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Advances in the synthesis and recent therapeutic applications of 1,2,4-thiadiazole heterocycles

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Abstract—Chemical properties of 1,2,4-thiadiazole have been reviewed in the last few years. However, the usefulness of 1,2,4-thiadiazole as a privileged system in medicinal chemistry has prompted the advances on the therapeutic potential of this system. This review provides a brief summary of the medicinal chemistry of 1,2,4-thiadiazole system and highlights some examples of 1,2,4-thiadiazole-containing drug substances in the current literature. A survey of representative literature procedures for the preparation of 1,2,4-thiadiazole is presented in sections by generalized synthetic methods.

1. Introduction

1,2,4-Thiadazoles are an important class of heterocycles, which have been the subject of great interest because of their biological activities. Very interesting therapeutic applications have been found in the 1,2,4-thiadiazole system. Although currently the only commercial 1,2,4-thiadiazole drug is the antibiotic cefozopram,[1] there are a number of synthetic products related to this system[2,3] with a broad range of biological activities (Fig. 1). For example, the thiadiazole SCH-202676 was identified in 2001 as a promising allosteric modulator of G-protein coupled receptors[4] and in 1998 KC 12291 showed the first evidence of its cardioprotective action.[5,6] More recently, in 2002, the small heterocyclic thiadiazolidinones (TDZD) were described as the first non-ATP competitive glycogen synthase kinase 3β inhibitors.[7] A number of derivatives have been prepared in order to improve the pharmacological properties of these interesting lead compounds. Also the properties of 1,2,4-thiadiazoles as thiol trapping agents have been recently reviewed.[8]

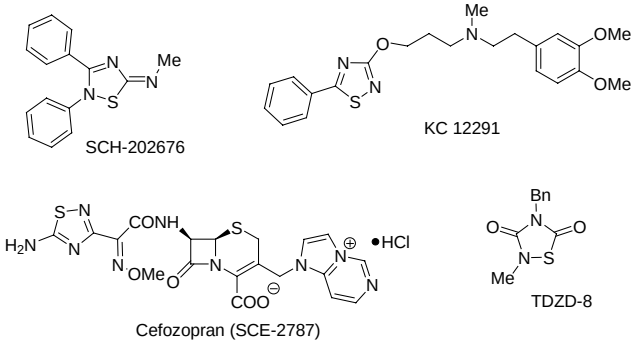

Figure 1. Some relevant structures with the 1,2,4-thiadiazole moiety.

The usefulness of 1,2,4-thiadiazole as pharmacophore in medicinal chemistry has prompted the advances on the chemistry of this system. This review covers a selection of the literature that describes the usefulness and efficiency of the 1,2,4-thiadiazole heterocycle in the medicinal chemistry area as well as recent chemical strategies on the synthesis of its main derivatives (Fig. 2).

2. Recent strategies on the synthesis of 1,2,4-thiadiazole

2.1. 3,5-Diaryl/dialkyl-1,2,4-thiadiazole (I)

The main synthetic procedure to obtain 3,5-diaryl/dialkyl-1,2,4-thiadiazole usually includes an oxidation step of compounds containing the thioamide group.[9] A variety of oxidizing agents as halogens, hydrogen peroxide or

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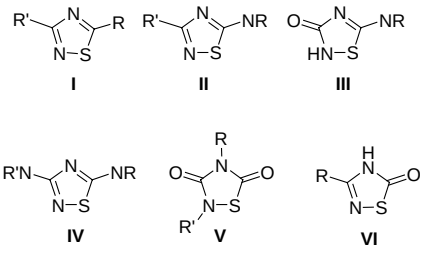


Figure 2. Main derivatives of the 1,2,4-thiadiazole heterocycles.

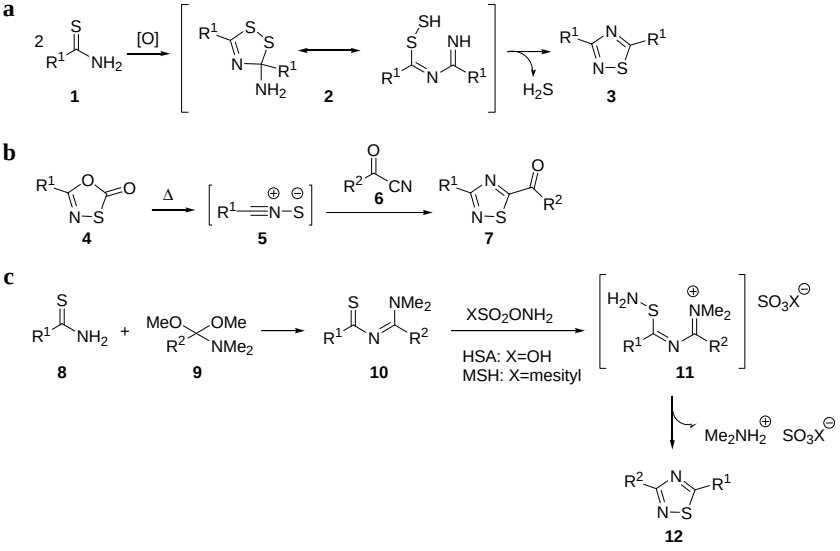
thionyl chloride yield 3,5-disubstituted 1,2,4-thiadiazole after cyclization reactions in moderate yields. Recently, it has been reported on the condensation reaction of thioamides (**1**) in the presence of oxidative DMSO–HCl mixtures.[10] This route has proved to be suitable to obtain symmetrically substituted derivatives (**3**) (Scheme 1a).[11]

Reaction of nitrile sulfides (**5**) with acyl cyanides (**6**) provides a versatile preparative route to 5-acyl 1,2,4-thiadiazole (**7**).[12] The 1,3-dipolar cycloaddition involving nitrile sulfide generally requires strongly activated dipolarophiles, as ethyl cyanoformate, tosyl cyanide or acyl cyanides.[13] As nitrile sulfides are short-life species, for preparative purposes they are usually generated in situ. The most widely used routes to nitrile sulfides are based on the thermal decarboxylation at 130–160 °C of 1,3,4-oxathiazol-2-ones (**4**), which are stable at room temperature and readily accessible (Scheme 1b).[14]

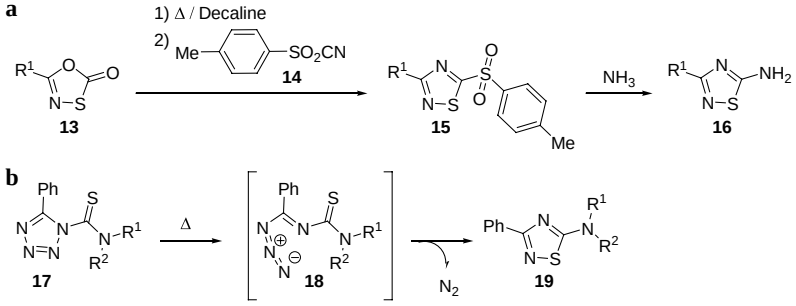
A more recent method based on the amination–cyclization of *N*′-(thioaroyl)-*N*,*N*-dimethylamidines (**10**) with an aminating agent such as hydroxylamine-*O*-sulfonic acid (HSA) or *O*-(mesitylenesulfonyl)hydroxylamine (MSH) provides 1,2,4-thiadiazole (**12**) in excellent yields. The *N*′-(thioaroyl)-*N*,*N*-dimethylamidines (**10**) are prepared by reaction of thioamide (**8**) with *N*,*N*-dimethylformamide dimethylacetal or *N*,*N*-dimethylacetamide dimethylacetal (**9**) in 90–99% yields (Scheme 1c).[15,16]

2.2. 3-Aryl/alkyl-5-amino-1,2,4-thiadiazole (II)

3-Alkyl-5-amino-1,2,4-thiadiazole derivatives were generated by thermolysis of different five-membered rings. By using the oxathiadiazole thermolysis approach, the reaction of the generated nitrile sulfide with tosyl cyanide (**14**) yielded a key intermediate with a labile tosyl substituent in the five position of the thiadiazole (**15**). Displacement of the tosyl group with ammonia provided 5-amino-3-substituted-thiadiazoles (**16**) (Scheme 2a).[13] These heterocycles have also been generated by thermolysis of 1-thiocarbamoyl-5-phenyl-tetrazoles (**17**) (Scheme 2b).[17]



Scheme 1. Synthesis of 3,5-diaryl/dialkyl-1,2,4-thiadiazole.

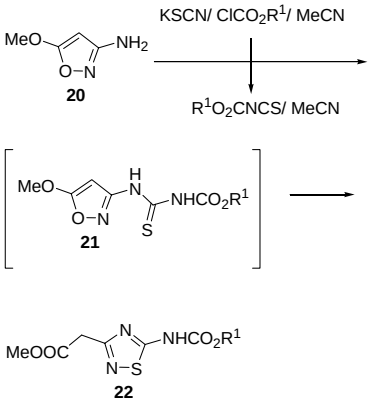


Scheme 2. Synthesis of 3-substituted-5-amino-1,2,4-thiadiazole by thermolysis.

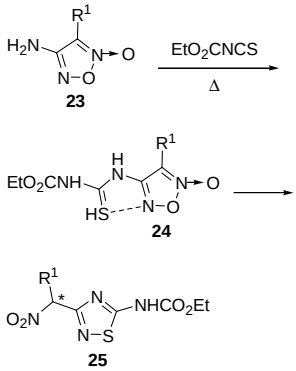
Methyl 2-(5-alkoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetates (**22**) were prepared by reaction of 3-amino-isoxazole (**20**) with isothiocyanates generated in situ, by the skeletal rearrangement of the intermediary thiourea derivative (**21**) (Scheme 3).[18]

Recently, 5-amino-3-(α-nitroalkyl)-1,2,4-thiadiazoles (**25**) have been obtained by thermal rearrangements of 3-substituted 4-(3-ethoxycarbonylthioureido)-1,2,5-oxadiazole 2-oxides (**24**). The reaction was performed by refluxing a mixture of aminofuroxans (**23**) with ethoxycarbonyl isothiocyanate in aprotic organic solvents (Scheme 4).[19]

Photoinduced molecular rearrangements of O–N bond-containing five-membered heterocycles can provide interesting methodologies in synthesis of 3-phenyl-5-substituted 1,2,4-thiadiazoles. In fact, photolytic species arising from the 1,2,4-oxadiazole ring do react with sulfur reagents by forming a N–S bond. The irradiation of 5-amino-3-phenyl-1,2,4-oxadiazole (**26**) in the presence



Scheme 3. Synthesis of methyl 2-(5-alkoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetates through skeletal rearrangement.

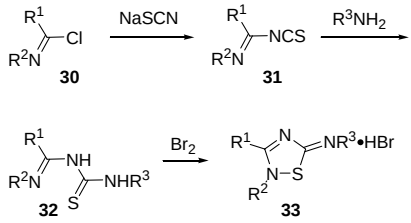


Scheme 4. Thermal rearrangement of 3-substituted 4-(3-ethoxycarbonylthioureido)-1,2,5-oxadiazole 2-oxides.

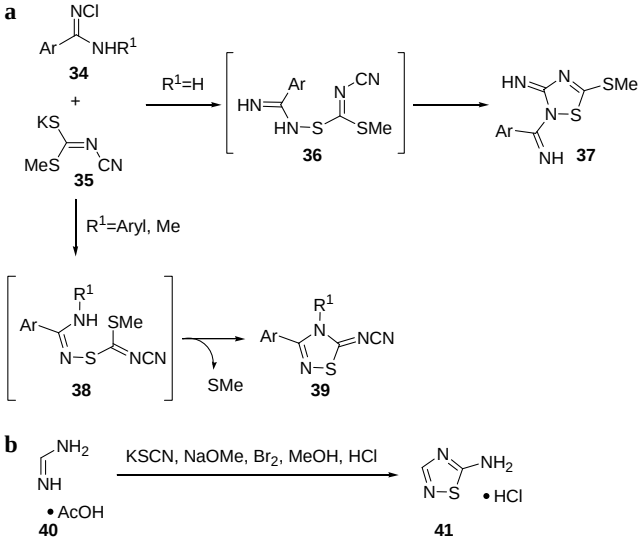
of thioureas (**28**) gives the target compound (**29**) because of the reaction between the ring-photolytic species (**27**) and the sulfur nucleophile (Scheme 5).[20]

Besides thermolysis and rearrangements, 1,2,4-thiadiazoles have been obtained by oxidative formation from imidoylthioureas (Scheme 6).[21,22] To prepare the compounds, benzamides were used as starting materials that were converted into benzimidoyl chlorides (**30**). Substitution of the chlorine atom in compound **30** by an SCN moiety to form intermediate **31**, followed by addition of an amine, afforded thioureas (**32**) and in the last step, an oxidation with bromine yielded the targeted 2,3,5-substituted [1,2,4]-thiadiazoles as their hydrobromide salts (**33**).

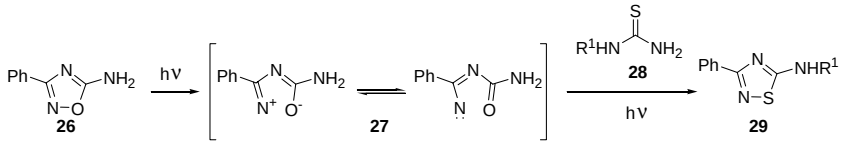
Reaction of *N*-unsubstituted *N*′-chlorobenzamidines (**34**, $R^1 = H$) with potassium *S*-methyl cyanimidodithiocarbonate (**35**) yielded 2-arylimidoyl-3-imino-5-methylthio-1,2,4-thiadiazoles (**37**).[23] In contrast, substituted amidines (**34**, R^1 = Aryl and Me) form 5-cyanimino-4,5-dihydro-3-aryl-1,2,4-thiadiazoles (**39**) containing both nitrogen atoms of amidines in the ring system.[24] The mechanisms for both synthetic pathways are depicted in



Scheme 6. Synthesis of 1,2,4-thiadiazole via imidoyl chlorides.



Scheme 7. Synthetic pathway for thiadiazoles from amidines.



Scheme 5. Synthesis of 1,2,4-thiadiazole by photoinduced molecular rearrangement.

Scheme 7a. At the same time, aminothiadiazoles can be obtained by cyclization of amidine with potassium thiocyanate and bromine (Scheme 7b).[25,26]

2.3. 5-Amino-1,2,4-thiadiazole-3-one (III)

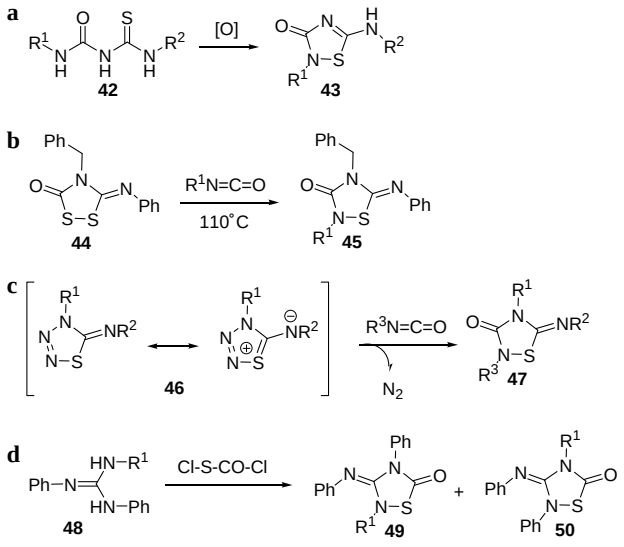
5-Amino-1,2,4-thiadiazole-3-ones can be obtained by three different routes: from cyclization of thiobiurets, from other heterocycles by reactions of cycloaddition–elimination or only addition with isocyanates and from guanidines. Some products were postulated several years ago, but in the last fourteen years, we can find an alternative synthesis or modified procedures to the same products (Scheme 8).

The synthesis of this nucleus (**43**) was achieved by ring closure of thiobiurets (**42**) in the presence of different oxidizing agents. In this way, 5-amino-1,2,4-thiadiazole-3-ones (**43**) were obtained via N–S bond formation with hydrogen peroxide in an alkaline solution.[27–29] Other oxidizing agents such as molecular bromine[30] and *N*-bromosuccinimide[31] were used for cyclization (Scheme 8a).

The 1,2,4-thiadiazole ring has been prepared from other heterocycles by a cycloaddition–elimination sequence. The reaction of 5-benzylimino-1,2,4-dithiazolidin-3-one (**44**) with isocyanates yields the corresponding 1,2,4-thiadiazole system (**45**) with elimination of carbonyl sulfide (Scheme 8b).[32]

An alternative way to obtain 5-imino-1,2,4-thiadiazole-3-ones (**47**) is by using 5-imino-1,2,3,4-thiatriazolines (**46**) as masked 1,3-dipoles with isocyanates via cycloaddition–elimination reactions (Scheme 8c).[33–35]

5-Amino-2*H*-1,2,4-thiadiazol-3-ones (**49**) and (**50**) can also be made available by reaction of substituted guanidines (**48**) with chlorocarbonyl sulfenylchloride (Scheme 8d).[36]



Scheme 8. Synthesis of 5-amino-1,2,4-thiadiazole-3-one.

2.4. 3,5-Diamino-1,2,4-thiadiazoles (IV)

Oxidation of binary mixtures of thioureas has been used as a general method for the preparation of different 1,2,4-thiadiazole derivatives via intramolecular heterocyclization processes.[37] Recently, 3,5-diamino-1,2,4-thiadiazoles (**52**) have been obtained by using [bis(acyloxy)iodo]arenes as a more specific oxidant reagent than the traditional ones (Scheme 9).[38]

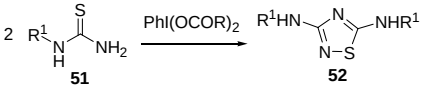
2.5. 1,2,4-Thiadiazolidine-3,5-diones (V)

Thiadiazolidinediones (**54**) were synthesized following a pathway which is based on the reactivity of *N*-alkyl-*S*-[*N*′-(chlorocarbonyl)amino]isothiocarbamoyl chlorides with isocyanates. Chlorination of *N*-alkyl or *N*-arylisothiocyanates in an inert atmosphere and subsequent reaction with *N*-alkyl or *N*-arylisocyanates produces sparingly soluble 3-oxothiadiazolium salts (**53**) via the intermediate iminochloromethylsulfenyl chloride. These heterocyclic salts are exceptionally reactive, and in the presence of moist air, it was possible to obtain through hydrolysis the 1,2,4-thiadiazolidine-3,5-diones after evolution of hydrogen chloride (Scheme 10).[39]

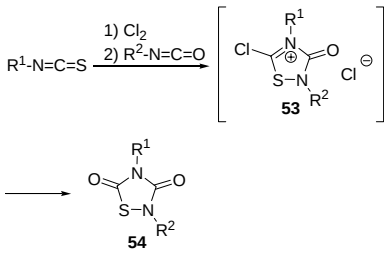
2.6. 3-Aryl/alkyl-1,2,4-thiadiazole-5-one (VI)

Usually, the preparation of 3,4-disubstituted-1,2,4-thiadiazole-5-ones (**60**) included the reaction of amidoximes (**55**) with chlorocarbonylsulfenyl chloride in the presence of base as a catalyst (Scheme 11a)[40] or the reaction with thiophosgene to afford 3,4-disubstituted 1,2,4-oxadiazoline-5-thiones (**61**), which, in the presence of a catalytic amount of copper powder, was converted into **60** (Scheme 11b).[41]

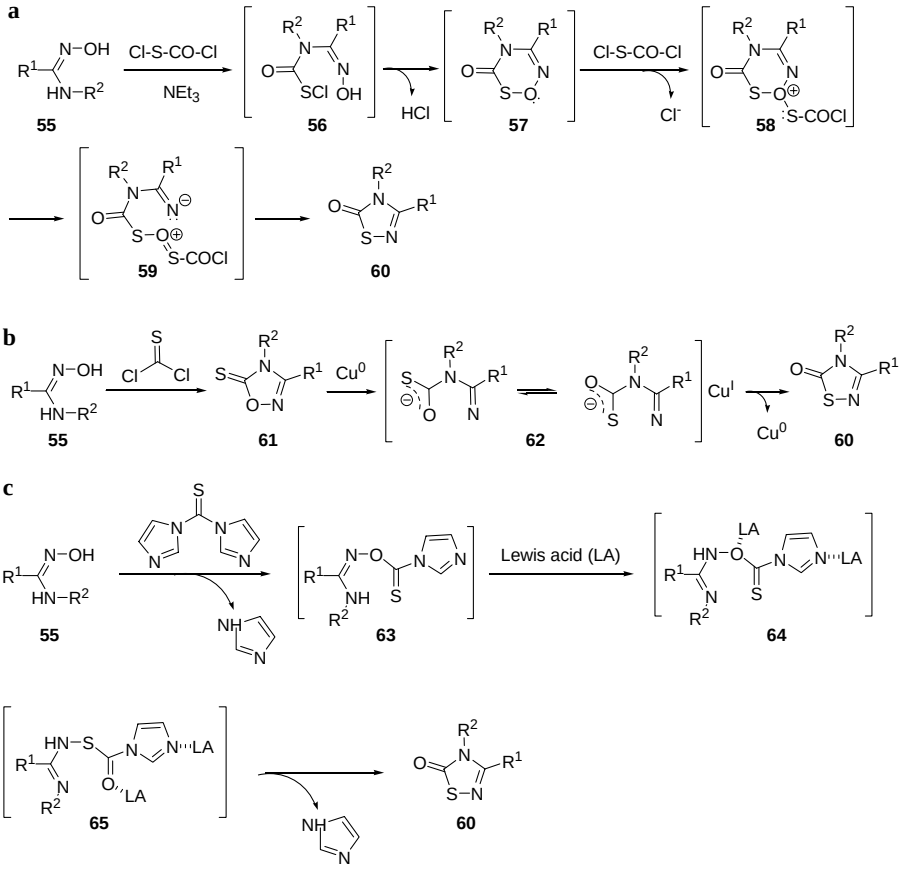
However, these methods require highly toxic reagents and often lead to a mixture of products. New methods for the synthesis of these derivatives have been developed from amidoximes by a Lewis acid-mediated rearrangement (Scheme 11c).[42] The detailed mechanisms for the synthetic procedures are all depicted in Scheme 11.



Scheme 9. Synthesis of 3,5-diamino-1,2,4-thiadiazoles.



Scheme 10. Synthesis of thiadiazolidinones through hydrolysis of iminochloromethylsulfenyl chloride.



Scheme 11. Synthesis of 3-substituted-1,2,4-thiadiazole-5-ones from amidoximes.

3. Therapeutic potential of 1,2,4-thiadiazole

During the last decade, very interesting therapeutic applications have been explored related to the 1,2,4-thiadiazole system. This nucleus is a fundamental constituent of a number of synthetic products with biological activities concerning central nervous system (CNS), G-protein coupled receptors, inflammation, cardiovascular system or antibiotic activity.

3.1. Central nervous system

One of the principal disorders of the central nervous system is the Alzheimer's disease (AD). This is a multifaceted progressive disorder characterized by a slow, progressive decline in cognitive function and behaviour. The biological mechanism underlying the formation of AD is complex, as several factors contribute to the neuropathology of the disease. Thiadiazole related compounds have been successfully described as potential drugs for the treatment of AD. The antioxidant and muscarinic receptor binding properties of 3-(thiadiazolyl)pyridine 1-oxide compounds (**66**) were reported,[43] and a family of 1,2,4-thiadiazolidinone derivatives containing the *N*-benzylpiperidine fragment (**67**) has also shown acetylcholinesterase inhibitory activity.[44] Moreover in a series of 1,2,4-thiadiazoles bearing a mono- or bicyclic amine at C5 (**68**), the ring represents an ester mimic in the binding of muscarinic ligands capable of displaying high receptor affinity over a wide efficacy

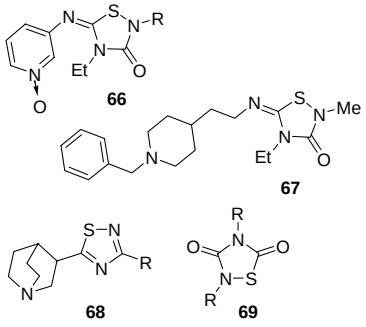


Figure 3. 1,2,4-Thiadiazole derivatives with activity in the central nervous system.

range.[45] Recently, the thiadiazolidin-3,5-dione (TDZD) derivatives (**69**)[7] were reported as the first non-ATP competitive inhibitors of glycogen synthase kinase 3β (GSK-3β). This enzyme has emerged as one of the most attractive therapeutic targets for the development of selective inhibitors as new promising drugs for unmet pathologies including Alzheimer's disease, stroke, bipolar disorders, chronic inflammatory processes, cancer and diabetes type II[46] (Fig. 3).

3.2. G-protein coupled receptors

In 2001, a novel thiadiazole compound, SCH-202676 (**70**), was identified as an allosteric modulator of a wide variety of unrelated G-protein coupled receptors

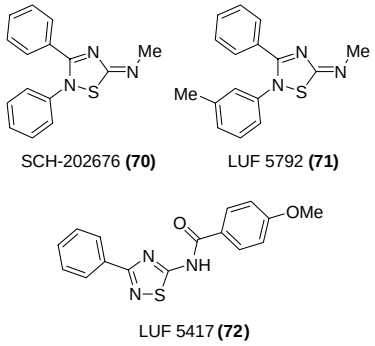


Figure 4. Allosteric modulators of adenosine receptors.

(GPCRs), including the human μ-, δ- and κ-opioid, α- and β-adrenergic, muscarinic M_1 and M_2 and dopaminergic D_1 and D_2 receptors.[4,47] Taking into account that GPCRs are a family of structurally related membrane-bound proteins that play a central role in the recognition and signal transduction of hormones and neurotransmitters, the allosteric modulation of GPCRs is an interesting pharmacological concept relatively novel and unexplored.

Adenosine receptors also belong to the superfamily of G-protein coupled receptors. By activation of these specific cell membrane receptors, extracellular adenosine regulates a number of physiological functions. Interestingly, SCH-202676 (**70**) modulates also adenosine A1, A2A and A3 receptors,[48] although derivative LUF 5792 (**71**) has proved to be more active than the reference compound as an allosteric inhibitor of agonist binding to human A1 receptors.[22] Recently, a new series of SCH-202676 (**70**) were synthesized with different *N*-imino substituents and the results of receptor–ligand binding experiments and stability studies by HPLC and HPLC–MS showed that these compounds are highly reactive sulfhydryl modifying agents rather than allosteric inhibitors.[49]

Furthermore, adenosine A3 receptor has been determined to show important roles in physiological systems, and antagonists may be useful in the treatment of inflammatory disease, such as asthma and glaucoma. Due to the fact that thiadiazolobenzamide derivatives as LUF5417 (**72**) had emerged as novel classes of adenosine receptor antagonists,[50] new analogues with more affinity and high selectivity at human adenosine A_3 receptors were identified[51] (Fig. 4).

3.3. Inflammation

Non-steroidal antiinflammatory drugs (NSAIDs) are important therapeutic agents for the treatment of pain and inflammation. However, their therapeutic use is often limited by common gastrointestinal side effects. A major mechanism of action of NSAIDs is lowering prostaglandin production through inhibition of cyclooxygenase (COX). This key enzyme in prostaglandin biosynthesis exists in two isoforms, COX-1 and COX-2. Their regulated expression suggests that a selective inhibitor of COX-2 might have antiinflammatory properties and lack gastrointestinal side effects. Prior to the discovery of these two isoforms of the COX, a number of 1,2,4-thiadiazoles containing a 2,6-di-*tert*-butylphenol substituent were identified as dual cyclooxygenase and 5-lipoxygenase inhibitors (**73**).[52] In 1999, the possibility that these compounds would be selective inhibitors of COX-2 was investigated, and the studies revealed that some members of the 1,2,4-thiadiazole series were active and selective for COX-2[53] (Fig. 5).

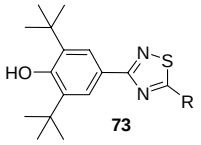


Figure 5. Dual cyclooxygenase and 5-lipoxygenase inhibitor.

3.4. Cardiovascular system

Drugs that affect the cardiovascular system functions could exert their effects on either the blood vessels or the heart itself. Among the thiadiazoles that act on cardiovascular system, KC 12291 (**74**) has shown cardioprotective actions because of the inhibition of voltage-gated Na^+ channels. The delay in ischaemia-induced Na^+ overload by KC 12291 (**74**) is cardioprotective upon reperfusion on a structural, metabolic and functional level.[5,6]

Remarkable antiplatelet and anticoagulant activities have been seen in 3,3′-benzene-bis-(and tris)-1,2,4-thiadiazolimines. This action is strongly dependent on the structure of the rest in 2-position of the 1,2,4-thiadiazole moiety. In fact, the most potent compound was the 3-phenylpropyl derivative **75**.[54] Besides, 5-oxo-1,2,4-thiadiazoles (**76**) were evaluated for in vitro and in vivo angiotensin II receptor antagonistic activities and also these derivatives showed efficient oral bioavailability[55] (Fig. 6).

3.5. Antibiotic activity

Methicilin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* are nosocomial pathogens associated with serious infections and considerable

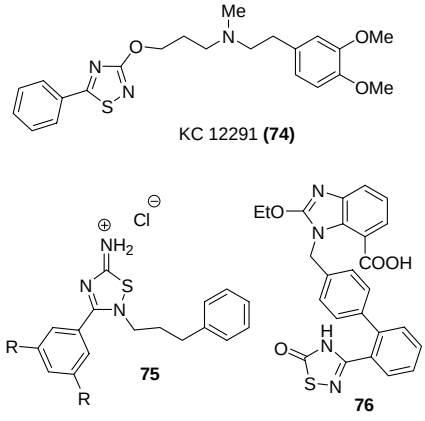


Figure 6. Relevant 1,2,4-thiadiazole derivatives with activity in the cardiovascular system.

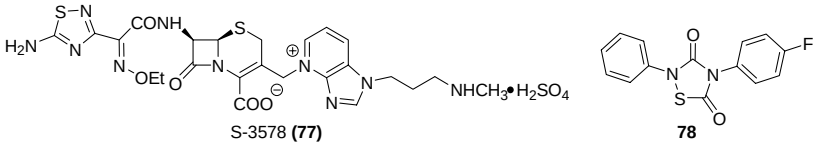


Figure 7. Novel antibiotic-based 1,2,4-thiadiazole compounds.

mortality. Although broad-spectrum cephalosporins have been useful against various infectious diseases, they are not active against MRSA. With the aim of developing a broad-spectrum cephalosporin, new β-lactams bearing various condensed-heterocycles were reported. Interestingly, improvement of antipseudomonal and anti-MRSA activities was accomplished by introducing a 5-amino-1,2,4-thiadiazol-3-yl moiety and hydroxyimino group as C-7 substituent.[56,57] A novel cephalosporin S-3578 (**77**) was selected because of its antibacterial activity, aqueous solubility and crystallinity.[58,59] It showed an extremely potent activity against Gram-positive bacteria including MRSA and Gram-negative bacteria including *P. aeruginosa*. Related to it, novel C-3′ condensed-heterocyclic pyridinium cephems were prepared in order to enhance its antibacterial spectrum and water solubility.[60,61]

The emergence of phatogenic bacteria that are resistant to current antibiotic therapies has prompted renewed interest in identifying novel molecular targets for new antibacterials. For example, the dihydroorotate dehydrogenase (DHOase), a critical enzyme of de novo pyrimidine biosynthesis, represents a valuable target for the development of novel antibiotic compounds. Thiadiazolidinediones (**78**) represent the first examples of potent and selective inhibitors of bacterial DHOases[62] (Fig. 7).

3.6. Miscellaneous

Besides the biological activities previously described, a variety of effects have been described for the 1,2,4-thiadiazole moiety as a result of different drug discovery programs. The biological screening of corporate collections led to the discovery of new lead compounds with a directed mechanism-based. 4-(Diethoxyphosphoryl)-methyl-*N*-(3-phenyl-[1,2,4]-thiadiazol-5-yl)benzamide (**79**) acted as a potent mesangial cell proliferation inhibitor,[63] 6-(1,2,4-thiadiazol-5-yl)-3-amino pyridazine derivatives (**80**) were identified as novel angiogenesis inhibitors[64] and 2,3-diaryl-5-anilino-[1,2,4]-thiadiazolium bromide (**81**) as a melanocortin-4 receptor agonist.[65]

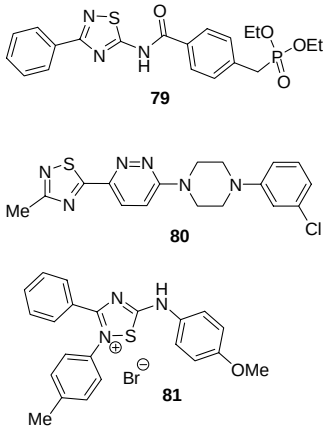


Figure 8. 1,2,4-Thiadiazole derivatives with a variety of effects.

Also, 1,2,4-thiadiazole derivatives are a distinctive class of small heterocyclic thiol trapping agents that serve as an interesting pharmacophore in the design of inhibitors targeting the cysteine residues of proteins.[8] Recently, new inhibitors of thiol-dependent enzymes as *trans*-glutaminases[66] or cathepsin B[67] inhibitors have been described (Fig. 8).

4. Conclusions

The synthesis of 1,2,4-thiadiazole heterocycles that have been reported to date illustrates different approaches to the challenge of preparing these bioactive products and allows the synthesis of many novel chemical derivatives. In general, 1,2,4-thiadiazole derivatives are prepared by appropriate intra- or intermolecular ring closure reactions and the substituents are then modified as required. A common procedure for their synthesis is the oxidative formation of the 1,2,4-thiadiazole ring by using a variety of oxidant reagents. Particularly useful is the thermolysis of different five-membered rings.

Cycloaddition/elimination reactions and also rearrangement have been widely used as synthetic routes.

The area of the synthesis of 1,2,4-thiadiazole rings continues to grow, and the organic chemistry will provide more and better methods for the synthesis of this interesting heterocycle, allowing the discovery of new drug candidates more active, more specific and safer.

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References and notes

1. Iizawa, Y.; Okonogi, K.; Hayashi, R.; Iwahi, T.; Yamazaki, T.; Imada, A. *Antimicrob. Agents Chemother.* **1993**, *37*, 100.

2. Kurzer, F. *Adv. Heterocycl. Chem.* **1982**, *32*, 285.
3. Franz, J. E.; Dhingra, O. P. In *Comprehensive Heterocyclic Chemistry. Five Membered Rings with Two or More O, S or N Atoms*; Katritzky, A. R., Rees, Ch. W., Eds.; V G Pergamon, 1984; pp 463–511.
4. Fawzi, A. B.; Macdonald, D.; Benbow, L. L.; Smith-Torhan, A.; Zhang, H. T.; Weig, B. C.; Ho, G.; Tulshian, D.; Linder, M. E.; Graziano, M. P. *Mol. Pharmacol.* **2001**, *59*, 30.
5. Decking, U. K. M.; Hartmann, M.; Rose, H.; Bruckner, R.; Meil, J.; Schrader, J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1998**, *358*, 547.
6. Hartmann, M.; Decking, U. K. M.; Schrader, J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1998**, *358*, 554.
7. Martínez, A.; Alonso, M.; Castro, A.; Pérez, C.; Moreno, F. J. *J. Med. Chem.* **2002**, *45*, 1292–1299.
8. Tam, T. F.; Leung-Toung, R.; Li, W.; Spino, M.; Karimian, K. *Mini Rev. Med. Chem.* **2005**, *5*, 367.
9. Hofmann, A. W.; Gabriel, S. *Ber* **1892**, *25*, 1578.
10. Miotti, U. *J. Chem. Soc., Perkin Trans. 2* **1991**, 617.
11. Forlani, L.; Boga, C. *J. Chem. Soc., Perkin Trans. 2* **2002**, 768.
12. McKie, M. C.; Paton, R. M. *ARKIVOC* **2002**, *6*, 15.
13. Unangst, P. C.; Shurum, G. P.; Connor, D. T. *J. Heterocycl. Chem.* **1993**, *30*, 357.
14. Paton, R. M. *Chem. Soc. Rev.* **1989**, *18*, 33.
15. Lin, Y.; Lang, S. A.; Petty, S. R. *J. Chem. Soc.* **1980**, *45*, 3750.
16. Pavlik, J. W.; Changtong, C.; Tantayanon, S. *J. Heterocycl. Chem.* **2002**, *39*, 237.
17. Rosenbaum, K.; Goldenberg, S.; Weber, G. *J. Prakt. Chem.* **1992**, *334*, 283.
18. Tatsuta, K.; Miura, S.; Gunji, H.; Tamai, T.; Yoshida, R.; Inagaki, T.; Kurita, Y. *Bull. Chem. Soc. Jpn.* **1994**, *1701*.
19. Molotov, S. I.; Kulikov, A. S.; Makhova, N. N.; Lyssenko, K. A. *Mendeleev Commun.* **2003**, *4*, 188.
20. Vivona, N.; Buscemi, S.; Asta, S.; Caronna, T. *Tetrahedron* **1997**, *53*, 12629.
21. Goerdeler, J.; Löbach, W. *Chem. Ber.* **1979**, *112*, 517.
22. van den Nieuwendijk, A. M. C. H.; Pietra, D.; Heitman, L.; Göblyös, A.; Ijzerman, A. P. *J. Med. Chem.* **2004**, *47*, 663.
23. Fuchigami, T.; Odo, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 310.
24. Sonnenschein, H.; Walek, W.; Schmitz, E.; Reck, G. *Liebigs Ann. Chem.* **1992**, *287*.
25. Smith, C. W.; Chakrabarti, J. K.; Williamson, W. R. N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1673.
26. Yoshida, Y.; Matsuda, K.; Sasaki, H.; Matsumoto, Y.; Matsumoto, S.; Tawara, S.; Takasugi, H. *Bioorg. Med. Chem.* **2000**, *8*, 2317.
27. Párkányi, C.; Yuan, H. L.; Cho, N. S.; Jaw, J.-H. J.; Woodhause, T. E.; Aung, T. L. *J. Heterocycl. Chem.* **1989**, *26*, 1331.
28. Cho, N. S.; Shon, H. I.; Párkányi, C. *J. Heterocycl. Chem.* **1991**, *28*, 1645.
29. Pískala, A.; Vachálková, A.; Masojídková, M.; Horváthová, K.; Ovesná, Z.; Pačes, V.; Novotný, L. *Pharmazie* **2004**, *59*, 756.
30. Cho, N. S.; Shon, H. I.; Párkányi, C. *J. Heterocycl. Chem.* **1991**, *28*, 1725.
31. Singh, R.; Choubey, A. K.; Bhattacharya, A. *J. Indian Chem. Soc.* **1998**, *75*, 430.
32. L'abbé, G.; Vandendriessche, A. *J. Heterocycl. Chem.* **1990**, *27*, 1629.
33. L'abbé, G.; Weyns, N. *Bull. Soc. Chim. Belg.* **1991**, *100*, 185.
34. L'abbé, G.; Weyns, N.; Sannen, I.; Delbeke, P.; Toppet, S. *J. Heterocycl. Chem.* **1991**, *28*, 405.
35. Kaugars, G.; Atherton, J. P.; Han, F. *J. Org. Chem.* **1992**, *57*, 1671.
36. Tittelbach, F.; Schellhaas, A. *J. Prakt. Chem.* **1992**, *334*, 685.
37. Joshua, C. P.; Sujatha, T. S. *Indian J. Chem.* **1990**, *29B*, 575.
38. Mamaeva, E. A.; Bakibaev, A. A. *Tetrahedron* **2003**, *59*, 7521.
39. Ottman, G.; Hooks, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 672.
40. Kawashima, E.; Ando, Y.; Takada, T.; Tabei, K. *Heterocycles* **1987**, *26*, 181.
41. Sümengen, D.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 687.
42. Kohara, Y.; Kubo, K.; Imamiya, E.; Naka, T. *J. Heterocycl. Chem.* **2000**, *37*, 1419.
43. Martínez, A.; Alonso, D.; Castro, A.; Arán, V. J.; Cardelus, I.; Baños, J. E.; Badía, A. *Arch. Pharm.* **1999**, *332*, 191.
44. Martínez, A.; Fernández, E.; Castro, A.; Conde, S.; Rodríguez-Franco, I.; Baños, J. E.; Badía, A. E. *J. Med. Chem.* **2000**, *35*, 913.
45. Macleod, A. M.; Baker, R.; Freedman, S. B.; Patel, S.; Merchant, K. J.; Roe, M.; Saunders, J. *J. Med. Chem.* **1990**, *33*, 2052.
46. Alonso, M.; Martínez, A. *Curr. Med. Chem.* **2004**, *11*, 755.
47. Lanzafame, A.; Christopoulos, A. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 830.
48. Gao, Z. G.; Gross, A. S.; Jacobson, K. A. *Life Sci.* **2004**, *74*, 3173.
49. Göblyös, A.; de Vries, H.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2005**, *48*, 1145.
50. van Muijlwijk-Koezen, J. E.; Timmerman, H.; Vollinga, R. C.; Kunzel, J. F. V.; de Groote, M.; Visser, S.; Ijzerman, A. P. *J. Med. Chem.* **2001**, *44*, 749.
51. Jung, K. Y.; Kim, S. K.; Gao, Z. G.; Gross, A. S.; Melman, N.; Jacobson, K. A.; Kim, Y. C. *Bioorg. Med. Chem.* **2004**, *12*, 613.
52. Unangst, P. C.; Shrum, G. P.; Connor, D. T.; Dyer, R. D.; Schrier, D. J. *J. Med. Chem.* **1992**, *35*, 3691.
53. Song, Y. T.; Connor, D. T.; Sercel, A. D.; Sorenson, R. J.; Doubleday, R.; Unangst, P. C.; Roth, B. D.; Beylin, V. G.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem.* **1999**, *42*, 1161.
54. Rehse, K.; Martens, A. *Arch. Pharm.* **1993**, *326*, 399.
55. Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228.
56. Hara, R.; Sakamoto, K.; Hisamichi, H.; Nagano, N. *J. Antibiot.* **1996**, *49*, 1162.
57. Ishikawa, T.; Iizawa, Y.; Okonogi, K.; Miyake, A. *J. Antibiot.* **2000**, *53*, 1053.
58. Fujimura, T.; Yamano, Y.; Yoshida, I.; Shimada, J.; Kuwahara, S. *Antimicrob. Agents Chemother.* **2003**, *47*, 923.
59. Miyazaki, S.; Okazaki, K.; Tsuji, M.; Yamaguchi, K. *Antimicrob. Agents Chemother.* **2004**, *48*, 378.
60. Yoshizawa, H.; Kubota, T.; Itani, H.; Ishitobi, H.; Miwa, H.; Nishitani, Y. *Bioorg. Med. Chem.* **2004**, *12*, 4211.
61. Yoshizawa, H.; Kubota, T.; Itani, H.; Minami, K.; Miwa, H.; Nishitani, Y. *Bioorg. Med. Chem.* **2004**, *12*, 4221.
62. Marcinkeviciene, J.; Rogers, M. J.; Kopcho, L.; Jiang, W.; Wang, K.; Murphy, D. J.; Lippy, J.; Link, S.; Chung, T. D. Y.; Hobbs, F.; Haque, T.; Trainor, G. L.; Slee, A.; Stern, A. M.; Copeland, R. A. *Biochem. Pharmacol.* **2000**, *60*, 339.
63. Kurogi, Y.; Miyata, K.; Okamura, T.; Hashimoto, K.; Tsutsumi, K.; Nasu, M.; Moriyasu, M. *J. Med. Chem.* **2001**, *44*, 2304.

64. Bongartz, J. P.; Stokbroekx, R.; van der Aa, M.; Luyckx, M.; Willems, M.; Ceusters, M.; Meerpoel, L.; Smets, G.; Jansen, T.; Wouters, W.; Bowden, C.; Valletta, L.; Herb, M.; Tominovich, R.; Tuman, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 589.
65. Pan, K.; Scott, M. K.; Lee, D. H. S.; Fitzpatrick, L. J.; Crooke, J. J.; Rivero, R. A.; Rosenthal, D. I.; Vaidya, A. H.; Zhao, B. Y.; Reitz, A. B. *Bioorg. Med. Chem.* **2003**, *11*, 185.
66. Marrano, C.; de Macédo, P.; Gagnon, P.; Lapierre, D.; Gravel, C.; Keillor, J. W. *Bioorg. Med. Chem.* **2001**, *9*, 3231.
67. Leung-Toung, R.; Wodzinska, J.; Li, W.; Lowrie, J.; Kukreja, R.; Desilets, D.; Karimian, K.; Tam, T. F. *Bioorg. Med. Chem.* **2003**, *11*, 5529.