Medicinal Chemistry Research (2020) 29:831–845
https://doi.org/10.1007/s00044-020-02530-7

MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Biologically active quinazoline-based hydroxamic acids

Vasily N. Osipov[1] · Derenik S. Khachatryan[2] · Alexandr N. Balaev[3]

Received: 26 November 2019 / Accepted: 4 March 2020 / Published online: 18 March 2020

Abstract

Molecular hybridization has become a new promising way to treat multifactorial diseases with a single compound that acts on multiple targets. The combination of several functional pharmacophore groups in one molecule can lead to a stronger therapeutic effect due to the ability to bind to several targets and possible synergistic interactions. The concept of multifunctional agents is being actively developed and has already produced some encouraging results. The quinazoline cycle and hydroxamic acids are unique pharmacophore groups that contribute to the structure of drug agents widely used in medical chemistry. The combination of these pharmacophores in one molecule leads to promising new compounds, which has been confirmed by many experimental studies in published literature across the world. Hybrid compounds of hydroxamic acids and the quinazoline cycle are a potential basis for the development of effective drugs used in the complex treatment of oncological, infectious and neurological diseases. This review provides information on the most significant developments in this area and discusses the bioactivity of important agents. Compounds with both linear hydroxamic acids and cyclic acids in which a hydroxamate group is integrated in the quinazoline ring are also covered in this review.

Keywords Hydroxamic acids · Quinazolines · Dual-targeted inhibitors · Hybrids.

Introduction

At present, one of the most promising strategies in creating new pharmaceuticals is the design and synthesis of hybrid compounds. These compounds typically consist of two or more different covalently linked bioactive fragments (pharmacophores) and operate via the activation of several mechanisms at single or multiple targets. Single agent therapy is not able to provide effective and long-term control of the malignant process due to the development of drug resistance, insufficient selectivity, and high toxicity (Lavi 2015; Bérubé 2016). Hybrid compounds overcome many of the disadvantages of individual drugs, such as low solubility, side effects, and multidrug resistance, which leads to a more pronounced therapeutic effect compared with individual components. Multipurpose hybrids also have certain advantages in comparison with the combined therapeutic approach such as superior bioavailability, low toxicity, they allow to more accurately predict the pharmacokinetic and pharmacodynamic profile, simpler patient compliance, higher treatment efficacy, and lower treatment costs. Multipurpose hybrids, as a rule, are created by linking the framework of two target selective ligands or pharmacophores with the total therapeutic effect exceeding the action of each individual ligand (Ganesan 2016; Musso et al. 2015; Kerru et al. 2017; Fortin and Bérubé 2013; Nepali et al. 2014).

Molecular modeling allows for the creation of drugs that combine the structural features of selective ligands to produce hybrids with several pharmacophore groups aimed at different types of targets. The most common design of multifunctional hybrids is based on the connection through a spacer of two selected pharmacophores with the ability to bind to different therapeutic targets.

The combination of the quinazoline cycle and hydroxamic acids is one of the unique pharmacophore groups that contributes to widely used medicinal agents in medical chemistry. The simplicity of their preparation and availability of feedstock, as well as the high biological activity of these

✉ Vasily N. Osipov
ovn65@yandex.ru

[1] Ph.D. in Chemistry, N.N. Blokhin Russian Cancer Research Center, Kashirskoye Shosse 24, Moscow, Russian Federation115478

[2] Ph.D. in Chemistry, National Research Centre "Kurchatov Institute", Akademika Kurchatova pl.1, Moscow, Russian Federation123182

[3] Ph.D. in Chemistry Pharm-Sintez JSC 2, 2nd Kabelnaya street 46, Moscow, Russian Federation111024

compounds, has led to the creation of multifunctional hybrid compounds that showed higher efficiency than the individual components or their additive use (Fortin and Bérubé 2013; Nepali et al. 2014; Hesham et al. 2018; Zhang et al. 2014; Schobert and Biersack 2017; Gupta 2013; Muri et al. 2002; Lou and Yang 2003). The creation and implementation of multifunctional preparations in the new generation of practice is actively developing throughout the world as evidenced by many experimental studies published across the world. This review is an attempt to detail and classify the most significant and promising developments based on the hybridization of hydroxamic acids and the quinazoline cycle.

Hydroxamic acid and the quinazoline cycle are important pharmacophore fragments

Hydroxamic acids and the quinazoline cycle are unique pharmacophore groups that are often present in drugs widely used in medical chemistry.

Hydroxamic acids, represented by the general formula RC(O)NR′OH, exhibit a wide spectrum of biological activity. In addition, they are easy to prepare and there is readily accessible feedstock, making them a desirable agent for both practical and research purposes (Gupta 2013).

Due to the ability of hydroxamic acids to form complexes with various metal ions, in particular iron, zinc, magnesium and calcium (the most common metals in metal-containing proteins), they possess a number of unique biological and pharmacological properties. Hydroxamic acids are capable of the inhibition of a variety of enzymes, including matrix metalloprotease, peroxidase, hydrolase, urease, lipoxygenase, cyclooxygenase, histone deacetylase, peptide deformylase (Gupta 2013; Muri et al. 2002; Lou and Yang 2003). In medical chemistry, hydroxamic acids are used in the design of therapeutic agents against hypertension (Zamora et al. 1995), cancer (Manal et al. 2016), malaria (Giannini et al. 2015), tuberculosis (Rao et al. 2018), HIV, Alzheimer's disease (Rao 1992; Xu et al. 2011), cardiovascular disorders (Yoon and Eom 2016), and others diseases (Qiu et al. 2017). Effective histone deacetylase inhibitors (HDACi) have been found among hydroxamic acid derivatives; in particular, Vorinostat (SAHA), Panobinostat (LBH589) and Belinostat have been approved by the US FDA for the treatment of cutaneous T-cell lymphoma and multiple myeloma (Mottamal et al. 2015) (Fig. 1).

It should be noted that although HDAC inhibitors during monotherapy showed moderately high antitumor activity, their combined use with many structurally and functionally diverse drugs and biologically active peptides was more effective (Bolden et al. 2006; Suraweera et al. 2018; Arrighetti et al. 2015). Modern methods of chemical synthesis make it possible to introduce a hydroxamate group into the molecules of various natural and synthetic compounds, including well-known pharmaceutical preparations. For example, derivatives of camptothecin, doxorubicin, and colchicine were synthesized (Fig. 2). These and many other examples are described in comprehensive reviews (Musso et al. 2015; Hesham et al. 2018; Papavassiliou and Papavassiliou 2013; Seo 2012). Such hybridization increases their therapeutic effect. The development of this direction led to the synthesis of new multitarget hybrid compounds.

In turn, the *quinazoline cycle* is also an important pharmacophore fragment. Derivatives of quinazoline and dihydroquinazoline are currently widely used in clinical practice (Khan et al. 2016; Shagufta and Ahmad 2017; Hemalatha and Madhumitha 2016), with preclinical studies of new derivatives at anongoing status. The quinazoline cycle is present both in various natural compounds and in the molecules of more than a hundred drugs. This can be attributed to its diverse activity, including antibacterial, antifungal, anti-inflammatory, antimalarial, antiviral, antituberculosis properties, as well as its inhibitory effect on thymidyl synthase, poly (ADP-ribose) polymerase and tyrosine kinase (Asif 2014) (Fig. 3).

The combination of these pharmacophores in one molecule can potentially lead to new promising compounds, as evidenced by numerous examples. In this review, we examined the biologically active compounds described in the literature that combine the quinazoline cycle and hydroxamate group in one molecule. Compounds with both linear hydroxamic acids and cyclic acids in which a hydroxamate group is integrated in the quinazoline ring are also covered.

Compounds with hydroxamate function included in the quinazoline cycle

The hydroxamate function in quinazolinones can be included in the heterocyclic ring as an endocyclic N-hydroxy group, forming a cyclic hydroxamic acid (Fig. 4).

One of the advantages of compounds with an endocyclic N-hydroxy group is their high metabolic stability, as it is known that in linear hydroxamic acids, single N–O bonds can be metabolized to highly reactive compounds that cause serious side effects (Rani and Granchi 2015).

Biological activity of cyclic hydroxamic acids

The endocyclic N-hydroxy group is present in a number of natural compounds, for example, in some siderophores (Carboxymycobactin, Heterobactin B, Cepabactin), which function as ligands and carriers of iron ions in bacteria (Hider and Kong 2010). The high affinity of hydroxates for iron ions allows the Fe^{3+} compounds to be dissolved and transported

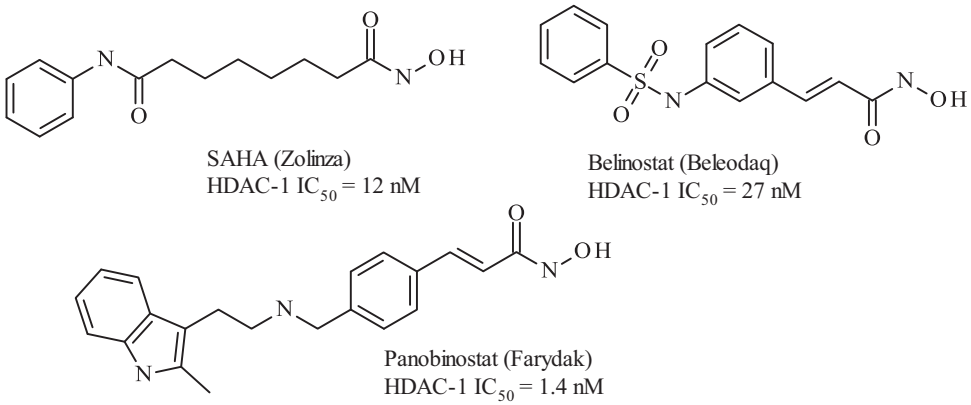


Fig. 1 Hydroxamic acids registered as HDACi

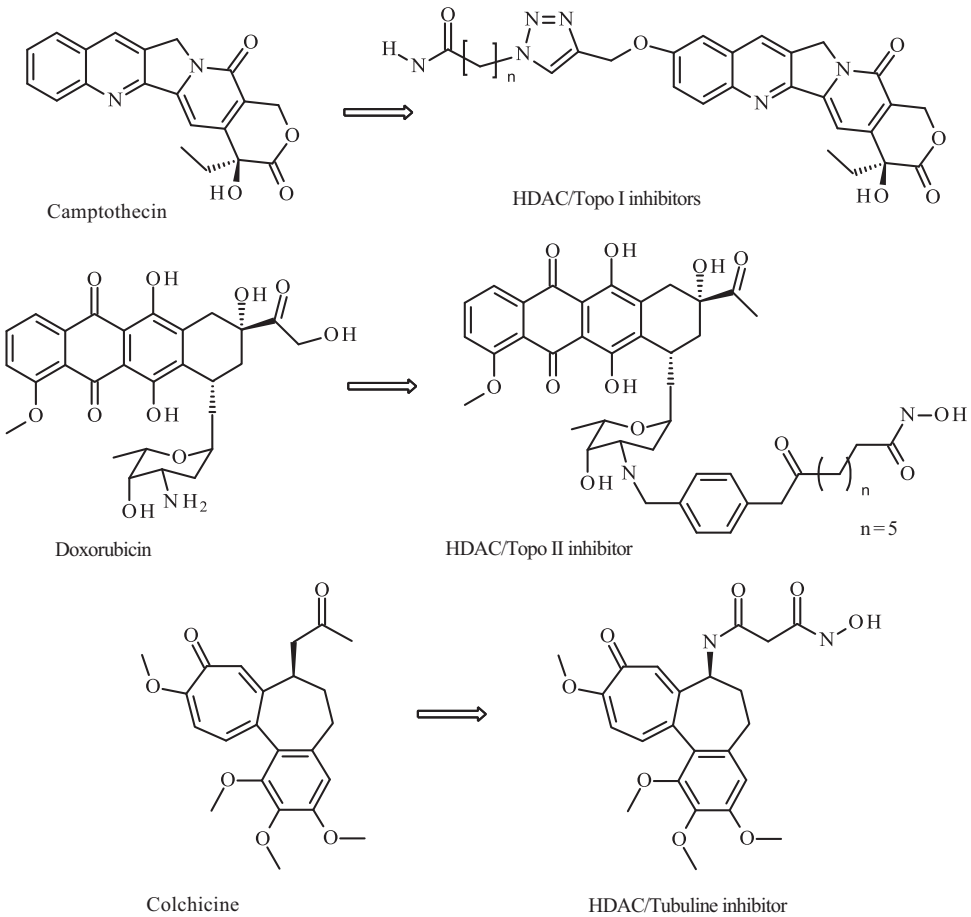


Fig. 2 Design of dual-acting hybrids with hydroxamate moiety

into the cell, where it is reduced to Fe^{2+}. Compounds of this class are also found in the products of fungal metabolism (Phaeosphaeride A) (Maloney et al. 2006; Abzianidze et al. 2015; Kobayashi et al. 2015) (Fig. 5).

One of the most studied natural compounds of this class are the benzaxazinoids, DIBOA, and DIMBOA (2,4-dihydroxy-2H-1,4-benzoxazin-3 (4H) -ones), which are responsible for the resistance of cereal plants to pests and diseases (Fig. 5) (Niemeyer 1988, 2009). In case of damage to plant tissue, these substances are formed in the form of secondary metabolites that have insecticidal and fungicidal effects.

Cyclic hydroxamic acids are a universal class of compounds that form the basis for the creation of many new therapeutic agents. In the last decade, active studies of cyclic hydroxamic acids have been conducted to create a class of antiretroviral drugs for the treatment of HIV-1 infection. A number of experimental studies have shown that clinical inhibitors of HIV-1 integrase (IN) effectively inhibit virus replication with a sharp decrease in viral load.

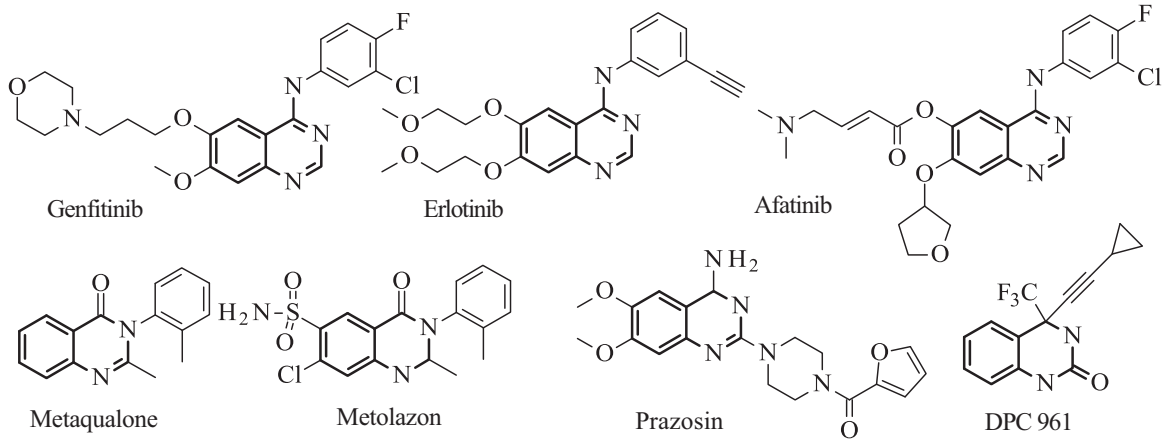


Fig. 3 Examples of quinazoline drugs

A series of N-hydroxy-dihydronaphthyridinone derivatives (compound 1), specific HIV-1 IN inhibitors with high efficiency and an excellent resistance profile, were designed, synthesized and evaluated (Fig. 4) (Pryde et al. 2013). A biological evaluation of a series of substituted 1,8-dihydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides (compounds 2 and 3) was completed, providing selective inhibition of not only IN but also RNase H, which until recently was the only enzyme clinically unconfirmed as an antiviral target (Zhao et al. 2014). However, the emergence of resistance to these drugs underlines the need to develop next-generation IN catalyst inhibitors with improved resistance profiles. One of the latest developments includes IN inhibitors, and derivatives of 2-hydroxyisoquinoline-1,3 (*2H,4H*)-dione (compound 4), which are potential agents for further preclinical development as a next-generation IN inhibitor (Fig. 6) (Tang et al. 2017; Billamboz et al. 2016).

A series of arylsulfonamide-based matrix metalloproteinase (MMP) inhibitors (compounds 5 and 6) with a cyclic hydroxamate fragment acting as Zn-binding groups selectively inhibiting MMP-2 and MMP-9 with IC_{50} values of 10.6 and 16.4 μM, respectively, were synthesized (Fig. 4) (Zhang et al. 2008a, 2008b). Also, HDACi were synthesized as a Zn-binding agent in the class of 5-membered cyclic hydroxamic acids (compound 7). However, these compounds showed low activity against extracts of HeLa cells; therefore, this group requires additional research in order to search and develop more active compounds (Mutule et al. 2014).

The biological activity of cyclic hydroxamic acids included in the quinazoline cycle

Until 2000, experimental studies on hydroxamic acids associated with quinazoline possessing biological activity were lacking. One of the first synthesized compounds with an endocyclic N-hydroxy group included in the quinazoline cycle was described in 1970 by Bonola and Sianesi (1970). The authors of the study synthesized a series of derivatives of 3-hydroxy-2,3-dihydro-4(*1H*)-quinazolines (compound 8) as potential antibacterial and antifungal agents (Fig. 7). Later, a derivative of 3-hydroxyquinazolin-4-one (compound 9), which exhibited an inhibitory effect on trypanosomal glycerol-3-phosphate oxidase, was reported (Grady et al. 1986). Jung et al. (1985) studied the genotoxicity of furan derivatives of 3-hydroxy-2,3-dihydroquinazolin-4-ones. The nitrofuran derivative (compound 10) was found to be the most active in mutagenicity tests (Fig. 7). Based on the test results, it was found that the carcinogenicity of this compound may be due to the ability to induce mutations in the hereditary apparatus of the cell.

As a result of the development of molecular modeling in recent decades, the list of pharmaceuticals that include quinazoline derivatives and hydroxamic acid in the molecule has expanded significantly. Compelling progress has been noted in the development of hybrid compounds, which are promising in the complex treatment of infectious and oncological diseases.

Compounds with antibacterial, antiviral, and fungicidal effects

Since the 2000s, a series of works has been executed on the synthesis of antibacterial and fungicidal drugs. During the experiments, 2,2′-disubstituted derivatives of 3-hydroxy-2,3-dihydro-4(*1H*)-quinazolinone (compound **11**) were developed, which are promising fungicides against fungi of various taxonomic classes (Fig. 8) (Kotov et al. 2001). Compounds of this series were also studied for antiglutamatergic activity (Fetisov et al. 1999). As a compound with fungicidal and growth-regulating properties, 3-hydroxy-2-thioxo-4(*3H*)-

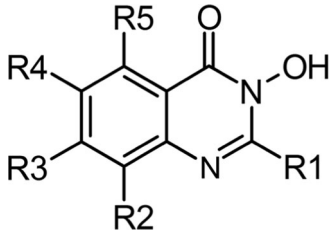


Fig. 4 The structure of compounds with hydroxamate function included in the quinazoline cycle

quinazolinone (compound **12**) was proposed (Khohlov et al. 2005). In continuation of the work, its derivatives were synthesized (Khohlov, Osipov 2011); compound 13 was declared as an antiviral, antibacterial, and fungicidal agent (Khokhlov et al. 2005, 2011).

The synthesis of a series of DNA gyrase inhibitors allowed an increase in the class of antibacterial agents. The most active compound from this series (compound 14) showed high intracellular activity (MIC = 0.13–4.0 mg/ml) against laboratory strains of model microorganisms (*Escherichia coli, Enterococcus faecalis, Staphylococcus aureus*, and *Streptococcus pyogenes*) which quantitatively corresponds to that for ciprofloxacin, a synthetic antibiotic with a similar pharmaceutical effect (MIC = 0.06–4.0 mg/ml) (Tran et al. 2004). In parallel, other experimental studies synthesized substituted 3-hydroxyquinazolin-4-ones (compound 15) with antimicrobial activity against model microorganisms of the ATCC collection *(S. aureus, B. subtilis, E. coli, P. aeruginosa*, and *S. albicans*) (Dikii et al. 2006).

One of the latest and promising antimicrobial developments relates to acetohydroxyacid synthase (AHAS) inhibitors, which are seen as a promising drug target against *Mycobacterium tuberculosis* (MTB). Using molecular docking followed by a search for similarities, 23 new AHAS inhibitors were found, including derivatives of 3-benzoyloxyquinazinone (Wang et al. 2013). The IC_{50} values for bacterial AHAS inhibitors for compounds 16 and 17 were 1.85 ± 0.19 and 2.02 ± 0.15 μM, respectively (Fig. 8). In continuation of these studies, 24 additional quinazolinonebenzoates were synthesized and their antituberculous activity was studied (Lu et al. 2015). Compound 18 showed significant inhibition of MTB-AHAS, with an IC_{50} value of 6.50 μM. It should be noted that this compound also showed in vitro intracellular activity against clinically isolated strains of drug-resistant MTB (MIC = 2.5–10 mg/L). These results showed that quinazolinone benzoate compounds should be considered as promising compounds for the development of effective anti-tuberculosis drugs with a possible new mode of action.

As mentioned above, cyclic hydroxamic acids have gathered strong interest as antiviral agents. One of the first studies was conducted by Bristol-Myers Squibb in 1996. Large-scale bioscreening revealed the active antiviral compounds BMY-183021 (19) and BMY-183355 (20) (Fig. 8), which are cyclic hydroxamic acids with the (*3H*)-quinazolinone ring, selectively inhibiting the transcriptases of influenza A and B viruses (IC_{50} = 40–50 μM) (Cianci et al. 1996).

Following these findings, substituted 3-hydroxyquinazolin-4-ones were synthesized that inhibit the hepatitis C virus (HCV) NS5B polymerase (Deore et al. 2012). The optimization of their structure led to the identification of N-phenylpropylcarboxamide (compound 21) (Fig. 8), which displayed activity against HCV NS5B polymerase with IC_{50} = 8.8 μM. Compound 21 has selectivity for Ava5 cells, HCV1b replicon (EC50 = 17.5 μM) when compared with parent HuH-7 human hepatocarcinoma cells (EC50 = 187.5 μM).

There is particular interest in the class of cyclic hydroxamic acids that is attracted by compounds that are potential antitumor drugs (Fig. 9). In a series of studies, the synthesis of 3-hydroxy-1H-quinazolin-2,4-dione (compound 22) was completed and the activity of these compounds as selective antagonists of the ionotropic glutamate receptors was confirmed, including the Gly/NMDA, AMPA and kainate (KARs) receptors (Colotta et al. 2004; Colotta et al. 2012; Catarzi et al. 2010). Most of the compounds in this series showed high affinity for both AMPA and KARs receptors, as well as for the Gly/NMDA site. The most active compound was 6-(2-carboxybenzoylamino)-3-hydroxy-*1H*-quinazoline-2,4-dione (compound 23), which not only showed high affinity for high-affinity and low-affinity CA receptors (Ki = 0.62 μM and Ki = 1.6 μM, respectively) but also high selectivity (Colotta et al. 2006). Substances from this class have also been shown to be potential inhibitors of tumor-associated human carbonic anhydrase. (hCAs) IX and XII isoforms (Falsini et al. 2017). 3-hydroxyquinazoline-2,4-diones were identified as inhibitors of flap endonuclease 1 (FEN1) (compound 24) (Tumey et al. 2005). It has been experimentally shown that the compounds of this group are 100 times more effective than known FEN1 inhibitors (IC_{50} 0.014–0.079 μM). Also, more than 1000-fold specificity was achieved in relation to the related endonuclease of pigment xeroderma G, the activity against which was IC_{50} = 0.16–0.19 μM.

Some of the considered group of hybrid compounds may be potential agents not only in the treatment of infectious and oncological diseases but also in the complex treatment of neurological pathologies. It was experimentally shown that the synthesized derivatives of quinazolin-4(*1H*)-one inhibit myeloperoxidase with IC_{50} values up to 100 nM, including the 3-hydroxyquinazolin-4 (*3H*)-one derivative (compound 25) (Li et al. 2015). Myeloperoxidase is a key antimicrobial enzyme that plays a key role in protecting the host and is able to participate in the development of inflammatory diseases, such as Parkinson's and Alzheimer's.

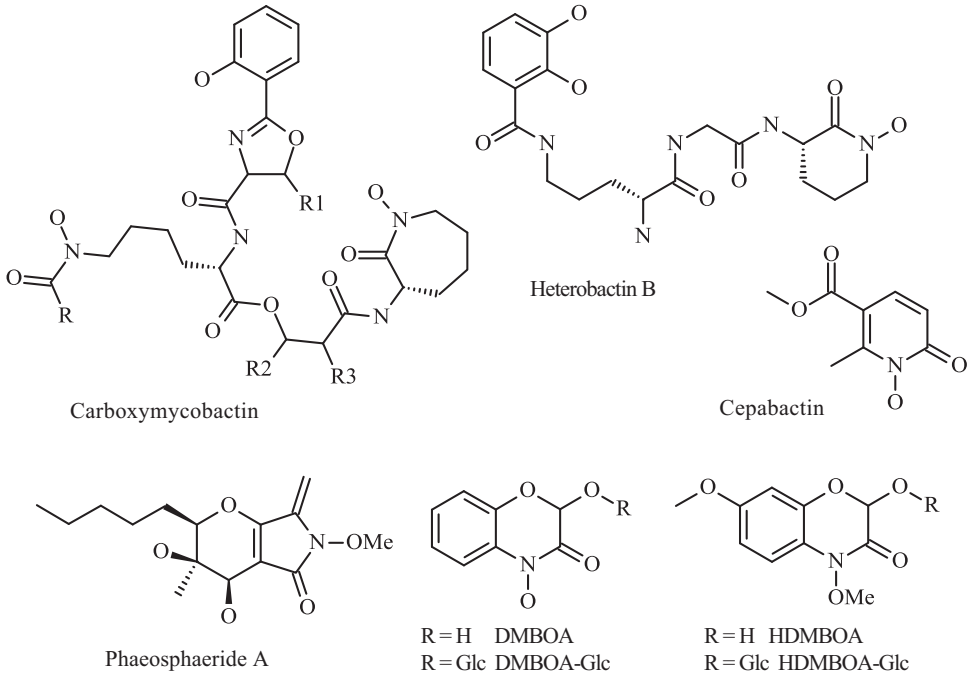


Fig. 5 Natural biologically active compounds with cyclic hydroxamate function

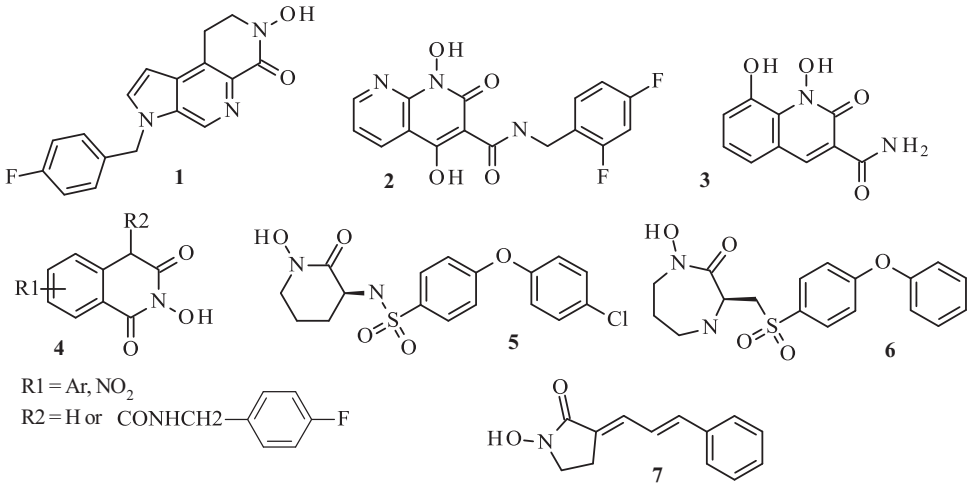


Fig. 6 Synthetic biologically active compounds with cyclic hydroxamate function

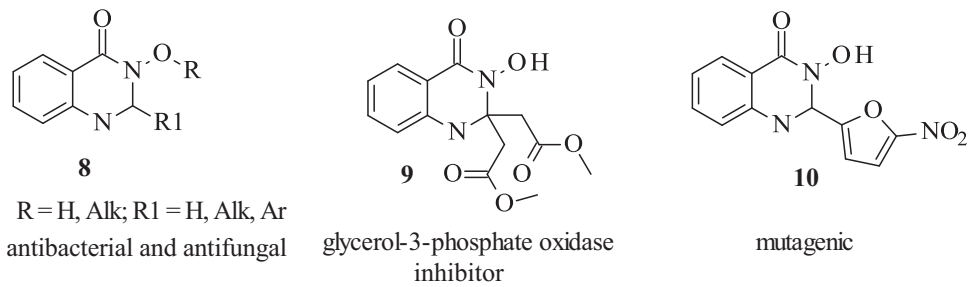


Fig. 7 Cyclic hydroxamic acids in the quinazoline cycle with potential biological activities

Linear hydroxamic acids linked to the quinazoline cycle

Hydroxamic acid and the quinazoline ring can be covalently connected via various linkers, allowing the molecule to freely interact with different targets. The chemical nature of hydroxamic acid and derivatives of quinazoline enables the creation of a variety of bifunctional molecules by varying the position at which hydroxamic acid is attached to the quinazoline cycle. Most often, hybrid compounds containing

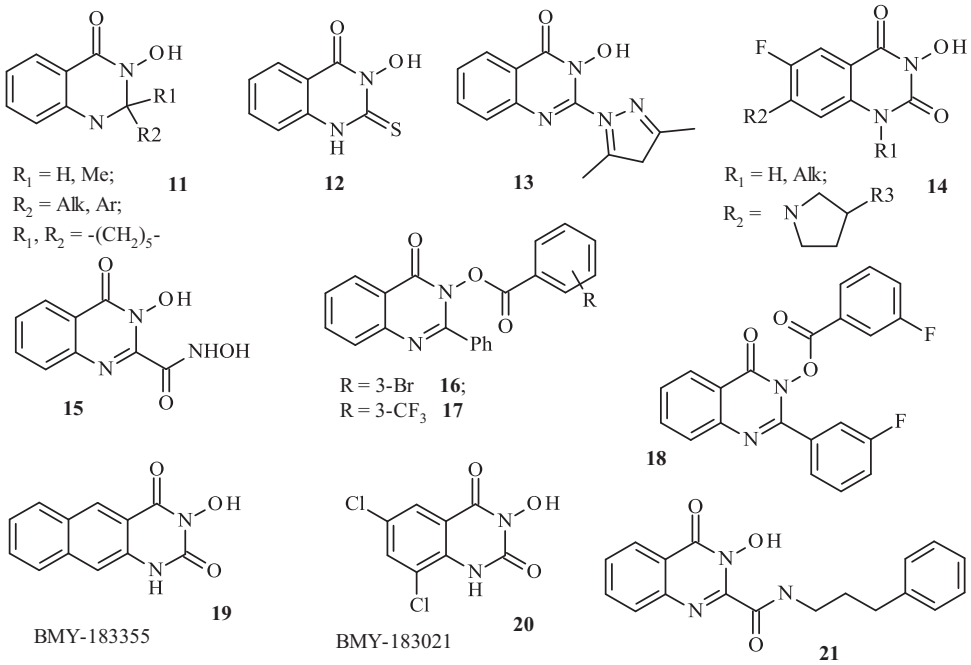


Fig. 8 A group of antibacterial, antifungal, and antiviral compounds based on cyclic hydroxamic acids and a quinazoline cycle

hydroxamic acids and the quinazoline cycle are used to increase the effectiveness of chemotherapy as multipurpose antitumor agents, which can be classified into several groups according to the type of action.

Selective MMP inhibitors

Selective MMP inhibitors were one of the first antitumor drugs based on the synthesis of hybrid compounds of hydroxamic acid and the quinazoline cycle. Overexpression of MMPs is involved in various pathological conditions, such as cancer, arthritis, cardiovascular disease, and neurological disorders. In this regard, MMPs are considered therapeutic targets and many MMP inhibitors have been developed over the past two decades, including hybrid compounds of quinazoline and hydroxamic acid. Thus, tumor necrosis factor α-convertase (TACE) is a metalloprotease-disintegrin closely associated with MMPs. Modern TACE inhibitors, such as succinate-based hydroxamic acids, for example Marimastat (TACE $IC_{50} = 3.8$ nM; blood $IC_{50} = 7$ μM), showed weak activity in vivo and in the blood. To solve this problem, volumetric substituents were introduced into succinate-based hydroxamic acids. The optimization of this series of sulfonamides resulted in the synthesis of heterocyclic bicyclic sulfonamides, of which compound 26 (Fig. 10) was selected for further studies (TACE $IC_{50} = 0.57$ nM; blood $IC_{50} = 0.28$ μM) (Barlaam et al. 1999). However, none of these compounds has been successfully tested in clinical trials due to insufficient efficacy and long-term dose-limiting side effects in diseases such as cancer and arthritis. Despite these disadvantages, inhibition of MMP is still considered an effective therapeutic approach. In the studied series of new hydroxamic acids, effective and specific inhibitors of MMP-2,3,9,13, one of the compounds is a derivative of 4-quinazolinone (Chollet et al. 2001). Among the latest developments of selective matrix metalloprotease-13 inhibitors (MMP-13), a Zn-linking group was used with the quinazoline-2-carboxamide system. The synthesized compounds 27, 28, 29 (Fig. 10) showed high activity and selectivity to other types of MMP (Nara et al. 2016, 2017).

HDAC inhibitors

Over the past few years, there has been developments to the synthesis of hydroxamic acid-based HDAC inhibitors with quinazoline fragments, where the latter act as an effective surface interaction domain (“cap”) with active enzyme sites (Fig. 11).

The 4-aminoquinazoline derivative (compound 30) significantly inhibited HDAC6 ($IC_{50} = 17$ nM) with 25-fold selectivity for HDAC1 and 200-fold selectivity for HDAC8 (Yang et al. 2015). It also inhibited the growth of 11 different hematologic and solid tumor cell lines more efficiently than SAHA, with IC_{50} in the low nanomolar ranges. It was determined that compound 30 increased the level of acetylation of α-tubulin in vitro. In in vivo experiments, compound 30 more effectively inhibited tumor growth in colorectal cancer (HCT116), acute myelocytic leukemia (MV4-11), and Romas xenograft B cell lymphoma when

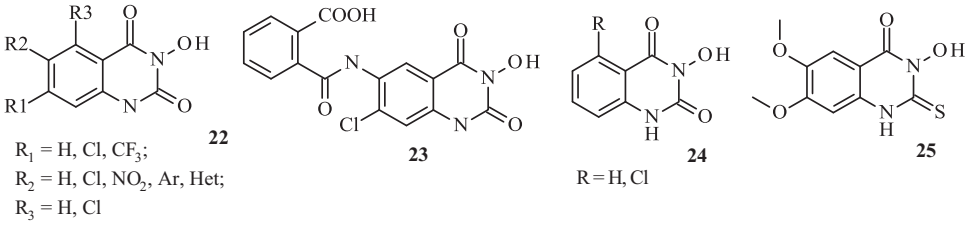


Fig. 9 Antineoplastic compounds based on cyclic hydroxamic acids included in the quinazoline cycle

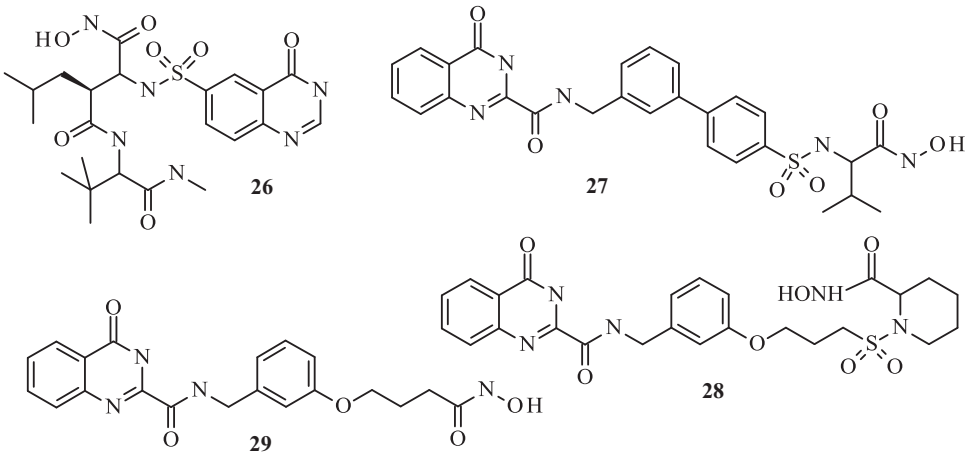


Fig. 10 Selective matrix metalloprotease inhibitors (MMPs)

compared with SAHA, even at a fourfold reduced dose. In addition, it had excellent oral bioavailability in rats (47%).

Based on compound 30, a further 58 more compounds were synthesized (Chen et al. 2018). Among which, compound 31 not only performed as the most potent inhibitor of HDAC1 and HDAC6 (HDAC1, $IC_{50} = 31.10$ nM; HDAC6, $IC_{50} = 16.15$ nM) double-acting with more than tenfold selectivity for other histone deacetylases (HDACs) but also showed activity against tubulin acetylation and histone H3 acetylation induction. It is important to note that compound 31 had strong antiproliferative activity against various in vitro tumor cell lines with IC_{50} values of <40 nM, particularly for hematological tumor cells (U266 and RPMI8226, $IC_{50} < 1$ nM), which was superior to compound 30 and SAHA. In addition, compound 31 showed significant inhibition of tumor growth in the MCF-7/ADR resistant xenograft model without any apparent changes in body weight or behavior.

Zhang et al. (2017) studied a series of hydroxamic acid-based HDACi with 4-aminoquinazolinyl fragments was studied. Most compounds showed stronger HDAC inhibition activity than SAHA. Some compounds selectively inhibited HDAC1,2 when compared with HDAC8, and exhibited strong activity on several cell lines while not having significant toxicity to primary human cells. The most promising agent was compound 32 ($R = 6$-Cl, $n = 6$) (Fig. 11) which had acceptable pharmacokinetic characteristics and showed significant antitumor activity in the study on the A549 xenograft model at well-tolerated doses.

Hieu et al. (2018a) studied hydroxamic acids analogous to compound 32 and new N-hydroxybenzamides, including a 4-aminoquinazolyl fragment (compound 33), were designed and synthesized. Biological evaluation showed that these hydroxamic acids and N-hydroxybenzamides are highly cytotoxic to three human cancer cell lines (SW620, colon cancer; PC-3, prostate cancer; NCI-H23, lung cancer). Regarding cytotoxicity, some compounds showed 5 to 10 times higher efficacy than SAHA. The compounds are also generally comparable with SAHA in HDAC inhibition with IC_{50} values in the submicromolar range.

The aforementioned authors (Hieu et al. 2018b) also synthesized several series of new N-hydroxybenzamides (compound 34) and N-hydroxypropenamides (compound 35) containing quinazolin-4 (3H)-one. Several compounds showed a fourfold higher cytotoxic activity than SAHA with respect to three human cancer cell lines (SW620, PC-3, and NCI-H23) and inhibited HDAC with IC_{50} values in the submicromolar range. It has been found that N-hydroxypropenamides (compound 36) are most effective both in terms of HDAC inhibition and cytotoxicity.

As HDAC6 inhibitors, a series of new quinazolin-4-one derivatives containing a conjugated hydroxamic acid fragment was studied (Yu et al. 2013). Most of these derivatives showed selective inhibition of HDAC6 with nanomolar IC_{50} values, caused neurite growth accompanied by the expression of growth-associated protein 43, and enhanced the synaptic activity of PC12 and SH-SY5Y neuronal cells without causing toxic or mitogenic effects. The most

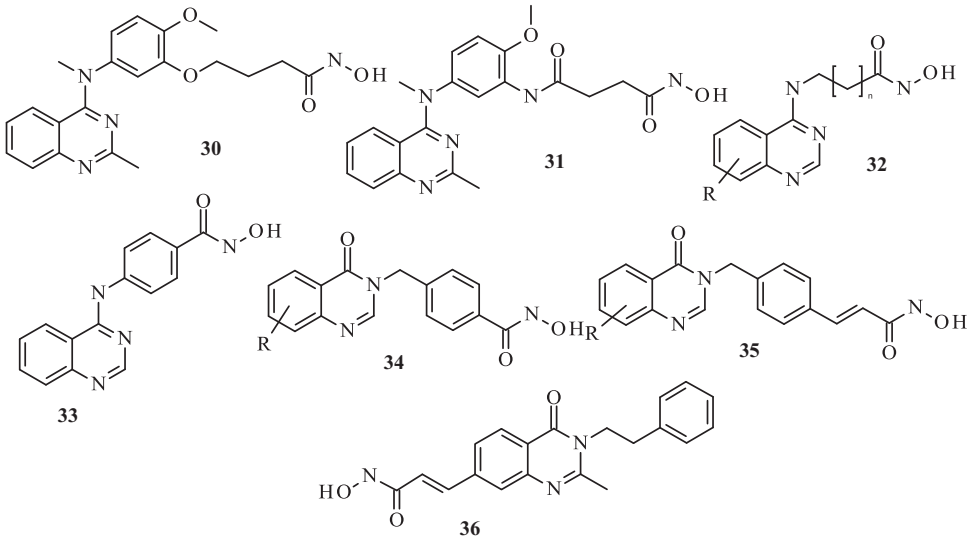


Fig. 11 Examples of HDAC inhibitors with a quinazoline cycle as the surface recognition domain of the enzyme site ("cap")

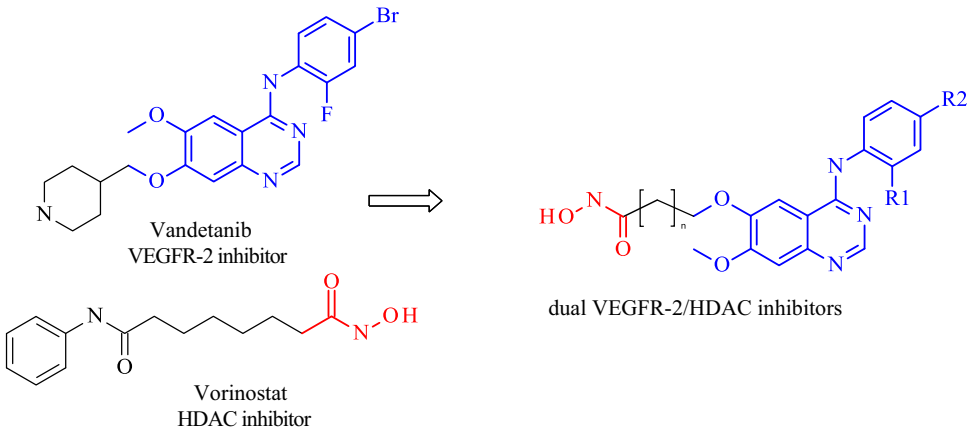


Fig. 12 Example strategy for creating multipurpose inhibitors using the binary VEGFR-2/HDAC inhibitor as an example (compound 38)

promising drug candidate, compound 36, selectively inhibits HDAC6 with an IC_{50} of 29 nM, increases α-tubulin acetylation, and reduces the aggregation of zinc-bound β-amyloid in vitro. In addition, this compound significantly improved performance in training mice with β-amyloid-induced hippocampal lesions. Compound 36 may be a good leader in the development of selective HDAC6 inhibitors for the treatment of Alzheimer's disease.

Multipurpose inhibitors

The discovery of the synergistic effect of the studied pharmacophores on cancer cells made it possible to apply a new method for constructing antitumor drugs (Fig. 12) where their action is based on the simultaneous inhibition of several targets involved in the protection and survival of tumor cells. Hybrid compounds directed at more than one target have proved to be more effective and powerful antitumor agents.

Dual inhibitors

Compound 37 and its analogs are patented as dual VEGFR-2/HDAC inhibitors (Fig. 13). However, the biological evaluation discussed in the patent only concerns HDAC inhibition; the question of the inhibition of VEGFR-2 by these compounds remains open (Qian et al. 2009). Later, studies were conducted on several similar hybrid molecules acting on HDAC and other targets. For example, compounds 38 (Fig. 13), including N-phenyl-4-aminoquinazoline and hydroxamic acid in the structure, were synthesized and studied as double VEGFR-2/HDAC inhibitors. The most active compound from this series inhibited HDAC with $IC_{50} = 2.2$ nM and VEGFR-2 with $IC_{50} = 74$ nM. Moreover, it significantly inhibited the enzymatic activity on lung cancer cells MCF-7 with $IC_{50} = 0.85$ μM (Peng et al. 2015; Peng et al. 2016), which is an example that perfectly illustrates the effectiveness of this strategy.

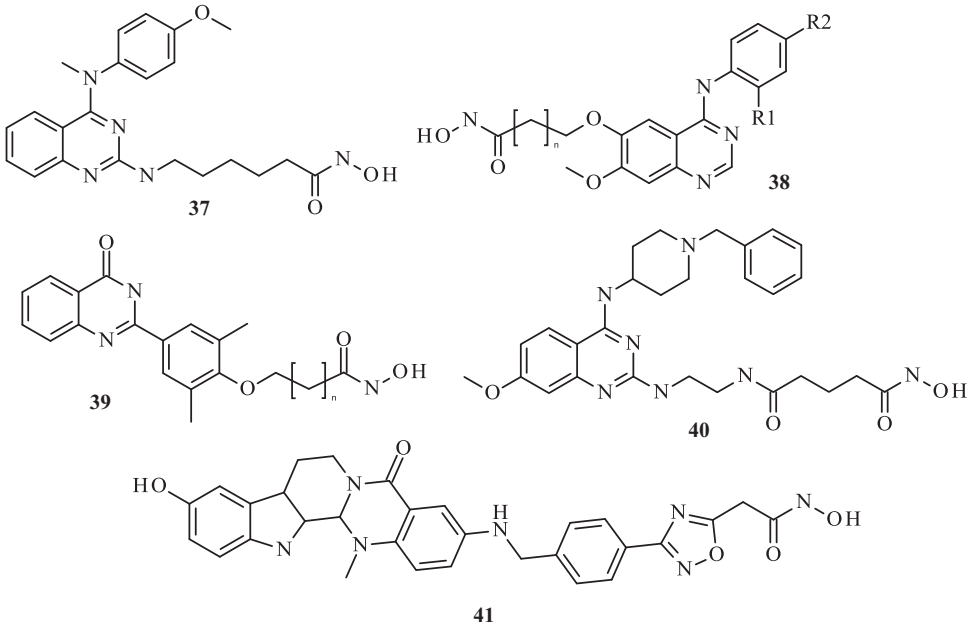


Fig. 13 Examples of double inhibitors with a quinazoline cycle in the molecule

Inhibitors of bromodomain and extra-terminal domain (BET) proteins and HDAC are known to kill cancer cells in murine lymphoma synergistically. The study (Shao et al. 2017) combined the fragments responsible for the inhibitory activity of BET and HDAC into one molecule using the structural design method using known inhibitors. Most synthesized compounds 39 (Fig. 13) showed inhibitory activity against bromdomains (BRD) BRD4 and histone deacetylase HDAC1.

Protein-lysine methyltransferase G9a (PKMT G9a) and HDACs are therapeutic targets for cancer therapy targeting identical substrates (H3K9 and p53 lysine 373). In search of a lead molecule with inhibition of both HDAC and G9a, the quinazoline core of G9a inhibitors was chosen as the main framework. As a result of the synthesis of more than 20 compounds and further investigation of the activity of in vitro, compound 40 was found (Fig. 13) which demonstrated significant inhibition of both G9a and HDAC in the low micromolar range in experiments on cells (Zang et al. 2017).

A series of novel hybrids based on the 3-amino-10-hydroxyl-evodiamine scaffold and SAHA were identified as triple inhibitors of topoisomerase I/II/ HDAC (He et al. 2015). In particular, compound 41 showed excellent antiproliferative activity against MDA-MB breast carcinoma cells ($IC_{50} = 2.3\ \mu M$), HCT116 colon carcinoma cells ($IC_{50} = 0.41\ \mu M$) and HLF liver cancer cells ($IC_{50} = 1.3\ \mu M$), provided good inhibitory activity against HDAC1 ($IC_{50} = 24\ nM$), HDAC6 ($IC_{50} = 13\ nM$) and HDAC8 ($IC_{50} = 2.5\ nM$), and topoisomerase I/II, comparable with standard inhibitors (Camptothecin and Etoposide). This proof-of-concept study also validated the effectiveness of discovering triple topoisomerase I/II and HDAC inhibitors as novel antitumor agents.

EGFR/HER2/HDAC inhibitors

The discovered synergistic effect of inhibition of epidermal growth factor receptor proteins (EGFR), human epidermal growth factor receptors 2 (HER2) and HDAC allowed us to apply a new drug development method (Fig. 14). Based on the Lapatinib EGFR/HER2 inhibitor (Lapatinib), chimeric HDAC inhibitors were obtained (compound 42). In biological trials, these analogs demonstrate selective and significant inhibition of EGFR/HER2, as well as the enzymatic activity of HDAC. In cell tests, using the Cal27 head and neck cell line as an example, a dose-dependent inhibition of EGFR phosphorylation and the induction of histone acetylation are observed (Mahboobi et al. 2010). In continuation of this work, a series of 43 hybrids based on Erlotinib (Erlotinib), inhibiting HDAC, EGFR, and HER2 kinases, was synthesized (Beckers et al. 2012).

Using a similar strategy for combining receptor tyrosine kinase inhibitors and Belinostat HDAC inhibitor, several dual-targeted inhibitors were constructed (Zhang et al. 2013). Among which, compound 44 showed anti-HDAC activity comparable with SAHA, however, the inhibitory effect against EGFR and HER2 was low.

By combining the pharmacophores of the EGFR/HER2 inhibitor Sapitinib (AZD-8931) and Vorinostat into a single compound, a new series of multipurpose inhibitors EGFR, HER2, and HDAC was synthesized (Ding et al. 2017). The compounds contain 4-anilinoquinazolines with C-6 triazole-linked long alkyl chains of hydroxamic acid. Compound

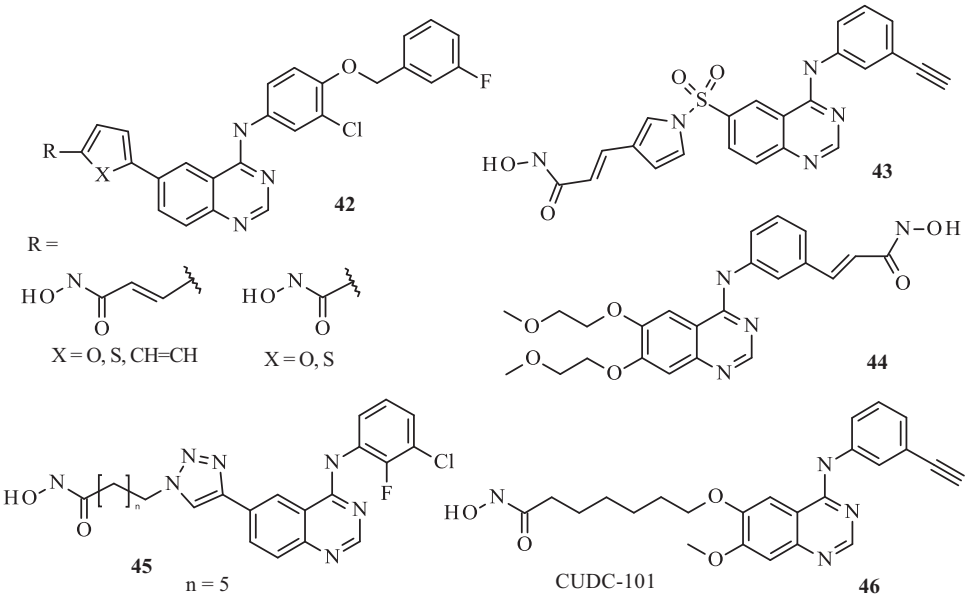


Fig. 14 EGFR/HER2/HDAC Inhibitors

45 showed the highest inhibitory activity against EGFR, HDAC1, and HDAC6 with IC_{50} values of 0.12, 0.72, and 3.2 nM, respectively. In addition, this compound significantly inhibited the proliferation of five human cancer cell lines: A549, BT-474, HER2-A431, SK-BR-3, and NCI-H1975(IC_{50} between 0.49 and 8.76 μM). Further studies showed that compound 45 regulated the phosphorylation of EGFR and HER2 and the hyperacetylation of histone H3 at the cellular level and caused apoptosis in BT-474 cells.

The most successful multipurpose antitumor drug was compound CUDC-101 (compound 46), created as an EGFR/HER2/HDAC inhibitor (Wang et al. 2013) (Fig. 14). In in vitro experiments, CUDC-101 effectively inhibits the activity of EGFR and HER2 kinase and HDAC enzymes with IC_{50} values of 2.4, 15.7, and 4.4 nM, respectively. This is ten times more effective than both HDAC inhibitor Vorinostat and EGFR inhibitor Erlotinib, and displays comparable activity against HER2 to Lapatinib, an inhibitor of HER2. In addition, when treating cancer cells, CUDC-101 increases the acetylation of p53 and α-tubulin; non-histone HDAC substrates. The results indicate that CUDC-101 effectively inhibits all three targets in cancer cells. CUDC-101 exhibits broad antiproliferative activity in many types of human cancer cells, including cancer of the lungs, pancreas, liver, colon, breast, prostate, and head and neck. Phase I clinical trials showed that the drug is well tolerated by patients and exhibits antitumor activity (Shimizu et al. 2014). However, phase II clinical trials were not conducted.

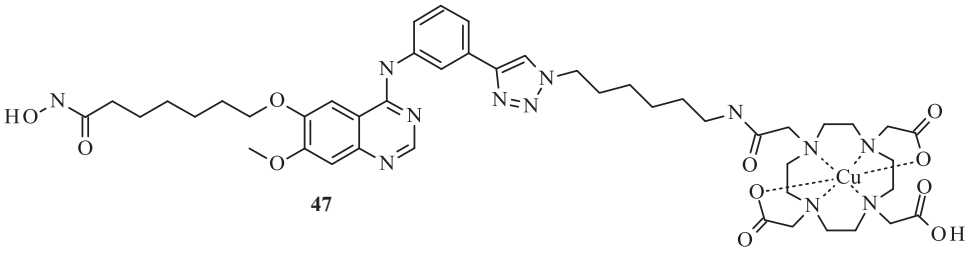
Inhibition of CUDC-10 was found for both the full length androgen receptor (flAR) and the androgen receptor of variant 7 (AR-V7), upon which prostate cancer resistant to complete sterilization depends (Sun et al. 2016). The effect of CUDC-101 on flAR and AR-V7 was shown to be duplicated only by other HDAC inhibitors or by killing HDAC isoforms HDAC5 and HDAC10. Thus, inhibition of HDAC signaling reduces the activity of flAR and AR-V7.

The design, synthesis, and biological evaluation of a ^{64}Cu-labeled agent (compound 47) for imaging HDAC in positron emission tomography, obtained by introducing a chelator by click reaction with CUDC-101 and then radiolabeled Cu-64 (Fig. 15) is reported (Meng et al. 2013).

The antitumor activity of CUDC-101 in combination with gemcitabine in pancreatic cancer has recently been investigated (Ji et al. 2018). In general, the combination of CUDC-101 and gemcitabine significantly increased antitumor activity when compared with gemcitabine alone, which provides the basis for studying the combination of gemcitabine and CUDC-101 as a potential therapeutic strategy for pancreatic cancer.

Potential therapeutic compounds

Among the drugs that have potential therapeutic activity and require further testing and implementation in medical practice, it should be noted that new classes of substances with the structure of 4-(*3H*)-quinazolinone and acylated hydroxamic acids (compound 48) (Bratu et al. 2014) and quinazoline-2,4(*1H*, *3H*)-dion derivatives (compounds 49 and 50) with a hydroxamate group are candidates for detecting antitumor activity (Fig. 16) (Zhou et al. 2013). Efficient and selective inhibitors of the enzyme Fe(II) peptide deformylase (PDF) *E. coli* (compound 51) were obtained by rational optimization of a weakly binding screening hit (hydrazide 5-chloro-2-oxo-1,4-dihydro-2H-quinazolin-3-yl) acetic acid (Apfel et al. 2001). However, it



47

Fig. 15 Agent for PET based on CUDC-101

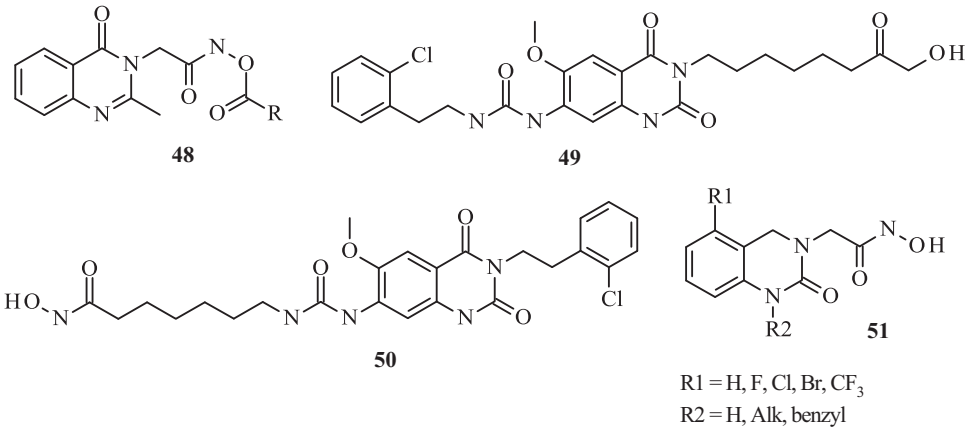


Fig. 16 Compounds with potential therapeutic activity

is noted that the synthesized compounds showed moderate antibacterial activity in vitro.

Conclusion

Quinazoline and hydroxamic acids create various classes of biologically active compounds with great therapeutic potential. The simplicity of their preparation, flexibility of structural modifications, and multifunctionality provide them with cause for widespread use; both for practical and research purposes. A number of currently available drugs are based on quinazoline/hydroxamic acid frameworks. Moreover, the combination of these two different pharmacophore groups in one molecule can lead to the creation of a drug that is more effective from the point of view of the combination of pharmaceutical properties and will allow the synthesis of a huge number of new compounds with promising properties.

It is interesting to note that among the latest available developments, many are dedicated to their promising antitumor activity. The strategy for creating multifunctional drugs is actively developing throughout the world and is promising in creating new-generation drugs, as evidenced by a number of studies presented in available literature. Among hybrid compounds of quinazoline and hydroxamic acid, selective inhibitors of MMPs and HDACs have been found.

The revealed synergistic effect of inhibiting EGFR, HER2, and HDAC has allowed a new method to develop multipurpose inhibitors of VEGFR-2/HDAC and EGFR/HER2/HDAC. One of the successful developments in this group of inhibitors, the CUDC-101 compound, has currently completed phase I clinical trials. The uniqueness of hybrid multifunctional compounds lies in the fact that they act on several targets responsible for the development of tumors. This reduces the resistance of the tumor to drugs and toxicity of drugs, and significantly increases the effectiveness of treatment.

However, the biological activity of the quinazoline/hydroxamic acid hybrid compounds is certainly not limited only to the antitumor effect. Interest in this group of compounds is constantly growing; a number of antibacterial and fungicidal preparations are currently under development. One of the latest favorable developments is the quinazoline–benzoate MTB-AHAS inhibitors, which are the basis for the development of potent anti-tuberculosis drugs. Also, within the last decade, active research is in progress to create a class of new antiviral drugs designed to treat influenza, hepatitis C, and other viral infections.

Thus, such compounds, due to the uniqueness of the set of properties of pharmacophore fragments, have high potential as the basis for the development of effective drugs.

Acknowledgements This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement No. 075-11-2018-172 dated 03.12.18). Unique project identifier RFMEFI62418X0051.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abzianidze VV, Prokofieva DS, Chisty LA, Bolshakova KP, Berestetskiy AO, Panikorovskii TL, Bogachenkov AS, Holder AA (2015) Synthesis of natural phaeosphaeride A derivatives and an in-vitro evaluation of their anti-cancer potential. Bioorg Med Chem Lett 25:5566–5569

Apfel C, Banner DW, Bur D, Dietz M, Hubschwerlen C, Locher H, Marlin F, Masciadri R, Pirson W, Stalder H (2001) 2-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)- and 2-(2,2-Dioxo-1,4-dihydro-2H-2λ6-benzo[1,2,6]thiadiazin-3-yl)-N-hydroxy-acetamides as potent and selective peptide deformylase inhibitors. J Med Chem 44:1847–1852

Arrighetti N, Corno C, Gatti L (2015) Drug combinations with HDAC inhibitors in antitumor therapy. Crit Rev Oncog 20:83–117

Asif M (2014) Chemical characteristics, synthetic methods, and biological potential of quinazoline and quinazolinone derivatives. Int J Med Chem 2014:1–27

Barlaam B, Bird TG, Lambert-van der Brempt C, Campbell D, Foster SJ, Maciewicz R (1999) New α-Substituted succinate-based hydroxamic acids as TNFα convertase inhibitors. J Med Chem 42:4890–4908

Beckers T, Mahboobi S, Sellmer A, Winkler M, Eichhorn E, Pongratz H, Maier T, Ciossek T, Baer T, Kelter G, Fiebig H, Schmidt M (2012) Chimerically designed HDAC- and tyrosine kinase inhibitors. A series of erlotinib hybrids as dual-selective inhibitors of EGFR, HER2 and histone deacetylases. MedChemComm 3:829

Bérubé G (2016) An overview of molecular hybrids in drug discovery. Expert Opin Drug Dis 11:281–305

Billamboz M, Suchaud V, Bailly F, Lion C, Andréola M-L, Christ F, Debyser Z, Cotelle P (2016) 2-hydroxyisoquinoline-1,3(*2H,4H*)-diones (HIDs) as human immunodeficiency virus type 1 integrase inhibitors: influence of the alkylcarboxamide substitution of position 4. Eur J Med Chem 117:256–268

Bolden JE, Peart MJ, Johnstone RW (2006) Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Disco 5:769–784

Bonola G, Sianesi E (1970) 2,3-Dihydro-4(*1H*)-quinazolinone derivatives. J Med Chem 13:329–332

Bratu M, Nuta DC, Caproiu MT, Missir AV, Limban C, Ileana C, Morusciag L (2014) New acylated derivatives of 2-methyl-4-oxo-quinazolin-3(*4H*)-yl-acetohydroxamic acid. Farmacia 62:664–673

Catarzi D, Lenzi O, Colotta V, Varano F, Poli D, Filacchioni G, Lingenhöhl K, Ofner S (2010) Pharmacological characterization of some selected 4,5-Dihydro-4-oxo-1,2,4-triazolo[1,5-a]quinoxaline-2-carboxylates and 3-Hydroxyquinazoline-2,4-diones as (S)-2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propionic Acid Receptor Antagonists. Chem Pharm Bull 58:908–911

Chen J, Sang Z, Jiang Y, Yang C, He L (2018) Design, synthesis, and biological evaluation of quinazoline derivatives as dual HDAC1 and HDAC6 inhibitors for the treatment of cancer. Chem Biol Drug Des 93:232–241

Chollet A-M, Le Diguarher T, Murray L, Bertrand M, Tucker GC, Sabatini M, Pierré A, Atassi G, Bonnet J, Casara P (2001) General synthesis of α-substituted 3-bisaryloxy propionic acid derivatives as specific mmp inhibitors. Bioorg Med Chem Lett 11:295–299

Cianci C, Chung TDY, Meanwell N, Putz H, Hagen M, Colonno RJ, Krystal M (1996) Identification of N-Hydroxamic acid and N-Hydroxyimide compounds that inhibit the influenza virus polymerase. Antivir Chem Chemother 7:353–360

Colotta V, Catarzi D, Varano F, Calabri FR, Filacchioni G, Costagli C, Galli A (2004) 3-Hydroxy-quinazoline-2,4-dione as a useful scaffold to obtain selective Gly/NMDA and AMPA receptor antagonists. Bioorg Med Chem Lett 14:2345–2349

Colotta V, Catarzi D, Varano F, Lenzi O, Filacchioni G, Costagli C, Galli A, Ghelardini C, Galeotti N, Gratteri P, Sgrignani J, Deflorian F, Moro S (2006) Structural investigation of the 7-chloro-3-hydroxy-1H-quinazoline-2,4-dione scaffold to obtain AMPA and kainate receptor selective antagonists. Synthesis, pharmacological, and molecular modeling studies. J Med Chem 49:6015–6026

Colotta V, Lenzi O, Catarzi D, Varano F, Squarcialupi L, Costagli C, Galli A, Ghelardini C, Pugliese AM, Maraula G, Coppi E, Pellegrini-Giampietro DE, Pedata F, Sabbadin D, Moro S (2012) 3-Hydroxy-1H-quinazoline-2,4-dione derivatives as new antagonists at ionotropic glutamate receptors: molecular modeling and pharmacological studies. Eur J Med Chem 54:470–482

Deore RR, Chen GS, Chang P-T, Chern T-R, Lai S-Y, Chuang M-H, Lin JH, Kung FL, Chen CS, Chiou CT, Chern J-W (2012) Discovery of N-Arylalkyl-3-hydroxy-4-oxo-3,4-dihydroquinazolin-2-carboxamide derivatives as HCV NS5B polymerase inhibitors. ChemMedChem 7:850–860

Dikii IL, Kris'kiv OS, Chernikh VP, Shemchuk LA, Dubinina NV (2006) Study of antimicrobial activity of quinazolin-4-ones and heterocyclic derivatives. Visn Farmatsii 2:64–67

Ding C, Chen S, Zhang C, Hu G, Zhang W, Li L, Chen YZ, Tan C, Jiang Y (2017) Synthesis and investigation of novel 6-(1,2,3-triazol-4-yl)-4-aminoquinazolin derivatives possessing hydroxamic acid moiety for cancer therapy. Bioorg Med Chem 25:27–37

Falsini M, Squarcialupi L, Catarzi D, Varano F, Betti M, Di Cesare Mannelli L, Tenci B, Ghelardini C, Tanc M, Angeli A, Supuran CT, Colotta V (2017) 3-Hydroxy-1H-quinazoline-2,4-dione as a new scaffold to develop potent and selective inhibitors of the tumor-associated carbonic anhydrases IX and XII. J Med Chem 60:6428–6439

Fetisov VI, Kotov AV, Gordeev PB, Bachurin SO, Petrova LN, Luk'janov OA, Martynov IV(1999) Sintez i izuchenie vlijanija prozvodnyh 3-gidroksi-1,2-digidrohinolin-4-onanaglutamat-inducirovannyj zahvat 45Ca2+ sinaptosomami mozga krys [The synthesis and the study of influence of derivatives of 3-hydroxy-1,2-dihydroquinoline-4-one on the glutamate-induced 45Ca2+-uptake by rat brain synaptosomes]. Dokl Akad Nauk Rep Acad Sci 367:776–779

Fortin S, Bérubé G (2013) Advances in the development of hybrid anticancer drugs. Expert Opin Drug Dis 8:1029–1047

Ganesan A (2016) Multitarget drugs: an epigenetic epiphany. ChemMedChem 11:1227–1241

Giannini G, Battistuzzi G, Vignola D (2015) Hydroxamic acid based histone deacetylase inhibitors with confirmed activity against the malaria parasite. Bioorg Med Chem Lett 25:459–461

Grady RW, Bienen EJ, Clarkson AB (1986) P-alkyloxybenzhydroxamic acids, effective inhibitors of the trypanosome glycerol-3-phosphate oxidase. Mol Biochem Parasit 19:231–240

Gupta SP, Sharma A (2013) Hydroxamic acids. A unique family of chemicals with multiple biological activities. Gupta SP (ed.), Springer-Verlag, Berlin

He S, Dong G, Wang Z, Chen W, Huang Y, Li Z, Jiang Y, Liu N, Yao J, Miao Z, Zhang W, Sheng C (2015) Discovery of novel multiacting topoisomerase I/II and histone deacetylase inhibitors. ACS Med Chem Lett 6:239–243

Hemalatha K, Madhumitha G (2016) Synthetic strategy with representation on mechanistic pathway for the therapeutic applications of dihydroquinazolinones. Eur J Med Chem 123:596–630

Hesham HM, Lasheen DS, Abouzid KAM (2018) Chimeric HDAC inhibitors: comprehensive review on the HDAC-based strategies developed to combat cancer. Med Res Rev 38:2058–2109

Hider RC, Kong X (2010) Chemistry and biology of siderophores. Nat Prod Rep 27:637

Hieu DT, Anh DT, Hai P-T, Huong L-T-T, Park EJ, Choi JE, Kang JS, Dung PTP, Han SB, Nam N-H (2018a) Quinazoline-based hydroxamic acids: design, synthesis, and evaluation of histone deacetylase inhibitory effects and cytotoxicity. Chem Biodivers 15:e1800027

Hieu DT, Anh DT, Tuan NM, Hai P-T, Huong L-T-T, Kim J, Kang JS, Vu TK, Dung PTP, Han SB, Nam NH, Hoa N-D (2018b) Design, synthesis and evaluation of novel N -hydroxybenzamides/ N -hydroxypropenamides incorporating quinazolin-4(*3H*)-ones as histone deacetylase inhibitors and antitumor agents. Bioorg Chem 76:258–267

Ji M, Li Z, Lin Z, Chen L (2018) Antitumor activity of the novel HDAC inhibitor CUDC-101 combined with gemcitabine in pancreatic cancer. Am J Cancer Res 8:2402–2418

Jung R, Le JY, Wengenmayer F, Wolf E, Kramer M (1985) Mutagenicity studies of a carcinogenic nitrofuran and some analogs. Biochimica Acta 44:485–492

Kerru N, Singh P, Koorbanally N, Raj R, Kumar V (2017) Recent advances (2015-2016) in anticancer hybrids. Eur J Med Chem 142:179–212

Khan I, Zaib S, Batool S, Abbas N, Ashraf Z, Iqbal J, Saeed A (2016) Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: an update on the development of synthetic methods and pharmacological diversification. Bioorg Med Chem 24:2361–2381

Khohlov PS, Osipov VN, Krivenko VI, Zubairov MM, Roshhin AV, Batuev EA (2011) 2-(2,5-Dimethyl)pyrazolyl-3-hydroxy-4(3H)-quinazolinone possessing antiviral, antibacterial and fungicidal activity and its production method. RU Patent RU2451683, 10 Mar 2011

Khohlov PS, Pavlova VV, Shumova TB, Poljanskaja SM (2005) 3-Hydroxy-2-thioxo-4(3h)-quinazolinone possessing fungicide and growth-regulating property and method for it preparing. RU Patent RU2275362, 27 Oct 2005

Khokhlov PS, Osipov VN, Roshchin AV (2011) 3-Hydroxy- and 3-alkoxy-2-sulfanylquinazolin-4(3H)-ones: synthesis and reactions with alkylating and acylating agents. Russ Chem Bull 60:153–156

Kobayashi K, Kobayashi Y, Nakamura M, Tamura O, Kogen H (2015) Establishment of relative and absolute configurations of Phaeosphaeride A: total synthesis of ent-Phaeosphaeride A. J Org Chem 80:1243–1248

Kotov AV, Zakharychev VV, Smirnov AG, Fetisov VI, Gordeev PB, Luk'yanov OA, Chimishkyan AL, Martynov IV (2001) The fungicidal activity of the 3-hydroxy-1,2,3,4-tetrahydroquinazoline-4-one derivatives and simulation of the structure-activity dependence. Dokl Biochem Biophysics 381:412–414

Lavi O (2015) Redundancy: a critical obstacle to improving cancer therapy. Cancer Res 75:808–812

Li Y, Ganesh T, Diebold BA, Zhu Y, McCoy JW, Smith SME, Sun A, Lambeth JD (2015) Thioxo-dihydroquinazolin-one compounds as novel inhibitors of myeloperoxidase. ACS Med Chem Lett 6:1047–1052

Lou B, Yang K (2003) Molecular diversity of hydroxamic acids. Part II: potential therapeutic applications. Mini-Rev Med Chem 3:609–620

Lu W, Baig IA, Sun H-J, Cui C-J, Guo R, Jung I-P, Wang J-G (2015) Synthesis, crystal structure and biological evaluation of substituted quinazolinone benzoates as novel antituberculosis agents targeting acetohydroxyacid synthase. Eur J Med Chem 94:298–305

Mahboobi S, Sellmer A, Winkler M, Eichhorn E, Pongratz H, Ciossek T, Baer T, Maier T, Beckers T (2010) Novel chimeric histone deacetylase inhibitors: a series of lapatinib hybrides as potent inhibitors of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and histone deacetylase activity. J Med Chem 53:8546–8555

Maloney KN, Hao W, Xu J, Gibbons J, Hucul J, Roll D, Brady SF, Schroeder FC, Clardy J (2006) Phaeosphaeride A, an inhibitor of STAT3-dependent signaling isolated from an Endophytic fungus. Org Lett 8:4067–4070

Manal M, Chandrasekar MJN, Gomathi Priya J, Nanjan MJ (2016) Inhibitors of histone deacetylase as antitumor agents: a critical review. Bioorg Chem 67:18–42

Meng Q, Li F, Jiang S, Li Z (2013) Novel 64Cu-labeled CUDC-101 for in vivo pet imaging of histone deacetylases. ACS Med Chem Lett 4:858–862

Mottamal M, Zheng S, Huang T, Wang G (2015) Histone deacetylase inhibitors in clinical studies as templates for new anticancer agents. Molecules 20:3898–3941

Muri E, Nieto M, Sindelar R, Williamson J (2002) Hydroxamic acids as pharmacological agents. Curr Med Chem 9:1631–1653

Musso L, Dallavalle S, Zunino F (2015) Perspectives in the development of hybrid bifunctional antitumour agents. Biochem Pharm 96:297–305

Mutule I, Borovika D, Rozenberga E, Romanchikova N, Zalubovskis R, Shestakova I, Trapencieris P (2014) 5-Membered cyclic hydroxamic acids as HDAC inhibitors. J Enzym Inhib Med Chem 30:216–223

Nara H, Kaieda A, Sato K, Naito T, Mototani H, Oki H, Yamamoto Yl, Kuno H, Santou T, Kanzaki N, Terauchi J, Uchikawa O, Kori M (2017) Discovery of novel, highly potent, and selective matrix metalloproteinase (MMP)-13 inhibitors with a 1,2,4-triazol-3-yl Moiety as a zinc binding group using a structure-based design approach. J Med Chem 60:608–626

Nara H, Sato K, Kaieda A, Oki H, Kuno H, Santou T, Kanzaki N, Terauchi J, Uchikawa O, Kori M (2016) Design, synthesis, and biological activity of novel, potent, and highly selective fused pyrimidine-2-carboxamide-4-one-based matrix metalloproteinase (MMP)-13 zinc-binding inhibitors. Bioorg Med Chem 24:6149–6165

Nepali K, Sharma S, Sharma M, Bedi PMS, Dhar KL (2014) Rational approaches, design strategies, structure activity relationship and mechanistic insights for anticancer hybrids. Eur J Med Chem 77:422–487

Niemeyer HM (1988) Hydroxamic acids (4-hydroxy-1,4-benzoxazin-3-ones), defence chemicals in the gramineae. Phytochemistry 27:3349–3358

Niemeyer HM (2009) Hydroxamic acids derived from 2-hydroxy-2H-1,4-benzoxazin-3(4H)-one: key defense chemicals of cereals. J Agric Food Chem 57:1677–1696

Papavassiliou KA, Papavassiliou AG (2013) Histone deacetylases inhibitors: conjugation to other anti-tumour pharmacophores provides novel tools for cancer treatment. Expert Opin Inv Drug 23:291–294

Peng F-W, Wu T-T, Ren Z-W, Xue J-Y, Shi L (2015) Hybrids from 4-anilinoquinazoline and hydroxamic acid as dual inhibitors of vascular endothelial growth factor receptor-2 and histone deacetylase. Bioorg Med Chem Lett 25:5137–5141

Peng F-W, Xuan J, Wu T-T, Xue J-Y, Ren Z-W, Liu D-K, Wang XQ, Chen XH, Zhang JW, Xu YG, Shi L (2016) Design, synthesis and biological evaluation of N-phenylquinazolin-4-amine hybrids as dual inhibitors of VEGFR-2 and HDAC. Eur J Med Chem 109:1–12

Pryde DC, Webster R, Butler SL, Murray EJ, Whitby K, Pickford C, Westby M, Palmer MJ, Bull DJ, Vuong H, Blakemore DC, Stead D, Ashcroft C, Gardner I, Bru C, Cheung W-Y, Roberts IO, Mortone J, Bissell RA (2013) Discovery of an HIV integrase inhibitor with an excellent resistance profile. MedChemComm 4:709

Qian Ch, Cai X, Zhai H (2009) Antiproliferative agents containing a zinc binding moiety. PCT International Application No. WO 2009036057 A1

Qiu X, Xiao X, Li N, Li Y (2017) Histone deacetylases inhibitors (HDACis) as novel therapeutic application in various clinical diseases. Prog Neuro-Psychoph 72:60–72

Rani R, Granchi C (2015) Bioactive heterocycles containing endocyclic N-hydroxy groups. Eur J Med Chem 97:505–524

Rao M, Valentini D, Zumla A, Maeurer M (2018) Evaluation of the efficacy of valproic acid and suberoylanilide hydroxamic acid (vorinostat) in enhancing the effects of first-line tuberculosis drugs against intracellular Mycobacterium tuberculosis. Int J Infect Dis 69:78–84

Rao MJ (1992) Antifungal potential of binary and mixed-ligand complexes of N,2′-diphenyl acetohydroxamic acid. J Inorg Biochem 46:207–214

Schobert R, Biersack B (2017) Multimodal HDAC inhibitors with improved anticancer activity Curr Cancer Drug Tar 18:39–56

Seo S-Y (2012) Multi-targeted hybrids based on HDAC inhibitors for anti-cancer drug discovery. Arch Pharm Res 35:197–200

Shagufta S, Ahmad I (2017) An insight into the therapeutic potential of quinazoline derivatives as anticancer agents. MedChemComm 8:871–885

Shao M, He L, Zheng L, Huang L, Zhou Y, Wang T, Chen Y, Shen M, Wang F, Yang Z, Chen L (2017) Structure-based design, synthesis and in vitro antiproliferative effects studies of novel dual BRD4/HDAC inhibitors. Bioorg Med Chem Lett 27:4051–4055

Shimizu T, LoRusso PM, Papadopoulos KP, Patnaik A, Beeram M, Smith LS, Rasco DW, Mays TA, Chambers G, Ma A, Wang J, Laliberte R, Voi M, Tolcher AW (2014) Phase I first-in-human study of CUDC-101, a multi-targeted inhibitor of HDACs, EGFR and HER2 in patients with advanced solid tumors. Clin Cancer Res 20:5032–5040

Sun H, Mediwala SN, Szafran AT, Mancini MA, Marcelli M (2016) CUDC-101, a novel inhibitor of full-length androgen receptor (flAR) and androgen receptor variant 7 (AR-V7) activity: mechanism of action and in vivo efficacy. Hormones Cancer 7:196–210

Suraweera A, O'Byrne KJ, Richard DJ (2018) Combination therapy with histone deacetylase inhibitors (HDACi) for the treatment of cancer: achieving the full therapeutic potential of HDACi Front Oncol 8:1–15

Tang J, Vernekar SKV, Chen Y-L, Miller L, Huber AD, Myshakina N, Wang Z (2017) Synthesis, biological evaluation and molecular modeling of 2-Hydroxyisoquinoline-1,3-dione analogues as inhibitors of HIV reverse transcriptase associated ribonuclease H and polymerase. Eur J Med Chem 133:85–96

Tran TP, Ellsworth EL, Stier MA, Domagala JM, Hollis Showalter HD, Gracheck SJ, Singh R (2004) Synthesis and structural-activity relationships of 3-hydroxyquinazoline-2,4-dione antibacterial agents. Bioorg Med Chem Lett 14:4405–4409

Tumey LN, Bom D, Huck B, Gleason E, Wang J, Silver D, Bennani YL (2005) The identification and optimization of a N-hydroxy urea series of flap endonuclease 1 inhibitors. Bioorg Med Chem Lett 15:277–281

Wang D, Zhu X, Cui C, Dong M, Jiang H, Li Z, Wang J-G (2013) Discovery of novel acetohydroxyacid synthase inhibitors as active agents against Mycobacterium tuberculosis by virtual screening and bioassay. J Chem Inf Model 53:343–353

Wang J, Pursell NW, Samson MES, Atoyan R, Ma AW, Selmi A, Xu W, Cai X, Voi M, Savagner P, Lai C-J (2013) Potential advantages of CUDC-101, a Multitargeted HDAC, EGFR, and HER2 inhibitor, in treating drug resistance and preventing cancer cell migration and invasion. Mol Cancer Ther 12:925–936

Xu K, Dai X-L, Huang H-C, Jiang Z-F (2011) Targeting HDACs: a promising therapy for Alzheimer's disease. Oxid Med Cell Longev 2011:1–5

Yang Z, Wang T, Wang F, Niu T, Liu Z, Chen X, Chen L (2015) Discovery of selective histone deacetylase 6 inhibitors using the quinazoline as the cap for the treatment of cancer. J Med Chem 59:1455–1470

Yoon S, Eom GH (2016) HDAC and HDAC inhibitor: from cancer to cardiovascular diseases. Chonnam Med J 52:1

Yu C-W, Chang P-T, Hsin L-W, Chern J-W (2013) Quinazolin-4-one derivatives as selective histone deacetylase-6 inhibitors for the treatment of Alzheimer's disease. J Med Chem 56:6775–6791

Zamora R, Grzesiok A, Weber H, Feelisch M (1995) Oxidative release of nitric oxide accounts for guanylyl cyclase stimulating, vasodilator and anti-platelet activity of Piloty's acid: a comparison with Angeli's salt. Biochemical J 312:333–339

Zang L, Kondengaden SM, Zhang Q, Li X, Sigalapalli DK, Kondengadan SM, Wang PG (2017) Structure based design, synthesis and activity studies of small hybrid molecules as HDAC and G9a dual inhibitors. Oncotarget 8:63187–63207

Zhang L, Han Y, Jiang Q, Wang C, Chen X, Li X, Xu W (2014) Trend of histone deacetylase inhibitors in cancer therapy: isoform selectivity or multitargeted strategy. Med Res Rev 35:63–84

Zhang Q, Li Y, Zhang B, Lu B, Li J (2017) Design, synthesis and biological evaluation of novel histone deacetylase inhibitors incorporating 4-aminoquinazolinyl systems as capping groups. Bioorg Med Chem Lett 27:4885–4888

Zhang X, Su M, Chen Y, Li J, Lu W (2013) The design and synthesis of a new class of RTK/HDAC dual-targeted inhibitors. Molecules 18:6491–6503

Zhang Y-M, Fan X, Yang S-M, Scannevin RH, Burke SL, Rhodes KJ, Jackson PF (2008a) Syntheses and in vitro evaluation of arylsulfone-based MMP inhibitors with heterocycle-derived zinc-binding groups (ZBGs). Bioorg Med Chem Lett 18:405–408

Zhang Y-M, Xiang B, Yang Sh-M, Rhodes K, Scannevin R, Jackson P, Chakravarty D, Karnachi P (2008b) Heterocyclic derived metalloprotease inhibitors. PCT International Application No. WO2008045668, 63187–63207

Zhao XZ, Smith SJ, Métifiot M, Johnson BC, Marchand C, Pommier Y, Hughes SH, Burke TR (2014) Bicyclic 1-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxamide-containing HIV-1 integrase inhibitors having high antiviral potency against cells harboring raltegravir-resistant integrase mutants. J Med Chem 57:1573–1582

Zhou X, Xie X, Liu G (2013) Quinazoline-2,4(1*H*,3*H*)-diones inhibit the growth of multiple human tumor cell lines. Mol Diversity 17:197–219