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8-Hydroxyquinoline: A Privileged Structure with Broad-ranging Pharmacological Potentials

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Abstract: Privileged structures could bind to diverse targets with high affinity, thus benefiting the discovery of novel bioactive agents. 8-Hydroxyquinoline derivatives represented an important type of "privileged structure" possessing a rich diversity of biological properties. Numerous encouraging investigations demonstrated that this privileged structure should be further exploited for the therapeutic applications in the future. In view of its predominance, and on the basis of our research interest involved in this scaffold, an updated and detailed account of the pharmacological properties of 8-hydroxyquinoline derivatives, as well as recent insights from structural biology were described. Finally, some outlooks on current issues and future directions in this field of research were also provided.

Keywords: Privileged structure; 8-Hydroxyquinoline; Pharmacological activities; Heterocycle; Drug design.

1. Introduction

Privileged structures, as defined in the literature, are chemical scaffolds with

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versatile binding properties, which could afford potent and specific ligands for diverse biotargets *via* proper structural modifications of functional groups.[1,2] Furthermore, privileged structures typically displayed favorable drug-like properties, which in turn provided more high-quality leads and compound libraries. No doubt, the identification of novel drug-like lead compounds is the solid base for research efforts aimed at discovery of a new drug. Over the past two decades, the application of privileged structure concept has emerged as a fertile strategy of overcoming shortcomings and improving the reliability of the bioactive compounds in drug discovery.[1,2]

Figure 1. Overview of broad-ranging pharmacological applications of 8-HQ derivatives.

In the field of drug discovery and development, there is now a wealth of published papers on the identification of biologically important heterocyclic "privileged structures" as promising drugs or candidates.[3-8] Quinoline has attracted considerable attention as an important heterocyclic pharmacophore, which is amply explored for broad-ranging biological effects. Among quinoline core compounds, the most frequently encountered in medicinal chemistry is the 8-hydroxyquinoline (8-HQ), which is one of the most important groups as strong metal ion chelators and represents an excellent scaffold with a wide spectrum of pharmacological applications such as iron-chelators for neuroprotection, anti-cancer agents, inhibitors of

2OG-dependent enzymes, chelators of metalloproteins, anti-HIV agents, antifungal agents, antileishmanial agents, anti-schistosomal agents, mycobacterium tuberculosis inhibitors, botulinum neurotoxin inhibitors and many others (**Figure 1**).

Hitherto, no comprehensive survey has been published to outline the wide spectrum of pharmaceutical activities of 8-HQ as a privileged heterocycle unit. Given this, fascinated by multifarious bioactivities of this heterocycle, we would like to comprehensively outline its pharmacological importance, which will provide insights for the further development of novel 8-HQ-based agents.

2. Broad-ranging pharmacological applications of 8-HQ derivatives

In this section, a broad range of pharmacological applications of 8-HQ derivatives were presented. It is hoped that the content and organization of this section will prove useful to the medicinal chemists embarking on the exploitation of 8-hydroxyquinolines in academia and industry.

2.1 Neuroprotection agents (As iron-chelators)

Neurodegenerative disorder diseases, such as Alzheimer's and Parkinson's diseases (AD and PD), represent one of the principal unmet medical needs, being the third highest cause of death just behind cancer and heart disease.[9] It was reported that metal-ion dysregulation and oxidative stress were involved in the progressive neurological decline (neurodegeneration) associated with neurodegenerative disorder.

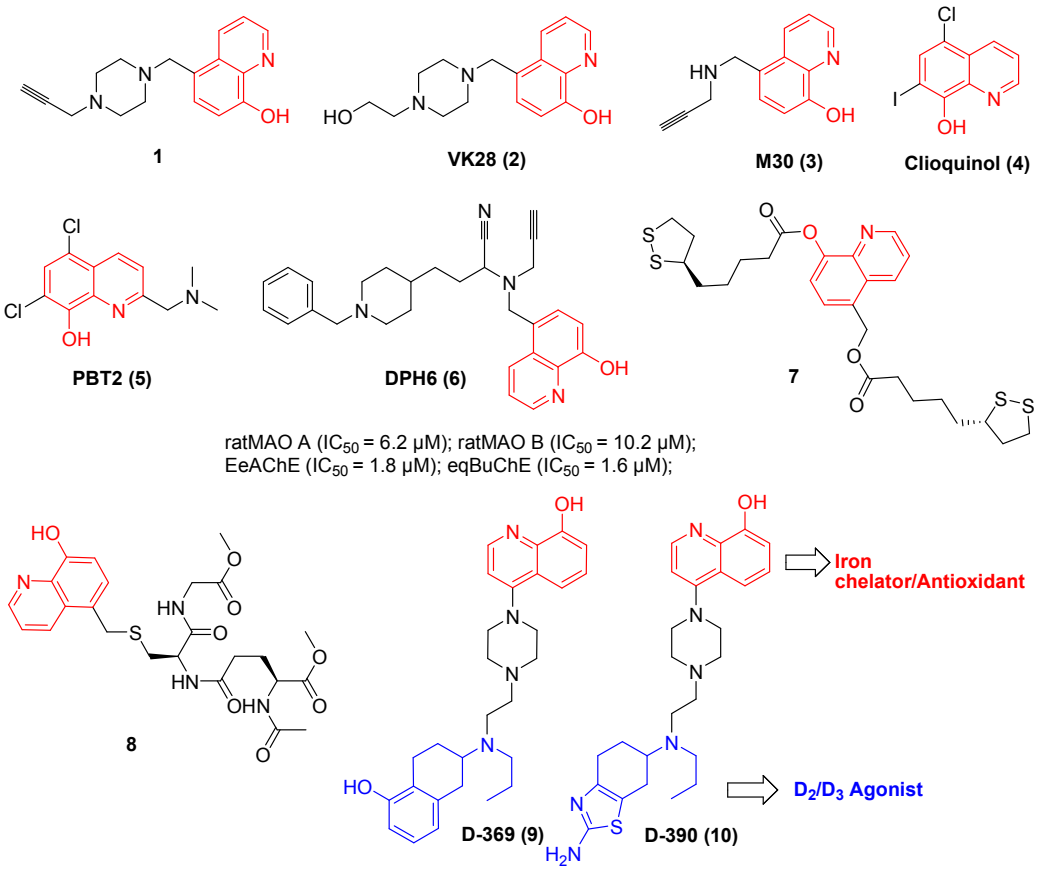


Figure 2. Structures of metal chelators with potentials for the treatment of neurodegenerative diseases.

Several 8-HQ derivatives were reported as multifunctional metal-chelators (metal-protein attenuating compound, MPAC), acetylcholinesterase (AChE) and monoamine oxidase (MAO) inhibitors for the potential treatment of neurodegenerative disorders (**Figure 2**). For instance, compound HLA20 (**1**), displayed strong iron(III) chelating, high antioxidant properties, favorable permeability into K562 cells and good selective MAO-B inhibition (IC_{50} = 110 μM), exhibited the hightest protective activities against differentiated P19 cell death induced by 6-hydroxydopamine. It was suggested that compound **1** also functions as radical scavenger to scavenge hydroxyl radical ($OH^{\bullet}$) directly.[10]

VK28 (**2**) was a brain permeable iron chelator with neuroprotection against 6-hydroxydopamine lession in rats.[11,12] From prototype VK-28 (**2**), M30 (**3**) was identified as a novel multifunctional neuroprotective agent with strong iron chelating

and brain selective MAO inhibitory effects for PD.[13-15]

Clioquinol (**4**) could cross the blood-brain barrier and sequester metal ions zinc and copper from amyloid β (Aβ) and redistribute them into the cell. A pilot phase II clinical trial with AD patients has finished through chelation therapy, in which patients dispalyed lower plasma levels of Aβ42 and improved cognition. PBT2 (**5**) is a new generation of 8-HQ-drived MPAC with improved cognition (metal-peptide attenuating properties) and oral activity. It is in a phase II clinical trial for the treatment of AD, and further clinical testing is currently underway.[16]

Recently, based on the 'multitarget-directed ligands' (MTDLs) strategy,[17a,b] a set of new multifunctional compounds against neurodegenerative diseases by combing 8-HQ and the pharmacophore elements of other bioactive fragments were designed and synthesised. For instance, DPH6 (**6**) was reported as an irreversible inhibitor of MAO A and B, a mixed-type AChE inhibitor, with metal-chelating effects.[18]

The bis-lipoyl derivative (LA-HQ-LA, **7**) and glutathione derivative (GS(HQ)H, **8**), endowed with an 8-HQ group exhibited pronounced chelant, antioxidant, and neuroprotective effects.[19,20] They could protect SHSY-5Y human neuroblastoma cells against H_2O_2- and 6-OHDA-induced damage.[19,20]

In particular, GS(HQ)H (**8**) showed high stability and could smoothly across the blood-brain barrier as assessed by in vitro assay. It is likely that this compound could selectively remove Zn(II) and Cu(II) from the Aβ peptide without leading to the depletion of copper or zinc in vivo.[20]

D-369 (**9**) and D-390 (**10**) were reported as highly active iron chelators, dopamine D2/D3 agonists and antioxidant agents. In vivo activity of a mouse neuroprotection model indicated potential usage in symptomatic and neuroprotective treatment of PD.[21,22]

In addition, the natural product resveratrol (**11**) displayed the Aβ anti-aggregative and cytoprotective activities in human neuroblastoma cell lines. However, the unfavorable bioavailability of resveratrol (dietary supplements) greatly limits its applications. The hybrid (*E*)-5-(4-hydroxystyryl)quinoline-8-ol (**12**) through combination of resveratrol (**11**) and Clioquinol (**4**) exhibited excellent potency to inhibit self-induced (IC_{50} =

8.50 μM) and Cu(II)-induced Aβ aggregation and to destroy the well-structured Aβ fibrils formed by self- and Cu(II)-induced Aβ aggregation (**Figure 3**). Importantly, the metal complexation of **12** could also halt copper redox cycling, then control Cu(I/II)-triggered hydroxyl radical production, as observed in a Cu-ascorbate redox system assay. Notably, **12** demonstrated extremely low acute toxicity (LD_{50} > 2000 mg/kg) and could cross the blood-brain barrier.[23]

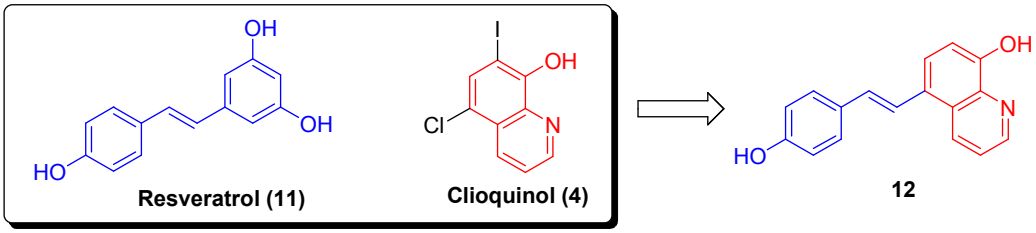


Figure 3. Design of the hybrid (*E*)-5-(4-hydroxystyryl)quinoline-8-ol (**12**) *via* the combination of resveratrol (**11**) and Clioquinol (**4**).

Collectively, these findings suggested that these 8-HQs could be potential neuroprotective agents for the treatment of neurodegenerative diseases, and 8-HQ will continue to offer a hugely explorable platform in the discovery of new chemical entities with neuroprotective properties for future perspective.

2.2 Anti-cancer agents

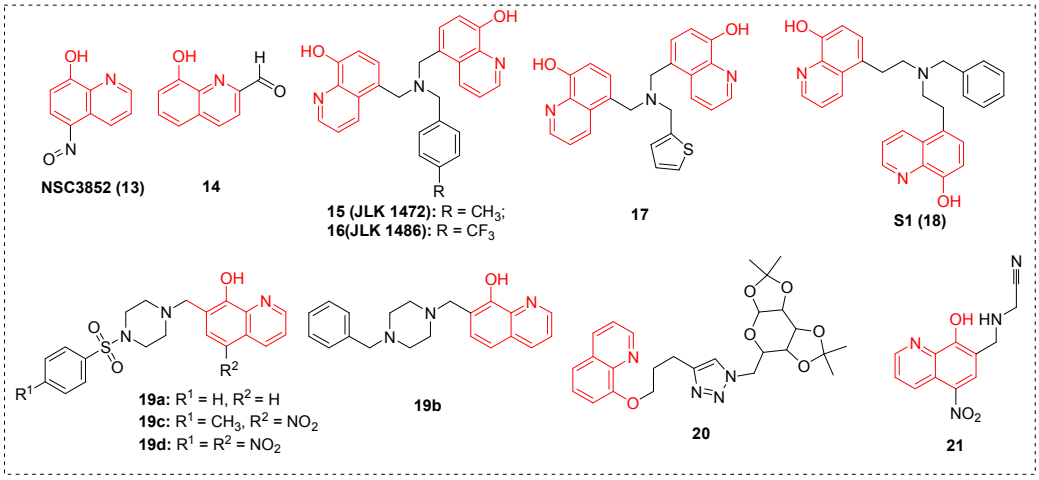


Figure 4. Structures of 8-HQ-based anti-cancer agents (part I).

In 2006, NSC3852 (**13**) was identified as a histone deacetylase (HDAC) inhibitor with cell differentiation and antiproliferative potency against human breast cancer cell lines

and antitumor property in mice model containing P388 and L1210 leukemic cells.[24] It was found that reactive oxygen species (ROS) formation was associated with the apoptotic and cell differentiation responses to NSC3852 in MCF-7 cells.[24]

8-Hydroxy-2-quinolinecarbaldehyde (**14**) displayed strong *in vitro* cytotoxicity against multiple cancer cells, including T-47D, Hs578t, SaoS2, K562, MDA231, SKHep1 (MTS_{50}: 12.5-25 μg/mL) and Hep3B (MTS_{50}: 6.25±0.034 μg/mL) [25]. The results demonstrated that the dosage of 10 mg/kg/day of **14** with intraperitoneal injection for 9 days completely suppressed the growth of the Hep3B xenograft tumor, and when compared with the control, no histological damage on vital organs was observed.[25]

Compounds JLK 1472 (**15**) and JLK 1486 (**16**) demonstrated high potency on KB3 cell line with EC_{50} values of 2.6 nM, 1.3 nM, respectively. But they were proven inactive on some cell lines including SF268 and PC3 while highly effective on other cell lines. It has tentatively been identified that their biotarget was probably located upstream from caspase 3/7. Furthermore, their cytotoxic effect was potentiated by the pro-apoptotic effects of TRAIL.[26a] Then, in 2011, it was reported that, JLK 1486 (**16**), displayed cytostatic (not cytotoxic) effects in experimental gliomas *via* MyT1 and STAT1 activation and, to a lesser extent, PPARγ activation.[26b]

It was showed in micro-array analysis that the best performing inhibitor **17** in 8-HQ substituted amines series could give covalent protein thiol adducts and induce the expression of various stress related genes involved in the cytotoxic and cytostatic activities in glioblastoma and carcinoma cells, which represent a novel promising anti-cancer candidate with unique mechanisms of action, targeting accessible thiols from specific proteins and inducing efficient anti-cancer activities.[26c,d]

As underlined in **Figure 5**, the mechanism of action of compound JLK1486 (**16**) was proposed and verified primarily, which requires two steps, a protonation process followed by a nucleophilic attack resulting in the formation of the quinone methide intermediate (**16b**).[26c]

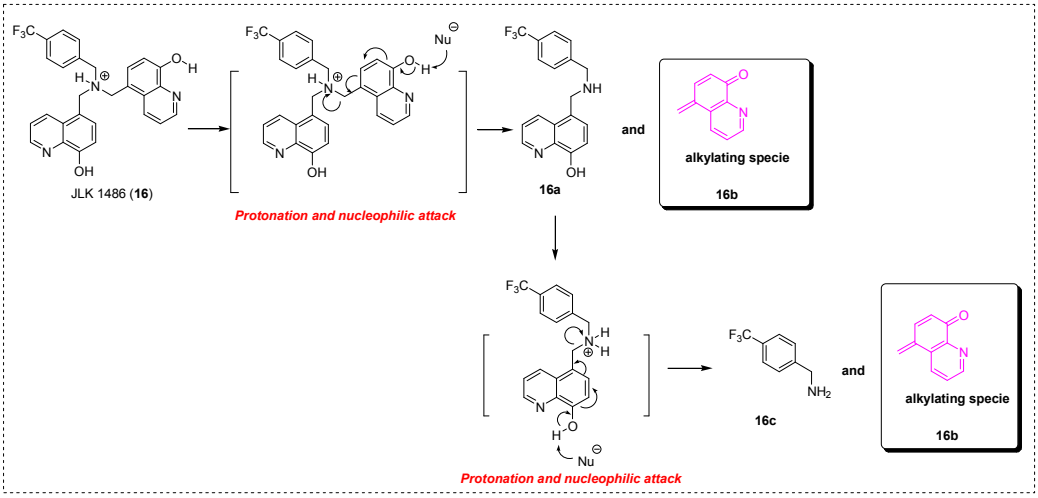


Figure 5. The proposed mechanism of action of compound JLK1486 (**16**).[26c]

In 2012, compound S1 (**18**) was reported as identified as a chelating agent binding ferric iron with a very high affinity (pFe^{3+}=29.5). It also exerted a marked cytostatic effect on hepatoma cells at concentrations as low as 0.1 μM.[27]

Taken Mannich base **19a** as a lead compound, in 2010, a series of 8-HQ-derived Mannich bases were prepared and assayed for their growth inhibition with intriguing structure-activity relationships (SARs) results in the lab of Shaw AY. All Mannich bases demonstrated moderate to low micromolar potency against four carcinoma cell lines. SARs results displayed that upon replacement of either sulfonyl moiety with methylene or piperazine ring with ethylenediamine group led to an appreciable increase in activity. Besides, as 8-hydroxyquinoline was replaced with 3-hydroxypyridine, phenol and 1-naphthol, a dramatic decrease in potency was observed. The structural modifications revealed that 8-hydroxyquinol skeleton appeared to be a crucial pharmacophore for inhibition

Among all the Mannich bases, **19b** exhibited the highest potencies against both SKHep and CE81T cells with GI_{50} values of 2.6 and 2.8 μM, respectively, while **19c** (GI_{50}, 0.7 and 1.9 μM against HeLa and BT483 cells, respectively) and **19d** showed the most high growth-inhibitory activity on CE81T and SKHep cells (GI_{50}, 2.8 μM against CE81T cells). These results demonstrated the sensibility of individual cell lines was closely related the structures of these derivatives.[28]

In 2014, 8-hydroxyquinoline derivative **20** containing a sugar and a 1,2,3-triazole

moiety was reported to show pomising antiproliferative potency and high selectivity toward ovarian cancer cells (OVCAR-03, GI_{50} < 0.25 μg/mL); this compound was more potent than the control drug doxorubicin (OVCAR-03, GI_{50} = 0.43 μg/mL).[29] Human cathepsin B, an enzyme belonging to the peptidase (or protease) families, is regarded as a promising therapeutic target for cancers. By combining structure-based design and focused library screening, the nitroxoline derivative **21** was identified as a new cathepsin B inhibitor, which was active in cell-based *in vitro* tumor invasion models, where it dramatically abolished invasion of MCF-10A neoT cells.[30] This research will afford valuable insights for further discovery of new anticancer agents with improved potency.

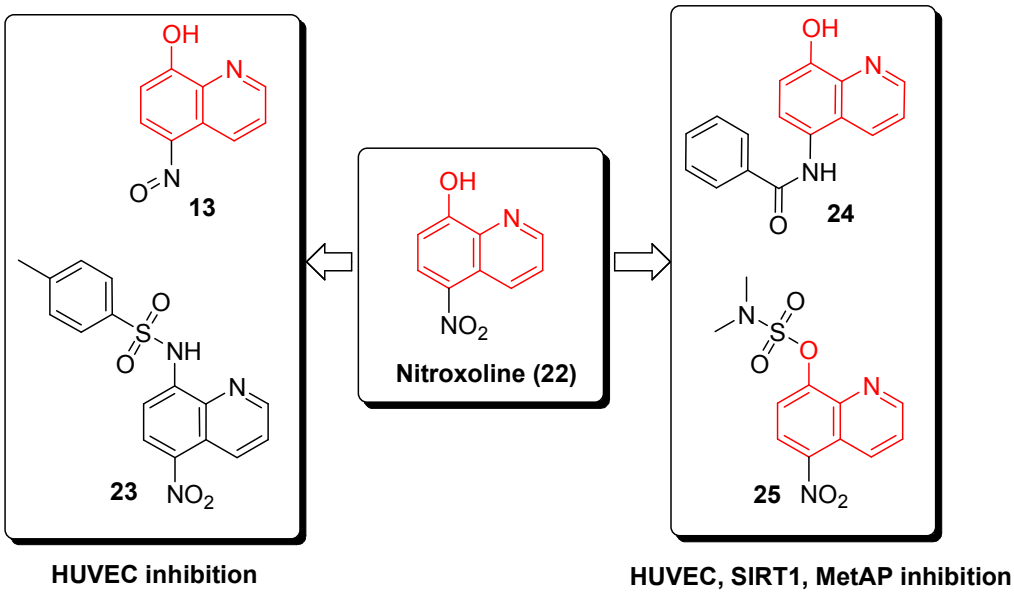


Figure 6. The structures of oxine derivatives with entirely different mechanism of action.

The nitroxoline (**22**) demonstrated antiproliferative activity in endothelial cells, it's action mechanisms included a dual inhibition of sirtuin 1 (SIRT1) and type 2 human methionine aminopeptidase (MetAP2). SARs investigation of nitroxoline derivatives afforded several substituted oxines (**13**, **23-25**, **Figure 6**) with potency against endothelial cell proliferation and angiogenesis. Minor modifications on 8-HQ core resulted in oxine derivatives with entirely different mechanisms of action.[31]

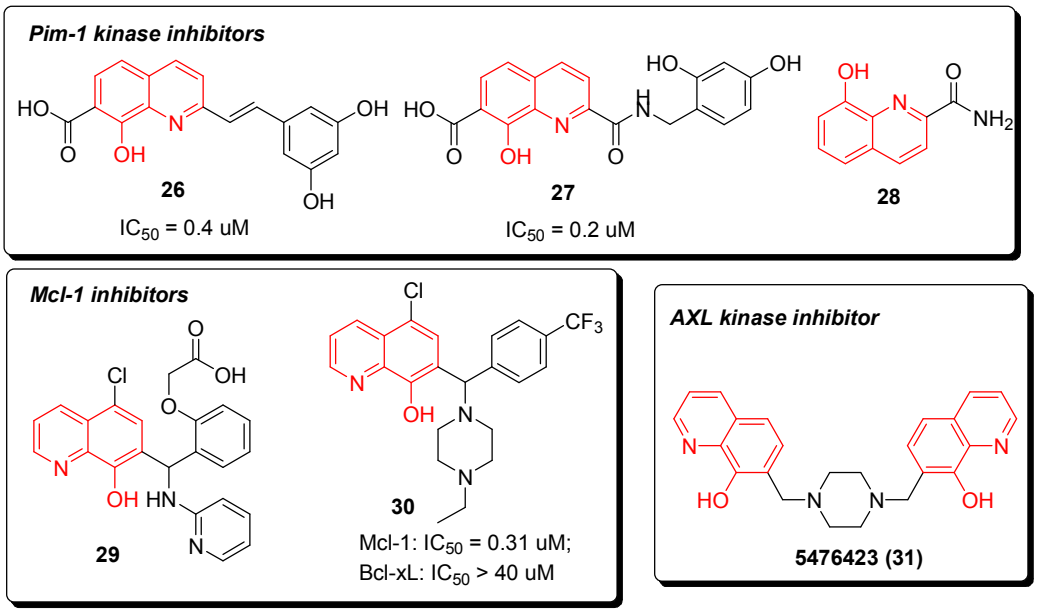


Figure 7. Structures of 8-HQ-based anti-cancer agents (part II).

The Pim-1 kinase was considered to be an important new target for anti-cancer drug discovery for its oncogenic potential. Compounds 2-styrylquinoline **26** and quinoline-2-carboxamide **27** were recently reported as novel and potent inhibitors of the Pim-1 kinase. The 8-hydroxy-quinoline 7-carboxylic acid skeleton was probably required for activity, which was preliminarily confirmed by molecular modeling.[32]

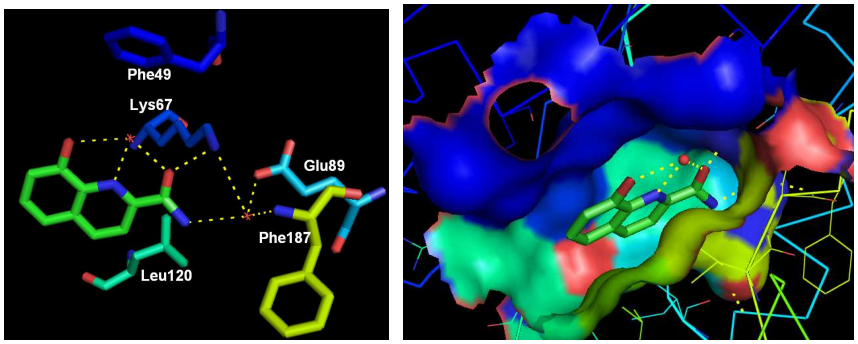


Figure 8. The crystal structure of a fragment **28** (IC_{50} = 10000 nM) bound to Pim-1 kinase (PDB code: 3VBV, resolution: 2.08 Å). Key H-bond interactions are shown as yellow dashed lines.

In addition, 8-hydroxyquinoline-2-carboxamide (**28**) was discoveryed as a fragment (IC_{50} = 10000 nM) bound to Pim-1 kinase *via* hydrogen bonding and hydrophobic interactions. The present co-crystal structure investigation demonstrated the rationale of further designing potent and selective Pim-1 kinase inhibitors based on this fragment and available structural information (**Figure 8**).[33]

The piperazine-substituted hydroxyquinoline **30**, which drived from a high-throughput screening (HTS) hit **29**, demonstrated selective inhibition of Mcl-1 (a target central to intrinsic apoptosis that has been implicated in a cancer) relative to the related Bcl-2 family protein Bcl-xL in the fluorescence polarization assay.

This compound also displayed efficacy in promoting death in a set of cell lines derived from diverse malignancies.[34]

In 2014, compound 5476423 (**31**) was identified as a lead with potential anti-proliferative effects on gallium-resistant lung cancer through an AXL kinase pathway through virtual screening of AXL kinase homology model. When compared with gallium acetylacetonate (GaAcAc), the IC_{50} values from treating gallium-resistant cells exhibited that compound **31** had 80 fold increased activity. The efficacy of GaAcAc against gallium-resistant cells was increased 2 fold combined to compound **31**.[35]

Obviously, these studies established proof-of-concept that 8-HQ could be employed as a favorable heterocyclic scaffold for development of omnifarious anticancer agents.

2.3 Inhibitors of 2-oxoglutarate (2OG) and iron dependent enzymes

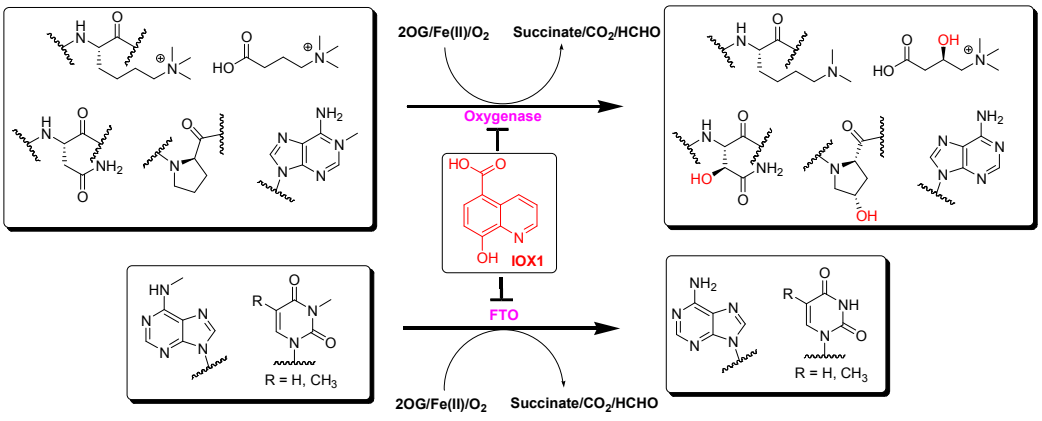
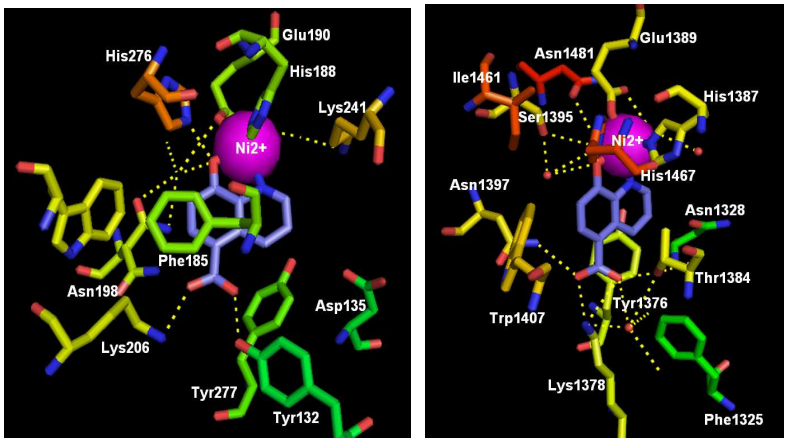


Figure 9. Reactions catalyzed by oxygenases and FTO.

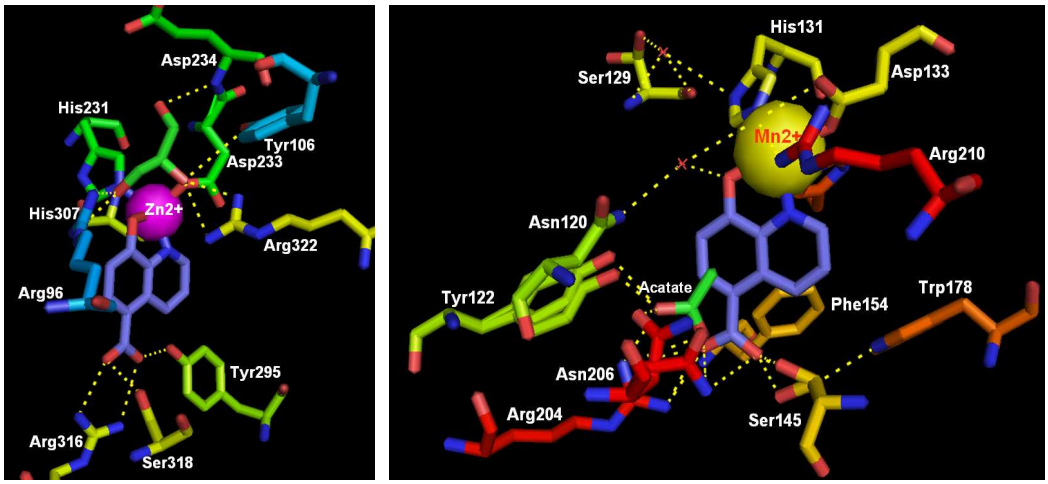
2-Oxoglutarate (2OG) and iron dependent oxygenases were considered to be promising therapeutic biotargets for omnifarious human diseases (**Figure 9**).[36] 5-Carboxy-8-hydroxyquinoline (IOX1, **32**) is the most effective broad-spectrum inhibitor of 2OG oxygenase subfamilies (including nucleic acid demethylases and γ-butyrobetaine hydroxylase), reported to date.[37] In 2010, IOX1 was validated as a

cell-active inhibitor of 2OG-dependent histone lysine demethylases (KDM) (namely, the Jumonji domain containing histone demethylases, JMJD) and inhibitor of fat mass and obesity associated protein (FTO, a 2OG-dependent *N*-methyl nucleic acid demethylase that acts on substrates including 3-methylthymidine, 3-methyluracil, and 6-methyladenine) *via* quantitative HTS of a collection of diverse compounds.[38a,b] Besides, it was also reported as a ligand of AlkB, which belongs to the Fe (II)/2OG-dependent dioxygenase superfamily and oxidatively demethylates the DNA substrate.[37] Though compound IOX1 suffers from low cell permeability, it has smaller and more compact chemical structure, and represents a lead compound for further modifications and a good tool compound for studies investigating the roles of 2OG-dependent enzymes in epigenetic processes. It was envisioned that by rationally changing substituents to maximize the key contacts between the ligand and the binding site, the potency and the selectivity profiles towards the desired target will be improved.

As shown in **Figure 10**, co-crystal structure analysis of oxygenases complexed with IOX1 displayed the binding modes and pivotal interactions involved in target recognition, which will aid the development of more potent and selective inhibitors .[38a,b]



(a) (b)



(c) (d)

Figure 10. Crystal structures of oxygenases in complex with the IOX1 (**32**). (a) JMJD2A complexed with IOX1 (blue); (PDB code: 3NJY, resolution: 2.60Å).[38a] (b) the human JMJD3 jumonji domain with IOX1; (PDB code: 2XXZ, resolution: 1.80Å). (c) the human FTO in complex with IOX1 (IC_{50} = 3.3 μM) (PDB code: 4IE4, resolution: 2.50 Å). (d) AlkB in complex with IOX1; (PDB code: 4JHT, resolution: 1.18 Å). Key H-bond interactions are shown as yellow dashed lines.

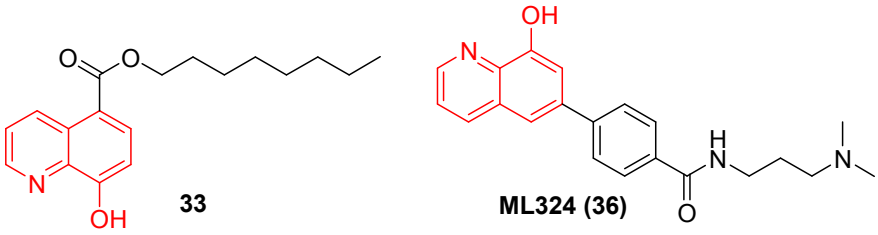


Figure 11. Structures of *n*-octyl ester (**33**) of IOX1 and ML324 (**36**).

As expected, the *n*-octyl ester (**33**) of IOX1 demonstrated improved cellular potency (30-fold) and enhanced selectivity over the parent IOX1.[39]

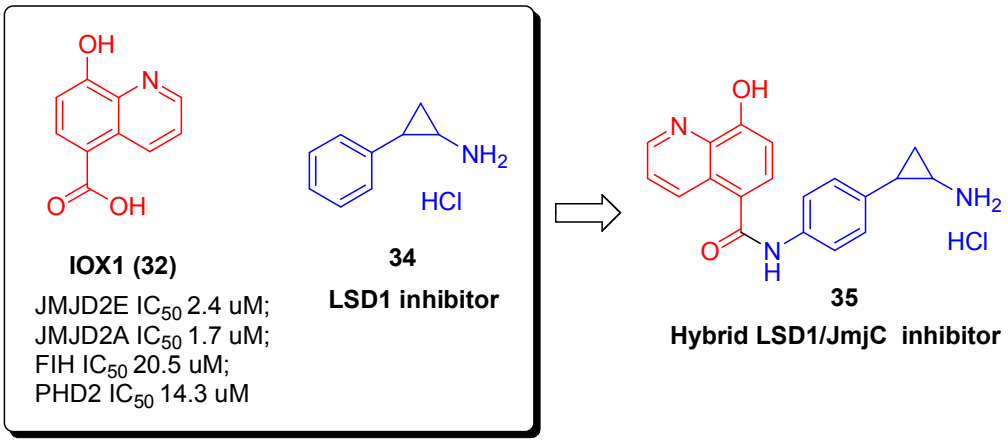


Figure 12. Design of dual inhibitor of JmiC and lysine-specific demethylases.

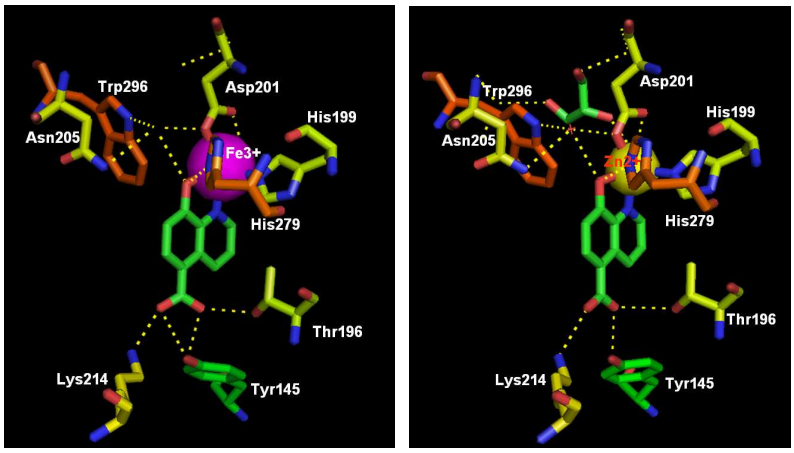
Currently, small molecule modulators of epigenetic regulation are employed as useful tools for probing biochemical mechanisms, and as lead compounds for discovery of anti-cancer therapeutic agents.[40] In prostate cancer, two different kinds of KDMs, KDM1 (lysine-specific demethylase 1, LSD1) and KDM4 (JMJD2), were coexpressed and colocalize with the androgen receptor. Inspired by this finding, recently, by coupling the skeleton of tranylcypromine **34**, a known LSD1 inhibitor, with IOX1 (**23**), a 2-OG competitive JmjC inhibitor, hybrid **35** was designed as a pan-histone demethylase inhibitor simultaneously targeting Jumonji C and lysine-specific demethylases, and displayed high anticancer activities in LNCaP prostate and HCT116 colon cancer cells (**Figure 12**).[41]

This needs to be stressed that inhibitors of the epigenetic-related targets are also showing great promise as antiviral agents. Through a quantitative HTS and subsequent structural optimization campaign, compound ML324 (**36**) was identified as a JMJD2E inhibitor (submicromolar inhibitory) with excellent cell permeability and *in vitro* absorption, distribution, metabolism and excretion (ADME) properties. In addition, ML324 showed potent antiviral effects against both human cytomegalovirus (HCMV) and herpes simplex virus (HSV) infection by inhibiting viral IE gene expression. In a mouse ganglia explant model of latently infected mice, ML324 can block the formation of HSV plaques and suppress HSV-1 reactivation.[42]

As a transcription factor under hypoxia, hypoxia-inducible factor-1 (HIF-1) was the master regulator of the cellular hypoxia response, which could activate a variety of

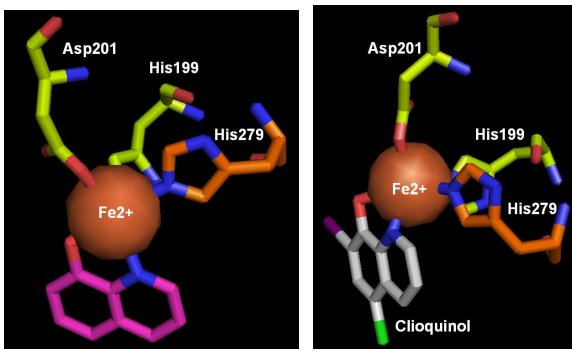
genes including those involved in glucose metabolisms, angiogenesis, cell proliferation and cell survival.[43] Among the isoforms, HIF-1α was a vital regulator of hypoxia responses in solid tumors, and its activity is indispensable for tumors to adapt to hypoxia conditions and recover from damages caused by hypoxic insult. The HIF-1α subunit was regulated by 2-OG- and Fe(II)-dependent hydroxylases, such as Factor Inhibiting HIF-1 (FIH-1). FIH-1 could hydroxylate Asn803 of HIF-1α and block its binding with co-activating factors. Quinol derivatives including IOX1 and Clioquinol, displayed inhibition against the hydroxylation effect of FIH-1.

The co-crystal structures of FIH-1 with IOX1, Clioquinol and 8-HQ (**37**) were determined respectively, giving an update on the molecular aspects at the basis of rational drug design. As shown in **Figures 13**,**14**, these three compounds bind to the active site of FIH-1 *via* chelating the Fe/Zn ion, then blocking the binding of a co-substrate, 2OG.[44] Contrary to the existing FIH-1 inhibitors with negative charges, these 8-HQ derivatives are neutral in charge and can afford a scaffold for further development as FIH-1 selective inhibitors.[44]



(a) (b)

Figure 13. Crystal structure of FIH-1α in complex with IOX1 (green) (a) PDB code: 4BIO, resolution: 2.45Å;[37] (b) PDB code: 3OD4, resolution: 2.20Å.



(a) (b)

Figure 14. FIH-1α in complex with (a) 8-HQ (pink) (PDB code: 3KCY, resolution: 2.59Å), (b) Clioquinol (white) (PDB code: 3KCX, resolution: 2.60Å).[44]

2.4 Chelators of metalloproteins (with miscellaneous therapeutic applications)

Metalloproteins afford an important class of biotargets currently receiving increased attention. The ability to bind with multiple metalloproteins is a main argument for using 8-HQ as a privileged structure in drug discovery. Recently, by screening of a metalloprotein-focused chelator fragment library, substituted 8-HQs at either the 5- or 7-positions were identified as active MMP-2 inhibitors (**38a-d**, **39a-d**), with low micromolar IC_{50} values (**Figure 15**).[45]

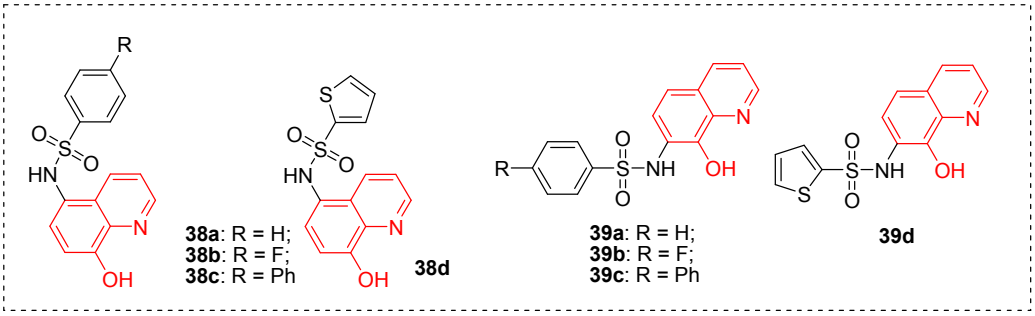


Figure 15. Structures of 8-HQ containing MMP-2 inhibitors.

In 2012, 8-HQ (**37**) and its 5-substituted derivatives were reported as competitive and selective inhibitors of an aminopeptidase from Aeromonas proteolytica (AAP, a dinuclear Zn^{2+} hydrolase) with K_i value of 0.16-29 μM at pH 8.0. The hydroxide at the 8-position and the nitrogen at the 1-position of 8-HQ were considered to be crucial for the inhibition of AAP. Co-crystal structure of AAP complexed with 8-HQ demonstrated that 8-HQ was able to interact with AAP in the metal-chelating mode, in which the nitrogen atom of 8-HQ coordinates to one Zn(II) ion and the hydroxide

anion bridges two Zn(II) ions in the active site of AAP (**Figure 16**).[46]

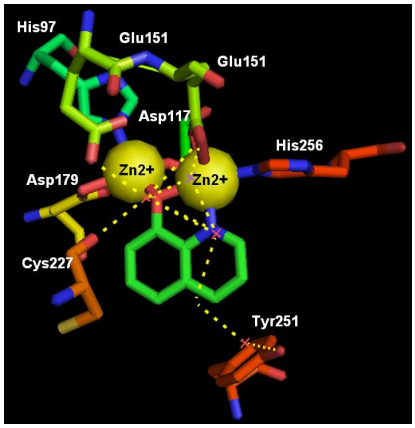


Figure 16. The X-ray co-crystal structure of AAP-8-HQ complex (PDB code: 3VH9, resolution: 1.29Å).

In sum, these two sections (**section 2.4** and **2.5**) introduced multiple cases of metal-chelating-related bioactivities of 8-HQs, suggesting that this heterocycle motif may be further exploited to seek novel therapeutic usages in the future. It should be pointed out that the propensity of 8-HQs to bind with multiple metalloproteins can underline their high promiscuity, which will result in unfavorable off-targets interactions. Therefore, considerable attention in the future should be focused on the optimization of 8-HQs into highly specific agents with minimum unwanted off-target activities.

2.5 Anti-HIV agents

Improving treatments for HIV infections still remain a challenge, especially new chemical entities are greatly needed to overcome the emergence of drug resistant viral mutants and enrich the current paradigm. As shown in **Figure 17**, several groups have already reported on the identification of 8-HQ analogues as excellent antiviral agents for targeting HIV-1 integrase (IN) (compounds **40**,**41**)[47,48] and IN-LEDGF/p75 interaction (compounds **42**,**43**).[49] We envisioned that with its broad-spectrum potential and flexibility of functionalization, 8-HQ will still function as an important scaffold in the discovery of HIV inhibitors in the future.

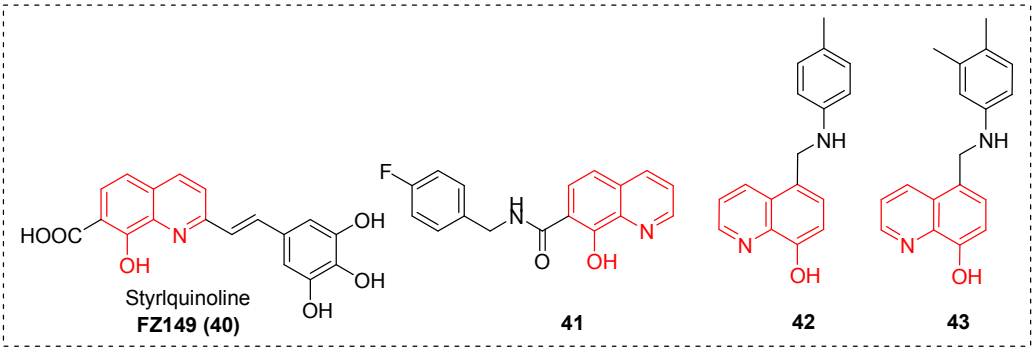


Figure 17. 8-HQs with anti-HIV activities.

2.6 Antifungal agents

8-HQ derivatives **44-46** exhibited antifungal potency *in vitro* comparable to or higher than that of the clinically used fluconazole (**Figure 18**).[50] These compounds are being carried forward as promising leads for the treatment of fungal infection.

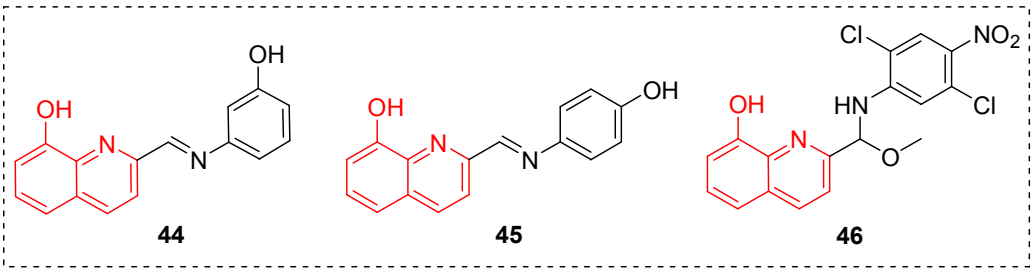


Figure 18. 8-HQs as antifungal agents.

2.7 Antileishmanial agents

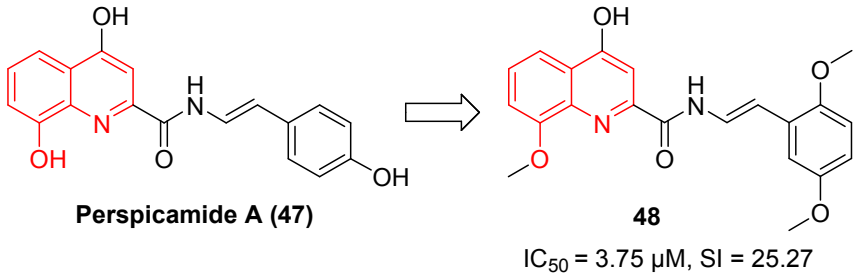


Figure 19. Discovery of 8-HQ derivative **48** as antileishmanial agent.

In 2005, the quinoline-2-carboxylic acid derivative perspicamide A (**47**) was originally isolated from the Australian ascidian *Botrylloides persipicuum*, which has received increased attention as quinoline-2-carboxylic acid is a common moiety in numerous drug-like molecules.[51] Recently, its analogue, **48** displayed potent inhibition

against *Leishmania donovani* with IC_{50} value of 3.75 μM and a selectivity index (SI) of 25.27, which was markedly increased compared to the approved drug Miltefosine (IC_{50} 12.4 μM; SI 4.1) (**Figure 19**).[52]

2.8 Anti-schistosomal agents

In 2013, the 8-hydroxyquinoline-5-sufonyl 1,4-diazepine **49** was identified as a potent anti-schistosomal agent (Figure **20**), which can significantly reduce oviposition of adult worms and totally diminish egg deposition *in vitro*. Molecular docking study displayed that this compound could exert its inhibitory property by binding with thioredoxin glutathione reductase (TGR), a vital protein for schistosome survival.[53]

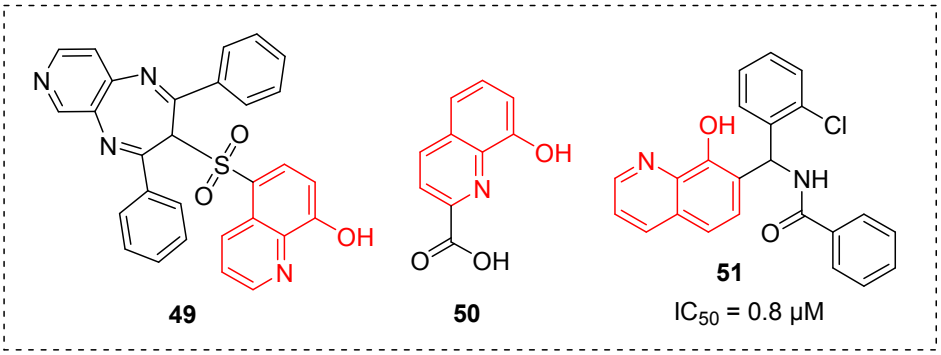


Figure 20. 8-HQ derivatives as anti-schistosomal agent, Mycobacterium tuberculosis inhibitor and Botulinum neurotoxin inhibitor, respectively.

2.7 Mycobacterium tuberculosis inhibitors

Class II fructose 1,6-bisphosphate aldolase (FBA) was regarded as a well-validated biotarget for the design of novel antibiotics against pathogenic bacteria including Mycobacterium tuberculosis, which is the causative agent for tuberculosis (TB). Very recently, *via* the enzymatic and structure-guided screening, 8-HQ carboxylic acid (**50**) was identified as a potent inhibitor of the class II FBA present in M. tuberculosis (MtFBA), with an IC_{50} of 10 μM, and possessed anti-TB properties (Figure **20**).

Compound **50** also showed inhibitory properties for other class II FBAs, including methicillin-resistant Staphylococcus aureus. As opposed to the existing inhibitors, Compound **50** functioned in a noncompetitive manner, exhibited no inhibitory effects toward class I FBAs in human and rabbit. Moreover, the complex crystal structure of **50** with MtFBA was determined (**Figure 21**), which would afford

more sophisticated, evidenced-based development of MtFBA inhibitors with improved target specificity.[54]

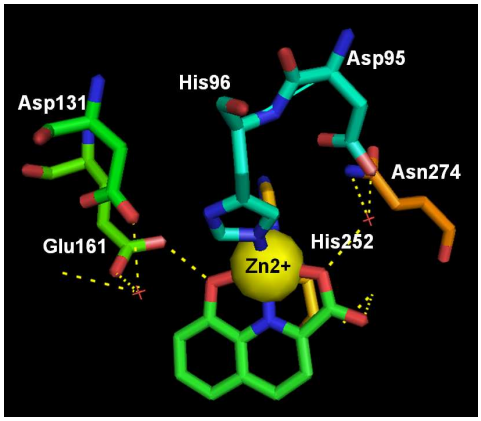


Figure 21. The crystal structure of **50** (green) bound to M. tuberculosis's class IIa FBA (PDB code: 4LV4, resolution: 2.08 Å). Key H-bond interactions are shown as yellow dashed lines.

2.8 Botulinum neurotoxin inhibitors

Botulinum neurotoxins (BoNT) were considered to be the most active toxins known and a severe bioterrorist threat. In 2014, compound **51** (Figure **20**) was reported as a potent BoNT inhibitor with favorable in vitro potencies (IC_{50} = 0.8 μM) and favorable ADME properties (excellent solubility at low pH) through the screening of commercially available and synthesized library.[55]

2.9 Miscellaneous activities

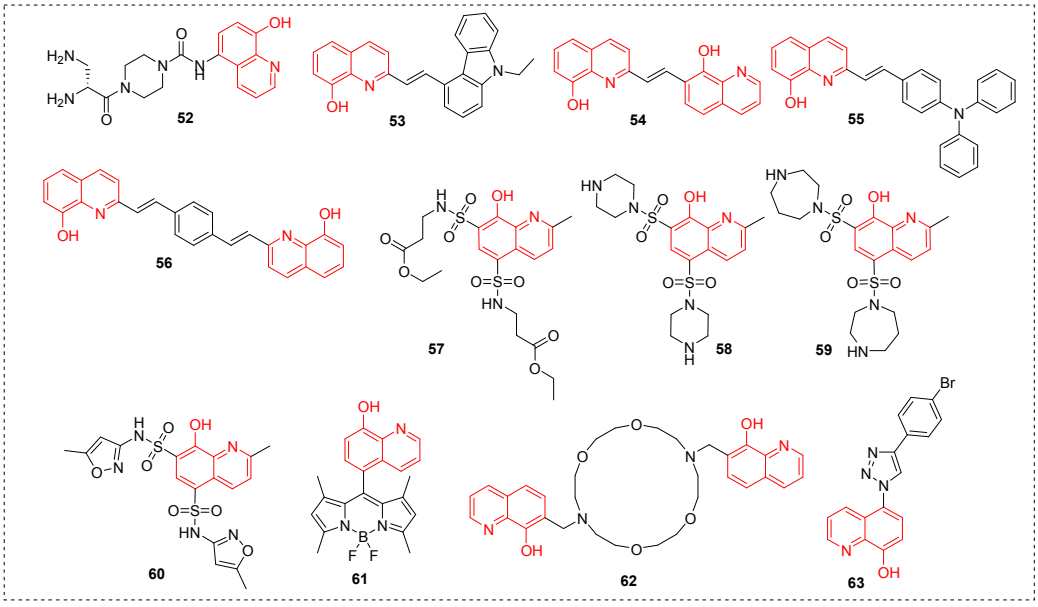


Figure 22. Other 8-HQ-containing compounds with potential applications.

Besides the contents described above, as shown in **Figure 22**, novel 8-HQ-containing 2,3-diaminopropionic acid **52** was validated as a glyoxal/methylglyoxal scavenger and as an AGE inhibitor.[56] 8-HQs **53-56** could induce the proliferation of rat mesenchymal stem cells (rMSCs).[57] In 2014, some 5,7-bis(alkylaminosulfonyl)-8HQs (**57-60**) were reported as highly effective radioprotective agents with low cytotoxicity for MOLT-4 cells.[58] 8-HQs **61-63** were identified as chemosensors or fluorescent sensors for their interesting electro-optical properties.[59-61]

3. Conclusions and perspectives

Undoubtedly, the 8-HQ core structure fits the definition of a "privileged structure" in medicinal chemistry, because it forms the centerpiece of small molecule chemical entities with a wide range of pharmacological properties, which have been presented in this review. 8-HQ was introduced into drug discovery programs for some different reasons. For instances, it was used as an essential part of the pharmacophore (usually as metal chelating moiety) favorably contributing to ligand binding. Besides, 8-HQ moiety was shown to function as a flat, aromatic linker to orient the pharmacophore elements into the proper geometry for binding, as well as modulating the physicochemical properties by placing them in the periphery of the molecule.

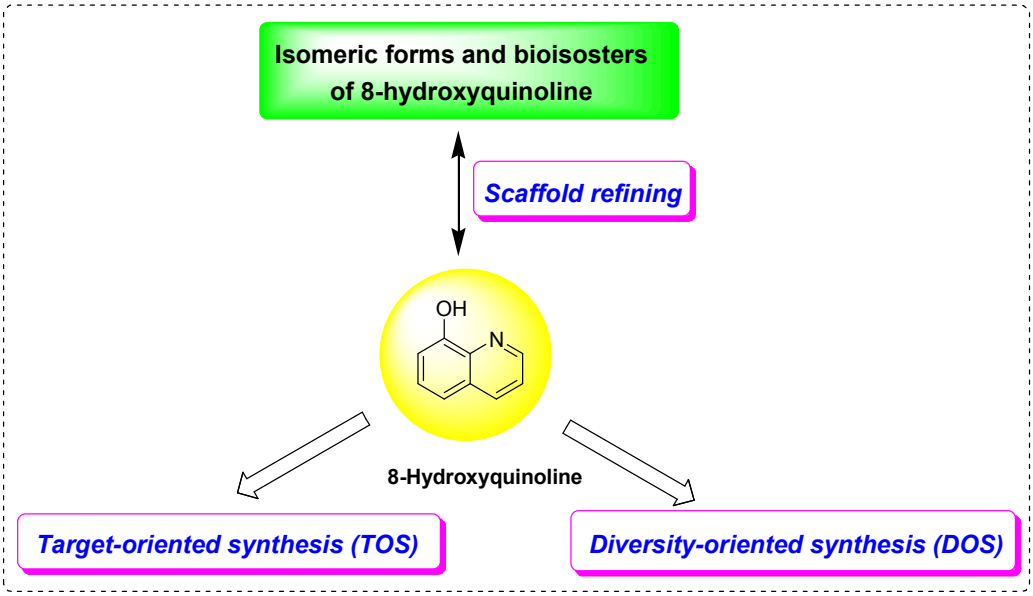


Figure 23. Graphical representation of the prospects of further exploitation of 8-HQ scaffold.

The prospects of 8-HQ will be represented from the following aspects (**Figure 23**): First, 8-HQ structure provides a versatile platform on which multiple functional substituents groups can be placed at various sites of core chemical skeleton, allowing medicinal chemistsus to utilize structure-based drug design or target-oriented synthesis (TOS) techniques to exquisitely tailor a molecule directly to its specific target, thereby to avoid or control unfavorable off-targets interactions. Consequently, novel derivatives towards a given target with improved potency, selectivity and minimum off-target activities will be obtained. Second, through design and synthesis of libraries around a given privileged structure to exploit unchartered territories in chemical and biological space, a higher hit rate and the identification of biologically relevant hits can be expected, thus we envision that there exists a great potential in chemical approaches such as multicomponent reactions (MCRs), diversity-oriented synthesis (DOS) methodologies and more efficient, expeditious straight-forward synthetic methods,[62,63] to further extend versatility of this scaffold in various medicinal areas. Lastly but also importantly, the "privileged structure"-guided scaffold repurposing is a useful strategy to identify structurally novel 8-HQ-related chemotypes with intellectual properties by switching the central core structure with its isomeric forms, bioisosters or structurally pertinent skeletons (towards or from 8-HQ) combined with decorating substituent groups.[8] It should be firmly convinced that the exploitation of 8-HQ scaffold remains an intriguing scientific endeavour, which will lead to the discovery of more clinically-relevant agents.

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8-Hydroxyquinoline: A Privileged Structure with Broad-ranging Pharmacological Potentials

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Overview of broad-ranging pharmacological applications of 8-HQ derivatives.