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Hydroxamate, a Key Pharmacophore Exhibiting a Wide Range of Biological Activities

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Abstract: Naturally occurring hydroxamic acid derivatives are biosynthesized by microorganisms (siderophores) and plants (benzoxazinoids). Recent developments in drug discovery have highlighted the numerous biological and pharmacological properties that the hydroxamic acid function may possess, leading to therapeutic applications. These properties may be explained by its ability to chelate metals *via* the presence of two oxygen atoms. Their pharmacological activities can be divided into three groups. The first concerns the ability of these hydroxamic acid derivatives to scavenge metals (particularly iron), which leads to antioxidant, antimicrobial and metal detoxification activities. The latter is largely used to treat iron overload in patients. The second group of activities is related to their ability to inhibit metallo-enzymes, which gives them a wide range of pharmacological effects: antimicrobial, anti-inflammatory and antitumor. The third group is linked to the capacity of these compounds to generate nitric oxide, which confers hypotensive activity. However, hydroxamates exhibit relatively low stability *in vivo*, which can be overcome by the synthesis of appropriately designed analogs. For this purpose, many different strategies have been proposed. In this review, we compare and discuss the various synthetic pathways used to obtain the most complex of them, the *N*-substituted hydroxamic acids. We conclude that among numerous protocols reported so far, the direct *N*-substitution of hydroxamic acids, the acylation of the appropriate *N-O* derivative and the direct oxidation of the corresponding amide allow for the synthesis of a wide range of new biologically active compounds.

Keywords: Biological activities, hydroxamates, hydroxamic acid derivatives, metal chelators, metallo-enzyme inhibitors, pharmacological properties, synthetic pathways.

INTRODUCTION

The hydroxamate function, formerly *N*-hydroxy-*N*-alkylamide, is found in various naturally occurring compounds. These molecules, called siderophores, are produced by microorganisms in order to form very stable complexes with ferric iron [1] (Fig. **1**) and they play a key role in the iron acquisition mechanisms of microorganisms. This mode of iron acquisition is energy-consuming and is only activated under iron stress conditions which frequently occur in natural environments [2]. Several types of siderophores are produced by a wide variety of microorganisms such as bacteria [3, 4], fungi [2, 5] and microalgae [6, 7]. In microorganisms which are pathogenic for humans or animals, these molecules play an important role as virulence factors [8].

In plants, siderophores have been found as cyclic hydroxamates which belong to the benzoxazinoid group (Fig. **2**) and are largely distributed in the families Acanthaceae, Lamiaceae, Poaceae, Ranunculaceae, Scrophulariaceae and Triticeae [9]. For the plants, they constitute defensive agents, acting as insecticides, antimicrobials and aphid anti-feedants [9-11].

Among the natural hydroxamic acid derivatives, deferoxamine B whose mesylate salt is known as Desferal© (Fig. **1**) is an important iron chelator clinically used worldwide to treat iron overload [12]. This linear siderophore was isolated from the bacteria *Streptomyces pilosus* [13]. It contains three hydroxamate functions and is able to bind ferric iron very strongly. This unusually strong affinity is due to the ideal positions in three-dimensional space of the three hydroxamate functions (Fig. **3**) [14].

Over the last few years, compounds containing hydroxamic acid function have been studied for other therapeutic applications [15-24]. Recent research in medicinal chemistry led to the development of anticancer drugs such as the recently FDA approved suberoylanilide hydroxamic acid which inhibits histone deacetylases (HDACs) (Vorinostat, Fig. **4**) [25]. The activities of hydroxamates can be sorted into three different groups according to their mode of action. The first group is related to their ability to scavenge metals (particularly iron), which leads to metal detoxification, antioxidant and antimicrobial properties. The second group of activities corresponds to

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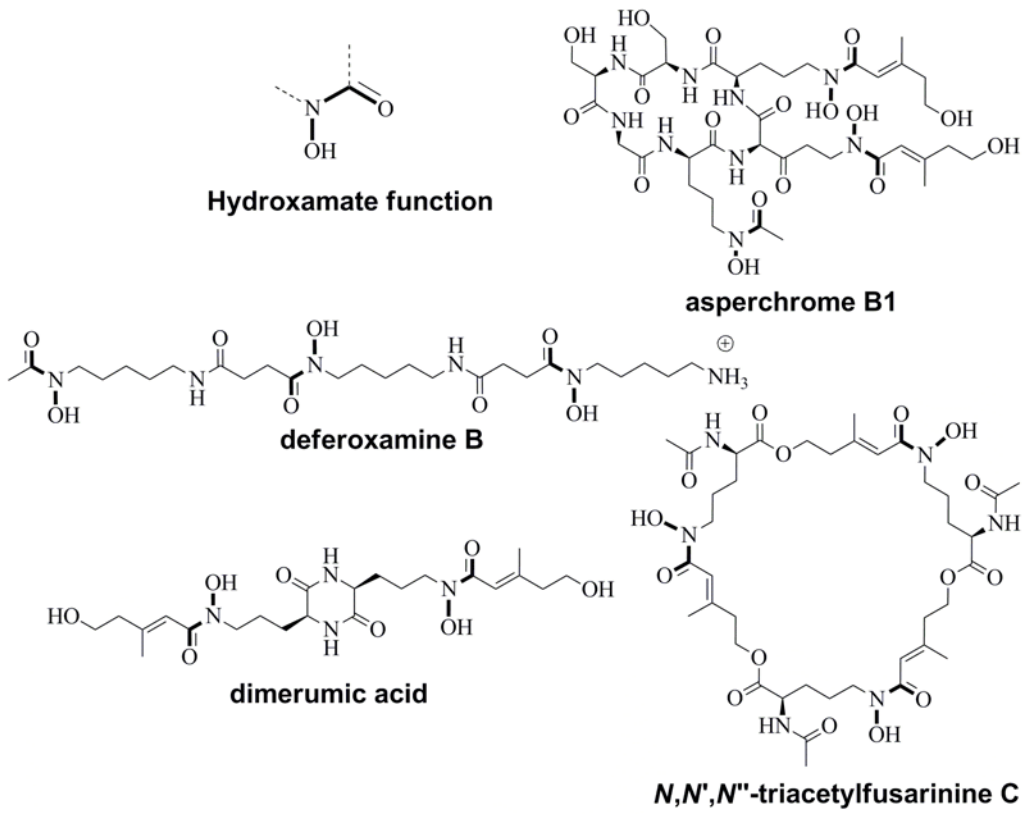

Fig. (1). Examples of naturally occurring hydroxamate siderophores.

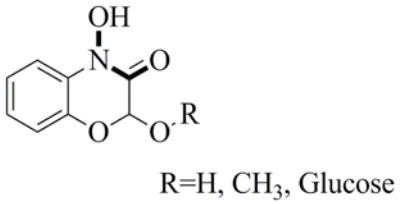

Fig. (2). Chemical structure of benzoxazinoids.

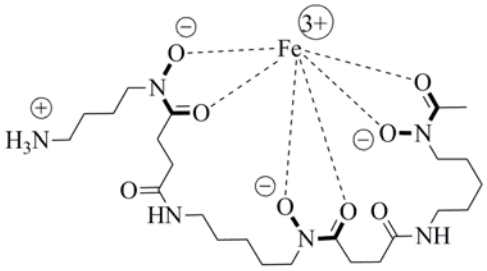

Fig. (3). Feroxamine B, complex of deferoxamine B with iron.

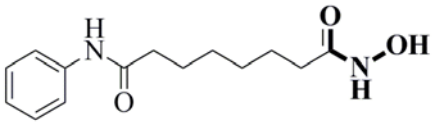

Fig. (4). Chemical structure of suberoylanilide hydroxamic acid (Vorinostat).

their capacity to inhibit metallo-enzymes [12] which permits a wide range of pharmacological activities such as antimicrobial, antitumor, anti-inflammatory, anti-fibrotic, antiviral, anti-neurodegenerative, anti-osteoarthritis and antidiabetic. In the third group, hydroxamic acid derivatives are characterized by their ability to generate nitric oxide, which leads to hypotensive effects.

The aim of this review is to consider the hydroxamate function as the pharmacophore of many biomolecules. In the first part, we will review the biological activities related to pharmacological applications of this function. In the second part different strategies for synthesizing the hydroxamate moiety will be discussed.

PHARMACOLOGICAL AND BIOLOGICAL ACTIVITIES OF HYDROXAMATE DERIVATIVES

Metal Detoxification

Iron in excess is toxic because it causes the production of reactive oxygen species (ROS) through the Fenton and Haber-Weiss reactions [26]. These ROS are responsible for

protein and lipid injuries, DNA degradation, alteration of cellular membranes, tissue damage and vascular permeability [27, 28]. These effects explain the pathologies observed in patients suffering from iron overload, which is a slow accumulation process [29]. Among these pathologies, there is the well-known idiopathic hemochromatosis. Iron accumulates principally in the liver of the patients affected by this disease and in the long term the organ develops serious complications, such as hepatocellular carcinoma [12]. Other iron overload pathologies exist, such as in *β*-thalassaemia [30] or sickle-cell disease [31], due to regular blood transfusions which lead to iron accumulation, each blood transfusion bringing approximately 250 mg of iron. Iron and aluminium overloads have also been observed in patients with renal failure who have to undergo repeated sessions of haemodialysis [32]. Finally, cerebral iron overload has been observed in neurodegenerative diseases [33] such as Alzheimer's disease [34], Huntington's disease [35], multiple sclerosis [36], Parkinson's disease [37] and Friedreich's ataxia [38].

As iron tends to be hoarded by organisms and eliminated in a very slow process, therapeutic treatment must be undertaken with the aim to protect organs against excess of this metal. In liver or heart, iron excess may cause irreversible damage, which could be fatal. The usual treatment is chelation therapy, which uses ligands to form complexes with the iron. Elimination by urinary or biliary tracks will then be facilitated [39]. Nowadays, the molecule of choice is deferoxamine B (Figs. **1**, **3**). Its tri-hydroxamate structure is highly specific for iron detoxification.

As these hydroxamate ligands are able to complex metal ions other than iron [40] they can also be used to treat metal intoxication such as that caused by aluminium, plutonium or actinides [41, 42].

Antioxidant Activities

Hydroxamate functions form part of the structure of compounds such as dimerumic acid [23], desferioxamines [43, 44], pectins modified to contain hydroxamates [45], caffeoyl-amino acidyl-hydroxamic acids [46] and ciclopirox olamine [47]. They contribute to their antioxidant capacity [48]. This property plays an important role in protecting organs such as liver [23] or the central nervous system from oxidative damage [49]. It has also been implicated in limiting retinal degeneration [50]. This antioxidant capacity of the hydroxamate function is attributable to an exchange of electrons between the hydroxamate group (donor) and ROS (acceptor) [51].

This property has been used to protect organs when oxidative damage is induced by certain drugs. For example, deferoxamine B is often used with doxorubicin [52] or catecholamine derivatives [48] in therapeutic protocols.

Anti-infective Activities

Antiparasitic Activities

Plasmodium sp., the causative agent of malaria, exhibits increasing resistance to antimalarial drugs. A strategy based on iron sequestration has been developed using deferoxamine B [18] which shows good antimalarial activity *in vitro* and *in vivo* [53]. In fact, this activity is explained by its ability to remove iron directly from the parasite [54], drastically reducing its replication rate. In addition, it protects the patient against oxidative damage induced by the parasite.

In conclusion, hydroxamate derivatives possess a therapeutic potential by exerting a double effect: iron chelation to the detriment of the pathogen and antioxidant protection of the patient [55]. In addition, it has been recently discovered that these compounds are able to inhibit various enzymes such as HDACs [56], aminopeptidase inhibitors [57] or specific metalloproteases (see antitumor activities), which may lead to promising antiparasitic applications (Fig. **5**) [58, 59].

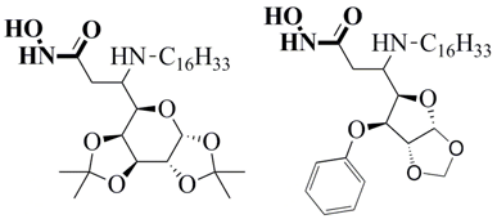

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Fig. (5). Examples of glycosylated β-amino hydroxamic acids with anti-infectious activities.

Antibacterial and Antifungal Activities

The iron complexation ability of hydroxamates may explain their bacterio- and fungi-static activities [60]. Unfortunately, their use in therapy may be complicated because the hydroxamate iron complexes may be captured by the microorganisms, inducing rapid growth [61].

Recently, peptidyl deformylase and methionine aminopeptidase inhibitors have been studied as potent antimicrobial compounds [62]. These enzymes are essential for bacterial growth. As hydroxamic acid derivatives are able to link with this ferrous-iron-containing peptidyl deformylase, they are able to inhibit it to lead to antibacterial activity [63]. The second enzyme, methionine aminopeptidase, is Zn-dependent and is involved the functional regulation of proteins [64]. Its inhibition by hydroxamates results in reduced bacterial growth [65]. The antibacterial potential of hydroxamates may also be due to their capacity to inhibiting numerous other metalloenzymes such as UDP-3-*O*-[R-3-hydroxymyristoy]-*N*-acetylglucosamine deacetylase [15, 66], glyoxalase [67], fructose *bis*-phosphate aldolases [68] or phosphomannose isomerases [69], Such a wide ranging inhibition of metallo-enzymes has been reported as a possible mode of action of the well-known antifungal ciclopirox olamine [70-72].

Other hydroxamates, such as enactins, neoenactins (Fig. **6**), benzoxazinoids (Fig. **2**), phenoxyacetohydroxamate or cinnamohydroxamate exhibit antifungal activity [73]. But no data regarding their biological targets has been reported so far [9, 74].

Natural hydroxamate ligands, such as albomycin, ferrimycin or salmycine also exhibit antibacterial activity

[75, 76]. In each of these molecules, there is a siderophore appendage, which is closely linked to the biologically active moiety (Fig. **7**). In fact, only the non-siderophore part of the molecule has antibacterial activity (tRNA synthetase inhibition), while the siderophore part allows the molecule to enter the bacterial cell to reach its target [76]. This "Trojan horse" strategy has provided ideas to design new antibacterial and antifungal molecules using natural synthetic siderophores [22].

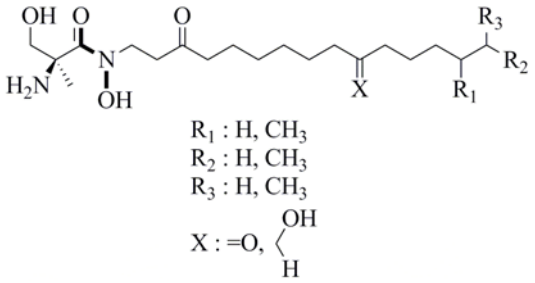

Fig. (6). Chemical structure of neoenactins.

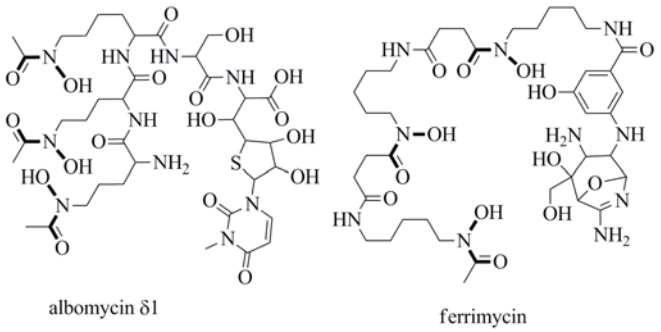

Fig. (7). Structure of natural antibacterial siderophore conjugate.

Anti-toxin Activities

Hydroxamate derivatives are known to limit the effects of toxins secreted by microorganisms, leading to a decrease of their virulence. Many of these toxins exert enzyme activity.

Botulinum neurotoxin, produced by *Clostridium botulinum* [77], is one of the most toxic proteins currently described [78]. Typically poisoning occurs through accidentally contaminated food. The neurotoxicity of this toxin is explained by its Zn(II) endopeptidase activity which cleaves membrane fusion proteins. Then, the release of acetylcholine by exocytosis is blocked, resulting in a flaccid muscle paralysis which can lead to death [79]. To reduce the toxic effects, researchers have developed effective inhibitors of Zn(II) endopeptidase based on hydroxamic acid derivatives (Fig. **8**) [80, 81].

Ureases are enzymes, which are produced by microorganisms in order to generate ammonia from urea. The bacterium *Helicobacter pylori* has recently been identified in the mucous layer of the stomach where the presence of urea was responsible to locally increase the pH. In these conditions urease is responsible for ammonia production by *H. pylori*. Ammonia is therefore responsible for stomach ulcers. Urea can also be degraded by urease positive microorganisms, facilitating urinary tract infections [82]. As various hydroxamic acid derivatives exhibit a relatively high affinity for the bi-nickel active site of ureases, such compounds [62, 83] may be useful to fight these types of infection.

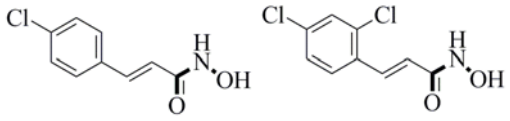

Fig. (8). Chemical structure of inhibitors of botulinum neurotoxin A [81].

Inhibition of other toxins, such as *Clostridium histolyticum* collagenase [84] and thermolysin [85, 86], has also been reported.

Antiviral Activities

Different hydroxamates possess activities against viruses such as herpes simplex [87], influenza A/H1N1 [88] or human immunodeficiency [20] viruses.

Replication of human immunodeficiency virus type 1, the causative pathogen of AIDS, involves three essential enzymes: reverse transcriptase, aspartyl-protease, and integrase. Recently, inhibitors of the latter have emerged as a new promising class of therapeutic agents. Among them, the hydroxamate group containing molecules is able to inhibit integrase by chelating the two metal ions essential for the activity of this enzyme. These promising compounds are similar to the currently marketed HIV integrase inhibitor raltegravir [20].

Another enzymatic target in HIV has recently been evidenced: the HDACs [89]. Inhibitors of these enzymes including hydroxamates, have given promising therapeutic results [90].

Antitumor Activities

Iron is an essential nutrient for cell growth and particularly for rapidly growing tumor cells. Formerly, iron depletion was considered as a therapeutic strategy to decrease cell proliferation but generally the tumor reacts by stimulating angiogenesis [26]. A complex equilibrium between the two processes is set up and cell proliferation is maintained. For this reason the strategy of iron depletion by the use of iron chelators such as hadacin [21], deferoxamine B [91] and ciclopirox olamine [92], has not proven effective in clinical trials [26].

Some hydroxamates can exhibit antitumor activity by inhibiting the ribonucleotide reductase, which is overexpressed in cancer cells and is responsible for the tight regulation of the pool of deoxyribonucleotides necessary for DNA replication and repair [26]. The di-ferric active site of the enzyme can be targeted by appropriate hydroxamates [16, 93], which leads to non-viable DNA and to the reduction of cell proliferation.

More generally, every metal containing enzyme, such as HDAC, matrix metalloproteinases (MMPs) or carbonic anhydrase, may be inhibited by appropriately designed hydroxamic acid derivatives.

HDACs are responsible for the removal of the acetyl group on histone, which closely interacts with DNA [19, 94]. Inhibition of this activity allows gene expression, particularly those implicated in apoptosis, a process which results in tumor cell elimination [95, 96]. Metal chelators, such as hydroxamates, are able to inhibit these zinc-dependent HDACs [15, 16]. For this reason, many different hydroxamic acid derivatives are currently under clinical trial [97]. Suberoylanilide hydroxamic acid (Vorinostat, Fig. **4**) has received FDA approval for the treatment of advanced primary cutaneous T-cell lymphoma [98] and many other antitumor activities have been evidenced [16].

MMPs are involved in various biological processes. They are responsible for tissue remodelling and degradation of the extracellular matrix proteins, including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycans [15, 99]. These enzymes contribute to tumor invasion and proliferation [100]. MMPs are considered to be the precursors of the metastatic process, which signal gravity in cancer evolution. MMP inhibitors are interesting molecules because they are able to limit this step of invasiveness and regulate cancer cells malignancy [16]. More precisely, MMPs exert their activity by cleaving amide bonds of peptides due to the presence of water, itself linked to the zinc (II) ion of the active site [99]. Hydroxamic acid derivatives can chelate the zinc ion replacing the water and leading to enzyme inactivation, which explains the antitumor effects of these molecules. Such a mode of action is exhibited by maramistat (Fig. **9**) a broad-spectrum inhibitor at the nanomolar level [101].

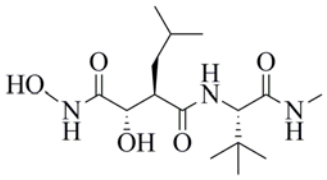

Fig. (9). Chemical structure of maramistat.

Carbonic anhydrases are also zinc-containing enzymes which catalyze the interconversion between carbon dioxide and the bicarbonate ion [62]. Thus they are involved in crucial physiological processes [102] such as respiration and transport of CO_2/bicarbonate, pH and CO_2 homeostasis, etc. Some carbonic anhydrase isoenzymes, which have a restricted expression in normal tissues, are predominantly found in tumor cells. These enzymes are responsible for the acidification of the tumor environment. Reversing this phenomenon by inhibiting the carbonic anhydrases results in limiting the cancer cells growth [103]. This therapeutic strategy has been well-considered because new potent carbonic anhydrase inhibitors have been designed utilizing the ability of hydroxamic acid derivatives to chelate zinc [62, 104].

A recent study on arachidonic acid and its metabolites seems to indicate the significance of cyclooxygenase and lipoxygenases inhibitors (see anti-inflammatory activities) in cancer treatment [105]. Hydroxamic acid derivatives have demonstrated their capacity to interfere not only in arachidonic acid metabolism but also in other biological processes involving enzymes such as phosphatase [106], methionine aminopeptidase (see anti-infectious activity) [65, 107], phospholipases C [108], glutamate carboxypeptidase II (see anti-neurodegeneration activity) [109], lysine demethylases [110], eukaryotic translation [111] or glyoxalase [67] whose inhibition leads to antitumor activity.

Anti-inflammatory Activities

Two major biochemical pathways leading to inflammation exist, both starting from arachidonic acid and resulting in the synthesis of physiological effectors grouped in two families [112]. The first pathway involves cyclooxygenase, and terminates in the production of prostaglandins and thromboxanes. The iron of the cyclooxygenase active site [113] can be chelated by hydroxamate ligands, leading to the blockade of this pathway. The second pathway involves enzymes called lipoxygenases which are non-heminic but still require iron to be active. These enzymes are responsible for the oxidation of fatty acids which produce physiological effects, such as leukotrienes and lipoxins [114]. These can also be inactivated by hydroxamate ligands. As these two pathways are tightly linked, efficient dual inhibitors have been designed to limit the process of inflammation [115].

Soluble TNF-α (tumor necrosis factor alpha) is responsible for inflammatory reactions linked to various diseases, such as inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, stroke and Crohn's disease. This factor comes from the peptide cleavage of TNF-α to a shorter soluble form by the TNF-α converting enzyme [116]. This enzyme is a metalloprotease whose active site is very similar to that of the MMPs. Interesting anti-inflammatory activity has been reported for many hydroxamic acids derivatives, known to inhibit members of this class of enzymes [15, 117].

Inhibition of other enzyme targets by hydroxamates such as 11β-hydroxysteroid dehydrogenases 2 [118], aminopeptidase, dipeptidylaminopeptidase [119], HDACs [120] or leukotriene A4 hydrolases [121] leading to anti-inflammatory activities has been reported. Therefore HDACs inhibition was also of interest in the treatment of asthma [122].

Anti-neurodegenerative Activities

Human serine racemase (a cytosolic pyridoxal-5′-phosphate dependent enzyme) is responsible for the production in the central nervous system of D-serine which acts as a neurotransmitter and an endogenous coagonist of the *N*-methyl-D-aspartate receptor ion channels [123]. Serine racemase inhibitors may be a tool for the treatment of neurodegenerative diseases such as amyotrophic lateral sclerosis [124] and Alzheimer's disease [125] because both diseases are associated with an increased level of D-serine. Very little information on the three-dimensional structure of the enzyme has been reported so far, limiting the *in silico*

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development of inhibitors, nonetheless the most potent ones seem to be hydroxamic acids [126].

Various degenerative diseases of the central and peripheral nervous system are associated with the production of an excess of glutamate which exerts neurotoxic effects. This glutamate comes from the hydrolysis of *N*-acetyl-aspartyl-glutamate, abundant in the brain, by glutamate carboxypeptidase II [127]. It seems obvious that inhibiting this enzyme should have a beneficial impact on the treatment of such degenerative diseases. Carboxypeptidase II is a metallopeptidase which contains two zinc ions forming a co-catalytic active site [128]. These two zinc ions can be complexed by hydroxamic acid derivatives leading to inactivation of the enzyme. This may constitute a way to design potent inhibitors [109].

In addition, inhibition of HDACs and MMPs has been tested and gave good results in the treatment of neurodegenerative pathologies [129-131]. It is now considered as an interesting new therapeutic strategy.

Cardiovascular Protective Activities

In addition to HDACs inhibition [132], various biological effects could be related to cardiovascular protective activities.

The formation of nitric oxide is recognized as an ubiquitous biochemical pathway involved in the regulation of the cardiovascular system [133, 134]. Hydroxamic acids are known to generate nitric oxide [135] and the *N*-substituted hydroxamic acids are also known to be nitric oxide donors [136]. This could explain their vasodilator properties [18] and thus, their potential significance in the development of hypotensive drugs.

Hydroxamates have also revealed antihypertensive activity by inactivating the vasopeptidase (neutral endopeptidase or angiotensin converting enzyme), which controls the blood pressure [137, 138].

Miscellaneous Activities

Many other metalloenzymes may be inhibited by hydroxamates leading to interesting biological effects.

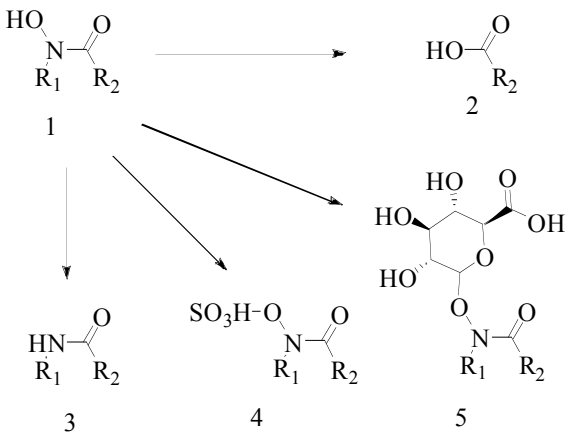
For example, anti-fibrotic activity (anti-scaring) is achieved by the inhibition of procollagen C-proteinase, which belongs to the MMP family (see antitumor activity) [139, 140]. Moreover, inhibition of other MMPs (see antitumor activity) can afford anti-osteoarthritis properties by limiting degradation of extracellular matrix components [141-145], activities against related to ischemia/reperfusion injury [146] or lung diseases [147]. Hydroxamates are able to inhibit enzymes such as aggrecanases [15, 141] and HDAC [148] making them good potential anti-osteoarthritis agents.

Recent development in designing inhibitors of insulin-degrading enzyme showed promising results in antidiabetic therapy [149]. Moreover, hydroxamates can act on the Akt signalling pathway [150]. Akt, also known as Protein Kinase B (PKB), is a serine/threonine-specific protein kinase that plays a key role in glucose metabolism, and also in other multiple cellular processes such as apoptosis, cell proliferation, transcription and cell migration. The mechanism is not elucidated because up to now, no specific targets have been identified.

Interesting enzyme inhibitions by hydroxamates have been reported for the snake venom metalloproteinase [151], the kynurenine aminotransferase, an enzyme related to schizophrenia [152] and recently, the tyrosinase whose inhibition favours a depigmenting activity [46] which may be of great interest in cosmetic [153].

STABILITY OF HYDROXAMIC ACID DERIVATIVES

Usually hydroxamic acid derivatives are very sensitive to hydrolysis [154]. This partially explains the low half-life of those molecules (less than 30 min for deferoxamine [39] and less than 1 hour for suberoylanilide hydroxamic acid [155]). Thus, the development of new drugs containing hydroxamate functions has to take into consideration the structural need for the specificity of biological targets without forgetting their pharmacokinetic properties. Four metabolites of the hydroxamate **1** are reported in the literature (Scheme **1**): the carboxylic acid **2**, the amide **3**, the *O*-sulfonate and the *O*-glucuronide conjugates, respectively **4** and **5** [156-158]. The carboxylic acid **2** is the result of acid hydrolysis of the hydroxamate 1 [159].



Scheme (1). Proposed metabolic scheme of hydroxamic acid derivative.

Overall stability of the hydroxamic acid derivatives against hydrolysis can be enhanced by choosing the appropriate substituent. A recent study has shown evidence of the influence of the R_1 substituent (Scheme **1**) of the hydroxamic acid **1** [160]. The presence of a methyl on the α position or α,β- unsaturation on the hydroxamic acid **1** will lead to greater stability. On the other hand, the presence of an electron-withdrawing group on the α position of the hydroxamate function enhances its hydrophobicity and decreases the stability of **1**.

As well as modifying the overall structure of the hydroxamic acid derivative to improve its stability, pro-drugs have been synthesised (Scheme **2**). For example the synthesis of *O*-glycosides of suberoylanilide hydroxamic acid led to an improved stability toward hydrolysis with a decrease of activity and toxicity [161]. In the case of the

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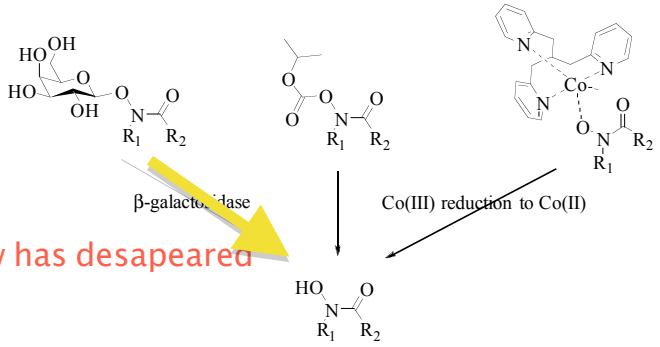
suberoylanilide hydroxamic acid *β*-galactoside, the drug could be efficiently released by enzymatic cleavage of the galactosyl moiety by β-galactosidase. Pro-drugs based on carbamate protection of the hydroxamate function also led to a better bio-availability [162] and need to be further explored in detail. Another strategy to improve stability is to use the hydroxamic acid derivative in a complex formed with another ligand and a metal ion such as cobalt (Scheme **2**), or iron [163-167]. For example, the use of the chaperone Co(III)-tris(2-methylpyridyl)amine with maramistat (Fig. **9**) led to a stable complexe which can reach cancer cells; the active hydroxamate may be released by Co(III) *in vivo* reduction to Co(II) [163]. This strategy allowed the targeting of hypoxic tumor environments where this reduction will occur and increase the biological effectiveness.



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Scheme (2). Pro-drugs of hydroxamic acid derivatives.

SYNTHESIS OF THE HYDROXAMATE FUNCTION

A wide variety of derivatives is necessary to study the structure-activity relationships and fully understand the metabolism of these compounds. Therefore, various synthetic approaches have been developed. Hydroxamic acids are easily synthesized by *N*-acylation of hydroxylamine or nucleophilic displacement of esters, strategies which were recently reviewed [168]. Acylation of hydroxylamine is achieved using activated carboxylic acids in the presence of hydroxylamine [160, 169, 170] or protected hydroxylamine (*N*-alkylhydroxylamine [160], *O*-alkylhydroxylamine [160, 170, 171] or *O*-polymer supported hydroxylamine [160]). Nucleophilic displacement of esters is realized by treatment of the corresponding ester with hydroxylamine (or protected hydroxylamine) under basic conditions [171]. These strategies have also been developed in a solid phase organic synthesis approach using various *N*- or *O*- polymer-supported hydroxylamine [160, 168, 172].

The synthesis of more complex *N*-substituted hydroxamic acid derivatives needs specific strategies. Three different synthetic pathways have been reported (Fig. **10**). The first approach corresponds to the *N*-addition of an alkyl group on the hydroxamic acid (Strategy 1). The second strategy consists in forming the hydroxamate function from the corresponding activated carboxylic acid and a *N*-substituted hydroxylamine (Strategy 2). The third strategy corresponds to the direct oxidation of amides (Strategy 3).

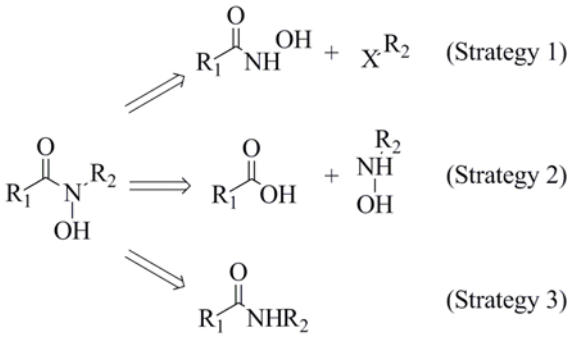


Fig. (10). Retrosynthetic strategies for the N-substituted hydroxamic acid (R_1, R_2: alkyl chains; X: OH, halogens).

Via the *N*-alkylation of an Hydroxamic Acid Function (Strategy 1)

Initially, the direct *N*-alkylation of the hydroxamic acid was considered as an interesting method in order to obtain the expected hydroxamate (Fig. **10**, strategy 1). Two synthetic pathways have been studied (Scheme **3**) [173] and will be described *via* the synthesis of **7.** Firstly, *N*-alkylation using the Mitsunobu reaction led to the corresponding hydroxamate **7** with two hydroximate side-products **8** and **9** (Scheme **3**). Formation of the latter products is due to the reactivity of the carbonyl oxygen of the *O*-benzyl acetohydroxamate. A second option involves alkyl bromide and *O*-benzyl acetohydroxamate. Such substitution leads to the expected structure **7** with just one side-product, compound **8**. Several other hydroxamates have been synthesized *via* this approach [174, 175]. In the case of intramolecular reactions, it appears that no side products are formed and only the hydroxamate-containing adduct is isolated [176].

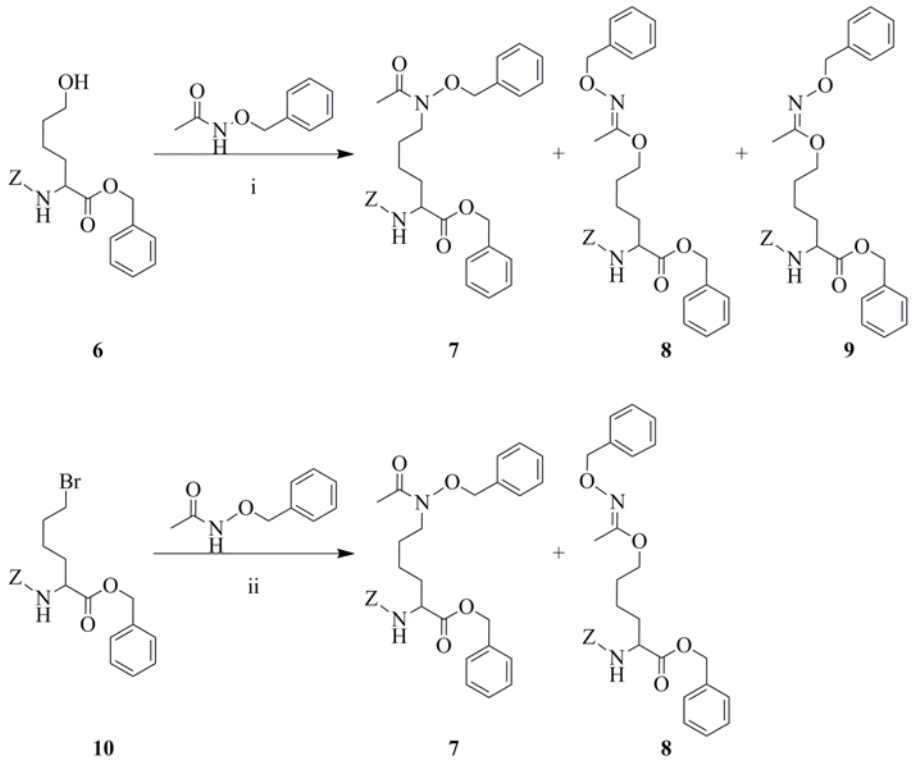
Recently, a third strategy involving iridium catalysis allows the formations of various hydroxamates through the alkylation of the *O*-protected hydroxamic acid function (Scheme **4**) [177].

Via the Final Acylation of *N*-substituted Hydroxylamine (Strategy 2)

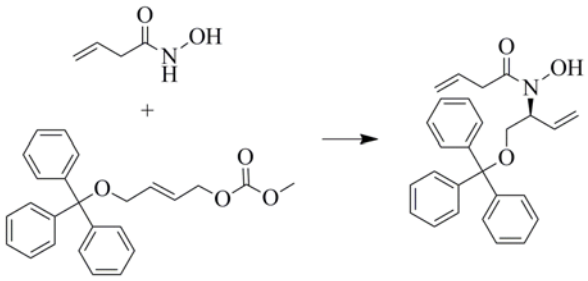
Most hydroxamate syntheses begin with the formation of the appropriate hydroxylamine. The second step consists of an acylation using conventional peptide synthesis strategies [178]. In order to obtain the suitable hydroxylamine, different strategies have been used depending on the substitution pattern required. They can be classified into two groups: the functionalization of hydroxylamine (this strategy can also be used using *O*-polymer supported hydroxylamine [172]), and the modification of a nitrogen containing function such as oxidation of an amine [179] or the reduction of a nitro group [180].

Functionalization of the hydroxylamine can be achieved in three ways: mainly nucleophilic substitution, addition to an *α,β*-unsaturated carbonyl group or the initial formation of a *N*-hydroxylimine.

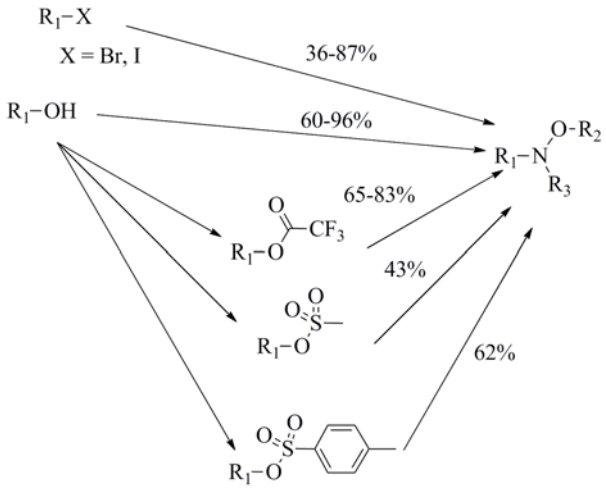
Nucleophilic substitution of hydroxylamine is the method of choice in order to prepare substituted hydroxylamines. It gives better results than the direct substitution of



Scheme (3). Formation of hydroxamate function by *N*-alkylation of hydroxamic acid; (i) PPh_3, DEAD, dry THF, 1.5h, RT; (ii) K_2CO_3, dry acetone, reflux, 24h.



Scheme (4). Preparation of hydroxamate using iridium catalyst; $[Ir(cod)Cl]_2$, phosphoramidite ligand, 1,5,7-triazabicyclo-[4.4.0]dec-5-ene, THF, 73%.

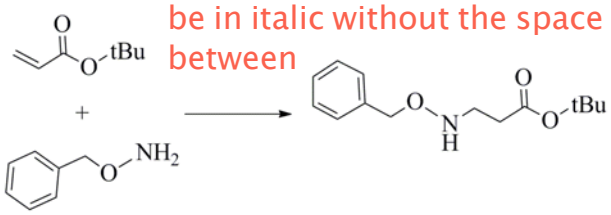


Scheme (5). Preparation of *N*-substituted hydroxylamine using nucleophilic substitution by hydroxylamine (R_2O-NHR_3).

hydroxamic acids [173]. Usually, alkyl bromides or iodides can be used in order to obtain the corresponding *N*-substituted hydroxylamine in the presence of a base [181, 182] or a palladium catalyst [183] (Scheme **5**). Hydroxylamines can also react with alcohols previously activated as trifluoroacetate [181], mesylate [184] or tosylate [185]. The Mitsunobu reaction involving *N*-carbamate-protected *O*-alkyl hydroxylamines as starting material has been used to transform alcohols into substituted hydroxylamines [181, 182]. Benzyl carbamates should be avoided as hydroxylamines can be cleaved in the presence of hydrogen during the deprotection steps [186].

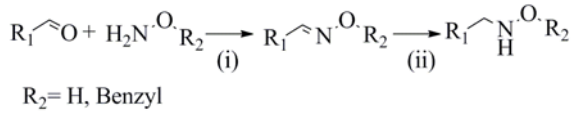
Other strategies were developed depending on the substitution pattern required. The Michael type addition of hydroxylamines on α, β-unsaturated esters leads to the corresponding *N*-substituted hydroxylamines (Scheme **6**) in good yield [65]. If a chiral centre is formed on the β-position of the carbonyl group, its stereochemistry can be controlled via the addition of a chiral catalyst [186].

"alpha,beta-" and "beta-" should be in italic without the space in between



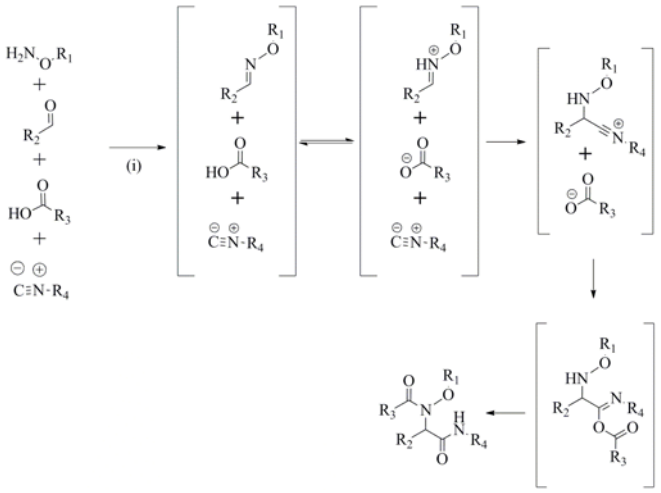
Scheme (6). Preparation of *N*-substituted hydroxylamine by addition on *α,β*-unsaturated ester; Et_3N, EtOH, 70%.

Functionalized hydroxylamines can be obtained in two steps from an aldehyde group (Scheme **7**). The first stage consists of the formation of an hydroxylimine by reaction of an *O*-substituted hydroxylamine with ketones [187] or alcohols [188]. The hydroxylimine is then reduced to the corresponding hydroxylamine [187]. This two step procedure can be also achieved in a one pot strategy [187]. Recently the Ugi multicomponent reaction was applied to the synthesis of hydroxamates [189]. The proposed mechanism (Scheme **8**) shows that it corresponds to a three step strategy. It started with the formation of the substituted hydroxylimine which was then reduced with sodium cyanoborohydride leading to the substituted hydroxylamine. The last step was a rearrangement corresponding to an *N*-acylation.



Scheme (7). Preparation of *N*-substituted hydroxylamine by initial formation *N*-hydroxylimine; (i) NaOAc, MeOH, H_2O, 87-96%; (ii) $NaBH_3CN$, AcOH, 80-91%.

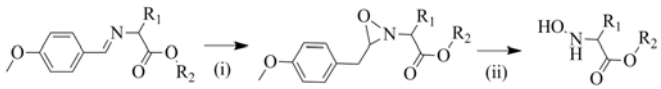
Formation of the functionalized hydroxylamine can also be achieved *via* the modification of a nitrogen-containing function: either reduction of a nitro group or oxidation of an imine or amine.



Scheme (8). Convergent synthesis strategy applied to the preparation of hydroxamates; (i) $ZnCl_2$, Et_2O, dry THF, inert atmosphere, RT, 2–3 days, 27-95%.

Nitro group reduction can be done with good yields using palladium supported barium sulphate [180], sodium borohydride [190] or hydrogen [191] with palladium catalyst or ammonium chloride with zinc [192]. Recently the formation of cyclic hydroxamate was achieved from a nitro group in one step by its reduction by hydrogen using an activated carboxylic acid to avoid overreduction to the amine [193].

The oxidation of an imine by monoperphthalic acid followed by acid hydrolysis can lead to the corresponding substituted hydroxylamine (Scheme **9**) [194].



Scheme (9). Preparation of *N*-substituted hydroxylamine by oxidation of the imine; (i) monoperphtalic acid, Et_2O, 0°C; (ii) H^+, H_2O, 35%.

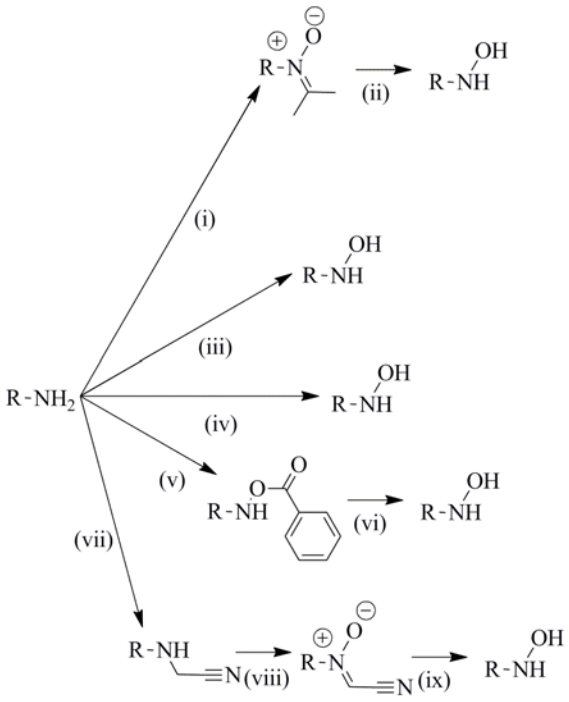
The latest approach, probably the most popular to access *N*-substituted hydroxylamines, is the direct oxidation of the corresponding amine (Scheme **10**) using either dimethyldioxirane [195], tertbutylperoxide [196], oxone [196], benzoyl peroxide [179, 197] or metachloroperoxybenzoic acid [198]. Most of the reagents lead to *O*-unprotected hydroxylamines. Benzoyl peroxide is the appropriate oxidant if the final *O*-protected derivative is expected [179, 197].

In some cases, access to *N*-monosubstituted hydroxylamines required an *N*-protection step. This could be realized through the preparation of *N*-benzylidene nitrones (Scheme **11**) [198].

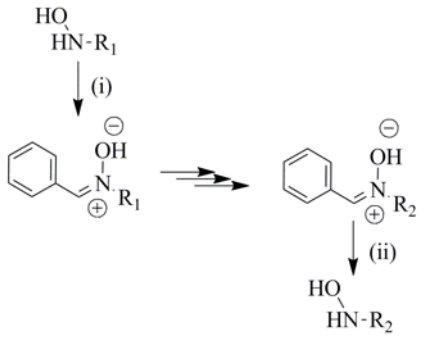
Via the Direct Oxidation of Amide (Strategy 3)

The oxidation of amides can be achieved using peroxo-molybdenum complexe with dimethylformamide [106, 190, 191]. This is a two step transformation starting with the trimethylsilylation of the amide. The *O*-silyliminoether is

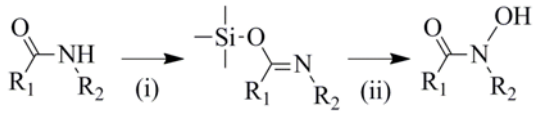
then oxidized (Scheme **12**). This strategy, mainly applied for the formation of cyclic hydroxamates, can also be used for the formation of various *N*-substituted hydroxamic acids [199].



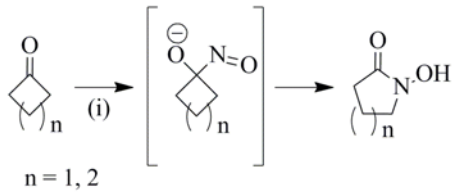
Scheme (10). Preparation of *N*-substituted hydroxylamine by oxidation of the amine; (i) dimetyldioxirane, 48%; (ii) H^+, H_2O; (iii) tertbutylperoxid, 10-50%; (iv) oxone, 10-50%; (v) benzoyl peroxide, 40-97%; (vi) NH_3, MeOH, 90%; (vii) $BrCH_2CN$, 100%; (viii) metachloroperoxibenzoic acid; (ix) $H_2NOH.HCl$, 53-77%.



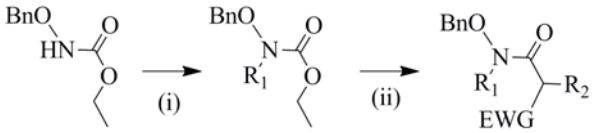
Scheme (11). Protection strategy of *N*-monosubstituted hydroxylamine as *N*-benzylidene nitrones; (i) benzaldehyde, CH_2Cl_2, TEA, 75-96%; (ii) $NH_2OH.HCl$, imidazole, MeOH, oxalic acid, 77%.



Scheme (12). Preparation of *N*-substituted hydroxamic acid by oxidation of silylated iminoethers; (i) bistrimethylsilylacetamide, 95%; (ii) MoO_5, DMF, 15-80%.



Scheme (13). Preparation of cyclic hydroxamates by NOH insertion on ketone; (i) *N*-hydroxybenzenesulfonamide, NaOH, EtOH, 18-69%.



Scheme (14). Preparation of hydroxamates by the reaction of a variety of stabilized carbon nucleophiles on *N*-alkyl-*N*-benzyloxy carbamates; (i) NaH, DMF, R_1X, rt, 81-87%; (ii) R2-CH2-EWG, Lithium bis(trimethylsilyl)amide, TH, 52-92%.

Miscellaneous Strategies

Other original strategies have been found to lead to hydroxamic acid derivatives, for example, cyclic hydroxamates throughout NOH insertion on ketones (Scheme **13**) [200] or the reaction of a variety of stabilized carbon nucleophiles on *N*-alkyl-*N*-benzyloxy carbamates (Scheme **14**) [201].

CONCLUSION

Hydroxamates possess specific biochemical activities associated with interesting pharmacological properties. They can be sorted into three different categories depending on their biochemical role. The first category corresponds to their iron (or other metal) chelating capacity, which leads to iron detoxification, antioxidant or anti-infective activities. The second category is related to their ability to inhibit metalloenzymes. This mode of action leads to multiple therapeutic properties such as anti-cancer, anti-infective, anti-inflammatory, anti-scarring, anti-toxin, antiviral, anti-neurodegeneration, or anti-osteoarthritis. The third category corresponds to the ability of hydroxamic acid derivatives to generate nitric oxide leading to cardiovascular protective effects, particularly hypotensive activity.

Owing to this wide range of activities, hydroxamates constitute an important class of compounds regularly found in chemical libraries devoted to high throughput screening.

Many strategies have been developed to synthesize these molecules. To access simple hydroxamic acids structures, the usual strategy followed is the direct coupling of carboxylic acids or esters with hydroxylamines (or substituted hydroxylamines). For more complex molecules such as *N*-substituted hydroxamic acids, their synthesis is more difficult. Nevertheless, it can be achieved either by direct oxidation of the corresponding amides, coupling the appropriate *N*-substituted hydroxylamines with carboxylic acids or the *N*-substitution of hydroxamic acids.

All these various strategies lead to structurally original derivatives, exhibiting potentially significant biological activities.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary material is available on the publisher's web site along with the published article.

ABBREVIATIONS

ROS = Reactive oxygen species

HDAC = Histone deacetylase

MMP = Matrix metalloproteinase

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