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Bioactive heterocycles containing endocyclic *N*-hydroxy groups

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Abstract

Drug-likeness rules consider N-O single bonds as “structural alerts” which should not be present in a perspective drug candidate. In most cases this concern is correct, since it is known that *N*-hydroxy metabolites of branded drugs produce reactive species that cause serious side effects. However, this dangerous reactivity of the *N*-OH species generally takes place when the nitrogen atom is not comprised in a cyclic moiety. In fact, the same type of metabolic behavior should not be expected when the nitrogen atom is included in the ring of an aromatic heterocyclic scaffold. Nevertheless, heterocycles bearing endocyclic *N*-hydroxy portions have so far been poorly studied as chemical classes that may provide new therapeutic agents. This review provides an overview of *N*-OH-containing heterocycles with reported bioactivities that may be considered as therapeutically relevant and, therefore, may extend the chemical space available for the future development of novel pharmaceuticals. A systematic treatment of the various chemical classes belonging to this particular family of molecules is described along with a discussion of the biological activities associated to the most important examples.

Keywords

N-hydroxy-heterocycles; bioactivity; metabolism

1. Introduction

The presence of N-O single bonds is generally considered as a structural element which poses serious risks to the drug-likeness of the resulting molecule [1-3]. This warning derives from the general observation that most of the drugs bearing amino- or nitro-moieties generate reactive *N*-OH metabolites. These *N*-OH metabolites are usually generated by biochemical transformation via hydroxylation or oxidation of amines or by reduction of nitro groups present in the parent drugs and are considered as toxic metabolites. In fact, these reactive metabolites can either covalently bind to nucleic acids or interact with proteins and, therefore, be responsible for several side effects *i.e.* cellular necrosis, hypersensitivity, blood dyscrasia, fetotoxicity, hepatotoxicity *etc*. [4,5]. The high reactivity

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of these *N*-OH metabolites (**1**, Fig. 1) towards nucleophilic species is generally promoted by an initial conjugation with inorganic sulfate to produce corresponding *O*-sulfate ester (**2**), which further ionizes to generate the electrophilic nitrenium species (**3**). These cationic species covalently bind to nucleic acids and/or other nucleophilic sites of cellular components, to produce stable adduct which generate severe toxicity and, ultimately, may lead to the formation of malignant tumor (Fig. 1) [6].

In details, primary *N*-hydroxy-substituted metabolites of drugs containing exocyclic and electron-rich nitrogen atoms are chemically unstable and susceptible to subsequent transformations, leading to the production of secondary metabolites in addition to nitrenium ions (**3**), such as: nitrones (**4**) if there are hydrogen atoms in α, nitroso- (**5**) and nitro- (**6**) metabolites if one of the two substituents is an hydrogen (R' = H, Fig. 2).

All these reactive secondary metabolites can cause severe toxicity and, for this reason in the past some drugs were withdrawn from the market. For example, Zimeldine (**7**, Fig. 3) a clinically effective antidepressant drug was withdrawn from the market due to unexpected incidences of the Guillain-Barré syndrome and other peripheral neuropathies [7], because of the formation of a *N*-hydroxy metabolite which is further metabolized to a nitrone derivative (90-95% of the total hydroxylamine metabolite) as shown in Fig. 3 [8].

In general, most of the drugs including aliphatic amines (primary, secondary and tertiary), alicyclic amines, aromatic amines (primary, secondary and tertiary), *N*-heterocycles are potentially susceptible to *N*-oxidation resulting to *N*-hydroxy metabolites. Thus, the knowledge of these metabolic transformations allows a rationale design of safer molecules either by changing the electron-density on these sensible portions, leading to the production of safer *N*-OH containing bioactive molecules, or by modifying the substituents present on the nitrogen atom. In any case, the design of new drugs generally avoids the introduction of *N*-OH structural portions for the abovementioned concerns.

Nowadays, a wide range of *N*-hydroxy derivatives included into acyclic portions have been identified to possess interesting pharmacological properties. Among them, chemistry of *N*-hydroxy derivatives such as hydroxamates (**8**), amidoximes (**9**), *N*-hydroxyurea (**10**) and aldoximes (**11**), have been explored in the production of various types of bioactive molecules (Fig. 4).

For example, some extensively explored hydroxamic acids have been identified to be able to inhibit histone deacetylase (HDAC) enzymes. Inhibition of HDACs is a clinically validated therapeutic strategy for treatment of various types of cancers [9-11]. Furthermore, some hydroxamates, *N*-hydroxyamidoximes, *N*-hydroxyureas displayed inhibitory activity against matrix metalloproteinases (MMPs), lysine-specific demethylase 1 (LSD1), human epidermal growth receptor 2 (HER2), TNF-α converting enzyme (TACE), inosine monophosphate dehydrogenase (IMPDH), and carbonic anhydrases (CA). All these effects were found to be potentially useful in the treatment of various pathologies, such as cancer, viral infections, rheumatoid arthritis and multiple sclerosis [12-20]. Furthermore, *N*-hydroxyamidoximes and *N*-hydroxyureas also showed antiprotozoal, antibacterial, anti-human immunodeficiency virus (HIV) and anti-leishmania activity [21,22]. In particular, several compounds belonging

to these classes proved to be useful drugs in clinical or preclinical studies, such as the HDAC inhibitors suberoylanilide hydroxamic acid (SAHA, Vorinostat, **12** in Fig. 5) [23], *m*-carbocinnamic acid bishydroxamide (CBHA, **13**) [24], Scriptaid (**14**) [25], the sulfonamide derivatives PXD101 (Belinostat, **15**) [26] and Oxamflatin (**16**) [27], and the 3-substituted indole derivatives LBH589 (Panobinostat, **17**) [28] and NVP-LAQ824 (Dacinostat, **18**) [29] (Fig. 5).

Finally, some aromatic aldoximes were developed as potent and selective estrogen receptor β (ERβ) agonists by both industrial [30-32] and academic groups [33,34].

The secret of success of these classes of exocyclic *N*-hydroxylated derivatives should be found in their metabolic stability. In fact, hydroxamates such as Vorinostat **12** (Fig. 5) are indeed metabolized by *O*-glucuronation or *O*-sulfation. However, the resulting conjugates are stable and are excreted as such without the generation of reactive intermediates, since the acyl-substituent on the nitrogen atom makes it quite electron-poor and, therefore, less prone to bear the positive charge of the nitrenium species, which are instead produced by electron-rich *N*-hydroxyamines (Fig. 2). For similar reasons, aromatic aldoximes are also stable towards this type of metabolism and, moreover, they are also quite resistant towards hydrolytic processes [35].

In spite of the success of the above-mentioned exocyclic (and electron-poor) *N*-hydroxy-derivatives, there is only a limited number of reports about heterocycles containing endocyclic *N*-hydroxy-portions, which should benefit from a comparable metabolic stability, since they are not prone to generate reactive intermediates, such as nitrenium ions and nitrones. There is a growing interest in expanding the chemical space of new potential therapeutic agents and *N*-hydroxy heterocycles may represent a newly emerging structural motif. Therefore, this review covers the scientific literature describing heterocycles containing endocyclic *N*-OH portions that proved to possess biorelevant properties. Fig. 6 gives a general overview of the various chemical classes which are systematically discussed herein. Chemical structures in red and green color are five-membered and six-membered heterocycles, respectively, which are shown in the inner yellow circle. Chemical structures in blue and black color respectively comprise five- and six-membered heterocyclic rings that are fused with other aromatic rings, and are placed in the outer black circle.

2. *N*-Hydroxy-substituted five-membered heterocycles

2.1. One endocyclic heteroatom

2.1.1. Pyrrolidinones, pyrrolidinethiones and pyrrolidinediones—*N*-Hydroxy-substituted pyrrolidinones, pyrrolidinethiones and pyrrolidindiones are heterocycles of great biopharmacological importance, because of their presence in numerous molecules showing interesting pharmacological applications. 3-Amino-1-hydroxypyrrolid-2-one, named as HA-966 (**19** in Fig. 7), was first synthesized in 1959 and displayed various neuropharmacological properties. Chemically, it is similar to the cyclic form of the well-known amino acid γ-aminobutyric acid (GABA), which is an important inhibitory neurotransmitter in mammalian central nervous system. Bonta *et al.* reported that HA-966 **19** showed various interesting properties, such as antitoxic effect against amphetamine-

induced motor activity, selective central antitremor effect against tremor induced by chemical agents, antidepressant and anticonvulsant effects in mammals [36]. Further studies reported that it was one of the first substances endowed with moderately strong and selective action in antagonizing L-glutamate- or L-aspartate-evoked excitation of single neurons in the cerebral cortex. It reduced the excitatory effect of L-glutamate- or L-aspartate, while it had either no effect or weak effect on acetylcholine response. Hence, HA-966 reduced aminoacid-evoked responses stronger than that induced by acetylcholine [37]. The same authors reported a weak depressant action of HA-966 on chemically and synaptically excited neurons in cat cerebral cortex nucleus and potency of HA-966 relative to GABA was similar. Direct action of HA-966 on synaptic responses of central neurons may contribute to its complex effects and a blockade of excitatory amino acid receptors may contribute substantially to the depressant action on L-glutamate- and L-aspartate-induced excitation [38,39]. Moreover, selective action of HA-966 at the glycine modulatory site of the *N*-methyl-D-aspartate (NMDA) receptor complex was reported as maximum interaction at the highest concentration of 250 μM, and further increasing the concentration of HA-966 did not increase the degree of antagonism. In radioligand binding experiments, this compound inhibited strychnine-insensitive [^{3}H]-glycine binding to rat cerebral cortex synaptic plasma membranes with an IC_{50} of 17.5 μM, and on increasing concentration up to 1 mM it caused minimal inhibition. These results demonstrated that the activity of HA-966 was due to the antagonism at the glycine modulatory site on the NMDA receptor complex [40-42]. Further studies of HA-966 suggested that (*R*)-(+)-enantiomer (**19a**, Fig. 7) was a selective inhibitor of glycine/NMDA receptor and this property was responsible for its anticonvulsant action *in vivo*. In contrast the (*S*)-(-)-enantiomer (**19b**, Fig. 7) showed only a weak interaction with glycine/NMDA receptor, but it displayed some significant muscle relaxation and sedative action. Nevertheless, the sedative/ataxic effect of racemic HA-966 was mainly attributable to the (*S*)-(-)-enantiomer which was 25-fold more potent than (*R*)-(+)-enantiomer [43]. Furthermore, the neuroprotective action of HA-966 was mainly due to its (*R*)-enantiomer **19a** and it reduced NMDA-induced brain injury, whereas the other enantiomer was ineffective. Intravenously, racemic HA-966 and its (*S*)-enantiomer **19b** prevented tonic extensor seizures from low-intensity electroshock with ED_{50} at 13.2 and 8.8 mg/kg, respectively, whereas the anticonvulsant effects of the (*R*)-enantiomer were much less potent (ED_{50} = 105.9 mg/kg) [44]. *R*-(+)-HA-966 **19a** significantly disinhibited both non-conditioned and conditioned suppressed behavior in rodents in preclinical models of anxiety, acting as anxiolytic without relevant side effects, while the *S*-(-) enantiomer **19b** was devoid of any anxiolytic activity and it only produced behavioral sedation [45]. The enantiomer **19b** also prevented *in vivo* restraint stress-induced dopamine utilization in brain regions in contrast to the lack of efficacy of its (*R*)-enantiomer, and it also suppressed fear-induced behaviors. At the dose of 3 mg/kg, **19b** prevented locomotor sensitization *in vivo*, and at the highest dose of 5 mg/kg, it blocked acute cocaine-induced locomotion, but this treatment resulted in sedation of the animal, because this compound seems to act through the γ-hydroxybutyrate (γHB) binding site on the GABA receptor. This compound may thus represent a novel structural example of potential anxiolytic agents with γHB-like actions [46]. Continuous efforts were made aimed at identifying more potent analogues of HA-966, devoid of side effects and characterized by an improved brain penetration [47]. In particular Leeson *et. al*. reported a (*3R, 4R*)-*cis*-4-methyl derivative of HA-966 (**20**, also named

L-687,414, Fig. 7), which was found to be a more potent glycine/NMDA receptor antagonist than HA-966,whereas its *trans* diastereoisomer was inactive [48]. The additional methyl group in **20**, when compared to compounds **19a** and **19b**, may increase the hydrophobic contribution to the binding process to the glycine site of the receptor, but it may also affect the conformation of the five- membered ring. In addition to the above-mentioned (*3R,4R*)-derivative **20**, the [3.2.l] bicyclic analogue **21** (Fig. 7) indicated that the energetically unfavorable conformation of the pyrrolidone ring, having the 3-amino group in a pseudoaxial situation, is essential for recognition by the glycine receptor. Hence, glycine receptor recognition requires the energetically less favoured 3-pseudoaxial conformation of the pyrrolidone ring, resulting in compound **20** being a more potent glycine/NMDA receptor antagonist than **19a** [49]. Further development of di-substituted derivatives of racemic HA-966 by the same group demonstrated that only the *cis* orientation at 4-position allowed substitution and there was a strict tolerance to substituent size by the receptor. Ethyl derivative **22a** (Fig. 7) displayed an IC_{50} value of 15 μM, which is equipotent to **19a** (IC_{50} = 12.5 μM), but less active than **20** having the IC_{50} value of 1.4 μM, in the [^{3}H]-glycine binding to rat cortical membrane assay. 4-Hydroxy-substituted derivative **22b** (Fig. 7) proved to have a similar antagonist activity (IC_{50} = 1.3 μM) to the corresponding methyl-substituted analogue **20**. Hence, the *cis*-4-methyl (**20**) and *cis*-4-hydroxy-substituted (**22b**) compounds exhibited similar *in vitro* anticonvulsant activities and good brain penetration levels, since they are not ionized at physiological pH. A smaller bicyclic analogue of compound **21** (IC_{50} = 19 μM) was also synthesized by reducing the length of the N-C5 ethylene bridge in **21** to a methylene portion, as in the [2.2.1]bicyclo-derivative **23** (Fig. 7), which proved to retain antagonist activity on the same receptor. However, the instability of **23** in aqueous solution did not allow an accurate determination of IC_{50} value [47]. *N*-hydroxy-2-pyrrolidinethione compound **24** (Fig. 7) when present in a zinc complex showed a good anti-microbial activity [50]. In addition, dioxopyrrolidine derivative **25** (Fig. 7) was an optically active derivative containing a sulfonylamino succinimide moiety, that showed some interesting inhibitory activity against the isoform 2 of matrix metalloprotease (MMP-2), an enzyme involved in tumor invasion. *In vitro* studies revealed that it exhibited a potent MMP-2 inhibitory activity, with an IC_{50} value of 0.0274 μM [51].

2.2. Two endocyclic heteroatoms

2.2.1. Imidazolidinones, imidazolidinediols and imidazolinethiones—*N*-

Hydroxy-imidazoles and derivatives are important bioactive small organic molecules. *N*Hydroxy imidazolidinone derivative **26** (Fig. 8) was found to exhibit affinity and efficacy similar to that of D-cycloserine, a representative partial agonist for the strychnine-insensitive glycine binding site of NMDA receptor. It was a potent ligand for strychnine-insensitive glycine binding site, with an IC_{50} value of 6.8 μM. It was reported that compound **26** possesses higher affinity than that of the partial agonist D-cycloserine, but it exhibits moderate affinity and an efficacy lower than the full agonist glycine, therefore it would be a useful tool in the exploration of the therapeutic potential of ligands interacting with glycine site of the NMDA receptor [52,53]. Compound **26** displayed an inhibitory activity against the interaction of glutamate with two receptors belonging to the same family of NMDA receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) and the kainate receptors, which play important functions in pathogenesis of cancer, thus proving to be

likely useful in treating cancer [54]. Similar kind of *N*-OH bearing small molecules, such as spiroimidazolidinone derivatives 1-hydroxy-7,7,9,9-tetramethyl-1,4,8-triazaspiro[4.5]decan-2-one **27a** (Fig. 8) and (±)-1-hydroxy-3,7,7,9,9-pentamethyl-1,4,8-triazaspiro[4.5]decan-2-one **27b** (Fig. 8) were reported by Vystorop *et al.* and ESR spectroscopy studies showed that these cyclic spirohydroxamic acids behave as NO donors in *in vitro* biological systems. The NO-donor activity of compounds **27a** and **27b** was found to be substantially higher in the presence of DMSO, compared to the aqueous medium. Compound **27b** was a stronger NO-donor than **27a** and it also exhibited a high antimetastatic activity on the B16-melanoma model, since NO-donor agents are known to display various pharmacological effects, including a cytotoxic action [55]. Nieto *et al.* presented a dimeric *N*-hydroxy-imidazole (**28**, Fig. 8), which is an analog of the trypanocidal agent 4,4'-bis(imidazolinylamino)diphenylamine. Compound **28** showed antiprotozoal activity in the submicromolar range, as shown by its IC_{50} values of 0.37 and 0.055 μM against *Trypanosoma brucei rhodesiense* and *Plasmodium falciparum*, respectively. Furthermore, compound **28** showed a significantly higher permeability through human blood-brain barrier, when compared to its non hydroxylated counterpart, as determined *in vitro* by transport assays through the human brain endothelial CMEC/D3 cell line. These results showed that the introduction of a hydroxyl group on the nitrogen atom of the imidazolyl ring enhanced the blood-brain barrier permeability of the resulting molecule (**28**). Furthermore, in the *T. brucei* STIB900 murine model of acute sleeping sickness, compound **28** was found to possess moderate activity at a dosage of 20 mg/kg by intraperitoneal administration and this modest effect might reflect an incomplete bioactivation of the molecule *in vivo* [56]. *N*-Hydroxy derivatives **29a-e** (Fig. 8) displayed inhibitory effects on platelet aggregation in the range 28.9-54.2% at the concentration of 0.2 mg/mL, thus proving to be more efficient than aspirin, which showed a 24.6% inhibitory effect at the same concentration. Compound **29c** displayed the most efficient inhibitory effect among the compounds of this series (54.2%), which was even higher than that of ticlopidine (44.6%) on platelet aggregation. A study of acute toxicity of these compounds showed that LD_{50} lay in the range 500-2500 mg/kg, thus proving that these compounds presented a low toxicity. Observation of the systemic arterial pressure variations after administration of these compounds suggested that compound **29e** exhibited a combination of antihypertensive activity and 32.1% inhibition of platelet antiaggregation, which resulted in a high clinical priority for this compound, since both mechanisms synergistically contribute to the treatment of hypertonic disease [57]. Compound **30** (Fig. 8) bearing two OH groups on its two nitrogen atoms was found to be active against *Bacillus cereus*. The mechanism of action of **30** was hypothesized to involve a bidentate chelation of zinc ions of the active site of the *Bacillus cereus* phospholipase C. In fact, it did not exhibit significant inhibition of this enzyme at pH 7.3, whereas it turned out to be active at pH 9.5, in fact ionized *N*-hydroxyl function would be expected to bind better than a neutral hydroxyl group to an active site zinc ion [58]. 1-Hydroxy-4-(4-methoxyphenyl)-1*H*-imidazole-2(3*H*)-thione **31** (Fig. 8) was prepared and tested as tyrosinase inhibitor, useful for the treatment and prevention of hyperpigmentation. In enzymatic assays, this compound exhibited a potent tyrosinase inhibitory activity with an IC_{50} value of 3.7 μM, so that it might find application in cosmetic preparations for the prevention or treatment of signs of aging or dry skin [59].

2.2.2. Thiazolidinones and thiazolidinethiones—Oxalatrunculin B **32** (Fig. 9), a natural product containing a *N*-hydroxylated thiazolidinone ring, was isolated from Red Sea sponge *Negombata corticata*. Actin polymerization inhibition assays and molecular modeling calculations demonstrated that oxalatrunculin B weakly bound to actin and exhibited significant antifungal and anticancer activity. Compound **32** displayed a significant antifungal activity against *Saccharomyces cerevisiae* with a MIC value of 56 μM. Cytotoxicity of oxalatrunculin B against several cancer cell lines suggested that compound **32** displayed nonspecific cytotoxicity against solid tumor cells and hematopoietic cancerous cells, possessing MIC value of 16.3 μM against hepatocellular carcinoma. The weak binding to actin and the stronger cytotoxic activity suggest that may exist a secondary target responsible for the different activities of **32** [60]. Austin *et al.* patented a series of *N*-hydroxy derivatives as industrial biocides. Out of these compounds, 3-hydroxy-4-methyl-thiazol-2(3*H*)thione **33** (Fig. 9) at the concentration of 25 ppm completely inhibited *Escherichia coli* proliferation and at 1 ppm completely inhibited viability of *Staphylococcus aureus* and *Aspergillus niger* [61]. A bivalent zinc complex of **33** at 1000 ppm inhibited the growth of bacteria and yeast such as *Escherichia coli*, *Enterococcus faecalis* and *Candida albicans*. This metal complex also reduced odor and inhibited the pH increase, hence it could be used as the absorbent layer in disposable articles for collecting body fluids [62]. Furthermore, the same author reported a similar derivative, *p*-chlorophenyl substituted compound **34** (Fig. 9), that showed an antimicrobial activity against *Pseudomonas aeruginosa* together with a low toxicity. This could be useful in a personal care formulation for cosmetic compositions containing compound **34** as an antimicrobial agent [63].

3. *N*-Hydroxy-substituted six-membered heterocycles

3.1. One endocyclic heteroatom

3.1.1. Piperidines—*N*-Hydroxy-substituted six membered ring systems, *i.e.* piperidine derivatives, have great importance due to their numerous biological applications. *N*-hydroxy-substituted piperidines displayed broad spectrum of biological activities, such as: antioxidant properties for the treatment of cellular oxidative stress, or anxiolytic and antidepressant activities, or they can be used in arresting the development of cataracts or macular degeneration, or they possess anti-inflammatory activity in the liver, which might be useful in the treatment of hepatitis, as well as an anti-angiogenic activity [64-68]. Komarov *et. al.* reported the antioxidant properties of some *N*-hydroxy derivatives of 2,2,6,6-tetramethylpiperidines, such as compound **35** (Fig. 10). **35** showed *in vitro* effective antioxidant properties on membrane models of lipid peroxidation, and significantly it slowed down the rate of peroxidation at concentrations of 10^{-6}-10^{-5} M. An increase in the length of the alkyl chain on the sulfur atom caused a reduction of the anti-oxidative effect of the resulting compound. The antioxidant effect observed with this compound is due to the oxidation to the corresponding nitroxyl radicals in aqueous medium. Moreover, compound **35** proved to be active in the treatment of ischemic and reperfusive injuries caused by lipid peroxidation in biomembranes. The anti-ischemic activity was demonstrated in models of long-term storage of isolate liver, as well as on models of ischemia of the liver, isolated ischemized heart, and ischemic shock [69]. *N*-hydroxytetramethylpiperidine derivatives **36**, **37a-b** and **38** (Fig. 10) showed interesting inhibitory activities against the cytokine Tumour

Necrosis Factor α (TNFα) protein: **36**, **37a-b** and **38** exhibited IC_{50} values of 3.8, 1.0, 0.9 and 6.7 μM, respectively. Compound **38** also exhibited lipid peroxidation inhibitory activity of 91.4% at 10 μM and 87% at 1 μM. The less active compounds **36**, **37a** and **37b** showed 64.4% 83.8% and 81.8% of lipid peroxidation inhibitory activity at 1 μM. Compound **38** alone efficiently exerted its cytotoxic action on both doxorubicin-resistant cells as well as sensitive cells, revealing that these type of inhibitors are able to bypass drug resistance. Further studies of compound **38** in combination with doxorubicin demonstrated that **38** displayed strong ability to reverse drug resistance in osteosarcoma, breast cancer and neuroblastoma [70,71].

3.2. Two endocyclic heteroatoms

3.2.2. Pyrazinones and piperazinones—Pyrazinones and piperazinones substituted with *N*-hydroxy groups have so far shown a significant biological importance, because of their emergence as subunits of various bioactive natural products as well as of other synthetic molecules. Natural product flutamide **39** in Fig. 11, a fully substituted 2,6-diketopirazine, which was isolated from fungus *Delitschia confertaspora*, exhibited inhibitory activity against cap-dependent transcriptase of influenza A and B viruses and it had no effect on the activities of other polymerases, hence it selectively inhibits the transcriptase of influenza viruses [72,73]. Both natural and synthetic flutamide [74,75] are endowed of inhibitory activity against influenza virus A transcription, with comparable IC_{50} values of 5.1 and 5.6 μM respectively, without showing any activity against other transcriptases. Compound **39** proved to efficiently inhibit the replication of influenza A and B viruses in cell culture. The selective antiviral properties of this natural product validate influenza virus endonuclease as a target for antiviral agents. A natural product known as scleriminol **40** (Fig. 11) was isolated from cultures of hypovirulent isolates of the fungal plant pathogen *Sclerotinia minor*, with a 1-hydroxy-2,6-pyrazinedione structure similar to flutamide. On the basis of the structural similarity with flutamide, scleriminol **40** was tested for the same biological activity, but this compound proved to be inactive on influenza virus cell lines. The role of this compound in the physiology of hypovirulent isolates of *S. minor* has not been determined yet [76]. Natural products NBRI16716A **41** and NBRI16716C **42** in Fig. 11 were isolated from the fermentation broth of *Perisporiopsis melioloides* and include in their structures several *N*-OH groups, in the endocyclic piperazine nitrogen atom and in the side chains. These compounds showed antitumor activities against human prostate cancer cells DU-145, and they inhibited the growth of these cells in their co-culture with human prostate stromal cells PrSCs without apparent cytotoxicity against PrSCs. Moreover, **41** showed efficient antitumor effect in xenograft models of DU-145 cells with PrSCs, without any effect on body weight of mice [77].

Synthetic small molecules deriving from natural product flutamide **39** were obtained by including various aromatic substituents in its structure and displayed interesting activities. Some of the most active compounds against cap-dependent endonuclease activity of influenza virus were obtained by replacing one of the isopropyl groups of flutamide with *p*-substituted phenyl groups, such as a *p*-fluorophenyl derivative **43a** and a *p*-methoxyphenyl derivative **43b** in Fig. 12. In fact, compounds **43a** and **43b** displayed IC_{50} values of 0.9 and 0.8 μM *in vitro*, respectively, *vs.* flutamide **39** which instead exhibited an IC_{50} of 5.1 μM in

the same assay. Monoaryl-substituted compounds **43a** and **43b** appeared to be more potent in the cell-based antiviral assay too, but unfortunately they showed a certain degree of cytotoxicity at concentrations greater than 10 μM, whereas natural product flutamide **39** did not show any appreciable toxicity at a concentration of 100 μM. Replacement of both alkyl substituents of flutamide with two phenyl rings (**44a-c**, Fig. 12), caused only a slight improvement in the activity for compounds **44b** and **44c** (IC_{50} = 2.8 and 3.5 μM, respectively) compared to the value of flutamide, whereas compound **44a** was nearly equipotent to flutamide (IC_{50} = 6.5 μM) [78]. Tomassini *et al.* studied the pharmacological activities of these chemically-modified analogs of flutamide. A structure-activity relationship analysis demonstrated that both *N*-hydroxy- and olefin groups in substituted 2,6-diketopirazine derivatives were required for activity. The aromatic substitution of the isopropyl side chains caused an increase in potency. Conversely, removal or transformation of *N*-hydroxy group resulted in a decrease of activity [73]. Marques *et al*. reported sulfonamide derivatives which displayed a good ability in inhibiting MMPs. These derivatives possess a new type of zinc-binding group at the enzyme catalytic center, and exhibited an inhibitory activity in the nanomolar range. The phenoxyphenly sulfonamide derivative **45** (Fig. 12) exhibited an efficient inhibitory activity against MMPs thanks to its ability to chelate the catalytic zinc ion of these enzymes. Compound **45** was screened against a broad spectrum of MMP isoforms and TACE and it showed a predominant inhibitory activity against MMP13 with an IC_{50} value of 9.5 nM, thus confirming that the 1-hydroxypiperazine-2,6-dione moiety may represent a valid potential substitute for the hydroxamate moiety as zinc binding group, typically present in most MMP inhibitors [79]. Other small heterocyclic molecules, such as pyrazinone derivative **46** in Fig. 12, were synthesized as artificial siderophores, as potential therapeutic agents for iron overloaded disease. Compounds **46** was reported as one of the first examples of microbial growth-promoters on *Aureobacterium flavescens* JG-9, showing the highest growth-promotion activity comparable to that of desferrioxamine B, which is a natural trihydroxamate siderophore [80].

4. *N*-Hydroxy-substituted fused five-membered ring systems

4.1. One endocyclic heteroatom

4.1.1. Indoles—*N*-Hydroxyindoles are fascinating molecular entities, which have attracted considerable attention of medicinal chemists. In fact, *N*-hydroxyindoles were found to be an integral part of the structure of some complex natural products (**47-48**, Fig. 13 and Table 1). Recently discovered natural products birnbaumin A **47a** and birnbaumin B **47b** in Fig. 13, having *N*-hydroxyindole moieties in their structure, were isolated from extract of yellow fruit bodies of the tropical mushroom *Leucocoprinus birnbaumii.* However, no biological properties for these two natural compounds have been identified yet [81].

N-Hydroxyindole-bearing natural product S-54832/A-I **48a** (Table 1), a thiazolyl peptide-based antibiotic, was isolated in 1984 from *Micromonospora globosa* cultures, and it exhibited excellent growth-inhibiting effect toward Gram-positive bacteria, including Staphylococci, Streptococci, Corynebacteria and Mycobacteria *in vitro* and against *Staphilococcus pyogenes*, *pneumoniae* and *S. aureus in vivo* [82,83]. *N*-Hydroxyindoles

were also found in nocathiacins I **48b**, III **48c** and IV **48d** in Table 1, a series of antibiotics that were independently isolated by two research groups from bacteria species *Nocardia* and the fungus *Amicolaptosis* and they closely resemble the structure of compound **48a** [84-86]. These nocathiacins (**48b-d**) exhibited *in vitro* and *in vivo* antibacterial activity against Gram-positive bacteria including multi drug-resistant strains, *Mycobacterium tuberculosis* and *Mycobacterium avium*. Nocathiacin I **48b** revealed a nanomolar potency against *S. aureus* strains and an excellent *in vivo* efficacy in a systemic *S. aureus* infection mice model. It was also active against Gram-positive anaerobes, revealing a clinical potential for these compounds to be used as antibiotics in humans [87,88]. Other natural products bearing *N*-hydroxyindole moiety are thiazomycin **48e** and thiazomycin A **48f** in Table 1. They are thiazole-rich potent antibacterial antibiotics that differ from nocathiacins for the oxazolidine ring as part of the amino-sugar moiety in contrast to the dimethyl amino group (R_2 in Table 1). They were isolated from *Amycolatopsis fastidiosa* and were found extremely potent and selective against Gram-positive pathogens *in vitro* and in *vivo* with MIC range 0.002-0.064 μg/ml. The *in vitro* activity of thiazomycin A **48f** was generally slightly lower than thiazomycin and nocathiacin I, suggesting a detrimental role of the methyl substitution in the sugar moiety. Thiazomycin **48e** showed ED_{99} value of 0.15 mg/kg and was highly efficacious against *Staphylococcus aureus via* subcutaneous administration in mice. Furthermore, nocathiacin and thiazomycin antibiotics exhibited antibacterial activity by selective inhibition of protein synthesis through a direct interaction with the L11 protein and 23S rRNA of the bacterial 50S ribosome. Moreover, they did not show any cross-resistance to clinically used antibiotic classes, such as vancomycin, oxazolidinones and quinolones [89-91]. Similarly, thiazomycin A **48f** selectively inhibited protein synthesis with IC_{50} value of 0.7 μg/ml and it did not inhibit any other macromolecules as RNA, DNA, peptidoglycan, and phospholipid of *S. aureus* [92]. In general, *N*-hydroxyindole scaffold-bearing natural products showed excellent activity against Gram-positive bacteria and could be further developed as anti-bacterial agents.

Due to the promising antibacterial activity of nocathiacins and to the presence of several functional groups in their structure suitable for chemical manipulation, some research groups reported the semi-synthetic derivatives of these natural products in order to improve aqueous solubility while maintaining the intrinsic biological activity [93,94]. Representative *N*-hydroxyindole scaffold-based semi-synthetic products **49a-c** in Table 2 were obtained by the addition of amines to the dehydroalanine side chain of nocathiacin I, in particular primary, secondary and cyclic amines with different functional groups were inserted to create analogues of nocathiacin I. The resulting compounds were endowed of potent antibacterial activity *in vitro* on a panel of Gram-positive bacteria along with good *in vivo* efficacy in a lethal *S. aureus* systemic infection model and good solubility. Among the primary amine analogues, the ethylendiamine derivative **49a** reached the best MIC values against methicillin-sensitive *Staphylococcus aureus* (MIC = 0.25 μg/mL), methicillin-sensitive *Enterococcus faecalis* (MIC = 0.5 μg/mL) and penicillin-resistant *Streptococcus pneumoniae* (MIC = 0.03 μg/mL), but it had overall decreased antibacterial activity compared to the parent compound nocathiacin I (MIC = 0.007, 0.03 and 0.001 μg/mL against *S. aureus*, *E. faecalis* and *S. pneumonia*, respectively). The 2-(methylamino)ethanol analogue **49b** and the morpholine analogue **49c** exhibited antibacterial profiles *in vivo* and *in*

vitro comparable to nocathiacin I. These derivatives showed better water solubility in comparison to the parent compound, especially **49b** possessed a solubility higher than 10 mg/mL, significantly improved compared to that of nocathiacin (0.34 mg/mL). Consequently, **49b** was proposed as a lead candidate for further study and safety evaluation on the basis of its promising properties and activity [95]. A different amide substitution on thiazole ring gave compounds **50a** and **50b** (Table 2) that exhibited potent *in vitro* antibacterial activity against *S. aureus*, *S. pneumoniae* and *E. faecalis*. The *N*-methyl-piperazinyl compound **50a** produced a significant reduction of kidney burden in a systemic *S. aureus* infection mouse model, with ED_{99} value of 0.28 mg/Kg comparable to that of vancomycin. Derivative **50b** with a neutral urea side chain displayed excellent antibacterial activity both *in vitro* (MICs range 0.0038-0.25 μg/mL) and *in vivo* and it exhibited acceptable aqueous solubility, thus revealing to be one of the most potent water-soluble nocathiacin analogues synthesized to date [96]. Finally, *O*-substituted derivative of nocathiacin I **51** in Table 2 also showed potent antibacterial activity with MICs ranging from 0.06 to 0.25 g/mL against the same series of pathogens. Compound **51** retained the *in vivo* potency of nocathiacin I (PD_{50} = 0.26 mg/Kg). Moreover, mono-methylphosphonate **51** possessed very good aqueous solubility [97].

Not only natural products and semi-synthetic compounds deriving from natural products showed excellent pharmacological properties, but recently also synthetic *N*-hydroxyindole heterocycles have acquired importance in the medicinal chemistry field. *N*-hydroxyindole-based compounds (NHIs) were reported as new and efficient inhibitors of the human isoform 5 of the enzyme lactate dehydrogenase (*h*LDH5), which is involved in the growth and survival of hypoxic tumours, with potential therapeutic applications of NHIs as anti-cancer agents [98,99]. *N*-hydroxyindole-based LDH inhibitors possess a hydroxyl group on the nitrogen atom at position 1, along with a carboxylic group at position 2 of the indole scaffold. The X-ray crystal structures of *h*LDH5 show that the enzymatic cavity is quite polar and rich in cationic residues such as arginines, because normally hosts the substrate pyruvate and the cofactor NADH, hence the OH/COOH moiety should bind in the catalytic binding site of the enzyme, as confirmed by molecular modeling studies. An extensive structure-activity relationship was made on the aryl-substituted NHIs and revealed that aryl substituents were generally beneficial for the activity, particularly if they were placed at position 5 and 6. Moreover, the presence of electron-withdrawing substituents in the aryl groups or of additional aryl portions generally improved inhibitory potency. Compound **52a** (Fig. 14), in which the phenyl group was present in position 5 and compound **52b** (Fig. 14) with the phenyl in position 6 showed 99% and 84% inhibitory activity of *h*LDH5, respectively, at 125 μM and less than 3% inhibition of the heart isoform *h*LDH1, thus revealing a good level of selectivity. The presence of the electron withdrawing group $-CF_3$ at 4 position and a phenyl ring at 6 position in compound **52c** (Fig. 14) caused a 87% inhibition of *h*LDH5 although against *h*LDH1 a minimal residual activity (11%) was observed. All these three compounds were competitive versus NADH and pyruvate, with K_i values in the low micromolar range (K_i's ranging from 4.7 to 35.4 μM). Cellular assays revealed that these NHIs were able to reduce lactate production in cancer cells and they possessed a strong antiproliferative activity, which was particularly pronounced under hypoxic conditions [100,101]. Further modification at 6 position with triazole ring in place

of phenyl ring decreased the inhibitory potency noticeably, but when the triazole ring was moved to position 4 it produced a good *h*LDH5 inhibitory activity, as for compound **53** (Fig. 14) that selectively inhibited of 73% the enzymatic activity. A sharp preference for *h*LDH5 was also found with dimeric compound **54** in Fig. 14, in which two *N*-hydroxyindole portions at their 6 positions are linked through a 1,3-bis(triazole)-propane chain, with a 83% inhibitory activity, but it also displayed 32% inhibitory activity against *h*LDH1 [102]. In the case of compound **55** (Fig. 20), insertion of *para*chloro atom in the *N*-phenyl ring of *N*-methylsulfonamide portion at position 6 of the indole scaffold led to efficient inhibition levels versus both the cofactor (K_i = 6.6 μM) and the substrate (K_i = 5.6 μM) [103]. *N*-hydroxy derivative **56** (Fig. 14) substituted at 2 position with an urea moiety and at 3 position with an unsubstituted amide revealed inhibitory activity on Iκb kinase β (IKKβ) of 86% at 1 μM. Thanks to the IKKβ inhibition activity, compound **56** could be useful as a prophylactic and/or therapeutic agent for several kinds of diseases associated with IKKβ activity [104]. Somei *et. al.* developed a variety of *N*-hydroxy derivatives with promising pharmacological application and they found that *N*-hydroxytryptamines play an important role in inhibition of blood platelet aggregation, hence they have potential utility for the treatment of erectile dysfunction and cerebral infarction. Compounds **57a-b** (Fig. 14) are tryptamine derivatives differing for the length of the acyl side chain and reached vascular relaxation effects about 66 and 79% respectively, compared to the α2-blocker yohimbine that was considered as a standard control (100%) [105]. Compound **58a-b** (Fig. 14) based on 3-cyano-2-phenyl-substituted-*N*-hydroxyindole scaffold exhibited fungicidal activity on leaf rust on wheat plant against pathogen *Puccinia recondita*, possessing EC_{50} values of 60 and 50 ppm, respectively [106].

4.1.2. Carbazoles and carbolines—*N*-hydroxy substituted carbazoles and carbolines are an important class of heterocycles, mainly present in natural products. Novel alkaloid coproverdine **59** (Fig. 15) possessing a *N*-hydroxycarbazole ring was isolated from marine organisms from New Zealand. Coproverdine displayed cytotoxic activity against a variety of murine and human tumor cell lines, with IC_{50} values ranging from 0.3 to 1.6 μM [107,108]. *N*-hydroxy pyrimidine-β-carboline alkaloid *N*-hydroxyannomontine **60** (Fig. 15) was isolated from the bark extract of *Annona foetida*, a plant of the Annonaceae family. The natural product **60** was characterized by antiparasitic activity against *Leishmania braziliensis* and *Leishmania guyanensis*, that are the main causes of leishmaniasis. It exhibited IC_{50} values of 437.5 and 252.7 μM against *L. guyanensis* and *L. braziliensis*, respectively [109]. Alkyl-guanidine-substituted β-carboline-based natural product opacaline B **61** (Fig. 15) was isolated from the New Zealand ascidian *Pseudodistoma opacum* and it exhibited a moderate antimalarial activity toward a chloroquine-resistant strain of *Plasmodium falciparum*, with an IC_{50} value of 4.5 μM (chloroquine was used as positive control, IC_{50} = 0.28 μM). Opacaline B was further screened against a wide range of parasites and it showed IC_{50} values of 27, 107 and 101 μM against *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi* and *Leishmania donovani* respectively, without being toxic toward the non-malignant L6 rat skeletal myoblast cell line [110].

4.1.3. Other *N*-hydroxy-heterocycles—Among the *N*-hydroxy five-membered rings in tricyclic, tetracyclic or more complex natural products, we can mention omphalotins F-I

62a-d in Fig. 16 that are *N*-hydroxylated tricyclic tryptophan derivatives isolated by Liermann *et. al*. from mycelial extracts of the basidiomycete *Omphalotus olearius*. Compounds **62a**, **62b**, **62c** and **62d** exhibited strong and selective nematicidal activity against the plant pathogen *Meloidogyne incognita*, with LD_{50} values of 2, 1, 0.5-1 and 1 μg/mL respectively, while the positive control ivermectin possessed a comparable LD_{50} value of 2 μg/mL. None of these compounds showed antibacterial or antifungal activities, neither cytotoxic effects towards mouse leukaemia cells or human colon adenocarcinoma cells at concentrations up to 50 μg/mL [111]. Notamide A **63** (Fig. 16) is an indole alkaloid bearing the bicyclo [2.2.2] diazaoctane, obtained from a culture of *Aspergillius* sp., which is a marine-derived fungus isolated from the common mussel *Mytilus edulis*. It showed modest biological properties, exerting only moderate cytotoxicity against some tumor cell lines [112]. The same pyranoindole ring present in the structure of notamide A was also found in the natural product stephacidin B **64** in Fig. 16, a very complex dimeric alkaloid isolated from the fungus *Aspergillus ochraceus*. Natural product **64** demonstrated potent *in vitro* cytotoxicity against several human tumor cell lines (IC_{50} range 0.26-0.46 μM) with a good selectivity observed for the testosterone-dependent LNCaP cells (IC_{50} = 0.06 μM), and the growth inhibition effect was exerted by strongly inducing apoptosis in cell cultures [113,114].

4.2. Two endocyclic heteroatoms

4.2.1. Benzimidazoles and benzimidazolones—In literature, some *N*-hydroxybenzimidazole-based compounds exhibited promising pharmaceutical applications, for example they were patented as anti-infective agents that decreased resistance, virulence or growth of microbes or as compounds endowed with fungicidal and fungistatic activity [115-117]. It is noteworthy to mention *N*-hydroxy-benzoimidazolones **65a-c** (Fig. 17) that showed *in vitro* potent inhibitory activity against human D-amino acid oxidase (DAAO), an enzyme that catalyzes the oxidation of D-amino acids to the corresponding imino acids and hydrogen peroxide. Compounds **65a-c** displayed IC_{50} values of 0.6, 0.1 and 0.08 μM respectively, but they also exhibited similar inhibitory activity against porcine isoform of DAAO. The inhibitory potency was largely dependent on the size and position of substituents on the benzene ring. The two substituted compounds **65b** and **65c** were administered to mice (30 mg/kg) along with D-serine at the same dosage in order to assess their effects on D-serine plasma levels. It was demonstrated that activation of NMDA receptor by D-serine provides a new therapeutic approach for the treatment of schizophrenia, but unfortunately D-serine nephrotoxicity was provoked by hydrogen peroxide generated by DAAO-mediated D-serine metabolism. Pharmacokinetics studies revealed that compound **65b** showed no effect on plasma D-serine due to the negligible oral bioavailability. Differently, the co-administration of **65c** and D-serine increased the levels of D-serine, but only in a short period of time, because of the poor bioavailability of **65c**. Metabolic stability tests of these compounds revealed that they were mainly metabolized by glucuronidation at the *N*-hydroxyl group, however this group was essential for the binding affinity to the DAAO active site. Therefore, new DAOO inhibitors should possess the *N*-OH group, but it would be necessary to optimize the presence of the surrounding substituents in order to improve the metabolic stability without compromise the activity [118]. *N*-hydroxybenzimidazole derivatives **66a-c** (Fig. 17) were reported as potent inhibitors of

LcrF, a multiple adaptational response transcription factor that regulates virulence in *Yersinia pestis* and *Yersinia pseudotuberculosis*. IC_{50} values of 3.9, 8.0 and 7.6 μM were reported for compounds **66a-c**, respectively, in LcrF-DNA binding assay. Similarly, **66a-c** were active also on ExsA, a multiple adaptational response transcription factor found in *Pseudomonas aeruginosa* with high homology with LcrF in the DNA binding domain, showing IC_{50} values of 3.5, 5.9 and 6.7 μM, respectively, in ExsA-DNA binding assay. In order to confirm their mechanism of action, these compounds were tested in an *in vitro* antimicrobial susceptibility test and they proved to be inactive against *Y. pseudotuberculosis* as well as *S. aureus* and *E. coli* bacteria, hence they did not target directly bacterial growth [119]. Similar *N*-hydroxybenzimidazoles **67a-c** (Fig. 17) were developed as anti-virulence agents against infections caused by *Pseudomonas aeruginosa* and they showed IC_{50} values of 3.0, 13 and 7.5 μM, respectively, in ExsA-DNA binding assay and they effectively reduced the cytotoxicity of *P. aeruginosa* in an *in vitro* whole cell assay. These compounds demonstrated good metabolic stability from *in vitro* human liver microsomal assay [120]. Compound **68** (Fig. 17) belongs to the same class of *N*-hydroxybenzimidazoles, but it is substituted on the distal phenyl with a triazole ring. It could be useful in treatment of infections, because it targeted transcription factors of the AraC-XylS family and inhibition of these factors reduced the virulence of microbial cells. Specifically, compound **68** showed EC_{50} <10 μM against *Pseudomonas aeruginosa* [121].

5. *N*-Hydroxy-substituted fused six-membered ring systems

5.1. One endocyclic heteroatom

5.1.1. Quinolinones and isoquinolinones—In the group of *N*-hydroxy-quinolinones, compound **69a** (Fig. 18), deriving from a HTS screening of the Pfizer compound collection, showed inhibitory activity against human kynurenine aminotransferase II (*h*KAT II), the primary enzyme in the brain responsible of catalyzing the formation of kynurenic acid from kynurenine, and this enzyme represents a potential target for the treatment of cognitive impairment associated with schizophrenia and other psychiatric disorders. Compound **69a** showed selective inhibitory activity of *h*KAT II with IC_{50} value of 23 nM, while for the rat isoform *r*KAT II the IC_{50} value was of 263 nM. The *R* isomer **70** (Fig. 18) of **69a** lost activity, displaying IC_{50} values of 219 nM for *h*KAT II and of 1170 nM for *r*KAT II. The methoxy derivative of the *S* isomer **69b** (Fig. 18) showed a potent activity on the human isoform similar to **69a**, but it was less selective (IC_{50} = 22 nM for *h*KAT II, IC_{50} = 137 nM for *r*KAT II). *In vivo* pharmacokinetic experiments revealed that after subcutaneous administration compound **69a** displayed excellent CNS exposure in rat and good *in vivo* efficacy [122]. Derivatives **69c** and **69d** (Fig. 18) of the *S* isomer **69a** were reported in a patent as the most potent *h*KAT II inhibitors of this chemical class, with IC_{50} values of 19 and 18 nM, respectively [123]. Compounds **71a-c** (Fig. 18) showed potent antimicrobial activity against *Enterobacter aerogenes*, *Serratia marcescens*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Lactobacillus casci*, *Lactobacillus plantarum*, *Leuconostoc dextranicum*, and *Streptococcus faecalis*. Compounds **71a**, **71b** and **71c** exhibited mean MIC values of 0.6, 0.6 and 0.2 μg/mL, respectively, on this panel of bacteria. In addition, chloro-substituted derivatives **71b** and **71c** weakly inhibited the growth of *Candida albicans*, with MICs of 20 μg/mL, and were 10-fold more effective than

unsubstituted **71a** (MIC = 200 μg/mL), even if they were less potent than the reference compound amphotericin B that exhibited MIC value of 0.6 μg/mL [124]. *N*-hydroxyquinolinone derivatives **72a-d** (Fig. 18) were potent 5-lipoxygenase enzyme inhibitors, with IC_{50} values of 0.87, 0.34, 0.98 and 0.84 μM, respectively, and isoquinolinone derivative **73** (Fig. 18) exhibited IC_{50} value of 0.45 μM against the same enzyme. For compounds **72a-c** and **73** the inhibition percentages against 12-lipoxygenase enzyme isolated from human platelets were evaluated and resulted of 97%, 98%, 97% and 99% at 100 μM, respectively. The same compounds **72a-c** and **73** also displayed inhibitory activity against 15-lipoxygenase enzyme obtained from soybean, with inhibition percentages of 100%, 100%, 97% and 50% at 100 μM, respectively [125]. 1-Hydroxy-3,4-dihydroquinolin-2(1*H*)-one **74a** and 1-hydroxy-6-chloro-3,4-dihydroquinolin-2(1*H*)-one **74b** in Fig. 18 are derivatives of a natural benzoxazinone compound that has been shown to cause symptomatic improvements in patients with benign prostatic hyperplasia, chronic prostatitis and prostatodynia. Compounds **74a** and **b** showed potent inhibitory effects on DU-145 prostate cancer cell growth, although they were not selective for this cell line because they inhibited MCF-7 cell growth at a concentration of 10 μg/mL [126].

5.1.2. Isoquinolinediones and benzo[*de*]isoquinolinediones—

N-hydroxyimide compound **75a** (Fig. 19) was initially reported as an inhibitor of the endonuclease dependent influenza polymerases, highlighting the absolute requirement of the *N*-hydroxy group for the activity [127]. Later, it was demonstrated that **75a** and the methyl ester analogue **75b** (Fig. 19) inhibited HIV-1 integrase and ribonuclease H and DNA polymerase functions of the HIV-1 reverse transcriptase. Interestingly, **75a** and **75b** complexed with magnesium ions were active, in particular these complexes required enolization of the ligands because magnesium cations were chelated by *N*-OH group and one of the adjacent OH groups of the corresponding tautomeric forms of **75a-b**, and these complexes released superoxide anion [128]. The insertion of an alkyl chain in position 4 of the scaffold as in compound **75c** (Fig. 19) did not improve the antiviral activity, but it conferred cytotoxicity to the compound. These inhibitors were only small prototype compounds with selectivity for two-metal ion enzymes, but they still need further optimization of substituents on the isoquinolinedione scaffold [129]. Representative 4-amide-substituted compound **75d** (Fig. 19) possessed the same scaffold and was patented as a potent inhibitor against HIV integrase (IC_{50} = 3 nM), thus it was considered a promising anti-HIV agent useful in the treatment of HIV infection and acquired immune deficiency syndrome (AIDS) [130]. Anti-viral compounds **76a-b** (Fig. 19) were characterized by the same scaffold with a substitution in position 7 of the fused phenyl ring. Compound **76a** showed a good RNase H inhibitory activity (IC_{50} = 5.7 μM) and **76b** showed noticeable overall integrase inhibitory activity (IC_{50} = 0.09 μM). Unfortunately, all the tested compounds possessing the 2-hydroxyisoquinoline-1,3(2*H*,4*H*)-dione scaffold exhibited high cellular cytotoxicity in cell cultures, which limits their applications as antiviral agents [131]. The 2-hydroxyisoquinolinedione **77** (Fig. 19) with a furan ring at the 6-position inhibited hepatitis C virus replication by targeting NS5B polymerase, which has a similar active site to that of HIV integrase and reverse transcriptase-associated ribonuclease H, showing IC_{50} value of 1.9 μM, and a similar value (1.3 μM) was obtained in a biochemical assay against recombinant NS5B [132]. Benzo[*de*]isoquinoline-1,3-dione derivatives **78** and **79** (Fig. 19) were developed as

antibacterial agents, inhibiting selectively bacterial DNA gyrase and DNA topoisomerase IV. The inhibition of two different targets offer advantages, by lowering the possibility of bacterial resistance. These two potent derivatives were tested against a wide panel of bacteria and proved to be active against some *Escherichia coli* strains, *Bacillus subtilis*, *Sthapylococcus aureus* and *pyogenes*; in particular **78**, in which the benzoisoquinoline ring was fused with a benzodioxin ring, showed MICs range of 0.13-8 μg/mL, whereas the pyrrolidine-substituted derivative **79** had MICs range of 0.06-2 μg/mL and it was nearly inactive against *S. pyogenes*. Moreover, it was confirmed that **79** had no any DNA intercalating or binding ability [133].

5.1.3. Acridone derivatives—Some acridone-based compounds are natural products, such as *N*-hydroxy-acridone alkaloid **80** (Fig. 20) isolated from the leaves of *Sarcomelicope dogniensis* [134]. Acridine-based drugs are well-known agents developed against malaria, and in particular floxacrine **81** (Fig. 20) exhibited *in vitro* and *in vivo* potent antimalarial activity (as racemic mixture). Floxacrine was able to bind heme, the by-product of parasite hemoglobin digestion, and to prevent heme crystallization, finally leading to parasite death, displaying IC_{50} value of 63 μM, comparable to the value of the reference anti-malarial drug chloroquine (IC_{50} = 56 μM) [135]. Unfortunately, its use would be limited only as a prophylactic agent, due to the requirement of high daily dosage, easy development of resistance to floxacrine and to the unwanted side effects produced by this molecule, such as chronic periarteritis and vascular cardiotoxicity. As a consequence, many floxacrine derivatives were synthesized to overcome the problems of the parent compound, but any small changes in inhibitor structure had negative effects on antimalarial activity, thus it was difficult to improve the activity-toxicity balance of the floxacrine derivatives [136-139]. Among the floxacrine analogues, *N*-hydroxy imine acridione derivative **82** (Fig. 20) was a potent antimalarial agent in both rodents and primates. In this structure, the replacement of the *N*-OH group with hydrogen did not completely remove the antimalarial activity, but the insertion of *N*-alkyl group caused a loss of activity. However, similarly to the parent compound floxacrine, **82** exerted some toxicity at higher doses [140].

5.2. Two endocyclic heteroatoms

5.2.1. Naphthyridinones—Compound **83** (Fig. 21) was a potent and selective RNase H inhibitor, showing IC_{50} value of 45 nM in biochemical assays, and it inhibited viral growth *in vitro*, without being cytotoxic [141]. A series of *N*-hydroxynaphthyridinone derivatives were patented as agents for the prophylaxis and treatment of infection by HIV, such as compound **84** (Fig. 21) that showed promising IC_{50} values in the low micromolar or nanomolar range in a RNase H-mediated RNA cleavage assay, in the integrase standard-transfer assay and against single-cycle HIV infectivity assay B, without being cytotoxic at this low concentrations [142]. Structurally similar representative derivative **85** (Fig. 21) showed inhibitory activity of *h*KAT II (IC_{50} = 52.7 nM), and therefore its potential use was for the treatment of cognitive deficits associated with schizophrenia and other neurodegenerative disorders [143].

5.2.2. Quinazolinediones and quinoxalinediones—*N*-hydroxyquinazoline-2,4-dione derivatives **86a-b** (Fig. 22) were designed as Gly/NMDA and AMPA receptor ligands and

their affinities were evaluated by measuring their ability to displace [^{3}H]-glycine or [^{3}H]-AMPA. Compound **86a** showed the best affinity toward Gly/NMDA receptor (K_i = 0.20 μM), differently **86b** substituted with a triazole ring showed a preferred binding to AMPA receptor (K_i = 0.25 μM), with a total selectivity for this receptor versus the Gly/NMDA receptor, that did not allow the presence of such a bulky substituent [144]. It is reasonable include in this group derivative **87**, in which the pyrimidinone ring was fused with a thiophene heterocycle, instead of a phenyl ring (Fig. 22). Compound **87** was one of the most active and selective flap endonuclease-1 (an enzyme involved in DNA repair) inhibitors (IC_{50} = 35 nM) compared to a related endonuclease, xeroderma pigmentosum G (IC_{50} of about 8 μM). The *N*-hydroxy-urea moiety was essential for the inhibition of the target enzyme by coordinating the two divalent metal ions needed for catalysis [145]. Compound **88** (Fig. 22) was a representative inhibitor endowed with potent anti-microbial activity, displaying MIC values lower than 2 ppm against *Candida albicans*, *Auresbasidium pulluans* and *Aspergillus niger* [146]. Hydroxamate-substituted quinoxalinedione **89** (Fig. 22) was a bidentate zinc chelating agent and it showed anticoagulant properties due to the replacement of calcium ions with zinc ions in the serine protease domain of factor VII, thus causing an inhibitory effect on factor VII itself. Compounds exhibiting chelating binding affinity to zinc ions were considered useful for the treatment of coagulation-related diseased states [147].

5.2.3. Benzoxazinones—2,4-Dihydroxy-1,4-benzoxazin-3-one (DIBOA) **90** (Fig. 23) is a cyclic hydroxamic acid possessing protective functions in plants against insects, bacteria and fungi, and it is abundant in sprouts of Gramineae family. In plants, it is stored in vacuoles as D-glycosides and the aglycone DIBOA is obtained after enzymatic hydrolysis. Compound **90** has been identified and quantified in grains and bakery products of rye and wheat. At present, uptake, metabolic fate and biological properties of this dietary compound in humans is still under study. Compound **90** was firstly isolated from commercial pollen extract, Cernitin T-60, and it proved to reduce the growth of a prostate cancer cell line [148]. Compound **90** and its methoxy derivative 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA) **91** (Fig. 23), which is the dominant benzoxazinoid compound found in wheat, exerted mutagenic activity against human liver cell line HepG2 and **91** caused stronger effects than the parent compound **90** [149]. Moreover, the cytotoxic effects of DIBOA were also observed on different cancer cell lines, such as DU-145 (prostate cancer) and MCF-7 (breast cancer) cells [126]. Derivatives of DIBOA such as compound **92** (Fig. 23) which bears a chlorine atom in position 6 and an ethyl chain in position 2 showed phytotoxic activity with IC_{50} value less of 1 μM against *Allium cepa* (onion) and *Lepidium sativum* (watercress) and it could be used for the development of a new generation of plant protection products of natural origin [150]. Halogenated benzoxazinone DIBOA derivative **93** (Fig. 23) was patented as a suitable agent for agricultural weed control. It showed phytotoxic activity, causing dose-dependent inhibitions of *Allium cepa*, *Triticum aestivum* (wheat), *Lepidium sativum*, *Lycopersicon esculentum* (tomato), *Lactuca sativa* (lettuce), *Avena fatua* (wild oats), *Echinochloa crus-galli* (barnyard grass) and *Lolium rigidum* (rigid ryegrass) [151]. Insertion of butyl group in place of the OH group of DIBOA produced compound **94** (Fig. 23) that possessed a potent phytotoxic activity making it useful as herbicide. The group in position 2 modulated the solubility and increased the phytotoxic

activity compared to the parent compound. It was found that compound **94** inhibited growth of *A. fatua* with IC_{50} value of 131 μM and *E. crus-galli* with IC_{50} value of 190 μM [152].

5.2.4. Other *N*-hydroxy heterocycles—*N*-hydroxy-containing natural products **95** and **96** (Fig. 24) are bispyrroloiminoquinone oximes isolated from the South African latrunculid sponge *Tsitsikamma favus*. Compounds **95** and **96** possessed interesting pharmacological properties, because they exhibited cytotoxicity against human colon tumor cell line HCT-116, with IC_{50} values of 128.2 and 16.5 μM, respectively, moreover they showed DNA intercalating ability [153]. Some studies demonstrated the weak oncogenic activity of 3-hydroxyxanthine **97** (Fig. 24), that may be due to its metabolization by xanthine oxidase that lead to the formation of oncogenic metabolites [154,155].

6. Conclusions

The presence of many *N*-hydroxylated heterocycles among pharmaceutical active derivatives attests the growing interest toward this varied chemical class of *N*-hydroxy-substituted compounds as building blocks. Anti-cancer and anti-microbial properties are the principal biological activities demonstrated by *N*-hydroxy-substituted compounds, suggesting that they may be therapeutically useful for some types of cancer and several other infection diseases. In some cases the role of the *N*OH group was clear, representing a pharmacophoric moiety necessary for the biological activity of the whole molecule on the related target, while in some compounds the need for this group was not adequately investigated and evaluated. The insertion of a *N*-OH group in a molecule significantly modifies some of its properties, for example it can increase solubility or modify the acid-base behavior of the compound. Importantly, the *N*-OH moiety affects the binding of the molecule to the target protein, increasing the possibility to establish some hydrogen bonds with the protein residues in the active site or with surrounding water molecules. Certainly, as previously discussed in the present review, one of the most represented classes is the *N*-hydroxyindole series which includes both synthetic and natural compounds, although these chemical entities are quite rare in nature. In order to obtain functionalized *N*-hydroxyindoles some synthetic methods for the construction of this kind of scaffold have been developed [156-159]. However, this scaffold is unstable if not adequately supported by some substitutions, such as electron withdrawing groups or resonance stabilizing substituents on the indole nucleus, or substituents in position 2 that can hydrogen-bond to the hydroxyl group.

The present review summarizes the main biologically active *N*-OH containing heterocycles along with a discussion of their medicinal importance, pointing out the increasing use of this structural motif in medicinal chemistry in view of their applications in several fields. It is concluded that *N*-OH-substituted bioactive molecules exhibit a wide spectrum of biological activities and this review would help and encourage further developments and modifications of *N*-OH containing compounds, highlighting the potentialities of this multifaceted chemical class.

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- Heterocycles containing endocyclic *N*-hydroxy portions are metabolically stable molecular entities
- We present several chemical classes of bioactive *N*-hydroxy heterocycles, according to the central scaffold of the molecules
- The main applications in medicinal chemistry of the compounds discussed in the present review are as anticancer and antibacterial agents

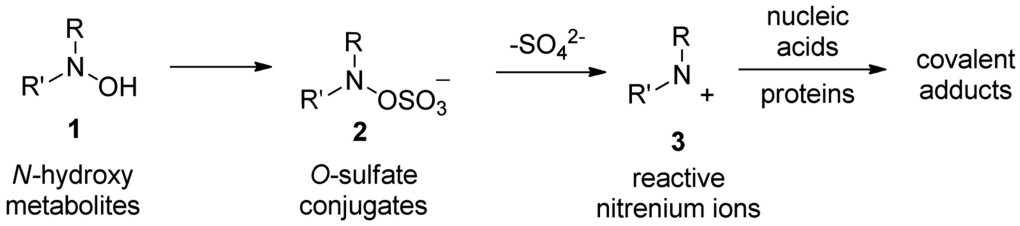


Fig. 1.

Schematic presentation of metabolic pathways involving primary *N*-hydroxy metabolites to electrophilic nitrenium species.

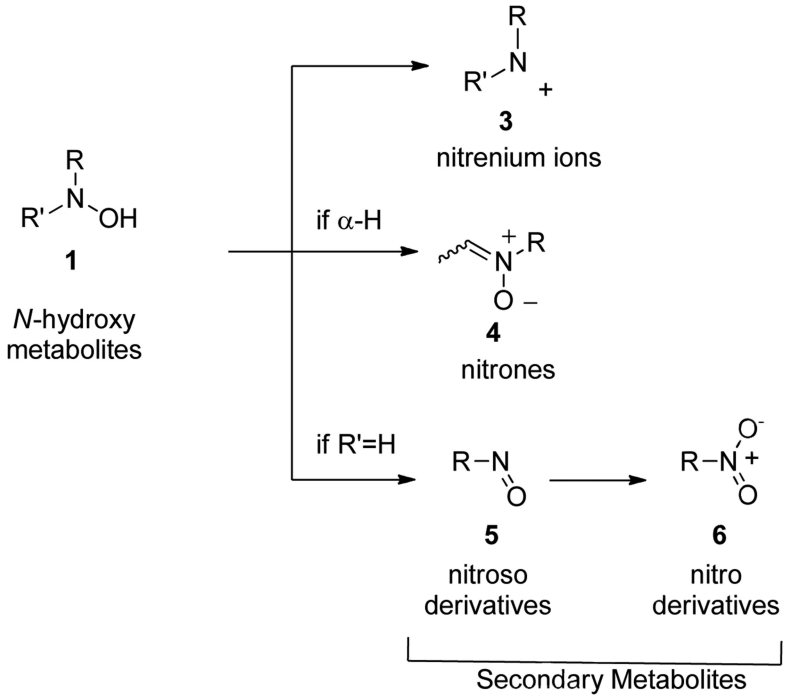


Fig. 2.
Reactive secondary metabolites generated from primary *N*-hydroxy metabolites.

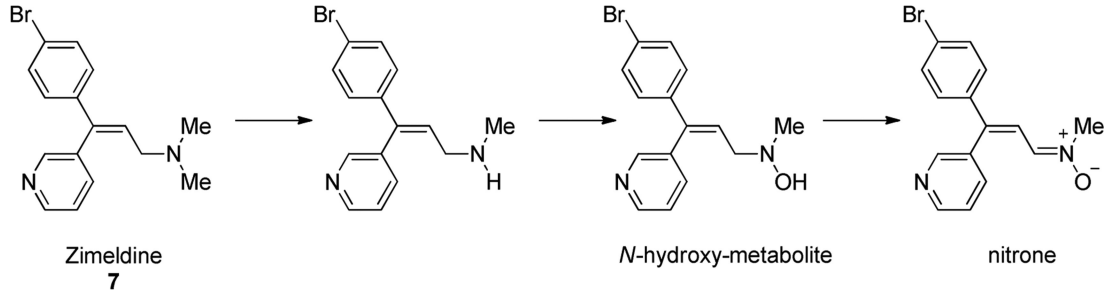


Fig. 3.

Reactive secondary nitrone metabolite generated from primary *N*-hydroxy metabolite of Zimeldine.

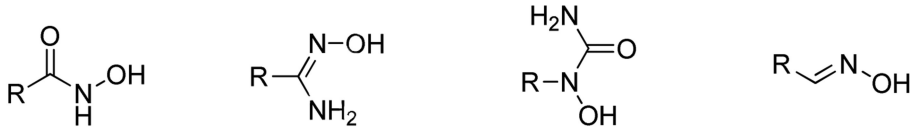


Fig. 4.
General representation of some biorelevant acyclic/exocyclic *N*-hydroxy-derivatives.

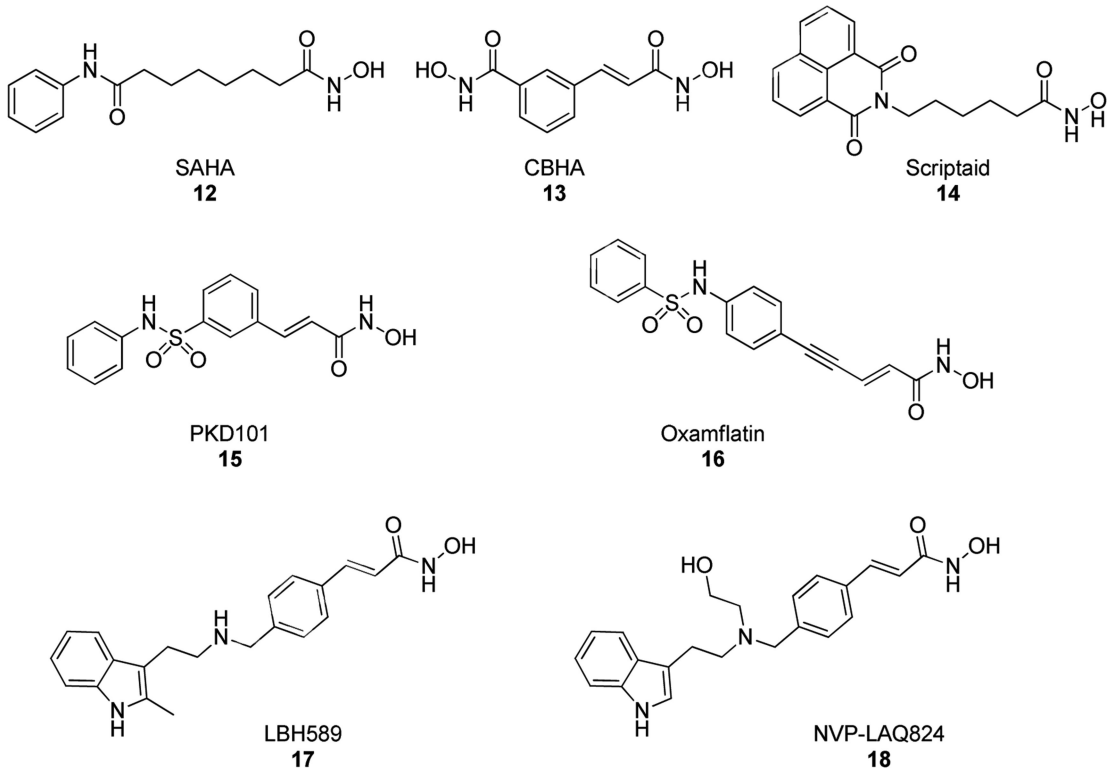


Fig. 5.
Structures of *N*-hydroxy-bearing clinical and preclinical small molecules.

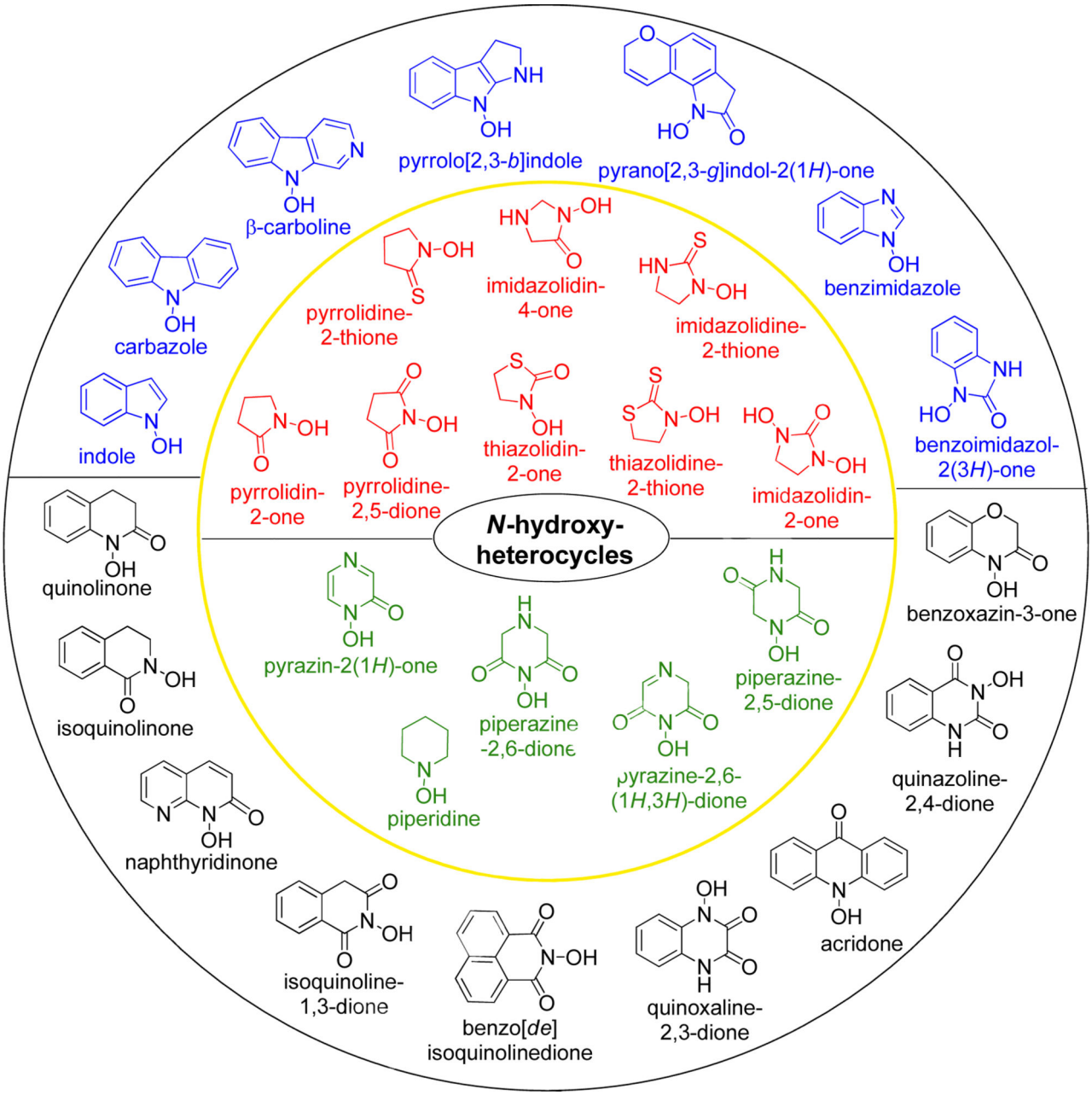


Fig. 6.

General structural overview of the types of endocyclic *N*-OH heterocyclic derivatives. Inner yellow circle: monocyclic 5-membered (red) and 6-membered (green) ring systems. Outer black circle: fused 5-membered (blue) and 6-membered (black) ring systems.

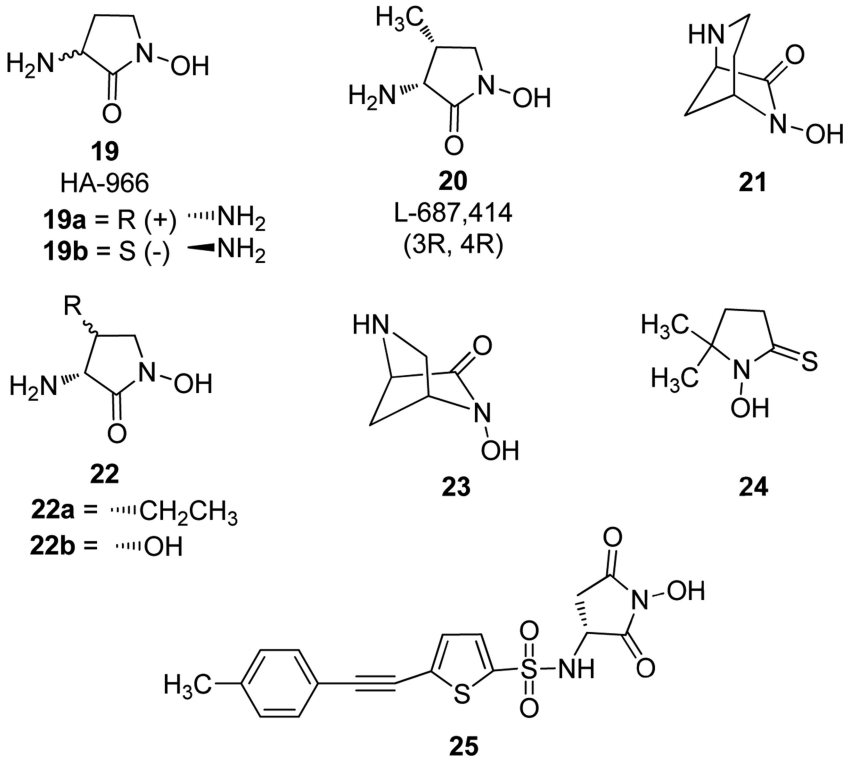


Fig. 7.
N-hydroxy-substituted pyrrolidinones, pyrrolidinethiones and pyrrolidindiones.

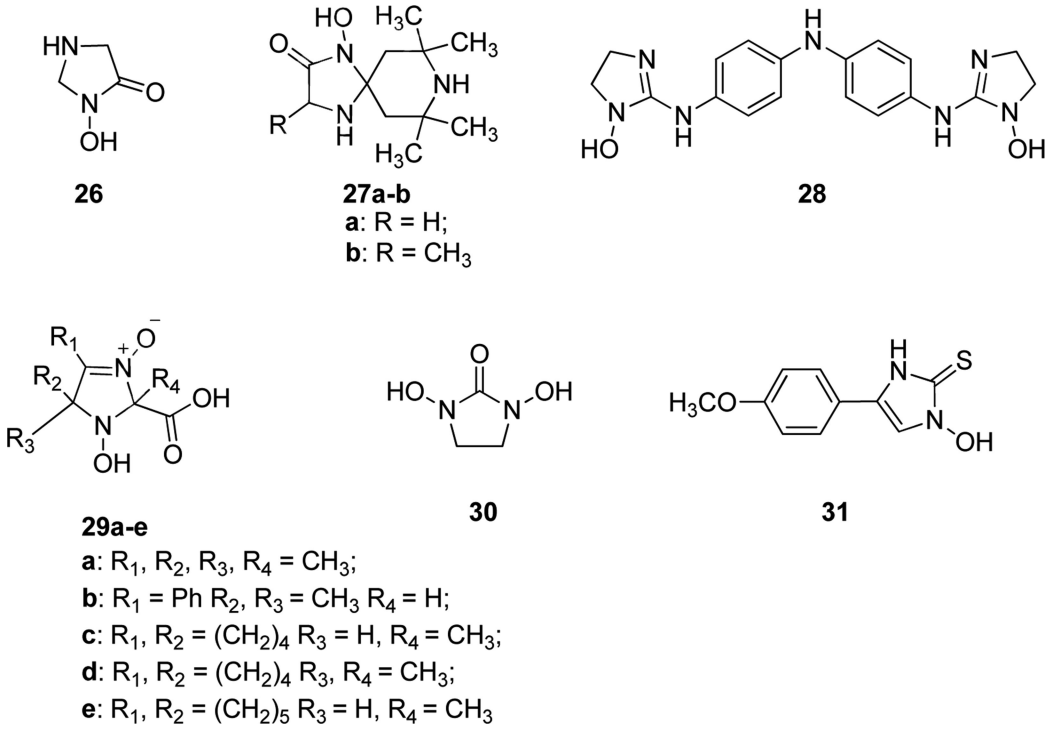
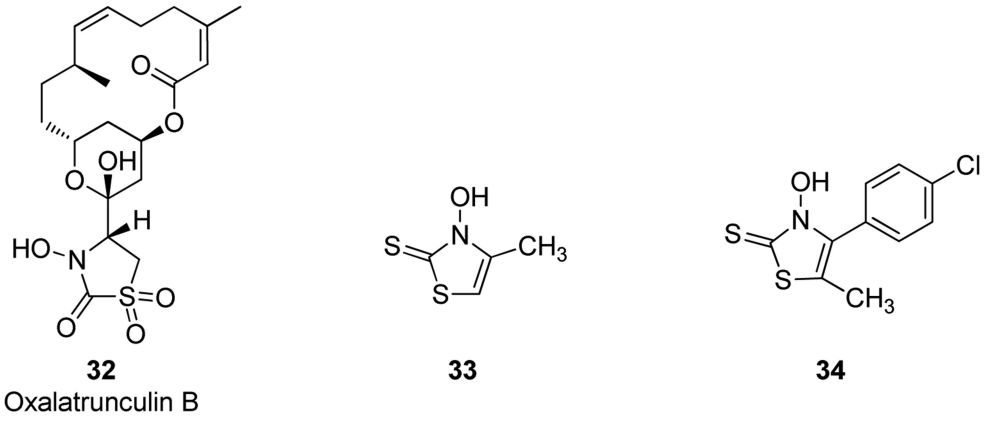


Fig. 8.

N-Hydroxy-substituted imidazolidinones, imidazolidinediols and imidazolinethiones.



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Oxalatrunculin B

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34

Fig. 9.
N-Hydroxy-substituted thiazolidinones and thiazolidinethiones.

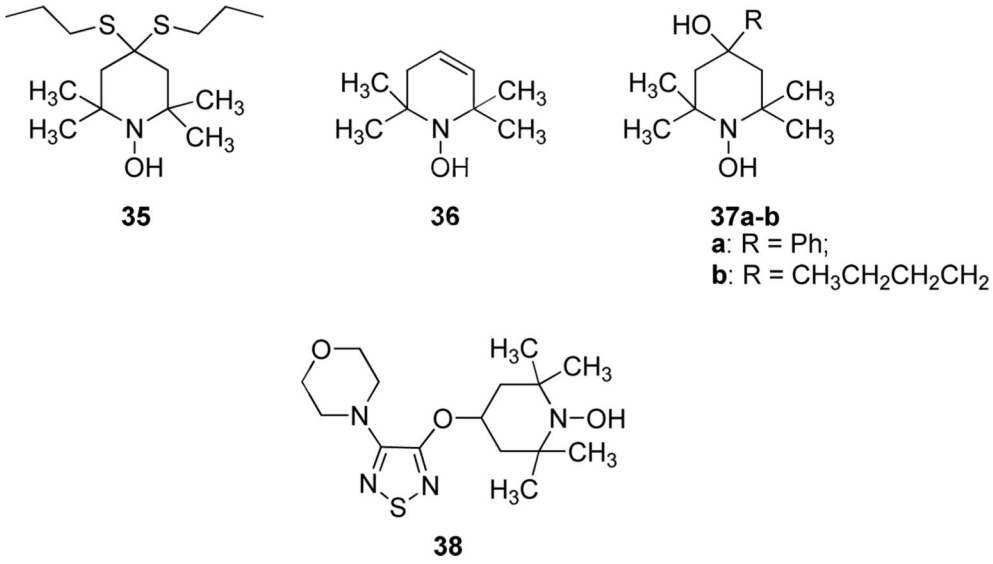


Fig. 10.
N-Hydroxy-substituted piperidine derivatives.

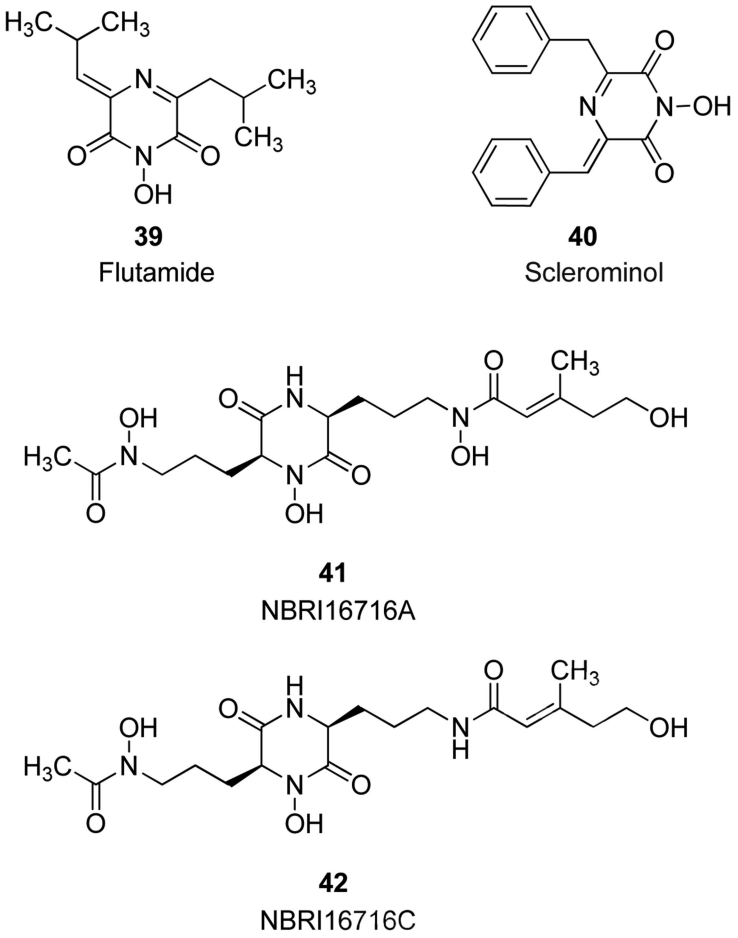


Fig. 11.
N-Hydroxy-substituted pyrazinone and piperazinone-based natural products.

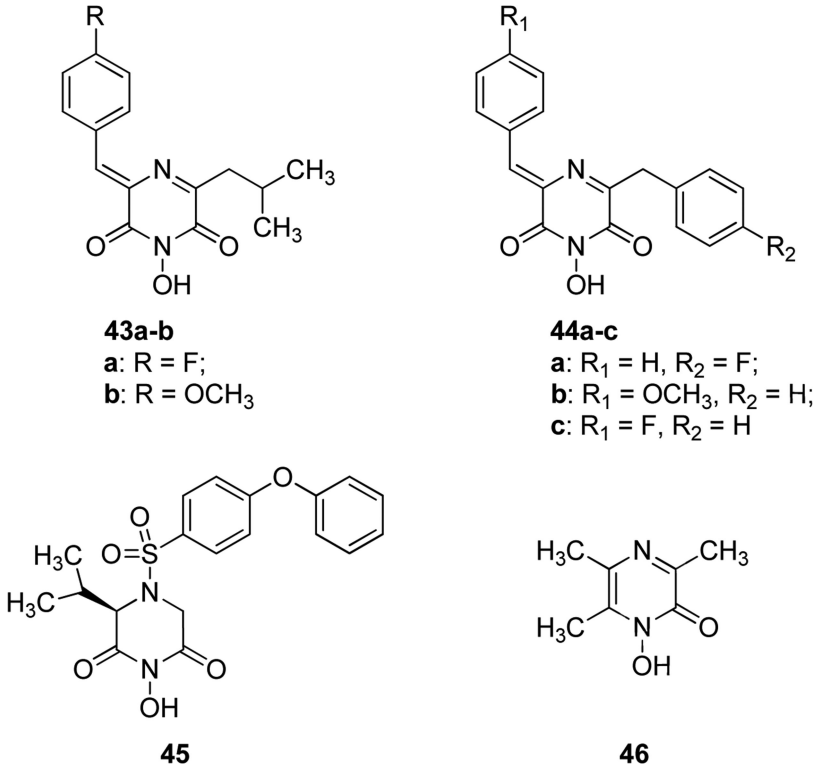
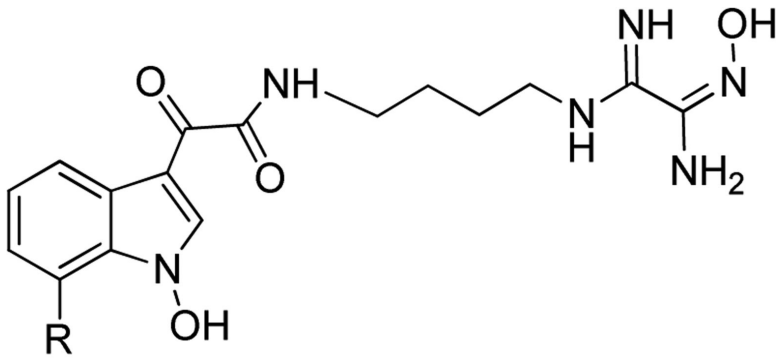


Fig. 12.

N-Hydroxy-substituted pyrazinone and piperazinone-based synthetic compounds.



47a-b

a: Birnbaumin A, R = H

b: Birnbaumin B, R = OH

Fig. 13.

N-Hydroxyindole-containing natural products.

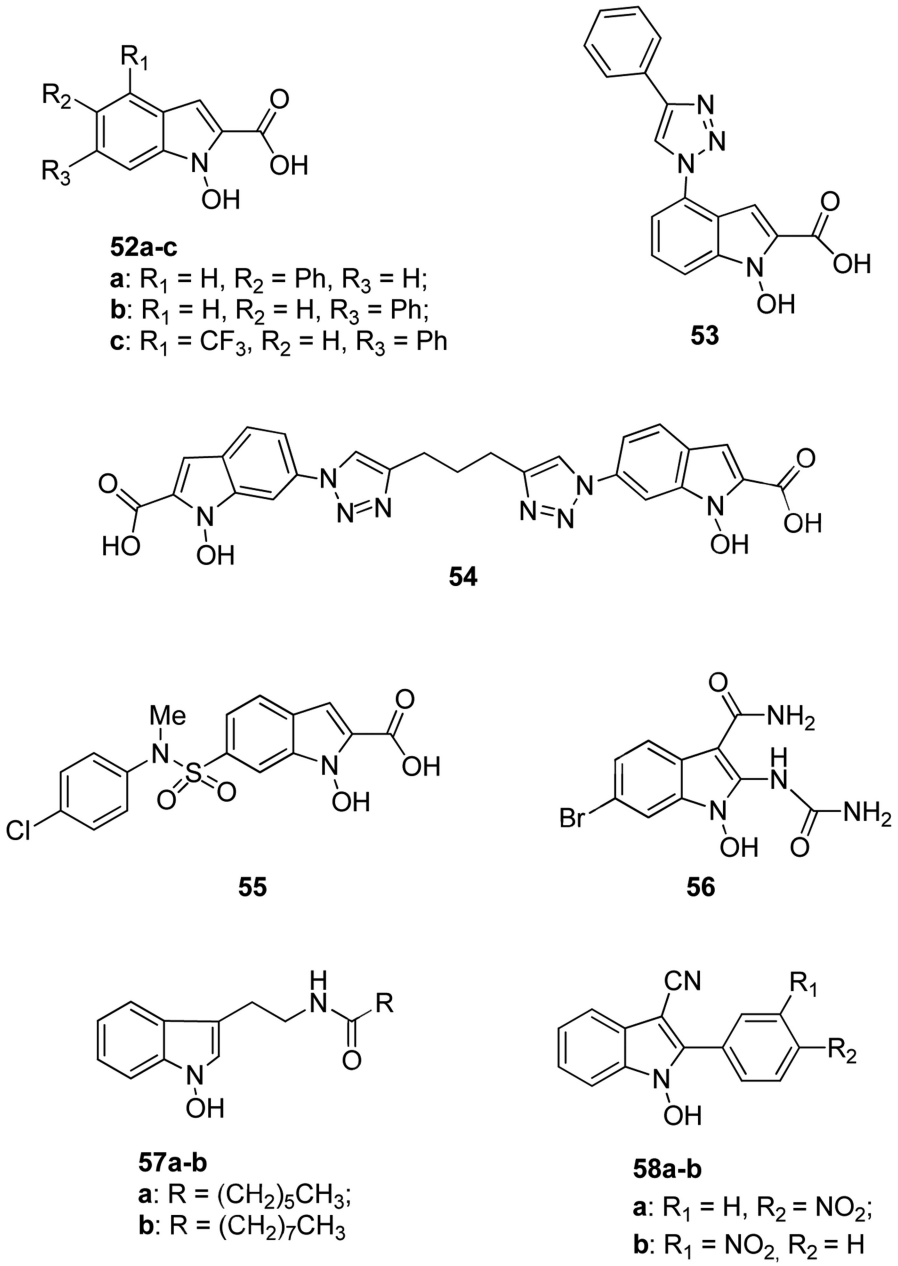


Fig. 14.
N-Hydroxyindole-based synthetic derivatives.

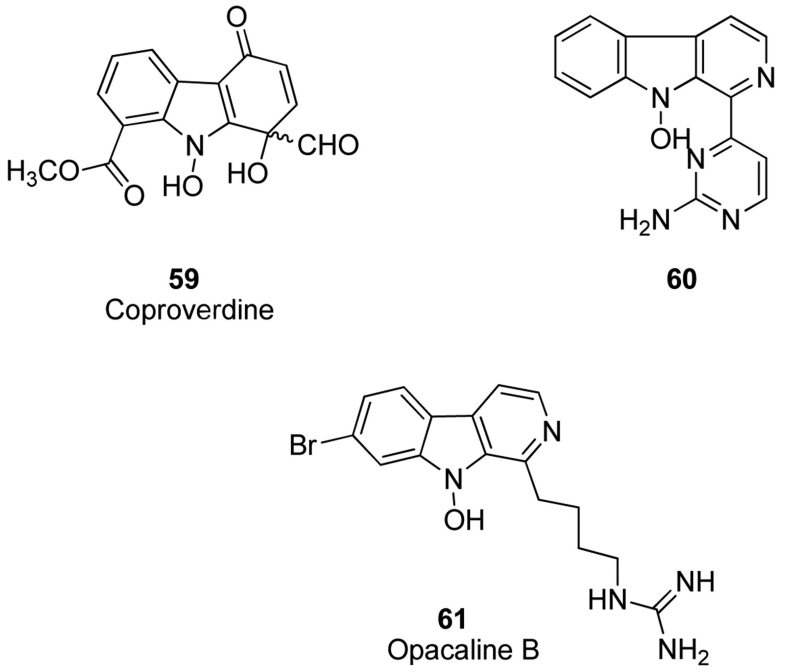


Fig. 15.
N-Hydroxy-substituted carbazole-based natural products.

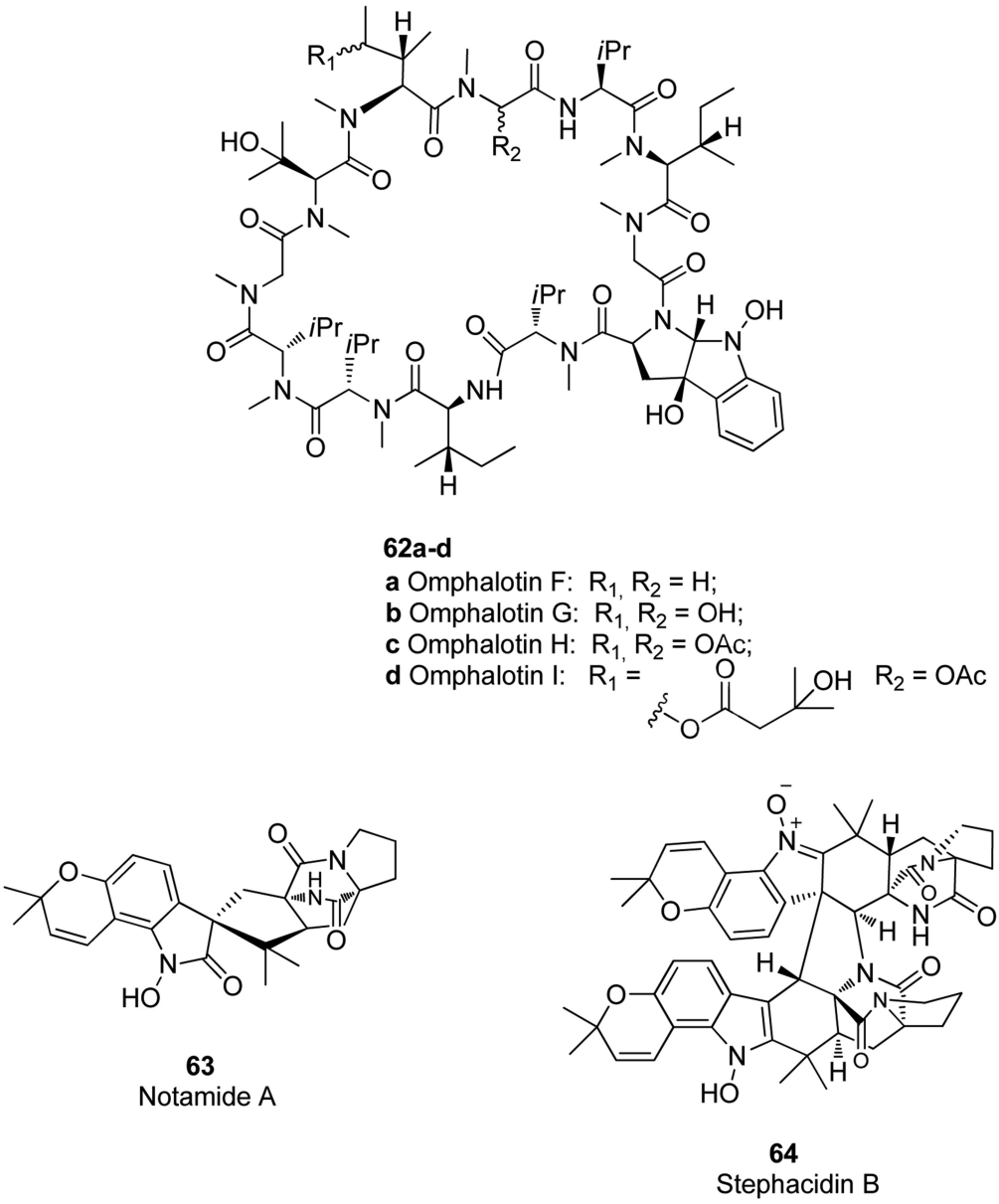
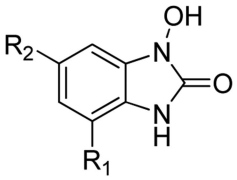
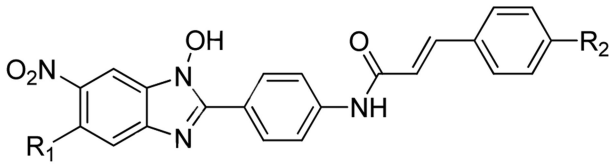


Fig. 16.
N-hydroxy five-membered rings in complex systems.



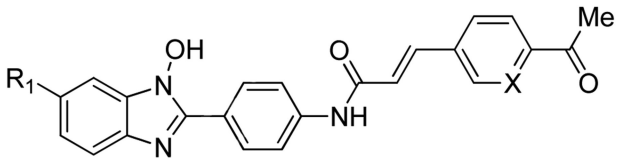
65a-c

a: $R_1 = R_2 = H$;
b: $R_1 = OCH_3$, $R_2 = H$;
c: $R_1 = F$, $R_2 = F$



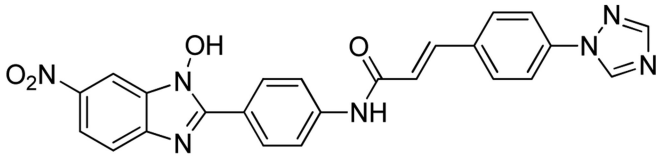
66a-c

a: R_1= H, R_2 = F;
b: R_1 = H, R_2 = OCH_3;
c: R_1= CH_3, R_2 = F



67a-c

a: $R_1 = NO_2$, X = C;
b: R_1 = CN, X = C;
c: $R_1 = NO_2$, X = N



68

Fig. 17.
N-hydroxy-substituted benzimidazoles and benzimidazolones.

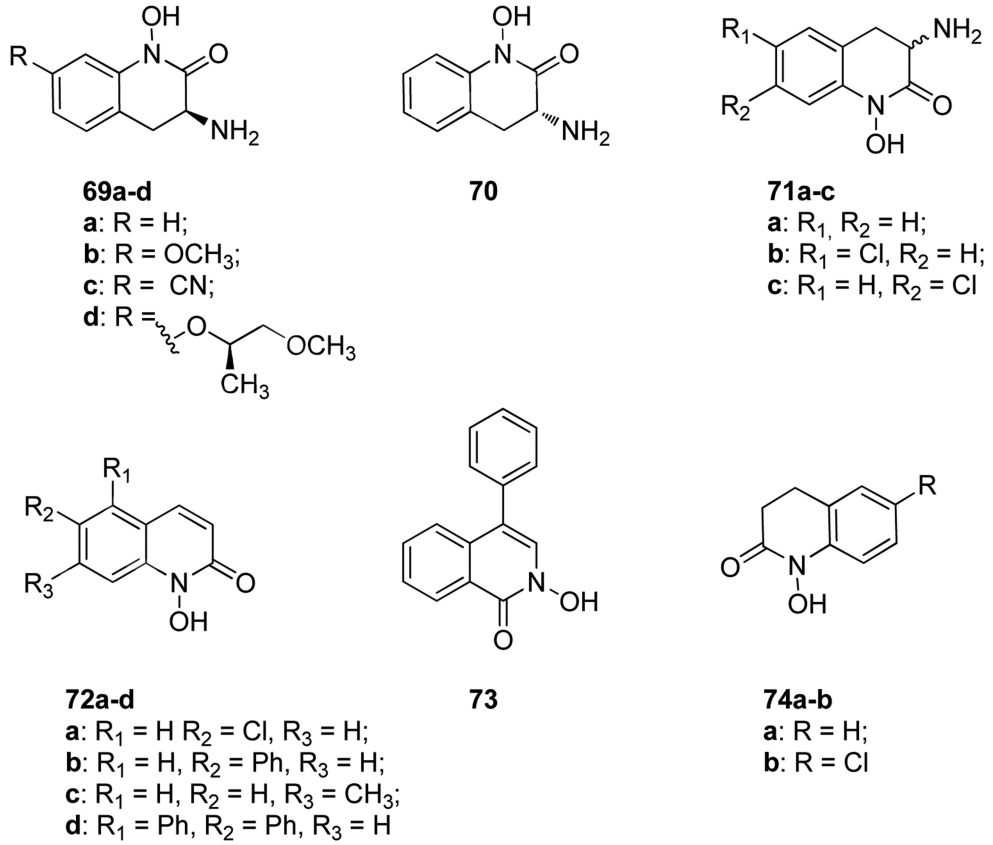


Fig. 18.

N-hydroxy-substituted quinolinones and isoquinolinones.

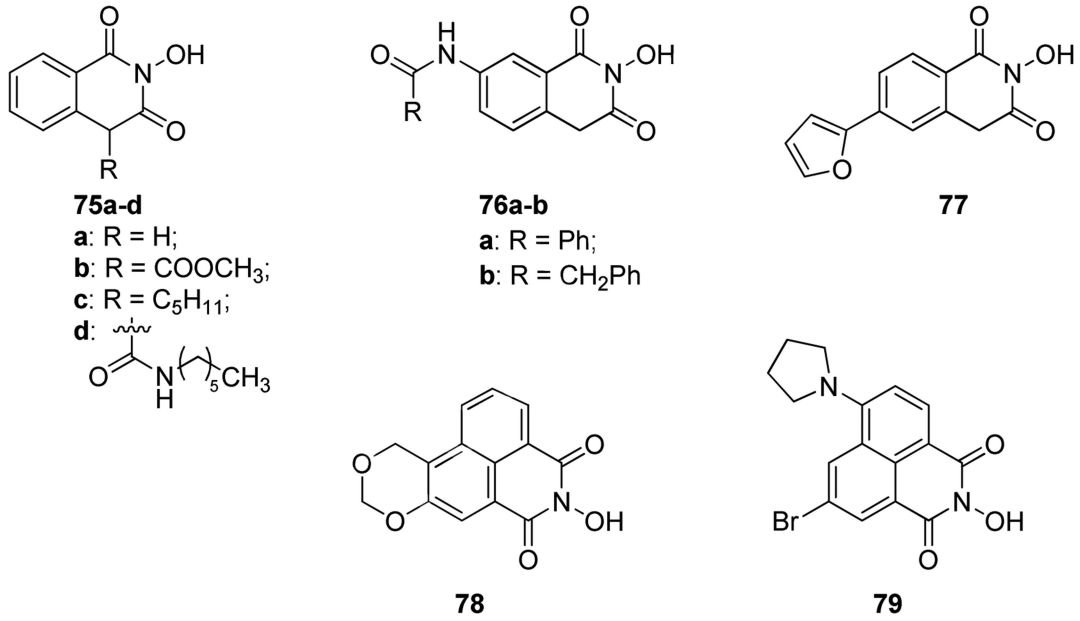


Fig. 19.

N-hydroxy-isoquinolinediones and benzo[*de*]isoquinolinediones.

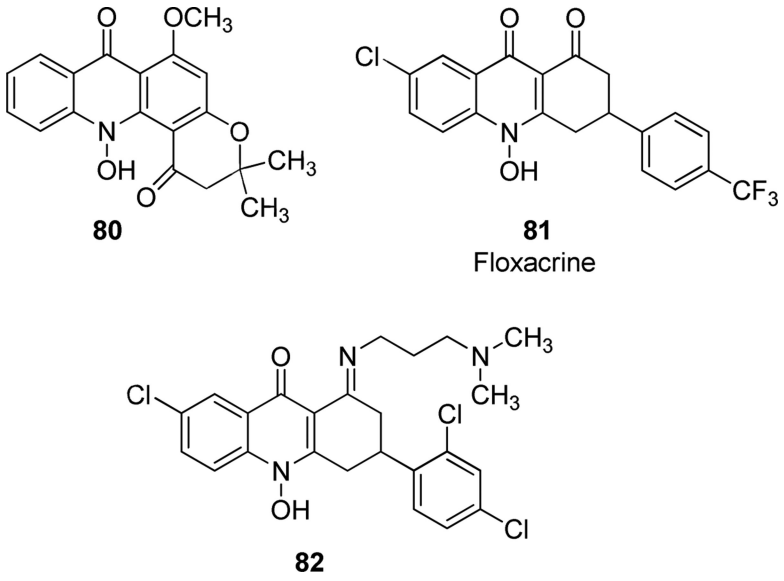


Fig. 20.
N-hydroxy-substituted acridone heterocycles.

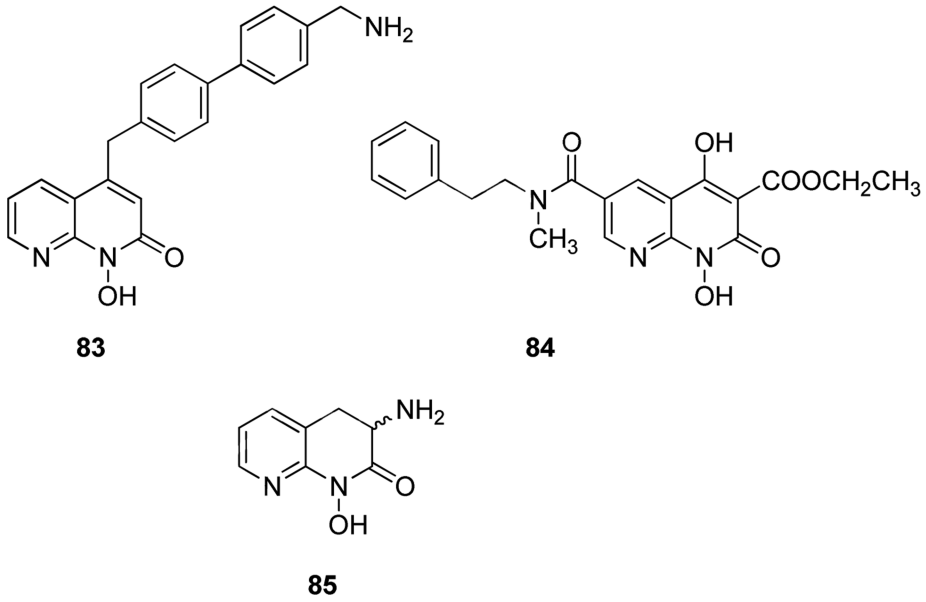


Fig. 21.
N-hydroxy-substituted naphthyridinones.

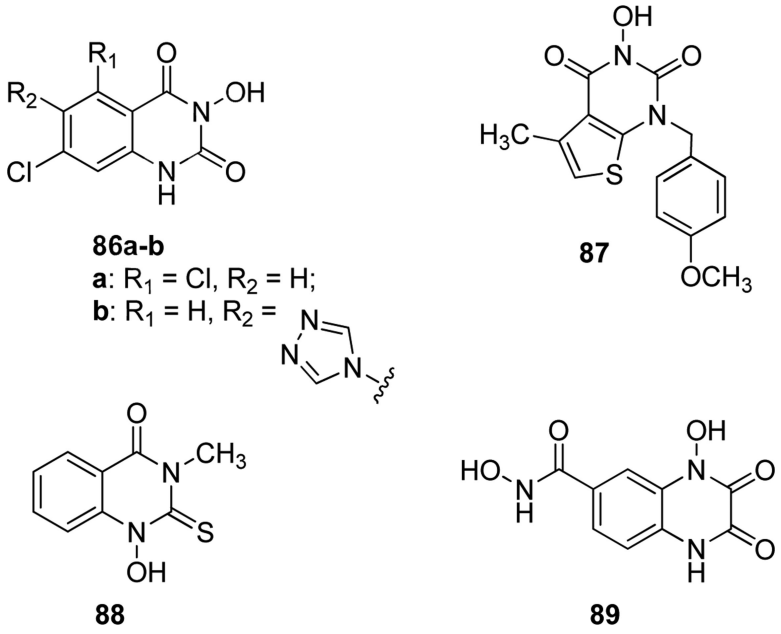


Fig. 22.
N-hydroxy-substituted quinazolinediones and quinoxalinediones.

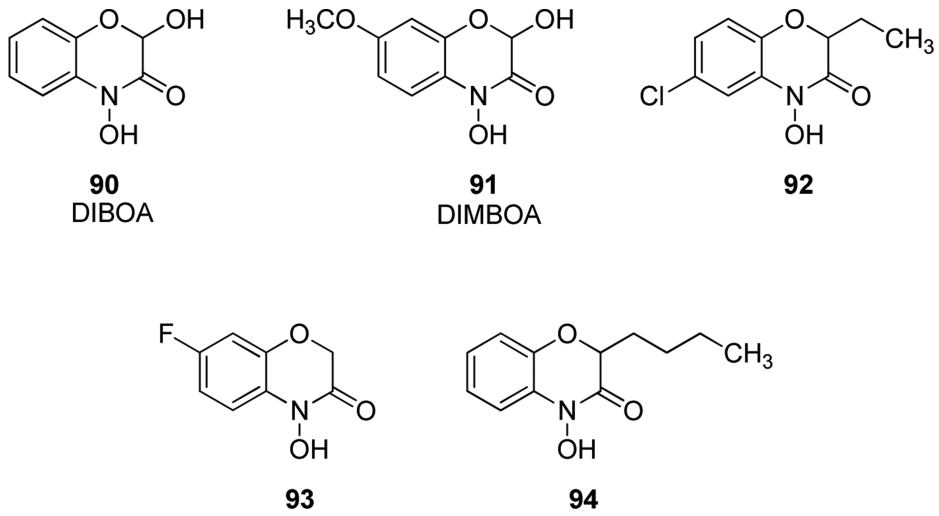


Fig. 23.
N-hydroxy-substituted benzoxazinones.

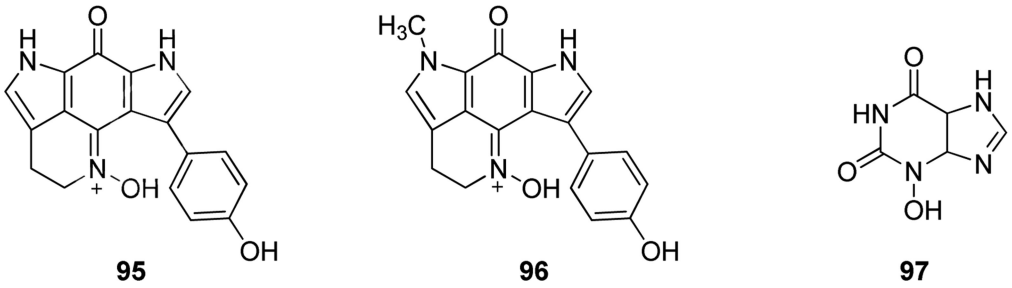
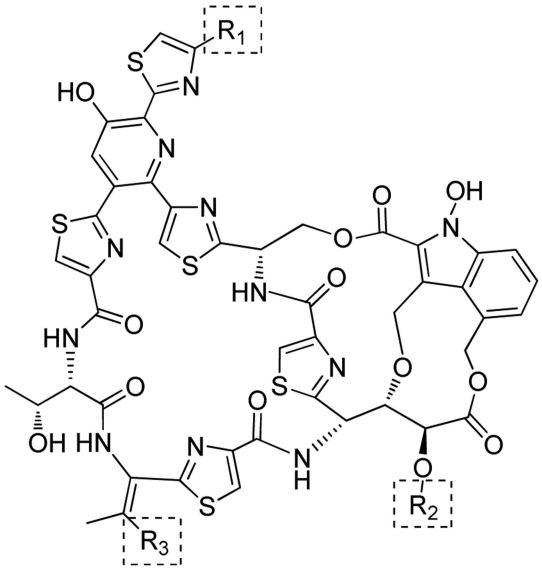
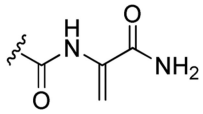
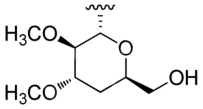
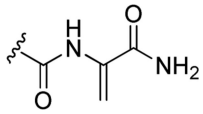
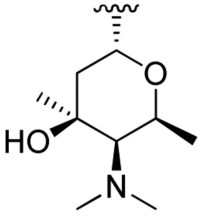
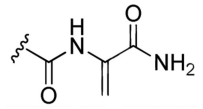
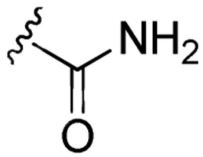
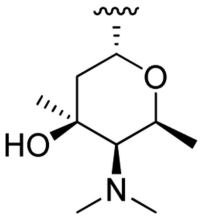


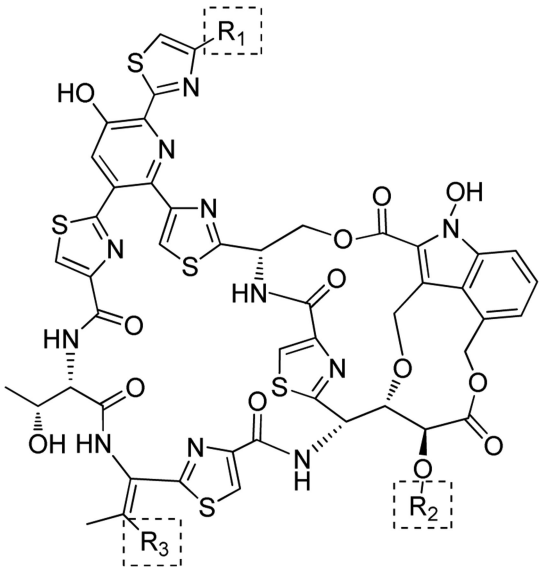
Fig. 24.
N-hydroxy six-membered rings in heterocyclic systems.

Table 1

Natural products S-54832/A-I, nocathiacins and thiazomycins.



		R_1	R_2	R_3
48a	S-54832/A-I			H
48b	Nocathiacin I			OCH_3
48c	Nocathiacin III		H	OCH_3
48d	Nocathiacin IV			OCH_3



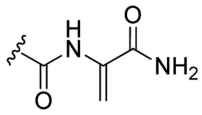
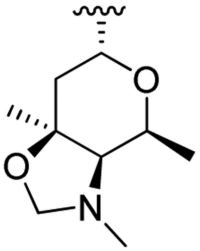
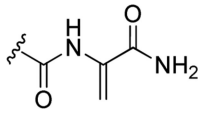
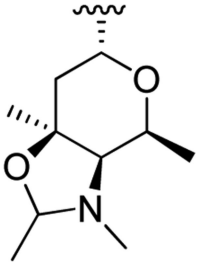
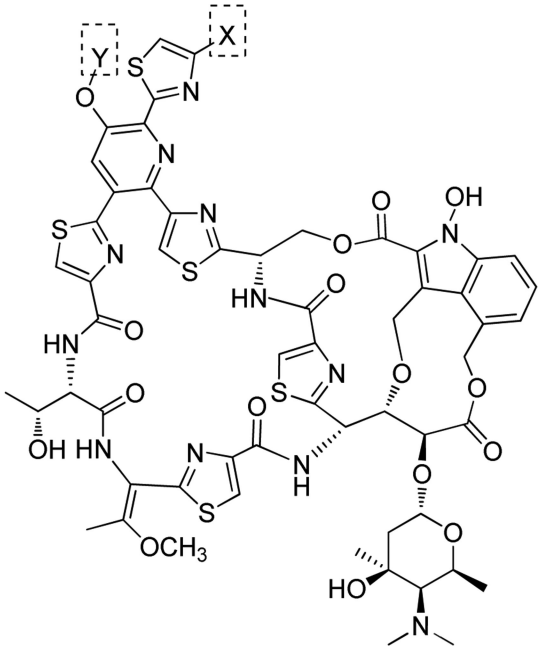
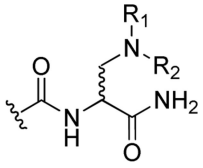
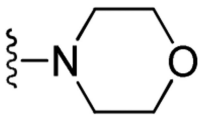
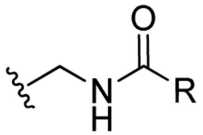
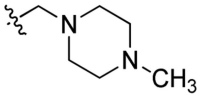
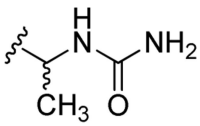
		R_1	R_2	R_3
48e	Thiazomycin			OCH_3
48f	Thiazomycin A			OCH_3

Table 2

Semisynthetic nocathiacin I derivatives.



		X	R_1	R_2	Y
49	**a**		H	$CH_2CH_2NHCH_3$	H
	b			CH_2CH_2OH	
	c				
		R			
50	**a**				H
	b				
51