Design, Synthesis and Biological Evaluation of Novel Benzoylimidazole Derivatives as Raf and Histone Deacetylases Dual Inhibitors

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In recent studies, combinations of histone deacetylases (HDACs) inhibitor with kinase inhibitor showed additive and synergistic effects. BRafV600E as an attractive target in many diseases treatments has been studied extensively. Herein, we present a novel design approach though incorporating the pharmacophores of BRafV600E inhibitor and HDACs inhibitor in one molecule. Several synthesized compounds exhibited distinct BRafV600E and HDAC1 inhibitory activities. The representative dual Raf/HDAC inhibitor, 7a, showed better antiproliferative activities against A549 and SK-Mel-2 in cellular assay than SAHA and sorafenib, with IC50 values of 9.11 µM and 5.40 µM, respectively. This work may lay the foundation for the further development of dual Raf/HDAC inhibitors as potential anticancer agents.

Key words BRafV600E; histone deacetylase 1 (HDAC1); antiproliferation; dual inhibitor; synthesis

Introduction

During the last few decades, developing mechanism-based targeted anticancer drugs has made great achievement. However, unsustainable clinical effectiveness and acquired drug resistance always limits the use of these agents.1 Since cancer is a disease involving complex signaling networks, blocking a single biological target may not completely shut off the core hallmark capability, allowing residual cancer cells to go on working. To address these problems, one particularly promising approach is incorporating the elements that simultaneously tackle multiple cancer-fighting targets into one molecule to obtain new chemical entity. Compared to single-target treatment, this kind of therapeutic regimens have superior efficacy and fewer side effects.2

Protein kinases are important participants in the processes of governing cellular proliferation, differentiation and evasion from apoptosis. BRaf, as one member of the Raf family, plays a crucial role in the Ras/Raf/Mek/Erk (mitogen-activated protein kinase, MAPK) signaling pathway.3,4) The Mutation of BRaf, especially BRafV600E, is the most common in human cancers. Up to data, a lot of BRafV600E inhibitors have been developed such as sorafenib,5) dabrafenib, and vemurafenib (Fig. 1). They effectively block the MAPK signaling pathway and inhibit proliferation of tumor cells expressing BRafV600E.

Histone deacetylases (HDACs) are important targets for tumor therapy.6–9) The HDACs family containing 18 isoforms is categorized into Class I (HDAC1, 2, 3, and 8), Class IIA (HDAC4, 5, 7, and 9), Class IIB (HDAC6 and 10), Class III (sirtuin1–7), and Class IV (HDAC11). Class I, II, and IV HDACs are all zinc-dependent deacetylases, and Class III HDACs are mechanistically distinct from other HDACs, which require nicotine adenine dinucleotide as a cofactor. The pharmacophore of HDACs inhibitors were generally composed of three parts: cap, linker, and zinc binding group (ZBG). Hydroxamic acid is the most frequently used ZBG group. Hydroxamic acid is the most frequently used ZBG group, three of which (i.e., vorinostat,10) belinostat,11) panobinostat12) have gained U.S. Food and Drug Administration approvals for clinical treatment.

A lot of literatures have described the synergistic and additive effects by the joint use of HDACs inhibitors and vari-
ous antitumor agents.\textsuperscript{13–15} Recently, Emmons \textit{et al.} revealed that HDACs inhibitor could enhance the durability of BRaf inhibitor therapy.\textsuperscript{16} Hence, the development of BRaf\textsuperscript{V600E} and HDACs dual inhibitors maybe a valuable strategy to circumvent resistance. Our group had previously reported a 2-(1H-imidazol-2-yl) pyridine derivative \textit{CLW27} possessing comparable antiproliferative activities to sorafenib \textit{in vitro} or \textit{in vivo}, and it showed inhibitory effect on BRaf and KDR-VEGFR2 kinases.\textsuperscript{17} In that compound, imidazole motif in the hinge region played a beneficial role for antitumor potency. For another, considering the genotoxicity of hydroxamic acid group and generated chromosomal aberrations in many cases,\textsuperscript{18,19} an alternative to hydroxamate as ZBG was tried in our design of novel Raf/HDAC dual inhibitors. Vasudevan \textit{et al.} reported the use of acyl imidazole as ZBG in HDAC inhibitors, but it did not show potent inhibitory activity.\textsuperscript{20} However, the HDAC activity is not be determined only by the ZBG group, the spatial structures of cap and linker parts also have influence on activity. In this study, we incorporated acyl imidazole motif as ZBG and retained key urea group in sorafenib, then synthesized a series of novel derivatives (Fig. 2).

**Chemistry**

Compounds \textit{7a--h} were synthesized as follows. Nucleophilic reaction of ethyl 4-hydroxybenzoate (1) with 1-fluoro-4-nitrobenzene yielded intermediate 2 using potassium carbonate with acetonitrile as solvent. Compound 4 was obtained by mannich reaction with imidazole (3), formaldehyde and dimethylamine hydrochloride as materials. Nucleophilic addition of 2 and 4 in tetrahydrofuran yielded key intermediate 5 with \textit{n-BuLi} as the base. Subsequently, reduction of 5 with iron powder as catalyst in ethanol afforded 6. Reaction of 6 with various amines in the presence of 1,1’-carbonyldimidazole at room temperature gave the target compounds \textit{7a--h} (Chart 1).

**Results and Discussion**

\textbf{Enzymatic Activities and Structure–Activity Relationship (SAR) Study of Target Compounds} The antitumor effect of the inhibition of the class I HDAC isoforms, especially HDAC1, was well confirmed.\textsuperscript{21–23} Therefore, all prepared derivatives were tested for their inhibitory ability against HDAC1, using SAHA as the reference compound. As shown in Table 1, IC\textsubscript{50} values illustrated that compound \textit{7c} bearing a terminal 4-methoxylphenyl, exhibited the best inhibitory activity against HDAC1 (IC\textsubscript{50} = 635 nM). However, it was much weaker than that of SAHA. While changing methoxyl from para-position to meta-position, compound \textit{7f} also showed a comparative activity (IC\textsubscript{50} = 679 nM). Additionally, compounds with groups such as –Me (\textit{7b}, \textit{7g}), –Cl or –CF\textsubscript{3} (\textit{7a}, \textit{7d}, and \textit{7e}) on phenyl inhibited HDAC1 with IC\textsubscript{50} values in submicromolar or micromolar range. The activities against BRaf\textsuperscript{V600E} of these derivatives were also evaluated. \textit{7a}, which reserved the same 4-chloro-3-trifluoromethyl substituent as sorafenib, had the strongest activity (IC\textsubscript{50} = 86 nM), although it was slightly less potent than sorafenib (IC\textsubscript{50} = 38 nM). Compound \textit{7d} and \textit{7e} with electron-withdrawing substitutions also showed moderate inhibitory activities. However, electron-donating substitutions such as -Me or -OMe, were detrimental to BRaf\textsuperscript{V600E} inhibition, exemplified by \textit{7b}, \textit{7c}, \textit{7f}, and \textit{7g}, with IC\textsubscript{50} values ranging from 0.840 to 4.727 \textmu M. When the phenyl was replaced with pyridyl, obvious declines on both enzymatic activities were observed.

\textbf{Raf and HDAC Isoforms Selectivity of Representative...
Compounds

Based on the enzymatic results, representative compounds 7a and 7c with better HDAC1 or BRafV600E activity were further evaluated against Raf and HDAC isoforms. As shown in Table 2, 7a also exhibited potent ARaf, BRafWT, and CRaf inhibitions. However, 7a and 7c showed no activities against HDAC6 and HDAC8. The most potent compound 7a was further tested against another six kinases which were frequently used in our lab to evaluate its selectivity and to discovery potential other molecular targets. The initial screening of 7a was conducted at 10 μM concentration for the inhibitory rates. As summarized in Table 3, compound 7a showed weak inhibitory effects against KDR-VEGFR2 and EGFR with IC50 values of 19.210 μM and 35.470 μM, respectively, and had no obvious inhibition against CDK4/6, FLT3, and BCR/ABL kinases.

Cell Proliferation Inhibition

We chose compounds 7a, 7b, 7c, and reference compounds sorafenib and SAHA to evaluate antiproliferative activities against tumor cell lines K562 (leukemia), HCT116 (colon cancer) and A549 (non-small cell lung cancer). As shown in Table 4, all three compounds demonstrated obvious antiproliferative activities against all tumor cells, especially 7a, although it had the weakest HDAC1 inhibition. Compared to sorafenib, 7a showed overall more potent antiproliferative activity. 7a also exhibited superior activity in solid tumor cell line A549 (IC50 = 9.11 μM) to that of SAHA (IC50 = 18.13 μM). Besides, 7a was further tested against another two tumor cells SK-Mel-2 (malignant melanoma) and MV4-11 (leukemia) which had extraordinary expression of BRafV600E or BRafWT. 7a displayed submicromolar inhibition toward MV4-11 with IC50 value of 0.38 μM. Especially, 7a had more potent activity against SK-Mel-2 than those of SAHA and sorafenib.

Molecular Docking Study

To further understand the interaction between the inhibitors and two proteins, we docked 7c in the active site of HDAC1 (PDB code: 5ICN) and 7a in BRafV600E (PDB code: 1UWJ) respectively. As shown in Fig. 3A, 7c exhibited excellent shape complementarity with the binding pocket of HDAC1. The acyl imidazole moiety could form bidentate coordination with zinc ion at the bottom of the pocket, with O-Zn2+ distance of 2.510 Å for C=O and N-Zn2+ distance of 2.731 Å for imidazole –NH–, respectively. Additionally, 7a also exhibited superior activity in solid tumor cell line A549 (IC50 = 9.11 μM) to that of SAHA (IC50 = 18.13 μM). Besides, 7a was further tested against another two tumor cells SK-Mel-2 (malignant melanoma) and MV4-11 (leukemia) which had extraordinary expression of BRafV600E or BRafWT. 7a displayed submicromolar inhibition toward MV4-11 with IC50 value of 0.38 μM. Especially, 7a had more potent activity against SK-Mel-2 than those of SAHA and sorafenib.

Table 1. Enzymatic Inhibitory Activities of Target Compounds 7a–h (IC50α, μM)

| Cpd. | R         | BRafV600E | HDAC1 | Cpd. | R         | BRafV600E | HDAC1 |
|------|-----------|-----------|-------|------|-----------|-----------|-------|
| 7a   |           | 0.086     | 1.710 | 7e   |           | 0.135     | 1.680 |
| 7b   |           | 0.840     | 0.882 | 7f   |           | 4.727     | 0.679 |
| 7c   |           | 1.853     | 0.635 | 7g   |           | 2.032     | 0.925 |
| 7d   |           | 0.221     | 1.850 | 7h   |           | >10       | 4.030 |
| Sorafenib | / | 0.038 | / | SAHA | / | / | 0.017 |

*We ran experiments in duplicate, SD <15%.

Table 2. Raf and HDAC Isoforms Selectivity of Compounds 7a and 7c (IC50α, μM)

| Cpd. | ARaf | BRafV600E | BRafWT | CRaf | HDAC1 | HDAC6 | HDAC8 |
|------|------|-----------|--------|------|-------|-------|-------|
| 7a   | 0.045| 0.086     | 0.134  | 0.102| 1.710 | NA    | NA    |
| 7c   | 1.103| 1.853     | 0.226  | 2.374| 0.635 | NA    | NA    |
| Sorafenib | 0.010 | 0.038 | 0.024 | 0.041| /     | /     | /     |
| SAHA | /    | /         | /      | /    | 0.037 | 0.026 | 3.21  |

*We ran experiments in duplicate, S.D. <15%. b) NA: no activity was observed at 50 μM concentration.

Table 3. Kinase Inhibitory Effects of Compound 7a

| Kinase        | Inhibition rate% | IC50 (μM) |
|---------------|------------------|-----------|
| KDR-VEGFR2    | 41.75%           | 19.210    |
| CDK4/cyclin D1| 0.08%            | /         |
| CDK6/cyclin D1| –2.05%           | /         |
| FLT3          | 9.20%            | /         |
| BCR-ABL       | –0.13%           | /         |
| EGFR          | 38.60%           | 35.470    |

KDR-VEGFR2 or BRafV600E. 7a displayed submicromolar inhibition toward MV4-11 with IC50 value of 0.38 μM. Especially, 7a had more potent activity against SK-Mel-2 than those of SAHA and sorafenib.
tionally, the O atom of carbonyl and the N atom of imidazole generated H-bond interactions with His178 and Cys151. Moreover, the phenyl linkage connected to acyl imidazole formed stacking $\pi - \pi$ interactions with the residues of Phe150 and Phe205. The urea group and two adjacent phenyls occupied the surface groove and came into close contact with the residues (Gln26, Gly27, and His28) at the rim region. Another H-bond was formed between NH of urea and Glu98 to enhance their binding (Fig. 3B). Comparing the binding modes of sorafenib (Fig. 3C) and 7a (Fig. 3D) in BRaf V600E, 7a reserved three key H-bond interactions between the urea group and the residues of Glu500 and Asp593, while the H-bond in the hinge was missed. This might be responsible for reduced potency against BRaf V600E of 7a.

**Conclusion**

In summary, we designed a series of novel Raf/HDAC dual inhibitors bearing acyl imidazole as ZBG. Eight target compounds were synthesized and tested against BRaf V600E and HDAC1, and most compounds exhibited obvious inhibitory activities. Among these, compounds 7a and 7c were the most potent compounds against BRaf V600E and HDAC1, respectively. Then 7a and 7c were submitted to evaluate the isoforms selectivities. The results showed these derivatives to be pan-Raf and selective HDAC1 inhibitors. Further *in vitro* antiproliferative assay showed that 7a, 7b, and 7c had inhibitory effects against several tumor cell lines including K562, HCT116, and A549. Moreover, 7a exhibited more potent antiproliferative activities against A549 and SK-Mel-2 cell lines than sorafenib and SAHA. Subsequently, molecular docking was performed to explain the structure–activity relationship. The demonstration of dual Raf/HDAC inhibitors in this paper provided useful tool compounds for further studies of multiple pathway inhibition achieved with a single molecule.

**Experimental**

**Chemistry** All of the starting materials were obtained commercially and were used without further purification. All of the reported yields were for isolated products and were not optimized. Melting points were determined in open capillaries.
on a WRS-1A digital melting point apparatus (Shenguang). The reduced pressure. The product was obtained as a white solid by chromatography on a silica gel column (1.66 g, 85.0%). mp: 192–194°C. 1H-NMR (500 MHz, DMSO-d6): δ: 13.36 (br, 1H), 8.53 (dd, J = 8.8, 2.7 Hz, 2H), 7.48 (s, 1H), 7.27 (s, 1H), 6.97 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 5.08 (s, 2H).

General Procedure for the Preparation of Target Compounds 7a–h

To a solution of 6 (3 mmol) in anhydrous dichloromethane (5 mL) was added CDI (0.58 g, 3.6 mmol) at room temperature. The resulting mixture was stirred for 12 h, then added iron powder (3.70 g, 70 mmol) in batches. The mixture was stirred for overnight. After completion of the reaction as monitored by TLC, the reaction mixture was filtered. The filter cake was washed with CH2Cl2 (2 mL × 2) and dried in vacuo. The crude product was recrystallized in mixed solvent of ethyl acetate and tetrahydrofuran (v/v = 1:1) to give the purified target compound.

1-(4-(4-(1H-imidazole-2-carbonyl)phenoxy)phenyl)-3-(4-chloro-3(trifluoromethyl)phenyl)urea (7a)

1H-NMR (500 MHz, DMSO-d6): δ: 13.37 (s, 1H), 9.16 (s, 1H), 8.91 (s, 1H), 8.58 (d, J = 9.0 Hz, 2H), 8.11 (d, J = 2.4 Hz, 1H), 7.66 (dd, J = 8.8, 2.4 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 2.4 Hz, 1H), 7.28 (s, 1H), 7.12 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H); ESI-MS m/z: 501.1 ([M + H]+), 523.1 ([M + Na]+); IR (KBr, cm⁻¹): 3344, 1674, 1591, 1547, 1489, 1323, 906, 775, 611.

1-(4-(1H-imidazole-2-carbonyl)phenoxy)phenyl)-3-(4-nitrophenyl)urea (7b)

1H-NMR (500 MHz, DMSO-d6): δ: 13.39 (s, 1H), 8.70 (s, 1H), 8.58 (d, J = 8.9 Hz, 2H), 8.55 (s, 1H), 7.53 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.28 (s, 1H), 7.12-7.04 (m, 6H), 2.25 (s, 3H); ESI-MS m/z: 413.1 ([M + H]+); IR (KBr, cm⁻¹): 3304, 1635, 1603, 1553, 1501, 1302, 1251, 1171, 823, 744, 665.

1-(4-(1H-imidazole-2-carbonyl)phenoxy)phenyl)-3-(4-methoxyphenyl)urea (7c)

1H-NMR (500 MHz, DMSO-d6): δ: 13.39 (s, 1H), 8.67 (s, 1H), 8.57 (d, J = 8.9 Hz, 2H), 8.47 (s, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.50 (s, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.28 (s, 1H), 7.10 (s, 2H), 7.05 (s, 2H), 6.88 (d, J = 8.9 Hz, 2H), 3.71 (s, 3H); ESI-MS m/z: 429.3 ([M + H]+); IR (KBr, cm⁻¹): 3348, 1634, 1591, 1501, 1475, 1389, 1225, 905, 773, 662.

1-(4-(1H-imidazole-2-carbonyl)phenoxy)phenyl)-3-(4-chlorophenyl)urea (7d)

1H-NMR (500 MHz, DMSO-d6): δ: 13.40 (s, 1H), 8.82 (s, 1H), 8.80 (s, 1H), 8.56 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.9 Hz, 2H), 7.51-7.47 (m, 7H), 7.33 (d, J = 8.9 Hz, 2H), 7.28 (s, 1H), 7.10 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H); ESI-MS m/z: 433.2 ([M + H]+); IR (KBr, cm⁻¹): 3360, 1686, 1595, 1497, 1389, 1229, 905, 839, 768, 598.

1-(4-(1H-imidazole-2-carbonyl)phenoxy)phenyl)-3-(3,4-dichlorophenyl)urea (7e)

1H-NMR (500 MHz, DMSO-d6): δ: 13.38 (s, 1H), 9.00 (s, 1H), 8.88 (s, 1H), 8.87 (d, J = 9.0 Hz, 2H), 7.88 (d, J = 2.4 Hz, 1H), 7.53 (d,
\[ J = 9.0 \text{ Hz}, \ 2H), \ 7.51 \ (d, \ J = 9.0 \text{ Hz}, \ 1H), \ 7.49 \ (d, \ J = 2.4 \text{ Hz}, \ 1H), \ 7.35 \ (dd, \ J = 8.9 \text{ Hz}, \ 1H), \ 7.28 \ (s, \ 1H), \ 7.12 \ (d, \ J = 8.9 \text{ Hz}, \ 2H), \ 7.06 \ (d, \ J = 9.0 \text{ Hz}, \ 2H), \ 7.01 \ (d, \ J = 9.0 \text{ Hz}, \ 2H), \ 6.94 \ (d, \ J = 8.0 \text{ Hz}, \ 1H), \ 6.55 \ (d, \ J = 7.51 \text{ Hz}, \ 1H), \ 3.29 \ (s, \ 3H); \ ESI-MS \ m/z: 429.3 ([M + H])^+; \ IR (KBr, \ cm^{-1}): 3265, 1659, 1572, 1499, 1420, 1393, 1232, 901, 849, 773. \]

In vitro HDAC Enzyme Assay The HDAC activity was determined using the HDAC fluorimetric activity assay kit (Biomol, Plymouth Meeting, PA, U.S.A.). Briefly, recombinant proteins of HDAC1, 6 and 8 was incubated with test molecules at indicated concentrations. The HDAC activity was expressed as arbitrary fluorescence units (AFU). The HDAC activity was calculated as a percentage of activity determined using the HDAC fluorimetric activity assay kit (Biomol, Plymouth Meeting, PA, U.S.A.).

In vitro Kinase Enzyme Assay Activity of full length BrAf\text{V600E} was determined using Hot-SpotSM kinase assay. 5nM of human GST-tagged BrAf\text{V600E} protein (AA416–766) (Invitrogen, Cat# PV3894) was mixed with 20µM of the substrate His 6-Tagged Full-length Human MEK1 (K97R) in reaction buffer (20mM Hepes pH 7.5, 10mM MgCl2, 1 mM ethylene glycol bis(2-aminoethyl ether)-N,N,N',N''-tetra-acetic acid (EGTA), 0.02% Brij35, 0.02mg/mL BSA (albumin from bovine serum), 0.1mM Na2VO3, 2 mM DTT, 1% DMSO at room temperature, the compounds dissolved in 100% DMSO at indicated doses (starting at 30µM with 3-fold dilution) was delivered into the kinase reaction mixture by Acoustic technology (Echo550; nanoliter range), incubate for 20 min at room temperature. After 10 µM 32P-γ-ATP (specific activity 10µCi/µL) (Perkin Elmer, NEG302H001 MC) was added to initiate the reaction, the reactions were carried out at 25°C for 2h. The kinase activities were detected by filter-binding method. IC\text{50} values and curve fits were obtained by Prism (GraphPad Software).

Computational Methods All computational work was performed in Discovery Studio 3.0 software (BIOVIA, 5005 Wateridge Vista Drive, San Diego, CA92121 U.S.A.). Docking was conducted using Cdocker module based on the cocrystal of BrAf\text{V600E} (PDB: 1UWJ) and HDAC1 (PDB: 5ICN). Water molecules outside the binding pockets were excluded. The energy minimization for compounds was performed by Powell’s method for 1000 iterations using tripos force field and with Gasteiger–Hückel charge. The other docking parameters were kept as default.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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