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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL IMIDAZOQUINAZOLINONE DERIVATIVES AS HDAC6 ISOFORM-SELECTIVE INHIBITORS

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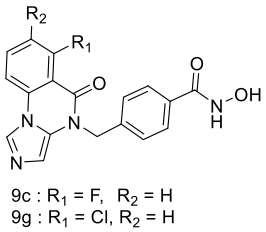
ABSTRACT

Synthesis and SAR of Isoform selective HDAC6 inhibitors of novel imidazoquinazolinones is shown. It demonstrates HDAC6 selective pharmacokinetic properties and has clean off-target profile. It shows efficacy comparable to approved HDAC inhibitors.



9c : R_1 = F, R_2 = H
9g : R_1 = Cl, R_2 = H

	HDAC6 (IC_{50} nm)	HDAC1 (IC_{50} nm)	Ratio
9c	1.3	181	137
9g	0.6	187	286

	MM1S (IC_{50} µM)	U266B1 (IC_{50} µM)	HLM	RLM
9c	1.2	1.32	83.5	88.9
9g	1.1	0.9	87.05	74.27

Figure 1.

KEYWORDS: Imidazoquinazolinones, Isoform-Selective Inhibitors, human deacetylase, HDAC6, Hydroxamic acid, Zinc binding groups.

INTRODUCTION

Hyper acetylation of histone is associated with transcriptional gene activation. Gene expression is a function of histones which in particular regulated by post-translational modifications such as acetylation and methylation, often called

epigenetic regulation. Histone deacetylases (HDACs) and histone acetyltransferases (HATs) play an important role in gene expression by controlling the potential acetylation status of histone proteins. Histones are highly basic proteins abundant in lysine and arginine residues and acetylation of the ε-amino group on lysine residues at *N*-terminal tails of histone opens up the chromatin structure and transcriptional gene activation. Conversely, the hypo-acetylation or de-acetylation of histone is associated with transcriptional gene repression. HDACs remove acetyl groups from hyper-acylated histones, which results in configurational change in chromatin that blocks transcription to DNA, consequently resulting into gene suppression.[1] HATs on the other hand, acetylate the lysine residue of histone leading to relaxing the chromatin structure to result in re-instating transcription to DNA.

There are 18 known human HDACs, which are divided into two main groups: zinc-dependent HDACs and NAD-dependent HDACs, also known as Sirtuins (Class III). These are further classified into four groups based on their sequence similarity and catalytic activity. Class I includes HDAC1, 2, 3, and 8; Class IIa includes HDAC4, 5, 7, and 9; Class IIb includes HDAC6 and 10; and Class IV consists of only HDAC11.

Many HDAC inhibitors have been created, most of which are identified by the presence of a hydroxamate group that binds to the zinc in the enzyme's active site.[2,3] Besides hydroxamates, other chemical groups are also known to inhibit HDACs. One of the most common types is 2-aminobenzamide derivatives. For example, Entinostat reached phase III clinical trials but did not improve patient life expectancy, so it was discontinued. Mocetinostat, on the other hand, is currently in phase II trials and shows great potential.[4] Four HDAC inhibitors have been approved by the US FDA for treating cutaneous T-cell lymphoma and multiple myeloma. Additionally, HBI-8000 has been approved by the Chinese FDA for treating cutaneous T-cell lymphoma.[5,9]

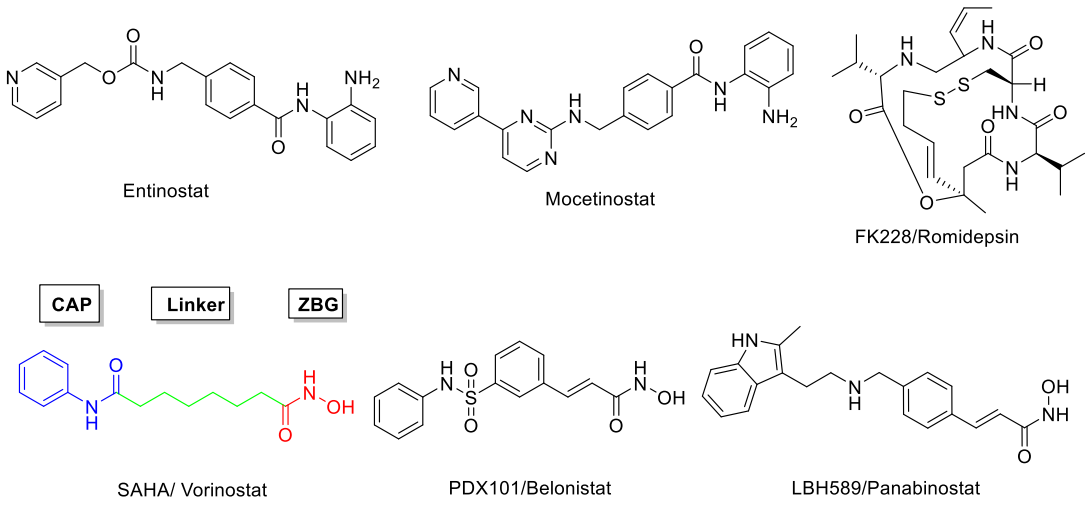


Figure 2.

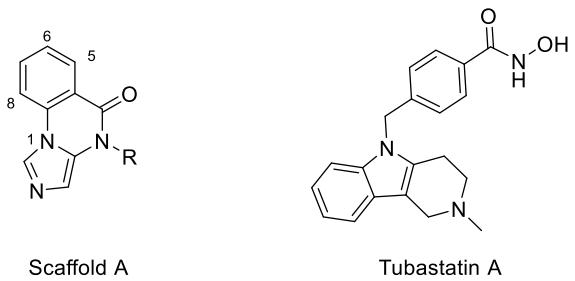
In spite of the success of HDAC inhibitors in cancer therapy, non-selective inhibition of HDACs result in side effects such as diarrhea, fatigue, neutropenia, decreased platelet levels and so on.[10-13] This has resulted in dose-limitations of HDAC inhibitors.[14] HDAC inhibitors are also being tested for CNS related diseases such as brain cancers, Alzheimer's disease, depression and drug addictions.[15,16] HDAC inhibitors such as SAHA, MS-275, Tubastatin-A, Valproic acid have low brain uptake due to poor blood- brain barrier (BBB) permeability, indicating their limitations for applications towards CNS diseases.[17-21]

Isoform selective inhibitors which target particular HDAC isoform, can provide a roadmap for the development of HDAC inhibitors with no or lesser side effects.[22] In the HDAC family, HDAC6 plays a pivotal role in myriad eukaryotic biological processes. HDAC6 is a unique member of the HDAC family that also targets various non-histone substrates such as α-tubulin, cortactin and heat shock protein 90 (HSP90) apart from regular histone acetylation and thereby regulate cell proliferation, metastasis, invasion and mitosis in tumors. HDAC6 is significantly expressed in various tissues such as liver, kidney, testis, brain, pancreas and heart. HDAC6 plays a central role in autophagic protein degradation by recruiting ubiquitinated proteins for transport to aggresomes and also targets various other non-histone substrates as well to modulate cell morphology, adhesion, migration, immune mediated cell-cell interactions, tumor cell invasion/metastasis and degradation of misfolded/unfolded proteins. Overexpression of HDAC6 is confirmed in many tumor cell lines and HDAC6 is also required for efficient oncogenic cell transformation.[23,24] Thus, HDAC6 selective inhibitors could be a potential targeting approach to overcome drug resistance in combination with various anti-cancer strategies while having reduced overall toxicity profile of pan-HDAC inhibitors.

Pharmacophore of HDAC inhibitor is divided into three parts *viz.* Zinc binding group (ZBG), linker and a cap group (**Fig 2**). In this article we try to develop and explore isoform specific inhibitor for HDAC6.

RESULT AND DISCUSSION

It has been recognised that cap group has significant effect in isoform selectivity in HDAC inhibitors.[25] Aryl substituted imidazolidinone based HDAC inhibitors are reported in 2015.[26] Previously, we have described our efforts to identify a tricyclic imidazole based scaffold (A, Fig. 3) as an IDO and or TDO modulator.[27] This tricyclic heterocycle contains imidazole ring fused with benzene ring with a Quinazolinone ring making a core or a cap group of the molecule. This idea emerged from the fact that recently reported molecule Tubastatin A (Fig. 3) is a tricyclic molecule with tremendous selectivity for HDAC6 and is considered a milestone in this area.[28]



Scaffold A Tubastatin A

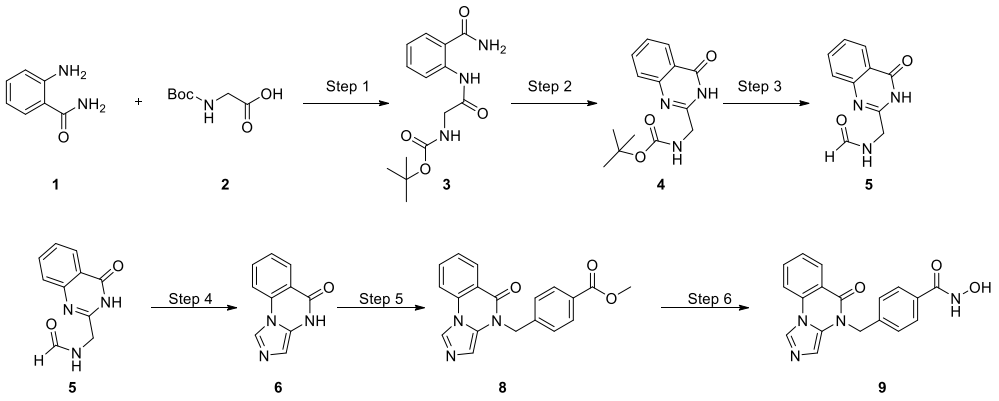
Figure 3.

Synthesis

Synthesis of (**9**) started from acid amine coupling of *N*-Boc glycine (**2**) and 2-aminobenzamide to obtain (**1**). In presence of sodium hydroxide, Quinazolinone ring (**4**) was formed with excellent conversion. *N*-Boc protection was removed by refluxing THF solution of (**4**) in TFA and consequently treatment of ethyl formate provided *N*-formyl derivative (**5**). Treatment of (**5**) with polyphosphoric acid in xylene facilitated formation of imidazole ring (**6**). This completed the synthesis of cap group.[27]

Compound (**6**) was then treated with 4-carbmethoxy benzyl bromide (**7**) in presence of Caesium carbonate to obtain (**8**) which was further converted to Hydroxamic acid (**9**) by treatment with Hydroxylamine hydrochloride.

Scheme 1



Reagents and conditions: **Step-1:** Isobutyl chloroformate, Et_3N, THF, rt, 16 h, 48%; **Step-2:** NaOH, EtOH, rt, 16 h, 93%; **Step-3:** TFA, MDC, reflux, 5h, 53%; Et_3N, ethyl formate, 60-70 °C, 14 h, 75%; **Step-4:** Polyphosphoric acid, xylene, 140 °C, 6 h, 82%; **Step-5:** 4-carbmethoxy benzyl bromide (**7**), Cs_2CO_3, DMF, 70 °C, 1 h, 90%; **Step-6:** Hydroxylamine HCl, 90%.

Structure activity relationship (SAR)

According to synthetic schemes initial two candidates viz. **9** and **21** were prepared.

In-vitro **HDAC6 and HDAC1 Biochemical Assay**

In the *in-vitro* human recombinant Histone deacetylase (HDAC) enzyme assay for screening of inhibitor compounds, human HDAC6 with an *N*-terminal GST tag and human HDAC1 with a *C*-terminal His tag expressed in a Baculovirus expression system were used (BPS Bioscience, San Diego, CA, USA). All other materials were procured from Sigma-Aldrich (St. Louis, MO, USA).

The HDAC6 and HDAC1 inhibitory activity for test compounds were assessed by using the substrate Boc-Ac-Lys-AMC. Assay buffer (50 mM Tris, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$ and 1 mg/ml BSA, 1% DMSO, pH 8.0) containing appropriate concentrations of compounds and 10 ng of HDAC6 or 20 ng of HDAC1 enzyme was pre-incubated at 37 °C for about 15 minutes before addition of the substrate. 10 µM substrate for HDAC6 or 30 µM substrate for HDAC1 were then added to the enzyme-compound mix and the assay plate incubated for about 1 hour at about 37 °C with slow shaking. The reaction was quenched by addition of a stop solution containing 10 mg/ml trypsin and 2 µM trichostatin A. The reaction mixture was further incubated at about 37 °C for about 15 minutes and the resulting fluorescence was read using a micro plate reader at an excitation wavelength of 360 nm and emission wavelength of 460 nm. Percent inhibition at each concentration of test compound(s) was determined by estimating the decrease in fluorescence signal.[29] Data were analyzed using nonlinear regression to generate IC_{50} values using GraphPad Prism 6 software..

Subsequent testing indicated 95.4% inhibition at 0.1 µM concentration and IC_{50} 8.19 [pIC50 (HDAC6) 8.08] nM for EPL 4009 and 95.5% inhibition at 0.1 µM concentration and IC50 5.93 nM [pIC50 (HDAC6) 8.08] for **21**. Starting SAR with testing of Zinc binding groups (ZBGs) looked like a logical step therefore, while keeping rest of the structure intact, different HDAC specific ZBGs were incorporated. Results are tabulated in **Table 1**.

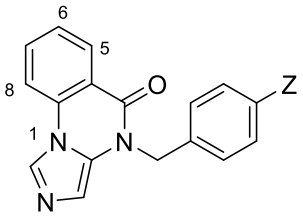
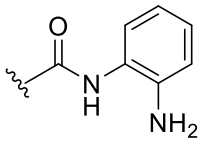
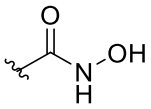
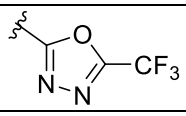
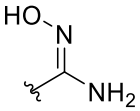
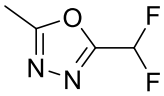
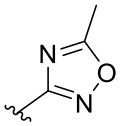
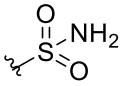


Table 1: SAR with testing of Zinc binding groups (ZBGs).

Compound Code	Zinc binding group (ZBG)	% inhibition (HDAC6) at 0.1 µM
10		1.0
9		95.4
11		0.9
12		19.7
13		9.4
14		16.6
15		NIL

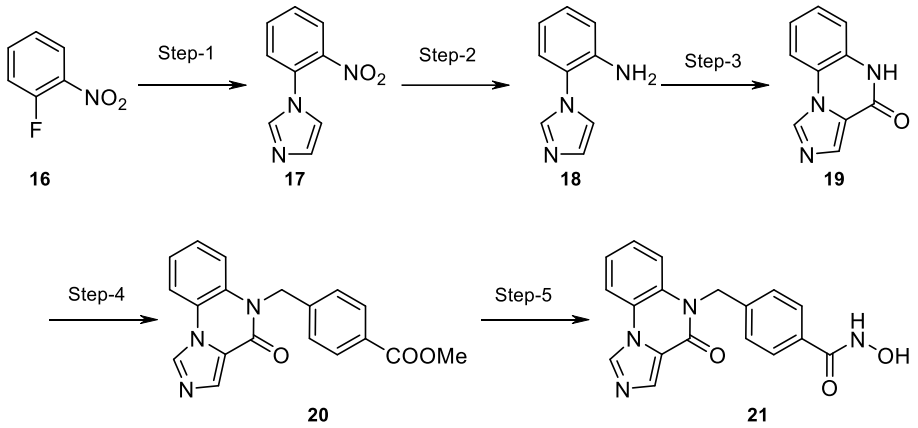
From all the known HDAC ZBGs' it was observed that, the Hydroxamate group showed excellent activity and other groups such as phenyldiamines, oxadiazoles, oxamidine and sulfonamides showed poor inhibition for HDAC6.

After preliminary trial of ZGB, we decided to evaluate Cap group. Since, Imidazo [1,5-a]quinazolin-5(4*H*)-one used as a model cap group with hydroxamic acid as ZGB showed excellent HDAC6 inhibition during preliminary testing, we decided to perform SAR on the same cap group. Four positions 5, 6 and 7 on quinazolinone ring and 2 and 4 positions of imidazole ring on Imidazo[1,5-a]quinazolin-5(4*H*)-one structural modifications were done. Additionally, Imidazole ring was replaced with Pyrrol, Pyrrolidine and Tetrahydrothiophene.

In parallel, synthesis of a reverse tricyclic scaffold (Scaffold B) was developed as well. 2-fluoro nitrobenzene was treated with imidazole in presence of potassium carbonate in acetonitrile under reflux conditions to obtain **2** in 65% yield. Nitro group was then reduced to amine by diazotization followed by hydrogenation under palladium in methanol.

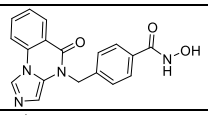
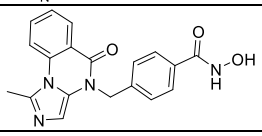
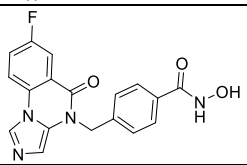
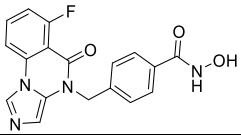
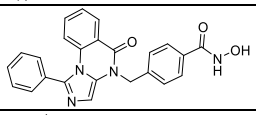
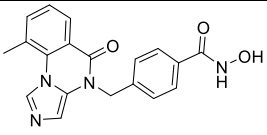
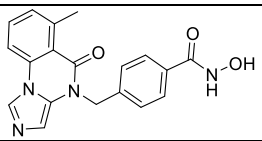
Carbonyl di-imidazole coupling of 3 yielded core frame of the reverse scaffold. Alkylation using caesium carbonate in DMF provided intermediate 5 which was then converted to Hydroxamic acid (Scheme 2).

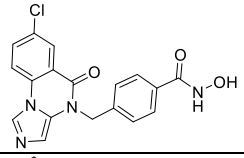
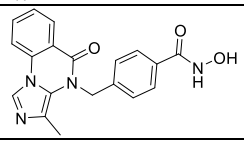
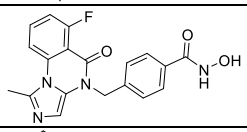
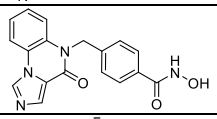
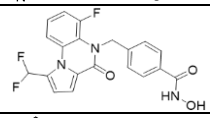
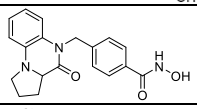
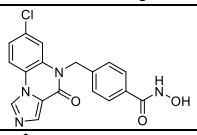
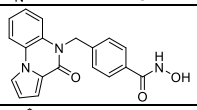
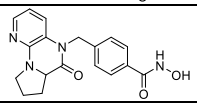
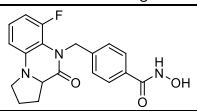
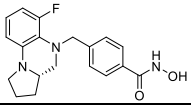
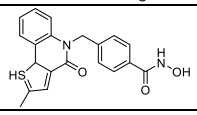
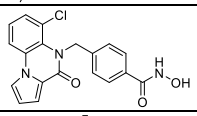
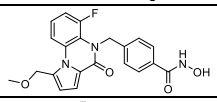
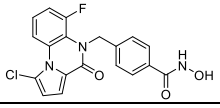
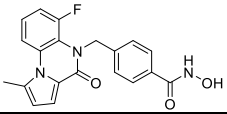
Scheme 2

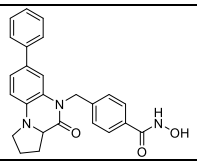


Reagents and conditions: **Step-1:** Imidazole, K_2CO_3, acetonitrile, reflux 24 h; 65%; Step-**2:** $NH_2NH_2.H_2O$, Pd/C, MeOH, reflux, 2 h, 93%; **Step-3:** CDI, 1,2,4-trichlorobenzene, 190 °C, 5h, 63%; **Step-4:** Cs_2CO_3, methyl(4-bromomethyl)benzoate (**7**), DMF, 0 °C-rt, 1 h; 44%; **Step-5:** 50% aq. hydroxyl amine, KOH, acetonitrile, rt, 1h; 95%

Table 2: SAR of the cap group of scaffold A and B.

Sr. No.	Code	Cap group	IC_{50} (nM) HDAC6	IC_{50} (nM) HDAC1	Fold selectivity (HDAC1/HDAC6)
1	**9**		8	329	41
2	**9a**		2	140	58
3	**9b**		6	210	35
4	**9c**		1.3	181	137
5	**9d**		11.4	180	16
6	**9e**		11.1	589	53
7	**9f**		4.3	428	99

8	**9g**		0.6	187	286
9	**9h**		13	501	39
10	**9i**		8.8	493	56
11	**21**		165	5.9	28
12	**21a**		2.4	552	227
13	**21b**		7.1	1046	147
14	**21c**		12.7	275	21
15	**21d**		3	298	95
16	**21e**		9	451	52
17	**21f**		5	1100	213
18	**21g**		74	5121	68
19	**21h**		2.1	317	149
20	**21i**		44.5	1001	225
21	**21j**		5.2	636	123
22	**21k**		3.5	695	198
23	**21l**		2.3	416	182

24	**21m**		11	298	26

SAR on the cap group furnished important data about the selectivity of the scaffold. Substitution at 5, 6, and 8 positions of Quinazolinone in (A and B scaffolds) was substituted with fluoro, chloro and methyl group. It was observed that when comparing data with **9** (Table 2, entry 1) and **21d** (Table 2, entry 15) substitution at 6th (Table 2, entry 3, 14 and 24) and substitution at 8th (**9e**, entry 6) position indicated diminished HDAC6/HDAC1 selectivity. Only one contrasting result was observed (**9g**, entry 8). Chloride substitution at 6th position in (B scaffold) indicated 286 fold HDAC6/HDAC1 selectivity. Contrary to this, substitution of chloride (**21i**, entry 20: 225.0), fluoride (entry 4: 136.9, entry 14: 56, entry 17: 213.4, entry 18: 68.4) and methyl (entry 7: 99.5) at 5th position indicated considerable upswing in HDAC6/HDAC1 selectivity. Substitution on imidazole ring were tested as well with alkyl (entry 9 and 10) and aryl groups.

Unsubstituted **21d** exhibited 95-fold selectivity. Saturation of pyrrole led to 21b with 147-fold selectivity and fluoride substitution and saturation led to **21f** with 213-fold selectivity.

HDAC-6 at low nM range with HDAC-1 at µM range is a desirable fold selectivity with greater than 100-fold difference in IC_{50} values.

Anticancer Activity Screening in multiple myeloma cell lines

Multiple myeloma cell lines MM.1S & U266B1 were purchased from ATCC and maintained in RPMI-1640 containing 10% FBS supplemented with antibiotics (100 units/mL penicillin, 100 µg/mL streptomycin).

Myeloma cell proliferation in response to the experimental drugs were assessed by using Cell Counting Kit-8 (CCK-8).

3000 cells/well were seeded in 96-well flat bottom microtiter plates and incubated for 24 hours at 37 °C, 5% CO_2. A separate plate with these cell lines are also inoculated for viability before the addition of the compounds (T_0). After 24 hours of incubation, test compounds at 8 different concentrations in triplicates were added to the plates and plates were further incubated for 72 hours. SAHA was used as a standard drug in these experiments.[30]

CCK-8 was added to the wells of control and test plates after 24 hours of incubation. The cell viability at time zero (T_0) was measured from the control plate wells. Plates were incubated at 37 °C, 5% CO_2 for 90 minutes and absorbance was recorded at 450 nm. IC_{50}, GI_{50}, TGI & LC_{50} were calculated by using[31] and graphs were plotted by using Graph Pad Prism6 software.

Table 3: Activity against MM1S and U266B1 cell lines.

Substrate	MM1S (IC_{50} - µM)	U266B1 (IC_{50} - µM)	HLM	RLM
9c	1.2	1.32	83.5	88.9
9g	1.1	0.9	87.05	74.27
9f	3.23	1.97	80.45	41.15
21b	8.1	4.1	70.1	23.6
21f	>3	>3	73.3	12.4
21j	2.02	1.12	1.5	X
21k	>3	>3	2.8	X

X: did not perform

Eight substrates from the pool with greater than 100-fold selectivity were further tested against MM1S and U266B1 cell lines. The results (table 3) indicate that compounds from **scaffold B** have diminished activity (>3 μM) against MM1S and U266B1 cell lines. In contrast, three compound of **scaffolds A** (**9c**, **9g** and **9f**) demonstrated activity of around 1 μM for both the cell lines.

Therefore, compounds from **scaffold A** were tested against human liver microsomes (HLM) and rat liver microsomes (RLM, Table 4); to evaluate their metabolic stability.

In vitro liver microsomal stability of selected compound

Some of the selected potent compounds were subjected to *in vitro* metabolic stability studies using pooled human and rat liver microsomes (Xenotech, Kansas City, USA). Briefly, the test compounds along with control compounds (Verapamil and Warfarin) were incubated at a final concentration of 1 μM with 20 ng/ml of microsomal protein along with the cofactor NADPH (1 mM) at 37 °C for 30 min in a potassium phosphate buffer (100 mM, pH 7.4) reaction mixture. The reaction samples were terminated with 100% cold acetonitrile at 0, 15 and 30 min, centrifuged at 10,000 rpm for 15 min at 4 °C and the collected supernatants were subjected to LC-MS/MS (AB Sciex4500, MA, USA) analysis to calculate the % remaining of the compound.[32]

Only one compound from **scaffold B** (**21b**) was tested for HLM and RLM owing to fold-selectivity of 196.

Table 4: Tests against HLM and RLM.

Substrate	HLM	RLM
9c	83.5	88.9
9g	87.05	74.27
9f	80.45	41.15
21b	70.1	23.6
21f	73.3	12.4
21i	1.5	X
21k	2.8	X

X: did not perform

Compounds **9c** (83.5, 88.9) and **9g** (87.05, 74.3) showed excellent metabolic stability against both HLM and RLM, respectively. However, **21b** (70.1, 23.6) and **9f** (80.45, 41.15) showed excellent metabolic stability against HLM but only low to moderate stability against RLM.

In summary, we have reported a HDAC6 selective inhibitor. **Scaffold B** demonstrated consistency in terms of fold selectivity compared to **scaffold A**. However, the **Scaffold A** based candidate with halogen substitution on the cap group indicated excellent fold selectivity additionally, **9c** and **9g** showed very good inhibition in multiple myeloma cell lines and exhibit good metabolic stability against human and rat liver microsomes. These compounds certainly qualify as initial lead compounds with selective HDAC6 inhibitory activity and will be explored further.

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Data supporting this study are included with available as supporting material file.

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