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Original article

Design, synthesis and structure–activity relationship of novel inhibitors against H5N1 hemagglutinin-mediated membrane fusion

Zhibo Zhu [a,1], Runming Li [a,b,1], Gaokeng Xiao [c], Zhipeng Chen [a], Jie Yang [a], Qiuhua Zhu [a], Shuwen Liu [a,*]

[a] School of Pharmaceutical Sciences, Southern Medical University, 1838 Guangzhou Avenue North, Guangzhou 510515, China
[b] Guangzhou Baidi Biotechnology Co. Ltd, Guangzhou 511495, China
[c] Institute of Traditional Chinese Medicine and Natural Products, Guangdong Province Key Laboratory of Pharmacodynamic Constituents of TCM and New Drugs Research, Jinan University, Guangzhou 510632, China

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ABSTRACT

We reported previously that a small molecule named CL-385319 could inhibit H5N1 influenza virus infection by targeting hemagglutinin, the envelope protein mediating virus entry. In the present study, a novel series of derivatives focused on the structural variation of CL-385319 were synthesized as specific inhibitors against the H5 subtype of influenza A viruses. These small molecules inhibited the low pH-induced conformational change of hemagglutinin, thereby blocking viral entry into host cells. Compound **1l** was the most active inhibitor in this series with an IC_{50} of 0.22 μM. The structure–activity relationships analysis of these compounds showed that the 3-fluoro-5-(trifluoromethyl)benzamide moiety was very important for activity, and the –F group was a better substituent group than $-CF_3$ group in the phenyl ring. The inhibitory activity was sensitive to the benzamide because the oxygen and hydrogen of the amide served as H-bond acceptor and donor, respectively.

1. Introduction

The H5N1 avian influenza A virus which caused significant morbidity and mortality is a serious threat to human health and has potential human-to-human transmission in the near future. Currently, only four drugs are available for the prevention and treatment of influenza virus, which fall into two categories, the M2 ion channel blockers and neuraminidase (NA) inhibitors [1]. However, most of the isolated H5N1 influenza A virus strains are now resistant to M2 inhibitors, and may rapidly develop resistance to NA inhibitors [2–5]. Therefore, it is urgently needed to develop new antiviral drugs, especially those with new mechanisms of action.

An effective antiviral strategy is to block virus entry into the target cell. Hemagglutinin (HA), the envelope protein of influenza A virus, is the key protein mediating influenza virus entry and is a target for developing influenza virus entry inhibitors. HA is a trimeric envelope glycoprotein, which can be cleaved into HA1 and HA2 subunits by host proteases [6]. The entry step of virus infection is initiated by HA1 binding to sialic acid receptor on the target cell membrane. The virion is then internalized to the endosome by endocytosis. The low endosomal pH leads to an irreversible conformational change of HA2 protein, resulting in the membrane fusion. Several small molecules, such as stachyflin [7], BMY-27709 [8] and CL-385319 [9], can stabilize the conformation of HA2 at neutral pH or destabilize the HA2 structure at low pH, leading to the blocking effect of membrane fusion between virus and endosome. These molecules can be lead compounds to develop new low molecular influenza virus entry inhibitors.

We reported previously that CL-385319 was effective in inhibiting the infection of H5N1 influenza A virus (A/Thailand/Kan353/2004) with an IC_{50} of 27.03 ± 2.54 μM [10]. Mechanism study showed that CL-385319 could interact with the H5-typed hemagglutinin and prevent the low pH-induced conformational change of the protein, thus blocking the fusion process [10]. In the present study, a series of derivatives which focused on structural variation of CL-385319 were synthesized. These novel compounds have potent activities against the infection of H5N1 pseudovirus which pseudotyped with hemagglutinin from A/Anhui/1/2005(H5N1) strain.

* Corresponding author. Tel.: +86 20 6164 8538; fax: +86 20 6164 8655.
E-mail address: liusw@smu.edu.cn (S. Liu).
[1] Both authors contributed equally.

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2. Results and discussion

2.1. Inhibition of the infection of H5N1 pseudovirus

Previously, we demonstrated that CL-385319 inhibited the highly pathogenic H5N1 avian influenza A virus by blocking viral entry [10]. CL-385319 could not inhibit N1-subtype neuraminidase activity and the absorption of H5-subtype HA to chicken erythrocytes. The inhibitory activity of CL-385319 is specific to hemagglutinin since it has no inhibitory activity on VSV-G pseudovirus, which the only difference is that the HA and NA were replaced by glycoproteins from vesicular stomatitis virus (VSV-G) [10].

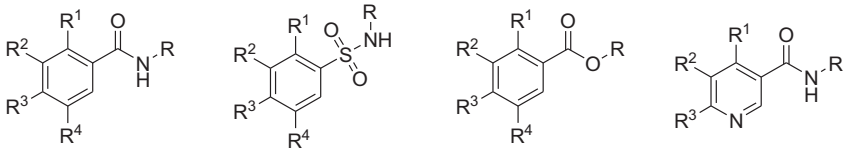
It is much more convenient and safer to use the single-cycle pseudovirus than live H5N1 avian influenza virus to evaluate the inhibitory activities of modified CL-385319 derivatives against H5N1 entry. The H5N1 pseudovirus was prepared by cotransfection of HA plasmid, NA plasmid and an HIV backbone plasmid (pNL4-3.luc.R$^-$E$^-$) to 293T cells.

The compounds designed and synthesized are listed in Table 1. Compounds **1a**–**t**, **2**–**3** and **4a**–**d** were evaluated for the inhibitory activity against the entry of H5N1 influenza virus. All compounds possess inhibitory activities against the infection of H5N1 virus with a potency ranging from moderate to potent. The IC_{50} values obtained for these compounds are also summarized in Table 1. The most active compounds in this series are **1k**, **1l**, **1m** and **1n**, with IC_{50} value lower than 1 μM (Fig. 1). Compounds **1k**, **1l** and **1m** had no effect on VSV-G pseudovirus infection (Fig. 1), which was similar to CL-385319, demonstrating that these compounds specifically interfere with the entry of influenza virus by targeting hemagglutinin.

2.2. SAR analysis of the compounds

From Table 1, the antiviral activities of compounds **1k**–**1n** were better than the others, which suggested that the incorporation of 3-fluoro-5-(trifluoromethyl)benzamide segment to the basic structure could increase the anti-H5N1 virus activity. Among them, compound **1l** is the most potent inhibitor with an IC_{50} of 0.22 μM. We also found that replacement of −H with CH_3 in R^4 substituent increases the activity (**1e** > **1r**; **1c** > **1t**). The structures of **1c** and **1l** are very similar, in which **1l** has an −F group in the phenyl ring, while the corresponding position of **1c** is a $-CF_3$ group. It is indicated that the −F group is a better substituent group than $-CF_3$ group, and $-CF_3$ is better substituent group than −H in R^4 substituent. This finding is also in agreement with the facts that replacement of $-CF_3$ with −F group or −H with $-CF_3$ enhances the inhibitory activity (**1l** > **1c** > **1t**; **1k** > **1b**; **1i** > **1h**; **1n** > **1e**). The inhibitory activity is sensitive to benzamide group since sulfonamides compounds **2** or **3** are much lower active than **1a**. The weaker activity may be ascribed to the fact that Arg106 from the HA2 chain of hemagglutinin can form hydrogen bond to the amide carbonyl oxygen of **1a** [9]. Glu105 and Asp109 from HA2 may participate in charge–charge interaction with the piperidine nitrogen and the pyrrole nitrogen. Interestingly, we found that **1g** and **1j** were less active although they can also form charge–charge interaction with Glu105 and Asp109, which may be due to the 3-carbon linker between the benzamide and piperazine. Therefore, a 2-carbon linker is a preference. It was reported that quinolizidine salicylamides can selectively inhibit the fusion process of the H1- and H3-subtypes influenza A by stabilizing hemagglutinin and prevent the essential conformational rearrangement [3–5]. We also

Table 1
Inhibitory activities of compounds against H5N1 pseudovirus.



Compounds	R^1	R^2	R^3	R^4	R	IC_{50} (μM)
CL-385319	H	CF_3	H	F	2-(Piperidin-1-yl)ethyl	0.37 ± 0.12
1a	H	CF_3	H	CF_3	2-(Piperidin-1-yl)ethyl	2.51 ± 0.16
1b	H	CF_3	H	CF_3	2-(Pyrrolidin-1-yl)ethyl	1.71 ± 0.26
1c	H	CF_3	H	CF_3	2-(Thiophen-2-yl)ethyl	2.44 ± 0.01
1d	H	CF_3	H	CF_3	(Pyridine-3-yl)methyl	2.46 ± 0.08
1e	H	CF_3	H	CF_3	Phenethyl	2.47 ± 0.34
1f	H	CF_3	H	CF_3	1-(Naphthalene-2-yl)ethyl	40.77 ± 4.31
1g	H	CF_3	H	CF_3	3-(4-Methylpiperazin-1-yl)propyl	66.64 ± 12.4
1h	H	CF_3	H	CF_3	2-Morpholinoethyl	9.89 ± 2.44
1i	H	CF_3	H	F	2-Morpholinoethyl	1.22 ± 0.17
1j	H	CF_3	H	F	3-(4-Methylpiperazin-1-yl)propyl	84.32 ± 15.06
1k	H	CF_3	H	F	2-(Pyrrolidin-1-yl)ethyl	0.38 ± 0.02
1l	H	CF_3	H	F	2-(Thiophen-2-yl)ethyl	0.22 ± 0.01
1m	H	CF_3	H	F	(Pyridine-4-yl)methyl	0.56 ± 0.01
1n	H	CF_3	H	F	Phenethyl	0.33 ± 0.01
1o	H	CF_3	H	F	1-(Naphthalene-2-yl)ethyl	49.00 ± 1.42
1p	H	CF_3	H	F	(3-Fluoro-5-(trifluoromethyl)benzamido)ethyl	59.97 ± 1.57
1q	OH	H	OH	OH	2-(Pyrrolidin-1-yl)ethyl	41.46 ± 1.35
1r	H	CF_3	H	H	Phenethyl	79.96 ± 4.27
1s	H	CF_3	H	H	Cyclohexyl	7.80 ± 0.01
1t	H	CF_3	H	H	2-(Thiophen-2-yl)ethyl	4.33 ± 0.12
2	H	CF_3	H	H	2-(Piperidin-1-yl)ethyl	54.87 ± 8.68
3	H	CF_3	H	F	2-(Piperidin-1-yl)ethyl	61.16 ± 8.61
4a	H	Cl	H	–	2-(Piperidin-1-yl)ethyl	6.25 ± 0.12
4b	H	Br	H	–	2-(Piperidin-1-yl)ethyl	5.13 ± 0.08
4c	H	Cl	H	–	2-(Thiophen-2-yl)ethyl	9.20 ± 0.50
4d	H	Br	H	–	2-(Thiophen-2-yl)ethyl	7.61 ± 0.35

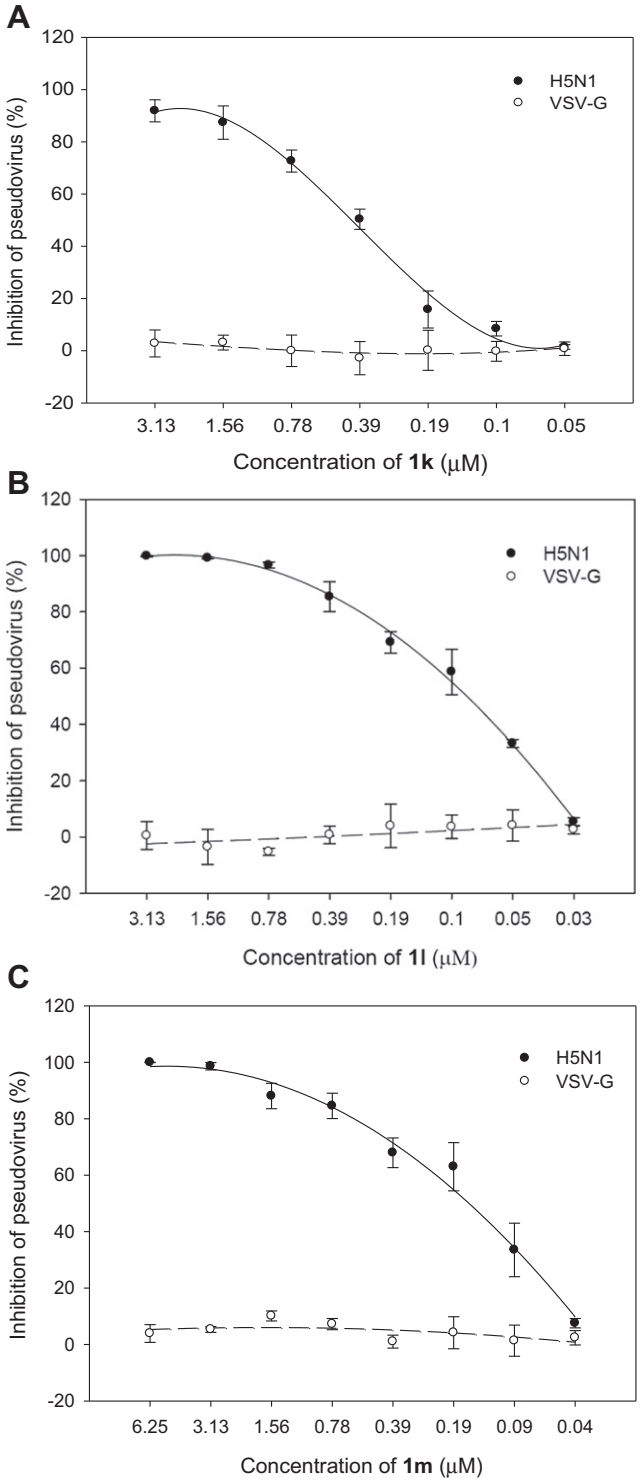


Fig. 1. The inhibitory activity of **1k** (A), **1l** (B) and **1m** (C) against A/Anhui/1/2005 H5N1 pseudovirus and VSV-G pseudovirus. The samples were tested in triplicate and the data were presented in mean ± SD. This experiment was repeated three times with similar results.

found that the inhibitory activities of **1k** and **1l** can not be improved by introduction of a −OH group at benzene moiety, such as compound **1q**. Compounds **1f** and **1o** had lower activities than compounds **1e** and **1n**, which suggests that bulky group in R moiety, could decrease the activity.

3. Conclusions

In the present study, a series of derivatives were synthesized based on the structure of CL-385319. These compounds could inhibit the infection of pseudoviruses carrying hemagglutinins from H5N1 strains. **1l** is the most active inhibitor in this series with an IC_{50} of 0.22 μM. The SAR analysis of these compounds showed that the 3-fluoro-5-(trifluoromethyl)benzamide moiety is very important for activity, while the F- group is a better substituent group than $-CF_3$ group and the $-CF_3$ group is better than H- group in the phenyl ring. The inhibitory activity is sensitive to the benzamide because the oxygen of amide is an H-bond acceptor, while the hydrogen of the amide served as H-bond donor, respectively.

4. Experimental protocols

4.1. Chemistry

All reagents and solvents were obtained from commercial suppliers and were used without further purification. The benzotriazole-l-yl-oxy-tris-pyrrolidino-phosphonium hexafluoro phosphate (PyBOP) was obtained from Aladdin (Shanghai, China). Most of reactions were monitored with a silica gel TLC plate under UV light followed by visualization with a *p*-anisaldehyde. ^{1}H NMR spectra were measured at 400 MHz in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm), and coupling constant in Hz. Melting points of solid compounds were observed on a Thomas Hoover capillary melting point apparatus.

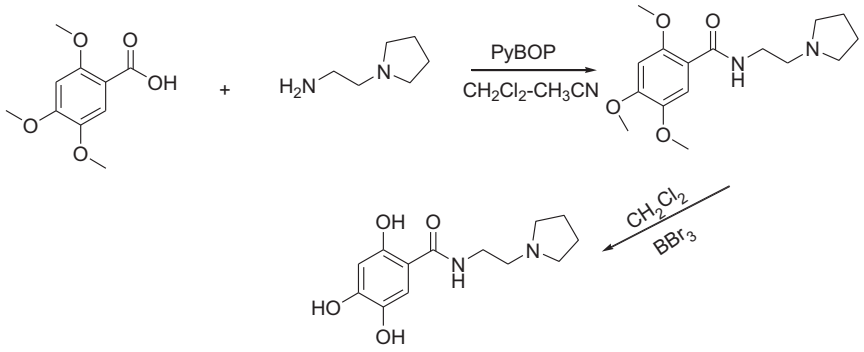
General synthesis of **1a**–**o**, **1r**–**t** and **4a**–**d** using Method A [11–13]: A mixture of 1 mmol (1 equiv.) of carboxylic acids, 1.4 mmol (1.4 equiv.) of amine, 552 mg (1.8 equiv.) of PyBOP and 2 mL of triethylamine was stirred overnight at room temperature in 40 ml of a 1:1 mixture of CH_2Cl_2 and CH_3CN. After solvent evaporation, the crude product was purified by column chromatography on silica ($CHCl_3$:CH_3CH_2OH = 9:1) resulting in yellow thick oil that slowly crystallized.

General synthesis of **1p**, **2** and **3** using Method B: To a solution of benzoyl chloride (1 mmol) in dry dichloromethane (10 ml) was added amine (1 mmol), and the mixture was stirred for 0.5 h at room temperature. After solvent evaporation, the crude product was purified by column chromatography on silica ($CHCl_3$:CH_3CH_2OH = 9:1) resulting in yellow thick oil and crystallized from the dichloromethane–petroleum ether mixture.

Synthesis of 2,4,5-*trihydroxy-N*-(2-(*pyrrolidin*-1-*yl*)*rthyl*)*benzamide* (**1q**) [14,15] (Scheme 1): 2,4,5-trimethoxybenzoic acid (1 mmol) was mixed with PyBOP (1.4 mmol, 1.4 equiv.), 1-(2-aminoethyl)pyrrolidine (1.8 mmol,1.8 equiv.) in 1:1 mixture of CH_2Cl_2 and CH_3CN at room temperature. After 2 h, the solvent (40 ml) was eliminated by normal pressure distillation. Then 20 ml of fresh CH_2Cl_2 and 2 ml of BBr_3 were added at −78 °C. After 4 h, 5 ml of H_2O were added to the mixture. After solvent evaporation, the crude product was purified by column chromatography on silica gel.

4.1.1. 3,5-Bis(trifluoromethyl)-N-(2-(piperidin-1-yl)ethyl) benzamide (*1a*)

The crude product was purified by column chromatography on silica gel and crystallized from dichloromethane–petroleum ether, 312 mg of **1a** as white solid, 85%. Mp 180–182 °C. CCDC:854218. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.87–1.91 (m, 4H, J = 16.0 Hz), 2.23–2.27 (m, 2H, J = 16.0 Hz), 2.73–2.78 (m, 2H, J = 20.0 Hz), 3.31–3.32 (d, 2H, J = 4.0 Hz), 3.66–3.69 (d, 2H, J = 12.0 Hz), 3.95–3.97 (d, 2H, J = 8.0 Hz), 7.97 (s, 1H), 8.66 (s, 2H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.9, 22.5, 34.6, 54.2, 57.4, 121.7, 124.4, 125.1, 128.4,



1q

Scheme 1.

131.7, 132.0, 135.3, 165.0. The X-ray structure of 1a was showed in supporting information (Fig. S1).

*4.1.2. 3,5-Bis(trifluoromethyl)-N-(2-(pyrrolidin-1-yl)ethyl) benzamide (**1b**)*

318 mg of **1b** as white solid, 90%. Mp 142–144 °C. MS (ESI) *m/z*: 355.1 $(M + H)^+$, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.13–2.25 (d, 4H, *J* = 46 Hz), 2.91 (s, 2H), 3.41 (s, 2H), 3.94 (s, 4H), 7.99 (s, 1H), 8.67 (s, 2H), 9.43 (s, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 23.3, 36.4, 54.5,55.8, 121.7, 124.4125.2, 128.4, 128.5, 131.8, 132.1, 135.3, 165.0; anal. cal. for $C_{14}H_{16}F_4N_2O$: C 61.74, H 4.21, N 4.50; found C 61.90, H 4.25, N 4.45.

*4.1.3. 3,5-Bis(trifluoromethyl)-N-(2-(thiophen-2-yl)ethyl) benzamide (**1c**)*

The crude product was purified by column chromatography on silica gel and crystallized from the dichloromethane–petroleum ether. 294 mg of **1c** as white solid, 85%. Mp 116–117 °C. CCDC:826436. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 3.18–3.26 (m, 2H, *J* = 32.0 Hz), 3.74–3.79 (m, 2H, *J* = 20.0 Hz), 6.85–6.96 (m, 2H, *J* = 44.0 Hz), 6.97–6.98 (m, 1H, *J* = 4.0 Hz), 7.19–7.20 (d, 1H, *J* = 4.0 Hz), (s, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 29.6, 41.7, 121.5, 124.2, 125.0, 125.1, 125.6, 127.2, 132.0, 136.6, 140.7, 164.8. The X-ray structure of **1c** was showed in supporting information (Fig. S2).

*4.1.4. 3,5-Bis(trifluoromethyl)-N-((pyridine-3-yl)methyl) benzamide (**1d**)*

296 mg of **1d** as white solid, 85%. Mp 152–154 °C. MS (ESI) *m/z*: 349.1$(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 4.68–4.70 (d, 2H, *J* = 6.0 Hz), 7.00 (s, 1H), 7.30–7.33 (m, 1H, *J* = 12.8 Hz), 7.74–7.77 (d, 1H, *J* = 11.6 Hz), 8.02 (s, 1H), 8.29 (s, 2H), 8.54–8.55 (m, 2H, *J* = 2.4 Hz);^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 41.9, 123.9, 125.3, 127.4, 127.5, 132.2, 132.5, 133.4, 136.0, 136.2, 149.3, 149.4, 164.6; anal. cal. for $C_{15}H_{10}F_6N_2O$: C 51.73, H 2.89, N 8.04; found C 51.90, H 2.92, N 8.15.

*4.1.5. 3,5-Bis(trifluoromethyl)-N-phenethylbenzamide (**1e**)*

314 mg of **1e** as white solid, 87%. Mp 64–66 °C. MS (ESI) *m/z*: 360.1$(M - H)^-$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 4.68–4.70 (d, 2H, *J* = 6.0 Hz), 7.00 (s, 1H), 7.30–7.33 (m, 1H, *J* = 12.8 Hz), 7.74–7.77 (d, 1H, *J* = 11.6 Hz), 8.02 (s, 1H), 8.29 (s, 2H), 8.54–8.55 (m, 2H, *J* = 2.4 Hz);^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 41.9, 123.9, 125.3, 127.4, 127.5, 132.2, 132.5, 133.4, 136.0, 136.2, 149.3, 149.4, 164.6; anal. cal. for $C_{17}H_{13}F_6NO$: C 51.73, H 2.89, N 8.04; found C 51.90, H 2.92, N 8.15.

*4.1.6. 3,5-Bis(trifluoromethyl)-N-(1-(naphthalene-2-yl)ethyl) benzamide (**1f**)*

175 mg of **1f** as white solid, 84%. Mp 133–135 °C. MS (ESI) *m/z*: 410.2$(M - H)^-$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.73–1.75 (d, 3H, *J* = 6.8 Hz), 5.48–5.52 (m, 1H, *J* = 14.4 Hz), 6.51–6.53 (d, 1H, *J* = 7.6 Hz), 7.48–7.52 (m, 3H, *J* = 16 Hz), 7.82–7.87 (m, 4H, *J* = 21.2 Hz), 7.99 (s, 1H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 21.4, 50.0, 124.6, 125.0, 126.3, 126.5, 127.3, 127.7, 127.9, 128.9, 132.0, 132.4, 133.3, 136.6, 139.5, 163.7; anal. cal. for $C_{21}H_{15}F_6NO$: C 61.32, H 3.68, N 3.41; found C 61.40, H 3.72, N 3.35.

*4.1.7. 3,5-Bis(trifluoromethyl)-N-(3-(4-methylpiperazin-1-yl) propyl)benzamide (**1g**)*

238 mg of **1g** as white solid, 60%. Mp 140–142 °C. MS (ESI) *m/z*: 398.3$(M + H)^+$,^{1}H NMR (D_2O, 400 MHz) *δ*: 2.04–2.08 (m, 2H, *J* = 1.6 Hz), 2.96 (s, 3H), 3.30–3.31 (m, 2H, *J* = 16 Hz), 3.45–3.48 (m, 2H, *J* = 12 Hz), 3.64 (s, 8H), 8.19 (s, 1H), 8.22 (s, 2H), ^{13}C NMR (D_2O, 100 MHz) *δ*: 23.6, 36.8, 42.8, 48.7, 54.6, 121.7, 124.4, 125.9, 127.8, 131.1, 131.5, 135.2, 168.1; anal. cal. for $C_{17}H_{21}F_6N_3O$: C 51.38, H 5.33, N 10.57; found C 51.58, H 5.23, N 10.51.

*4.1.8. 3,5-Bis(trifluoromethyl)-N-(2-morpholinoethyl)benzamide (**1h**)*

260 mg of **1h** as white solid, 70%. Mp 95–97 °C. MS (ESI) *m/z*: 369.1$(M - H)^-$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.54 (s, 4H), 2.64–2.67 (m, 2H, *J* = 12.0 Hz), 3.58–3.62 (m, 2H, *J* = 16.8 Hz), 3.73–3.75 (m, 4H, *J* = 8.8 Hz), 7.12 (s, 1H), 8.00 (s, 1H), 8.23 (s, 2H);^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 36.4, 53.3, 55.7, 66.9, 121.6, 124.3, 124.9, 125.0, 127.3, 127.3, 132.0, 132.3, 136.7, 164.5; anal. cal. for $C_{15}H_{16}F_6N_2O_2$: C 48.65, H 4.36, N 7.57; found C 48.80, H 4.26, N 7.51.

*4.1.9. 3-Fluoro-5-(trifluoromethyl)-N-(2-morpholinoethyl) benzamide (**1i**)*

224 mg of **1i** as white solid, 70%. Mp 78–79 °C. MS (ESI) *m/z*: 321.2$(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.53–2.55 (m, 4H, *J* = 8.4 Hz), 2.63–2.66 (m, 2H, *J* = 12 Hz), 3.56–3.60 (m, 2H, *J* = 16.8 Hz), 3.74–3.76 (m, 4H, *J* = 8.8 Hz), 6.90 (s, 1H), 7.47–7.49 (d, 1H, *J* = 8.0 Hz), 7.68–7.71 (d, 1H, *J* = 8.8 Hz), 7.83 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 36.3, 53.3, 56.7, 67.0, 115.5, 115.8, 115.8, 117.7, 117.9, 119.5, 119.6, 138.0, 161.3, 163.7, 164.7; anal. cal. for $C_{14}H_{16}F_4N_2O_2$: C 52.50, H 5.04, N 8.75; found C 52.60, H 5.03, N 8.71.

*4.1.10. 3-Fluoro-5-(trifluoromethyl)-N-(3-(4-methylpiperazin-1-yl) propyl)benzamide (**1j**)*

261 mg of **1j** as white solid, 75%. Mp 177–179 °C. MS (ESI) *m/z*: 348.2 $(M + H)^+$,^{1}H NMR (D_2O, 400 MHz) *δ*: 2.02–2.08 (m, 2H, *J* = 24 Hz), 2.96 (s, 3H), 3.29–3.31 (m, 2H, *J* = 8.0 Hz), 3.42–3.46 (m, 2H, *J* = 16 Hz), 3.63 (s, 8H), 7.60–7.66 (m, 2H), 7.81 (s, 1H), ^{13}C NMR (D_2O, 100 MHz), *δ*: 23.6, 36.7, 42.8, 54.6, 116.1, 116.4, 117.9, 118.2, 120.1, 136.4, 136.5, 160.9, 163.4, 168.1; anal. cal. for $C_{16}H_{21}F_4N_3O$: C 55.32, H 6.09, N 12.10; found C 55.42, H 6.13, N 12.05.

*4.1.11. 3-Fluoro-5-(trifluoromethyl)-N-(2-(pyrrolidin-1-yl)ethyl) benzamide (**1k**)*

280 mg of **1k** as white solid, 92%. Mp 163–164 °C. MS (ESI) *m*/*z*: 304.98 $(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.19(s, 4H), 3.38–3.41 (m, 4H, *J* = 10.8 Hz), 3.90–3.94 (m, 4H, *J* = 16.0 Hz), 7.42–7.44 (d, 1H, *J* = 8.0 Hz), 8.09–8.11 (d, H, *J* = 8.8 Hz), 8.21 (s, 1H), 9.19 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 23.3, 36.4, 54.6, 55.8, 115.7, 118.4, 118.6, 120.9, 136.5, 136.6, 161.1, 165.3; anal. cal. for $C_{14}H_{16}F_4N_2O$: C 55.26, H 5.30, N 9.21; found C 55.89, H 5.37, N 9.25.

*4.1.12. 3-Fluoro-5-(trifluoromethyl)-N-(2-(thiophen-2-yl)ethyl) benzamide (**1l**)*

307 mg of **1l** as white solid, 97%. Mp 86–88 °C. MS (ESI) *m*/*z*: 316.10 $(M - H)^-$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 3.16–3.20 (m, 2H, *J* = 13.2 Hz), 3.73–3.77 (m, 2H, *J* = 18.8 Hz), 6.88–6.89 (m, 1H, *J* = 3.2 Hz), 6.97–6.99 (m, 1H, *J* = 8.8 Hz), 7.19–7.20 (d, H, *J* = 1.2 Hz), 7.20–7.21 (d, 1H, *J* = 1.2 Hz), 7.45–7.47 (d, 1H, *J* = 8.0 Hz), 7.62–7.64 (d, 1H, *J* = 8.4 Hz), 7.75 (s, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 29.7, 41.6, 117.7, 117.9, 119.4, 119.5, 124.3, 125.6, 127.3, 140.8, 163.7, 164.9; anal. cal. for $C_{14}H_{11}F_4NOS$: C 52.99, H 3.49, N 4.41, S 10.11; found C 52.89, H 3.47, N 4.45, S 10.18.

*4.1.13. 3-Fluoro-5-(trifluoromethyl)-N-((pyridine-4-yl)methyl) benzamide (**1m**)*

268 mg of **1m** as white solid, 90%. Mp 99–101 °C. MS (ESI) *m*/*z*: 299.1$(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 4.70–4.71 (d, 2H, *J* = 6.0 Hz), 7.43–7.47 (m, 2H, *J* = 16.8 Hz), 7.50–7.52 (d, 1H, *J* = 8.0 H), 7.78–7.80 (d, 1H, *J* = 8.8 Hz), 7.87–7.94 (m, 2H, *J* = 26.4 Hz), 7.96–7.98 (d, 1H, *J* = 8.0 Hz), 8.13 (s, 1H), 8.54–8.55 (d, 1H, *J* = 4.8 Hz), 8.77 (s, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 41.5, 118.1, 119.8, 119.9, 124.7, 135.5, 138.9, 145.8, 146.7, 166.2; anal. cal. for $C_{14}H_{10}F_4N_2O$: C 56.38, H 3.38, N 9.39; found C 56.41, H 3.35, N 9.40.

*4.1.14. 3-Fluoro-5-(trifluoromethyl)-N-phenethylbenzamide (**1n**)*

288 mg of **1n** as white solid, 95%. Mp 163–164 °C. MS (ESI) *m*/*z*: 312.1 $(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.93–2.97 (m, 2H, *J* = 16 Hz), 3.70–3.75 (m, 2H, *J* = 20 Hz), 6.18 (s, 1H), 7.22 (s, 1H), 7.24 (s, 1H), 7.28 (s, 1H), 7.32–7.36 (m, 2H, *J* = 14.4 Hz), 7.43–7.45 (d, 1H, *J* = 8.0 Hz), 7.58–7.61 (d, 1H, *J* = 8.4 Hz), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 35.5, 41.4, 115.5, 115.6, 115.8, 117.7, 117.9, 119.4, 119.5, 128.8, 128.9, 138.0, 138.5, 161.2, 163.7, 164.8; anal. cal. for $C_{14}H_{16}F_4N_2O$: C 61.74, H 4.21, N 4.50; found C 61.90, H 4.25, N 4.45.

*4.1.15. 3-Fluoro-5-(trifluoromethyl)-N-(1-(naphthalene-2-yl)ethyl) benzamide (**1o**)*

343 mg of **1o** as white solid, 95%. Mp 183–184 °C. MS (ESI) *m*/*z*: 362.4 $(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.60–1.62 (d, 3H, *J* = 6.8 Hz), 4.56–4.58 (m, 1H, *J* = 6.8 Hz), 7.55–7.58 (m, 2H, *J* = 8.8 Hz), 7.67–7.69 (d, 1H, *J* = 8.4 Hz), 7.88–7.90 (d, 1H, *J* = 4.8 Hz), 7.91–7.96 (m, 2H, *J* = 18.8 Hz), 7.98 (s, 1H), 8.00 (s, 2H), 8.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 20.6, 50.1, 124.5, 125.7, 126.5, 126.6,127.6, 127.8, 128.4, 132.6, 136.7; anal. cal. for $C_{20}H_{15}F_4NO$: C 66.48, H 4.18, N 3.88; found C 66.70, H 4.25, N 3.65.

*4.1.16. 2-(3-Fluoro-5-(trifluoromethyl)benzamido)ethyl 3-fluoro-5-(trifluoromethyl) benzoate (**1p**)*

344 mg of **1p** as white solid,78%. Mp 193–184 °C. MS (ESI) *m*/*z*: 464.6(M + Na),^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 3.88–3.90 (m, 2H, *J* = 5.2 Hz), 4.60–4.61 (m, 2H, *J* = 4.8 Hz), 6.87 (s, 1H), 7.44–7.46 (d, 1H, *J* = 7.2 Hz), 7.52–7.54 (d, 1H, *J* = 7.2 Hz), 7.66–7.68 (d, 1H, *J* = 7.6 Hz), 7.79(s, 1H), 7.89–7.91 (d, 1H, *J* = 8.0 Hz), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 39.9, 64.4, 105.0, 115.8, 117.5, 117.7, 118.0, 119.5, 120.0, 120.20, 122.3, 132.8, 137.3, 161.7, 164.6, 165.1; anal. cal. for $C_{18}H_{11}F_8NO_3$: C 48.99, H 2.51, N 3.17; found C 48.90, H 2.54, N 3.15.

*4.1.17. 2,4,5-Trihydroxy-N-(2-(pyrrolidin-1-yl)ethyl)benzamide (**1q**)*

133 mg of **1q** as white solid, 50%. Mp 164–166 °C. MS (ESI) *m*/*z*: 267.3$(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 0.45 (s, 2H), 1.50–1.51 (d, 2H, *J* = 4.8 Hz), 1.62–1.66 (m, 2H, *J* = 16.8 Hz), 2.59–2.62 (m, 2H, *J* = 11.6 Hz), 3.51 (s, 2H), 6.56 (s, 1H), 6.58–6.59 (d, 1H, *J* = 2.8 Hz), 6.60–6.61 (d, 1H, *J* = 2.4 Hz), 6.64–6.65 (d, 1H, *J* = 2.4 Hz), 6.67–6.68 (d, 1H, *J* = 2.4 Hz), 7.39–7.43 (d, 1H, *J* = 15.2 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 24.2, 25.9, 35.7, 54.2, 56.5, 105.0, 105.2, 106.4, 106.6, 127.4, 127.6, 163.8, 163.9, 164.8, 167.3, 169.3; anal. cal. for $C_{13}H_{18}N_2O_4$: C 58.63, H 6.81, N 10.52; found C 58.80, H 6.66, N 10.51.

*4.1.18. 3-(Trifluoromethyl)-N-phenethylbenzamide (**1r**)*

205 mg of **1r** as white solid, 70%. Mp 104–105 °C. MS (ESI) *m*/*z*: 281.1$(M + H)^+$,^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 2.96–3.00 (m, 2H, *J* = 13.6 Hz), 3.74–3.79 (m, 2H, *J* = 19.2 Hz), 6.22 (s, 1H), 7.26 (s, 1H), 7.30 (s, 1H), 7.35–7.38 (m, 2H, *J* = 14.4 Hz), 7.55–7.59 (m, 1H, *J* = 15.6 Hz), 7.75–7.77 (d, 1H, *J* = 7.6 Hz), 7.87–7.89 (d, 1H, *J* = 7.6 Hz), 7.97 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 35.6, 41.3, 123.9, 126.8, 128.0, 128.8, 129.2, 130.1, 135.5, 138.7, 166.1; anal. cal. for $C_{15}H_{12}F_3NO$: C 64.51, H 4.33, N 5.02; found C 64.60, H 4.23, N 5.01.

*4.1.19. N-cyclohexyl-3-(trifluoromethyl)benzamide (**1s**)*

203 mg of **1s** as white solid, 75%. Mp 122–123 °C. MS (ESI) *m*/*z*: 272.2 $(M + H)^+$, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.20 (m, 2H, *J* = 30.8 Hz), 1.39–1.47 (m, 2H, *J* = 28.8 Hz), 1.58–1.66 (m, 2H, *J* = 31.2 Hz), 1.75–1.81 (m, 2H, *J* = 20.8 Hz), 2.03–2.07 (m, 2H, *J* = 16 Hz), 3.97–4.01 (m, 1H, *J* = 14.0 Hz), 5.97 (s, 1H), 7.55–7.59 (m, 1H, *J* = 15.6 Hz), 7.74–7.76 (d, 1H, *J* = 7.6 Hz), 7.93–7.95 (d, 1H, *J* = 7.6 Hz), 7.99 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 24.9, 25.6, 33.2, 49.1, 123.8, 127.9, 129.2, 130.2, 130.9, 135.9, 165.2; anal. cal. for $C_{14}H_{16}F_3NO$: C 61.98, H 5.94, N 5.16; found C 61.88, H 5.78, N 5.31.

*4.1.20. 3-(Trifluoromethyl)-N-(2-(thiophen-2-yl)ethyl)benzamide (**1t**)*

195 mg of **1t** as white solid, 65%. Mp 62–64 °C. MS (ESI) *m*/*z*: 322.7(M + Na), ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 3.16–3.20 (m, 2H, *J* = 12.8 Hz), 3.73–3.78 (m, 2H, *J* = 18.8 Hz), 6.29 (s, 1H), 6.88–6.89 (m, 1H, *J* = 3.2 Hz), 6.97–6.99 (m, 1H, *J* = 8.4 Hz), 7.19–7.20 (m, 1H, *J* = 6.4 Hz), 7.54–7.58 (m, 1H, *J* = 15.6 Hz), 7.74–7.76 (d, 1H, *J* = 7.6 Hz), 7.88–7.90 (d, 1H, *J* = 8.0 Hz), 7.99 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 29.8, 41.5, 123.9, 124.0, 124.2, 125.6, 127.2, 128.1, 129.2, 130.1, 135.4, 141.0, 166.0; anal. cal. for $C_{13}H_{12}F_3NOS$: C 56.18, H 4.04, N 4.68, S 10.71; found C 56.32, H 4.13, N 4.61, S 10.61.

*4.1.21. 3-(Trifluoromethyl)-N-(2-(piperidin-1-yl)ethyl) benzensulfonamide (**2**)*

238 mg of **3** as white solid, 71%. Mp 171–172 °C. MS (ESI) *m*/*z*: 337.0 $(M + H)^+$, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.85–1.96 (m, 4H, *J* = 44 Hz), 2.20–2.26 (m, 2H, *J* = 24 Hz), 2.75–2.82 (m, 2H, *J* = 28 Hz), 3.29 (s, 2H), 3.46(s, 2H), 3.62–3.65 (d, 2H, *J* = 12 Hz), 7.69–7.71 (m, 1H, *J* = 8.0 Hz), 7.83 (d, 1H), 8.12 (s, 1H), 8.19–8.23 (m, 2H, *J* = 16 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 21.8, 22.6, 54.3, 57.5, 121.9, 124.1, 124.1, 124.6, 129.4, 130.6, 140.9; anal. cal. for $C_{14}H_{19}F_3N_2O_2S$: C 49.99, H 5.69, N 8.33,S 9.53; found C 49.86, H 5.63, N 8.31,S 9.43.

*4.1.22. 2-(Piperidin-1-yl)ethyl 3-fluoro-5-(trifluoromethyl) benzoate (**3**)*

207 mg of **2** as white solid, 65%. Mp 179–181 °C. MS (ESI) *m*/*z*: 320.0 $(M + H)^+$, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.89–2.05 (m, 4H, *J* = 40 Hz), 2.29–2.32 (d, 2H, *J* = 12.0 Hz), 2.77–2.85 (m, 2H, *J* = 32 Hz), 3.44–3.45 (d, 2H, *J* = 4.0 Hz), 3.66–3.69 (d, 2H, *J* = 12 Hz), 4.99 (s, 2H), 7.57–7.58 (d, 1H, *J* = 4.0 Hz), 7.96–7.9 8(d,

1H, $J = 8.0$ Hz), 8.09 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.8, 22.6, 53.9, 55.5, 59.9, 117.8, 120.2, 120.4, 122.4, 132.2, 161.2, 163.5, 163.7; anal. cal. for $C_{15}H_{17}F_4NO_2$: C 56.42, H 5.37, N 4.39; found C 56.32, H 5.23, N 4.31.

4.1.23. 5-Chloro-N-(2-(piperidin-1-yl)ethyl)pyridine-3-carboxamide (**4a**)

192 mg of **4a** as white solid, 72%. Mp 102–103 °C. MS (ESI) m/z: 268.9 $(M + H)^+$, ^{1}H NMR (DMSO-d6, 400 MHz) δ: 1.44 (s, 2H), 1.56–1.57 (m, 4H, $J = 4.4$ Hz), 2.41 (s, 4H), 2.53–2.54 (d, 2H, $J = 4.8$ Hz), 3.49–3.50 (d, 2H, $J = 4.4$ Hz), 7.28 (s, 2H), 8.11 (s, 1H), 8.62–8.64 (d, 1H, $J = 5.2$ Hz), 8.81(s, 1H), ^{13}C NMR (DMSO-d6, 100 MHz) δ: 24.3, 26.0, 36.6, 54.2, 56.7, 131.4, 135.0, 145.5, 150.9, 164.0; anal. cal. for $C_{13}H_{18}ClN_3O$: C 58.31, H 6.78, N 15.69; found C 58.32, H 6.73, N 15.61.

4.1.24. 5-Bromo-N-(2-(piperidin-1-yl)ethyl)pyridine-3-carboxamide (**4b**)

218 mg of **4b** as white solid, 70%. Mp 96–97 °C. MS(ESI) m/z: 312.8, 314.8 $(M + H)^+$, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.44 (s, 2H), 1.57–1.59 (d, 4H, $J = 5.2$ Hz), 2.41 (s, 4H), 2.53–2.56 (m, 2H, $J = 12$ Hz), 3.49–3.53 (m, 2H, $J = 16$ Hz), 7.28 (s, 2H), 8.23–7.27 (m, 1H, $J = 8.4$ Hz), 8.71–8.75 (d, 1H, $J = 12.4$ Hz), 8.85 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.3, 26.0, 36.6, 54.2, 56.7, 56.7, 121.0, 131.8, 137.9, 145.8, 145.9, 153.0, 153.1, 164.0; anal. cal. for $C_{13}H_{18}BrN_3O$: C 50.01, H 5.81, N 13.46; found C 50.12, H 5.76, N 13.61.

4.1.25. 5-Chloro-N-(2-(thiophen-2-yl)ethyl)pyridine-3-carboxamide (**4c**)

200 mg of **4c** as white solid, 75%. Mp 124–125 °C. MS (ESI) m/z: 267.9 $(M + H)^+$, ^{1}H NMR (DMSO-d6, 400 MHz) δ: 3.09–3.12 (m, 2H, $J = 14.4$ Hz), 3.55–3.56 (m, 2H, $J = 5.6$ Hz), 6.94–6.98 (m, 2H, $J = 15.2$ Hz), 7.34–7.36 (d, 1H, $J = 5.2$ Hz), 8.28–8.29 (m, 1H, $J = 4.0$ Hz), 8.78–8.79 (d, 1H, $J = 2.0$ Hz), 8.96–8.97 (d, 2H, $J = 1.6$ Hz), ^{13}C NMR (DMSO-d6, 100 MHz) δ: 29.0, 41.0, 124.1, 125.3, 126.9, 131.0, 131.1, 134.5, 141.2, 146.7, 150.3, 163.4; anal. cal. for $C_{12}H_{11}ClN_2OS$: C 54.03, H 4.16, N 10.50,S 12.02; found C 54.12, H 4.13, N 10.61, S 12.08.

4.1.26. 5-Bromo-N-(2-(thiophen-2-yl)ethyl)pyridine-3-carboxamide (**4d**)

239 mg of **4d** as white solid, 77%. Mp 114–115 °C. MS (ESI) m/z: 312.2 $(M + H)^+$, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.13–3.16 (m, 2H, $J = 13.2$ Hz), 3.68–3.73 (m, 2H, $J = 19.2$ Hz), 6.84–6.85 (d, 2H, $J = 3.2$ Hz), 6.93–6.95 (m, 1H, $J = 8.4$ Hz), 7.03 (s, 1H), 7.15–7.16 (d, 1H, $J = 5.2$ Hz), 8.20 (s, 1H), 8.68–8.69 (d, 1H, $J = 2.0$ Hz), 8.77–8.78 (d, 1H, $J = 1.6$ Hz), ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 29.7, 41.6, 121.0, 124.2, 125.6, 127.2, 131.6, 137.9, 140.8, 145.9, 153.2, 164.4; anal. cal. for $C_{12}H_{11}BrN_2OS$: C 46.31, H 3.56, N 9.00,S 10.30; found C 46.22, H 3.58, N 9.02, S 10.28.

4.2. Measurement of the inhibitory activity against H5N1 pseudovirus

MDCK cells and 293T cells were obtained from the American Type Culture Collection (ATCC). Cells were grown in Dulbecco's Modified Eagle Medium (DMEM, Gibco) containing glutamine, supplemented with 10% fetal calf serum (FCS).

The H5N1 pseudoviruses were prepared by transfecting HA plasmid from the H5 subtype strain A/Anhui/1/2005(H5N1) strain and the NA plasmid from the N1 subtype strain A/Thailand/Kan353/2004. Briefly, 293T cells (60–70% confluent) were co-transfected with 2 μg HA plasmid, 2 μg NA plasmid and 3 μg HIV backbone plasmid (pNL4-3.luc.R$^-$E$^-$) into six-well plate using the calcium phosphate precipitation method [10]. Forty-eight hours after transfection, the culture supernatants were harvested and centrifuged at 2000 rpm for 5 min. Aliquots were stored at −70 °C. The amount of pseudotyped particles was quantitated using the HIV-1 p24 ELISA kit from Retro-Tek (Buffalo, NY).

For measuring the inhibitory activities of test compounds, MDCK cells (1×10^4/well) were seeded in 96-well plates and grown overnight. Tested compounds at indicated concentrations were incubated with pseudotyped particles (1 ng p24/well) for 30 min at 37 °C. Subsequently, the virus–compound mixture was transferred to the cells and incubated for an additional 48 h. Cells were washed with phosphate buffer saline (PBS) and lysed with the lysing reagent included in the luciferase kit (Promega, Madison, WI). Aliquots of cell lysates were transferred to 96-well flat bottom luminometer plates (Costar), followed by the addition of luciferase substrate (Promega). The luciferase activity was measured in a microplate luminometer. As a negative control, VSV-G pseudotyped particles were incubated with the tested compound instead of H5N1 pseudovirus.

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Appendix A. Supporting information

Supporting information related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.08.041.

References

[1] H.P. Hsieh, J.T. Hsu, Curr. Pharm. Des. 13 (2007) 3531–3542.
[2] K.E. Doucette, F.Y. Aoki, Expert Opin. Pharmacother. 2 (2001) 1671–1683.
[3] R.K. Gupta, J.S. Nguyen-Van-Tam, N. Engl. J. Med. 355 (2006) 1419–1431.
[4] Q.M. Le, M. Kiso, K. Someya, Y.T. Sakai, T.H. Nguyen, K.H. Nguyen, N.D. Pham, H.H. Ngyen, S. Yamada, Y. Muramoto, T. Horimoto, A. Takada, H. Goto, T. Suzuki, Y. Suzuki, Y. Kawaoka, Nature 437 (2005) 1108.
[5] A. Moscona, N. Engl. J. Med. 360 (2009) 953.
[6] J. Skehel, Biologicals 37 (2009) 177–178.
[7] J. Yoshimoto, M. Kakui, H. Iwasaki, H. Sugimoto, T. Fujiwara, N. Hattori, Microbiol. Immunol. 44 (2000) 677–685.
[8] G. Luo, A. Torri, W.E. Harte, S. Danetz, C. Cianci, L. Tiley, S. Day, D. Mullaney, K.L. Yu, C. Ouellet, P. Dextraze, N. Meanwell, R. Colonno, M. Krystal, J. Virol. 71 (1997) 4062–4070.
[9] S.J. Plotch, B. O'Hara, J. Morin, O. Palant, J. LaRocque, J.D. Bloom Jr., S.A. Lang, M.J. DiGrandi, M. Bradley, R. Nilakantan, Y. Gluzman, J. Virol. 73 (1999) 140–151.
[10] S.W. Liu, R.M. Li, R.T. Zhang, C. Chan, B.M. Xi, Z.B. Zhu, J. Yang, K.M.P. Vincent, J. Zhou, M. Chen, M. Jan, K. Frank, P. Stephan, H. Thomas, D. Ursula, P. Pan, L. Du, S.B. Jiang, B. Zheng, Eur. J. Pharmacol. 660 (2011) 460–467.
[11] L. Maton, D. Taziaux, J.P. Soumillion, J.H. Jiwan, J. Mater. Chem. 15 (2005) 2928–2937.
[12] C.A.G.N. Montalbetti, V. Falque, Tetrahedron 61 (2005) 10827–10852.
[13] W. Wang, J.S. McMurray, Tetrahedron Lett. 40 (1999) 2501–2504.
[14] I. Ryu, H. Matsubara, S. Yasuda, H. Nakamura, D.P. Curran, J. Am. Chem. Soc. 124 (2002) 12946–12947.
[15] A.K. Chakraborti, L.A. Sharma, M.K. Nayak, J. Org. Chem. 67 (2002) 6407–6414.