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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of 5-chloro-2-hydroxy-3-triazolylbenzoic acids as HIV integrase inhibitors

Jie Chen · Cheng-Fu Liu · Cheng-Wen Yang · Cheng-Chu Zeng · Wei Liu · Li-Ming Hu

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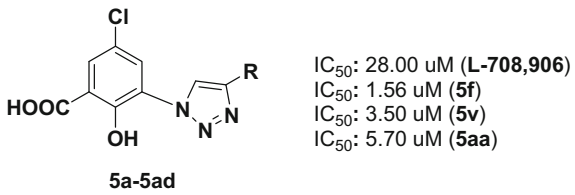
Abstract A series of potential HIV-1 integrase inhibitors based on 5-chloro-2-hydroxy-3-triazolylbenzoic acid scaffold was designed and synthesized. Some of these compounds exhibit potent inhibitory activities at micromolar concentrations against HIV-1 integrase in the 3′-end processing and the strand transfer step.

Graphical Abstract



Keywords Click chemistry · Diketo acids · HIV IN inhibitors · 2-Hydroxy-3-triazolylbenzoic acids · Metal ion binding

Introduction

HIV-1 integrase (IN), along with reverse transcriptase and protease, are encoded by HIV genome. HIV IN functions through catalyzing the insertion and integration of the proviral DNA into the genome of the host cell in 3′-end processing and strand transfer steps (LaFemina *et al.*, 1992; Chiu and Davies, 2004); therefore, it is essential for HIV-1 replication. Moreover, since there is no corresponding known human counterpart, HIV IN is regarded as a promising chemotherapeutical target to treat AIDS (Esposito and Craigie, 1999; Gupta and Nagappa, 2003; Anthony, 2004).

During the past decades, much attention has been paid to the design and synthesis of HIV IN inhibitors and a large number of compounds, with great structural diversity, have been synthesized and evaluated as possible HIV IN inhibitors, which lead to the discovery of many typical HIV IN inhibitors, including aryl β-diketo acids (such as s-1360 and L-708,906) (Fig. 1) (Hazuda *et al.*, 2004; Bacchi *et al.*, 2011a, b), styrylquinones (Fig. 1) (Mouscadet and Desmaele, 2010), polyhydroxylated aromatics (Wang *et al.*, 2009; Yang *et al.*, 2010; Reddy *et al.*, 1999) and oligonucleotides (Drake *et al.*, 1998; Jing *et al.*, 2000). Among these discoveries and advances, the most representative achievement is the disclosure of the keto-enol acid scaffold for the IN inhibitory activity, and the most successful one is the raltegravir (Fig. 1), the first integrase inhibitor (INI) approved by the Food and Drug Administration (FDA) for the treatment of AIDS (Evering and Markowitz, 2008; Temesgen and Siraj, 2008).

The general structure of aryl β-diketo acid inhibitors, taking L-708,906 as an example, is comprised of a pharmacophore(s) and an appending hydrophilic subunit(s) (Fig. 2, top) (Kawasuji *et al.*, 2006a, b). An indole ring or a benzene ring appended by one or two arylalkyl substituents is a typical hydrophobic moiety, which has a specific interaction with an adjacent hydrophobic pocket or surface. Meanwhile, the pharmacophore, typically being aryl diketo acid or its bioisoster, functions through a competitive binding of two divalent metallic ion in the IN active core, and thus blocking the access of a host DNA to the integrase enzyme.

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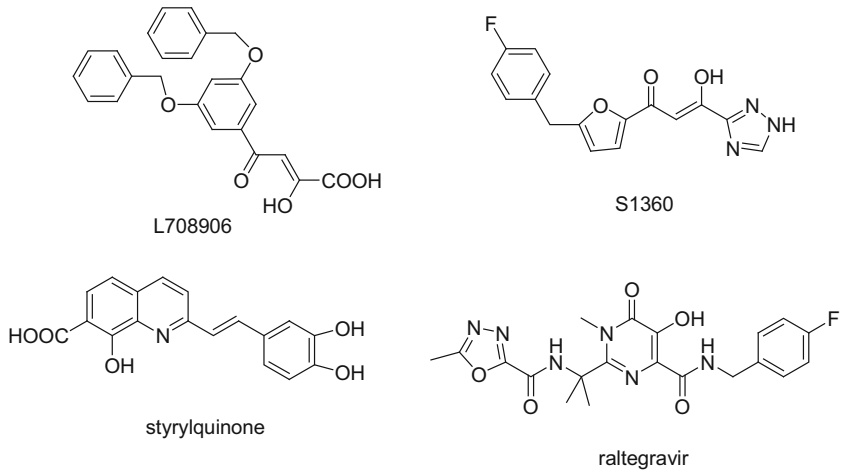


Fig. 1 The structures of some typical HIV IN inhibitors

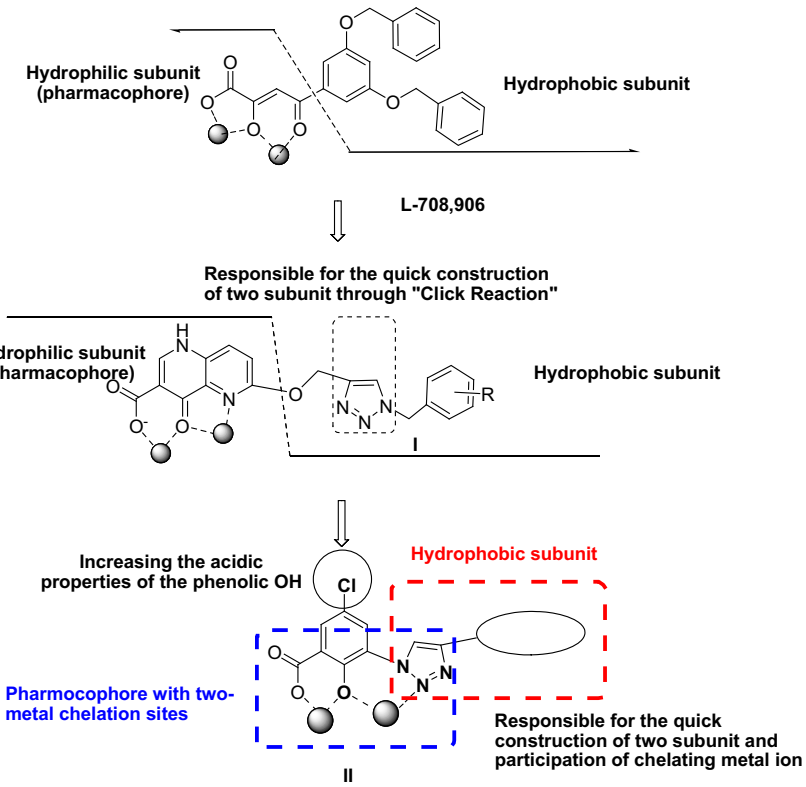


Fig. 2 Design of 5-chloro-2-hydroxy-3-triazolylbenzoic acids as HIV integrase inhibitors

Based on the understanding of the structural feature of diketo acid type of HIV IN inhibitors, we have carried out a project (Xu *et al.*, 2009; Zeng *et al.*, 2009) with the basic assumption that the development of HIV IN inhibitors can be in principle performed by a combination of appropriate pharmacophore and a hydrophobic moiety linked by an efficient method, such as click chemistry (Hou *et al.*, 2012; Bock *et al.*, 2005). In this regard, we have designed and synthesized a series of 1,4-dihydro-4-oxo-1,5-naphthyridine-3-carboxylic acid derivatives (see structure I in Fig. 1, middle) as potential HIV IN inhibitors; however, expected anti-HIV IN activity was not observed (Fig. 2, middle) (Zeng *et al.*, 2009).

Continuing on the basis of the previous project, we further modified structure I, the pharmacophore, to structure II, a 5-chloro-2-hydroxy-3-triazolylbenzoic acid subunit. In this design, the N-5 position of the former is replaced by an aromatic carbon atom and the fused pyridine ring is modified to be a triazolyl group (Fig. 2, bottom). We anticipate that the triazole ring plays a double role, namely, it does not only serve as a linker but would also participate in metal ion binding. In addition, to

increase the acidic properties of the phenolic OH at C-2 position, a chloride atom was introduced on the C-5 of the benzoic acid (Jiao *et al.*, 2010). Herein, we reported the synthesis of 5-chloro-2-hydroxy-3-triazolylbenzoic acids. The preliminary HIV IN inhibitory activity evaluation shows that some of these compounds can inhibit the replication of HIV-1 in vitro against integrase at micromolar concentration (Zeng *et al.*, 2010).

Results and discussion

The synthesis of 5-chloro-2-hydroxy-3-triazolylbenzoic acids **5** is depicted in Scheme 1. Nitration of 5-chloro-2-hydroxybenzoic acid **1** gave 5-chloro-2-hydroxy-3-nitrobenzoic acid **2**, which was reduced by $Na_2S_2O_4$ at room temperature to afford compound **3**. The key intermediate azidobenzoic acid **4** was produced in a good yield by using *tert*-butyl nitrite and azidotrimethylsilane under mild conditions (Barral *et al.*, 2007). Target 5-chloro-2-hydroxy-3-triazolylbenzoic acids **5a–5ad** were finally obtained in good to excellent yields by copper (I)-catalyzed Huisgen 1,3-dipolar cycloaddition of **4** and terminal alkynes (Scheme 1; Table 1).

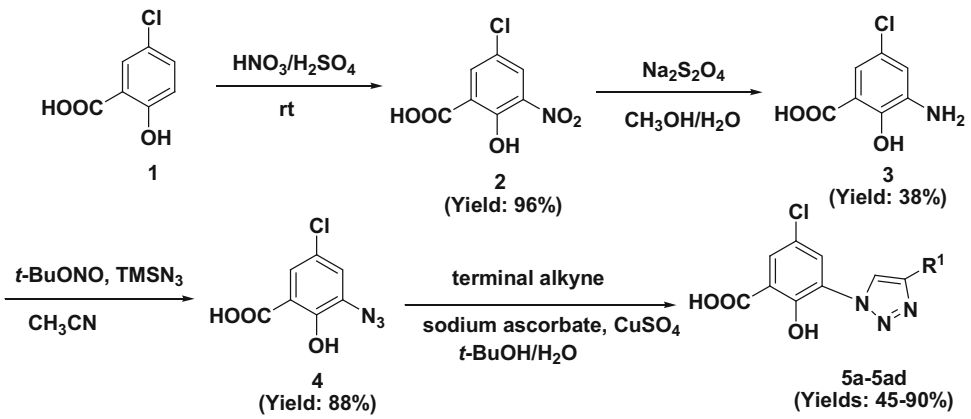
As mentioned above, we selected 5-chloro-2-hydroxy-3-triazolylbenzoic acid subunit as the pharmacophore wherein the triazole ring may function not only as part of the pharmacophore, but also as a linker to assemble the pharmacophore and hydrophobic unit. The hydrophobic subunit was the main modified moiety, and as a result, the designed target compounds **5a–5ad** differ only in the structure of the side chain attached to the triazolyl ring (both as a whole using as hydrophobic subunit). As shown in Table 1, for compound **5a**, a benzene ring appends directly to the triazole unit. In order to adjust its flexibility and improve the possible hydrophobic interaction with the hydrophobic pocket of HIV IN, the side chain of the target compounds is introduced through oxygen or nitrogen atom to the triazole ring. For example, **5b–5j** are substituted by phenoxymethyl groups and compounds **5k–5r** benzyloxymethyl groups, whereas, in the cases of **5t–5ad**, a dibenzylaminomethyl group is introduced (benzylaminomethyl for **5s**).

All title compounds **5a–5ad** were preliminarily tested against purified HIV IN to determine any possible inhibitory activity, and the results are summarized in Table 1. Under the activity evaluation conditions, the IC_{50} values of compounds L-708,906 and raltegravir are 28.0 and 0.00427 μg/mL, respectively, notably, the IC_{50} of L-708,906 for strand transfer is ~0.06 μM (Marchand *et al.*, 2003). It was observed that the HIV IN inhibitory effect of compound **5a** and most of the *O*-bridged compounds (**5b–5d** and **5g–5r**) were less than 50 % at an initial concentration of 20 μg/mL. Structurally, these *O*-bridged compounds possess only one side-chain (whereas two side-chain for L-708,906), which may lead to lower hydrophobic interaction with the hydrophobic pocket of HIV IN compared with the positive compound. To our delight, most of the *N*-bridged compounds (**5t–5v** and **5w–5ad**) exhibit a higher potency than L-708,906. For example, the IC_{50} of compound **5z** (bearing two *o*-fluorobenzyl groups) and **5ac** (bearing two *o*-bromobenzyl groups) are 17.5 μM and 12.8 μM, respectively. In addition, the corresponding **5p** (bearing one *o*-fluorobenzyl group) and **5r** (bearing one *o*-bromobenzyl group) show less than 50 % inhibitory effect at initial 20 μg/mL. As expected, this outcome may be the result of the increase in hydrophobic interaction of the *N*-bridged compounds with the hydrophobic pocket of HIV IN.

In addition, the screening results reveal that the IC_{50} of compounds **5v** and **5aa** are less than 6.0 μM, and the best result is afforded for *p*-bromophenoxy methyl triazolylbenzoic acid (**5f**), with an IC_{50} of 1.56 μM.

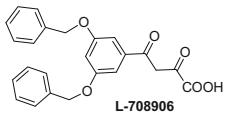
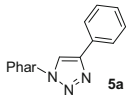
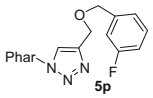
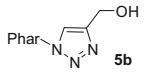
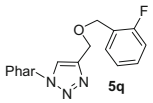
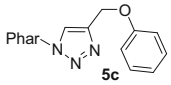
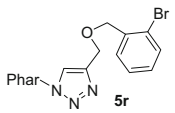
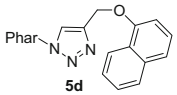
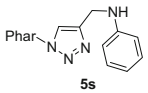
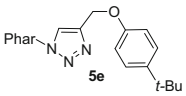
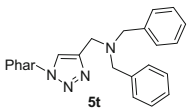
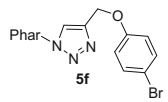
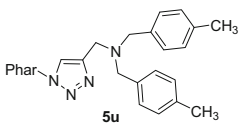
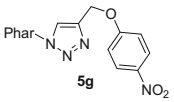
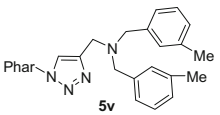
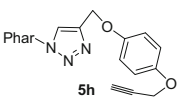
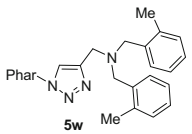
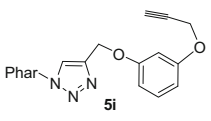
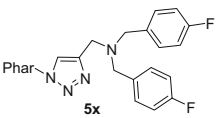
Conclusion

In summary, HIV IN inhibitors based on 5-chloro-2-hydroxy-3-triazolylbenzoic acid scaffold were designed; their



Scheme 1 Synthesis of 5-chloro-2-hydroxy-3-triazolylbenzoic acids **5a–5ad**

Table 1 Inhibitory activity results of target compounds **5a–5ad** in vitro

Structure of compound	IC_{50} (μg/mL)	Structure of compound	IC_{50} (μg/mL)
 L-708906	28.0	raltegravir	0.00427
 5a	–	 5p	–
 5b	–	 5q	–
 5c	–	 5r	–
 5d	29.1	 5s	33.1
 5e	21.6	 5t	26.3
 5f	1.56	 5u	18.4
 5g	–	 5v	3.50
 5h	–	 5w	23.7
 5i	–	 5x	19.0

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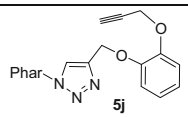
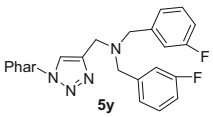
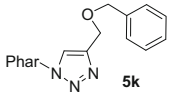
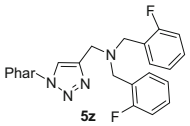
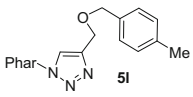
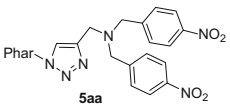
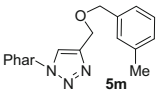
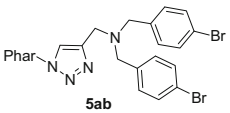
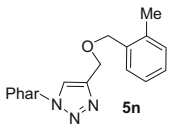
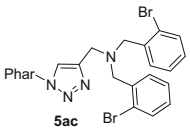
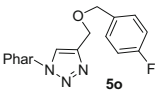
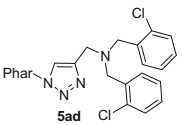
 5j	–	 5y	38.2
 5k	–	 5z	17.5
 5l	32.9	 5aa	5.70
 5m	–	 5ab	13.8
 5n	34.8	 5ac	12.8
 5o	49.3	 5ad	19.8

For clarity, *Phar* in the Table is referred to 5-chloro-2-hydroxy-benzoic acid

"–" The HIV-IN inhibitory effect was less than 50 % at the initial concentration of 20 μg/mL

synthesis follows a straightforward pathway by using a click chemistry reaction. Compared with *O*-bridged compounds, most of the *N*-bridged compounds inhibit replication of HIV -1 integrase more efficiently than the positive compound L-708,906. The work has demonstrated that our click chemistry reaction methodology has been quite useful in the design of HIV IN inhibitors, producing a promising new starting point for further optimization.

Experimental

Materials and methods

All melting points were measured using an XT4A electrothermal instrument equipped with a microscope and are uncorrected. Infrared spectra (IR) were measured as thin films on KBr plates on a Bruker IR spectrophotometer and are expressed in v (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on an AV 400M Bruker spectrometer (400 MHz for ^{1}H frequency, 100 MHz for ^{13}C frequency) in solvent ($CDCl_3$, CD_3OD or DMSO-d_6) with TMS as an internal reference. ESI–MS was measured on a Bruker esquire 6000 mass spectrometer. All solvents were available from commercial source and used directly without further purification. All starting terminal alkynes (Trost and Xie, 2006; Inamoto *et al.*, 2005; Dinges *et al.*, 2007; Ma *et al.*, 2005; Brouillette *et al.*, 1994) and compounds **2** (Musser *et al.*, 1985) and **3** (Von Plessing and Carlos, 1963) were synthesized according to known procedures. *Cautions for using $TMSN_3$*: to work in a fume hood with good ventilation.

*Synthesis of 3-azido-5-chloro-2-hydroxybenzoic acid (**4**)[31]*

In a 100-mL round-bottom flask was added 50 mL of acetonitrile containing 3-amino-5-chloro-2-hydroxybenzoic acid (0.94 g, 5 mmol) and cooled in an ice-water bath.

To the flask was added dropwise *t*-BuONO (7.5 mmol, 975 μL) and $TMSN_3$ (6 mmol, 755 μL). After stirring for about 30 min, the ice-water bath was removed and the stirring was continued for about 3 h. Upon completion, most of the solvents were evaporated under reduced pressure and the product then was precipitated to give gray solid. The reaction mixture was filtered and washed with petroleum ether and then water. After drying under vacuum, a red solid (938 mg) was obtained in 88 % yield. M.P.: 138–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35 (d, 1H, J = 2.8 Hz, Ar–*H*), 7.54 (d, 1H, J = 2.8 Hz, Ar–*H*), 12.41 (bs, 1H, COO*H*);^{13}C NMR (100 MHz, DMSO-d_6): δ 115.6, 122.9, 125.8, 125.9, 129.3, 153.7, 171.2; IR (KBr): ν 3,439.6, 2,135, 1,676, 1,464, 1,292, 1,232, 1,171 cm^{-1}; MS (ESI): *m/z* 211.6 [M−H]$^-$.

*The general procedure for the synthesis of 5-chloro-2-hydroxy-3-triazolylbenzoic acids (**5**)*

In a 250-mL three-necked round-bottom flask was added 20 mL of *tert*-butanol/water (*V*:*V* = 1:1) mixed solution containing 3-azido-5-chloro-2-hydroxybenzoic acid (427 mg, 2 mmol) and terminal alkyne (2.2 mmol). To this solution were then added sodium ascorbate (200 mg, 1 mmol, 50 % equiv.) and $CuSO_4{\cdot}5H_2O$ (50 mg, 0.2 mmol, 10 % equiv.). The reaction mixture was stirred for about 8–12 h at room temperature. The precipitate was filtered, washed with water and then petroleum ether, and dried under vacuum to give gray solid.

*5-Chloro-2-hydroxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)benzoic acid (**5a**)* Yield: 69 %; M.P.: 260–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 (t, 1H, J = 7.2 Hz, Ar–*H*), 7.47 (t, 2H, J = 7.6 Hz, Ar–*H*), 7.77 (d, 2H, Ar–*H*), 7.95 (d, 2H, J = 7.6 Hz, Ar–*H*), 9.12 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.5, 121.1, 124.3, 125.5, 125.9, 126.8, 128.6, 129.2, 130.8, 132.1, 148.4, 157.6, 169.5; IR (KBr): ν 3,437, 1,637, 1,469, 1,418, cm^{-1}; MS (ESI): *m/z* 313.6 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-[4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]benzoic acid (**5b**)* Yield: 52 %; M.P.: 175–177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.60 (s, 2H, OCH_2), 7.70–7.73 (m, 2H, Ar–*H*), 8.58 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.4, 117.7, 122.2, 124.2, 125.8, 126.6, 129.4, 148.1, 157.3, 169.7; IR (KBr): ν 3,435, 1,635 cm^{-1}; MS (ESI): *m/z* 267.5 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-[4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl]benzoic acid (**5c**)* Yield: 69 %; M. P.: 230–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.23 (s, 2H, OCH_2), 6.95 (t, 1H, J = 7.2 Hz, Ar–*H*), 7.07 (d, 2H, J = 8.0 Hz, Ar–*H*), 7.30 (t, 2H, J = 8.0 Hz, Ar–*H*), 7.91 (d, 1H, J = 2.8 Hz, Ar–*H*), 8.01 (d, 1H, J = 2.8 Hz, Ar–*H*), 8.69 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 61.2, 115.2, 121.4, 122.4, 126.8, 130.0, 130.3, 130.5, 143.4, 153.5, 158.5, 170.8; IR (KBr): ν 3,438, 2,927, 1,638, 1,472 cm^{-1}; MS (ESI): *m/z* 343.6 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-[4-(naphthalen-1-yloxymethyl-1H-1,2,3-triazol-1-yl)benzoic acid (**5d**)* Yield: 65 %; M. P.: 231–233 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.44 (s, 2H, OCH_2), 7.22–7.53 (m, 4H, Ar–H), 7.86 (d, 1H, J = 7.6 Hz, Ar–H), 7.91 (d, 1H, J = 2.4 Hz, Ar–H), 8.04 (d, 1H, J = 2.4 Hz, Ar–H), 8.13 (d, 1H, J = 8.4 Hz, Ar–H), 8.82 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 62.0, 106.4, 120.9, 122.0, 122.2, 125.4, 125.8, 126.6, 126.7, 126.8, 126.9, 127.9, 130.2, 130.5, 134.5, 143.4, 153.8, 154.0, 170.8; IR (KBr): ν 3,437, 1,634 cm^{-1}; MS (ESI): *m/z* 393.7 [M−H]$^-$; HRMS (ESI) calcd for $C_{20}H_{15}ClN_3O_4$ [M+H]: 396.0751, found: 396.0750.

*5-Chloro-2-hydroxy-3-[4-(4-tert-butylphenoxymethyl)-1H-1,2,3-triazol-1-yl]benzoic acid (**5e**)* Yield: 48 %; M. P.: 226–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (s, 9H, C(CH_3)$_3$), 5.19 (s, 2H, OCH_2), 6.98 (d, 2H, J = 8.8 Hz, Ar–*H*), 7.29 (d, 2H, J = 8.8 Hz, Ar–*H*), 7.83 (d, 1H, J = 2.0 Hz, Ar–*H*), 7.89 (d, 1H, J = 2.0 Hz, Ar–*H*), 8.74 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.8, 34.2, 61.4, 114.7, 120.2, 126.3, 126.6, 126.7, 128.4, 130.1, 143.3, 143.5, 155.4, 156.3, 170.8; IR (KBr): ν 3,436, 1,633 cm^{-1}; MS (ESI): *m/z* 399.7 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-[4-(4-bromophenoxymethyl)-1H-1,2,3-triazol-1-yl]benzoic acid (**5f**)* Yield: 90 %; M. P.: 234–236 °C; ^{1}H NMR (400 MHz, MeOH-d_4): δ 5.19 (s, 2H, OCH_2), 6.95 (d, 2H, J = 8.8 Hz, Ar–*H*), 7.38 (d, 2H, J = 8.4 Hz, Ar–*H*), 7.83 (s, 1H, Ar–*H*), 8.00 (s, 1H, Ar–*H*), 8.57 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 61.3, 115.3, 117.5, 121.2, 124.2, 125.6, 125.7, 126.7, 129.2, 130.5, 132.2, 148.6, 156.3, 170.1; IR (KBr): ν 3,437, 2,925, 1,639, 1,488, 1,469, 1,424, 1,384, 1,241, 1,173, 1,102, 1,074, 1,024, 886, 817, 776, 727, 527 cm^{-1}; MS (ESI): *m/z* 421.6 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-[4-(4-nitrophenoxymethyl)-1H-1,2,3-triazol-1-yl]benzoic acid (**5g**)* Yield: 71 %: M. P.: >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.41 (s, 2H, OCH_2), 7.31 (d, 2H, J = 8.4 Hz, Ar–*H*), 7.75 (s, 2H, Ar–*H*), 8.23 (d, 2H, J = 8.8 Hz, Ar–*H*), 8.90 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 62.3, 115.8, 118.0, 126.3, 126.4, 126.6, 129.9, 141.5, 141.9, 157.3, 163.8, 169.7; IR (KBr): ν 3,438, 1,637 cm^{-1}; MS (ESI): *m/z* 388.6 [M−H]$^-$; HRMS (ESI) calcd for $C_{16}H_{12}ClN_4O_6$ [M+H]: 391.0445, found: 396.0509.

*5-Chloro-2-hydroxy-3-{4-[(4-prop-2-ynyloxy)phenoxy]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5h**)* Yield: 42 %; M. P.: 217–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.51 (t,

1H, $J = 2.4$ Hz, ≡ C–*H*), 4.72 (d, 2H, $J = 2.4$ Hz, ≡ C–CH_2), 5.17 (s, 2H, OCH_2), 6.94 (d, 2H, $J = 8.8$ Hz, Ar–*H*), 7.02 (d, 2H, $J = 8.8$ Hz, Ar–*H*), 7.76 (s, 2H, Ar–*H*), 8.80 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.4, 61.9, 78.4, 80.0, 116.1, 116.4, 117.6, 122.1, 126.0, 126.1, 126.5, 129.7, 143.0, 152.0, 153.1, 157.6, 169.6; IR (KBr):ν 3,436, 1,637, 1,507 cm^{-1}; MS (ESI): *m/z* 397.6 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-{4-[(3-prop-2-ynyloxy)phenoxy]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5i**)* Yield: 80 %; M. P.: 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.53 (t, 1H, $J = 2.4$ Hz, ≡ C–*H*), 4.78 (d, 2H, $J = 2.4$ Hz, ≡ C–CH_2), 5.22 (s, 2H, OCH_2), 6.59–6.61 (m, 1H, Ar–*H*), 6.70 (s, 1H, Ar–H), 6.71–6.72 (m, 1H, Ar–*H*), 7.22 (t, 1H, $J = 8.4$ Hz, Ar–*H*), 7.76 (d, 1H, $J = 2.8$ Hz, Ar–*H*), 7.78 (d, 1H, $J = 2.8$ Hz, Ar–*H*), 8.82 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.0, 61.6, 78.7, 79.8, 102.5, 108.1, 117.8, 122.2, 126.2, 126.3, 126.5, 129.8, 130.5, 142.8, 157.5, 159.0, 159.8, 169.7; IR (KBr): ν 3,437, 1,636, 1,469 cm^{-1}; MS (ESI): *m/z* 397.6 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-{4-[(2-prop-2-ynyloxy)phenoxy]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5j**)* Yield: 56 %; M. P.: 206–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.50 (t, 1H, $J = 2.4$ Hz, ≡ C–*H*), 4.78 (d, 2H, $J = 2.4$ Hz, ≡ C–CH_2), 5.23 (s, 2H, OCH_2), 6.93–7.24 (m, 4H, Ar–*H*), 7.78 (s, 2H, Ar–*H*), 8.82 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.6, 62.1, 78.6, 79.9, 114.8, 115.3, 117.9, 121.6, 121.9, 122.3, 126.2, 126.3, 126.5, 129.8, 142.9, 147.4, 148.6, 157.4, 169.7; IR (KBr): ν 3,437, 1,637, 1,502 cm^{-1}; MS (ESI): *m/z* 397.6 [M−H]$^-$;

*5-Chloro-2-hydroxy-3-[4-(benzyloxymethyl-1H-1,2,3-triazol-1-yl)]benzoic acid (**5k**)* Yield: 85 %; M. P.: 225–227 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.59 (s, 2H, OCH_2Ar), 4.69 (s, 2H, OCH$_2$), 7.31–7.38 (m, 5H, Ar–*H*), 7.93–7.99 (m, 2H, Ar–*H*), 8.68 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 63.2, 71.8, 127.9, 127.9, 128.1, 128.6, 128.7, 138.5, 169.7; IR (KBr): ν 3,436, 1,638, 1,471 cm^{-1}; MS (ESI): *m/z* 357.8 [M−H]$^-$, 359.8 [M+H]$^+$, HRMS: *m/z* calcd for $C_{17}H_{14}N_3O_4Cl$: 358.06001; found: 358.0590.

*5-Chloro-2-hydroxy-3-{4-[(4-methylbenzyloxy)methyl]-1H-1,2,3-triazol-1-yl}benzoic acid (**5l**)* Yield: 63 %; M. P.: 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3H, Ar–CH_3), 4.53 (s, 2H, OCH_2Ar), 4.65 (s, 2H, OCH_2), 7.17 (d, 2H, $J = 7.6$ Hz, Ar–*H*), 7.25 (d, 2H, $J = 8.0$ Hz, Ar–*H*), 7.87 (s, 1H, Ar–*H*), 7.93 (s, 1H, Ar–*H*), 8.64 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2, 63.1, 72.0, 120.5, 125.2, 126.1, 128.5, 128.6, 128.7, 130.0, 130.1, 137.8, 138.5, 155.3, 170.1; IR (KBr): ν 3,436, 1,636, 1,471 cm^{-1}; MS (ESI): *m/z* 371.8 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-{4-[(3-methylbenzyloxy)methyl]-1H-1,2,3-triazol-1-yl}benzoic acid (**5m**)* Yield: 69 %; M. P.: 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H, Ar–CH_3), 4.55 (s, 2H, OCH_2Ar), 4.67 (s, 2H, OCH_2), 7.10–7.17 (m, 3H, Ar–*H*), 7.25 (t, 1H, $J = 7.2$ Hz, Ar–*H*), 7.86 (s, 1H, Ar–*H*), 7.93 (s, 1H, Ar–*H*), 8.64 (s, 1H, Ar–*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.4, 63.2, 71.8, 120.7, 125.2, 126.0, 128.6, 128.6, 128.7, 128.9, 130.1, 137.8, 138.5, 155.0, 170.2; IR (KBr): ν 3,436, 1,637, 1,472, 1,423 cm^{-1}; MS (ESI): *m/z* 371.6 [M−H]$^-$; HRMS (ESI) calcd for $C_{18}H_{17}ClN_3O_4$ [M+H]: 374.0908, found: 374.0894.

*5-Chloro-2-hydroxy-3-{4-[(2-methylbenzyloxy)methyl]-1H-1,2,3-triazol-1-yl}benzoic acid (**5n**)* Yield: 54 %; M. P.: 195–197 °C; ^{1}H NMR (400 MHz, DMSO-d6): δ 2.27 (s, 3H, Ar–*CH$_3$*), 4.58 (s, 2H, OCH_2Ar), 4.68 (s, 2H, OCH_2), 7.18–7.34 (m, 4H, Ar–*H*), 7.86 (d, 1H, $J = 2.4$ Hz, Ar–*H*), 7.93 (d, 1H, $J = 2.4$ Hz, Ar–*H*),8.63 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.8, 63.2, 70.3, 121.2, 125.9, 126.0, 126.7, 128.1, 128.9, 129.0, 130.2, 130.4, 136.5, 136.8, 144.5, 154.5, 170.5; IR (KBr): *v* 3,437, 1,637, 1,471, 1,422 cm^{-1}; MS (ESI): *m/z* 371.8 [M−H]$^-$; HRMS (ESI) calcd for $C_{18}H_{17}ClN_3O_4$ [M+H]: 374.0908, found: 374.0886.

*5-Chloro-2-hydroxy-3-{4-[(4-fluorobenzyloxy)methyl]-1H-1,2,3-triazol-1-yl}benzoic acid (**5o**)* Yield: 51 %; M. P.: 201–203 °C; ^{1}H NMR (400 MHz, CD$_3$OD): δ 4.60 (s, 2H, OCH_2Ar), 4.72 (s, 2H, OCH$_2$), 7.05–7.09 (m, 2H, Ar–*H*), 7.38–7.41 (m, 2H, Ar–*H*), 7.85 (s, 1H, Ar–*H*), 8.02 (s, 1H, Ar–*H*), 8.52 (s, 1H, triazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 63.2, 71.0, 115.4, 115.6, 120.0, 126.3, 127.0, 128.0, 130.2, 130.3, 134.8, 134.8, 155.4, 160.8, 163.3, 170.3; IR (KBr): *v* 3,437, 1,638, 1,511,1,471 cm^{-1}; MS (ESI): *m/z* 375.9 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-{4-[(3-fluorobenzyloxy)methyl]-1H-1,2,3-triazol-1-yl}benzoic acid (**5p**)* Yield: 67 %; M.P.: 204–206 °C; ^{1}H NMR (400 MHz, DMSO-d6): δ 4.61 (s, 2H, OCH_2Ar), 4.70 (s, 2H, OCH_2), 7.12–7.41 (m, 4H, Ar–*H*), 7.92 (s, 1H, Ar–*H*), 8.02 (s, 1H, Ar–*H*), 8.63 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 63.1, 71.2, 115.3, 115.7, 120.2, 126.1, 127.0, 128.2, 130.1, 130.3, 134.7, 134.8, 155.3, 160.9, 163.1, 170.0; IR (KBr): ν 3,437, 1,638, 1,471 cm^{-1}; MS (ESI): *m/z* 375.8 [M−H]$^-$.

*5-Chloro-2-hydroxy-3-{4-[(2-fluorobenzyloxy)methyl]-1H-1,2,3-triazol-1-yl}benzoic acid (**5q**)* Yield: 53 %; M.P. 208–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.62 (s, 2H, OCH_2Ar), 4.67 (s, 2H, OCH_2), 7.18–7.48 (m, 4H, *Ar–H*), 7.73–7.74 (m, 2H, Ar–*H*), 8.71 (s, 1H, triazole-*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ 63.4, 65.5, 115.6, 119.7, 120.6, 124.8, 125.4, 126.4, 128.7, 129.6, 130.8. 135.6,

144.2, 155.0, 159.5, 162.0, 170.3; IR (KBr): ν 3,444, 1,639, 1,466, 1,420 cm^{-1}; MS (ESI): *m/z* 375.7 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[(2-bromobenzyloxy)methyl]-1H-1,2,3-triazol-1-yl}benzoic acid (**5r**)* Yield: 48 %; M. P.: 189–191 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 4.63 (s, 2H, OCH_2Ar), 4.75 (s, 2H, OCH_2), 7.25 (t, 1H, $J = 7.6$ Hz, Ar–H), 7.40 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.53 (d, 1H, $J = 7.2$ Hz, Ar–H), 7.60 (d, 1H, $J = 7.6$ Hz, Ar–H), 7.83 (s, 1H, *Ar–H*), 7.85 (s, 1H, Ar–H), 8.71 (s, 1H, triazole-H); ^{13}C NMR (DMSO-d_6): δ 63.7, 71.3, 119.5, 122.7, 125.9, 126.7, 127.6, 128.2, 129.9, 132.8, 137.6, 156.1, 169.5; IR (KBr): ν 3,437, 1,638, 1,469 cm^{-1}; MS (ESI): *m/z* 435.7 $[M-H]^-$; HRMS (ESI) calcd for $C_{17}H_{12}BrClN_3O_4$ [M−H]: 435.9700, found: 435.9710.

*5-Chloro-2-hydroxy-3-[4-(phenylaminomethyl)-1H-1,2,3-triazol-1-yl]benzoic acid (**5s**)* Yield: 90 %; M.P.: 177–179 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 4.38 (s, 2H, NCH_2), 6.11 (s, 1H, N–*H*), 6.53–7.09 (m, 5H, Ar–*H*), 7.75 (s, 2H, Ar–*H*), 8.62 (s, 1H, triazole-H); ^{13}C NMR (DMSO-d_6): δ 39.0, 112.9, 116.6, 117.8, 124.2, 125.6, 126.6, 129.3, 129.4, 146.0, 148.8, 157.1, 169.7; IR (KBr): ν 3,436, 1,637, 1,578, 1,507 cm^{-1}; MS (ESI): *m/z* 342.6 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-[4-(N,N-dibenzylamino)methyl-1H-1,2,3-triazol-1-yl]benzoic acid (**5t**)* Yield: 47 %; M.P.: 171–172 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 4.21 (s, 4H, *Ar–*CH_2), 4.32 (s, 2H, *N–*CH_2), 7.44–7.54 (m, 10H, Ar–*H*), 7.77 (d, 1H, $J = 2.8$ Hz, Ar–*H*), 7.86 (s, 1H, $J = 2.8$ Hz, Ar–*H*), 8.93 (s, 1H, triazole-H); ^{13}C NMR (DMSO-d_6): δ 46.8, 56.6, 118.5, 120.9, 126.4, 126.8, 128.1, 129.2, 129.5, 129.9, 131.2, 138.9, 139.0, 156.8, 169.8; IR (KBr): ν 3,440, 1,638, 1,501, 1,467, 1,425 cm^{-1}; MS (ESI): *m/z.* 447.1 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(4-methylbenzyl)amino]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5u**)* Yield: 66 %; M. P.: 144–146 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 6H, Ar–CH_3), 4.18 (s, 4H, Ar–CH_2), 4.29 (s, 2H, N–CH_2), 7.26 (d, 2H, $J = 7.2$ Hz, Ar–*H*), 7.41 (d, 2H, $J = 7.2$ Hz, Ar–*H*), 7.75 (s, 1H, Ar–*H*), 7.82 (s, 1H, Ar–*H*), 8.89 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 21.3, 46.5, 56.3, 117.8, 126.2, 126.4, 129.5, 129.7, 129.8, 130.0, 130.4, 131.3, 138.9, 139.0, 157.5, 169.5; IR (KBr): ν 3,437, 1,637, 1,502, 1,468, 1,424 cm^{-1}; MS (ESI): *m/z* 474.8 $[M-H]^-$, 476.9 $[M+H]^+$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(3-methylbenzyl)amino]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5v**)* Yield: 45 %; M. P.: 108–109 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 6H, $2CH_3$), 4.33–4.35 (s, br, 6H, *Ar–*CH_2, *N–*CH_2), 7.24–7.45 (m, 8H, Ar–*H*), 8.13 (s, 2H, Ar–*H*), 9.03 (s, 1H, triazole-*H*), 14.8 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 21.4, 46.9, 56.7, 117.8, 121.3, 126.3, 126.4, 128.3, 128.5, 128.8, 129.1, 129.8, 130.1, 131.8, 138.0, 138.5, 157.5, 169.6; IR (KBr): ν 3,441, 1,637, 1,502, 1,465, 1,425 cm^{-1}; MS (ESI): *m/z* 475.2 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(2-methylbenzyl)amino]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5w**)* Yield: 48 %; M. P.: 132–133 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 2.11 (s, 6H, $2CH_3$), 4.02–4.15 (s, br, 6H, *Ar–*CH_2, *N–*CH_2), 7.24–7.58 (m, 8H, Ar–*H*), 7.81 (s, 1H, Ar–*H*), 7.91 (s, 1H, Ar–*H*), 8.95 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 19.1, 47.6, 54.3, 119.3, 126.4, 126.7, 127.5, 128.0, 129.1, 130.0, 131.1, 131.8, 138.6, 157.6, 169.3.; IR (KBr): ν 3,435, 1,640, 1,503, 1,467, 1,423 cm^{-1}; MS (ESI): *m/z.* 475.2 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(4-fluorobenzyl)amino]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5x**)* Yield: 48 %; M. P.: 197–198 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 4.13–4.15 (s, br, 6H, *Ar–*CH_2, *N–*CH_2), 7.24–7.56 (m, 8H, Ar–*H*), 7.79 (s, 1H, Ar–*H*), 7.86 (s, 1H, Ar–*H*), 8.86 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 46.6, 55.5, 115.9, 116.1, 118.8, 126.9, 128.2, 129.3, 130.9, 132.3, 133.2, 155.7, 161.5, 163.9, 170.2; IR (KBr): ν 3,445, 1,635, 1,500, 1,465, 1,423 cm^{-1}; MS (ESI): *m/z* 483.1 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(3-fluorobenzyl)amino]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5y**)* Yield: 52 %; M. P.: 204–205 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 4.01 (s, 4H, *Ar–*CH_2), 4.13 (s, 2H, *N–*CH_2), 7.20–7.65 (m, 8H, Ar–*H*), 7.85 (s, 1H, Ar–*H*), 7.94 (s, 1H, Ar–*H*), 8.76 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 46.5, 55.6, 115.6, 116.1, 118.8, 126.9, 128.2, 129.3, 130.9, 134.7, 134.9, 155.7, 161.2, 163.3, 170.0; IR (KBr): ν 3,437, 1,636, 1,503, 1,468, 1,423 cm^{-1}; MS (ESI): *m/z* 483.1 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(2-fluorobenzyl)amino]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5z**)* Yield: 66 %; M.P.: 212–213 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 4.02 (s, 4H, *Ar–*CH_2), 4.12 (s, 2H, *N–*CH_2), 7.17–7.48 (m, 8H, Ar–*H*), 7.85 (s, 1H, Ar–*H*), 7.92 (s, 1H, Ar–*H*), 8.77 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 46.7, 55.4, 115.7, 116.2, 118.7, 126.9, 128.3, 129.4, 130.9, 134.6, 134.8, 155.5, 161.5, 163.4, 170.1; IR (KBr): ν 3,441, 1,637, 1,502, 1,465, 1,428 cm^{-1}; MS (ESI): *m/z.* 483.1 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(4-nitrobenzyl)amino]methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5aa**)* Yield: 56 %; M.P.: 225–226 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 3.81 (s, br, 6H, *Ar–*CH_2, *N–*CH_2), 7.72 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.86 (s, 2H, Ar–*H*), 8.20 (d, 4H, $J = 8.4$ Hz, Ar–H), 8.65 (s, 1H, triazole-*H*); ^{13}C NMR

(DMSO-d_6): δ 47.8, 56.8, 121.4, 123.9, 126.5, 126.9, 129.3, 130.2, 130.5, 146.7, 147.2, 154.4, 170.1; IR (KBr): ν 3,440, 1,638, 1,501, 1,467, 1,423 cm^{-1}; MS (ESI): *m/z* 537.1 $[M-H]^-$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(4-bromobenzyl)amino] methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5ab**)* Yield: 62 %; M.P.: 135–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.02 (s, 4H, *Ar–CH_2*), 4.13 (s, 2H, *N–CH_2*), 7.46 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.62 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.82 (d, 1H, $J = 2.8$ Hz, Ar–*H*), 7.89 (d, 1H, $J = 2.8$ Hz, Ar–*H*), 8.75 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 47.8, 56.1, 119.6, 119.7, 122.2, 126.5, 127.5, 127.8, 130.0, 132.0, 132.8, 139.4, 155.8, 170.1; IR (KBr): ν 3,439, 1,636, 1,503, 1,465, 1,428 cm^{-1}; MS (ESI): *m/z* 604.9 $[M+H]^+$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(2-bromobenzyl)amino] methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5ac**)* Yield: 56 %; M.P.: 175–177 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 4H, *Ar–CH_2*), 3.93 (s, 2H, *N–CH_2*), 7.18–7.70 (m, 8H, Ar–*H*), 7.88 (s, 1H, Ar–*H*), 7.97 (s, 1H, Ar–*H*), 8.65 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 48.1, 54.4, 119.3, 120.4, 121.7, 127.5, 128.3, 129.5, 129.8, 130.2, 131.6, 133.9, 134.5, 134.6, 138.5, 157.9, 170.1; IR (KBr): ν 3,441, 1,640, 1,503, 1,470, 1,425 cm^{-1}; MS (ESI): *m/z* 604.9 $[M+H]^+$.

*5-Chloro-2-hydroxy-3-{4-[N,N-bis(2-chlorobenzyl)amino] methyl-1H-1,2,3-triazol-1-yl}benzoic acid (**5ad**)* Yield: 54 %; M.P.: 201–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.90 (s, 4H, *Ar–CH_2*), 3.98 (s, 2H, *N–CH_2*), 7.28–7.71 (m, 8H, Ar–*H*), 7.88 (s, 1H, Ar–*H*), 7.98 (s, 1H, Ar–*H*), 8.67 (s, 1H, triazole-*H*); ^{13}C NMR (DMSO-d_6): δ 48.2, 54.4, 119.4, 120.3, 121.7, 127.6, 128.4, 129.6, 129.8, 130.1, 131.7, 133.9, 134.6, 134.7, 138.7, 157.9, 170.2; IR (KBr): ν 3,439, 1,640, 1,503, 1,465, 1,423 cm^{-1}; MS (ESI): *m/z* 515.1 $[M-H]^-$.

HIV IN inhibitory activity screening

The possible HIV IN inhibitory activity of all desired compounds was evaluated by a procedure developed by us (Zeng *et al.*, 2009). The detail is as follows: A synthesized 30 oligonucleotide and a 20 oligonucleotide, purchased from Shanghai Sangon Biological Engineering Technology & Services Co. Ltd., were used as donor DNA and target DNA, respectively. The donor DNA was biotinylated at the 5′ end (5′ bio-DNA) and immobilized on streptavidin-coated 96-well microtiter plates. After addition of desired compound, 3′ digoxigenin-labeled target DNA (3′ dig-DNA) and recombinant HIV integrase, the plate was subjected to incubation in optimized condition.

After incubation, the plate was washed using phosphate-buffered saline (PBS) containing 0.1 % Tween 20, and then 100 μL of antidigoxigenin peroxidase (POD) was added to each well. After incubation at 37 °C for 60 min, the plates were washed by PBS again. The digoxigenin-labeled products were visualized by adding tetramethylbenzidine (TMB) and a POD substrate. H_2SO_4 (0.5 M, 100 μL) was added to stop the colorimetric reaction. The absorbance intensity was recorded at 450 nm by a microplate reader, and finally total inhibitory effect (including inhibiting 3′-end process reaction and strand transfer reaction) was obtained by comparing the absorbance of drug group with that of control group (without test compound).

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

References

Anthony NJ (2004) HIV-1 integrase: a target for new AIDS chemotherapeutics. Curr Top Med Chem 4:979–990

Bacchi A, Carcelli M, Compari C, Fisicaro E, Pala N, Rispoli G, Rogolino D, Sanchez TW, Sechi M, Neamati N (2011a) HIV-1 IN strand transfer chelating inhibitors: a focus on metal binding. Mol Pharm 8:507–519

Bacchi A, Carcelli M, Compari C, Fisicaro E, Pala N, Rispoli G, Rogolino D, Sanchez TW, Sechi M, Sinisi V, Neamati N (2011b) Investigating the role of metal chelation in HIV-1 integrase strand transfer inhibitors. J Med Chem 54:8407–8420

Barral K, Moorhouse AD, Moses JE (2007) Efficient conversion of aromatic amines into azides: a one-pot synthesis of triazole linkages. Org Lett 9:1809–1811

Bock VD, Hiemstra H, van Maarseveen JH (2005) Cu(I)-catalyzed alkyne-azide click cycloadditions from a mechanistic and synthetic perspective. Eur J Org Chem 2006:51–68

Brouillette WJ, Saeed A, Abuelyaman A, Hutchison TL, Wolkowicz PE, McMillin JB (1994) Synthesis and enzymic evaluation of conformationally defined carnitine analogs. J Org Chem 59:4297–4303

Chiu TK, Davies DR (2004) Structure and function of HIV-1 integrase. Curr Top Med Chem 4:965–977

Dinges J, Albert DH, Arnold LD, Ashworth KL, Akritopoulou-Zanze I, Bousquet PF, Bouska JJ, Cunha GA, Davidsen SK, Diaz GJ, Djuric SW, Gasiecki AF, Gintant GA, Gracias VJ, Harris CM, Houseman KA, Hutchins CW, Johnson EF, Li H, Marcotte PA, Martin RL, Michaelides MR, Nyein M, Sowin TJ, Su Z, Tapang PH, Xia Z, Zhang HQ (2007) 1,4-Dihydroindeno[1,2-c]pyrazoles with acetylenic side chains as novel and potent multitargeted receptor tyrosine kinase inhibitors with low affinity for the hERG ion channel. J Med Chem 50:2011–2029

Drake R, Neamati N, Hong H (1998) Identification of a nucleotide binding site in HIV-1 integrase. Proc Natl Acad Sci USA 95:4170–4175

Esposito D, Craigie R (1999) HIV integrase structure and function. Adv Virus Res 52:319–333

Evering TH, Markowitz M (2008) Raltegravir: an integrase inhibitor for HIV-1. Expert Opin Invest Drug 17:413–422

Gupta SP, Nagappa AN (2003) Design and development of integrase inhibitors as anti-HIV agents. Curr Med Chem 10:1779–1794

Hazuda DJ, Yong SD, Guare JP, Anthony NJ, Gomez RP, Wai JS, Vacca JP, Handt L, Motzel SL, Klein HJ, Tussey L, Schleif WA, Gabryelski LS, Jin L, Miller MD, Casimiro DR, Emini EA, Shiver JW (2004) Integrase inhibitors and cellular immunity suppress retroviral replication in Rhesus Macaques. Science 305:528–532

Hou JL, Liu XF, Shen J, Zhao GL, Wang PG (2012) The impact of click chemistry in medicinal chemistry. Expert Opin Drug Discov 7:489–501

Inamoto K, Yamamoto A, Ohsawa K, Hiroya K, Sakamoto T (2005) Highly regioselective palladium-catalyzed annulation reactions of heteroatom-substituted allenes for synthesis of condensed heterocycles. Chem Pharm Bull 53:1502–1507

Jiao ZG, He HQ, Zeng CC, Tan JJ, Hu LM, Wang CX (2010) Design, synthesis and anti-HIV integrase evaluation of N-(5-chloro-8-hydroxy-2-styrylquinoline-7-yl)benzenesulfonamide derivatives. Molecules 15:1903–1917

Jing N, Marchad C, Liu J (2000) Mechanism of inhibition of HIV-1 integrase by G-tetrad-forming oligonucleotides in vitro. J Biol Chem 275:21460–21467

Kawasuji T, Fuji M, Yoshinaga T, Sato A, Fujiwara T, Kiyama R (2006a) A platform for designing HIV integrase inhibitors. a two-metal binding model as a potential mechanism of HIV integrase inhibitors. Bioorganic Med Chem 14:8420–8429

Kawasuji T, Yoshinaga T, Sato A, Yodo M, Fujiwara T, Kiyama R (2006b) A platform for designing HIV integrase inhibitors. 2-Hydroxy-3-heteroaryl acrylic acid derivatives as novel HIV integrase inhibitor and modeling of hydrophilic and hydrophobic pharmacophores. Bioorganic Med Chem 14:8430–8445

LaFemina RL, Schneider CL, Robbins HL, Callahan PL, LeGrow K, Roth E, Schleif WA, Emini EA (1992) Requirement of active human immunodeficiency virus type 1 integrase enzyme for productive infection of human T-lymphoid cells. J Virol 66:7414–7419

Ma SM, Wu B, Jiang XF (2005) $PdCl_2$-catalyzed efficient transformation of propargylic amines to (E)-α-chloroalkylidene-β-lactams. J Org Chem 70:2588–2593

Marchand C, Christophe AA, Karki RG, Pais GC, Zhang XC, Cowansage K, Patel TA, Nicklaus MC, Burke TR, Pommier Y (2003) Metal-dependent inhibition of HIV-1 integrase by β-diketo acids and resistance of the soluble double-mutant (F185K/C280S). Mol Pharm 64:600–609

Mouscadet JF, Desmaele D (2010) Chemistry and structure-activity relationship of the styrylquinoline-type HIV integrase inhibitors. Molecules 15:3048–3078

Musser JH, Jones H, Sciortino S, Bailey K, Coutts SM, Khandwala A, Sonnino-Goldman P, Leibowitz M, Wolf P, Neiss ES (1985) Synthesis and antiallergic activities of 1,3-oxazolo[4,5-h]quinolines. J Med Chem 28:1255–1259

Reddy MV, Rao MR, Rhodes D, Hansen MS, Rubins K, Bushman FD, Venkateswarlu Y, Faulkner DJ (1999) Lamellarin α 20-sulfate, an inhibitor of HIV-1 integrase active against HIV-1 virus in cell culture. J Med Chem 42:1901–1907

Temesgen Z, Siraj DS (2008) Raltegravir: first in class HIV integrase inhibitor. Ther Clin Risk Manag 4:493–500

Trost BM, Xie J (2006) Palladium-catalyzed asymmetric ring expansion of allenylcyclobutanols: an asymmetric Wagner-Meerwein shift. J Am Chem Soc 128:6044–6045

Von Plessing B, Carlos (1963) Derivatives of 5-chlorosalicylic acid. Farm Nueva (Madrid) 28:439–446

Wang P, Liu C, Sanches T, Zhong Y, Liu B, Xiong J, Neamato N, Zhao GS (2009) Design and synthesis of novel nitrogen-containing polyhydroxylated aromatics as HIV-1 integrase inhibitors from caffeic acid phenethyl ester. Bioorganic Med Chem Lett 19:4574–4578

Xu YS, Zeng CC, Jiao ZG, Hu LM, Zhong RG (2009) Design, synthesis and anti-HIV integrase evaluation of 4-Oxo-4H-quinolizine-3-carboxylic acid derivatives. Molecules 14:868–883

Yang LF, Xu XM, Huang YL, Zhang B, Zeng CC, He HQ, Wang CX, Hu LM (2010) Synthesis of polyhydroxylated aromatics having amidation of piperazine nitrogen as HIV-1 integrase inhibitor. Bioorganic Med Chem Lett 20:5469–5471

Zeng J, Lu XH, Zeng CC, Hu LM, Zhong RG (2009) Design, synthesis and anti-HIV integrase evaluation of 1,2,3-triazol-4-yl-substituted 1,4-dihydro-4-oxo-1,5-naphthyridine-3-carboxylic acids. Chin J Chem 27:953–962

Zeng CC, Yang CW, Liu CF, Hu LM, Sheng W (2010) Preparation of 5-chloro-2-hydroxy-3-(4-substituted-1*H*-1,2,3-triazolyl)benzoic acid derivatives as HIV-1 integrase inhibitors Faming Zhuanli Shenqing, CN 101812028 A 20100825