Top Heterocycl Chem (2007) 9: 179–264
DOI 10.1007/7081_2007_081

Published online: 8 September 2007

Chemistry of Biologically Active Isothiazoles

Francesca Clerici · Maria Luisa Gelmi (✉) · Sara Pellegrino · Donato Pocar

Istituto di Chimica Organica "A. Marchesini", Facoltà di Farmacia, Università di Milano, Via Venezian 21, 20133 Milano, Italy
marialuisa.gelmi@unimi.it

To our dear Prof Pocar for his retirement

Abstract The isothiazole ring as well as the corresponding benzo- and heterocondensed rings are present in many chemically interesting compounds. The isothiazole ring can be a substituent of a bioactive scaffold or the pharmacophore of bioactive molecules. New compounds have been designed, synthesised and tested towards different biological targets and, in many cases, they display interesting pharmaceutical activities. Different SAR studies are reported starting from already known isothiazole derivatives or from

new compounds characterised by a particular substitution pattern aiming to improve the biological activity. Agrochemical applications are also reported.

Keywords Benzisothiazoles · Biologically active compounds · Isothiazoles · Pyridoisothiazoles · Saccharins · Sultams

1 Introduction

The importance of isothiazoles and of compounds containing the isothiazole nucleus appears to have grown over the years. New synthetic approaches and unprecedented reactions have recently been reported and numerous technical and pharmaceutical applications have been discovered [1–6]. This review is based on the fact that the isothiazole ring is present in many chemically interesting compounds that display biological activity. The isothiazole ring can be a substituent of a bioactive scaffold or the pharmacophore of bioactive molecules. A great number of SAR studies have been carried out starting from already prepared isothiazole derivatives or from new compounds characterised by a particular substitution pattern aiming to ameliorate the biological activity. Among the benzisothiazoles the best-known derivative is the noncaloric sweetener saccharin [7]. Due to the large amount of literature on this compound and its biological activity, it is considered in this review only for particular and original applications.

Regarding other isothiazole derivatives, different activities have been claimed such as antimicrobial, antibacterial, antifungal, antiviral, antiproliferative and anti-inflammatory activities. They have also been tested as inhibitors of proteases, for the treatment of anxiety and depression, for their action on the 5-HT receptor, and as inhibitors of aldoso reductase. Patented compounds for agrochemical applications are of old interest. This review is concerned with recent results, mainly limited to the last decade. Previous references have been taken into account only if they are of particular relevance or necessary for a better understanding of the text. Furthermore, patents have been included only if they add important information to the existing scientific literature. Articles exclusively dedicated to biological investigations without chemical interest have not been considered.

The review is divided into four main chapters concerning isothiazoles, sultams, benzisothiazoles and benzisothiazolones of biological interest. In these last two cases, heterocondensed compounds are included. In each chapter, the corresponding dioxides as well as partially hydrogenated rings are considered. For each class of compounds, the following is reviewed: i) procedures by direct synthesis of the above rings pointed out as synthetic *methods A–V*, and ii) the reactivity insofar as related to biologically interesting transformations of functional groups present on the isothiazole ring or related to the functionalisation of the isothiazole nucleus with a proper pharmacophore.

A chapter on biological applications of selected compounds has also been inserted in which the main activities are depicted and in which, for each class of bioactive compounds, the lead compound has been selected. A short account of the main biological mechanisms in which the target compounds are involved has also been reported when of strong relevance.

2
Isothiazoles

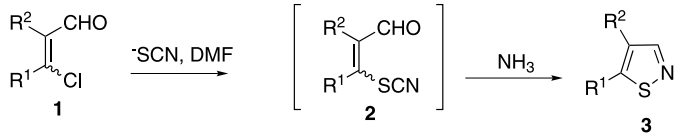
Isothiazoles constitute a relatively novel class of heterocyclic compounds, the first preparation being reported in the mid 1950s [8]. The rapid progress in their chemistry and intense studies on the synthesis and chemical conversion of their derivatives are due primarily to the extraordinarily broad range of useful properties manifested by various representatives of this class of compounds. Data on the chemistry of isothiazoles are documented in several monographs and reviews disclosing both synthetic and reacting aspects [1–6]. Below only few general synthetic methods based on the construction of the ring are reported if useful for the preparation of compounds characterised by a claimed activity. Analogously, the reactivity of the isothiazole system is related to the preparation of active or potentially active compounds.

Many 3-heterosubstituted isothiazoles characterised by interesting biological applications have been prepared, in which the heteroatom can be oxygen, sulphur, nitrogen and a halogen. In particular, depending on the substitution at the nitrogen atom, the oxygen substituted compounds can exist as enoles, when nitrogen is unsubstantiated, or as isothiazol-3(2H)ones when nitrogen is substituted.

2.1
Synthesis of Carbon Linked Isothiazoles

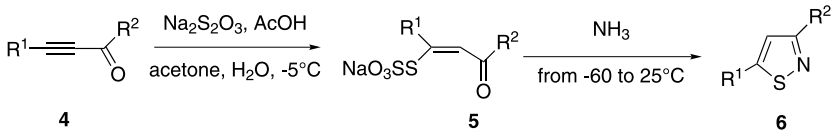
The well-known synthesis from 3-halogeno-α,β-unsaturated aldehydes **1** and ammonium thiocyanate, via intermediate **2**, is very useful for the preparation of substituted isothiazoles **3** and for fused analogues (Scheme 1, *Method A*) [1, 2].

A number of modifications of this method has been described. For example, the alkinyl carbonyl compounds **4** and $Na_2S_2O_3$ afforded the dithion-



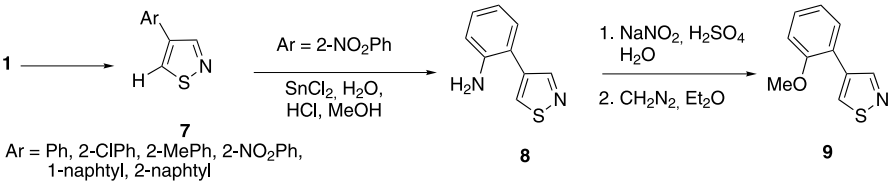
Scheme 1 Synthesis of isothiazoles: *Method A*

ites **5** then cyclised in liquid NH_3 to the corresponding isothiazoles **6** [1, 2] (Scheme 2, *Method B*).



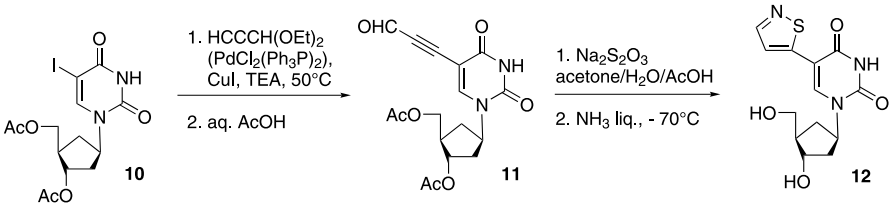
Scheme 2 Synthesis of isothiazoles: *Method B*

Several antifungal 4-arylisothiazoles **7** (25–54% yields) were prepared taking advantage of the classical procedure described in *Method A* [9] from **1** ($R^1 = H$, $R^2 = Ar$) and ammonium thiocyanate in DMF. 4-(2-Methoxyphenyl)isothiazole (**9**) was also prepared from the corresponding 2-nitro derivative **7** (Ar = 2-NO_2Ph) in 26% overall yield via intermediate **8** (Scheme 3) (see Sect. 4.1, analogue compounds of brassilexin.



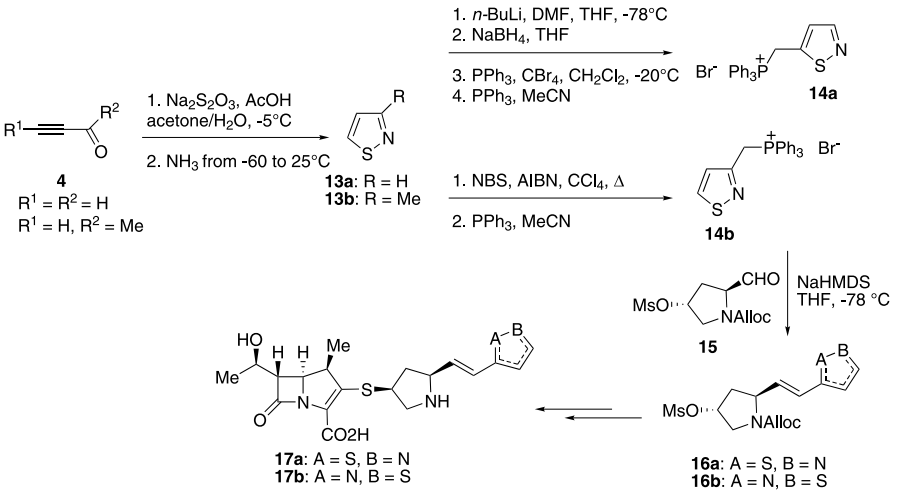
Scheme 3 Synthesis of 4-arylisothiazoles

The 5-substituted isothiazole **12** is a substrate for viral HSV-1 thymidine kinase [10]. The isothiazole ring was built according to *Method B* starting from the alkinyl aldehyde **11** prepared from 2′-desoxy-5-iodouridine **10** and propiolaldehyde diethyl acetal in presence of ($PdCl_2(Ph_3P)_2$), CuI and TEA at 50 °C. Acetal intermediate (91%) was formed, which was then deprotected with aqueous AcOH (80%) giving aldehyde **11** (51%). Its reaction with $Na_2S_2O_3$ in acetone/H_2O/AcOH afforded a *cis/trans* mixture of a thiosulfate (1 : 1, not isolated) then treated with liq. NH_3 at – 70 °C to give **12** (13%) (Scheme 4).



Scheme 4 Synthesis of 2′-deoxy(5-isothiazol-5-yl)uridine

The synthesis of isothiazoles **13a,b** (R = H, 30% yield, R = Me, 38% yield) was performed according to the same *Method B* from the propioaldehyde **4** ($R^1 = R^2 = H$) or 1-butin-3-one **4** ($R^1 = H$, $R^2 = Me$). Compounds **13a,b** were then transformed into the regioisomeric phosphonium salts **14a–b**, which are the key intermediates for the preparation of several antimicrobic agents based on a carbapenem structure [11]. Compounds **13a** was transformed into the phosphonium salt **14a** through formylation (*n*-BuLi, DMF, 73%), reduction with $NaBH_4$ (83%), substitution of the hydroxy group with bromine (PPh_3, CBr_4, 80%) and reaction with PPh_3 (63%). On the other hand, **13b** was first brominated (NBS, AIBN, CCl_4, 45%) and then transformed into the phosphonium salt **14b** (63%) as reported in Scheme 5. The preparation of 1-β-methylcarbapenems **17a,b**, bearing isothiazoloethenyl moieties al C-5 position of the pyrrolidine ring, was achieved using as key reaction the Wittig reaction from salts **14** and aldehyde **15** operating with NaHMDS as the base in THF at – 78 °C. Alkenes **16a,b** were isolated in 76 and 73% yield, respectively. The *E*-isomers were obtained exclusively. Mesylates **16** were then used for the preparation of carbapenem derivatives **17**.

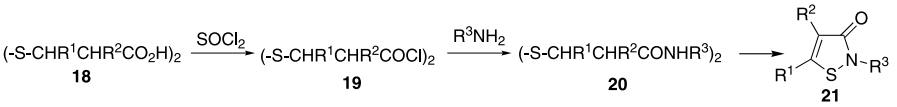


Scheme 5 Synthesis of 1-β-methylcarbapenems with an isothiazoloethenyl side chain

2.2
Synthesis of 3-Heterosubstituted Isothiazoles

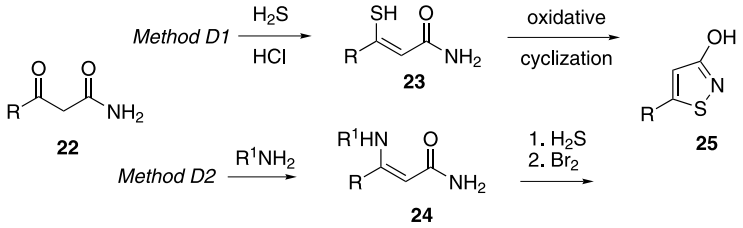
The main method for the formation of the 3-heterosubstituted isothiazole ring is, even today, a ring closing reaction based on the formation of an S – N bond [1, 2].

The well-known synthesis based on the oxidative cyclisation of dithiopropionamides **20**, obtained from acids **18** via dichlorides **19**, is considered an efficient and simple procedure affording good yields of isothiazol-3(2H)ones **21** (Scheme 6, *Method C*). Different reagents were tested aiming to ameliorate the yield and the efficiency of the strategy depending on the different dithiopropionic acids **18** and amines used in the process. This synthetic approach was also used for the preparation of the corresponding benzoderivatives [1, 2, 4].



Scheme 6 Synthesis of isothiazol-3(2*H*)ones: *Method C*

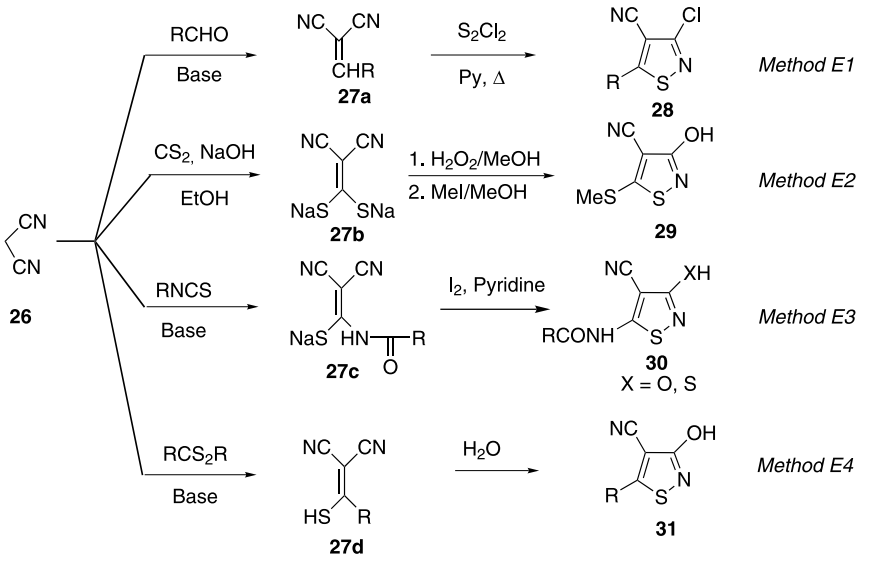
The *Methods D* outlined in Scheme 7 are also based on S – N bond formation. Thioenols **23** and enamines **24**, prepared from β-ketoamides **22**, represent the starting compounds in a number of procedures based on oxidative cyclisation with different reagents. 3-Hydroxy substituted isothiazoles **25** can be obtained this way [1, 3].



Scheme 7 Synthesis of 3-hydroxy substituted isothiazoles: *Methods D*

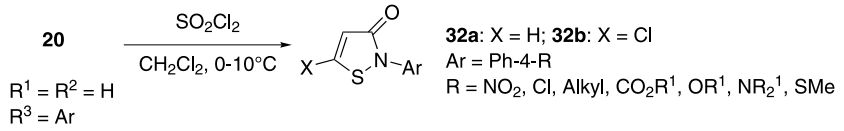
A different synthetic pathway, which is useful for the preparation of 4-cyano-isothiazoles **28–31** substituted at C-3 with different heteroatoms (Hal, S, O), is exploited by *Methods E* (Scheme 8). These procedures start from dicyanomalonate **26** and different electrophiles giving the key intermediates **27a–d**, subsequently cyclised to the isothiazole-4-carbonitriles **28–31**. A number of modifications of these procedures are known and are very useful for obtaining different starting materials for the preparation of isothiazole derivatives of biological interest [1, 2, 4].

Several antibacterial compounds containing substituted 3(2H)-isothiazolones as scaffold and, among them, a series of 3(2H)-isothiazolones **32**, substituted at the nitrogen atom with an aryl moiety functionalised with groups that are different in hydrophobicity, size, steric and electronic parameters, were prepared (Scheme 9). They were synthesised adopting *Method C* starting from dithiodipropionamides **20** ($R^1 = R^2 = H$, $R^3 = Ar$). By incremental addition to **20** of a dichloromethane solution of sulfuryl chloride, as



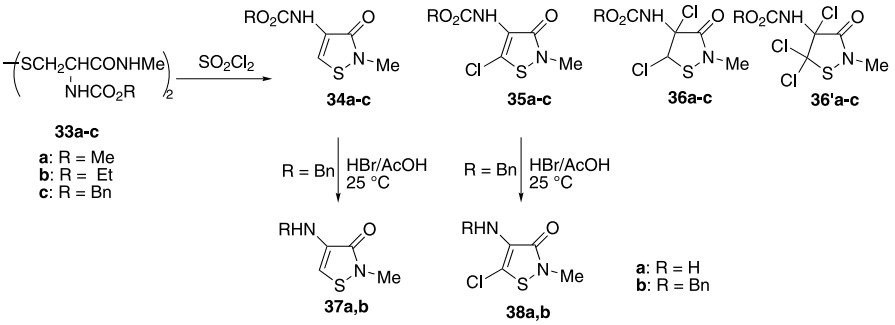
Scheme 8 Synthesis of 4-cyano-3-heterosubstituted isothiazoles: *Methods E*

an oxidizing agent, a mixture of isothiazolones **32a** and **32b**, unsubstituted and chloro substituted in position 5, respectively, was obtained [12]. The authors found that by manipulation of the stoichiometry SO_2Cl_2/amide, a different distribution of the products **32a/b** was observed. The use of an excess of SO_2Cl_2 favours the formation of chloro compounds **32b**, while the 1 : 1 stoichiometry favours the formation of **32a** which were obtained in variable yields (16–70%) depending on the aniline derivative.



Scheme 9 Synthesis of 2-aryl-isothiazol-3(2*H*)ones

A similar synthetic scheme was adopted by Nadel [13] to prepare isothiazolones **34** and **35** from L-cystine derivatives transformed into the corresponding cystine *bis*-*N*-(methylamides) **33a–c** ($EtOCO_2Cl$, TEA in CH_2Cl_2 then $MeNH_2/H_2O$, 69–73%) (Scheme 10). As reported in Table 1, several parameters were evaluated in order to find the best reaction conditions to produce the different isothiazolone derivatives **34** (43–63%) or **35** (52–66%). As by-products, the polyhalogenated compounds **36** and **36′** (not separable) were formed in some instances. Finally, the deprotection of the amino group



Scheme 10 Synthesis of 4-amino-isothiazol-3(2*H*)ones

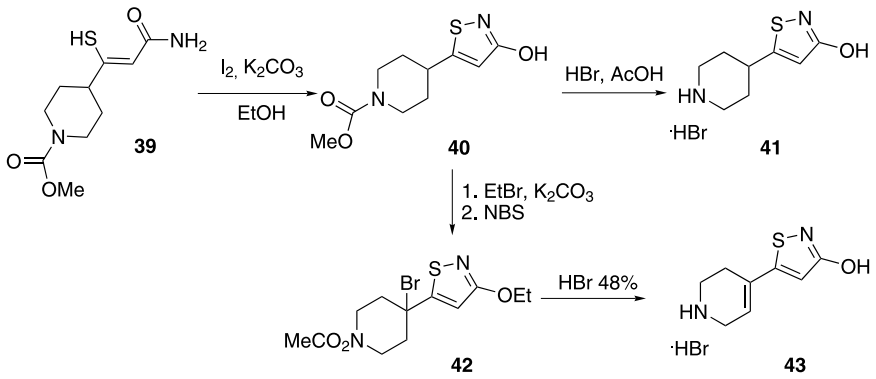
Table 1 Summary of ring closing reactions of the amino blocked cystine *bis*(methylamides)

33	Solvent	SO_2Cl_2/**45** Molar ratio	Rate of feeding (mL/h)	Temp. (°C)	Product
33a	CH_2Cl_2/C_6H_{12} (1 : 1)	4	9.6	35–40	**34a**
33a	hexane	6	19.2	30	**35a**
33b	$CHCl_3$	3.5	3.4	boiling	**34b**
33b	CCl_4	6.5	20.8	25	**35b**
33c	CH_2Cl_2/C_6H_{12} (1 : 1)	4	6.4	35–40	**34c**
33c	$CHCl_3$	6.5	31.2	50	**35c**
33a	CCl_4	7	20	35–40	**34a** + **35a** + **36/36′a**
33b	CCl_4	7.5	20	20	**34b** + **35b** + **36/36′b**
33c	CCl_4	7.5	25	55	**34c** + **35c** + **36/36′c**

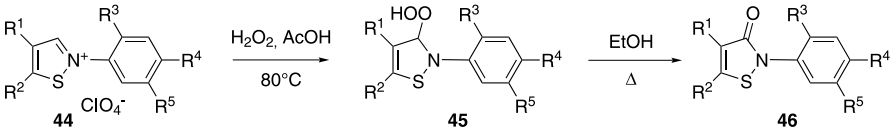
of **34c** and **35c** was performed using a mixture of HBr in AcOH and compounds **37** (78%) and **38** (65%) were formed (Scheme 10).

Recently, a series of analogues of thio-THIP (4,5,6,7-tethrahydroisothiazolo[5,4-*c*]pyridine-3-ol see Sect. 6), 5-(4-piperidyl)isothiazol-3-ol **41** and 5-(1,2,3,6-tetrahydro-pyrid-4-yl)isothiazol-3-ole **43** were developed basing their preparation on the same general strategy as described in *Method D1* from the enolised β-thioxoamide **39**, as shown in Scheme 11. Oxidation of **39** with I_2 under basic conditions afforded **40**, which was deprotected to give **41** by treatment with HBr in AcOH. Compound **42**, obtained from **40** by alkylation of the oxygen atom followed by bromination (EtBr, K_2CO_3, then NBS) and was dehalogenated and deprotected by treatment with 48% HBr to give the target compound **43** [14].

Isothiazol-3-ones **46** were prepared and their activity was evaluated on different serine proteases [15]. The key isothiazole salts **44** were prepared according to *Method A* by reacting isothiocyanate intermediates **2** and several aniline derivatives operating in AcOH in the presence of $HClO_4$. They



Scheme 11 Synthesis of 5-(4-piperidyl)- and 5-(1,2,3,6-tetrahydro-pyrid-4-yl)isothiazol-3-ols



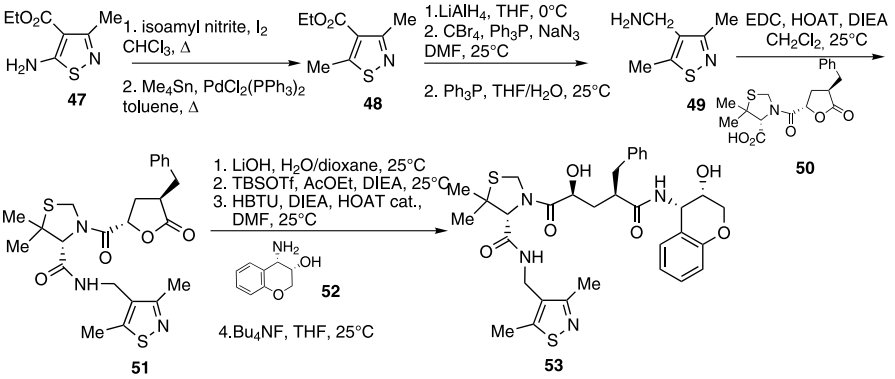
Scheme 12 Synthesis of substituted 2-aryl-isothiazol-3(2*H*)ones

were oxidised to peroxides **45** with H_2O_2 in AcOH and then transformed (EtOH, reflux) into isothiazol-3-ones **46** in moderate to good yields (20–65%) (Scheme 12).

2.3 Reactivity of Isothiazoles

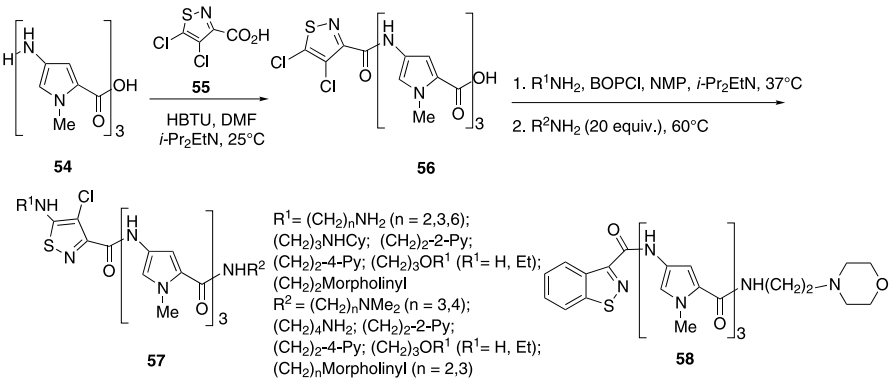
A series of new HIV protease inhibitors were designed and synthesised [16] (Scheme 13). One of the most active compounds is derivative **53** functionalised with the 3,5-dimethylisothiazole-4-methylamide ring. The latter was synthesised from the commercially available ethyl 5-amino-3-methylisothiazole-4-carboxylate **47**, which was converted into the 5-methyl derivative **48** (40%) by treatment with first isoamyl nitrite and I_2 and then with Me_4Sn and $PdCl_2(PPh_3)_2$. Its reduction with $LiAlH_4$ followed by treatment of the alcohol intermediate with CBr_4, Ph_3P, NaN_3, afforded the azido intermediate then reduced to amine **49** with Ph_3P (39%). By condensation of amine **49** with **50** (EDC, HOAT, DIEA, 60%), **51** was formed then hydrolyzed at the lactone function (LiOH, H_2O, dioxane), protected at hydroxyl group (TBSOTf, AcOEt, DIEA), condensed with **52** (HBTU, DIEA, HOAT cat.) then deprotected at the oxygen atom with Bu_4NF to give **53**.

An efficient synthesis of DNA binding tetrameric acid derivatives **57** [17], consisting of an isothiazole and three *N*-methylpyrrole carboxamide units,



Scheme 13 Synthesis of new HIV protease inhibitors

was performed and various substituents at both termini were introduced (Scheme 14). The coupling of trimeric *N*-methylpyrrole amino acid **54** with isothiazole **55** (HBTU in DMF and *i*-Pr_2EtN, 91%) resulted in the desired tetramer **56.** The two amino groups were then introduced in sequence by performing a "one pot" reaction. First Cl-5 was selectively substituted by the proper amine operating in presence of BOPCl and NMP/*i*-Pr_2EtN. Then the amide function was formed using a large excess of a second amine and **57** was obtained. Benzisothiazole derivative **58** was also prepared [18].

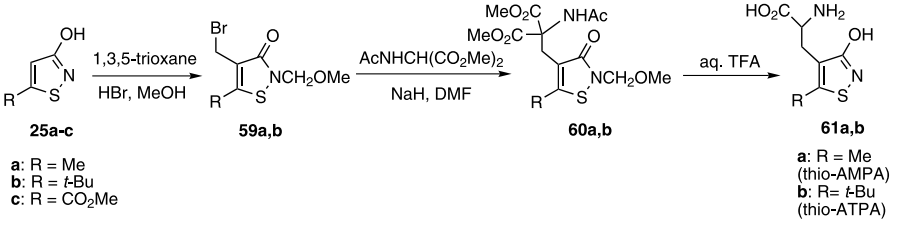


Scheme 14 Synthesis of tetrameric acid containing isothiazole and pyrazole rings

Many isothiazoles containing an amino acid functionality, analogues of isoxazole-based molecules, acting on glutamate receptors have been prepared in the last two decades. The isothiazole ring has mainly been synthesised according to *Method D1*. Afterwards, functionalisation of the ring was performed affording the biologically interesting target compounds, which can

be divided into two groups: i) isothiazoles with the characteristic amino acid group at C-4 and ii) isothiazoles with the characteristic amino acid group at C-5. The methodologies for the synthesis of such compounds are described in the following.

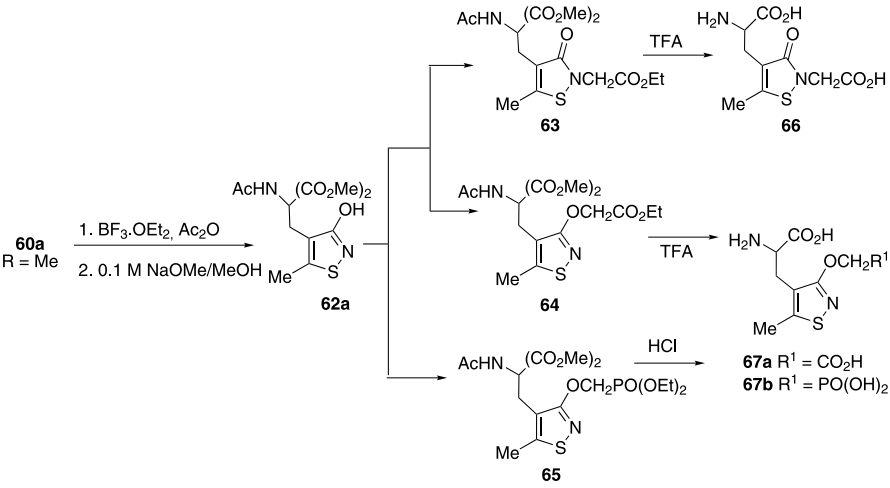
i) Isothiazoles with the characteristic amino acid group on C-4 [19]. Thio-AMPA (**61a**) and thio-ATPA (**61b**) were synthesised as outlined in Scheme 15. Compounds **25**, prepared from **23** with I_2 as oxidizing agent, were treated with trioxane, HBr/MeOH affording **59a,b** (27%, 39% respectively). Several reaction conditions (times and temperatures) were tested in attempts to increase the yields without appreciable results. Dimethyl acetamidomalonate reacted easily in basic conditions with **59a,b** affording **60a,b** which were deprotected under acidic conditions providing thio-AMPA (**61a**, 28%) and thio-ATPA (**61b**, 31%). Chiral chromatographic resolution of **61b** was also performed (Scheme 15).



Scheme 15 Synthesis of thio-AMPA and thio-ATPA

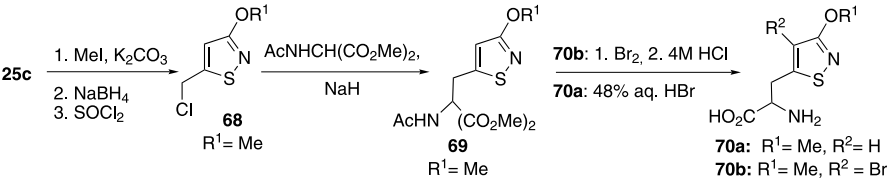
From **60a** the isothiazole amino acids **66** and **67a,b** were synthesised as outlined in the Scheme 16 [20]. Treatment of **60a** with $BF_3{\cdot}Et_2O$ in the presence of Ac_2O and subsequent heating under reflux of the intermediate product in methanolic sodium methoxide provided the 3-isothiazolol **62** (60% yield). Alkylation of **62** with ethyl chloroacetate gave a reaction mixture containing two main components **63** (26%) and **64** (31%), which were deprotected using 1M TFA to give **66** (14%) and **67a** (31%), respectively. The synthesis of **65** by alkylation of compound **62** with diethyl 4-toluenesulfonyloxymethylphosphonate under basic conditions was accompanied by extensive decomposition products. Compound **65** was thus obtained in a low yield (15%) without the formation of the isomeric *N*-alkylated product and then deprotected to give the target phosphono-amino acid **67b** (32% yield).

ii) Isothiazoles with the characteristic amino acid group at C-5 [19]. The functionalisation of C-5 with an amino acid function linked to the ring through a methylene bridge was accomplished by elaboration of a preexisting carboxy group. Methylation of **25c** (R = CO_2Me) followed by reduction and substitution of alcohol with $SOCl_2$ provided **68**, which was further converted into the fully protected compound **69**. The deprotection of **69**, which required conc. HBr, was accompanied by a marked decomposition of the



Scheme 16 Synthesis of thio-AMPA and thio-ATPA derivatives

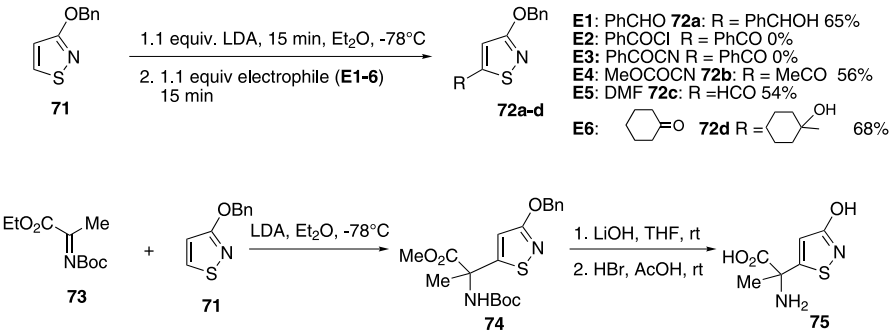
product and provided **70a** as the hydrobromide (25%). Bromination of **69** and deprotection by refluxing in 4 M HCl for a period of less than 4 h, resulted in a pronounced decomposition and in a low yield (20%) of **70b** as the hydrochloride (Scheme 17).



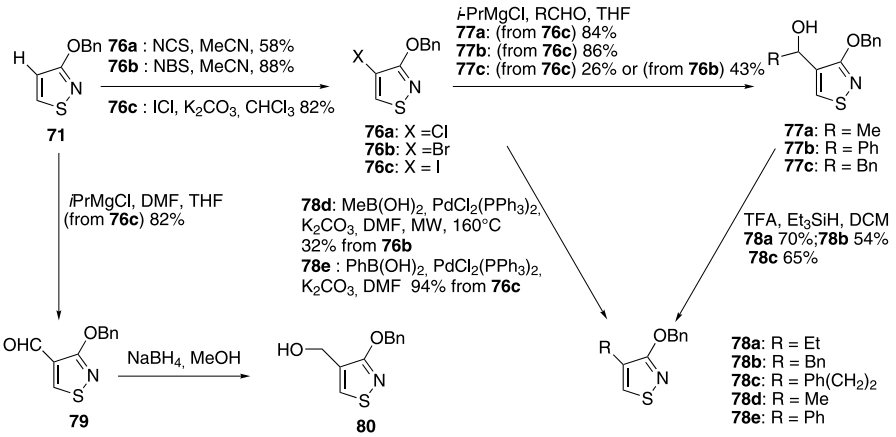
Scheme 17 Preparation of β-isothiazol-5-yl alanines

Differently from the case reported above (compounds **70**), thioibotenic acid derivatives like **75** and **83a–g**, NO the isothiazole analogues of ibotenic acid, were prepared taking advantage of a general methodology enabling the direct introduction of a substituent in the 5-position of 3-(benzyloxy)isothiazoles **71** [21]. The reaction of a series of electrophiles (**E1-6**) with **71** in the presence of LDA (1.1 equiv., 0.1 M in Et_2O) produced compounds **72a–d** (54–68% yields). When an amino acid synthon, i.e. **73**, was used in the reaction as the electrophile, the protected amino acid **74** (36%) was obtained. The ester **74** was hydrolyzed under basic conditions and subsequent treatment with HBr in AcOH removed the Boc and benzyl groups to give compound **75** (18%) (Scheme 18).

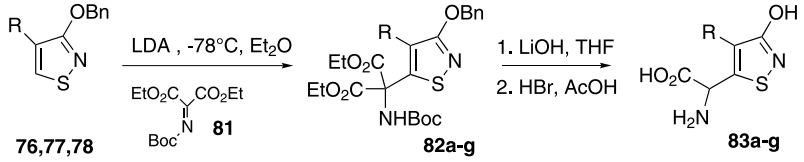
The 4-substituted Thio-Ibo derivatives **83a–g** (Scheme 20) were prepared with similar chemistry from the corresponding 4-substituted 3-benzyloxy-isothiazoles **76, 77** and **78** synthesised as outlined in Scheme 19. The use



Scheme 18 Preparation of α-isothiazol-5-yl alanine



Scheme 19 Synthesis of 4-substituted 3-benzyloxyisothiazoles



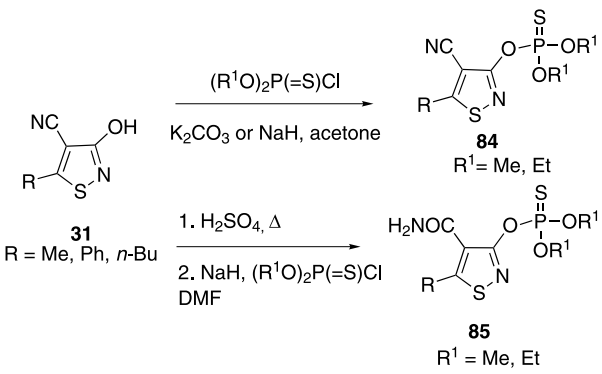
Scheme 20 Synthesis of 4-substituted Thio-Ibo

of 3-*O*-protected-isothiazolols **71** as key reagents to functionalise the C-4 position represent a convenient approach. Compound **71** can be synthesised through cyclisation reaction of 3,3-dithiodipropionamide according to *Method C* followed by *O*-protection. The benzyl protecting group in compound **71** did not withstand acidic halogenation conditions and the syntheses

of **76a–c** were accomplished employing non-acidic conditions (ICl or NCS or NBS). The 4-iodo **76c** or 4-bromo **76b** compounds were suitable starting materials for magnesium–halogen exchange followed by Grignard reactions with various aldehydes leading to alcohols **77**. Treatment of **77** with TFA and Et_3SiH gave the respective isothiazoles **78a–c**. However, the final step was not applicable for the synthesis of the methyl compound **78d**; for this reason alcohol **80** was effectively prepared via aldehyde **79** and various reductive methods were tried aiming to the synthesis of **78d** from **80**, but all were unsuccessful. Due to the difficulty of reducing the alcohol functionality in **80**, the possibility of introducing the methyl group by a Suzuki cross-coupling reaction from **76** was investigated. Microwave heating and the use of methyl boronic acid and $PdCl_2(PPh_3)_2$ limited by-product formation sufficiently to give an isolated yield of 32% of **78d**. Standard aryl–aryl Suzuki reaction was applied to give the phenyl compound **78e** in excellent yield.

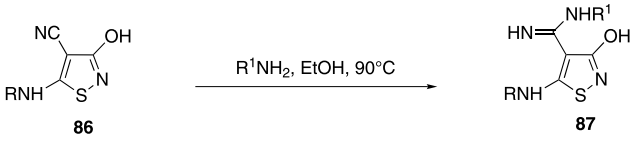
Starting from **76**, **77**, **78**, in the presence of LDA (1.1 equiv., 0.1 M in Et_2O), the 2-(*N*-*t*-butoxycarbonylimino) malonic acid diethyl ester (**81**) was added and the desired products **82a–g** were obtained. The hydrolysis of the ester functionality and the deprotection of nitrogen and oxygen atoms gave **83a–g** as the zwitterion upon treatment of the corresponding hydrobromides with propylene oxide.

Isothiazole esters of phosphorothioic acid were prepared for their interest as harmful organism-controlling agents [22]. Numerous examples of these compounds are patented and the syntheses of the isothiazole nucleus were usually done by the way of *Method E4* or slightly modified methodologies. As examples of the above interesting derivatives, the preparation of compounds **84** and **85** are reported in Scheme 21. Compound **31** was treated with anhydrous K_2CO_3 in acetone and dialkyl-chlorothiophosphate was added affording **84**. For the preparation of **85**, compound **31** was firstly transformed into the corresponding carbamoyl derivative (H_2SO_4), which was treated in DMF with NaH and subsequently made to react with dialkyl-chlorothiophosphate.



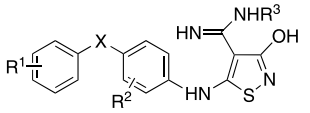
Scheme 21 Synthesis of alkyl 3-isothiazolyl-thiophosphonates

3-Hydroxy-4-carboxyalkylamidino-5-amino-isothiazole derivatives **87** were discovered as potent MEK1 inhibitors (Scheme 21) [23–25]. 5-Amino-isothiazoles **86** were prepared according to *Method E3* from the isothiocyanate, which was treated with cyanoacetamide (KOH in DMF) and then cyclised with bromine. By reaction of the nitrile group with an amine, usually cyclohexylmethylamine, in EtOH at reflux, the corresponding amidines **87** were formed. Following the same synthetic scheme a series of amidine compounds of general formula **88** were also prepared [26].



R = *n*-Pr, 4-MeO-Bu, *i*Pr, 3-morpholinyl-$(CH_2)_3$, cyclohexyl-CH_2,2-thienyl-$(CH_2)_2$, Ph-$(CH_2)_2$, 4-HO-Ph-$(CH_2)_2$, MeCH(Ph), 3-Py, pyrazolyl, Ar
Ar = 2- or 3- or 4-Me-Ph; 2- or 3- or 4-MeO-Ph; 2- or 3- or 4-O_2N-Ph, 4-NC-Ph, 2-F_3C-Ph, 4-EtO_2C-Ph, 3-Br-Ph, 4-Cl-Ph, 3,5-Cl_2-Ph, 2,5-Cl_2-Ph, 2,4-Cl_2-Ph, 3-F_3C-4-Cl-Ph

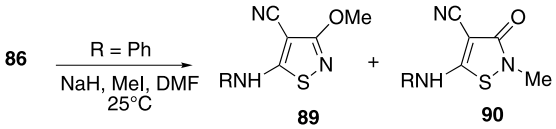
R^1 = Cyclohexyl-CH_2, R = 4-Me-Ph, 2-MeO-Ph 3- or 4-Cl-Ph; 3- or 4-Br-Ph; 2-F-Ph; 3-O_2N-4-Cl-Ph, 4-O_2N-2-MeO-Ph, 2,4-Me_2-Ph, 3,5-Cl_2-Ph, 2,4-Cl_2-Ph



X = O, NH, CH_2, CO, S, SO_2, CMe_2, N=N
R^3 = alkylalcohols, alkylamines,alkyldiols, alkyl
R^1 = H, Cl, F, Me
R^2 = Cl, F, CF_3, NMe_2

Scheme 22 Synthesis of 3-hydroxy-4-carboxyalkylamidino-isothiazoles

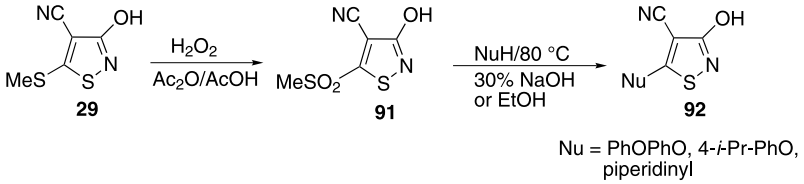
Starting from **86** (R = Ph), a mixture of 3-methoxy compound **89** and 3-isothiazolone **90** was obtained using NaH and MeI (Scheme 23) [23].



Scheme 23 Methylation of 3-hydroxy-isothiazoles

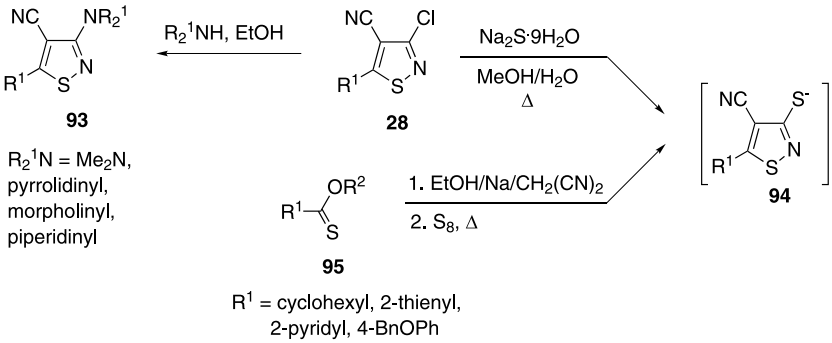
An alternative and more general approach to functionalisation at C-5 with the nucleophilic group was found from sulfone **91**, which derives from oxidation of **29** (H_2O_2 in Ac_2O/AcOH). By the way of a nucleophilic substitution reaction with the proper nucleophile, compounds **92** were prepared (Scheme 24) [23].

3-Chloroisothiazoles **28** functionalised with a cyano group at C-4 were the starting materials for the preparation of a series of molecules characterised by antiviral activity [27]. Depending on the substituent at C-5, they were prepared in 60–72% yields according to *Method E1*. They were then functionalised at C-3 both with an amino group and with a thio group. The reaction of



Scheme 24 General procedure for nucleophilic substitution at C-5

chloroisothiazole **28** with secondary amines in EtOH at reflux gave derivatives **93** (70–84%). Instead, the functionalisation at C-3 with a sulphur atom was made by making **28** react first with $Na_2S{\cdot}9H_2O$, affording the intermediate **94.** Intermediate **94** can be also prepared by condensation of O-alkyl thioates **95** with $CH_2(CN)_2$ in EtONa/EtOH and treatment with S_8 at reflux (*Method E*) (Scheme 25).

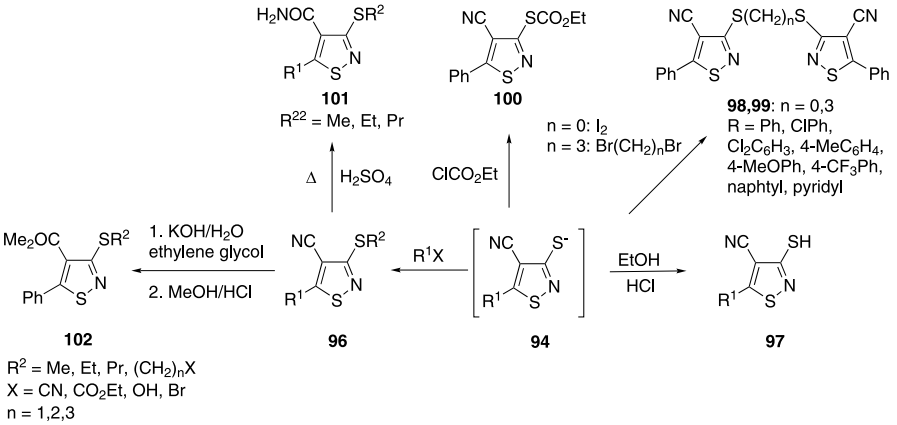


Scheme 25 Preparation of 4-cyano-isothiazole synthons

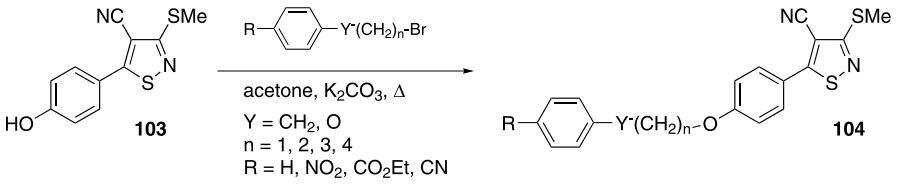
From **94**, several compounds were generated such as the 3-thioalkyl compounds **96** (40–67%) by reaction with alkyl bromides. Intermediate **94** was also treated with HCl, iodine, 1,3-dibromopropane or with ethyl chlorocarbonate affording the mercaptane **97** (68%), the disulfide **98** (45%, $n = 0$), compound **99** (37%, $n = 3$) and the thiocarbonate **100** (67%), respectively. By a partial hydrolysis of the nitrile group with H_2SO_4 at reflux, carboxamides **101a–b** (92%) were prepared from **96.** The same reagents **96** can be transformed into methyl esters **102** (Scheme 26).

Because compound **96** (R^1 = Me, R = BnOPh) exhibited a broad antipicornavirus spectrum of action, it was selected as a model and a series of new functionalised aryl compounds **104** (66–82%) was synthesised from compound **103**, which was functionalised at the oxygen atom with a proper chain operating in acetone in the presence of K_2CO_3 at reflux (Scheme 27) [27].

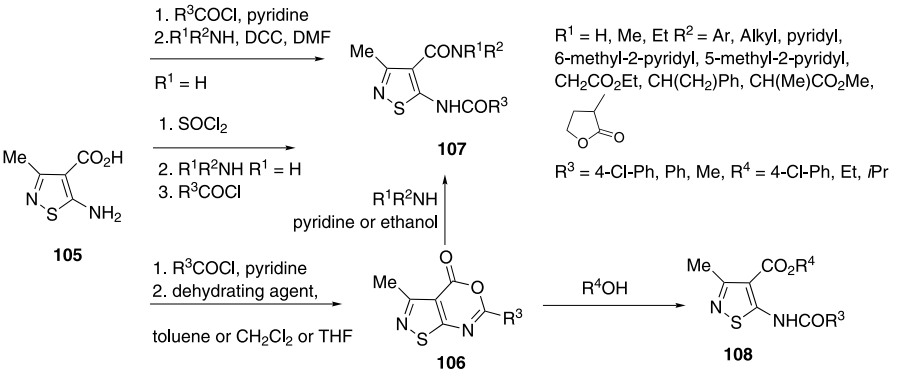
Anti-inflammatory compounds **107** and **108** (Scheme 28) were prepared from the known amino acid **105** following three different strategies, the first



Scheme 26 Chemical applications of synthon **94**



Scheme 27 Synthesis 4-cyano-3-methylthio-5-substituted isothiazoles as potential antipicornavirus agents

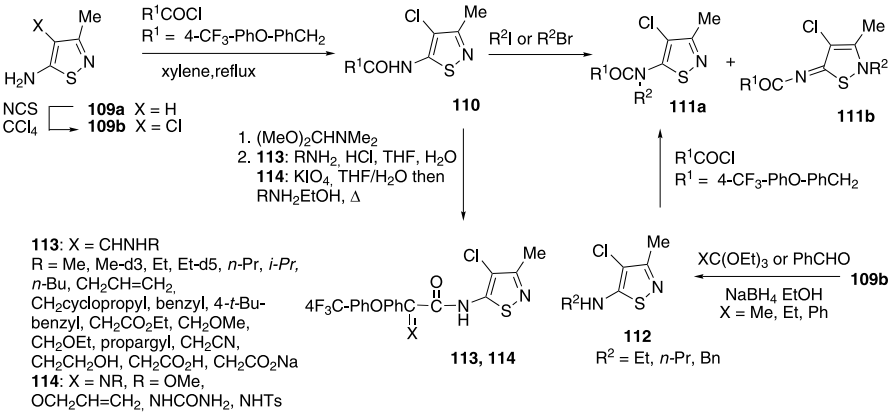


Scheme 28 Synthesis of 5-acylamino-isothiazol-4-carboxylic acid derivatives

one consisting in the preparation of 4-carboxamides via 4-carbonyl chloride, then acylated to nitrogen in position 5. Alternatively, **105** can be firstly reacted with acyl chloride affording 5-carboxyamides then converted into **107**

with amines in DMF/DCC. The same 5-carboxyamides can be converted into the semi-anhydride **106** under the influence of dehydrating reagents such as $SOCl_2$, DCC, $POCl_3$, and ethyl chloroformate in solvents such as benzene, toluene, chloroform, methylene chloride and THF. Oxazinone **106** was used to obtain the diamides **107** and the proper ester **108** by reacting with alcohols [28].

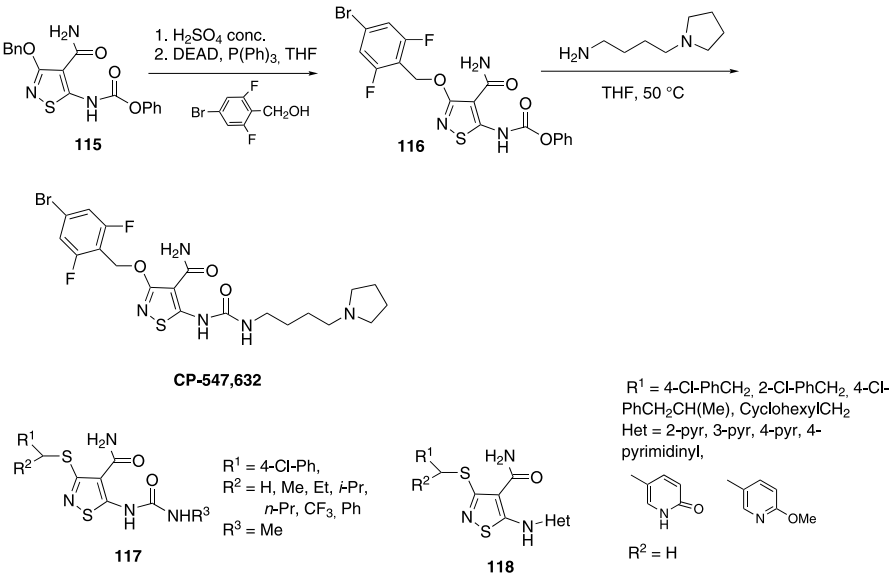
Other 5-carboxamidoisothiazoles, which are interesting as insecticides, functionalised with a chloro atom in position 4, were prepared with a standard procedure [29, 30]. Some of them were prepared by reacting **109b** with an acyl chloride in boiling xylene. Alkylation of **110** with several alkyliodides or bromides resulted in the formation of both the *N*-substituted isomeric product **111a** and **b** [31] (Scheme 29). In order to obtain exclusively the structures **111a**, the alkyl group was introduced at the amine stage using reductive amination on **109b** affording **112**, which was subsequently acylated. To enhance biological selectivity, other derivatives were prepared with substituents at the α-methylene position [32]. Compound **110** was converted to the enamineamide **113**, via the Mannich intermediate, followed by substitution of the dimethylamino group with several amines. The same Mannich intermediate was transformed into derivatives **114**.



Scheme 29 Synthesis of 5-carboxamido-4-chloroisothiazole

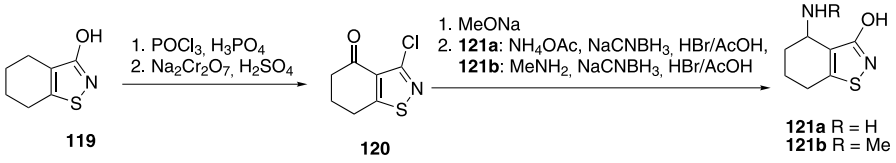
CP 547, 632 was identified as a potent inhibitor of the VEGFR-2 and basic fibroblast growth factor (FGF) kinases [33, 34] (Scheme 30). The synthesis of this compound, and of several other derivatives, starts from compound **115** prepared according to *Method E3*. The hydrolysis of benzyl ether of **115** (H_2SO_4) followed by alkylation with 2,6-difluoro-4-bromobenzylalcohol in THF/DEAD/$P(Ph)_3$ afforded the intermediate **116**, which was reacted with 4-pyrrolidin-1-yl-butylamine affording the target compound **CP 547, 632**.

A similar chemistry was employed for the preparation of a series of isothiazoles **117** and **118** under study as TrkA kinase inhibitors (Scheme 30) [35].



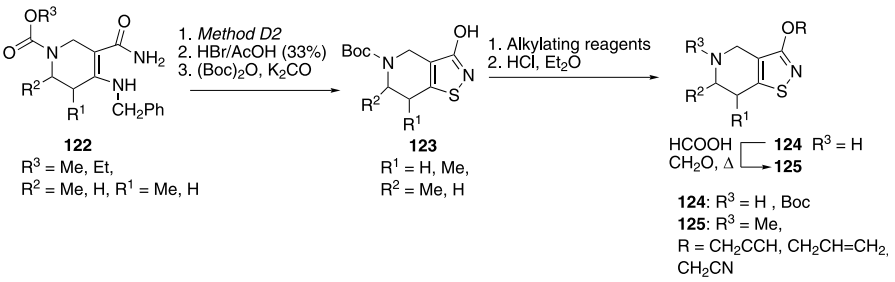
Scheme 30 Synthesis of **CP 547,632** and TrkA kinase inhibitors

Following *Method D2*, **119** (Scheme 31) was obtained, which could be transformed into the corresponding 3-ketoderivative **120** with $POCl_3$ and then with $Na_2Cr_2O_7/H_2SO_4$. Transformation of **120** afforded 4-amino derivatives **121** [37].



Scheme 31 Synthesis of 4-amino-3-hydroxy-4,5,6,7-tetrahydrobenzo[*d*]isothiazoles

A series of 4-hydroxy-4,5,6,7-tetrahydroisothiazolo[4,5-*c*]pyridines **124** and **125** were synthesised and pharmacologically characterised as conformationally restricted mAChR ligands (Scheme 32) [38]. Their synthesis was based on the corresponding enamines **122** transformed according to *Method D2* into isothiazoles **123**. From **123** with different alkylating reagents and employing proper conditions (RX, K_2CO_3, Bu_4NHSO_4; RX, K_2CO_3; R_2SO_4, Bu_4NHSO_4; NaOH, CH_2N_2) **124** was obtained (R^3 = Boc), which was



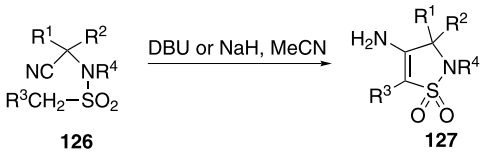
Scheme 32 Synthesis of 3-alkoxy-4,5,6,7-tetrahydroisothiazolo[4,5-*c*]pyridines

deprotected to nitrogen ($R^3 = H$) and then methylated at the nitrogen atom to afford **125** (HCHO/HCOOH at reflux).

2.4
Synthesis of 2,3-Dihydro-, 4,5-Dihydro- and Isothiazole *S*,*S*-Dioxides

2.4.1
Isothiazole and dihydroisothiazole *S*,*S*-dioxides

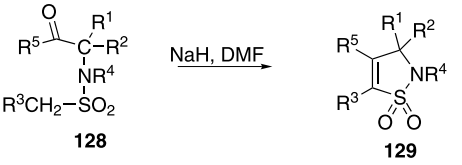
The main synthetic method to prepare the isothiazole *S*,*S*-dioxide ring and analogous dihydro compounds takes advantage of the intramolecular condensation with different electrophiles of the anion generated in position α to the SO_2 group. A very interesting class of isothiazoles is represented by the 4-amino-2,3-dihydroisothiazole *S*,*S*-dioxide series **127**. These compounds were synthesised from **126** through the well-studied [39] procedure known as CSIC (carbanion-mediated-sulfonamide-intramolecular cyclisation) shown in the Scheme 33 (*Method F*).



Scheme 33 General synthesis of 4-amino-2,3-dihydroisothiazole *S*,*S*-dioxides: *Method F*

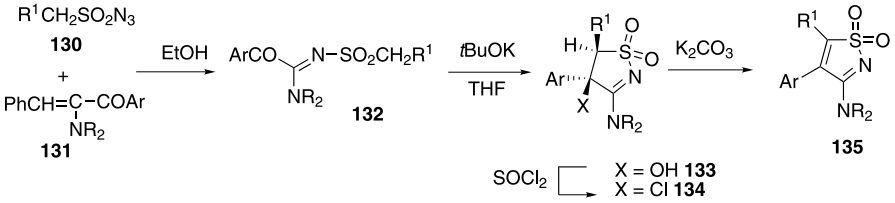
An intramolecular cyclisation is also at the basis of the synthetic strategy outlined in Scheme 34 (*Method G*), which can afford 2,3-dihydroisothiazoles **129** from **128** operating with NaH, DMF (Scheme 34) [40–42].

When the starting compounds are sulfonylamidines **132**, prepared via a cycloaddition reaction of azide **130** and enamine **131**, 3-aminosubstituted-4,5-dihydroisothiazol *S*,*S*-dioxides **133** can be obtained by base catalyzed in-



Scheme 34 General synthesis of 2,3-dihydroisothiazole *S*,*S*-dioxides: *Method G*

tramolecular cyclisation (*Method H*). Substitution of the hydroxy group with a halogen (compound **134**) followed by dehydrohalogenation, affords the corresponding unsaturated isothiazole *S*,*S*-dioxides **135** [43] (Scheme 35).

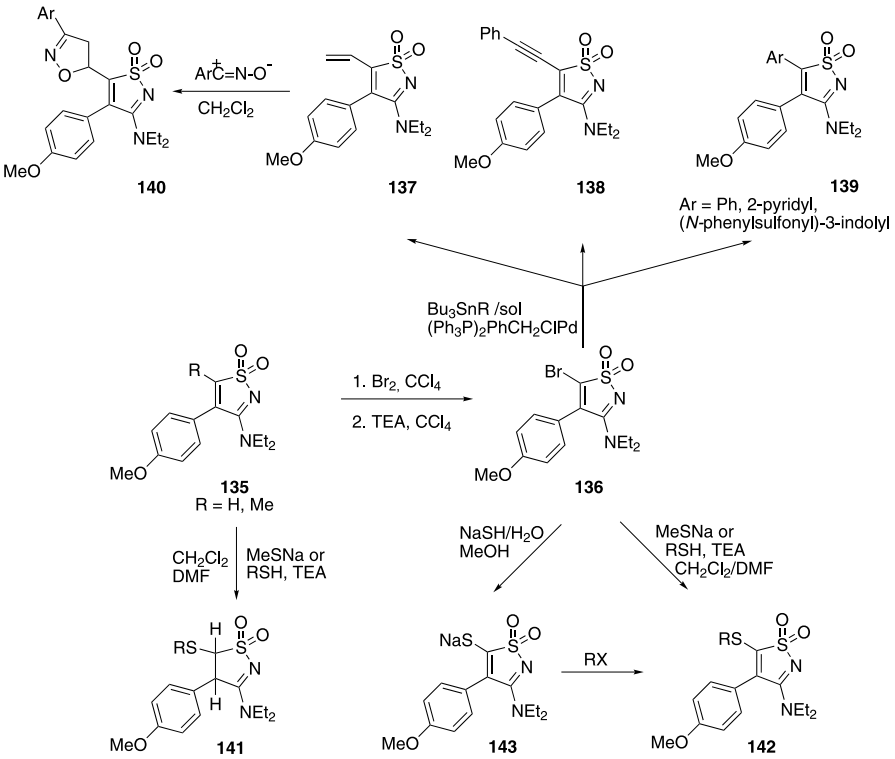


Scheme 35 General synthesis of 3-amino-isothiazole *S*,*S*-dioxide derivatives: *Method H*

Isothiazole dioxides **135** are the key intermediates for the preparation of a series of compounds for which the inhibitory activity on protein farnesyltransferase from *Tripanosoma brucei* was evaluated (Scheme 36) [44, 45]. Compounds used in these studies belong to two different classes in the isothiazole dioxide series. The first class includes 3-dimethylamino-4-(4-methoxyphenyl)-isothiazole *S*,*S*-dioxides **135**, unsubstituted or methyl substituted on C-5, respectively [43], or functionalised at C-5 with substituents ranging from alkenyl to aryl or heteroaryl groups. The second class consists of a series of 3-dimethylamino-4-(4-methoxyphenyl)-isothiazole *S*,*S*-dioxides and the corresponding 4,5-dihydro derivatives whose main feature is an *S*-atom as a linker between the isothiazole moiety and the substituent.

The 5-bromo derivative **136** was the key starting material for the preparation of both classes of compounds. It was obtained from **135** (R = H) by addition of bromine to the C4–C5 double bond followed by elimination of HBr, which can be spontaneous or induced by TEA. Stille reaction on **136** (Bu_3SnR, $(Ph_3P)_2BnClPd$) performed in toluene afforded the vinyl compound **137** (70%), the ethenyl derivative **138** (86%), and the aryl or heteroaryl compounds **139** (45–70%). Isothiazoles **140** functionalised at C-5 with an isoxazoline ring were prepared by a regioselective cycloaddition reaction starting from the vinyl derivative **137** and nitrile oxides [46].

The Michael addition of different mercaptans to isothiazoles **135** and **136** was regioselective and occurred at C-5 [47]. The addition to **135** of mercaptans gave a mixture of *trans* (major isomer) and *cis* diastereomers **141**

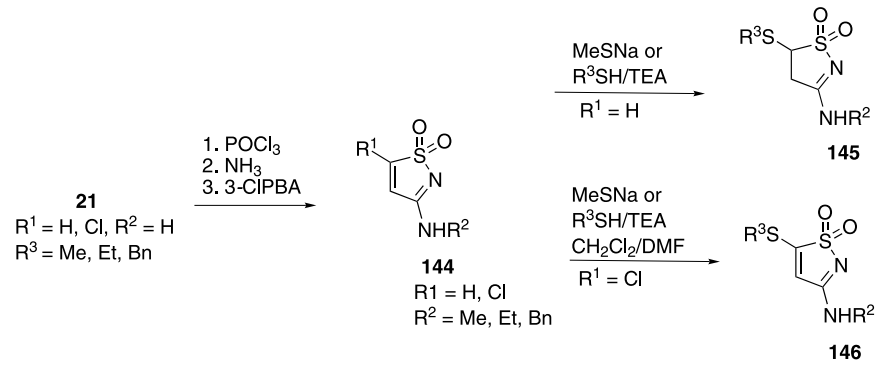


Scheme 36 General reactivity of 3-amino-5-bromo-isothiazole *S*,*S*-dioxide derivatives

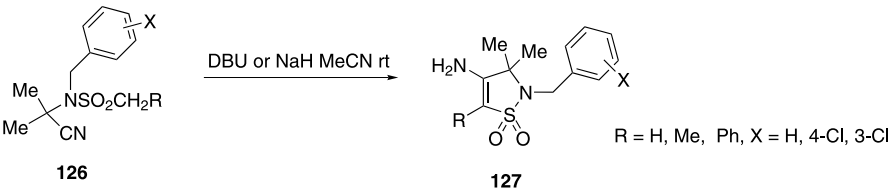
(60–90%). Compound **136** gave the addition elimination products **142** with methyl thiolate (R = Me, 68%) or mercaptans (R = alkyl, aryl and heteroaryl, 31–88%) in CH_2Cl_2/DMF. The use of sodium thiolate in MeOH afforded **143**, which was alkylated at a sulfur atom to give **142** (R = Bn 79% yield, R = farnesyl 47% yield) using alkyl bromides and a base.

Analogues **145** and **146**, unsubstituted at C-4, were prepared as inhibitors of rat aortic myocyte proliferation [45] starting from isothiazoles **144** ($R^1 = H$, Cl) bearing different amino groups at C-3. Compounds **144** were synthesised from the corresponding isothiazolones prepared according to *Method C* followed by reaction with $POCl_3$ and NH_3 and oxidation of the sulfur atom with 3-chloroperbenzoic acid (Scheme 37) [48]. By reacting **144** ($R^1 = H$) with mercaptans, dihydro isothiazole derivatives **145** were formed in 40–91% yield. Through an addition–elimination process, compounds **146** (56–89%) were obtained from **144** ($R^1 = Cl$) and mercaptans.

According to *Method F* 4-amino-2,3-dihydroisothiazole *S*,*S*-dioxides **127** were synthesised through base-catalyzed ring closure starting from a variety of alkylsulfonamides **126** (Scheme 38). Several compounds belonging to this class have been studied for their potential anti-HIV activity [49–51].

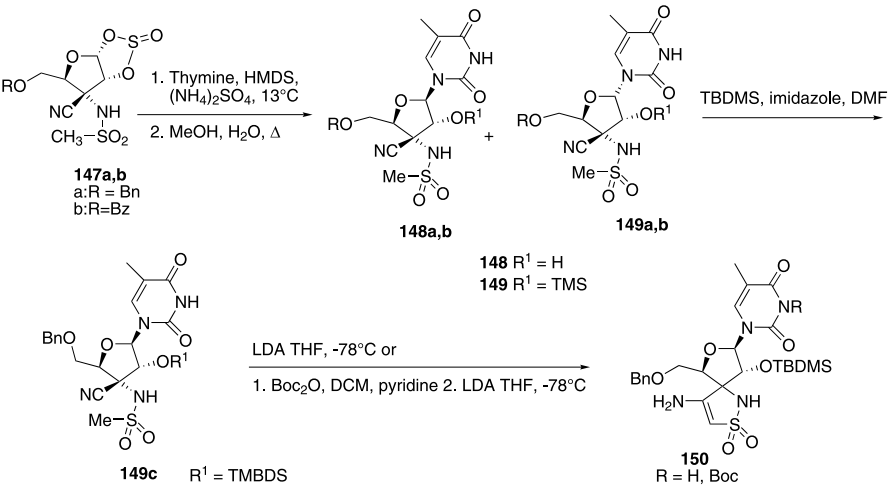


Scheme 37 Reactivity of 3-alkylamino-isothiazole *S*,*S*-dioxides with mercaptans



Scheme 38 Synthesis of 4-amino-2,3-dihydroisothiazole *S*,*S*-dioxides

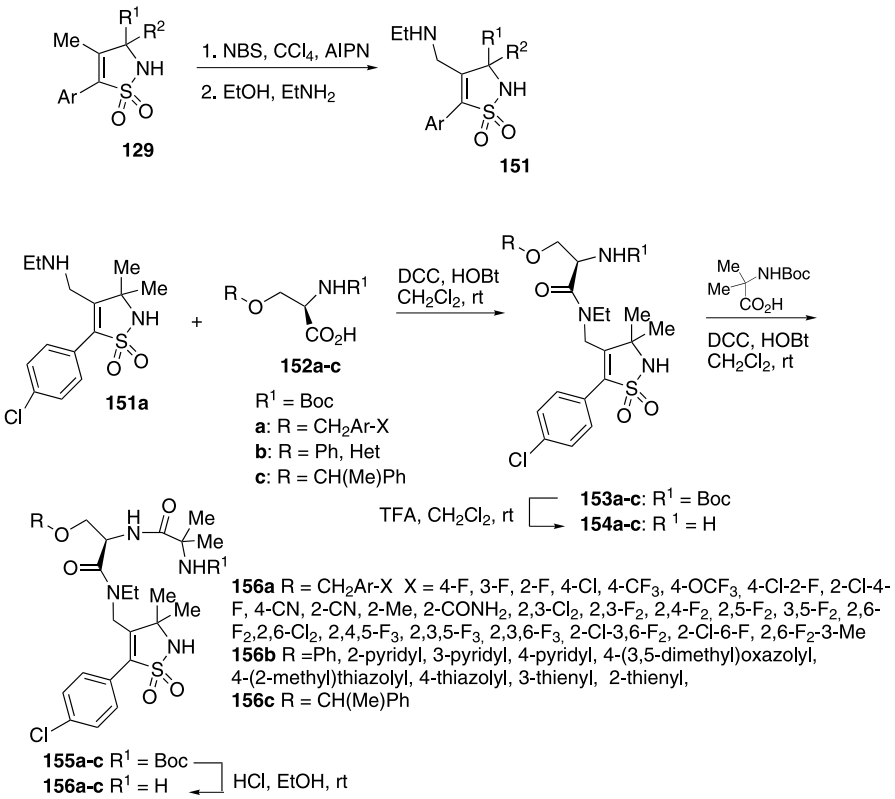
More recently, several studies on alkanesulfonamides located on monosaccharide backbones have been performed due to the biological interest of spiro products like **150** (Scheme 39) [49]. These new bicyclic systems were used as glycone precursor for aza analogues of TSAO RT inhibitors. Several families of



Scheme 39 Synthesis of aza analogues of TSAO RT inhibitors

compounds, depending on the substitution at both *N*-3 and *N*-2″, were synthesised. Sulfite derivatives **147** as *end*o and *exo* mixtures (*endo/exo* 1 : 1 to 3 : 2) were prepared by reaction of the corresponding dihydroxy derivatives with $SO(Im)_2$ in THF. Compounds **147** were treated with silylated thymine in dry conditions at 125 °C to give a mixture of regioisomeric 2′-*O*-silylated and 2′-hydroxy-5-methyluridine derivatives **148a,b** and **149a,b**. After protection of **148a** as TBDMS giving **148c** followed by cyclisation using LDA in THF, compound **150** (R = H) was obtained (*Method F*). Alternatively, the protection as *N*-Boc derivative of **148c** and subsequent cyclisation afforded compound **150** (R= Boc). Several aza derivatives were evaluated for their inhibitory activity against HIV-1 (III_B) and HIV-2(ROD).

2,3-Dihydro-4-ethylaminomethylisothiazole *S*,*S*-dioxide (**151**) is the key compound for the preparation of a large series of compounds like **156** designed as growth hormone secretagogues (GHSs) (Scheme 40) [52]. Their synthesis is based on the coupling of derivatives **151**, prepared according to *Method G*, with the opportune carboxylic acid derivatives and subsequent

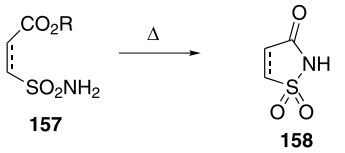


Scheme 40 Synthesis of growth hormone segretatgogues (GHSs) based on the 2,3-dihydroisothiazole nucleus

deprotection steps. Among the large number of differently substituted derivatives claimed in the patents [40–42], the synthesis of D-serine derivatives **156** are reported starting from **151a** as shown in Scheme 40.

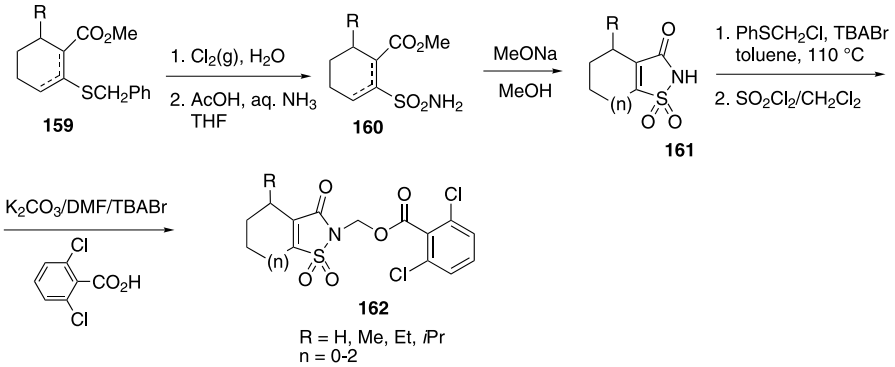
2.4.2 Isothiazol- and Dihydroisothiazol-3-One *S*,*S*-Dioxides

Formation of the C – N bond through a cyclisation process is the key step for the synthesis of the isothiazolone *S*,*S*-oxide ring **158** from the corresponding **157** according to *Method I*, which is also general for dihydroderivatives and for benzisothiazolones [1, 2].



Scheme 41 Synthesis of isothiazol-and dihydro-isothiazol-3-one *S*,*S*-dioxides: *Method I*

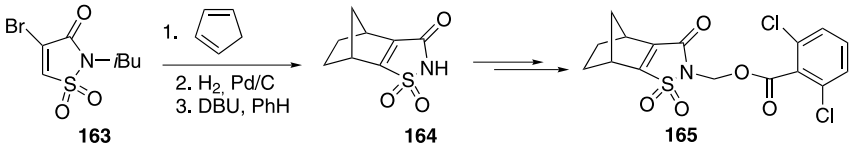
This scaffold characterises several potent mechanism-based inhibitors of HLE (see Sect. 5.3) such as tetrahydrobenzisothiazolones **162** (R = alkyl, n = 1) [53], which were prepared according to *Method I* from **159**, oxidised with Cl_2 in AcOH to the corresponding intermediates, which were transformed into the sulfonamides **160**. Their cyclisation with MeONa afforded isothiazoles **161** (70–80% overall yield). The functionalisation of the nitrogen atom was performed using $PhSCH_2Cl$ and $(t\text{-}Bu)_4NBr$ (70–80%) followed by treatment of the intermediate with SO_2Cl_2 in CH_2Cl_2 giving the *N*-chloromethyl intermediate (60–80%). Their reaction with the benzoic acid derivative in basic conditions afforded compounds **162** (50–60%) (Scheme 42). Compounds



Scheme 42 Synthesis of 4,5,6,7-tetrahydrobenzo[*d*]isothiazolones

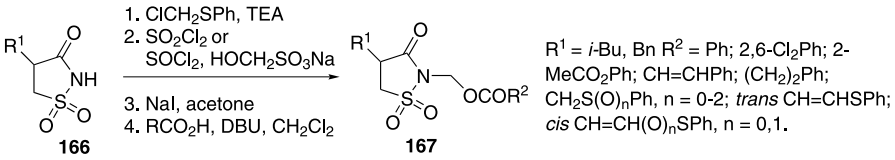
162 (R = H, $n = 0.2$) were also prepared from the available intermediates **161** ($n = 0.2$).

The analogue norbornane compound **165** was obtained from bromo isothiazolone dioxide **163** and cyclopentadiene, which gave the intermediate cycloadduct (95%), which was transformed into derivative **164** (40% overall yield) by reduction of the double bond followed by elimination of hydrogen bromide and deprotection (48%). The latter was converted to the target dichlorobenzoate **165** as described before for compounds **162** (Scheme 43) [53].



Scheme 43 Synthesis of norbornane-isothiazole derivative **165**

Following *Method I* simple isothiazolidin-3-one *S*,*S*-dioxide derivatives of general formula **166** were synthesised from intermediates like **157** [54]. The functionalisation of nitrogen gave **167** (Scheme 44).



Scheme 44 Synthesis of isothiazolidin-3-one *S*,*S*-dioxide derivatives

Phosphate derivatives **168** (Fig. 1) were also prepared starting from racemic 4-*i*-propyl-2-bromomethyl-isothiazolidin-3-one *S*,*S*-dioxide and di *n*-butyl- and benzyl phosphate in the presence of DBU [55].

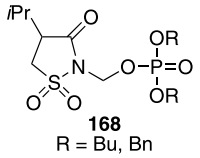
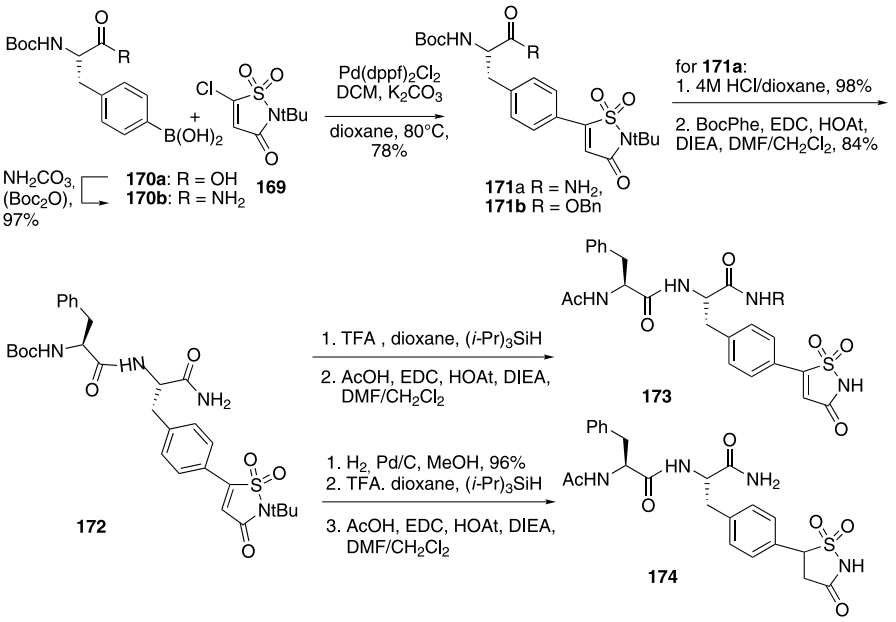


Fig. 1 *N*-Methylen-isothiazolidin-3-one *S*,*S*-dioxide phosphate

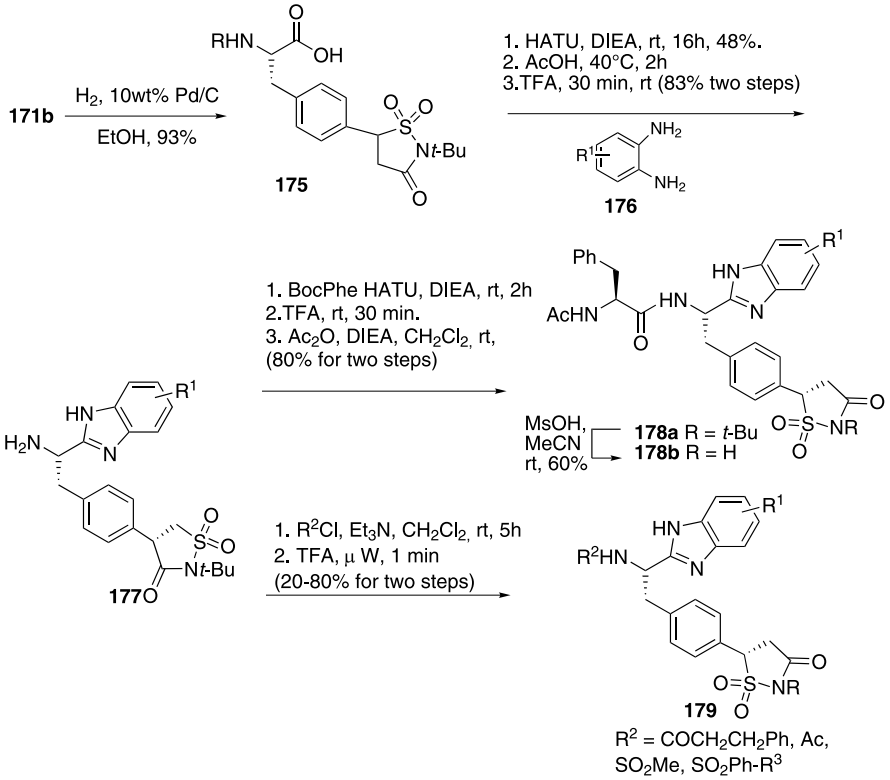
Functionalisation of the isothiazol-3-one *S*,*S*-dioxide system at C-5 provided several interesting derivatives. An example regarding the synthesis of some protein tyrosine phosphatase inhibitors [56] is reported below in

Scheme 45. Peptides containing the IZD heterocyclic pTyr mimetics were synthesised in 10–11 linear steps from readily available starting materials such as 5-chloro-isothiazol-3-one **169**, synthesised according to *Method C*, and amino acid derivatives **170**. The key synthetic reaction was a novel Suzuki coupling of chloroheterocycle **169** with 4-phenylalanineboronic acid **170** to afford the fully protected scaffold **171**. The *N*-terminus of **171** was subsequently elaborated via peptide coupling and the dipeptide **172** was deprotected to give inhibitor **173**. The 4,5 double bond of **172** was reduced, isomers were separated, and each of them was further elaborated to afford compounds **174** (Scheme 45).



Scheme 45 Synthesis of peptidomimetics **173** and **174** containing the isothiazolidin-3-one *S*,*S*-dioxide scaffold

From the optimisation of the above compounds, potent nonpeptidic benzimidazole sulfonamide inhibitors were disclosed [57]. The synthesis followed the route previously depicted. The ester **171b** was reduced and deprotected giving **175** in high yield and its coupling with substituted phenylendiamine **176** followed by cyclisation under acidic conditions afforded the desired benzimidazole **177**. Careful control of the temperature was critical because ring closure at higher temperatures proceeded more rapidly but returned mixtures of diastereomers at the α-centre of the amino acid. The (*R*/*S*)-IZD diastereomers were easily separated by chiral HPLC to afford two discrete isomers. Both diastereomers were further elaborated to the final compounds providing



Scheme 46 Synthesis of peptidomimetics **178** and **179** containing the isothiazolidin-3-one *S*,*S*-dioxide scaffold

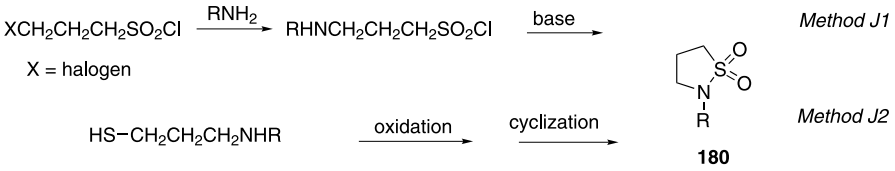
an active (*S*) and inactive pair. The removal of Boc group with TFA furnished the free amine, which was acylated with a variety of reagents under mild conditions to give amides, ureas, sulfonamides and carbamates **179** (Scheme 46).

3 Sultams

γ-Sultams are useful heterocycles for asymmetric synthesis and medicinal chemistry. Several compounds of biological interest containing the sultam moiety were synthesised and in many cases their preparation can be performed by simple functionalisation of the unsubstituted sultam or by modification of preexisting functional groups. Most compounds are *N*-substituted sultams but there are also several interesting derivatives substituted at C-2, C-3 or/and C-4. Some examples of the synthesis of sultams with a particular substitution pattern were reported.

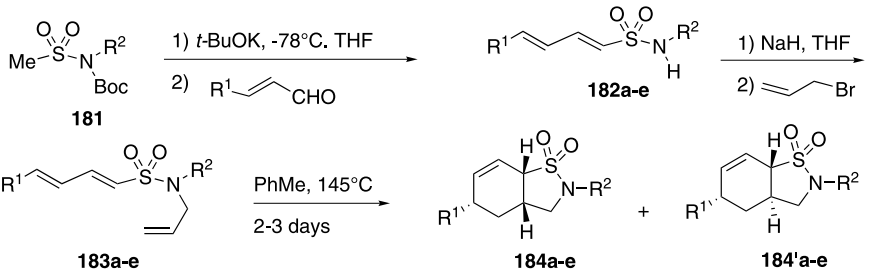
3.1
Synthesis of Sultams

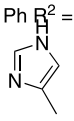
Various protocols for the synthesis of the substituted sultams have been developed using as the ring formation step either C – N, C – C or C – S bond formation [1, 2]. Very often the cyclisation of a γ-aminosulfonyl chloride deriving from nucleophilic substitution of an opportune amine on a γ-halosulfonyl chloride is used. In such a case the resulting sultam can be substituted or not at the ring nitrogen depending on the amine used in the process (*Method J1*). In the case of γ-aminopropanethiols oxidation of the thiol function and cyclisation was done in a one-step procedure (*Method J2*) (Scheme 47). A large number of different combination of reagents were used in the sultam ring synthesis based on this procedure and will be described for each significant compound.



Scheme 47 Synthesis of sultams: *Method J*

Recently developed powerful methodologies for the generation of these cyclic sulfonamides include pericyclic reactions as the intramolecular Diels–Alder reaction affording bi- or polycyclic sultams (*Method K*) (Scheme 48).



182, 183,184, 184' a R^1 = H R^2 = 4-Cl-Bn
182, 183,184, 184' b R^1 = Me R^2 = 4-Cl-Bn
182, 183,184, 184' c R^1 = Ph R^2 = 4-Cl-Bn
182, 183,184, 184' d R^1 = Ph R^2 = *n*-Bu
182, 183,184, 184' e R^1 =  R^2 = 4-Cl-Bn

Scheme 48 Synthesis of polycyclic sultams via Diels–Alder reaction: *Method K*

Such a procedure has been exploited for the synthesis of several derivatives for which an anti-inflammatory activity has been claimed [58]. A derivative under study as the Histamine H3 antagonist was prepared by the thermal intramolecular Diels–Alder reaction of a triene derivative of buta-1,3-diene-1-sulfonic acid amide. 1,3-Butadiene sulfonamides **182** (**a**: 67%, **b**: 69%, **c**: 99%, **d**: 51%) were prepared by the base mediated condensation of *N*-Boc-methanesulfonamides (**181**) with a series of aldheydes. *N*-akylation of **182** to give trienes **183** (**a**: 69%, **b**: 76%, **c**: 82%, **d**: 59%) was achieved by reacting the sodium salts with allyl bromide in THF at reflux. The intramolecular Diels–Alder reactions of compounds **183** were performed at 145 °C in toluene in a sealed vessel under argon. Under these conditions compounds **184** and **184′** were obtained in good yields (**a**: 76% ratio 6 : 1, **b**: 71% ratio 6 : 1, **c**: 92% ratio 3 : 1, **d**: 87% ratio 3 : 1).

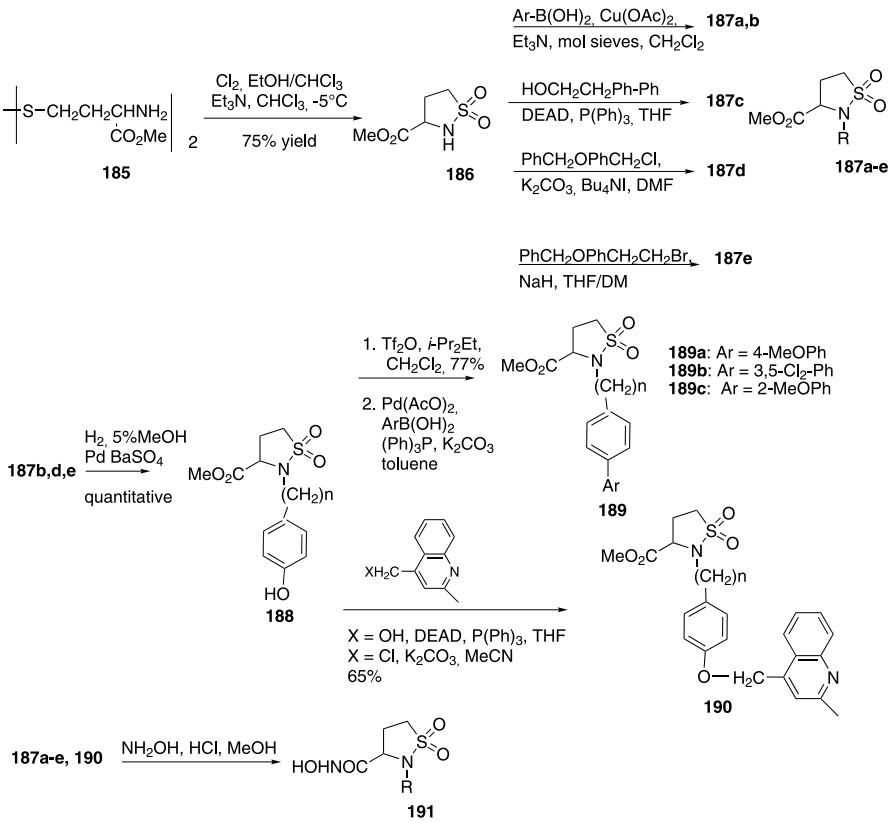
3.2 Reactivity of Sultams

N-Unsubstituted γ-sultams can be easily substituted at the nitrogen ring by alkylation, arylation or acylation. Arylation can be performed efficiently via copper promoted chemistry by using arylboronic acids. Alkylation is usually performed with halogen derivatives by using bases such as K_2CO_3, NaH, TEA. In some cases good results were obtained from hydroxy substituted compounds and DEAD/PPh_3 [59, 60].

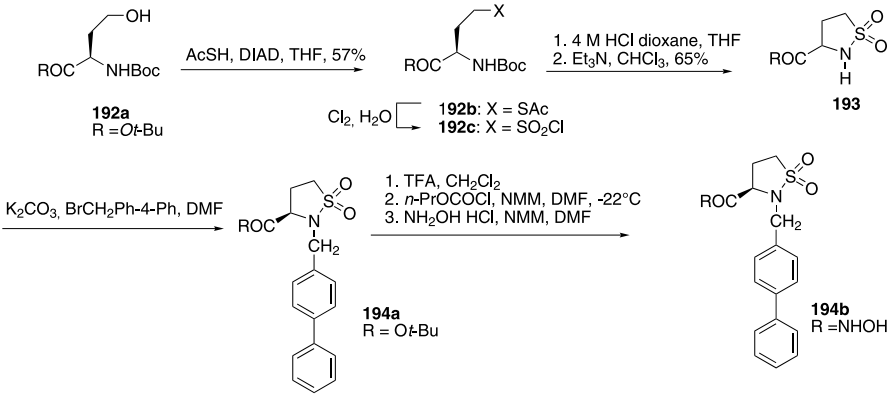
Synthesis of sultam hydroxamates prepared as potential anti-inflammatory agents was accomplished as shown in Scheme 49 by applying the methodology already described (*Method C*). Racemic homocystine **185** was oxidised to the sulfonyl chloride and cyclised. The resulting sultam **186** was arylated or alkylated affording **187a–e** (**a**: R = 4-Ph – Ph, 13%; **b**: R = 4-$PhCH_2O$ – Ph, 26%; **c**: R = Ph – $PhCH_2CH_2$, 88%; **d** R = $PhCH_2OPhCH_2$, 44%; **e**: R = $PhCH_2OPhCH_2CH_2$). Deprotection of oxygen in **187b,d,e** and transformation of the phenolic group of **188** into OTf followed by Suzuki reaction gave the bis-aryls **189a–c**. When **188** was treated with 4-(hydroxymethyl)- or with 4-(chloromethyl)-2-methylquinoline, **190** was formed (Scheme 49). Treatment of **187** and **190** with basic hydroxylamine gave the corresponding hydroxamates **191**.

Enantiopure homochiral sultams were prepared from chiral alcohol **192a** that was converted to the thioacetate **192b** (R = AcS) prior to chlorine oxidation, selective *N*-Boc removal and cyclisation to **193**. A similar chemistry as that reported in Scheme 49 afforded the target compound **194b** (R = NHOH) (Scheme 50).

A novel series of HIV protease inhibitors containing the sultam scaffold **197** has been synthesised [61]. Compound **197** was prepared (Scheme 50) starting from the thioacetate **195** prepared as described in the literature [61]. The usual oxidation/chlorination one-pot process (*Method J1*) with Cl_2 gas

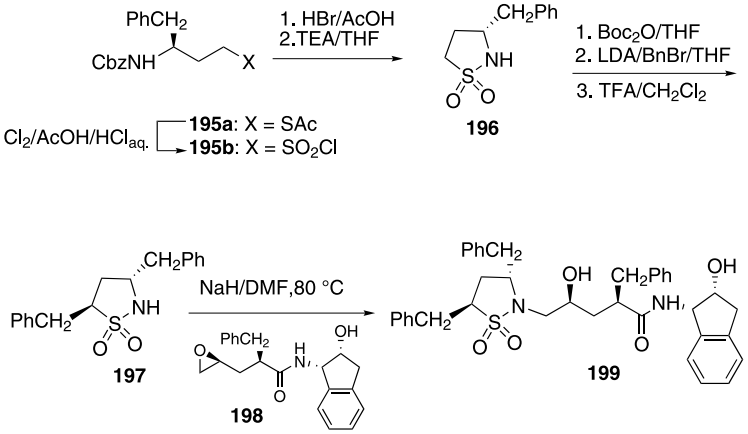


Scheme 49 Synthesis of sultam hydroxamates



Scheme 50 Synthesis of homochiral sultams **194**

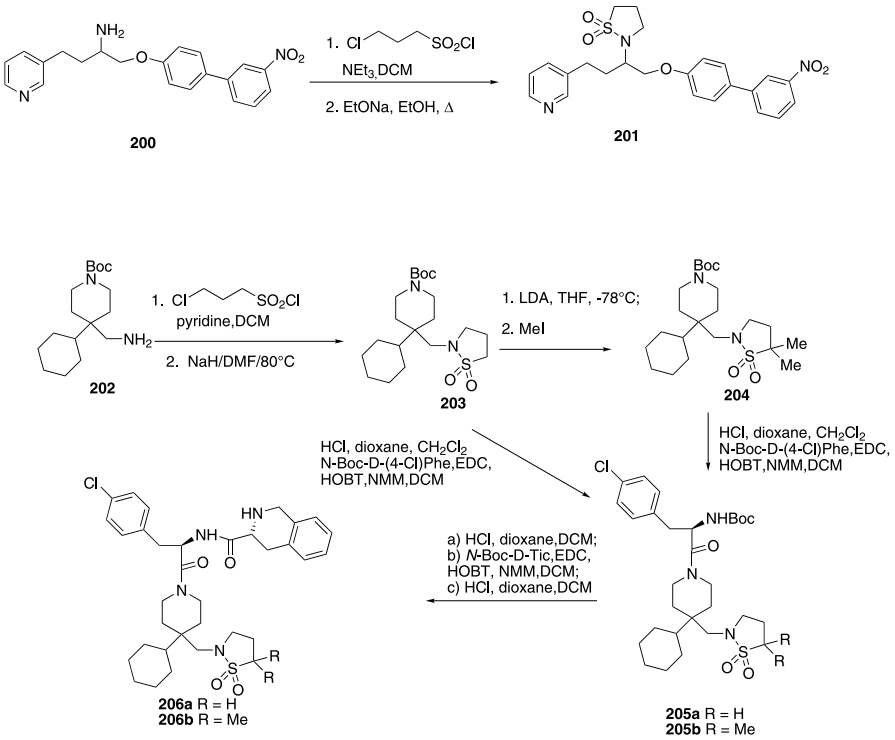
in AcOH/aq. HCl produced sulfonyl chloride **195b** (95%). The Cbz group was removed (48% HBr/AcOH) and the cyclisation to **196** (58%) was performed using TEA. The benzyl substituent was introduced starting from the *N*-Boc derivative, obtained from **196** (Boc_2O/THF), which was treated with LDA and BnBr in THF. Finally, the nitrogen atom was deprotected (TFA/CH_2Cl_2) and the isothiazolidine *S*,*S*-dioxide **197** was isolated. Compound **197** was then coupled with epoxide **198** using NaH in DMF at 80 °C. A partial isomerisation occurred and a mixture of *trans/cis* epimers (3 : 1) was formed (the *trans* isomer **199** is shown in Scheme 51).



Scheme 51 Synthesis of 3,5-dibenzyl-*N*-substituted sultams

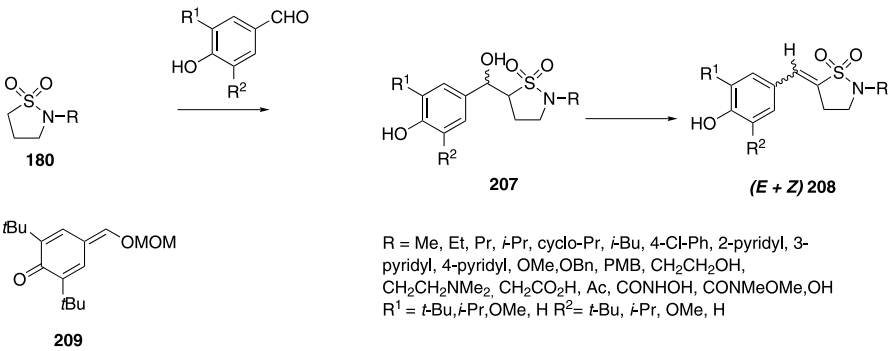
By the same chemistry based on the reaction of 3-chloropropanesulfonyl chloride with amines as shown in *Method J1*, compounds **201** [62] and **203** were prepared from amines **200** and **202**, respectively (Scheme 52). Further alkylation of **203** with methyl iodide resulted in the formation of **204**. Removal of the Boc group in **203** and **204** with HCl followed by coupling with *N*-Boc-D-(4-Cl)Phe under EDC conditions gave **205**. Removal of Boc protection followed by EDC coupling with *N*-Boc-Tic and subsequent Boc removal furnished **206a** and **206b** [63]. Compound **201** showed anti-inflammatory activity, whereas **206a** and **206b** were synthesised as selective human melanocortin subtype-4 receptor ligands.

Taking advantage of the nucleophilic character of the C-5 atom due to the electron-withdrawing effect exerted by the SO_2 group, condensation reactions with aldheydes are possible giving rise to the alkylidene derivatives [64, 65]. By this way, through an aldol condensation, antiarthritic drug candidates, were prepared. The *N*-substituted sultam ring, from the cyclisation process, was condensed with 3,5-di-*t*-butyl-4-hydroxybenzaldehyde affording the corresponding adducts **207** as diastereomeric mixture. Treatment of the crude aldol adducts with a catalytic amount of *p*TsOH resulted in dehydration and



Scheme 52 Synthesis of *N*-functionalised sultams as selective human melanocortin subtype-4 receptor ligands

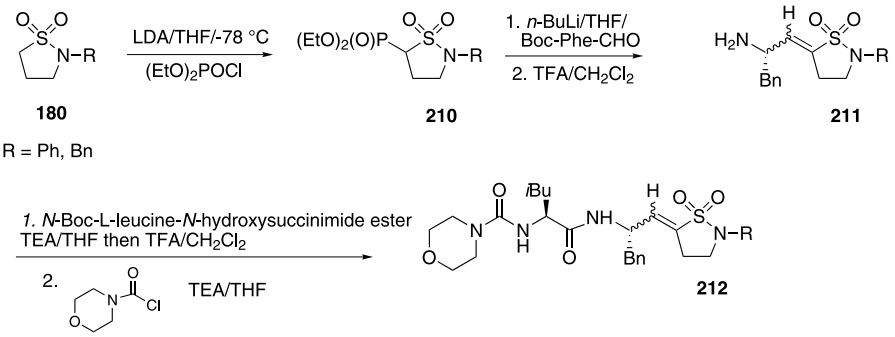
removal of the MOM group yielded an *E*/*Z* mixture of 5-benzylidene-γ-sultam derivatives **208.** Starting from the *N*-unprotected sultam **208,** several alkylated or acylated derivatives were formed by introduction of an alkyl or acyl substituent at the nitrogen atom. The use of the *p*-quinone methide



Scheme 53 Synthesis of 5-benzylidene-γ-sultam derivatives

derivative **209**, generated from the corresponding benzaldehyde, allows to obtain a single *E*-isomer (R = Et), via a 1,6-Michael addition (Scheme 53).

By a Wittig-Horner reaction, alkylidene derivatives **212** were similarly prepared and tested on *Plasmodium falciparum*. Phosphonates **210** were obtained from sultams **180** by using $(EtO)_2POCl$ and LDA at – 78 °C and used in a Wittig-Horner reaction with Boc-Phe-CHO (*n*BuLi in THF) affording **211** (*E*: 60%, *Z*: 16–29%) after deprotection of the nitrogen atom (TFA in CH_2Cl_2). The dipeptides **212** (56–88%) were obtained by condensation of **211** with *N*-Boc-L-leucine-*N*-hydroxysuccinimide ester in presence of TEA in THF and deprotection of nitrogen with TFA in CH_2Cl_2. Carbamates **212** (R = $PhCH_2$) were obtained in low yield from **212** (R = H) and 4-morpholinecarbonyl chloride in presence of TEA in THF (Scheme 54) [66].



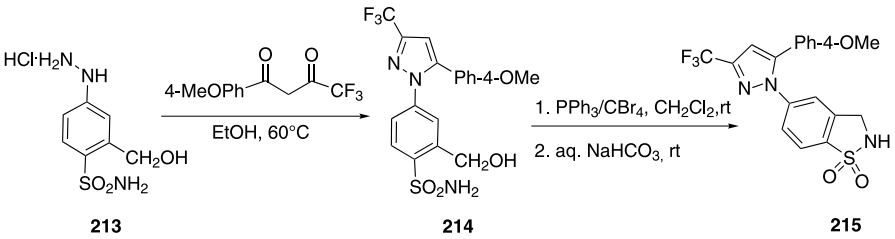
Scheme 54 Synthesis of 5-alkylidene-γ-sultam dipeptides

4
Benzisothiazoles

Examples of new synthetic approaches to the benzisothiazole ring are related to compounds characterised by a particular substitution pattern or to heterobicyclic derivatives. Instead, the preformed benzisothiazole ring was extensively used for the preparation of biological compounds functionalised with several heterosubstituted chains at C-3 or at the nitrogen atom. Naphtho[1,8-*c*,*d*]isothiazole (naphtosultam) represents the most used ring when functionalisation at the nitrogen atom with pharmacophores was done.

4.1
Synthesis of Benzisothiazoles and Heterobicyclic Isothiazoles

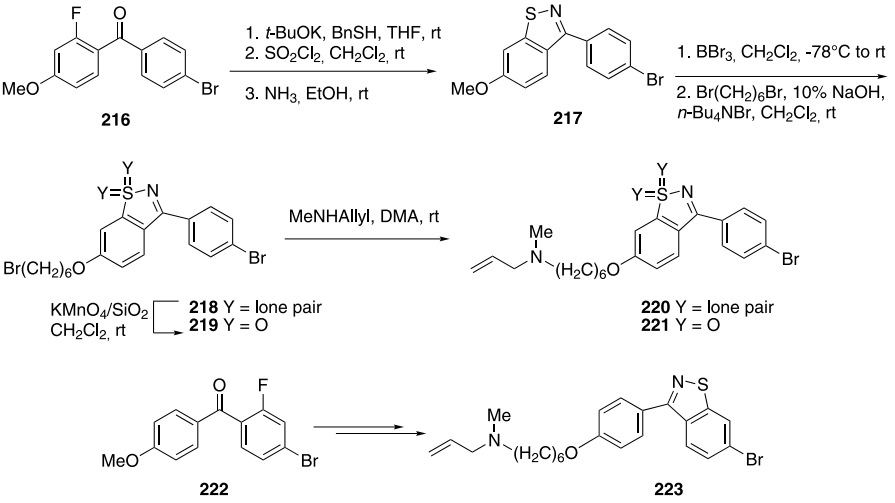
S,*S*-Dioxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl-pyrazole (**215**) [67], an anti-inflammatory agent, was synthesised from compound **214** by treatment with CBr_4, Ph_3P and aqueous $NaHCO_3$. Preparation of the reagent **214** was ac-



Scheme 55 Synthesis of *S*,*S*-dioxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl-pyrazole

complished as shown in Scheme 55 by simple coupling of phenylhydrazine hydrochloride **213** with 1-(4-methoxyphenyl)-3-trifluoromethyl-1,3-propane dione in EtOH.

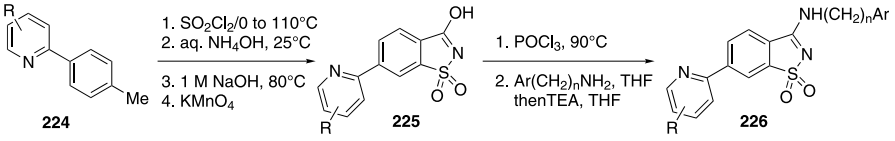
Benzo[*d*]isothiazoles **220** and **221** (Scheme 56) were synthesised as oxidosqualene cyclase inhibitors. By reaction of fluorobenzophenones **216** with potassium benzylthiolate followed by *S*-chlorination, cleavage of the benzyl group with SO_2Cl_2 and reaction with NH_3, compound **217** was formed. Methoxy deprotection and alkylation with 1,6-dibromohexane gave intermediate **218**, which was converted to **220** with *N*-allylmethylamine. Intermediate **218** was oxidised to the *S*,*S*-dioxide **219** and then functionalised at C-6 affording **221**. Similarly, benzo[*d*]isothiazole **223** was prepared from benzophenone **222** [68].



Scheme 56 Synthesis of 3-aryl substituted benzisothiazoles as oxidosqualene cyclase inhibitors

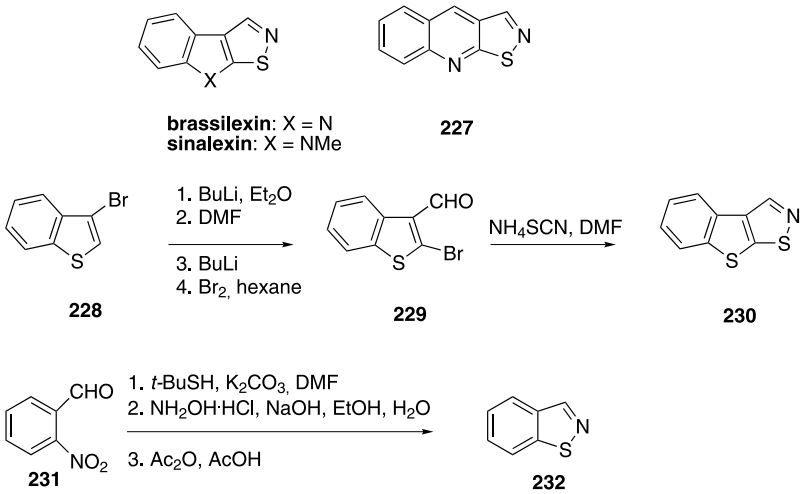
A series of benzisothiazoles *S*,*S*-dioxides functionalised with a nitrogen-linked chain at C-3 and with different substituents on the benzene ring, which

are particularly useful in the treatment of pain, inflammatory hyperalgesia, and urinary disfunctions, were patented [69]. As an example, the synthesis of compounds **226** was reported (Scheme 57). From substituted chloropyridine derivatives and by using a Suzuki reaction, the *bis*-aryl derivatives **224** were synthesised. Their treatment, in sequence, with SO_2Cl_2, aq. NH_4OH, 1 M NaOH and with $KMnO_4$ afforded the 3-hydroxy-benzisothiazoles **225**. Their reaction with $POCl_3$ followed by treatment of the corresponding 3-chloro intermediates with a proper amine gave **226**.



Scheme 57 Synthesis of 3-aminosubstituted benzisothiazoles *S*,*S*-dioxides

Potential new inhibitors of *Leptospheria maculansi* mediated detoxification of phytoalexin brassilexin were designed and synthesised by analogy with the heteroaromatic structure of isothiazolo[5,4-*b*]indole (brassilexin) [9]. The above ring was replaced by quinolino[5,4-*b*]-isothiazole **227**, benzothiophene[5,4-*b*]-isothiazole **230** and the simple benzoisothiazole **232** rings. In addition, 4-arylisothiazoles **7** resulting from disconnecting the "*a*" bond of the indole ring of brassilexin and replacing the NH group *ortho* to isothiazole with different substituents were prepared (see Sect. 2.1). Even if the synthesis of the above ring is known in general, some changes in the



Scheme 58 Synthesis of benzothiopheneisothiazole and benzisothiazole

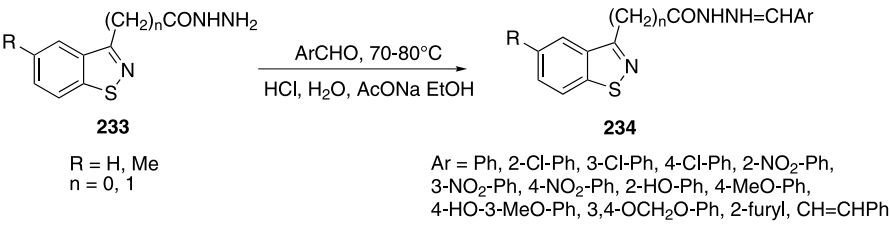
use of the reagents were made aiming to improve the yield or to find less harsh conditions or to simplify the purification processes. A new synthetic approach was adopted for the preparation of **230** starting from 3-bromobenzo[*b*]thiophene **228** was treated with *t*-BuLi then quenched with DMF. After bromination in basic conditions, **229** (35% overall yield) was obtained and then heated with NH_4SCN affording **230** (11%). Aiming to avoid several chromatographic steps and to increase the yields, the synthesis of unsubstituted 1,2-benzoisothiazole **232** (64%, overall yield), starting from aldehyde **231**, was revisited. New conditions are reported in Scheme 58.

4.2
Reactivity of Benzisothiazoles and Heterobicyclic Isothiazoles

Several compounds of biological interest containing the benzisothiazole ring were prepared and, in many cases, well-known starting materials were used. In general, their chemistry is related to the simple functionalisation of preexisting substituents. They can be divided into two main classes, i.e. benzisothiazoles functionalised at C-3 or at nitrogen. The majority of C-3 functionalised compounds bears a nitrogen atom directly linked to C-3 or a carbon chain containing a nitrogen. Other heteroatoms can be directly linked to C-3, such as oxygen and sulphur.

4.2.1
3-Carbon Linked Benzisothiazoles

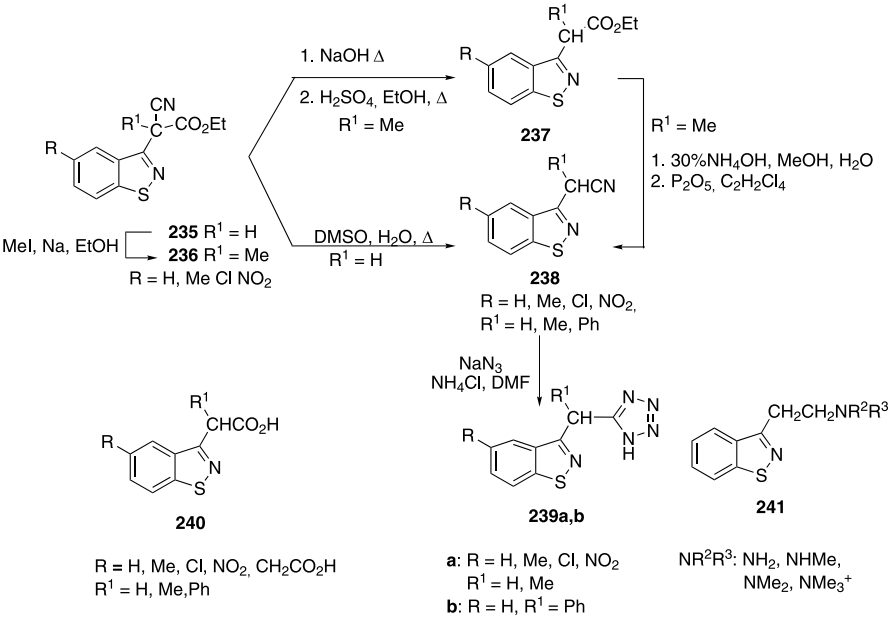
Vicini et al. reported on the preparation of hydrazones **234** obtained from the condensation of a proper aldehyde with 1,2-benzisothiazole hydrazide derivatives **233** characterised by a different length of the linker chain (Scheme 59) [70] and their antimicrobial [71, 72] and anti-inflammatory [73] activities were evaluated. Both theoretical and experimental lipophilic indices were calculated and QSAR studies were also reported [70].



Scheme 59 Synthesis of hydrazones of hydrazido benzisothiazole derivatives

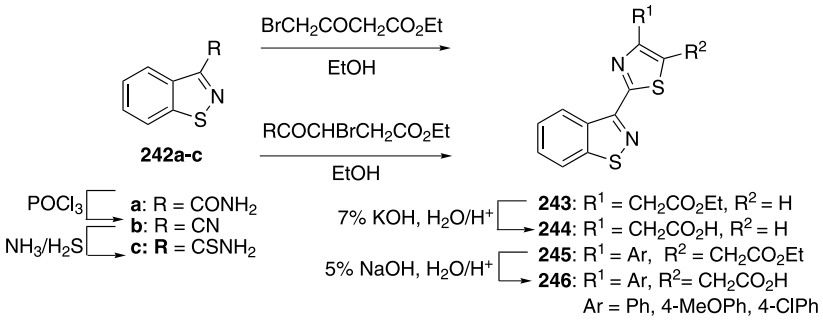
Below two examples of benzisothiazole derivatives characterised by anti-inflammatory activity functionalised at C-3 with a heterocyclic ring, which

was built starting from homologous nitrile compounds **238** and **242b**, are given. Compound **238** was prepared by using two different synthetic strategies starting from the available 3-chlorobenzisothiazole (see Sect. 4.2.2) condensed with both ethyl cyanoacetate and phenylacetonitrile in EtOH/Na affording **235** and **238** (R^1 = Ph, R = H), respectively [74]. The alkylation of **235** with MeI gave **236** hydrolyzed and esterified to **237** (R^1 = Me), then transformed into nitrile **238** (R^1 = Me), by treatment first with NH_4OH and then with P_2O_5. Compound **235** was directly hydrolyzed in aqueous DMSO to **238** (R^1 = H). Tetrazolyl derivatives **239a,b** were prepared by treatment of **238** with NaN_3 in DMF in the presence of NH_4Cl. The benzisothiazolylalkanoic acids **240** were simply prepared by alkaline hydrolysis of the corresponding nitriles. From ethyl 2-(1,2-benzisothiazol-3-yl)-acetate (**237**, R^1 = H) some new 2-(1,2-benzisothiazol-3-yl)ethylamine derivatives **241** were synthesised and their putative histaminergic activity was investigated [75]. 2-(1,2-Benzisothiazol-3-yl)ethanol was obtained by reduction of ester **237** ($LiAlH_4$, Et_2O), which was treated with $SOCl_2$ to obtain the chloro derivative, and then reacted with a suitable amine in EtOH affording the targeted compounds **241** (Scheme 60).



Scheme 60 Synthesis of 3-tetrazolyl- and 3-carboxymethyl-benzisothiazoles

Benzisothiazole 3-carboxamide **242a** was converted, through the intermediate nitrile **242b**, into the thioamide **242c** ($POCl_3$ then NH_3/H_2S), the key starting material for the preparation of several 2-(1,2-benzisothiazol-

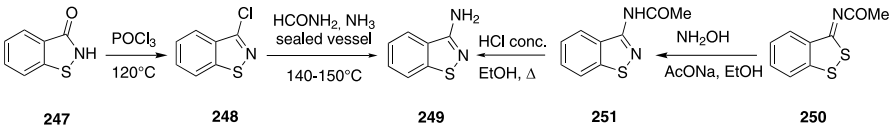


Scheme 61 Synthesis 2-(1,2-benzisothiazol-3-yl)-thiazolyl-4- or 5-acetic acid derivatives

3-yl)-thiazolyl-4- or 5-acetic esters **243** and **245** obtained by reaction with bromo ketoesters. The hydrolysis of the ester function gave acids **244** and **246** (Scheme 61) [76].

4.2.2
3-Heterosubstituted Benzisothiazoles

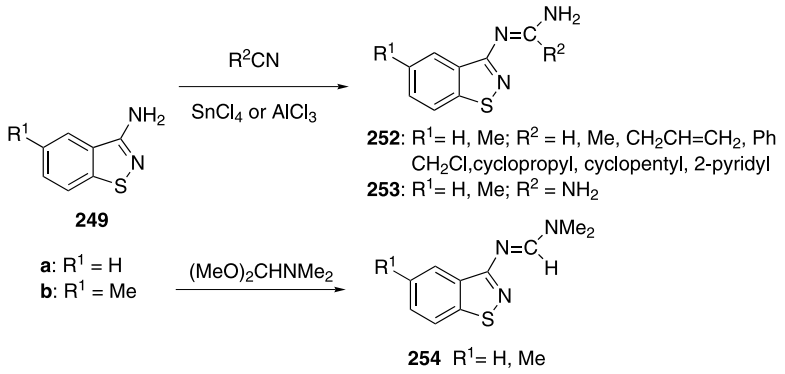
A large number of biologically interesting compounds were synthesised from two key reagents represented by 3-chloro-1,2-benzisothiazole (**248**) and 3-amino-2-benzisothiazole (**249**) (Scheme 62). The chloro derivative was prepared from 1,2-benzisothiazolone (**247**) obtained according to *Method C* from 2,2′-dithiosalicyclic acid ($SOCl_2$, DMF, toluene, 75 °C; Cl_2, CH_2Cl_2, then NH_4OH). By adding $POCl_3$ to **247** and heating it gradually to 120 °C, the 3-chloro derivative **248** was obtained (77% yield) [77]. Other recent preparations of **248** are claimed in several patents [78, 79].



Scheme 62 Synthesis of 3-chloro- and 3-amino-1,2-benzisothiazole

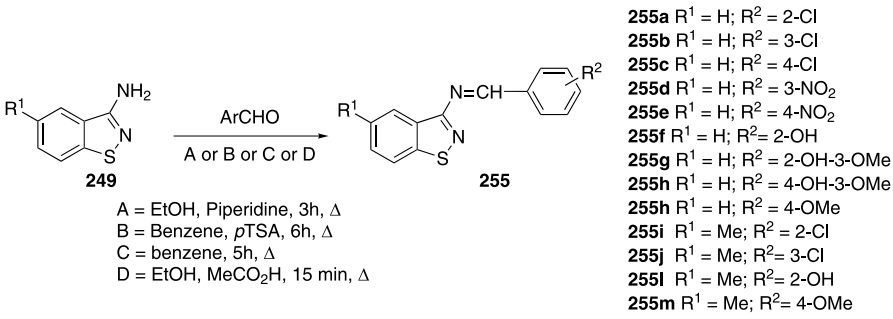
The preparation of 3-amino-1,2-benzisothiazole **249** can be done in different ways. A well-known method started from **248**, which was treated with a formamide solution containing NH_3 [80] (Scheme 62). An alternative method started from hydroxylamine and *N*-(3*H*-benzo[*c*]1,2-dithiol-3-ylidene) acetamides (**250**) (obtained from **248** and thioacetic acid), and gave *N*-(3-benzisothiazolyl)acetamide (**251**) (52–62%) hydrolyzed to amine **249** (48–88%) [81].

Several 3-amino substituted benzisothiazoles, in which the amino group is involved in the formation of an amide, amidino, imino, guanidino groups or is a part of a cyclic amine (e.g. piperazine) were prepared and evaluated for different activities. 3-Amidinobenzisothiazole compounds **252** displayed remarkable analgesic action and an interesting antiphlogistic action that is often dissociated from antipyretic activity [82]. Their antimicrobial activity in vitro was also evaluated [83]. The main procedure for their preparation involved a nucleophilic addition of 3-amino-1,2-benzisothiazoles **249a,b** to the carbon of selected nitriles used both as reagent and solvent. The majority of the target compounds were obtained by heating the amine with the suitable cyanide and acidic catalyst enhancing the CN group reactivity (i.e. $SnCl_4$ or $AlCl_3$). Guanidino derivatives **253** and formamidino compounds **254** were prepared by reacting **249a,b** with cyanamine in HCl and *N*,*N*-dimethylformamide dimethylacetal in benzene, respectively (Scheme 63).



Scheme 63 Synthesis of 3-amidino- and 3-guanidino-1,2-benzisothiazoles

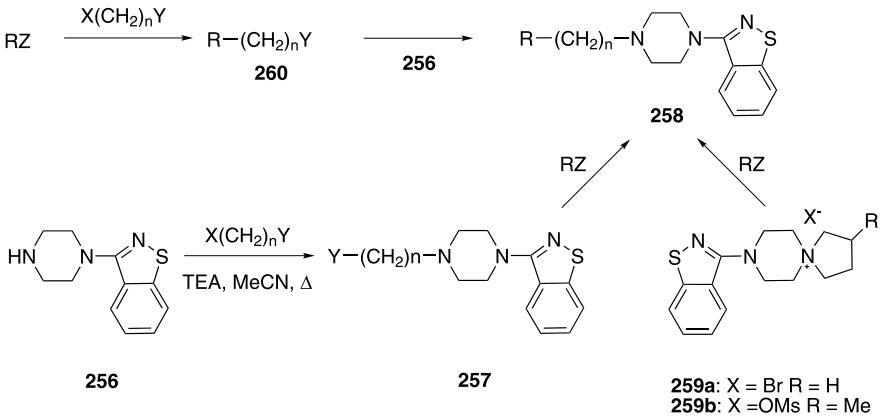
3-Aminoarylidene-1,2-benzisothiazol **255** were also prepared from 3-aminobenzisothiazole **249** and an opportune aldehyde (Scheme 64). This



Scheme 64 Synthesis of 3-aminoarylidene-1,2-benzisothiazoles

reaction was not always straightforward and different experimental conditions (A, B, C or D) were developed [73].

There is a large literature concerning the preparation and the evaluation of the 3-(piperazinyl)-1,2-benzisothiazole derivatives **258** (Tables 2, 3) substituted at nitrogen atom with different oxygen functionalized chains [84–88] as antipsychotic agents. Three main synthetic strategies were adopted for their preparation (Scheme 65). The first one used as key reagent the 3-(piperazinyl)-1,2-benzisothiazole (**256**), which was appropriately alkylated to introduce a chain of suitable length (n = 2, 3, 4) affording the intermediate **257** and then made to react with the characteristic terminal group (reagent RZ) affording **258**. Some examples of the very large number of derivatives that have been synthesised are given in Table 2 (entries 1–9). The second strategy took advantage of reagents **259a**,**b** from which compounds of type **258** (Table 2, entries 10–12) were prepared. The use of reagent **259b** gave a mixture of two regioisomers (entries 11 and 12).



Scheme 65 Synthesis of 3-(piperazinyl)-1,2-benzisothiazole derivatives **258**

According to the third strategy, the chain was first linked to the terminal characteristic group (intermediate **260**) and then the piperazinylbenzisothiazole (**256**) was alkylated with the whole substituent **260** affording **258** (Table 3 entries 1–5).

3-Phenylpropionic acid derivatives of general formula **261**, functionalised at C-2 with a 3-heterosubstituted benzisothiazole, were patented for use in the treatment and/or prevention of peroxysome proliferator-activated receptor gamma (PPARgamma) mediated diseases [89]. Only the synthesis of the 3-sulfur linked compound **264** (40%) was extensively described starting from methyl 3-[4-(benzyloxy)phenyl]-2-chloropropionate (**263**) and benzoisothiazol-3(2*H*)-thione (**262**) operating in the presence of MeONa/MeOH (Scheme 66).

Table 2 Antipsychotic 3-(piperazinyl)-1,2-benzisothiazole derivatives **258** (part I)

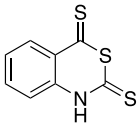
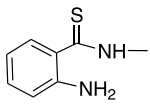
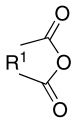
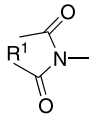
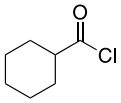
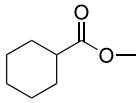
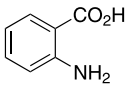
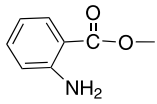
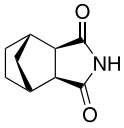
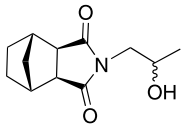
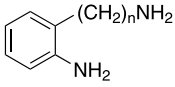
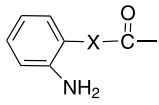
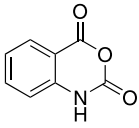
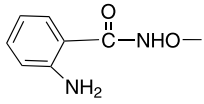
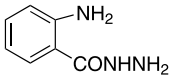
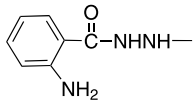
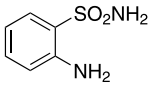
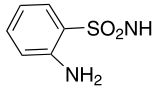
Entry	n	Y	RZ	**258**, R:	Refs.
1	4	NH_2			[85]
2	4	NH_2			[86]
3	4	OH			[86]
4	4	OH			[85]
5	2				[86]
6	3	CO_2Et		 X = CH_2NH, NH	[85]
7	3	ONH_2			[85]
8	3	Cl			[85]
9	2	Cl	Het	Het	[87]
10	4	–			[85]

Table 2 (continued)

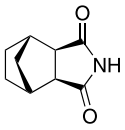
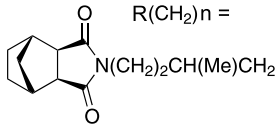
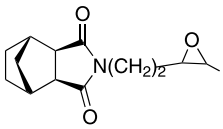
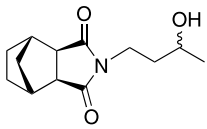
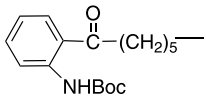
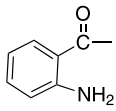
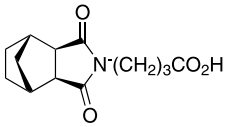
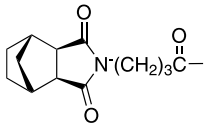
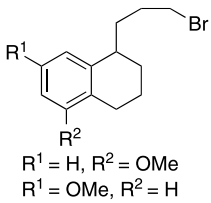
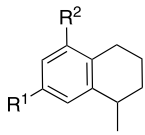
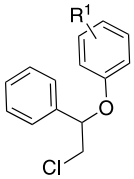
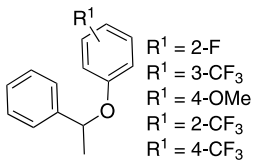
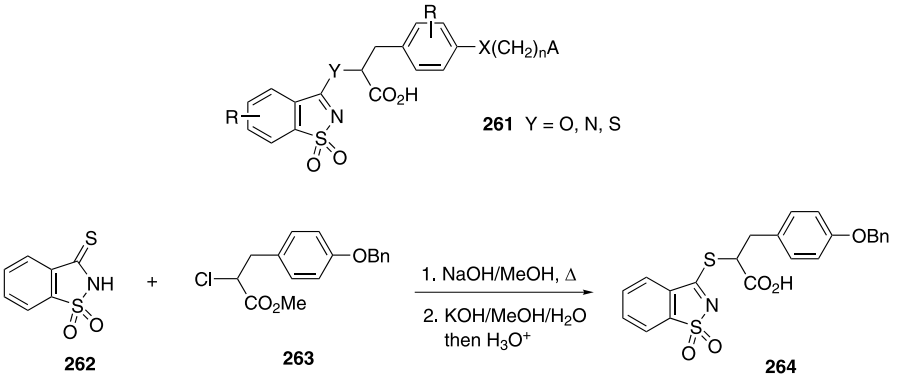
Entry	n	Y	RZ	**258**, R:	Refs.
12	4	–			[85]

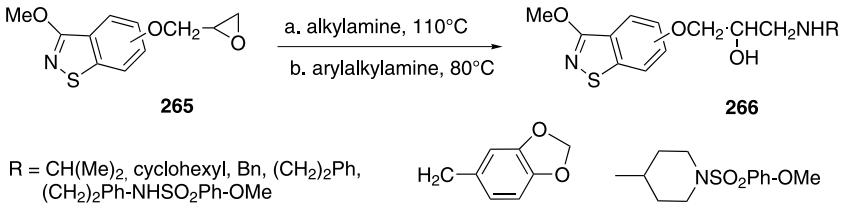
Table 3 Antipsychotic 3-(piperazinyl)-1,2-benzisothiazole derivatives **258** (part II)

Entry	R $(CH_2)_n$Y **260**	**258**, R:	Refs.
1			[86]
2			[85]
3			[86]
4			[88]
5			[89]



Scheme 66 Synthesis of 2-hetero-(benzisothiazol-3-yl)(3-phenyl)propionic acids

Benzisothiazole moieties substituted at C-3 with an oxygen are also present in compounds studied for β-adrenoceptor blocking activity such as **266** [90]. These compounds were prepared as racemic mixtures from **265** by a coupling reaction of the epoxide function of the benzene ring with the various amine derivatives (Scheme 67).

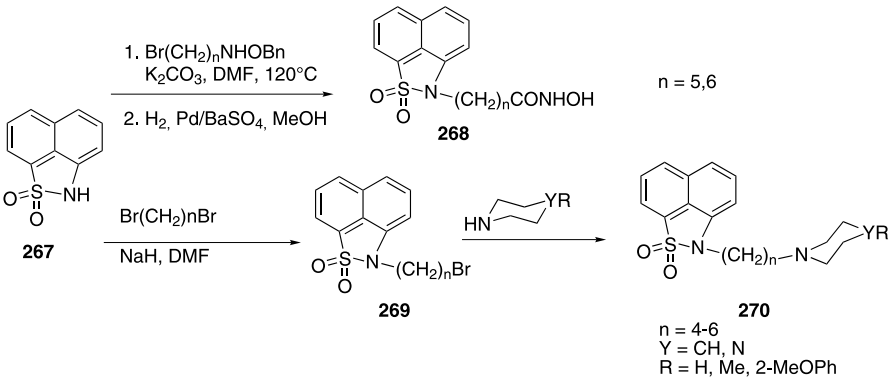


Scheme 67 Synthesis of 3-methoxybenzisothiazolyl substituted propanolamines

4.2.3
2-Substituted Benzisothiazoles and Naphtosultams

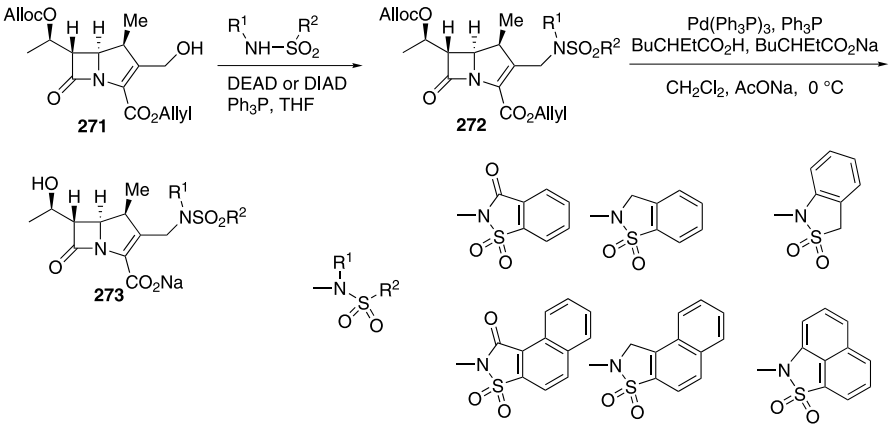
S,*S*-Dioxo-2*H*-naphtho[1,8-*c*,*d*]isothiazole (naphtosultam) is in general the more represented ring of this class of nitrogen functionalised compounds. A series of naphtosultams **268** substituted at nitrogen with a functionalised C-7 and C-8 chain were patented for their anti-cell-proliferation activity (Scheme 68) [91]. They were prepared from naphthalenesultam **267** and a ω-bromo-hexanoic or -heptanoic acid benzyloxy-amides in the presence of K_2CO_3. The resulting intermediates were reduced with H_2 and $Pd/BaSO_4$ giving **268** (60–70%).

The naphtosultam derivatives **270** characterised by anti-inflammatory activity are strictly correlated to the above compounds. They were prepared via intermediate **269**, obtained by reaction of **267** with dibromoalkyl compounds followed by treatment with the proper amine (Scheme 68) [92].



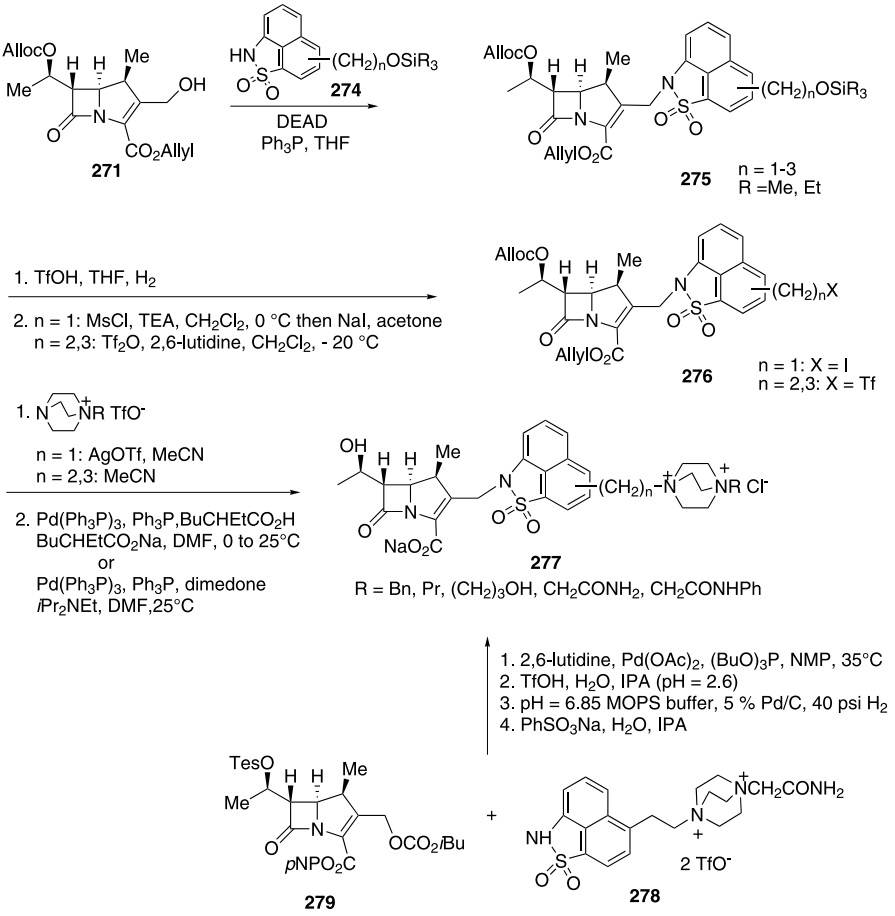
Scheme 68 Synthesis *N*-naphtosultam-substituted alkanoic acid hydroxyamides and alkylamines

Aryl sulfonamides were targeted as potential anti-MRS pharmacophores of 1-β-methylcarbapenems characterised by antimicrobic activity (Scheme 69). The functionalisation of carbapenem **272** with naphtosultam as well as with other isothiazole derivatives was achieved through a Mitsunobu reaction, taking advantage of the acidity of the arylsulfonamide function. The reaction of *bis*(allyl)protected hydroxymethylcarbapenem **271** and the proper sulfonamido compound in THF and in the presence of DEAD or DIAD and Ph_3P afforded **272** (average yield: 49%). The deprotection of oxygen atoms performed with a mixture of $Pd(Ph_3P)_3$, Ph_3P, $BuCHEtCO_2H$, $BuCHEtCO_2Na$ afforded **273** (average yield: 67%) [93].



Scheme 69 General synthesis of carbapenems functionalized with benzisothiazole *S*,*S*-dioxide rings

In this case, the naphthosultamyl-methyl group was also selected as a good candidate and the structure was optimised to improve water solubility, pharmacokinetics and chemical stability. The Mitsunobu reaction of carbapenem **271** with a series of homologous silyloxyalkyl-1,8-naphtosultams **274** produced compounds **275** in good yields. Deprotection of the *O*-silyl group (TfOH, THF/H_2O, 55–65% from **271**) followed by activation of the hydroxy group as mesylate (n = 1: MsCl, TEA then NaI) or triflate (n = 2, 3: Tf_2O, 2,6-lutidine) gave compounds **276**. Their reaction with substituted DABCO salts (n = 1: AgOTf, MeCN; n = 2, 3: MeCN) followed by deprotection of oxygen atoms using the above reported McCombi procedure or, preferably, using dimedone as allyl scavenger ($Pd(Ph_3P)_3/Ph_3P$, dimedone, iPr$_2$NEt, DMF) gave the cationic zwitterion products **277** (24–72%) purified by tandem ion-exchange and reverse-phase chromatography [94]. Being biologically optimised the linker between naphtosultam and amino group, and aiming to

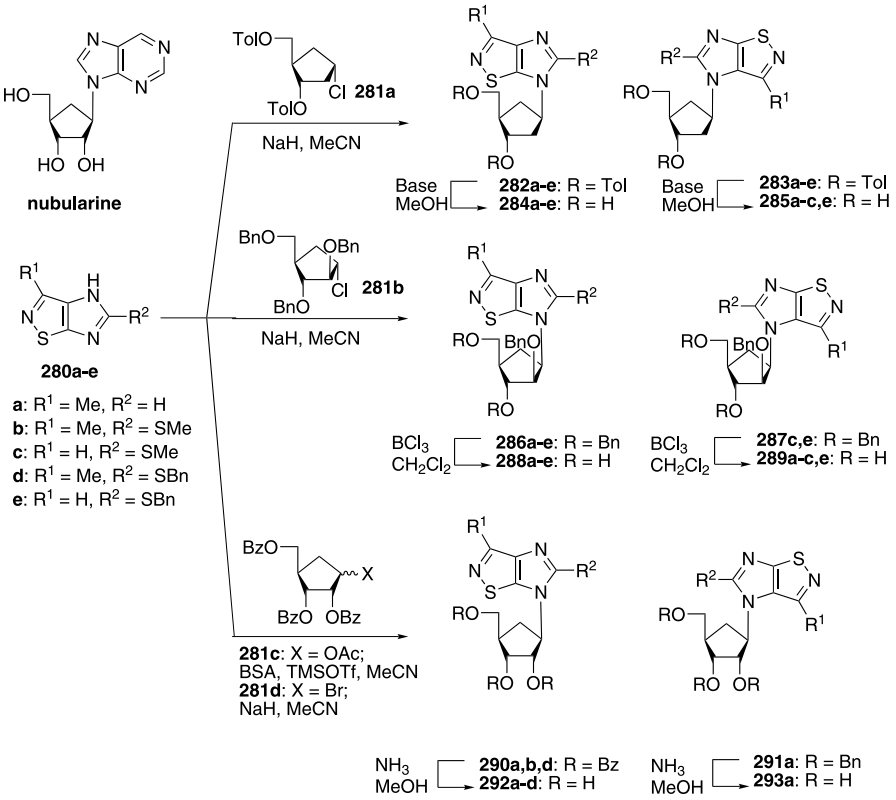


Scheme 70 Synthesis of carbapenems containing the naphtosultam scaffold

minimise manipulations with the sensitive carbapenem, the next synthetic challenge was the coupling of the preformed naphthosultam intermediate **278**, prepared as described in the literature, to carbapenem **279.** Compound **277** (**L-786, 392,** $R^1 = CH_2CONH_2$) was obtained in 97% yield [95] (Scheme 70).

4.2.4
Reactivity of Heterobicyclic Isothiazoles

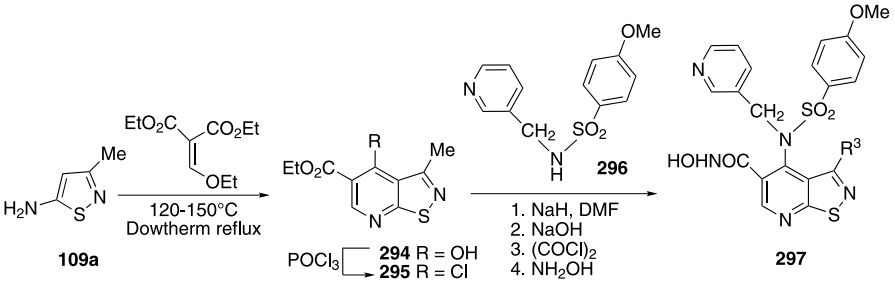
Nucleosides **282–293** functionalised with the imidazo[4,5-*d*]isothiazole ring were prepared by reaction with different glycosides and their cytotoxic activity was evaluated (Scheme 71) [96]. Studies concerning the regiochemistry of the formation of the β-*N*-glycosyl bond between the sugar and the nitrogen atom of the imidazole ring were performed. The sodium salts of imidazo[4,5-*d*]isothiazoles **280a–e**, generated in situ using NaH, were condensed with different chloro sugars **281a,b.** From the α-chlorodesoxyribose derivative



Scheme 71 Synthesis of imidazo[4,5-d]isothiazole-containing nucleosides

281a, a mixture of *N*-6 and *N*-4 β-nucleosides **282** and **283** (63–88%) then deprotected affording **284** and **285** (27–94%). The regiochemistry was governed by steric principles, as heterocycles bearing both 3- and 5-substituents gave primarily the *N*-6 nucleosides, while less hindered derivatives afforded the *N*-4 and *N*-6 products approximately in 1 : 1 ratio. The glycosylation of **280** with the more hindered α-chloroarabinose derivative **281b** is more regioselective and the *N*-6 nucleoside derivatives **286** were formed (46–68%) together with lesser amounts of the *N*-4 isomers **287** (4–30%). In particular, starting from **280c,e**, which do not have a substituent at C-3, compounds **287c,e** were obtained in 24% and 30% yields, respectively. A small amount of the corresponding α-anomers of **286** (3–5%) and **287c** (20%) and **288e** (7%) were detected (^{1}H NMR). The benzyl group was then removed affording the nucleosides **288a–e** and **289c,e**. Apart from compound **289a**, the 5-substituted compounds were subject to decomposition and were isolated in very low yields. The glycosylation of **280a,b,d** with β-D-ribofuranose **281c** was performed by in situ generation of the *N*-silyl derivatives with *N*,*O*-*bis*(trimethylsilylacetamide) ion followed by glycosylate with TMSOTf as catalyst and compounds **290a** (37%) and **291a** (23%) were formed. The reaction was not successful starting from 5-substituted **280b–d**. When the reaction of **280b,d** and **281c** was directly performed in presence of TMSOTf, the single *N*-6 regioisomers **290b** and **290d** were isolated in 52 and 21% yields, respectively. Deprotection of compounds **290ab,d** and **291a** with methanolic ammonia provided the nucleosides **292a,b,d** and **293a** in good yield. The *N*-6 isomer **292c** (11%) was prepared via the sodium salt of **280c** (MeONa/MeOH), which was treated with bromo sugar **281d** (large excess) to give **290c**, which was then deprotected.

To synthesise potent inhibitors of MMP-13 and MMP-9 with selectivity versus MMP-1 and TACE, the isothiazole derivatives **297** were prepared [97] as outlined in the Scheme 72. The bicyclic heteroaryl system of **297** was accessible by condensation of the isothiazole **109a** with diethyl ethoxymethylenemalonate followed by thermally induced cyclisation to give alcohol **294.** Treatment with $POCl_3$ converted the hydroxy substituent to a chloro group



Scheme 72 Synthesis of isothiazolopyridine hydroxamic acids

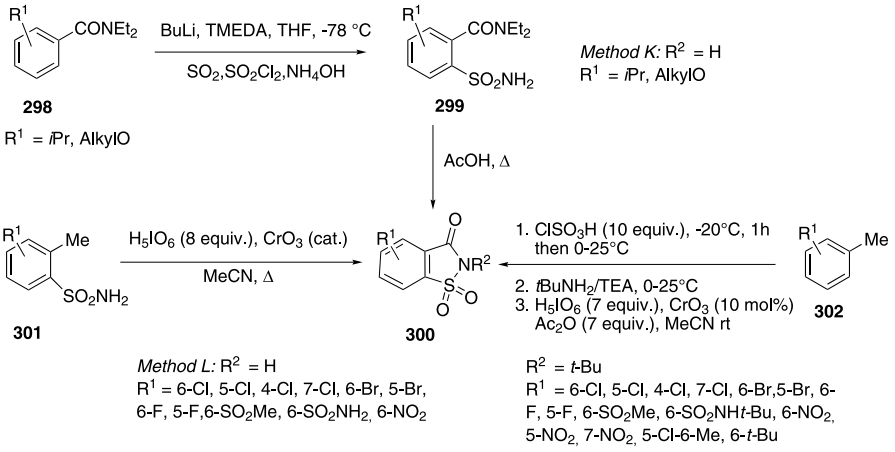
and **295** was formed. The anion of the sulfonamide **296** displaced chlorine from the pyridine ring. Hydrolysis of the ester with NaOH followed by activation of the acid with oxalyl chloride and reaction of the intermediate acid chloride with hydroxylamine gave the hydroxamic acids **297**.

5
Benzisothiazolones

In this chapter benzisothiazolones and benzisothiazolone *S*,*S*-dioxides are separately treated. According to the large amount of literature already available on the second group of compounds (saccharin derivatives), most of all for their interest as sweetener, here only some examples of synthesis or reactivity that appear particularly appealing are considered. Regarding the benzisothiazolones, not oxidised at the sulphur atom, several synthetic methods were described and substitutions with different alkyl or heteroalkyl chain at the nitrogen atom considered. In many cases competitive *N*- and *O*-alkylation was observed. 3-Oxoisothiazolo[5,4-*b*]pyridines were also considered.

5.1
Synthesis of Benzisothiazol-3-One *S*,*S*-Dioxides

Methods L and *M* were the common methods used to prepare NH saccharins **300** ($R^2 = H$). Starting from substituted diethylbenzamides **298** (*Methods L*) (Scheme 73) bearing at the benzene ring a 4-*iso*-propyl or a 4-methoxy group or alkoxy groups in one of the four positions of the ring, intermediates **299** (80–84%) were prepared by introducing a sulfonamido group at the *or-*



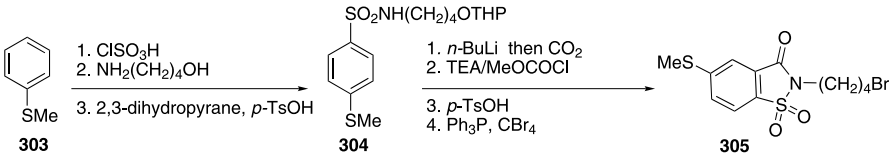
Scheme 73 Synthesis of benzisothiazolone *S*,*S*-dioxides: *Methods L* and *M*

tho position (BuLi in TMEDA then, in sequence, SO_2, SO_2Cl_2 and NH_4OH). By heating of **299** in acetic acid, **300** ($R^2 = H$) was obtained in 90–95% yield (Scheme 73) [98].

The practical and general *Method M* (Scheme 73) starts from various substituted *o*-toluenesulfonamides **301**, which were oxidised to the corresponding substituted saccharin derivatives **300** ($R^2 = H$) by refluxing with 8 equiv. of H_5IO_6 and a catalytic amount of CrO_3 in MeCN. A higher catalyst loading of CrO_3 was required for complete oxidation of substrates with strong electron-withdrawing groups.

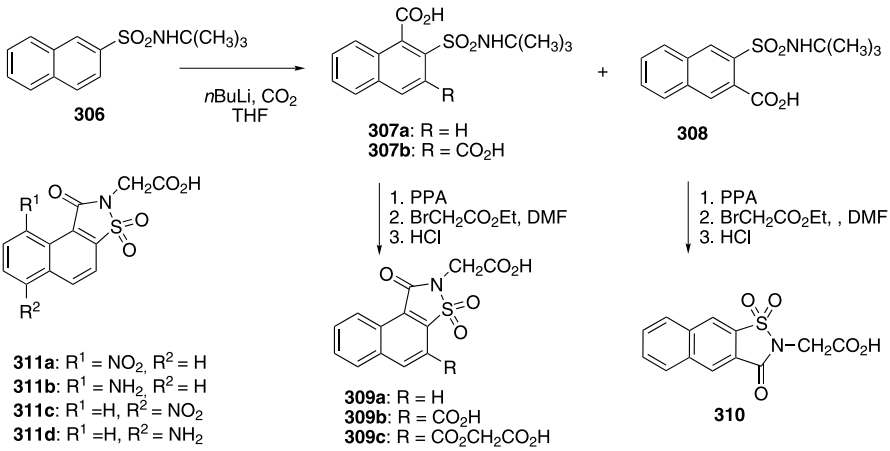
In some cases, starting from the substituted toluene **302**, it is possible to perform a "one-pot reaction" (Scheme 73) with formation of the *N*-*t*-butyl saccharine derivatives, the *N*-*t*-butyl group being very useful as an *N*-protecting group for the preparation of other protected saccharin derivatives. *N*-*t*-Butyl-*o*-methyl arenesulfonamides were easily prepared by chlorosulfonation of substituted toluene derivatives with chlorosulfonic acid. The resulting sulfonyl chlorides were treated with *t*-$BuNH_2$ to afford the *N*-*t*-butyl-*o*-toluenesulfonamide derivatives, which were subjected to the oxidation step without purification, affording **300** ($R^2 = t$-Bu) [99].

The preparation of the saccharin derivative **305** (Scheme 74), substituted with thiomethyl group at C-5 and directly functionalised at nitrogen with a chain containing the bromo atom at C-4′, was prepared according to *Method N*. The substituted sulfonamide **304** was prepared by reaction of **303** in sequence with $ClSO_3H$, 4-aminobutanol and 2,3-dihydropyran. **304** was *ortho*-lithiated and carbonylated and the corresponding intermediate was finally cyclised, deprotected at the oxygen atom and transformed into the *N*-bromobutylsaccharin **305** [100].



Scheme 74 Synthesis of *N*-4′-bromobutylsaccharin: *Method N*

Method N was also applied to the preparation of the naphto[1,2-*d*]- and naphto[2,3-*d*]isothiazole *S*,*S*-dioxide nuclei (NiT) by *ortho*-carbonylation of 2-(*N*-*t*-butyl)naphtalenesulfonamide (**306**). A mixture of three compounds **307a**,**b** and **308** was obtained, which were separated by chromatography and treated with PPA resulting in the corresponding naphtoisothiazoles. The compounds were then reacted with ethyl bromo acetate and hydrolyzed to esters **309a**,**b** and **310** as shown in Scheme 75. The nitration of ethyl ester of **309** (fuming HNO_3) gave regioisomeric esters hydrolyzed to **311a**,**c**. Alternatively,

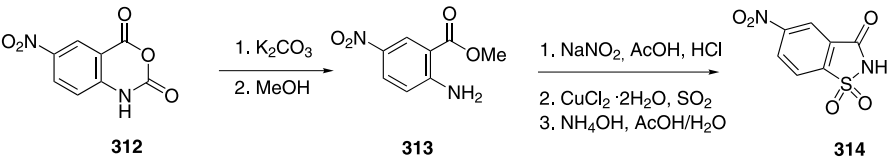


Scheme 75 Synthesis of naphto[1,2-*d*]- and naphto[2,3-*d*]isothiazolone *S*,*S*-dioxide derivatives

the nitrocompounds were first reduced to the corresponding amines and then hydrolyzed to **311b,d** (H_2, Pd/C) [101].

Another two methods (*Methods O, P*) were reported to obtain saccharin derivatives from heterocylic starting materials.

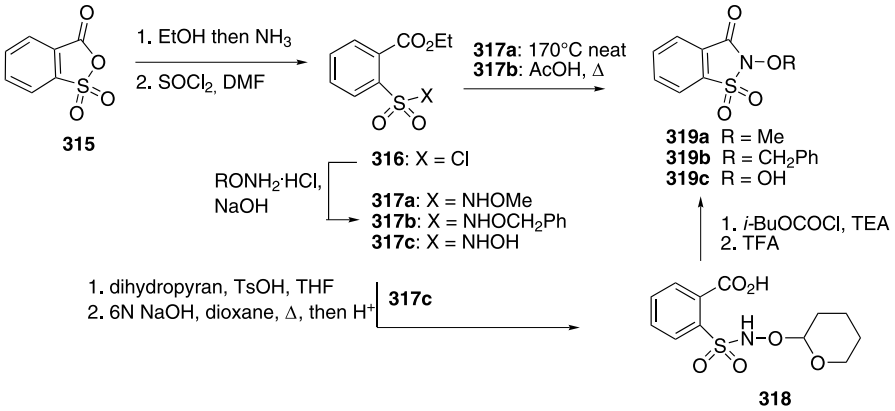
The preparation of all four mononitro aromatic derivatives of 1,2-benzisothiazol-3-one *S*,*S*-dioxide was reported. As an example, the preparation of the 5-nitrosaccharin **314** (*Method O*) from nitro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione **312** is outlined in the Scheme 76. Starting from **312,** which was treated with K_2CO_3 in MeOH, the methyl 2-amino-5-nitrobenzoate **313** was formed. The amino group was transformed into the diazonium salt ($NaNO_2$ in AcOH/HCl). Its reaction with $CuCl_2$ and sulphur dioxide afforded the corresponding sulfonyl chloride, which was added to cold concentrated ammonium hydroxide and **314** was isolated in 74% yield [100].



Scheme 76 Synthesis of nitro-substituted benzisothiazolone *S*,*S*-dioxides: *Method O*

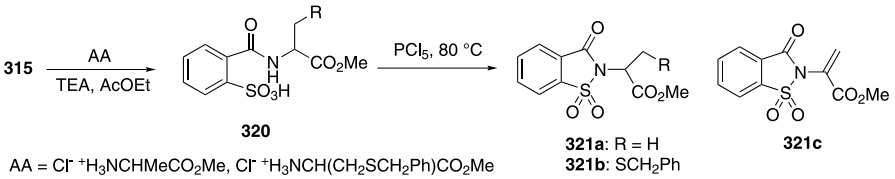
Saccharin substituted at nitrogen with an OR group can be obtained in good yield starting from *O*-sulfobenzoic anhydride **315** according to *Method P*, via the synthon *O*-carbethoxybenzenesulfonyl chloride **316**, which was condensed with the corresponding *O*-alkylhydroxylamine to give intermediates **317a,b,c.** Thermal cyclisation, either neat or in refluxing AcOH,

afforded **319a,b** from **317a,b.** The synthesis of *N*-hydroxysaccharin **319c** could not be done by deprotection of **317a,b** but through protection of compound **317c** as the dihydropyranyl derivative **318.** Its cyclisation in smooth conditions (*i*-butyl chloroformate, TEA) followed by acid-catalyzed removal of the THP group afforded **319c** (61% yield) (Scheme 77) [102].



Scheme 77 Synthesis of *N*-hydroxy-benzisothiazolone *S,S*-dioxides: *Method P*

Compounds **321** (Scheme 78) were prepared as potential protease inhibitors [103] according to *Method Q* using the 2-sulfobenzoic anhydride **315,** which by reaction with alanine or *S*-benzyl-L-cysteine methyl esters gave intermediates **320** directly treated with PCl_5 at 80 °C. Compounds **321a** (16%, racemic) and **321b** (11%) were formed, respectively. As a by-product in the case of the cysteine starting material, compound **321c** was formed.

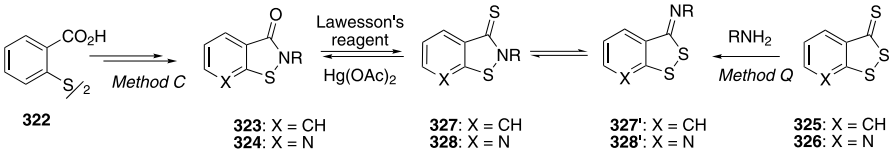


Scheme 78 Synthesis of methyl *N*-saccarinyl acetate derivatives: *Method Q*

5.2
Synthesis of Benzisothiazol-3-Ones and Heterobicyclic Isothiazolones

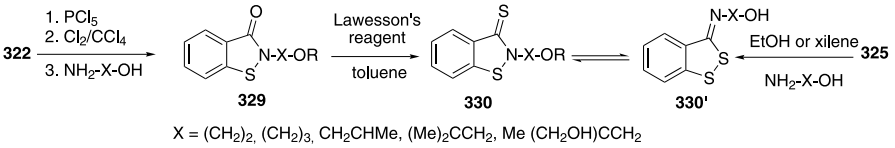
1,2-Benzisothiazol-3-ones **323** and 3-oxoisothiazolo[5,4-*b*]pyridines **324** were prepared by modification of known synthetic protocols and, usually, the *N*-substituted compounds were obtained directly. Different reagents were used to achieve this synthetic target according to *Methods C, M-T*. The

main synthetic procedure follows the general *Method C* using the 2,2′-dithiobis(benzoic acid) (**322**) as building block, which after activation of the carboxylic function and reaction with different nitrogen donors gave the 1,2-benzisothiazol-3-one derivatives **323** (Scheme 79). 3*H*-1,2-Benzodithiole-3-thione **325** and pyrido derivative **326** are the starting materials for the preparation of 1,2-benzisothiazol-3(2H)-thione **327** and 3-oxoisothiazolo [5,4-*b*]pyridine **328**, respectively, by reaction with a proper amino derivative (*Method R*). The thione derivatives are not stable and can equilibrate in solution affording 3-imino compounds **327′** and **328′**. The transformation of **323** into the corresponding thione **327** was possible by using the Lawesson's reagent (Scheme 79).



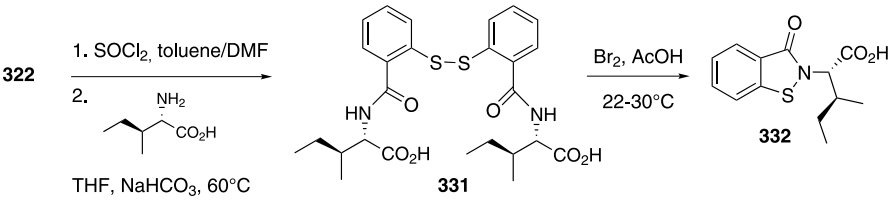
Scheme 79 Synthesis of 1,2-benzoisothiazol-3(2*H*)-ones and 3-oxoisothiazolo[5,4-*b*]pyridines: *Methods C* and *R*

According to both *Methods C* and *R*, a series of 1,2-benzisothiazol-3(2H)-ones **329** and the corresponding thiones **330**, substituted at the nitrogen atom with a chain having a hydroxy group, were prepared and tested as antimicrobics (Scheme 80). Compounds **329** were prepared through a "one-pot" procedure starting from **322** [104, 105]. The reaction of thione **325** with hydroxyamines gave compounds **330**, which are in equilibrium with **330′** [105]. Depending on the nature of the amine, the solvent polarity and the temperature, different ratios of the two isomers were obtained. Using ethanolamine as coupling reagent a dynamic equilibrium occurs in solution, making the isomers inseparable. This last synthetic approach was unsatisfactory in the case of compounds **330**, where $X = (Me)_2CCH_2$, $Me(CH_2OH)CCH$, which were prepared in better yields by treating the corresponding compounds **329** with the Lawesson's reagent.



Scheme 80 Synthesis of 2-hydroxyalkyl-1,2-benzoisothiazol-3(2*H*)-ones and thiones

(*S*-(*R**, *R**))-3-Methyl-2-(oxo-3*H*-benzo[*d*]isothiazol-2-yl)pentanoic acid (**332**) (Scheme 81) was prepared by using *Method C* on a pilot scale (amount of **332** produced: 37 Kg) from **322**, which was transformed into the dichloride



Scheme 81 Synthesis of (*S*-(*R**, *R**))-3-Methyl-2-(oxo-3*H*-benzo[*d*]isothiazol-2-yl)pentanoic acid

(toluene/DMF/$SOCl_2$, 83%). Several esters of leucine were used and reacted with the dichloride, but the best result was found using L-leucine itself. The choice of the reaction solvent was critical and THF was found to give the product in satisfactory yield and purity. The addition to the reaction mixture of a base such as $NaHCO_3$ at 60 °C improved the yield and purity: compound **331** was obtained in 75% yield, without epimerisation at the amino acid stereocentre. The oxidative cyclisation of **331** afforded compound **332** in 74% yield [106].

From **322** and using *Method C*, a large class of benzisothiazolones, named **BITA1–3**, substituted at nitrogen atom with an aryl or heteroaryl nucleus bearing a SO_2 group at the *para* position were prepared and tested for anti-HIV activity (Fig. 2) [107].

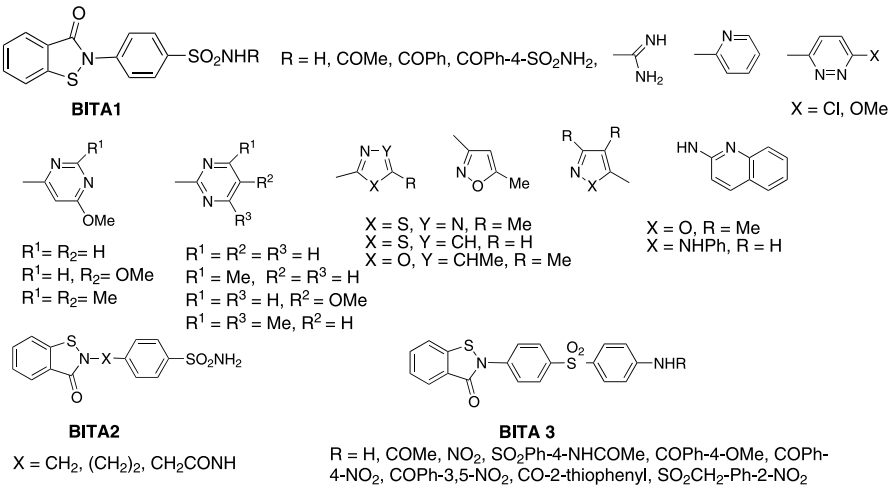
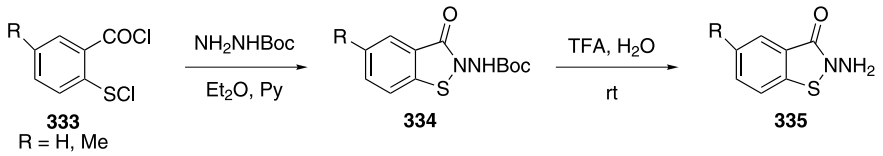


Fig. 2 Synthesis of **BITA** compounds

A different way was used to build the *N*-amino substituted benzisothiazolone nucleus from chlorocarbonylphenylsulfenylchlorides (**333**) (*Method S*) which, on reaction with *N*-Boc-hydrazine in pyridine and

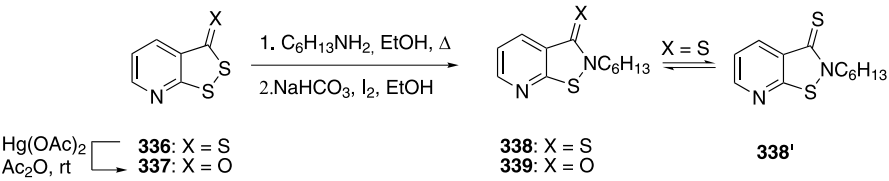
ether gave compounds **334.** The deprotection was achieved using TFA and *N*-amino-benzisothiazol-3-ones **335** were isolated in 70–75% yields (Scheme 82) [71–73].



333 R = H, Me **334** **335**

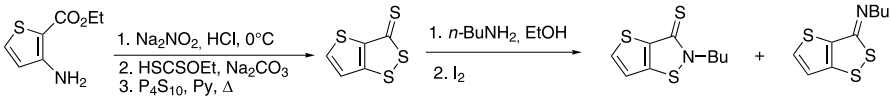
Scheme 82 Synthesis of 2-*N*-amino-benzisothiazolones: *Method S*

Pyridoisothiazolones and the corresponding thiones were prepared according to *Method R* and used for evaluations in vitro of anti-*micobacterium* activity. 3*H*-1,2-Dithiol-[3,4-*b*]pyridin-3-thione (**326**) was transformed into the corresponding oxo compound **337** (98%) with $Hg(OAc)_2$ in AcOH [108]. The reaction of **336** with hexylamine gave the thioamide intermediate, which was then oxidised with I_2 in basic conditions affording **338**, which equilibrates to **338′** in different solvents such as DMSO, DMF, acetone and H_2O. From **337**, *N*-hexylisothiazolo[5,4-*b*]pyridine-3-(2H)-one (**339**) (36%) was prepared using the sequence shown above (Scheme 83) [109].



Scheme 83 Synthesis of *N*-hexylpyridoisothiazol-3-ones and -3-thiones

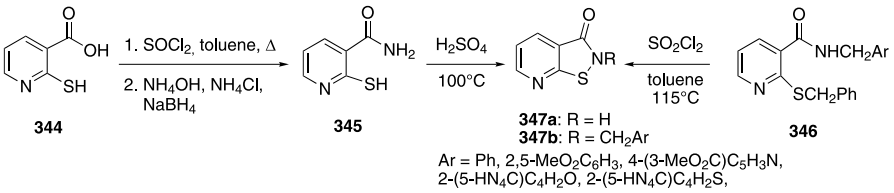
The above authors also reported on the synthesis of *N*-butylthieno[3,2-*c*]isothiazole-3(2H)-thione (**342**) from compounds **341** according to *Method R* (Scheme 84). The latter was obtained from 2-chloroacrylonitrile and ethylthioglycolate in a EtOH/EtONa solution affording **340** (80%). Then it was transformed into **341** (32%) by reaction with i) $NaNO_2$, ii) potassium ethyl xantogenate and iii) P_4S_{10}. The reaction of **341** with *n*-butylamine followed by oxidation with I_2, afforded a mixture of **342** and **343** (57%) [110].



340 **341** **342** **343**

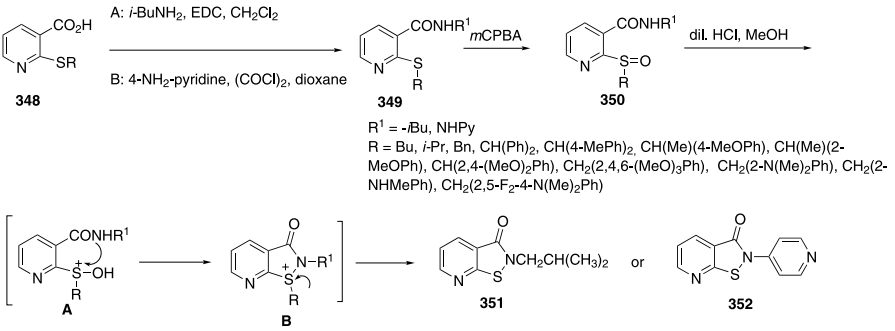
Scheme 84 Synthesis of butylthieno[3,2-*c*]isothiazole-3(2*H*)-thione

An efficient method to prepare *N*-substituted pyridoisothiazol-3-ones is shown in Scheme 85 (*Method R*). It employs a readily available starting material and inexpensive reagents, and can be carried out on a large scale without purification of the intermediate. Commercially available mercaptonicotinic acid (**344**) was converted into mercaptonicotinamide by sequential treatment with thionyl chloride, buffered NH_4OH and $NaBH_4$. The use of $NaBH_4$ improved the yield by reducing the disulfide *bis*-amide preventing its disproportionation in the reaction mixture. 2-Mercaptonicotinamide (**345**) was oxidatively cyclised to the 2H-pyridoisothiazolone **347a** in H_2SO_4, which acts as oxidant and solvent. This avoids use of chlorine, hydrogen peroxide or peracids to effect this transformation [111]. Similarly, a large number of pyridoisothiazol-3-ones **347b**, substituted with a functionalised benzyl group at the nitrogen atom, can be prepared from the 2-(benzylthio)nicotinamides **346**, which were synthesised by standard methods [112]. This method is particularly useful when the substituted benzylamine is readily available and the alkylation at nitrogen of compound **347** is not feasible because of the instability of the benzyl halide (*Method D1*). The oxidative cyclisation of **346b** to **347b** was carried out in one step by heating with sulfuryl chloride. Some selected examples are listed in Scheme 85.

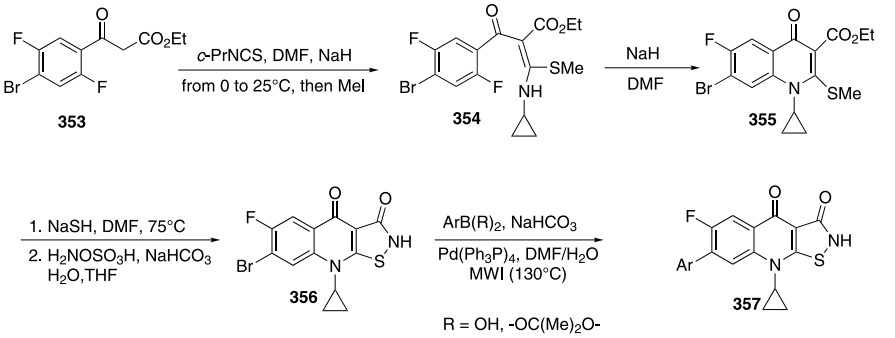


Scheme 85 Synthesis of pyridoisothiazol-3-ones: *Method R*

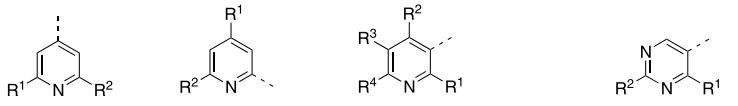
N-Substituted pyridoisothiazolones **351** and **352** displayed a high inhibitory activity of H+/K+ ATPase in vitro but non in vivo (see Sect. 6). A study was undertaken on finding prodrugs that are more stable at neutral and weakly acidic pH than pyrido derivatives and that are converted into the active isothiazolopyridines only in the acid department of the parietal cells. These prodrugs were identified in nicotinamides **349** [113]. *S*-Alkylnicotinic acids **348** were prepared by condensation of 2-mercaptonicotinic acid **344** with the corresponding benzyl chlorides operating in DMF or with the corresponding benzyl alcohols under acidic conditions (HCl/acetone). Their reaction with *i*-$BuNH_2$ by the use of EDC (procedure A) or with 4-aminopyridine and oxalyl chloride (procedure B) gave the nicotinamides **349** then oxidised with *m*-CPBA to sulfoxides **350**. The conversion of **350** (R^1 = *i*-Bu, Py) into the respective *N*-*i*-butyl (**351**) or -pyridyl (**352**) isothiazolopyridines was done and a study on the efficacy of R as a leaving group was performed (Scheme 86).



Scheme 86 Synthesis of pyridoisothiazol-3-ones: *Method T*



Ar: Ph, 3-NH_2COPh, 3-AcPh, 2- or 3- or 4-NCPh, 4-$NCCH_2$Ph, 2- or 3- or 4-FPh, 3- or 4-HOPh, 2- or 3- or 4-MeOPh, 3-MeO-4-HOPh, 3-HO-3,5-Me_2Ph, 3- or 4-$HOCH_2$Ph, 2- or 3- or 4-H_2NPh, 3-H_2N-4-MePh, 3-H_2N-4-FPh, 3- or 4-Me_2NPh, 3- or 4-H_2NCH_2Ph, 4-$H_2N(CH_2)_2$Ph, 4-H_2NCH_2COPh, 3-(2-piperidinyl), 4-(2-piperidinyl), 2-pyrrolyl, 2-indolyl, 5-indolyl, *N*-Me-5-indolyl, 3-chinolinyl, 4- or 5- or 6- or 7-quinolinyl, 6-isoquinolinyl, 5-pyrimidinyl, 7-benzopyrimidinyl



R1 = R2 = H
R1 = H, R2 = F
R^1 = H, R^2 = Me
R^1 = H, R^2 = CH_2OH
R^1 = R^2 = Me

R^1 = Me, R^2 = H
R^1 = H, R^2 = Me
R^1 = H, R^2 = Me

R^1 = R^2 = R^3 = R^4 =H
R^1 = Me, R^2 = R^3 = R^4 = H
R^1 = R^2 = R^3 = H, R^4 = Me
R^1 = F, R^2 = R^3 = R^4 = H
R^1 = R^2 = R^3 = H, R^4 = F
R^1 = R^2 = R^3 = H, R^4 = CH_2NH_2
R^1 = R^4 = Me, R^2 = R^3 = H
R^1 = R^2 = R^3 = H, R^4 = OMe
R^1 = R^3 = R^4 =H, R^2 = OMe
R^1 = R^2 = R^4 =H, R^3 = OMe
R^1 = R^2 = R^3 = H, R^4 = *N*-pyrrolyl
R^1 = R^2 = R^4 =H, R^3 = 3-pyrrolidinyl
R^1 = R^2 = R^4 =H, R^3 = 3-tetrahydropyridinyl

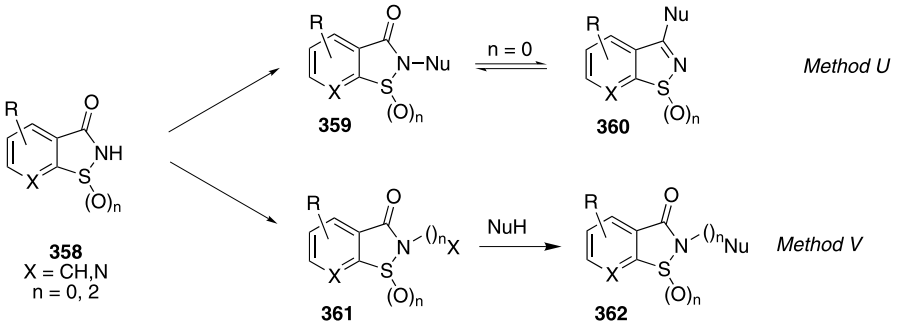
R^1 = R^2 = H
R^1 = H, R^2 = OMe
R^1 = R^2 =O Me

Scheme 87 Synthesis of isothiazoloquinolone derivatives

SAR studies were performed on compounds containing the 9*H*-isothiazolo[5,4-*b*]quinoline-3,4-dione (ITQ) nucleus and it was found that some of them are potent antibacterial agents (see Scheme 101) [114, 115]. They were prepared from compound **353**, which was treated with cyclopropyl isothiocyanate in DMF and then with MeI. Compound **354** (94%) was obtained and treated with in NaH in DMF to give the isothiazolo[5,4-*b*]quinoline compound **355** (93%). Its treatment with anhydrous NaSH gave the corresponding mercaptan (84%), which was directly cyclised without purification to **356** (85%) in the presence of hydroxylamine-*O*-sulfonic acid. Microwave-assisted Suzuki–Miyaura cross-coupling of the ITQ nucleus **356** with the desired arylboronic esters or acids afforded derivatives **357**, typically, in 30–50% yield after HPLC purification (Scheme 87).

5.3
Reactivity of Benzisothiazol-3-Ones and Benzisothiazol-3-One *S,S*-Dioxides

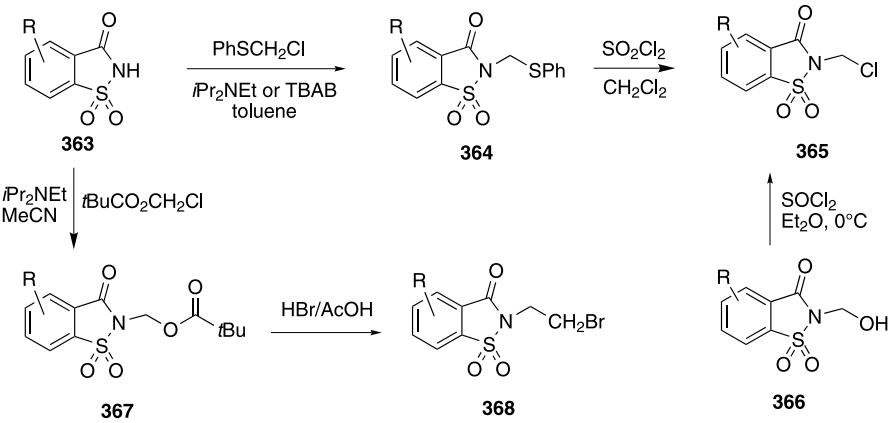
Several functionalisations were introduced at the nitrogen atom of benzisothiazol-3-ones and 3-oxo-isothiazolo[5,4-*b*]pyridines of general formula **358**, in which $n = 0$ or 2, adopting two main synthetic strategies consisting in i) the formation of the sodium salt, which was then reacted with electrophiles to directly give the compound **359** (*Method U*), or ii) the preparation of key reagents in which the nitrogen atom of saccharin was substituted with an activated methylgroup (intermediate **361**), which was then reacted with a proper nucleophile affording **362** (*Method V*). The choice of the above methods is strictly dependent on the kind of chain. The main limitation of *Method U* is related to the possibility to obtain the product of *N*-alkylation **359** and of the *O*-alkylation **360**. This occurs particularly for non-oxidised compounds ($n = 0$) (Scheme 88).



Scheme 88 Synthesis of *N*-substituted saccharin key reagents: *Methods U* and *V*

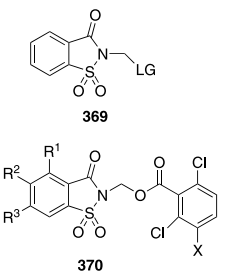
When *Method V* was adopted, the nitrogen atom was functionalised with both the chloromethyl and bromomethyl groups. By treating saccharins **363**

with $PhSCH_2Cl$ and TEBABr [116] or *i*-Pr_2NEt [117] in toluene at reflux, compounds **364** were obtained, which were then treated with SO_2Cl_2 in CH_2Cl_2, and the chloromethyl compounds **365** (80–90%) were formed. Alternatively, **365** were prepared from the corresponding alcohols **366** with $SOCl_2$ [118]. The bromomethyl derivatives **368** (95% overall yield) were obtained by treating **363** with chloromethyl pivalate and Hünig's base affording **367**, then treated with HBr in acetic acid (Scheme 89) [116].



Scheme 89 Synthesis of saccharin key reagents

A large number of molecules containing the benzisothiazolone *S*,*S*-dioxide scaffold (BIT) of the general formula **369** were prepared to find molecules characterised by protease inhibition activity (Fig. 3). Analogous isothiazole derivatives are reported in Sect. 2.4.2. SAR studies were done both considering the substitution pattern of the benzene ring and, most of all, the substituent on the nitrogen atom represented by the CH_2LG group, in which LG is a different leaving group such as substituted benzoic acids, amino



LG = OR, OHet, OCOR, $OPO_2(R)$, SO_2R

[**115**]
R^1 = *i*Pr, R^2 = R^3 = H, X = O-$(CH_2)_2$-4-morpholinyl
R^1 = *i*Pr, R^2 = H, R^3 = OMe, X = O-$(CH_2)_2$-1-pyrrolidinyl
R^1 = *i*Pr, R^2 = H, R^3 = OMe, X =OCH_2CO_2H
R^1 = *i*Pr, R^2 = H, R^3 = OMe, X =$SO_2NMe(CH_2)_2NMe_2$
R^1 = *i*Pr, R^2 = H, R^3 = OMe, X =SO_2-1-piperazinyl-4-Me
R^1 = *i*Pr, R^2 = H, R^3 = OH, X =SO_2-1-piperazinyl-4-Me

[**96**]
R^1 = R^2 = OEt, R^3 = H, X = O-$(CH_2)_2$-4-morpholinyl
R^1 = R^2 = OEt, R^3 = H, X = O-$(CH_2)_2$-1-pyrrolidinyl
R^1 = OEt, R^2 = H, R^3 = OMeX = O-$(CH_2)_2$-4-morpholinyl

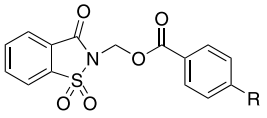
[**96**]
X = H
R^1 = OEt, R^2 = R^3 = H
R^1 = *i*Pr, R^2 = R^3 = H
R^1 = R^2 = OMe, R^3 = H
R^1 = R^3 = OMe, R^2 = H
R^1 = OEt, R^2 = H, R^3 = OMe
R^1 = OPr, R^2 = H, R^3 = OMe
R^1 = R^3 = OMe, R^2 = H
R^1 = R^2 = H, R^3 = OMe

[**117**]
R^1 = *i*Pr, R^2 = H, R^3 = F
R^1 = *i*Pr, R^2 = H, R^3 = OMe
R^1 = *i*Pr, R^2 = H, R^3 = NMe_2
R^1 = *i*Pr, R^2 = H, R^3 = 1-Me-4piperazinyl

Fig. 3 General formula of several protease inhibitors and 3-oxo-1,2-benzisothiazolone-3(2*H*)-yl]methyl benzoate *S*,*S*-dioxide derivatives

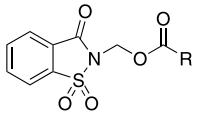
acids, hydroxy-heterocycles or cyclic enolates, phosphinates or phosphonates and sulfinates. The above compounds were prepared directly from saccharin derivatives or, generally, from the key reagents **365** and **368** by reaction with nucleophiles. The reaction of chloroderivatives **365** with 2,6-dichlorobenzoic acids, having a further *meta*-substituent, in the presence of K_2CO_3/TEBABr in DMF afforded compounds **370** (75–95%) [98, 117, 119].

A library of *N*-(acyloxymethyl)benzisothiazolone *S*,*S*-dioxide derivatives **371** and **372**, in which the acyl group represents a *para* substituted benzoate or an amino acid or a dipeptide, was prepared using parallel synthetic methods and automated purification, when possible, starting from bromo compound **368** (R = H) and 300 commercially available carboxylic acids using, as reaction conditions, K_2CO_3/DMF (23 °C) or K_2CO_3/MeCN (60 °C) or *i*-Pr_2EtN/DMF (23 °C), depending on the solubility of the acid [120]. Selected compounds are shown in Fig. 4.



371

R = NHCbz, $CONH(CH_2)_2Ph$, $NHCO(CH_2)_2Ph$, $CH_2NHCONHPh$, CH_2NHCO_2Ph, $NHCONHCH_2Ph$, $CH_2NHCOCH_2Ph$, NH_2, $CH_2NHCO^2CH_2Ph$, $O(CH_2)_2OPh$



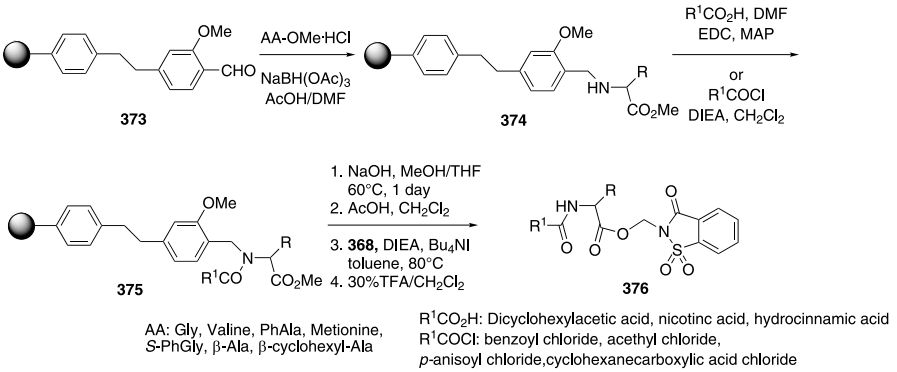
372

R = $(CH_2)_nNHR^1$, n = 1-5, R^1 = Cbz, Boc
R = L-Ala-Gly-*N*-Cbz, -Gly-Gly-*N*-Cbz, N_α-Boc-N_δCbz-L-lysine, N_α-Boc-N_δ-Cbz-D-lysine
Gly-β-Ala-*N*Cbz, β-Ala-β-Ala-*N*Cbz

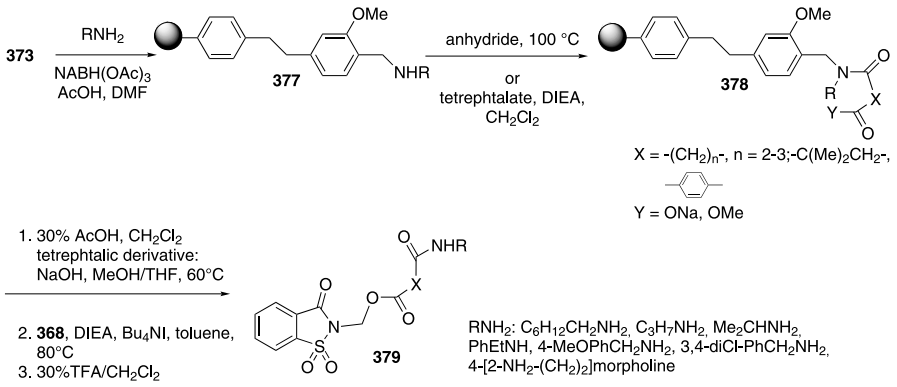
Fig. 4 Selected compounds of a library of *N*-(acyloxymethyl)benzisothiazolone *S*,*S*-oxide derivatives

Aiming to avoid basic treatment, which causes instability of these derivatives, an alternative synthetic approach was found that operates in the solid phase [121]. To prepare libraries of acyl *N*-(acyloxymethyl)benzisothiazolone *S*,*S*-dioxides, those authors applied split/pool methodology. Two different series of compounds were prepared such as compounds **376** containing an amino acid group acylated at the nitrogen atom. According to strategy I shown in Scheme 90, a series of structurally diverse carboxylic acid derivatives were prepared from supported aldehyde **373** condensed with different protected amino acids in the presence of $NaBH(OAc)_3$ to afford intermediate **374**, which was then acylated affording **375**. After hydrolysis of ester and reaction with bromo derivative **368** (R = H) in PTC conditions, compounds **376** were obtained.

A different series of carboxylic acid derivatives **379** was prepared according to strategy II (Scheme 91) starting from **373**, which was treated with an alkylamine in reductive conditions. The acylation of amine **377** gave **378**, which was transformed into amide **379** by condensation with **368** (R = H). According to the protocol depicted in Scheme 91, the elaboration of the intermediated so formed gave **379**.



Scheme 90 Solid phase synthesis of *N*-(acyloxymethyl)benzisothiazolone *S*,*S*-dioxide derivatives: strategy I



Scheme 91 Solid phase synthesis of *N*-(acyloxymethyl)benzisothiazolone *S*,*S*-dioxide derivatives: strategy II

Both chloro- and bromomethyl aryl substituted derivatives **365** and **368** were used for the preparation of *N*-(heteroaryloxymethyl)benzisothiazolone *S*,*S*-dioxide derivatives **380**, obtained in low to good yields, using different bases (NaH/DMF, $CsCO_3$/DMF, *i*-Pr_2NEt/DMF, MTBD/MeCN). This way, compounds containing cyclic enolates were also prepared (Fig. 5) [116, 122].

Benzisothiazolones with a phosphonate leaving group were also prepared. Substituted chloro derivatives **365** were used to prepare the dialkyl phosphates **381a** and dialkyl phosphinate **381b** by using a proper dialkyl phosphate or dialkyl phosphinate in CH_2Cl_2 in the presence of TEA. Only the yield (66%) of compound **381** (R^1 = 4-*i*-Pr, 6-OMe; R^2 = OEt) is reported (Fig. 6) [123].

SAR studies were performed to find the more active tetrazolyloxy substituted compounds **382**, and the 4-*i*-propyl-6-methoxy derivative showed an improved activity and blood stability (Fig. 6) [119].

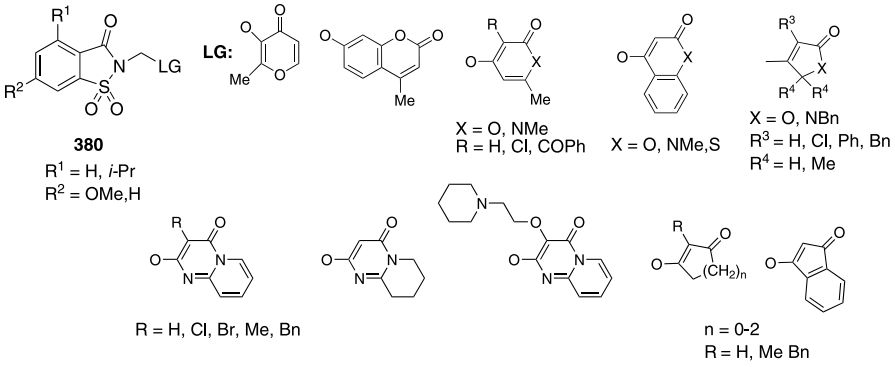


Fig. 5 *N*-(heteroaryloxyymethyl)benzisothiazolone *S*,*S*-oxide

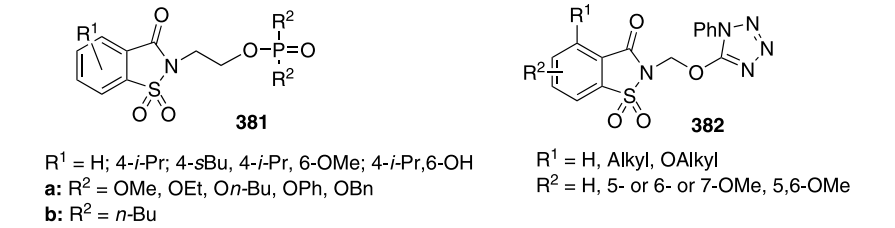
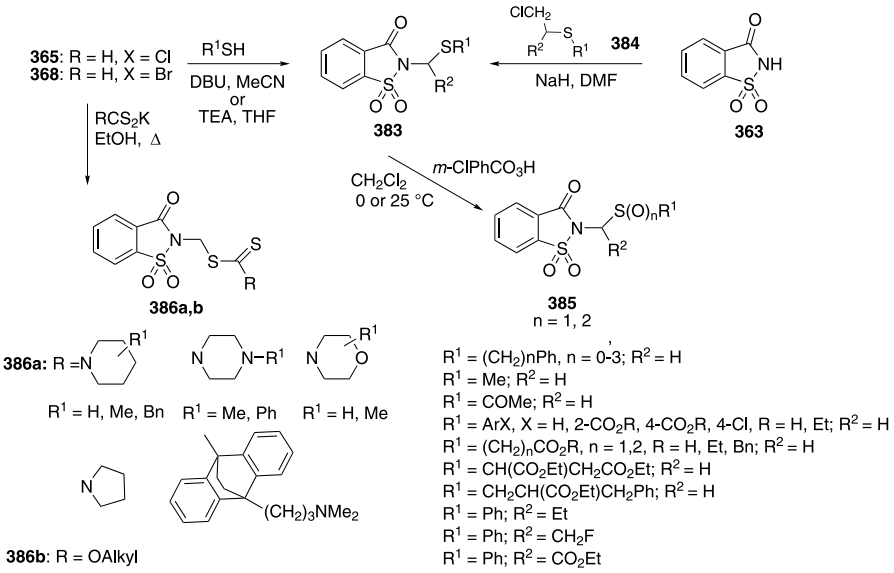


Fig. 6 *N*-(Phosphoxymethyl)- and *N*-(tetrazolylmethyl)benzisothiazolone *S*,*S*-oxide derivatives

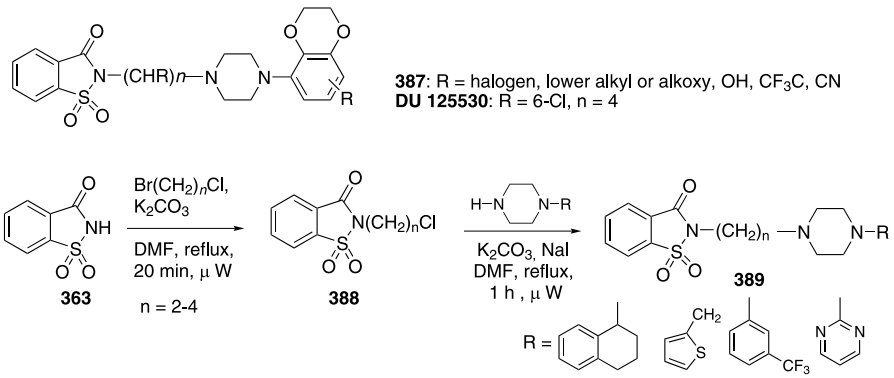
Benzisothiazolones **385** containing sulphur leaving groups were prepared via thioderivatives **383** [103, 124]. The functionalisation of the nitrogen atom with a sulphur containing chain was achieved in two different ways depending on the substituent linked to the sulphur atom. The first one consists in the reaction of sulfides **384** (R^2 = Me, Ph) with the sodium salt of saccharin **363** (R = H) in DMF affording **383**. Alternatively, compounds **383** (25–60 overall yields) were prepared from the chloromethyl derivative **365** (R = H) and the appropriate mercaptan in the presence of DBU/MeCN or TEA/THF. Thiophenol reacted with bromo derivative **368** (R = H) in the presence of TEA. Sulfones (n = 2) or sulfoxides (n = 1) **385** were prepared with *m*-chloroperbenzoic acid and their distribution depended on the stoichiometry of the oxidant and on the kind of R^1 and R^2 on **383** (Scheme 92).

Dithiocarbamates **386a** (10–62%) or *O*-alkylthiocarbonates **386b** (37–46%) were prepared from potassium *N*,*N*-disubstituted dithiocarbamates or potassium *O*-alkyl dithiocarbonates and **365** (Scheme 92). Their antimicobacterial activity was checked [118].

Several *N*-(4-substituted piperazin-1-yl-alkyl)benzisothiazol-3-one *S*,*S*-dioxides of general formula **387**, which were studied as 5-HT_{1A} receptor ligands, were prepared (Scheme 93). They are described in a patent applica-



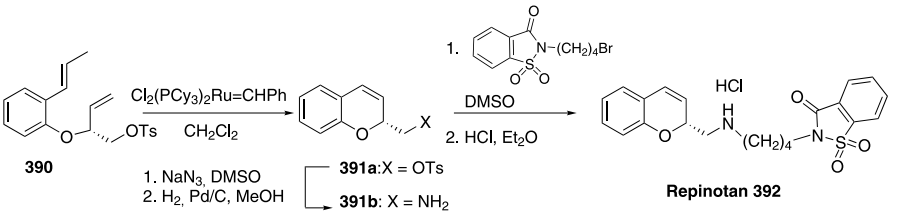
Scheme 92 Synthesis of *N*-(thiomethyl)-benzisothiazolone *S*,*S*-dioxide derivatives



Scheme 93 *N*-(4-Substituted piperazin-1-yl-alkyl)benzisothiazol-3-one *S*,*S*-dioxides

tion [125] and were obtained according to *Method U* starting from saccharin **363** (R = H), which was deprotonated with NaH and alkylated with a functionalised piperazine. This way, 6-chloro compound **DU 125530** was obtained and was claimed as the most active. Compounds **389** were obtained according to the *Method V* by alkylation of saccharin **363** (R = H) with dihaloalkanes to afford **388**, which was then condensed with 4-alkyl-piperazines to obtain the final products **389**. Syntheses were performed by microwave heating to obtain the compounds in better yields (80–95%) than those obtained by conventional heating [126, 127].

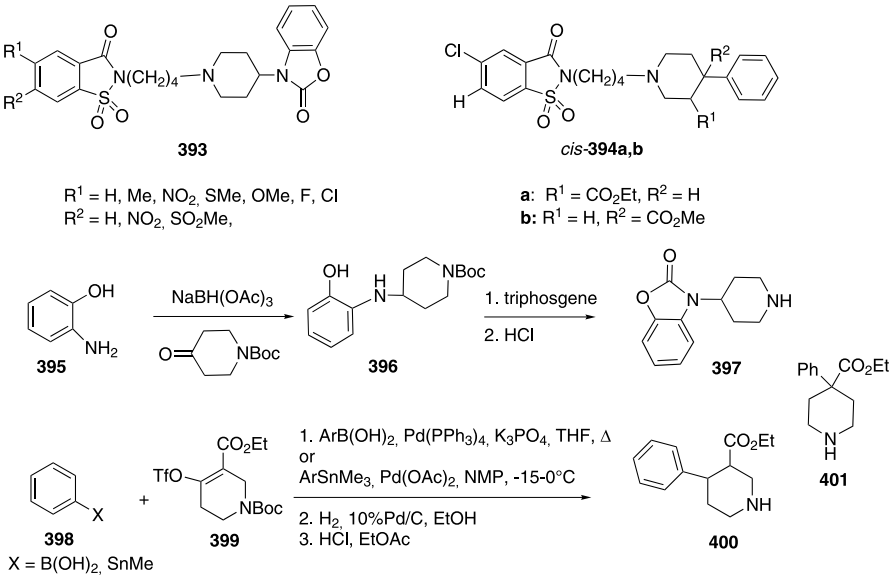
A concise asymmetric synthesis of the 2-(aminomethyl)chroman derivative repinotan (**392**), a potent 5-HT_{1A} receptor agonist, has been described (Scheme 94) [128]. In this case, the synthetic pathway is also based on the alkylation of the saccharin nitrogen followed by reaction with a suitable amine as outlined in *Method V*. The synthesis started from allylphenol. Rearrangement of the double bond ($PdCl_2(MeCN)_2$, CH_2Cl_2, Δ) afforded the corresponding styrene, which underwent a Mitsunobu reaction with the commercially available (*S*)-2-hydroxy-3-buten-1-yl *p*-tosylate providing the requisite diene **390** (64%). An RCM reaction was performed using 0.2 equiv. of Grubb's catalyst and 2-(hydroxymethyl) chromene **391a** (78%) was obtained as *p*-toluenesulfonyl ester and then transformed into 2-(aminomethyl)chroman **391b** (83%). Its alkylation with *N*-4-bromobutylsaccharin followed by conversion to the hydrogen chloride salt provided repinotan **392** as a pure enantiomer.



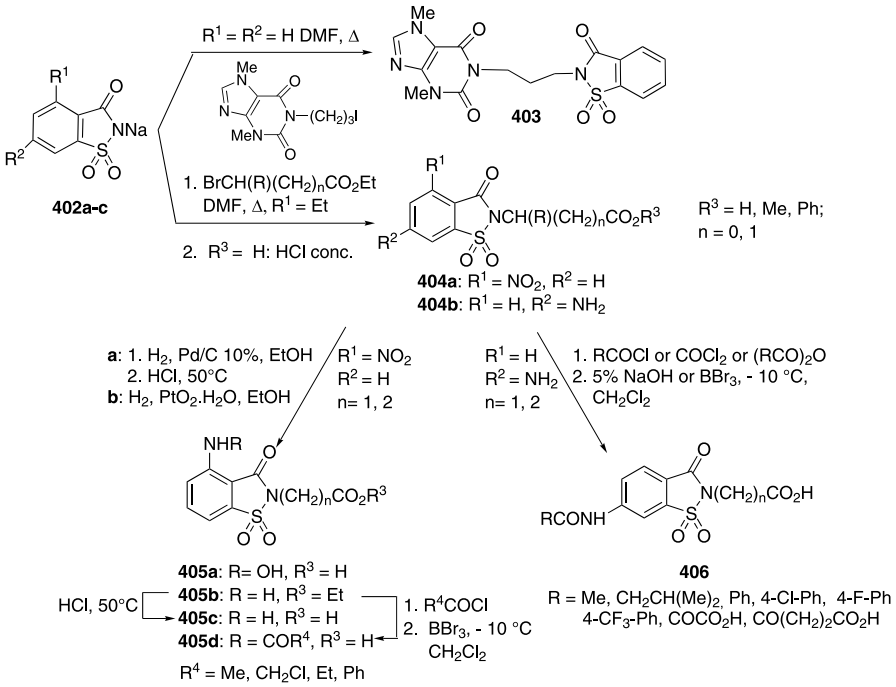
Scheme 94 Synthesis of Repinotan

Compounds **393** and **394** were prepared from 5- or 6-substituted *N*-bromobutylsaccharin and the proper amine **397**, **400** and the commercial available meperidine **401**, following *Method V* (*i*-Pr_2NEt or Et_3N, DMF) (Scheme 95) [129]. Amine **397** was obtained from 2-aminophenol **395**, which was reductively alkylated with *N*-Boc-piperidone affording **396** (90%). Its cyclisation with triphosgene and deprotection of nitrogen provided piperidine **397** (90%). Concerning the preparation of amine **400**, the synthesis consisted first in a palladium mediated coupling of either phenylboronic acid or phenyltrimethyl stannane **398** with enoltriflate **399**, which gave the 4-phenylsubstituted racemic amine *cis*-**400** (80–90% overall yield) after reduction of the alkene intermediate and deprotection of nitrogen. The base catalyzed epimerisation of *cis*-**400** to the *trans* epimer at carboxy linked carbon was reported. The chiral HPLC separation of racemic *cis*-**400** was done as well as the chemical resolution of the corresponding *cis*-acid using (*S*)-α-methylbenzylamine as the resolving agent. Racemic **393a** was also separated by chiral HPLC (Chiralcel OD column).

The direct alkylation of the nitrogen atom of salt **402a** with 1-(3-iodopropyl)-3,7-dimethylxanthine afforded compound **403** (80%), which antagonised glutamate induced neurotoxicity [130] (Scheme 96).



Scheme 95 Synthesis of saccharin derivatives containing a piperidine side chain

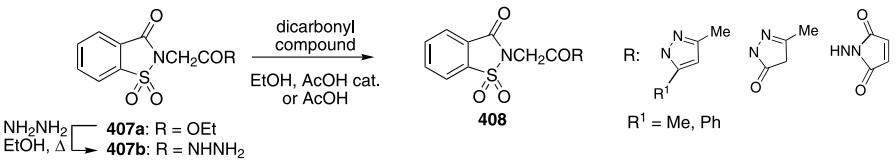


Scheme 96 Synthesis of *N*-saccharinylalkylcarboxylic acids

There is a particular interest in the study of several alkanoic acid derivatives of benzo- and naphto[1,2-*d*]- or naphto[2,3-*d*]isothiazole-3-one *S*,*S*-dioxides as ARIs (Aldoso reductase inhibitors) [131, 132]. As usual, the synthesis of target benzo derivatives was performed starting from the sodium salt of saccharins **402b,c** which were alkylated with an halogeno ester as outlined in Scheme 96 affording compounds **404a,b**. Different substituents on the benzene ring such as the 4-nitro group transformed both into hydroxylamine derivative **405a** or into amine **405b**, depending on the reductive conditions. The latter was hydrolised to acid **405c** or acylated to give amides **405d**. The 6-amino group in compound **404b** was also acylated and a series of amides **406** were obtained (Scheme 96).

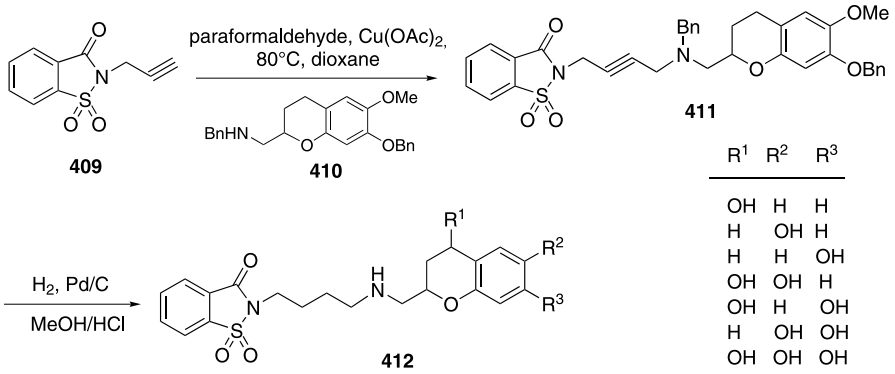
Other alkanoic acid derivatives, i.e. the naphto[1,2-*d*]- and naphto[2,3-*d*]isothiazole-3-one *S*,*S*-dioxide derivatives **309** and **310**, as well as the nitro and the amino compounds **311**, have already been cited in Scheme 75.

N-Acetylsaccharinyl acid derivatives **408**, which are structurally related to COX-2 inhibitor celecoxib, were designed and synthesised [133] from *N*-saccharinyl acetate **407a**, prepared via the reaction of ethyl bromoacetate with sodium saccharin by heating the reactants in DMF (see [133]). Its transformation into the corresponding hydrazide **407b** and subsequent reaction with ethyl acetoacetate, β-diketones and maleic anhydride, afforded the heterocyclic compounds **408** [134] (Scheme 97).



Scheme 97 Synthesis of *N*-alkylheterosubstituted saccharins

The carbon chain functionalised with the chromone nucleus characterises the patented saccharin derivatives **412** as agents for treating disorders of the central nervous system. As an example, the synthesis of (*R*)-(–)-[2-[4-(benzyl [7-(benzyloxy)-6-methoxy-3,4-dihydro-2*H*-chromen-2-yl]methylamino)-2-butynyl]-1,2-benzisothiazol-3(2*H*)-one *S*,*S*-dioxide (**412**: R^1 = H, R^2 = OMe, R^3 = OH) is reported. The reaction of (*R*)-(–)-[*N*-benzyl-*N*-[7-(benzyloxy)-6-methoxy-3,4-dihydro-2*H*-chromen-2-yl]methylamine (**410**) was performed in the presence of paraformaldehye/$Cu(OAc)_2$ and alkynyl saccharin **409**, prepared from the sodium salt of saccharine and the alkynyl bromide. Compound **411** (90%) was obtained and reduced with H_2 and10% Pd/C in MeOH/HCl affording **412** (R^1 = H, R^2 = OMe, R^3 = OH) (64%) (Scheme 98).



Scheme 98 Synthesis of (chromenyl)methylaminobutyryl-1,2-benzisothiazol-3(2*H*)-one *S*,*S*-dioxides

To increase the hydrophilicity of compounds **329** and of the corresponding thio compounds **330**, the hydroxy group was transformed and benzisothiazolones **413** and thiones **414/414′** functionalised with a carbamate chain were prepared (Fig. 7). Their activity against representative bacterial and fungal strains was tested. The reaction of **329** with a series of isothiocyanates was done in presence of DABCO in xylene, and compounds **413** were obtained in 75–90% yields [104]. The reaction of **330** with the same reagent was performed using DABCO or $Fe(acac)_3$ as catalyst in benzene at reflux and the mixture of carbamates **414/414′** was obtained and separated by column chromatography. Equilibration between **414/414′** takes place in DMSO or acetone/water [105].

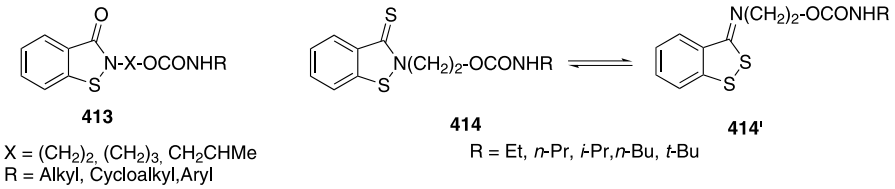
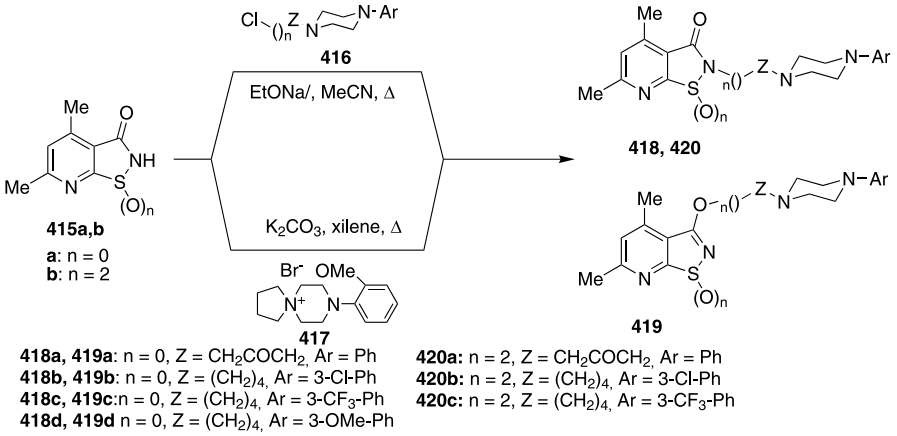


Fig. 7 *N*-2-Hydroxyalkyl-benzisothiazol-one and -thione carbamic esters

4-Arylpiperazin-1-ylalkyl chains are the common feature of a series of isothiazolo[5,4-*b*]pyridine derivatives **418** and **419** and of the corresponding *S*,*S*-dioxides **420**, tested as antimicrobials. Two reagents were used to alkylate **415a,b**, i.e. the chloroalkylpiperazine **416** and the quaternary salt **417** (*Method U*). A mixture of compounds of *N*-alkylation **418a–c** (47–53%) and *O*-alkylation **419a–c** (8–11%) was isolated from **415a**. Instead, using isothiazolopyridine *S*,*S*-dioxide **415b**, only isomers **418a–c** (42–65%) were formed. Compounds **418d** (42%) and **419d** (11%) were obtained using **417** as chain donor (Scheme 99) [135].



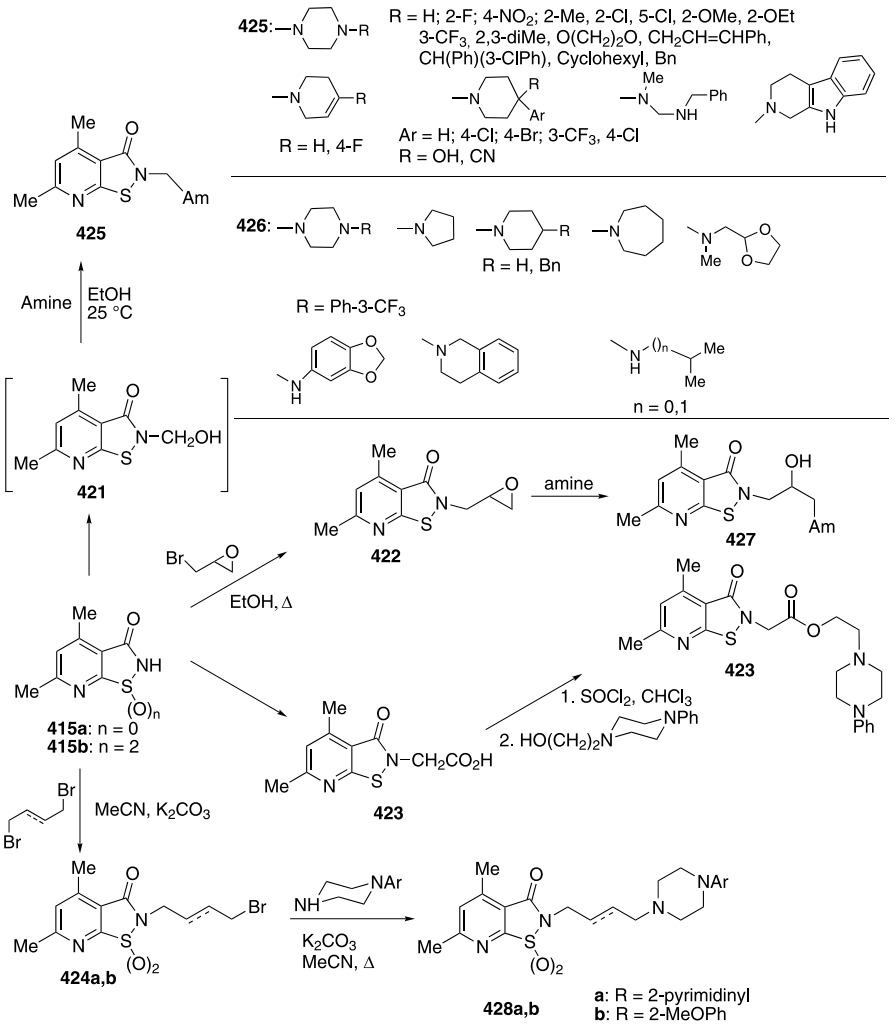
Scheme 99 Synthesis of *N*-(4-arylpiperazin-1-ylalkyl)-3-oxo-isothiazolo[5,4-*b*]pyridines

Another strategy was used to obtain a large number of saccharin analogues substituted at the nitrogen atom with polyfunctionalised chains (Scheme 100). In this case, compounds **421** [136], **422** [137], **423** [138] and **424a** containing a saturated chain [139] were first prepared according to known procedures by substitution of the nitrogen atom of **415** with a proper linker. Instead, **424b** (40%) was obtained by reaction of **415** with *trans* 1,4-dibromo-2-propene in MeCN and using K_2CO_3 as the base [135].

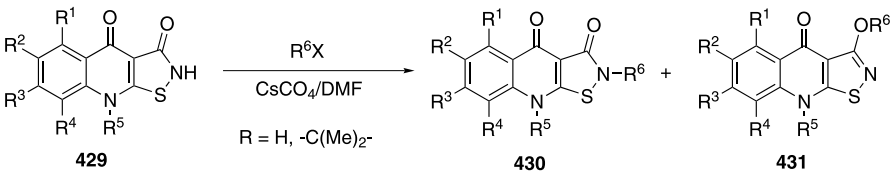
Compounds **425** (50–85%) were obtained from intermediate **421** (not isolated) by reaction with different cyclic amines [135, 136]. Indeed, epoxide **422** afforded compounds **426** (40–70%) containing hydroxy amine functionalised chains [139]. For the preparation of **427** (11%), **423** was first transformed into the corresponding acyl chloride using $SOCl_2$, then reacted with 1(hydroxyethyl)-4-phenylpyperazine. Instead, from **424a,b**, containing the unsaturated and saturated chin, respectively, compounds **428a** (70%) and **428b** (55%) were formed by reaction with *N*-(2-pyridinyl)pyperazine and *o*-methoxyphenyl-pyperazine.

The alkylation of the ITQ nucleus of general formula **429** is reported in a patent as well as the parent compounds **357** (see Sect. 5.2) [140]. They were prepared as inhibitors of bacterial DNA synthesis and replication. As the parent benzisothiazolones, a mixture of *N*- and *O*-alkyl derivatives **430** and **431** (major isomer) was obtained performing the reaction in DMF and $CsCO_3$ at 25 °C (Scheme 101).

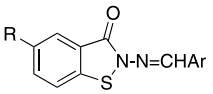
The reaction of *N*-amino compounds **335** with a series of substituted benzaldehydes, 1-furanaldehyde and cinnamaldehyde, operating in the classical conditions (H_2O/EtOH/AcONa, 70 °C) afforded 2-benzilidene-amino compounds **432** (57–89%) [70–72] which were tested as antimicrobials and antifungals (Fig. 8).



Scheme 100 General procedures for the alkylation of 3-oxo-isothiazolo[5,4-*b*]pyridines with polyfunctionalised chains



Scheme 101 Alkylation of ITQs



432a,b

a: R = H; Ar = 2-F-Ph, 3-F-Ph, 4-F-Ph, 3-HO-Ph, 4-HO-Ph Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 2-NO_2-Ph, 3-NO_2-Ph, 4-NO_2-Ph, 2-HO-Ph, 4-MeO-Ph, 4-HO-3-MeO-Ph, 3,4-OCH_2O-Ph, 2-furyl, CH=CHPh
b: R = Me, Ar = Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 2-NO_2-Ph, 3-NO_2-Ph, 4-NO_2-Ph, 2-HO-Ph, 4-MeO-Ph, 4-HO-3-MeO-Ph, 3,4-OCH_2O-Ph, 2-furyl, CH=CHPh

Fig. 8 *N*-(Benzylidene-amino)-benzisothiazolones

6 Biologically Active Compounds

While saccharin remains one of the most important, widely used and best known isothiazole derivatives, many other isothiazole derivatives manifest a broad spectrum of useful properties and have applications in several fields. In these compounds the isothiazole ring can be both the pharmacophore or a scaffold with no direct biological activity. In order to obtain biologically active compounds, different approaches were used, which are represented by random library screenings of different heterocycle containing molecules, or by rational design. In this last case, bioisosteric replacement of isoxazole ring in known pharmacological active compounds was widely used and, although the isothiazole moiety is markedly less acidic and more lipophilic, this approach very often led to active compounds.

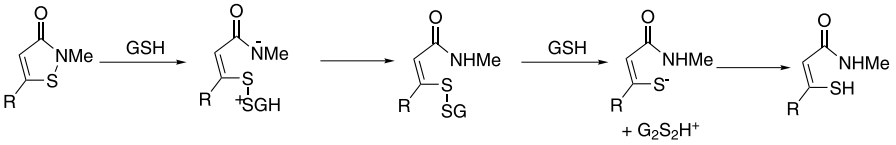
Below isothiazole derivatives are classified according to their activity and for each section the most active compounds are cited. When important, a short account of the mechanism of the action is discussed.

Pesticides. Isothiazoles are known as harmful organism-controlling agents and have been widely cited as agrochemicals since the 1970s [22, 141]. Recent developments in this field are represented by 5-thio-isothiazole derivatives **433**, which are claimed as termite controlling agents [142] and by 5-amino-isothiazole derivatives **434**. Among them, derivative **434a** possesses pesticidal activity against the larvae of *Spodoptera littoralis*, *Heliothis armigera*, *Plutella xylostella* [143], compound **434b** is claimed as a pesticide against *Plasmopara viticola* on vines [144] and compounds of general formula **434c** (R^1 = Cl, R^2 = substituted alkylaromatic group) are claimed as strongly active insecticides with good compatibility with crops [145].

Substituted *N*-(5-isothiazolyl)phenylacetamides **110** (R^1 = CH_2PhOPh-4-CF_3) possess an excellent broad spectrum of activity against insects by acting on mitochondrial respiration as inhibitors of MET at Complex 1 (NADH dehydrogenase), but they have been found to be toxic to fish. In order to improve safety to non-target organisms various *N*-alkylated derivatives **111a** were synthesised as proinsecticides [32], while derivatives **114** (X = NHR, R = OMe, $OCH_2CH{=}CH_2$, $NHCONH_2$, NHTs) substituted at the α-methylene position were prepared to enhance selectivity [33].

Antimicrobial. The antimicrobial activity of 1,2-benzisothiazoles and of 3-isothiazolones has been intensively studied and various derivatives are

known to be effective against a wide range of bacteria and fungi. The biological activity of such compounds arises from their ability to readily pass into membranes and fungal cell walls and then react with important intracellular sulphur containing proteins, or simpler molecules, such as glutathione, causing impairment of the cell function. The S – S bond formation with a biological target is strictly related to the lability of the S – N bond [105]. The mechanism of this reaction involves a nucleophilic attack by the sulphur atom at the sulphur atom of the isothiazolone, followed by the cleavage of the S – N bond to give the ring opened amidodisulfide, which reacts further with the same nucleophile to give the mercaptoacrylamide (Scheme 102). This causes the cell's death.



Scheme 102 Mode of action isothiazolones

The extent of activity of mononuclear isothiazoles, is strictly dependent on the nature and position of substituents on the heterocyclic ring. 5-Chloro-*N*-methylisothiazolone **21a** (R^1 = Cl, R^2 = H, R^3 = Me), the main active component of the commercial biocide Katon [2], is several orders of magnitude more active against bacteria and fungi with respect to the corresponding 4-Cl-*N*-alkylisothiazolones. Unfortunately, **21a** is a strong skin sensitiser and this unlikely characteristic is due to its ability to react with histidine and lysine, two nucleophilic amino acids that are present in epidermal proteins. This interaction causes chemical modifications of such proteins, leading to allergic contact dermatitis. Curiously, the 5 unsubstituted derivative is a very weak sensitiser, as it reacts exclusively with thiol nucleophiles [146]. 4-Benzylamino-2-methylisothiazolones unsubstituted (**37b**) or chloro substituted on C-5 (**38b**) were prepared, but their activity is lower with respect to **21a** [13].

The general interest in BIT derivatives has shifted to their industrial application as biocides even if the parent BIT compound is not recommended for pharmaceutical, cosmetic, and toiletry preparation because it is a skin sensitiser. Nevertheless, many BIT derivatives have been prepared in the last years and extensive studies on the influence of substituents in the molecule on biological activity led to the conclusion that their activity results from a concurrence of steric effects and S – N bond reactivity induced by electronic effects of the substituents [105]. As examples, hydrazones **432** were assayed against gram-positive bacteria and gram negative bacteria and on PRS but they were less active or comparable to BIT and possess an activity equal or superior to the reference drugs ampicillin and miconazole [71]. The substi-

tution of sulphur for oxygen in the keto-benzisothiazole system (compound **414**) increases the strength of the S – N bond and lowers the antibacterial activity with respect to keto derivatives [105, 147, 148]. These compounds were found to be less active than reference compounds (cefotaxime, gentamicin). A series of compounds **413** were prepared in order to enhance lipophilicity and to facilitate membrane crossing but they were less active than BIT [149]. Some of them were active in vitro against anti-*Mycobacterium avium* [105].

In the last years other isothiazole derivatives showing antimicrobial activity and with a different mode of action have been prepared. 4-Arylpiperazin-1-ylalkyl chains are the common feature of a series of thiazolo[5,4-*b*]pyridine derivatives **418** (Ar = Ph, 3-Cl – Ph) characterised by both antimicrobial and CNS activity. [135]. 3-Amidinobenzisothiazole compounds **252** (R^1 = Me, R^2 = $CH_2 - CH = CH_2$) are active against gram positive bacteria and yeasts. The unsaturated aliphatic moiety is essential for antimicrobial activity [83]. A small library of minor groove binding ligands **57** (R^1 = $H_2N(CH_2)_3$, R^2 = $(CH_2)_4NMe_2$) consisting of a four heterocyclic ring core was synthesised. The position of basic groups in the molecule strongly influences the antimicrobial activity and DNA binding affinity [17].

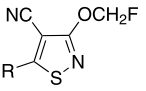
ITQs have tricyclic structures comprising a quinolone nucleus with an annelated isothiazolone ring, which replaces the archetypal 3-carboxylic group of typical quinolones. ITQs inhibit type II topoisomerases, such as DNA girase and topoisomerase IV. The first examples were synthesised in the late 1980s but they exerted mammalian cytotoxicity [150]. Recently compounds of type **429a**,**b** (X = CH, N) have been prepared and tested on MRS. Considering the ITQ nucleus, the addition of a methoxy group at C-8 on compounds **429a** increased the activity, while the removal of fluorine at C-6 or replacement of C-8 carbon with a nitrogen (compounds **429b**) compromised activity against MRS. For amino groups linked to C-7 in compound **429**, the activity decreased in the order 6-isoquinolinyl > 4-piridinyl > 5-dihydroisoindolyl > 6-tetrahydroisoquinolinyl. The most active compound is **429a** (R^1 = H, R^2 = F, R^3 = 2-methyl-4-pyridyl, R^4 = OMe). By modulating the substituent at C-7 it is possible to reduce cytotoxicity [115, 151].

Carbapenem derivatives of general formula **434** acylate a broad spectrum of PBP with high affinity, and they are rapidly bactericidal, with potent activity against methicillin sensitive staphylococci. In addition the carbapenem nucleus is resistant to most serine β-lactamases [152]. Attached to the carbapenem nucleus is a lipophilic side chain, which is further substituted with a cationic group. The lipophilic component provides for potent binding to the target penicillin binding proteins, including the MRS. Unfortunately, first generation derivatives provoked immune responses in toxicological tests. In compound **277** (n = 2, R = CH_2CONH_2) the presence of a naphtosultam side chain, attached to the carbapenem through a metylene linker, lowers the immunotoxicity. The expulsion of the side chain occurs when the β-lactam has

acylated the surface of red blood cells ("Releasable Hapten" hypothesis). Consequently, the red blood cells are not labelled with the potential immunogenic naphtosultam side chain [94, 95, 152]. Also carbapenem **17a** exerts potent antibacterial activity, excellent stability and a good pharmacokinetics profile [11].

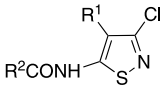
Antiviral and antitumor. Purine nucleosides analogues have been investigated as antitumor and antiviral agents. Bioisosteric derivatives of nucleobases have been proposed. In particular, as the sulphur atoms is analogous to a – CH = CH – group because of its steric and electronic properties, different imidazo[4,5-*d*]isothiazoles **292** (R^1 = H, Me; R^2 = H, SMe, SBu) have been synthesised. All compounds were cytotoxic at micromolar concentrations, but showed no antiviral activity on human cytomegalovirus and herpes simplex virus type 1 [96]. The nucleoside analogue **12** was also prepared, but showed none antiviral activity nor cytotoxicity [10].

Aza-TSAO is a bioisosteric derivative of the spiro nucleoside TSAO (Fig. 9), which is a potent HIV-1 inhibitor. The bioisosteric replacement leads to less active compounds [49]. The binding mode of several aza-TSAO derivatives of type **150** which show HIV RT inhibitory activity, was in-



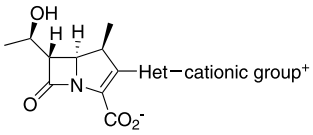
433

RS: Me, thiocyclopentyl, trimethylsilylmethylthio, OEt, OPh, SPh, pyrimidylthio, isopropylamino, 3-methylphenoxy, p-chlorophenylthio,

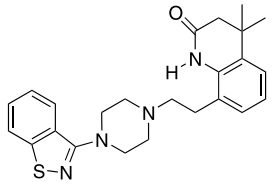


434a,c

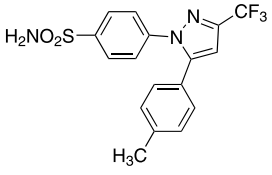
434a: R^1 = CN, R^2 = 3-Cl-Ph
434b: R^1 = Me, R^2 = 2-propyl-benzofuran-5-yl
434c: R^1 = Cl, R^2 = substituted alkylaromatic group



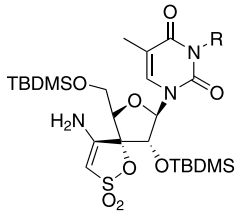
435



436



celecoxib



TSAO

Fig. 9 Biological active compounds

vestigated by a thorough conformational search at the MM, HF and DFT level [153]

Compound **332** is an antriretroviral agent that interferes with the HIV-1 nucleocapsid protein, a highly conserved zinc finger protein. It affects the zinc finger region causing rapid extrusion of zinc and subsequent denaturation of the viral protein [106].

Compound **53** is a potent HIV protease inhibitor, which is more active than indinavir [16].

Isothiazole-4-carbonitrile derivatives exert antiviral activity, showing different selectivity depending on the substituents on the ring [25]. Compound **86** represents a novel class of active-site inhibitors of hepatitis C virus (HCV) NS5B polymerase. They act by preventing proper positioning of natural template in the active-site, by disrupting the suitable entry path of initiating rNTP substrate and by locking the C-terminus into an inactive conformation [27, 154, 155]. The most active compound is the *N*-3,5-dichlorophenyl compound, which has an IC_{50} of 200 nM and EC_{50} of 100 nM.

3-Thio derivatives **96** (R = Ar, R^1 = H, Me) are active against picornaviruses, such as rhinoviruses and enteroviruses, but also against HIV. The biological activity depends on the presence of bulky substituents at the para position of the phenyl ring and of the presence of a low molecular thioalkyl chain at 3. These compounds act by interfering with early events of viral replication and it has been postulated that they have a capsid-binding activity and that they induce some conformational changes in the binding site [27].

Antifungal and antimycobacterial. Brassilexin and the sinalexin (see Scheme 58) are the most potent antifungal phytoalexins produced by crucifer plants. Many fungal pathogens, i.e. *Leptospheria maculans*, have evolved enzymatic systems that are able to detoxify phytoalexins. Potential inhibitors of brassilexin detoxification were used to protect plants against the fungal invader. The indole-isothiazole fused-ring system of brassilexin was replaced with quinoline-isothiazole **227**, benzothiophene-isothiazole **230**, isothiazoles **7** and benzisothiazole **232**. Compound **227** and **230** displayed the strongest growth inhibitor activity [9].

The equilibrium mixture of compounds **342** and **343** shows antimicotic and antibacterial activity in vitro [110].

Dithiocarbamate **386a** and dithiocarbonate **386b** show activity against *Mycobacterium tuberculosis* and antitumor activity [118].

Compounds of type **135** and **141** have been synthesised as inhibitors of PFT, an enzyme that catalyses the transfer of the farnesyl group from farnesyl pyrophosphate to the cysteine SH in the protozoan parasite *Trypanosoma brucei*, the causative agent of African sleeping sickness. The parent compound **140** (Ar = (2,4,6-trimethylphenyl) is the most active (ED_{50} 10 μM) [44, 45]. This class of compounds has been tested also on mammalian PFTase and some of them showed inhibitory activity. In particular, none of the dihydroderivatives affects the enzyme in a concentration-dependent manner,

while compounds with a C4-C5 double bond and sulfanyl substituents (**142**) showed both inhibitory and antiproliferative activity by inhibiting G0/G1 phase of the cell cycle. The activity in such compounds is affected by two principals factors such as the planarity of the isothiazole ring and the nature of substituent at the 5-position [25].

Anti-inflammatory. The conventional NSAID's exert they activity by inhibiting the COX enzyme, which synthesises prostaglandins, the major mediators of inflammation. Two isoforms of this enzyme were identified: the constitutive COX-1 and the inducible COX-2. Celecoxib is a selective COX2 inhibitor, which was recently removed from the market for its cardiovascular toxicity. Compound **408** (R = 3-methyl-5-phenyl-pyrazol-1-yl) is a *N*-benzesulfonamide analogue of celecoxib with higher analgesic and anti-inflammatory activity [133]. Instead the benzisothiazolyl analogue **215** of celecoxib is a selective inhibitor of COX-1 [67]. Compound **208** ($R^1 = R^2$ = t-Bu, R = Et) is a potent inhibitor of cyclooxygenase-2 and 5-lipooxigenase as well as of production of IL 1 [64, 65]. Compound **246** (R^1 = 4-Cl-Ph, R^2 = CH_2CO_2H) is an arylacetic acid derivative that exerts high anti-inflammatory activity [76].

Compound **107** (R^1 = H, $R^2 = R^2$ = 4-Cl – Ph) possesses antiviral activity, and different derivatives containing its scaffold have been tested as anti-inflammatory and immunosuppressant agents. Electron withdrawing, lipophylic and small substituents such as Cl or Me of the aromatic group in the carboxamide fragment increase immunosuppressant activity [28, 29]. Compounds **255** and **234** have been tested in vitro and in vivo for anti-inflammatory activity. Hydrazones are more active than Schiff bases [73]. Pyridoisothiazolones represent a class of compounds with high analgesic activity. For example, derivatives **426** (R = Ar) have analgesic action two to ten times more potent than acetylsalicylic acid. [136]

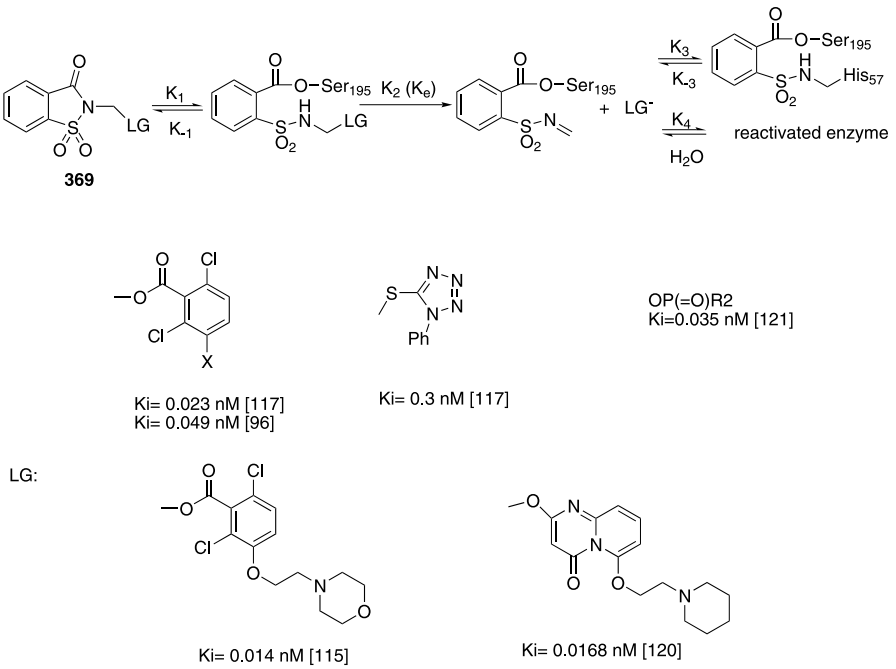
The aryl derivatives **347b** inhibit the IL-1β induced cartilage breakdown associated with osteoarthritis. These compounds are relatively resistant to reductive metabolism by liver microsomial preparations and act by interfering with the proteolytic activation of matrix metalloproteinases [112].

Inhibitor of H^+/K^+ ATPase. H^+/K^+ ATPase is responsible of the acidic secretion in stomach and is a pharmacological target in peptic ulcers. Compounds **351** and **352** show a high inhibitory activity in vitro, but no action in vivo. The potent in vitro activities are due to its high-thiophilic properties, which are not selective for the target enzyme. Prodrugs **350** have been prepared that are converted in the active isothiazolopyridines only within the acidic compartment of the parietal cells, avoiding interaction with thiol groups on other proteins except H^+/K^+-ATPase (see Scheme 87) [113].

Human leukocyte elastase inhibitors. HLE belongs to the chymotrypsin family of serine proteinases: the enzyme consists of a single polypeptide chain of 218 amino acid residues and four disulfide bridges. HLE has been proposed to be a primary mediator of many pulmonary disorders such as em-

physema, acute respiratory distress syndrome and chronic bronchitis. Orally bioavailable inhibitors of HLE belong to the BIT class and are characterised by their specificity and incorporation of a built-in mechanism for regeneration of enzyme activity [98, 124]. Thus, rapid acylation of the active site serine is followed by ring opening and simultaneous departure of the leaving group, yielding a reactive electrophilic species. Deacylation gives active enzyme, while subsequent reaction with an active site nucleophile yields inactive enzyme (Scheme 103).

The heterocyclic scaffold allows the attachment and optimal spatial orientation of peptidyl and nonpeptidyl recognition elements, leading to exploitation of favourable binding interactions with specific subsites of HLE. Different leaving groups have been proposed and studied for compound of general formula **369**. The most active are reported in Scheme 103. Tetrahydrobenzisothiazolone derivative **162** (R = Et, $n = 1$) has been tested as an HLE inhibitor, but it showed less activity than the BIT containing compound [53].



Scheme 103 Mode of action of HLE inhibitors

Recently, closely related isothiazolidin-3-one *S*,*S* dioxide **167** was prepared and tested in vitro [54]. The R^1 residue binds to primary specificity pockets of HLE and by modulating the R1 substitutent it is possible to obtain highly potent HLE inhibitors or compounds that are highly selective for other types of serine proteases (R^1 = isobutyl for HLE inhibitors, R^1 = Ph for cathepsin

G inhibitors, R^1 = small group for PR3 proteinase inhibitors). In all cases the leaving group is represented by carboxylic acid derivatives [54].

Other derivatives tested on HLE are the ortophosphoric derivatives **168** [55] and compound **46** ($R^1 = R^2$ = Ph, $R^3 = R^5$ = Cl, R^4 = O-*i*-Pr) [15].

Inhibitor of mast cell tryptase. Starting from the consideration that BIT derivatives act on HLE, a library of BIT was tested on HMCT. This is a trypsin-like serine protease which is the major product secreted from mast cells during their activation. Elevated tryptase levels have been observed in various diseases such as asthma and inflammatory skin diseases. The most active BIT compound is **371** (R = C_6H_4-4-NHCbz, IC_{50}(μM) = 0.0643). Modeling studies suggest that such compounds recognise a hydrophobic binding pocket on the *S′* side of tryptase that prefers a benzyloxycarbamate group approximately nine atoms from the electrophilic benzisothiazolone *S*,*S*-dioxide carbonyl [120].

Inhibitors of Aldoso reductase. Aldoso reductase catalyses the NADPH-dependent reduction of glucose to sorbitol, whose activity is higher in hyperglycaemic conditions leading to elevated intracellular concentration of sorbitol and, as a consequence, high cellular osmolarity. This fact is dramatically relevant in the development of long-term diabetic complications. NiT **309a** belong to a novel class of aldoso reductase inhibitors, possessing benzisothiazoles scaffold. The presence of a planar aromatic moiety and of an acidic function is important for activity. Also the disposition of the second aromatic ring is crucial for the biological activity. In fact, compound **310**, having a linear tricyclic moiety, is not active. The functionalisation with a second carboxylic group on the phenyl ring (**309b**,**c**) leads to an enhancement of the activity [101]. This class of compounds is selective for Aldoso reductase, while is not active against other enzymes, e.g. aldehyde dehydrogenase.

Kinase inhibitors. Protein kinases are key regulators of different biological pathways. Different kinases are present in the cell and represent an intriguing biological target for several diseases. MEK has a central role in regulating cell growth and survival, differentiation and angiogenesis. Overexpression and activation of these enzymes are associated with various human cancers. Compound **86** was found as lead for in vitro inhibitors of MEK and different derivatives have been synthesised in order to evaluate structure–activity relationship. In particular, a free hydroxyl group at C-3 and, a hydrogen bond donor at C-5 are essential for activity (bioisosteric derivatives with S and O are not active) and the inclusion of a spacer between 5-alkyl or aromatic group and isothiazole core lead to no activity [23]. The replacement of the cyano group with an amidino group in compound **88** (R^1 = 2,5-Cl_2, R^2 = H, R^3 = $CH_2CH(Me)OH$) and the introduction of a bulky *para*-substituent on the aromatic ring produced an improvement of oral activity [26].

ChK 1 and ChK 2 are the major effectors of the replication checkpoint: the fail-safes, which ensure that the cell cycle does not progress to the next stage

until the previous step is completed. Carboxamidine isothiazole derivatives **87** (R^1= cyclohexyl, pyrazolyl, *i*Pr, alkylalcohol) are potent ChK2 inhibitors. They act by direct binding to the ATP site of ChK2 and are ATP-competitors. They possess cellular activity to regulate the ChK2 mediated cell cycle arrest and apoptosis [24].

Isothiazoles have been found to be active also as inhibitors of TrKA, kinases receptors for the neurotrophin family of ligands. Compound **117** (R^1 = 4-Cl – Ph, R^2 = H, R^3 = Me) is a potent inhibitor of this enzyme and its derivatives have been prepared. *N*-Amino-heteroaryl substituted compounds **118** (R^1 = 4-Cl – Ph, R^2 = H) were shown to be good urea surrogates, whereas thioindanyl substituted at C-3 **117** were shown to be very potent inhibitors [35].

CP-547,632 is a potent inhibitor of the VEGFR-2 and basic fibroblast growth factor kinases at nanomolar concentration. It is undergoing clinical trials (2007) [34].

Tyrosine phosphatase inhibitors. PTPs in concert with tyrosine kynases, control the phosphorilation state of many proteins involved in signal transduction pathways. Deregulation of these signalling pathways is involved in numerous diseases, such as cancer and diabetes. PTP1B was the first purified PTP and it is considered one of the best validated drug targets in type2 diabetes and obesity. The design of inhibitors of PTP1B has focused on binding to the active site and on discovery of mimetics of pTyr. Isothiazolidinone peptides have been designed as inhibitors of PTP1B and they show binding activity at nanomolar concentration. In particular, compounds containing a saturated isothiazolidinone scaffold bind the active site much more strongly than the corresponding unsaturated derivatives [156, 157].

In order to improve cellular permeability nonpeptidic pTyr mimetics have been designed and compound **179** was found as a potent, cell permeable inhibitor of PTP1B [57].

Interaction with GABA receptors. GABA is an inhibitory neurotransmitter in the CNS that operates through different receptors: ionotropic $GABA_A$ and $GABA_C$ receptors, and metabotropic $GABA_B$ receptors. $GABA_A$ receptors have been implicated in different neurological diseases and represent important therapeutic targets [14]. A number of different heterocyclic $GABA_A$ agonists, such as muscimol, THIP, isoguvacine have been synthesised (see Scheme 11). $GABA_A$ agonists are zwitterionic compounds and the structure of the heterocyclic ring is a factor of critical importance for the interaction with receptors. In fact compounds with highly delocalised negative charges on the ring have low affinity for the receptors. Other important factors that contribute to biological effects are steric effects, acidity, and tautomeric equilibria. All these factors were examined in depth using ab initio calculations [158]. Another critical factor is represented by the ability of such compounds to penetrate the blood–brain barrier and it is determined by the concentrations of the ionised and unionised form. (I/U ratio) [159]. The

isothiazolyl derivatives thiomuscimol and thio-THIP exert a lower activity with respect to the isoxazolyl compounds. Furthermore the bioisosteric substitution of sulphur for the oxygen atom of THIP converts an agonist to a competitive antagonist. Other isothiazole analogues of THIP have been been prepared. They show affinity for $GABA_A$ receptors at low-micromolar range, which is higher for the satured compound 41 [14, 160, 161].

Interaction with glutamic acid receptors. S – Glu is the main excitatory neurotransmitter in CNS and activates two different types of receptors: ionotropic and metabotropic receptors. Glu is involved in many physiological processes, such as learning, memory, and vision. An altered Glu function is implicated in various neuropathologies, such as epilepsy, stroke, cognitive disorders, and neurogenerative deseases. Ionotropic receptors are subdivided into three groups: NMDA, AMPA, and KA receptors. Furthermore Ibo is a naturally occurring excitotoxin isolated from the mushroom *Amanita muscaria*, which activates KA, NMDA, and several metabotropic receptors. Considering the presence in both AMPA and Ibo structure of an isoxazolyl ring, isothiazolyl bioisoteric derivatives have been prepared in the last years, and in most cases the isothiazolyl derivatives show the same potency as the isoxazolyl ones [19–21]. Only thio-ATPA is considerably less active than ATPA on AMPA receptors, but it is a potent and selective agonist at homomerically expressed ionotropic GluR5. In particular, it has been demonstrated that the activity is solely due to the *S*-enantiomer. Thio-AMPA, as well as AMPA, penetrates the blood-brain barrier as a net uncharged diprotonated species (see Scheme 15) [19].

A **67a** series was designed as structural hybrids between agonist and antagonists ligands showing different receptor selectivity. Such compounds are bioisosteric modified analogues of the dipeptide Glu-Gly [20].

Thioibotenic acid is active both on ionotropic and cloned metabotropic Glu receptors. The different behaviour between isoxazolyl and isothiazolyl derivatives has been studied by using computational and experimental methods [162]. Thio-ibo analogues (see Scheme 20) have been synthesised in order to investigate the structure–activity relationship at both iGlu and mGlu receptors. Analogues containing smaller substituents retained affinity similar to thio-Ibo at NMDA receptors, while by increasing the bulkiness of the substituent the activity is lost. It is notable that the change in efficacy is different between individual subtypes [21]. The xantine derivative **403** significantly antagonised glutamate induced neurotoxicity [130].

Interaction with muscarinic receptors. Deficit in central cholinergic transmission causes the learning and memory impairments seen in patients with Alzhiemer's disease ("cholinergic hypothesis"). The natural alkaloid arecoline is an agonist of muscarinic AChRs, and has been shown to improve cognition when administered to Alzheimer's patients, although the pharmacological effects are shortlived. Compounds **124** and **125** (R = Me, Et, allyl, CH_2CN; $R^1 = R^2 = R^3 = H$, Me) represent conformationally restricted bicyclic analogues

of arecoline, with potent inhibitor activity of the binding of mAChR radioligands [37].

Interaction with serotonin receptors. Serotonin is involved in several diseases, such as depression, schizophrenia, nad psychoses. Seven families of receptors have been discovered (5-HT1-7). Compounds such as buspirone and ipsapirone **389** (R = Ar, $n = 4$), which belong to the class of heteroarylpiperazines, are clinically effective dugs for the treatment of anxiety and depression. It is now generally accepted that the clinical effects are due to the interaction with 5-HT receptors. This class comprises five different receptors (5-$HT1_{a-f}$). 5-HT1a receptors are involved in anxiety and depression. Ipsaspirone is a partial agonist of 5-HT1a, while **DU1255530** (see Scheme 93) is an antagonist [126].

Repinotan (**392**) is a 5-HT1a agonist, in which the 2-(aminomethyl)-1,4-benzodioxan group bioisosterically replaces the arylpiperazine. Repinotan is being developed by Bayer as a potential treatment for ischemic stroke and traumatic brain injury [128].

It is thought that 5-HT2a antagonism together with relatively weaker dopamine antagonism are principal features that differentiate the side-effect profile of atypical antipsychotic agents of the first generation treatments. 5-HT2a antagonist with benzisothiazole scaffold has the general formula **258** (see Tables 2 and 3). Among this class compound **436** is a new atypical antipsychotics for the treatment of schizophrenia [163]. Other benzisothiazolyl substituted piperazines have been prepared, but the activity is low [87, 88].

Interaction with adrenergic receptors. Adrenergic receptors belong to the family of G-protein couplet receptors and have been classified as α (1–3) and β (1–3). Selective α-1 anatagonists represent a target for the treatment of benign prostatic hyperplasia. Ipsaspirone, a 5-HT1 partial agonist, has a modest affinity for α-1 receptors and different derivatives have been prepared in order to gain a potent antagonist activity. As an example, a chlorine atom has been introduced on the benzene ring of saccharin and the piperazine group was replaced with a piperidine derivative, leading to the high selective compound **394** ($R^1 = CO_2Et$, $R^1 = H$). The stereochemistry is important for the activity [129]. Compound **393** ($R^1 = Cl$, $R^1 = H$), is selective for α-1 receptors with no interaction with other protein G-coupled receptors [100].

References

1. Clerici F, Gelmi ML, Pellegrino S (2008) Comp Heterocycl Chem III, (in press)
2. Chapman RF, Peart BJ (1996) Comp Heterocycl Chem II 3:319
3. Kaberdin RV, Potkin VI (2002) Russ Chem Rev 71:673
4. Taubert K, Kraus S, Schulze B (2002) Sulf Rep 23:79
5. Taubert K, Siegemund A, Schulze B (2002) Sulf Rep 24:279
6. Hamad Elgazwy A-SS (2003) Tetrahedron 59:7445

7. Ager DJ, Pantaleone DP, Henderson SA, Katritzky AR, Prakash I, Walters DE (1998) Ang Chem Int Ed 37:1802
8. Adams A, Slask R (1956) Chem Ind 42:1232
9. Soledade M, Pedras C, Suchy M (2006) Bioorg Med Chem 14:714
10. Luyten I, De Winter H, Busson R, Lescrinier T, Creuven I, Durant F, Balzarini J, De Clercq E, Herdewijn P (1996) Helv Chim Acta 79:1462
11. Kang YK, Lee KS, Yoo KH, Shin KJ, Kim DC, Lee C-S, Kong JY, Kim DJ (2003) Bioorg Med Chem Lett 13:463
12. Khalaj A, Adibpour N, Shahverdi AR, Daneshtalab M (2004) E J Med Chem 39:699
13. Nádel A, Pálinkás J (2000) J Het Chem 37:1463
14. Ebert B, Mortensen M, Thompson SA, Kehler J, Wafford KA, Krogsgaard-Larsen P (2001) Bioorg Med Chem Lett 11:1573
15. Gütschow M, Pietsch M, Taubert K, Freysoldt THE, Schulze B (2003) Z Naturforsch B: Chem Sci 58:111
16. Lu Z, Raghavan S, Bohn J, Charest M, Stahlhut MW, Rutkowski CA, Simcoe AL, Olsen DB, Schleif WA, Carella A, Gabryelski L, Jin L, Lin JH, Emini E, Chapman K, Tata JR (2003) Bioorg Med Chem Lett 13:1821
17. Bürli RW, Ge Y, White S, Baird EE, Touami SM, Taylor M, Kaizerman JA, Moser HE (2002) Bioorg Med Chem Lett 12:2591
18. Kaizerman JA, Gross MI, Ge Y, White S, Hu W, Duan J-X, Baird EE, Johnson KW, Tanaka RD, Moser HE, Bürli RW (2003) J Med Chem 46:3914
19. Matzen L, Engesgaard A, Ebert B, Didriksen M, Frølund B, Krogsgaard-Larsen P, Jaroszewski JW (1997) J Med Chem 40:520
20. Matzen L, Ebert B, Stensbøl TB, Frølund B, Jaroszewski JW, Krogsgaard-Larsen P (1997) Bioorg Med Chem 5:1569
21. Jørgensen CG, Clausen RP, Hansen KB, Bräuner-Osborne H, Nielsen B, Metzler BB, Kehler J, Krogsgaard-Larsen P, Madsen U (2007) Org Biomol Chem 5:463
22. Perronnet J, Taliani L, Girault P, Poittevin A (1976) US Patent 3 983 129
23. Varaprasad CVNS, Barawkar D, El Abdellaoui H, Chakravarty S, Allan M, Chen H, Zhang W, Wu JZ, Tam R, Hamatake R, Lang S, Hong Z (2006) Bioorg Med Chem Lett 16:3975
24. Larson G, Yan S, Chen H, Rong F, Hong Z, Wu JZ (2007) Bioorg Med Chem Lett 17:172
25. Yan S, Appleby T, Gunic E, Shim JE, Tasu T, Kim H, Rong F, Chen H, Hamatake R, Wu JZ, Hong Z, Yao N (2007) Bioorg Med Chem Lett 17:28
26. El Abdellaoui H, Varaprasad CVNS, Barawkar D, Chakravarty S, Maderna A, Tam R, Chen H, Allan M, Wu JZ, Appleby T, Yan S, Zhang W, Lang S, Yao N, Hamatake R, Hong Z (2006) Bioorg Med Chem Lett 16:5561
27. Cutri CCC, Garozzo A, Siracusa MA, Castro A, Tempera G, Sarva MC, Guerrera F (2002) Antiviral Res 55:357
28. Lipnicka U, Regiec A, Sulkowski E, Zimecki M (2006) Arch Pharm Chem Life Sci 339:401
29. Schieweck F, Tormo I Blasco J, Blettner C, Mueller B, Gewehr M, Grammenos W, Grote T, Gypser A, Rheinhimer J, Schaefer P, Schwoegler A, Wagner O, Rack M, Baumann E, Strathmann S, Schoefl U, Scherer M, Stierl R, Treacy MF, Culbertson DL, Bucci T (2005) WO Patent 2 005 040 162
30. Watanabe Y, Yamazaki D, Otsu Y, Shibuya K (2003) WO Patent 2 003 051 123
31. Samaritoni JG, Arndt L, Bruce TJ, Dripps JE, Gifford J, Hatton CJ, Hendrix WH, Schoonover JR, Johnson GW, Hegde VB, Thornburgh S (1997) J Agric Food Chem 45:1920

32. Samaritoni JG, Babcock JM, Schlenz ML, Johnson GW (1999) J Agric Food Chem 47:3381
33. Larson ER, Noe MC, Gant TG (1999) WO Patent 9 962 890
34. Beebe JS, Jani JP, Knauth E, Goodwin P, Higdon C, Rossi AM, Emerson E, Finkelstein M, Floyd E, Harriman S, Atherton J, Hillerman S, Soderstrom C, Kou K, Gant T, Noe MC, Foster B, Rastinejad F, Marx MA, Schaeffer T, Whalen PM, Roberts WG (2003) Cancer Res 63:7301
35. Lippa B, Morris J, Corbett M, Kwan TA, Noe MC, Snow SL, Gant TG, Mangiaracina M, Coffey HA, Foster B, Knauth EA, Wessel MD (2006) Bioorg Med Chem Lett 16:3444
36. Falch E, Perregaard J, Frølund B, Søkilde B, Buur A, Hansen LM, Frydenvang K, Brehm L, Bolvig T, Larsson OM, Sanchez C, White HS, Schousboe A, Krogsgaard-Larsen P (1999) J Med Chem 42:5402
37. Pedersen H, Bräuner-Osborne H, Ball RG, Frydenvang K, Meier E, Bøgesø KP, Krogsgaard-Larsen P (1999) Bioorg Med Chem 7:795
38. Marco JL, Ingate ST, Chinchòn PM (1999) Tetrahedron 55:7625
39. Dodge JA, Evers B, Jungheim LN, Muehl BS, Ruehter G, Thrasher KJ (2002) WO Patent 2 002 032 888
40. Evers B, Ruehter G, Tebbe MJ, Martin de la Nava EM (2003) WO Patent 2 003 087 069
41. Evers B, Ruehter G, Martin de la Nava EM, Tebbe MJ (2003) WO Patent 2 003 087 070
42. Clerici F, Marazzi G, Taglietti M (1992) Tetrahedron 48:3227
43. Clerici F, Gelmi ML, Yokoyama K, Pocar D, Van Voorhis WC, Buckner FS, Gelb MH (2002) Bioorg Med Chem Lett 12:2217
44. Clerici F, Contini A, Corsini A, Ferri N, Grzesiak S, Pellegrino S, Sala A, Yokoyama K (2006) Eur J Med Chem 41:675
45. Clerici F, Erba E, Gelmi ML, Valle M (1997) Tetrahedron 53:15859
46. Beccalli EM, Clerici F, Gelmi ML (1999) Tetrahedron 55:2001
47. Clerici F, Contini A, Gelmi ML, Pocar D (2003) Tetrahedron 59:9399
48. Van Nhien AN, Tomassi C, Len C, Marco-Contelles JL, Balzarini J, Pannecouque C, De Clercq E, Postel D (2005) J Med Chem 48:4276
49. Alvarez R, Jimeno M-L, Gago F, Balzarini J, Perez-Perez M-J, Camarasa M-J (1998) Antiviral Chem Chemother 9:333
50. Marco JL, Ingate ST, Jaime C, Bea I (2000) Tetrahedron 56:2523
51. Evers B, Ruehter G, Berg M, Dodge JA, Hankotius D, Hary U, Jungheim LN, Mest H-J, de la Nava E-MM, Mohr M, Muehl BS, Petersen S, Sommer B, Riedel-Herold G, Tebbe MJ, Thrasher KJ, Voelkers S (2005) Bioorg Med Chem 13:6748
52. Subramanyam C, Bell MR, Ghose AK, Kumar V, Dunlap RP, Franke C, Mura AJ (1995) Bioorg Med Chem Lett 5:325
53. Kuang R, Epp JB, Ruan S, Chong LS, Venkataraman R, Tu J, He S, Truong TM, Groutas WC (2000) Bioorg Med Chem 8:1005
54. Kuang R, Venkataraman R, Ruan S, Groutas WC (1998) Bioorg Med Chem Lett 8:539
55. Yue EW, Wayland B, Douty B, Crawley ML, McLaughlin E, Takvorian A, Wasserman Z, Bower MJ, Wei M, Li Y, Ala PJ, Gonneville L, Wynn R, Burn TC, Liu PCC, Combs AP (2006) Bioorg Med Chem 14:5833
56. Combs AP, Zhu W, Crawley ML, Glass B, Polam P, Sparks RB, Modi D, Takvorian A, McLaughlin E, Yue EW, Wasserman Z, Bower M, Wei M, Rupar M, Ala P, Reid BM, Ellis D, Gonneville L, Emm T, Taylor N, Yeleswaram S, Li Y, Wynn R, Burn TC, Hollis G, Liu PCC, Metcalf B (2006) J Med Chem 49:3774
57. Greig IR, Tozer MJ, Wright PT (2001) Org Lett 3:369

58. Cherney RJ, Mo R, Meyer DT, Hardman KD, Liu R-Q, Covington MB, Qian M, Wasserman ZR, Christ DD, Trzaskos JM, Newton RC, Decicco CP (2004) J Med Chem 47:2981
59. Cherney RJ, King BW, Gilmore JL, Liu R-Q, Covington MB, Duan JJ-W, Decicco CP (2006) Bioorg Med Chem Lett 16:1028
60. Spaltenstein A, Almond MR, Bock WJ, Cleary DG, Furfine ES, Hazen RJ, Kazmierski WM, Salituro FG, Tung RD, Wright LL (2000) Bioorg Med Chem Lett 10:1159
61. Alcaraz L, Baxter A, Bent J, Bowers K, Braddock M, Cladingboel D, Donald D, Fagura M, Furber M, Laurent C, Lawson M, Mortimore M, McCormick M, Roberts N, Robertson M (2003) Bioorg Med Chem Lett 13:4043
62. Bakshi RK, Hong Q, Tang R, Kalyani RN, MacNeil T, Weinberg DH, Van der Ploeg LHT, Patchett AA, Nargund RP (2006) Bioorg Med Chem Lett 16:1130
63. Inagaki M, Tsuri T, Jyoyama H, Ono T, Yamada K, Kobayashi M, Hori Y, Arimura A, Yasui K, Ohno K, Kakudo S, Koizumi K, Suzuki R, Kato M, Kawai S, Matsumoto S (2000) J Med Chem 43:2040
64. Inagaki M, Haga N, Kobayashi M, Ohta N, Kamata S, Tsuri T (2002) J Org Chem 67:125
65. Valente C, Guedes RC, Moreira R, Iley J, Gut J, Rosenthal PJ (2006) Bioorg Med Chem Lett 16:4115
66. Singh SK, Reddy PG, Rao KS, Lohray BB, Misra P, Rajjak SA, Rao YK, Venkateswarlu A (2004) Bioorg Med Chem Lett 14:499
67. Dehmlow H, Aebi JD, Jolidon S, Ji Y-H, Von der Mark EM, Himber J, Morand OH (2003) J Med Chem 46:3354
68. Brown BS, Jinkerson TK, Keddy RG, Lee C-H (2006) WO Patent 2 006 065 646
69. Vicini P, Zani F, Cozzini P, Doytchinova I (2002) Eur J Med Chem 37:553
70. Zani F, Vicini P, Incerti M (2004) Eur J Med Chem 39:135
71. Vicini P, Fisicaro E, Lugari MT (2000) Arch Pharm 333:135
72. Geronikaki A, Vicini P, Incerti M, Hadjipavlou-Litina D (2004) Arzneim Forsch 54:530
73. Vicini P, Incerti M, Amoretti L, Ballabeni V, Tognolini M, Barocelli E (2002) Farmaco 57:363
74. Morini G, Pozzoli C, Adami M, Poli E, Coruzzi G (1999) Farmaco 54:740
75. Sharma PK, Sawhney SN (1997) Bioorg Med Chem Lett 7:2427
76. Yevich JP, New JS, Smith DW, Lobeck GW, Catt JD, Minielli LJ, Eison MS, Taylor DP, Riblet LA, Temple DL (1986) J Med Chem 29:359
77. Su W, Chen Z, Lou F, Xu Y, Wang B (2006) CN Patent 1 850 811
78. Kraus H, Krebs A, Sollner R (1998) EU Patent 846 692
79. Vicini P (1986) Farmaco 41:808
80. Böshagen H, Geiger W (1977) J Liebigs Ann Chem, p 20
81. Panico A, Vicini P, Incerti M, Cardile V, Gentile B, Ronsisvalle G (2002) Farmaco 57:671
82. Vicini P, Zani F (1997) Farmaco 52:21
83. Navas FIII, Tang FLM, Schaller LT, Norman MH (1998) Bioorg Med Chem 6:811
84. Ishizumi K, Kojima A, Antoku F, Saji I, Yoshigi MC (1995) Chem Pharm Bull 43:2139
85. Orjales A, Mosquera R, Toledo A, Pumar C, Labeaga L, Innerarity A (2002) Eur J Med Chem 37:721
86. Perrone R, Berardi F, Colabufo NA, Leopoldo M, Tortorella V (2000) Bioorg Med Chem 8:873
87. Orjales A, Mosquera R, Toledo A, Pumar MC, Garcia N, Cortizo L, Labeaga L, Innerarity A (2003) J Med Chem 46:5512

88. Zbigniew M, Rusin KE, Sawicki AW, Kurowski K, Matusiewicz KJ, Stawinski T, Sulikowski D, Ktudkiewicz DD (2006) US Patent 2 006 160 870
89. Morini G, Pozzoli C, Menozzi A, Comini M, Poli E (2005) Farmaco 60:810
90. Xie W, Herbert B, Schumacher RA, Ma J, Nguyen TM, Gauss CM, Tehim A (2005) WO Patent 2 005 111 038
91. López-Rodríguez ML, Porras E, Benhamú B, Ramos JA, Morcillo MJ, Lavandera JL (2000) Bioorg Med Chem Lett 10:1097
92. Wilkening RR, Ratcliffe RW, Wildonger KJ, Cama LD, Dykstra KD, DiNinno FP, Blizzard TA, Hammond ML, Heck JV, Dorso KL, St Rose E, Kohler J, Hammond GG (1999) Bioorg Med Chem Lett 9:673
93. Ratcliffe RW, Wilkening RR, Wildonger KJ, Waddell ST, Santorelli GM, Parker DL Jr, Morgan JD, Blizzard TA, Hammond ML, Heck JV, Huber J, Kohler J, Dorso KL, St Rose E, Sundelof JG, May WJ, Hammond GG (1999) Bioorg Med Chem Lett 9:679
94. Humphrey GR, Miller RA, Pye PJ, Rossen K, Reamer RA, Maliakal A, Ceglia SS, Grabowski EJJ, Volante RP, Reider PJ (1999) J Am Chem Soc 121:11261
95. Swayze EE, Drach JC, Wotring LL, Townsend LB (1997) J Med Chem 40:771
96. Zask A, Gu Y, Albright JD, Du X, Hogan M, Levin JI, Chen JM, Killar LM, Sung A, Di Joseph JF, Sharr MA, Roth CE, Skala S, Jin G, Cowling R, Mohler KM, Barone D, Black R, March C, Skotnicki JS (2003) Bioorg Med Chem Lett 13:1487
97. Desai RC, Dunlap RP, Farrell RP, Ferguson E, Franke CA, Gordon R, Hlasta DJ, Talomie TG (1995) Bioorg Med Chem Lett 5:105
98. Xu L, Shu H, Liu Y, Zhang S, Trudell ML (2006) Tetrahedron 62:7902
99. Nerenberg JB, Erb JM, Thompson WJ, Lee H-Y, Guare JP, Munson PM, Bergman JM, Huff JR, Broten TP, Chang RSL, Chen TB, O'Malley S, Schorn TW, Scott AL (1998) Bioorg Med Chem Lett 8:2467
100. Da Settimo F, Primofiore G, La Motta C, Sartini S, Taliani S, Simorini F, Marini AM, Lavecchia A, Novellino E, Boldrini E (2005) J Med Chem 48:6897
101. Nagasawa HT, Kawle SP, Elberling JA, DeMaster EG, Fukuto JM (1995) J Med Chem 38:1865
102. Groutas WC, Chong LS, Venkataraman R, Epp JB, Kuang R, Houser-Archield N, Hoidal JR (1995) Bioorg Med Chem 3:187
103. Carmellino ML, Pagani G, Terreni M, Pregnolato M, Borgna P, Pastoni F, Zani F (1997) Farmaco 52:359
104. Borgna P, Carmellino ML, Natangelo M, Pagani G, Pastoni F, Pregnolato M, Terreni M (1996) Eur J Med Chem 31:919
105. Fiore PJ, Puls TP, Walker JC (1998) Org Proc Res Dev 2:151
106. Turpin JA, Song Y, Inman JK, Huang M, Wallqvist A, Maynard A, Covell DG, Rice WG, Appella E (1999) J Med Chem 42:67
107. Borgna P, Pregnolato M, Invernizzi AG, Mellerio G (1993) J Het Chem 30:1079
108. Pagani G, Pregnolato M, Ubiali D, Terreni M, Piersimoni C, Scaglione F, Fraschini F, Rodríguez Gascón A, Pedraz Munoz JL (2000) J Med Chem 43:199
109. Pregnolato M, Borgnan P, Terreni M (1995) J Het Chem 32:847
110. Wright SW, Corbett RL (1993) Org Prep Proc Int 25:247
111. Wright SW, Petraitis JJ, Batt DG, Corbett RL, Di Meo SV, Freimark B, Giannaras JV, Orwat MJ, Pinto DJ, Pratta MA, Sherk SR, Stampfli HF, Williams JM, Magolda RL, Arner EC (1995) Bioorg Med Chem 3:227
112. Terauchi H, Tanitame A, Tada K, Nishikawa Y (1996) Heterocycles 43:1719
113. Wiles JA, Song Y, Wang Q, Lucien E, Hashimoto A, Cheng J, Marlor CW, Ou Y, Podos SD, Thanassi JA, Thoma LC, Deshpande M, Pucci MJ, Bradbury BJ (2006) Bioorg Med Chem Lett 16:1277

114. Wiles JA, Wang Q, Lucien E, Hashimoto A, Song Y, Cheng J, Marlor CW, Ou Y, Podos SD, Thanassi JA, Thoma LC, Deshpande M, Pucci MJ, Bradbury BJ (2006) Bioorg Med Chem Lett 16:1272
115. Hlasta DJ, Ackerman JH, Court JJ, Farrell RP, Johnson JA, Kofron JL, Robinson DT, Talomie TG, Dunlap RP, Franke CA (1995) J Med Chem 38:4687
116. Hlasta DJ, Subramanyam C, Bell MR, Carabateas PM, Court JJ, Desai RC, Drozd ML, Eickhoff WM, Ferguson EW, Gordon RJ, Dunlap RP, Franke CA, Mura AJ, Rowlands A, Johnson JA, Kumar V, Maycock AL, Mueller KR, Pagani ED, Robinson DT, Saindane MT, Silver PJ, Subramanian S (1995) J Med Chem 38:739
117. Guzel O, Salman A (2006) Biorg Med Chem 14:7804
118. Hlasta DJ, Bell MR, Court JJ, Cundy KC, Desai RC, Ferguson EW, Gordon RJ, Kumar V, Maycock AL, Subramanyam C (1995) Biorg Med Chem Lett 5:331
119. Combrink KD, Gülgeze HB, Meanwell NA, Pearce BC, Zulan P, Bisacchi GS, Roberts DGM, Stanley P, Seiler SM (1998) J Med Chem 41:4854
120. Yu K-L, Civiello R, Roberts DGM, Seiler SM, Meanwell NA (1999) Bioorg Med Chem Lett 9:663
121. Varga M, Kapui Z, Batori S, Nagy LT, Vasvari-Debreczy L, Mikus E, Urbán-Szabó K, Arányi P (2003) Eur J Med Chem 38:421
122. Desai RC, Court JC, Ferguson E, Gordon R, Hlasta DJ (1995) J Med Chem 38: 1571
123. Groutas WC, Epp JB, Venkataraman R, Kuang R, Truong TM, McClenahan JJ, Prakash O (1996) Biorg Med Chem 4:1393
124. Hartog J, Van Steen BJ, Mos J, Schipper J (1995) EU Patent 0 633 260
125. Van Steen BJ, Van Wijngaarden I, Ronken E, Soudijn W (1998) Bioorg Med Chem Lett 8:2457
126. Caliendo G, Fiorino F, Perissutti E, Severino B, Scolaro D, Gessi S, Cattabriga E, Borea PA, Santagada V (2002) Eur J Pharm Sci 16:15
127. Gross JL (2003) Tetrahedron Lett 44:8563
128. Patane MA, Di Pardo RM, Price RAP, Chang RSL, Ransom RW, O'Malley SS, Di Salvo J, Bock MG (1998) Bioorg Med Chem Lett 8:2495
129. Zlatkov A, Peikov P, Rodriguez-Alvarez J, Danchev N, Nikolova I, Mitkov J (2000) Eur J Med Chem 35:941
130. Primofiore G, Da Settimo F, La Motta C, Simorini F, Minutolo A, Boldrini E (1997) Farmaco 52:583
131. Da Settimo A, Primofiore G, La Motta C, Da Settimo F, Simorini F, Boldrini E, Bianchini P (1996) Farmaco 51:261
132. Aal EHA, El-Sabbagh OI, Youssif S, El-Nabtity (2002) Monats Chem 133:255
133. Scherling D, Karl W, Seidel D, Weinz C, Schohe-loop R, Mauler F (2003) WO Patent 2 003 029 250
134. Malinka W, Sieklucka-Dziuba M, Rajtar G, Zgodzinski W, Kleinrok Z (2000) Pharmazie 6:416
135. Malinka W, Swiatek P, Flipek B, Sapa J, Jezierska A, Koll A (2005) Farmaco 60:961
136. Malinka W, Sieklucka-Dziuba M, Rajtar G, Marowska D, Kleinrok Z (1995) Farmaco 50:769
137. Malinka W, Rutkowska M (1997) Farmaco 52:595
138. Malinka W, Ryng S, Sieklucka-Dziuba M, Rajtar G, Głowniak A, Kleinrok Z (1998) Farmaco 53:504
139. Bradbury BJ, Pais G, Wang Q, Deshpande M, Pucci MJ, Song Y, Lucien E, Wiles JA, Hashimoto A (2006) WO Patent 2 006 089 054
140. Singerman GM (1976) US Patent 3 997 548

141. Ikeda K, Abe N, Katoh C, Kanaoka A (1994) EU Patent 578 246
142. Davis RH, Krummel G (1994) EU Patent 623 282
143. Pilkington BL, Armstrong S, Barnes NJ, Barnett SP, Clarke ED, Crowley PJ, Fraser TEM, Hughes D, Methews CJ, Salmon R, Smith SC, Viner R, Whittingham WG, Williams J, Whittle AJ, Mound WR, Urch CJ (2001) WO Patent 2 001 090 105
144. Watanabe Y, Yamazaki D, Otsu Y, Shibuya K (2003) (2003) WO 2 003 051 123
145. Morley JO, Oliver AJ, Charlton MH (1998) J Mol Struct 429:103
146. Alvarez-Sanchez R, Basketter D, Pease C, Lepoittevin J-P (2004) Bioorg Med Chem Lett 14:365
147. Zani F, Pregnolato M, Zampollo F (1999) Farmaco 54:643
148. Pagani G, Borgna P, Piersimoni C, Nista D, Terreni M, Pregnolato M (1996) Arch Pharm 329:421
149. Chu DTW, Fernandes PB, Claiborne AK, Shen L, Pernet AG (1988) Drugs Exp Clin Res 14:379
150. Wang Q, Lucien E, Hashimoto A, Pais GCG, Nelson DM, Song Y, Thanassi JA, Marlor CW, Thoma CL, Cheng J, Podos SD, Ou Y, Deshpande M, Pucci MJ, Buechter DD, Bradbury BJ, Wiles JA (2007) J Med Chem 50:199
151. Yasuda N, Yang C, Wells KM, Jensen MS, Hughes DL (1999) Tetrahedron Lett 40:427
152. Soriano E, Marco-Contelles J, Tomassi C, Van Nhien AN, Postel D (2006) J Chem Inf Model 46:1666
153. Cutri CCC, Garozzo A, Siracusa MA, Sarva MC, Tempera G, Geremia E, Pinizzotto MR, Guerrera F (1998) Biorg Med Chem 6:2271
154. Cutri CCC, Garozzo A, Siracusa MA, Sarva MC, Castro A, Geremia E, Pinizzotto MR, Guerrera F (1999) Biorg Med Chem 7:225
155. Ferri N, Clerici F, Yokoyama K, Pocar D, Corsini A (2005) Biochem Pharmacol 70:1735
156. Combs AP, Yue EW, Bower M, Ala PJ, Wayland B, Douty B, Takvorian A, Polam P, Wasserman Z, Zhu W, Crawley ML, Pruitt J, Sparks R, Glass B, Modi D, McLaughlin E, Bostrom L, Li M, Galya L, Blom K, Hillman M, Gonneville L, Reid BG, Wei M, Becker-Pasha M, Klabe R, Huber R, Li Y, Hollis G, Burn TC, Wynn R, Liu P, Metcalf B (2005) J Med Chem 48:6544
157. Yue EW, Wayland B, Douty B, Crawley ML, McLaughlin E, Takvorian A, Wasserman Z, Bower MJ, Wei M, Li Y (2006) Bioorg Medl Chem 14:5833
158. Brehm L, Ebert B, Kristiansen U, Wafford KA, Kemp JA, Krogsgaard-Larsen P (1997) Eur J Med Chem 32:357
159. Frolund B, Kristiansen U, Brehm L, Hansen AB, Krogsgaard-Larsen P, Falch E (1995) J Med Chem 38:3287
160. Ebert B, Mortensen M, Thompson SA, Kehler J, Wafford KA, Krogsgaard-Larsen P (2001) Bioorg Med Chem Lett 11:1573
161. Krogsgaard-Larsen P, Mikkelsen H, Jacobsen P, Falch E, Curtis DR, Peet MJ, Leah JD (1983) J Med Chem 26:895
162. Hermit MB, Greenwood JR, Nielsen B, Bunch L, Jorgensen CG, Vestergaard HT, Stensbol TB, Sanchez C, Krogsgaard-Larsen P, Madsen U, Brauner-Osborne H (2004) Eur J Pharm 486:241
163. Singer JM, Barr BM, Coughenour LL, Gregory TF, Walters MA (2005) Bioorg Med Chem Lett 15:4560