New Applications of Methyl 2-Chloro-2-cyclopropylideneacetate Towards the Synthesis of Biologically Important Heterocycles

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Meinem Lehrer, Herrn Prof. A. de Meijere, möchte ich an dieser Stelle für die Überlassung des interessanten Themas, seine hilfreichen Anregungen, seine Diskussionsbereitschaft und die stete Unterstützung während der Anfertigung dieser Arbeit herzlich danken.

To My Parents

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1. Introduction

Organic synthesis has a long history that can be traced back to ancient times, although it was not recognized as such, due to lack of scientific knowledge. As a science, arguably the synthesis of urea by Wöhler in the year 1828 is the beginning of organic synthesis. This synthesis was followed by other milestones such as synthesis of acetic acid (Kolbe, 1885), glucose (Fisher, 1890), α-terpineols (Perkin, 1904), camphor (Komppa, 1903), torpinone (Robinson, 1917), quinine (Woodward, 1944), and many other natural products.[1] Today, organic synthesis can be broadly divided into two main parts: target oriented (total synthesis) and method oriented. The target oriented molecule can be a natural product or a designed molecule. The organic chemist is free to imagine and design unlimited numbers of new molecules never seen before either in nature or in the laboratory. This molecular design process is often guided by the particular interests of the chemist and can be aided by molecular modeling studies. These designed molecules can be of theoretical, physical, material science or biological interest. Undoubtedly, the most fertile area of molecular design for the organic chemist is that of biologically interesting molecules. Frequently the designed molecule are based on the structures of bioactive natural products (natural product analogue) or a completely imagined molecule targeted towards a specific biological action. Today molecular design, chemical synthesis and the biological evaluation is a powerful multidisciplinary approach to drug discovery and development. For this reason it has been a great challenge for a synthetic chemist to synthesize analogues of natural products.

From the last twenty years there has been a lot of work directed towards the cyclopropyl group as a special substituent in biologically active molecules. Natural and synthetic compounds bearing a cyclopropyl group are endowed with large spectrum of biological properties ranging from enzyme inhibitions to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor and antiviral activities.[2] The cyclopropane ring, due to its unusual bonding and inherent ring strain (27.5 kcal/mol) is unique among carbocycles in both its properties and reactions.[3] Consequently numerous methods have been developed for the construction of cyclopropanes. Among them metal-catalyzed cyclopropanation, in particular that of alkenes with ethyl diazoacetate, is one of the most simple and straightforward approaches for the preparation of cyclopropanes. Initially copper complexes were widely used as catalysts for the cyclopropanation of alkenes with diazo compounds.[4] Subsequently, rhodium carboxylates have been reported to be highly effective catalyst for cyclopropanation.[5] Among cyclopropanes, cyclopropanols have long

stimulated a spate of synthetic and mechanistic studies due to their unique reactivity.[6] Cyclopropanols are prone to ring-opening reaction and can easily be converted into certain classes of organic compounds in particular, to carbonyl compounds by ring opening followed by reaction with electrophiles.[7] In 1989, Kulinkovich et al. have developed a synthetically useful reaction in which a titanacyclopropane intermediate act as a formal 1,2-dicarbanionic equivalent, and thus leads to the formation of two new carbon-carbon bonds, allowing the conversion of ester to caclopropanols.[8] This Kulinkovich reaction has been extended by de Meijere et al. for the synthesis of cyclopropyl amines from *N*,*N*-dialkycarboxamide.[9]

This is an important milestone in the field of cyclopropane chemistry, because around 200 pharmaceutically relevant compounds contains cyclopropyl amine moiety. Some examples of biologically important molecules containing cyclopropyl group are Ciprofloxacin (**1**)[10] and Trovaflaxine (**2**)[11] (Figure 1) which belong to a major class of fluoroquinolones antibacterials with great therapeutic potential and are widely used to treat patients with infections.

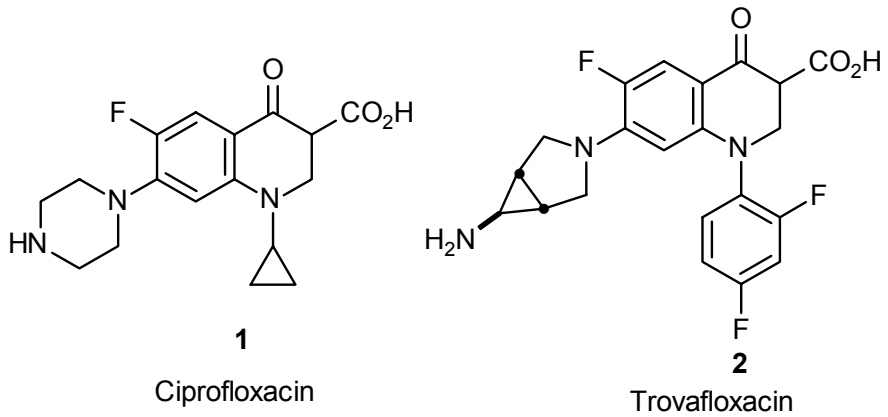


Figure 1. Sructure of quinolone antibacterial agents, Ciprofloxacin (**1**), Trovafloxacin (**2**).

Nature also makes use of cyclopropyl groups even in amino acids,[12] and most of the naturally occurring amino acids with a cyclopropyl group, as well as most of the cyclopropyl analogues of natural amino acids, are responsible for the observed biological activities of compounds containing them as constituents. The design and synthesis of unnatural amino acid for incorporation into peptides in order to confer conformational constraint, leading to potential improvements in biological activity, as well as to increase biostability, continues to be of great interest.[13] The studies by Hruby et al. have shown that topographically constrained amino acid analogues can lead to dramatic change in potency and receptor selectivity of the peptide and have

provided valuable insights about the role which play in amino acid residues in the peptide interaction with the receptor.[14]

The synthetic methodology based on the reactions of highly functionalized methylene-cyclopropanes, has been growing steadily over the past decade.[15] In particular the acceptor-activated methylenecyclopropanes, like (substituted) alkyl cyclopropylideneacetates (**3**),[16] alkyl 2-bromo-2-cyclopropylideneacetates (**4**)[17] and methyl 2-chloro-2-cyclopropylideneacetates (**5**)[18] (Figure 2) are highly functionalized valuable building blocks for organic synthesis.

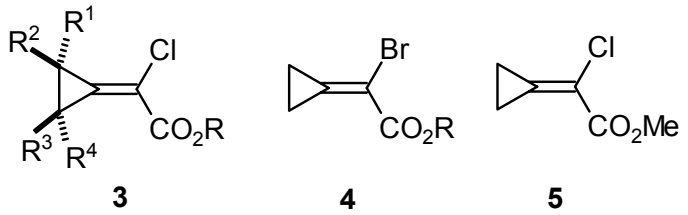
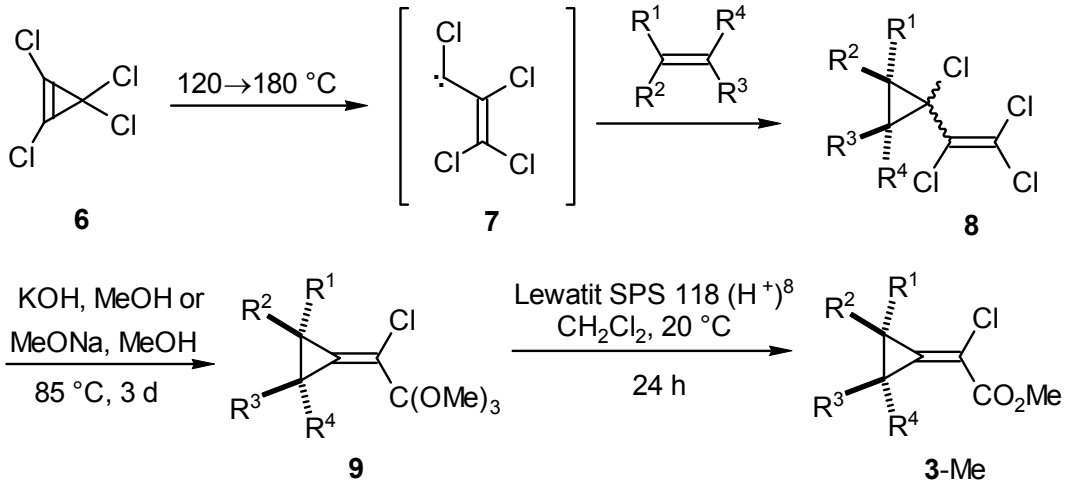


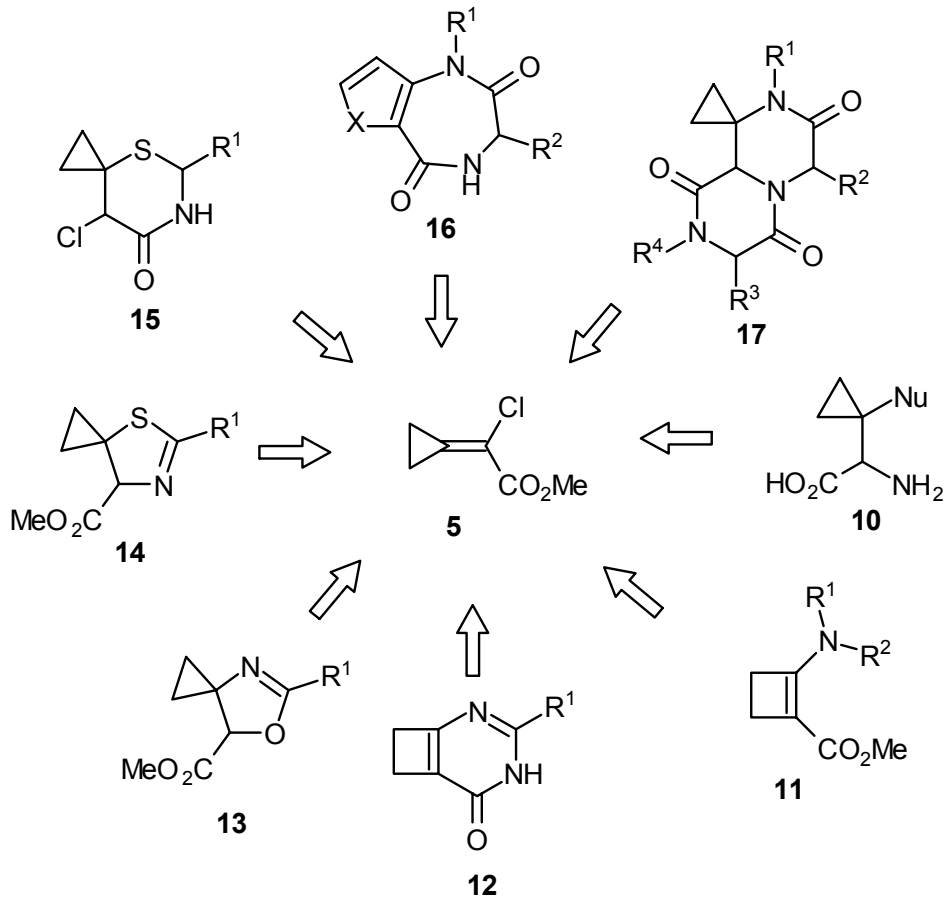
Figure 2. Alkyl 2-chloro-2-cyclopropylideneacetates **3**, **5** and the bromo analogue **4**.

In the year 1982 de Meijere et al. has described a synthetic method for synthesis of variously substituted methyl 2-chloro-2-cyclopropylideneacetates (**3**-Me) starting from tetrachloro-cyclopropene (**6**).[18] Tetrachlorocyclopropene readily available from tetrachloroethane and sodium trichloro-acetate,[19] undergoes thermal ring opening in an autoclave to perchloro-vinylcarbene (**7**), which can be efficiently trapped with a large number of alkenes to form 1-chloro-1-(trichloroethenyl)-cyclopropane **8**.



Scheme 1. Synthesis of substituted methyl 2-chloro-2-cyclopropylideneacetates (**3**-Me).

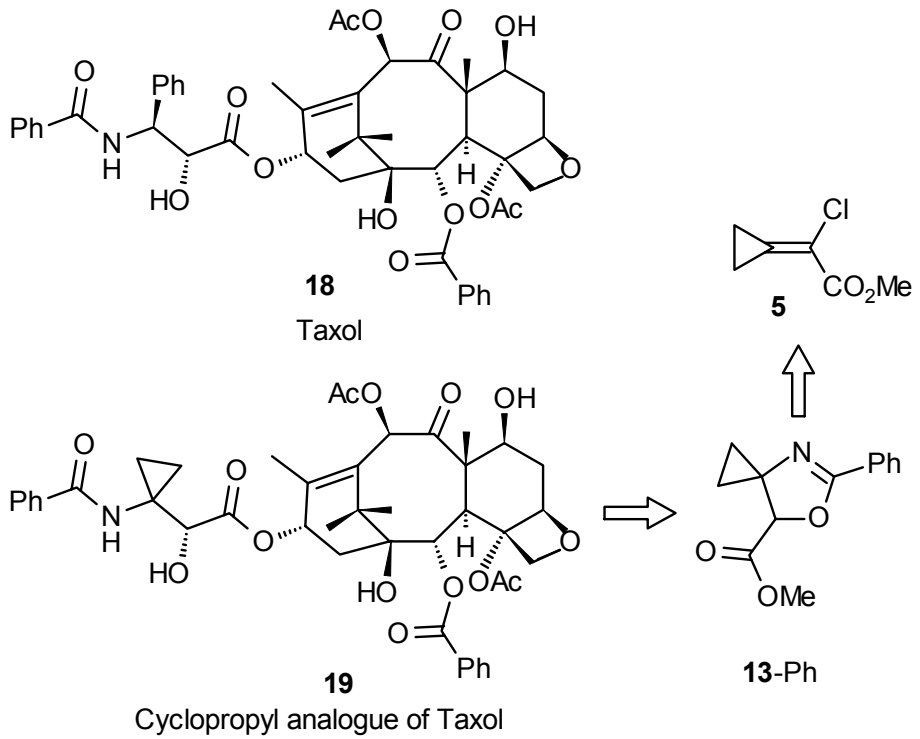
From these intermediates, substituted methyl 2-chloro-2-cyclopropylideneacetates (**3**-Me) can be obtained by treatment with potassium hydroxide or sodium methoxide in methanol followed by acidic hydrolysis of the resulting orthoesters **9** (Scheme 1). The bromo analogues alkyl 2-bromo-2-cyclopropylideneacetates **4** can be synthesized by the Wittig olefinations of cyclopropanone ethyl hemiacetal with appropriately substituted triphenyl methylenephosphoranes.[17] These methylene cyclopropanes, in particular methyl 2-chloro-2-cyclopropylideneacetate (**5**) are very reactive Michael acceptor than any other 3,3-di-substituted acrylates. The addition of most nucleophiles occurs smoothly and this is partly due to the strain release upon conversion of *sp*- to sp^2-hybridized carbon[3] and is also due to the presence of the α-chloro substituent.[20] Due to its enhanced reactivities and multi-functionalities, **5** can be applied in a broad sense towards elegant syntheses of spirocyclopropanated carbo-[21] and heterocycles,[22] various cyclopropyl-group containing amino-acids[23] as well as biologically active conformationally restricted peptide mimics[24] with different ring size and substituent. This can be achieved either by chemical transformations of the primary Michael adducts or by addition of a bidentate nucleophile on to **5**. The 1,4-addition of the nitrogen nucleophile with **5** proceeds very smoothly which after nucleophilic substitution of chlorine give the alanine analogue **10**.[25] The Michael adducts of diphenymethylene-amine (benzophenone imine) or benzylamine with **5** efficiently undergo further transformation to give cyclobutene derivatives (**11**).[23] Amidines react with **5** in the presence of triethyl amine in dioxane to give cyclobutene annelated pyrimidinones (**12**) by Michael reaction followed by domino transformation.[26] The reaction of **5** with aryl amides in presence of NaH or with aryl thioamide in presence of $NaHCO_3$ in acetonitrile generates spirocyclopropane oxazolines (**13**)[27] and thiazolines (**14**).[28] The kind of product obtained by Michael addition depends on the nature of reagents used. When $Ti(iPrO)_4$ is used, reaction of aryl thioamides with **5** undergoe a six-membered ring-closure to give the corresponding 5,6-dihydro-1,3-thiazin-4-ones (**15**).[28] Pyrrolo[3,2-e]diazepinedione derivatives (**16**) can also be prepared from **5**.[24] A broad variety of geometrically defined spirocyclopropane bicyclic peptides **17** can also be obtained from **5** by sequence of reactions[24] (Scheme 2).



Scheme 2. Retrosynthetic analysis of cyclobutene derivatives, spirocyclopropanated carbo- and hetero-cycles from methyl 2-chloro-2-cyclopropylideneacetate (**5**).

The reaction of aryl amides or thioamide with **5** for the synthesis of oxazolines (**13**) or thiazolines (**14**) are particularly very interesting from a biological point of view, since oxazolines and thiazolines are present in many biologically active natural products[29] and are found as a peptide link modification widespread into metabolites from bacterial and merine origin.[30] The conformation constraint introduced by these "peptide mimic" can be used for the design of peptide analogue of pharmacologically interesting molecules. For this reason, these heterocyclic units have been used as scaffolding devices in peptide sequences which lead to the stabilization of the reverse turn secondary structure.[31] Chiral oxazoline derivatives are used for enantiospecific total synthesis of natural products[32] and are also widely applied as ligands in asymmetric synthesis.[33] Oxazolines have been also shown to be suitable precursors for the paclitaxel side chain.[34] Paclitaxel (Taxol®) **18**, originally isolated from the pacific yew (*Taxus brevifolia*),[35] has become an important anticancer drug, especially for the treatment of refractory ovarian cancer, small-cell

lung cancer, and metastatic breast disease.[36] The first total synthesis of Taxol was achieved by Nicolaou et al.,[37] where the side chain was attached by ring-opening condensation with an appropriately substituted β-lactam. Since cyclopropyl groups have been proved to be highly effective in improving the activity of many biologically active compounds,[2a,b][38] several cyclopropane-bearing analogues of paclitaxel have been synthesized and shown to have improved or retained anticancer activity.[39] The phenyl derivative of the above spirocyclopropanated oxazoline (**13**-Ph) has been used for the synthesis of C-3'-cyclopropanated Taxol analogue **19** (Scheme 3).[40]



Scheme 3. Structure of Taxol and retrosynthetic analysis for the cyclopropane derivatives of it.

The reaction of methyl 2-chloro-2-cyclopropylideneacetate **5** with amidine producing cyclobutene-annelated pyrimidinones (**12)** resemble hetero analogues of benzocyclobutenes and undergo cyclobutene ring opening followed by Diels-Alder reaction with dienophile to give tetrahydroquinazolinone derivatives.[26] Tetrahydroquinazolinones are important class of heterocycles and have found to be attracted by pharmaceutical chemists.[41] One good example containing tetrahydroquinazolinones is the Folic acid analogue (**20**). Folic acid (**21**) (Figure 3) one of the important B vitamins, is a precursor for the biogenetic synthesis of the cofactor,

tetrahydrofolic acid conjugate.[42] This later in turn, serves both as a formyl and hydroxymethyl transfer agent in a variety of biological system. The analogue 5,8-dideaza-5,6,7,8-tetrahydrofolic acid (**20**) have attracted considerable attention in chemistry[43] and biology.[44] A wide range of biological activities has been discovered for such compound, like anticancer properties, antimicrobial activity against *Streptococcus feacium*, inhibition of dihydrofolate reductive and thymidilate synthase,[45] as well as an ability to be a good substrate for mouse liver folylpolyglutamate synthetase.[46]

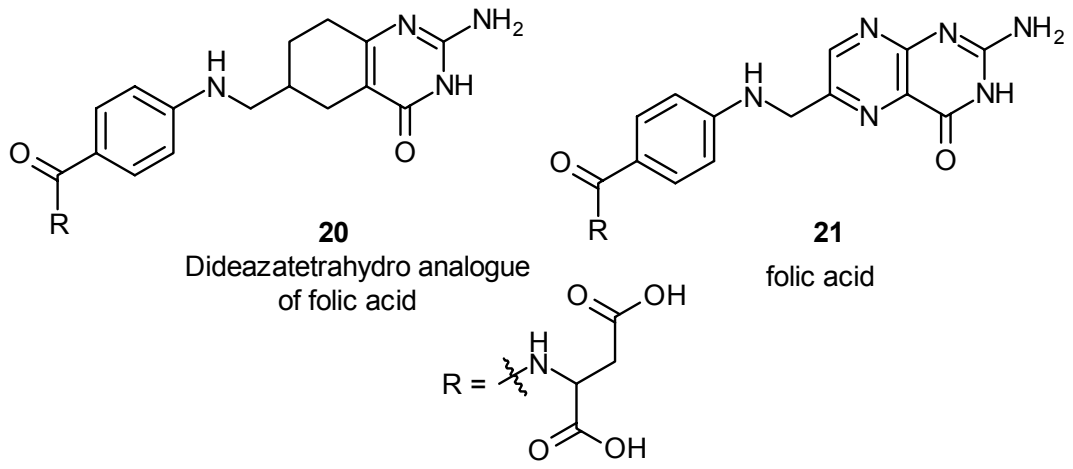
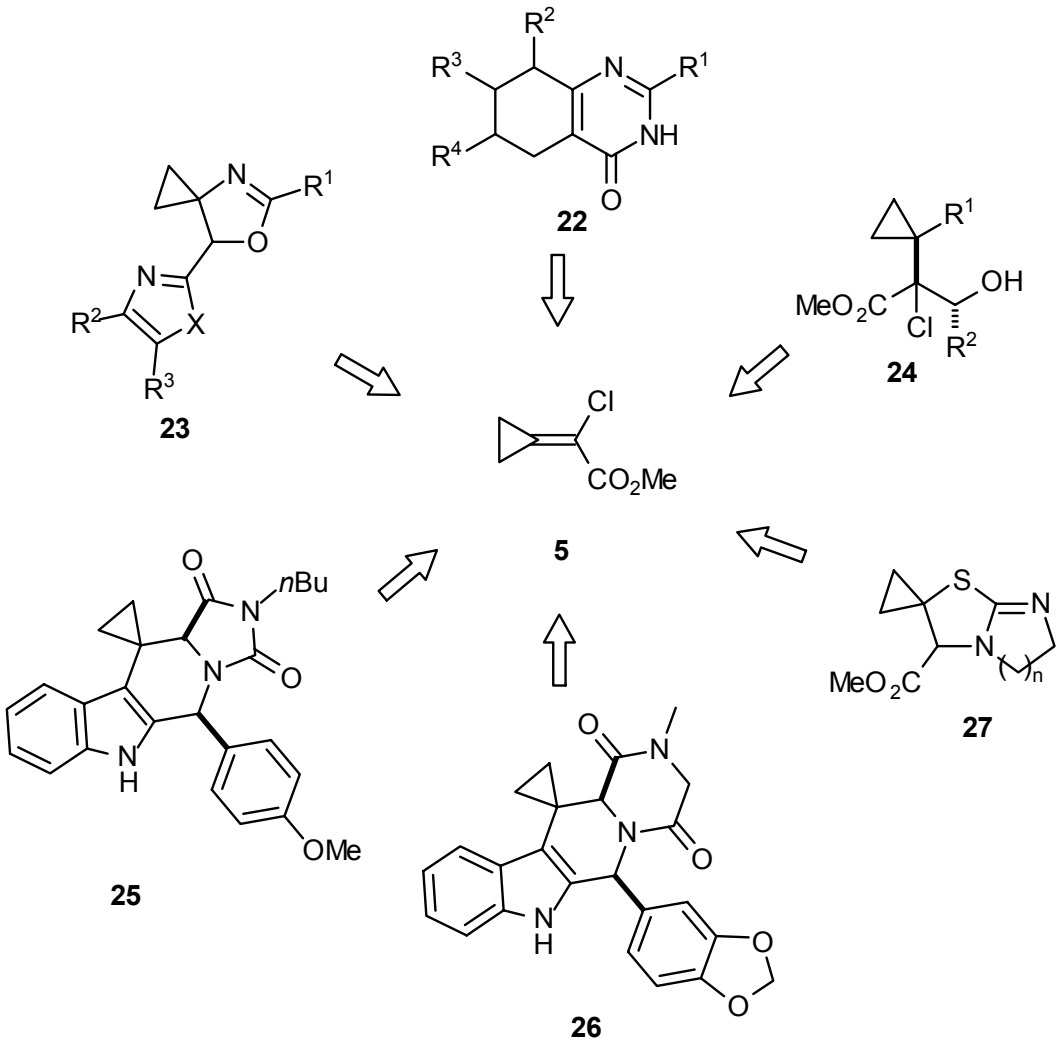


Figure 3. Structure of Folic acid and tetrahydro analogue of Folic acid.

Although methyl 2-chloro-2-cyclopropylideneacetate (**5**) have shown to be potential Michael acceptor, this building block have not really been easily available yet. The method described by de Meijere et al. requires a halide-resistant autoclave for the thermal ring opening reaction and the overall atom economy is rather poor.[18] The previously developed synthesis of the bromo derivative (**4**-Me) starts from cyclopropanone ethyl hemiacetal (the preparation of which requires the generation as well as handling of finely dispersed sodium) and the Wittig olefinations with the appropriately substituted triphenyl-methylenephosphoranes do not provide good yields of the product. With the more recently developed conversion of carboxylic acid esters to cyclopropanols, the Kulinkovich reaction[8] in hand, an advanced synthesis of **5** or **4**-Me ought to be developed.

It is mentioned before that pyrimidinones and tetrahydroquinazolinones are among the most important class of heterocycles that are present in many biologically active molecules. Literature shows that, only a few different methods for the synthesis of tetrahydroquinazolinone derivatives are described.[47] Since a versatile method for the synthesis of cyclobutene annelated

pyrimidinones is known,[26] an appropriate method has to be developed for conversion to variously substituted tetrahydro quinazolinones (**22**). Lewis-acid catalyzed Michael addition of indoles onto Michael acceptors[48] provides 3-substituted tryptophane analogues[49] and other indole derivatives.[50] In view of the fact that methyl 2-chloro-2-cyclopropylideneacetate (**5**) is a particularly reactive Michael acceptor a synthetic method to cyclopropane analogue of tryptophan ought to be achieved by Michael addition of **5** onto indole, and to use it as a precursor for the synthesis of cyclopropane analogue of the PDE5 inhibitors, the hydrantoin lead structure to Tadalafil (**25**)[51] and Tadalafil (**26**)[52] itself.



Scheme 4. Retrosynthetic analysis for the synthesis of different molecule from **5**.

Since a method for the synthesis of spirocyclopropane oxazoline carboxylate is well established the conversion of the carboxylate group to a herterocycle such as oxazole, thiazole or benzoxazole

(**23**) has to be found out. In a same way as with thioamides, the Michael addition of alkylated thiourea to produce thiazolines (**27**) has to be studied.

Domino processes[53] consisting of a Michael addition and an aldol reaction,[54] especially the one known as the Robinson annelation[55] were the first of these now extremely popular sequential reactions which provide a one-pot access to complex skeletons from relatively simple starting materials.[56] After the successful Michael addition, a sequential Michael addition-aldol reaction of Grignard reagents and aldehydes onto **5** for the synthesis of chlorohydrins (**24**) has to be investigated (Scheme 4).

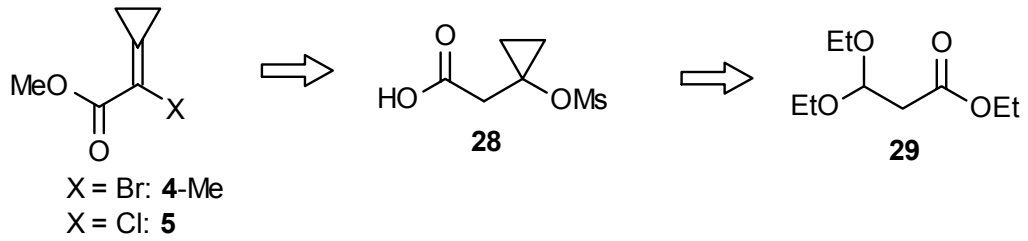
The aim of this work can be summarized as follows:

1. An advanced, simple and economical method for the synthesis of the acceptor-activated methylenecyclopropanes **5** and **4**-Me.
2. Synthesis of dihydro- and tetrahydro-quinazolinones by Michael addition of amidine onto **5** followed by Diels-Alder reaction with suitable dienophiles.
3. Synthesis of variously substituted spirocyclopropane oxazolines containing benzoxazole.
4. Synthesis of spirocyclopropane analogue of tryptophane and its use for the synthesis of Tadalafil (**26**) and hydrantoin lead structure to Tadalafil (**25**).
5. Sequential addition of Grignard reagent and aldehydes with **5** for synthesis of chlorohydrins (**24**).

2. Main Part

2.1. An Advanced Synthesis of Methyl 2-chloro- and 2-bromo-2-cyclopropylideneacetate

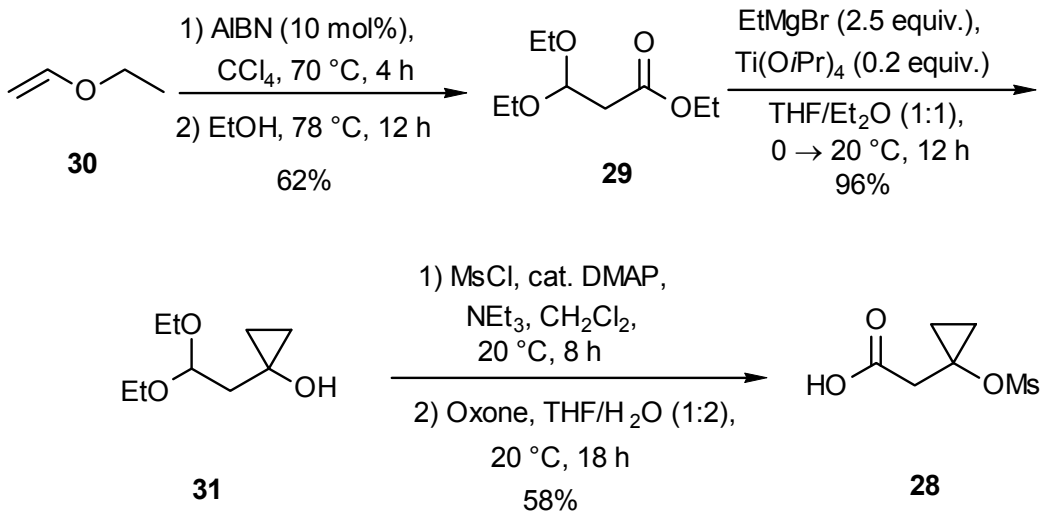
The first aim of this project was to develop a advanced method for the preparation of the methylenecyclopropane **4**-Me and **5** by the use of the Kulinkovich reaction.[8] It was assumed that the cyclopropanol obtained form the Kulinkovich reaction of the ester **29** could be converted to the carboxylic acid **28** as a key intermediate which in turn could be transformed to the desired methylene cyclopropanes. The retrosynthetic analysis to **4**-Me and **5** is presented in Scheme 5.[57]



Scheme 5. Retrosynthetic analysis for the synthesis of Methyl 2-chloro- and 2-bromocyclo-propylideneacetate.

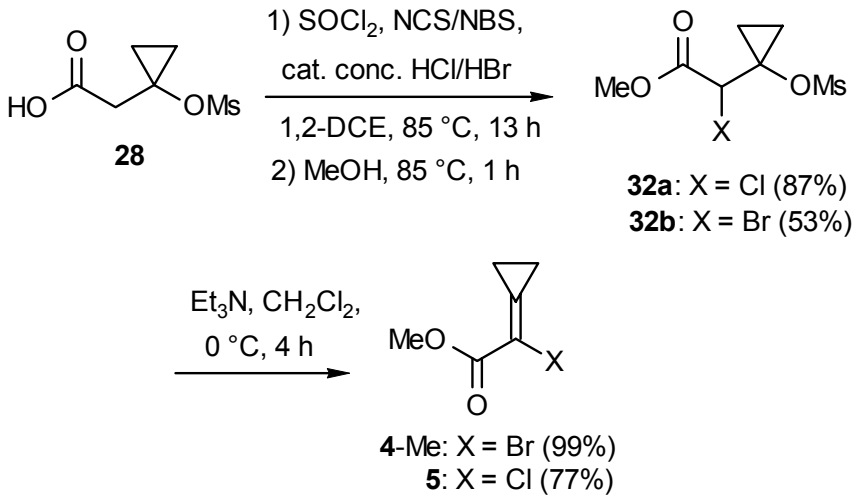
Having the 2-(1'-mesyloxycyclopropyl)acetic acid (**28**) in mind as a key intermediate for the synthesis of **4**-Me and **5**, compound **29** with a masked carboxyl group was considered as a precursor. Although the methyl analogue (methyl 3,3-dimethoxypropionate) is commercially available or easily prepared by Walker oxidation of methyl acylate,[58] the ethyl 3,3-dimethoxypropionate (**29**) could be prepared on a large scale (4 mol) starting from ethyl vinyl ether, tetrachloromethane and ethanol by a little modification of the method described in the literature.[59] When the reaction was carried out at 50 °C, as described in the literature, the product (**29**) was obtained only in 12% after 2 days. However, by increasing the reaction temperature to 70 °C the product could be isolated in 62% yield after 15 h. The Kulinkovich reductive cyclopropanation of **29** under the established conditions yielded the cyclopropanol **31** in 96% yield even on a reasonably large scale (ca. 1 mol).[60] The cyclopropanol **31** was cleanly transformed under DMAP-catalysis (5 mol%) in the presence of triethylamine as to the corresponding mesylate. It has been observed that this mesylate is not stable and decomposes when standing for a long time at room temperature. Anyway, this compound could be deprotected

and oxidized in situ with 1.5 equiv. of Oxone, crystallization from diethyl ether afforded the pure acid **28** as a colorless crystalline compound (Scheme 6).



Scheme 6. Preparation of 2-(1'-mesyloxycyclopropyl)acetic acid from ethyl vinyl ether.

Attempted α-bromination of the in situ generated acid chloride of **28** with a catalytic amount of chlorosulfonic acid and molecular bromine at 85 °C failed, just like the first attempts to halogenate **28** with NCS in dichloromethane, probably because of the poor solubility of **28** and the acid chloride of **28** in tetrachloromethane. However, 1,2-dichloroethane as a better solvent for the starting material upon chlorination with NCS and subsequent treatment with methanol led to the α-chloro ester **32a** in 87% yield (Scheme 3).



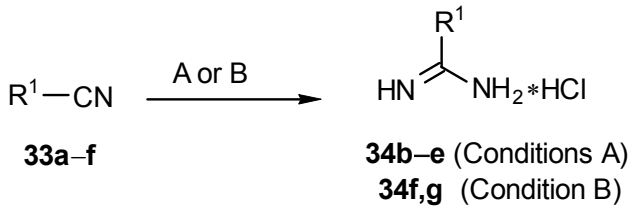
Scheme 7. Transformation of **28** to methyl 2-halo-2-cyclopropylideneacetates **4**-Me and **5**.

Under the same conditions, the acid chloride of **28** could be transformed to the α-bromo ester **32b** with NBS and a catalytic amount of concentrated hydrobromic acid in 53% yield. Although **32a** and **29b** could be purified by silica gel chromatography, they appeared not to be very stable under these conditions. Therefore, the crude halogenated esters **32a** and **32b** were directly subjected to dehydrohalogenation by treatment with triethylamine in dichloromethane at 0 °C. The resulting methyl 2-chloro-2-cyclopropylideneacetate (**5**) could be purified by bulb to bulb distillation and crystallization from pentane/Et_2O while bromo analogue **4**-Me was purified by chromatography in very good yields (Scheme 7).[61]

2.2. Tetrahydroquinazolinone Derivatives

2.2.1. Synthesis of amidines from nitriles

Among various methods for preparation of amidines from nitriles,[62] we found that the method described by Reed et al.[62b] was the best for our substrates. When a THF solution of p-chlorobenzyl nitrile was added to a 1 N solution of LiHMDS in hexane, followed by quenching with 6 N isopropanolic HCl, the corresponding amidine **34b** was isolated in 93% yield. Following the same method other amidines **34c–e** were formed and isolated in good to excellent yield. Surprisingly, under the same conditions *o*-phenyl benzonitrile failed to give the corresponding amidine **34f**. This compound was prepared by the method descried by Wolfgang von der Sall et al.[62e] When a solution of *o*-phenyl benzonitrile in toluene was added to a freshly prepared solution of $MeAl(Cl)NH_2$ in toluene, **34f** was isolated in 58% yield. In the same way **34g** was prepared with 84% yield. These results are summarized in Scheme 8 and Table 1.



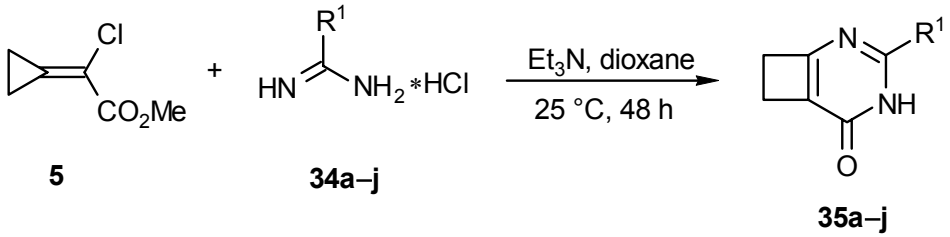
Scheme 8. Synthesis of amidines (**34b–g**) from nitriles **33a–f**. Conditions A: LiHMDS (1 N , hexane), THF, 25 °C, 4 h, 6 N HCl (iPrOH); conditions B: Me_3Al (1 M, toluene), NH_4Cl, toluene, 120 °C, 15 h.

Table 1. Yield and reaction conditions of preparation of amidines **34b–g** from nitriles.

Entry	R^1	Reaction Conditions	Product	Yield (%)
	p-ClC_6H_4	**A**	**34b**	93
	o-BrC_6H_4	**A**	**34c**	91
	o-FC_6H_4	**A**	**34d**	80
	p-$(C_6H_5CH_2O)C_6H_4$	**A**	**34e**	92
	o-PhC_6H_4	**B**	**34f**	58
	3-(5-chloro-benzo[b]thiophene)	**B**	**34g**	84

2.2.2. Synthesis of cyclobutene-annelated pyrimidinones

When a mixture of methyl 2-chloro-2-cyclopropylidineacetate **5** and 2 equivalents of benzamidine hydrochloride **34a** was stirred in dioxane in the presence of 4 equivalents of triethylamine for 48 h at room temperature, 3-phenyl-2,4-diazabicyclo[4.2.0]octa-1(6),2-diene-5-one (**35a**) was isolated in 83% yield.[63]The product **35a** is very less soluble either in Et_2O or in dichloromethane but could be easily precipitated from MeOH. Similarly, under the same conditions the other pyrimidinones **35b–j** were obtained in good yields (68–82 %).



Scheme 9. Michael addition of amidines (**34a–j**) to **5** for the synthesis of cyclobutene annelated pyrimidinones **35a–j**.

Table 2. Yields of the pyrimidinones from Michael addition of amidines onto **5**.

Entry	Amidines	R^1	Product	Yield (%)
1	**34a**	Ph	**35a**	83
2	**34b**	*p*-ClC_6H_4	**35b**	78
3	**34c**	*o*-BrC_6H_4	**35c**	76
4	**34d**	*o*-FC_6H_4	**35d**	82
5	**34e**	*p*-$(C_6H_5CH_2O)C_6H_4$	**35e**	68
6	**34f**	*o*-PhC_6H_4	**35f**	80
7	**34g**	3-(5-chloro-benzo[b]thiophene)	**35g**	74
8	**34h**	SMe	**35h**	74
9	**34i**	$N(Bn)_2$	**35i**	66
10	**34j**	OMe	**35j**	38

Less reactive *S*-methylisothiourea hemisulpahte and dibenzyl guanidine[64] produced the corresponding pyrimidinones **35h** and **35i** at 50 °C in 74% and 66% yield respectively. Similarly the *O*-methylurea also furnished the pyrimidinone **35j** in 38% yield(Scheme 9, Table 2).

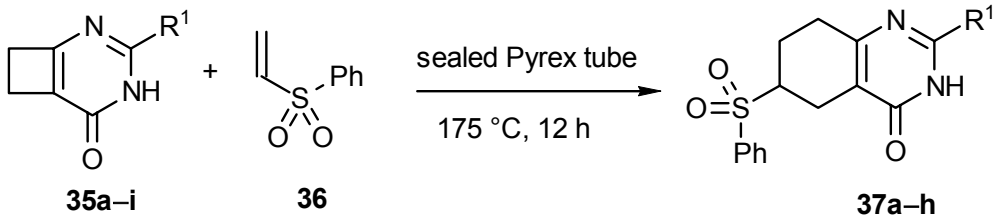
2.2.3. Cyclobutene ring opening and subsequent Diels-Alder reaction

Diels-Alder reaction[65] is a powerful construction protocol in organic synthesis, an easy method for the synthesis of the carbon-carbon bond formation of cyclic and bicyclic organic compounds. A wide variety of natural products skeleton has been constructed using this method.[66] The above cyclobutene-annelated pyrimidinones **35** resemble hetero analogues of benzocyclobutene and it was interesting to open the cyclobutene ring so that the in situ formed butadiene would react with a suitable ethylene equivalent dienophile to give tetrahydroquinazolinone derivatives. The low reactivity of alkenes and alkynes as dienophilic reagents rank as one of the foremost limitations of Diels-Alder cycloaddition chemistry. It is well known that to achieve the [4+2] cycloaddition of ethylene to butadienes a temperature of 175 °C and a pressure of 6000 psi or more are require.[67] Therefore, a number of ethylene and acetylene equivalents have been developed to circumvent this problem. Among them, of particular interest and synthetically important are the dienophiles that are activated by sulphur, such as sulphoxide and sulfone. The best known is phenyl vinyl sulfone developed by L. P. Paquette et al.[68] Although this sulfone has been used as a dienophile in an intramolecular Diels-Alder reaction with cyclobutene ring,[69] a regioselective intermolecular addition to cyclobutene ring has never been achieved. In order to optimize the reaction conditions, we chose the compound **35a**. The reactions of **35a** with excess of phenyl vinyl sulfone (**36**) in toluene or in 1,2-dichlorobenzene at 175 °C in a closed Pyrex tube for 12 h gave the corresponding Diels-Alder adduct **37a** in very poor yields (Table 1, entries 1, 2), but interestingly only one regioisomer was found. As the melting point of **36** is 68 °C, the reaction was carried out in liquid of **36**. When a mixture of **35a** and 10-fold excess of **36** were heated at 175 °C for 12 h under solvent free conditions, 2-phenyl-6-benzenesulfonyl-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one **37a** was isolated in 84% yield as one regioisomer (entry 3). Its structure was assigned on the basis of ^{1}H-NMR, ^{13}C-NMR, HMBC, HMQC, MS as well as single crystal structure of the 6-ethyl derivative of it (**41b**). Decreasing the amount of **36** to 4 equivalents did not alter the yield (entry 4), but further going down to 1.5 equiv. or decreasing the temperature substantially reduced the yield (entries 5 and 6). These results are summarized in Table 3.

Table 3. Optimization of reaction conditions and yield of Diels-Alder reactions of **35a** with phenyl vinyl sulfone **36**.

Entry	Equiv. of **33**	Reaction conditions	Yield of **37a**(%)
1	excess	1,2-dichlorobenzene, 175 °C, 12 h	25
2	excess	toluene, 175 °C, 12 h	32
3	10	neat, 175 °C, 12 h	84
4	4	neat, 175 °C, 12 h	83
5	1.5	neat, 175 °C, 12 h	49
6	4	neat, 165 °C, 12 h	39

Once the optimal conditions were found for **35a** (entry 4), we performed the ring-opening reactions to **35a**–**i** and synthesized the corresponding adducts **37a**–h in good yields (Scheme 10, Table 4). Surprisingly **35i** decomposed under these reaction conditions.



Scheme 10. Thermal Diels-Alder reaction of **35** with phenyl vinyl sulfone.

Tabale 4: Yeild of Diels-Alder reaction products **37a**–**h** from the starting material **35a**–**h**.

Entry	Compound **35**	R^1	Product	Yield (%)
1	**35a**	Ph	**37a**	83
2	**35b**	*p*-ClC_6H_4	**37b**	59
3	**35c**	*o*-BrC_6H_4	**37c**	43
4	**35d**	*o*-FC_6H_4	**37d**	70
5	**35e**	*p*-$(C_6H_5CH_2O)C_6H_4$	**37e**	66
6	**35f**	*o*-PhC_6H_4	**37f**	65
7	**35g**	3-(5-chloro-benzo[b]thiophene)	**37g**	88
8	**35h**	SMe	**37h**	56
9	**35i**	$N(Bn)_2$	**37i**	00

2.2.4. Microwave assisted Diels-Alder reaction

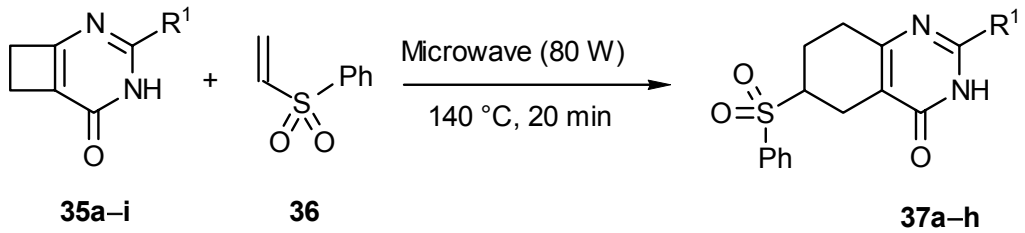
Microwave-assisted organic reactions have attracted the attention of synthetic chemists[70] as they can decrease the reaction time, can be performed efficiently with less byproducts and most importantly in solvent free conditions. Due to all these factors more focus is been paid now a days to microwave assisted organic reaction. Microwaves have been used to carry out organometallic cross-coupling reactions, heterocycles synthesis, solid-phase synthesis, condensations as well as cycloaddition reactions.[71] Since the Diels-Alder reaction carried out above is a thermal reaction and needed temperature of at least 175 °C, the application of microwaves irradiation in this case is very significant. Although efforts have been paid to promote the Diels-Alder reaction [72] by microwave irradiation, a cyclobutene ring-opening followed by Diels-Alder reactions has never been achieved before. For this reason we were interested in carrying out the ring-opening reaction and Diels-Alder reaction using microwaves. For optimizing the reaction conditions, we tried the reaction between **35a** and **36** at 170 °C for 10 min. Although the reaction was completed (as observed by HPLC) the crude reaction mixture was completely black, which might be due to decomposition of sulfone in these conditions. Despite the difficulty of purifying by column chromatography, 59% of product **37a** was isolated. It was surprising that the yield increased to 64% and 70% when the temperature was decreased to 160 and 150 °C respectively, the crude reaction mixture was still black in colour.

Table 5. Optimisation of the reaction conditions and yield for microwave assisted reaction.

Entry	Temperature	Time	Yield **37a** (%)
1	170 °C	10 min	59
2	160 °C	10 min	64
3	150 °C	10 min	70
4	140 °C	10 min	57
5	140 °C	20 min	69
6	130 °C	20 min	55
7	130 °C	30 min	66
8	120 °C	20 min	20

Further decreasing the temperature to 140 °C for 10 min, led to decrease in yield to 57% (entry 4), as 21% of starting material was recovered. The extension of the reaction time to 20 min increased the yield to 69% (entry 5). Other conditions tried (entries 6,7,8) never gave better yields than entry 5. These results are summarized in Table 5.

Once the optimal conditions (entry 5) were found the other cyclobutene pyrimidinones were also reacted with **36** to give the products **37a**–**h** in yield ranging from 52 to 69%. Although the yields are lower in comparision with the use of oil bath, the higher reaction temperature and longer time could be avoided by using microwaves. As observed before, the reaction with **37i** did not give any product. These results are summarized in Scheme 11 and Table 6.



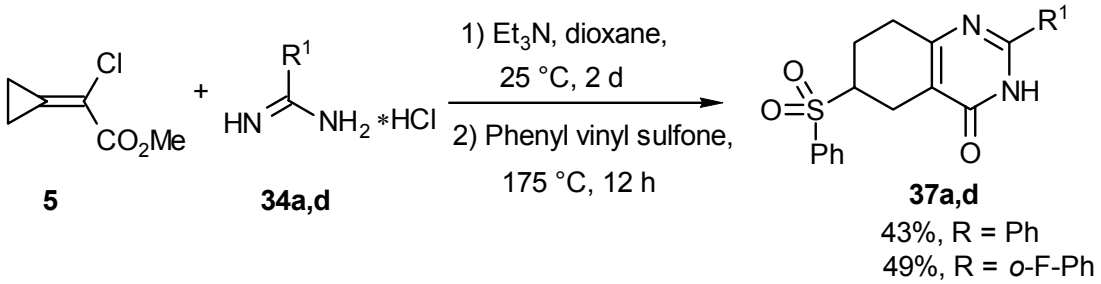
Scheme 11. Optimised conditions for the microwave assisted Diels-Alder reaction.

Table 6. Yields of the microwave assisted Diels-Alder reaction.

Entry	R^1	Product	Yield (%)
1	Ph	**37a**	69
2	*p*-Cl-Ph	**37b**	57
3	*o*-Br-Ph	**37c**	62
4	*o*-F-Ph	**37d**	57
5	*p*-($C_6H_5CH_2O$)Ph	**37e**	63
6	*o*-biphenyl	**37f**	63
7	3-(5-chloro-benzo[b]thiophene)	**37g**	52
8	SMe	**37h**	63
9	$N(Bn)_2$	**37i**	Decomposition

2.2.5. "One pot" synthesis of tetrahydroquinazolinones

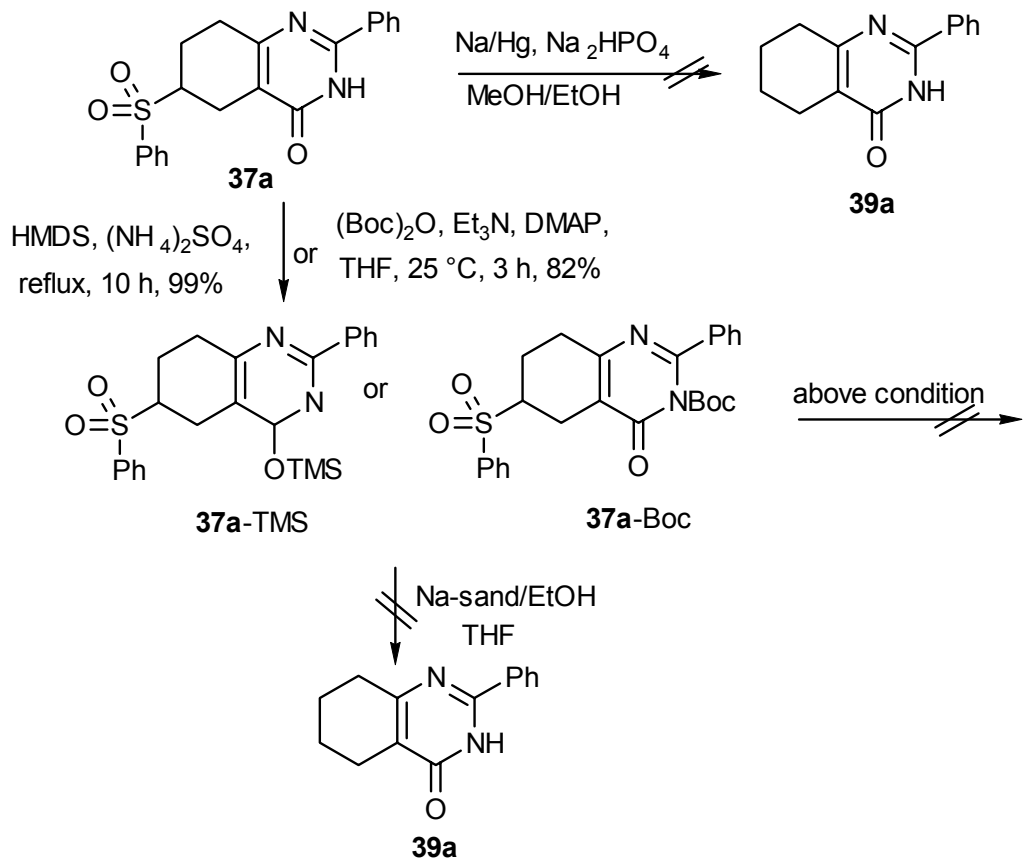
After the stepwise Michael addition and Diels-Alder reactions were successfully performed, it was interesting to carry out these two operations in "one pot" fashion. Indeed, when phenyl vinyl sulfone was added to the crude reaction mixture of benzamidine hydrochloride **34a** and **5** in presence of triethyl amine after 48 h in a Pyrex bottle and heated to 175 °C for 12 h, **37a** was isolated in 43% yield. A little higher yield was obtained in case of **34d** (Scheme 12).



Scheme 12. One pot synthesis of tetrahydroquinazolinones **37a,d** from **5** and amidines **34a,d**.

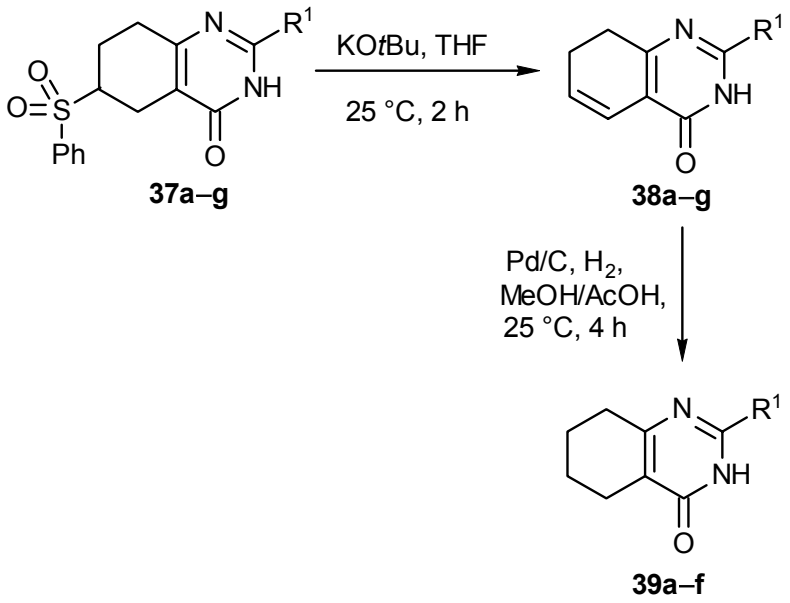
2.2.6. Reductive elimination of sulfone group

Once the tetrahydroquinazoline ring has been formed, the next issue was to remove the sulfonyl group. Although several methods are reported for this purpose, the one which involvs Na/Hg amalgam in the presence of Na_2HPO_4[73] has been most widely used. However, when **34a** (as well as its *O*-TMS protected or *N*-Boc protected equivalent) was reacted with Na/Hg and Na_2HPO_4 (4 equiv. each) in MeOH, only (deprotected) starting material was isolated without any reductive elimination. By changing the reagents to Na-sand/EtOH,[74] only substantial amount of benzaldehyde was isolated (Scheme 13).



Scheme 13. Removal of sulfone group by using Na/Hg amalgam or Na-sand/EtOH.

This problem was solved by using a two step procedure: basic elimination of the $PhSO_2$-group followed by Pd-catalysed hydrogenation of the resulting double bond. When 3 equiv. of KO*t*Bu were added to a THF solution of **37a**, the elimination product **38a** was obtained in 96% yield after 2 h. The subsequent hydrogenation of **38a** under Pd/C, in methanol led to the target substance 2-phenyl-5,6,7,8-tetrahydroquinazolinone **39a** in 91% yield. In a similar manner, **39c–f** were obtained from **37c–f** in excellent yields over two steps. Due to the low solubility of **38b** and **38e** in MeOH, the reaction was carried out in AcOH to give **39b** and **39e** in 94% and 93% yield respectively. In case of **38g**, the hydrogenation reaction was not successful due to the presence of *S*Me group which may be due to poisoning of the catalyst. Instead of the desired product, some amount of the material without *S*Me group was isolated. These results are summarised in Scheme 14 and Table 7.



Scheme 14. Basic elimination of $PhSO_2H$ group followed by hydrogenation: preparation of 2-substituted tetrahydroquinazolinones **39a**–**f**.

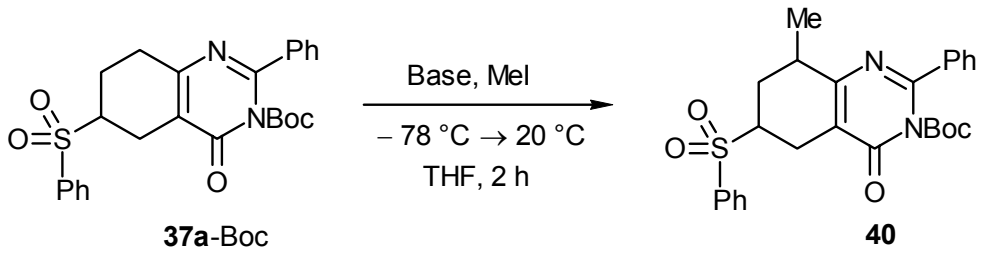
Table 7. Yields of elimination and hydrogenation reaction.

Entry	R^1	**38**	Yield (%)	**39**	Yield (%)
1	Ph	**38a**	96	**39a**	91
2	*p*-Cl-Ph	**38b**	95	**39b**	94
3	*o*-Br-Ph	**38c**	93	**39c**	91
4	*o*-F-Ph	**38d**	94	**39d**	92
5	*p*-($C_6H_5CH_2O$)Ph	**38e**	92	**39e**	93*
6	*o*-biphenyl	**38f**	87	**39f**	93
7	SMe	**38g**	98	**39g**	00
8	3-(5-Cl-1-benzo-thiophene)	**38h**	00		

*) With out benzyl group.

2.2.7. Alkylation of tetrahydroquinazolinones

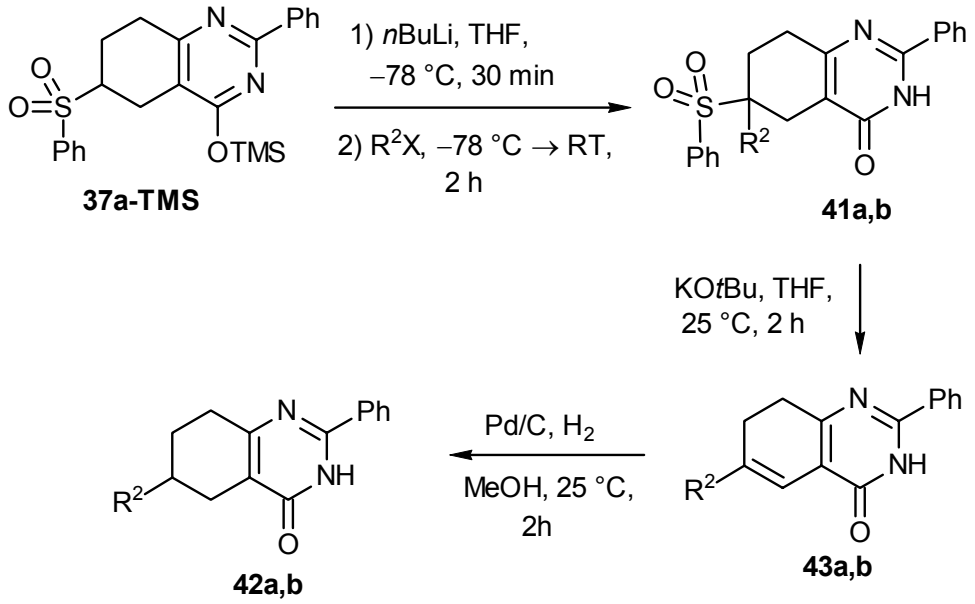
The presence of a strong electron acceptor at C-6 position – phenyl sulfonyl group – makes possible further derivatization at this centre, namely alkylation of the corresponding anion generated from an *O*- or *N*-protected precursor. Surprisingly, when a THF solution of *N*-Boc protected compound (**37a**-Boc) was subjected to *n*BuLi conditions followed by treatment with MeI, no alkylation was observed at C-6 instead, *N*-Boc-2-phenyl-8-methyl-6-phenylsulfonyl-tetrahydroquinazolin-one **40** was isolated. Changing the base from *n*BuLi to either LDA or NaHMDS gave the same product in lower yield (Scheme 15).



Entry	Base	Yield **40** (%)
1	*n*BuLi	28
2	LDA	19
3	NaHMDS	14

Scheme 15. Alkylation at C-8 of *N*- **37a**-Boc.

However, substitution at C-6 position could be achieved by changing the protecting group. Thus, when *O*-TMS protected compound (**37a**-TMS) was subjected to *n*BuLi conditions followed by treatment with alkyl halides, the desired products **41a**–**b** were obtained in good yields. The structure of **41b** could be known from X-ray crystallographic analysis (Figure 4) in which the sulfonyl group is attached to C-6 of the tetrahydro-ring to correspond to the outcome of a rigioselective Diels-Alder reaction. Elimination of sulfone group followed by hydrogenation lead to 2-phenyl-6-alkyltetrahydroquinazolinones **42a**–**b** (Scheme 16).



Scheme 16. Alkylation at C-6 position of tetrahydroquinazolinone

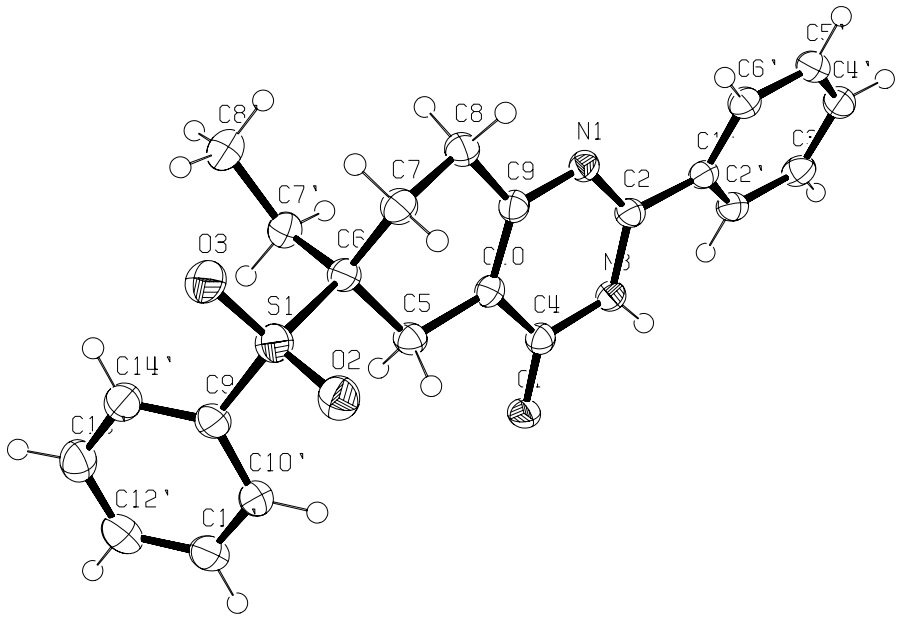
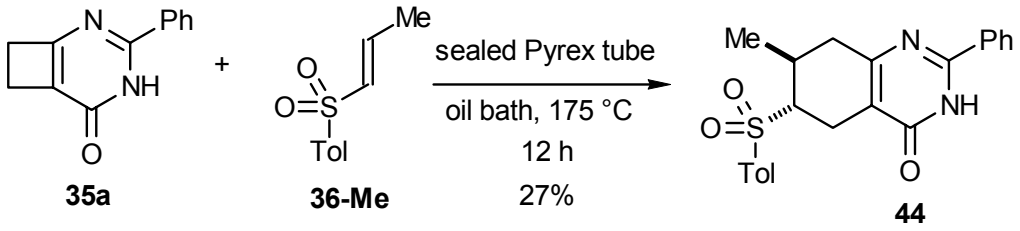


Figure. 4. Molecular structure of **41b** in crystal.

Table 8. Alkylation at sulfone centre (C-6) followed by the removal of $PhSO_2$-group to prepare 2-alkyl-tetrahydroquinazolinones **42a,b**.

R^2X	**41**	Yield (%)	**43**	Yield (%)	**42**	Yield (%)
MeI	**41a**	83	**43a**	95	**42a**	96
EtBr	**41b**	86	**43b**	97	**42b**	96

After successful substitution at C-6, the intention was to explore the possibility of getting a substituent also at the position C-7. An obvious option was to use a phenyl propenyl sulfone. Indeed, when **35a** was reacted with (*E*)-*p*-tolyl-1-propenyl sulfone (**36**-Me), the corresponding cycloaddition product (**44**) was isolated, albeit in 27% yield, as a mixture of two diasteriomers in a ratio of 1:1. An attempt to introduce an ethyl group failed, because the corresponding sulfone polymerized under these reaction conditions (Scheme 17).

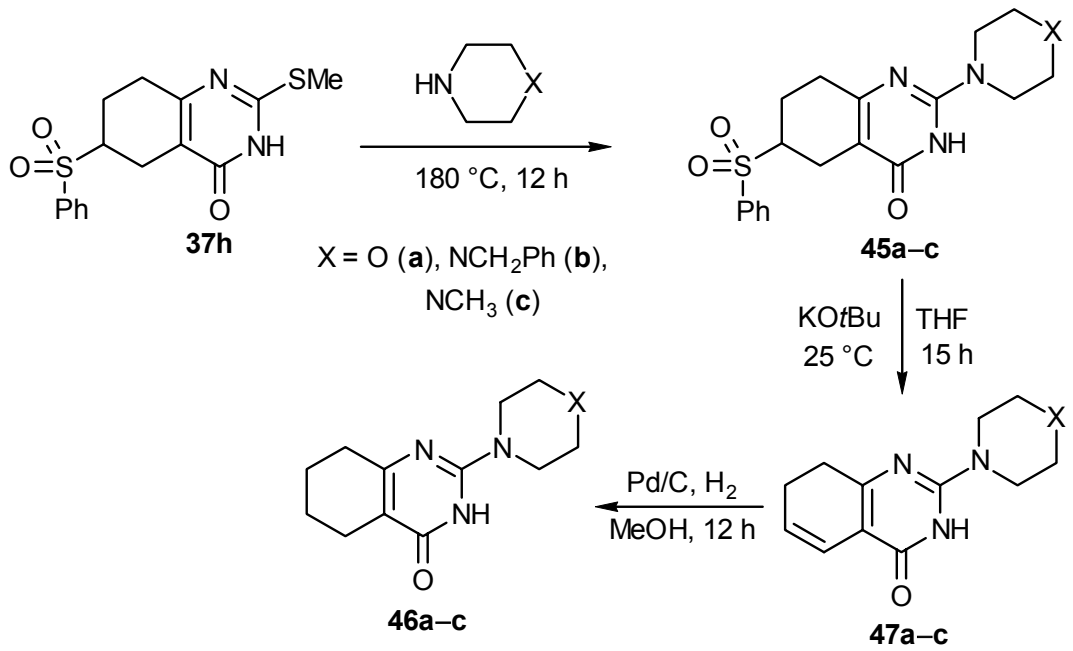


Scheme 17. Reaction of *p*-tolyl-1-propenyl sulfone **36**-Me with **35a**.

2.2.8. Nucleophilic substitution of SMe group for the synthesis of 2-amino tetrahydroquinazolinones

In order to check the opportunity of further derivatization at C-2, we intended to substitute the *S*Me group in **37h** by secondary amines. Initial attempt to get 2-morpholino-tetrahydroquinazolinone by reacting **37h** with 2 equivalents of morpholine in DMF at 180 °C for 12 h in a sealed Pyrex bottle failed, and this experiment afforded only 2-dimethylamino-6-phenylsulfonyltetrahydroquinazolinone (**48**) in 78% yield. Obviously, this product has been formed due to the instability of DMF at higher temperature and substitution of *S*Me by dimethyl amine. This was confirmed by heating **37h** in an excess of DMF at 180 °C without morpholine: the same product (**48**) was isolated in 86% yield. When **37h** was heated at 180 °C with an excess of morpholine without solvent for 12 h, 2-morpholino-6-phenylsulfonyl tetrahydroquinazolinone

(**45a**) was obtained in 93% yield. In a similar way, *N*-benzyl and *N*-methyl piperazine successfully gave the corresponding substitution products **45b**,**c** in 92% and 91% yield, respectively. Unlike before, 5 equiv. of KO*t*Bu and a longer period of time (15 h) were necessary to complete the elimination reaction in **45a**–**c** to prepare **47a**–**c**. Hydrogenation of **47a**–**c** by using standard conditions gave 2-morpholinyl, 2-piperazinyl and 2-*N*-methylpiperazinyl derivatives **46a**–**c** in very good yield (Scheme 18, Table 9).



Scheme 18. Nucleophilic substitution of *S*Me group with secondary amines.

Table 9. Yields of nucleophilic substitution of *S*Me group in **37h** with amines.

Amines	**45**	Yield (%)	**47**	Yield (%)	**46**	Yield (%)
morpholine	**45a**	93	**47a**	84	**46a**	94
N-benzylpiperazine	**45b**	92	**47b**	94	**46b***	87
N-Methypiperazine	**45c**	91	**47c**	88	**46c**	83

*) Without benzyl group.

2.3. Cyclopropane Analogue of Tadalafil

2.3.1. Considerations

In recent years there has been an increasing interest for the phosphodiesterases (PDEs) inhibitors. PDEs are super-family of enzymes that degrades the intracellular messenger cyclic guanosine monophosphate (cGMP) and are distributed throughout the vascular smooth muscle tissue and to a lesser extends in the lung, kidney, and platelets.[75] Of the 12 PDE gene families discovered till now, cGMP-specific PDE5 carries out the principal cGMP hydrolyzing activities in human corpus cavernosum tissue. PDE5 are drug targets for the treatment of various diseases, particularly for the treatment of cardiovascular disease, such as hypertension, and congestive heart failure.[76] More interestingly it is reported that PDE5 plays an important role in the mechanism of penile erection. The most promising PDE5 inhibitors are Zaprinast (**49**), Sildenafil (**50**) (Viagra®, Pfizer) and Vardenafil (**51**) (Levirta®, Bayer) and for that reason Sildenafil and Verdanafil were approved for the treatment of erectile disfunction (ED).[77]

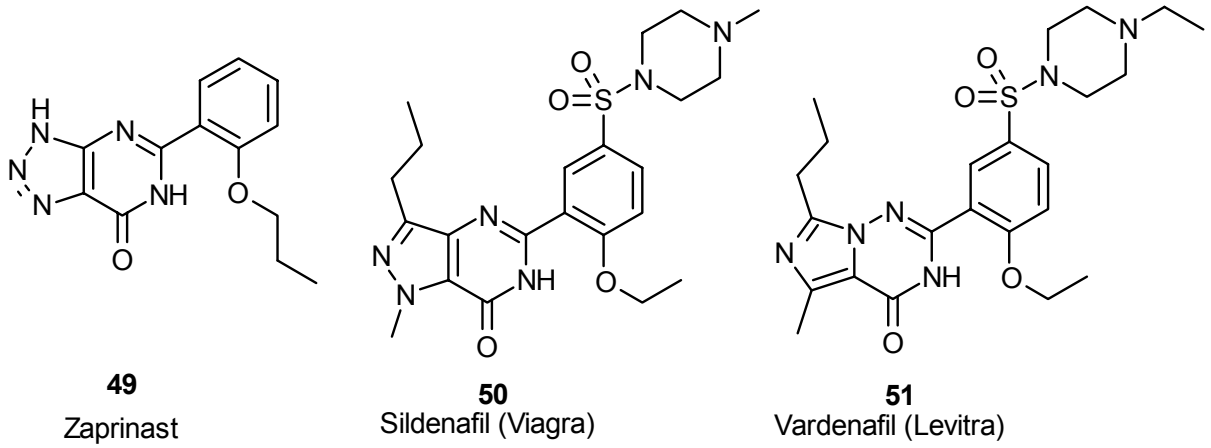


Figure 5. Structures of PDE5 inhibitors: Zaprinast, Vardenafil and Sildenafil.

Despite the efficacy of Sildenafil, clinically significant adverse effect has been noted,[78] and it has been proposed that some of the side effects may be due to lack of selectivity for PDE5.[79] The search for a better PDE5 inhibitor compared to PDE6 led to the discovery of Tadalafil (**52**) (Cialis®, Lilly ICOS),[52] via the hydantoin lead structure (**53**). It was found that Tadalafil has 1000-fold selectivity for PDE5 versus PDE6 as against 12-fold in case of Sildenafil.[80] These

hererocycles (**52** and **53**) have a common heterocyclic skeleton (β-carboline ring) which is present in many indole alkaloids.[81]

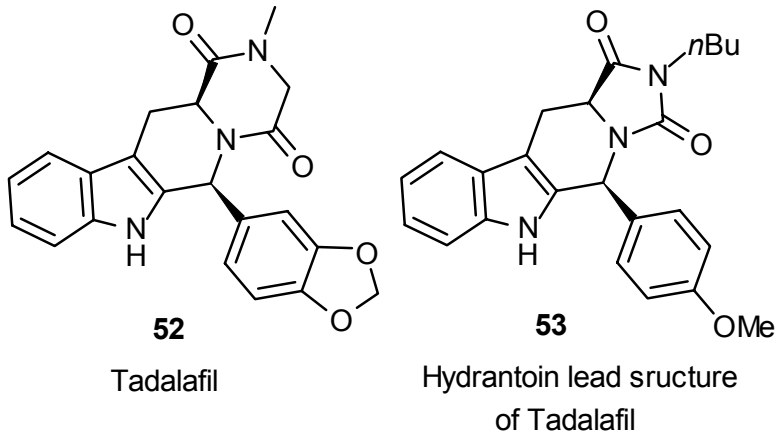


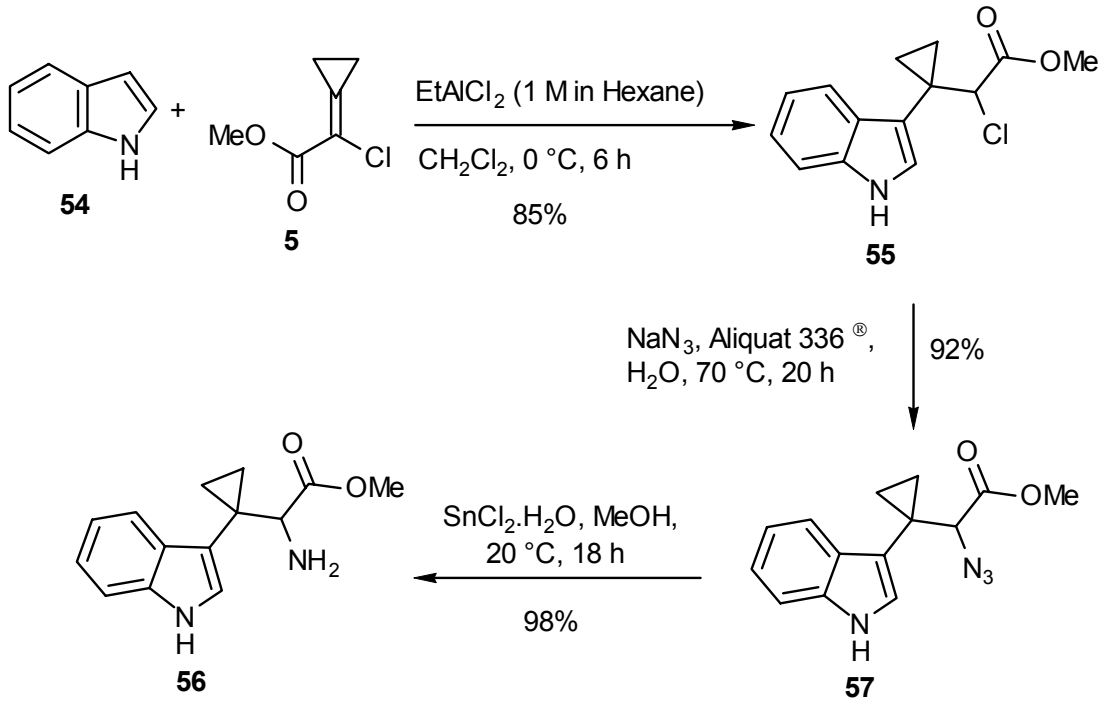
Figure 6. Structure of Tadalafil, hydrantoin lead structure of Tadalafil, and natural product Fumitremorgine C and Demethoxyfumitremorgine C.

The synthesis of all these tetrahydro-β-carbolines (**52** and **53**) have been achieved starting from tryptophan.[80] Tryptophane is an essential residue in numerous peptide hormones and is a part of many naturally occurring indole alkaloids[82] for which its replacement by conformationally restricted analogues e.g. dimethyl or cyclopropyl derivatives has considerable potential.[83] Since cyclopropyl groups have proved to be highly effective in improving the activity of many biologically active compounds,[2a,b][38] it was interesting to synthesize cyclopropyl analogue of tryptophane and using it as a precursor to synthesize spirocyclopropyl analogue of hydrantoin lead structute to Tadalafil (**25**) and Tadalafil (**26**) it self.[57] This idea was executed to demonstrate once again the enhanced tendency with which a suitable 1,1-disubstituted cyclopropane derivative undergoes ring closure due to the enforced favorable conformation just like a correspondingly substituted 2,2-disubstituted propane derivative.[84]

2.3.2. Synthesis of a spirocyclopropanated tryptophan methyl ester

The potent Michael acceptor methyl 2-chloro-2-cyclopropylideneacetate (**5**), in presence of ethylaluminum dichloride undergoes addition of indole **54** to furnish **55** in 85% yield after 6 h. The cyclopropanated tryptophane methyl ester **56** could be prepared by nucleophilic substitution

of the chloride under phase transfer catalysis with sodium azide in water and subsequent reduction of the azido ester **57** with tin(II) chloride with an overall yield of 90%. These results are summerised in Scheme 19.

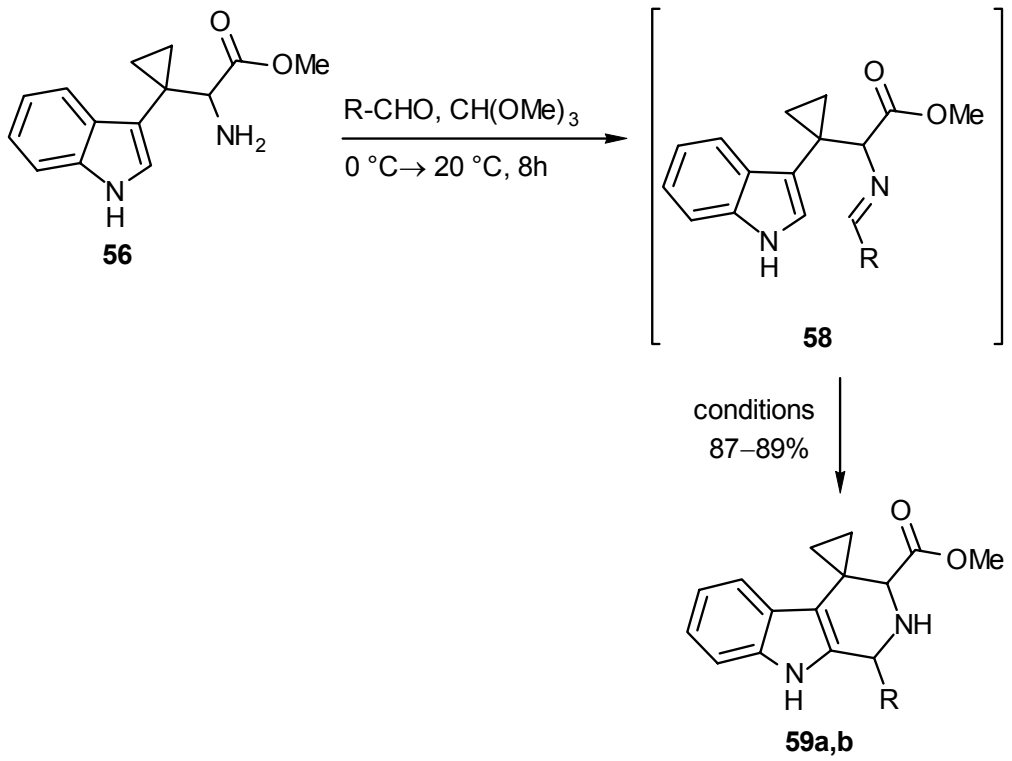


Scheme 19. Michael addition of **5** onto indole (**54**) and synthesis of cyclopropanated tryptophan methyl ester (**56**).

2.3.3. The Pictet–Spengler reaction for synthesis of tetrahydro-β-carbolines

The Pictet–Spengler reaction has long been an important reaction for the synthesis of both indole and isoquinoline alkaloids and also has been of vital importance in the synthesis of numerous tetrahydro-*β*-Carbolines which is a common skeleton in indole alkaloids and their analogues mostly with interesting biological activities.[82] As expected condensation of **56** with *p*-anisaldehyde in trimethyl orthoformate yielded the corresponding imine **58a** after 8 h at 20 °C almost quantitatively. Treatment with 4 equiv. of trifluoroacetic acid at 0 °C and subsequent stirring at 20 °C for 15 h gave the tetrahydro-β-carboline **59a** in 87% yield as a mixture of two diastereomers (*cis*/*trans* = 1 : 1.7) which could not be separated by column chromatography. The pure *trans*-isomer was separated by crystallization from ethyl acetate and the mother liquer was found to contain a mixture of both isomers (*cis*/*trans* = 5 : 1). In a similar way the reaction of **56**

with piperonal yielded the corresponding tetrahydro-β-carbolines **59b** in 89% with a ratio of *cis*/*trans* = 1 : 2.5 (Scheme 20). In this case the *trans*-isomer could be separated by crystallization from ethyl acetate/pentane and the mother liquer was found to contain *cis*/*trans* = 3 : 1. The assignment of *cis*/*trans*-steriochemistry for tetrahydro-β-carbolines **59a**,**b** were based on a detailed study of the ^{1}H and ^{13}C spectroscopy and by comparison with the literature data, well established by Cook.[85] Thus, the signals for C-1 and C-3 in *trans*-isomers appear at higher field in carbon spectrum than the analogous carbons of the corresponding *cis*-isomer probably due to 1,3 interactions present in *trans*-isomer. Moreover, the ^{1}H-NMR signals at C-1 is more shielded in the *cis*-isomer compared to the *trans*-isomer.

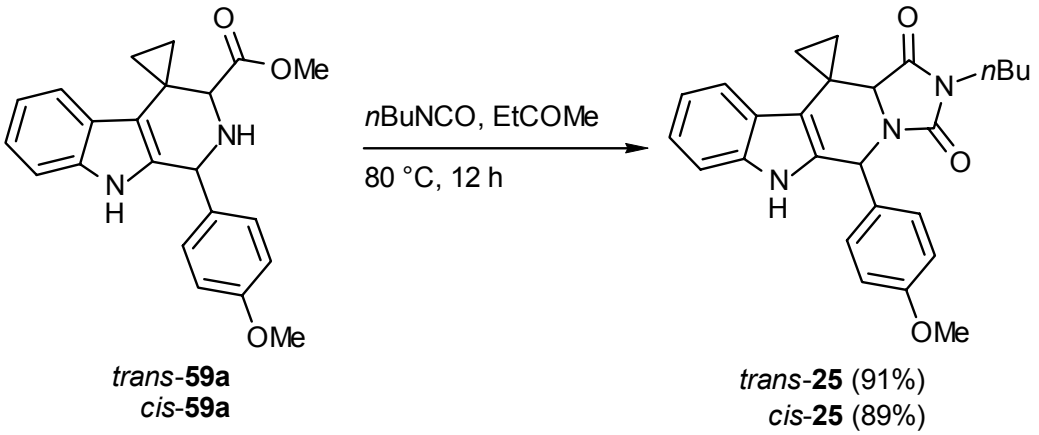


Compound	R	Conditions	Yield (%)	d.r. (*cis*/*trans*)
59a	*p*-anisyl	TFA, CH_2Cl_2, 0 → 20 °C, 15 h	87	(1 : 1.7)
59b	piperonyl	TFA, CH_2Cl_2, 0 → 20 °C, 12 h	89	(1 : 2.5)

Scheme 20. Pictet–Spengler reactions of **56** with aldehydes.

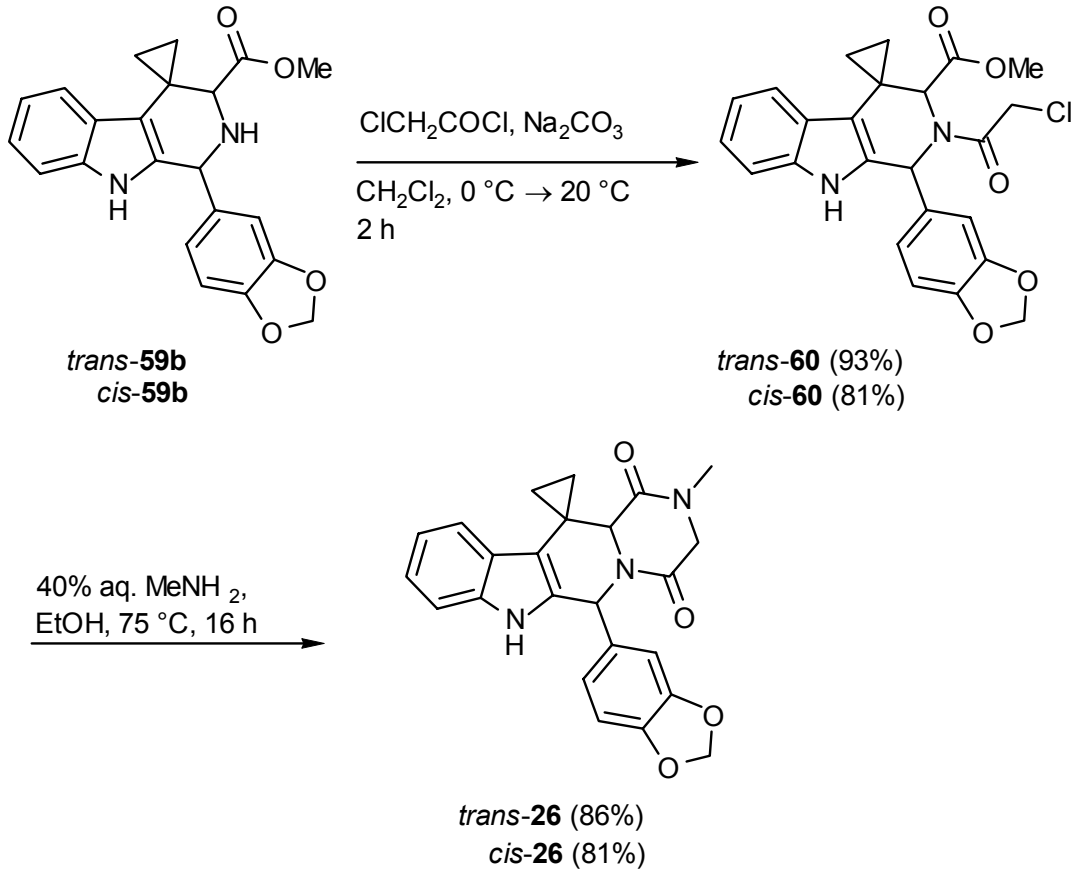
2.3.4. Synthesis of cyclopropyl analogue of hydantoin lead to Tadalafil and Tadalafil

Treatment of the tetrahydrocarboline *trans*-**59a** with *n*-butyl isocyanate in refluxing ethyl methyl ketone for 12 h led to the hydantoin lead structure *trans*-**25** (91%) and similarly when a mixture of *cis*/*trans*-**59a** (5 : 1) was refluxed in ethyl methyl ketone with *n*-butyl isocyanate, the resulted mixture could be purified by column chromatography to give *cis*-**25** in 89% yield, calculated according to the starting *cis*-**59a**.



Scheme 21. Synthesis spirocyclopropyl analogue of hydrantion lead to tadalafil **25** from the corresponding β-carboline **59**.

In order to synthesize the tadalafil analogue the tetrahydrocarboline derivative, *trans*-**59b** was acylated with chloroacetyl chloride to provide the *N*-(chloroacetyl) derivative *trans*-**60** in 93% yield, which upon reaction with 40% aq. methylamine in ethanol underwent nucleophilic substitution and subsequent ring-closing amide formation to lead to the spirocyclopropanated tadalafil analogue *trans*-**26** in 86% yield. In a similar way *cis*/*trans*-**59b** (3 : 1) was acylated to provide a chromatograpically separable product to give *cis*-**60** in 81% yield (calculated from pure *cis*-**59**) which upon reaction with 40% aq. methylamine in ethanol generated the *cis*-**26** in 81% yield (Scheme 22).[86]

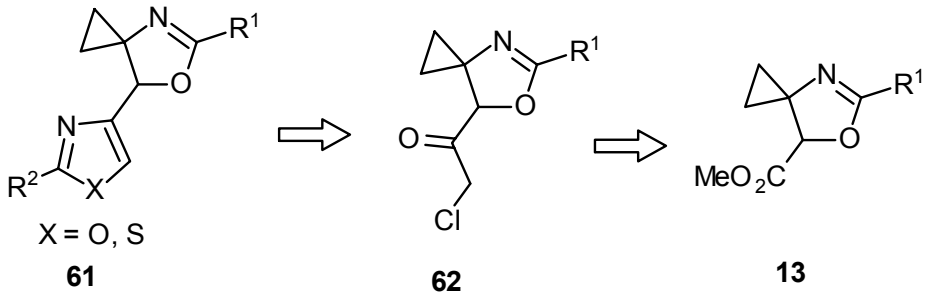


Scheme 22. Synthesis of spirocyclopropane analogue of Tadalafil (**26**).

2.4. Synthesis of Spirocyclopropyl Oxazolines

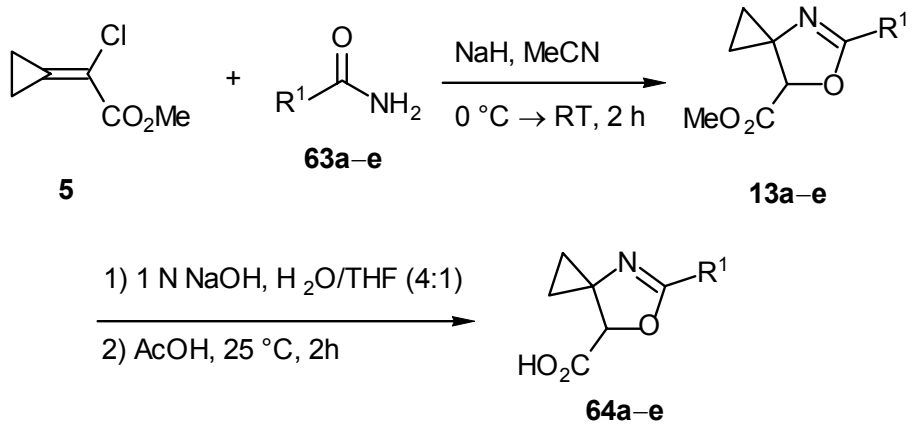
2.4.1. *Synthesis of spirocyclopropane oxazoline carboxylic acid and attempted transformation to oxazole or thiazole derivatives*

Recently, a new and efficient method for the preparation of spirocyclopropane substituted oxazoline carboxylic acid methyl ester by the reaction of carboxamides with methyl 2-chloro-2-cyclopropylideneacetate (**5**) has been developed.[27] On the basis of this work further effords were directed to the transformation of the methyl ester group to heterocycle derivatives such as oxazole and thiazole (**61**). The conceivable synthesis of the target molecule (**61**) was considered from the α-chloro ketone (**62**) which could be easily obtained from the corresponding oxazoline methyl ester (**13**) (Scheme 23).



Scheme 23. Retrosynthetic analysis for the synthesis of heterocycles from oxazoline methyl ester.

By adopting the method described by de Meijere et al., when methyl 2-chloro-2-cyclopropylideneacetate (**5**) in acetonitrile solution was treated with 4-bromo benzamide (**63a**) in the presence of sodium hydride at 0 °C and the mixture was allowed to warm up to room temperature after 2 h, the 5-(4-bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester (**13a**) was isolated in 51% yield. Under the same conditions, other aryl amides gave the corresponding oxazolines **13b**–**e** in yields ranging from 54 to 81%. Under basic conditions (1 N aq. NaOH in H_2O/THF), the hydrolysis of **13a** gave the oxazoline carboxylic acid **64a** in excellent yield (91%) after 2 h. The product could be purified by column chromatography using Et_2O/AcOH as eluent. In the similar procedure other oxazoline methyl esters were converted to the corresponding carboxylic acid (**64b**–**e**) in very good yield. These results are summarized in Scheme 24 and Table 10.



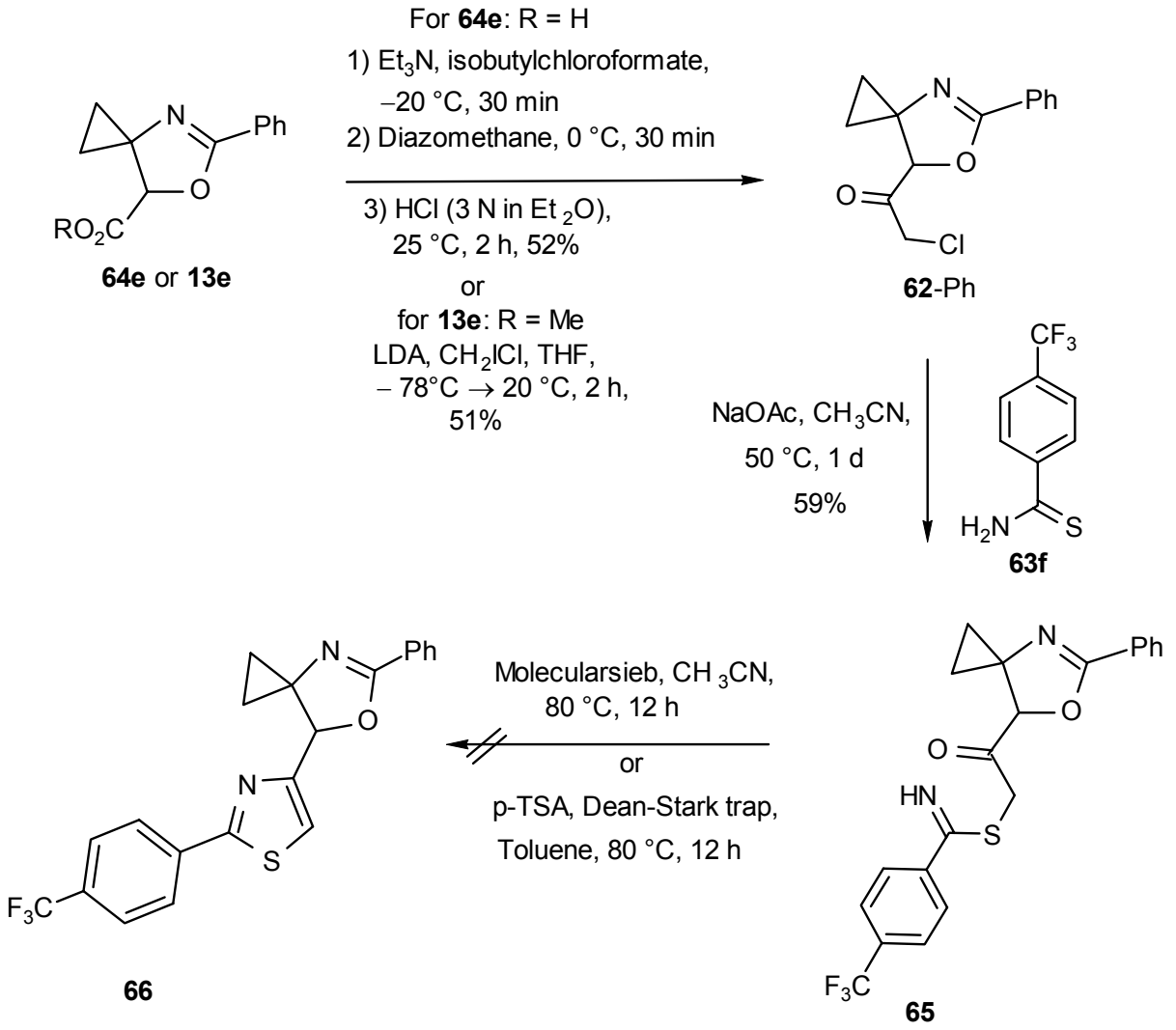
Scheme 24. Michael addition of aryl amides onto methyl 2-chloro-2-cyclopropylideneacetate **5** with ensuing intramolecular nucleophilic substitution to yield spirocyclopropaneoxazoline-carboxylic acids **64a**–**e**.

Table 10. Yields of methyl spirocyclopropaneoxazoline carboxylates **13a**–**e** from **5** and arenecarboxamides and hydrolysis of **13a**–**e** to oxazolinecarboxylic acids **64a**–**e**.

Entry	R^1	**13**	Yield (%)	**64**	Yield (%)
1	4-Br-C_6H_4	**13a**	51	**64a**	91
2	3-Br-C_6H_4	**13b**	64	**64b**	90
3	3-CF_3-C_6H_4	**13c**	47	**64c**	89
4	4-CF_3-C_6H_4	**13d**	81	**64d**	93
5	Ph	**13e**	54	**64e**	89

With the oxazolinecarboxylic acids in hand further effords were made to convert them into α-chloro ketone. The classical method for the synthesis of α-chloroketones involves the conversion of the carboxylic acid to an α-diazoketone and the subsequent acidolysis with HCl.[87] When the half ester formed from **64e** and isobutylchloroformate was treated with diazomethane followed by reaction with HCl (3 N in Et_2O) the corresponding α-chloroketone (**62**-Ph) was obtained in 52% yield. The same product (**62**-Ph) could also be obtained in 51% yield by using the method described by Polniaszek and coworkers by using LDA (5 equiv.) and CH_2ICl (4 equiv.)[88] directly from the ester **13e** in one step without the use of diazomethane. However, the reaction of α-chloroketone (**62**-Ph) with benzamide or benzothioamide either in NaH/DMF at 45 °C or in

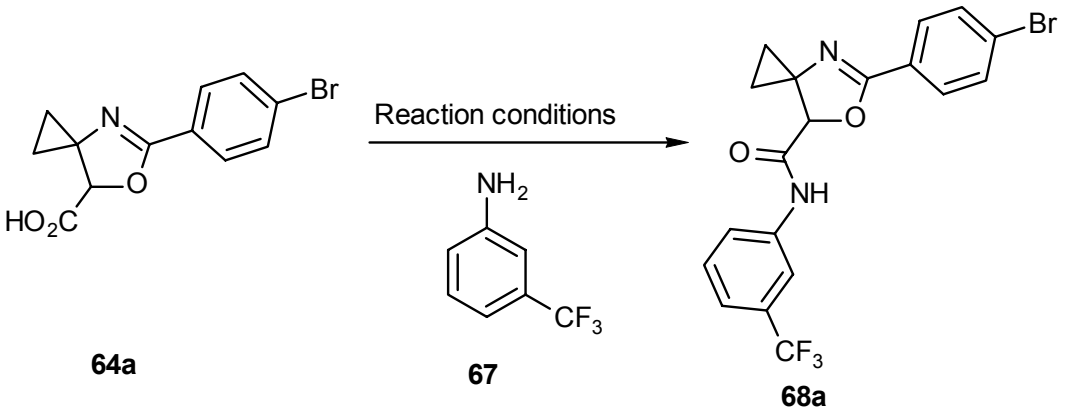
Et_3N/EtOH at 70 °C for 15 h did not lead to any product containing oxazole or thiazole ring, only starting material was recovered. Only in the case when the reaction was carried out with 4-(trifluoromethyl)-benzothioamide in the presence of NaOAc in CH_3CN at 50 °C for 24 h, the nucleophilic substitution product (**65**) was isolated in 59% yield. Several trials for the ring closure reaction by using molecularsieve or by using para-toluenesulfonic acid in a Dean-Stark apparatus did not lead to the thiazole ring. These resuts are presented in the Scheme 25.



Scheme 25. Synthesis of α-chloroketone derivative (**62**-Ph) from oxazoline carboxylic acid (**64e**) or methyl ester (**13e**) and conceivable further transformation to thiazoline ring (**66**).

2.4.2. Coupling of oxazoline carboxylic acids with anilines and subsequent Mitsunobu reaction for the synthesis of benzoxazole derivatives

After failing to produce the oxazole or thiazole ring it was interesting to synthesize a benzoxazole derivative of spirocyclopropane oxazolines. The obvious choice was to consider the orthohydroxy aniline so that the coupling reaction with oxazoline carboxylic acid followed by ring closing reaction would afford the desired benzoxazole. In order to optimize the condition for coupling reaction, 5-(4-bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (**64a**) and 3-trifluoromethyl aniline was chosen. When the reaction was carried out in the presence of DCC and DMAP in DCM as solvent at 20 °C for 18 h, no product was obtained. The reaction also failed in a condition of DCC, HOBT in DCM for 18 h.[89]



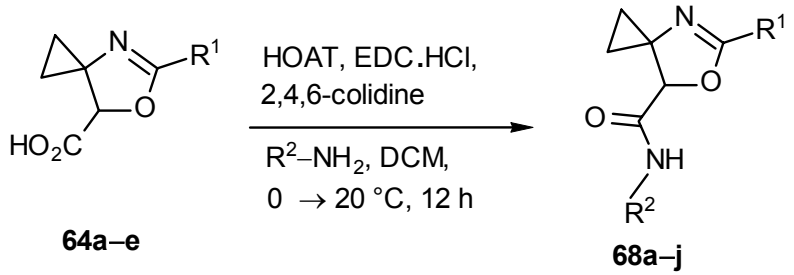
Scheme 26. Optimization of reaction conditions for the coupling reaction of **64a** with 4-CF_3-aniline.

Table 11. Reaction conditions and yield for the coupling reaction of **46a** with paratrifluoromethyl-aniline.

Entry	Reaction conditions	**68a** Yield (%)
1	DCC, DMAP, DCM, 18 h	00
2	DCC, HOBT, colidine, DCM, 18 h	00
3	$SOCl_2$, DCM, 60 °C, 12 h	decomposition
4	HOAt, EDC·HCl, colidine, 20 °C, 12 h	92%

Another idea to convert the carboxylic group to acid chloride by $SOCl_2$ and then reacting with the aniline also failed. Finally when the reaction was carried out in the presence of HOAt, EDC•HCl and colidine at 20 °C for 12 h in DCM, the coupling product **68a** was obtained in 92% yield (Scheme 27, Table 12).

With the optimal conditions the oxazolines **64b–d** were coupled with 3-trifluoromethyl aniline to give the corresponding amide **68b–d** in good yield. The reaction of **46d** with 3-chloro-6-hydroxy-aniline gave the product **68e** in 85% yield. The other substituted 6-hydroxy anilines also coupled with **64d** to give the product **68f–h** in yield ranging from 55 to 78%. The reaction of **64e** with 3-chloro-6-hydroxy-aniline under the same conditions gave the product **68i** in 92% yield. These results are summerized in Scheme 27 and Table 12.

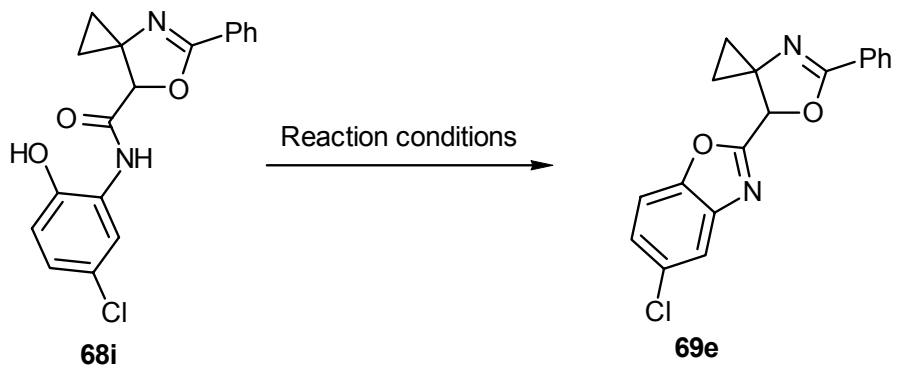


Scheme 27. Coupling reaction of oxazoline carboxylic acids (**64a–e**) with anilines for the synthesis of amide **68a–j**.

Table 12. Yields of the coupling of oxazoline carboxylic acids with anilines.

Entry	**64**	R^1	R^2	**68**	Yield (%)
1	**64a**	4-Br-C_6H_4	3-CF_3-C_6H_4	**68a**	92
2	**64b**	3-Br-C_6H_4	3-CF_3-C_6H_4	**68b**	82
3	**64c**	3-CF_3-C_6H_4	3-CF_3-C_6H_4	**68c**	81
4	**64d**	4-CF_3-C_6H_4	3-CF_3-C_6H_4	**68d**	90
5	**64d**	4-CF_3-C_6H_4	3-Cl-6-OH-C_6H_3	**68e**	85
6	**64d**	4-CF_3-C_6H_4	3-OCF_3-6-OH-C_6H_3	**68f**	55
7	**64d**	4-CF_3-C_6H_4	3,5-di-Cl-6-OH-C_6H_2	**68g**	79
8	**64d**	4-CF_3-C_6H_4	3-CF_3-6-OH-C_6H_3	**68h**	78
9	**64e**	C_6H_5	3-Cl-6-OH-C_6H_3	**68i**	92
10	**64d**	C_6H_5	6-SH-C_6H_4	**68j**	0

When **68i** was reacted with P_2O_5 in CCl_4, no product was found, only the starting material was recovered. A very small amount of the product **69e** (12%) was isolated when the reaction was carried out in PPTS in DCE at 85 °C for 12 h. The desired product was not observed when the same reaction was done in toluene in a Dean-Stark trap at 85°C. Finnaly under the Mitsunobu condition[90] (Ph_3P, DEAD) the product was isolated in 85% yield. These results are given in Scheme 28, Table 13.

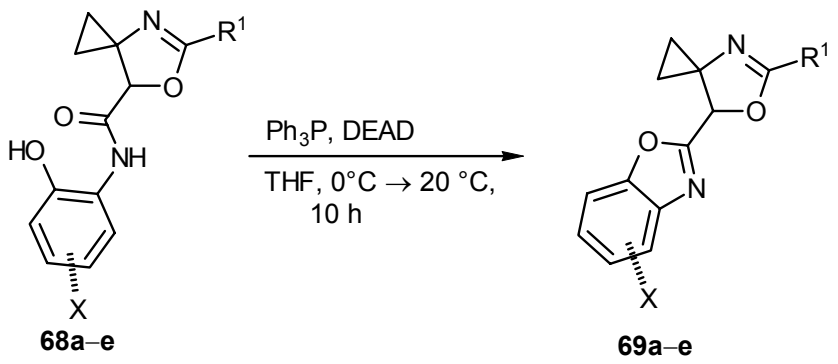


Scheme 28. Optimisation of reaction conditions for synthesis of bezoxazole derivatives.

Table 13. Reaction conditions and yield of dehydro cyclization reaction for synthesis of benzoxazole derivative.

Entry	Raction conditions	Yield **69e** (%)
1	P_2O_5, CCl_4, 80 °C, 10 h	00
2	PPTS, DCE, 85 °C, 12 h	12
3	PPTS, Dean-Stark trap, toluene, 80 °C, 12 h	00
4	Ph_3P, DEAD, THF, 0 → 20 °C, 10 h	83

After finding the optimized condition for the dehydro cyclisation reaction, other *o*-hydroxy amides **68f–i** were also transformed to the corresponding benzoxazoles in very good yield. These resuts are given in Scheme 29.



Scheme 29. Synthesis of benzoxazole derivatives of oxazolines by Mitsunobu reaction conditions.

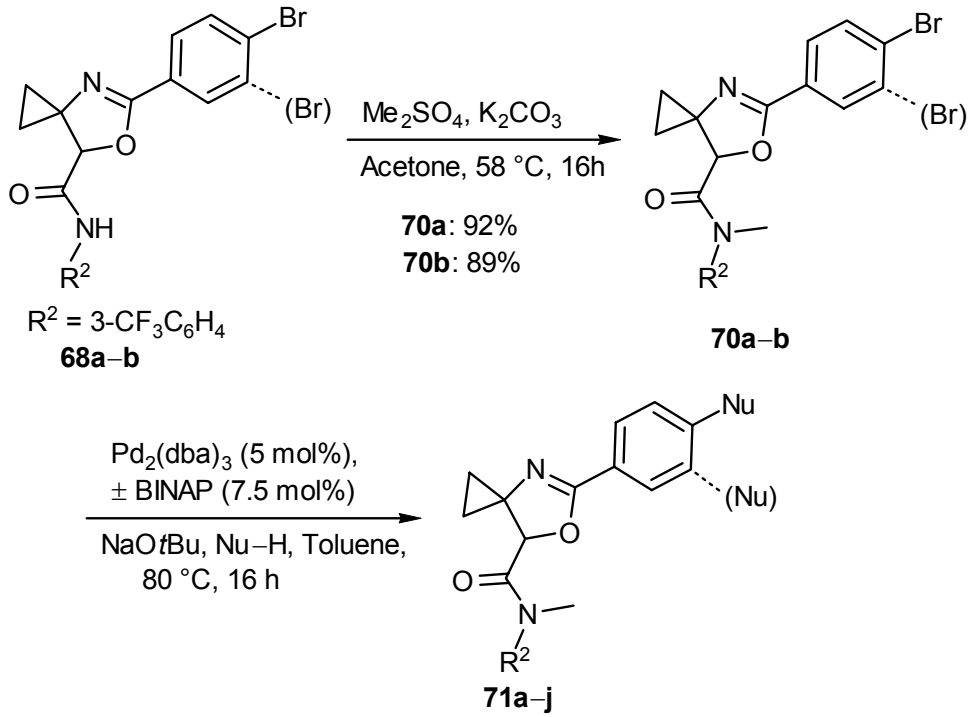
Table 13. Yields of benzoxazole derivatives of oxazolines by Mitsunobu reaction.

Entry	**68**	R^1	X	**69**	Yield (%)
1	**68e**	4-CF_3-C_6H_4	3-Cl	**69a**	85
2	**68f**	4-CF_3-C_6H_4	3-OCF_3	**69b**	81
3	**68g**	4-CF_3-C_6H_4	3,5-di-Cl	**69c**	88
4	**68h**	4-CF_3-C_6H_4	3-CF_3	**69d**	81
5	**68i**	C_6H_5	3-Cl	**69e**	83

2.4.3. Pd-Catalyzed C–N or C–C bond formation reaction for the synthesis of amino-aryl or biaryl substituted oxazolines.

The palladium-catalyzed coupling of amines with aryl halides, commonly known as Buchwald–Hartwig reaction[91] has matured from a synthetic loboratory procedure to a technique that is widely used in natural product synthesis as well as in other field of academic interest. This reaction also opened a new chapter in the field of transition metal-catalyzed cross coupling chemistry with a new approach for the synthesis of aniline derivatives.[92] After successful synthesis of benzoxazole derivatives, it was interesting to try Buchwald–Hartwig reaction of the aryl bromide group present in 5-(4-bromo-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (3-trifluoromethyl-phenyl)-amide (**68a**). The initial attempts for the reaction of **68a** with the well established condition [$Pd_2(dba)_3$, BINAP, Na*t*OBu] in toluene for 18 h failed to give any desired products with complete decomposition of **68a**. It was concluded that the free amide group might not be stable in the reaction conditions. So by methylating the amide group of **68a** with

Me_2SO_4, K_2CO_3 in acetone followed by the palladium-catalyzed reaction with morpholine, the coupling product **71a** was isolated in 71% yield after 16 h. In order to optimize the amount of catalyst we found that the best yield was obtained when 5 mol% of $Pd_2(dba)_3$ and 7.5 mol% of ± BINAP were used. Other secondary amines such as pyrolidine under the same reaction condition gave the product **71b** in 90% yield, but in the case of *N*-methyl and *N*-benzyl piperazine the decreased yield (59 and 62% respectively, entries 3 and 4) was observed. Another interesting amine, *N,N*-dibenzyl-3-azabicyclo[3.1.0]hexane also proceeded smoothly to afford the product **71e** in 67% yield . These five different amines were also reacted with 5-(3-bromo-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**70b**) to give the corresponding aminated products. In the case of *N*-methyl and *N*-benzyl piperazine very poor yield (13 and 12% respectively, entry 8 and 9) was obtained and the reaction was not finished even if the reaction time was increased to 40 h. These results are given in Scheme 30 and Table 14.

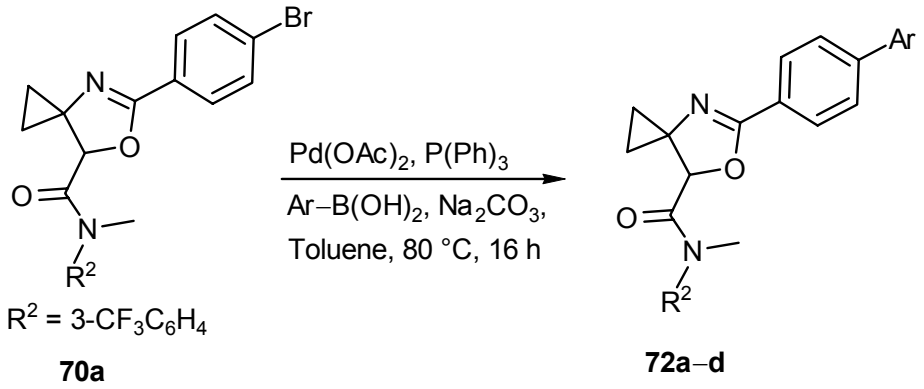


Scheme 30. Methylation of amide group followed by Buchwald amination of aryl-bromides (**70a,b**) for the synthesis of aminoaryl substituted oxazolines (**71a–j**).

Table 14. Yield of Buchwald–Hartwig amination of aryl-bromides for the synthesis of aminoaryl substituted oxazolines

Entry	**70**	Nu-H	**71**	Yield (%)
1	**70a**	morpholine	**71a**	71
2	**70a**	pyrolidine	**71b**	90
3	**70a**	*N*-methylpiperazine	**71c**	59
4	**70a**	*N*-Benzylpiperazine	**71d**	62
5	**70a**	*N,N*-dibenzyl-3-azabicyclo[3.1.0]hexane	**71e**	67
6	**70b**	morpholine	**71f**	82
7	**70b**	pyrolidine	**71g**	73
8	**70b**	*N*-methylpiperazine	**71h**	13
9	**70b**	*N*-Benzylpiperazine	**71i**	12
10	**70b**	*N,N*-dibenzyl-3-azabicyclo[3.1.0]hexane	**71j**	81

Another interesting Pd-catalyzed reaction of aryl halides with boronic acid the Suzuki reaction represents a powerful means for the preparation of numerous products important in pharmaceutical and material science.[93] After successful Buchwald–Hartwig reaction the scope of the Suzuki reaction of the aryl bromide group present in 5-(4-bromo-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethylphenyl)-amide (**70a**) was also tested. After trying several reaction of **70a** with phenyl boronic acid it was found that 10 mol% of $Pd(OAc)_2$ and 40 mol% of Ph_3P was necessary to complete the reaction and the product **72a** was isolated in 90% yield after 16 h. *p*-Trifluoromethoxy phenyl boronic acid under the same reaction condition gave the product **72b** in 84% yield. 3-Thiophene- and 2-naphthaleneboronic acid also yielded the product **72c,d** in 65 and 85% respectively. These results are given in Scheme 31 and Table 15.



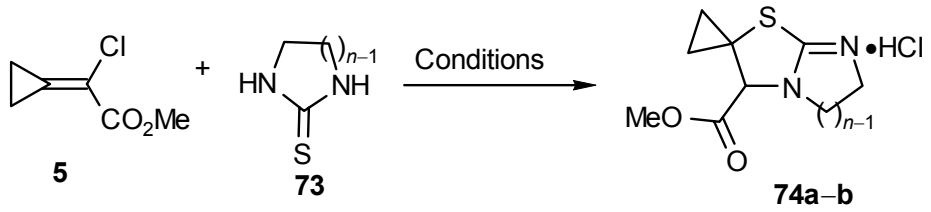
Scheme 31. Palladium catalyzed cross-coupling reaction of **70a** with aryl boronic acids.

Table 15.Yield of the Palladium catalyzed cross-coupling reaction of **72a** with aryl boronic acids.

Entry	Ar	**72**	Yield
1	C_6H_5	**72a**	90
2	4-OCF_3-C_6H_4	**72b**	80
3	C_4H_3S	**72c**	65
4	$C_{10}H_6$	**72d**	85

2.5. Reaction of Tetra- and trimethylenethiourea with Methyl 2-Chloro-2-cyclopropylideneacetate

After the successful synthesis of spirocyclopropanated oxazolines it was interesting to study the Michael addition of urea or thiourea derivatives. Dimethyl urea or dimethyl thiourea did not react with the Michael acceptor **5** either in the presence of Et_3N in dioxane or NaH in acetonitrile. Under the same reaction conditions, tetramethylene urea also did not give any product corresponding to a Michael addition. But in the case of tetramethylene thiourea, when the reaction was carried out in the presence of Et_3N in a solution of dioxane, the tricyclic product **74a** corresponding to the Michael addition and ring closure reaction was isolated in 82% yield as a hydrochloride salt. The same product **74a** was also be obtained, when the reaction was carried out in the presence of NaH but in lower yield (49%). The reaction also occurs with trimethylene-thioura in presence of either Et_3N or NaH to give the product **74b** in 41 and 29% yield respectively. The hydrochloride moiety could not be detected by mass spectrometry.



Scheme 32. Michael reaction of oligomethylenethioureas with **5**.

Table 16. Yields of the reaction of oligomethylenethioureas with **5**.

Entry	Conditions	*n*	**74**	Yield (%)
1	Et_3N, dioxane, 20 °C, 15 h	4	**74a**	82
2	Same as above	3	**74b**	41
3	same	2	**74c**	00
4	NaH, MeCN, 0 → 20 C, 12 h	4	**74a**	49
5	same	3	**74**b	29
6	same	2	**74**c	00

Since the product **74b** could be readily crystallized from Et_2O, the structure was rigorously proved by an X-ray crystal structure alalysis (Figure 7). The reaction did not occur with

diethylenethiourea (Scheme 32, Table 16). The compound **74b** decomposed when washed with 1 N NaOH in order to get the free base.

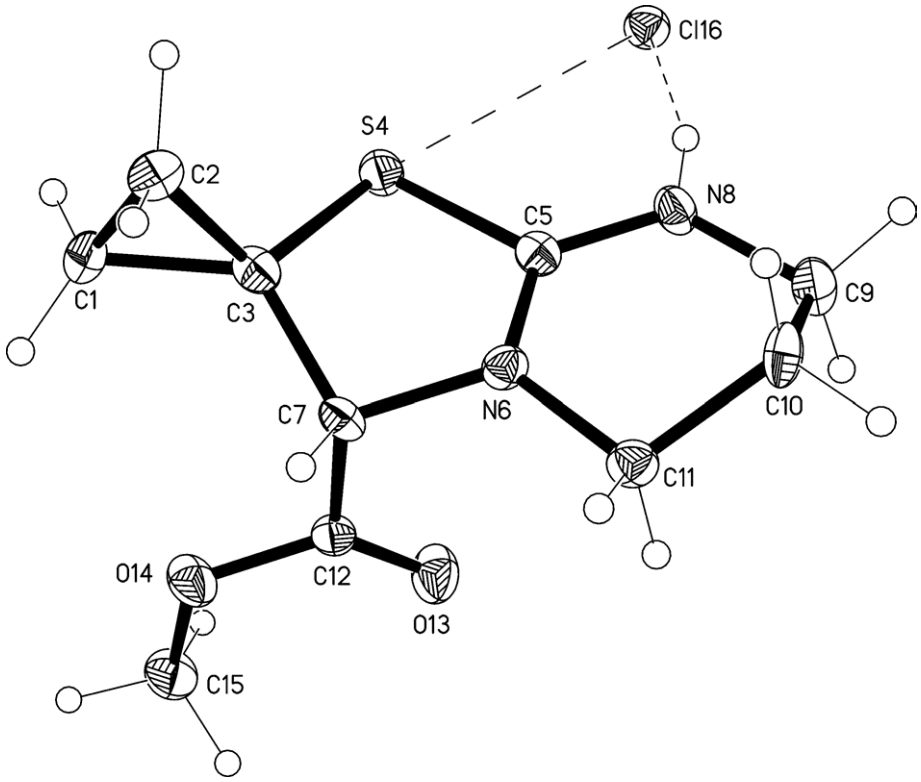
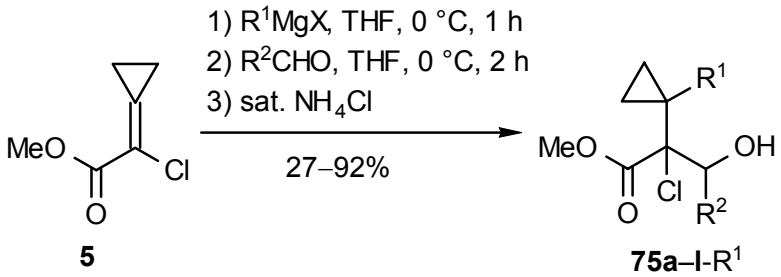


Figure. 7. Molecular structure of **74b** in crystal.

2.6. Sequential Addition of Grignard Reagents and Aldehydes to Methyl 2-chloro-2-cyclopropylideneacetate

The smooth bromine-magnesium exchange on Michael-acceptors like *tert*-butyl bromocrotonate and even β,β-disubstituted α-bromoacrylonitriles with isopropylmagnesium halides as reported by Knochel et al.,[94] led to functionalised alkenylmagnesium halides which cleanly reacted with various electrophilies. In an attempt to adopt these conditions for the conversion of the very reactive Michael acceptor methyl 2-chloro-2-cyclopropylideneacetate (**5**) to the corresponding methyl 2-cyclopropylidene-2-(chloro-magnesuim)acetate, treatment of **5** with one equivalent of iPrMgCl at 0 °C apparently did not lead to the insertion of the metal into the carbon-chlorine bond, but to 1,4-addition of the Grignard reagent on to the α,β-unsaturated ester. Upon trapping of the magnesium enolate with benzaldehyde, the Michael-aldol product **75a**-iPr was isolated in very good yield (92%, Table 17) and as a single diastereomer (>97% *anti* 2*S**,3*R**) as indicated by the ^{1}H-NMR spectrum of the crude product. The scope of this reaction sequence of **5** was screened varying the Grignard reagents and the aldehydes to lead to the corresponding β-chloroalcohols **75a**–**l**-R^1 in moderate to excellent yield (27–92%, Scheme 33, Table 17), all of which could be purified by column chromatography. The same diastereoselectivity was observed for the reactions with cyclohexyl- and ethylmagnesium bromide, albeit the yields were poor (27 and 32%, respectively).



Scheme 33. Addition of Grignard reagents to methyl 2-chloro-cyclopropylideneacetate (**5**) and trapping of the formed magnesium enolate with aldehydes.

However, the reaction with phenyl- and *p*-fluorophenyl-magnesium chloride did not proceed as cleanly as those with isopropylmagnesium chloride, albeit the product could be purified by crystallization followed by column chromatography (Table 1, entries 4, 6). The reactions of

vinylmagnesium bromide and phenylethynylmagnesium chloride led to an unidentified mixture of products and a 60% yield of 1,3-diphenylprop-2-ynol, respectively, the latter resulting from a direct attack of the Grignard reagent on benzyldehyde. Mesitylmagnesium bromide did not react cleanly with **5** to yield the Michael adduct, most probably due to its steric bulk. Upon addition of 1 equiv. of cuprous cyanide to the reaction mixture from **5** and vinylmagnesium bromide prior to the addition of benzaldehyde, the Michael-aldol adduct **75**-Vin was formed, but as a mixture of *anti*- and *syn*-diastereomers (69:31). The same decreased diastereoselectivity was observed in the reaction of **5** with PhMgCl and PhCHO in the presence of CuCN (entries 8 and 5). Since compound **75b**-iPr readily crystallized, the relative configurations of the quaternary and the tertiary stereogenic center could be deduced from a single crystal X-ray structure analysis (Figure 7) to correspond to the outcome of an *anti*-diastereoselective aldol reaction in the second step.

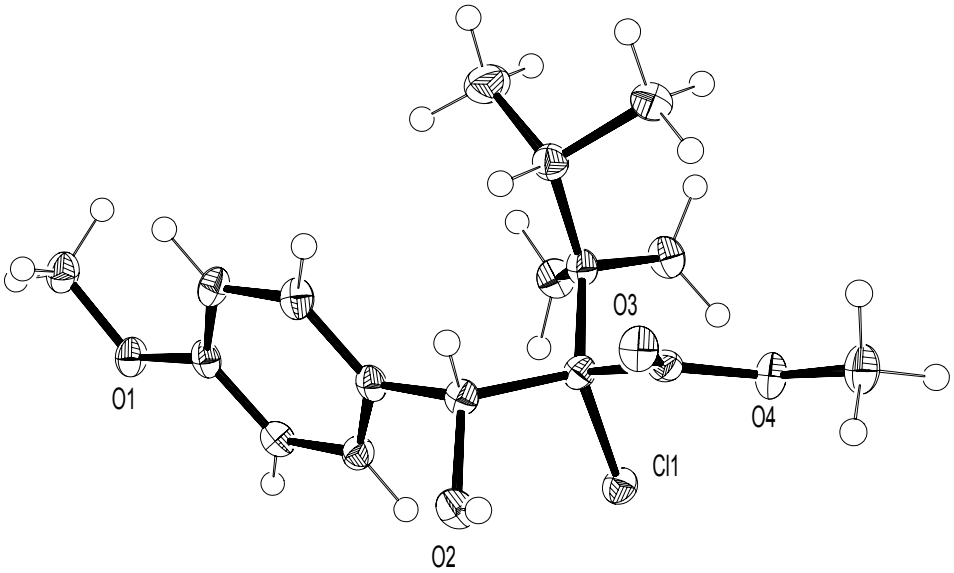


Figure 7. Structure of compound **75b**-iPr in the crystal indicating a (2*S**,3*R**)-configuration corresponding to an *anti*-aldol.

Table 17. Addition of organomagnesium halides to methyl 2-chloro-cyclopropylideneacetate (**17**) and trapping of the formed magnesium enolate with aldehydes

Entry	R^1	X	R^2	Product	Yield ((%)[a] [d.r.])
1	iPr	Cl	Ph	**75a**-iPr	92 [>97:3]
2	cHex	Br	Ph	**75a**-cHex	27 [>97:3]
3	Et	Br	Ph	**75a**-Et	32 [>97:3]
4	Ph	Cl	Ph	**75a**-Ph	42 [>97:3]
5	Ph	Cl	Ph	**75a**-Ph	35[b] [66:34]
6	4-F-C_6H_4	Cl	Ph	**75a**-4-FC_6H_4	39 [>97:3]
7	Vin	Br	Ph	**75a**-Vin	–[c]
8	Vin	Br	Ph	**75a**-Vin	64[b] [69:31]
9	PhC≡C	Cl	Ph	**75a**-PhC≡C	–[d]
10	2,4,6-Me_3-C_6H_2	Br	Ph	**75a**-2,4,6-$Me_3C_6H_2$	0[c]
11	iPr	Cl	4-$OMeC_6H_4$	**75b**-iPr	72 [>97:3]
12	iPr	Cl	3,4-(OCH_2O)C_6H_3	**75c**-iPr	78 [>97:3]
13	iPr	Cl	4-$NMe_2C_6H_4$	**75d**-iPr	80 [>97:3]
14	iPr	Cl	3,4,5-$(OMe)_3C_6H_2$	**75e**-iPr	72 [>97:3]
15	iPr	Cl	C_6F_5	**75f**-iPr	78 [>97:3]
16	iPr	Cl	2-F-4-$NO_2C_6H_3$	**75g**-iPr	83 [>97:3]
17	iPr	Cl	4-FC_6H_4	**75h**-iPr	80 [>97:3]
18	iPr	Cl	4-$NO_2C_6H_4$	**75i**-iPr	73 [>97:3]
19	iPr	Cl	H	**75j**-iPr	61[e] [>97:3]
20	iPr	Cl	CO_2Et	**75k**-iPr	72 [>97:3]
21	iPr	Cl	C_3H_7	**75l**-iPr	32[e] [>97:3]

[a] Stoichiometry used normally: **5** : R^1MgX : R^2CHO = 1:1:1.05; isolated yields.

[b] 1 Equivalent of CuCN was added prior to the aldehyde.

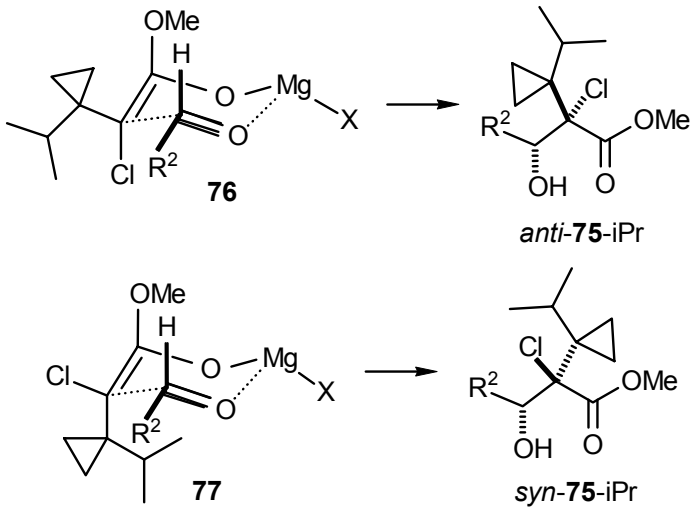
[c] Complicated mixture of unidentified products.

[d] Only 1,3-diphenylprop-2-ynol was isolated in 60% yield.

[e] 5 Equivalents each of paraformaldehyde and butyraldehyde were used.

As far as the aldehydes were concerned, various substituted benzaldehydes were screened and found to give consistently good yields (72–83%) independent of their substituents and substitution pattern (Table 17, entries 11–18). In case of aliphatic aldehyde five equiv. each of paraformaldehyde and butyraldehyde was used to complete the reaction although the yields were only 61 and 32% respectively (Table 17, entries 19,21). Another interesting aldehyde, ethylglyoxylate reacted in the general way to give the corresponding product in 72% yield.

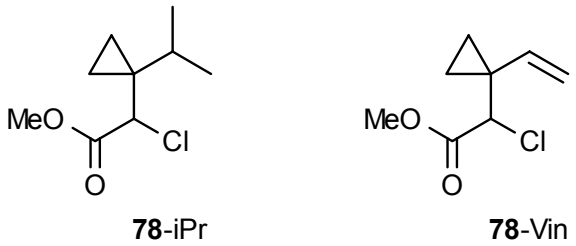
Comparable processes with trialkylboranes[95] yielded mixtures of *syn*- and *anti*-diastereomers (20:80 to 70:30, in the best cases) in good chemical yields but with the waste of two organyl residues from the borane. The extraordinarily high diastereoselectivity upon the addition of the enolate formed upon reaction of isopropylmagnesium chloride with **5** and benzaldehyde may be rationalized with the six-membered transition structure, typical for aldol additions, in which the bulky alkyl residue containing the 1,1-disubstituted cyclopropane ring, prefers an equatorial as in **76** rather than an axial position as in **77** (Scheme 34).



Scheme 34. Rationalization of the selective formation of the anti-aldols in the sequential addition of iPrMgCl and aldehydes to **5**.

The Michael adduct **78**-iPr of isopropylmagnesium chloride to **5** was obtained in virtually quantitative yield (98%), upon quenching the reaction before adding an aldehyde, after 30 min with aqueous ammonium chloride solution. The corresponding adduct **78**-Vin of vinylmagnesium bromide could also be obtained in 80% yield by adding **5** to the Grignard reagent in the presence of one equiv. of cuprous cyanide, and 0.5 equiv. of BF_3•OEt_2 at –78 °C, followed by aqueous

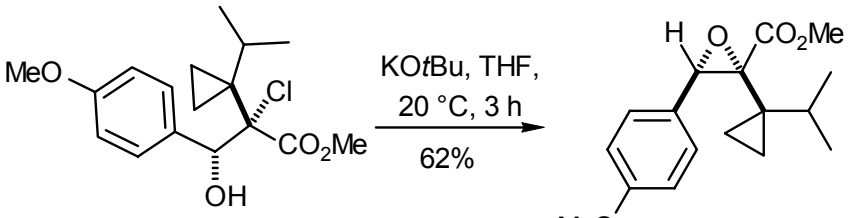
work-up. The adduct **78**-iPr was also obtained as the sole product when benzonitrile was added to the enolate formed from isopropylmagnesium bromide and **5**.



78-iPr **78**-Vin

Figure 10. Structures of the Michael adduct of **5** with Grignard reagents.

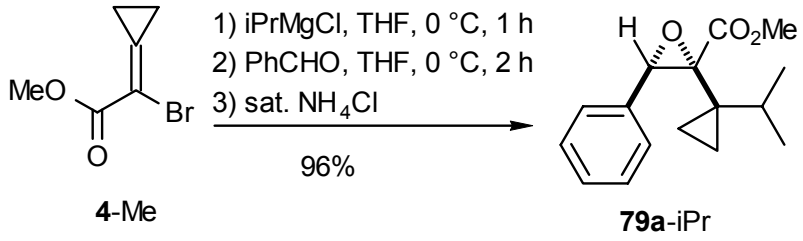
The α-chloro-β-hydroxy esters 2 which are – in most cases – diastereoselectively formed in this one-pot sequential Michael addition-aldol reaction from **5**, isopropylmagnesium chloride and an aldehyde, offer themselves as precursors to α,β-epoxy esters of type **79** which can also be made by a Darzens reaction. In fact, when **75**-iPr in tetrahydrofuran was treated at ambient temperature with potassium *tert*-butoxide, it underwent clean cyclization to the diastereomerically pure α,β -epoxyester **79**-iPr with the aryl and the 1-isopropylcyclopropyl group on the same side of the oxirane ring.



75b-iPr **79b**-iPr

Scheme 35. Diastereoselective formation of the Darzen-type α,β-epoxy ester **79b**-iPr.

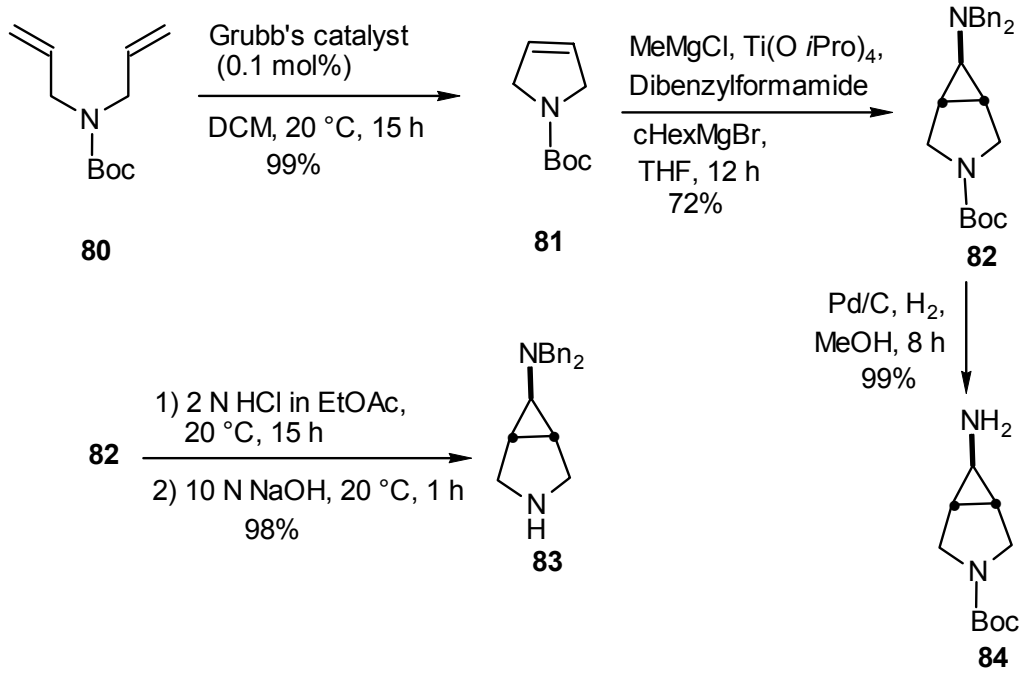
The analogous α,β-epoxy esters **79a**-iPr was obtained directly from methyl 2-bromo-2-cyclopropylideneacetate (**4**-Me) upen treatment with isopropylmagnesium chloride and benzaldehyde in 96% yield (Scheme 36). Apparently the bromohydrine analogous to **75a**-iPr is not stable under the work-up condition and undergoes cyclisation by intramolecular nucleophilic displacement even in the ammonium chloride-buffered medium.



Scheme 36. Diastereoselective formation of the Darzen-type α,β-epoxy ester **79a**-iPr directly from **5**.

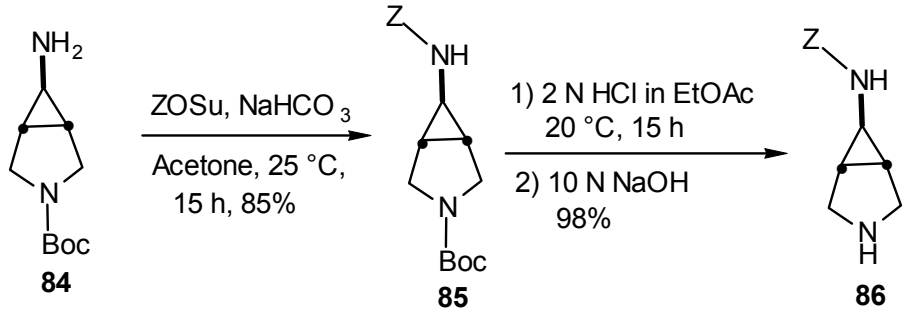
2.7. Synthesis of 6-amino-3-azabicyclo[3.1.0]hexane

It has already noted before that Trovafloxacin (**11**)[11] which has a potent activity against Gram-negative, Gram-positive and anaerobic bacteria contains a 3-azabicyclo[3.1.0]hex-6-yl amine substituent on C-7 of the naphthyridinon moiety. Very recently 3,6-disubstituted azabicyclo[3.1.0]hexyl amine derivatives has reported to be muscarinic receptor antagonist.[96] In view of the biological activity of the compound containing 3-azabicyclo[3.1.0]hex-6-yl amine it was interesting to synthesize this amine as well as other orthogonally protected derivative of it and find out a condition for the nucleophilic substitution with aryl halides. Recently Kulinkovich has developed a method in which a titanacyclopropane intermediate has been used for the synthesis of cyclopropanol from ester.[8] A analogous method has been developed by de Meijere for the synthesis of cyclopropyl amine from ester.[9] In the mean time Helmchen et al.[97] has described an efficient synthesis of 1-Boc-2,5-dihydro-1*H*-pyrrole (**81**) by protection reaction of dially amine followed by ring closing metathesis using Grubbs first generation catalyst.[98] Initial attempts to prepare (**81**) from Boc-diallyl amine as described by Helmchen was not successful. The reaction did not come to end and only 30% of starting material was converted to product even if after stirring for 24 h and increasing the catalyst loading to 2 mol%. This problem was solved by distilling the starting material and storing it in the presence small amount of molecular sieb prior to the metathesis reaction and by using glove box for transferring the catalyst. In this way the reaction was successful and gave the product in 99% yield even in large scale (1.1 mol) and with the use of only 0.1 mol% of catalyst. The orthogonally protected diamine *exo*-6-(*N*,*N*-dibenzylamino)-3-aza-bicyclo[3,1,0]hexane-3-carboxylic acid tert-butyl ester (**82**) was prepared from (**81**) in 71% yield (270 g, from 1 mol of starting material). Debenzylation of **82** by using Pd/C in methanol gave the mono-Boc protected diamine (**84**). It must be noted that for the debenzylation reaction Pd/C purchased from the Merck was the best. The same reaction carried out by using Pd/C from Aldrich, Fluka or Lancaster did not go to the end even after 4 days of stirring. The reaction of **82** with 2 N HCl in EtOAc resulted in deprotection of Boc group and gave the hydrochloride salt of **83** from which the free amine **83** was liberated in 98% by treatment with 10 N aq. NaOH solution. These results are given in Scheme 37.



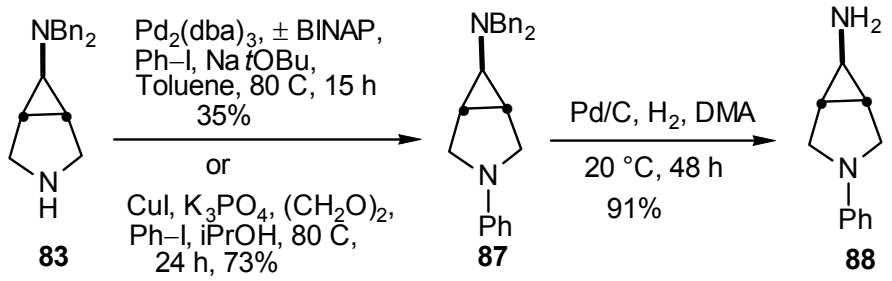
Scheme 37. Synthesis of *exo*-6-(*N*,*N*-dibenzylamino)-3-aza-bicyclo[3,1,0]hexane-3-carboxylic acid tert-butyl ester (**82**) and mono-deprotected products **83** and **84**.

Since the protecting group play and important role in organic synthesis[99] it was interesting to change the protection of the primary amine group from dibenzyl group to benzyloxy carbonyl group (Z group). When a solution of **84** in acetone was treated with 1.1 equiv. of ZOSu in presence of 1 N aq. $NaHCO_3$ the orthogonally protected product **85** was obtained in 85% of yield. Deprotection of the Boc group was achieved by using the same method described for compound **83**. These results are summarized in Scheme 38.



Scheme 38. Protection of primary and deprotection of secondary anine group.

Since aromatic amines plays an important role in many areas including pharmaceutical, agrochemicals, photography and electronic materials[100] it was interesting to study the reactivity towards the nucleophilic substitution of benzyl iodide with the free amine **83**. By adopting the palladium-catalyzed amination protocol developed by Buchwald[91a] by using 10 mol% $Pd_2(dba)_3$, 30 mol% ± BINAP in the presence of Na*t*OBu in a solution of toluene the product (**8**) was isolated only in 35% yield. Recently Buchwald et al. has reported a Copper-catalyzed amination of alkyl amine with aryl iodide in the presence of K_3PO_4 and ethylene glycol.[101] By using this method when 2.1 equiv. of benzyl iodide was reacted with **83** in the presence of 10 mol% of CuI in a solvent isopropanol at 80 °C for 24 h the compound **87** was isolated in 73% yield. It is noted that the product **87** is very sensitive towards silica gel but could be purified by crystallized from methanol. The attempted debenzylation of **87** with Pd/C, H_2 in methanol did not give any product even after 48 h, instead, only starting material and 30% of product corresponding to the mono-debenzylation reaction was identified by NMR spectra. By changing the solvent to MeOH/AcOH (20:1) or MeOH/6 N HCl in isopropanol did not give any product. The reaction also failed by changing the catalyst to $Pd(OH)_2$/C in ethyl acetate as solvent. Finally by changing the solvent to dimethyl acetamide the product **88** was isolated in 90% yield after 48 h by using Pd/C as catalyst. These results are presented in Scheme 39.



Scheme 39. Metel-catalyzed amination of aryl iodide with **83**.

3. Experimental Part

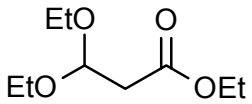
3.1. General Remarks

All reagents were used as purchased from commercial suppliers without further purification. All reactions in non-aq. solvents were carried out using standard Schlenk techniques under an atmosphere of dry nitrogen. Solvents were purified and dried according to conventional methods prior to use; diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. – Solvents are abbreviated as follows: EtOAc = ethyl acetate, MEK = ethyl methyl ketone, MeOH = methanol, EtOH = ethanol, DCM = dichloromethane, AcOH = acetic acid, DMF = dimethyl formamide. – ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature with a Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C), a Varian UNITY-200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) or a Varian UNITY-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) instrument. Chemical shifts δ are given in ppm relative to resonances of solvent (^{1}H: 7.26 ppm for $CHCl_3$; ^{13}C: 77.0 ppm for $CDCl_3$), coupling constants *J* are given in Hertz. Characterization of the multiplicity of signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet. – The multiplicities of signals were determined by the DEPT or the APT technique: DEPT: + = primary or tertiary (positive DEPT-signal), – = secondary (negative DEPT-signal), C_{quat} = quaternary C-atom; APT: + = primary or tertiary (positive APT-signal), – = secondary or quaternary C-atom (negative APT-signal). – IR: Bruker IFS 66. – MS: Finnigan MAT 95, 70 eV. – HRMS: Finnigan MAT 95 using preselected ion peak matching at R = 10000 to be within ± 2 ppm. – Chromatography: Separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). The dimensions of the columns are given as "diameter × height of the silica column". – TLC: Macherey-Nagel, TLC plates Alugram® Sil G/UV_{254}. Detection under UV-light at 254 nm, development with MOPS reagent (10% molybdophosphoric acid, solution in ethanol). – Melting points: apparatus according to Dr. Tottoli (Büchi); values are uncorrected. – Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

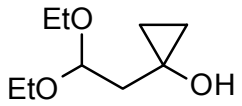
3.2. Synthesis of Compounds

3.2.1. Advanced synthesis of methyl 2-chloro- and 2-bromo-2-cyclopropylideneacetate

Ethyl 3,3-diethoxypropionate (**29**): Into a two litre three necked round-bottomed flask equipped with magnetic stirring bar, reflux condenser, addition funnel and a thermometer, 400 mL of CCl_4 was taken with 3.3g (20 mmol, 10 Mol %) of azobisisobutyronitrile. This solution was heated to 70 °C and Etyl vinyl ether (144 g, 2 Mol) was added over a period of 1 h. After stirring for 3 hour at this temperature, at which point the vapour temperature increased from 50 °C to 70 °C, the reaction mixture was cooled down to RT and 400 mL of EtOH was added to it and the reaction mixture was refluxed for 12 h, cooled down to RT, diluted with 500 mL of ether and washed with H_2O (2×300 mL), sat. aq. $NaHCO_3$ (2×300 mL), dried over $MgSO_4$ and solvent removed in vacuo. The crude product was distilled at reduced pressure (b.p. 86–89 °C, 30 mbar) to yield 236 g (62%) of pure product as a colourless oil. Other physical properties are same with the literature.[59]



1-(2,2-Diethoxyethyl)cyclopropanol (**31**): To a solution of 190 g (1.0 mol) of **29** in 1.5 L of THF/Et_2O (1:1) was added 59.5 mL (200 mmol) of titanium(IV) isopropoxide at 0 °C and 1.25 L of EtMgBr (2.0 M solution in Et_2O, 2.50 mol) over 2 h. The deep black solution was stirred at 20 °C for 12 h then 1 L of Et_2O was added and the reaction was quenched by slow addition of 200 mL of water at 0 °C, and the mixture stirred until the precipitation was complete. After filtration of the precipitate, the filtrate was dried over $MgSO_4$ and then filtered over Celite®. Removal of the solvent in vacuo (water bath < 40 °C) yielded 171 g (96%) of **17** as a slightly yellow liquid. – IR (film): ν = 3420 cm^{-1}, 2938, 2835, 1717, 1700, 1457, 1387, 1192, 1122, 1053. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.41–0.44 (m, 2 H, cPr-CH_2), 0.73–80 (m, 2 H, cPr-CH_2), 1.21 (t, ^3J = 7.3 Hz, 6 H, 2 CH_3), 1.85 (d, ^3J = 7.2 Hz, 2 H, CH_2), 3.42–3.78 (m, 5 H, 2 CH_2 + OH), 4.77 (t, ^3J = 7.2 Hz, 1 H, CH). – ^{13}C-NMR ($CDCl_3$, 62.9 MHz, DEPT): δ = 12.4 (–, 2 C, cPr-C), 15.3 (+, 2 C, CH_3), 40.8 (–, CH_2), 53.1 (C_{quat}, cPr-C), 61.7 (–, 2 C, OCH_2), 102.9 (+, CH). – MS (EI, 70 eV), *m*/*z* (%): 129 (6), 128 (10), 103 (49), 83 (92), 75 (48), 55 (63), 47 (100). – $C_9H_{18}O_3$ (174.2): calcd. C 62.04, H 10.41, found: C 61.79, H 10.38.

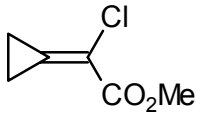


2-(1'-Mesyloxycyclopropyl)acetic acid (**28**). To a solution of 171 g (955 mmol) of **31** in 1.5 L of DCM were added 121 g (1.2 mol) of triethyl-amine, 6.10 g (50 mmol) of DMAP and slowly within 30 min 120 g (1.05 mmol) of mesyl chloride. The solution was stirred for 8 h at 20 °C, extracted with 1 N HCl (1×500 mL) and water (1×500 mL). Drying over Na_2SO_4 yielded the raw mesylate as brown oil, which was dissolved in 1.20 L of THF/H_2O (1:2). To this solution was added 922 g (1.50 mol) of Oxone® and the suspension was stirred at 20 °C for 18 h. Water (1 L) was added and the aq. phase was extracted with ethyl acetate (3×1 L). Drying over $MgSO_4$, evaporation of the solvent and recrystallization of the residue from Et_2O yielded 108 g (58%) of **28** as colorless crystals, m. p. = 96–98 °C. – IR (film): ν = 3032 cm^{-1}, 1710, 1424, 1408, 1331, 1265, 1230, 1184, 1155, 942, 907. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.90–0.96 (m, 2 H, cPr-CH_2), 1.39–1.47 (m, 2 H, cPr-CH_2), 2.91 (s, 2 H, CH_2), 3.05 (s, 3 H, CH_3), 10.85–11.23 (br. s., 1 H, CO_2H). – ^{13}C-NMR ($CDCl_3$, 50.3 MHz, APT): δ = 12.5 (–, 2 C, cPr-C), 39.9 (+, CH_3), 41.7 (–, CH_2), 63.6 (C_{quat}, cPr-C), 173.6 (C_{quat}, C=O). – MS (DCI, 70 eV), *m/z* (%): 406 (3) [$2M^+ + NH_4^+$], 212 (100) [$M^+ + NH_4^+$]. – $C_6H_{10}O_5S$ (194.2): calcd. C 37.11, H 5.19, found: C 37.39, H 4.96.

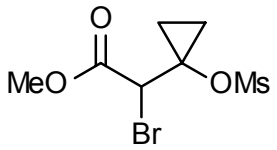
Methyl 2-chloro(1-methanesulfonyloxycyclopropyl)acetate (**32a**)*:* To a solution of 108 g (557 mmol) of **28** in 1.5 L of 1,2-dichloroethane was added 51.3 mL (696 mmol) of thionyl chloride, and the solution was heated under reflux for 60 min. At room temperature were added 111 g (836 mmol) of NCS and 1 mL of conc. aq. HCl, and the solution was heated at 90 °C for 12 h. At 20 °C MeOH (100 mL) was added, and the solution stirred at this temperature for an additional 1 h. The solvent was removed in vacuo, the residue suspended in cold (0 °C) tetrachloromethane, and the mixture was filtered to remove succinamide. Removal of the solvent afforded 130.1 g (97%) of **32a** as yellow oil, which was 90% pure by NMR and used in the next step without further purification. An analytical sample was purified on 100 g of silica gel (column, 4×20 cm, PE/Et_2O = 3:1; R_f = 0.16). – IR (film): ν = 3045 cm^{-1}, 2830, 1717, 1456, 1424, 1408, 1329, 1175, 987, 935, 882. –^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.84 (m, 2 H, cPr-CH_2), 1.33 (m, 2 H, cPr-CH_2), 3.01 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 4.58 (s, 1 H, Cl-CH). – ^{13}C-NMR ($CDCl_3$, 62.9 MHz): δ = 10.0 (–, 2 C, cPr-C), 39.3 (+, CH_3), 52.0 (+, OCH_3), 62.0 (C_{quat}, cPr-C), 63.2 (+,

Cl-CH), 170.8 (C_{quat}, C=O). – MS (DCI, 70 eV), *m/z* (%): 244/242 (2/7) [M^+], 207 (63) [M^+ – Cl], 129 (100), 99 (35), 97 (28). – $C_7H_{11}ClO_5S$ (242.7): calcd. C 34.65, H 4.57, found: C 34.60, H 4.56.

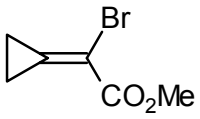
Methyl 2-chloro-2-cyclopropylideneacetate (**5**). To a solution of 130.1 g of the above crude **32a** in 1 L of DCM kept at 0 °C was added 81 g (55.2 mmol) of triethylamine, and the solution was stirred at this temperature for 8 h. DCM (500 mL) and aq. 1 N HCl (3×100 mL) were added and the phases were separated. Drying of the organic phase over $MgSO_4$ and removal of the solvent in vacuo yielded the crude product which was bulb to bulb distilled at 1 torr with a dry-ice cooling bath, crystallized with PE/Et_2O (100 mL) at –20 °C to yield 58 g (77% from **28**) of **5** as colorless crystals. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.41–1.50 (m, 2 H, cPr-CH_2), 1.66–1.75 (m, 2 H, cPr-CH_2), 3.83 (s, 3 H, CH_3). – ^{13}C-NMR ($CDCl_3$, 62.9 MHz): δ = 5.5 (–, cPr-C), 9.7 (–, cPr-C), 52.9 (+, CH_3), 114.7 (C_{quat}, cPr-C), 139.1 (C_{quat}, Cl-C), 162.7 (C_{quat}, C=O). The additional experimental data are identical to those reported in literature.[18]



Methyl 2-bromo(1-methanesulfonyloxycyclopropyl)acetate (**32b**). To a solution of 4.00 g (20.6 mmol) of **28** in 50 mL of DCE was added 1.82 mL (25.0 mmol) of thionyl chloride, and the solution was heated under reflux for 30 min. At ambient temperature were added 4.44 g (25.0 mmol) of NBS and 4 drops of conc. aq. HBr, and the solution was heated under reflux at 90 °C for 4 h. MeOH (50 mL) was added at 20 °C, and the solution was stirred for an additional 1 h. The solvents were removed in vacuo, the residue suspended in tetrachloromethane, and the mixture filtered. Removal of the solvent and chromatographic purification of the residue on 40 g of silica gel (column, 3×20 cm, PE/Et_2O = 3:1; R_f = 0.19) afforded 2.98 g (53%) of **32b** as colourless oil. – IR (film): ν = 3031 cm^{-1}, 2944, 1423, 1366, 1168. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.82 (m, 2 H, cPr-CH_2), 1.21 (m, 2 H, cPr-CH_2), 3.08 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 4.85 (s, 1 H, Br-CH). – ^{13}C-NMR ($CDCl_3$, 62.9 MHz): δ = 11.2 (–, 2 C, cPr-C), 40.4 (+, CH_3), 52.5 (+, OCH_3), 62.3 (C_{quat}, cPr-C), 63.2 (+, Br-CH), 171.2 (C_{quat}, C=O). – MS (70 eV), *m/z* (%): 288/286 (3/4) [M^+], 209 (63) [M^+ – Br], 207 (19), 129 (100), 79 (28), 56 (75). – $C_7H_{11}BrO_5S$ (287.1): calcd. C 29.28, H 3.86, found: C 29.17, H 3.83.



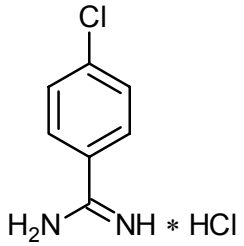
Methyl 2-bromo-2-cyclopropylideneacetate (**4**-Me). To a solution of 2.18 g (15.6 mmol) of **32b** in 25 mL of DCM kept at 0 °C were added 1.21 g (12.4 mmol) of triethylamine, and the solution was stirred at this temperature for 4 h. DCM (100 mL) and 1 N aq. HCl (10 mL) were added. Separation of the phases, drying of the organic phase over $MgSO_4$ and removal of the solvent in vacuo yielded 1.52 g (99%) of **32**b as a colourless crystalline solid. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.39 (m, 2 H, cPr-CH_2), 1.76 (m, 2 H, cPr-CH_2), 3.82 (s, 3 H, CH_3). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 7.0 (–, cPr-C), 12.1 (–, cPr-C), 53.2 (+, CH_3), 103.7 (C_{quat}, cPr-C), 143.6 (C_{quat}, Br-C), 162.6 (C_{quat}, C=O).



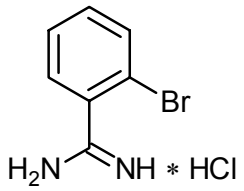
3.2.2. Synthesis of 5,6,7,8-tetrahydroquinazolinone derivatives

General procedure for synthesis of amidine from nitriles (GP 1): Into a dry reaction flask charged with 1 M LiHMDS in THF, the corresponding solution of nitriles (**33a–d**) in THF was added, and the reaction mixture was kept stirring at 20 °C for 4 h, at which point 6 N isopropanolic HCl (4 equiv) was added. The crude reaction mixture was kept at 0 °C overnight. The precipitated product was filtered, washed with diethyl ether, dried to yield the amidine hydrochlorides as colourless solids.

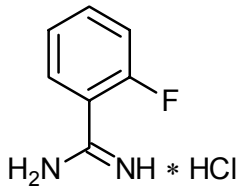
p-Chlorobenzamidine hydrochloride (**34b**): Using the GP 1, 3.5 g (91%) of **34b** were obtained from *p*-chlorobenzonitrile (2.76 g, 20.0 mmol) and 22.0 mL of 1 M LiHMDS as a white solid, m.p. 238 °C (lit. m.p. 243–245 °C)[102]. – IR (KBr): ν = 3239 cm^{-1}, 3054, 1678, 1460, 1401, 1036, 715. – ^{1}H-NMR (250 MHz, [D_6]DMSO): δ = 7.60–7.77 (m, 2 H), 7.85–7.97 (m, 2 H), 8.4 (br. s, NH). – ^{13}C-NMR (62.9 MHz, [D_6]DMSO), δ = 126.8 (C_{quat}, aryl-C), 129.4 (+, 2 C, aryl-C), 130.6 (+, 2 C, aryl-C), 139.1 (C_{quat}, aryl-C), 165.1 (C_{quat}, NCN).



o-Bromobenzamidine hydrochloride (**34c**): Using the GP 1, 4.3 g (91%) of **34c** were obtained from *o*-bromobenzonitrile (3.68 g, 20.0 mmol) and 22 mL of 1 M LiHMDS as a white solid, m.p. > 250 °C. – IR (KBr): ν = 3228 cm^{-1}, 3059, 1669, 1458, 1401, 1030, 728. – ^{1}H-NMR (250 MHz, CD_3OD): δ = 4.92 (br. s, NH), 7.54–7.68 (m, 3 H), 7.74–7.86 (m, 1 H). – ^{13}C-NMR (62.9 MHz, CD_3OD): δ = 121.1 (C_{quat}), 129.5 (+), 131.0 (+), 133.3 (C_{quat}), 134.8 (+), 135.0 (+), 168.4 (NCN). – MS (DCI, 70 eV) *m/z* (%): 399 (6) [2M – 2Na + H^+], 216 [M – HCl + NH_4^+], 199 (100) [M – HCl + H^+].

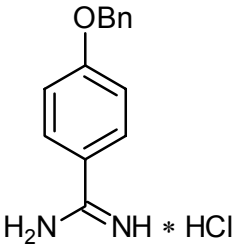


o-Fluorobenzamidine hydrochloride (**34d**): Using the GP 1, 2.8 g (80%) of **34d** were obtained from *o*-fluorobenzonitrile (2.40 g, 20.0 mmol) and 22.0 mL of 1 M LiHMDS as a white solid, m.p. 98–100 °C. – IR (KBr): ν = 3477 cm^{-1}, 3144, 1701, 1674, 1476, 1401, 1228, 774, 684. – ^{1}H-NMR (250 MHz, CD_3OD): δ = 4.98 (br. s, NH), 7.38–7.49 (m, 2 H), 7.64–7.80 (m, 1 H). – ^{13}C-NMR (62.9 MHz, CD_3OD, DEPT): δ = 118.2 (+, d, $^2J_{C\text{-}F}$ = 9.2 Hz, aryl-C), 118.8 (C_{quat}, d, $^2J_{C\text{-}}$

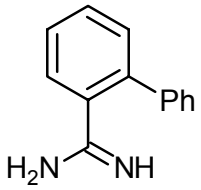


$_F$ = 3.2 Hz, aryl-C), 126.6 (+, aryl-C), 131.4 (+, aryl-C), 136.8 (+), 161.2 (C_{quat}, d, $^1J_{C\text{-}F}$ = 253.7 Hz, aryl-C), 164.9 (C_{quat}, NCN).

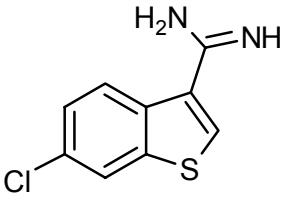
p-Benzyloxybenzamidine hydrochloride (**34e**): Using the GP 1, 2.42 g (92%) of **34e** were obtained from *o*-benzyloxybenzonitrile (2.09 g, 10 mmol) and 11 mL of 1 M LiHMDS as a white solid, m.p. 181–182 °C (lit. m.p. 179–180 °C).[103] – IR (KBr): ν = 3317 cm^{-1}, 3125, 1677, 1609, 1486, 1267, 1190, 1010, 837, 763. – ^{1}H-NMR (250 MHz, CD_3OD): δ = 4.92 (br. s, NH), 5.24 (s, 2 H), 7.19–7.28 (m, 2 H), 7.32–7.52 (m, 5 H) 7.79–7.84 (m, 2 H). – ^{13}C-NMR (75.5 MHz, CD_3OD): δ = 71.4 (–, OCH_2), 116.7 (+, aryl-C), 121.14 (C_{quat}, aryl-C), 128.7 (+, aryl-C), 129.2 (+, aryl-C), 129.6 (+, aryl-C), 131.1 (+, aryl-C), 137.6 (C_{ipso}), 164.9 (C_{ipso}), 168.4 (NCN).



o-Phenylbenzamidine (**34f**)**:** To a suspension of NH_4Cl (2.14 g, 40.0 mmol) in 40 mL of toluene was added Me_3Al (2 M in toluene, 40.0 mmol) over a period of 30 min at 5 °C. The temperature was then allowed to reach 25 °C, and stirring was continued until evolution of methane ceased (~ 2 h). To this solution of $MeAl(Cl)NH_2$, *o*-biphenyl nitrile (2.86 g, 16.0 mmol) was added in 5 mL of toluene during a period of 5 min, and the resulting solution was refluxed for 20 h. After cooling, the crude reaction mixture was poured onto a suspension of 20 g of SiO_2 in 100 mL of dichloromethane, filtered and the solid residue was washed with 2 × 50 mL of MeOH. The solvent was removed in vacuo from the combined solutions. The residue was suspended in 100 mL of water, 30 mL of 2 N HCl were added and the suspension was extracted with ethylacetate (2 × 50 mL). To the aq. layer 60 mL of 2 N NaOH were added and the solution was extracted with DCM (3 × 50 mL). This DCM layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to yield 1.83 g (58%) of **34f** as a white solid, m.p. 148–150 °C (lit. m.p. 149–151 °C).[62e] – IR (KBr): ν = 3408 cm^{-1}, 3059, 1674, 1639, 1600, 1427, 1199, 744, 701. – ^{1}H-NMR (250 MHz, [D_6]DMSO): δ = 5.4 (br. s, NH), 7.31–7.55 (m, 9 H). – ^{13}C-NMR (62.9 MHz, [D_6]DMSO): δ = 127.3 (aryl-C), 128.1 (aryl-C), 128.3 (aryl-C), 128.6 (aryl-C), 129.2 (aryl-C), 136.2 (aryl-C), 137.5 (aryl-C), 139.0 (aryl-C), 140.5 (aryl-C), 165.9 (NCN). – MS (70 eV), *m/z* (%): 196 (10) [M^+], 195 (100) [M^+ –1], 178 (31), 77 (8).



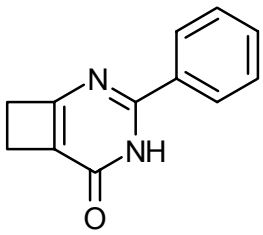
3-(5-chloro-benzo[b]thiophene) amidine (**34g**): Following the method described for **34f** 420 mg (84%) of **34g** were obtained from the corresponding nitrile (460 mg, 2.38 mmol), as a white solid, m.p. > 250 °C. – IR (KBr): $\nu = 3042$ cm^{-1}, 1656, 1551, 1639, 1408, 1082, 866, 829. – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 7.46$ (dd, $^3J = 8.4$ Hz, $^4J = 1.8$ Hz, 1 H, Ar-H), 7.83 (d, $^3J = 8.3$ Hz, 1 H, Ar-H), 7.98 (d, $^4J = 1.3$ Hz, 1 H, Ar-H), 8.17 (s, 1 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): $\delta = 106.5$ (C_{quat}, aryl-C), 113.7 (C_{quat}, aryl-C), 122.1 (+, aryl-C), 123.8 (+, aryl-C), 126.9 (+, aryl-C), 132.7 (C_{quat}, aryl-C), 136.5 (C_{quat}, aryl-C), 138.3 (C_{quat}, aryl-C), 139.1 (+, aryl-C), 163.3 (NCN). – MS (70 eV), *m/z* (%): 210 (100) [M$^+$], 194 (75), 159 (40),



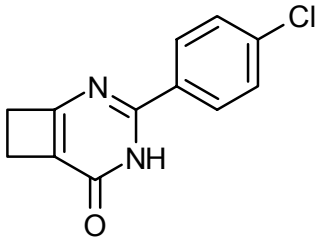
General Procedure for Michael addition of amidines 34a–j onto 5 (GP 2):

A solution of methyl 2-chloro-2-cyclopropylidineacetate **5**, amidine **34** (2 eqiv.) and of Et_3N (4 equiv.) was stirred in anhydrous dioxane at room temp. for 48 h. After filtration the solid residue was suspended in DCM and washed with water. The aq. layer was washed three times with DCM. The organic layers were combined with the filtrate, dried over $MgSO_4$, evaporated in vacuo and the crude product was purified by column chromatography.

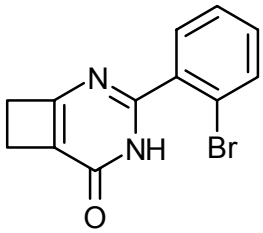
3-Phenyl-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35a**): The crude product obtained from **5** (365 mg, 2.50 mmol) and benzamidine hydrochloride (**34a**, 793 mg, 5.00 mmol) in 25 mL of dioxane according to GP 2 was purified by column chromatography (R_f = 0.3, Et_2O, 1.5 × 30 cm, 30 g SiO_2) to yield 411 mg (83%) of **35a** as a white solid, m.p. 191 °C. – IR (KBr): $\nu = 3008$ cm^{-1}, 2937, 1670, 1557, 1498, 1321, 1082, 838, 766. – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.01$ (t, $J = 3.2$ Hz, 2 H), 3.22 (t, $J = 3.2$ Hz, 2 H), 7.47–7.53 (m, 3 H, aryl-H), 8.05–8.2 (m, 2 H, aryl-H), 12.54 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): $\delta = 25.7$ (–, CH_2), 33.7 (–, CH_2), 124.1 (C_{quat}, C-6), 127.6 (+, aryl-C), 128.9 (+, aryl-C), 131.7 (+, aryl-C), 132.5 (C_{ipso}, aryl-C), 158.6 (C_{quat}, C-1/C-3), 160.52 (C_{quat}, C-3/C-1), 171.9 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 198 (100) [M$^+$], 170 (7) [M$^+$ – C_2H_4], 104 (91) [HN=CPh$^+$], 77 (44) [$C_5H_5^+$]. – $C_{12}H_{10}N_2O$ (198.2): calcd. C 72.71, H 5.08, N 14.13; found C 72.44, H 5.38, N 14.03.



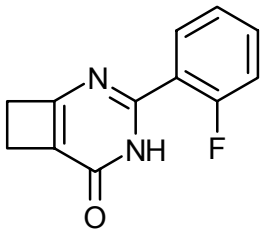
3-(p-Chlorophenyl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35b**): The crude product obtained from **5** (365 mg, 2.50 mmol), *p*-chlorobenzamidine hydrochloride (**34b**, 955 mg, 5.00 mmol) and triethylamine (1.01 g, 10.0 mmol) in 25 mL of dioxane according to GP 2 was purified by column chromatography (R_f = 0.31, DCM/MeOH = 25:1, 1.5×20 cm, 25 g SiO_2) to yield 455 mg (78%) of **35b** as a white solid, m.p. 218–219 °C. – IR (KBr): ν = 3078 cm^{-1}, 2938, 1668, 1520, 1491, 1322, 1092, 1076, 837, 760. – ^{1}H-NMR (250 MHz, [D_6]DMSO): δ = 2.9 (t, *J* = 3.1 Hz, 2 H), 3.15 (t, *J* = 3.1 Hz, 2 H), 7.6 (d, *J* = 8.5 Hz, 2 H, aryl-H), 8.05 (d, *J* = 8.5 Hz, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, [D_6]DMSO), δ = 25.1 (–, CH_2), 33.6 (–, CH_2), 126.1 (C_{quat}, C-6), 128.9 (+, aryl-C), 129.8 (+, aryl-C), 136.6 (C_{quat}, C_{ipso}), 152.1 (C_{quat}, C-Cl), 158.2 (C_{quat}, C-1/C-3), 159.6 (C_{quat}, C-3/C-1), 171.5 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 234/232 (33/100) [M^+], 204 (6) [$M^+ – C_2H_4$], 138/140 (57/18) [$HN{=}CC_6H_4Cl^+$], 111 (15) [$C_5H_4Cl^+$]. – $C_{12}H_9ClN_2O$ (232.7): calcd. C 61.95, H 3.90, N 12.04; found C 61.63, H 3.78, N 11.83.



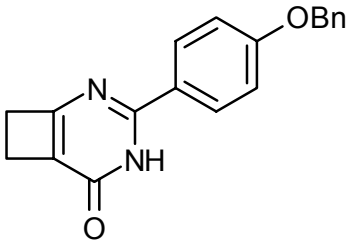
3-(o-Bromophenyl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35c**): The crude product obtained from **5** (1.10 g, 7.50 mmol) *o*-bromobenzamidine hydrochloride (**34c**, 3.50 g, 15.0 mmol) and triethylamine (3.03 g, 30.0 mmol) in 60 mL of dioxane according to GP 2 was purified by column chromatography (R_f = 0.35, Et_2O/MeOH = 50:1, 3×30 cm., 50 g SiO_2) to yield 1.59 g (76%) of **35c** as a white solid, m.p. 178–179 °C. – IR (KBr): ν = 2925 cm^{-1}, 2847, 1662, 1540, 1472, 1326, 1089, 778, 762. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.0 (t, *J* = 4.2 Hz, 2 H), 3.2 (t, *J* = 4.2 Hz, 2 H), 7.3–7.5 (m, 2 H, aryl-H), 7.52–7.7 (m, 2 H, aryl-H), 11.0 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 25.4 (–, CH_2), 33.7 (–, CH_2), 120.9 (C_{quat}, C-6), 125.1 (C_{quat}, C-Br), 127.7 (+, aryl-C), 130.9 (+, aryl-C), 132.0 (+, aryl-C), 133.7 (+, aryl-C), 134.6 (C_{quat}, C_{ipso}), 157.6 (C_{quat}, C-1/C-3), 160.3 (C_{quat}, C-3/C-1), 171.2 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 279/277 (21/22) [M^+ + 1], 278/276 (97/100) [M^+], 184/182 (41/42) [$HNCC_6H_4Br^+$], 102 (58), 95 (79). – $C_{12}H_{10}BrN_2O$ (277.1): calcd. C 52.01, H 3.27, N 10.11; found C 51.92, H 3.37, N 9.94.



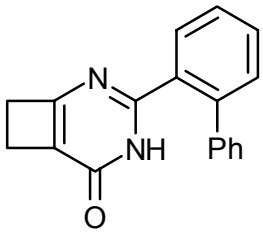
3-(o-Fluorophenyl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35d**): The crude product obtained from **5** (730 mg, 5.00 mmol), *o*-fluorobenzamidine hydrochloride (**34d**, 1.75 g, 10.0 mmol) and triethylamine (2.02 g, 20.0 mmol) in 50 mL of dioxane according to GP 2 was purified by column chromatography (R_f = 0.5, Et_2O/MeOH = 25:1, 3 × 30 cm, 50 g SiO_2) to yield 884 mg (82%) of **35d** as a white solid, m.p. 184–185 °C. – IR (KBr): ν = 3095 cm^{-1}, 2976, 2947, 1668, 1617, 1532, 1319, 1223, 1084, 753. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.04 (t, *J* = 4.2 Hz, 2 H), 3.25 (t, *J* = 4.2 Hz, 2 H), 7.16–7.42 (m, 2 H, aryl-H), 7.48–7.62 (m, 1 H, aryl-H), 7.91–8.20 (m, 1 H, aryl-H), 10.22 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 25.4 (–, CH_2), 33.8 (–, CH_2), 116.6 (+, d, $^2J_{C\text{-}F}$ = 22.9 Hz) 120.1 (d, $^2J_{C\text{-}F}$ = 22.9 Hz, C_{ipso}), 125.0 (+, d, $^3J_{C\text{-}F}$ = 3.5 Hz), 130.9 (+, d, $^4J_{C\text{-}F}$ = 1.5 Hz), 133.6 (+, d, $^3J_{C\text{-}F}$ = 9.2 Hz), 156.7 (C_{quat}, C-1/C-3), 156.8 (C_{quat}, C-3/C-1), 160.2 (C_{quat}, d, $^1J_{C\text{-}F}$ = 251 Hz), 171.0 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 217 (17) [M^+ + 1], 216 (100) [M^+], 122 (42) [$HN{=}CC_6H_4F^+$], 102 (20), 95 (24) [$C_6H_4F^+$]. – $C_{12}H_{10}FN_2O$ (116.2): calcd. C 66.66, H 4.20, N 12.96; found C 66.50, H 4.28, N 13.03.



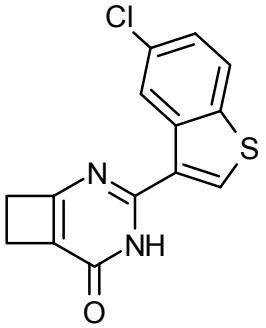
3-(p-Benzyloxyphenyl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35e**): The crude product obtained from **5** (660 mg, 4.50 mmol) *p*-benzyloxybenzamidine hydrochloride (**34e**, 2.4 g, 9.00 mol) and triethylamine (1.82 g, 18.0 mol) in 50 mL of dioxane according to GP 2 was purified by column chromatography (R_f = 0.34, DCM/MeOH = 25:1, 3 × 30 cm, 50 g, SiO_2) to yield 930 mg (68%) of **35e** as a white solid, m.p. 212–213 °C. – IR (KBr): ν = 3088 cm^{-1}, 2936, 1664, 1608, 1504, 1303, 1252, 1189, 843, 762. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.01 (t, *J* = 3.8 Hz, 2 H), 3.20 (t, *J* = 3.8 Hz, 2 H), 5.15 (s, 2 H, OCH_2), 7.04–7.12 (m, 2 H, aryl-H), 7.30–7.47 (m, 5 H, aryl-H), 7.95–8.22 (m, 2 H, aryl-H), 11.48 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, [D_6]DMSO): δ = 24.6 (–, CH_2), 32.9 (–, CH_2), 69.4 (–, OCH_2), 114.7 (+, aryl-C), 122.5 (C_{quat}, C-6), 124.9 (C_{ipso}), 127.6 (+, aryl-C), 127.8 (+, aryl-C), 128.4 (+, aryl-C), 129.4 (+, aryl-C), 136.5 (C_{ipso}, aryl-C), 156.7 (C_{ipso}, aryl-C), 159.9 (C_{quat}, C-1/C-3), 160.9 (C_{quat}, C-3/C-1), 169.9 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 304 (8) [M^+], 91 (100) [$C_7H_7^+$]. – $C_{19}H_{16}N_2O_2$ (304.6): calcd. C 74.98, H 5.30, N 9.20; found C 74.78, H 5.01, N 8.98.



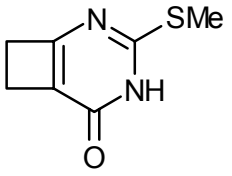
3-(Biphenyl-2-yl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35f**): The crude product obtained from **5** (527 mg, 3.6 mmol) *o*-biphenylbenzamidine (**34f**, 1.40 g, 7.20 mole) and triethylamine (1.44 g, 14.2 mol) in 25 mL of dioxane according to GP 2 was purified by column chromatography (R_f = 0.41, Et_2O, 1.5 × 20 cm, 20 g SiO_2) to yield 425 mg (80%) of **35f** as a white solid, m.p. 176–177 °C. – IR (KBr): ν = 2928 cm^{-1}, 1675, 1540, 1478, 1323, 1088, 976, 745, 698. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.92 (t, *J* = 4.2 Hz, 2 H), 3.18 (t, *J* = 4.2 Hz, 2 H), 7.22–7.41 (m, 5 H, aryl-H), 7.44–7.78 (m, 4 H, aryl-H), 9.22 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 25.0 (–, CH_2) 33.5 (–, CH_2), 123.8 (C_{quat}, C-6), 127.7 (+, aryl-C), 128.1 (+, aryl-C), 128.8 (+, aryl-C), 129.8 (+, aryl-C), 130.7 (+, aryl-C), 132.3 (C_{ipso}, aryl-C), 139.2 (C_{ipso}, aryl-C), 140.6 (C_{ipso}, aryl-C), 157.3 (C_{quat}, C-1/C-3), 161.9 (C_{quat}, C-3/C-1), 170.8 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 274 (42) [M^+], 273 (100) [M^+ – 1], 245 (8), 178 (11).



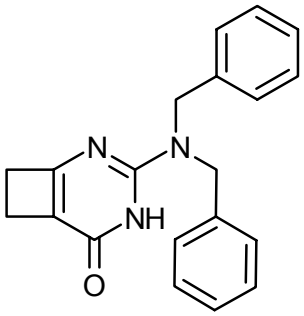
3-(5-chloro-benzo[b]thiophene)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35g**): The crude product obtained from **5** (219 mg, 1.50 mmol) 5-chloro-benzo[b]thiophen-3-yl-amidine (**34g**, 420 mg, 2.0 mol) and triethylamine (404 g, 4.0 mol) in 25 mL of dioxane according to GP 2 was purified by column chromatography (R_f = 0.37, DCM/MeOH = 25:1, 1.5 × 20 cm, 20 g SiO_2) to yield 330 mg (74%) of **35g** as a white solid, m.p. 218 °C. – IR (KBr): ν = 3109, cm^{-1}, 2985, 1934, 1664, 1552, 1538, 1245, 1075, 858, 757. – ^{1}H-NMR (200 MHz, [D_6]DMSO): δ = 2.90 (t, *J* = 3.2 Hz, 2 H), 3.20 (t, *J* = 3.2 Hz, 2 H), 7.46 (dd, ^3J = 8.2 Hz, ^4J = 1.83 Hz, 1 H, aryl-H), 8.05 (d, ^3J = 8.9 Hz, 1 H, aryl-H), 8.72 (s, 2 H, aryl-H), 11.9 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, [D_6]DMSO): δ = 24.8 (–, CH_2), 33.1 (–, CH_2), 124.0 (C_{quat}, C-6), 124.2 (+, aryl-C), 124.5 (+, aryl-C), 125.1 (+, aryl-C), 127.4 (–, aryl-C), 130.3 (–, aryl-C), 134.7 (+, aryl-C), 137.4 (–, aryl-C), 138.2 (–, aryl-C), 155.9 (C_{quat}, C-1/C-3), 156.7 (C_{quat}, C-3/C-1), 169.6 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 288 (100) [M^+], 193 (45), 159 (40), 95 (89). – $C_{14}H_9ClN_2OS$ (288.8): calcd. C 58.23, H 3.14, N 9.70; found C 58.53, H 3.07, N 9.67.



3-Methylthio-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35h**): In 50 mL of Schlank flask **5** (365 mg, 2.50 mmol), *S*-methylisothiourea hemisulphate **34h** (1.39 g, 5.00 mmol) and triethylamine (1.52g, 15.0 mmol) in 25 mL of anhydrous dioxane were stirred at 50 °C for 48 h. After filtration, the solid residue was dissolved in water and extracted with DCM (2 × 25 mL). After removing the solvent in vacuum, the crude product was purified by column chromatography (R_f = 0.3, DCM/MeOH = 25:1, 1.5 × 30 cm, 30 g SiO_2) to yield 310 mg (74%) of **35h** as a white solid, m.p. 215 °C. – IR (KBr): ν = 2996 cm^{-1}, 2928, 1654, 1541, 1456, 1396, 1297, 1189, 922, 751. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, SMe), 2.95 (t, *J* = 3.1 Hz, 2 H, CH_2), 3.15 (t, *J* = 3.1 Hz, 2 H, CH_2), 11.5 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, [D_6]DMSO, DEPT): 13.4 (–, CH_2), 24.9 (–, CH_2), 33.2 (+, CH_3), 120.4 (C_{quat}, C-6), 152.3 (C_{quat}, C-1/C-3), 156.6 (C_{quat}, C-3/C-1), 164.98 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 169 (12) [M^+ + 1], 168 (100) [M^+], 121 (14) [M^+ – SMe], 93 (22), 74 (16). – $C_7H_8N_2OS$ (168.2): calcd. C 49.98, H 4.79, N 16.65; found C 49.66, H 5.14, N 16.50.

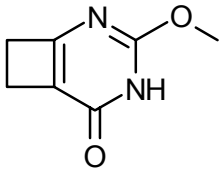


3-Dibenzylamino-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35i**): The crude product obtained from **5** (366 mg, 2.5 mmol), dibenzylguanidine (1.38 g, 5 mmol) was subjected to chromatography to get 520 mg (66%) of **35i** as a white solid, m.p. 204 °C, R_f = 0.5 (DCM:MeOH = 25:1). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.77 (t, ^3J = 3.3 Hz, 2 H, CH_2), 3.03 (t, ^3J = 3.3 Hz, 2 H, CH_2), 4.75 (s, 4 H, Bn-H), 7.17–7.20 (m, 4 H, aryl-H), 7.23–7.33 (m, 6 H, aryl-H), 9.60 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, CD_3OD): δ = 23.9 (–, CH_2), 33.5 (–, CH_2), 50.4 (–, Bn-CH_2), 112.2 (C_{quat}, C-6), 127.1 (+, aryl-C), 127.7 (+, aryl-C), 128.8 (+, aryl-C), 135.8 (C_{quat}, aryl-C), 157.5 (C_{quat}, C-1/C-3), 157.9 (C_{quat}, C-3/C-1), 173.0 (C_{quat}, C-5). – MS (70 eV), *m/z* (%): 317 (10) [M^+], 227 (15), 226 (100) [M^+], 91 (35). HRMS 317.1528 (correct mass).



3-Methoxy-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35j**): The crude product obtained from **5** (366 mg, 2.50 mmol), Omethyl-urea (1.23 g, 10 mmol) and Et_3N (1.52 g, 15 mmol) in 25 mL of dioxane at 50 °C according to GP 2 was subjected to column chromatography (R_f = 0.20, Et_2O) to yield 144 mg (38%) of **35j** as a white solid, m.p.198°C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.92

(t, J = 3.2 Hz, 2 H, CH_2), 3.08 (t, J = 3.1 Hz, 2 H, CH_2), 3.98 (s, 3 H, OMe), 11.5 (br. s, 1 H, NH). – ^{13}C NMR (62.9 MHz, [D_6]DMSO, DEPT): 24.2 (–, CH_2), 33.1 (–, CH_2), 55.5 (+, CH_3), 117.9 (C_{quat}, C-6), 159.7 (C_{quat}, C-1/C-3), 160.6 (C_{quat}, C-3/C-1), 171.5 (C_{quat}, C-5). –MS (70 eV), *m/z* (%): 152 (100) [M^+], 122 (21), 94 (15), 58 (33). – $C_7H_8N_2O2$ (152.2): calcd. C 55.26, H 5.30, N 18.41; found C 55.50, H 5.30, N 18.64.



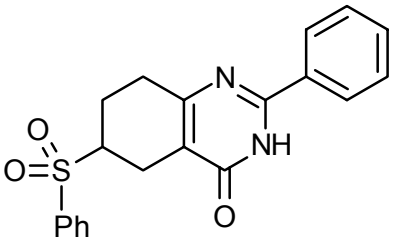
General Procedure for Diels-Alder reaction of 35 with phenyl vinyl sulfone (GP 3):

6-Benzenesulfonyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37**): In a sealed Pyrex tube, 1 equiv. of 2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-ones (**35**) were stirred with 4 equiv. of phenyl vinyl sulfone (**36**) at 175 °C for 12 h. The mixture was allowed to cool down to room temperature, dissolved in DCM/MeOH (10:1) and was purified by column chromatography.

General Procedure for microwave assisted Diels.Alder reaction (GP 4):

6-Benzenesulfonyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37**): In a 10 mL glass tube, 2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-ones (**35**) (0.5 mmol) and phenyl-vinyl sulphone (336 mg, 2 mmol) were taken. The vessel was sealed with a septum and placed in to a microwave cavity. Microwave irradiation of 80 W was used, the temperature being ramped from RT to 140 °C. Once 140 °C was reached, the reaction mixture was held at this temperature for 20 min. After allowing the mixture to cool to RT, the reaction vessel was opened. This crude product was purified by column chromatography.

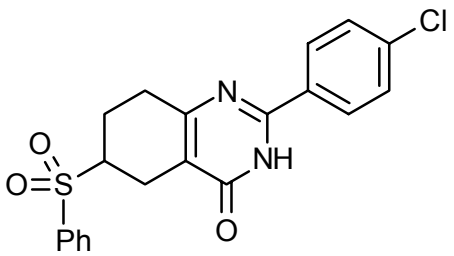
6-Benzenesulfonyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37a**): The crude product obtained from 3-phenyl-2,4-diazabicyclo[4.2.0]octa-1(6),2-diene-5-one (**35a**, 198 mg, 1.00 mmol) and phenyl vinyl sulfone (670 mg, 4.00 mmol) according to GP 3 was purified by column chromatagraphy (R_f = 0.41, Et_2O/MeOH = 25:1, 1 × 30 cm, 25 g SiO_2) to yield 303 mg (81%) of **37a** as a white solid, m.p. > 250 °C. – IR (KBr): ν = 2931 cm^{-1}, 1637, 1551, 1316, 1146, 1085, 699. – ^1H-NMR (200 MHz, [D_6]DMSO): δ = 1.60–1.83 (m, 1 H), 2.10–2.30 (m, 1 H), 2.30–2.45 (m, 1 H), 2.65–2.82 (m, 3 H), 3.6–3.8 [m, 1 H, C(6)-H], 7.4–7.6 (m, 3 H, aryl-H), 7.60–7.85 (m, 3 H, aryl-H), 7.85–8.10 (m, 4 H, aryl-H), 12.6 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, [D_6]DMSO): δ = 21.1



(–, CH_2), 21.7 (–, CH_2), 29.8 (–, CH_2), 57.4 (+, C-6), 115.9 (C-4a), 127.5 (+), 128.5 (+), 128.5 (+), 129.5 (+), 131.3 (+), 132.2 (C_{ipso}), 134.1 (+), 136.9 (C_{ipso}), 153.9 (C-8a), 159.0 (C-2/C-4), 162.5 (C-4/C-2). – MS (70eV), *m/z* (%): 366 (2) [M^+], 225 (24) [$M^+ – SO_2Ph$], 224 (100) [$M^+ – SO_2Ph$ – H], 180 (8), 104 (12), 77 (18) [Ph^+]. – $C_{20}H_{18}N_2O_3S$ (366.5): calcd. C 65.56, H 4.95, N 7.64; found C 65.89, H 4.86, N 7.49.

Using microwaves 126 mg (69%) of **37a** was obtained according to GP 4 which has same physical datas as given above.

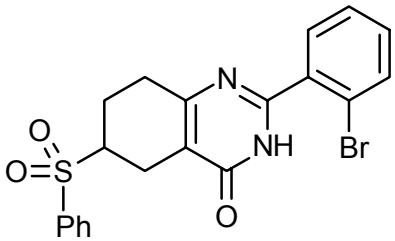
6-Benzenesulfonyl-2-(p-chlorophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37b**): The crude product obtained from 3-(*p*-chlorophenyl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-diene-5-one (**35b**, 400 mg, 1.70 mmol) and phenyl vinyl sulfone (1.15 g, 6.80 mmol) according to GP 3 was purified by column chromatagraphy (R_f = 0.41, DCM/MeOH = 25:1, 3 × 30 cm, 50 g SiO_2) to yield 410 mg (59%) of **37b** as a white solid, m.p. > 250 °C. – IR (KBr): ν = 3067 cm^{-1}, 2946, 1655, 1548, 1506, 1321, 1146, 1087, 842, 749, 689. – ^{1}H-NMR (250 MHz , [D_6]DMSO): δ = 1.68–1.80 (m, 1 H), 2.20–2.75 (m, 5 H), 3.60–3.71 [m, 1 H, C(6)-H], 7.52–7.62 (m, 2 H, aryl-H), 7.71–7.80 (m, 3 H, aryl-H), 7.85–7.97 (m, 2 H, aryl-H), 8.02–8.11 (m, 2 H, aryl-H). –^{13}C-NMR (63.9 MHz, [D_6]DMSO): δ = 21.5 (–, CH_2), 22.0 (–, CH_2), 30.0 (–, CH_2), 57.5 (+, C-6), 117.0 (C_{qaut}, C-4a), 128.8 (+, aryl-C), 128.9 (+, aryl-C), 129.5 (+, aryl-C), 129.8 (+, aryl-C), 131.0 (C_{qaut}, C-Cl), 134.4 (+, aryl-C), 136.6 (C_{ipso}), 137.1 (C_{ipso}), 153.1 (C-8a), 159.6 (C_{qaut}, C-2/C-4), 162.5 (C_{qaut}, C-4/C-2). – MS (70 eV), *m/z* (%): 400 (1) [M^+], 261/259 (10/36) [$M^+ – SO_2Ph$], 260/258 (32/100) [$M^+ – HSO_2Ph$], 140/138 (5/13) [$HN{=}CC_6H_4Cl^+$]. – $C_{20}H_{17}ClN_2O_3S$ (400.9): calcd. C 59.92, H 4.27, N 6.99; found C 59.70, 4.04, 6.67.



Using microwaves 114 mg (57%) of **37b** was obtained according to GP 4 which has same physical datas as given above.

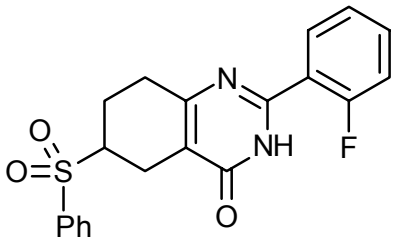
6-Benzenesulfonyl-2-(o-bromophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37c**): The crude product obtained from 3-(*o*-bromophenyl)-2,4-diazabicyclo-[4.2.0]octa-1(6),2-dien-5-one (**35c**, 1.10 g, 3.60 mmol) and phenyl vinyl sulfone (2.32 g, 12.0 mmol), according to GP 3 was purified by column chromatagraphy (R_f = 0.43, Et_2O/MeOH = 25:1, 3 × 30 cm, 50 g SiO_2) to yield 683 mg

(43%) of **37c** as a white solid, m.p. 221–222 °C. – IR (KBr): ν = 3064 cm^{-1}, 2932, 1653, 1604, 1544, 1447, 1301, 1147, 1084, 764, 690. –^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.80–2.01 (m, 1 H), 2.42–3.01 [m, 1 H, C(6)-H], 7.35–7.45 (m, 2 H, aryl-H), 7.53–7.75 (m, 5 H, aryl-H), 7.95–8.01 (m, 2 H, aryl-H), 11.04 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 21.5 (–, CH_2), 22.1 (–, CH_2), 30.6 (–, CH_2), 58.6 (+, C-6), 117.6 (C_{qaut}, C-4a), 120.9 (C_{qaut}, C-Br), 127.8 (+, aryl-C), 129.0 (+, aryl-C), 129.3 (+, aryl-C), 130.9 (+, aryl-C), 132.1 (+, aryl-C), 133.6 (+, aryl-C), 134.0 (+, aryl-C), 134.6 (C_{ipso}), 136.8 (C_{ipso}), 154.3 (C_{qaut}, C-8a), 160.3 (C_{qaut}, C-2/C-4), 162.4 (C_{qaut}, C-4/C-2). – MS (70 eV), *m/z* (%): 446/444 (1/1) [M^+], 318/316 (9/10), 304/302 (95/100) [M^+ – HSO_2Ph], 260/258 (11/11) 141 (18) [$PhSO_2^+$], 77 (52) [Ph^+]. – $C_{20}H_{17}BrN_2O_3S$ (445.3): calcd. C 53.93, H 3.85, N6.29; found C 54.22, H 3.71, N 6.34.



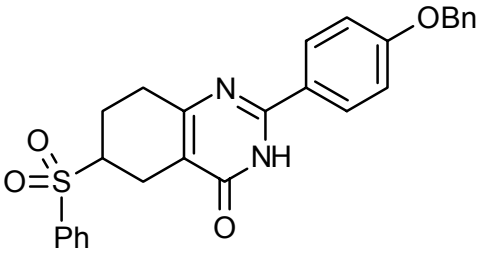
Using microwaves 138 mg (62%) of **37c** was obtained according to GP 4 which has same physical datas as given above.

6-Benzenesulfonyl-2-(o-fluorophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37d**): The crude product obtained from 3-(*o*-fluorophenyl)-2,4-diazabicyclo-[4.2.0]octa-1(6),2- dien-5-one (**35d**, 648 mg, 3 mmol) and phenyl vinyl sulfone (2.01 g, 12.0 mmol), according to GP 3 was purified by column chromatagraphy (R_f = 0.45, Et_2O/MeOH = 25:1, 3×30 cm, 50 g SiO_2) to yield 881 mg (70%) of **37d** as a white solid, m.p. 201–202 °C. – IR (KBr): ν = 3073 cm^{-1}, 2941, 1672, 1603, 1558, 1449, 1308, 1146, 1084, 779, 689. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.81–2.12 (m, 1 H), 2.48–3.11 (m, 5 H), 3.22–3.40 [m, 1 H, C(6)-H], 7.10–7.38 (m, 3 H, aryl-H), 7.50–7.81 (m, 4 H, aryl-H), 7.95–8.20 (m, 2 H, aryl-H), 10.67 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 21.4 (–, CH_2), 22.3 (–, CH_2), 30.7 (–, CH_2), 59.0 (+), 116.6 (+, d, $^2J_{C\text{-}F}$ = 22.9 Hz), 117.7 (C-4a), 119.4 (d, $^2J_{C\text{-}F}$ = 9.2 Hz, C_{ipso}), 125.1 (+, d, $^3J_{C\text{-}F}$ = 3.1 Hz), 129.0 (+), 129.3 (+, aryl-C), 131.0 (+, d, $^4J_{C\text{-}F}$ = 1.1 Hz, aryl-C), 133.7 (+, d, $^3J_{C\text{-}F}$ = 9.2 Hz, aryl-C), 133.9 (+, aryl-C), 136.8 (C_{ipso}, aryl-C), 150.5 (d, $^3J_{C\text{-}F}$ = 1.5 Hz, aryl-C), 160.1 (C_{qaut}, C-2), 160.5 (d, $^1J_{C\text{-}F}$ = 250.6 Hz, C-F), 163.0 (C_{qaut}, C-4). – MS (70 eV), *m/z* (%): 384 (1) [M^+], 243 (23) [M^+ – SO_2Ph], 242 (100) [M^+ – HSO_2Ph], 122 (16), 77 (22) [Ph^+]. – $C_{20}H_{10}FN_2O_3S$ (384.4): calcd. C 62.49, H 4.46, N 7.29; found C 62.30, H 4.30, N 7.11.



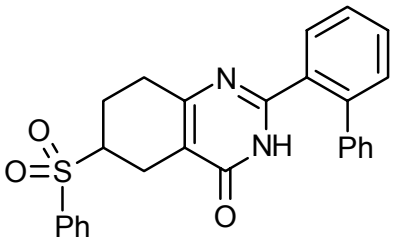
Using microwaves 110 mg (57%) of **37d** was obtained according to GP 4 which has same physical datas as given above.

6-Benzenesulfonyl-2-(p-benzyloxyphenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)one (**37e**): The crude product obtained from 3-(*p*-benzyloxyphenyl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35e**, 652 mg, 2.1 mmol) and phenyl vinyl sulfone (2.43 g, 8.50 mmol), according to GP 3 was purified by column chromatagraphy (R_f = 0.40, DCM/MeOH = 25:1, 3 × 30 cm, 50 g SiO_2) to yield 670 mg (66%) of **37e** as a white solid, m.p. > 250 °C. – IR (KBr): ν = 3072 cm^{-1}, 2939, 1649, 1607, 1547, 1516, 1304, 1259, 1144, 1085, 837, 742, 687. – ^{1}H-NMR (300 MHz, [D_6]DMSO): δ = 1.71–1.84 (m, 1 H), 2.18–2.31 (m, 1 H), 2.40–2.58 (m, 1 H), 2.64–2.78 (m, 3 H), 3.55–3.73 [m, 1 H, C(6)-H], 5.21 (s, 2 H), 7.05–7.12 (m, 2 H, aryl-H), 7.31–7.48 (m, 5 H, aryl-H), 7.64–7.8 (m, 3 H, aryl-H), 7.90–7.98 (m, 2 H, aryl-H), 8.04–8.11 (m, 2 H, aryl-H), 12.15 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, [D_6]DMSO): δ = 21.1 (–, CH_2), 22.0 (–, CH_2), 29.7 (–, CH_2), 57.4 (+, CH), 69.3 (–, Bn-CH_2), 114.7 (+, aryl-C), 114.9 (C_{quat}, C-4a), 124.3 (C_{quat}, C_{ipso}), 127.6 (+, aryl-C), 127.8 (+, aryl-C), 128.4 (+, aryl-C), 128.4 (+, aryl-C), 129.2 (+, aryl-C), 129.5 (+, aryl-C), 134.0 (+, aryl-C), 136.5 (C_{ipso}), 136.9 (C_{ipso}), 153.8 (C_{quat}, C-8a), 160.8 (C_{quat}, C-2/C-4), 162.5 (C_{quat}, C-4/C-2). – MS (70eV), *m/z* (%): 472 (2) [M^+], 330 (49) [M^+ – SO_2Ph], 91 (100) [$C_7H_7^+$]. – $C_{27}H_{24}N_2O_4S$ (472.6): calcd. C 68.63, H 5.12, N 5.93; found C 68.80, H 5.04, N 6.08.



Using microwaves 149 mg (63%) of **37e** was obtained according to GP 4 which has same physical datas as given above.

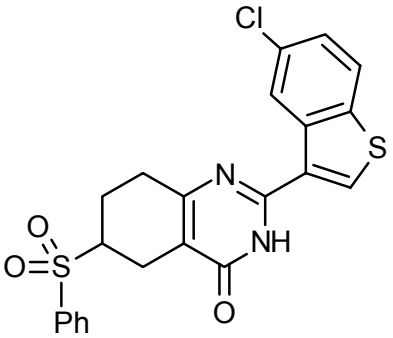
6-Benzenesulfonyl-2-(o-biphenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37f**): The crude product obtained from 3-(*o*-biphenyl)-2,4-diazabicyclo[4.2.0]-octa-1(6),2-dien-5-one (**35f**, 501 mg, 1.83 mmol) and phenyl vinyl sulfone (1.23 g, 7.32 mmol), according to GP 3 was purified by column chromatagraphy (R_f = 0.31, Et_2O/MeOH = 25:1, 3 × 30 cm, 50 g SiO_2) to yield 522 mg (65%) of **37f** as a white solid, m.p. 194–195 °C. – IR (KBr): ν = 3059 cm^{-1}, 3059, 2933, 1647, 1546, 1447, 1320, 1302, 1145, 1085, 742, 688. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.82–1.95 (m, 1 H), 2.42–2.95 (m, 5 H),



3.21–3.31 [m, 1 H, C(6)-H], 7.20–7.39 (m, 5 H, aryl-H), 7.42–7.78 (m, 7 H, aryl-H), 7.90–8.02 (m, 2 H, aryl-H), 9.1 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.3 (–, CH_2), 22.1 (–, CH_2), 30.5 (–, CH_2), 59.1 (+, CH), 116.5 (C_{quat}, C-4a), 127.7 (+, aryl-C), 128.1 (+, aryl-C), 128.4 (+, aryl-C), 128.9 (+, aryl-C), 129.0 (+, aryl-C), 130.0 (+, aryl-C), 130.9 (+, aryl-C), 131.0 (+, aryl-C), 131.7 (+, aryl-C), 133.9 (C_{ipso}), 136.9 (C_{ipso}), 139.2 (C_{ipso}), 140.7 (C_{ipso}), 155.7 (C_{quat}, C-8a), 160.1 (C_{quat}, C-2/C-4), 162.0 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 442 (4) [M^+], 300 (100) [$M^+ – SO_2Ph$], 180 (16), 122 (17). – $C_{26}H_{22}N_2O_3S$ (442.5): calcd. C 70.57, H 5.01, N 6.33; found C 70.53, H 4.98, N 6.04.

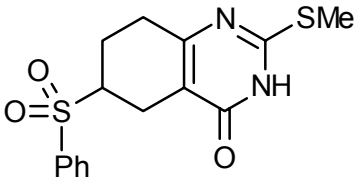
Using microwaves 139 mg (63%) of **37f** was obtained according to GP 4 which has same physica datas as given above.

6-Benzenesulfonyl-2-(5-chloro-benzo[b]thiophene-3-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37g**): The crude product obtained from 3-(5-chloro-benzo[b]thiophene)-2,4-diazabicyclo[4.2.0]-octa-1(6),2-dien-5-one (**35g**, 180 mg, 0.63 mmol) and phenyl vinyl sulfone (420 mg, 4.00 mmol), according to GP 3 was purified by column chromatagraphy (R_f = 0.45, DCM/MeOH = 25:1, 1.5 × 15 cm, 20 g SiO_2) to yield 256 mg (88%) of **37g** as a pale yellow solid, m.p. > 250 °C. – IR (KBr): ν = 3084 cm^{-1}, 1640, 1563, 1417, 1312, 1147, 1078, 806. – ^{1}H-NMR (200 MHz, [D_6]DMSO): δ = 1.60–1.89 (m, 2 H), 2.08–2.56 (m, 2 H), 2.59–3.02 (m, 2 H), 3.48–3.67 [m, 1 H, C(6)-H], 7.41–7.54 (m, 1 H, aryl-H), 7.68–7.80 (m, 3 H, aryl-H), 7.85–8.00 (m, 2 H, aryl-H), 8.04–8.19 (m, 2 H, aryl-H), 8.52–8.73 (m, 1 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.0 (–, CH_2), 21.8 (–, CH_2), 29.8 (–, CH_2), 57.4 (+, aryl-C), 116.3 (C-4a), 124.4 (+, 2 C, aryl-C), 125.1 (+, aryl-C), 126.8 (–, aryl-C), 128.5 (+, 2 C, aryl-C), 129.5 (+, 2 C, aryl-C), 130.2 (+, aryl-C), 134.1 (+, aryl-C), 134.4 (+, aryl-C), 136.9 (C_{ipso}), 137.4 (C_{ipso}), 138.2 (C_{ipso}), 150.0 (C_{quat}, C-8a), 158.9 (C_{quat}, C-2/C-4), 162.0 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 456 (1) [M^+], 314 (100) [$M^+ – SO_2Ph$], 125 (20), 77 (57). – $C_{22}H_{17}ClN_2O_3S_2$ (457.0): calcd. C 57.83, H 3.75, N 6.13; found C 57.52, H 3.55, N 6.02.



Using microwaves 118 mg (52%) of **37g** was obtained according to GP 4 which has same physical datas as given above.

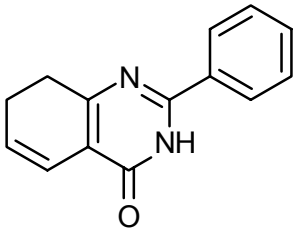
6-Benzenesulfonyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37h**): The crude product obtained from **35h** (168 mg, 1.00 mmol) and phenyl vinyl sulfone (672 g, 7.32 mmol), according to GP 3 was purified by column chromatagraphy (R_f = 0.41, DCM/MeOH = 25:1, 1.5 × 20 cm, 25 g SiO_2) to yield 189 mg (56%) of **37h** as a white solid, m.p. > 250 °C. – IR (KBr): ν = 3059 cm^{-1}, 2918, 2847, 1644, 1576, 1448, 1315, 1150, 1088, 723, 689. – ^{1}H-NMR (200 MHz, [D_6]DMSO): δ = 1.57–1.79 (m, 1 H), 2.11–2.38 (m, 3 H), 2.43 (s, 3 H), 2.58–2.70 (m, 2 H), 3.52–3.73 [m, 1 H, C(6)-H], 7.60–7.81 (m, 3 H, aryl-H), 7.85–7.95 (m, 2 H, aryl-H), 12.56 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, [D_6]DMSO): δ = 12.5 (+, CH_3), 21.0 (–, CH_2), 21.4 (–, CH_2), 29.8 (–, CH_2), 57.3 (+, CH), 117.2 (C_{quat}, C-4a), 128.4 (+, aryl-C), 129.5 (+, aryl-C), 134.0 (+, aryl-C), 136.9 (C_{ipso}) 154.3 (C_{quat}, C-8a), 159.8 (C_{quat}, C-2/C-4), 162.7 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 336 (2) [M^+], 195 (18), 194 (100) [$M^+ – SO_2Ph$]. – $C_{15}H_{16}N_2O_3S_2$ (336.4): calcd. C 53.55, H 4.79, N 8.33; found C 53.56, H 4.52, N 8.20.



Using microwaves 106 mg (63%) of **37h** was obtained according to GP 4 which has same physical datas as given above.

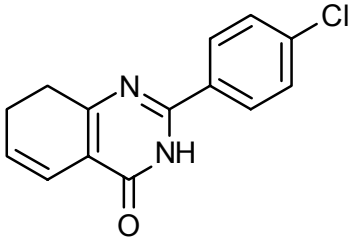
General Procedure for elimination of solfonyl group (GP 5): *2-Aryl-7,8-dihydroquinazolin-4(3H)-one* (**38**): To a suspension of above sulfone **37** in THF, 3 equiv. of KO*t*Bu were added and the resulting solution was stirred for 2 h at room temperature, poured into a separating funnel with sat. aq. NH_4Cl solution (10 mL) and extracted with DCM (3 × 20 mL). The organic layer was dried over $MgSO_4$, after filtration, the solvent was evaporated in vacuum to yield **38** which was used for the next reaction without further purification.

2-Phenyl-7,8-dihydroquinazolin-4(3H)-one (**38a**): From the sulfone **37a** (366 mg, 1.00 mmol) and KO*t*Bu (336 mg, 3.00 mmol) were obtained according to GP 5, 210 mg (96%) of **38a** as a pale yellow solid (R_f = 0.5, hexane/ethylacetate = 1:1), m.p. 241 °C. – IR (KBr): ν = 3032 cm^{-1}, 2932, 1653, 1505, 1317, 930, 718. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.42–2.58 [m, 2 H, C(7)-H], 2.89 [t, *J* = 9.7 Hz, 2 H, C(8)-H], 6.04 [dt, *J* = 9.7, 4.3 Hz, 1 H, C(6)-H], 6.73 [dt, *J* = 9.7, 1.8 Hz, 1 H, C(5)-H], 7.48–7.56 (m, 3 H, aryl-H), 8.14–8.22 (m, 2 H, aryl-H), 12.58 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.7 (–, CH_2), 29.6 (–, CH_2), 117.2 (C-4a), 119.5 (+, C-5), 127.4 (+, aryl-C), 127.6 (+, aryl-C), 128.9 (+, aryl-C), 131.7 (+, C-

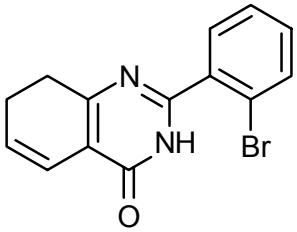


6), 132.1 (C_{ipso}), 154.6 (C_{quat}, C-8a), 161.4 (C_{quat}, C-2/C-4), 161.9 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 224 (100) [M^+], 223 (98), 180 (19) [$M^+ – CONH_2$], 104 (14) [$PhCNH^+$], 77 (20) [Ph^+]. – $C_{14}H_{12}N_2O$ (224.3): calcd. C 74.98, H 5.39, N 12.55; found C 74.71, H 5.31, N 12.31.

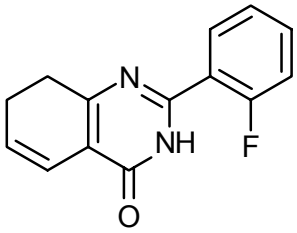
2-(p-Chlorophenyl)-7,8-dihydroquinazolin-4(3H)-one (**38b**)**:** From the sulfone **37b** (200 mg, 0.50 mmol) and KO*t*Bu (168 mg, 1.50 mmol) were obtained according to GP 5, 123 mg (95%) of **38b** as a pale yellow solid (R_f = 0.48, hexane/ethylacetate = 1:1), m.p. > 250 °C. – IR (KBr): ν = 3029 cm^{-1}, 2934, 1652, 1504, 1389, 1176, 1091, 738. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.42–2.56 [m, 2 H, C(7)-H], 2.87 [t, *J* = 9.6 Hz, 2 H, C(8)-H], 6.06 [dt, *J* = 9.5, 4.3 Hz, 1 H, C(6)-H], 6.71 [dt, *J* = 9.5, 1.8 Hz, 1 H, C(5)-H], 7.48–7.56 (m, 2 H), 8.16–8.27 (m, 2 H), 13.1 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.3 (–, CH_2), 28.7 (–, CH_2), 116.8 (C-4a), 119.6 (+, C-5), 127.7 (+), 128.9 (+, aryl-C), 129.5 (+, aryl-C), 131.7 (+, C-6), 136.5 (C_{ipso}), 153.3 (C_{quat}, C-8a), 159.6 (C_{quat}, C-2/C-4), 162.5 (C_{quat}, C-4/C-2). – MS (70 eV) *m/z* (%): 260/258 (32/100) [M^+], 259/257 (40/98) [M^+ – H], 216/214 (28/8), 104 (14), 77 (20) [Ph^+]. – $C_{14}H_{11}ClN_2O$ (258.7): calcd. C 65.00, H 4.29, N 10.83; found C 64.93, H 4.08, N 10.99.



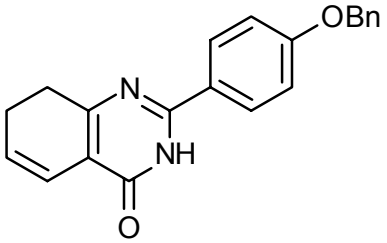
2-(o-Bromophenyl)-7,8-dihydroquinazolin-4(3H)-one (**38c**): From the sulfone **37c** (400 mg, 0.90 mmol) and KO*t*Bu (302 mg, 2.70 mmol) was obtained according to GP 5, 285 mg (94%) of **38c** as a pale yellow solid (R_f = 0.55, Et_2O), m.p. 202 °C. – IR (KBr): ν = 3035 cm^{-1}, 2836, 1665, 1491, 1324, 1183, 928, 767, 735. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.15–2.30 [m, 2 H, C(7)-H], 2.85 [t, *J* = 9.1 Hz, 2 H, C(8)-H], 6.04 [dt, *J* = 9.6, 4.4 Hz, 1 H, C(6)-H], 6.59 [dt, *J* = 9.6, 1.7 Hz, 1 H, C(5)-H], 7.28–7.81 (m, 4 H), 11.55 (br. s, 1 H, N-H). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 22.5 (–, CH_2), 29.0 (–, CH_2), 118.0 (C-8a), 119.3 (+, C-5), 121.1 (C_{quat}, C-Br), 127.7 (+, C-6), 127.9 (+, aryl-C), 131.1 (+, aryl-C), 131.8 (+, aryl-C), 133.7 (+, aryl-C), 134.3 (C_{ipso}), 154.4 (C_{quat}, C-8a), 160.6 (C_{quat}, C-2/C-4), 160.6 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 304/302 (96/100) [M^+], 203/301 (98/80), 259/257 (24/26), 102 (28). – $C_{14}H_{11}BrN_2O$ (303.2): calcd. C 55.47, H 3.66, N 9.24; found C 55.22, H 3.70, N 9.03.



2-(o-Fluorophenyl)-7,8-dihydroquinazolin-4(3H)-one (**38d**): From the sulfone **37d** (384 mg, 1.00 mmol) and KO*t*Bu (336 mg, 3.00 mmol) were obtained according to GP 5, 223 mg (92%) of **38d** as a pale yellow solid (R_f = 0.51, Et_2O), m.p. 191 °C. – IR (KBr): ν = 3043 cm^{-1}, 2934, 2886, 1653, 1559, 1327, 1220, 1181, 1122, 774. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.38–2.52 [m, 2 H, C(7)-H], 2.85 [t, *J* = 9.4 Hz, 2 H, C(8)-H], 5.98 [dt, ^3J = 9.4, 4.4 Hz, 1 H, C(6)-H], 6.61 [dt, *J* = 9.5, 1.7 Hz, 1 H, C(5)-H], 7.12–7.35 (m, 2 H), 7.41–7.54 (m, 1 H), 7.98–8.12 (m, 1 H), 11.51 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.5 (–, CH_2), 29.0 (–, CH_2), 116.5 (+, d, $^2J_{C\text{-}F}$ = 22.7 Hz), 118.0 (C-4a), 119.4 (+, C-5), 120.1 (C_{quat}, d, $^2J_{C\text{-}F}$ = 9.0 Hz, aryl-C), 124.8 (+, d, $^3J_{C\text{-}F}$ = 3.1 Hz, aryl-C), 127.8 (+, C-6), 133.3 (+, d, $^3J_{C\text{-}F}$ = 9.2 Hz, aryl-C), 134.5 (C_{ipso}), 155.3 (C_{quat}, d, $^1J_{C\text{-}F}$ = 250.6 Hz), 157.5 (C_{quat}, C-8a), 158.4 (C_{quat}, C-2/C-4), 162.4 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 242 (100) [M^+], 241 (85), 198 (24), 102 (12). – $C_{14}H_{11}FN_2O$ (242.3): calcd. C 69.41, H 4.58, N 11.56; found C 69.22, H 4.83, N 11.45.

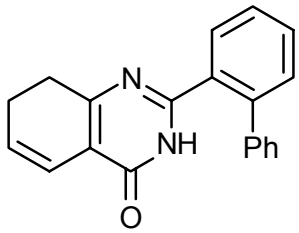


2-(p-Benzoyloxyphenyl)-7,8-dihydroquinazolin-4(3H)-one (**38e**): From the sulfone **37d** (400 mg, 0.85 mmol) and KO*t*Bu (285 mg, 2.50 mmol) were obtained according to GP 5, 258 mg (92%) of **38e** as a pale yellow solid (R_f = 0.62, DCM/MeOH = 25:1), m.p. 247 °C. – IR (KBr): ν = 3032 cm^{-1}, 2943, 1646, 1606, 1512, 1305, 999, 753, 677. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.40–2.58 (m, 2 H), 2.85 [t, *J* = 9.1 Hz, 2 H, C(8)-H], 5.15 (s, 2 H), 6.01 [dt, *J* = 9.6, 4.4 Hz, 1 H, C(6)-H], 6.7 [dt, *J* = 9.6, 1.7 Hz, 1 H, C(5)-H], 7.02–7.18 (m, 2 H, aryl-H), 7.30–7.62 (m, 5 H, aryl-H), 8.06–8.22 (m, 2 H, aryl-H), 12.23 (br. s, 1 H, NH). – ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 22.7 (–, CH_2), 28.6 (–, CH_2), 69.4 (–, Bn-CH_2), 114.8 (C-4a), 119.5 (+, C-5), 126.34 (+, C-6), 127.7 (+, aryl-C), 127.9 (+, aryl-C), 128.4 (+, aryl-C), 129.2 (+, aryl-C), 131.5 (C_{ipso}), 136.5 (C_{ipso}), 140.8 (C_{ipso}), 155.9 (C_{quat}, C-8a), 159.9 (C_{quat}, C-2/C-4), 160.9 (C_{quat}, C-4/C-2).– MS (70 eV), *m/z* (%): 330 (55) [M^+], 239 (8), 91 (100) [$C_7H_7^+$].

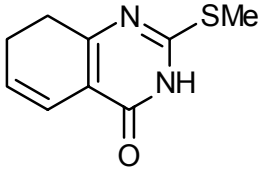


2-(o-Biphenyl)-7,8-dihydroquinazolin-4(3H)-one (**38f**): From the sulfone **37f** (300 mg, 0.68 mmol) and KO*t*Bu (224 mg, 2.00 mmol) was obtained according to GP 5, 177 mg (87%) of **38f** as a pale yellow solid (R_f = 0.55, Et_2O), m.p. 193 °C. – IR (KBr): ν = 3070 cm^{-1}, 2936, 1634, 1549,

1507, 1321, 1165, 979, 699. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.38–2.51 [m, 2 H, C(7)-H], 2.88 [t, *J* = 9.2 Hz, 2 H, C(8)-H], 5.98 [dt, *J* = 9.5 and 4.4 Hz, 1 H, C(6)-H], 6.57 [dt, *J* = 9.5, 1.7 Hz, 1 H, C(5)-H], 7.22–7.36 (m, 5 H), 7.44–7.62 (m, 3 H), 7.76–7.82 (m, 1 H) 9.51 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.5 (–, CH_2), 28.7 (–, CH_2), 117.2 (C-4a), 119.3 (+, C-5), 127.8 (+, C-6), 127.9 (+, 2 C, aryl-C), 128.6 (+, 2 C, aryl-C), 129.1 (+, 2 C, aryl-C), 130.2 (+, aryl-C), 130.9 (+, aryl-C), 131.1 (+, aryl-C), 131.5 (C_{ipso}), 139.1 (C_{ipso}), 140.8 (C_{ipso}), 155.8 (C_{quat}, C-8a), 159.8 (C_{quat}, C-2/C-4), 160.0 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 301 (28) [M^+ + 1], 300 (100) [M^+], 299 (40), 180 (38), 122 (43), 77 (78). – $C_{20}H_{16}N_2O$ (300.4): calcd. C 79.98, H 5.37, N 9.33; found C 79.64, H 5.24, N 9.57.



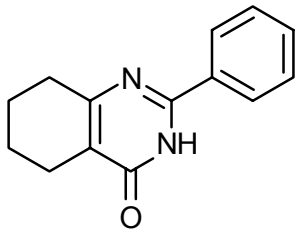
2-Methylthio-7,8-dihydroquinazolin-4(3H)-one (**38h**): From the sulfone **37h** (336 mg, 1.00 mmol) and KO*t*Bu (336 mg, 3.00 mmol) was obtained according to GP 5, 181 mg (98%) of **38h** as a pale yellow solid (R_f = 0.45 Et_2O), m.p. 214 °C. – IR (KBr): ν = 2922 cm^{-1}, 2836, 1641, 1623, 1540, 1271, 1138, 1203, 943. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.38–2.49 [m, 2 H, C(7)-H], 2.60 (s, 3 H), 2.76 [t, *J* = 9.3 Hz, 2 H, C(8)-H], 5.98 [dt, *J* = 9.7 and 4.3 Hz, 1 H, C(6)-H], 6.61 [dt, *J* = 9. and 1.8 Hz, 1 H, C(5)-H], 12.9 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 13.3 (+, CH_3), 22.4 (–, CH_2), 29.4 (–, CH_2), 114.6 (C-4a), 119.3 (+, C-5), 126.0 (+, C-6), 157.0 (C_{quat}, C-8a), 161.2 (C_{quat}, C-2/C-4), 162.2 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 194 (100) [M^+], 147 (12), 121 (16), 92 (14). – $C_9H_{10}N_2OS$ (194.3): calcd. C 55.65, H 5.19, N 14.42; found C 55.39, H 5.32, N 14.16.



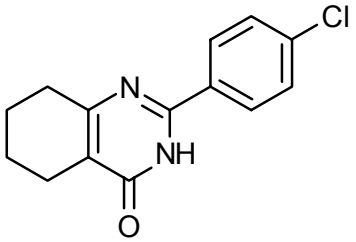
General Procedure for hydrogenation reaction (GP 6):

2-Aryl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**39**): Into a 50 mL flame-dried flask flushed with nitrogen, Pd/C (10% Pd w/w) was added, followed by 10 mL of MeOH. This mixture was stirred under hydrogen atmosphere and after 30 min a solution of **38** in MeOH was added with a syringe and stirring was continued at room temperature until the reaction completed. Reaction mixture was filtered through a pad of Celite®, and the solvent was removed in vacuo to yield **39** as a white solid.

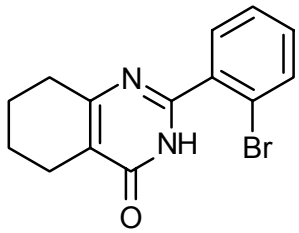
2-Phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**39a**): The crude reaction mixture obtained from **38a** (224 mg, 1.00 mmol), 10 mg of Pd/C in 20 mL of MeOH after 4 h, according to GP 6, afforded 206 mg (91%) of **39a** as a solid, m.p. 224 °C. – IR (KBr): ν = 2934 cm^{-1}, 2848, 1634, 1550, 1319, 1165, 979, 698. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.75–1.91 (m, 4 H), 2.50–2.65 (m, 2 H), 2.71–2.78 (m, 2 H), 7.40–7.58 (m, 3 H, aryl-H), 8.11–8.22 (m, 2 H, aryl-H), 12.4 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.8 (–, CH_2), 21.9 (–, CH_2), 22.3 (–, CH_2), 31.9 (–, CH_2), 120.2 (C_{quat}, C-4a), 127.5 (+, aryl-C), 128.8 (+, aryl-C), 131.4 (+, aryl-C), 132.5 (C_{ipso}), 153.2 (C_{quat}, C-8a), 162.5 (C_{quat}, C-2/C-4), 164.5 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 227 (19) [M^+ + 1], 226 (100) [M^+], 225 (51), 211 (31), 198 (10), 104 (21). – $C_{14}H_{14}N_2O$ (226.3): calcd. C 74.31, H 6.24, N 12.38; found C 74.34, H 6.55, N 12.29.



2-(p-Chlorophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**39b**): The crude reaction mixture obtained from **38b** (51.6 mg, 0.20 mmol), 20 mg of Pd/C in 10 mL of AcOH after 8 h according to GP 6, afforded 49 mg (94%) of **39b** as a solid, m.p. = 255 °C. – IR (KBr): ν = 3070 cm^{-1}, 2936, 1634, 1549, 1507, 1321, 1014, 929, 699. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.74–1.93 (m, 4 H), 2.50–2.62 (m, 2 H), 2.66–2.79 (m, 2 H), 7.42–7.58 (m, 2 H, aryl-H), 8.13–8.24 (m, 2 H, aryl-H), 12.92 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.8, (–, CH_2), 21.9 (–, CH_2), 22.4 (–, CH_2), 32.0 (–, CH_2), 120.4 (C_{quat}, C-4a), 127.4 (+, aryl-C), 128.9 (+, aryl-C), 129.0 (C_{ipso}), 131.4 (C_{quat}, C-Cl), 157.5 (C_{quat}, C-2/C-8a), 157.6 (C_{quat}, C-8a/C-2), 162.5 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 262/260 (16/51) [M^+], 226 (100) [M^+ – C1 + 1], 225 (52) [M^+ – Cl], 211 (37), 104 (32), 77 (26).

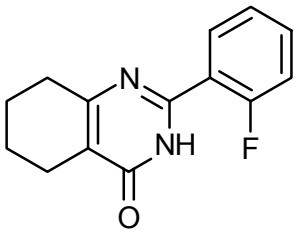


2-(o-Bromophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**39c**): The crude reaction mixture obtained from **38c** (100 mg, 0.33 mmol) 20 mg of Pd/C (10% by weight) in 20 mL MeOH after 4 h, according to GP 6, yielded 93 mg (92%) of **39c** as a white solid, m.p. 193 °C. – IR (KBr): ν = 3035 cm^{-1}, 2944, 1648, 1559, 1319, 1227, 1031, 977, 927, 760, 728. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.72–1.91 (m, 4 H), 2.38–2.51 (m, 2 H), 2.60–2.78 (m, 2 H), 7.28–7.42 (m, 2 H, aryl-H), 7.51–7.68 (m, 2 H, aryl-H), 12.12 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.5 (–, CH_2), 21.8 (–, CH_2), 22.1 (–,

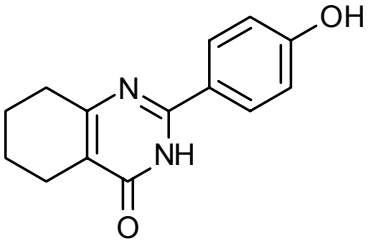


CH_2), 31.6 (–, CH_2), 121.1 (C_{quat}, C-4a), 127.6 (+, aryl-C), 131.0 (+, aryl-C), 131.7 (+, aryl-C), 133.4 (+, aryl-C), 134.6 (C_{ipso}), 156.2 (C_{quat}, C-8a), 161.8 (C_{quat}, C-2), 163.6 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 304/306 (100/95) [M^+], 289/291 (28/27), 225 (11) [M^+ – Br].– $C_{14}H_{13}BrN_2O$ (305.2): calcd. C 55.10, H 4.29, N 9.18; found C 55.32, H 4.14, N 8.97.

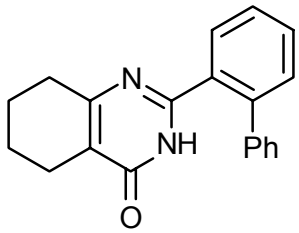
2-(o-Fluorophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**39d**): The crude reaction mixture obtained from **38d** (100 mg, 0.41 mmol), 20 mg of Pd/C in 20 mL of MeOH after 4 h according to GP 6, afforded 93 mg (92%) of **39d** as a solid, m.p. 170 °C. – IR (KBr): ν = 3026 cm^{-1}, 2952, 1647, 1564, 1327, 1233, 1163, 979, 928, 761. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.66–1.92 (m, 4 H), 2.49–2.61 (m, 2 H), 2.63–2.74 (m, 2 H), 7.16–7.34 (m, 2 H, aryl-H), 7.22–7.58 (m, 1 H, aryl-H), 8.14–8.25 (m, 1 H, aryl-H), 10.2 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.6, (–, CH_2), 21.9 (–, CH_2), 22.2 (–, CH_2), 31.7 (–, CH_2), 116.4 (+, d, $^2J_{C\text{-}F}$ = 22.9 Hz), 120.3 (C_{quat}, d, $^2J_{C\text{-}F}$ = 9.2 Hz), 121.2 (C_{quat}, C-4a), 124.8 (+, d, $^3J_{C\text{-}F}$ = 3.1 Hz), 130.9 (+, aryl-C), 132.5 (+, d, $^3J_{C\text{-}F}$ = 9.2 Hz, aryl-C), 154.0 (C_{quat}, d, $^1J_{C\text{-}F}$ = 250.6 Hz, aryl-C), 161.5 (C_{quat}, C-8a), 162.4 (C_{quat}, C-2/C-4), 162.7 (C_{quat}, C-4/C-2). – MS (70eV), *m/z* (%): 244 (100) [M^+], 243 (48), 229 (28), 122 (16). – $C_{14}H_{13}FN_2O$ (244.3): calcd. C 68.84, H 5.56, N 11.47; found C 69.09, H 5.21, N 11.61.



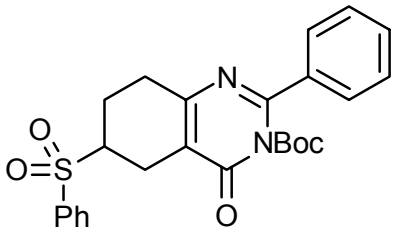
2-[(p-Benzoyloxy)phenyl]-5,6,7,8-tetrahydroquinazoline-4(3H)-one (**39e**): The crude reaction mixture obtained from **38e** (165 mg, 0.50 mmol), 25 mg of Pd/C in 10 mL of AcOH after 8 h according to GP 6, afforded 113 mg (93%) of **39e** as a solid, m.p. > 250 °C. – IR (KBr): ν = 3430 cm^{-1}, 2940, 1641, 1515, 1324, 1289, 1182, 1113, 932, 847, 768. – ^{1}H-NMR (300 MHz, [D_6]DMSO): δ = 1.61–1.80 (m, 4 H), 2.31–2.41 (m, 2 H), 2.54–2.61 (m, 2 H), 6.78–6.89 (m, 2 H, aryl-H), 7.88–7.99 (m, 2 H, aryl-H), 10.6 (br. s, 1 H, NH). – ^{13}C-NMR (75.5 MHz, [D_6]DMSO): δ = 21.5, (–, CH_2), 21.6 (–, CH_2), 21.9 (–, CH_2), 31.1 (–, CH_2), 115.2 (+, 2 C, aryl-C), 118.0 (C_{ipso}), 122.8 (C_{ipso}), 129.1 (+, 2 C, aryl-C), 153.0 (C_{quat}, C-8a), 160.5 (C_{quat}, C-2/C-4), 162.9 (C_{quat}, C-4/C-2).– MS (70 eV), *m/z* (%): 242 (100) [M^+], 241 (44), 227 (27), 120 (31).



2-(o-Biphenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**39f**): The crude reaction mixture obtained from **38f** (120 mg, 0.40 mmol), 10 mg of Pd/C in 20 mL of MeOH after 4 h according to GP 6 afforded 112 mg (93%) of **39f** as a solid, m.p. 190 °C. – IR (KBr): ν = 3027 cm^{-1}, 2936, 1643, 1566, 1324, 1225, 1170, 978, 764. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.66–1.84 (m, 4 H), 2.38–2.48 (m, 2 H), 2.57–2.66 (m, 2 H), 7.21–7.42 (m, 5 H, aryl-H), 7.48–7.61 (m, 2 H, aryl-H), 7.72–7.79 (m, 2 H, aryl-H), 11.1 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.6 (–, CH_2), 21.7 (–, CH_2), 22.1 (–, CH_2), 31.6 (–, CH_2), 119.9 (C_{quat}, C-4a), 127.3 (+, aryl-C), 127.4 (+, aryl-C), 128.1 (+, aryl-C), 128.3 (+, aryl-C), 129.0 (+, aryl-C), 130.0 (+, aryl-C), 130.7 (+, aryl-C), 132.1 (C_{ipso}), 139.5 (+, aryl-C), 140.7 (C_{ipso}), 156.1 (C_{quat}, C-8a), 161.5 (C_{quat}, C-2/C-4), 163.3 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 302 (72) [M^+], 301 (35), 180 (58), 124 (100). – $C_{22}H_{18}N_2O$ (302.4): calcd. C 79.44, H 6.00, N 9.26; found C 79.89, H 5.68, N 9.49.



6-Benzenesulfonyl-4-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline-4(H)-3-carboxylic acid tert-butyl ester (**37a-Boc**): To a suspension of **37a** (183 mg, 0.50 mmol) in 10 mL of THF was added $(Boc)_2O$ (218 mg, 1.00 mmol), Et_3N (50.6 mg, 0.50 mmol) and DMAP (122 mg, 0.5 mmol) at room temperature, and the resulting solution was stirred for 2 h. The reaction mixture was diluted with 25 mL of DCM and washed with 10 mL 1 N HCl. The oganic layer was separated, aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed and the crude product was purified by column chromatography (R_f = 0.5, hexane/ethylacetate = 2:1, 1 × 20 cm, "flash" SiO_2) to yield 191 mg (82%) of the product as a white solid, m.p. 153 °C. – IR (KBr): ν = 3066 cm^{-1}, 2985, 1752, 1595, 1421, 1249, 1146. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.62 (s, 9 H), 1.84–2.04 (m, 1 H), 2.40–2.56 (m, 1 H), 2.79–3.25 (m, 4 H), 3.31–3.44 [m, 1 H, C(6)-H], 7.42–7.51 (m, 3 H, aryl-H), 7.58–7.78 (m, 3 H, aryl-H), 7.95–8.02 (m, 2 H, aryl-H), 8.28–8.39 (m, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.8 (–, CH_2), 22.0 (–, CH_2), 27.5 (+), 31.0 (–, CH_2), 58.9 (+, CH), 85.2 (C_{quat}), 114.5 (C_{quat}, C-4a), 128.2 (+, aryl-C), 128.4 (+, aryl-C), 129.0 (+, aryl-C), 129.4 (+, aryl-C), 130.6 (+, aryl-C), 134.2 (C_{ipso}), 136.4 (+, aryl-C), 136.5 (C_{ipso}), 148.9 (C_{quat}, C-8a), 162.6 (C_{quat}, C-2/C-4), 163.4 (C_{quat}, C-4/C-2), 167.0 (C_{quat}, C=O). – MS (70eV), *m/z* (%): 466 (1) [M^+], 225 (20), 224 (100) [M^+ –



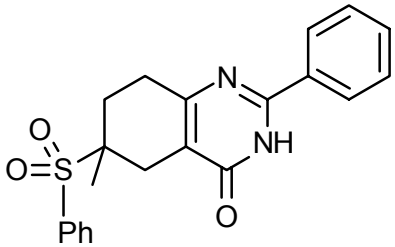
SO_2Ph – Boc – H], 57 (16). – $C_{25}H_{26}N_2O_5S$ (466.6): calcd. C 64.36, H 5.62, N 6.00; found C 64.22, H 5.51, N 5.86.

6-Benzenesulfonyl-8-methyl-4-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline-4(H)-3-carboxylic acid tert-butyl ester (**40**): To a solution of **37a-Boc** (233 mg, 0.50 mmol) in 10 mL of THF was added *n*BuLi (0.24 mL, 2.45 M in hexane) at −78 °C over a period of 15 min. The dark red solution was stirred at this temperature and after 15 min MeI (92 mg, 0.65 mmol) in 1 mL THF was added, cooling bath was removed, and stirring was continued at room temperature for 2 h. The reaction mixture was poured into a separating funnel containing 10 mL of sat. aq. NH_4Cl solution and extracted with Et_2O (3 × 15 mL). Combined organic solutions were dried over $MgSO_4$. Removal of the solvent, followed by column chromatography (R_f = 0.55, hexane/ethylacetate = 2:1, 1 × 20 cm, "flash" SiO_2) yielded 66 mg (28%) of the title product as a white solid, m.p. 98 °C. – IR (KBr): ν = 3029 cm^{-1}, 2981, 1762, 1540, 1410, 1243, 1148, 856. – ^{1}H-NMR (300 MHz,$CDCl_3$): δ = 1.35 (d, *J* = 7.3 Hz, 3 H), 1.58 (s, 9 H) 2.04–2.32 (m, 2 H), 2.75–3.12 (m, 2 H), 3.25–3.39 (m, 1 H), 3.40–3.52 [m, 1 H, C(6)-H], 7.38–7.46 (m, 3 H, aryl-H), 7.58–7.77 (m, 3 H, aryl-H), 7.92–7.98 (m, 2 H, aryl-H), 8.30–8.39 (m, 2 H, aryl-H). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 21.6 (+), 22.2 (–, CH_2), 27.9 (+), 28.4 (–, CH_2), 34.8 (+), 55.8 (+), 85.4 (C_{quat}), 114.0 (C-4a), 128.1 (+, aryl-C), 128.3 (+, aryl-C), 129.1 (+, aryl-C), 129.5 (+), 131.2 (+, aryl-C), 134.2 (+, aryl-C), 136.4 (C_{ipso}), 149.2 (C_{quat}, C-8a), 162.5 (C_{quat}, C-2/C-4), 163.4 (C_{quat}, C-4/C-2). – MS (DCI, 70 eV), *m/z* (%): 498 (5) [$M^+ + NH_4$], 481 (100) [$M^+ + H$], 381 (79), 341 (82). – $C_{26}H_{28}N_2O_5S$ (480.6): calcd. C 64.98, H 5.87, N 5.83; found C 64.62, H 5.57, N 5.85.

6-Benzenesulfonyl-2-phenyl-4-trimethylsilyloxy-5,6,7,8-tetrahydroquinazolin (**37a-TMS**): Into a 25 mL dry reaction flask **37a** (1.60 g, 4.40 mmol) and 20 mg of $(NH_4)_2SO_4$ was added in 15 ml of HMDS. This reaction mixture was refluxed for 15 h. After cooling to 20 °C HMDS was removed in vacuo, the reaction mixture was taken in 20 mL of DCM, washed with 5 mL of water and dried over $MgSO_4$. After filtration, removal of the solvent yielded 1.91 g (99%) of **37a-TMS** as a white solid, m.p. > 250 °C. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.45 (s, 9 H), 1.80–1.98 (m, 1 H), 2.35–2.51 (m, 1 H),

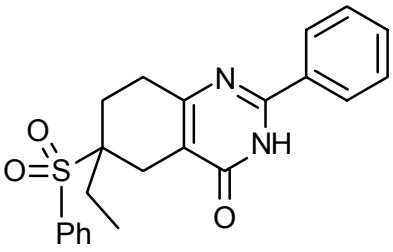
2.75–2.87 (m, 2 H), 3.02–3.21 (m, 2 H), 3.25–3.41 (m, 1 H), 7.18–7.32 (m, 3 H, aryl-H), 7.58–7.75 (m, 3 H, aryl-H), 7.95–8.03 (m, 2 H, aryl-H), 8.25–8.36 (m, 2 H, aryl-H). –^{13}C-MNR (62.9 MHz, $CDCl_3$): δ = 0.31 (+, TMS-CH_3), 21.9 (–, CH_2), 22.2 (–, CH_2), 30.81 (–, CH_2), 59.5 (+), 112.3 (C-4a), 127.3 (+), 127.8 (+), 128.4 (+, aryl-C), 128.9 (+, aryl-C), 129.0 (+, aryl-C), 130.2 (+, aryl-C), 134.0 (+, aryl-C), 136.8 (C_{ipso}), 137.5 (C_{ipso}), 161.4 (C_{quat}, C-8a), 164.1 (C_{quat}, C-2/C-4), 166.4 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 438 (2) [M^+], 296 (100) [M^+ – SO_2Ph], 281 (23) [M^+ – SO_2Ph – Me], 247 (63), 175 (25).

6-Benzenesulfonyl-6-methyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**41a**): To a cooled solution of sulfone **37a-TMS** (439 mg, 1.00 mmol) in 15 mL THF, *n*BuLi (1.77 M in hexane, 0.62 mL) was added at –78 °C over a period of 15 min. The resulting mixture was stirred for additional 15 min. and MeI (156 mg, 1.10 mmol) in 1 ml THF was added. The cooling bath was removed, and stirring was continued at RT for 2 h. The reaction mixture was poured into a separating funnel containing 10 mL of sat. aq. NH_4Cl solution and extracted with DCM (3 × 15 mL). Removal of solvent followed by column chromatography (R_f = 0. 32, DCM/MeOH = 25:1, 1.5 × 30 cm, 25 g SiO_2) yielded 315 mg (83%) of **41a** as a white solid, m.p. > 250 °C. – IR (KBr): ν = 3057 cm^{-1}, 2943, 1644, 1553, 1447, 1300, 1153, 1088, 701. – ^{1}H-NMR (250 MHz, [D_6]DMSO): δ = 1.22 (s, 3 H), 1.84–2.51 (m, 3 H), 2.62–2.83 (m, 3 H), 7.38–7.60 (m, 3 H, aryl-H), 7.63–8.10 (m, 7 H, aryl-H). – ^{13}C-NMR (62.9 MHz, [D_6]DMSO): δ = 18.1 (+), 26.2 (–, CH_2), 27.8 (–, CH_2), 28.1 (–, CH_2), 60.4 (C_{quat}), 115.7 (C_{quat}, C-4a), 127.8 (+, aryl-C), 128.8 (+, aryl-C), 129.6 (+), 130.5 (+, aryl-C), 132.4 (+, aryl-C), 134.6 (C_{ipso}), 154.1 (C_{quat}, C-8a), 158.4 (C_{quat}, C-2), 164.2 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 380 (1) [M^+], 238 (100) [M^+ – SO_2Ph], 77 (30). – $C_{21}H_{20}N_2O_3S$ (380.5): calcd. C 66.30, H 5.30, N 7.36; found C 66.13, H 5.60, N 7.61.

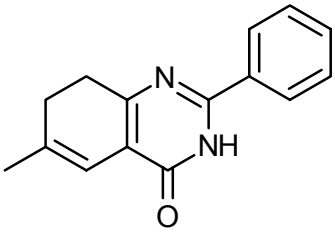


6-Benzenesulfonyl-6-ethyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**41b**): The crude mixture obtained from **37a-TMS** (439 mg, 1.00 mmol), *n*BuLi (1.77 M in hexane, 0.62 mL) and EtBr (119 mg, 1.1 mmol) according to the method given above for **41a** was purified by column chromatography (R_f = 0.38, DCM/MeOH = 25:1, 1.5 × 30 cm, 25 g SiO_2) to afford 339 mg (86%) of **41b** as a white solid, m.p. 242 °C. – IR (KBr): ν = 3065 cm^{-1}, 2941, 1644, 1554, 1447, 1301,

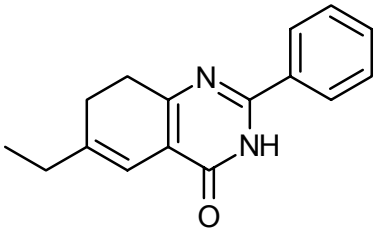
1151, 1079, 763, 692. – ^{1}H-NMR (250 MHz, [D$_6$]DMSO): δ = 1.11 (t, *J* = 7.3Hz, 3 H), 1.62–1.81 (m, 2 H), 2.12–2.44 (m, 3 H), 2.71–3.02 (m, 3 H), 7.41–7.74 (m, 6 H, aryl-H), 7.91–8.21 (m, 4 H, aryl-H), 12.7 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, [D$_6$]DMSO): δ = 8.6 (+), 23.3 (–, CH$_2$), 24.4 (–, CH$_2$), 28.4 (–, CH$_2$), 28.8 (–, CH$_2$), 67.9 (C$_{quat}$), 116.2 (C$_{quat}$, C-4a), 127.5 (+, aryl-C), 128.8 (+, aryl-C), 129.0 (+), 130.1 (+, aryl-C), 131.8 (+, aryl-C), 133.8 (C$_{ipso}$), 135.7 (+, aryl-C), 153.9 (C$_{quat}$, C-8a), 160.7 (C$_{quat}$, C-2/C-4), 164.4 (C$_{quat}$, C-4/C-2) – MS (70 eV), *m/z* (%): 394 (1) [M$^+$], 253 (52) [M$^+$ – SO$_2$Ph], 252 (100) [M$^+$ – SO$_2$Ph – H], 237 (14), 211 (15), 104 (11).



6-Methyl-2-phenyl-7,8-dihydroquinazolin-4(3H)-one **(43a)**: From the sulfone **41a** (265 mg, 0.70 mmol) and KO*t*Bu (235 mg, 2.10 mmol) according to the GP 5 were obtained 160 mg (96%) of **43a** as a pale yellow solid, m.p. 218 °C, R_f = 0.6 (hexane/ethyl acetate = 1:2). – IR (KBr): ν = 3031 cm^{-1}, 2924, 1636, 1506, 1436, 1314, 1182, 932, 772, 699. – ^{1}H-NMR (250 MHz, CDCl$_3$): δ = 1.96 (s, 3 H), 2.39 [t, *J* = 9.1 Hz, 2 H, C(7)-H], 2.89 [t, *J* = 9.1 Hz, 2 H, C(8)-H], 6.46 [s, 1 H, C(5)-H], 7.42–7.61 (m, 3 H, aryl-H), 8.18–8.36 (m, 2 H, aryl-H), 13.3 (br. s, 1 H, NH). –^{13}C-NMR (62.9 MHz, CDCl$_3$): δ = 23.4 (+, CH$_3$), 28.3 (–, CH$_2$), 29.9 (–, CH$_2$), 114.3 (+, C-5), 117.8 (C$_{quat}$, C-4a), 127.5 (+, aryl-C), 128.8 (+, aryl-C), 131.3 (+, aryl-C), 132.3 (C$_{ipso}$), 137.7 (C$_{quat}$, C-6), 153.4 (C$_{quat}$, C-8a), 159.4 (C$_{quat}$, C-2/C-4), 161.9 (C$_{quat}$, C-4/C-2). – MS (70 eV), *m/z* (%): 238 (100) [M$^+$] 237 (38), 223 (50) [M$^+$ – Me], 194 (10) [M$^+$ – CONH$_2$], 104 (14), 77 (10) [Ph$^+$].

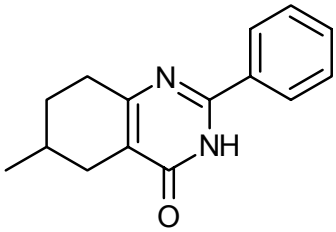


6-Ethyl-2-phenyl-7,8-dihydroquinazolin-4(3H)-one (**43b**): From the sulfone **41b** (197 mg, 0.50 mmol) and KO*t*Bu (168 mg, 1.50 mmol) according to the GP 5 were obtained 118 mg (98%) of **43b** as a pale yellow solid m.p. 198 °C, R_f = 0.6 (hexane/-ethylacetate = 1:2). – IR (KBr): ν = 3020 cm^{-1}, 2955, 2922, 1630, 1532, 1321, 1098, 922, 699. – ^{1}H-NMR (250 MHz, CDCl$_3$): δ = 1.16 (t, *J* = 7.3 Hz, 3 H), 2.26 (q, *J* = 7.3 Hz, 2 H), 2.40 [t, *J* = 8.9 Hz, 2 H, C(7)-H], 2.89 [t, *J* = 8.9 Hz, 2 H, C(8)-H], 6.47 [s, 2 H, C(5)-H], 7.42–7.61 (m, 3 H, aryl-H), 8.22–8.38 (m, 2 H, aryl-H), 13.45 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, CDCl$_3$): δ = 11.8 (+), 26.9 (–, CH$_2$), 23.0 (–, CH$_2$), 30.1 (–, CH$_2$), 112.4 (+, C-

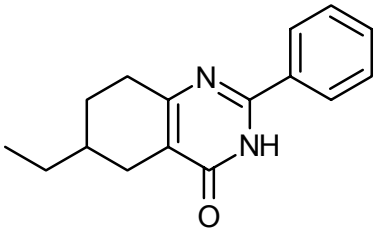


5), 117.8 (C_{quat}, C-4a), 127.5 (+, aryl-C), 128.7 (+, aryl-C), 131.3 (+, aryl-C), 132.3 (C_{quat}, C-6), 143.2 (C_{ipso}), 153.4 (C_{quat}, C-8a), 159.7 (C_{quat}, C-2/C-4), 162.0 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 252 (100) [M^+], 237 (80) [M^+ – Me], 223 (25) [M^+ – Et], 180 (20).

6-Methyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**42a**): The crude reaction mixture obtained from **43a** (100 mg, 0.42 mmol), 22 mg of Pd/C in 25 mL of MeOH after 4 h according to the GP 6 afforded 97 mg (96%) of **42a** as a solid, m.p. 237 °C. – IR (KBr): ν = 3072 cm^{-1}, 2948, 1641, 1507, 1316, 1073, 697. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.38–1.56 (m, 1 H), 1.76–2.15 (m, 3 H), 2.68–2.86 (m, 3 H), 7.20–7.38 (m, 3 H, aryl-H), 8.02–8.14 (m, 2 H, aryl-H), 11.68 (br. s, 1 H, NH). –^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.5 (+), 28.0 (+), 30.1 (–, CH_2), 30.4 (–, CH_2), 31.8 (–, CH_2), 119.6 (C_{quat}, C-4a), 127.5 (+, aryl-C), 128.8 (+, aryl-C), 131.3 (+, aryl-C), 132.4 (C_{ipso}), 153.3 (C_{quat}, C-8a), 162.2 (C_{quat}, C-2/C-4), 164.8 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 240 (100) [M^+], 225 (90) [M^+ – Me], 198 (49), 104 (31), 77 (16). – $C_{15}H_{16}N_2O$ (240.3): calcd. C 74.97, H 6.71, N 11.66; found C 74.77, H 6.99, N 11.53.

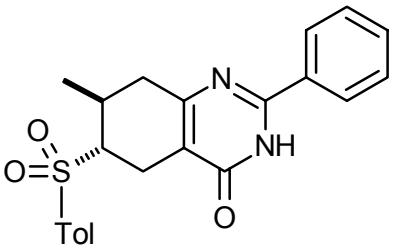


6-Ethyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**42b**): The crude reaction mixture obtained from **43b** (76 mg, 0.30 mmol), 15 mg of Pd/C in 25 mL MeOH after 4 h, according to the GP 6, afforded 74 mg (96%) of **42b** as a solid, m.p. 221 °C. – IR (KBr): ν = 2922 cm^{-1}, 1642, 1549, 1315, 919, 697. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.3 Hz, 3 H), 1.24–1.68 (m, 4 H), 1.80–2.15 (m, 2 H), 2.55–3.00 (m, 3 H), 7.36–7.60 (m, 3 H, aryl-H), 8.10–8.32 (m, 2 H, aryl-H), 13.12 (br. s, 1 H, NH). –^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 11.5 (+), 27.9 (–, CH_2), 28.1 (–, CH_2), 28.8 (–, CH_2), 31.8 (–, CH_2), 34.7 (+), 119.6 (C_{quat}, C-4a), 127.5 (+, aryl-C), 128.7 (+, aryl-C), 131.3 (+, aryl-C), 132.4 (C_{ipso}), 153.2 (C_{quat}, C-8a), 162.4 (C_{quat}, C-2/C-4), 164.9 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 254 (80) [M^+], 225 (100) [M^+ – Et], 198 (36), 104 (22). – $C_{16}H_{18}N_2O$ (254.3): calcd. C 75.56, H 7.15, N 11.01; found. C 75.36, H 7.45, N 10.88.



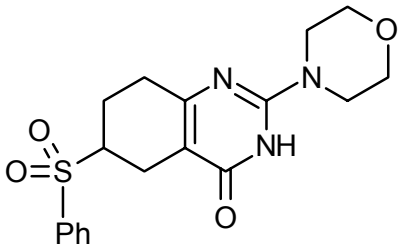
6-p-Toluenesulfonyl-7-methyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)one (**44**): **35a** (99 mg, 0.50 mmol) and (*E*)-*p*-tolyl-1-propenyl sulfone **36-Me** (392 mg, 2.00 mmol) were heated at 175

°C for 12 h in 10 mL Pyrex tube. After cooling down to room temperature, the reaction mixture was dissolved in DCM/MeOH and purified by column chromatography (R_f = 0.40, hexane/ethyl acetate = 1:2) to yield 53 mg (27%) of the title compound as a white solid, m.p. = 247 °C. – IR (KBr): ν = 3034 cm^{-1}, 2927, 1653, 1507, 1302, 1142, 1018. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 7.8 Hz, 3 H), 2.41–2.76 (m, 4 H), 2.88–3.04 (m, 1 H), 3.13–3.36 (m, 1 H), 7.32–7.55 (m, 6 H), 7.72–7.82 (m, 2 H, aryl-H), 8.06–8.16 (m, 2 H, aryl-H), 12.8 (br. s, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 20.4 (+, CH_3), 21.7 (+, CH_3), 27.2 (–, CH_2), 37.3 (–, CH_2), 63.2 (+, CH), 115.6 (C-4a), 127.5 (+, aryl-C), 128.7 (+, aryl-C), 128.9 (+, aryl-C), 130.0 (+, aryl-C), 131.7 (+, aryl-C), 132.0 (+, aryl-C), 135.2 (C_{ipso}), 144.8 (C_{quat}, C-8a), 154.1 (C_{quat}, C-2), 163.7 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 394 (2) [M^+], 239 (36), 238 (100), 223 (28), 180 (20).



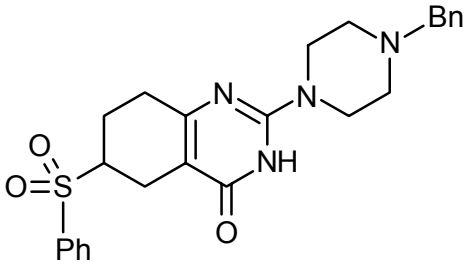
Nucleophilic substitution of SMe group by amines

6-Benzenesulfonyl-2-(morpholine-4-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**45a**): **37h** (168 mg, 0.5 mmol) and morpholine (2 mL) were tightly sealed in a 10 mL of Pyrex bottle and heated at 180 °C for 15 h. The reaction mixture was cooled to RT, excess of morpholine was removed in vacuo, and crude product was filtered through a pad of SiO_2 (2 × 3 cm, 10 g, DCM/MeOH = 10:1) to yield 175 mg (93%) of **31a** as a white solid, m.p. > 250 °C. – IR (KBr): ν = 2902 cm^{-1}, 2848, 1656, 1590, 1395, 1300, 1267, 1146, 1114, 979, 742, 722. – ^{1}H-NMR (250 MHz, [D_6]DMSO): δ = 1.55–1.72 (m, 1 H), 2.05–2.32 (m, 2 H), 3.21–3.72 (m, 12 H), 7.60–7.81 (m, 3 H, aryl-H), 7.82–7.92 (m, 2 H, aryl-H), 8.86 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, [D_6]DMSO): δ = 21.5 (–, CH_2), 21.7 (–, CH_2), 44.8 (–, 2C, NCH_2), 58.1 (+), 65.8 (–, 2 C, OCH_2), 128.7 (+, aryl-C), 129.8 (+, aryl-C), 134.3 (+, aryl-C), 137.2 (C_{ipso}) 151.9 (C_{quat}, C-8a), 159.1 (C_{quat}, C-2), 163.4 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 375 (8) [M^+], 233 (100) [$M^+ - SO_2Ph$], 202 (23), 176 (10). – $C_{18}H_{21}N_3O_4S$ (375.5): calcd. C 57.58, H 5.64, N 11.19; found C 57.26, H 5.65, N 11.53.

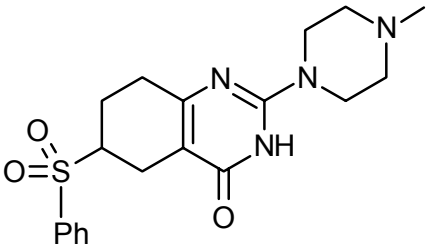


2-(4-benzylpiperazin-1-yl)-6-Benzenesulfonyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**45b**): Following the method given above for **45a**, **45b** was obtained from **37h** (750 mg, 2.23 mmol) and *N*-benzylpiperazine (1.57 g, 8.92 mmol) in 92% (953 mg) yield as a white solid, m.p. > 250 °C. –

IR (KBr): ν = 2937 cm^{-1}, 2816, 1653, 1576, 1304, 1262, 1144, 745. – ^{1}H-NMR (250 MHz, [D_6]DMSO): 1.52–1.71 (m, 1 H), 2.08–2.42 (m, 7 H), 3.41–3.63 (m, 9 H), 7.17–7.38 (m, 5 H, aryl-H), 7.62–7.94 (m, 5 H, aryl-H). –^{13}C-NMR (50.3 MHz, [D_6]DMSO): δ = 20.9 (–, CH_2), 21.2 (–, CH_2), 29.6 (–, CH_2), 43.9 (–, NCH_2), 51.6 (–, NCH_2), 58.1 (+), 61.4 (–, Bn-CH_2), 104.4 (C-4a), 126.4 (+, aryl-C), 127.6 (+, aryl-C), 128.0 (+, aryl-C), 128.3 (+, aryl-C), 128.9 (+, aryl-C), 133.4 (+, aryl-C), 137.1 (C_{ipso}), 137.5 (C_{ipso}), 152.5 (C_{quat}, C-8a), 159.4 (C_{quat}, C-2), 163.1 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 464 (14) [M^+], 429 (12), 412 (16), 318 (68), 159 (96), 91 (100). – $C_{25}H_{28}N_4O_3S$ (464.6): calcd. C 64.63, H 6.07, N 12.06; found C 64.48, H 6.17, N 11.97.

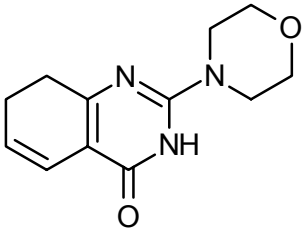


6-Benzenesulfonyl-2-(4-methylpiperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one **(45c)**: Following the method given above for **45a**, **45c** was obtained from **37h** (336 mg, 1.00 mmol) and *N*-methyl piperazine (2 mL) in 91% yield (352 mg) as a white solid, m.p. > 250 °C. – IR (KBr): ν = 3232 cm^{-1}, 2930, 2797, 1631, 1585, 1301, 1266, 1147, 1083, 1003, 721. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.78–1.92 (m, 1 H, CH_2), 2.38 (s, 3 H, CH_3), 2.41 (m, 4 H, CH_2), 2.43–2.80 (m, 5 H, NCH_2), 3.13–3.26 (m, 1 H, CH), 3.68–3.81 (m, 4 H, NCH_2), 7.52–7.71 (m, 3 H, aryl-H), 8.89–8.98 (m, 2 H, aryl-H) 11.42 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, [D_6]DMSO): δ = 21.0 (–, CH_2), 21.2 (–, CH_2), 29.6 (–, CH_2), 43.8 (–, NCH_2), 45.1 (+), 53.7 (–, NCH_2), 58.0 (+), 104.4 (C-4a), 128.0 (+, aryl-C), 129.0 (+, aryl-C), 133.4 (+, aryl-C), 137.1 (C_{ipso}), 152.6 (C_{quat}, C-8a), 159.3 (C_{quat}, C-2), 163.2 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 388 (16) [M^+], 318 (100), 306 (24), 176 (74), 83 (55), 71 (26). – $C_{19}H_{22}N_4O_3S$ (388.5): calcd. C 58.74, H 6.23, N 14.42; found C 58.64, H 6.14, N 14.29.

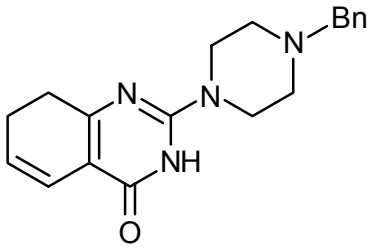


2-(Morpholin-4-yl)-7,8-dihydroquinazolin-4(3H)-one (**47a**): The crude product obtained from **45a** (175 mg, 0.47 mmol), KO*t*Bu (264 mg, 2.35 mmol) in 10 mL THF, according to GP 5, after 15 h was purified by column chromatography (R_f = 0.45, Et_2O/MeOH = 25:1, 1.5 × 30 cm, 25 g SiO_2) to yield 60 mg (84%) of **47a** as a white solid, m.p. 228–230 °C. – IR (KBr): nu(tilde) = 2924 cm^{-1}, 2849, 1637, 1585, 1382, 1263, 1171, 1115, 987, 862, 729. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ =

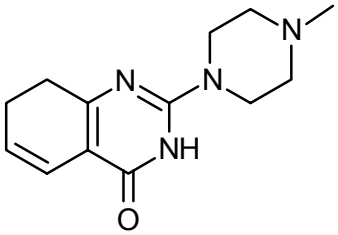
2.28– 2.40 (m, 2 H, CH_2), 2.62 [t, J = 9.6 Hz, 2 H, C(8)-H], 3.77–3.84 (m, 8 H, NCH_2), 6.45 [dt, J = 9.7 and 4.3 Hz, 1 H, C(6)-H], 6.73 [dt, J = 9.7 and 1.8 Hz, 1 H, C(5)-H], 12.12 (br. s, 1 H, NH). – ^{13}C-NMR (62.9 MHz $CDCl_3$): δ = 22.6 (–, CH_2), 30.2 (–, CH_2), 44.9 (–, NCH_2), 66.4 (–, NCH_2), 107.5 (C_{quat}, C-4a), 119.6 (+, C-5), 122.1 (+, C-6), 152.4 (C_{quat}, C-8a), 162.5 (C_{quat}, C-2/C-4), 164.2 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 234 (11) [M^+ + 1], 233 (100) [M^+], 202 (62) [M^+ – CH_2OH], 188 (16), 176 (30). – $C_{12}H_{15}N_3O_2$ (233.3): calcd. C 61.79, H 6.48, N 18.01; found C 61.54, H 6.72, N 17.91.



2-(4-Benzylpiperazin-1-yl)-7,8-dihydroquinazolin-4(3H)-one **(47b)**: The crude product obtained from **45b** (200 mg, 0.43 mmol) and KO*t*Bu (480 mg, 4.30 mmol) according to GP 5, was purified by column chromatography (R_f = 0.41, DCM/MeOH = 25:1, 1.5 × 30 cm, 25 g SiO_2) to yield 131 mg (94%) of **47b** as a white solid, m.p. = 196–197 °C. – IR (KBr): ν = 3040 cm^{-1}, 2953, 1636, 1576, 1388, 1311, 1277, 1170, 1005, 848, 726. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.22–2.40 (m, 2 H), 2.49–2.63 (m, 6 H), 3.54 (s, 2 H), 3.72–3.82(m, 4 H), 5.68 [dt, J = 9.5 and 4.3 Hz, 1 H, C(6)-H], 6.42 [dt, J = 9.5, 1.7 Hz, 1 H, C(5)-H], 7.26–7.38 (m, 5 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.7 (–, CH_2), 29.7 (–, CH_2), 44.5 (–, NCH_2), 46.0 (–, NCH_2), 54.5 (–, Bn-CH_2), 107.1 (C-4a), 119.8 (+, C-5), 121.6 (+, C-6), 127.2 (+, aryl-C), 128.3 (+, aryl-C), 137.6 (C_{ipso}), 152.2 (C_{quat}, C-8a), 162.5 (C_{quat}, C-2/C-4), 164.2 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 322 (71) [M^+], 189 (30), 176 (100), 146 (38), 91 (53). – $C_{19}H_{22}N_4O$ (322.4): calcd. C 70.78, H 6.88, N 17.38; found C 70.45, H 6.47, N 17.50.

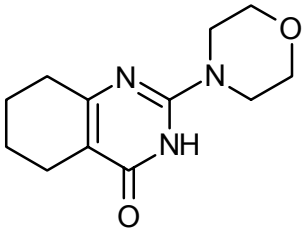


2-(4-Methylpiperazin-1-yl)-7,8-dihydroquinazolin-4(3H)-one (**47c**): The crude product obtained from **45c** (220 mg, 0.57 mmol) and KO*t*Bu (638 mg, 5.70 mmol) according to the GP 5 was purified by column chromatography (R_f = 0.40, DCM/MeOH = 25:1, 1.5 × 20 cm, 25 g Al_2O_3) to yield 121 mg (94%) of **47c** as a white solid, m.p.= 188 °C. – IR (KBr): ν = 3101 cm^{-1}, 2935, 2792, 1654, 1582, 1387, 1267, 1140, 1005, 727. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.21–2.38 (m, 5 H), 2.41–2.54 (m, 4

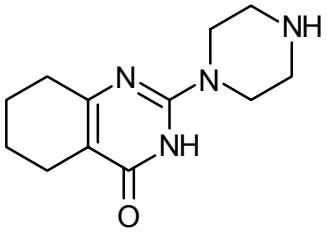


H), 2.55–2.66 (m, 2 H), 3.64–3.81(m, 4 H), 5.72 [dt, *J* = 9.7 and 4.3 Hz, 1 H, C(6)-H], 6.48 [dt, *J* = 9.7 and 1.8 Hz, 1 H, C(5)-H]. –^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.6 (–, CH_2), 25.5 (–, CH_2), 44.4 (–, NCH_2), 46.0 (+), 54.5 (–, NCH_2), 107.1 (C-4a), 119.8 (+, C-5), 121.6 (+, C-6), 156.9 (C_{quat}, C-8a), 162.5 (C_{quat}, C-2/C-4), 164.2 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 246 (49) [M^+], 189 (12), 176 (100). – $C_{13}H_{18}N_4O$ (246.3): calcd. C 62.39, H 7.37, N 22.75; found C 62.37, H 7.23, N 22.59.

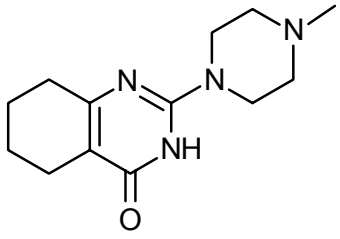
2-(Morpholin-4-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**46a**): The crude reaction mixture obtained from **47a** (100 mg, 0.43 mmol), 15 mg of Pd/C in 25 mL MeOH after 15 h according to the GP 6 afforded 97 mg (96%) of **46a** as a white solid, m.p. 204–205 °C. – IR (KBr): ν = 2925 cm^{-1}, 2856, 1640, 1576, 1386, 1270, 1165, 1121, 1001, 877, 767. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.63–1.90 (m, 4 H), 2.30–2.42 (m, 2 H), 2.43–2.58 (m, 2 H), 3.56–3.92 (m, 8 H), 11.6 (br. s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 21.3 (–), 23.2 (–, CH_2), 22.5 (–, CH_2), 32.2 (–, CH_2), 44.9 (–, NCH_2), 66.5 (–, OCH_2), 109.7 (C_{quat}, C-4a), 156.6 (C_{quat}, C-8a), 163.6 (C_{quat}, C-2/C-4), 165.7 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 235 (84) [M^+], 204 (100) [$M^+ - CH_2OH$], 190 (40), 178 (90), 150 (47). – $C_{12}H_{17}N_3O_2$ (235.3): calcd. C 61.26, H 7.28, N 17.86; found C 61.41, H 7.40, N 17.65.



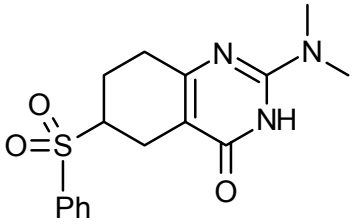
2-Piperazin-1-yl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**46b**): The crude reaction mixture obtained from **47b** (150 mg, 0.47 mmol), 15 mg of Pd/C in 25 mL of MeOH after 15 h according to the GP 6 afforded 99 mg (90%) of **46b** as a white solid, m.p. = 121 °C. – IR (KBr): ν = 2930 cm^{-1}, 1700, 1635, 1576, 1437, 1398, 1267, 998. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.60–1.82 (m, 4 H), 2.28–2.54 (m, 4 H), 2.84–3.02 (m, 4 H), 3.62–3.71 (m, 4 H), aryl H 11.81 (br. s, 1 H, NH). –^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 21.4 (–, CH_2), 22.3 (–, CH_2), 22.6 (–, CH_2), 32.3 (–, CH_2), 45.6 (–, CH_2), 109.2 (C_{quat}, C-4a), 151.7 (C_{quat}, C-8a), 163.5 (C_{quat}, C-2), 165.5 (C_{quat}, C-4). – MS (70 eV), *m/z* (%): 234 (21) [M^+], 192 (33), 178 (55), 166 (74), 72 (100).



2-(4-Methylpiperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**46c**): The crude reaction mixture obtained from **47c** (100 mg, 0.41 mmol), 15 mg of Pd/C in 25 mL of MeOH after 15 h according to the GP 6 afforded 74 mg (96%) of **46c** as a white solid, m.p. 210 °C. – IR (KBr): $\nu = 3091$ cm^{-1}, 2934, 2785, 1642, 1576, 1387, 1308, 1267, 1150, 1000, 845. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.61–1.80 (m, 4 H), 2.24–2.40 (m, 5 H), 2.42–2.58 (m, 6 H), 3.64–3.74 (m, 4 H), 11.81 (br. s, 1 H, NH). –^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.3 (–, CH_2), 22.3 (–, CH_2), 22.6 (–, CH_2), 32.3 (–, CH_2), 44.5 (–, NCH_2), 46.0 (+, CH_3), 54.6 (–, NCH_2), 109.7 (C_{quat}, C-4a), 151.5 (C_{quat}, C-8a), 163.6 (C_{quat}, C-2/C-4), 165.6 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 248 (17) [M^+], 178 (100), 166 (12), 83 (28), 71 (19). – $C_{13}H_{20}N_4O$ (248.3): calcd. C 62.88, H 8.12, N 22.56; found C 62.59, H 8.12, N 22.40.

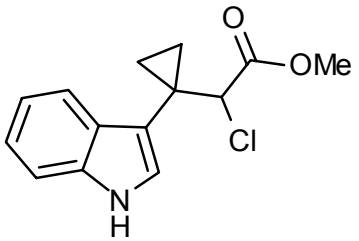


2-Dimethylamino-6-benzenesulfonyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**48**): **37h** (168 mg, 0.5 mmol) was dissolved in 2 mL of DMF in a 10 ml pyrex bottle. This bottle was tightly sealed and heated at 180 °C for 12 h. The reaction mixture was cooled to room temperature, excess of DMF was removed at reduced pressure, and the crude product was filtered through a pad of SiO_2 (2 × 3 cm, 10 g, DCM/MeOH = 10:1) to yield 143 mg (86%) of **48** as a white solid, m.p. = 249 °C. – IR (KBr): $\nu = 2929$ cm^{-1}, 1635, 1586, 1302, 1138, 1084. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.71–1.92 (m, 1 H), 2.31–2.87 (m, 4 H), 3.11 (s, 3 H), 3.13–3.26 (m, 1 H), 3.58–3.72 (m, 1 H), 7.53–7.74 (m, 3 H, aryl-H), 7.90–7.99 (m, 2 H, aryl-H), 11.59 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.5 (–, CH_2), 22.0 (–, CH_2), 31.1 (–, CH_2), 37.4 (+, CH_3), 59.9 (+, CH_3), 104.1 (C_{quat}, C-4a), 128.9 (+, aryl-C), 129.1 (+, aryl-C), 133.8 (+, aryl-C), 137.1 (C_{ipso}), 152.5 (C_{quat}, C-8a), 161.9 (C_{quat}, C-2/C-4), 164.8 (C_{quat}, C-4/C-2). – MS (70 eV), *m/z* (%): 333 (6) [M^+], 192 (20), 191 (100), 162 (10), 77 (15). – $C_{16}H_{19}N_3O_3S$ (333.4): calcd. C 57.64, H 5.74, N 12.60; found C 57.58, H 5.45, N 12.48.

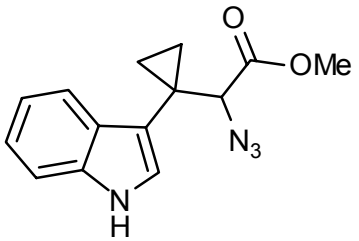


3.2.3. Synthesis of cyclopropyl analogue of Tadalafil

Methyl 2-chloro-2-[1-(1H-indol-3-yl)cyclopropyl]acetate (**55**). To a solution of methyl 2-chloro-2-cyclopropylidineacetate (4.40 g, 30.0 mmol) and indole (5.97 g, 51.0 mmol) in CH_2Cl_2 (150 mL) was added ethylaluminum dichloride (51.0 mL, 51.0 mmol, 1 M solution in hexane) at 0 °C, and the mixture was stirred at this temperature for 6 h. The mixture was carefully poured into an ice-cold saturated Na_2CO_3 solution (150 mL). Extraction of the aq. phase with CH_2Cl_2 (3 × 200 mL), drying of the combined organic phases over $MgSO_4$, evaporation of the solvents and chromatographic purification of the residue on 80 g of silica gel (4.5 × 20 cm, R_f = 0.45, pentane/Et_2O = 5 : 1) yielded 6.70 g (85%) of **55** as a pale yellow oil. – IR (film): ν = 3306 cm^{-1}, 3008, 2949, 1747, 1456, 1420, 1313, 1195, 1170, 1010. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.02–1.24 (m, 3 H, cPr-H), 1.35–1.46 (m, 1 H, cPr-H), 3.60 (s, 3 H, OCH_3), 4.31 (s, 1 H, 2-H), 7.06–7.38 (m, 4 H, aryl -H), 7.65–7.72 (m, 1 H, aryl-H), 8.00–8.14 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 13.6 (–, cPr-C), 21.6 (C_{quat}, cPr-C), 52.8 (+, OCH_3), 69.2 (+, 2-H), 111.4 (+, aryl-C), 113.9 (C_{quat}, aryl-C), 118.9 (+, aryl-C), 119.4 (+, aryl-C), 121.8 (+, aryl-C), 125.8 (+, aryl-C), 127.2 (C_{quat}, aryl-C), 135.7 (C_{quat}, aryl-C), 169.2 (C_{quat}, C=O). – MS (70 eV); *m/z* (%): 265/263 (14/52) [M^+], 228 (100) [M^+ – Cl], 196 (73), 168 (35), [M^+ – Cl – CO_2Me – H], 130 (29), 83 (28). – $C_{14}H_{14}ClNO_2$ (263.7): calcd. 263.0713 (correct HRMS).



Methyl 2-azido-2-[1-(1H-indol-3-yl)cyclopropyl]acetate (**57**). A suspension of **55** (6.50 g, 24.7 mmol), NaN_3 (4.80 g, 73.9 mmol) and Aliquat 336® (12.4 g,12.4 mmol) in water (60 mL) was heated at 70 °C for 20 h. After cooling to 20 °C the reaction mixture was extracted with Et_2O (3 × 100 mL), and the combined organic phases were dried over Na_2SO_4. Removal of the solvent in vacuo and column chromatography of the residue on 80 g of silica gel (4.5 × 20 cm, R_f = 0.36, CH_2Cl_2/MeOH = 10 : 1) yielded 6.10 g (91%) of **57** as a slightly yellow oil. – IR (KBr): ν = 3329 cm^{-1}, 2923 , 2104, 1743, 1442, 1338, 1270, 1233, 1033, 746. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.00–1.18 (m, 3 H, cPr-H), 1.24–1.42 (m, 1 H, cPr-H), 3.68 (s, 3 H, OCH_3), 3.75 (s, 1 H, 2-H), 7.10–7.21 (m, 3 H, aryl-H), 7.33 (d,

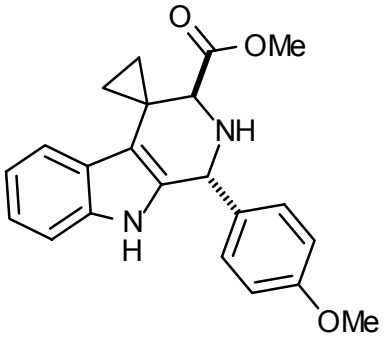


^3J = 7.5 Hz, 1 H, aryl-H), 7.70 (d, ^3J = 7.5 Hz, 1 H, aryl-H), 8.00–8.14 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.9 (–, cPr-C), 11.9 (–, cPr-C), 20.1 (C_{quat}, cPr-C), 52.4 (+, OCH_3), 69.2 (+, C-2), 111.4 (+, aryl-C), 114.6 (C_{quat}, aryl-C), 119.0 (+, aryl-C), 119.6 (+, aryl-C), 122.0 (+, aryl-C), 125.3 (+, aryl-C), 127.3 (C_{quat}, aryl-C), 135.8 (C_{quat}, aryl-C), 169.6 (C_{quat}, C=O). – MS (70 eV); *m/z* (%): 270 (71) [M^+], 228 (100) [$M^+ - N_3$], 196 (56), 183 (58) [$M^+ - N_2 - CO_2Me$], 168 (20) [$M^+ - N_3 - CO_2Me - H$], 156 (62), 129 (47), 117 (12). – $C_{14}H_{14}N_4O_2$ (270.3): calcd. C 62.21, H 5.22; found: C 62.12, H 5.33.

Methyl 2-amino-2-[1-(1H-indol-3-yl)cyclopropyl]acetate (**56**). To a solution of **57** (6.00 g, 22.2 mmol) in MeOH (80 mL) was added tin(II) chloride dihydrate (9.90 g, 43.9 mmol), and the solution was stirred at 20 °C for 18 h. After removal of the solvent in vacuo, the residue was taken up in CH_2Cl_2 (150 mL), the solution extracted with sat. Na_2CO_3 solution (100 mL) and the aq. layer reextracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were dried over $MgSO_4$, the solvents removed, and the residue purified by column chromatography on 100 g of silica gel (3 × 30 cm, R_f = 0.30, CH_2Cl_2/MeOH = 10 : 1) to yield 5.22 g (98%) of **56** as a pale yellow solid (m. p. 127 °C). – IR (film): ν = 3348 cm^{-1} (NH), 3136, 2986, 2945, 2919, 1736 (C=O), 1584, 1435, 1199, 1015, 919, 741. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.85–1.09 (m, 3 H, cPr-H), 1.21–1.29 (m, 1 H, cPr-H), 1.65 (s, 2 H, NH_2), 3.08 (s, 1 H, 2-H), 3.65 (s, 3 H, OCH_3), 7.07–7.20 (m, 3 H, aryl-H), 7.31 (d, ^3J = 7.7 Hz, 1 H, aryl-H), 7.70 (d, ^3J = 7.7 Hz, 1 H, aryl-H), 8.21–8.33 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 11.6 (–, cPr-C), 12.2 (–, cPr-C), 22.2 (C_{quat}, cPr-C), 51.8 (+, OCH_3), 62.6 (+, C-2), 111.3 (+, aryl-C), 115.3 (C_{quat}, aryl-C), 119.3 (+, aryl-C), 119.5 (+, aryl-C), 122.0 (+, aryl-C), 124.9 (+, aryl-C), 127.8 (C_{quat}, aryl-C), 135.9 (C_{quat}, aryl-C), 174.7 (C_{quat}, C=O). – MS (70 eV); *m/z* (%): 244 (28) [M^+], 215 (12), 185 (38) [$M^+ - CO_2Me$], 168 (25), 156 (100), 129 (42), 117 (9). – $C_{14}H_{16}N_2O_2$ (244.3): calcd. C 68.83, H 6.60; found: C 68.65, H 6.84.

Methyl 1'-(4-methoxyphenyl)-2',3',4',9'-tetrahydrospiro-(cyclopropane-1,4'-1H-β-carboline)-3'-carboxylate (**59a**). To a solution of **56** (1.22 g, 5.00 mmol) in trimethyl orthoformate (25 mL) was added *p*-anisaldehyde (694 mg, 5.10 mmol) and the solution was stirred at 25 °C for 8 h. After

removal of the volatiles in vacuo and dissolving of the residue in CH_2Cl_2 (25 mL), at 0 °C trifluoroacetic acid (2.24 g, 19.6 mmol) was added over a period of 5 min, and the resulting red solution was stirred at 25 °C for 15 h. Dilution with sat. aq. $NaHCO_3$ (20 mL), extraction of the aq. phase with CH_2Cl_2 (2 × 25 mL), washing of the combined organic phases with brine (50 mL), drying over $MgSO_4$ and column chromatography of the residue on 50 g of silica gel (3 × 15 cm, R_f = 0.54, Et_2O) yielded 1.57 g (87%) of **59a** as a mixture of *cis*- and *trans*-diastereomers (1 : 1.7). Recrystallization from EtOAc yielded the *trans*-diastereomer (830 mg, 46%), as a colorless solid, m. p. 190 °C.



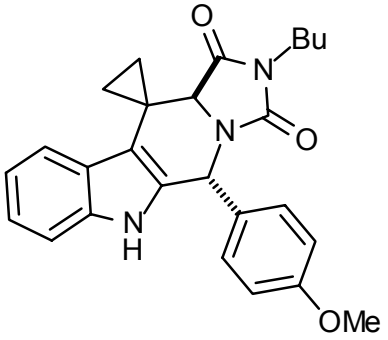
The residue from the mother liquor contained the *cis*- and *trans*-diastereomers in a ratio of 5:1, m. p. 91–98 °C. – *trans*-**59a**: – IR (KBr): ν = 3393 cm^{-1}, 3171, 2956, 1725, 1514, 1246, 1178, 1027. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.06–1.12 (m, 2 H, cPr-H), 1.40–1.48 (m, 1 H, cPr-H), 1.80–1.88 (m, 1 H, cPr-H), 2.20–2.81 (br s, 1 H, NH), 3.44 (s, 1 H, CH), 3.70 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 5.52 (s, 1 H, CH), 6.84–6.90 (m, 2 H, aryl-H), 6.94–7.12 (m, 2 H, aryl-H), 7.16–7.42 (m, 4 H, aryl-H), 7.55 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.7 (–, cPr-C), 13.6 (–, cPr-C), 20.0 (C_{quat}, cPr-C), 51.8 (+, OCH_3), 54.2 (+, OCH_3), 55.3 (+, CH), 62.2 (+, CH), 111.2 (+, aryl-C), 111.5 (C_{quat}, aryl-C), 114.1 (+, 2 C, aryl-C), 118.8 (+, aryl-C), 119.3 (+, aryl-C), 121.4 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 130.0 (+, 2 C, aryl-C), 133.3 (C_{quat}, aryl-C), 134.8 (C_{quat}, aryl-C), 136.0 (C_{quat}, aryl-C), 159.5 (C_{quat}, aryl-C), 172.7 (C_{quat}, C=O). – MS (70 eV), *m/z* (%): 362 (100) [M^+], 303 (75) [$M^+ – CO_2Me$], 195 (50), 168 (18), 121 (22). – $C_{22}H_{22}N_2O_3$ (362.4): C 72.91, H 6.12, N 7.73; found: C 72.83, H 6.05, N 7.58. – *cis*-**59a**: – IR (KBr): ν = 3394 cm^{-1}, 3004, 2950, 1734, 1512, 1457, 1251, 1174, 1030. –^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.86–0.91 (m, 1 H, cPr-H), 1.04–1.40 (m, 2 H, cPr-H), 1.68–1.80 (m, 1 H, cPr-H), 2.21–2.80 (br s, 1 H, NH), 3.46 (s, 1 H, CH), 3.74 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.23 (s, 1 H, CH), 6.84–6.92 (m, 2 H, aryl-H), 6.94–7.12 (m, 2 H, aryl-H), 7.16–7.42 (m, 4 H, aryl-H), 7.52 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 9.0 (–, cPr-C), 11.8 (–, cPr-C), 20.2 (C_{quat}, cPr-C), 51.8 (+, OCH_3), 55.3 (+, CH), 57.1 (+, OCH_3), 62.5 (+, CH), 111.3 (+, aryl-C), 113.4 (C_{quat}, aryl-C), 114.3 (+, 2 C, aryl-C), 118.8 (+, aryl-C), 119.5 (+, aryl-C), 121.6 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 129.8 (+, 2 C, aryl-C), 132.1 (C_{quat}, aryl-C), 135.9 (C_{quat}, aryl-C), 159.7 (C_{quat}, aryl-C), 170.9 (C_{quat}, C=O). – MS (70 eV), *m/z* (%): 363/362 (20/100) [M^+], 303 (75) [$M^+ – CO_2Me$], 302 (35), 195

(50), 168 (18), 121 (22). – $C_{22}H_{22}N_2O_3$ (362.4): calcd. C 72.91, H 6.12, N 7.73; found: C 72.49, H 5.98, N 7.61.

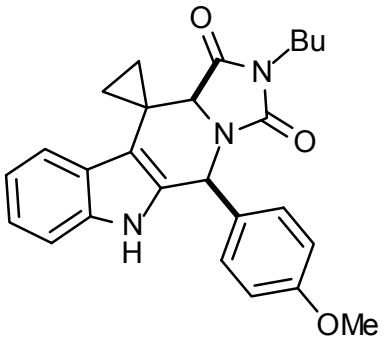
Methyl 1'-(1,3-benzodioxole-5-yl)-2',3',4',9'-tetrahydrospiro[cyclopropane-1,4'-(1H-β-carboline)]-3'-carboxylate (**59b**). To a solution of **56** (1.22 g, 5.00 mmol) in trimethyl orthoformate (25 mL) was added piperonal (750 mg, 5.00 mmol), and the solution was stirred at 25 °C for 8 h. After removal of the volatiles in vacuo the residue was taken up in CH_2Cl_2 (30 mL), at 0 °C trifluoroacetic acid (2.28 g, 20.0 mmol) was added over a period of 5 min, and the solution was stirred at 25 °C for 12 h. Dilution with CH_2Cl_2 (50 mL), adding of sat. aq. $NaHCO_3$ (25 mL), extraction of the aq. phase with CH_2Cl_2 (2 × 30 mL), drying of the combined organic phases over $MgSO_4$, evaporation of the solvents and column chromatography of the residue on 50 g of silica gel (3 × 15 cm, R_f = 0.40, pentane/Et_2O = 2 : 1) yielded 1.67 g (89%) of **59b** as a mixture of the *cis*- and *trans*-diastereomer (1 : 2.5). recrystallization from EtOAc/pentane yielded the *trans*-diastereomer (980 mg, 52%) as a colorless solid, m. p. 190 °C. The residue from the mother liquor showed a ratio of 3 : 1 for the *cis*- and *trans*-diastereomer, m. p. 79–85 °C. – *trans*-**59b**: IR (KBr): ν = 3271 cm^{-1}, 2972, 2892, 1740, 1487, 1354, 1238, 1111, 1038. –^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.06–1.12 (m, 2 H, cPr-H), 1.38–1.42 (m, 1 H, cPr-H), 1.80–1.82 (m, 1 H, cPr-H), 2.20 (br s, 1 H, NH), 3.42 (s, 1 H, CH), 3.71 (s, 3 H, OCH_3), 5.61 (s, 1 H, CH), 5.94 (s, 2 H, OCH_2O), 6.72–6.92 (m, 3 H, aryl-H), 6.96–7.14 (m, 2 H, aryl-H), 7.18–7.38 (m, 2 H, aryl-H), 7.60 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.7 (–, cPr-C), 13.6 (–, cPr-C), 15.2 (C_{quat}, cPr-C), 51.7 (+, OCH_3), 54.6 (+, CH), 62.3 (+, CH), 101.1 (–, OCH_2O), 108.1 (+, aryl-C), 108.9 (+, aryl-C), 111.2 (+, aryl-C), 111.5 (C_{quat}, aryl-C), 118.8 (+, aryl-C), 119.4 (+, aryl-C), 121.4 (+, aryl-C), 122.0 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 134.3 (C_{quat}, aryl-C), 135.5 (C_{quat}, aryl-C), 136.1 (C_{quat}, aryl-C), 147.5 (C_{quat}, aryl-C), 148.0 (C_{quat}, aryl-C), 172.9 (C_{quat}, C=O). – MS (70 eV), *m/z* (%): 376 (100) [M^+], 359 (20), 317 (64) [M^+ – CO_2Me], 195 (10), 168 (18). – $C_{22}H_{20}N_2O_4$ (376.4): calcd. C 70.20, H 5.36, N 7.44; found: C 69.90, H 5.60, N 7.55. – *cis*-**59b**: IR (KBr): ν = 3302 cm^{-1}, 3013, 2890, 2773, 1735, 1697, 1487, 1443, 1248, 1039. –^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.85–0.92 (m, 1 H, cPr-H), 1.38–1.42 (m, 2 H, cPr-H), 1.72–1.80 (m, 1 H, cPr-H), 3.10 (br s, 1 H, NH), 3.75 (s, 3 H,

OCH_3), 4.28 (s, 1 H, CH), 5.20 (s, 1 H, CH), 5.96 (s, 2 H, OCH_2O), 6.72–6.94 (m, 3 H, Ar-H), 6.98–7.14 (m, 2 H, aryl-H), 7.18–7.38 (m, 2 H, aryl-H), 7.55 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.7 (–, cPr-C), 13.6 (–, cPr-C), 20.0 (C_{quat}, cPr-C), 51.8 (+, OCH_3), 54.2 (+, CH), 62.2 (+, CH), 101.4 (–, OCH_2O), 108.2 (+, aryl-C), 111.2 (+, aryl-C), 111.5 (C_{quat}, aryl-C), 114.1 (+, aryl-C), 118.8 (+, aryl-C), 119.3 (+, aryl-C), 121.4 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 130.0 (+, aryl-C), 133.3 (C_{quat}, aryl-C), 134.2 (C_{quat}, aryl-C), 134.8 (C_{quat}, aryl-C), 136.0 (C_{quat}, aryl-C), 159.5 (C_{quat}, aryl-C), 172.7 (C_{quat}, C=O). – MS (70 eV), *m/z* (%): 376 (100) [M^+], 359 (20), 317 (64) [$M^+ - CO_2Me$], 315 (20), 289 (12), 195 (10), 168 (18). – $C_{22}H_{20}N_2O_4$ (376.4): calcd. C 70.20, H 5.36, N 7.44; found: C 70.48, H 5.56, N 7.13.

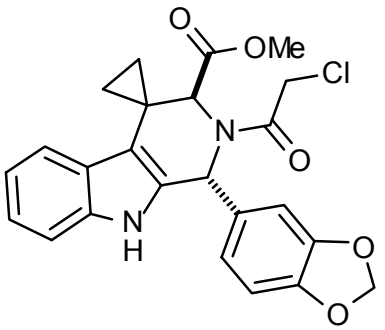
trans-2'-Butyl-10'-(4-methoxyphenyl)-3a',4',9',10'-tetrahydrospiro[cyclopropane-1,4'-(2',9',10a'-triazacyclopenta[b]fluorene)]-1',3'-dione (*trans*-**25**). To a solution of *trans*-**59a** (100 mg, 276 μmol) in methyl ethyl ketone (5 mL) was added *n*butyl isocyanate (31 mg, 313 μmol), and the mixture was stirred at 100 °C for 18 h. The solvent was removed in vacuo, and the residue purified by chromatography on 15 g of silica (3 × 15 cm, R_f = 0.35, pentane/Et_2O = 1 : 1) to yield 108 mg (91%) of *trans*-**25** as a colorless solid, m. p.178 °C. – IR (KBr): ν = 3309 cm^{-1}, 2959, 2933, 2866, 1761, 1708, 1512, 1457, 1249, 1174, 1078. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 8.0 Hz, 3 H, CH_3), 1.08–1.42 (m, 4 H, cPr-H), 1.55–1.62 (m, 3 H, Bu-H), 1.92–2.04 (m, 1 H, Bu-H), 3.40–3.52 (m, 2 H, NCH_2), 3.77 (s, 3 H, OCH_3), 4.48 (s, 1 H, CH), 6.3 (s, 1 H, CH), 6.80–6.91 (m, 2 H, aryl-H), 7.04–7.5 (m, 6 H, aryl-H), 8.04 (br s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$, APT): δ = 7.8 (–, cPr-C), 11.7 (–, cPr-C), 13.6 (+, CH_3), 18.9 (–, CH_2), 19.9 (–, cPr-C), 30.1 (–, CH_2), 38.5 (–, NCH_2), 51.1 (+, OCH_3), 55.3 (+, CH), 56.4 (+, CH), 111.5 (+, aryl-C), 113.3 (–, aryl-C), 114.4 (+, 2 C, aryl-C), 119.0 (+, aryl-C), 120.0 (+, aryl-C), 122.4 (+, aryl-C), 123.9 (–, aryl-C), 129.6 (+, 2 C, aryl-C), 131.1 (–, aryl-C), 131.4 (–, aryl-C), 136.8 (–, aryl-C), 154.7 (–, aryl-C), 159.9 (–, C=O), 170.0 (–, C=O). – MS (70 eV), *m/z* (%): 430/429 (30/100) [M^+], 322 (35), 301 (10), 195 (10). – $C_{26}H_{27}N_3O_3$ (429.5): calcd. C 72.71, H 6.34, N 9.78; found: C 72.57, H 6.32, N 9.57.



cis-2'-Butyl-10'-(4-methoxyphenyl)-3a',4',9',10'-tetrahydrospiro[cyclopropane-1,4'-(2',9',10a'-triazacyclopenta[b]fluorene)]-1',3'-dione (*cis*-**25**). To a solution of **59a** (480 mg, 1.33 mmol, *cis*/*trans* = 5 : 1) in MEK (20 mL) was added *n*butyl isocyanate (158 mg, 1.60 mmol), and the mixture was stirred at 100 °C for 18 h. Evaporation of the solvents and chromatographic purification of the residue on 20 g of silica (3 × 15 cm, pentane/Et_2O = 1 : 2) yielded 84 mg (89% from starting *trans*-diastereomer) of *trans*-**25** (R_f = 0.71), and 426 mg (90% from starting *cis*-diastereomer) of *cis*-**25** (R_f = 0.30) the latter as a colorless solid, m. p. 104–105 °C. – IR (KBr): ν = 3290 cm^{-1}, 2961 2933, 2871, 1766, 1702, 1512, 1447, 1331, 1244, 1173, 1063. –^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 8.0 Hz, 3 H, CH_3), 1.12–1.38 (m, 4 H, cPr-H), 1.55–1.62 (m, 2 H, CH_2), 1.85–2.04 (m, 2 H, CH_2), 3.40–3.52 (m, 2 H, NCH_2), 3.80 (s, 3 H, OCH_3), 4.65 (s, 1 H, CH), 5.84 (s, 1 H, CH), 6.85–6.91 (m, 2 H, aryl-H), 7.04–7.36 (m, 6 H, aryl-H), 7.52 (br s, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 7.1 (–, cPr-C), 11.0 (–, cPr-C), 13.6 (+, CH_3), 18.9 (–, CH_2), 19.9 (C_{quat}, cPr-C), 30.0 (–, CH_2), 38.3 (–, NCH_2), 55.1 (+, OCH_3), 56.3 (+, CH), 60.5 (+, CH), 111.4 (+, aryl-C), 112.0 (C_{quat}, aryl-C), 114.1 (+, 2 C, aryl-C), 119.0 (+, aryl-C), 119.9 (+, aryl-C), 122.2 (+, aryl-C), 124.0 (C_{quat}, aryl-C), 129.1 (+, 2 C, aryl-C) 130.7 (C_{quat}, aryl-C), 134.3 (C_{quat}, aryl-C), 136.9 (C_{quat}, aryl-C), 154.7 (C_{quat}, aryl-C), 159.5 (C_{quat}, C=O), 169.1 (C_{quat}, C=O). – MS (70 eV), *m*/*z* (%): 430/429 (30/100) [M^+], 322 (38), 301 (10), 223 (10) 195 (10). – $C_{26}H_{27}N_3O_3$ (429.5): calcd. C 72.71, H 6.34, N 9.78; found: C 72.45, H 6.29, N 9.81.



Methyl trans-1'-(1,3-benzodioxole-5-yl)-2'-(2-chloroacetyl)-2',3',4',9'-tetrahydrospiro-[cyclopropane-1,4'-(1H-β-carboline)]-3'-carboxylate (*trans*-**60**). To a mixture of *trans*-**59b** (619 mg, 1.65 mmol) and 1 N Na_2CO_3 (8.25 mL, 8.25 mmol) in CH_2Cl_2 (30 mL) was added chloroacetyl chloride (372 mg, 3.30 mmol) at 0 °C, the mixture was stirred at 20 °C for 2 h, diluted with CH_2Cl_2 (25 mL) and washed with a sat. $NaHCO_3$ solution (20 mL). Drying over $MgSO_4$, evaporation of the solvents and chromatographic purification of the residue on 25 g of silica (1.5 × 20 cm, R_f = 0.40, pentane/Et_2O = 1 : 2) yielded 697 mg



(93%) of *trans*-**60** as a colorless solid, m. p. 118 °C. – IR (KBr): ν = 3302 cm^{-1}, 2890, 1739, 1662, 1487, 1444, 1394, 1240, 1039. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.06–1.12 (m, 1 H, cPr-H), 1.24–1.30 (m, 1 H, cPr-H), 1.52–1.64 (m, 1 H, cPr-H), 2.18–2.26 (m, 1 H, cPr-H), 3.65 (s, 3 H, OCH_3), 3.74–4.15 (m, 3 H, CH_2,CH), 5.81–5.93 (m, 2 H, CH_2), 6.12 (s, 1 H, CH), 6.72–6.80 (m, 1 H, aryl-H), 6.86–7.00 (m, 2 H, aryl-H), 7.02–7.28 (m, 3 H, aryl-H), 7.40–7.51 (m, 1 H, aryl-H), 8.60 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.3 (–, cPr-C), 15.3 (–, cPr-C), 19.5 (C_{quat}, cPr-C), 43.1 (–, CH_2), 52.8 (+, OCH_3), 57.6 (+, CH), 62.2 (+, CH), 101.2 (–, OCH_2O), 106.4 (C_{quat}, aryl-C), 107.3 (+, aryl-H), 108.6 (+, aryl-H), 111.5 (+, aryl-H), 118.4 (+, aryl-H), 118.8 (C_{quat}, aryl-H), 119.3 (+, aryl-H), 121.4 (+, aryl-H), 124.5 (+, aryl-H), 135.0 (C_{quat}, 2 C, aryl-H), 136.2 (C_{quat}, 2 C, aryl-H), 149.2 (C_{quart}, aryl-H), 169.4 (C_{quart}, C=O), 171.8 (C_{quat}, C=O). – MS (70 eV), *m*/*z* (%): 454/452 (22/63) [M^+], 417 (36) [M^+ – Cl], 375 (100) [M^+ – $COCH_2Cl$], 315 (40), 195 (20). – $C_{24}H_{21}ClN_2O_5$ (452.9): calcd. C 63.65, H 4.67, N 6.19; found: C 63.82, H 4.92, N 5.96.

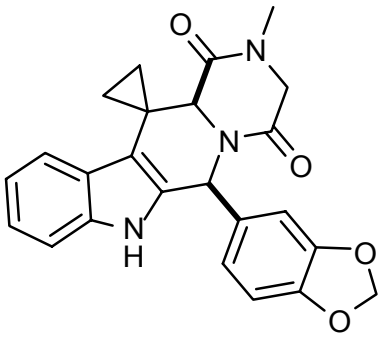
Methyl cis-1'-(1,3-benzodioxole-5-yl)-2'-(2-chloroacetyl)-2',3',4',9'-tetrahydrospiro-[cyclopropane-1,4'-(1H-β-carboline)]-3'-carboxylate (*cis*-**60**). To a mixture of *cis*-**59b** (752 mg, 2.00 mmol, mixture of *cis*/*trans* = 3 : 1) and 1 N Na_2CO_3 (10.0 mL, 10.0 mmol) in CH_2Cl_2 (25 mL) was added chloroacetyl chloride (452 mg, 4.00 mmol) at 0 °C, the mixture was stirred at 20 °C for 2 h, diluted with CH_2Cl_2 (25 mL) and washed with sat. $NaHCO_3$ solution (20 mL). Drying over $MgSO_4$, evaporation of the solvents and chromatographic purification on 25 g of silica (1.5 × 20 cm, R_f = 0.51, pentane/Et_2O = 1 : 1) yielded 551 mg (81% from pure *cis*-**59**) of *cis*-**60** as a colorless solid, m. p. 125–132 C. – IR (KBr): ν = 3295 cm^{-1}, 2891, 1738, 1670, 1486, 1395, 1040. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.86–0.92 (m, 1 H, cPr-H), 0.96–1.15 (m, 1 H, cPr-H), 142–1.58 (m, 1 H, cPr-H), 2.05–2.21 (m, 1 H, cPr-H), 3.58 (s, 3 H, OCH_3), 3.92–4.10 (m, 3 H, CH_2, CH), 5.78–5.95 (m, 2 H, OCH_2O), 6.08 (s, 1 H, CH), 6.63–6.76 (m, 1 H, aryl-H), 6.82–7.13 (m, 4 H, aryl-H), 7.21–7.40 (m, 2 H, aryl-H), 7.82 (br s, 1 H, NH). – ^{13}C-NMR (50.3 MHz, $CDCl_3$, APT): δ = 10.2 (–, cPr-C), 15.1 (–, cPr-C), 19.6 (–, cPr-C), 43.3 (–, CH_2), 52.7 (+, OCH_3), 57.7 (+, CH), 64.1 (+, CH), 101.3 (–, OCH_2O), 106.4, (–, aryl-C), 108.7 (+, aryl-C), 107.4 (+, aryl-C), 111.4 (+, aryl-C), 118.8 (–, aryl-C), 119.2 (–, aryl-C), 119.8

(+, aryl-C), 122.1 (+, aryl-C), 124.2 (+, aryl-C), 136.3 (–, 2 C, aryl-C), 136.8 (–, 2 C, aryl-C), 147.5 (–, aryl-C), 166.2 (–, C=O), 171.5 (–, C=O). – MS (70 eV), *m/z* (%): 454/452 (30/79) [M^+], 417 (48) [M^+ – Cl], 375 (100) [M^+ – $COCH_2Cl$], 315 (46), 195 (20). – $C_{24}H_{21}ClN_2O_5$ (452.9): calcd. C 63.65, H 4.67, N 6.19; found: C 63.90, H 5.31, N 6.16.

trans-6'-(1,3-Benzodioxole-5-yl)-2'-methyl-12'-spirocyclopropyl-2',3',6',7',12',12a'-hexa-hydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1',4'-dione (*trans*-**26**). A solution of *trans*-**60** (596 mg, 1.32 mmol) and methylamine (1 mL, 40% in H_2O) in EtOH (25 mL) was heated at 75 °C for 16 h. All volatiles were removed in vacuo, the residue was dissolved in CH_2Cl_2 (30 mL), the solution washed with water (20 mL) and dried over $MgSO_4$. Evaporation of the solvent and chromatographic purification of the residue on 25 g of silica (1.5 × 20 cm, R_f = 0.23, pentane/Et_2O = 1 : 2) yielded 470 mg (86%) of *trans*-**26** as a colorless solid, m. p. > 250 °C. – IR (KBr): ν = 3299 cm^{-1}, 2888, 1664, 1488, 1330, 1236, 1036, 935. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.70–0.78 (m, 1 H, cPr-H), 1.24–1.32 (m, 1 H, cPr-H), 1.54–1.82 (m, 2 H, cPr-H), 2.98 (s, 3 H, CH_3), 3.86–4.20 (m, 2 H, CH_2), 4.56 (s, 1 H, CH), 5.32 (s, 1 H, CH), 5.95 (s, 2 H, CH_2), 6.68–6.82 (m, 3 H, aryl-H), 6.96–7.20 (m, 2 H, aryl-H), 7.28–7.39 (m, 2 H, aryl-H), 8.12 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 8.2 (–, cPr-C), 11.2 (–, cPr-C), 21.0 (C_{quat}, cPr-C), 33.5 (+, CH_3), 51.5 (–, CH_2), 53.4 (+, CH), 56.8 (+, CH), 101.3 (–, CH_2), 108.3 (C_{quat}, aryl-C), 109.1 (+, aryl-C), 111.5 (+, aryl-C), 113.6 (+, aryl-C), 118.9 (C_{quat}, aryl-C), 120.0 (+, aryl-C), 122.4 (+, aryl-C), 122.5 (+, aryl-C), 123.9 (+, aryl-C), 130.4 (C_{quat}, aryl-C), 131.4 (C_{quat}, aryl-C), 136.5 (C_{quat}, aryl-C), 148.0 (C_{quat}, aryl-C), 148.2 (C_{quat}, aryl-C), 162.9 (C_{quat}, C=O), 163.0 (C_{quat}, C=O). – MS (70 eV), *m/z* (%): 415 (100) [M^+], 315 (15), 289 (48). – $C_{24}H_{21}N_3O_4$ (415.5): calcd. 415.1532 (correct HRMS).

cis-6'-(1,3-Benzodioxole-5-yl)-2'-methyl-12'-spirocyclopropyl-2',3',6',7',12',12a'-hexahydropyra-zino[1',2':1,6]pyrido[3,4-b]indole-1',4'-dione (*cis*-**26**). A solution of *cis*-**60** (226 mg, 500 µmol) and methylamine (0.4 mL, 40% in H_2O) in EtOH (10 mL) was heated at 75 °C for 16 h. The volatiles were removed in vacuo, the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (10 mL) and dried over $MgSO_4$. Evaporation of the solvents and chromatographic

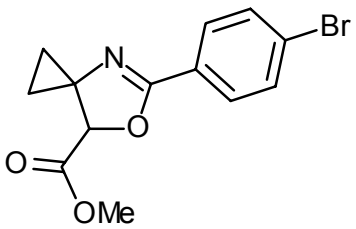
purification of the residue on 20 g of silica (1.5 × 20 cm, R_f = 0.40, pentane/Et_2O = 1 : 1) yielded 168 mg (81%) of *cis*-**26** as a colorless solid, m. p. > 250 °C. – IR (KBr): ν = 3245 cm^{-1}, 2890, 1668, 1489, 1465, 1332, 1040. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.10–1.16 (m, 2 H, cPr-H), 1.36–1.40 (m, 1 H, cPr-H), 1.72–1.78 (m, 1 H, cPr-H), 3.01 (s, 3 H, CH_3), 3.85–4.20 (m, 2 H, CH_2), 4.52 (s, 1 H, CH), 5.22 (s, 1 H, CH), 5.98 (s, 2 H, CH_2), 6.71–6.84 (m, 3 H, aryl-H), 6.96–7.20 (m, 2 H, aryl-H), 7.26–7.38 (m, 2 H, aryl-H), 8.12 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 8.2 (–, cPr-C), 11.2 (–, cPr-C), 21.0 (C_{quat}, cPr-C), 33.5 (+, CH_3), 51.5 (–, CH_2), 53.4 (+, CH), 56.8 (+, CH), 101.3 (–, CH_2), 108.3 (C_{quat}, aryl-C), 109.1 (+, aryl-C), 111.5 (+, aryl-C), 113.6 (+, aryl-C), 118.9 (C_{quat}, aryl-C), 120.0 (+, aryl-C), 122.4 (+, aryl-C), 122.5 (+, aryl-C), 123.9 (+, aryl-C), 130.4 (C_{quat}, aryl-C), 131.4 (C_{quat}, aryl-C), 136.5 (C_{quat}, aryl-C), 148.0 (C_{quat}, aryl-C), 148.2 (C_{quat}, aryl-C), 162.9 (C_{quat}, C=O), 163.0 (C_{quat}, C=O). – MS (70 eV), *m*/*z* (%): 416 (32), 415 (100) [M^+], 315 (15), 289 (50), 274 (10). – $C_{24}H_{21}N_3O_4$ (415.5): calcd. C 69.39, H 5.10, N 10.11; found: C 69.12, H 5.09, N 9.91.



3.2.4. Synthesis of spirocyclopropyl oxazolines

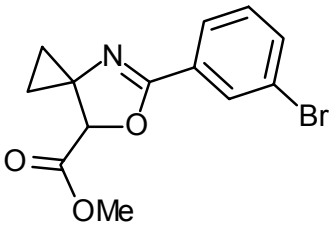
General procedure for Michael reaction of carboxamides with 5 (GP 7): A solution of Methyl-2-chloro-2-cyclopropylideneacetate (**5)** and the corresponding amide in anhydrous acetonitrile was treated with NaH (60% dispersion in mineral oil) at 0 °C. The resulting suspension was subsequently stirred for 1 h at this temperature and 2 h at 20 °C. After removing solvent the pale yellow residue was taken with 300 mL of diethyl ether, poured into a separating funnel and washed with 100 mL of water. The aq. layer was extracted with 2 × 100 mL of diethyl ether and combined organic layer was dried over $MgSO_4$. After removing the solvent in vacuo the crude product was purified by column chromatography.

5-(4-Bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester (**13a**): The crude product obtained from **5** (5.86 g, 40.0 mmol), 4-bromobenzamide (**63a**, 8.0 g, 40.0 mmol) and NaH (1.60 g, 40.0 mmol) in 150 mL of anhydrous acetonitrile according to GP 7 was purified by column chromatography (R_f = 0.35, Pentane/Et_2O = 5:1, 3 × 20 cm, 100 g SiO_2) to yield 6.20 g (51%) of **13a** as a white solid, m.p. = 102 °C. – IR (KBr): ν = 3087 cm^{-1}, 2954, 1767, 1651, 1403, 1214, 1066, 1011, 725. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.85–1.01 (m, 2 H, cPr-H), 1.14–1.22 (m, 1 H, cPr-H), 1.28–1.35 (m, 1 H, cPr-H), 3.78 (s, 3 H, CH_3), 4.91 (s, 1 H, CH), 7.52–7.58 (m, 2 H, aryl-H), 7.78–7.82 (m, 2 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.5 (–, cPr-C), 14.8 (–, cPr-C), 52.3 (+, CH_3), 53.4 (–, cPr-C), 79.8 (+, CH-C), 125.9 (–, aryl-C), 126.1 (–, aryl-C), 129.4 (+, 2 C, aryl-C), 131.7 (+, 2 C, aryl-C), 162.7 (–, CN-C), 169.3 (–, CO-C). – MS (70 eV), *m/z* (%): 311/309 (32/36) [M^+], 252/250 (100/96) [$M^+ – CO_2Me$], 224/222 (22/20), 143 (33). – $C_{13}H_{12}BrNO_3$ (310.2): calcd. C 50.35, H 3.90, N 4.52; found C 50.36, H 3.64, N 4.41.

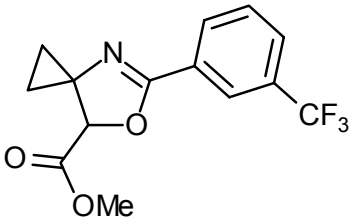


5-(3-Bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester (**13b**): The crude product obtained from **5** (6.15 g, 42.0 mmol), 3-bromobenzamide (**63b,** 8.40 g, 42.0 mmol) and NaH (1.68 g, 42.0 mmol) in 150 mL of anhydrous acetonitrile according to GP 7 was purified by column chromatography (R_f = 0.42, Pentane/Et_2O = 5:1, 3 × 20 cm, 100 g SiO_2) to yield 9.36 g (64%) of **13b** as a solid, m.p. = 79 °C. – IR (KBr): ν = 3066 cm^{-1}, 2958, 1738, 1653, 1423, 1074, 1025, 1012, 888, 708. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.95–1.05 (m, 2 H, cPr-H), 1.20–1.42

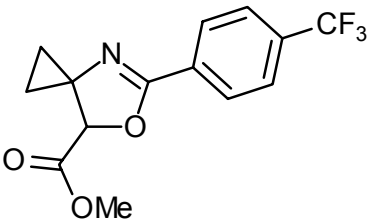
(m, 2 H, cPr-H), 3.80 (s, 3 H, CH_3), 4.90 (s, 1 H), 7.22–7.34 (m, 1 H, aryl-H), 7.58–7.64 (m, 1 H, aryl-H), 7.82–7.90 (m, 1 H, aryl-H), 8.06–8.11 (m, 1 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.5 (–, cPr-C), 14.8 (–, cPr-C), 52.3 (+, CH_3), 53.4 (–, cPr-C), 79.8 (+, CH-C), 122.5 (–, aryl-C), 126.5 (+, aryl-C), 128.9 (–, aryl-C), 129.9 (+, aryl-C), 130.9 (+, aryl-C), 134.4 (+, aryl-C), 162.1 (–, CN-C), 169.3 (–, CO-C). – MS (70 eV), *m/z* (%): 311/309 (24/24) [M^+], 252/250 (92/100) [M^+ – CO_2Me], 224 (27), 143 (72). – $C_{13}H_{12}BrNO_3$ (310.2): calcd. C 50.35, H 3.90, N 4.52; found C 50.16, H 3.71, N 4.38.



5-(3-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester (**13c**): The crude product obtained from **5** (7.32 g, 50.0 mmol), 3-trifluoromethylbenzamide (**63c**, 8.65 g, 50.0 mmol) and NaH (2 g, 50.0 mmol) in 180 mL of anhydrous acetonitrile according to GP 7 was purified by column chromatography (R_f = 0.35, Pentane/Et_2O = 5:1, 3 × 20 cm, 100 g SiO_2) to yield 7.03 g (47%) of **13c** as a viscous oil. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.90–1.05 (m, 2 H, cPr-H), 1.20–1.42 (m, 2 H, cPr-H), 3.82 (s, 3 H, CH_3), 4.95 (s, 1 H, CH), 7.50–7.61 (m, 1 H, aryl-H), 7.68–7.75 (m, 1 H, aryl-H), 8.10–8.21 (m, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.4 (–, cPr-C), 14.7 (–, cPr-C), 52.2 (+, CH_3), 53.4 (–, cPr-C), 79.7 (+, CH-C), 123.6 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 124.8 (+, q, aryl-C), 127.8 (+, aryl-C), 127.9 (+, q, $^3J_{C\text{-}F}$ = 3.9 Hz, aryl-C) 128.9 (+, aryl-C), 130.9 (C_{quat}, q, $^2J_{C\text{-}F}$ = 32.8 Hz, aryl-C), 131.0 (C_{quat}, aryl-C), 162.1 (–, CN-C), 169.1 (–, CO-C). – MS (70 eV), *m/z* (%): 299 (11) [M^+], 240 (100) [M^+ – CO_2Me], 212 (49), 145 (30). – $C_{14}H_{12}F_3NO_3$ (299.3): calcd. C 56.19, H 4.04, N 4.68; found;

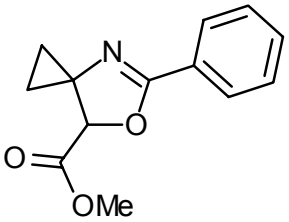


5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester (**13d**). The crude product obtained from **5** (4.03 g, 27.5 mmol), 4-trifluoromethylbenzamide **63d** (5.20 g, 27.5 mmol) and NaH (1.1 g, 27.5 mmol) in 120 mL of anhydrous acetonitrile according to GP 7 was purified by column chromatography (R_f = 0.4, Pentane/Et_2O = 5:1, 3 × 20 cm) to yield 6.60 g (81%) of title compound as a oil which solidified at 0 °C m.p. = 75–77 °C. – IR (KBr): ν = 3021 cm^{-1}, 2967, 1768, 1648, 1415, 1317, 1170, 1080, 859. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.92–1.08 (m, 2 H, cPr-



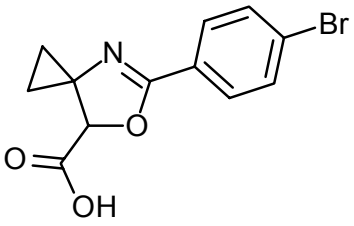
H), 1.20–1.28 (m, 1 H, cPr-H), 1.33–1.41 (m, 1 H, cPr-H), 3.78 (s, 3 H, CH_3), 4.92 (s, 1 H, CH), 7.67 (d, ^3J = 8.3 Hz, 2 H, aryl-H), 8.05 (d, ^3J = 8.3 Hz, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.6 (–, cPr-C), 14.9 (–, cPr-C), 52.3 (+,CH_3), 53.4 (–, cPr-C), 79.8 (+, CH-C), 123.4 (C_{quat}, q, $^1J_{C\text{-}F}$ = 242 Hz, CF_3), 124.8 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, 2 C, aryl-C), 128.3 (+, 2 C, aryl-C), 130.2 (C_{quat}, aryl-C), 132.3 (C_{quat}, q, $^2J_{C\text{-}F}$ = 32.8 Hz, aryl-C), 162.2 (C_{quat}, CN-C), 169.1 (C_{quat}, CO-C). – MS (70 eV), *m/z* (%): 299 (20) [M^+], 240 (100) [M^+ – CO_2Me], 212 (60), 172 (23), 145 (25). – $C_{14}H_{12}F_3NO_3$ (299.3): calcd. C 56.19, H 4.04, N 4.68; found C 56.09, H 3.80, N 4.77.

5-Phenyl-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester (**13e**): The crude product obtained from **5** (2.50 g, 17.0 mmol), benzamide (**63e**, 5.20 g, 17.0 mmol) and NaH (595 mg, 17.0 mmol) in 50 mL of anhydrous acetonitrile according to GP 7 was purified by column chromatography (R_f = 0.38, Pentane/Et_2O = 4:1, 3 × 10 cm) to yield 2.2 g (54%) of title compound as a solid, m.p. = 48 °C. – IR (KBr): ν = 2948 cm^{-1}, 1732, 1449, 1284, 1057, 694. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.91–1.08 (m, 2 H, cPr-H), 1.18–1.27 (m, 1 H, cPr-H), 1.32–1.42 (m, 1 H, cPr-H), 3.80 (s, 3 H, CH_3), 4.93 (s, 1 H, CH), 7.39–7.54 (m, 3 H, aryl-H), 7.91–7.99 (m, 2 H, aryl-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 10.4 (–, cPr-C), 14.7 (–, cPr-C), 52.3 (+, CH_3), 53.3 (–, cPr-C), 79.7 (+, CH-C), 127.0 (–, aryl-C), 128.0 (+, 2 C, aryl-C), 128.4 (+, 2 C, aryl-C), 131.5 (+, aryl-C), 163.5 (–, CN-C), 169.5 (–, CO-C). – MS (70 eV), *m/z* (%): 231 (35) [M^+], 172 (100) [M^+ – CO_2Me], 144 (60), 105 (26).

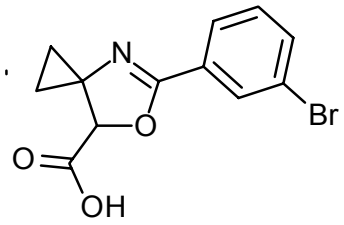


General procedure for synthesis of oxazoline carboxylic Acid 64a–e from the ester 13a–e (GP 8): To a solution of oxazoline carboxylic acid methyl ester (**13a–e)** in MeOH/THF (4:1) at room temperature aq. NaOH (1 N, 5 equiv.) was added. The resulting solution was stirred for 30 min, then glacial AcOH (10 equiv.) was added, stirred for additional 15 min. and the solvent was evaporated in vacuo. The residue was filtered over SiO_2 gel (Et_2O/AcOH = 50:1), and the product crystallized from ether/hexane.

5-(4-Bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (**64a**).The crude product obtained from **13a** (3.70 g, 12 mmol), NaOH (2.40 g) and AcOH (7.20 g, 120 mmol) according to GP 8 yielded 3.21 g (91%) of **64a** as white solid, m.p. 199 °C. – IR (KBr): ν = 3093 cm^{-1}, 1745, 1633, 1591, 1491, 1199, 1092, 838. – ^{1}H-NMR (300 MHz, CD_3OD): δ = 0.96–1.02 (m, 1 H, cPr-H), 1.09–1.20 (m, 2 H, cPr-H), 1.22–1.32 (m, 1 H, cPr-H), 4.95 (s, 1 H, CH), 7.61–7.68 (m, 2 H, aryl-H), 7.80–7.85 (m, 2 H, aryl-H). – ^{13}C-NMR (75.5 MHz, CD_3OD, APT): δ =10.7 (–, cPr-C), 15.0 (–, cPr-C), 53.9 (–, cPr-C), 81.0 (+, CH-C), 127.2 (–, aryl-C), 127.4 (–, aryl-C), 130.7 (+, 2 C, aryl-C), 133.0 (+, 2 C, aryl-C), 164.9 (–, CN-C), 171.9 (–, CO-C). – MS (70 eV), *m/z* (%): 297/255 (46/44) [M^+], 252/250 (100/96) [M^+ – CO_2H], 224/222 (36/40), 143 (71). – $C_{12}H_{10}BrNO_3$ (296.1): calcd. C 48.67, H 3.40, N 4.73; found C 48.39, H 3.15, N 4.65.

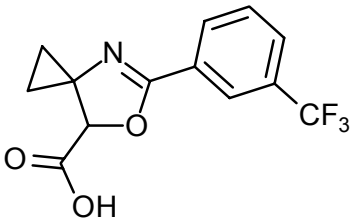


5-(3-Bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (**64b**). The crude product obtained from **13b** (8.5 g, 27.5 mmol), NaOH (5.5 g, 138 mmol) and AcOH (16.5 g, 275 mmol) according to GP 8 yielded 7.31 g (90%) of **64b** as a white solid, m.p. = 196 °C. – IR (KBr): ν = 3108 cm^{-1}, 1728, 1637, 1431, 1201, 1096, 1032, 791. – ^{1}H-NMR (300 MHz, CD_3OD): δ = 0.96–1.04 (m, 1 H, cPr-H), 1.11–1.22 (m, 2 H, cPr-H), 1.23–1.37 (m, 1 H, cPr-H), 5.01 (s, 1 H, CH), 7.39 (m, 1 H, aryl-H), 7.68–7.75 (m, 1 H, aryl-H), 7.86–7.94 (m, 1 H, aryl-H), 8.05–8.10 (m, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, CD_3OD, APT): δ = 10.8 (–, cPr-C), 15.1 (–, cPr-C), 53.9 (–, cPr-C), 81.0 (+, CH-C), 123.4 (–, aryl-C), 127.7 (+, aryl-C), 130.2 (–, aryl-C), 131.6 (+, aryl-C), 131.8 (+, aryl-C), 135.8 (+, aryl-C), 164.3 (–, CN-C), 171.8 (–, CO-C). – MS (70 eV), *m/z* (%): 297/295 (42/37) [M^+], 252/250 (98/100) [M^+ – CO_2H], 143 (68), 116 (20). – $C_{12}H_{10}BrNO_3$ (296.1): calcd. C 48.67, H 3.40, N 4.73; found C 48.76, H 3.21, N 4.80.

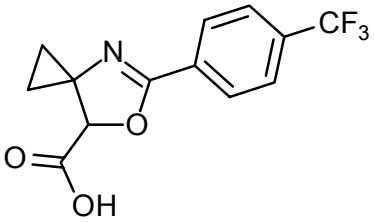


5-(3-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (**64c**): The crude product obtained from **13c** (6.70 g, 22.0 mmol), NaOH (4.40 g, 110 mmol) and AcOH (1.32 g, 220 mmol) according to GP 8 yielded 5.60 g (89%) of **64c** as a white solid, m.p. = 171 °C. – IR (KBr): ν = 3015 cm^{-1}, 1734, 1641, 1447, 1329, 1303, 1135, 1027, 919. – ^{1}H-NMR (250 MHz, DMSO-D_6): δ = 0.98–1.07 (m, 1 H, cPr-H), 1.13–1.23 (m, 2 H, cPr-H), 1.26–1.37 (m, 1 H, cPr-H),

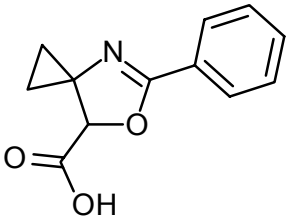
5.05 (s, 1 H, CH), 7.71 (m, 1 H, aryl-H), 7.87 (m, 2 H, aryl-H), 8.14–8.23 (m, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, [D$_6$]DMSO, DEPT): δ = 10.0 (–, cPr-C), 14.5 (–, cPr-C), 53.3 (–, cPr-C), 79.1 (+, CH-C), 123.9 (C$_{quat}$, q, $^1J_{C-F}$ = 272 Hz, CF$_3$), 123.8 (+, q, $^3J_{C-F}$ = 3.2 Hz, aryl-C), 127.8 (+, aryl-C), 128.5 (+, q $^3J_{C-F}$ = 3.2 Hz, aryl-C), 129.8 (C$_{quat}$, q, $^2J_{C-F}$ = 33.2 Hz, aryl-C), 130.5 (+, aryl-C), 131.5 (C$_{quat}$, aryl-C), 161.4 (–, CN-C), 170.3 (–, CO-C). – MS (70 eV), *m/z* (%): 285 (24) [M$^+$], 240 (100) [M$^+$ – CO$_2$H], 212 (81), 172 (36), 145 (44).



5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (**64d**): The crude product obtained from **13d** (5.90 g, 19.2 mmol), NaOH (3.84 g, 94 mmol) and AcOH (11.5 g, 192 mmol) in MeOH/THF (500 mL) according to GP 8 (R_f = 0.40, Et$_2$O/AcOH = 50:1) to yield 5.11 g (93%) of **64d** as white solid, m.p. = 190–191 °C. – IR (KBr): ν = 2755 cm^{-1}, 1740, 1646, 1417, 1332, 1168, 1093, 852. – ^{1}H-NMR (300 MHz, CD$_3$OD): δ = 0.95–1.06 (m, 1 H, cPr-H), 1.11–1.23 (m, 2 H, cPr-H), 1.06–1.15 (m, 1 H, cPr-H), 5.03 (s, 1 H, CH), 7.78 (d, ^3J = 8.2 Hz, 2 H, aryl-H), 8.10 (d, ^3J = 8.2 Hz, 2 H, aryl-H). – ^{13}C-NMR (75.5 MHz, CDCl$_3$, APT): δ = 10.9 (–, cPr-C), 15.2 (–, cPr-C), 54.1 (–, cPr-C), 81.1 (+, CH-C), 125.3 (–, q, $^1J_{C-F}$ = 272 Hz, CF$_3$), 126.6 (+, q, $^3J_{C-F}$ = 3.8 Hz, 2 C, aryl-C), 129.6 (+, 2 C, aryl-C), 131.8 (–, aryl-C), 134.2 (–, q, $^2J_{C-F}$ = 32.8 Hz, aryl-C), 164.3 (–, CN-C), 171.8 (–, CO-C). – MS (70 eV), *m/z* (%): 285 (38) [M$^+$], 240 (100) [M$^+$ – CO$_2$H], 212 (75), 172 (32). – C$_{13}$H$_{10}$F$_3$NO$_3$ (285.2): calcd. C 54.74, H 3.53, N 4.91; found C 54.35, H 3.25, N 5.11.

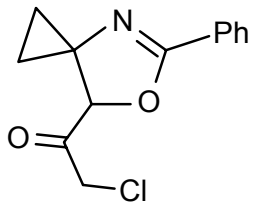


5-Phenyl-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (**64e**): The crude product obtained from **13e** (3.40 g, 14.7 mmol), NaOH (2.96 g, 74 mmol) and AcOH (8.80 g, 147 mmol) in MeOH/THF (200 mL) according to GP 8 (R_f = 0.40, Et$_2$O/AcOH = 50:1), yielded 5.10 g (93%) of **64e** as a white solid, m.p 182 °C. – IR (KBr): ν = 3061 cm^{-1}, 3009, 1717, 1638, 1457, 1364, 1211, 1069, 735. – ^{1}H-NMR (250 MHz, CD$_3$OD): δ = 0.95–1.03 (m, 1 H, cPr-H), 1.05–1.34 (m, 3 H, cPr-H), 4.99 (s, 1 H, CH), 7.40–7.59 (m, 3 H, aryl-H), 7.86–7.98 (m, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, CD$_3$OD, DEPT): δ = 11.0 (–, cPr-C), 15.3 (–,



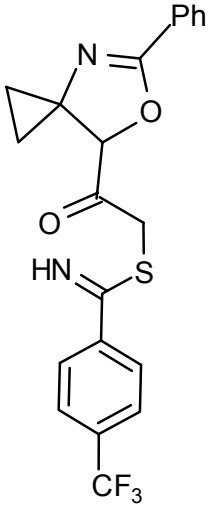
cPr-C), 54.0 (C_{quat}, cPr-C), 81.3 (+, CH-C), 128.3 (C_{quat}, aryl-C), 129.3 (+, 2 C, aryl-C), 129.9 (+, 2 C, aryl-C), 133.3 (+, aryl-C), 166.2 (–, CN-C), 172.4 (–, CO-C). – MS (70 eV), *m/z* (%): 217 (48) [M^+], 172 (100) [$M^+ – CO_2H$], 144 (57), 104 (28).

2-Chloro-1-(5-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl)-ethanone (**62**-Ph): A solution of lithium diisopropyl amine(35.7 mmol) in 40 mL THF was added dropwise over a period of 30 min to a solution 5-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester **13e** (1.71 g, 7.14 mmol) and CH_2ICl in 30 mL of THF at –78 °C and the reaction mixture was stirred for 10 min at this temperature. At 25 °C a solution of acetic acid (10 mL) in 20 mL of THF was added slowly over a period of 10 min. After stirring for an additional 10 min the reaction mixture was partitioned between Et_2O and brine. Organic layer was washed with sat. NaHCO3, 5% $NaHSO_3$ and brine, dried over $MgSO_4$. After removing the solvent the crude product was purified by column chromatography (R_f = 0.31, pentane/Et_2O = 5:1) to yield 900 mg (51%) of 62-Ph as a white solid, m.p. 168 °C. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.89–1.00 (m, 2 H, cPr-H), 1.15–1.24 (m, 1 H, cPr-H), 1.36–1.42 (m, 1 H, cPr-H), 4.37 (d, ^2J = 14.2 Hz, 1 H, CH_2), 4.57 (d, ^2J = 14.2 Hz, 1 H, CH_2), 4.98 (s, 1 H, CH), 7.38–7.59 (m, 3 H, aryl-H), 7.88–8.00 (m, 2 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = δ = 10.4 (–, cPr-C), 14.4 (–, cPr-C), 46.5 (–, CH_2), 53.3 (C_{quat}, cPr-C), 84.6 (+, CH-C), 126.3 (C_{quat}, aryl-C), 127.9 (+, 2 C, aryl-C), 128.6 (+, 2 C, aryl-C), 131.9 (+, aryl-C), 162.8 (C_{quat}, CN-C), 198.9 (C_{quat}, CO-C). – MS (70 eV), *m/z* (%): 451/449 (32/30) [M^+], 184/182 (95/100), 156/154 (32/31).



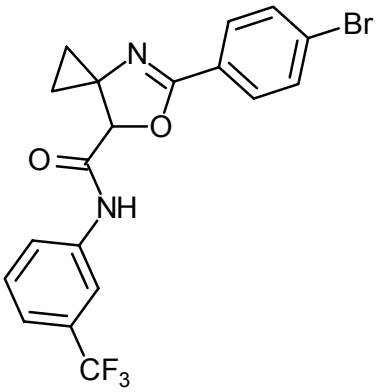
4-Trifluoromethyl-thiobenzimidic acid 2-oxo-2-(5-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl)-ethyl ester (**65**): To a mixture of **62**-Ph (100 mg, 0.40 mmol) and NaOAc (41 mg, 0.50 mmol) in 5 mL of CH_3CN was added 4-trifluoromethy benzthioamide (102 mg, 0.50 mmol) and the reaction mixtute was stirrred at 50 °C

for 48 h. After removing solvent the reaction mixture was taken in 25 mL of Et_2O and wased with water, dried over MgSO4. After removing solvent the crude reaction mixture was purified in column chromatography (R_f = 0.28, pentane/Et_2O = 5:1) to yield 99 mg (59%) of 65 as a white solid, m.p. 191 °C. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.78–0.83 (m, 1 H, cPr-H), 1.30–1.41 (m, 2 H, cPr-H), 3.58 (d, ^2J = 12.5 Hz, 1 H, CH_2), 3.79 (d, ^2J = 14.2 Hz, 1 H, CH_2), 4.92 (s, 1 H, CH), 7.36–7.55 (m, 3 H, aryl-H), 7.63–7.75 (m, 2 H, aryl-H), 7.83–8.01 (m, 4 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = δ = 10.6 (–, cPr-C), 14.7 (–, cPr-C), 39.8 (–, CH_2), 50.4 (C_{quat}, cPr-C), 85.0 (+, CH-C), 109.2 (C_{quat}, CNH-C), 125.6 (C_{quat}, aryl-C), 127.1 (+, aryl-C), 127.8 (+, 2 C, aryl-C), 128.3 (+, 2 C, aryl-C), 128.8 (+, 2 C, aryl-C), 131.3 (C_{quat}, aryl-C). – MS (70 eV), *m/z* (%): 418 (< 1) [M^+], 246 (40), 173 (100), 172 (78).



General procedure for coupling of oxazoline carboxylic acid with anilines (GP 9): To an ice-cold solution of oxazoline carboxylic acid (**64**) and HOAt in dry DCM was added EDC·HCl in one portion, stirred for 15 min. followed by addition of 2,4,6-colidine and respective anilines. The cooling bath was removed and the resulting pale yellow reaction solution was stirred for 12 h at 20 °C. The reaction mixture was filtered through a pad of SiO_2 and the crude product was purified by column chromatography.

5-(4-Bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (3-trifluoromethyl-phenyl)-amide (**68a**): The crude product obtained from **64a** (1.20 g, 4.05 mmol), HOAt (606 mg, 4.45 mmol), EDC·HCl (1.16g, 6.07 mmol), 2,4,6-colidine (980 mg, 8.1 mmol) and 3-trifluoro-methyl aniline (977 mg, 6.07 mmol) following GP 9 was purified by column chromatography (R_f = 0.52, Pentane /Et_2O = 1:1) to yield 1.64 g (92%) of **68a** as white solid, m.p. 194 °C. – IR (KBr): ν = 3327 cm^{-1}, 1670, 1557, 1453, 1336, 1125, 1069. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.97–1.16 (m, 2 H, cPr-H), 1.34–1.48 (m, 2 H, cPr-H), 4.98 (s, 1 H, CH), 7.38–7.50 (m, 2 H, aryl-H), 7.59–7.63 (m, 2 H, aryl-H) 7.72–7.87 (m, 4 H, aryl-H), 8.02 (br s, 1 H, NH). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.6

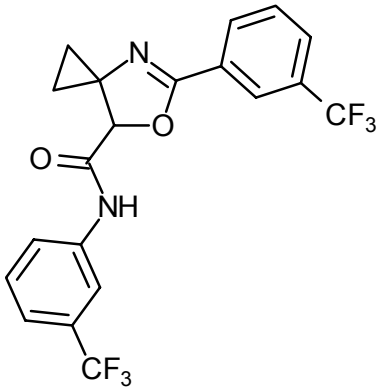


(–, cPr-C), 14.4 (–, cPr-C), 53.5 (–, cPr-C), 80.3 (+, CH-C), 116.8 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 121.7 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 123.2 (+, aryl-C), 125.5 (–, aryl-C), 126.6 (–, aryl-C), 129.2 (+, aryl-C), 129.7 (+, 2 C, aryl-C), 131.8 (–, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 132.0 (+, 2 C, aryl-C), 136.9 (–, aryl-C), 160.7 (–, CN-C), 166.5 (–, CO-C). – MS (70 eV), *m/z* (%): 440/438 (21/20) [M^+], 280/278 (46/44) [M^+ – Br], 253/251 (58/62), 252/250 (68/62), 161 (100). – $C_{19}H_{14}BrF_3N_2O_2$ (439.2): calcd. C 51.96, H 3.21, N 6.38; found C 52.13, H 3.07, N 6.16.

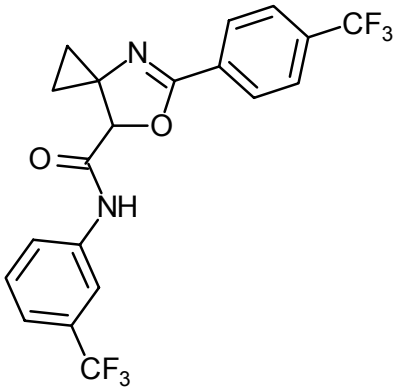
5-(3-Bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (3-trifluoromethyl-phenyl)-amide (**68b**): The crude product obtained from **64b** (250 mg, 0.85 mmol), HOAt (139 mg, 1.02 mmol), EDC·HCl (244 mg, 1.27 mmol), 2,4,6-colidine (206 mg, 1.70 mmol) and 3-trifluoromethyl aniline (178 mg, 1.1 mmol) in 20 mL of DCM following GP 9 was purified by column chromatography (R_f = 0.40, Pentane/Et_2O = 2:1) to yield 307 mg (82%) of **68b** as a white solid, m.p. = 171–172 °C. – IR (KBr): ν = 3269 cm^{-1}, 3077, 1668, 1552, 1338, 1168, 1063, 810. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.98–1.11 (m, 2 H, cPr-H), 1.36–1.47 (m, 2 H, cPr-H), 5.00 (s, 1 H, CH), 6.76–6.99 (m, 1 H, aryl-H), 7.30–7.47 (m, 2 H, aryl-H), 7.63–7.78 (m, 1 H, aryl-H), 7.82 (s, 1 H, aryl-H), 7.84–7.93 (m, 1 H, aryl-H), 8.06 (br. s, 1 H, NH), 8.11–8.15 (m, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ =10.7 (–, cPr-C), 14.4 (–, cPr-C), 53.5 (–, cPr-C), 80.3 (+, CH-C), 116.9 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 121.7 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 122.8 (–, aryl-C), 123.2 (+, aryl-C), 126.4 (+, aryl-C), 128.5 (–, aryl-C), 129.7 (+, aryl-C), 130.3 (+, aryl-C), 130.8 (+, aryl-C), 131.3 (–, aryl-C), 131.5 (+, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C) 134.8 (+, aryl-C), 136.9 (–, aryl-C), 160.2 (–, CN-C), 166.4 (–, CO-C). – MS (70 eV), *m/z* (%): 440/438 (83/81) [M^+], 280/278 (67/69), 253/251 (98/100), 252/250 (92/84), 161 (69). – $C_{19}H_{14}BrF_3N_2O_2$ (439.2): calcd. C 51.96, H 3.21, N 6.38; found C 52.25, H 2.96, N 6.24.

5-(3-Trifluromethylphenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (3-trifluoro-methylphenyl)-amide (**68c**): The crude product obtained from **64c** (100 mg, 0.35 mmol), HOAt (57 mg, 0.42 mmol), EDC·HCl (101 mg, 0.53 mmol), 2,4,6-colidine (85 mg, 0.7 mmol) and 3-trifluoro-methyl aniline (86 mg, 0.53 mmol) in 10 mL of DCM following the GP 9 was purified by column chromatography (R_f = 0.35, Pentane/Diethylether 2:1) to yield 121 mg (81%) of the title

compound as a white solid m.p. = 135 °C. – IR (KBr): ν = 3259 cm^{-1}, 3074, 1672, 1549, 1324, 1110, 1075, 696. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.00–1.16 (m, 2 H, cPr-H), 1.34–1.52 (m, 2 H, cPr-H), 5.04 (s, 1 H, CH), 7.37–7.50 (m, 2 H, aryl-H), 7.62 (t, ^3J = 8.2 Hz, 1 H, aryl-H), 7.71–7.84 (m, 3 H, aryl-H), 8.03 (br. s, 1 H, NH), 8.17 (d, ^3J = 8.2 Hz, 1 H, aryl-H), 8.23 (s, 1 H, aryl-H), – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.8 (–, cPr-C), 14.4 (–, cPr-C), 53.5 (–, cPr-C), 80.4 (+, CH-C), 116.9 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 121.7 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 123.3 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.8 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 127.4 (–, aryl-C), 128.4 (+, aryl-C), 129.4 (+, aryl-C), 129.7 (+, aryl-C), 130.9 (+, aryl-C), 131.2 (–, q, $^2J_{C\text{-}F}$ = 33.5 Hz, aryl-C), 131.5 (–, q, $^2J_{C\text{-}F}$ = 33.5 Hz, aryl-C), 136.9 (–, Ar-C), 160.3 (–, CN-C), 166.3 (–, CO-C). – MS (70 eV), *m/z* (%): 428 (32) [M^+], 268 (48), 241 (100), 240 (86), 173 (56), 161 (52). – $C_{20}H_{14}F_6N_2O_2$ (428.3): calcd. C 56.08, H 3.29, N 6.54; found C 56.29, H 3.20, N 6.42.



5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (3-trifluro-methyl-phenyl)-amide (**68d**): The crude product obtained from **64d** (285 mg, 1.00 mmol), HOAt (163 mg, 1.20 mmol), EDC·HCl (286 mg, 1.50 mmol), 2,4,6-colidine (242 mg, 2.00 mmol) and 3-trifluoro-methyl aniline (209 mg, 1.30 mmol) in 15 mL of DCM following the GP 9 was purified by column chromatography (R_f = 0.43, Pentane:Et_2O = 2:1) to yield 385 mg (90%) of **68d** as a white solid, m.p. = 162 °C. – IR (KBr): ν = 3335 cm^{-1}, 2927, 1671, 1558, 1447, 1338, 1128, 1054, 851. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.98–1.17 (m, 2 H, cPr-H), 1.38–1.50 (m, 2 H, cPr-H), 5.02 (s, 1 H, CH), 7.38–749 (m, 2 H, aryl-H), 7.70–7.78 (m, 3 H, aryl-H), 7.82 (s, 1 H, aryl-H), 8.04 (br. s, 1 H, NH), 8.08–8.14 (m, 2 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ =10.8 (–, cPr-C), 14.5 (–, cPr-C), 53.6 (–, cPr-C), 80.4 (+, CH-C), 116.9 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 121.7 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 123.2 (+, aryl-C), 123.2 (+, aryl-C), 125.7 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 126.4 (+, aryl-C), 128.2 (+, 2 C, aryl-C), 129.7 (+, aryl-C), 129.9 (–, aryl-C), 131.3 (–, q, $^2J_{C\text{-}F}$ = 33.5 Hz, aryl-C), 133.5 (–, q, $^2J_{C\text{-}F}$ = 33.5 Hz, aryl-C), 136.9 (–, aryl-C), 160.3 (–, CN-C), 166.4 (–, CO-C). – MS (70 eV), *m/z* (%): 428 (44) [M^+],



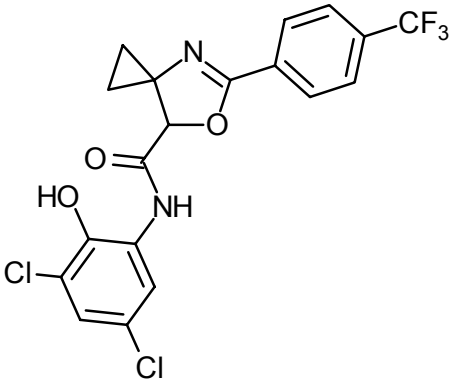
268 (51), 241 (100), 240 (86), 161 (31). – $C_{20}H_{14}F_6N_2O_2$ (428.3): calcd. C 56.08, H 3.29, N 6.54; found C 56.37, H 3.50, N 6.61.

5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (5-chloro-2-hydroxy-phenyl)-amide (**68e**): The crude product obtained from **64d** (285 mg, 1.0 mmol), HOAt (163 mg, 1.20 mmol), EDC·HCl (286 mg, 1.5 mmol), 2,4,6-colidine (242 mg, 2.0 mmol) and 5-chloro-2-hydroxyaniline (187 mg, 1.3 mmol) in 15 mL of DCM following GP 9 was purified by column chromatography (R_f = 0.50, Pentane/Et_2O 1:1) to yield 349 mg (85%) of the **68e** as white solid, m.p. 238 °C. – IR (KBr): ν = 3380 cm^{-1}, 3102, 1653, 1552, 1428, 1327, 1136, 1176, 854. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.76–0.92 (m, 1 H, *c*Pr-H), 0.97–1.17 (m, 2 H, cPr-H), 0.76–0.92 (m, 1 H, cPr-H), 5.01 (s, 1 H, CH), 6.87–6.92 (m, 1 H, aryl-H), 7.05 (m, 1 H, aryl-H), 7.42–7.58 (m, 3 H, aryl-H), 7.77 (s, 1 H, aryl-H), 7.96–8.00 (m, 2 H, aryl-H), 8.27 (br s, 1 H, NH). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.6 (–, cPr-C), 14.7 (–, cPr-C), 53.8 (–, cPr-C), 80.6 (+, CH-C), 117.3 (+, aryl-C), 120.8 (+, aryl-C), 125.4 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 126.6 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 128.2 (+, 2 C, aryl-C), 130.1 (–, aryl-C), 131.3 (–, q, $^2J_{C\text{-}F}$ = 33.5 Hz, aryl-C), 146.8, 160.6 (–, CN-C), 166.7 (–, CO-C). – MS (DCI), *m/z* (%): 411 (100) [M + H^+]. – $C_{19}H_{14}ClF_3N_2O_3$ (410.8): calcd. C 55.56, H 3.44, N 6.82; found C 55.69, H 3.18, N 7.06.

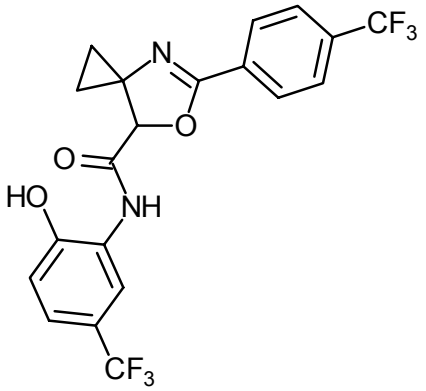
5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (5-trifluoro-methoxy-2-hydroxy-phenyl)-amide (**68f**) The crude product obtained from **64d** (143 mg, 0.50 mmol), HOAt (82 mg, 0.60 mmol), EDC·HCl (143 mg, 0.75 mmol), 2,4,6-colidine (121 mg, 1.0 mmol) and 5-trifluoromethoxy-2-hydroxy aniline (125 mg, 0.65 mmol) in 10 mL of DCM following the general procedure 1 (GP 1) was purified by column chromatography (R_f = 0.45, Pentane/Et_2O = 1:1) to yield 127 mg (55%) of **68f** as colourless solid, m.p. = 135 °C. – IR (KBr): ν = 3378 cm^{-1}, 3122, 1654, 1559, 1447, 1251, 1136, 1069, 854. – ^{1}H-NMR (300 MHz, CD_3OD): δ = 1.04–1.20 (m, 2 H, cPr-H), 1.30–1.41 (m, 2 H,

cPr-H), 5.18 (s, 1 H, CH), 6.82–6.93 (m, 2 H, aryl-H), 7.83 (d, ^3J = 8.2 Hz, 2 H, aryl-H), 8.02–8.08 (m, 1 H, aryl-H), 8.18 (d, ^3J = 8.2 Hz, 2 H, aryl-H). – ^{13}C-NMR (75.5 MHz, CD_3OD, APT): δ = 10.7 (–, cPr-C), 15.0 (–, cPr-C), 54.7 (–, cPr-C), 81.8 (+, CH-C), 115.2 (+, aryl-C), 116.0 (+, aryl-C), 118.8 (+, aryl-C), 121.7 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 126.7 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 127.1 (–, aryl-C), 129.6 (+, 2 C, aryl-C), 131.6 (–, aryl-C), 134.4 (–, q, $^2J_{C\text{-}F}$ = 33.5 Hz, aryl-C), 142.3 (–, aryl-C), 147.7 (–, aryl-C), 163.1 (–, CN-C), 168.4 (–, CO-C). – MS (70 eV), *m/z* (%): 460 (35) [M^+], 296 (15), 268 (54), 241 (100), 240 (61), 173 (57).

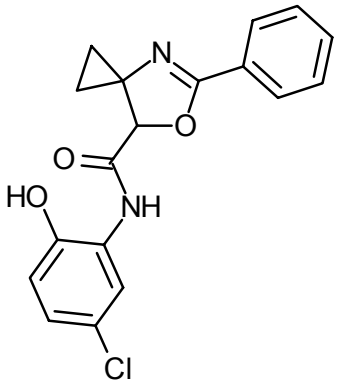
5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (3,5-dichloro-2-hydroxy-phenyl)-amide (**68g**) The crude product obtained from **64d** (143 mg, 0.50 mmol), HOAt (82 mg, 0.60 mmol), EDC·HCl (143 mg, 0.75 mmol), 2,4,6-colidine (121 mg, 1.0 mmol) and 3,5-dichloro-2-hydroxy aniline (126 mg, 0.65 mmol) in 10 mL of DCM following GP 9 was purified by column chromatography (R_f = 0.41, Pentane:Et_2O = 1:1) to yield 175 mg of **68g** (79%) as colourless solid, m.p. = 185 °C. – IR (KBr): ν = 3392 cm^{-1}, 3132, 1676, 1596, 1412, 1326, 1140, 1056, 852. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.99–1.20 (m, 2 H, cPr-H), 1.37–1.51 (m, 2 H, cPr-H), 5.00 (s, 1 H, CH), 6.21 (br s, 1 H, OH), 7.12 (d, ^4J = 2.5 Hz, 1 H, aryl-H), 7.71 (d, ^3J = 8.0 Hz, 2 H, aryl-H), 8.07 (d, ^3J = 8.0 Hz, 2 H, aryl-H), 8.17 (d, ^4J = 2.5 Hz, 1 H, aryl-H), 8.78 (br s, 1 H, NH) . – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.5 (–, cPr-C), 14.9 (–, cPr-C), 53.8 (–, cPr-C), 80.3 (+, CH-C), 119.1 (+, aryl-C), 120.5 (–, aryl-C), 123.6 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 124.1 (+, aryl-C) 125.7 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 125.8 (–, aryl-C), 126.0 (–, aryl-C), 128.1 (+, 2 C, aryl-C), 129.8 (–, aryl-C), 133.7 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 140.0 (–, aryl-C), 160.3 (–, CN-C), 166.7 (–, CO-C). – MS (70 eV), *m/z* (%): 446/444 (15/21) [M^+], 268 (59), 241 (100), 240 (60), 173 (51). – $C_{19}H_{13}Cl_2F_3N_2O_3$ (445.2) calcd. C 51.26, H 2.94, N 6.29; found C 51.51, H 2.95, N 6.53.



5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (5-trifluoro-methyl-2-hydroxy-phenyl)-amide (**68h**): The crude product obtained from **64d** (143 mg, 0.50 mmol), HOAt (82 mg, 0.60 mmol), EDC·HCl (143 mg, 0.75 mmol), 2,4,6-colidine (121 mg, 1.0 mmol) and 5-trifluoromethyl-2-hydroxy aniline (115 mg, 0.65 mmol) in 10 mL of DCM following GP 9 was purified by column chromatography (R_f = 0.45, Pentane/Et_2O = 1:1) to yield 167 mg (78%) of **68h** as colourless solid, m.p. 134-136 °C. – IR (KBr): ν = 3383 cm^{-1}, 3122, 1664, 1559, 1414, 1336, 1160, 1069, 856. – ^{1}H-NMR (300 MHz, CD_3OD): δ = 1.04–1.20 (m, 2 H, cPr-H), 1.24–1.40 (m, 2 H, cPr-H), 5.09 (s, 1 H, CH), 6.97 (d, ^3J = 7.5 Hz, 1 H, aryl-H), 7.25–7.32 (m, 1 H, aryl-H), 7.82 (d, ^3J = 8.1 Hz, 2 H, aryl-H), 8.18 (d, ^3J = 8.1 Hz, 2 H, aryl-H), 8.39 (br. s, 1 H, NH), 8.64–8.70 (m, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.8 (–, cPr-C), 14.4 (–, cPr-C), 54.7 (–, cPr-C), 81.8 (+, CH-C), 115.8 (+, aryl-C), 119.2 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 122.5 (+, q, $^3J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 123.5 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.8 (q, $^1J_{C\text{-}F}$ = 271 Hz, CF_3), 125.3 (q, $^1J_{C\text{-}F}$ = 262 Hz, CF_3), 126.7 (+, aryl-C), 129.6 (+, 2 C, aryl-C), 131.6 (–, aryl-C), 134.3 (q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 151.8 (–, aryl-C), 163.1 (–, CN-C), 168.6 (–, CO-C). – MS (70 eV), *m/z* (%): 444 (20) [M^+], 268 (52), 241 (100), 140 (57), 173 (53). – $C_{20}H_{14}F_6N_2O_3$ (444.3). – calcd. C 54.06, H 3.14, N 6.30; found C 54.16, H 3.40, N 6.45.



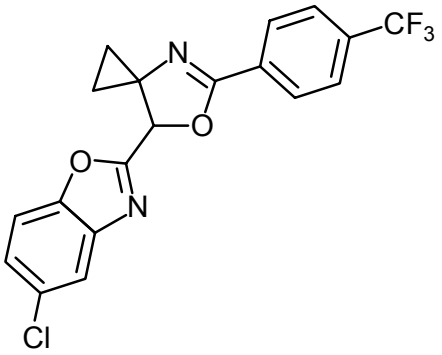
5-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (5-chloro-2-hydroxy-phenyl)-amide (**68i**): The crude product obtained from **64e** (185 mg, 0.85 mmol), HOAt (139 mg, 1.02 mmol), EDC·HCl (244 mg, 1.27 mmol), 2,4,6-colidine (206 mg, 1.70 mmol) and 5-chloro-2-hydroxyaniline (146 mg, 1.1 mmol) in 15 mL of DCM following GP 9 was purified by column chromatography (R_f = 0.25, Pentane:Et_2O = 1:1) to yield 268 mg (92%) of **68i** as a white solid, m.p. 211 °C. – IR (KBr): ν = 3381 cm^{-1}, 3052, 1668, 1558, 1431, 1339, 1195, 1033. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.96–1.18 (m, 2 H, cPr-H), 1.34–1.50 (m, 2 H, cPr-H), 5.01 (s, 1 H, CH), 6.87–6.92 (m, 1 H, Ar-H), 7.05 (dd, ^3J = 8.2 Hz, ^4J = 2.5 Hz, 1 H, aryl-H) 7.42–7.58 (m, 3 H, aryl-H), 7.77 (s, 1 H, aryl-H), 7.96–8.00 (m, 2 H, aryl-H), 8.27 (br s, 1 H, NH). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 10.6 (–, cPr-C),



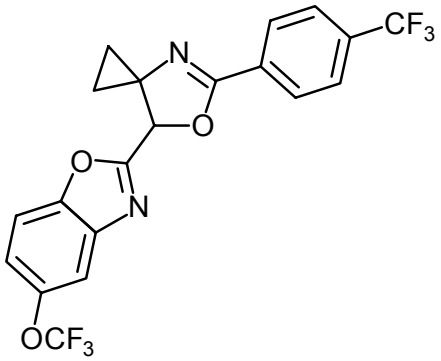
14.5 (–, cPr-C), 53.7 (–, cPr-C), 80.2 (+, CH-C), 120.1 (+, aryl-C), 121.9 (+, aryl-C), 125.5 (–, aryl-C), 126.6 (–, aryl-C), 127.0 (+, aryl-C), 127.9 (+, 2 C, aryl-C), 128.7 (+, 2 C, aryl-C), 131.9 (+, aryl-C), 146.8 (–, aryl-C), 161.5 (–, CN-C), 168.2 (–, CO-C). – MS (70 eV), *m/z* (%): 344/342 (6/20) [M^+], 200 (55), 173 (100), 172 (58), 105 (54). – $C_{18}H_{15}ClN_2O_3$ (342.8): calcd. C 63.07, H 4.41, N 8.17; found C 63.32, H 4.18, N 8.02.

General procedure for synthesis of Oxazoline benzoxazole derivatives (Mitsunabu reaction) (GP 10): To a solution of the the above amides (**68e-h)** and Ph_3P (2.2 equiv.) in 10 mL of dry THF was added drop wise a solution of DEAD (2.2 equiv.) in an ice bath. The resulting solution was stirred at 20 °C for 10 h. This reaction mixture was taken in Et_2O (25 mL), H_2O was added, the organic layer was separated. The aq. layer was extracted with Et_2O (2 × 25 mL), the combined etheral layer was dried over $MgSO_4$, concentrated and purified by column chromatography to yield the corresponding benzooxazoles.

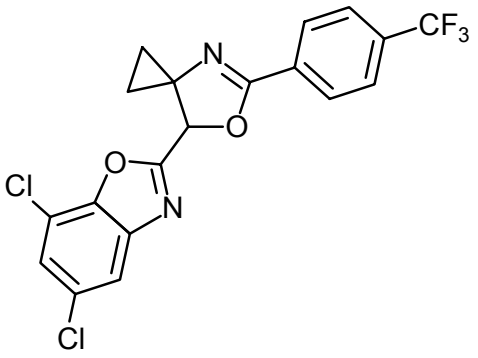
5-Chloro-2-[5-(4-trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl]-benzooxazole (**69a**): The crude product obtained from (**68e**, 205mg, 0.50 mmol), Ph_3P (288 mg, 1.10 mmol) and DEAD (174 mg, 1.10 mmol) according to GP 10, was purified by column chromatography (R_f = 0.40, Pentane/Et_2O = 5:1) to yield 162 mg (83%) of **69a** as a white solid, m.p. = 129 °C. – IR (KBr): ν = 3105 cm^{-1}, 1652, 1453, 1324, 1173, 1130, 1122, 857. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.59–0.66 (m, 1 H, cPr-H), 1.00–1.12 (m, 1 H, cPr-H), 1.21–1.32 (m, 1 H, cPr-H), 1.38–1.47 (m, 1 H, cPr-H), 5.74 (s, 1 H, CH), 7.33 (dd, ^3J = 8.7 Hz, ^4J = 1.87 Hz, 1 H, aryl-H), 7.44 (d, ^3J = 8.7 Hz, 1 H, aryl-H), 7.65 (d, ^3J = 8.1 Hz, 2 H, aryl-H), 7.71 (s, 1 H, aryl-H), 8.08 (d, ^3J = 8.1 Hz, 2 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.3 (–, cPr-C), 14.9 (–, cPr-C), 54.4 (–, cPr-C), 78.0 (+, CH-C), 111.9 (+, aryl-C), 120.5 (+, aryl-C), 123.2 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 125.5 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 125.6 (+, aryl-C), 128.4 (+, 2 C, aryl-C), 130.1 (–, aryl-C), 130.4 (–, aryl-C), 132.7 (–, q, $^2J_{C\text{-}F}$ = 32.1 Hz, aryl-C), 141.5 (–, aryl-C), 149.5 (–, aryl-C), 162.0 (–, CN-C), 163.3 (–, CN-C). – MS (DCI), *m/z* (%): 393 (100) [M^+ + H]. – $C_{19}H_{12}ClF_3N_2O_2$ (392.8): calcd. C 58.10, H 3.08, N 7.13; found C 58.31, H 2.94, N 6.99.



5-(Trifluoromethoxy)-2-[5-(4-trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl]-benzooxazole (**69b**): The crude product obtained from (**68f**, 91mg, 0.20 mmol), Ph_3P (115 mg, 0.44 mmol) and DEAD (77 mg, 0.44 mmol) according to GP 10 was purified by column chromatography (R_f = 0.42, Pentane/Et_2O = 5:1) to yield 72 mg (81%) of **69b** as white solid, m.p. = 105 °C. – IR (KBr): ν = 3093 cm^{-1}, 1651, 1569, 1475, 1348, 1255, 1160, 810. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.20–0.30 (m, 1 H, cPr-H), 0.98–1.12 (m, 1 H, cPr-H), 1.23–1.34 (m, 1 H, cPr-H), 1.39–1.50 (m, 1 H, cPr-H), 5.74 (s, 1 H, CH), 7.20–7.29 (m, 1 H, aryl-H), 7.43 – 7.58 (m, 1 H, aryl-H), 7.61 (s, 1 H, aryl-H), 7.68 (d, ^3J = 8.0 Hz, 2 H, aryl-H), 8.09 (d, ^3J = 8.0 Hz, 2 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.3 (–, cPr-C), 14.9 (–, cPr-C), 54.4 (–, cPr-C), 78.0 (+, CH-C), 111.7 (+, aryl-C), 113.7 (+, aryl-C), 115.4 (–, q, $^1J_{C\text{-}F}$ = 234 Hz, CF_3), 119.7 (+, aryl-C), 122.1 (–, aryl-C), 125.5 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 128.4 (+, 2 C, aryl-C), 130.1 (–, aryl-C), 133.2 (+, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 141.2 (–, aryl-C), 149.2 (–, aryl-C), 162.0 (–, CN-C), 163.4 (–,CN-C). – MS (70 eV), *m/z* (%): 442 (80) [M^+], 441 (100), 173 (97), 145 (60). – $C_{20}H_{12}F_6N_2O_3$ (442.3): calcd. C 54.31, H 2.73, N 6.33; found C 54.37, H 2.92, N 6.18.

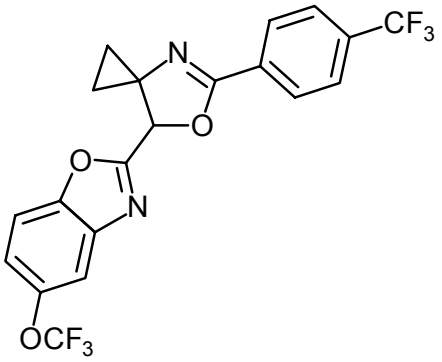


5,7-(Dichloro)-2-[5-(4-trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl]-benzo-oxazole (**69c**): The crude product obtained from (**68g**, 125mg, 0.28 mmol), Ph_3P (161 mg, 0.62 mmol) and DEAD (108 mg, 0.62 mmol) according to GP 10 was purified by column chromatography (R_f = 0.45, Pentane/Et_2O 5:1), to yield 105 mg (88%) of **69c** as colourless solid, m.p. = 120 °C. – IR (KBr): ν = 3074 cm^{-1}, 1657, 1562, 1328, 1348, 1167, 1119, 848. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.63–0.75 (m, 1 H, cPr-H), 1.02–1.13 (m, 1 H, cPr-H), 1.26–1.37 (m, 1 H, cPr-H), 1.01–1.50 (m, 1 H, cPr-H), 5.77 (s, 1 H, CH), 7.39 (d, ^4J = 2.4 Hz, 1 H, aryl-H), 7.62 (d, ^4J = 2.4 Hz, 1 H, aryl-H), 7.69 (d, ^3J = 8.0 Hz, 1 H, aryl-H), 8.09 (d, ^3J = 8.0 Hz, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.5 (–, cPr-C), 14.9 (–, cPr-C), 54.5 (–, cPr-C), 77.7 (+, CH-C), 117.0 (–, aryl-C), 119.2 (+, aryl-C), 123.8 (–, q, $^1J_{C\text{-}F}$ = 262 Hz, CF_3), 125.5 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 126.4 (+, aryl-C), 128.5 (+, 2 C, aryl-C), 130.1 (–, aryl-

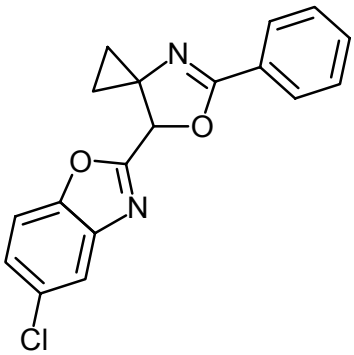


C), 130.7 (–, aryl-C), 133.7 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 142.3 (–, aryl-C), 146.4 (–, aryl-C), 161.9 (–, CN-C), 163.7 (–,CN-C). – MS (70 eV), *m/z* (%): 328/326 (24/16) [M^+], 327/325 (39/28), 173 (100), 145 (65).

5-(Trifluoromethyl)-2-[5-(4-trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl]-benzooxazole (**69d**): The crude product obtained from (**68h**, 105mg, 0.24 mmol), Ph_3P (136 mg, 0.52 mmol) and DEAD (90 mg, 0.52 mmol) according to GP 10 was purified by column chromatography (R_f = 0.40 Pentane/Et_2O = 5:1) to yield 85 mg (81%) of **69d** as solid m.p. = 145 °C. – IR (KBr): ν = 3075 cm^{-1}, 3046, 1650, 1628, 1579, 1439, 1336, 1187, 1072, 815. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.60–0.72 (m, 1 H, cPr-H), 1.02–1.14 (m, 1 H, cPr-H), 1.23–1.34 (m, 1 H, cPr-H), 1.40–1.52 (m, 1 H, cPr-H), 5.78 (s, 1 H, CH), 7.58–7.66 (m, 2 H, aryl-H), 7.73 (d, ^3J = 8.1 Hz, 2 H, aryl-H), 8.02 (s, 1 H, aryl-H), 8.11 (d, ^3J = 8.1 Hz, 2 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ =11.3 (–, cPr-C), 15.0 (–, cPr-C), 54.4 (–, cPr-C), 77.9 (+, CH-C), 111.7 (+, aryl-C), 118.4 (+, q, $^3J_{C\text{-}F}$ = 4.5 Hz, aryl-C), 123.2 (+, q, $^3J_{C\text{-}F}$ = 4.5 Hz, aryl-C), 124.2 (–, q, $^1J_{C\text{-}F}$ = 268 Hz, CF_3), 124.8 (–, q, $^1J_{C\text{-}F}$ = 264 Hz, CF_3), 125.5 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 127.8 (–, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 128.5 (+, 2 C, aryl-C), 130.1 (–, aryl-C), 133.2 (–, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 140.6 (–, aryl-C), 152.6 (–, aryl-C), 162.0 (–, CN-C), 163.7 (–, CN-C). – MS (DCI), *m/z* (%): 870 (1) [2 M + NH_4^+], 853 (18) [2 M + H^+], 444 (12) [M + NH_4^+], 427 (100) [M + H^+]. – $C_{20}H_{12}F_6N_2O_2$ (426.3): calcd. C 56.35, H 2.84, N 6.57; found C 56.21, H 2.79, N 6.62.

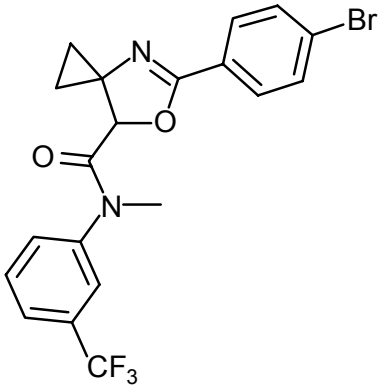


5-Chloro-2-(5-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl)-benzooxazole (**69e**): the crude product obtained from 5-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (5-chloro-2-hydroxy-phenyl)-amide (**68e**, 103mg, 0.3 mmol), Ph_3P (173 mg, 0.66 mmol) and DEAD (115 mg, 0.66 mmol) according to GP 10 was purified by column chromatography (R_f = 0.35, Pentane/Et_2O = 5:1) to yield 83 mg (85%) of product **69e** as white solid, m.p. = 129 °C. – IR (KBr): ν = 3077 cm^{-1}, 2971, 1653, 1569, 1427, 1335, 1293, 1078, 698. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.54–0.63 (m, 1 H, cPr-H), 0.98–1.06 (m, 1 H, cPr-H), 1.18–



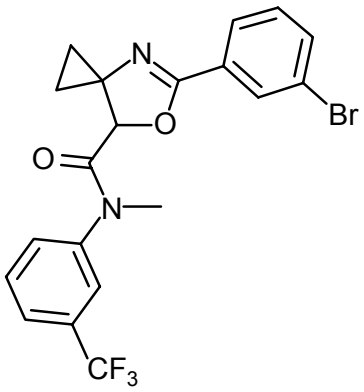
1.28 (m, 1 H, cPr-H), 1.36–1.45 (m, 1 H, cPr-H), 5.70 (s, 1 H, CH), 7.28–7.39 (m, 1 H, aryl-H), 7.40 –7.57 (m, 4 H, aryl-H), 7.69 (s, 1 H, aryl-H), 7.95–8.02 (m, 2 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.1 (–, cPr-C), 14.7 (–, cPr-C), 54.2 (–, cPr-C), 77.8 (+, CH-C), 111.9 (+, aryl-C), 120.4 (+, aryl-C), 126.1 (+, aryl-C), 126.8 (–, aryl-C), 128.1 (+, 2 C, aryl-C), 128.5 (+, 2 C, aryl-C), 130.2 (–, aryl-C), 131.6 (+, aryl-C), 141.5 (–, aryl-C), 149.5 (–, aryl-C), 163.2 (–, CN-C), 163.7 (–, CN-C). – MS (70 eV), *m/z* (%): 325/323 (2/8) [M^+], 172 (16), 155 (100), 105 (18), 91 (82). – $C_{18}H_{13}ClN_2O_2$ (324.8): calcd. C 66.57, H 4.03, N 8.63; found C 66.58, H 3.84, N 8.55.

5-(4-Bromo-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoro-methyl-phenyl)-amide (**70a**): To a solution of 5-(4-bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (3-trifluoromethyl-phenyl)-amides (**68a**) (1.50 g, 3.42 mol) in 50 mL acetone was added Me_2SO_4 (657 mg, 5.13 mmol) and K_2CO_3 (1.42 g, 10.3 mmol) and the resulting reaction mixture was refluxed for 16 h. After cooling the crude product was filtered through SiO_2 (eluent Et_2O, 3 × 4 cm, 20 g Si_2O) and the product purified by column chromatography (R_f = 0.35, Pentane/Et_2O = 1:1) to yield 1.43 g (92%) of **70a** as a white solid, m.p. = 89–90 °C. – IR (KBr): ν = 3073 cm^{-1}, 2924, 1655, 1507, 1333, 1180, 1128, 936, 833, 794. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.72–0.84 (m, 1 H, cPr-H), 1.06–1.39 (m, 3 H, cPr-H), 3.29 (s, 3 H, CH_3), 5.07 (s, 1 H, CH), 7.21–7.48 (m, 8 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.7 (–, cPr-C), 39.0 (+, CH_3), 53.7 (–, cPr-C), 80.9 (+, CH-C), 119.8 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 124.3 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.5 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.9 (–, aryl-C), 129.1 (+, 2 C, aryl-C), 130.3 (+, aryl-C), 131.2 (+, 2 C, aryl-C), 132.0 (–, q, $^2J_{C\text{-}F}$ = 33.0 Hz, aryl-C), 143.1 (–, aryl-C), 161.6 (–, CN-C), 167.8 (–, CO-C). – MS (70 eV), *m/z* (%): 454/452 (7/9) [M^+], 280/278 (34/36), 202 (100), 174 (86).



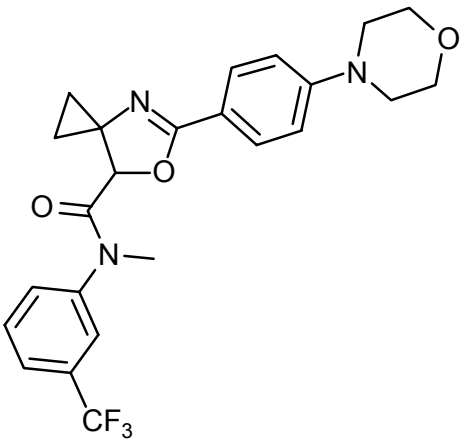
5-(3-Bromo-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoro-methyl-phenyl)-amide (**70b**): The crude product obtained from **68b** (220 mg, 0.5 mol), Me_2SO_4 (96 mg, 0.75 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in 10 mL of acetone according to the method described for **70a** was purified by column chromatography (R_f = 0.2, Pentane/Et_2O = 2:1) to yield

203 g (89%) of **70b** as white solid, m.p. = 110 °C. – IR (KBr): ν = 2956 cm^{-1}, 1663, 1340, 1255, 1124, 1061, 799. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.75–0.87 (m, 1 H, cPr-H), 1.10–1.38 (m, 3 H, cPr-H), 3.31 (s, 3 H, CH_3), 5.07 (s, 1 H, CH), 7.08–7.17 (m, 1 H, aryl-H), 7.21–7.54 (m, 7 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ =12.1 (–, cPr-C), 14.8 (–, cPr-C), 39.1 (+, CH_3), 53.7 (–, cPr-C), 80.9 (+, CH-C), 122.0 (–, aryl-C), (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.2 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 126.2 (+, aryl-C), 128.2 (+, aryl-C), 129.6 (+, aryl-C), 130.3 (+, aryl-C), 131.5 (+, aryl-C), 131.9 (–, aryl-C), 134.2 (–, aryl-C), 143.1 (–, aryl-C), 161.1 (–, CN-C), 167.8 (–, CO-C). – MS (70 eV), *m/z* (%): 454/452 (21/19) [M^+], 280/278 (43/42), 202 (100), 175 (80), 174 (60). – $C_{20}H_{16}BrF_3N_2O_2$ (453.3): calcd. C 53.00, H 3.56, N 6.18; found C 53.28, H 3.41, N 6.27.



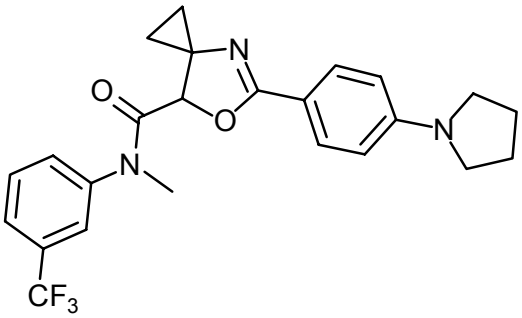
General procedure for amination of aryl bromide in 70 (GP 11) (Buchwald-Hartwig Reaction): To an oven-dried Schlenk flask purged with nitrogen, was taken $Pd_2(dba)_3$ (2.0 mol%) and (±)-BINAP (3.0 mol%) in 5 mL of toluene. The mixture was heated to 80 °C with stirring for 5 min to dissolve the BINAP. After cooling, the aryl-bromide (**70a** or **70b**), the corresponding amine and NaO*t*Bu was added and the mixture was heated to 80 °C for 16 h. the mixture was cooled to room temperature, diluted with Et_2O (25 mL), filtered, and concentrated in vacuo. The crude product was then purified by column chromatography.

5-(4-Morpholin-4-yl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71a**): The crude product obtained from **70a** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (3.65 mg), (±)-BINAP (3.74 mg), morpholine (26.0 mg, 0.30 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) according to GP 12 was purified by column chromatography (R_f = 0.25, Et_2O) to yield 65 mg (71%) of product which crystallized from Et_2O at 0 °C to give the product **71a** as a white solid, m.p. = 159–160 °C. – IR (KBr): ν = 3084 cm^{-1}, 2969, 2864, 1655, 1607, 1521, 1335, 1228, 1119. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.62–0.83 (m, 1 H, cPr-H), 0.98–1.33 (m, 3 H, cPr-H), 3.02–3.20 (m, 2

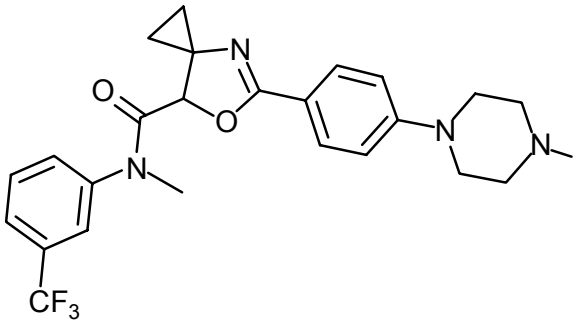


H), 3.28 (s, 3 H, CH_3), 3.66–3.91 (m, 2 H), 4.97 (s, 1 H, CH), 6.62 (d, ^3J = 8.2 Hz, 2 H, aryl-H) 7.03–7.50 (m, 6 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.8 (–, cPr-C), 14.4 (–, cPr-C), 39.0 (+, CH_3), 48.1 (–, 2 C, CH_2-C), 53.4 (–, cPr-C), 66.6 (–, 2 C, CH_2-C), 80.8 (+, CH-C), 113.6 (+, 2 C, aryl-C), 117.0 (–, aryl-C), 123.3 (–, q, $^1J_{C\text{-}F}$ = 264 Hz, CF_3), 124.2 (+, q, $^3J_{C\text{-}F}$ = 4.3 Hz, aryl-C), 124.3 (+, q, $^3J_{C\text{-}F}$ = 3.2 Hz, aryl-C), 129.0 (+, 2 C, aryl-C), 130.1 (+, aryl-C), 131.8 (–, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 143.2 (–, aryl-C), 153.1 (–, aryl-C), 162.4 (–, CN-C), 168.2 (–, CO-C). – MS (70 eV), *m/z* (%): 459 (22) [M^+], 285 (16), 257 (20), 190 (100).

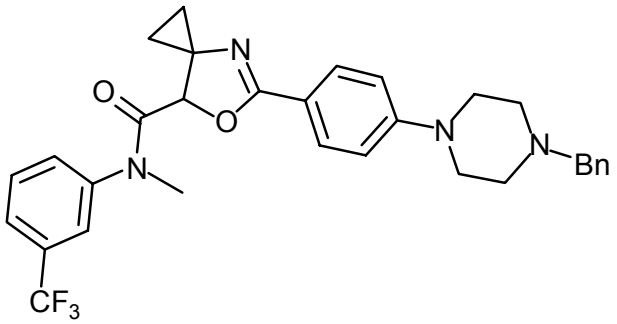
5-(4-Pyrrolidin-1-yl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71b**): The crude product obtained from **70a** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (3.65 mg), (±)-BINAP (3.74 mg), pyrrolidine (28 mg, 0.40 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified by column chromatography (R_f = 0.42, Et_2O) to yield 80 mg (90%) of **71b** as white solid, m.p. = 152–153 °C. – IR (KBr): ν = 3083 cm^{-1}, 2961, 2852, 1637, 1607, 1527, 1387, 1334, 1130, 1061. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.72–0.80 (m, 1 H, cPr-H), 1.03–1.14 (m, 1 H, cPr-H), 1.18–1.34 (m, 2 H, cPr-H), 1.94–2.02 (m, 4 H), 3.11–3.35 (m, 7 H), 4.98 (s, 1 H, CH), 6.32 (d, 2 H, ^3J = 8.1 Hz, aryl-H), 7.18–7.38 (m, 5 H, aryl-H), 7.47 (s, 1 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.7 (–, cPr-C), 14.3 (–, cPr-C), 25.4 (–,2 C, CH_2-C), 39.0 (+, CH_3), 47.4 (–, 2 C, CH_2-C), 53.3 (–, cPr-C), 80.8 (+, CH-C), 110.5 (+, 2 C, aryl-C), 112.8 (–, aryl-C), 123.2 (–, q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 123.9 (+, q, $^3J_{C\text{-}F}$ = 3.2 Hz, aryl-C), 124.3 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 129.2 (+, 2 C, aryl-C), 130.1 (+, aryl-C), 131.8 (–, q, $^2J_{C\text{-}F}$ = 32.1 Hz, aryl-C), 143.2 (–, aryl-C), 149.7 (–, aryl-C), 163.1 (–, CN-C), 168.4 (–, CO-C). – MS (70 eV), *m/z* (%): 443 (16) [M^+], 241 (18), 213 (22), 174 (100). – $C_{24}H_{24}F_3N_3O_2$ (443.5): calcd. C 65.00, H 5.45, N 9.48; found C 64.69, H 5.16, N 9.22.



5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71c**): The crude product obtained from **70a** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (3.65 mg), (±)-BINAP (3.74 mg), *N*-methylpiperazine (40 mg, 0.40 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified by column chromatography (R_f = 0.20, CH_2Cl_2/ MeOH = 10:1) to yield 55 mg (59%) of **71c** as white solid, m.p. = 147–148 °C. – IR (KBr): ν = 2948 cm^{-1}, 2843, 2794, 1653, 1644, 1611, 1520, 1330, 1233, 1133, 1068. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.69–0.81 (m, 1 H, cPr-H), 1.05–1.14 (m, 1 H, cPr-H), 1.18–1.35 (m, 2 H, cPr-H), 2.35 (s, 3 H, CH_3), 2.51–3.58 (m, 4 H, NCH_2), 3.20–3.28 (m, 4 H, NCH_2), 3.30 (s, 3 H, CH_3), 4.98 (s, 1 H, CH), 6.70 (d, ^3J = 8.7 Hz, 2 H, aryl-H), 7.15–7.40 (m, 5 H, aryl-H), 7.44 (s, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.8 (–, cPr-C), 14.4 (–, cPr-C), 39.0 (+, CH_3), 46.1 (+, CH_3), 47.7 (–, 2 C, CH_2-C), 53.4 (–, cPr-C), 54.7 (–, 2 C, CH_2-C), 80.8 (+, CH-C), 113.9 (+, 2 C, aryl-C), 116.5 (–, aryl-C), 123.2 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 124.1 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 124.3 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 128.9 (+, 2 C, aryl-C), 130.1 (+, aryl-C), 131.8 (–, q, $^2J_{C\text{-}F}$ = 32.1 Hz, aryl-C), 143.1 (–, aryl-C), 153.0 (–, aryl-C), 162.4 (–, CN-C), 168.3 (–, CO-C). – MS (70 eV), *m/z* (%): 472 (22) [M^+], 270 (19), 242 (16), 203 (100).

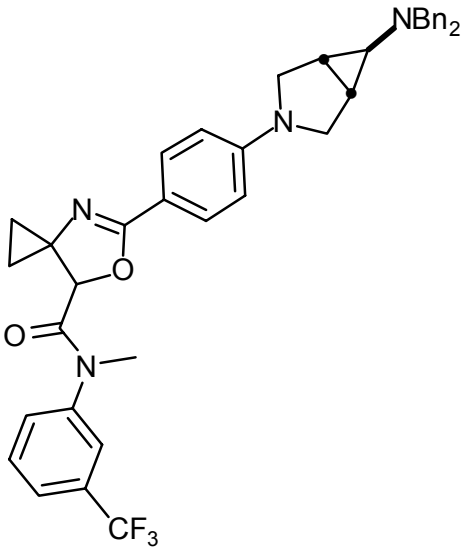


5-[4-(4-Benzyl-piperazin-1-yl)-phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71d**): The crude product obtained from **70a** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (3.65 mg), (±)-BINAP (3.74 mg), *N*-benzylpiperazine (53 mg, 0.30 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified by column chromatography (R_f = 0.30, DCM/MeOH = 10:1) to yield 68 mg (62%) of **71d** as white solid, m.p. = 144–146 °C. – IR (KBr): ν = 2945 cm^{-1}, 2830, 2814, 1653, 1611, 1520, 1333, 1134, 700. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.71–0.82 (m, 1 H, cPr-H), 1.04–1.14 (m, 1 H, cPr-H), 1.18–1.37 (m, 2 H, cPr-H), 2.54–2.62 (m, 4 H, NCH_2), 3.18–3.27 (m, 4 H, NCH_2), 3.29 (s, 3 H, CH_3), 3.57 (s, 2 H, Bn-H), 5.00 (s, 1 H, CH), 6.67 (d, ^3J = 8.7 Hz, 2 H, aryl-



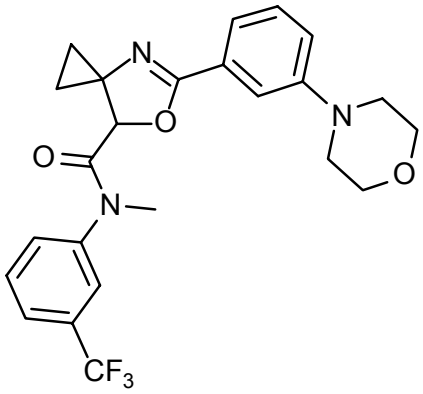
H), 7.14–7.39 (m, 10 H, aryl-H), 7.41 (s, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.8 (–, cPr-C), 14.4 (–, cPr-C), 39.0 (+, CH_3), 47.8 (–, 2 C, *N*CH_2-C), 52.7 (–, 2 C, *N*CH_2-C), 53.4 (–, cPr-C), 62.9 (–, Bn-C), 80.8 (+, CH-C), 113.8 (+, 2 C, aryl-C), 116.4 (–, aryl-C), 123.2 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 124.1 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 124.2 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 127.2 (+, aryl-C), 128.3 (+, 2 C, aryl-C), 128.9 (+, aryl-C), 129.2 (+, 2 C, aryl-C), 130.1 (+, aryl-C), 130.2 (+, aryl-C), 131.8 (–, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 137.6 (–, aryl-C), 143.2 (–, aryl-C), 153.1 (–, aryl-C), 162.5 (–, CN-C), 168.3 (–, CO-C). – MS (70 eV), *m/z* (%): 548 (62) [M^+], 279 (58), 185 (18), 91 (100) [$C_7H_7^+$]. – $C_{31}H_{31}F_3N_4O_2$ (541.6): calcd. C 67.87, H 5.71, N 10.21; found C 67.66, H 5.85, N 10.07.

5-[4-(6-Dibenzylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71e**): The crude product obtained from **70a** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (3.65 mg), (±)-BINAP (3.74 mg), *exo*-6-(*N*,*N*-dibenzylamino)-3-azabicyclo[3,1,0]hexane (83 mg, 0.30 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified in column chromatography (R_f = 0.45, Et_2O) to yield 87 mg (67%) of **71e** as pale yellow solid, m.p. = 96 °C. – IR (KBr): ν = 3061 cm^{-1}, 2841, 1684, 1611, 1524, 1388, 1332, 1186, 1130, 699. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.70–0.80 (m, 1 H, cPr-H), 1.02–1.14 (m, 1 H, cPr-H), 1.16–1.34 (m, 2 H, cPr-H), 1.44–1.58 (m, 2 H), 1.61–1.64 (m, 1 H), 3.12–3.20 (m, 2 H, *N*CH_2-H), 3.24–3.35 (m, 5 H, CH_3 and *N*CH_2-H), 3.68 (s, 4 H, Bn-H), 5.00 (s, 1 H, CH), 6.24 (d, 2 H, ^3J = 8.2 Hz, aryl-H), 7.18–7.38 (m, 15 H, aryl-H), 7.45 (s, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 11.8 (–, cPr-C), 14.3 (–, cPr-C), 25.9 (+, CH-C), 26.0 (+, CH-C), 39.0 (+, CH_3), 48.6 (+, CH-C), 49.7 (–, 2 C, CH_2-C), 53.4 (–, cPr-C), 59.0 (–, 2 C, Bn-C), 80.7 (+, CH-C), 110.9 (+, 2 C, aryl-C), 113.7 (–, aryl-C), 123.1 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 123.9 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 124.3 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 127.1 (+, aryl-C), 128.1 (+, 2 C, aryl-C), 129.0 (+, aryl-C), 129.4 (+, aryl-C), 130.1 (+, aryl-C), 130.2 (+, aryl-C), 131.8 (–, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 138.6 (–, aryl-C), 143.2 (–, aryl-C), 149.6 (–, aryl-C), 162.9 (–, CN-C), 168.4 (–, CO-C). – MS (70 eV), *m/z* (%):

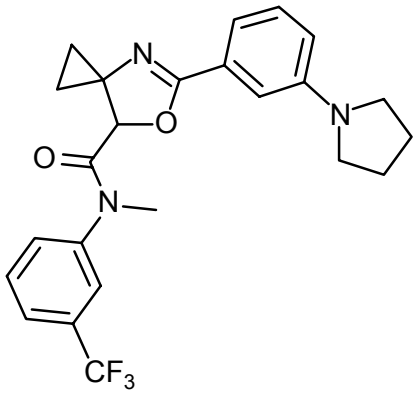


650 (19) [M^+], 559 (29) [$M^+ - C_7H_7$], 249 (34), 158 (57), 91 (100) [$C_7H_7^+$]. – $C_{39}H_{37}F_3N_4O_2$ (650.7): calcd. C 71.98, H 5.73, N 8.61; found C 71.75, H 5.57, N 8.79.

5-(3-Morpholino-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluromethyl-phenyl)-amide (**71f**): The crude product obtained from **70b** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (9.1 mg, 5 mol%), (±)-BINAP (9.3 mg, 7.5 mol%), morpholine (26 mg, 0.30 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified by column chromatography (R_f = 0.25, Et_2O) to yield 75 mg (82%) of **71f** which crystallized from Pentane/Et_2O at 0 °C to get white solid, m.p. = 122 °C. – IR (KBr): ν = 2959 cm^{-1}, 2924, 2853, 1684, 1653, 1599, 1331, 1265, 1220. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.72–0.80 (m, 1 H, cPr-H), 1.04–1.14 (m, 1 H, cPr-H), 1.21–1.38 (m, 2 H, cPr-H), 3.08 (d, ^3J = 4.8 Hz, 4 H), 3.30 (s, 3 H, CH_3), 3.81 (d, ^3J = 4.8 Hz, 4 H), 5.00 (s, 1 H, CH), 6.88–7.00 (m, 2 H, aryl-H), 7.03–7.18 (m, 2 H, aryl-H), 7.20–7.40 (m, 3 H, aryl-H), 7.42 (s, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.6 (–, cPr-C), 38.9 (+, CH_3), 49.1 (–, 2 C, CH_2-C), 53.5 (–, cPr-C), 66.8 (–, 2 C, CH_2-C), 80.6 (+, CH-C), 114.5 (+, aryl-C), 118.6 (+, aryl-C), 123.3 (–, q, $^1J_{C\text{-}F}$ = 274 Hz, CF_3), 123.9 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 124.4 (+, q, $^3J_{C\text{-}F}$ = 3.4 Hz, aryl-C), 127.2 (–, aryl-C), 128.7 (+, aryl-C), 130.2 (+, aryl-C), 131.0 (–, q, $^2J_{C\text{-}F}$ = 32.2 Hz, aryl-C), 143.1 (–, aryl-C), 150.9 (–, aryl-C), 162.7 (–, CN-C), 168.1 (–, CO-C). – MS (DCI), *m/z* (%): 919 (2 M + H^+), 460 (100) [M + H^+].

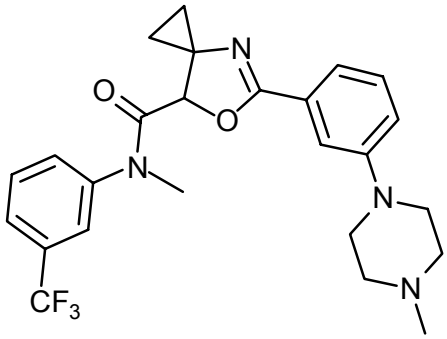


5-(3-Pyrrolidin-1-yl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoro-methylphenyl)-amide (**71g**): The crude product obtained from **70b** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (9.1 mg, 5 mol%), (±)-BINAP (9.3 mg, 7.5 mol%), pyrrolidin (26 mg, 0.30 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified by column chromatography (R_f = 0.40, Et_2O) to yield 65 mg (73%) of **71g** which crystallized from Pentane/Et_2O at 0 °C to give white solid, m.p. = 122 °C. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.71–0.80 (m, 1 H, cPr-H), 1.06–1.15 (m, 1 H, cPr-H), 1.21–1.39 (m, 2 H, cPr-H), 1.92–2.02 (m, 4 H), 3.18–3.30 (m, 4 H), 3.33 (s, 3 H, CH_3),

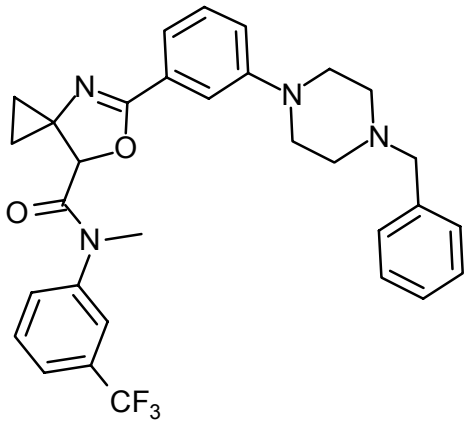


5.03 (s, 1 H, CH), 6.54–6.61 (m, 1 H, aryl-H), 6.69–6.82 (m, 2 H, aryl-H), 7.03–7.16 (m, 1 H, aryl-H), 7.22–7.40 (m, 3 H, aryl-H), 7.46 (s, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.5 (–, cPr-C), 25.4 (–, 2 C, CH_2-C), 38.9 (+, CH_3), 47.6 (–, 2 C, CH_2-C), 53.5 (–, cPr-C), 80.6 (+, CH-C), 110.5 (+, aryl-C), 114.7 (+, aryl-C), 123.3 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 123.9 (+, q, $^3J_{C\text{-}F}$ = 3.5 Hz, aryl-C), 124.4 (+, q, $^3J_{C\text{-}F}$ = 3.5 Hz, aryl-C), 127.0 (–, aryl-C), 128.5 (+, aryl-C), 130.2 (+, aryl-C), 131.9 (–, q, $^2J_{C\text{-}F}$ = 32.5 Hz, aryl-C), 143.1 (–, aryl-C), 147.5 (–, aryl-C), 163.3 (–, CN-C), 168.2 (–, CO-C). – MS (70 eV), *m/z* (%): 443 (23) [M^+], 241 (62), 174 (100), 84 (68).

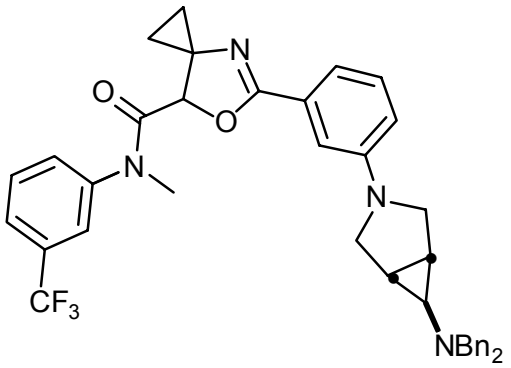
5-[3-(4-Methyl-piperazin-1-yl)-phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71h**): The crude product obtained from **70b** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (9.1 mg, 5 mol%), (±)-BINAP (9.3 mg, 7.5 mol%), piperonyl (100 mg, 1.00 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified by column chromatography (R_f = 0.25, DCM/MeOH = 10:1) to yield 12 mg (13%) of **71h**. – IR (KBr): ν = 2925 cm^{-1}, 1684, 1653, 1600, 1457, 1331, 1131. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.63–0.80 (m, 1 H, cPr-H), 0.99–1.12 (m, 1 H, cPr-H), 1.18–1.31 (m, 2 H, cPr-H), 2.29 (s, 3 H, CH_3), 2.49 (t, ^3J = 4.9 Hz, 4 H), 3.14 (t, ^3J = 4.9 Hz, 4 H), 3.24 (s, 3 H, CH_3), 4.98 (s, 1 H, CH), 6.83–6.96 (m, 2 H, aryl-H), 7.01–7.17 (m, 2 H, aryl-H), 7.18–7.37 (m, 3 H, aryl-H), 7.39 (s, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.0 (–, cPr-C), 38.9 (+, CH_3), 46.1 (+, CH_3), 47.8 (–, 2 C, CH_2-C), 53.6 (–, cPr-C), 55.0 (–, 2 C, CH_2-C), 80.7 (+, CH-C), 114.8 (+, aryl-C), 118.9 (+, aryl-C), 119.0 (+, aryl-C), 123.0 (–, q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 124.0 (+, q, $^3J_{C\text{-}F}$ = 3.5 Hz, aryl-C), 124.4 (+, q, $^3J_{C\text{-}F}$ = 3.5 Hz, aryl-C), 127.1 (–, aryl-C), 128.6 (+, aryl-C), 130.2 (+, aryl-C), 130.3 (+, aryl-C), 132.0 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 143.1 (–, aryl-C), 150.8 (–, aryl-C), 162.8 (–, CN-C), 168.1 (–, CO-C). – MS (70 eV), *m/z* (%): 472 (100) [M^+], 198 (28), 270 (65), 203 (60).



5-[3-(4-Benzyl-piperazin-1-yl)-phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71i**): The crude product obtained from **70b** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (9.1 mg, 5 mol%), (±)-BINAP (9.3 mg, 7.5 mol%), N-benzylpiperazine (70.4 mg, 0.40 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified by column chromatography (R_f = 0.25, DCM/MeOH = 10:1) to yield 13 mg (12%) of **71i** as a viscous oil. – IR (KBr): ν = 2962 cm^{-1}, 2925, 2855, 1675, 1653, 1457, 1331, 1167, 1069, 701. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.70–0.85 (m, 1 H, cPr-H), 1.05–1.15 (m, 1 H, cPr-H), 1.20–1.35 (m, 2 H, cPr-H), 2.63–2.78 (m, 4 H, NCH_2), 3.18–3.24 (m, 4 H, NCH_2), 3.25 (s, 3 H, CH_3), 3.67 (s, 2 H, Bn-H), 5.01 (s, 1 H, CH), 6.87–7.00 (m, 2 H, aryl-H), 7.08–7.17 (m, 2 H, aryl-H), 7.27–7.45 (m, 9 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.6 (–, cPr-C), 38.9 (+, CH_3), 48.4 (–, 2 C, NCH_2-C), 52.6 (–, 2 C, NCH_2-C), 53.6 (–, cPr-C), 62.5 (–, Bn-C), 80.7 (+, CH-C), 115.1 (+, aryl-C), 119.0 (+, aryl-C), 119.3 (+, aryl-C), 123.6 (–, q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 123.9 (+, aryl-C), 124.4 (+, aryl-C), 128.9 (+, aryl-C), 127.0 (–, aryl-C), 127.8 (+, aryl-C), 128.5 (+, aryl-C), 128.7 (+, aryl-C), 129.7 (+, aryl-C), 130.3 (+, aryl-C), 132.0 (–, q, $^2J_{C\text{-}F}$ = 33.1 Hz, aryl-C), 143.1 (–, aryl-C), 150.6 (–, aryl-C), 162.7 (–, CN-C), 168.1 (–, CO-C). – MS (70 eV), *m/z* (%): 548 (100) [M^+], 346 (31), 146 (39), 91 (83) [$C_7H_7^+$].



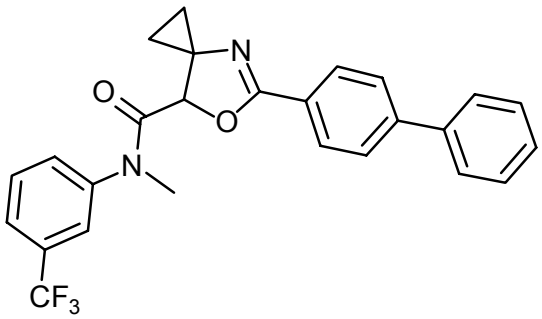
5-[3-(6-Dibenzylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71j**): The crude product obtained from **70b** (90.6 mg, 0.20 mmol), $Pd_2(dba)_3$ (9.1 mg, 5 mol%), (±)-BINAP (9.3 mg, 7.5 mol%), *exo*-6-(*N*,*N*-dibenzylamino)-3-azabicyclo[3,1,0]hexane (139 mg, 0.50 mmol) and NaO*t*Bu (28.8 mg, 0.30 mmol) was purified in column chromatography (R_f = 0.40, Pentane/Et_2O = 1:2) to yield 105 mg (81%) of **71j** as pale-yellow solid, m.p. = 85–88 °C. – IR (KBr): ν = 3025 cm^{-1}, 2887, 2812, 1653, 1599, 1493, 1332, 1129, 699. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.74–0.85 (m, 1 H, cPr-H), 1.12–1.20 (m, 1 H, cPr-H), 1.22–1.40 (m, 2 H, cPr-H), 1.50–1.61 (m, 2 H), 1.71–1.79 (m, 1 H), 3.08–3.20 (m, 2 H,



NCH_2-H), 3.32–3.48 (m, 5 H, CH_3 and *N*CH_2-H), 3.73 (s, 4 H, Bn-H), 5.09 (s, 1 H, CH), 6.48–6.80 (m, 1 H, aryl-H), 6.72–6.93 (m, 2 H, aryl-H), 7.05–7.19 (m, 1 H, aryl-H), 7.24–7.47 (m, 13 H, aryl-H), 7.52 (s, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.5 (–, cPr-C), 26.0 (+, CH-C), 38.9 (+, CH_3), 48.3 (+, CH-C), 49.8 (–, 2 C, CH_2-C), 53.5 (–, cPr-C), 59.0 (–, 2 C, Bn-C), 80.5 (+, CH-C), 110.9 (+, aryl-C), 114.9 (+, aryl-C), 115.7 (+, aryl-C), 123.2 (–, q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 123.9 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.4 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 127.0 (+, 2 C, aryl-C), 128.1 (+, 4 C, aryl-C), 128.5 (+, aryl-C), 129.4 (+, 4 C, aryl-C), 130.2 (+, aryl-C), 131.9 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 138.7 (–, 2 C, aryl-C), 143.3 (–, aryl-C), 147.4 (–, aryl-C), 163.1 (–, CN-C), 168.2 (–, CO-C). – MS (70 eV), *m/z* (%): 650 (17) [M^+], 559 (14) [M^+ – C_7H_7], 249 (19), 158 (18), 91 (100) [$C_7H_7^+$].

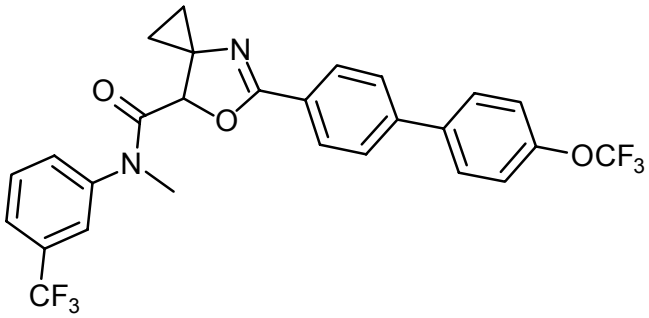
General procedure for reaction of aryl boronic acid with aryl-bromide (70) (The Suzuki reaction) (GP 13): To a 25 mL Schlenk flask $Pd(OAc)_2$ (4.5 mg, 10 mol%) and $P(Ph)_3$ (21 mg, 40 mol%) were taken in 5 mL of toluene. The mixture was degassed for 5 min. by bubbling nitrogen through it. To this solution **70a** (90.6 mg, 0.2 mmol), the corresponding boronic acid (0.30 mmol) and Na_2CO_3 (0.40 mmol, aq. 2 N) was added and the mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature, taken in Et_2O (25 ml), washed with water (10 mL) and the aq. layer was extracted with Et_2O (2 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography.

5-Biphenyl-4-yl-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**72a**): The crude product obtained from **70a**, phenyl boronic acid (36.5 mg) according to the GP 13 was purified by column chromatography (R_f = 0.30, pentane/Et_2O = 1:2), to yield 81 mg (90%) of **72a** as a white solid, m.p. = 136–137 °C. – IR (KBr): ν = 3081 cm^{-1}, 1660, 1643, 1334, 1128, 1067, 705. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.74–0.83 (m, 1 H, cPr-H), 1.03–1.38 (m, 3 H, cPr-H), 3.25 (s, 3 H, CH_3), 5.02 (s, 1 H, CH-H), 7.09–7.59 (m, 13 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.7 (–, cPr-C), 39.1 (+, CH_3), 53.7 (–, cPr-C), 81.0 (+, CH-C), 123.2 (–, q, $^1J_{C\text{-}F}$ = 262 Hz, CF_3),



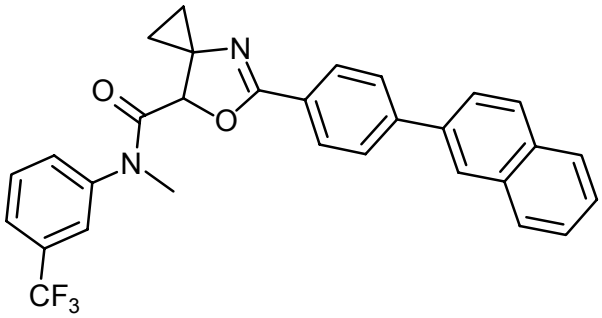
124.1 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.4 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 125.2 (–,aryl-C), 126.6 (+, 2 C, aryl-C), 127.1 (+, 2 C, aryl-C), 127.9 (+, aryl-C), 128.1 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 130.2 (+, aryl-C), 132.0 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 140.1 (–, aryl-C), 143.2 (–, aryl-C), 143.9 (–, aryl-C), 162.2 (–, CN-C), 168.0 (–, CO-C). – MS (70 eV), *m/z* (%): 450 (92) [M^+], 276 (91), 248 (61), 181 (100). – calcd. $C_{26}H_{21}F_3N_2O_2$ (450.5) C 69.33, H 4.70, N 6.22; found C 69.26, H 4.48, N 6.18.

5-(4'-Trifluoromethoxy-biphenyl-4-yl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**72b**): The crude product obtained from **70a**, 4-(trifluoromethoxy)phenyl boronic acid (66.5 mg) according to the GP 13 was purified by column chromatography (R_f = 0.26, pentane/Et_2O = 1:2), to yield 85 mg (80%) of **72b** as colourless solid, m.p. = 136–138 °C. – IR (KBr): ν = 2943 cm^{-1}, 1654, 1646, 1494, 1331, 1270, 1178, 1068.

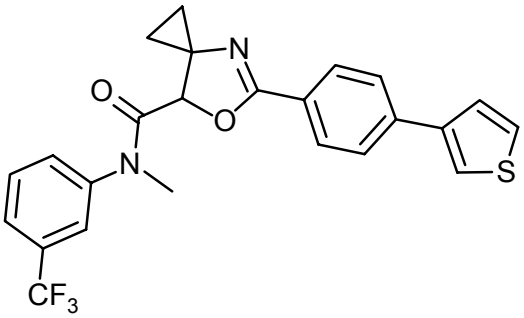


– ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.78–0.87 (m, 1 H, cPr-H), 1.12–1.40 (m, 3 H, cPr-H), 3.34 (s, 3 H, CH_3), 5.07 (s, 1 H, CH), 7.15–7.23 (m, 1 H, aryl-H), 7.28–7.32 (m, 3 H, aryl-H), 7.35–7.40 (m, 1 H, aryl-H), 7.41–7.49 (m, 3 H, aryl-H), 7.55–7.62 (m, 4 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.7 (–, cPr-C), 39.1 (+, CH_3), 53.7 (–, cPr-C), 80.9 (+, CH-C), 120.4 (–, q, $^1J_{C\text{-}F}$ = 235 Hz, CF_3), 121.3 (+, 2 C, aryl-C), 124.1 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.4 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 125.6 (–, aryl-C), 126.5 (+, 2 C, aryl-C), 128.2 (+, 2 C, aryl-C), 128.5 (+, 2 C, aryl-C), 130.2 (+, 2 C, aryl-C), 130.2 (+, aryl-C), 132.1 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 138.8 (–, aryl-C), 142.4 (–, aryl-C), 143.1 (–, aryl-C), 149.1 (–, aryl-C), 162.1 (–, CN-C), 168.0 (–, CO-C). – MS (70 eV), *m/z* (%): 534 (27) [M^+], 360 (43), 304 (32), 265 (100), 202 (76), 174 (86). – calcd. $C_{27}H_{20}F_6N_2O_2$ (534.5) C 60.68, H 3.77, N 5.24; found C 60.41, H 3.58, N 5.06.

5-(4-Naphthalen-2-yl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**72c**): The crude product obtained from **70a**, 4-naphthalyl boronic acid (51.5 mg) according to the GP 13 was purified by column chromatography (R_f = 0.24, pentane/Et_2O = 1:2), to yield 85 mg (85%) of **72c** as colourless solid, m.p. = 144 °C. – IR (KBr): ν = 3066 cm^{-1}, 1658, 1492, 1330, 1170, 1118, 1053, 818. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.73–0.84 (m, 1 H, cPr-H), 1.03–1.39 (m, 3 H, cPr-H), 3.24 (s, 3 H, CH_3), 5.02 (s, 1 H, CH), 7.11–7.38 (m, 3 H, aryl-H), 7.40–7.48 (m, 3 H, aryl-H), 7.52–7.60 (m, 4 H, aryl-H), 7.61–7.70 (m, 1 H, aryl-H), 7.74–7.90 (m, 3 H, aryl-H), 7.96–8.01 (m, 1 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.1 (–, cPr-C), 14.7 (–, cPr-C), 39.1 (+, CH_3), 53.7 (–, cPr-C), 80.9 (+, CH-C), 124.0 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.5 (+, q, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 125.1 (+, aryl-C), 125.2 (–, aryl-C), 126.1 (+, aryl-C), 126.3 (+, aryl-C), 126.5 (+, aryl-C), 126.8 (+, aryl-C), 127.7 (+, aryl-C), 128.2 (+, 2 C, aryl-C), 128.3 (+, 2 C, aryl-C), 128.6 (+, aryl-C), 130.3 (+, aryl-C), 132.1 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 132.9 (–, aryl-C), 133.6 (–, aryl-C), 137.4 (–, aryl-C), 143.6 (–, aryl-C), 143.8 (–, aryl-C), 162.1 (–, CN-C), 168.0 (–, CO-C). – MS (70 eV), *m/z* (%): 500 (35) [M^+], 326 (53), 298 (42), 231 (100), 202 (68), 174 (28). – $C_{30}H_{23}F_3N_2O_2$ (500.5): calcd. C 71.99, H 4.63, N 5.60; found C 72.25, H 4.46, N 5.35.



5-(4-Thiophen-3-yl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**72d**): The crude product obtained from **70a**, 4-(thiophen-3-yl) boronic acid (26 mg) according to the GP 13 was purified by column chromatography (R_f = 0.25, pentane/Et_2O = 1:2) to yield 59 mg (65%) of **72d** as colourless solid, m.p. = 141–142 °C. – IR (KBr): ν = 2955 cm^{-1}, 1664, 1644, 1340, 1165, 1127, 1070, 792. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.78–0.88. (m, 1 H, cPr-H), 1.11–1.40 (m, 3 H, cPr-H), 3.32 (s, 3 H, CH_3), 5.06 (s, 1 H, CH), 7.17–7.35 (m, 2 H, aryl-H), 7.36–7.41 (m, 4 H, aryl-H), 7.43–7.57 (m, 5 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 12.0 (–, cPr-C), 14.7 (–, cPr-C), 39.1 (+, CH_3), 53.7 (–, cPr-C), 80.9 (+, CH-C), 121.3 (+, aryl-C), 124.0 (+, d, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 124.4 (+, d, $^3J_{C\text{-}F}$ =

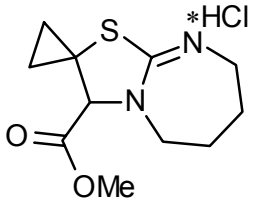


3.8 Hz, aryl-C), 125.0 (–, aryl-C), 125.8 (+, 2 C, aryl-C), 126.1 (+, 2 C, aryl-C), 126.5 (+, aryl-C), 128.2 (+, 2 C, aryl-C), 128.3 (+, 2 C, aryl-C), 130.2 (+, aryl-C), 132.0 (–, q, $^2J_{C\text{-}F}$ = 33.2 Hz, aryl-C), 138.4 (–, aryl-C), 141.3 (–, aryl-C), 143.1 (–, aryl-C), 162.2 (–, CN-C), 168.0 (–, CO-C). – MS (70 eV), *m/z* (%): 456 (27) [M^+], 282 (53), 254 (38), 202 (42), 187 (100), 175 (42). – $C_{24}H_{19}F_3N_2O_2S$ (456.5): calcd. C 63.15, H 4.20, N 6.14; found C 63.18, H 4.14, N 6.6.02.

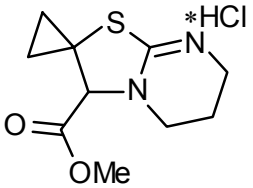
3.2.5. Michael addition of dialky thiourea onto methyl 2-chloro-2-cyclopropyledeneacetate

General Procedure: To a solution of meth (**5**) in 25 mL of dioxane in a 50 mL of flamed dried reaction flask, the corresponding dialkyl thiourea and Et_3N were added. The resulting slurry was stirred for 15 h, solvent was removed in vacuum. The resulting crude product was dissolved in DCM/MeOH (25:1) and purified in column chromatography to yield the product as white solid.

2-cyclopropyl-2,3,5,6,7,8-hexahydro-thiazolo[3,2-a][1,3]diazepine-3-carboxylic acid methyl ester (**74a**): The crude product obtained from methyl 2-chloro-2-cyclopropylideneacetate (366 mg, 2.5 mmol), tetramethylenethiourea (650 mg, 5 mmol) and Et_3N (1.01 g, 10 mmol) was purified in column chromatography (R_f = 0.22, DCM/MeOH = 9:1) to yield 568 mg (82%) of product **74a** as a white solid, m.p. = 175–176 °C. The product was crystallized from Et_2O/MeOH (50/1) at 0 °C. – IR (KBr): ν = 3171, 3117, 2929, 2869, 1741, 1616, 1559, 1359, 1039, 994, 856 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.10–1.18 (m, 2 H, cPr-H), 1.34–1.48 (m, 2 H, cPr-H), 2.01–2.20 (m, 4 H, CH_2), 3.68–3.80 (m, 4 H, NCH_2), 3.81 (s, 3 H, OMe), 4.38 (s, 1 H, CH), 12.11 (br s, 1 H, NH). – ^{13}C-NMR (63.9 MHz, $CDCl_3$, DEPT): δ = 6.4 (–, cPr), 18.4 (–, cPr), 25.0 (–, CH_2), 25.6 (–, CH_2), 29.3 (C_{quat}, cPr), 44.8 (–, NCH_2), 50.7 (–, NCH_2), 53.2 (+, OMe), 74.5 (+, CH), 167.5 (C_{quat}, C=O), 171.4 (C_{quat}, C=N). – MS (DCI), *m/z* (%): 241 (100) [M^+ + H – HCl].



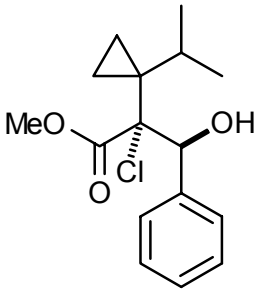
2-cyclopropyl-2,3,7,8-tetrahydro-5H-thiazolo[3,2-a]pyrimidine-3-carboxylic acid methyl ester (**74b**):The crude product obtained from methyl 2-chloro-2-cyclopropylidene acetate (366 mg, 2.5 mmol), trimethylenethiourea (580 mg, 5 mmol) and Et_3N (1.01 g, 10 mmol) was purified in column chromatography (R_f = 0.20, DCM/MeOH = 9:1) to yield 235 mg (41%) of product **74b** as a white solid, m.p. = 180°C. – IR (KBr): ν = 3093, 2955, 1880, 2767, 2680, 1734, 1630, 1548, 1312, 1225, 1004 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.12–1.36 (m, 3 H, cPr-H), 1.38–1.50 (m, 1 H, cPr-H), 2.12–2.21 (m, 2 H, CH_2), 3.48–3.67 (m, 4 H, NCH_2), 3.83 (s, 3 H, OMe), 4.18 (s, 1 H, CH). – ^{13}C-NMR (75.6 MHz, $CDCl_3$, APT): δ = 6.7 (–, cPr), 18.6 (–, cPr), 18.8 (–, CH_2), 29.0 (–, cPr), 39.7 (–, CH_2), 44.8 (–, NCH_2), 53.5 (+, OMe), 72.0 (+, CH), 166.9 (C_{quat}, C=O), 167.1 (C_{quat}, C=N). – MS (70 eV), *m/z* (%): 226 (23) [M^+ – CO_2Me–HCl], 140 (29).



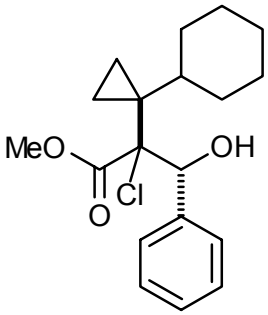
3.2.6. Sequential addition of Grignard reagent and aldehyde with methyl 2-chloro-2-cylopropylideneacetate

General procedure for the one-pot reaction of methyl 2-chloro-2-cylopropylideneacetate (5) with Grignard reagents and benzaldehydes: To a solution of **5** (147 mg, 1.00 mmol) in THF (10 mL) was slowly (within 10 min) added at 0 °C a solution of the Grignard reagent (1.00 mmol). The mixture was stirred for 30 min under rewarming to 20 °C, and then cooled again, at 0 °C a solution of the respective aldehyde (1.05 mmol) in THF (2 mL) was added, and the mixture was stirred for an additional 30 min under rewarming to 20 °C. The mixture was cooled again to 0 °C, the reaction was quenched with sat. NH_4Cl solution (4 mL), and the mixture was stirred at 20 °C for 15 min, Et_2O (20 mL) was added, the phases were separated, the aq. phase was extracted with 20 mL of Et_2O, the combined organic phase was dried over Na_2SO_4, and the volatiles removed in vacuo. Chromatographic purification of the residue on silica gel yielded the products.

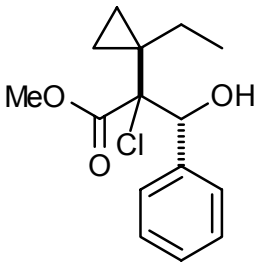
Methyl 2-chloro-3-hydoxy-2-(1-isopropylcylopropyl)-3-phenylpropionate (**75a-iPr**):From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and benzaldehyde (111 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (R_f = 0.30, pentane/Et_2O = 3:1, 1.5 × 15 cm) yielded 273 mg (92%) of **75a**-iPr as a colorless oil. – IR (film): ν = 3516 cm^{-1}, 2960, 2929, 2873, 1723, 1454, 1262, 1054, 702. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = –0.14 to 0.08 (m, 1 H, cPr-H), 0.16–0.26 (m, 2 H, cPr-H), 0.69 (d, ^3J = 6.7 Hz, 3 H, CH_3), 0.78 (d, ^3J = 6.7 Hz, 3 H, CH_3), 0.85–1.03 (m, 1 H, cPr-H), 2.42 (sept, ^3J = 6.7, 6.97 Hz, 1 H, CH), 3.82 (s, 3 H, OCH_3), 5.64 (s, 1 H, CH), 7.21–7.51 (m, 5 H, aryl-H) ppm. – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 5.1 (–, cPr-C), 8.5 (–, cPr-C), 20.9 (+, CH_3), 21.2 (+, CH_3), 26.1 (+, CH), 28.0 (C_{quat}, cPr-C), 53.1 (+, OCH_3), 75.1 (+, CH), 81.8 (C_{quat}, Cl-C), 127.5 (+, 2 C, aryl-C), 128.3 (+, aryl-C), 128.7 (+, 2 C, aryl-C), 138.3 (C_{quat}, C_{ipso}), 172.4 (C_{quat}, C=O) ppm. – MS (DCI), *m*/*z* (%): 610.6 (< 1) [2 M^+ + NH_4], 314.3 (100) [M^+ + NH_4]. – $C_{16}H_{21}ClO_3$ (296.8): calcd. C 64.75, H 7.13; found C 64.97, H 6.86.



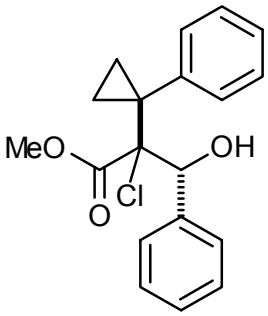
Methyl 2-chloro-2-(1-cyclohexylcyclopropyl)-3-hydroxy-3-phenylpropionate (**75a-cHex**): From **5** (147 mg, 1.00 mmol), cHexMgBr (2 M in Et_2O, 0.5 mL, 1.00 mmol), and benzaldehyde (111 mg, 1.05 mmol), chromatographic purification on 30 g of silica gel (R_f = 0.13, pentane/Et_2O = 3:1, 3 × 10 cm) yielded 91 mg (27%) of **75a**-cHex as a colorless oil. – IR (film): ν = 3521 cm^{-1}, 2928, 1718, 1453, 1263, 701. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = –0.02 to 0.07 (m, 1 H, cPr-H), 0.18–0.32 (m, 2 H, cPr-H), 0.45–0.60 (m, 1 H, cHex-H), 0.92–1.93 (m, 10 H, cHex-H, 1 H, cPr-H), 3.14 (br s, 1 H, OH), 3.84 (s, 3 H, OCH_3), 5.62 (s, 1 H, OCH), 7.26–7.34 (m, 3 H, aryl-H), 7.40–7.44 (m, 2 H, aryl-H) ppm. – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 5.9 (–, cPr-C), 7.1 (–, cPr-C), 26.1 (–, CH_2, cHex), 26.8 (–, CH_2, cHex), 27.1 (–, CH_2, cHex), 28.0 (C_{quat}, cPr-C), 31.3 (–, CH_2, cHex), 32.1 (–, CH_2, cHex), 36.5 (+, CH, cHex), 53.0 (+, OCH_3), 75.3 (+, OCH), 82.4 (C_{quat}, Cl-C), 127.5 (+, 2 C, aryl-C), 128.2 (+, aryl-C), 128.6 (+, 2 C, aryl-C), 138.4 (C_{quat}, C_{ipso}), 172.1 (C_{quat}, C=O) ppm. – MS (DCI), *m*/*z* (%): 690.9 (20) [2 M^+ + NH_4], 354.5 (100) [M^+ + NH_4]. – $C_{19}H_{25}ClO_3$ (336.9): calcd. C 67.75, H 7.48; found C 67.82, H 7.36.



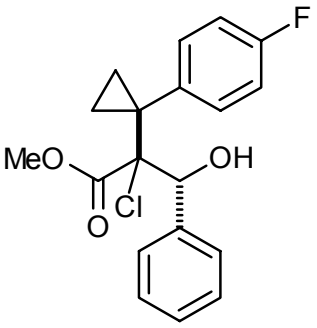
Methyl 2-chloro-2-(1-ethylcyclopropyl)-3-hydroxy-3-phenylpropionate (**75a-Et**): From **5** (294 mg, 2.0 mmol), EtMgBr (2 M in Et_2O, 1.1 mL, 2.2 mmol), and benzaldehyde (233 mg, 2.2 mmol), chromatographic purification on 30 g of silica gel (R_f = 0.60, pentane/Et_2O = 5:1, 3 × 10 cm) yielded 180 mg (32%) of **75a**-Et as a colorless oil. – IR (film): ν = 3530 cm^{-1}, 3030, 2970, 2945, 1721, 1453, 1269. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.01–0.07 (m, 1 H, cPr-H), 0.31–0.37 (m, 1 H, cPr-H), 0.74 (t, ^3J = 7.5 Hz, 3 H, CH_3), 0.86–0.93 (m, 2 H, cPr-H), 1.63–1.88 (m, 2 H, CH_2), 2.90–3.40 (br s, 1 H, OH), 3.84 (s, 3 H, OCH_3), 5.59 (s, 1 H, OCH), 7.26–7.33 (m, 3 H, aryl-H), 7.43–7.47 (m, 2 H, aryl-H) ppm. – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 15.4 (–, cPr-C), 16.5 (–, cPr-C), 18.2 (+, CH_3), 31.2 (C_{quat}, cPr-C), 33.4 (–, CH_2), 61.5 (+, OCH_3), 82.9 (+, OCH), 88.6 (C_{quat}, Cl-C), 135.7 (+, 2 C, aryl-C), 136.5 (+, aryl-C), 136.9 (+, 2 C, aryl-C), 146.4 (C_{quat}, C_{ipso}), 180.8 (C_{quat}, C=O) ppm. – MS (DCI), *m*/*z* (%): 582.6 (75) [2 M^+ + NH_4], 300.3 (100) [M^+ + NH_4]. – $C_{15}H_{19}ClO_3$ (282.8): calcd. C 63.72, H 6.77; found C 63.76, H 6.44.



Methyl 2-chloro-3-hydroxy-3-phenyl-2-(1-phenyl-cyclopropyl)propionate (**75a-Ph**): From **5** (147 mg, 1.00 mmol), PhMgCl (2 M in THF, 0.5 mL, 1.00 mmol), and benzaldehyde (111 mg, 1.10 mmol), chromatographic purification on 20 g of silica gel (R_f = 0.30, pentane/Et_2O = 3:1, 1.5 × 15 cm) and subsequent crystallization from Pentane/Et_2O gave the pure product **75a**-Ph (139 mg, 42%) as colorless crystals, m.p. 105–107 °C. – IR (KBr): ν = 3549 cm^{-1}, 1729, 1320, 1182, 700. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.88–0.94 (m, 2 H, cPr-H), 1.08–1.16 (m, 1 H, cPr-H), 1.48–1.54 (m, 1 H, cPr-H), 3.75 (s, 3 H, OCH_3), 4.30 (br s, 1 H, OH), 4.79 (br s, 1 H, OCH), 7.23–7.37 (m, 8 H, aryl-H), 7.62–7.66 (m, 2 H, aryl-H) ppm. – ^{13}C-NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.8 (–, cPr-C), 14.3 (–, cPr-C), 31.8 (C_{quat}, cPr-C), 53.2 (+, OCH_3), 77.5 (+, OCH), 79.9 (C_{quat}, Cl-C), 127.5 (+, 2 C, aryl-C), 127.6 (+, 2 C, aryl-C), 127.7 (+, aryl-C), 128.1 (+, aryl-C), 128.7 (+, 2 C, aryl-C), 132.4 (+, 2 C, aryl-C), 138.8 (C_{quat}, C_{ipso}), 140.4 (C_{quat}, C_{ipso}), 171.0 (C_{quat}, C=O) ppm. – MS (DCI), *m/z* (%): 678.6 (3) [2 M^+ + NH_4], 348.3 (100) [M^+ + NH_4]. – $C_{19}H_{19}ClO_3$ (330.8): calcd. C 68.98, H 5.79; found: C 69.00, H 5.51.



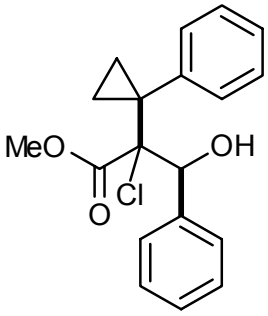
Methyl 2-chloro-2-[1-(4-fluorophenyl)cyclopropyl]-3-hydroxy-3-phenylpropionate (**75a-4-F-C_6H_4**): From **5** (147 mg, 1.0 mmol), 4-F-PhMgCl (1 M in THF, 0.5 mL, 1.0 mmol), and benzaldehyde (111 mg, 1.05 mmol), and chromatographic purification on 25 g of silica gel (R_f = 0.52, pentane/Et_2O = 5:11, 5 × 20 cm) and subsequent crystallization from Pentane/Et_2O gave 136 mg (39%) of **75a**-4-FC_6H_4 as a colorless solid, m.p. 125–127 °C. – IR (KBr): ν = 3548 cm^{-1}, 1731, 1217, 701, 557. – ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 0.86–0.96 (m, 2 H, cPr-H), 1.03–1.13 (m, 1 H, cPr-H), 1.45–1.54 (m, 1 H, cPr-H), 3.74 (s, 3 H, OCH_3), 4.40 (br s, 1 H, OH), 4.66 (br s, 1 H, OCH), 6.97–7.05 (m, 2 H, aryl-H), 7.26–7.29 (m, 6 H, aryl-H), 7.61–7.67 (m, 1 H, aryl-H) ppm. – ^{13}C-NMR (APT, $CDCl_3$, 75.5 MHz): δ = 11.1 (–, cPr-C), 14.8 (–, cPr-C), 31.0 (–, cPr-C), 53.4 (+, OCH_3), 77.9 (+, OCH), 79.8 (–, Cl-C), 114.6 (+, d, $^2J_{C\text{-}F}$ = 21.1 Hz, aryl-C), 127.7 (+, 2 C, aryl-C), 128.2 (+, aryl-C), 128.6 (+, 2 C, aryl-C), 134.2 (+, d, *J* = 8.3 Hz, aryl-C), 136.23 (–, d, *J* = 3.0 Hz, aryl-C), 138.7 (–, aryl-C), 162.1 (–, d, $^1J_{C\text{-}F}$ = 247 Hz, aryl-C-F), 170.8 (–, C=O) ppm. – $C_{19}H_{18}ClFO_3$ (348.8): calcd. C 65.43, H 5.20; found: C 65.43, H 5.04.



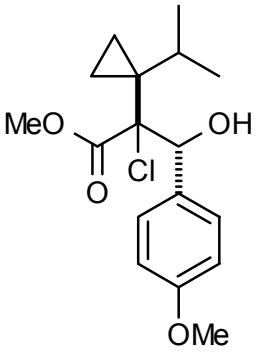
Methyl 2-chloro-3-hydroxy-2-(1-vinylcyclopropyl)-3-phenylpropionate (**75a**-Vin): To a solution of vinyl-magnesiumbromide (1.12 mL, 1.4 mmol, 1.25 M) in THF (10 mL) was added CuCN (126 mg, 1.4 mmol) at –78 °C, the solution was stirred for 15 min, then $BF_3{\cdot}OEt_2$ (100 mg, 0.70 mmol) and **5** (147 mg, 1.00 mmol) was added and the solution was stirred at –78 °C for 1 h at which point benzaldehyde (148 mg, 1.4 mmol) was added and stirring was continued for 12 h at 20 °C. Water (10 mL) and Et_2O (20 mL) was added, layers were separated and the aq. layer was extracted with Et_2O (2×10 mL) drying over Na_2SO_4, removal of the solvent in the vacuum and chromatografic purification of the residue on 20 g of silica (1.5 ×20 cm, R_f = 0.28 pentane/Et_2O = 5 : 1) to yield 55 mg (20%) of *syn* isomer as a colorless oil and 122 mg (44%) of anti isomer, (R_f = 0.21 Pentane / Et_2O = 5:1) as a colorless oil. – *Syn* isomer: IR (film):= ν = 3523, 3086, 3031, 2951, 1734, 1453, 1386, 1264, 1031, 916, 701 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.51–0.60 (m, 1 H, cPr-H), 0.79–0.98 (m, 2 H, cPr-H), 1.13–1.23 (m, 1 H, cPr-H), 3.05 (d, ^3J = 5.50 Hz, 1 H, OH), 3.74 (s, 3 H, CH_3), 5.04 (d, ^3J = 10.0 Hz, 1 H, vinyl-H), 5.10 (d, ^3J = 3.7 Hz, 1 H, vinyl-H), 5.42 (d, ^3J = 5.5 Hz, 1 H, CH), 6.48 (dd, ^3J = 17.0 Hz, ^2J = 10.1 Hz, 1 H, vinyl-H), 7.27–7.37 (m, 3 H, aryl-H), 7.42–7.51 (m, 2 H, aryl-H). – ^{13}C-NMR (DEPT, 62.9 MHz, $CDCl_3$): δ = 11.0 (–, cPr-C), 11.9 (–, cPr-C), 27.3 (C_{quat}, cPr-C), 53.0 (+, OCH_3), 77.2 (+, CH), 78.6 (C_{quat}, Cl-C), 114.4 (–, vinyl-C), 127.5 (+, 2 C, aryl-C), 128.2 (+, aryl-C), 128.6 (+, 2 C, aryl-C), 138.1 (C_{quat}, C_{ipso}), 138.7 (+, vinyl-C), 170.2 (–, CO-C). – MS (DCI), *m*/*z* (%): 578 (7) [2 M^+ + NH_4], 315 (60) [M^+ + NH_3 + NH_4], 298 (100) [M^+ + NH_4]. *anti* isomer: IR (film): ν = 3523, 3089, 3032, 2953, 1718, 1454, 1266, 1069, 911, 701 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.14–0.23 (m, 1 H, cPr-H), 0.38–0.56 (m, 2 H, cPr-H), 1.18–1.28 (m, 1 H, cPr-H), 3.68 (br s, 1 H, OH), 3.87 (s, 3 H, CH_3), 4.98 (d, ^3J = 17.0 Hz, 1 H, vinyl-H), 5.10 (d, ^3J = 6.5 Hz, 1 H, vinyl-H), 5.52 (s, 1 H, CH-H), 6.14 (dd, ^3J = 16.3 Hz, ^2J = 10.5 Hz, 1 H, vinyl-H), 7.27–7.37 (m, 3 H, aryl-H), 7.42–7.56 (m, 2 H, aryl-H). – ^{13}C-NMR (DEPT, 62.9 MHz, $CDCl_3$): δ = 9.84 (–, cPr-C), 13.86 (–, cPr-C), 26.5 (C_{quat}, cPr-C), 53.4 (+, OCH_3), 75.1 (+, CH-C), 78.3 (C_{quat}, Cl-C), 114.8 (–, vinyl-C), 127.3 (+, 2 C, aryl-C), 128.2 (+, aryl-C), 128.7 (+, 2 C, aryl-C), 137.6 (+,

vinyl-C), 137.7 (C_{quat}, C_{ipso}), 172.1 (–, CO-C). – MS (DCI), *m/z* (%): 578 (27) [2 M^+ + NH_4], 298 (100) [M^+ + NH_4]. – $C_{15}H_{17}ClO_3$ (280.8): calcd. C 64.17, H 6.17; found: C 64.27, H 5.88.

Methyl 2-chloro-3-hydroxy-3-phenyl-2-(1-phenyl-cyclo-propyl)propionate (**75a**-Ph): From phenylmagnesiumchloride (0.55 mL, 1.1 mmol, 2 M), CuCN (99 mg, 1.1 mmol), $BF_3{\cdot}OEt_2$ (100 mg, 0.70 mmol), **5** (147 mg, 1.00 mmol) and benzaldehyde (148 mg, 1.4 mmol), chromatographic purification on 20 g of silica (1.5 ×20 cm, R_f = 0.45 pentane/Et_2O = 5 : 1) yielded 39 mg (12%) of *syn* isomer as a colorless oil and 77 mg (23%) of *anti* isomer, (R_f = 0.30 Pentane / Et_2O = 5:1) as a colorless oil. *Anti* isomer: (same as described before). – *Syn* isomer: IR (film): ν = 3523, 2961, 1734, 1456, 1264, 1069, 1031, 703 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.80–0.91 (m, 1 H, cPr-H), 1.05–1.18 (m, 1 H, cPr-H), 1.52–1.61 (m, 1 H, *c*Pr-H), 1.67–1.79 (m, 1 H, cPr-H), 2.56 (d, ^3J = 5.7 Hz, 1 H, OH), 3.54 (s, 3 H, OCH_3), 5.24 (d, ^3J = 5.7 Hz, 1 H, CH), 7.24–7.36 (m, 6 H, aryl-H), 7.39–7.43 (m, 2 H, aryl-H), 7.48–7.55 (m, 2 H, aryl-H) ppm. – ^{13}C-NMR (DEPT, $CDCl_3$, 62.9 MHz): δ = 9.91 (–, cPr-C), 12.7 (–, cPr-C), 32.4 (C_{quat}, cPr-C), 52.3 (+, OCH_3), 74.9 (+, OCH_3), 82.2 (C_{quat}, Cl-C), 115.2 (+, aryl-C), 120.6 (+, aryl-C), 127.7 (+, 2 C, aryl-C), 128.2 (+, 2 C, aryl-C), 128.2 (+, aryl-C), 128.7(+, 2 C, aryl-C), 129.6 (+, aryl-C), 131.9 (+, 2 C, aryl-C), 139.3 (C_{quat}, C_{ipso}), 141.4 (C_{quat}, C_{ipso}), 168.6 (C_{quat}, C=O) ppm. – MS (DCI), *m/z* (%): 678.6 (2) [2 M^+ + NH_4], 348.3 (100) [M^+ + NH_4].

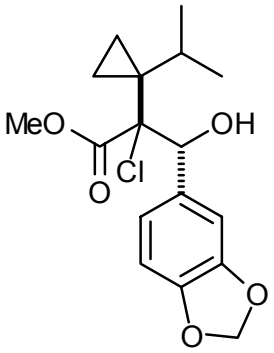


Methyl 2-chloro-3-hydoxy-2-(1-isopropylcylopropyl)-3-(4-methoxyphenyl)propionate (**75b**-iPr): From **5** (800 mg, 5.46 mmol), iPrMgCl (2 M in Et_2O, 3.00 mL, 6.00 mmol), and 4-methoxybenzaldehyde (818 mg, 6.00 mmol), chromatographic purification on 30 g of silica gel (3 × 10 cm, pentane/Et_2O = 3:1, R_f = 0.13, *p*-anisaldehyde) yielded 1.29 g (72%) of **75b**-iPr as a colorless oil, which crystallized spontaneously, m. p. 95 °C. – IR (KBr): ν = 3505, 2968, 2947, 2841, 1715, 1613, 1516, 1252, 1034, 835 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = –0.12 to 0.10 (m,1 H, cPr-H), 0.11–0.35 (m, 2 H, cPr-H), 0.68 (d, ^3J = 6.4 Hz, 3 H, CH_3), 0.77 (d, ^3J = 6.4 Hz, 3 H, CH_3), 0.85–1.03 (m, 1 H, cPr-H), 2.40 (sept, ^3J = 6.4 Hz, 1 H, CH), 3.81 (s, 6 H, 2 × OCH_3), 3.84 (s, 1 H, OH),



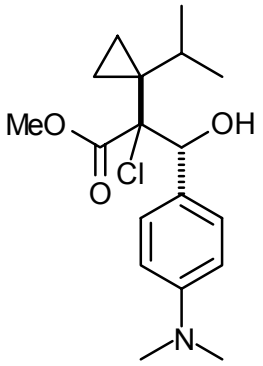
5.59 (s, 1 H, CH), 6.85 (d, ^3J = 8.8 Hz, 2 H, aryl-H), 7.35 (d, ^3J = 8.8 Hz, 2 H, aryl-H) ppm. – ^{13}C-NMR (DEPT, $CDCl_3$, 62.9 MHz): δ = 5.1 (–, cPr-C), 8.5 (–, cPr-C), 20.9 (+, CH_3), 21.2 (+, CH_3), 26.1 (+, CH), 28.1 (C_{quat}, cPr-C), 53.0 (+, OCH_3), 55.2 (+, OCH_3), 74.7 (+, CH), 82.0 (C_{quat}, Cl-C), 112.8 (+, 2 C, aryl-C), 129.8 (+, 2 C, aryl-C), 130.5 (C_{quat}, C_{ipso}), 159.5 (C_{quat}, C_{ipso}), 172.5 (C_{quat}, C=O) ppm. – $C_{17}H_{23}ClO_4$ (326.8): calcd. C 62.48, H 7.09; found: C 62.53, H 6.80.

Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)-3-(1,3-benzodioxole-5-yl)propionate (**75c**-iPr): From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and piperonal (158 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (3 × 10 cm, pentane/Et_2O = 2:1, R_f = 0.31, *p*-anisaldehyde) yielded 264 mg (78%) of **75c**-iPr as a colorless solid, m. p. 113–115 °C. – IR (KBr): ν = 3544, 2975, 2872, 1712, 1440, 1248, 1041, 929 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.04–0.18 (m, 1 H, cPr-H), 0.22–0.36 (m, 2 H, cPr-H), 0.68 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.80 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.95–1.02 (m, 1 H, cPr-H), 2.41 (sept, ^3J = 7.0 Hz, 1 H, iPr-H), 3.38 (d, ^3J = 5.7 Hz, 1 H, OH), 3.84 (s, 3 H, CH_3), 5.59 (d, ^3J = 5.7 Hz, 1 H, CH), 5.98 (s, 2 H, CH_2), 6.72–6.94 (m, 2 H, aryl-H), 7.02 (s, 1 H, aryl-H) ppm. – ^{13}C-NMR (DEPT, 62.9 MHz, $CDCl_3$): δ = 5.25 (–, cPr-C), 8.50 (–, cPr-C), 20.9 (+, iPr-C), 21.2 (+, iPr-C), 26.1 (+, iPr-C), 28.0 (C_{quat}, cPr-C), 53.1 (+, OCH_3), 74.8 (+, CH), 81.8 (C_{quat}, Cl-C), 101.0 (–, CH_2), 107.2 (+, aryl-C), 109.0 (+, aryl-C), 122.4 (+, aryl-C), 132.2 (C_{quat}, aryl-C), 147.0 (C_{quat}, aryl-C), 147.4 (C_{quat}, aryl-C), 172.4 (–, C=O) ppm. – MS (70 eV), *m/z* (%): 340 [M^+] (1), 151 (100), 93 (64), 65 (66). – $C_{17}H_{21}ClO_5$ (340.8): calcd. C 59.91, H 6.21; found: C 60.27, H 5.96.

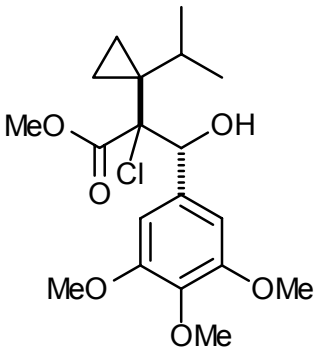


Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)-3-(4-dimethylaminophenyl)propionate (**75d**-iPr): From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and 4-dimethylaminobenz-aldehyde (156 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (3 × 10 cm, pentane/Et_2O = 1:1, R_f = 0.40, *p*-anisaldehyde) yielded 270 mg (80%) of **75d**-iPr as a colorless solid, m. p. 88 °C. – IR (KBr): ν = 3529, 2974, 2953, 2796, 1716, 1617, 1525, 1344,

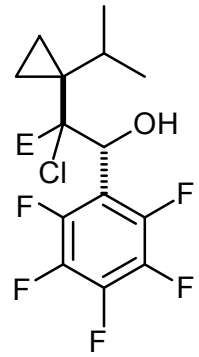
1271, 945, 821 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.03–0.14 (m, 1 H, cPr-H), 0.20–0.31 (m, 2 H, cPr-H), 0.67 (d, ^3J = 6.9 Hz, 3 H, CH_3), 0.78 (d, ^3J = 6.9 Hz, 3 H, CH_3), 0.90–0.98 (m, 1 H, cPr-H), 2.38 (sept, ^3J = 6.9 Hz, 1 H, iPr-H), 2.98 (s, 6 H, NMe_2), 3.19 (d, ^3J = 5.8 Hz, 1 H, OH), 3.82 (s, 3 H, CH_3), 5.55 (d, ^3J = 5.8 Hz, 1 H, CH), 6.63–6.72 (m, 2 H, aryl-H), 7.24–7.32 (m, 2 H, aryl-H) ppm. – ^{13}C-NMR (APT, 75.5 MHz, $CDCl_3$): δ = 5.36 (–, cPr-C), 8.61 (–, cPr-C), 21.0 (+, iPr-C), 21.3 (+, iPr-C), 26.1 (+, iPr-C), 28.4 (–, cPr-C), 40.5 (+, NCH_3), 53.0 (+, OCH_3), 75.1 (+, CH), 82.7 (–, Cl-C), 111.5 (+, 2 C, aryl-C), 126.2 (–, aryl-C), 129.3 (+, 2 C, aryl-C), 150.5 (–, aryl-C), 172.4 (–, C=O) ppm. – MS (DCI), *m/z* (%): 679 (2) [2 M^+ + H], 340 (38) [M^+ + H], 150 (100). – $C_{18}H_{26}ClNO_3$ (339.9): calcd. C 63.61, H 7.71, N 4.12; found: C 63.91, H 7.46, N 4.21.



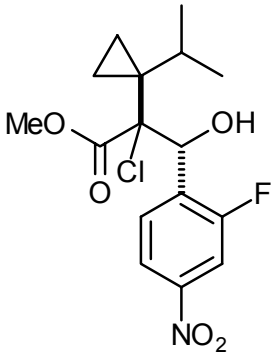
Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopro-pyl)-3-(3,4,5-trimethoxyphenyl)propionate (**75e**-iPr): From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and 3,4,5-trimethoxybenzalde-hyde (206 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (3 × 10 cm, pentane/Et_2O = 1:2, R_f = 0.50, *p*-anisaldehyde) yielded 278 mg (72%) of **75e**-iPr as a colorless solid, m. p. 105 °C. – IR (KBr): ν = 3533, 3026, 2951, 2916, 2882, 1722, 1593, 1506, 1462, 1266, 1122, 846 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.05–0.13 (m, 1 H, cPr-H), 0.18–0.28 (m, 2 H, cPr-H), 0.67 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.77 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.89–0.97 (m, 1 H, cPr-H), 2.38 (sept, ^3J = 7.0 Hz, 1 H, iPr-H), 3.32–3.42 (br s, 1 H, OH), 3.80 (s, 3 H, CH_3), 3.82 (s, 9 H, CH_3), 5.54 (s, 1 H, CH), 6.67 (s, 2 H, aryl-H) ppm. – ^{13}C-NMR (APT, 75.5 MHz, $CDCl_3$): δ = 5.38 (–, cPr-C), 8.49 (–, cPr-C), 21.0 (+, iPr-C), 21.2 (+, iPr-C), 26.2 (+, iPr-C), 28.1 (–, cPr-C), 53.1 (+, OCH_3), 56.1 (+, 2 C, OCH_3), 60.9 (+, OCH_3), 75.2 (+, CH), 81.7 (–, Cl-C), 106.2 (+, 2 C, aryl-C), 133.9 (–, aryl-C), 138.1 (–, aryl-C), 152.4 (–, aryl-C), 172.5 (–, C=O) ppm. – MS (DCI), *m/z* (%): 790 (45) [2 M^+ + NH_4], 404 (100) [M^+ + NH_4], 369 (90). – $C_{19}H_{27}ClO_6$ (386.9): calcd. C 58.99, H 7.03; found: C 59.21, H 6.88.



Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)-3-(pentafluorophenyl)propionate (**75f**-iPr): From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and pentafluorobenzaldehyde (206 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (3 × 10 cm, pentane/Et_2O = 3:1, R_f = 0.50, *p*-anisaldehyde) yielded 302 mg (78%) of **75f**-iPr as a colorless solid, m. p. 74 °C. – IR (KBr): ν = 3389, 3032, 2992, 2962, 2880, 1753, 1658, 1528, 1500, 1237, 999, 946 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.40–0.54 (m, 3 H, cPr-H), 0.67 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.78 (d, ^3J = 7.0 Hz, 3 H, CH_3), 1.00–1.08 (m, 1 H, cPr-H), 2.28 (sept, ^3J = 7.0 Hz, 1 H, iPr-H), 3.83 (s, 3 H, CH_3), 4.07 (d, J = 5.6 Hz, 1 H, OH), 5.80 (d, ^3J = 5.6 Hz, 1 H, CH) ppm. – ^{13}C-NMR (APT, 75.5 MHz, $CDCl_3$): δ = 6.94 (–, cPr-C), 8.71 (–, cPr-C), 21.1 (+, iPr-C), 21.5 (+, iPr-C), 26.6 (+, iPr-C), 29.5 (–, cPr-C), 53.6 (+, OCH_3), 70.1 (+, CH), 80.7 (–, Cl-C), 113.5 (–, m, aryl-C), 135.8 (–, m, aryl-C), 139.1 (–, m, aryl-C), 142.8 (–, m, aryl-C), 143.6 (–, m, aryl-C), 146.9 (–, m, aryl-C), 170.6 (–, C=O) ppm. – MS (DCI), *m/z* (%): 790 (10) [2 M^+ + NH_4], 404 (100) [M^+ + NH_4]. – $C_{16}H_{16}ClF_5O_3$ (386.7): calcd. C 49.69, H 4.17; found: C 49.81, H 3.96.

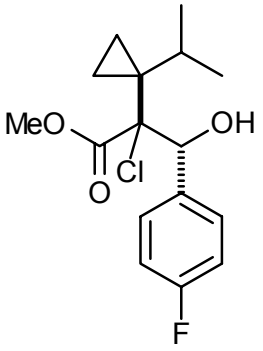


Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)-3-(2-fluoro-4-nitrophenyl)propio-nate (**75g**-iPr): From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and 2-fluoro-4-nitrobenzaldehyde (177 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (3 × 10 cm, pentane/Et_2O = 3:1, R_f = 0.45, *p*-anisaldehyde) yielded 299 mg (83%) of **75g**-iPr as a colorless solid, m. p. 98 °C. – IR (KBr): ν = 3530, 3199, 2999, 2978, 2878, 1717, 1616, 1539, 1357, 1242, 876, 801 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.11–0.20 (m, 1 H, cPr-H), 0.42–0.54 (m, 2 H, cPr-H), 0.62 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.83 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.95–1.02 (m, 1 H, cPr-H), 2.25 (sept, ^3J = 7.0 Hz, 1 H, iPr-H), 3.74 (s, 3 H, CH_3), 4.35 (br s, 1 H, OH), 6.42 (s, 1 H, CH), 7.26–7.31 (m, 1 H, aryl-H), 7.58 (m, 1 H, aryl-H), 7.80 (m, 1 H, aryl-H) ppm. – ^{13}C-NMR (APT, 75.5 MHz, $CDCl_3$): δ = 7.88 (–, cPr-C), 8.35 (–, cPr-C), 21.2 (+, iPr-C), 21.3 (+, iPr-C), 26.5 (+, iPr-C), 29.4 (–, cPr-C), 53.4 (+, OCH_3), 68.9 (+, CH), 81.5 (–, Cl-C), 111.9 (+, d, $^2J_{C\text{-}F}$ = 26.4 Hz, aryl-C), 119.4 (+, d, $^3J_{C\text{-}F}$ = 20.4 Hz, aryl-C), 129.9 (–, d, $^3J_{C\text{-}F}$ = 3.8 Hz, aryl-C), 132.0 (+, d, $^4J_{C\text{-}F}$ = 7.5 Hz, aryl-C), 150.3 (–, d, $^2J_{C\text{-}F}$ = 15.1 Hz, aryl-C), 161.5 (–, d, $^1J_{C\text{-}F}$ = 252 Hz, aryl-C),

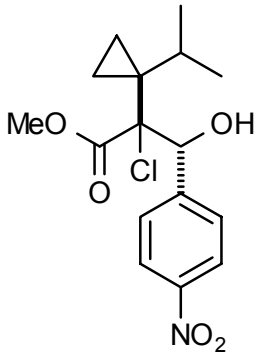


171.6 (–, C=O) ppm. – MS (DCI), *m/z* (%): 736 (56) [2 M^+ + NH_4], 377 (100) [M^+ + NH_4]. – $C_{16}H_{19}ClFNO_5$ (359.8): calcd. C 53.41, H 5.32, N 3.89; found: C 53.58, H 5.11, N 3.97.

Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)-3-(4-fluorophenyl)propionate (**75h**-iPr*):* From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and 4-fluorobenzaldehyde (129 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (3 × 10 cm, pentane/Et_2O = 3:1, R_f = 0.35, *p*-anisaldehyde) yielded 252 mg (80%) of **75h**-iPr as a colorless solid, m. p. 78 °C. – IR (KBr): ν = 3556, 3002, 2981, 2955, 2877, 1716, 1604, 1511, 1267, 1218, 840 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = –0.13 to 0.04 (m, 1 H, cPr-H), 0.12–0.33 (m, 2 H, cPr-H), 0.67 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.79 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.86–1.00 (m, 1 H, cPr-H), 2.38 (sept, ^3J = 7.0 Hz, 1 H, iPr-H), 3.43 (d, ^3J = 5.6 Hz, 1 H, OH), 3.83 (s, 3 H, CH_3), 5.63 (d, ^3J = 5.6 Hz, 1 H, CH), 6.97–7.08 (m, 2 H, aryl-H), 7.37–7.46 (m, 2 H, aryl-H) ppm. – ^{13}C-NMR (APT, 50.3 MHz, $CDCl_3$): δ = 5.09 (–, cPr-C), 8.51 (–, cPr-C), 20.9 (+, iPr-C), 21.2 (+, iPr-C), 26.1 (+, iPr-C), 28.0 (–, cPr-C), 53.1 (+, OCH_3), 74.4 (+, CH), 81.5 (C_{quat}, Cl-C), 114.4 (+, d, $^2J_{C\text{-}F}$ = 21.6 Hz, 2 C, aryl-C), 130.4 (+, d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 C, aryl-C), 134.1 (–, d, $^4J_{C\text{-}F}$ = 3.0 Hz, aryl-C), 162.7 (–, d, $^1J_{C\text{-}F}$ = 247 Hz, aryl-C), 172.6 (–, C=O) ppm. – MS (DCI), *m/z* (%): 296 (100) [M^+ –F + H], 332 (62) [M^+ + NH_4]. – $C_{16}H_{20}ClFO_3$ (314.8): calcd. C 61.05, H 6.40; found C 61.30, H 6.21.

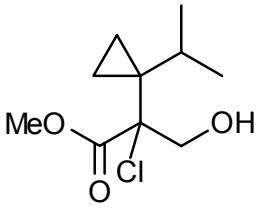


Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)-3-(4-nitrophenyl)propionate (**75i**-iPr): From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and 4-nitrobenzaldehyde (159 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (3 × 10 cm, pentane/Et_2O = 2:1, R_f = 0.35, *p*-anisaldehyde) yielded 250 mg (73%) of **75i**-iPr as a colorless solid, m. p. 138 °C. – IR (KBr): ν = 3580, 2972, 2950, 2877, 1729, 1515, 1346, 1250, 1078, 855 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = –0.18 to 0.02 (m, 1 H, cPr-H), 0.16–0.39 (m, 2 H, cPr-H), 0.67 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.82 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.95–1.00 (m, 1 H, cPr-H), 2.46 (sept, ^3J = 7.0 Hz, iPr-H), 3.67 (d, ^3J = 5.7 Hz, 1 H, OH), 3.85 (s, 3 H, CH_3), 5.78 (d, ^3J = 5.7 Hz, 1 H, CH),

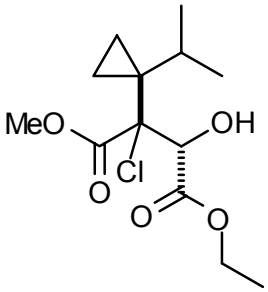


7.61 (m, 2 H, aryl-H), 8.19 (m, 2 H, aryl-H) ppm. – ^{13}C-NMR (DEPT, 62.9 MHz, $CDCl_3$): δ = 5.08 (–, cPr-C), 8.66 (–, cPr-C), 20.8 (+, iPr-C), 21.2 (+, iPr-C), 26.2 (+, iPr-C), 27.8 (C_{quat}, cPr-C), 53.3 (+, OCH_3), 74.1 (+, CH), 80.5 (C_{quat}, Cl-C), 122.5 (+, 2 C, aryl-C), 129.8 (+, 2 C, aryl-C), 145.4 (C_{quat}, aryl-C), 147.7 (C_{quat}, aryl-C), 172.4 (–, C=O) ppm. – MS (DCI), *m/z* (%): 359 (5) [$M^+ + NH_4$], 210/208 (32/100), 139 (93). – $C_{16}H_{20}ClNO_5$ (341.8): calcd. C 56.23, H 5.90, N 4.10; found: C 56.38, H 5.80, N 4.00.

Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)propionate (**75j**-iPr): From **5** (147 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.5 mL, 1.0 mmol), paraformaldehyde (150 mg, 5 mmol of monomer) after 15 h, Chromatografic purification on 20 g of silica (1.5 × 15 cm, pentane/Et_2O = 3 : 1, R_f = 0.35) yielded 135 mg (61%) of **75j**-iPr as colorless oil. – IR (film): ν = 3464, 2961, 2875, 1733, 1436, 1266, 1077, 1031, 733 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.48–0.61 (m, 2 H, cPr-H), 0.78 (d, ^3J = 2.1 Hz, 3 H, CH_3), 0.81 (d, ^3J = 2.1 Hz, 3 H, CH_3), 0.85–0.93 (m, 2 H, cPr-H), 2.08 (sept, ^3J = 6.8 Hz, iPr-H), 2.37 (br s, 1 H, OH), 3.71 (d, ^3J = 12.3 Hz, CH_2), 3.81 (s, 3 H, CH_3), 4.19 (d, ^3J = 12.3 Hz, CH_2). – ^{13}C-NMR (DEPT, 62.9 MHz, $CDCl_3$): δ = 7.76 (–, cPr-C), 8.33 (–, cPr-C), 21.2 (+, iPr-C), 27.8 (+, iPr-C), 29.1 (C_{quat}, cPr-C), 53.0 (+, OCH_3), 67.3 (–, CH_2), 80.6 (C_{quat}, Cl-C), 170.8 (–, CO-C). – MS (DCI), *m/z* (%): 458 (1) [2 $M^+ + NH_4$], 255 (13) [$M^+ + NH_3 + NH_4$], 238 (100) [$M^+ + NH_4$]. – $C_{10}H_{17}ClO_3$ (220.7): calcd. C 54.42, H 7.76; found: C 54.67, H 5.51.

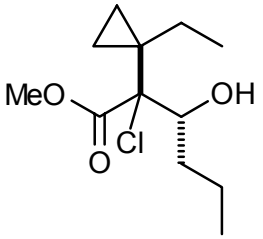


2-Chloro-3-hydroxy-2-(1-isopropyl-cyclopropyl)-succinic acid 4-ethyl ester 1-methyl ester (**75k**-iPr): From **5** (147.0 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and ethylglyoxylate (224 mg, 50% solution in toluene, 1.1 mmol), chromatographic purification on 20 g of silica (1.5 × 15 cm, pentane/Et_2O = 5 : 1, R_f = 0.35) yielded 211 mg (72%) of **75i**-iPr as colorless oil. – IR (film): ν = 3496, 2968, 1734, 1436, 1268, 1121, 1029, 763 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.39–0.46 (m, 1 H, cPr-H), 0.65–0.74 (m, 1 H, cPr-H), 0.76 (d, ^3J = 6.8 Hz, 3 H, CH_3), 0.85 (d, ^3J = 6.8 Hz, 3 H, CH_3), 1.01–1.09 (m, 2 H, CH_2), 1.27 (t, ^3J = 7.0 Hz, 3 H, CH_3), 2.39 (sept, ^3J = 6.8 Hz, iPr-H), 3.20 (d, ^3J = 6.8 Hz, 1 H, OH), 3.81 (s, 3 H, OCH_3), 4.15–4.32 (m, 2 H, CH_2), 5.03 (d, ^3J = 6.8 Hz,

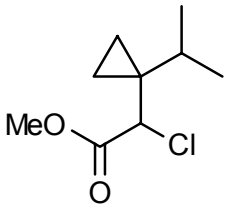


1 H, CH). – ^{13}C-NMR (DEPT, $CDCl_3$, 62.9 MHz): δ = 6.31 (–, cPr-C), 9.73 (–, cPr-C), 13.9 (+, CH_3), 21.1 (+, CH, iPr-C), 21.7 (C_{quat}, cPr-C), 26.6 (+, CH), 30.2 (C_{quat}, cPr-C), 53.0 (+, OCH_3), 62.7 (–, CH_2), 74.4 (+, CH), 80.3 (C_{quat}, Cl-C), 169.2 (C_{quat}, C=O), 171.2 (C_{quat}, C=O) ppm. – MS (DCI), *m*/*z* (%): 602.6 (1) [2 M^+ + NH_4], 310.3 (100) [M^+ + NH_4]. – $C_{13}H_{21}ClO_5$ (292.8): calcd. C 53.34, H 7.23; found: C 53.54, H 7.11.

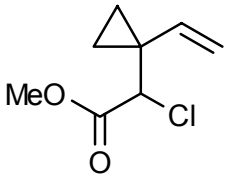
Methyl 2-chloro-3-hydroxy-2-(1-isopropylcyclopropyl)-3-butyl propionate (**75l**-iPr): From **5** (147.0 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.5 mL, 1.0 mmol), butyraldehyde (260 mg, 5 mmol), chromatografic purification on 20 g of silica (1.5 × 15 cm, pentane/Et_2O = 5 : 1, R_f = 0.35) yielded 85 mg (32%) of **75l**-iPr as colorless oil. – IR (film): ν = 3530, 2962, 2873, 1717, 1467, 1260, 1123, 1079, 1033, 1013 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.42–0.66 (m, 2 H, cPr-H), 0.75 (d, ^3J = 3.6 Hz, 3 H, CH_3), 0.79 (d, ^3J = 3.6 Hz, 3 H, CH_3), 0.87–1.11 (m, 5 H), 1.38–1.56 (m, 2 H, CH_2), 1.61–1.77 (m, 2 H, CH_2), 2.12 (sept, ^3J = 6.8 Hz, iPr-C), 3.80 (s, 3 H, OCH_3), 4.38–4.46 (m, 1 H, CH). – ^{13}C-NMR (DEPT, $CDCl_3$, 62.9 MHz): δ = 7.16 (–, cPr-C), 8.13 (–, cPr-C), 14.1 (+, CH_3), 19.0 (–, CH_2), 21.2 (+, CH_3), 21.4 (+, CH_3), 26.6 (+, CH, iPr), 28.0 (C_{quat}, cPr-C), 33.3 (–, CH_2), 52.9 (+, OCH_3), 73.0 (+, CH), 81.8 (C_{quat}, Cl-C), 172.5 (C_{quat}, C=O) ppm. – MS (DCI), *m*/*z* (%): 280.3 (100) [M^+ + NH_4]. – $C_{13}H_{23}ClO_3$ (262.8): calcd. C 59.42, H 8.82; found: C 59.34, H 8.54.



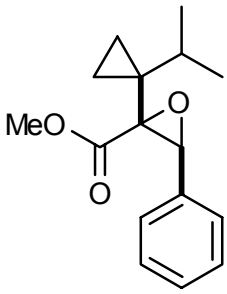
Methyl chloro(1-isopropylcyclopropyl)acetate (**78**-iPr): From **5** (294 mg, 2.0 mmol), iPrMgCl (2 M in Et_2O, 1.1 mL, 2.2 mmol) and aq. sat. NH_4Cl, chromatographic purification on 20 g of silica gel (1.5 × 10 cm, pentane/Et_2O = 5:1, R_f = 0.80) yielded 373 mg (98%) of **78**-iPr as a colorless oil. – IR (film): ν = 3085, 2960, 2875, 1758, 1434, 1168, 1015, 772 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.61–0.56 (m, 4 H, cPr-H), 0.94–0.85 (m, 6 H, 2 CH_3), 1.64–1.72 (m, 1 H, CH), 3.73 (s, 3 H, OCH_3), 4.38 (s, 1 H, CH) ppm. – ^{13}C-NMR (DEPT, $CDCl_3$, 62.9 MHz): δ = 10.4 (–, cPr-C), 11.9 (–, cPr-C), 19.5 (+, iPr-C), 20.0 (+, iPr-C), 28.1 (C_{quat}, cPr-C), 31.3 (+, iPr-C), 52.6 (+, C-Cl), 62.7 (+, OCH_3), 169.3 (C_{quat}, C=O) ppm. – MS (DCI), *m*/*z* (%): 225.3 (50) [M^+ + NH_3 + NH_4], 208.2 (100) [M^+ + NH_4].



Methyl chloro-(1-vinylcyclopropyl)acetate (**78**-Vin): To a solution of vinylmagnesium bromide (4.78 mL, 9.56 mmol, 2 M) in THF (40 mL) was added at –78 °C CuCN (855 mg, 9.55 mmol), the mixture was stirred for 15 min, then $BF_3 \cdot OEt_2$ (600 µl, 4.78 mmol) and **5** (1.00 g, 6.82 mmol) were added, and the mixture was stirred at –78 °C for 3 h. Water (20 mL) was added at this temperature and the mixture was allowed to warm to 20 °C. Extraction of the aq. phase with Et_2O (3 × 30 mL), drying over Na_2SO_4, removal of the solvent in vacuo and chromatographic purification of the residue on 20 g of silica gel (1.5 × 20 cm, pentane/Et_2O = 100:1, R_f = 0.42 [pentane/Et_2O = 10:1]) yielded 957 mg (80%) of **78**-Vin as a colorless oil. – IR (film): ν = 3087, 3010, 2955, 1756 (C=O), 1699, 1653, 1641, 1436, 1289, 1195, 1168, 1014, 908, 808, 668 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.85–1.13 (m, 4 H, cPr-H), 3.78 (s, 3 H, OCH_3), 4.01 (s, 1 H, CH), 5.02 (dd, ^3J = 17.3, ^2J = 0.7 Hz, 1 H, vinyl-H), 5.06 (dd, ^3J = 10.6, ^2J = 0.7 Hz, 1 H, vinyl-H), 6.05 (dd, ^3J = 17.3 Hz, ^3J = 10.6 Hz, 1 H, vinyl-H) ppm. – ^{13}C-NMR (DEPT, 62.9 MHz, $CDCl_3$): δ = 14.8 (–, cPr-C), 15.1 (–, cPr-C), 26.3 (C_{quat}, cPr-C), 52.6 (+, CHCl), 64.3 (+, OCH_3), 114.0 (–, vinyl-C), 136.8 (+, vinyl-C), 168.5 (C_{quat}, C=O) ppm. – MS (70 eV), *m/z* (%): 174 (<1) [M^+], 173 (1) [M^+ – H], 139 (100) [M^+ – Cl], 107 (12), 79 (35), 67 (10), 59 (8). – $C_8H_{11}ClO_2$ (174.6): calcd. C 55.02, H 6.35, Cl 20.30; found C 55.09, H 6.31, Cl 20.24.

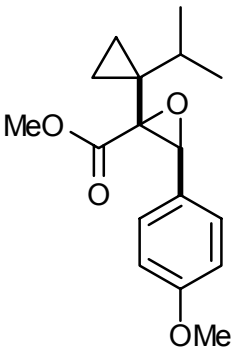


Methyl 2-bromo-3-hydoxy-2-(1-isopropylcylopropyl)-3-phenylpropionate (**79a-iPr**): From **1**-Br (191.0 mg, 1.00 mmol), iPrMgCl (2 M in Et_2O, 0.50 mL, 1.00 mmol), and benzaldehyde (111 mg, 1.05 mmol), chromatographic purification on 20 g of silica gel (1.5 × 15 cm, pentane/Et_2O = 10:1, R_f = 0.50, MOPS) yielded 249 mg (73%) of **75a**-iPr as a colorless oil. – IR (film): ν = 2959 cm^{-1}, 2875, 1738, 1453, 1268, 1038, 699. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.24–0.41 (m, 3 H, cPr-H), 0.47 (d, ^3J = 6.9 Hz, 3 H, CH_3), 0.78 (d, ^3J = 6.9 Hz, 3 H, CH_3), 0.84–0.94 (m, 1 H, cPr-H), 2.42 (sept, ^3J = 6.9 Hz, 1 H, CH), 3.78 (s, 3 H, OCH_3), 4.31 (s, 1 H), 7.28–7.40 (m, 5 H, aryl-H) ppm. – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 7.7 (–, cPr-C), 9.3 (–, cPr-C), 19.9 (+, CH_3), 20.0 (+, CH_3), 22.7 (–, cPr-C), 30.1 (+, CH), 52.5 (+, OCH_3), 63.6 (+, CH), 66.6 (–, Br-C), 127.2 (+, 2 C, aryl-C), 127.9 (+, 2 C, aryl-C), 128.0 (+, aryl-C), 134.3 (–,



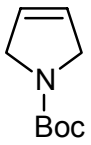
C_{ipso}), 171.1 (–, C=O) ppm. – MS (DCI), *m/z* (%): 538.5 (< 1) [2 M^+ + NH_4 – 2 HBr], 278.2 (100) [M^+ + NH_4 – HBr]. – $C_{16}H_{20}O_3$ (260.3): calcd. C 73.82, H 7.74; found C 73.69, H 7.39.

Methyl 2-(1-isopropylcyclopropyl)-3-(4-methoxyphenyl)oxirane-2-carboxylate (**79b**-iPr): To a solution of **75b**-iPr (222 mg, 679 µmol) in THF (20 mL) was added at 20 °C KO*t*Bu (80 mg, 713 µmol), and the suspension was stirred at this temperature for 3 h. Removal of all volatiles in vacuo and chromatographic purification of the residue on 20 g of silica gel (3 × 20 cm, pentane/Et_2O = 3:1, R_f = 0.75, MOPS) yielded 122 mg (62%) of **79b**-iPr as a colorless oil. – IR (film): ν = 2957, 2874, 2837, 1734, 1614, 1516, 1436, 1251, 1038, 831 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 0.21–0.50 (m, 3 H, cPr-H), 0.58 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.81 (d, ^3J = 7.0 Hz, 3 H, CH_3), 0.85–1.03 (m, 1 H, cPr-H), 2.65 (sept, ^3J = 7.0, Hz, 1 H, iPr), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.24 (s, 1 H, CH), 6.84 (d, ^3J = 8.8 Hz, 2 H, aryl-H), 7.28 (d, ^3J = 8.8 Hz, 2 H, aryl-H) ppm. – ^{13}C-NMR (DEPT, $CDCl_3$, 62.9 MHz): δ = 7.7 (–, cPr-C), 9.3 (–, cPr-C), 19.9 (+, CH_3, 2 C), 22.5 (C_{quat}, cPr-C), 30.1 (+, CH), 52.4 (+, OCH_3), 55.2 (+, OCH_3), 63.4 (+, CH), 66.4 (C_{quat}, C-O), 113.4 (+, 2 C, aryl-C), 126.1 (C_{quat}, C_{ipso}), 128.3 (+, 2 C, aryl-C), 159.3 (C_{quat}, C_{ipso}), 171.1 (C_{quat}, C=O) ppm. – MS (DCI), *m/z* (%): 598.7 (1) [2 M^+ + NH_4], 308.3 (100) [M^+ + NH_4], 291.3 (46) [M^+ + H]. – $C_{17}H_{22}O_4$ (290.4): calcd. C 70.32, H 7.64; found C 70.23, H 7.35.

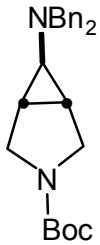


3.2.7. Synthesis of 6-amino-3-azabicyclo[3,1,0]hexanes

N-tert-Butoxycarbonyl-3-pyrroline (**81**): *N-tert*-butoxycarbonyl diallylamine (216 g, 1.1 mol) was added over 1.5 h at 20 °C into a two litre round bottomed flask equipped with stirrer, dropping funnel and thermometer containing *bis*(tricyclohexylphosphine)benzylidene ruthenium(IV)dichloride (Grubbs catalyst, 905 mg, 1.1 mmol, 0.1 mol%) in dichloromethane (1.2 L). After 15 h of stirring at 20 °C the solvent was removed by reduced pressure and the remaining dark oil was distilled (bp = 60 °C, 1 torr) to get the pure product (184 g, 99 %) as a colourless oil which crystallized on standing at 0 °C to give the pure *N-tert*-butoxycarbonyl-3-pyrroline. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.43 (s, 9 H, CH_3), 3.99–4.13 (m, 4 H, CH_2), 5.60–5.78 (m, 2 H, CH). – ^{13}C-NMR ($CDCl_3$, 62.9 MHz, DEPT): δ = 28.3 (+, CH_3), 48.6 (–, CH_2), 79.5 (C_{quat}, Boc-C), 133.9 (+, CH), 155.3 (C_{quat}, CO).

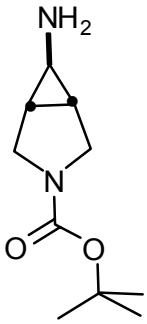


exo-6-(N,N-dibenzylamino)-3-aza-bicyclo[3,1,0]hexane-3-carboxylic acid tert-butyl ester (**82**):In to a four litre 3 necked flask equipped with a mechanical stirrer, reflux condenser and dropping funnel and thermometer, *N-tert*-butoxycarbonyl-3-pyrroline (169 g, 1.00 mol) was taken in 1.5 litre of dry THF. To this solution Ti(O*i*Pr)$_4$ (313 g, 1.10 mol) was added in one portion followed by addition of CH_3MgCl (3 M in THF, 367 mL, 1.1 mol) at 10 °C within a period of 30 min. The ice bath was removed and *N,N*-dibenzyl formamide (148 g, 0.65 mol) was added at a time to the above solution. After stirring for 15 min cyclohexyl magnesium bromide (2 M in Et_2O, 1.10 L, 2.2 mol) was added slowly within a period of 4 hours. Then the resulting black solution was refluxed for 1 h, cooled down to 0 °C and quenched with 200 ml of H_2O and stirred for 10 h in the presence of air. The reaction mixture was filtered and the solid material was washed with Et_2O (3×500 mL), combined organic phahe dried over $MgSO_4$, concentrated to ~ 700 mL and the crude product was filtered through a small column (Al_2O_3 with 2% water, 600 g, 10 cm height). The product was crystallized from pentane/ether (10:1, 800 mL) at 0 °C to get (270 g, 71 %) as a colourless crystals m.p. xx °C. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.30–1.37, (m, 2 H, CH), 1.45 (s, 9 H, CH_3), 1.58–1.60 (m, 1 H, *N*CH), 3.17–3.27 (m, 2 H, CH_2), 3.29–3.47 (m, 2 H, CH_2), 3.58–3.76 (m, 4 H, Bn-H), 7.20–7.39 (m, 10 H, aryl-H). – ^{13}C-NMR ($CDCl_3$, 62.9 MHz, DEPT): δ = 25.2 (+, CH), 25.8 (+, CH), 28.4 (+, CH_3), 47.5 (+, CH), 47.6 (–, CH_2), 47.8 (–, CH_2), 58.7 (–, Bn-CH_2), 79.1 (C_{quat}, Boc-C), 126.9

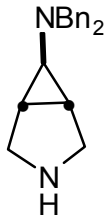


(+, 2 C, aryl-C), 128.0 (+, 4 C, aryl-C), 129.3 (+, 4 C, aryl-C), 138.4 (C_{quat}, C_{ipso}), 154.4 (C_{quat}, CO).

exo-6-Amino-3-azabicyclo[3,1,0]hexane-3-carboxylic acid tert-butyl ester (**84**): To a 500 mL flask equipped with stirrer, flushed with nitrogen, Pd/C (10% Pd, Merck, 2.3 g) was taken followed by careful addition of methanol (100 mL). The resulting mixture was stirred in the presence of H_2 (1 atm). After 30 min *exo*-6-(*N*,*N*-dibenzylamino)-3-*tert*-butoxycarbonyl-3-azabicyclo[3,1,0]hexane (37.8 g, 0.1mol) dissolved in methanol (150 mL) was added to it. The resulting mixture was stirred under H_2 until the H_2 uptake became equal to the theoretical value (4.48 L). Then the crude product was filtered through a pad of Celite®, the solvent was removed under reduced pressure. The product crystallised on standing at 5 °C (18.9 g, 96 %) as a white solid, m.p. = 51 °C. – ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.37 (s, 9 H, CH_3), 1.39–1.42, (m, 2 H, CH), 1.65 (br s, 2 H, NH), 2.03 (br s, 1 H, *N*CH), 3.22–3.36 (m, 2 H, CH_2), 3.38–3.52 (m, 2 H, CH_2). – ^{13}C-NMR ($CDCl_3$, 62.9 MHz, DEPT): δ = 25.2 (+, CH), 26.0 (+, CH), 28.4 (+, CH_3), 35.2 (+, CH), 47.5 (–, CH_2), 47.8 (–, CH_2), 154.4 (C_{quat}, CO).



exo-6-(N,N-dibenzylamino)-3-aza-bicyclo[3,1,0]hexane (**83**)*:* To a suspension of *exo*-6-(*N*,*N*-dibenzylamino)-3-aza-bicyclo[3,1,0]hexane-3-carboxylic acid tert-butyl ester (18.9 g, 50 mmol) in 20 mL of EtOAc was added HCl (2 N in EtOAc, 250 mL) over 15 min. The resulting white slurry was stirred at 20 °C for 15 h. To this was added 10 N NaOH (100 mL), the organic layer was separated, aq. layer extracted with EtOAc (3 × 100 mL), dried over Na_2SO_4, concentrated and the product crystallized on standing at room temperature to give 13.5 g (97%) as white solid, m.p 68 °C. – IR (KBr): ν = 3283, 3026, 2919, 2850, 1495, 1453, 1093, 826, 746, 698 cm^{-1}. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.25 (m, 2 H, CH), 1.48–1.55 (m, 1 H, *N*CH), 1.57 (br s, 1 H, NH), 2.72–2.91 (m, 4 H, CH_2), 3.63 (s, 4 H, Bn-CH_2), 7.21–7.37 (m, 10 H, aryl-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 27.3 (CH), 44.1 (*N*CH), 48.7 (CH_2), 58.7 (Bn-CH_2), 126.9 (aryl-C), 128.0 (aryl-C), 129.4 (aryl-C), 138.5 (aryl-C).

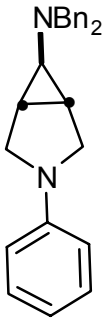


exo-6-Benzyloxycarbonylaminoexo-3-aza-bicyclo[3,1,0]hexane-3-carboxylic acid tert-butyl-ester (**85**): To a solution of *exo*-6-Amino-3-azabicyclo[3,1,0]hexane-3-carboxylic acid *tert*-butyl ester

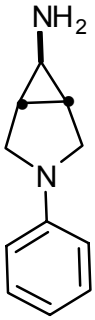
(12.9 g, 65 mmol) in 200 mL of acetone was added N-(benzyloxy-carbonyloxy)-succinamide (17.8 g, 71.5 mmol) and $NaHCO_3$ (aq. 1 N, 130 mL). This mixture was stirred for 15 h at 20 °C. Acetone was removed, aq. layer extracted with Et_2O (3×200 mL), dried over MgSO4. After removing solvent the crude product was crystallized from Et_2O to yield the title compound (18.3 g, 85%) as white solid, m.p. = 111–112 °C. – IR (KBr): ν = 3289, 3068, 2974, 2941, 2872, 1676, 1540, 1390, 1164, 1105, 745 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, Boc-CH_3), 1.58–1.70 (m, 2 H, CH), 2.31–2.36 (m, 1 H, *N*CH), 3.27–2.39 (m, 2 H, CH_2), 3.27–2.39 (m, 2 H, CH_2), 4.96 (br. s, 1 H, NH), 5.07 (s, 2 H, Bn-CH_2), 7.30–7.37 (m, 5 H, aryl-C). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 24.1 (+, CH), 25.3 (+, CH), 28.4 (+, Boc-CH_3), 33.3 (+, CH), 47.4 (–, CH_2), 47.7 (–, CH_2), 66.8 (–, Bn-CH_2), 79.5 (–, Boc-C), 128.2 (+, aryl-C), 128.5 (+, 4 C, aryl-C), 136.3 (–, C_{ipso}), 154.5 (–, C=O), 156.6 (–, C=O). – MS (70 eV) *m/z* (%): 332 (1) [M^+], 232 (6), 203 (7), 91 (100) [C_7H_7]. – $C_{18}H_{24}N_2O_4$ (332.4): calcd. C

exo-6-Benzyloxycarbonylamin-3-aza-bicyclo[3,1,0]hexane (**86**): To a suspension of *exo*-6-Benzyloxycarbonylamino-3-aza-bicyclo[3,1,0]hexane-3-carboxylic acid *tert*-butyl-ester (17 g, 51 mmol) in 25 mL of EtOAc was added HCl (2 N in EtOAc, 255 mL) over 15 min. The resulting white slurry was stirred at 20 °C for 15 h. To this was added 10 N NaOH (100 mL), organic layer was separated, aq. layer extracted with EtOAc (2 × 100 mL), combined organic layer was dried over Na_2SO_4, concentrated and the product crystallized from Pentane/Et_2O (1:1) to give 11.6 g (98%) of product as a white solid, m.p. = 141 °C. – IR (KBr): ν = 3325, 3166, 2950, 2874, 1703, 1567, 1297, 1179, 1037, 895 cm^{-1}. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 1 H, NH), 1.52–1.58 (m, 2 H, CH), 2.32–2.37 (m, 1 H, *N*CH), 2.86 (m, 2 H, CH_2), 3.10 (m, 2 H, CH_2), 5.00 (br. s, 1 H, NH), 5.05 (s, 2 H, Bn-CH_2), 7.30–7.38 (m, 5 H, aryl-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, APT): δ = 26.1 (+, 2 C, CH), 30.3 (+, CH), 48.5 (–, CH_2), 66.7 (–, Bn-CH_2), 128.1 (+, 2 C, aryl-C), 128.2 (+, aryl-C), 128.5 (+, 2 C, aryl-C), 136.4 (–, C_{ipso}), 156.6 (–, C=O). – MS (70 eV) *m/z* (%): 232 (1) [M^+], 203 (7), 91 (100) [C_7H_7]. – $C_{13}H_{16}N_2O_2$ (232.3): calcd. C 67.22, H 6.94, N 12.06; found C 67.57, H 6.97, N 11.89.

exo-6-(N,N-dibenzylamino)-3-pheny-3-aza-bicyclo[3,1,0]hexane (**87**): To an oven-dried Schlenk flask purged with nitrogen *exo*-6-(*N*,*N*-dibenzylamino)-3-aza-bicyclo[3,1,0]hexane (274 mg, 1.00 mmol) was taken with CuI (19 mg, 10.0 mol%) ethylene glycol (124 mg, 2 mmol) K_3PO_4 (425 mg, 2.2 mmol) and iodobenzene (449 mg, 2.2 mmol) in 2 mL of isopropanol. The mixture was heated to 80 °C for 16 h. The mixture was cooled to room temperature, diluted with Et_2O (25 mL), filtered over a pad of Al_2O_3, and concentrated in vacuo. The crude product was then purified by crystallization from pentane/Et_2O m.p. = 79 °C. – IR (KBr): ν = 3022, 2829, 1602, 1508, 1508, 1360, 1162, 753, 702 cm^{-1}. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.56 (m, 2 H, CH), 2.70–2.75 (m, 1 H, CH), 3.08–3.16 (m, 2 H, CH_2), 3.37 (m, 2 H, CH_2), 3.67 (s, 4 H, Bn-H), 6.48 (d, *J* = 8.2 Hz, 2 H, aryl-H), 6.66 (t, *J* = xx Hz, 1 H, aryl-H), 7.16–7.38 (m, 12 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.1 (+, 2 C, CH), 48.2 (+, CH), 49.7 (–, CH_2), 59.0 (–, Bn-CH_2), 112.0 (+, 2 C, aryl-C), 116.0 (+, aryl-C), 127.0 (+, 2 C, aryl-C), 128.1 (+, 4 C, aryl-C), 129.1 (+, 2 C, aryl-C), 129.4 (+, 4 C, aryl-C), 138.7 (–, 2 C, C_{ipso}), 147.8 (–, C_{ipso}). – MS (DCI), *m/z* (%): 709 $[2\ M+H]^+$ (1), 372 $[M+NH_4]^+$ (8), 355 $[M+H^+]$ (100). – $C_{25}H_{26}N_2$ (354): calcd. C 84.71, H 7.39, N 7.97, found; C 84.99, 7.16, 8.08.



3-pheny-3-aza-bicyclo[3,1,0]hexylamine (**88**): Into a 100 mL flame-dried flask flushed with nitrogen, Pd/C (540 mg, 10% Pd w/w) was added, followed by 20 mL of DMA. This mixture was stirred under hydrogen atmosphere and after 30 min a solution of **87** (1.77g, 5 mmol) in 25 mL of DMA was added with a syringe and stirring was continued at room temperature for 2 d. Reaction mixture was filtered through a pad of Celite®, and the solvent was removed in vacuo, the product was crystallized by standing at 4 °C to yield 793 mg (91%) of **88** as a white solid, m.p. = 121 °c, – IR (KBr): ν = 3340, 2935, 2841, 1629, 1600, 1505, 1448, 1355, 1160, 745 cm^{-1}. –^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.66 (m, 2 H, CH), 1.71 (br. s, 2 H NH), 2.20–2.25 (m, 1 H, CH), 3.19–3.27 (m, 2 H, CH_2), 3.44–3.57 (m, 2 H, CH_2), 6.48 (d, *J* = 8.2 Hz, 2 H, aryl-H), 6.64 (t, *J* = 7.8 Hz, 1 H, aryl-H), 7.16–7.24 (m, 2 H, aryl-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.2 (+, 2 C, CH), 35.8 (+, CH), 49.6 (–, CH_2), 112.0 (+, 2 C, aryl-C), 116.0 (+, aryl-C), 129.0 (+, 2 C, aryl-C), 147.8 (–, C_{ipso}). – MS (70 eV) *m/z* (%): 174 (20) $[M^+]$, 106 (12), 69 (100).



4. Summary

The work in this thesis starts with the advanced synthesis of methyl 2-chloro- and 2-bromo-2-cyclopropyledeneacetate (**4**-Me and **5**). The cyclopropanol derivative (**31**) obtained by Kulinkovich reductive cyclopropanation of 3,3-diethoxy propionate, was easily converted to 2-(1'-mesyloxycyclopropyl)-acetic acid (**28**) by mesylating the alcohol group followed by oxidation. α-Chlorination of the in situ formed acid chloride of the acid **28** with *N*-chlorosuccinamide in presence of catalytic amount of HCl generated the chloride **32a** which under basic elimination furnished the methyl 2-chloro-2-cyclopropyledeneacetate (**5**). In the similar way the bromo analogue **4-Me** was prepared by using *N*-bromosuccinamide.

A series of different amidines (**34b**–**f**) was easily prepared from the corresponding nitriles which underwent Michael addition followed by domino transformation in presence of triethyl amine to afford cyclobutene annelated pyrimidinones (**35a**–**j**). These pyrimidinones were reacted with phenyl vinyl sulfone to produce 6-sulfone substituted tetrahydroquinazolinones (**37a**–**h**) under thermal or microwave assisted conditions. Basic elimination of **37a**–**h** followed by hydrogenation led to 2-substituted 5,6,7,8-tetrahydroquinazolinones (**39a**–**f**). Alkylation of the tetrahydro- ring was done by use of base such as *n*-BuLi to get the alkylated product (**40**, **42a**,**b**). Nucleophilic substitution of *S*Me group of the compound **37h** with different secondary amines produced the 2-amino derivative of 5,6,7,8-tetrahydroquinazolinones **46a**–**c**.

Michael addition of indole onto methyl 2-chloro-2-cyclopropylideneacetate (**5**) in presence of a Lewis acid furnished the methyl 2-chloro-2-[1-(1H-indol-3-yl)cyclopropyl]acetate **(55)**. The cyclopropanated tryptophane methyl ester **56** was prepared by nucleophilic substitution of the chloride **55** with sodium azide under phase transfer catalysis followed by subsequent reduction of the azido ester **57**. The Pictet–Spengler reaction of the ester **56** with *p*-anisaldehde or piperonal produced the tetrahydro-β-carbolines (**59a**,**b**) with greater efficiency than the corresponding non-cyclopropanated precursor. In both cases products were obtained as a mixture of two diasteriomers (*cis*/*trans* = 1 : 1.7 for **59a** and 1 : 2.5 for **59b**) from which the *trans*-isomers were easily separated by crystallization from ethyl acetate. Treatment of the tetrahydro-β-carboline **59a** with *n*-butyl isocyanate gave the cyclopropanated hydantoin lead structure to Tadalafil (**25**). The tetrahydro-β-carboline **59b** was efficiently converted to the spirocyclopropanated analogue of Tadalafil (**26**) in two steps with a very good yield.

Michael addition of carboxamides with compound **5** gave the spirocyclopropanated oxazoline carboxylate methyl esters (**13a**–**e**), from which free carboxylic acids (**64a**–**e**) were obtained under basic hydrolysis. Coupling reaction of **64a**–**e** with different anilines in presence of HOAt/EDC and colidine gave the amide **68a**–**j** with very good yields. The coupling products with α-hydroxy anilines under Mitsunobu reaction conditions (Ph_3P/DEAD) gave the benzoxazole derivatives of oxazolines (**69a**–**e**). The bromide group present in the *N*-methylated products of **70a**,**b** were reacted with varieties of amines under Buchwald reaction conditions to give the amino-aryl derivatives **71a**–**j**. Similarly, Suzuki reaction conditions were successfully applied to synthesize the biary-derivatives of oxazolines (**72a**–**d**).

Sequential Michael reaction of Grignard reagent and aldol reaction with the compound **5** produced the β-chloro alcohols **75a**–**l** and in most cases single diasteriomers (> 97%, *anti* 2S*,2R*) were obtained. The structure was deduced from a single crystal X-ray structure analysis. These β-chloro alcohols **75a**–**l** are good precursors for the synthesis of α,β-epoxyesters. The β-chloro alcohol **75b**-iPr underwent clean cyclization under basic condition to produce diasteriomerically pure α,β-epoxyester **79b**-iPr. The analogous α,β-epoxyester **79a**-iPr was obtained directly from methyl 2-bromo-2-cyclopropylideneacetate (**4**-Me) upon treatment with isopropylmagnesium chloride and benzaldehyde. Apparently, the bromohydrine analogous to **75a**-iPr is not stable under the work-up conditions and undergoes cyclization by intramolecular nucleophilic displacement.

The orthogonally protected diamine *exo*-6-(*N*,*N*-dibenzylamino)-3-aza-bicyclo[3,1,0]hexane-3-carboxylic acid *tert*-butyl ester (**82**) was also prepared from *N*-*tert*-butoxycarbonyl-3-pyrroline (**81**). Selective deprotection of either the *tert*-butoxycarbonyl group or dibenzyl group provided monoprotected derivatives **83** and **84** with good yields. The phenylation reaction of **83** catalyzed by CuI was found to be more efficient than the corresponding $Pd_2(dba)_3$ catalyzed reaction to produce **87** Unlike in the case of **84** the debenzylation reaction was successful in dimethy acetamide to give the product **88**.

4. Zusammenfassung

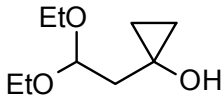
In der vorliegenden Arbeit wurde zunächst eine verbesserte Synthese von 2-Chlor- und 2-Brom-2-cyclopropylidenessigsäuremethylester (**4**-Me und **5**) vorgestellt. Hierzu wurde das Cyclopropanol-Derivat **31**, das durch eine Kulinkovich-Reaktion von 3,3-Diethoxypropionsäuerester dargestellt wurde, durch Mesitylierung und nachfolgender Oxidation in die 1'-Mesityloxycyclopropansäure (**28**) überführt. α-Chlorierung des in situ gebildeten Säurechlorids mit N-Chlorsuccinimid in Gegenwart katalytischer Mengen Chlorwasserstoff ergab das Chlorid **32a**, welches durch basische Eliminierung 2-Chlor-2-cyclopropylidenessigsäuremethylester (**5**) ergibt. Durch die analoge Reaktion mit *N*-Bromosuccinimid wurde **4**-Me dargestellt.

Eine Reihe verschiedener Amidine (**34b**–**f**) wurde aus den Nitrilen durch eine Michael-Addition mit nachfolgender Domino-Reaktion in Gegenwart von Triethylamin zu den Cyclobuten-annelierten Pyrimidinonen (**35a**–**j**) synthetisiert. Diese wurden dann thermisch oder durch Mikrowellen mit Vinylsulfon zu den substituierten Tetrahydrochinolidinen (**37a**–**h**) umgesetzt. Basische Eliminierung gefolgt von Hydrogenolyse fuehrte zu den 2-substituierten 5,6,7,8-Tetrahydrochinolidinen **39a**–**f**. Alkylierung nach der Deprotonierung mit einer Base wie *n*-BuLi ergab die Produkte **40**, **42a,b**. Durch nucleophile Substitution der SMe-Gruppe in der Verbindung **37h** mit verschiedenen sekundären Aminen konnten die 2-Amino-Derivate **46a**–**c** erhalten werden. Mittels Michael-Addition von Indol an 2-Chlor-2-cyclopropylidenessigsäuremethylester (**5**) in Gegenwart einer Lewis-Säure wurden 2-Chlor-2-[1-(1H-indol-3-yl)-cyclopropyl)-essigester (**55**) dargestellt. Der cyclopropanierte Tryptophanester **56** wurde durch die nucleophile Substitution von **55** mit Natriumazid unter Phasentransferbedingungen und nachfolgender Reduktion erhalten. Die Pictet-Spengler-Reaktion mit *p*-Anisaldehyd oder Piperonal ergab die Tetrahydro-β-carboline **59a,b** effizienter als der entsprechende nicht-cyclopropanierte Vorläufer. In beiden Fällen wurde eine Mischung aus zwei Diastereomeren (*cis/trans* = 1 : 1.7 fuer **59a** bzw. 1 : 2.5 fuer **59b**) isoliert. Das *trans*-Isomer konnte durch Kristallisation aus Essigester erhalten werden. Die Reaktion von **59a** mit *n*-Butylisocyanate ergab die cyclopropanierte Hydantoin Leitstruktur für Tadalafil (**25**). Das Tetrahydro-β-carbolin **59b** wurde in zwei Stufen mit guter Ausbeute in das spirocyclopropanierte Analogon von Tadalafil (**26**) ueberfuehrt.

Eine weitere Michael-Addition von Carboxamiden mit Verbindung **5** ergab die spirocyclopropanierten Oxazolinecarbonsaeuremethylester **13a**–**e**, aus denen die freie Carbonsaeure (**64a**–**e**) durch Hydrolyse erhalten wurde. Kupplung mit verschiedenen Anilinen in Gegenwart von HOAt/EDC und Colidin ergab die Amide **68a**–**j** in guten Ausbeuten. Die Reaktion mit α-Hydroxyanilinen unter Mitsunobu-Bedingungen (Ph_3P/DEAD) erbrachte die Benzoxazol-Derivate **69a**–**e**. Eine Buchwald-Reaktion der *N*-methylierten Produkte **70a,b** mit einer Vielzahl von Aminen fuehrte zu den Aminoaryl-Derivaten **71a**–**j**. Analog fuehrte die Suzuki-Reaktion erfolgreich zu den Biaryl-Oxazolinen **72a**–**d**.

Die Addition von Grignard-Reagenzien an Verbindung **5** und nachfolgende Aldol-Reaktion fuehrte zu den β-Chloralkoholen **75a**–**l** meist in Form eines einzigen Diastereomers (> 97%, *anti* 2S*,2R*). Die Struktur wird durch die Röntgenstruktur belegt. Die Verbindungen **75a**–**I** sind hervorragende Ausgangsverbindungen zur Synthese von α,β-Epoxyestern. Der β-Chloralkohol **75b**-*i*Pr konnte zu dem α,β-Epoxyester **79b**-*i*Pr in Form eines einzigen Diastereomers cyclisiert werden. Der analoge α,β-Epoxyester **79a**-iPr wurde direkt aus 2-Brom-2-cyclopropylidenessigsäuremethylester (**4**-Me) durch Reaktion mit Isobutylmagnesiumchlorid und Benzaldehyd erhalten. Offensichtlich ist das Bromhydrin nicht stabil und cyclisiert durch eine intramolekulare nucleophile Substitution.

Der orthogonal geschuetzte *exo*-6-(*N,N*-Dibenzylamino)-3-aza-bicyclo[3.1.0]hexan-3-carbonsaeure-tert-butylester (**82**) wurde ebenfalls aus *N*-*tert*-Butoxycarbonyl-3-pyrrolin (**81**) hergestellt. Selektive Entfernung der tert-Butoxycarbonylgruppe bzw. der Dibenzylgruppe ergab die Derivate **83** und **84**. Die Kupfer-katalysierte Phenylierung von **83** zu **87** erwies sich als effizienter als die entsprechende Palladium-katalysierte Reaktion. Im Gegensatz dazu war die Dibenzylierung von **84** zu **88** mit Dimethylacetamid erfolreich.



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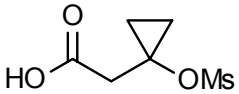

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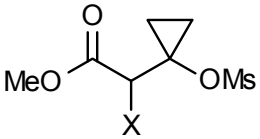
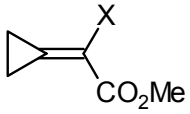
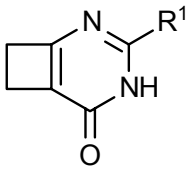


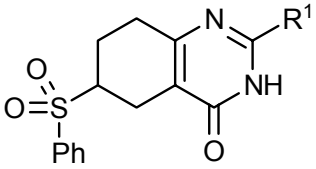
32a: X = Cl
32b: X = Br



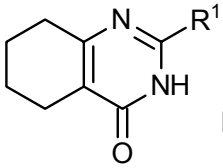
5: X = Cl
4-Me: X = Br



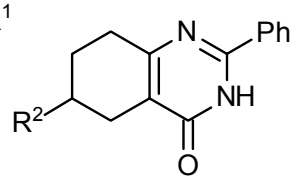
35a–i



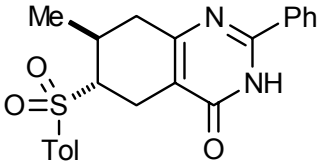
37a–h



39a–f



42a,b



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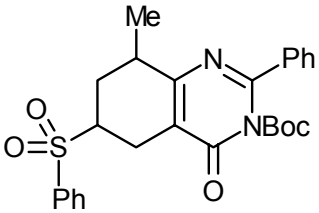

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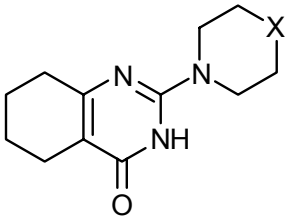
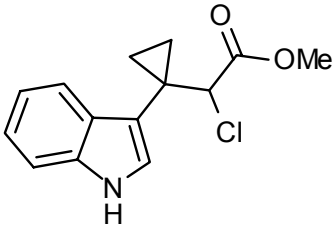


46a–c



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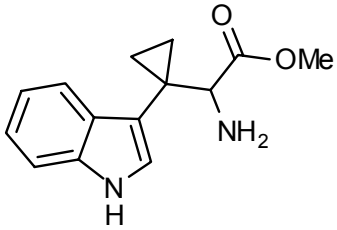

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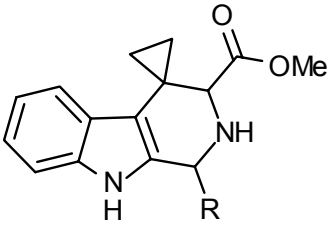
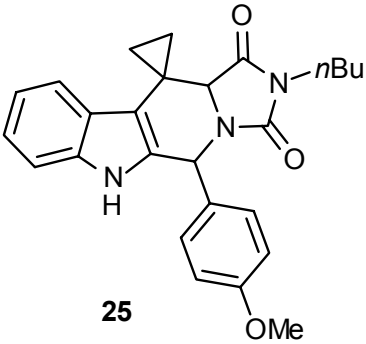


59a,b



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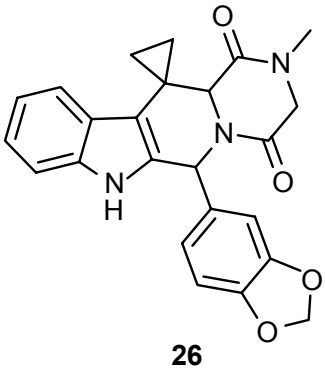

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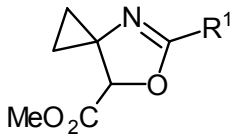
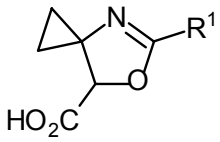
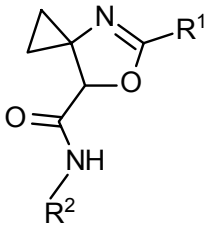


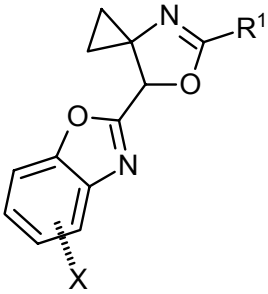
13a–e



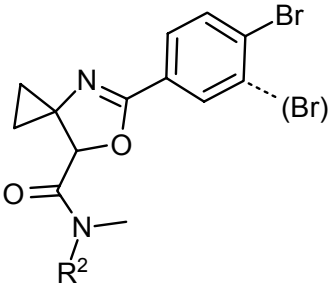
64a–e



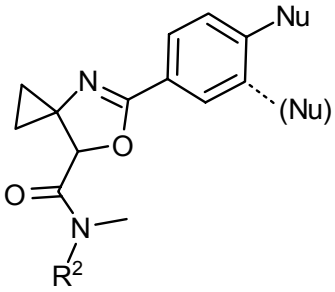
68a–j



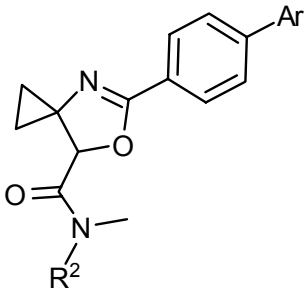
69a–e



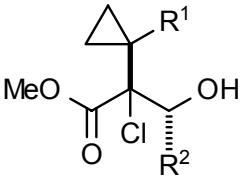
70a–b



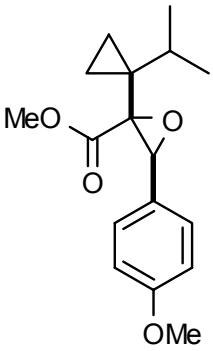
71a–j



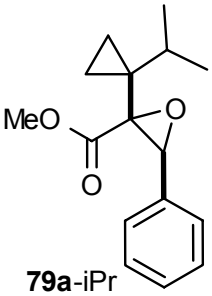
72a–d



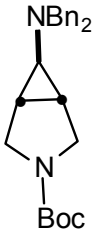
75a–l-R^1



79b-iPr



79a-iPr



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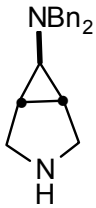

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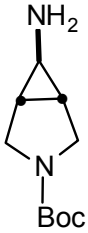

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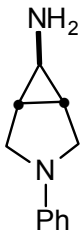
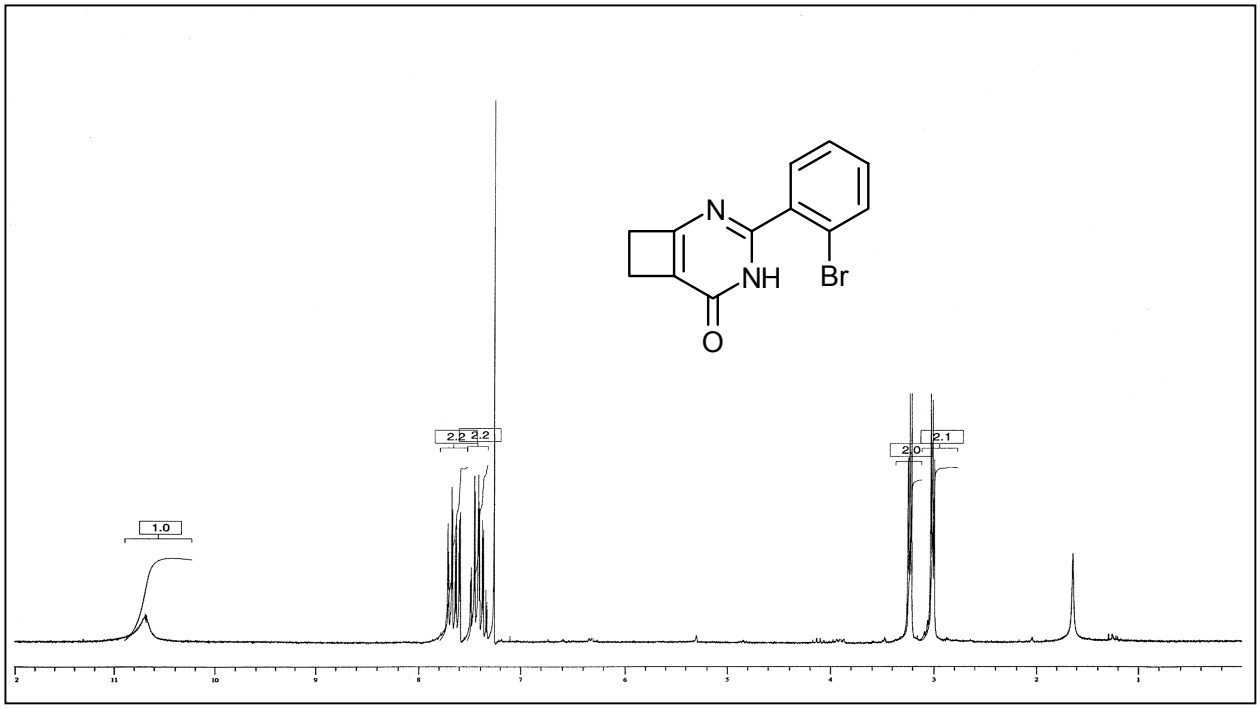
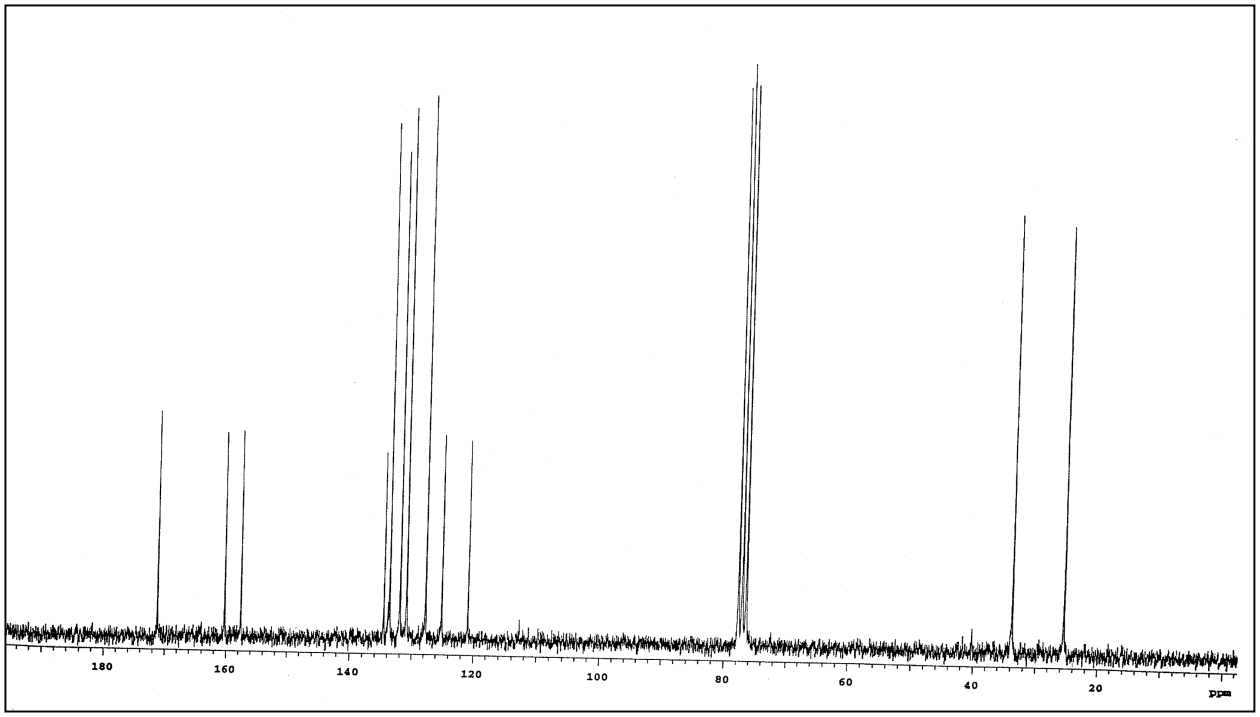


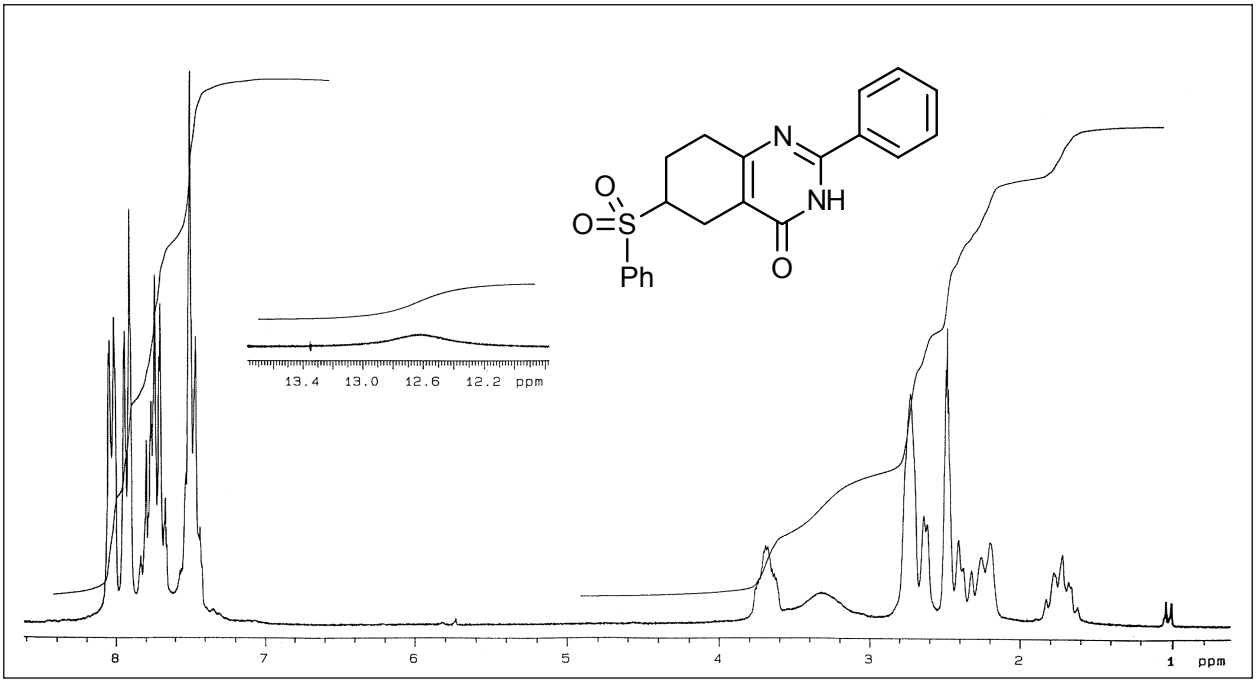
88

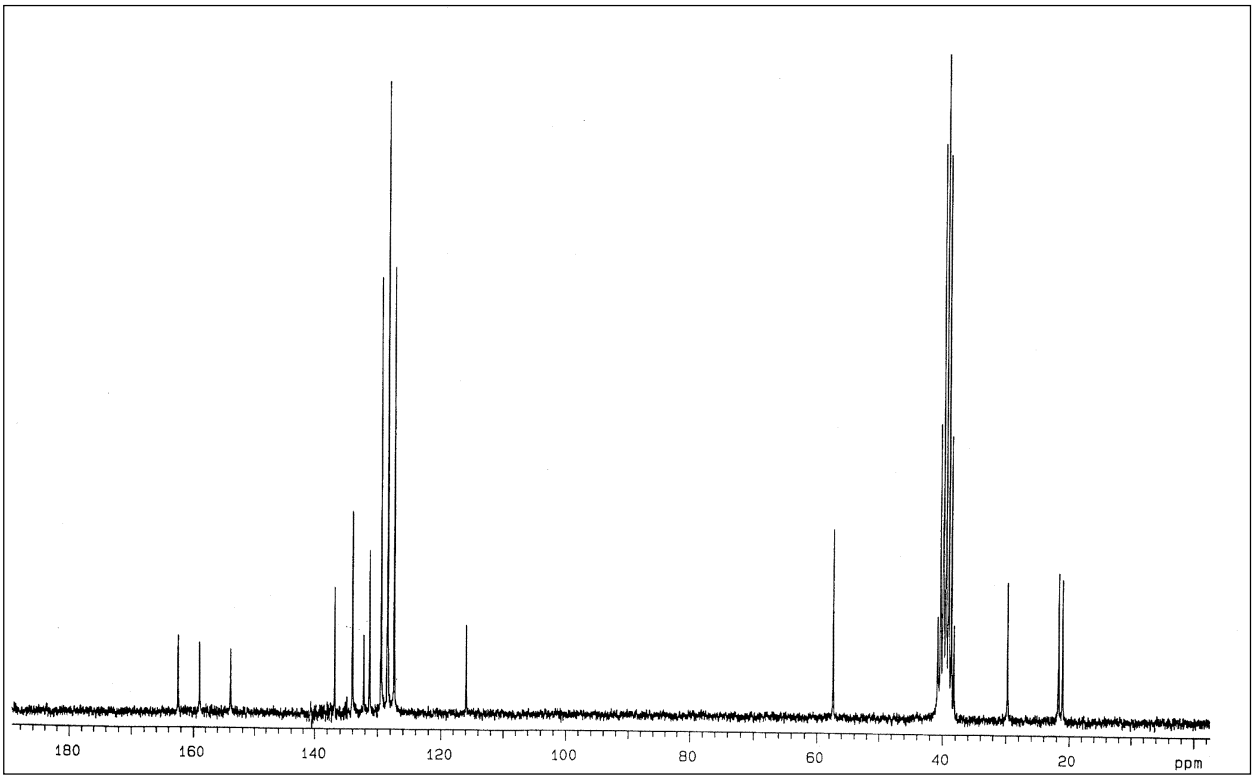
5. Spectral Data



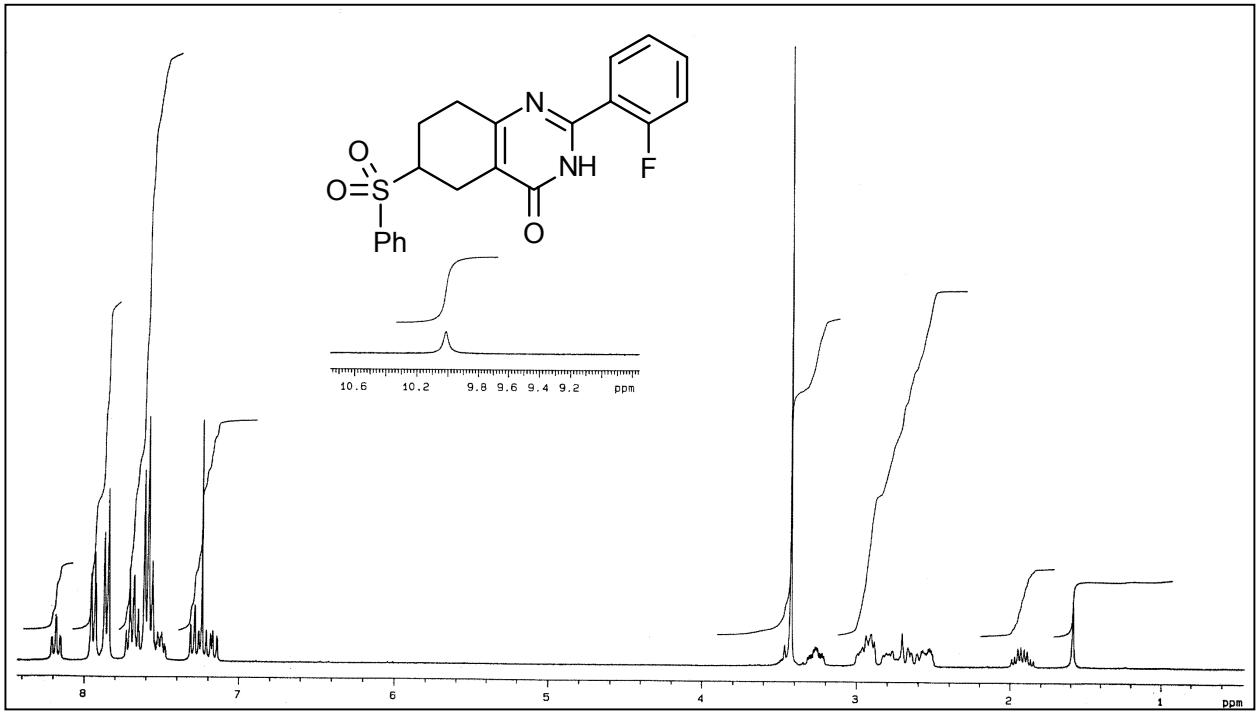


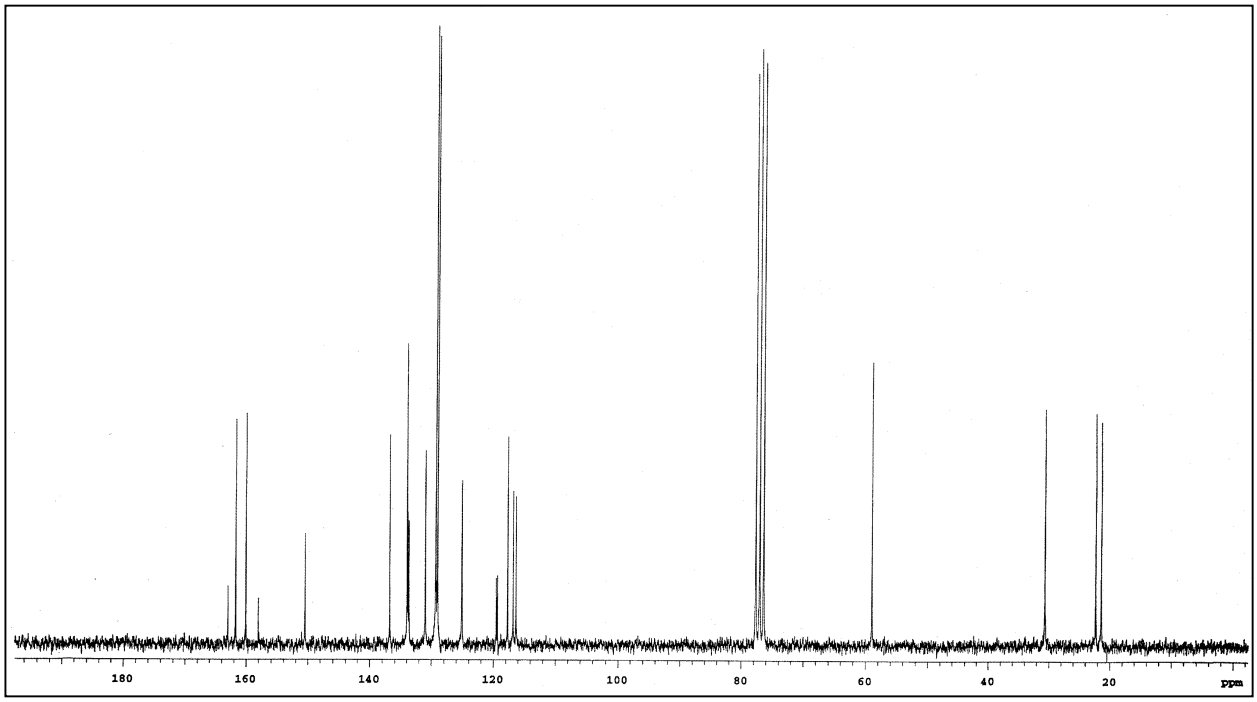
3-(o-Bromophenyl)-2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**35c**)



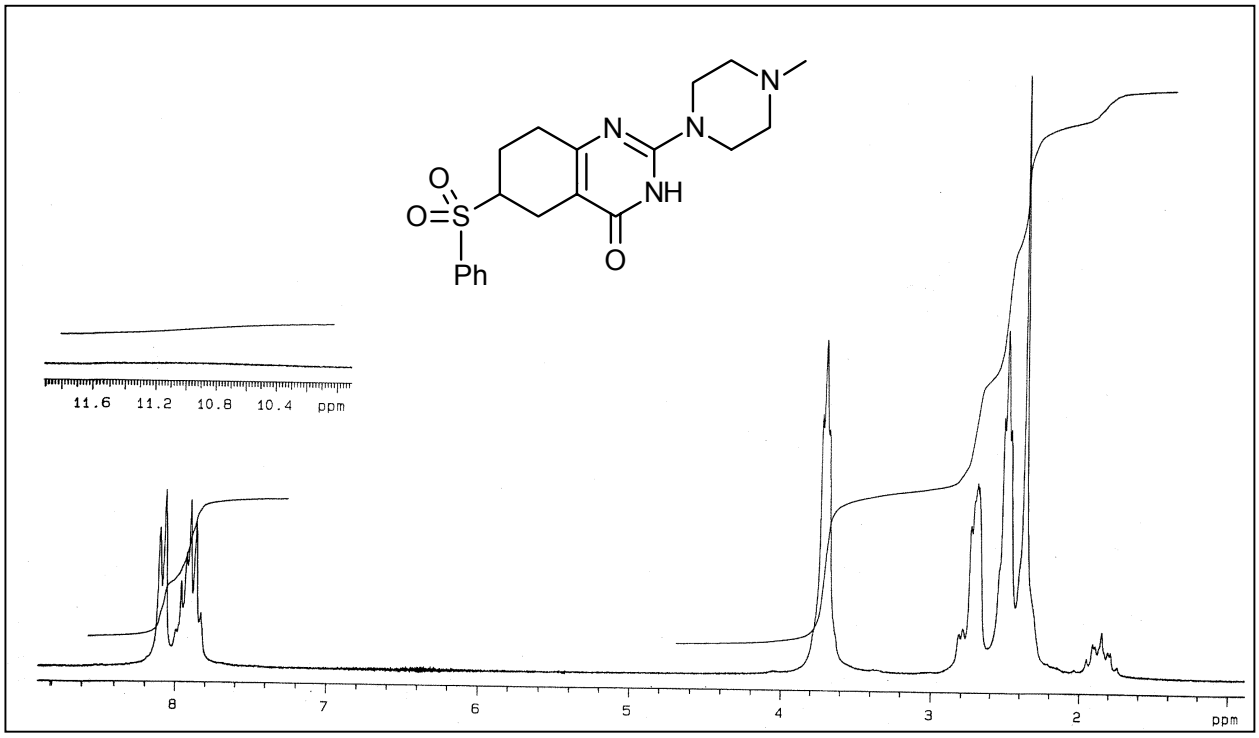


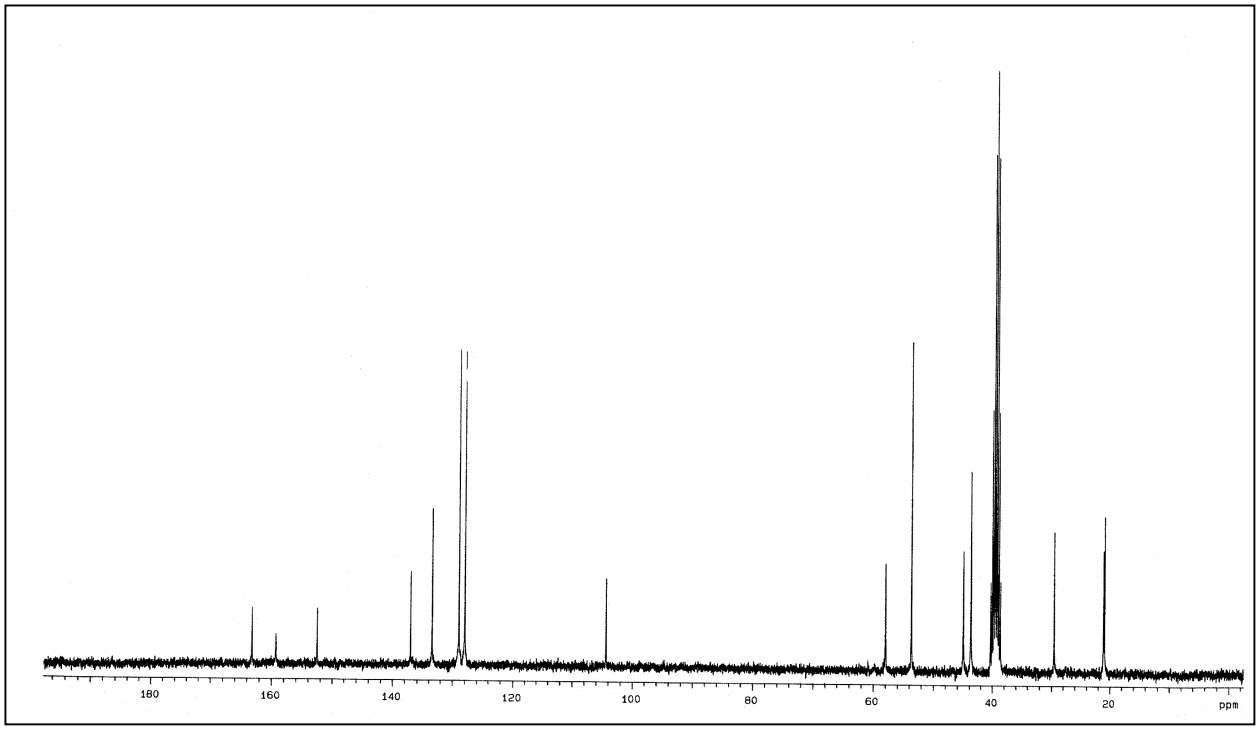
6-Benzenesulfonyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37a**)



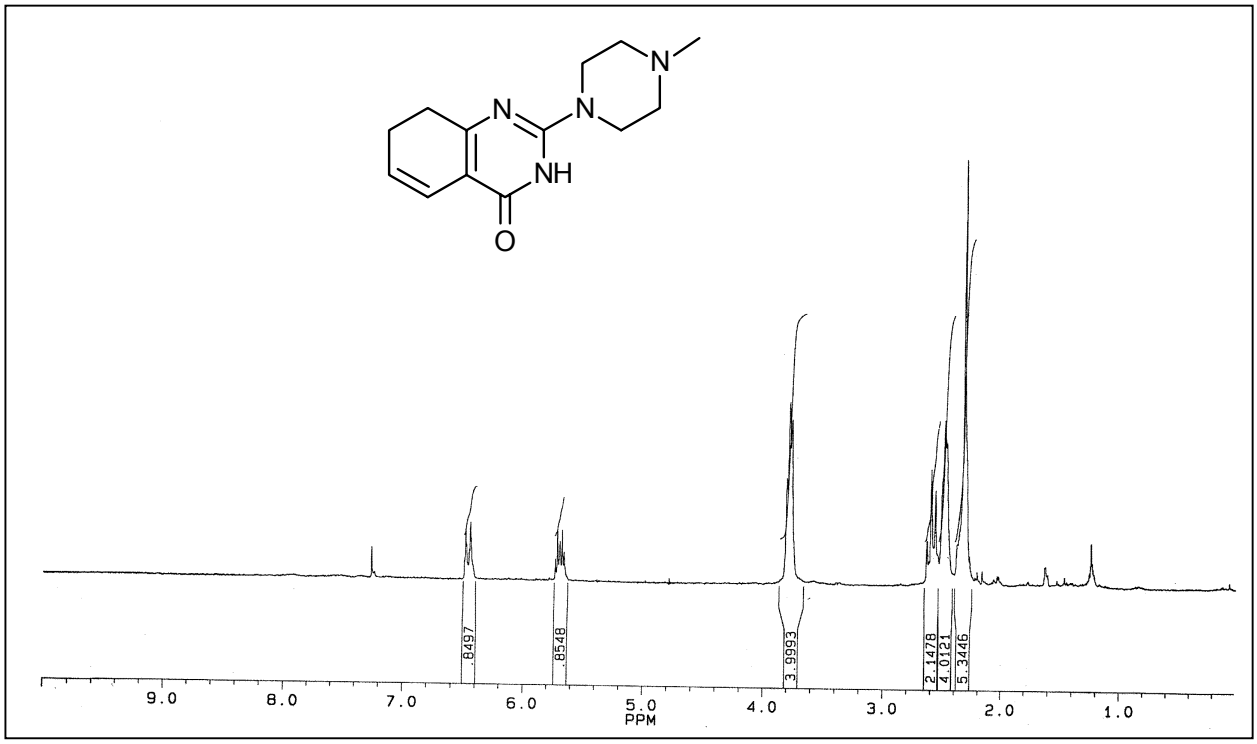


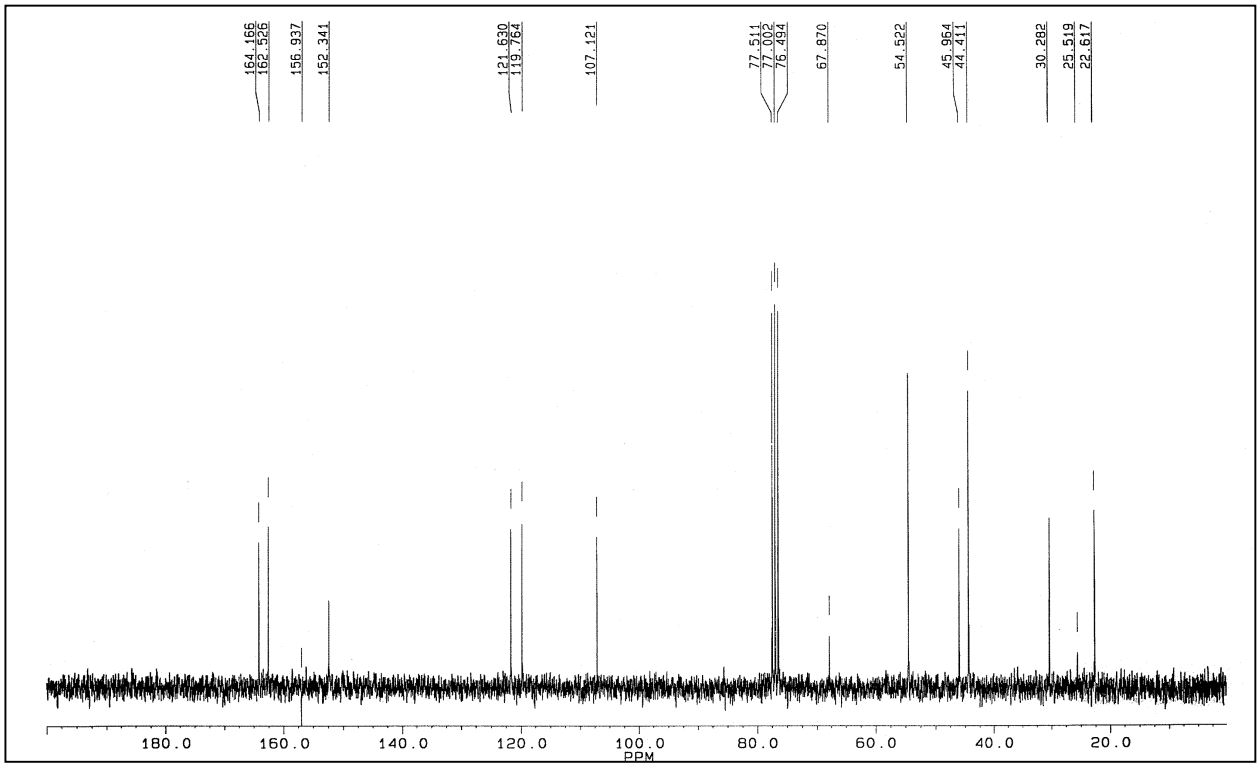
6-Benzenesulfonyl-2-(o-fluorophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**37d**)



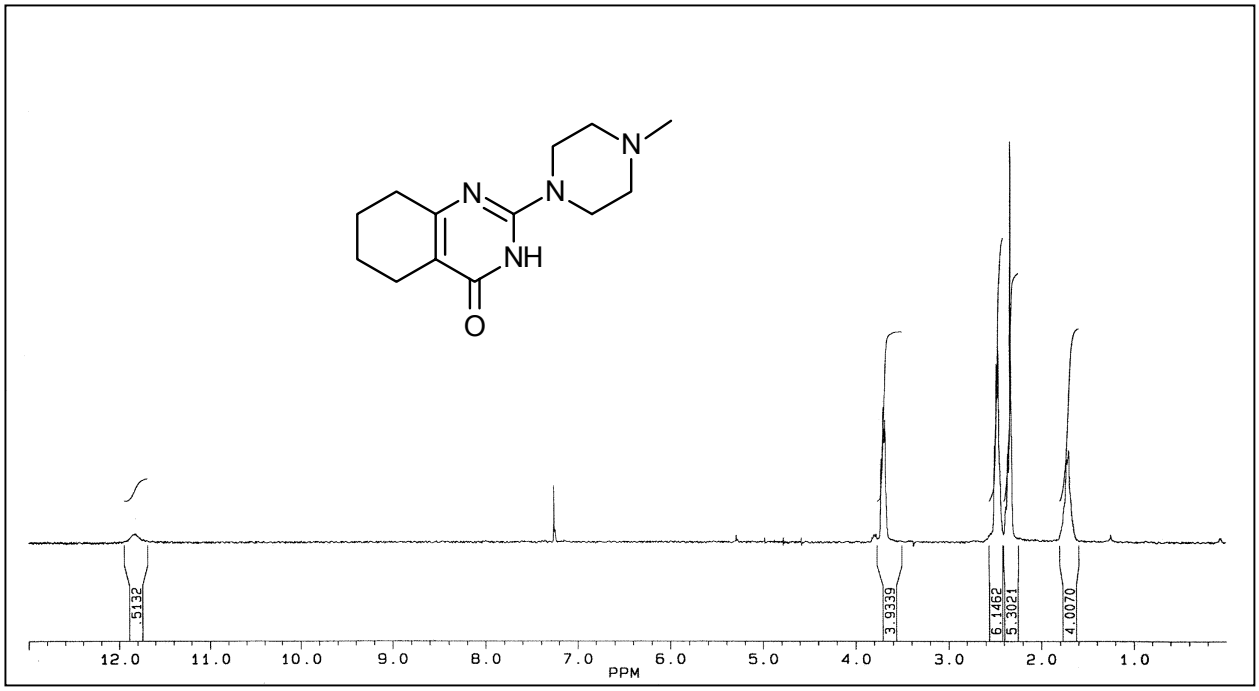


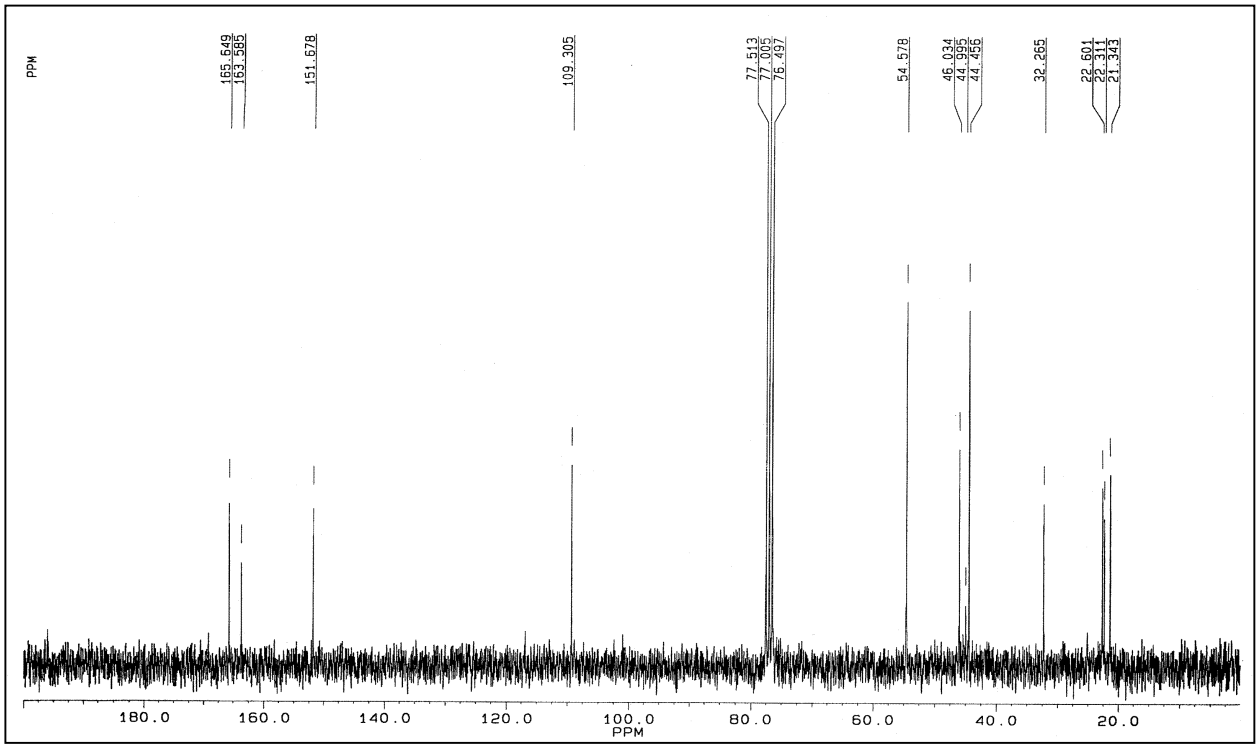
6-Benzenesulfonyl-2-(4-methylpiperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one **(45c)**



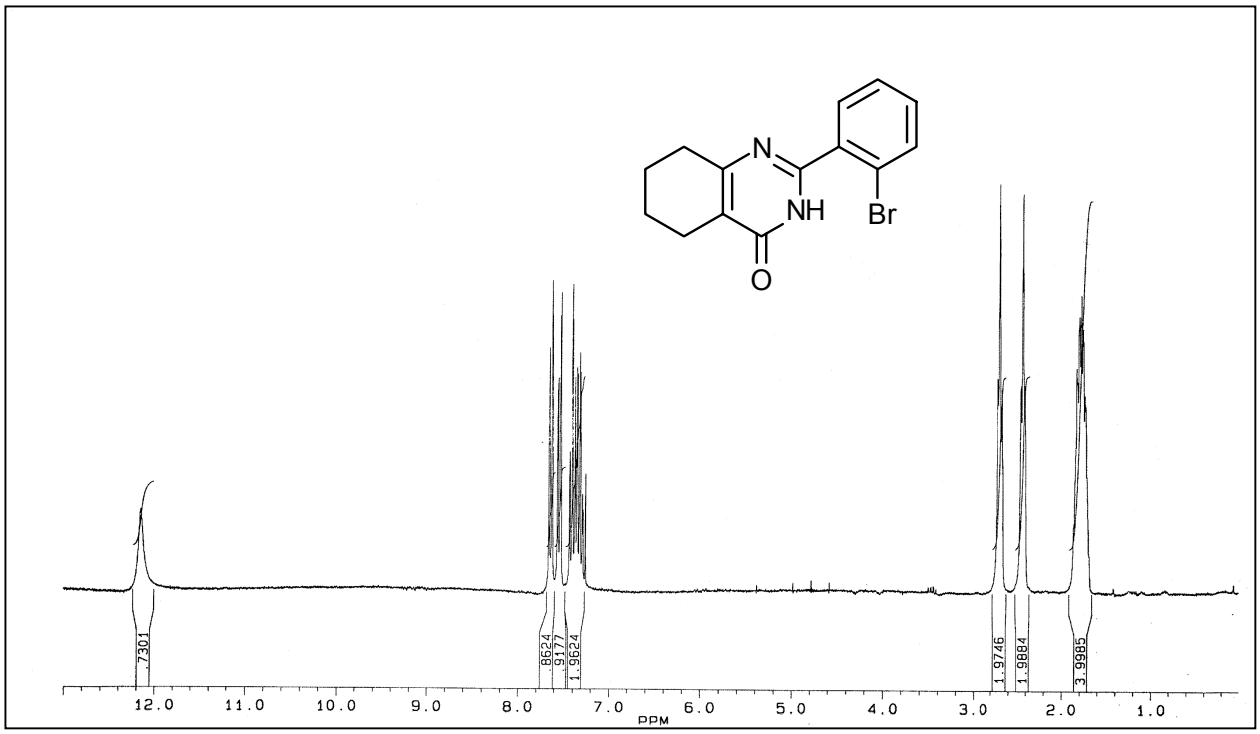


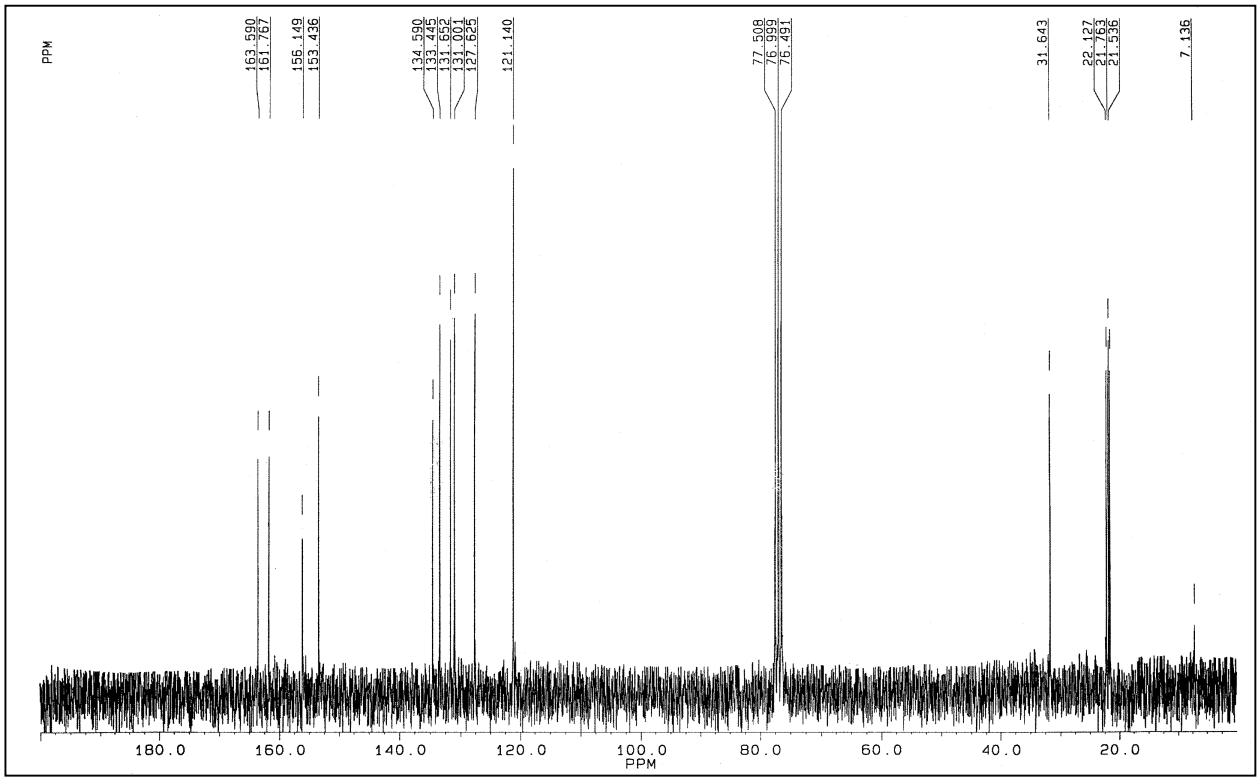
2-(4-Methylpiperazin-1-yl)-7,8-dihydroquinazolin-4(3H)-one (**47c**)



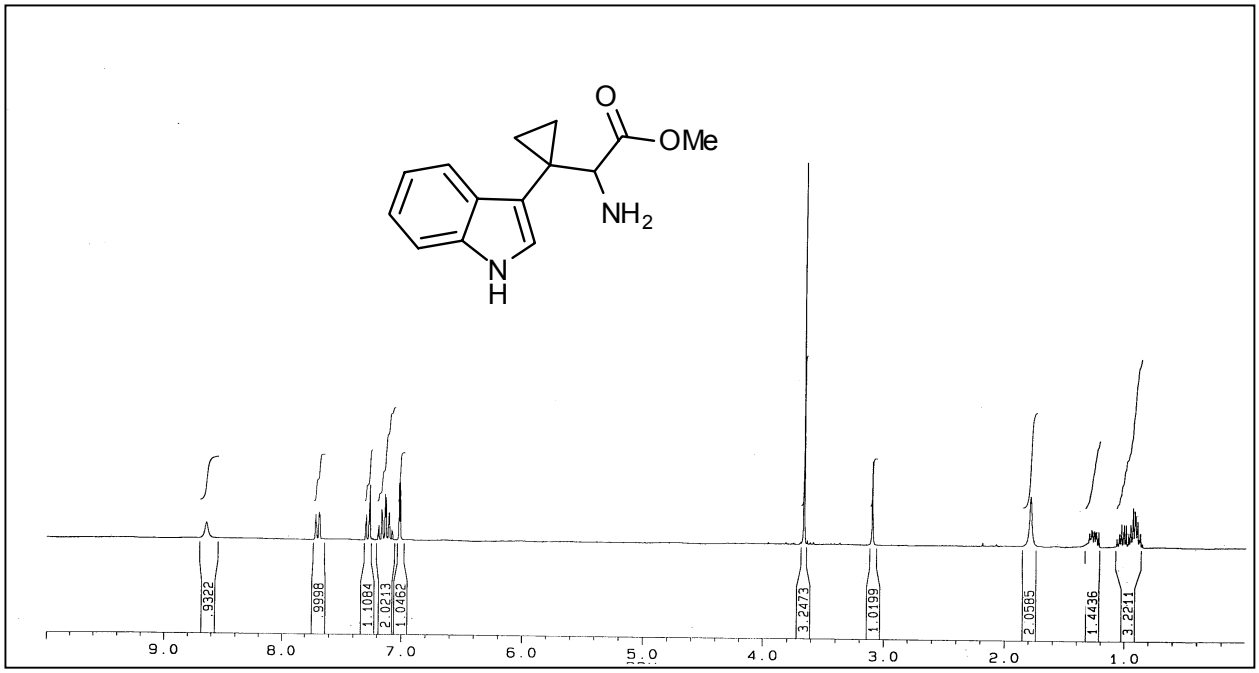


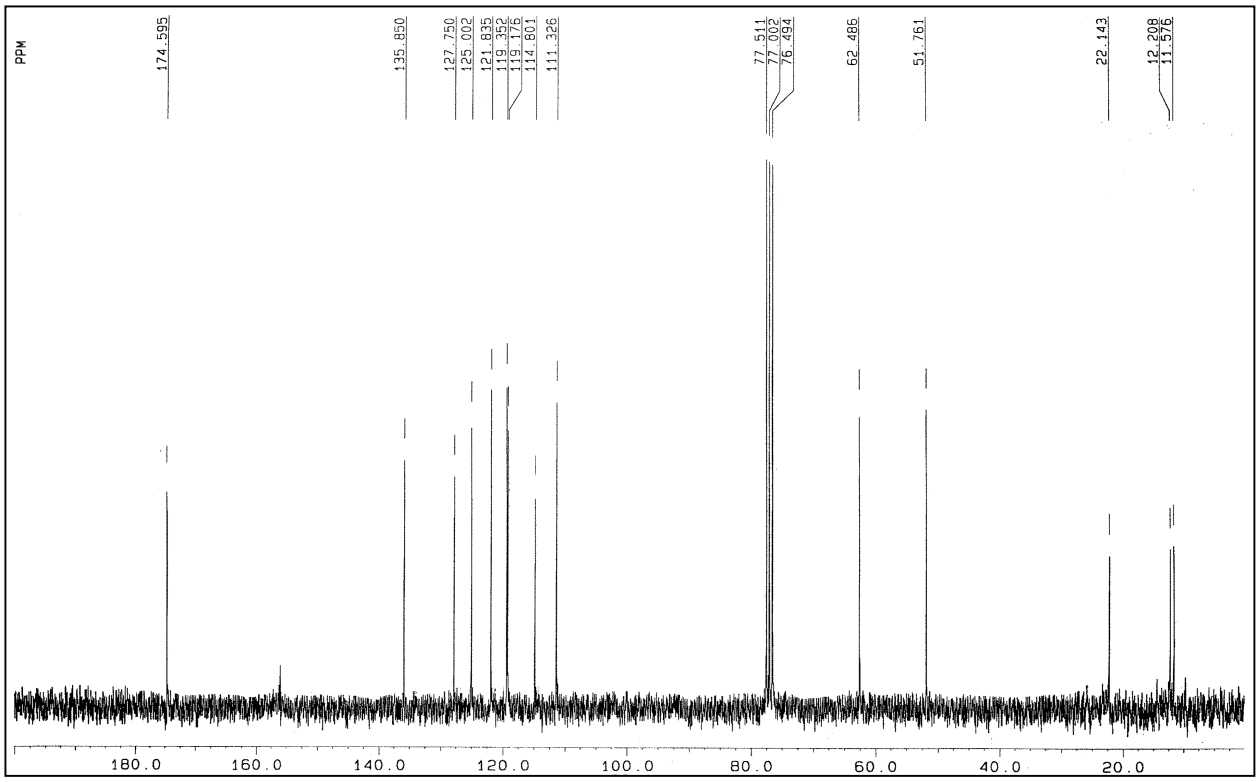
2-(4-Methylpiperazin-1-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**46c**)



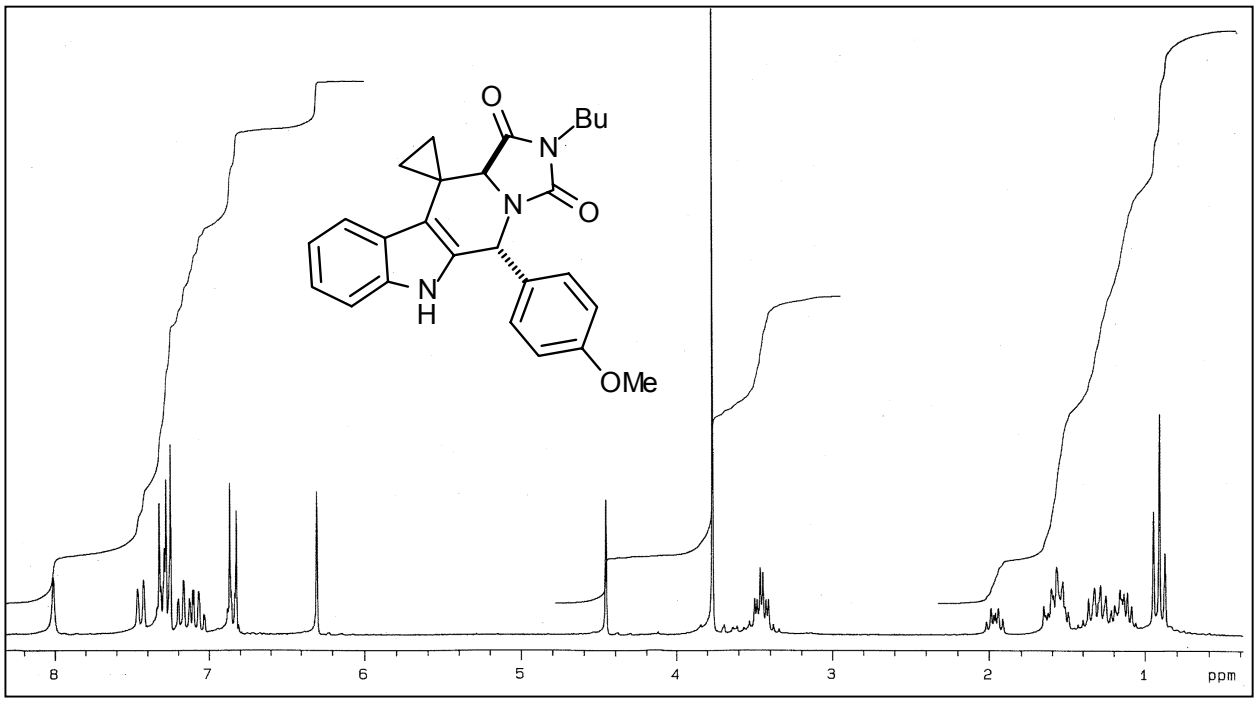


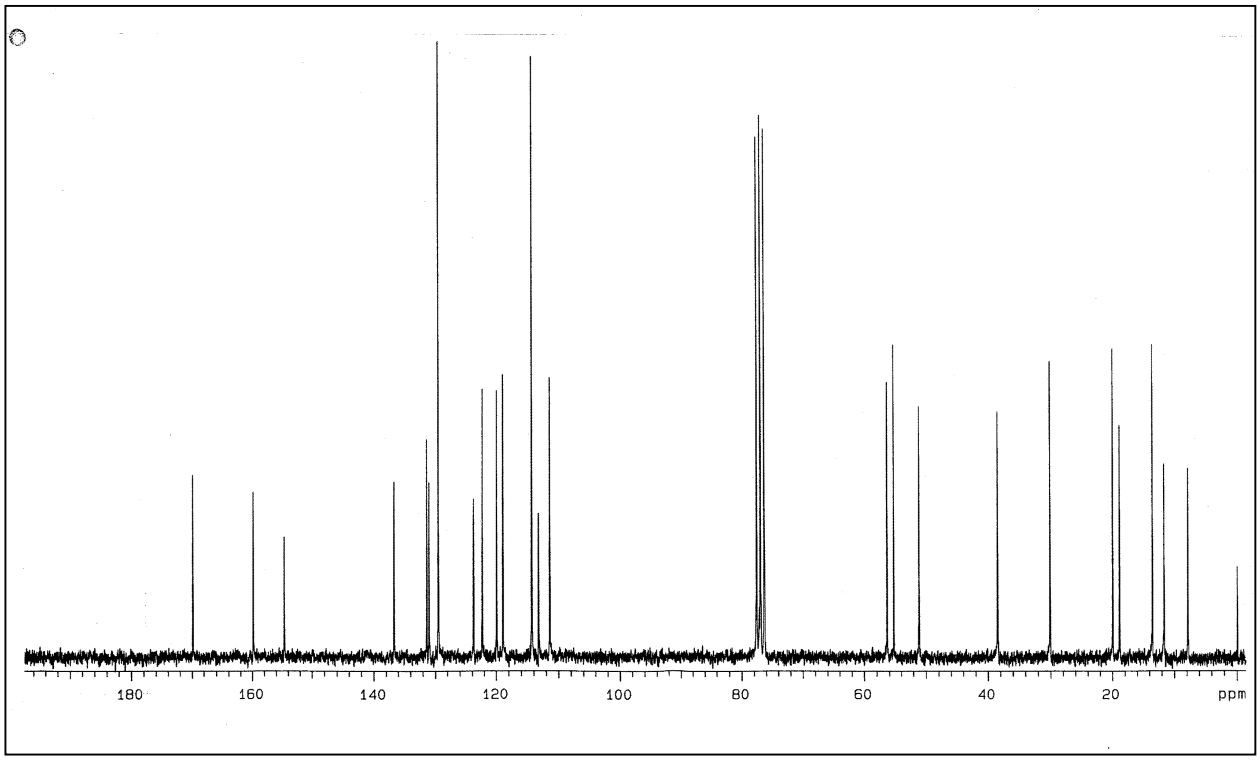
2-(o-Bromophenyl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**39c**)



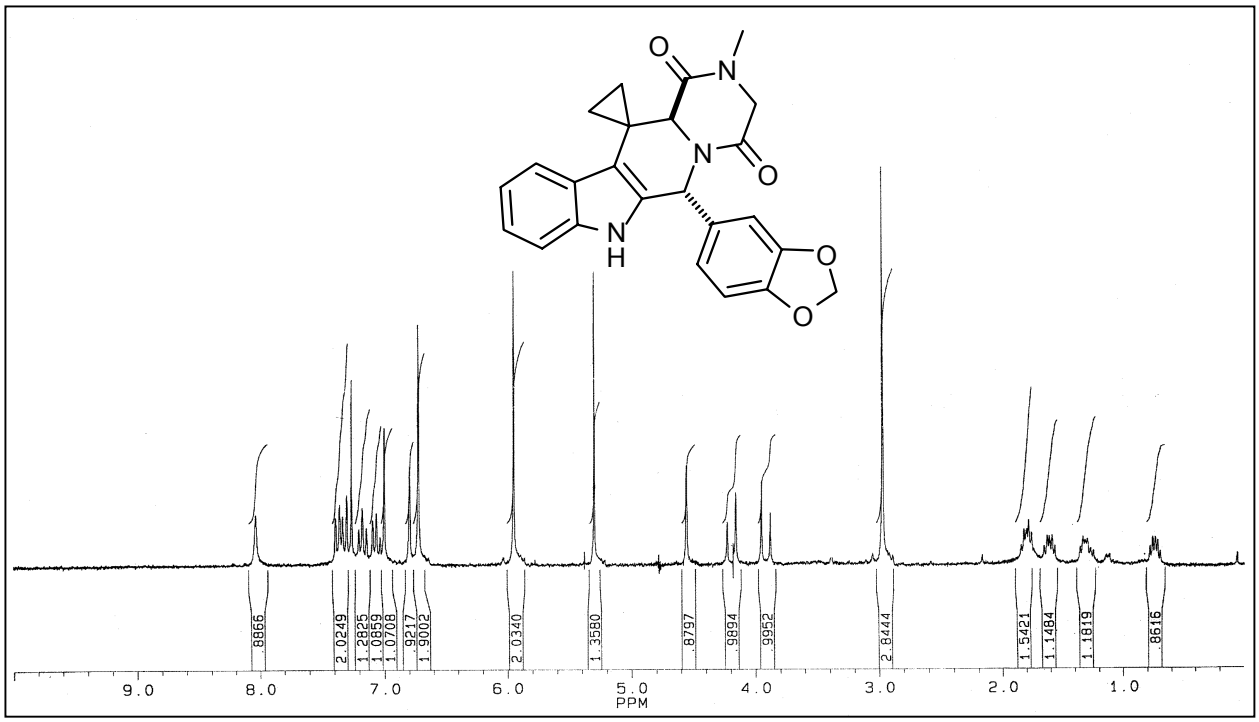


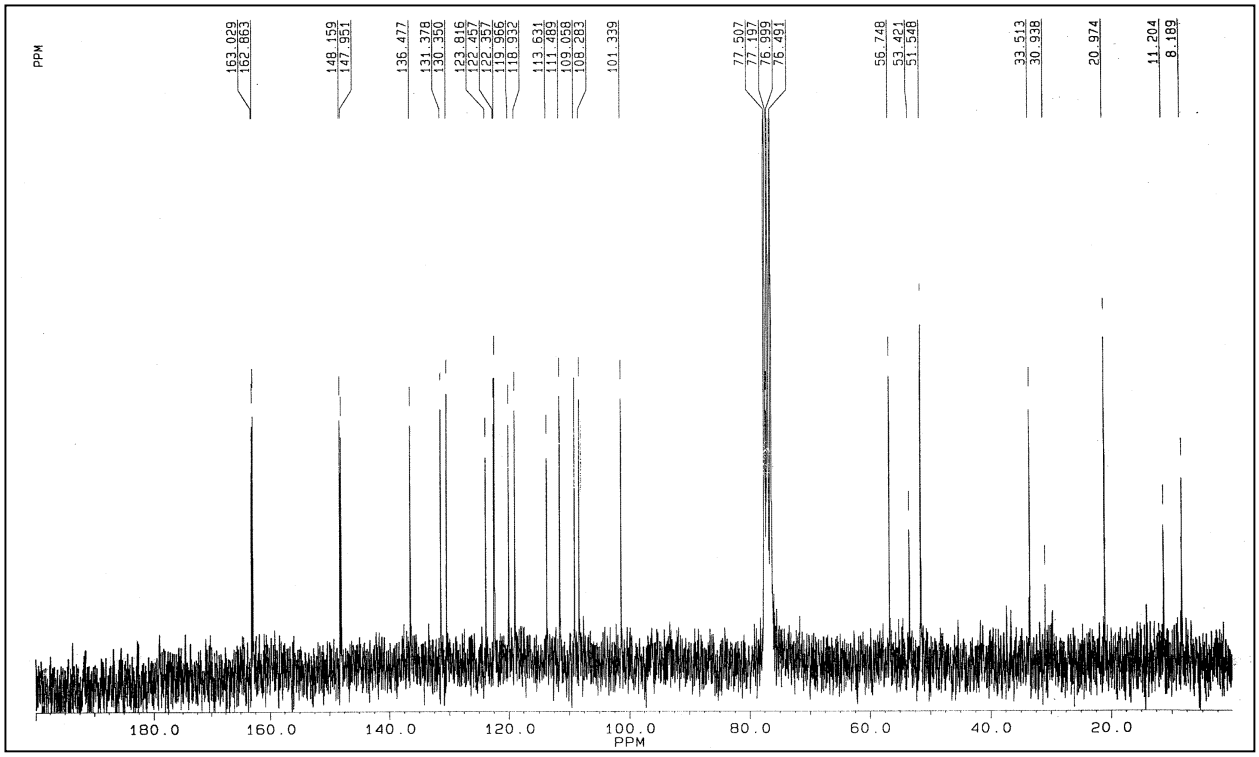
Methyl 2-amino-2-[1-(1H-indol-3-yl)cyclopropyl]acetate (**56**)



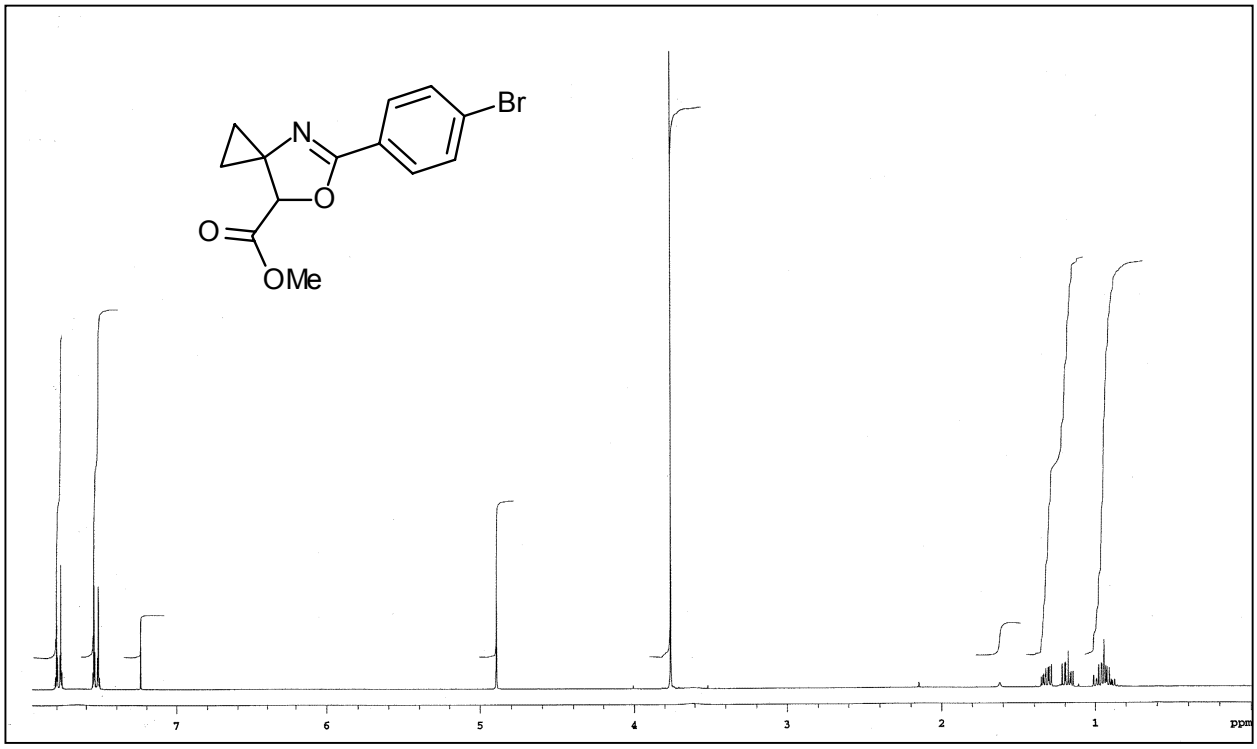


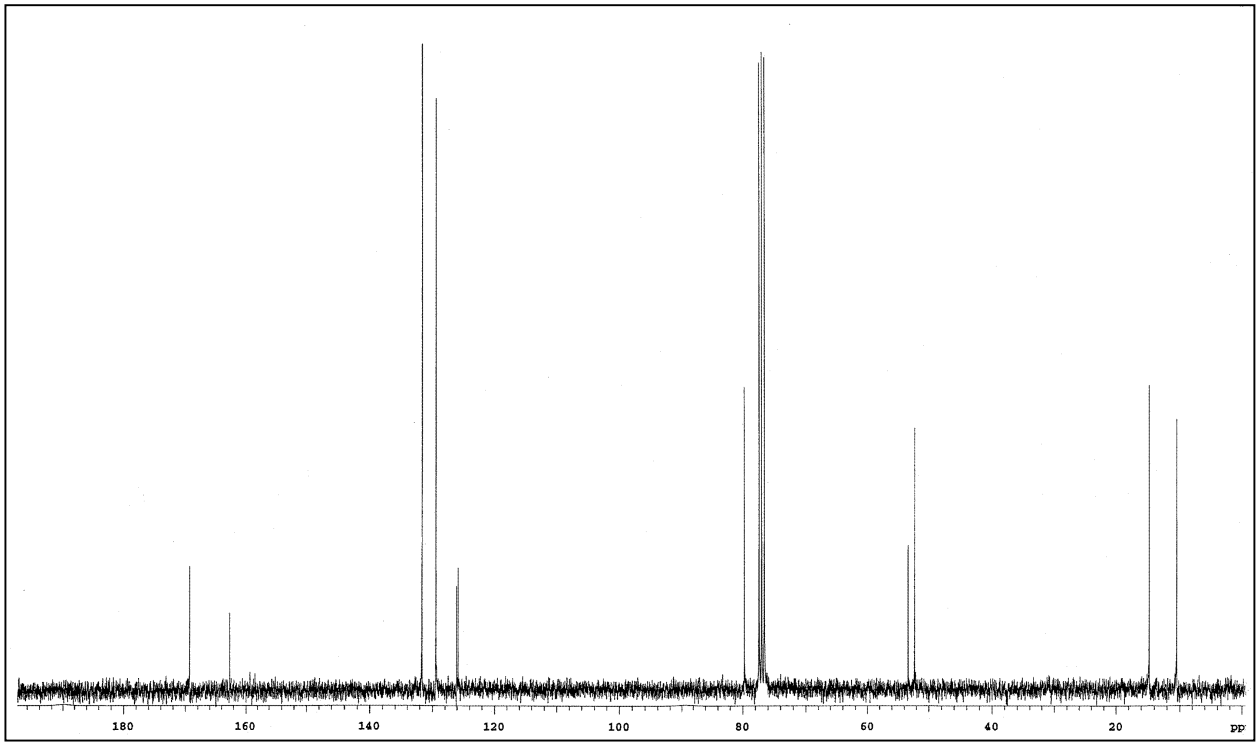
trans-2'-Butyl-10'-(4-methoxyphenyl)-3a',4',9',10'-tetrahydrospiro[cyclopropane-1,4'-(2',9',10a'-triazacyclopenta[b]fluorene)]-1',3'-dione (*trans*-**25**)



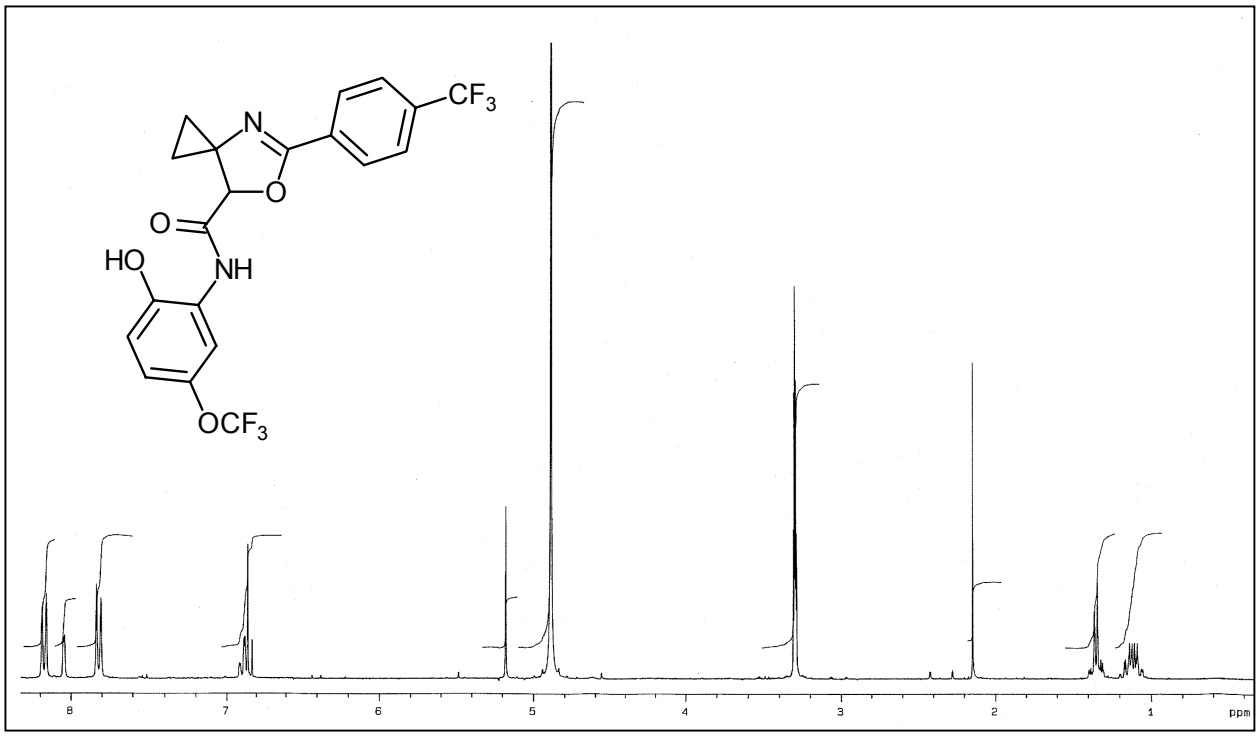


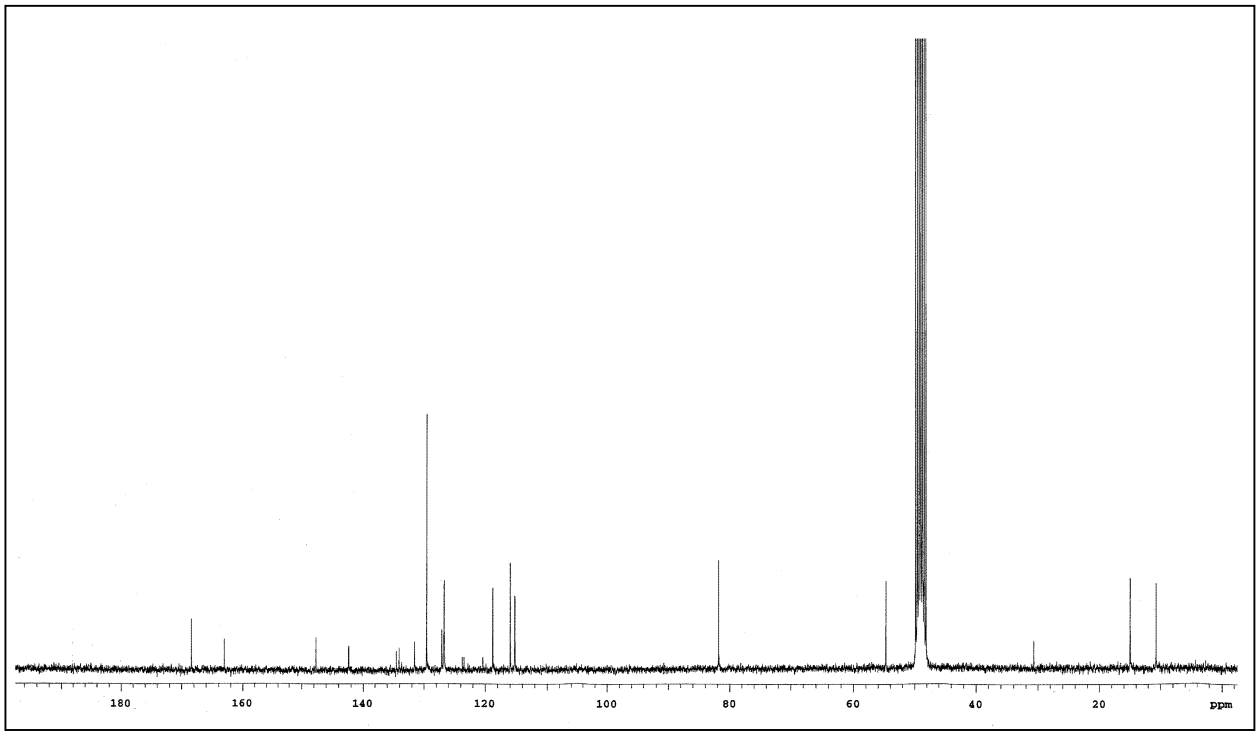
trans-6'-(1,3-Benzodioxole-5-yl)-2'-methyl-12'-spirocyclopropyl-2',3',6',7',12',12a'-hexa-hydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1',4'-dione (*trans-***26**)



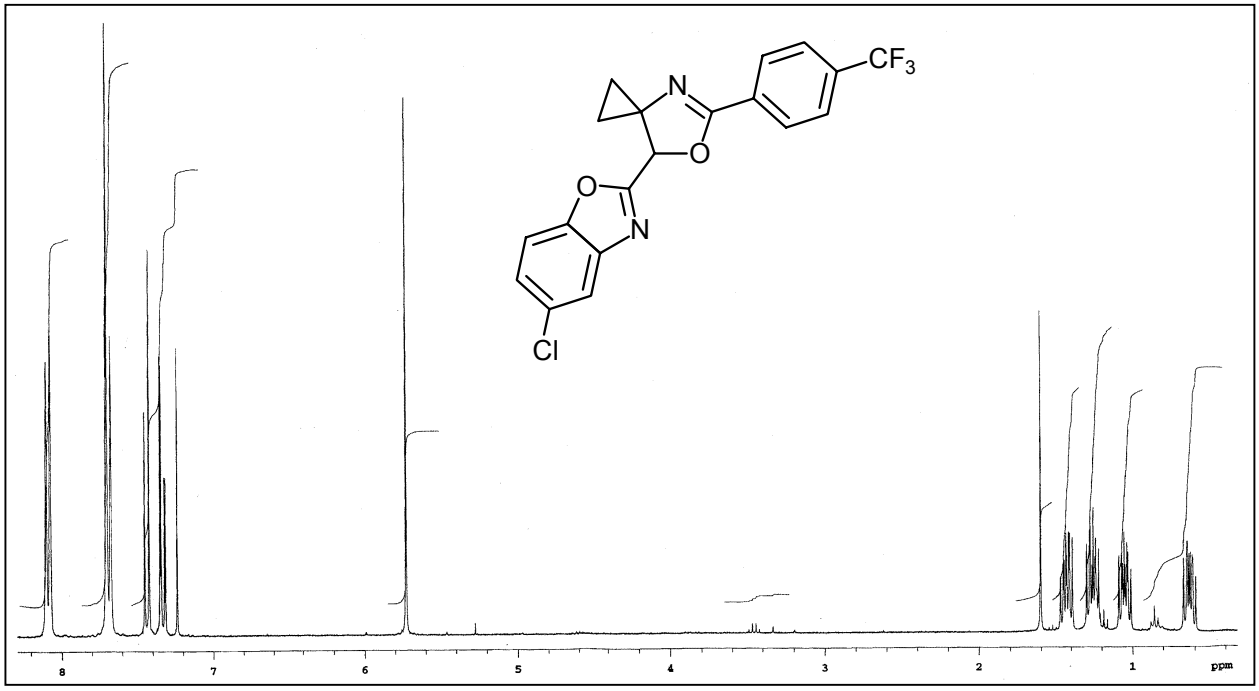


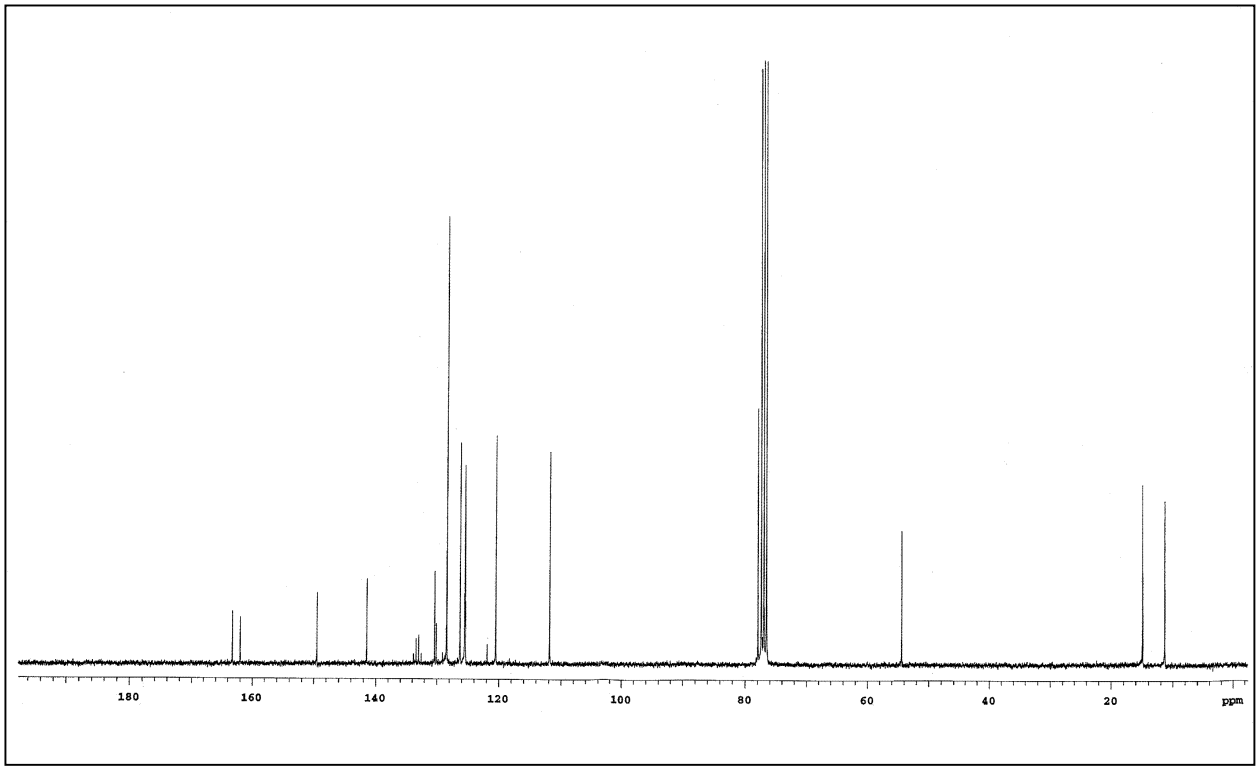
5-(4-Bromophenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl ester (**13a**)



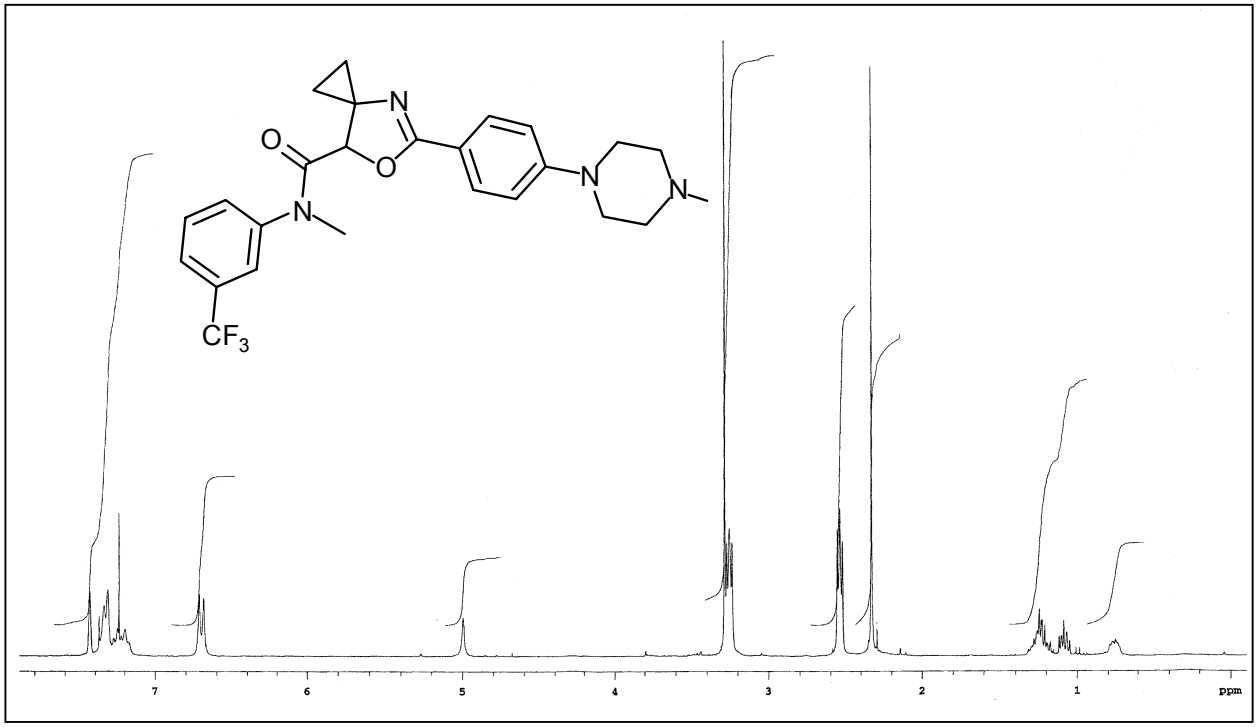


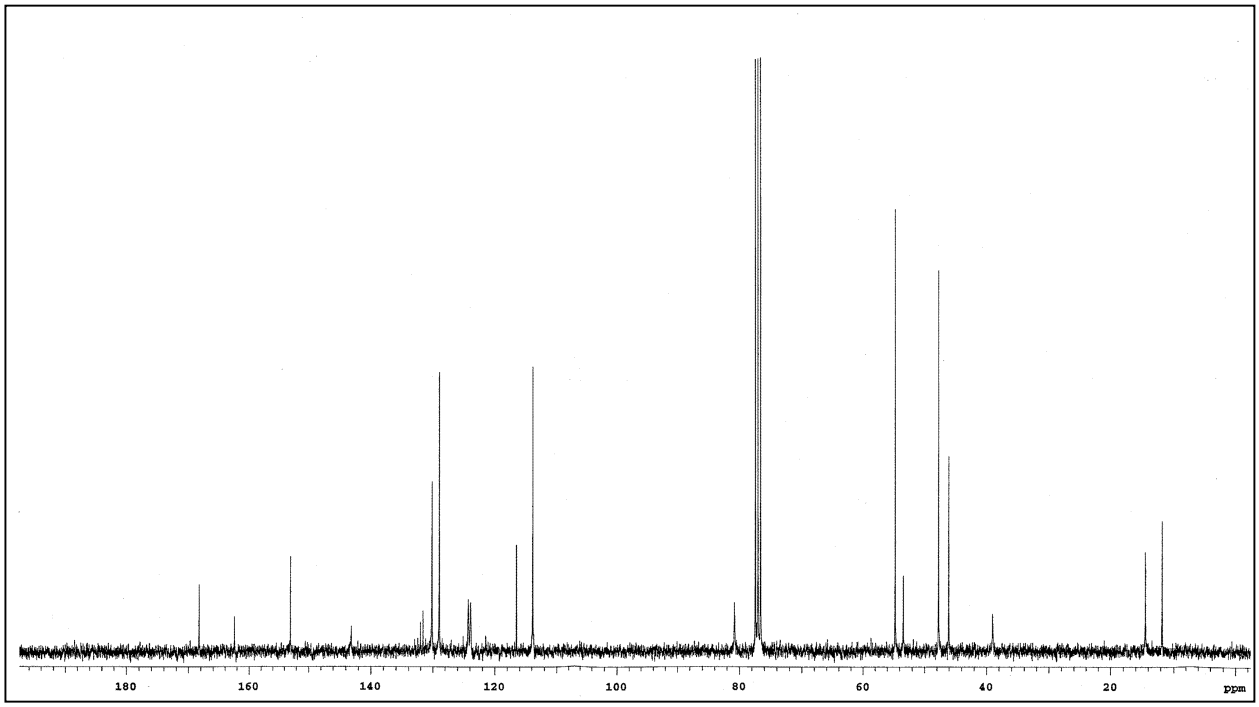
5-(4-Trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid (5-trifluoro-methoxy-2-hydroxy-phenyl)-amide (**68f**)



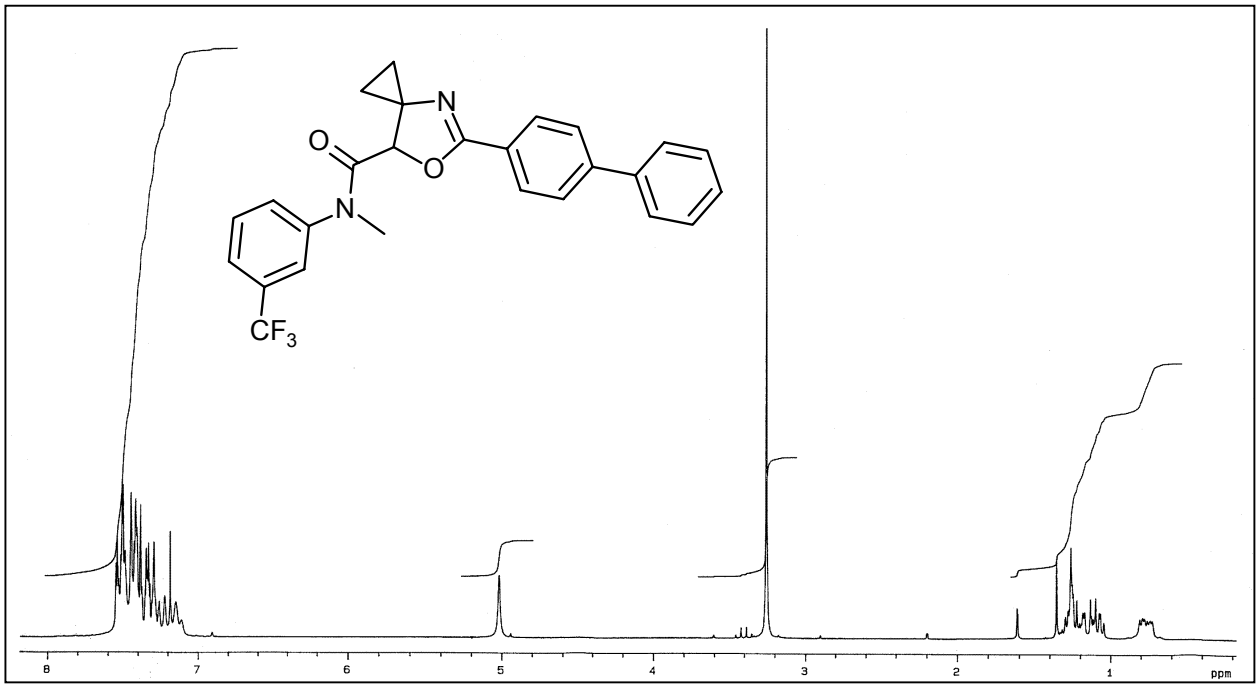


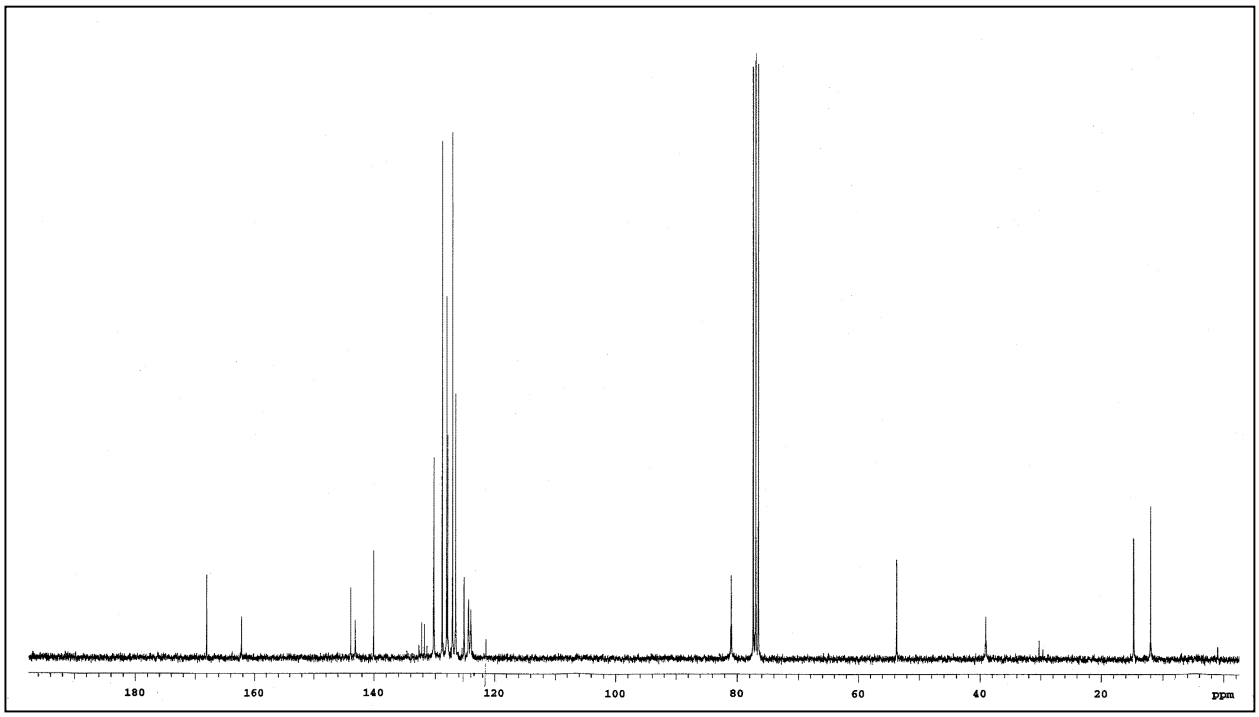
5-Chloro-2-[5-(4-trifluoromethyl-phenyl)-6-oxa-4-aza-spiro[2.4]hept-4-en-7-yl]-benzooxazole (**69a**)





5-[4-(4-Methyl-piperazin-1-yl)-phenyl]-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**71c**)





5-Biphenyl-4-yl-6-oxa-4-aza-spiro[2.4]hept-4-ene-7-carboxylic acid methyl-(3-trifluoromethyl-phenyl)-amide (**72a**)

6. Crystal Data

1. 6-Benzenesulfonyl-6-ethyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one (**41b**)

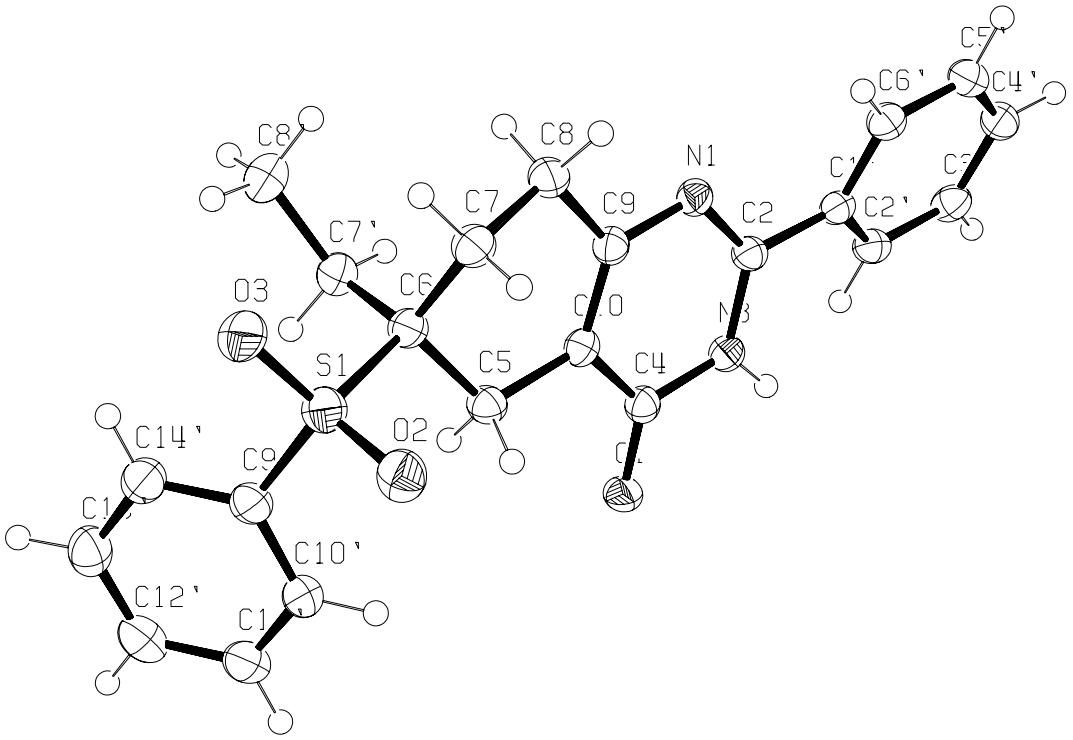


Table 18.. Crystal data and structure refinement for **41b**

Empirical formula	$C_{22} H_{22} N_2 O_3 S$	
Formula weight	394.48	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 13.17(2) Å	α = 90 deg.
	b = 10.98(4) Å	β = 94.05(6) deg.
	c = 13.03(3) Å	γ = 90 deg.
Volume	1881(8) $Å^3$	
Z	4	
Density (calculated)	1.393 Mg/m^3	
Absorption coefficient	1.748 mm^{-1}	
F(000)	832	
Crystal size	0.2 x 0.2 x 0.2 mm^3	
Theta range for data collection	3.36 to 56.74°.	
Index ranges	-14<=h<=12, -11<=k<=11, -14<=l<=14	
Reflections collected	12555	
Independent reflections	2461 [R(int) = 0.0525]	
Completeness to theta = 56.74°	98.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2461 / 0 / 253	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0366, wR2 = 0.0843	
R indices (all data)	R1 = 0.0493, wR2 = 0.0900	
Largest diff. peak and hole	0.152 and -0.329 e.$Å^{-3}$	

Table 19. Atomic coordinates (x 10^4) equivalent isotropic displacement parameters (Å^{2}x 10^3) for **41b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	8017(1)	2131(1)	1182(1)	32(1)
O(3)	8944(1)	2122(2)	657(1)	39(1)
N(1)	8180(1)	-425(2)	5217(1)	24(1)
C(5')	8347(2)	-1523(2)	8313(2)	30(1)
O(2)	7734(1)	3232(2)	1692(1)	37(1)
N(3)	6404(1)	-352(2)	5200(1)	24(1)
C(4')	7521(2)	-2115(2)	8687(2)	30(1)
O(1)	5397(1)	299(2)	3809(1)	29(1)
C(3')	6628(2)	-2247(2)	8066(2)	29(1)
C(2')	6556(2)	-1776(2)	7080(2)	26(1)
C(1')	7379(2)	-1164(2)	6703(2)	24(1)
C(6')	8277(2)	-1046(2)	7330(2)	28(1)
C(2)	7337(2)	-625(2)	5664(2)	23(1)
C(4)	6276(2)	117(2)	4218(2)	24(1)
C(10)	7192(2)	368(2)	3740(2)	23(1)
C(9)	8103(2)	109(2)	4261(2)	24(1)
C(8)	9089(2)	382(2)	3807(2)	29(1)
C(7)	8963(2)	1290(2)	2916(2)	30(1)
C(6)	8080(2)	918(2)	2143(2)	28(1)
C(7')	8217(2)	-346(2)	1646(2)	32(1)
C(5)	7084(2)	935(2)	2684(2)	26(1)
C(8')	9249(2)	-660(3)	1239(2)	41(1)
C(9')	7001(2)	1744(2)	280(2)	31(1)
C(10')	6002(2)	1998(2)	498(2)	35(1)
C(11')	5214(2)	1663(3)	-211(2)	41(1)
C(12')	5426(2)	1118(2)	-1128(2)	40(1)
C(13')	6419(2)	903(2)	-1353(2)	39(1)
C(14')	7212(2)	1199(2)	-641(2)	35(1)

Table 20. Bond lengths [Å] and angles [°] for **41b**.

S(1)-O(3)	1.441(3)
S(1)-O(2)	1.442(4)
S(1)-C(9')	1.769(3)
S(1)-C(6)	1.827(4)
N(1)-C(2)	1.308(3)
N(1)-C(9)	1.375(4)
C(5')-C(6')	1.382(4)
C(5')-C(4')	1.384(4)
N(3)-C(2)	1.364(3)
N(3)-C(4)	1.379(4)
C(4')-C(3')	1.387(4)
O(1)-C(4)	1.257(3)
C(3')-C(2')	1.383(4)
C(2')-C(1')	1.394(4)
C(1')-C(6')	1.395(4)
C(1')-C(2)	1.476(4)
C(4)-C(10)	1.422(4)
C(10)-C(9)	1.367(4)
C(10)-C(5)	1.508(4)
C(9)-C(8)	1.496(4)
C(8)-C(7)	1.531(4)
C(7)-C(6)	1.540(4)
C(6)-C(5)	1.534(4)
C(6)-C(7')	1.547(5)
C(7')-C(8')	1.533(4)
C(9')-C(14')	1.387(4)
C(9')-C(10')	1.394(4)
C(10')-C(11')	1.390(4)
C(11')-C(12')	1.382(4)
C(12')-C(13')	1.381(4)
C(13')-C(14')	1.387(4)
O(3)-S(1)-O(2)	118.69(13)
O(3)-S(1)-C(9')	108.02(18)

O(2)-S(1)-C(9')	107.46(14)		
O(3)-S(1)-C(6)	108.74(13)		
O(2)-S(1)-C(6)	107.2(2)		
C(9')-S(1)-C(6)	106.01(17)		
C(2)-N(1)-C(9)	117.6(2)		
C(6')-C(5')-C(4')	120.1(2)		
C(2)-N(3)-C(4)	122.8(2)		
C(5')-C(4')-C(3')	119.9(2)		
C(2')-C(3')-C(4')	120.2(2)		
C(3')-C(2')-C(1')	120.3(2)		
C(2')-C(1')-C(6')	119.1(2)		
C(2')-C(1')-C(2)	122.5(2)		
C(6')-C(1')-C(2)	118.4(2)		
C(5')-C(6')-C(1')	120.4(2)		
N(1)-C(2)-N(3)	122.2(2)		
N(1)-C(2)-C(1')	119.8(2)		
N(3)-C(2)-C(1')	118.0(2)		
O(1)-C(4)-N(3)	120.1(2)		
O(1)-C(4)-C(10)	124.6(2)		
N(3)-C(4)-C(10)	115.2(2)		
C(9)-C(10)-C(4)	119.0(2)		
C(9)-C(10)-C(5)	124.2(2)		
C(4)-C(10)-C(5)	116.8(2)		
C(10)-C(9)-N(1)	123.0(2)		
C(10)-C(9)-C(8)	121.2(2)	C(8')-C(7')-C(6)	118.6(2)
N(1)-C(9)-C(8)	115.7(2)	C(10)-C(5)-C(6)	112.7(2)
C(9)-C(8)-C(7)	112.4(2)	C(14')-C(9')-C(10')	120.8(2)
C(8)-C(7)-C(6)	111.1(2)	C(14')-C(9')-S(1)	119.4(2
C(5)-C(6)-C(7)	109.1(2)	C(10')-C(9')-S(1)	119.8(2)
C(5)-C(6)-C(7')	109.5(2)	C(11')-C(10')-C(9')	118.9(3)
C(7)-C(6)-C(7')	114.0(2)	C(12')-C(11')-C(10')	120.2(3)
C(5)-C(6)-S(1)	107.91(17)	C(13')-C(12')-C(11')	120.7(3)
C(7)-C(6)-S(1)	104.5(2)	C(12')-C(13')-C(14')	119.8(3)
C(7')-C(6)-S(1)	111.6(3)	C(9')-C(14')-C(13')	119.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 21. Anisotropic displacement parameters ($Å^2$x 10^3)for **41b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	32(1)	34(1)	31(1)	7(1)	7(1)	1(1)
O(3)	32(1)	48(1)	38(1)	13(1)	14(1)	0(1)
N(1)	22(1)	28(1)	23(1)	-1(1)	3(1)	-1(1)
C(5')	27(1)	35(2)	28(1)	1(1)	-2(1)	2(1)
O(2)	45(1)	32(1)	36(1)	4(1)	7(1)	0(1)
N(3)	19(1)	30(1)	24(1)	1(1)	5(1)	-1(1)
C(4')	34(2)	30(1)	26(1)	5(1)	2(1)	5(1)
O(1)	20(1)	41(1)	26(1)	5(1)	2(1)	3(1)
C(3')	28(1)	28(1)	33(1)	4(1)	8(1)	3(1)
C(2')	25(1)	25(1)	29(1)	0(1)	1(1)	2(1)
C(1')	23(1)	24(1)	25(1)	0(1)	3(1)	3(1)
C(6')	23(1)	32(1)	28(1)	1(1)	4(1)	0(1)
C(2)	21(1)	23(1)	24(1)	-3(1)	0(1)	0(1)
C(4)	26(1)	23(1)	23(1)	-1(1)	2(1)	1(1)
C(10)	23(1)	24(1)	23(1)	-1(1)	5(1)	-1(1)
C(9)	24(1)	25(1)	23(1)	-2(1)	2(1)	-1(1)
C(8)	22(1)	39(2)	27(1)	1(1)	2(1)	-1(1)
C(7)	24(1)	36(2)	30(1)	3(1)	5(1)	-2(1)
C(6)	23(1)	35(2)	26(1)	6(1)	5(1)	1(1)
C(7')	30(1)	36(2)	29(1)	0(1)	4(1)	1(1)
C(5)	23(1)	29(1)	26(1)	3(1)	2(1)	0(1)
C(8')	40(2)	47(2)	37(1)	-3(1)	11(1)	6(1)
C(9')	33(2)	30(1)	29(1)	9(1)	5(1)	5(1)
C(10')	38(2)	40(2)	27(1)	6(1)	6(1)	10(1)
C(11')	36(2)	51(2)	36(2)	11(1)	2(1)	10(1)
C(12')	46(2)	39(2)	35(2)	7(1)	-5(1)	1(1)
C(13')	54(2)	31(2)	32(1)	-1(1)	5(1)	5(1)
C(14')	40(2)	32(2)	35(2)	6(1)	10(1)	6(1)

Table 22. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **41b**.

	x	y	z	U(eq)
H(1C)	8962	-1446	8733	36
H(2B)	5862	-480	5541	29
H(2C)	7566	-2429	9367	36
H(3A)	6065	-2662	8320	35
H(4A)	5944	-1870	6657	32
H(6A)	8843	-634	7079	33
H(11A)	9380	-385	3556	35
H(11B)	9575	718	4348	35
H(12A)	9602	1328	2560	36
H(12B)	8830	2111	3189	36
H(14A)	8067	-971	2162	38
H(14B)	7693	-426	1067	38
H(01A)	6854	1789	2747	31
H(01B)	6554	490	2257	31
H(15A)	9223	-1484	950	61
H(15B)	9780	-620	1804	61
H(15C)	9403	-76	703	61
H(17A)	5862	2393	1121	42
H(18A)	4528	1808	-65	49
H(19A)	4883	890	-1608	48
H(20A)	6558	552	-1995	46
H(21A)	7895	1030	-783	42

2. 2-cyclopropyl-2,3,7,8-tetrahydro-5*H*-thiazolo[3,2-a]pyrimidine-3-carboxylic acid methyl ester (**74b**)

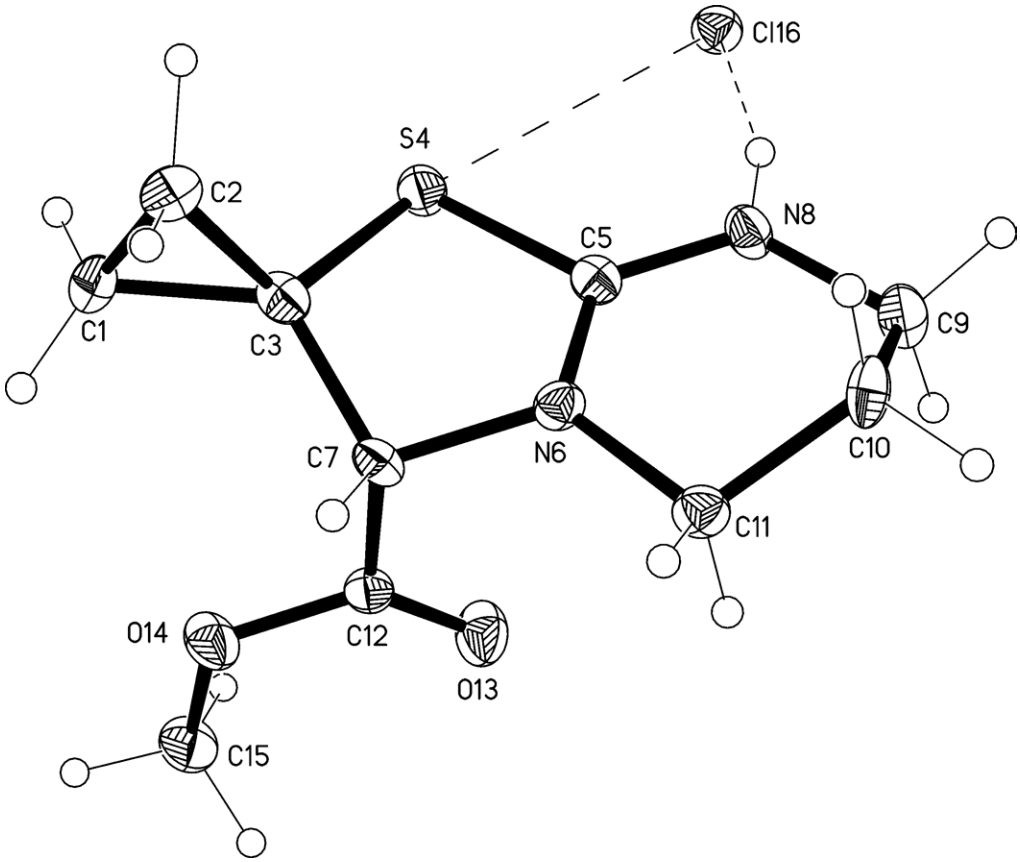


Table 23. Crystal data and structure refinement for **74b**.

Identification code	**74b**	
Empirical formula	$C_{10} H_{15} Cl N_2 O_2 S$	
Formula weight	262.75	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.9542(2) Å	α = 90°.
	b = 10.3036(3) Å	β = 90°.
	c = 12.8711(3) Å	γ = 90°.
Volume	1187.49(5) $Å^3$	
Z	4	
Density (calculated)	1.470 Mg/m^3	
Absorption coefficient	4.404 mm^{-1}	
F(000)	552	
Theta range for data collection	5.50 to 58.66°.	
Index ranges	-9<=h<=9, -10<=k<=11, -14<=l<=13	
Reflections collected	7764	
Independent reflections	1667 [R(int) = 0.0325]	
Completeness to theta = 58.66°	99.7 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1667 / 0 / 146	
Goodness-of-fit on F^2	0.722	
Final R indices [I>2sigma(I)]	R1 = 0.0246, wR2 = 0.0761	
R indices (all data)	R1 = 0.0252, wR2 = 0.0771	
Absolute structure parameter	0.054(15)	
Extinction coefficient	0.0046(6)	
Largest diff. peak and hole	0.272 and -0.271 $e.Å^{-3}$	

Table 24. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3)
for **74b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(13)	-1158(2)	7253(2)	975(1)	26(1)
N(6)	194(2)	5115(2)	1795(1)	16(1)
C(12)	-1908(2)	6564(2)	1514(1)	16(1)
Cl(16)	3838(1)	7829(1)	3796(1)	20(1)
S(4)	296(1)	6339(1)	3547(1)	19(1)
N(8)	2576(2)	5860(2)	2241(1)	18(1)
O(14)	-3350(2)	6766(1)	1741(1)	23(1)
C(7)	-1372(2)	5320(2)	2050(2)	16(1)
C(3)	-1369(2)	5437(2)	3225(2)	18(1)
C(1)	-2737(2)	5556(2)	3883(2)	20(1)
C(2)	-1843(3)	4315(2)	3896(2)	24(1)
C(5)	1140(2)	5724(2)	2427(2)	16(1)
C(9)	3241(3)	5356(2)	1272(2)	22(1)
C(10)	2330(2)	4201(2)	897(2)	21(1)
C(11)	690(2)	4581(2)	796(2)	18(1)
C(15)	-4007(3)	7956(2)	1335(2)	24(1)

Table 25. Bond lengths [Å] and angles [°] for **74b**.

O(13)-C(12)	1.198(3)		
N(6)-C(5)	1.332(3)		
N(6)-C(7)	1.456(3)		
N(6)-C(11)	1.467(2)		
C(12)-O(14)	1.340(3)		
C(12)-C(7)	1.533(3)		
S(4)-C(5)	1.747(2)		
S(4)-C(3)	1.806(2)		
N(8)-C(5)	1.316(3)		
N(8)-C(9)	1.477(3)		
O(14)-C(15)	1.457(3)		
C(7)-C(3)	1.517(3)		
C(3)-C(1)	1.494(3)		
C(3)-C(2)	1.504(3)		
C(1)-C(2)	1.510(3)		
C(9)-C(10)	1.521(3)		
C(10)-C(11)	1.525(3)		
C(5)-N(6)-C(7)	114.01(17)		
C(5)-N(6)-C(11)	121.26(18)		
C(7)-N(6)-C(11)	122.93(17)		
O(13)-C(12)-O(14)	125.0(2)		
O(13)-C(12)-C(7)	125.50(19)	C(1)-C(3)-S(4)	120 .32(15)
O(14)-C(12)-C(7)	109.48(17)	C(2)-C(3)-S(4)	119.80(15)
C(5)-S(4)-C(3)	88.91(10)	C(7)-C(3)-S(4)	105.74(14)
C(5)-N(8)-C(9)	120.67(19)	C(3)-C(1)-C(2)	60.10(14)
C(12)-O(14)-C(15)	116.19(17)	C(3)-C(2)-C(1)	59.44(14)
N(6)-C(7)-C(3)	103.56(16)	N(8)-C(5)-N(6)	124.1(2)
N(6)-C(7)-C(12)	108.76(17)	N(8)-C(5)-S(4)	122.30(17)
C(3)-C(7)-C(12)	112.48(17)	N(6)-C(5)-S(4)	113.56(16)
C(1)-C(3)-C(2)	60.46(15)	N(8)-C(9)-C(10)	109.07(18)
C(1)-C(3)-C(7)	124.73(18)	C(9)-C(10)-C(11)	110.01(18)
C(2)-C(3)-C(7)	120.70(19)	N(6)-C(11)-C(10)	108.27(16)

Symmetry transformations used to generate equivalent atoms:

Table 26. Anisotropic displacement parameters ($Å^2 x 10^3$) for **74b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(13)	23(1)	25(1)	29(1)	7(1)	6(1)	0(1)
N(6)	17(1)	16(1)	14(1)	-2(1)	0(1)	-1(1)
C(12)	16(1)	19(1)	14(1)	-3(1)	-2(1)	-1(1)
Cl(16)	20(1)	21(1)	19(1)	-1(1)	-2(1)	-1(1)
S(4)	16(1)	23(1)	17(1)	-4(1)	-1(1)	0(1)
N(8)	13(1)	21(1)	21(1)	-4(1)	-1(1)	0(1)
O(14)	18(1)	22(1)	28(1)	8(1)	-1(1)	3(1)
C(7)	12(1)	18(1)	18(1)	-1(1)	-3(1)	-1(1)
C(3)	16(1)	17(1)	21(1)	1(1)	-2(1)	-1(1)
C(1)	19(1)	24(1)	18(1)	3(1)	5(1)	-1(1)
C(2)	24(1)	29(1)	19(1)	7(1)	0(1)	0(1)
C(5)	16(1)	13(1)	18(1)	1(1)	-1(1)	1(1)
C(9)	17(1)	25(1)	25(1)	-2(1)	3(1)	1(1)
C(10)	20(1)	20(1)	23(1)	-5(1)	9(1)	4(1)
C(11)	18(1)	18(1)	17(1)	-2(1)	-2(1)	-2(1)
C(15)	22(1)	23(1)	27(1)	4(1)	-2(1)	6(1)

Table 27. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **74b**.

	x	y	z	U(eq)
H(8A)	3147	6255	2699	22
H(7A)	-1987	4560	1825	19
H(1A)	-3718	5544	3528	25
H(1B)	-2684	6124	4502	25
H(2A)	-1240	4124	4522	29
H(2B)	-2275	3544	3548	29
H(9A)	4287	5087	1399	27
H(9B)	3244	6044	734	27
H(10A)	2431	3475	1396	25
H(10B)	2712	3906	215	25
H(11A)	569	5238	242	21
H(11B)	84	3811	613	21
H(15A)	-5057	8007	1545	36
H(15B)	-3941	7955	575	36
H(15C)	-3464	8707	1611	36

3. Methyl 2-chloro-3-hydoxy-2-(1-isopropylcylopropyl)-3-(4-methoxyphenyl)propionate (**75b**-iPr).

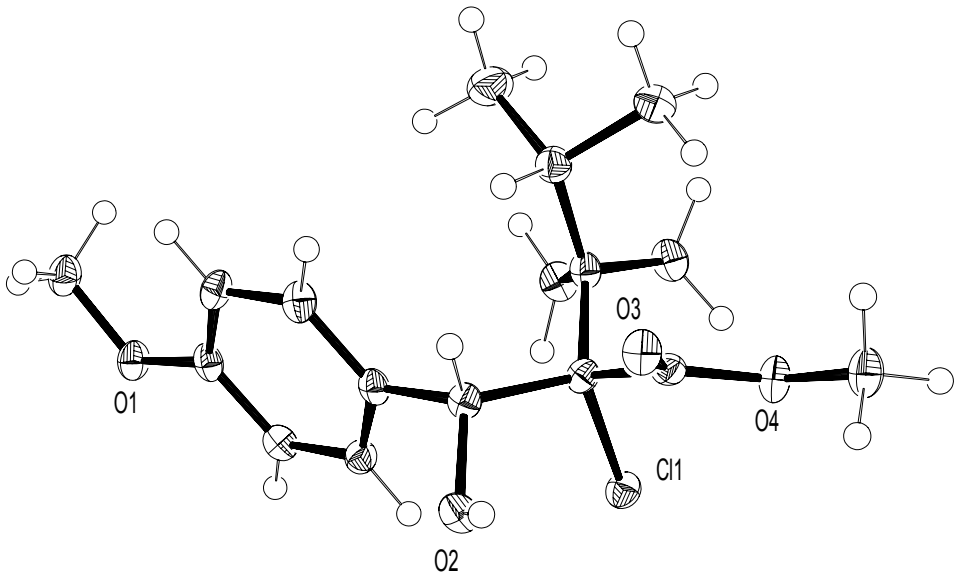


Table 28. Crystal data and structure refinement for **75b**-iPr.

Empirical formula	$C_{17} H_{23} Cl O_4$	
Formula weight	326.80	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 13.008 Å	α = 90°.
	b = 8.581 Å	β = 93.42°.
	c = 14.591 Å	γ = 90°.
Volume	1625.8 $Å^3$	
Z	4	
Density (calculated)	1.335 Mg/m^3	
Absorption coefficient	2.214 mm^{-1}	
F(000)	696	
Crystal size	0.5 x 0.5 x 0.5 mm^3	
Theta range for data collection	4.42 to 56.97°.	
Index ranges	-14<=h<=14, -9<=k<=9, -15<=l<=15	
Reflections collected	12541	
Independent reflections	2186 [R(int) = 0.0272]	
Completeness to theta = 56.97°	99.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2186 / 0 / 200	
Goodness-of-fit on F^2	1.137	
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0848	
R indices (all data)	R1 = 0.0343, wR2 = 0.0849	
Extinction coefficient	0.0242(9)	
Largest diff. peak and hole	0.242 and -0.334 $e.Å^{-3}$	

Table 29. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3)
for **75b**-iPr. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	3720(1)	1859(1)	2574(1)	20(1)
O(2)	5619(1)	1849(1)	3752(1)	21(1)
O(4)	2944(1)	-632(1)	3634(1)	22(1)
O(3)	4486(1)	-1085(1)	4352(1)	21(1)
O(1)	8119(1)	2181(1)	232(1)	22(1)
C(1)	7514(1)	1687(2)	915(1)	19(1)
C(4)	6222(1)	968(2)	2328(1)	17(1)
C(8)	4444(1)	102(2)	2853(1)	17(1)
C(3)	7020(1)	-16(2)	2111(1)	21(1)
C(16)	4253(1)	-3863(2)	2675(1)	24(1)
C(13)	4937(1)	-2625(2)	2257(1)	21(1)
C(10)	4356(1)	-1079(2)	2051(1)	18(1)
C(2)	7670(1)	322(2)	1412(1)	21(1)
C(6)	6708(1)	2678(2)	1111(1)	20(1)
C(15)	2463(1)	-1285(2)	4415(1)	25(1)
C(9)	3970(1)	-586(2)	3700(1)	17(1)
C(5)	6079(1)	2329(2)	1813(1)	19(1)
C(11)	4269(1)	-425(2)	1086(1)	23(1)
C(7)	5583(1)	569(2)	3125(1)	18(1)
C(12)	3350(1)	-1175(2)	1480(1)	23(1)
C(14)	5433(2)	-3309(2)	1420(1)	33(1)
C(17)	8899(1)	1131(2)	-32(1)	25(1)

Table 30. Bond lengths [Å] and angles [°] for **75b**-iPr.

Cl(1)-C(8)	1.8121(16)
O(2)-C(7)	1.429(2)
O(4)-C(9)	1.333(2)
O(4)-C(15)	1.445(2)
O(3)-C(9)	1.209(2)
O(1)-C(1)	1.373(2)
O(1)-C(17)	1.426(2)
C(1)-C(2)	1.386(3)
C(1)-C(6)	1.392(3)
C(4)-C(3)	1.390(3)
C(4)-C(5)	1.395(3)
C(4)-C(7)	1.508(2)
C(8)-C(9)	1.533(2)
C(8)-C(10)	1.547(2)
C(8)-C(7)	1.563(2)
C(3)-C(2)	1.393(3)
C(16)-C(13)	1.535(3)
C(13)-C(14)	1.530(3)
C(13)-C(10)	1.548(2)
C(10)-C(12)	1.511(2)
C(10)-C(11)	1.515(2)
C(6)-C(5)	1.381(3)
C(11)-C(12)	1.502(3)
C(9)-O(4)-C(15)	115.69(13)
C(1)-O(1)-C(17)	116.63(13)
O(1)-C(1)-C(2)	124.60(16)
O(1)-C(1)-C(6)	115.57(15)
C(2)-C(1)-C(6)	119.81(16)
C(3)-C(4)-C(5)	117.57(15)
C(3)-C(4)-C(7)	119.44(15)
C(5)-C(4)-C(7)	122.93(15)
C(9)-C(8)-C(10)	110.03(13)
C(9)-C(8)-C(7)	108.37(13)

C(10)-C(8)-C(7)	112.79(13)
C(9)-C(8)-Cl(1)	105.79(11)
C(10)-C(8)-Cl(1)	111.17(11)
C(7)-C(8)-Cl(1)	108.40(11)
C(4)-C(3)-C(2)	122.32(16)
C(14)-C(13)-C(16)	109.48(15)
C(14)-C(13)-C(10)	113.47(15)
C(16)-C(13)-C(10)	112.44(14)
C(12)-C(10)-C(11)	59.54(11)
C(12)-C(10)-C(8)	118.42(14)
C(11)-C(10)-C(8)	117.29(14)
C(12)-C(10)-C(13)	117.23(14)
C(11)-C(10)-C(13)	120.43(14)
C(8)-C(10)-C(13)	113.67(13)
C(1)-C(2)-C(3)	118.85(16)
C(5)-C(6)-C(1)	120.44(16)
O(3)-C(9)-O(4)	123.58(16)
O(3)-C(9)-C(8)	122.60(15)
O(4)-C(9)-C(8)	113.77(14)
C(6)-C(5)-C(4)	121.00(16)
C(12)-C(11)-C(10)	60.11(11)
O(2)-C(7)-C(4)	108.74(13)
O(2)-C(7)-C(8)	110.74(13)
C(4)-C(7)-C(8)	114.82(13)
C(11)-C(12)-C(10)	60.35(11)

Symmetry transformations used to generate equivalent atoms:

Table 31. Anisotropic displacement parameters ($Å^2$x 10^3)for **75b**-iPr. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	19(1)	21(1)	21(1)	3(1)	0(1)	3(1)
O(2)	26(1)	25(1)	12(1)	-2(1)	0(1)	-5(1)
O(4)	15(1)	32(1)	19(1)	4(1)	2(1)	-1(1)
O(3)	20(1)	29(1)	15(1)	2(1)	-1(1)	-1(1)
O(1)	20(1)	29(1)	17(1)	2(1)	5(1)	-2(1)
C(1)	16(1)	27(1)	12(1)	-2(1)	-2(1)	-5(1)
C(4)	15(1)	22(1)	14(1)	-2(1)	-4(1)	-3(1)
C(8)	15(1)	19(1)	16(1)	1(1)	-1(1)	2(1)
C(3)	18(1)	25(1)	18(1)	5(1)	-2(1)	0(1)
C(16)	27(1)	22(1)	24(1)	-1(1)	0(1)	-1(1)
C(13)	21(1)	22(1)	20(1)	-1(1)	1(1)	-1(1)
C(10)	16(1)	23(1)	15(1)	0(1)	0(1)	-2(1)
C(2)	15(1)	29(1)	19(1)	0(1)	0(1)	3(1)
C(6)	22(1)	21(1)	16(1)	2(1)	-2(1)	-2(1)
C(15)	21(1)	35(1)	21(1)	3(1)	5(1)	-2(1)
C(9)	18(1)	17(1)	17(1)	-4(1)	-1(1)	0(1)
C(5)	17(1)	22(1)	20(1)	-3(1)	0(1)	0(1)
C(11)	26(1)	28(1)	14(1)	0(1)	1(1)	-3(1)
C(7)	17(1)	21(1)	15(1)	0(1)	-2(1)	0(1)
C(12)	21(1)	30(1)	18(1)	0(1)	-5(1)	-3(1)
C(14)	39(1)	27(1)	35(1)	-4(1)	14(1)	2(1)
C(17)	20(1)	33(1)	21(1)	-2(1)	5(1)	-1(1)

Table 32. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **75b**-iPr.

	x	y	z	U(eq)
H(2A)	5585	1513	4290	32
H(3A)	7127	-953	2451	25
H(16A)	4654	-4817	2793	37
H(16B)	3664	-4090	2246	37
H(16C)	4006	-3471	3253	37
H(13A)	5508	-2389	2726	25
H(2B)	8211	-371	1278	25
H(6A)	6590	3599	760	23
H(15A)	1713	-1268	4300	38
H(15B)	2654	-668	4963	38
H(15C)	2695	-2363	4510	38
H(5A)	5541	3027	1947	23
H(11A)	4264	723	1015	27
H(11B)	4616	-999	603	27
H(7A)	5918	-340	3451	21
H(12A)	3132	-2208	1238	28
H(12B)	2780	-487	1650	28
H(14A)	5787	-4282	1595	50
H(14C)	5930	-2563	1196	50
H(14D)	4898	-3520	935	50
H(17C)	9279	1603	-521	37
H(17D)	8579	157	-254	37
H(17A)	9374	911	499	37

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