The new era of 1,2,4-oxadiazoles†

Andrea Pace* and Paola Pierro

Received 6th May 2009, Accepted 11th August 2009
First published as an Advance Article on the web 16th September 2009
DOI: 10.1039/b908937c

The synthesis, the chemical and photochemical reactivity, and the use of 1,2,4-oxadiazoles in materials and as bioactive compounds have been reviewed. The material in this survey includes some historical background, general features, state-of-the-art applications together with a critical discussion about current limitations and suggestions for future developments.

Introduction

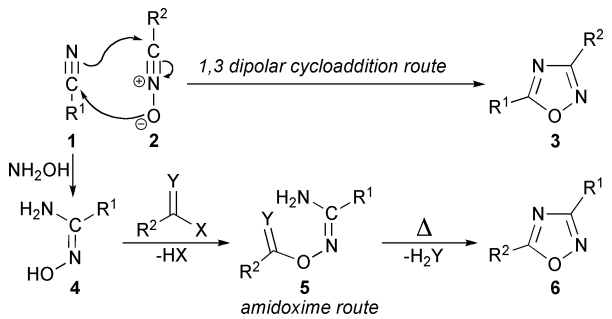
The first synthesis of 1,2,4-oxadiazoles, initially named furo[ab$_1$]diazoles, was achieved 125 years ago by Tiemann and Krüger.[1] Since then, and until the early 1960's, only a few articles were occasionally published on this five-membered heterocyle. In the next decade, 1,2,4-oxadiazoles, mostly because of their peculiar tendency to undergo molecular rearrangements, gained a lot of interest in the chemistry community. In recent years the increased rate of publication on 1,2,4-oxadiazoles points to a revitalized interest fuelled by the use of this heterocycle in medicinal chemistry and in new materials. 1,2,4-Oxadiazole's rich chemistry has been reviewed several times,[2] the latest of which covered 1997–2006 literature, with only two 2007 articles cited.[2a] For these reasons, without any intention to write an exhaustive review, we decided to present an organized discussion of current strategies about the synthesis and reactivity of 1,2,4-oxadiazoles and their use in materials or as bioactive compounds with a touch of historical background, an overview of the state-of-the-art research and some insights for future developments.

Dipartimento di Chimica Organica "E. Paternò", Viale delle Scienze–Parco d'Orleans II–Edificio 17, Palermo, 90128 Italy. E-mail: pace@unipa.it; Fax: +39 091 596825; Tel: +39 091 596903

† On the occasion of his 70th birthday, this article is dedicated to Professor Nicolò Vivona, who devoted his scientific life to 1,2,4-oxadiazoles and instilled in the authors the passion for this heterocycle.

Synthesis of 1,2,4-oxadiazoles

"Give me a nitrile and I will build you a 1,2,4-oxadiazole!" This sentence humorously summarizes the two most common routes among the known synthetic strategies to obtain 1,2,4-oxadiazoles[2] (Scheme 1): (i) the 1,3-dipolar cycloaddition of nitriles **1** to nitrile oxides **2**; (ii) the cyclization of amidoxime derivatives **5**. The latter compound, in fact, can be easily prepared by reaction of nitriles **1** with hydroxylamine followed by reaction with activated carboxylic acids or a wide variety of their derivatives including amidoxime itself. One of the main advantages of these strategies is their complementarity. In fact, depending on the approach used, the nitrile precursor substituent (R^1 in the scheme) can end up being linked at either C(5), as in **3**, or C(3), as in **6**, of the final



Scheme 1 Common synthetic strategies towards 1,2,4-oxadiazoles.

Andrea Pace

Andrea Pace was appointed Assistant Professor of Organic Chemistry at the University of Palermo in 1997. He joined the research group of Prof. Vivona working on heterocyclic chemistry. Tenured in 2000, between 2001 and 2003 he joined the group of Prof. Clennan at the University of Wyoming. His current interests regard heterocycles, photochemistry, fluorinated molecules, and intrazeolite reactions.

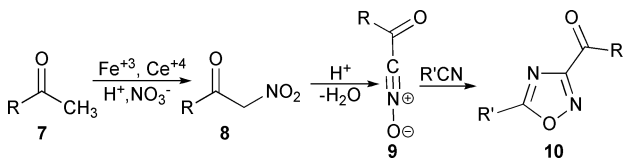
Paola Pierro

Paola Pierro graduated in Chemistry and Pharmaceuticals Technologies in 1998 and received her PhD in Technologies of Bioactive Compounds in 2005 from the University of Palermo. In Palermo, she worked as a post-doc investigating polymerization in supercritical CO_2, synthesis of hydrogels and synthesis of heterocyclic compounds in constrained media. She is mother of Mattia born during the preparation of this review.

1,2,4-oxadiazole. On the other hand, the main limitation is that the choice between these two or other alternative methods is often a matter of the precursors' availability, which sometimes could be compromised by the need for a particular functional group on the final heterocycle. In this chapter, the synthesis of either 3,5-diaryl- or 3,5-dialkylsubstituted 1,2,4-oxadiazoles will not be discussed since it is generally straightforward due to the commercial availability of a wide variety of alkanoates, substituted benzoate esters, alkanoyl or aroyl chlorides, as well as the corresponding nitriles.

Keto-1,2,4-oxadiazoles

Aside from being biologically active themselves,[3] α-keto-1,2,4-oxadiazoles also present an important linking site, for instance, for terminal amino groups of biologically important molecules. By using orthogonal protecting groups, a library of 3-keto-1,2,4-oxadiazole antiasthmatics has been obtained through the amidoxime route. The carbonyl functionality was formed in the last steps by liberating a TBS-protected secondary alcohol and oxidation with Dess–Martin periodinane.[3a] An interesting alternative involves the one-pot synthesis of 3-acyl-1,2,4-oxadiazole **10** by reaction of a methyl ketone with a nitrile in the presence of iron(III) nitrate. Similar to the Mukaiyama–Hoshino method, the proposed mechanism involves an initial α-nitration of the ketone **7** followed by loss of water to form the nitrile oxide **9** *in situ* which will cyclize with the nitrile (Scheme 2).[4] A recent example involving 5-keto-1,2,4-oxadiazoles as anti-inflammatory agents has been reported.[3b]



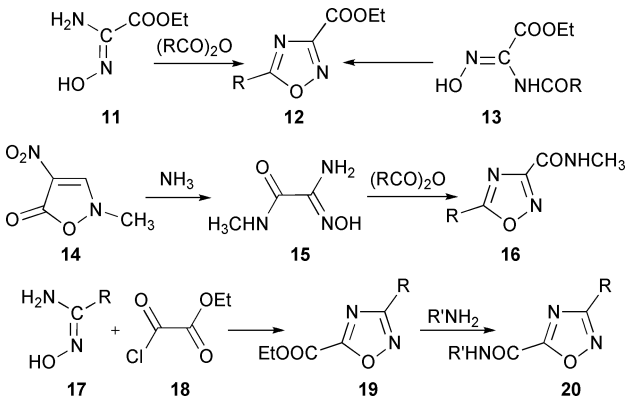
Scheme 2 One-pot synthesis of 3-keto-1,2,4-oxadiazoles.

Ethoxycarbonyl- and carbamoyl-1,2,4-oxadiazoles

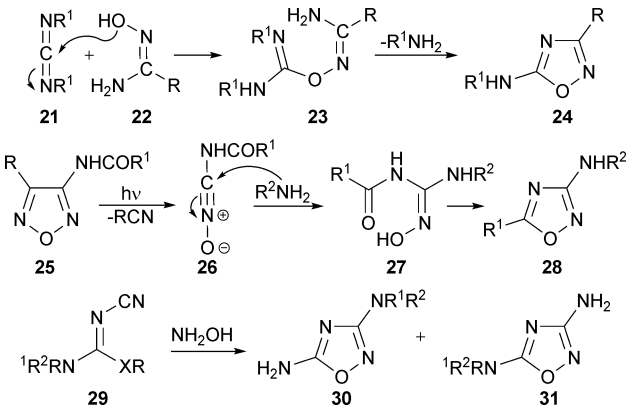
These compounds are very useful precursors for further modification of the side chains. 3-Ethoxycarbonyl derivatives **12** can be synthesized from either amidoxime **11**, by reaction with anhydrides,[5] or *N*-acylamidoxime **13** (Scheme 3).[6] 3-Carbamoyl derivatives **16** can be obtained from nitroisoxazolone **14** by generating the amidoxime **15** which then reacts with anhydrides.[7] 5-Ethoxycarbonyl derivatives **19**, instead, can be synthesized by reacting the desired amidoxime with ethyl oxalyl chloride.[8] The aminolysis of the resulting oxadiazole produces 5-carbamoyl derivatives **20**.[8]

Amino-1,2,4-oxadiazoles

A variety of methods,[2f,9] not all for general application, have been reported for the synthesis of amino-1,2,4-oxadiazoles. Among these, cyclization of amidoxime with carbodiimdes[9a] (Scheme 4) and aromatic nucleophilic substitution (SN_{Ar}) of 5-trichloromethyl-1,2,4-oxadiazoles[9b,9c] appear to be the most convenient routes to 5-amino-1,2,4-oxadiazoles **24**. In turn, 3-amino-1,2,4-oxadiazoles **28** can be achieved by photochemical reaction



Scheme 3 Syntheses of ethoxycarbonyl- and carbamoyl-1,2,4-oxadiazoles.



Scheme 4 Examples of amino-1,2,4-oxadiazoles syntheses.

of 3-acylamino-1,2,5-oxadiazoles **25**[9e] in the presence of amines. 3,5-Diamino derivatives **30** and **31** can be synthesized by the reaction of 3-cyanoisothioureas **29** (X = S) with hydroxylamine.[9g] Similarly, a recent microwave assisted reaction between *N*-cyano-*O*-phenylisoureas **29** (X = O) and hydroxylamine produced 3-arylalkoxyamino-5-amino-1,2,4-oxadiazoles in good yields.[9h]

Fluorinated 1,2,4-oxadiazoles

Fluorinated azoles are important heterocycles with application in both the pharmaceutical industry and new materials science. The synthesis of fluorinated 1,2,4-oxadiazoles was reviewed in 2005[10] and, more recently, various 3-substituted 5-pentafluorophenyl-1,2,4-oxadiazoles **32** (Fig. 1) have been used as fluorinated oxadiazole arylating reagents (FOXARs)[11] for the attachment of fluorinated moieties to nucleophilic pendants of polymers[12] and macromolecules.[13] Fluorinated 1,2,4-oxadiazoles **33** (Fig. 1) have been employed, in the presence of sodium dithionite, as reagents to introduce the difluoromethylene moiety into organic

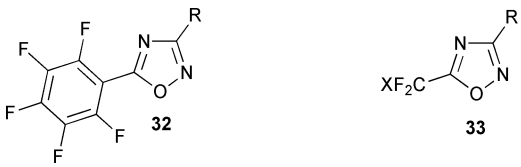


Fig. 1 Examples of fluorinated 1,2,4-oxadiazoles reagents.

compounds.[14] To date, there is still no literature on the synthesis of 1,2,4-oxadiazoles bearing a fluorine atom directly linked to the heterocyclic ring.

Chirally substituted 1,2,4-oxadiazoles

Chirality in 1,2,4-oxadiazole based molecules is important to confer new properties to light interacting materials[15] and increase selectivity as bioactive molecules.[5,16] In this context, while the introduction of elicity into 1,2,4-oxadiazole systems remains relatively unexplored, the direct linkage of a chiral center into 1,2,4-oxadiazoles can be easily achieved using a *N*-protected activated amino acid as a source for the C(5)[16] such as in the case of compound **34** bearing two chiral orthogonally protected amino moieties (Fig. 2).[17]

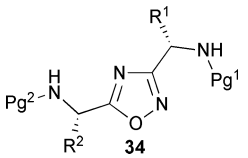
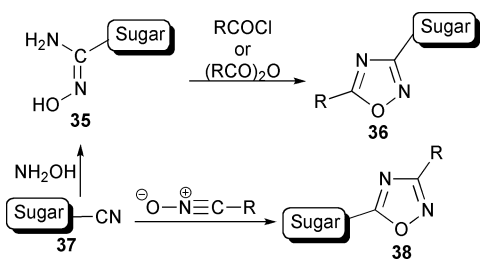


Fig. 2 An example of orthogonally protected chiral 1,2,4-oxadiazoles.

Sugar-linked 1,2,4-oxadiazoles

In addition to introducing chirality, the linking of carbohydrate moieties to bioactive 1,2,4-oxadiazoles is important for improving their pharmacological properties such as increasing their water solubility. Easily accessible sugar cyanohydrins **37** can be used as 1,2,4-oxadiazole synthons in the amidoxime route, producing 3-glycosyl-1,2,4-oxadiazoles **36**,[18] or in the cycloaddition with nitrile oxides, yielding 5-glycosyl derivatives **38** (Scheme 5).[19]



Scheme 5 Synthesis of directly-linked glycosyl-1,2,4-oxadiazoles.

Recently, the synthesis of 1,2,4-oxadiazole linked to a carbohydrate through a 1,2,3-triazole spacer has been achieved from either azidoglycosides or azidophenyl-1,2,4-oxadiazoles.[20,21]

Heterocycle-linked 1,2,4-oxadiazoles

These represent a rather general class of compounds where the coupled heterocyclic systems may play either a complementary or a cooperative function. For instance, a given heterocycle can be introduced into a 1,2,4-oxadiazole compound to enhance or tune some of its physico-chemical properties or biological activity. Alternatively the 1,2,4-oxadiazole ring can be introduced into a heterocyclic system because of its stereoelectronic properties or as a photochemically active site. For example, 3-[(1,2,4-oxadiazol-3-yl)-methyl]-3,4-dihydropyrimidine-2(1*H*)-ones, where the 1,2,4-oxadiazole moiety has been introduced as a bioisostere of esters and amides, have been synthesized by ionic liquid-phase organic synthesis (IoLiPOS).[22]

Recent syntheses of bis(1,2,4-oxadiazole) involve various spaced bis[(1,2,4-oxadiazol)-benzaldehyde] building blocks **39**[23] (Fig. 3) and *N*,*N*′-protected bis(5-aminoalkyl-1,2,4-oxadiazol-3-yl)methane.[24] As for directly-linked systems, tris(heterocycle) **40** has been recently reported in an unprecedented combination of 1,2,3-triazole, 1,2,4- and 1,2,5-oxadiazole rings (Fig 3).[25] This, and similar poly(hererocycles) (see below), could be used as novel metal ligands in the development of metal organic frameworks (MOFs).

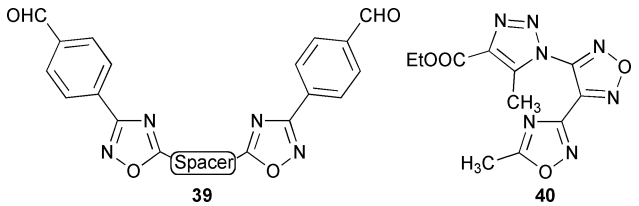


Fig. 3 1,2,4-Oxadiazole bis- and tris- heterocyclic systems.

Metal complexes of 1,2,4-oxadiazoles

Coordination compounds of 1,2,4-oxadiazoles have been occasionally reported.[2a,26–30] Complexes with the oxadiazole acting as a monodentate ligand have been obtained with Cu(II), Co(II), Zn(II), Pt(II) and Pd(II).[26] Other palladium and platinum complexes containing the 1,2,4-oxadiazole directly involved as a ligand have been synthesized by 1,3-dipolar cycloaddition of nitrile oxide on the activated nitrile metal complexes.[27] As for chelated systems, iron and copper complexes of 1,2,4-oxadiazol-3-yl-bipyridine showed similar structural features of terpyridyl complexes.[28] Surprisingly, 3,3′-bis[1,2,4-oxadiazole] **41** (Fig. 4), synthesized by Moussebois and Eloy in 1964[31] has only recently been considered as a ligand for palladium and silver complexes.[29]

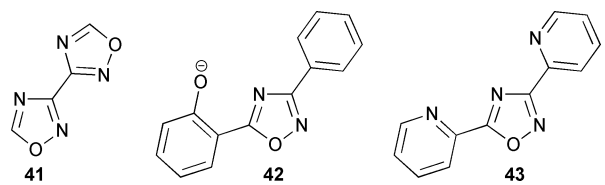


Fig. 4 Examples of 1,2,4-oxadiazole metal ligands.

Interestingly, room temperature fluorescence was observed for the Cu(II) complex of 5-(2′-oxyphenyl)-3-phenyl-1,2,4-oxadiazole **42**.[30] Most recently, copper, nickel and zinc complexes of 3,5-bis(2′-pyridyl)-1,2,4-oxadiazoles **43** have been synthesized, and their DNA-binding interactions evaluated,[32] opening the way for further studies on their anti-tumor activity.

New methodologies for the synthesis of 1,2,4-oxadiazoles

With the increasing number of applications of the 1,2,4-oxadiazole, greener, faster and higher yielding synthetic methodologies are being developed which also aim at obtaining various substituted derivatives in a library fashion. Following the first synthesis of 1,2,4-oxadiazoles under microwave irradiation,[33] modern methodologies have been used alone, or in combination with

other techniques, to improve the synthesis of this heterocycle.[2a] In 1,2,4-oxadiazole synthesis, microwaves have generally been used to facilitate the cyclocondensation of amidoxime and esters under solvent-free conditions.[34,35] In this respect, it is worth noting that the use of terms such as "microwave-induced" or "microwave-accelerated", especially when using non-controllable conditions (domestic microwave, non-homogeneous stirring, non-monitorable temperatures, *etc.*), have been strongly debated and the reaction acceleration due to either anisotropical heating or to the so-called "microwave effect" has been recently rationalized.[36] Nevertheless, if no speculative mechanistic hypothesis is proposed, this approach remains a very attractive alternative for quick *lab-bench* preparations of 1,2,4-oxadiazoles even in the absence of precise temperature measurements or homogeneous stirring.[34]

The recent achievement of a multi-step synthesis of aryl- and alkyl-substituted 1,2,4-oxadiazoles in a single continuous microreactor sequence has been an important advance in this field. The sequence used three microreactors, two of which involved solvent superheating, which allowed the synthesis of one derivative in about 30 min.[37] This very promising strategy requires further development both in terms of obtained yield of pure product and applicability toward the synthesis of other 1,2,4-oxadiazoles.

Chemical reactivity of 1,2,4-oxadiazoles

In the class of five-membered heterocyclic systems, 1,2,4-oxadiazole is among the least aromatic with an index of aromaticity $I_5 = 39$ or $I_A = 48$.[38] Therefore, the 1,2,4-oxadiazole has a high tendency to rearrange into other, more stable, heterocycles. Its thermal or photochemical reactivity is also a consequence of: (i) the labile O–N bond;[39] (ii) the electrophilic character of C(3) and C(5),[9b,40] the latter enhanced by the presence of electron-withdrawing substituents; (iii) the nucleophilic[41] or weakly basic[42] character of the pyridine-like N(4) nitrogen; (iv) the ambiphilic[43] character of N(2); (v) the ability of the ring oxygen to act as a good internal leaving-group;[44] (vi) the presence of a side-chain which might be involved in intramolecular rearrangements. These features make the 1,2,4-oxadiazole ring itself a multi-functional heterocycle (Fig. 5) whose reactivity strongly depends on the type of substituents, reagents and reaction media used.

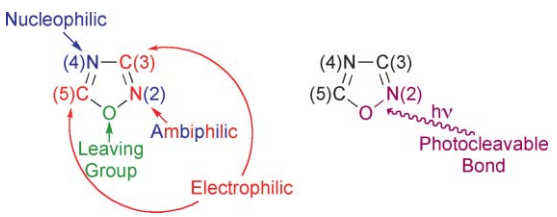
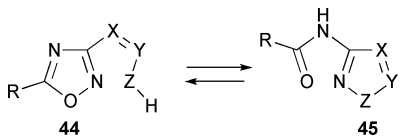


Fig. 5 Chemical and photochemical features of 1,2,4-oxadiazole.

Thermal reactions

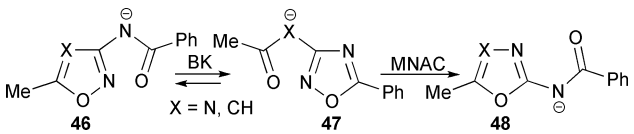
Aside from reduction occurring at either the N–O or the C–O bond[45] and pyrolytic fragmentation,[46] reactions of 1,2,4-oxadiazoles can be classified as follows.

Reactions at the electrophilic N(2). Despite the weakness of the O–N bond and the electron-withdrawing character of O(1) coupled with its good leaving-group ability, no reaction is known where the N(2) nitrogen of the 1,2,4-oxadiazole is attacked by an external nucleophile. The latter, in fact, would usually prefer to react with the C(5) or the C(3) electrophilic sites. Nevertheless, in the presence of a nucleophilic center in the C(3)-linked side-chain, the 1,2,4-oxadiazole can undergo several intramolecular ring rearrangements involving a nucleophilic attack on N(2) and the cleavage of the O(1)–N(2) bond. A classical rearrangement is represented by the so called Boulton–Katritzky (BK) reaction[47] whose general pattern for 1,2,4-oxadiazoles **44** is illustrated in Scheme 6.



Scheme 6 General BK rearrangement of 1,2,4-oxadiazoles.

Besides the ring-degenerate rearrangement involving an X–Y–Z = N–C–O side-chain and transforming a 1,2,4-oxadiazole into another 1,2,4-oxadiazole,[48] several other BK reactions of 1,2,4-oxadiazoles bearing a C–N–O, C–C–O, N–C–S, N–C–C, C–C–N, C–N–N, N–C–N and N–N–N C(3)-linked side-chains have been reported.[49] A recent example involves the reaction of 3-amino-5-phenyl-1,2,4-oxadiazoles with fluorinated β-diketones in the presence of Montmorillonite-K10. Here, the formation of final imidazoles is the result of an acid-catalyzed BK reaction involving a N–C–C side-chain.[50] Interestingly, 1,2,4-oxadiazoles produced by BK rearrangement of some arylazofuroxans, are proposed as key intermediates in cascade BK–BK rearrangements leading to a series of 1,2,3-triazoles.[51] This ancillary feature of 1,2,4-oxadiazoles has been confirmed by both theoretical and experimental data in two other base- and thermally-induced cascade rearrangements involving a BK and a migration–nucleophilic attack–cyclization (MNAC) reaction sequence (Scheme 7).[52] The first one involves the transformation of the anion of 3-benzoylamino-1,2,4-oxadiazoles **46** (X = N) into that of 2-benzoylamino-1,3,4-oxadiazoles **48** (X = N) (Scheme 7).[52a] The second one involves the isoxazole-to-oxazole rearrangement between **46** (X = CH) and **48** (X = CH) involving the formation of the less stable, but isolable, 1,2,4-oxadiazole **47** (X = CH).[52b]

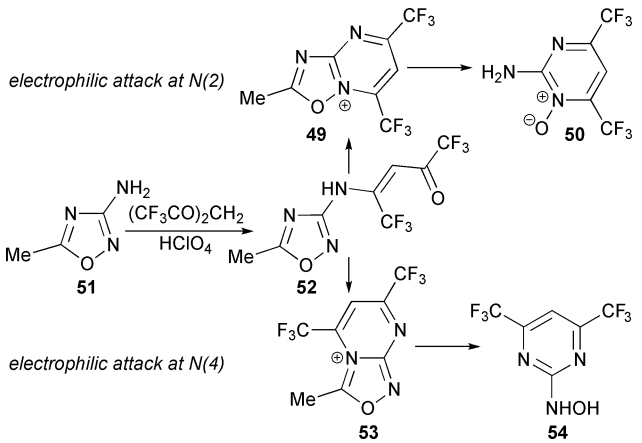


Scheme 7 Cascade BK–MNAC rearrangements of 1-oxa-2-azoles.

From a mechanistic point of view, the most studied BK reaction is the transformation of the arylhydrazones of 3-aroyl-1,2,4-oxadiazoles. This rearrangement has been thoroughly investigated by Spinelli and coworkers as a function of the reaction environment and substituent effects. Recent studies involve the reactivity in cyclodextrins,[53] in ionic liquids[54] and in the gas phase.[55] The plethora of data collected about this rearrangement allowed its applicative use as a probe reaction to gather information about new reaction media.[55d]

Reactions at the nucleophilic N(2). Because of the inductive effect of the O(1), the lone pair electrons of N(2) are not easily

available to undergo an electrophilic attack. Nevertheless, one cannot exclude that, in the presence of favorable stereoelectronic conditions and strong electrophiles, the N(2) might be involved as a base,[42] a ligand, for example in chelated systems,[56] or a nucleophilic center.[41] In the only example of the latter case, N(2) competes with N(4) for the intramolecular reaction with the electrophilic site on the C(3)-linked side-chain. In fact, differently from the 5-phenyl derivative,[41] the reaction of 3-amino-5-methyl-1,2,4-oxadiazole with a series of fluorinated β-diketones in the presence of $HClO_4$, yields 2-amino-pyrimidine-*N*-oxides **50** and 2-hydroxyamino-pyrimidine **54** through two isomeric bicyclic cationic intermediates **49** and **53**, respectively (Scheme 8).[41]

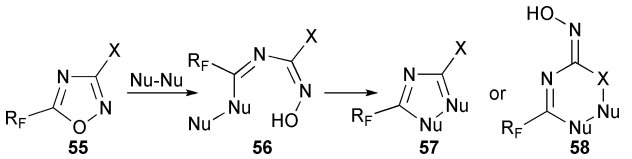


Scheme 8 Reactions involving N(2) and N(4) as nucleophilic sites.

Reactions at the electrophilic C(3). If compared to C(5), the C(3) is a much weaker electrophilic center. Therefore SN_{Ar} reactions in this position may occur only in the presence of good leaving-groups such as chlorine.[2d] Nevertheless, the C(3) can be considered as an *in fieri* electrophilic center especially in reactions with bidentate nucleophiles involving ring-opening and subsequent cyclization.[39]

Reactions at the nucleophilic N(4). Even though the 1,2,4-oxadazole is highly resistant to electrophilic attack,[2] the N(4) remains the preferred site for the reaction with external electrophilic reagents. Therefore, protonation,[42] and metal complexation[28] of 1,2,4-oxadiazoles usually involve the N(4) position. This site can also be involved in intramolecular rearrangements as discussed above (Scheme 8).[41]

Reactions at the electrophilic C(5). Due to the electron-withdrawing effect of both O(1) and N(4), the C(5) position is the most electrophilic site of the 1,2,4-oxadiazole.[2] Therefore, in the presence of a variety of leaving-groups, SN_{Ar} reactions can easily take place.[2d] Moreover, through its C(5) position, the 1,2,4-oxadiazole can activate vinyl[57] and fluoroaryl[10–13,58] groups towards nucleophilic attack. However, when the C(5) is linked to a perfluoroalkyl, with scarce leaving-group ability, the C(5)–O(1) bond will break as a consequence of the nucleophilic attack. This is the first step of the addition of a nucleophile–ring opening–ring closure (ANRORC) reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles **55** (Scheme 9). Depending on the nature of the 3-substituent, the cyclization step of the open-chain intermediate can involve either the C(3),[39] leading to **57**, or an electrophilic site

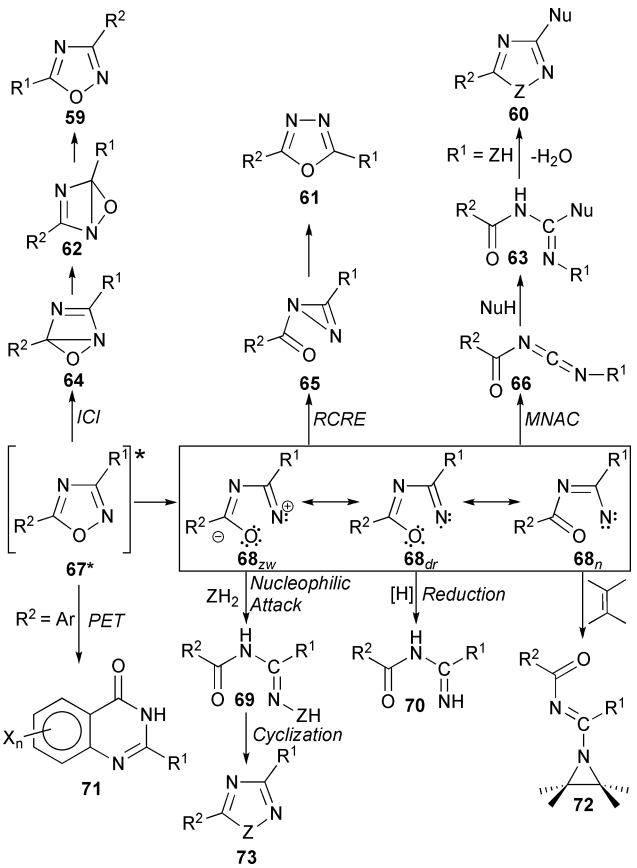


Scheme 9 ANRORC of 1,2,4-oxadiazole with bidentate nucleophiles.

of the original C(3)-linked side-chain, leading to **58**. Although many combinations of bidentate nucleophiles and substituted oxadiazoles still need to be explored, this reaction has been applied as an important synthetic strategy towards different types of perfluoroalkylated heterocycles. Very recent applications[59] of the ANRORC of 1,2,4-oxadiazoles lead to 1,2,4-triazoles carboxamides,[59a] 1,2,4-triazin-6-ones,[59a] and to 1,2,4-oxadiazin-6-ones with interesting water gelation ability.[59b]

Photochemical reactions

If Tiemann and Krüger[1] can be considered the parents of the 1,2,4-oxadiazole, Newman[60] can definitely be appointed as the pioneering father of its photochemistry later developed by Buscemi and Vivona. A recent rationale of 1,2,4-oxadiazole photoreactivity in solution is illustrated in Scheme 10.[61]



Scheme 10 General photoreactivity of 1,2,4-oxadiazoles.

Besides following the internal cyclization–isomerization (ICI) route, or undergoing a photoinduced electron transfer (PET) to produce quinazolinones **71**, the 1,2,4-oxadiazole excited state **67*** can develop into a photolytic intermediate with either a zwitterionic $\mathbf{68}_{zw}$, diradical $\mathbf{68}_{dr}$, or nitrene-like $\mathbf{68}_{n}$ character.

This species will then develop through a MNAC or a ring contraction–ring expansion (RCRE) route. Furthermore, in the presence of a nucleophilic reagent (including a solvent or a nucleophilic site in the side-chain), it can undergo a nucleophilic attack eventually followed by cyclization. If an hydrogen donor is present, the open-chain reduction product **70** is observed. Finally, the nitrene-*like* photoreactivity of 1,2,4-oxadiazoles has been very recently exploited in the presence of external or tethered alkenes.[62] Surprisingly, the RCRE, which in solution is restricted to compounds bearing a tautomerizable group (*e. g.* **67***; $R^1 = XH$) at C(3), was the main pathway observed in zeolite NaY during the irradiation of **67** ($R^1 = R^2 = Ph$).[61b]

Further developments

Due to the growing importance of 1,2,4-oxadiazoles in both materials and bioactive compounds, the study of their reactivity remains a crucial step for the assessment of their stability under the most variable environmental conditions. So far, with few recent exceptions,[53,54,61b] the reactivity of 1,2,4-oxadiazoles has been investigated mostly in solution or in homogeneous phases. In this context, a deeper study of 1,2,4-oxadiazole chemical and photochemical behaviour in organized media which may mimic either biological or nanostructured environments is needed.

1,2,4-Oxadiazoles in materials

Polymers

Polymers containing 1,2,4-oxadiazole repeating units were synthesized in the late 1960's by either 1,3-dipolar cyclization of dinitrile oxides with various dinitriles, homopolymerization of 3-cyanobenzonitrile oxide, or cyclodehydration of bisamidoximes with diacid chlorides.[63] The obtained polymers were infusible,[63b] soluble only in sulfuric acid[63b] and thermally degraded below 400 °C.[63a] The introduction of two methyl groups in the aromatic spacers of 1,2,4-oxadiazoles improved solubility but compromised thermal stability.[63b] When the 1,2,4-oxadiazoles were present as pendant groups, such as in the terpolymer **74** (Fig. 6), solubility in polar solvents improved, while thermal decomposition was still observed even at temperatures below 200 °C.[64]

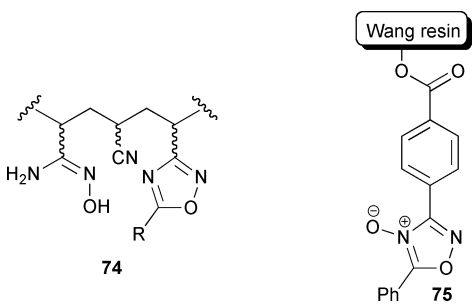


Fig. 6 Examples of 1,2,4-oxadiazole polymers.

Potential artificial oxygen carriers, based on new water-soluble fluorinated polymers, were obtained by using FOXARs[11] to introduce fluorinated pendants in the α,β-poly(*N*-2-hydroxyethyl)-DL-aspartamide (PHEA) and polyethylenglycol–PHEA (PHEA–PEG) biocompatible polymers. The introduction of the fluorinated moiety increased the polymer's oxygen-dissolving ability without compromising its biocompatibility which was checked by an *in vitro* viability assay.[12] Polymer bound 1,2,4-oxadiazoles-4-oxides **75** were synthesized as a solid phase supported photochemical source of nitrosocarbonyls for hetero Diels–Alder reactions.[65]

Liquid crystals and ionic liquids

The physico-chemical properties of thermotropic liquid crystals (LC) can be strongly affected by the introduction of heteroaromatic moieties because of the presence of polarizable heteroatoms.[66] Compared to 1,3,4-oxadiazole, a commonly used heterocycle in optoelectronics, the peculiar exocyclic bond angle of 140° between the C(3) and the C(5) substituted positions of 1,2,4-oxadiazole allows a lesser deviation from linearity and a better molecular organization in the mesophase. Moreover, due to its asymmetry and the strong lateral O–N dipole, mesomorphic compounds containing this heterocycle possess a generally wider temperature range of the mesophase and lower melting points and decomposition temperatures than those of liquid crystals containing 1,3,4-oxadiazoles.[67] In this context, hockey-stick liquid crystals consisting of two terminal ten-carbon alkyl chains and a 1,2,4-oxadiazole core substituted with a "monodirectional" aromatic–C≡C–aromatic moiety have been obtained through a Sonogashira coupling of 5-(4′-halophenyl)-3-[4″-(decyloxy)phenyl]-1,2,4-oxadiazoles with the corresponding arylacetylene.[68] Chiral liquid crystals such as **75** (Fig. 7), where the asymmetric carbon is not directly attached to the 1,2,4-oxadiazole, were obtained from enantiopure secondary alcohols linked, through an aromatic ester spacer, to the C(3) of the 1,2,4-oxadiazole.[15] H-bond induced liquid crystals such as **76** could be formed between pyridyl-1,2,4-oxadiazole dervatives and carboxylic acids.[69] In the case of diacids, nicely C-shaped LCs have been obtained.[69b] Fluorinated ionic liquid crystals (ILC) **77** were synthesized by quaternization of pyridyl-1,2,4-oxadiazoles with CH_3I.[70] Interestingly, replacing the rigid perfluoroalkyl moiety with a more disordered alkyl chain resulted in a dramatic change of the salt's physico-chemical properties. In the series of ionic liquids (IL) **78**, the 1,2,4-oxadiazole-pyridinium linking position strongly affects the melting points.[71]

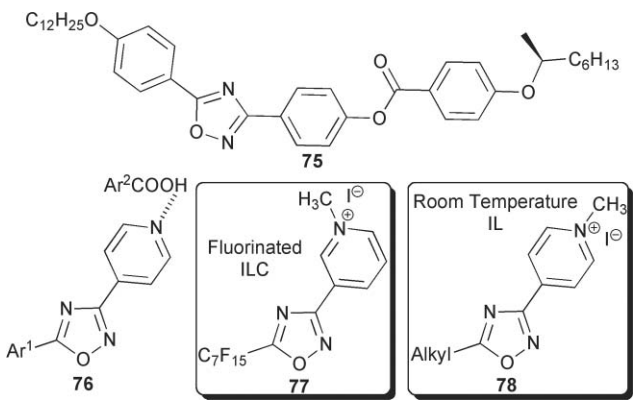


Fig. 7 Examples of 1,2,4-oxadiazole LC and IL.

Luminescent materials

While the photoluminescence of 1,3,4-oxadiazoles is well-known, 1,2,4-oxadiazoles rarely, and usually with low quantum yields,

show fluorescence in the visible region. In this context, an interesting comparison between the fluorescence of two identically substituted series of 1,2,4- and 1,3,4-oxadiazoles has been reported.[67b] In some cases the luminescent properties of a system can be designed to be a function of a measure such as the concentration of a given species in solution. For example, the fluorescence of the star-shaped molecule **79** (Fig. 8) is self-quenched by the tertiary amino moiety of its core and is strongly dependant on the medium's acidity.[13b]

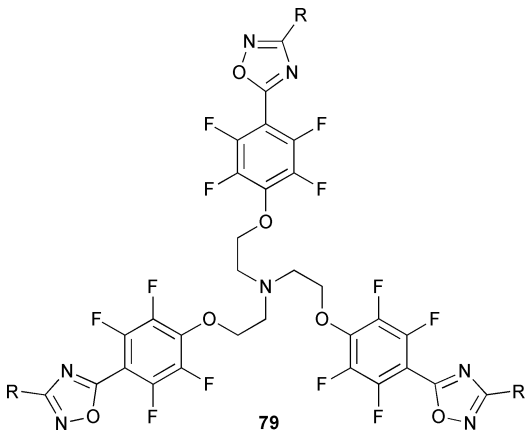


Fig. 8 pH sensitive luminescent 1,2,4-oxadiazole.

By opportunely choosing the substituents on the side chains, it is also possible to design push–pull systems (*i.e.* a conjugated system containing both electron-withdrawing and electron-donating functional groups) with a large Stokes shift. For instance, some of the hockey-stick shaped 1,2,4-oxadiazoles described above as liquid crystals showed significant blue emission (400–470 nm) both in solution and in the solid phase.[67a]

New challenges

Despite the fact that initial studies about the use of 1,2,4-oxadiazoles in polymers could have been frustrated by solubility and thermal stability issues,[63,64] recent work showed how their use as biocompatible pendants for biomedical application could be an intriguing aspect to pursue.[12] Similarly, the application of 1,2,4-oxadiazoles in materials for optoelectronics has been somewhat limited by the photoreactivity of this heterocycle. Nevertheless, 1,2,4-oxadiazole properties, including its non-symmetrical core, could turn out to be useful for the design of photoswitchable/photoactive materials.

1,2,4-Oxadiazoles as bioactive compounds

Anti-asthmatics

Selective α-keto-1,2,4-oxadiazoles **80** (Fig. 9) were synthesized as inhibitors of human mast cell tryptase, an enzyme associated with immediate and long-term effects of asthma. The presence of a 3,4-dichlorophenethyl group aided in blocking oxidative processes and improved pharmacokinetic parameters, such as clearance and half-life time.[3]

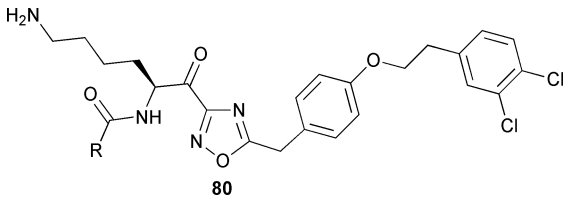


Fig. 9 Examples of 1,2,4-oxadiazole anti-asthmatics.

Anti-diabetics

Since glycogen phosphorylase (GP) is responsible for the release of glucose-1-phosphate from glycogen, its inhibition might be a valid approach for the treatment of diabetes. In this context, a series of 3-β-D-glucopyranosyl-1,2,4-oxadiazoles **81** (Fig. 10) possessing different substituents at the C(5) of the oxadiazole ring were tested as GP inhibitors. The data showed that the presence of a heteroatom or a polar group at the C(5)-linked R^1 is not favourable in terms of GP inhibition, which increased according to the sequence R^1 = phenyl < *p*-methoxyphenyl < *p*-tolyl < 2-naphthyl, the last being the most potent inhibitor.[18] Another approach used in diabetes treatment is the inhibition of the dipeptidyl peptidase IV enzyme (DPP-IV). Aiming at synthesizing novel α-amino acid pyrrolidide analogs as DPP-IV inhibitors, the introduction of the polar acidic heterocycle 5-oxo-1,2,4-oxadiazole at the 3′ position of the terminal phenyl group of compound **82** improved both potency and selectivity.[72]

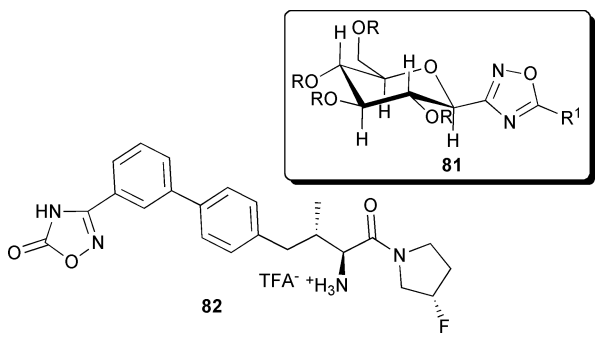


Fig. 10 Examples of 1,2,4-oxadiazole anti-diabetics.

Anti-inflammatory agents

In 1972, 5-methyl-3-phenyl-1,2,4-oxadiazole was examined for anti-inflammatory properties showing similar activity to that of the phenylbutazone.[73] Twenty years later other examples of anti-inflammatory agents based on this heterocycle have been reported,[74,75] including dual cyclooxygenase/5-lypoxygenase inhibitors,[74a] coumarin[74b] and 3-phenyl-1,2,4-oxadiazole-5-carbohydrazide derivatives.[75a]

More recently, the first example of 1,2,4-oxadiazoles having a fatty acid chain at C(5) **83** (Fig. 11) as isosters of palmitic acid derivatives were reported to possess pharmacological activity similar to aspirin and ibuprofen by inhibiting the function of fatty acid amide hydrolase (FAAH). The increased anti-inflammatory activity obtained from the introduction of a long hydrocarbon chain on the 1,2,4-oxadiazole nucleus was explained by considering the increased hydrophobicity which allows these compounds to enter the cells more quickly and leave them more slowly than

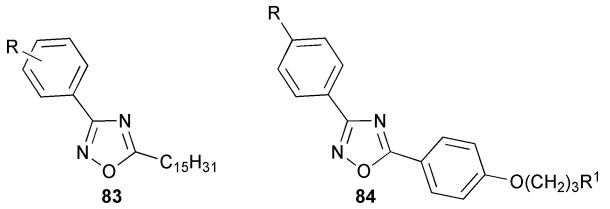


Fig. 11 Examples of 1,2,4-oxadiazole anti-inflammatory agents.

derivatives with shorter alkyl chains.[76] Very recently, the synthesis and evaluation of new ketoheterocycles, incorporating as a central heterocycle the 1,2,4-oxadiazoles with an oleyl acyl chain at C(5) or its regioisomer, proved more active than the corresponding oxazoles as FAAH inhibitors.[3b]

With a different action mechanism, a new class of interleukin-8 antagonists incorporating the 3,5-diaryl-1,2,4-oxadiazole ring system **84** were introduced as potential anti-inflammatory agents where the basicity of the nitrogen in the side-chain substituent is crucial for the activity.[77]

Anti-microbial agents

1,2,4-Oxadiazoles **85** (X = C, CH, N; POM = pivaloyloxymethyl) (Fig. 12), isosteres of pyridine- and pyrazine-carboxylic acids, were synthesized and tested for their anti-mycobacterial activity evidencing potency from 2 to 8 times higher than that of reference compound pyrazinamide.[78]

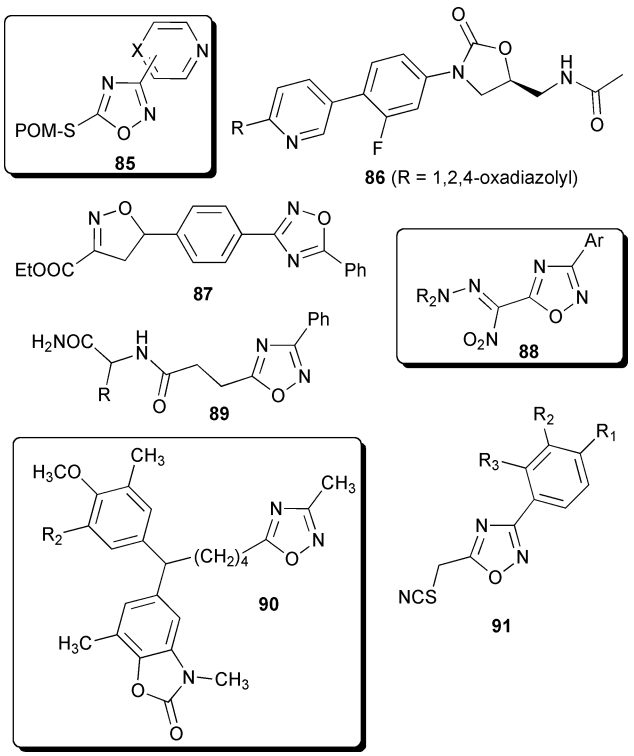


Fig. 12 Examples of 1,2,4-oxadiazole antimicrobials.

1,2,4-Oxadiazoles were also used, together with triazoles and tetrazoles, as heteroaromatic substituents on the pyridine ring to enhance up to 16 times the activity of some linezolid-like molecules **86** against six strains of resistant bacteria. This effect has been attributed to the increased hydrophobic interaction of the heterocyclic moieties with the binding pocket in the site of action.[79]

Throughout the course of development of anti-tuberculosis drugs, substitution of the benzyl-piperazine ring of the lead compound with a 5-phenyl-1,2,4-oxadiazol-3-yl moiety lead to compound **87** with improved activity.[80]

The synthesis of new ω-nitro-1,2,4-oxadiazole-5-carbaldehyde hydrazones **88** was reported together with their activity against a series of standard bacterial strains. The most pronounced anti-microbial activity was observed for compounds characterized by more conjugated chains (R = C_6H_5) having values of MIC comparable with that of the reference drug gentamicin.[81]

Seven 1,2,4-oxadiazoles **89**, carrying a terminal amino-acidic residue at the C(5) position, showed a novel profile of anti-microbial activity for this class of heterocyclic compounds. Compounds with leucine, isoleucine or aspartic acid residues were the most active against different Gram positive and negative bacteria although their activity was lower than ciprofloxacin. Interestingly, after intravenous administration, compounds with phenylalanine, valine, aspartic acid or glutamic acid residues were the most active in inhibiting the rat paw oedema induced by carragenin.[82] The 1,2,4-oxadiazole system has also been used as a hydrolysis-resisting substituent in some human immunodeficiency virus type 1 (HIV-1) non-nucleoside reverse transcriptase inhibitors (NNRTs). In particular, the 3-methyl-1,2,4-oxadiazol-5-yl system in compound **90** was the best bioisosteric replacement for the methyl ester group, maintaining an anti-HIV activity with submicromolar EC_{50} values.[83] Finally, antikinetoplastids based on 5-thiocyanomethyl-3-aryl-1,2,4-oxadiazoles **91** have been synthesized and evaluated, based upon the aryl substituent, as potential drugs for the treatment of Leishmaniasis and African trypanosomiasis.[84]

Anti-tumoral agents

Cancer, often referred to as a single condition, actually consists of more than one hundred different diseases, all characterized by uncontrolled growth and spread of abnormal cells. In this context, the identification of drugs acting as apoptosis inducers represents an attractive approach for the discovery of new anti-cancer agents.

By means of a high-throughput screening (HTS) assay, 1,2,4-oxadiazole **92** (Fig. 13) was discovered acting as an apoptosis agent.[85] Furthermore, the structure–activity relationship (SAR) of a series of 3,5-diaryl-1,2,4-oxadiazoles showed that the 4′-position of the C(3)-linked phenyl can tolerate different

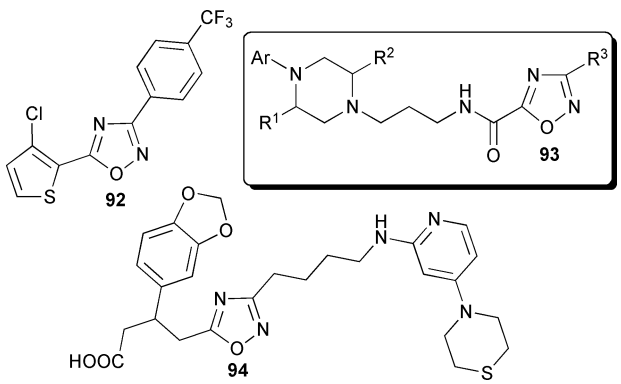


Fig. 13 Examples of 1,2,4-oxadiazole antitumorals.

non-basic groups and that there are no additive effects *via* 3,4-disubstitution. The replacement of the phenyl group by a pyridyl group, with the aim to improve the solubility profile, leads to compounds with similar activity. The SAR of the C(5)-linked aryl substituent showed that the thiophene ring is important for these compounds to act as apoptosis inducers. Nevertheless, furan can successfully replace the thiophene moiety with an additional improvement of the solubility profile.[85] Additionally, the HTS assay showed that these 3,5-diaryl-1,2,4-oxadiazoles selectively induced apoptosis in breast and colorectal cancer without affecting the vitality of primary normal cells.[86]

Most recently, a series of 1,2,4-oxadiazole-5-carboxamides **93** have been synthesized and tested as inhibitors of the glycogen synthase kinase 3 (GSK-3), a key regulator of both differentiation and cellular proliferation.[8] Interestingly, bioisosteric transformation of the 1,2,4-oxadiazole ring into the 1,3,4-oxadiazole resulted in loss of activity.[8] Several pyridine and pyrimidine derivatives showed a moderate to high inhibitory activity in the *in vitro* kinase assay suggesting that the position of the nitrogen in the pyridine and oxadiazole rings, as well as the nature of the substituents in the phenyl ring, were decisive for the biological activity.[8] According to the results of competitive binding assay, the 1,2,4-oxadiazole-5-thione and, to a lesser extent, the 1,2,4-oxadiazole-5-one were considered efficacious bioisosteres of nitro- and cyano group in the hydrophilic pharmacophore of known non-steroidal androgen receptor antagonists for the treatment of prostate cancer.[87]

An alternative anti-tumoral strategy involves the inhibition of processes involved in tumor growth, such as angiogenesis. In this context, the antagonists of the integrin $\alpha_v\beta_3$, a receptor which has been found on the surface of many tumor cells and recognizes the arginine–glycine–aspartic acid (RGD) sequence, are able to inhibit angiogenesis. 1,2,4-Oxadiazolebutanoic acids such as **94**, in which the heterocyclic ring acts as ester/amide isoster, were tested as non-peptidic analogs of $\alpha_v\beta_3$ antagonists. With the appropriate substitution at the β-position and by the introduction of a guanidine mimetic, it is possible to obtain derivatives with $\alpha_v\beta_3$ antagonistic activity characterized by a low to sub-nanomolar $\alpha_v\beta_3$ potency, good bioavailability and promising pharmacokinetic properties.[88]

Immunosuppressors

The suppression of the body's immune system may be induced with drugs, as in preparation for organ transplantation to prevent rejection of the donor tissue, or for the treatment of auto-immune diseases such as rheumatoid arthritis or Crohn's disease.

The zeta chain-associated protein kinase 70 (ZAP-70) is a member of the protein-tyrosine kinase family that plays a critical role in T-cell activation by its SH2 domains. Agents that bind to SH2 domains would prevent ZAP-70 from triggering the intracellular cascade and might be a potential immunosuppressor.[89] The 1,2,4-oxadiazole scaffold **95** (Fig. 14) was identified as an effective mimetic for the monophosphorylated tetrapeptide sequence found in SH2 domains of ZAP-70.[89b] Further SAR studies led to the synthesis of series of ZAP-70 SH2 inhibitors in which the tyrosine moiety of **95** was replaced with other functional groups with the advantage of removing most of the peptidic nature of these inhibitors.[89a]

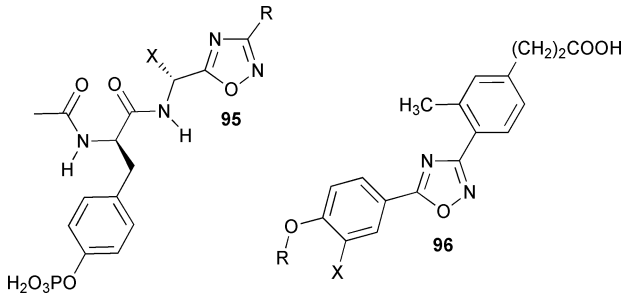


Fig. 14 Examples of 1,2,4-oxadiazole immunosuppressors.

In recent years, the sphingosine-1-phosphate (S1P) receptors have emerged as targets of immunosuppressant drugs. Based on previous SAR studies, a series of 3-arylpropionic acids **96** as $S1P_1$ agonists has been reported. Compound **96** (R = *i*-Pr; X = CF_3) was a 90 pM $S1P_1$ agonist and its selectivity against $S1P_3$ and $S1P_5$ was much greater than that of 3-(*o*-tolyl)-5-(*p*-cyclohexylphenyl)-1,2,4-oxadiazole reference. Replacement of the trifluoromethyl group with bromide or nitrile yielded full agonist ($S1P_1$ binding affinity <80 pM).[90] All the 3-arylpropionic acids showed overall good pharmacokinetic properties with the exception of a short half-life value. With the aim to improve this parameter, the same authors suggested further modifications at the α and β positions of the propionic acid chain.[91]

Neuroprotective agents

Sirtuins are a class of seven proteins (SIRT1–7) which play a major role in age-related diseases. Based on a virtual database screening, a series of 1,2,4-oxadiazole-carbonylaminourea derivatives **97** (Fig. 15) have been synthesized and tested for their SIRT1 and SIRT2 activity.[92] The results showed that modifications, such as the introduction of bulky and lipophilic substituents at the R^1 position or the presence of a trifluoromethyl-phenyl substituent at the R^2 position, were important for the inhibitory activity. Compound (**97**; R^1 = naphthyl, X = S, R^2 = 3-CF_3-C_6H_4) was the most potent SIRT1 inhibitor in the series.[92]

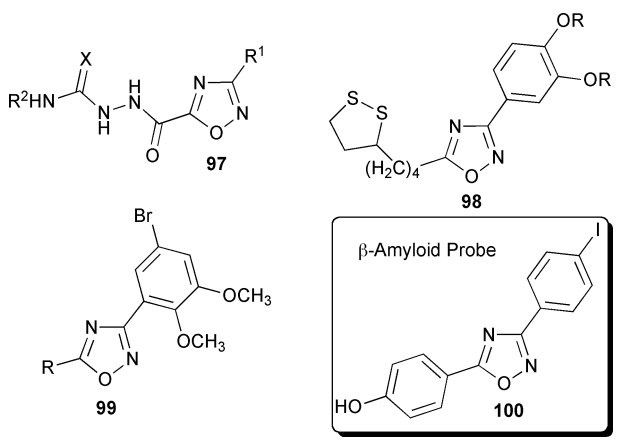


Fig. 15 Examples of 1,2,4-oxadiazole neuroprotecting agents.

Another approach against neurodegenerative processes involves the use of neuroprotective antioxidants. Considering that 1,2-dithiolane-3-pentanoic acid (α-lipoic acid) and its amides are very reactive against a variety of ROS *in vitro*, a series of lipoic

acid derivatives have been synthesized and their neuroprotective activity evaluated. This study showed that it is possible to obtain strong neuroprotective compounds by inserting a heterocyclic ring, whose nature has a strong effect on the activity, in the alkyl-1,2-dithiolane moiety in conjunction with another antioxidant entity such as a free or protected catechol moiety. Compound **98**, containing the 1,2,4-oxadiazole linker as amide bioisostere, was among the most potent in the series.[93]

A recent approach towards the therapy of Parkinson's disease considers the development of new dopamine agonists. Based on molecular modelling studies, a series of 3-(5-bromo-2,3-dimethoxyphenyl)-1,2,4-oxadiazoles **99** has been synthesized and evaluated as potential dopamine agonists. Once again, the choice of the 1,2,4-oxadiazole system was the result of its efficiency in replacing the amide group in a series of benzamide analogues with high affinity for dopamine receptors.[94] All the synthesized compounds showed a log $P > 2.6$, indicating that they should easily cross the blood-brain barrier.

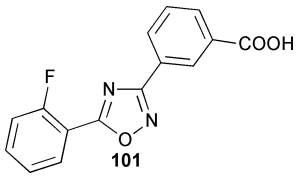
As for Alzheimer's disease, another common neurodegenerative process, an emerging research field is the development of new probes for the *in vivo* imaging of β-amyloid (Aβ) plaques which are formed in the brain during the early stage of the disease. For this purpose, a series of 3,5-diaryl-1,2,4-oxadiazoles have been designed as potential probes for Aβ plaques imaging.

All of the synthesized compounds, especially the hydroxy derivative **100**, showed a high affinity for the plaques, as deduced from the values of the inhibition constant. Favorable absorption by the brain was confirmed by the biodistribution experiments in normal mice performed with the corresponding ^{125}I radioiodinated derivatives. However, since these compounds have an unfavorable *in vivo* pharmacokinetic profile due to non-specific binding, further development should involve structure modification to reduce the lipophilicity of these 1,2,4-oxadiazole derivatives.[95]

Nonsense mutation readthrough promoters

Nonsense mutations are single-point alterations in genetic code due to nucleotide changes, which convert an amino acid-encoding codon to a translational stop codon (UAA, UAG or UGA) in the protein coding region of the mRNA with consequent premature interruption of the mRNA translation and production of a truncated protein. In terms of specific diseases, these mutations are responsible for ~5% of cases of cystic fibrosis (CF) and ~15% of Duchenne muscolar dystrophy (DMD).[96] It is, therefore, extremely important to search for molecules which can promote the readthrough of premature stop codons and allow the synthesis of functional proteins. Gentamicin, an aminoglycoside, is the most used drug for the pharmacologic treatment, although it is limited by the need for intravenous administration and by renal and otic toxicities.[97] Recently, a new 1,2,4-oxadiazole derivative has been successfully tested against both CF and DMD. 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-benzoic acid **101**, also known as *Ataluren* or PTC124 (Fig. 16), was identified in an HTS for compounds that promote suppression of UGA stop codon and specifically correct the processing of the gene in patients whose diseases are caused by nonsense mutations.[97,98]

PTC124 selectively allows the ribosome to bypass the premature stop signal, without affecting the correct reading of normal stop codons in mRNA, and continue the translation process to make a full-length and functional protein. In mice, high dosages of an aqueous suspension of PTC124 were needed due to the scarce bioavailability.[98] In humans, PTC124's safety and tolerability have been demonstrated in phase I clinical trials in healthy adult volunteers. During the drafting of this review, phase IIb clinical studies in patients with nonsense mutation DMD and CF were being enrolled. Due to the success of this approach, future developments should address the improvement of PTC124's bioavailability and a better interpretation of the mechanism of action at the molecular level.[99]



101

Fig. 16 Structure of PTC124.

Conclusions

In their attempt to merge material about the synthesis and reactivity of 1,2,4-oxadiazoles with that about their applications, the authors often felt they were dealing with literature belonging to very separate research fields. The authors hope that this review unites this gap by providing the reader a broad and up-to-date vision of 1,2,4-oxadiazoles chemistry, application and biological activity while including suggestions for further developments. The reviewed material may provoke many interesting questions, especially regarding the action mechanism of biologically active 1,2,4-oxadiazoles which, due to its importance, the authors emphasize in this conclusive chapter.

On one hand, it is true that the 1,2,4-oxadiazoles are highly resistant to hydrolysis and electrophilic attack. However, due to their relatively high tendency to rearrange and the strong dependence of their reactivity upon structural as well as environmental factors (temperature, sterical restraints, solvent polarity, acidity or basicity of the media, exposure to light, *etc.*) one cannot exclude the possibility that the actual active molecule is a product of some *in vivo* reaction of the used 1,2,4-oxadiazoles. In this context, the study of enzyme-catalyzed reactions of 1,2,4-oxadiazoles may represent a new challenging area for both chemists and biologists involved in the use of this heterocycle.

References

1 F. Tiemann and P. Krüger, *Chem. Ber.*, 1884, **17**, 1685–1698.

2 See for example: (*a*) K. Hemming, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, London, UK, 3rd edn, 2008, vol 5, pp. 243-314; (*b*) L. A. Kayukova, *Pharm. Chem. J.*, 2005, **39**, 539–547; (*c*) K. Hemming, *J. Chem. Res. Synop.*, 2001, 209–216; (*d*) J. C. Jochims, in *Comprehensive Heterocycle Chemistry II*, ed. C. W. Rees, A. R. Katritzky and E. F. V. Scriven, Pergamon, Oxford, U.K., 2nd edn., 1996, Vol. 4, pp. 179-228; (*e*) L. B. Clapp, in *Comprehensive Heterocycle Chemistry*, ed. C. W. Rees, A. R. Katritzky, Pergamon, Oxford, U.K., 1st edn., 1984, Vol. 6, pp. 365-392; (*f*) L. B. Clapp, *Adv. Heterocycl. Chem.*, 1976, **20**, 65–116; (*g*) F. Eloy, *Fortschr. Chem Forsh.*, 1965, **4**, 807–876.

3 (*a*) J. T. Palmer, R. M. Rydzewski, R. V. Mendonca, D. Sperandio, J. R. Spencer, B. L. Hirschbein, J. Lohman, J. Beltman, M. Nguyen and L. Liu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3434–3439; (*b*) J. Garfunkle,

C. Ezzili, T. J. Rayl, D. G. Hochstatter, I. Hwang and D. L. Boger, *J. Med. Chem.*, 2008, **51**, 4392–4403.
4 K. Itoh, H. Sakamaki and C. A. Horiuchi, *Synthesis*, 2005, 1935–1938.
5 S. Borg, G. Estenne-Bouhtou, K. Luthman, I. Csoregh, W. Hesselink and U. Hacksell, *J. Org. Chem.*, 1995, **60**, 3112–3120.
6 M. Kmetic and B. Stanovnik, *J. Heterocycl. Chem.*, 1995, **32**, 1563–1565.
7 M. Tamua, Y. Ise, Y. Okajima, N. Nishiwaki and M. Ariga, *Synthesis*, 2006, 3453–3461.
8 A. G. Koryakova, Y. A. Ivanenkov, E. A. Ryzhova, E. A. Bulanova, R. N. Karapetian, O. V. Mikitas, E. A. Katrukha, V. I. Kazey, I. Okun, D. V. Kravchenko, Y. V. Lavrovsky, O.M. Korzinov and A. V. Ivachtchenko, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3661–3666.
9 See among others: (*a*) M. Ispikoudi, K. E. Litinas and K. Fylaktakidou, *Heterocycles*, 2008, **75**, 1321–1328 and reference therein cited; (*b*) S. Buscemi, A. Pace, I. Pibiri and N. Vivona, *Heterocycles*, 2002, **57**, 1891–1896; (*c*) F. Eloy and R. Lenaers, *Helv. Chim. Acta*, 1966, **49**, 1430–1432; (*d*) U. Kraatz, in *Houben-Weyl E 8c, Heteroarenes III/3*, Georg Thieme Verlag, Stuttgart, 1994, pp. 409-525; (*e*) S. Buscemi, N. Vivona and T. Caronna, *Synthesis*, 1995, 917–919; (*f*) S. Buscemi, A. Pace, V. Frenna and N. Vivona, *Heterocycles*, 2002, **57**, 811–823; (*g*) J. W. Tilley and H. Ramuz, *Helv. Chim. Acta*, 1980, **63**, 832–840; (*h*) T. Kurz, N. Lolak and D. Geffken, *Tetrahedron Lett.*, 2007, **48**, 2733–2735.
10 A. Pace, S. Buscemi and N. Vivona, *Org. Prep. Proced. Int.*, 2005, **37**, 447–506.
11 A. Pace, I. Pibiri, A. Palumbo Piccionello, S. Buscemi and N. Vivona, *Book of Abstract of the 20th International Congress of Heterocyclic Chemistry*, Palermo, 2005, p. 435.
12 (*a*) D. Mandracchia, A. Palumbo Piccionello, G. Pitarresi, A. Pace, S. Buscemi and G. Giammona, *Macromol. Biosci.*, 2007, **7**, 836–845; (*b*) G. Pitarresi, A. Palumbo Piccionello, R. Calabrese, A. Pace, S. Buscemi and G. Giammona, *J. Fluorine Chem.*, 2008, **129**, 1096–1103.
13 (*a*) S. Buscemi, A. Pace, A. Palumbo Piccionello, S. Pappalardo, D. Garozzo, T. Pilati, G. Gattuso, A. Pappalardo, I. Pisagatti and M. F. Parisi, *Tetrahedron Lett.*, 2006, **47**, 9049–9052; (*b*) S. Buscemi, A. Pace, A. Palumbo Piccionello and N. Vivona, *J. Fluorine Chem.*, 2006, **127**, 1601–1605.
14 X. Yang, Z. Wang, X. Fang, X. Yang, F. Wu and Y. Shen, *Synthesis*, 2007, 1768–1778.
15 M. Parra, P. Hidalgo and E. Y. Elgueta, *Liq. Cryst.*, 2008, **35**, 823–832.
16 A. R. Katritzky, A. A. Shestopalov and K. Suzuki, *ARKIVOC*, 2005, **7**, 36–55.
17 V. V. Sureshbabu, H. P. Hemantha and S. A. Naik, *Tetrahedron Lett.*, 2008, **49**, 5133–5136.
18 M. Benltifa, S. Vidal, B. Fenet, M. Msaddek, P. G. Goekjian, J.-P. Praly, A. Brunyánszki, T. Docsa and P. Gergely, *Eur. J. Org. Chem.*, 2006, 4242–4256.
19 M. Benltifa, S. Vidal, D. Gueyrard, P. G. Goekjian, M. Msaddek and J.-P. Praly, *Tetrahedron Lett.*, 2006, **47**, 6143–6147.
20 J. V. dos Anjos, D. Sinou, R. M. Srivastava and S. Carneiro do Nascimento, *J. Carbohydr. Chem.*, 2008, **27**, 258–277.
21 J. V. dos Anjos, D. Sinou, S. J. de Melo and R. M. Srivastava, *Carbohydr. Res.*, 2007, **342**, 2440–2449.
22 J. C. Legeay, J. J. Vanden Eynde and J. P. Bazureau, *Tetrahedron Lett.*, 2007, **48**, 1063–1068.
23 F. Crestey, C. Lebargy, M.-C. Lasne and C. Perrio, *Synthesis*, 2007, 3406–3410.
24 J. Huck, M. L. Roumestant and J. Martinez, *J. Pept. Res.*, 2003, **62**, 233–237.
25 V. Yu. Rozhkov, L. V. Batog and M. Struchkova, *Mendeleev Commun.*, 2008, **18**, 161–163.
26 M. Massacesi, G. Devoto and G. Gelli, *Spectrochim. Acta*, 1985, **41Ab**, 1433–1436.
27 (*a*) N. A. Bokach, V. Yu. Kukushkin, M. Haukka and A. J. L. Pombeiro, *Eur. J. Inorg. Chem.*, 2005, 845–853; (*b*) N. A. Bokach, A. V. Khripoun, V. Yu Kukushkin, M. Haukka and A. J. L. Pombeiro, *Inorg. Chem.*, 2003, **42**, 896–903.
28 B. J. Childs, D. C. Craig, M. L. Scudder and H. A. Goodwin, *Aust. J. Chem.*, 1999, **52**, 673–680.
29 C. Richardson and P. J. Steel, *Inorg. Chem. Commun.*, 2007, **10**, 884–887.
30 A. S. da Silva, M. A. A. da Silva, C. E. M. Carvalho, O. A C. Antunes, J. O. M. Herrera, I. M. Brinn and A. S. Mangrich, *Inorg. Chim. Acta*, 1999, **292**, 1–6.
31 C. Moussebois and F. Eloy, *Helv. Chim. Acta*, 1964, **47**, 838–848.
32 A. Terenzi, *Book of Abstracts of the Scuola Nazionale di Chimica Bioinorganica per Dottorandi*, Napoli, 2008, p. 12.
33 B. Oussaid, L. Moeini, B. Martin, D. Villemin and B. Garrigues, *Synth. Commun.*, 1995, **25**, 1451–1459.
34 J. J. R. de Freitas, J. C. R. de Freitas, L. P. da Silva, J. R. de Freitas Filho, G. Y. V. Kimura and R. M. Srivastava, *Tetrahedron Lett.*, 2007, **48**, 6195–6198.
35 B. Kaboudin and F. Saadati, *Tetrahedron Lett.*, 2007, **48**, 2829–2832and references therein cited.
36 M. A. Herrero, J. M. Kremsner and C. O. Kappe, *J. Org. Chem.*, 2008, **73**, 36–47.
37 D. Grant, R. Dahl and N. D. P. Cosford, *J. Org. Chem.*, 2008, **73**, 7219–7223.
38 (*a*) C. V. Bird, *Tetrahedron*, 1985, **41**, 1409–1414; (*b*) C. V. Bird, *Tetrahedron*, 1992, **48**, 335–340.
39 A. Pace, I. Pibiri, S. Buscemi and N. Vivona, *Heterocycles*, 2004, **63**, 2627–2648.
40 (*a*) S. Buscemi, A. Pace, A. Palumbo Piccionello, G. Macaluso, N. Vivona, D. Spinelli and G. Giorgi, *J. Org. Chem.*, 2005, **70**, 3288–3291; (*b*) S. Buscemi, A. Pace, I. Pibiri, N. Vivona and D. Spinelli, *J. Org. Chem.*, 2003, **68**, 605–608; (*c*) S. Buscemi, A. Pace, I. Pibiri, N. Vivona, C. Z. Lanza and D. Spinelli, *Eur. J. Org. Chem.*, 2004, 974–980.
41 S. Buscemi, A. Pace, A. Palumbo Piccionello, N. Vivona and M. Pani, *Tetrahedron*, 2006, **62**, 1158–1164.
42 R. E. Trifonov, A. P. Volovodenko, S. N. Vergizov, N. I. Shirinbekov, V. A. Gindin, A. O. Koren and V. A. Ostrovskii, *Helv. Chim. Acta*, 2005, **88**, 1790–1797.
43 S. V. Volovik, V. I. Staninets and N. S. Zefirov, *Theor. Exp. Chem.*, 1991, **26**, 390–398.
44 B. Cosimelli, S. Guernelli, D. Spinelli, S. Buscemi, V. Frenna and G. Macaluso, *J. Org. Chem.*, 2001, **66**, 6124–6129.
45 A. G. Tyrkov and A. N. Usova, *Russ. J. Org. Chem.*, 2004, **40**, 286–287.
46 J. L. Cotter and G. J. Knight, *Chem. Comm.*, 1966, 336–337.
47 A. J. Boulton, A. R. Katritzky and A. M. Hamid, *J. Chem. Soc. C*, 1967, 2005–2007.
48 S. Buscemi, V. Frenna, A. Pace, N. Vivona, B. Cosimelli and D. Spinelli, *Eur. J. Org. Chem.*, 2002, 1417–1423.
49 (*a*) M. Ruccia, N. Vivona and D. Spinelli, *Adv. Heterocycl. Chem.*, 1981, **29**, 141–169; (*b*) N. Vivona, S. Buscemi, V. Frenna and G. Cusmano, *Adv. Heterocycl. Chem.*, 1993, **56**, 49–154.
50 A. Palumbo Piccionello, A. Pace, S. Buscemi, N. Vivona and M. Pani, *Tetrahedron*, 2008, **64**, 4004–4010.
51 N. N. Makhova, I. V. Ovchinnikov, A. S. Kulikov, S. I. Molotov and E. L. Baryshnikova, *Pure Appl. Chem.*, 2004, **76**, 1691–1703.
52 (*a*) A. Pace, I. Pibiri, A. Palumbo Piccionello, S. Buscemi, N. Vivona and G. Barone, *J. Org. Chem.*, 2007, **72**, 7656–7666; (*b*) A. Pace, P. Pierro, S. Buscemi, N. Vivona and G. Barone, *J. Org. Chem.*, 2009, **74**, 351–358.
53 S. Guernelli, P. Lo Meo, S. Morganti, R. Noto and D. Spinelli, *Tetrahedron*, 2007, **63**, 10260–10268.
54 (*a*) F. D'Anna, V. Frenna, S. Marullo, R. Noto and D. Spinelli, *Tetrahedron*, 2008, **64**, 11209–11217; (*b*) F. D'Anna, V. Frenna, R. Noto, V. Pace and D. Spinelli, *J. Org. Chem.*, 2006, **71**, 9637–9642; (*c*) F. Bessac and F. Maseras, *J. Comput. Chem.*, 2008, **29**, 892–899; (*d*) F. D'Anna, V. Frenna, S. La Marca, R. Noto, V. Pace and D. Spinelli, *Tetrahedron*, 2008, **64**, 672–680.
55 A. Fontana, S. Guernelli, P. Lo Meo, E. Mezzina, S. Morganti, R. Noto, E. Rizzato, D. Spinelli and R. Zappacosta, *Tetrahedron*, 2008, **64**, 733–740.
56 A. Pace, N. Vivona and G. Barone, Unpublished results.
57 J. E. Macor, T. Ordway, R. L. Smith, P. R. Verhoest and R. A. Mack, *J. Org. Chem.*, 1996, **61**, 3228–3229.
58 A. Palumbo Piccionello, A. Pace, P. Pierro, I. Pibiri, S. Buscemi and N. Vivona, *Tetrahedron*, 2009, **65**, 119–127.
59 (*a*) A. Palumbo Piccionello, A. Pace, S. Buscemi and N. Vivona, *ARKIVOC*, 2009, **4**, 235–244; (*b*) A. Palumbo Piccionello, A. Pace, S. Buscemi, N. Vivona and G. Giorgi, *Tetrahedron Lett.*, 2009, **50**, 1472–1474.
60 (*a*) H. Newman, *Tetrahedron Lett.*, 1968, **9**, 2417–2420; (*b*) H. Newman, *Tetrahedron Lett.*, 1968, **9**, 2421–2424.

61 (*a*) A. Pace, S. Buscemi, N. Vivona, A. Silvestri and G. Barone, *J. Org. Chem.*, 2006, **71**, 2740–2749; (*b*) A. Pace, S. Buscemi and N. Vivona, *J. Org. Chem.*, 2005, **70**, 2322–2324.
62 (*a*) A. Palumbo Piccionello, I. Pibiri, A. Pace, R. A. Raccuglia, S. Buscemi, N. Vivona and G. Giorgi, *Heterocycles*, 2007, **71**, 1529–1537; (*b*) A. Palumbo Piccionello, A. Pace, I. Pibiri and S. Buscemi, *ARKIVOC*, 2009, **8**, 156–167.
63 (*a*) D. A. Klein and R. A. Fouty, *Macromolecules*, 1968, **1**, 318–324 and references therein cited; (*b*) E.-J. Choi and J. C. Jung, *Polym. J.*, 1992, **24**, 121–125and references therein cited.
64 (*a*) I. Vega, W. Morris and N. D'Accorso, *React. Funct. Polym.*, 2006, **66**, 1609–1618; (*b*) I. Vega, L. Sanchez and N. D'Accorso, *J. Heterocycl. Chem.*, 2007, **44**, 389–392.
65 P. Quadrelli, R. Scrocchi, A. Piccanello and P. Caramella, *J. Comb. Chem.*, 2005, **7**, 887–892.
66 A. Seed, *Chem. Soc. Rev.*, 2007, **36**, 2046–2069.
67 (*a*) H. Gallardo, R. Cristiano, A. A. Vieira, R. A. W. Neves Filho, R. M. Srivastava and I. H. Bechtold, *Liq. Cryst.*, 2008, **35**, 857–863; (*b*) M. Parra, P. Hidalgo, E. Carrasco, J. Barberá and L. Silvino, *Liq. Cryst.*, 2006, **33**, 875–882; (*c*) S. Torgova, T. Geivandova, O. Francescangeli and A. Strigazzi, *Pramana*, 2003, **61**, 239–248.
68 H. Gallardo, R. Cristiano, A. A. Vieira, R. A. W. Neves Filho and R. M. Srivastava, *Synthesis*, 2008, 605–609.
69 (*a*) M. Parra, P. Hidalgo, J. Barberá and J. Alderete, *Liq. Cryst.*, 2005, **32**, 573–577; (*b*) M. Parra, P. Hidalgo and J. Alderete, *Liq. Cryst.*, 2005, **32**, 449–455.
70 (*a*) I. Pibiri, A. Pace, S. Buscemi, N. Vivona and L. Malpezzi, *Heterocycles*, 2006, **68**, 307–321; (*b*) F. Lo Celso, I. Pibiri, A. Triolo, R. Triolo, A. Pace, S. Buscemi and N. Vivona, *J. Mater. Chem.*, 2007, **17**, 1201–1208.
71 I. Pibiri, A. Pace, A. Palumbo Piccionello, P. Pierro and S. Buscemi, *Heterocycles*, 2006, **68**, 2653–2661.
72 J. Xu, L. Wei, R. Mathvink, J. He, Y.-J. Park, H. He, B. Leiting, K. A. Lyons, F. Marsilio, R. A. Patel, J. K. Wu, N. A. Thornberry and A. E. Weber, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2533–2536.
73 S. E. Dahlgren and T. Dalhamn, *Acta Pharmacol. Toxicol.*, 1972, **31**, 193–202.
74 (*a*) P. C. Unangst, G. P. Shrum, D. T. Connor, R. D. Dyer and D. J. Schrier, *J. Med. Chem.*, 1992, **35**, 3691–3698; (*b*) D. N. Nicolaides, K. C. Fylaktakidou, K. E. Litinas and D. Hadjipavlou-Litina, *Eur. J. Med. Chem.*, 1998, **33**, 715–724.
75 (*a*) L. F. C. C. Leite, M. N. Ramos, J. B. P. Da Silva, A. L. P. Miranda, C. A. M. Fraga and E. J. Barreiro, *Il Farmaco*, 1999, **54**, 747–757; (*b*) R. M. Srivastava, A. De Almeida Lima, O. S. Viana, M. J. Da Costa Silva, M. T. J. A. Catanho and J. O. F. De Morais, *Bioorg. Med. Chem.*, 2003, **11**, 1821–1827.
76 N. M. M. Bezerra, S. P. De Oliveira, R. M. Srivastava and J. R. Da Silva, *Il Farmaco*, 2005, **60**, 955–960.
77 M. A. Weidner-Wells, T. C. Henninger, S. A. Fraga-Spano, C. M. Boggs, M. Matheis, D. M. Ritchie, D. C. Argentieri, M. P. Wachter and D. J. Hlasta, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4307–4311.
78 M. H. Gezginci, A. R. Martin and S. G. Franzblau, *J. Med. Chem.*, 2001, **44**, 1560–1563.
79 Y. W. Jo, W. B. Im, J. K. Rhee, M. J. Shim, W. B. Kim and E. C. Choi, *Bioorg. Med. Chem.*, 2004, **12**, 5909–5915.
80 D. Rakesh, R. B. Sun, R. P. Lee Tangallapally and R. E. Lee, *Eur. J. Med. Chem.*, 2009, **44**, 460–472.
81 A. G. Tyrkov and L. T. Sukhenko, *Pharm. Chem. J.*, 2004, **38**, 376–378.
82 A. C. L. Leite, R. F. Vieira, A. R. De Faria, A. G. Wanderley, P. Afiatpour, E. C. P. A. Ximenes, R. M. Srivastava, C. F. de Oliveira, M. V. Medeiros, E. Antunes and D. J. Brondani, *Il Farmaco*, 2000, **55**, 719–724.
83 T. Sakamoto, M. D. Cullen, T. L. Hartman, K. M. Watson, R. W. Buckheit, C. Pannecouque, E. De Clercq and M. Cushman, *J. Med. Chem.*, 2007, **50**, 3314–3321.
84 D. M. Cottrell, J. Capers, M. M. Salem, K. DeLuca-Fradley, S. L. Croft and K. A. Werbovetz, *Bioorg. Med. Chem.*, 2004, **12**, 2815–2824.
85 H.-Z. Zhang, S. Kasibhatla, J. Kuemmerle, W. Kemnitzer, K. Ollis-Mason, L. Qiu, C. Crogan-Grundy, B. Tseng, J. Drewe and S. X. Cai, *J. Med. Chem.*, 2005, **48**, 5215–5223.
86 K. A. Jessen, N. M. English, J. Y. Wang, S. Maliartchouk, S. P. Archer, L. Qiu, R. Brand, J. Kuemmerle, H.-Z. Zhang, K. Gehlsen, J. Drewe, B. Tseng, S. Xiong Cai and S. Kasibhatla, *Mol. Cancer Ther.*, 2005, **4**, 761–771.
87 S. Fujii, K. Ohta, T. Goto, H. Kagechika and Y. Endo, *Bioorg. Med. Chem.*, 2009, **17**, 344–350.
88 M. L. Boys, L. A. Schretzman, N. S. Chandrakumar, M. B. Tollefson, S. B. Mohler, V. L. Downs, T. D. Penning, M. A. Russell, J. A. Wendt, B. B. Chen, H. G. Stenmark, H. Wu, D. P. Spangler, M. Clare, B. N. Desai, I. K. Khanna, M. N. Nguyen, T. Duffin, V. Wayne Engleman, M. B. Finn, S. K. Freeman, M. L. Hanneke, J. L. Keene, J. A. Klover, G. A. Nickols, M. A. Nickols, C. N. Steininger, M. Westlin, W. Westlin, Y. X. Yu, Y. Wang, C. R. Dalton and S. A. Norring, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 839–844.
89 (*a*) C. B. Vu, E. G. Corpuz, S. G. Pradeepan, S. Violette, C. Bartlett and T. K. Sawyer, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3009–3014; (*b*) C. B. Vu, E. G. Corpuz, T. J. Merry, S. G. Pradeepan, C. Bartlett, R. S. Bohacek, M. C. Botfield, C. J. Eyermann, B. A. Lynch, I. A. MacNeil, M. K. Ram, M. R. van Schravendijk, S. Violette and T. K. Sawyer, *J. Med. Chem.*, 1999, **42**, 4088–4098.
90 L. Yan, P. Huo, G. Doherty, L. Toth, J. J. Hale, S. G. Mills, R. Hajdu, C. A. Keohane, M. J. Rosenbach, J. A. Milligan, G.-J. Shei, G. Chrebet, J. Bergstrom, D. Card, E. Quackenbush, A. Wickham and S. M. Mandala, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3679–3683.
91 L. Yan, P. Huo, J. J. Hale, S. G. Mills, R. Hajdu, C. A. Keohane, M. J. Rosenbach, J. A. Milligan, G.-J. Shei, G. Chrebet, J. Bergstrom, D. Card and S. M. Mandala, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 828–831.
92 T. Huhtiniemi, T. Suuronen, V. M. Rinne, C. Wittekindt, M. Lahtela-Kakkonen, E. Jarho, E. A. A. Wallén, A. Salminen, A. Poso and J. Leppänen, *J. Med. Chem.*, 2008, **51**, 4377–4380.
93 M. Koufaki, C. Kiziridi, F. Nikoloudaki and M. N. Alexis, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4223–4227.
94 S. B. Tiwari and D. V. Kohli, *Med. Chem. Res.*, 2008, **17**, 386–398.
95 M. Ono, M. Haratake, H. Saji and M. Nakayama, *Bioorg. Med. Chem.*, 2008, **16**, 6867–6872.
96 (*a*) S. Hirawat, E. M. Welch, G. L. Elfring, V. J. Northcutt, S. Paushkin, S. Hwang, E. M. Leonard, N. G. Almstead, W. Ju, S.W. Peltz and L. L. Miller, *J. Clin. Pharmacol.*, 2007, **47**, 430–444; (*b*) S. A. Hamed, *Drugs*, 2006, **9**, 783–789.
97 S. Aurino and V. Nigro, *Acta Myol.*, 2006, **25**, 5–12.
98 (*a*) E. M. Welch, E. R. Barton, J. Zhuo, Y. Tomizawa, W. J. Friesen, P. Trifillis, S. Paushkin, M. Patel, C. R. Trotta, S. Hwang, R. G. Wilde, G. Karp, J. Takasugi, G. Chen, S. Jones, H. Ren, Y.-C. Moon, D. Corson, A. A. Turpoff, J. A. Campbell, M. M. Conn, A. Khan, N. G. Almstead, J. Hedrick, A. Mollin, N. Risher, M. Weetall, S. Yeh, A. A. Branstrom, J. M. Colacino, J. Babiak, W. D. Ju, S. Hirawat, V. J. Northcutt, L. L. Miller, P. Spatrick, F. He, M. Kawana, H. Feng, A. Jacobson, S. W. Peltz and H. L. Sweeney, *Nature*, 2007, **447**, 87–91; (*b*) S. Davies, N. Serradell, E. Rosa and R. Castaner, *Drugs Future*, 2008, **33**, 733–736; (*c*) E. Kerem, S. Hirawat, S. Armoni, Y. Yaakov, D. Shoseyov, M. Cohen, M. Nissim-Rafinia, H. Blau, J. Rivlin, M. Aviram, G. L. Elfring, V. J. Northcutt, L. L. Miller, B. Kerem and M. Wilschanski, *Lancet*, 2008, **372**, 719–727.
99 S. Wilton, *Neuromuscular Disord.*, 2007, **17**, 719–720.

