Supplementary Information

Design, synthesis and biological evaluation of 2,3-dihydroimidazo[1,2-c]quinazoline derivatives as novel phosphatidylinositol 3-kinase and histone deacetylase dual inhibitors

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General experimental

All chemicals were reagent grade and purchased from commercial suppliers. Melting points were determined in open capillaries on a WRS-1A digital melting point apparatus (Shenguang). NMR spectra was recorded in $CDCl_3$ and DMSO–d6 on a Bruker DRX–300 (300 MHz) using TMS as internal standard. The chemical shifts are reported in ppm (δ) and coupling constants (*J*) values are given in Hertz (Hz). Mass spectra were obtained from Agilent 1100 LC/MSD (Agilent) or Q-tof micro MS (Micromass) and the high-resolution (HR) electrospray ionization-time of flight (ESI-TOF)-MS was recorded on Agilent 6224 A (TOF) LC/MS. The purity of all tested compounds was established by HPLC to be >95.0%. HPLC analysis was performed at room temperature using an Agilent Eclipse XDB–C18 (250 mm × 4.6 mm) and 35% MeOH/H_2O as a mobile phase and plotted at 254 nm. All cells were obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China).

Functional assay

Computational Methods

All computational work was performed in Discovery Studio (2.5). Docking was conducted using cdocker based on the cocrystal of PI3K and Copanlisib (PDB: 5G2N). PI3K was used as receptor. The cavity occupied by Copanlisib was selected as the ligand binding site. The docking sphere radius value based on Copanlisib is default. Water molecules outside the binding pocket were excluded. The energy minimization for compounds **12b, 12c and 12e** was performed by Powell's method for 1000 iterations using Tripos force field and with Gasteiger-Hückel charge. The other docking parameters were kept at default. The same approach is used to the cocrystal of HDAC1 homolog protein and Vorinostat (PDB: 1C3S).

HDAC enzymatic assay in vitro

All three full-length recombinant human HDACs (rhHDACs) 1, 6 and 8 were expressed in insect High5 cells using a baculoviral expression system, and all His6-tagged and GST-fusion proteins was purified using Ni-NTA (QIAGEN). The deacetylase activity of HDAC1 and 8 were assayed with a HDAC substrate (Ac-Lys-Tyr-Lys(e-acetyl)-AMC), and HDAC6 was assayed with another HDAC substrate (Boc-Lys(e-acetyl)-AMC).The total HDAC assay volume was 25 μL and all the assay components were diluted in HEPES buffer (25 mM HEPES, 137 mM NaCl, 2.7 mM KCl and 4.9 mM $MgCl_2$, pH = 8.0). The reaction was carried out in the 384-well plate (OptiPlateTM-384F, PerkinElmer). In brief, the HDAC assay mixture contained the substrate (5-50 μM, 5 μL), rhHDAC isoforms (20-200 nM) and inhibitor (1 μL). Positive controls contained all the above components except the inhibitor. The negative controls contained neither enzyme nor inhibitor. The HDAC6 assay

components were incubated at room temperature for 3 h, and HDAC1 and 8 were incubated for 24 h. The reaction was quenched with the addition of 25 μL Trypsin with the final concentration of 0.31%. After 30 min incubation at room temperature, the 384-well plate was read at wavelengths 355 nm (excitation) and 460 nm (emission) using Envision (PerkinElmer). Each experiment was done in triplicate.

PI3K enzymatic assay in vitro

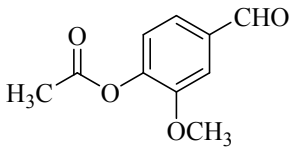
The inhibition of PI3Ks (P110α/85α, Promege; P110β, Millipore; P110γ, Invitrogen; P110 δ , Millipore) activity was determined using the Kinase-Glo Plus Luminescent Kinase assay (PI3Kα, Promege) and ADP-Glo Kinase assay (PI3Kβ, γ and δ, Promege), respectively. Test compounds were serially diluted to the desired concentrations and then 2.5 mL of each of them was added to a 384-well plate (Corning) as assay plate. 1x kinase buffer was prepared contained 50 mM HEPES (pH 7.5), 3 mM $MgCl_2$, 1 mM EGTA, 100 mM NaCl, 0.03% CHAPS, 2 mM DTT. PI3K enzyme was diluted in the 1x kinase buffer to give 4x kinase solutions. PI3Kα, β, δ and δ were diluted to the final concentrations of 1.65 nM, 4.8 nM, 7.6 nM and 5.7 nM, respectively. 2.5 mL of kinase solution was then added to each well of the assay plate, except for control well without enzyme (add 2.5 mL of 1x kinase buffer instead). Meanwhile, PIP2 substrate and ATP were diluted in the 1x kinase buffer to give 2x substrate solution with final concentrations of 50 mM of PIP2 and 25 mM of ATP. After that, 5 mL of substrate solution was added to each well of the assay plate to start reaction. The assay plate was covered and incubated at room temperature for 1 h. As for PI3Kα, 10 mL of Kinase-Glo reagent was then added to each well of the assay plate to stop the reaction. Subsequently, the mixture was treated briefly with centrifuge, shaked slowly on the shaker for 15 min before reading on a plate reader for luminescence. As for PI3Kβ, γ and δ, 5 mL reaction mixture was transferred from 384-well to a new 384 plate and 5 mL of ADP-Glo reagent was added to each well to stop the reaction. The mixture was treated briefly with centrifuge, shaked slowly on the shaker and equilibrated for 40 min. 10 mL Kinase Detection reagentwas added to each wells, shaked for 1 min and equilibrated for 1 h before reading on a plate reader for luminescence. Finally, conversion datawas collected on Flex station and RLU values were converted to inhibition values using the formula of (sample RLU - min)/(max-min)×100. Herein, “min” means the RLU of no enzyme control and “max” means the RLU of DMSO control.

Cell culture and Cytotoxicity/proliferation assay

The antiproliferative activitives of compounds **12b, 12c, 12e, 12h and 12i** were evaluated against HCT116, K562 and Hut78 cell lines by the standard MTT assay in vitro, with Vorinostat and Copanlisib as the positive control. The cancer cell line was cultured in RPMI 1640 medium with 10% fetal bovine serum (FBS). Approximate 2.5×10^3 cells, suspended in RPMI 1640 medium, were plated into each well of a 96-well plate and incubated in 5% CO_2 at 37ºC for 24 h. The tested compounds at the

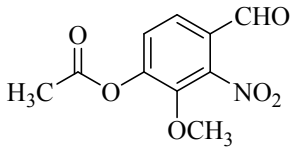
indicated final concentrations were added to the culture medium and incubated for 48 h. Fresh MTT was added to each well at the terminal concentration of 0.5 mg/mL, and incubated with cells at 37ºC for 4 h. After the supernatant was discarded, 150 μL DMSO was added to each well, and the absorbance values were determined by a microplate reader (Bio-Rad, Hercules, CA, USA) at 490 nm.

Synthetic Procedure and analytic data



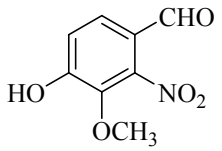
4-formyl-2-methoxyphenyl acetate (**2**)

Vanillin (**1**; 20g, 131mmol), acetic anhydride (26 mL, 275 mmol) were stirred in 80 mL CH_2Cl_2 at 0℃ for 5 min. Then triethylamine (Et_3N) (48 mL, 346 mmol) and DMAP (0.2 g, 1.64 mmol) were added and stirred for 3 h at room temperature. After the completion of reaction, the organic phase was washed with dilute HCl, water and brine, dried over with magnesium sulfate. The solvent was removed by distillation under reduced pressure, the crude product was recrystallized from petroleum ether/ethyl acetate to give compound **2** as a white solid (21.1 g, 85 %); mp: 76~78℃; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H, -C*H*O), 7.51 (m, 2H, *H*-Ar), 7.23 (d, J = 7.7 Hz, 1H, *H*-Ar), 3.94 (s, 3H, -OC*H*$_3$), 2.35 (s, 3H, -COC*H*$_3$); ^{13}C-NMR (300M, $CDCl_3$) δ (ppm): 190.1, 167.8, 151.8, 145.2, 134.7, 124.8, 123.9, 110.7, 55.4, 20.1; ESI-MS *m/z*: 195.1 $[M+H]^+$.



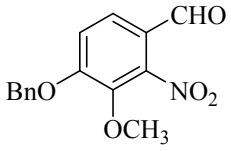
4-formyl-2-methoxy-3-nitrophenyl acetate (**3**)

Fuming nitric acid (80 mL) was cooled to 0 °C and compound **2** (34 g, 175 mmol) was added portionwise, keeping the internal temperature below 5 °C. After 2 h the resulting mixture was poured over ice with stirring. The slurry was filtered and the resulting solids were washed with water (10 mL×3) and air-dried to give the desired product **3** as a yellow solid (17 g, 41 %); mp: 86~88℃; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.90 (s, 1H, -C*H*O), 7.94 (d, 1H, *H*-Ar), 7.75 (d, 1H, *H*-Ar), 3.87 (s, 3H, -OC*H*$_3$), 2.40 (s, 3H, -COC*H*$_3$); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 186.2, 168.0, 150.1, 146.1, 145.2, 126.2, 126.0, 125.5, 62.3, 21.2; ESI-MS *m/z*: 240.0 $[M+H]^+$.



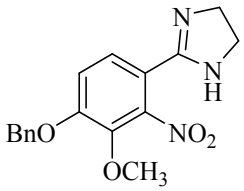
4-hydroxy-3-methoxy-2-nitrobenzaldehyde (**4**)

Compound **3** (17 g, 71.1 mmol), KOH (11.8 g, 210 mmol) were stirred in 120 mL H_2O at 100℃ for 15 min. The reaction mixture was cooled to 0℃ and acidified with dilute HCl (pH 5-6). The precipitant was filtered, washed by water and air-dried to give the corresponding compound **4** as a yellow solid (11g, 79%); mp: 134~137℃; ^{1}H-NMR (300 MHz, DMSO-*d*6) δ 9.69 (s, 1H, -C*H*O), 7.68 (d, , *J* = 7.7, 1H, *H*-Ar), 7.19 (d, *J* = 7.7, 1H, *H*-Ar), 3.82 (s, 3H, -OCH_3); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 190.9, 162.2, 148.6, 144.1, 133.7, 123.1, 122.4, 66.0; ESI-MS m/z: 198.0 $[M+H]^+$.



4-(benzyloxy)-3-methoxy-2-nitrobenzaldehyde (**5**)

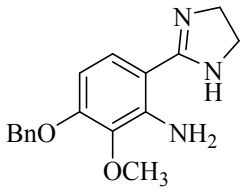
Compound **4** (11 g, 55.8 mmol) was dissolved in 50mL DMF and the stirred solution was treated with potassium carbonate (10 g, 72.4 mmol) followed by benzyl bromide (11 g, 64.3 mmol) at the room temperature. After stirring for 4 h the reaction mixture was poured into 60 mL water, then extracted with EtOAc (30 mL×2). The organic layer was washed with brine (30 mL×2), dried over sodium sulfate and concentrated under reduced pressure. The resulting solids were triturated with Et_2O (300 mL) to give the corresponding compound **5** as a yellow solid (9.8 g, 61%); mp: 110~112℃; ^{1}H-NMR (300 MHz, DMSO-*d*6) δ 9.79 (s, 1H, -C*H*O), 7.88 (d, *J* = 7.6, 1H, *H*-Ar), 7.59 (d, *J* = 7.6, 1H, *H*-Ar), 7.52 (1H, m, *H*-Ar), 7.49 (1H, m, *H*-Ar), 7.39 (3H, m, H-Ar), 5.38 (2H, s, -CH2), 3.06 (3H, s, -CH3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 188.1, 159.7, 143.6, 137.1, 131.1, 130.9, 130.1, 129.7, 127.9, 122.7, 116.5, 73.8, 64.6; ESI-MS m/z: 288.1$[M+H]^+$.



2-(4-(benzyloxy)-3-methoxy-2-nitrophenyl)-4,5-dihydro-1H-imidazole (**6**)

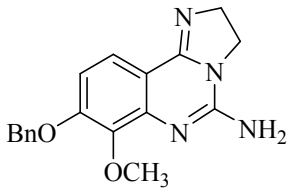
Compound **5** (9.5 g, 33.1 mmol) and ethane-1, 2-diamine (3.8 mL, 56.9 mmol) were stirred in 160 mL tert-butanol at room temperature for 0.5 h. Then, potassium carbonate (10 g, 72.4 mmol) and iodine (11 g, 43.3 mmol) were added and stirred for 4 h at 85℃. The solution was concentrated under reduced pressure. The oil, thus

obtained, was treated with 80 mL water and extracted with CH_2Cl_2 (40 mL×2). Then the organic layer was washed with saturated sodium thiosulfate solution (50 mL×2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was further purified by column chromatography to afford white solid **6** (6.1g, 56%); ^{1}H-NMR (300 MHz, DMSO-*d*6) δ 7.51 (m, 3H, *H*-Ar), 7.44 (m, 3H, *H*-Ar), 7.38 (m, 1H, *H*-Ar), 6.90 (s, 1H, -N*H*-), 5.30 (s, 2H, -CH_2Ph), 3.85 (3H, s, -CH_3), 3.32 (s, 4H, -CH_2CH_2-); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 168.1, 157.6, 142.8, 136.7, 131.1, 130.9, 130.1, 129.7, 122.2, 120.7, 120.1, 73.9, 64.8, 49.7; ESI-MS *m/z*: 328.1 $[M+H]^+$.



3-(benzyloxy)-6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxyaniline (**7**)

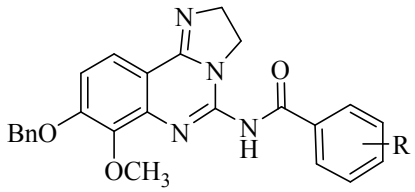
Compound **6** (6.1g, 18.6mmol) and iron powder (5.2g, 93 mmol) were suspended in 100 mL glacial acetic acid and 40 mL water. Then the mixture was stirred at room temperature for 24 h at which time the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The resulting residue was further purified by column chromatography to afford white solid **7** (4.2 g, 76 %); ^{1}H-NMR (300 MHz, DMSO-*d*6) δ 7.49-7.28 (m, 5H, *H*-Ar), 7.16 (d, *J* = 7.6 Hz, 1H, *H*-Ar), 6.92 (brs, 2H, -NH_2), 6.70 (s, 1H, *H*-Ar), 6.35 (d, *J* = 7.6 Hz, 1H, *H*-Ar), 5.13 (s, 2H, -CH_2Ph), 3.82 (t, *J* = 7.0 Hz, 2H, -CH_2CH$_2$-), 3.65 (s, 3H, -OCH_3), 3.26 (t, *J* = 7.0, 2H, -CH$_2$CH_2-); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 168.2, 156.9, 144.6, 137.8, 131.5, 131.1, 130.9, 130.1, 122.8, 104.7, 102.1, 73.8, 68.2, 49.5; ESI-MS *m/z*: 298.2 $[M+H]^+$.



8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (**8**)

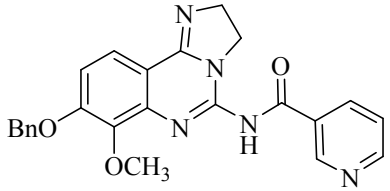
Cyanogen bromide (3.4 g, 32.1 mmol) was added to a mixture of compound **7** (4.2 g, 14.1 mmol) and triethylamine (8.5 mL, 61.3 mmol) in 125 mL CH_2Cl_2 precooled to 0°C. The reaction mixture was stirred and allowed to warm to room temperature gradually. After 4 h it was diluted with saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was further purified by column chromatography to afford white solid **8** (4.1 g，90 %); ^{1}H-NMR (300 MHz, DMSO-*d*6) δ 7.30-7.47 (m, 7H, *H*-Ar), 5.31 (s, 2H, -CH_2Ph), 4.32 (m, 2H, -CH_2CH$_2$-), 4.13 (m, 2H, -CH$_2$CH_2-), 3.81 (s, 3H, -CH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 158.1,

157.3, 150.1, 145.8, 135.5, 130.6, 128.7, 128.0, 127.7,124.5, 118.6, 111.2, 71.8, 51.2, 46.6, 45.1; ESI-MS *m/z*: 323.2 $[M+H]^+$.



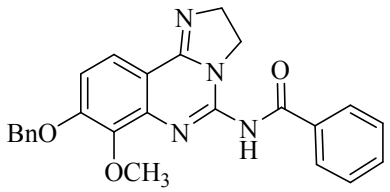
General synthesis of amides of 5-amino-7-methoxy-8-benzyloxy-2,3-dihydroimidazo [1,2-c]quinazoline (**9a-9f**)

Carboxylic acid (1.20 mmol), DMF (0.05 mL) and $SOCl_2$ (6.00 mL) were mixed and stirred at reflux for 4 h, then cooled and evaporated to give reactive acyl chloride. Then the solution of acyl chloride in CH_2Cl_2 (5.00 mL) was added dropwise to the solution of compound **8** (1.00 mmol) and triethylamine (0.50 mL, 3.60 mmol) in 20 mL CH_2Cl_2 at 0°C. After stirring overnight at room temperature, the reaction mixture was then poured in excess of diluted NaOH and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over with sodium sulfate and concentrated under reduced pressure. The crude product was further purified by column chromatography to afford solids **9a-9f**.



N-(8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (**9a**)

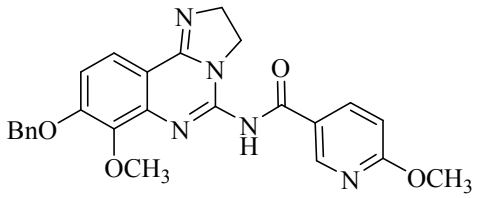
Compound **9a** was synthesized as a yellow solid (720 mg, 85 %) by treatment of nicotinic acid (291 mg，2.38 mmol), $SOCl_2$ (12 mL) , DMF (0.10 mL), compound **8** (640 mg，1.99 mmol) and triethylamine (1 mL, 7.20 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M，DMSO-d_6) δ (ppm): 12.75 (s, 1H, -N*H*CO-), 9.33 (s, 1H, *H*-Py), 8.73 (m, 1H, *H*-Py), 8.45 (m, 1H, *H*-Py), 7.62 (m, 1H, *H*-Py), 7.50 (m, 2H, *H*-Ar), 7.43 (m, 3H, *H*-Ar), 7.32 (m, 1H, *H*-Ar), 7.16 (m, 1H, *H*-Ar), 5.29 (s, 2H, -OC*H*$_2$Ar), 4.10 (m, 2H, =NC*H*$_2$CH$_2$N), 4.06 (m, 2H, =NCH$_2$C*H*$_2$N), 3.93 (s, 3H, -OC*H*$_3$); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 157.0, 149.3, 148.3, 147.7, 146.1, 136.2, 134.1, 133.0, 131.7, 130.9, 128.7, 128.0, 127.7, 126.2, 123.8, 112.6, 101.2, 73.1, 51.2, 46.0, 45.2; ESI-MS *m/z*: 428.2 $[M+H]^+$.



N-(8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide

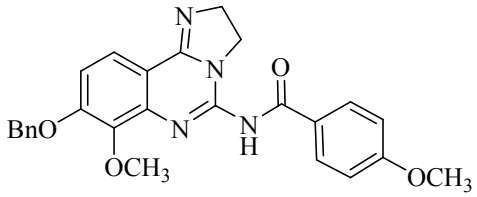
(**9b**)

Compound **9b** was synthesized as a yellow solid (726 mg, 86 %) by treatment of benzoic acid (300 mg，2.44 mmol), $SOCl_2$ (12 mL) , DMF (0.1 mL), compound **8** (640 mg，1.99 mmol) and triethylamine (1 mL, 7.20 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M，DMSO-d_6) δ (ppm): 12.91 (s, 1H, -N*H*CO-), 8.20 (m, 2H, *H*-Ar), 7.66 (m, 1H, *H*-Ar), 7.57 (m, 2H, *H*-Ar), 7.50 (m, 2H, *H*-Ar), 7.43 (m, 3H, *H*-Ar), 7.36 (m, 1H, *H*-Ar), 7.17 (m, 1H, *H*-Ar), 5.28 (s, 2H, -OCH_2Ar), 4.10 (m, 2H, =NCH_2CH$_2$N), 4.06 (m, 2H, =NCH$_2$CH_2N), 3.94 (s, 3H, -OCH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 157.0, 149.3, 146.1, 134.1, 133.8, 133.0, 132.5, 130.9, 129.8, 128.9, 128.7, 128.0, 127.7, 123.8, 112.6, 101.2, 73.1, 51.2, 46.0, 45.2; ESI-MS *m/z*: 427.2 $[M+H]^+$.



N-(8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methoxynicotinamide (**9c**)

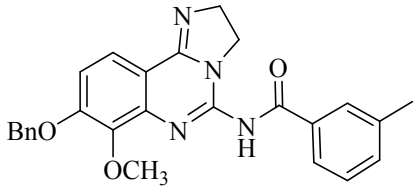
Compound **9c** was synthesized as a yellow solid (740 mg, 81 %) by treatment of 6-methoxynicotinic acid (370 mg，2.42 mmol), $SOCl_2$ (12 mL) , DMF (0.1 mL), compound **8** (640 mg，1.99 mmol) and triethylamine (1 mL, 7.20 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M，DMSO-d_6) δ (ppm): 12.73 (s, 1H, -N*H*CO-), 8.23 (m, 1H, *H*-Py), 7.92 (m, 1H, *H*-Py), 7.51 (m, 2H, *H*-Ar), 7.43 (m, 3H, *H*-Ar), 7.33 (m, 1H, *H*-Ar), 7.15 (m, 1H, *H*-Ar), 7.09 (m, 1H, *H*-Py); 5.28 (s, 2H, -OCH_2Ar), 4.10 (m, 2H, =NCH_2CH$_2$N), 4.06 (m, 2H, =NCH$_2$CH_2N), 3.93 (s, 3H, -OCH_3); 3.83 (s, 3H, -OCH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 164.7, 157.0, 152.1,149.3, 146.1, 140.3, 134.1, 133.0, 130.9, 128.7, 128.0, 127.7, 123.8, 117.7, 113.9, 112.6, 101.2, 73.1, 51.2, 50.8, 46.0, 45.2; ESI-MS *m/z*: 427.2 $[M+H]^+$.



N-(8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-4-methoxybenzamide (**9d**)

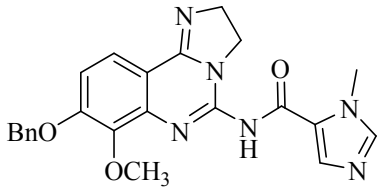
Compound **9d** was synthesized as a yellow solid (730 mg, 81 %) by treatment of 4-methoxybenzoic acid (362 mg，2.38 mmol), $SOCl_2$ (12 mL) , DMF (0.1 mL), compound **8** (640 mg，1.99 mmol) and triethylamine (1 mL, 7.20 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.91 (s, 1H, -N*H*CO-), 8.09 (m, 2H, *H*-Ar), 7.57 (m, 2H, *H*-Ar), 7.50 (m, 2H, *H*-Ar), 7.43 (m, 3H, *H*-Ar), 7.36 (m, 1H, *H*-Ar), 7.18 (m, 1H, *H*-Ar), 7.13 (m, 1H, *H*-Ar), 5.28 (s, 2H, -OCH_2Ar), 4.10 (m, 2H, =NCH_2CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$CH_2NH-), 3.94 (s,

3H, -OCH_3), 3.89 (s, 3H, -OCH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 165.1, 157.0, 149.1, 146.1, 134.0, 133.0, 130.9, 128.7, 128.0, 127.6, 126.2, 125.2, 123.8, 115.7, 112.6, 101.2, 73.1, 51.3, 51.0 46.0, 45.2; ESI-MS *m/z*: 457.2 $[M+H]^+$.



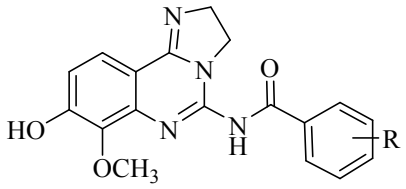
N-(8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-methylbenzamide (**9e**)

Compound **9e** was synthesized as a yellow solid (720 mg, 82 %) by treatment of 3-methylbenzoic acid (324 mg，2.38 mmol), $SOCl_2$ (12 mL) , DMF (0.1 mL), compound **8** (640 mg，1.99 mmol) and triethylamine (1 mL, 7.20 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.91 (s, 1H, -N*H*CO-), 7.97 (m, 1H, *H*-Ar), 7.91 (m, 1H, *H*-Ar), 7.50 (m, 2H, *H*-Ar), 7.43 (m, 3H, *H*-Ar), 7.36 (m, 1H, *H*-Ar), 7.31 (m, 1H, *H*-Ar), 7.26 (m, 1H, *H*-Ar), 7.17 (m, 1H, *H*-Ar), 5.28 (s, 2H, -OCH_2Ar), 4.10 (m, 2H, =NCH_2CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$CH_2NH-), 3.94 (s, 3H, -OCH_3), 2.46 (s, 1H, -CH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 157.0, 149.3, 146.1, 139.6, 134.9, 134.1, 133.5, 133.0, 132.3, 130.9, 129.8, 128.7, 128.1, 127.7, 125.4, 123.8, 112.6, 101.2, 73.1, 51.3, 46.0, 45.2, 23.1; ESI-MS *m/z*: 441.2 $[M+H]^+$.



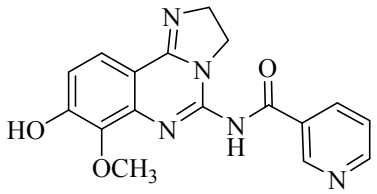
N-(8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-methyl-1H-imidazole-5-carboxamide (**9f**)

Compound **9f** was synthesized as a yellow solid (710 mg, 83 %) by treatment of 1-methyl-1H-imidazole-5-carboxylic acid (300 mg，2.38 mmol), $SOCl_2$ (12 mL), DMF (0.1 mL), compound **8** (640 mg，1.99 mmol) and triethylamine (1 mL, 7.20 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.91 (s, 1H, -N*H*CO-), 8.59 (m, 1H, *H*-imidazole), 8.01 (m, 1H, *H*-imidazole), 7.50 (m, 2H, *H*-Ar), 7.43 (m, 3H, *H*-Ar), 7.36 (m, 1H, *H*-Ar), 7.17 (m, 1H, *H*-Ar), 5.28 (s, 2H, -OCH_2Ar), 4.10 (m, 2H, =NCH_2CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$CH_2NH-), 3.94 (s, 3H, -OCH_3), 3.90 (s, 1H, -NCH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 157.0, 155.6, 149.3, 146.1, 134.1, 133.0, 132.6, 132.1, 130.9, 128.7, 128.1, 127.7, 123.8, 112.6, 101.2, 73.1, 51.3, 46.0, 45.2, 35.1; ESI-MS *m/z*: 431.2 $[M+H]^+$.



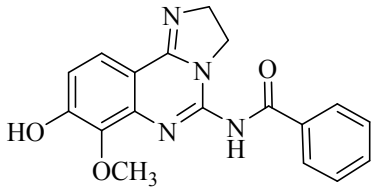
General synthesis of amides of 5-amino-7-methoxy-8-hydroxy-2,3-dihydroimidazo [1,2-c]quinazoline (**10a-10f**)

Compound **9** (1 mmol) was added portionwise to a round-bottom flask containing trifluoroacetic acid (TFA) (25 mL) precooled with an ice bath. The reaction mixture was heated at 60℃ and allowed to stir at this temperature for 5 h, at which time it was cooled to RT. Then, it was concentrated under reduced pressure. The resulting residue was further purified by column chromatography to afford solids **10a-10f**.



N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (**10a**)

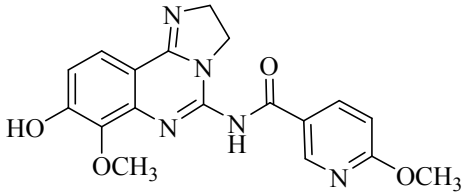
Compound **10a** was synthesized as a white solid (440 mg, 80 %) by treatment of compound **9a** (700mg, 1.64mmol) and trifluoroacetic acid (40 mL) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.77 (s, 1H, -N*H*CO-), 9.33 (s, 1H, *H*-Py), 8.73 (m, 1H, *H*-Py), 8.46 (m, 1H, *H*-Py), 7.54-7.48 (m, 2H, *H*-Py and *H*-Ar), 6.84 (m, 1H, *H*-Ar), 5.31 (s, 1H, *H*OAr), 4.10 (m, 2H, =NCH_2CH$_2$NH-), 4.07 (m, 2H, =NCH$_2$CH_2NH-), 3.92 (s, 3H, -OCH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 153.1, 149.3, 148.3, 147.7, 146.9, 136.2, 134.8, 133.0, 131.7, 126.2, 124.3, 112.9, 105.6, 51.2, 46.0, 45.2; ESI-MS *m/z*: 338.2 $[M+H]^+$.



N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide (**10b**)

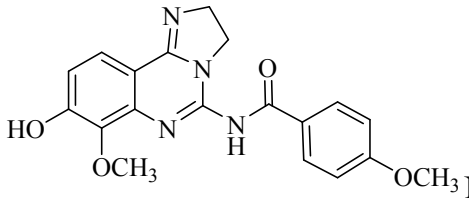
Compound **10b** was synthesized as a white solid (452 mg, 82 %) by treatment of compound **9b** (700 mg, 1.64 mmol) and trifluoroacetic acid (40 mL) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.90 (s, 1H, -N*H*CO-), 8.20 (m, 2H, *H*-Ar), 7.67 (m, 1H, *H*-Ar), 7.58 (m, 2H, *H*-Ar), 7.45 (m, 1H, *H*-Ar), 6.83 (m, 1H, *H*-Ar), 5.31 (s, 1H, *H*OAr), 4.11 (m, 2H, =NCH_2CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$CH_2NH-), 3.94 (s, 3H, -OCH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 153.1, 149.3, 146.9, 134.8, 133.8, 133.0, 132.5, 129.8, 128.9, 124.3,

112.9, 105.6, 51.2, 46.0, 45.2; ESI-MS *m/z*: 337.2 $[M+H]^+$.



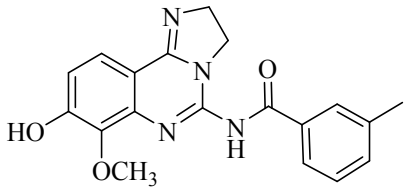
N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methoxynicotinamide (**10c**)

Compound **10c** was synthesized as a white solid (450 mg, 78 %) by treatment of compound **9c** (720 mg, 1.57 mmol) and trifluoroacetic acid (40 mL) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.73 (s, 1H, -N*H*CO-), 8.23 (m, 1H, *H*-Py), 7.92 (m, 1H, *H*-Py), 7.47 (m, 1H, *H*-Ar), 7.10 (m, 1H, *H*-Py), 6.84 (m, 1H, *H*-Ar), 4.11 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$C*H*$_2$NH-), 3.94 (s, 3H, -OC*H*$_3$), 3.83 (s, 3H, -OC*H*$_3$); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 164.7, 153.1, 152.1, 149.3, 146.9, 140.3, 134.8, 133.0, 124.2, 117.7, 113.9, 112.9, 105.6, 51.2, 50.8, 46.0, 45.2; ESI-MS *m/z*: 368.2 $[M+H]^+$.



N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-4-methoxybenzamide (**10d**)

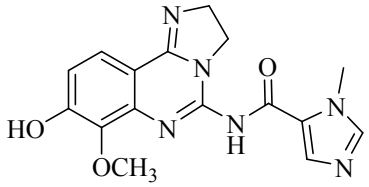
Compound **10d** was synthesized as a white solid (450 mg, 79 %) by treatment of compound **9d** (710 mg, 1.56 mmol) and trifluoroacetic acid (40 mL) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.91 (s, 1H, -N*H*CO-), 8.10 (m, 2H, *H*-Ar), 7.58 (m, 2H, *H*-Ar), 7.44 (m, 1H, *H*-Ar), 7.14 (m, 1H, *H*-Ar), 6.83 (m, 1H, *H*-Ar), 5.31 (s, 1H, *H*OAr), 4.11 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$C*H*$_2$NH-), 3.94 (s, 3H, -OC*H*$_3$), 3.89 (s, 3H, -OC*H*$_3$); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 165.1, 153.0, 149.1, 146.9, 134.9, 133.0, 126.2, 125.2, 124.3, 115.7, 113.0, 105.8, 51.3, 51.0 46.0, 45.2; ESI-MS *m/z*: 367.2 $[M+H]^+$.



N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-methylbenzamide (**10e**)

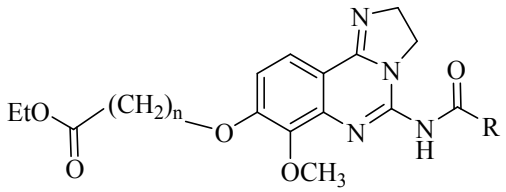
Compound **10e** was synthesized as a white solid (420 mg, 75 %) by treatment of compound **9e** (700 mg, 1.59 mmol) and trifluoroacetic acid (40 mL) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.91 (s, 1H, -N*H*CO-), 7.98 (m, 1H, *H*-Ar), 7.91 (m, 1H, *H*-Ar), 7.45 (m, 1H, *H*-Ar), 7.32 (m,

1H, *H*-Ar), 7.26 (m, 1H, *H*-Ar), 6.83 (m, 1H, *H*-Ar), 5.29 (s, 1H, *H*OAr), 4.11 (m, 2H, =NCH_2CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$CH_2NH-), 3.94 (s, 3H, -OCH_3), 2.46 (s, 3H, -CH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 153.1, 149.3, 146.9, 139.6, 134.9, 134.7, 133.5, 133.0, 132.3, 129.8, 125.4, 124.3, 113.0, 105.8, 51.3, 46.0, 45.2, 23.1; ESI-MS *m/z*: 351.2 $[M+H]^+$.



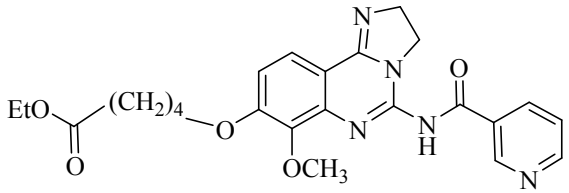
N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-methyl-1H-imidazole-5-carboxamide (**10f**)

Compound **10f** was synthesized as a white solid (410 mg, 74 %) by treatment of compound **9f** (700 mg, 1.63 mmol) and trifluoroacetic acid (40 mL) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d$_6$) δ (ppm): 12.91 (s, 1H, -N*H*CO-), 8.59 (m, 1H, *H*-imidazole), 8.01 (m, 1H, *H*-imidazole), 7.45 (m, 1H, *H*-Ar), 6.84 (m, 1H, *H*-Ar), 5.35 (s, 1H, *H*OAr), 4.11 (m, 2H, =NCH_2CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$CH_2NH-), 3.94 (s, 3H, -OCH_3), 3.89 (s, 3H, -NCH_3); ^{13}C-NMR (300M, DMSO-d6) δ (ppm): 176.1, 153.1, 155.6, 149.3, 146.9, 134.8, 133.0, 132.6, 132.1, 124.3, 113.1, 105.8, 51.3, 46.0, 45.2, 35.1; ESI-MS *m/z*: 341.2 $[M+H]^+$.



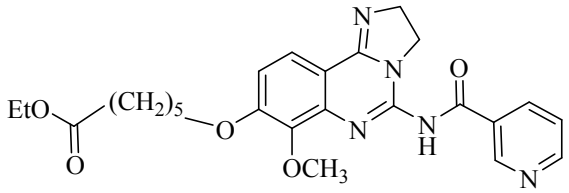
General synthesis of amides of ethyl 6-((7-methoxy-5-amido-2,3-dihydroimidazo [1,2-c]quinazolin-8-yl)oxy)alkanoate (**11a-11j**)

Compound **10** (1 mmol) was solubilized in DMF (8 mL) and Cs_2CO_3 (2.5 mmol) was added. The mixture was stirred at 50℃ for 0.5 h, then ethyl bromoalkanoate (1.5 mmol) was added. The reaction mixture was stirred at 80℃ for 2 h, then cooled to the room temperature and poured into 30 mL water. The solution was extracted with CH_2Cl_2 and the extract was concentrated under reduced pressure. The resulting residue was further purified by column chromatography to afford solids.



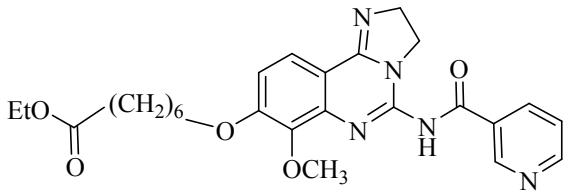
ethyl 5-((7-methoxy-5-(nicotinamido)-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy) pentanoate (**11a**)

Compound **11a** was synthesized as a white solid (177 mg, 64 %) by treatment of compound **10a** (200 mg, 0.59 mmol), Cs_2CO_3 (484 mg, 1.50 mmol) and ethyl 5-bromopentanoate (186 mg, 0.89 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.75 (s, 1H, -N*H*CO-), 9.33 (s, 1H, *H*-Py), 8.73 (s, 1H, *H*-Py), 8.45 (m, 1H, *H*-Py), 7.62 (m, 1H, *H*-Py), 7.53 (m, 1H, *H*-Ar), 7.05 (m, 1H, *H*-Ar), 4.10 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.94 (s, 3H, -OC*H*$_3$), 2.29 (t, 2H, *J* = 7.0 Hz, EtOOCC*H*$_2$-), 1.79 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.66 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.17 (t, 3H, *J* = 7.0 Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 180.3, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 68.4, 61.2, 51.2, 46.0, 45.2, 33.5, 27.9, 22.7, 14.2; ESI-MS *m/z*: 466.2 [M+H]$^+$.



ethyl 6-((7-methoxy-5-(nicotinamido)-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy) hexanoate (**11b**)

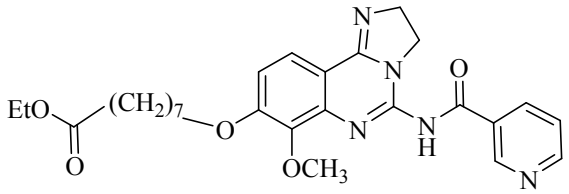
Compound **11b** was synthesized as a white solid (185 mg, 65.1%) by treatment of compound **10a** (200 mg, 0.59 mmol), Cs_2CO_3 (484 mg, 1.50 mmol) and ethyl 6-bromohexanoate (200 mg, 0.89 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.75 (s, 1H, -N*H*CO-), 9.33 (s, 1H, *H*-Py), 8.73 (s, 1H, *H*-Py), 8.45 (m, 1H, *H*-Py), 7.62 (m, 1H, *H*-Py), 7.53 (m, 1H, *H*-Ar), 7.05 (m, 1H, *H*-Ar), 4.10 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.94 (s, 3H, -OC*H*$_3$), 2.29 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.79 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.56 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.30 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.17 (t, 3H, J=7Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 180.3, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 69.5, 61.2, 51.2, 46.0, 45.2, 33.3, 29.6, 25.8, 25.5, 14.2; ESI-MS *m/z*: 480.2 [M+H]$^+$.



ethyl 7-((7-methoxy-5-(nicotinamido)-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy) heptanoate (**11c**)

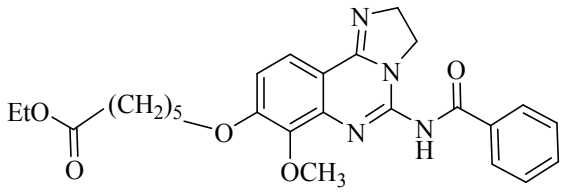
Compound **11c** was synthesized as a white solid (180 mg, 62 %) by treatment of compound **10a** (200 mg, 0.59 mmol), Cs_2CO_3 (484 mg, 1.50 mmol) and ethyl 7-

bromoheptanoate (211 mg, 0.89 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.75 (s, 1H, -N*H*CO-), 9.33 (s, 1H, *H*-Py), 8.73 (s, 1H, *H*-Py), 8.45 (m, 1H, *H*-Py), 7.62 (m, 1H, *H*-Py), 7.53 (m, 1H, *H*-Ar), 7.05 (m, 1H, *H*-Ar), 4.10 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.94 (s, 3H, -OC*H*$_3$), 2.29 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.78 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.56 (m, 2H, -C*H*$_2$(CH$_2$)$_4$OAr), 1.46 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.37 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.17 (t, 3H, J=7Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 180.3, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 69.3, 61.2, 51.2, 46.0, 45.2, 33.9, 29.8, 29.0, 25.6, 24.7, 14.2; ESI-MS *m/z*: 494.2 [M+H]$^+$.



ethyl 8-((7-methoxy-5-(nicotinamido)-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy) octanoate (**11d**)

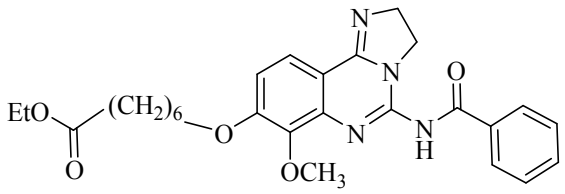
Compound **11d** was synthesized as a white solid (192mg, 66 %) by treatment of compound **10a** (200 mg, 0.59 mmol), Cs_2CO_3 (484 mg, 1.50 mmol) and ethyl 7-bromoheptanoate (211 mg, 0.89 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.75 (s, 1H, -N*H*CO-), 9.33 (s, 1H, *H*-Py), 8.73 (s, 1H, *H*-Py), 8.45 (m, 1H, *H*-Py), 7.62 (m, 1H, *H*-Py), 7.53 (m, 1H, *H*-Ar), 7.05 (m, 1H, *H*-Ar), 4.10 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.94 (s, 3H, -OC*H*$_3$), 2.29 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.78 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.57 (m, 2H, -C*H*$_2$(CH$_2$)$_5$OAr), 1.46 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.37 (m, 2H, -C*H*$_2$(CH$_2$)$_4$OAr), 1.27 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.17 (t, 3H, J=7Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 180.3, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 69.2, 61.2, 51.1, 46.0, 45.1, 33.9, 29.7, 29.4, 29.0, 26.4, 24.8, 14.2; ESI-MS *m/z*: 408.2 [M+H]$^+$.



ethyl 6-((5-benzamido-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy) hexanoate (**11e**)

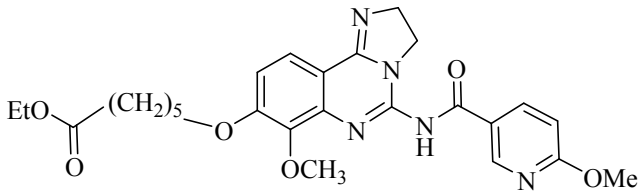
Compound **11e** was synthesized as a white solid (190 mg, 67 %) by treatment of compound **10b** (200 mg, 0.59 mmol), Cs_2CO_3 (484 mg, 1.50 mmol) and ethyl 6-bromohexanoate (200 mg, 0.89 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.90 (s, 1H, -N*H*CO-), 8.20 (m, 2H,

H-Ar), 7.67 (m, 1H, *H*-Ar), 7.58 (m, 2H, *H*-Ar), 7.51 (m, 1H, *H*-Ar), 7.06 (m, 1H, *H*-Ar), 4.11 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.94 (s, 3H, -OC*H*$_3$), 2.29 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.79 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.61 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.48 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.17 (t, 3H, J=7Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d$_6$) δ (ppm): 180.3, 173.6, 157.3, 149.0, 146.1, 134.3, 134.0, 133.0, 132.5, 129.8, 128.6, 124.0, 112.6, 101.2, 69.5, 61.2, 51.2, 46.0, 45.2, 33.8, 29.9, 25.5, 25.1, 14.2; ESI-MS *m/z*: 479.2 [M+H]$^+$.



ethyl 7-((5-benzamido-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy) heptanoate (**11f**)

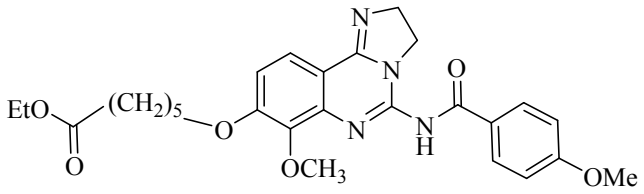
Compound **11f** was synthesized as a white solid (180 mg, 61.5 %) by treatment of compound **10b** (200 mg, 0.59 mmol), Cs_2CO_3 (484 mg, 1.50 mmol) and ethyl 7-bromoheptanoate (212 mg, 0.89 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d$_6$) δ (ppm): 12.90 (s, 1H, -N*H*CO-), 8.20 (m, 2H, *H*-Ar), 7.67 (m, 1H, *H*-Ar), 7.58 (m, 2H, *H*-Ar), 7.51 (m, 1H, *H*-Ar), 7.06 (m, 1H, *H*-Ar), 4.11 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.94 (s, 3H, -OC*H*$_3$), 2.29 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.78 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.56 (m, 2H, -C*H*$_2$(CH$_2$)$_4$OAr), 1.46 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.37 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.17 (t, 3H, J=7Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d$_6$) δ (ppm): 180.3, 173.6, 157.3, 149.0, 146.1, 134.3, 134.0, 133.0, 132.5, 129.8, 128.6, 124.0, 112.6, 101.2, 69.3, 61.2, 51.2, 46.0, 45.2, 34.2, 29.7, 29.0, 25.5, 25.0, 14.2; ESI-MS *m/z*: 493.3 [M+H]$^+$.



ethyl 6-((7-methoxy-5-(6-methoxynicotinamido)-2,3-dihydroimidazo[1,2-c] quinazolin-8-yl)oxy)hexanoate (**11g**)

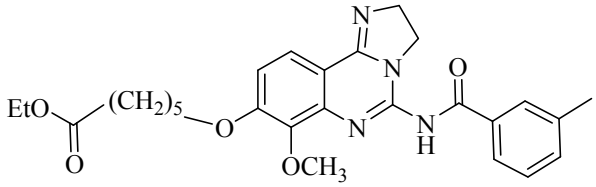
Compound **11g** was synthesized as a white solid (170 mg, 61 %) by treatment of compound **10c** (200 mg, 0.54 mmol), Cs_2CO_3 (443 mg, 1.40 mmol) and ethyl 6-bromohexanoate (182 mg, 0.82 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d$_6$) δ (ppm): 12.78 (s, 1H, -N*H*CO-), 9.02 (m, 1H, *H*-Py), 8.40 (m, 1H, *H*-Py), 7.59 (m, 1H, *H*-Ar), 7.08 (m, 1H, *H*-Py), 6.88 (m, 1H, *H*-Ar), 4.11 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.93 (s, 3H, -OC*H*$_3$), 3.92 (s, 3H, -OC*H*$_3$), 2.33 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.79 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.62 (m, 2H, -

C*H*$_2$(CH$_2$)$_3$OAr), 1.48 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.17 (t, 3H, J=7Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d$_6$) δ (ppm): 180.3, 176.1, 164.6, 157.3, 152.1, 149.1, 146.1, 140.3, 134.3, 133.0, 124.0, 117.7, 113.9, 112.6, 101.2, 69.5, 61.2, 51.2, 50.8, 46.0, 45.2, 33.9, 30.1, 25.3, 24.9, 14.2; ESI-MS *m/z*: 510.2[M+H]$^+$.



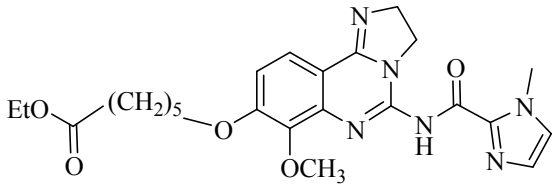
ethyl 6-((7-methoxy-5-(4-methoxybenzamido)-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy)hexanoate (**11h**)

Compound **11h** was synthesized as a white solid (170 mg, 59 %) by treatment of compound **10d** (210 mg, 0.57 mmol), Cs$_2$CO$_3$ (465 mg, 1.43 mmol) and ethyl 6-bromohexanoate (191 mg, 0.86 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d$_6$) δ (ppm): 12.90 (s, 1H, -N*H*CO-), 8.16 (d，2H，J=9Hz, *H*-Ar), 7.58 (d, 1H, J=9Hz，*H*-Ar), 7.02 (m, 3H, *H*-Ar), 4.10 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.94 (s, 3H, -OC*H*$_3$), 2.29 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.78 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.46 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.37 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.17 (t, 3H, J=7Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d$_6$) δ (ppm): 180.2, 176.1, 165.2, 157.3, 149.1, 146.1, 134.3, 133.0, 126.2, 125.2, 124.0, 115.7, 112.6, 101.2, 69.5, 61.2, 51.2, 51.0, 46.0, 45.2, 33.9, 30.0, 25.3, 24.9, 14.2; ESI-MS *m/z*: 509.2 [M+H]$^+$.



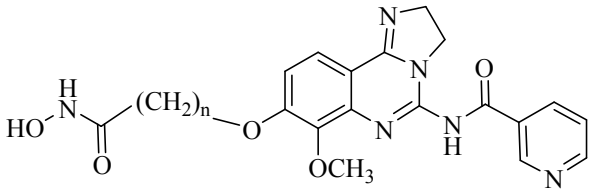
ethyl 6-((7-methoxy-5-(3-methylbenzamido)-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl)oxy)hexanoate (**11i**)

Compound **11i** was synthesized as a white solid (170 mg, 60 %) by treatment of compound **10e** (200 mg, 0.57 mmol), Cs$_2$CO$_3$ (465 mg, 1.43 mmol) and ethyl 6-bromohexanoate (191 mg, 0.86 mmol) according to above-mentioned general procedure; ^{1}H-NMR (300M, DMSO-d$_6$) δ (ppm): 12.89 (s, 1H, -N*H*CO-), 8.01 (m，2H， *H*-Ar), 7.58 (m, 1H, *H*-Ar), 7.36 (m, 2H, *H*-Ar), 7.01 (m, 1H, *H*-Ar), 4.11 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.09 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, CH$_3$C*H*$_2$OOC-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.93 (s, 3H, -OC*H*$_3$), 2.37 (s，3H，ArC*H*$_3$), 2.32 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.78 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.62 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.48 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.17 (t, 3H, J=7.0 Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d$_6$) δ (ppm): 180.3, 176.1, 157.3, 149.1, 146.1, 139.6, 134.9, 134.3, 133.5, 133.0, 132.3, 129.8, 125.4, 124.0, 112.6, 101.2, 69.5, 61.3, 51.2, 46.0, 45.2, 34.0, 30.1, 25.3, 24.9, 22.9, 14.2; ESI-MS *m/z*: 493.2 [M+H]$^+$.



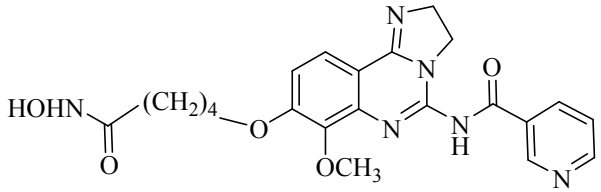
ethyl 6-((7-methoxy-5-(1-methyl-1H-imidazole-2-carboxamido)-2,3-dihydroimidazo [1,2-c]quinazolin-8-yl)oxy)hexanoate (**11j**)

Compound **11j** was synthesized as a white solid (180 mg, 63 %) by treatment of compound **10e** (200 mg, 0.59 mmol), Cs_2CO_3 (479 mg, 1.47 mmol) and ethyl 6-bromohexanoate (197 mg, 0.88 mmol) according to above-mentioned general procedure. ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.53 (s, 1H, -N*H*CO-), 7.78 (m, 1H, *H*-imidazole), 7.67 (m, 1H, *H*-imidazole), 7.57 (d, 1H, J = 9.0 Hz, *H*-Ar), 7.02 (d, 1H, J = 9.0 Hz, *H*-Ar), 4.09 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.06 (m, 4H, =NCH$_2$C*H*$_2$NH- and CH$_3$C*H*$_2$OOC-), 4.02 (m, 2H, -C*H*$_2$OAr), 3.92 (s, 3H, -OC*H*$_3$), 3.90 (s, 3H, -NC*H*$_3$), 2.32 (t, 2H, *J*=7.0Hz, EtOOCC*H*$_2$-), 1.77 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.62 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.48 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.17 (t, 3H, J=7.0 Hz, C*H*$_3$CH$_2$OOC-); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 180.3, 176.1, 157.3, 155.4 149.1, 146.1, 134.3, 133.0, 132.5, 131.9, 124.0, 112.6, 101.2, 69.5, 61.3, 51.2, 46.0, 45.2, 35.6, 33.9, 30.1, 25.3, 24.9, 14.2; ESI-MS *m/z*: 483.2 $[M+H]^+$.



General synthesis of amides of N-(8-(hydroxyaminooxoalkanyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (**12a-12j**)

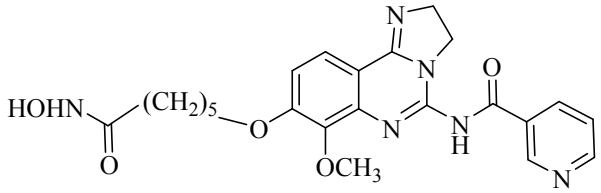
KOH (15 mmol) was added to a solution of hydroxyamine hydrochloride (10 mmol) in methanol (15 mL) cooled by an ice bath. The mixture was stirred for another 1 h. The resulting precipitate was filtered off, and the solution of free hydroxylamine was prepared. The above freshly prepared hydroxyamine solution was placed in a round bottom flask cooled by an ice bath and compound **11** (1 mmol) was added to the solution. After the mixture was stirred over night at the room temperature, water (25 mL) and AcOH were added to adjust pH to 4-5. The solution was keeping in a refrigerator for 3 h. The precipitate was collected by filtration, washed with water, then crystallized from acetone/THF to afford the white solids.



N-(8-((5-(hydroxyamino)-5-oxopentyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-

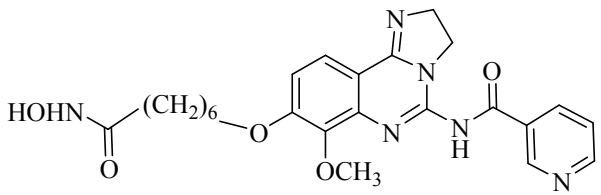
c]quinazolin-5-yl)nicotinamide (**12a**)

Compound **12a** was synthesized as a white solid (77 mg, 53 %) by treatment of compound **11a** (150 mg, 0.32 mmol), hydroxyamine hydrochloride (224 mg, 3.22 mmol) and KOH (271 mg, 4.83 mmol) according to above-mentioned general procedure; mp: 204~206℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.83 (s, 1H, -N*H*CO-), 10.26 (s, 1H, *H*ONH-), 9.25 (s, 1H, *H*-Py), 8.76 (m, 1H, *H*-Py), 8.56 (s, 1H, HON*H*-), 8.37 (m, 1H, *H*-Py), 7.59 (m, 1H, *H*-Py), 7.45 (m, 1H, *H*-Ar), 7.04 (m, 1H, *H*-Ar), 4.07 (m, 2H, =NCH_2CH$_2$NH-), 4.05 (m, 2H, =NCH$_2$CH_2NH-), 4.01 (m, 2H, -CH_2OAr), 3.94 (s, 3H, -OCH_3), 1.98 (t，2H，J = 7.0 Hz，HONHCOCH_2-), 1.82 (m, 2H, -CH_2CH$_2$OAr), 1.58 (m, 2H, -CH_2(CH$_2$)$_2$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 68.1, 51.2, 46.0, 45.2, 33.3, 27.8, 22.7; HRMS (ESI): m/z calcd for $C_{22}H_{24}N_6O_5Na^+$ (M + Na^+): 475.1700, found: 475.1723.



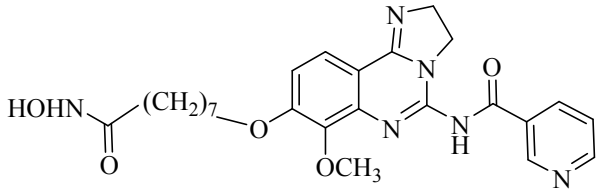
N-(8-((6-(hydroxyamino)-6-oxohexyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (**12b**)

Compound **12b** was synthesized as a white solid (73 mg, 50 %) by treatment of compound **11b** (150 mg, 0.31 mmol), hydroxyamine hydrochloride (217 mg, 3.13 mmol) and KOH (263 mg, 4.69 mmol) according to above-mentioned general procedure; mp: 238~240℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.82 (s, 1H, -N*H*CO-), 10.26 (s, 1H, *H*ONH-), 9.24 (s, 1H, *H*-Py), 8.76 (m, 1H, *H*-Py), 8.56 (s, 1H, HON*H*-), 8.36 (m, 1H, *H*-Py), 7.58 (m, 1H, *H*-Py), 7.45 (m, 1H, *H*-Ar), 7.04 (m, 1H, *H*-Ar), 4.07 (m, 2H, =NCH_2CH$_2$NH-), 4.04 (m, 2H, =NCH$_2$CH_2NH-), 4.01 (m, 2H, -CH_2OAr), 3.93 (s, 3H, -OCH_3), 1.99 (t，2H，J = 7.0 Hz，HONHCOCH_2-), 1.79 (m, 2H, -CH_2CH$_2$OAr), 1.58 (m, 2H, -CH_2(CH$_2$)$_3$OAr), 1.44 (m, 2H, -CH_2(CH$_2$)$_2$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 69.5, 51.2, 46.0, 45.2, 32.9, 29.6, 25.8, 24.7; HRMS (ESI): m/z calcd for $C_{23}H_{26}N_6O_5Na^+$ (M + Na^+): 489.1857, found: 489.1883.



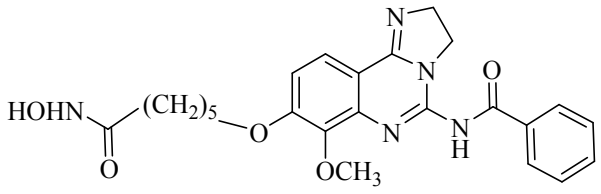
N-(8-((7-(hydroxyamino)-7-oxoheptyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (**12c**)

Compound **12c** was synthesized as a white solid (75mg, 51%) by treatment of compound **11c** (150 mg, 0.30 mmol), hydroxyamine hydrochloride (211 mg, 3.04 mmol) and KOH (256 mg, 4.56 mmol) according to above-mentioned general procedure; mp: 209~211℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.73 (s, 1H, -N*H*CO-), 10.30 (s, 1H, *H*ONH-), 9.32 (s, 1H, *H*-Py), 8.72(m, 1H, *H*-Py), 8.61(s, 1H, HON*H*-), 8.45 (m, 1H, *H*-Py), 7.59 (m, 1H, *H*-Py), 7.51(m, 1H, *H*-Ar), 7.04 (m, 1H, *H*-Ar), 4.11(m, 2H, =NCH_2CH$_2$NH-), 4.09 (m, 2H, =NCH$_2$CH_2NH-), 4.04 (m, 2H, -CH_2OAr), 3.94 (s, 3H, -OCH_3), 1.96 (t，2H，J = 7.0 Hz，HONHCOCH_2-), 1.77 (m, 2H, -CH_2CH$_2$OAr), 1.54 (m, 2H, -CH_2(CH$_2$)$_4$OAr), 1.49(m, 2H, -CH_2(CH$_2$)$_2$OAr), 1.34 (m, 2H, -CH_2(CH$_2$)$_3$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 69.3, 51.2, 46.0, 45.2, 33.6, 29.7, 28.7, 25.8, 25.1; HRMS (ESI): m/z calcd for $C_{24}H_{28}N_6O_5Na^+$ (M + Na^+): 503.2013, found: 503.2035.



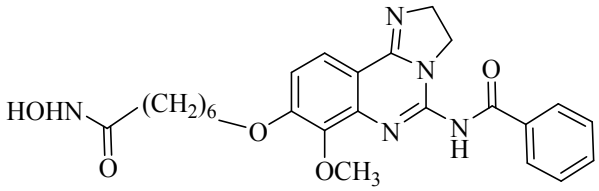
N-(8-((8-(hydroxyamino)-8-oxooctyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (**12d**)

Compound **12d** was synthesized as a white solid (74mg, 51%) by treatment of compound **11d** (150 mg, 0.30 mmol), hydroxyamine hydrochloride (205 mg, 2.96 mmol) and KOH (249 mg, 4.43 mmol) according to above-mentioned general procedure; mp: 236~238℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.70 (s, 1H, -N*H*CO-), 10.29 (s, 1H, *H*ONH-), 9.32 (s, 1H, *H*-Py), 8.72 (m, 1H, *H*-Py), 8.60 (s, 1H, HON*H*-), 8.45 (m, 1H, *H*-Py), 7.59 (m, 1H, *H*-Py), 7.51 (m, 1H, *H*-Ar), 7.04 (m, 1H, *H*-Ar), 4.11(m, 2H, =NCH_2CH$_2$NH-), 4.09 (m, 2H, =NCH$_2$CH_2NH-), 4.04 (m, 2H, -CH_2OAr), 3.94 (s, 3H, -OCH_3), 1.98 (t，2H，J = 7.0 Hz，HONHCOCH_2-), 1.79 (m, 2H, -CH_2CH$_2$OAr), 1.55 (m, 2H, -CH_2(CH$_2$)$_5$OAr), 1.49(m, 2H, -CH_2(CH$_2$)$_2$OAr), 1.34-1.30 (m, 4H, -CH_2(CH$_2$)$_4$OAr and -CH_2(CH$_2$)$_3$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 157.3, 149.1, 148.3, 146.1, 136.2, 134.3, 133.0, 131.7, 126.2, 124.0, 112.6, 101.2, 69.2, 51.1, 46.0, 45.1, 33.5, 29.7, 29.3, 28.8, 26.3, 25.2; HRMS (ESI): m/z calcd for $C_{25}H_{30}N_6O_5Na^+$ (M + Na^+): 517.2170, found: 517.2187.



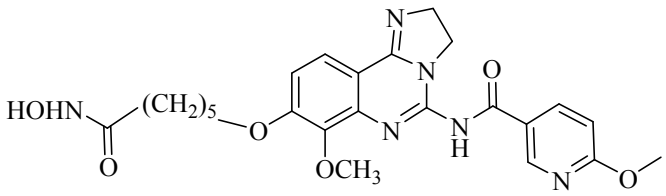
N-(8-((6-(hydroxyamino)-6-oxohexyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide (**12e**)

Compound **12e** was synthesized as a white solid (79 mg, 54 %) by treatment of compound **11e** (150 mg, 0.31 mmol), hydroxyamine hydrochloride (218 mg, 3.13 mmol) and KOH (264 mg, 4.70 mmol) according to above-mentioned general procedure; mp: 233~234℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.89 (s, 1H, -N*H*CO-), 10.35 (s, 1H, *H*ONH-), 8.66 (s, 1H, HON*H*-), 8.21 (d, 2H, *J* = 7.0 Hz, *H*-Ar), 7.60 (m, 1H, *H*-Ar), 7.55 (d, 1H, *J* = 7.0 Hz, *H*-Ar), 7.49 (m, 1H, *H*-Ar), 7.45 (s, 1H, *H*-Ar), 7.04 (d, 1H, *J* = 9.0 Hz, *H*-Ar), 4.12 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.09 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.04 (m, 2H, -C*H*$_2$OAr), 3.93 (s, 3H, -OC*H*$_3$), 1.99 (t, 2H, *J* = 7.0 Hz, HONHCOC*H*$_2$-), 1.79 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.58 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.44 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.1, 173.6, 157.3, 149.0, 146.1, 134.3, 134.0, 133.0, 132.5, 129.8, 128.6, 124.0, 112.6, 101.2, 69.5, 51.2, 46.0, 45.2, 32.9, 29.6, 25.8, 24.7; HRMS (ESI): m/z calcd for $C_{24}H_{27}N_5O_5Na^+$ (M + Na^+): 488.1904, found: 488.1927.



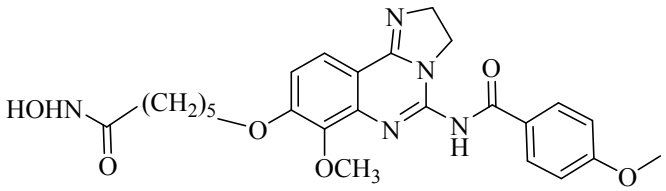
N-(8-((7-(hydroxyamino)-7-oxoheptyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide (**12f**)

Compound **12f** was synthesized as a white solid (74 mg, 51 %) by treatment of compound **11f** (150 mg, 0.30 mmol), hydroxyamine hydrochloride (212 mg, 3.05 mmol) and KOH (256 mg, 4.56 mmol) according to above-mentioned general procedure; mp: 199~202℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.81 (s, 1H, -N*H*CO-), 10.36 (s, 1H, *H*ONH-), 8.21 (s, 1H, HON*H*-), 8.18 (s, 1H, *H*-Ar), 7.57 (m, 2H, *H*-Ar), 7.51 (m, 2H, *H*-Ar), 7.46 (m, 1H, *H*-Ar), 7.00 (m, 1H, *H*-Ar), 4.08 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.06 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.01 (m, 2H, -C*H*$_2$OAr), 3.93 (s, 3H, -OC*H*$_3$), 1.96 (t, 2H, *J* = 7.0 Hz, HONHCOC*H*$_2$-), 1.76 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.50 (m, 2H, -C*H*$_2$(CH$_2$)$_4$OAr), 1.44 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr), 1.34 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.1, 173.6, 157.3, 149.0, 146.1, 134.3, 134.0, 133.0, 132.5, 129.8, 128.6, 124.0, 112.6, 101.2, 69.3, 51.2, 46.0, 45.2, 33.6, 29.7, 28.7, 25.7, 25.0; HRMS (ESI): m/z calcd for $C_{25}H_{29}N_5O_5Na^+$ (M + Na^+): 502.2061, found: 502.2086.



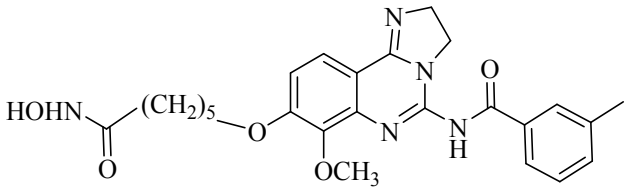
N-(8-((6-(hydroxyamino)-6-oxohexyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methoxynicotinamide (**12g**)

Compound **12g** was synthesized as a white solid (74 mg, 51 %) by treatment of compound **11g** (150 mg, 0.29 mmol), hydroxyamine hydrochloride (205 mg, 2.94 mmol) and KOH (248 mg, 4.42 mmol) according to above-mentioned general procedure. mp: 230~233℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.74 (s, 1H, -N*H*CO-), 10.35 (s, 1H, *H*ONH-), 8.97 (s, 1H, *H*-Py), 8.67 (s, 1H, HON*H*-), 8.35 (d, 1H, *J* = 7.0 Hz, *H*-Py), 7.57 (d, 1H, *J* = 9.0 Hz, *H*-Ar), 7.02 (d, 1H, *J* = 9.0 Hz, *H*-Ar), 6.86 (d, 1H, *J* = 9.0 Hz, *H*-Py), 4.10 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.08 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.06 (m, 2H, -C*H*$_2$OAr), 3.92 (s, 6H, -OC*H*$_3$), 1.99 (t, 2H, *J* = 7.0 Hz, HONHCOC*H*$_2$-), 1.78 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.58 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.44 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 164.6, 157.3, 152.1, 149.1, 146.1, 140.3, 134.3, 133.0, 124.0, 117.7, 113.9, 112.6, 101.2, 69.5, 51.2, 50.8, 46.0, 45.2, 32.9, 29.6, 25.8, 24.7; HRMS (ESI): m/z calcd for $C_{24}H_{28}N_6O_6Na^+$ (M + Na^+): 519.1963, found: 519.1981.



N-(8-((6-(hydroxyamino)-6-oxohexyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-4-methoxybenzamide (**12h**)

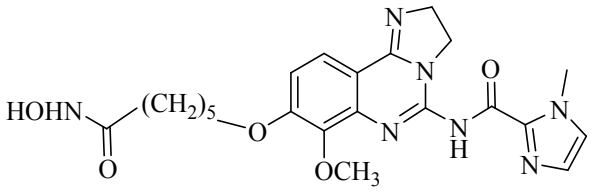
Compound **12h** was synthesized as a white solid (70 mg, 48 %) by treatment of compound **11g** (150 mg, 0.29 mmol), hydroxyamine hydrochloride (205 mg, 2.94 mmol) and KOH (248 mg, 4.42 mmol) according to above-mentioned general procedure; mp: 229~231℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.97 (s, 1H, -N*H*CO-), 10.35 (s, 1H, *H*ONH-), 8.68 (s, 1H, HON*H*-), 8.19 (m, 2H, *H*-Ar), 7.57 (m, 1H, *H*-Ar), 7.03 (m, 3H, *H*-Ar), 4.13 (m, 2H, =NC*H*$_2$CH$_2$NH-), 4.10 (m, 2H, =NCH$_2$C*H*$_2$NH-), 4.07 (m, 2H, -C*H*$_2$OAr), 3.92 (s, 3H, -OC*H*$_3$), 3.83 (s, 3H, -OC*H*$_3$), 1.99 (t, 2H, *J* = 7.0 Hz, HONHCOC*H*$_2$-), 1.79 (m, 2H, -C*H*$_2$CH$_2$OAr), 1.58 (m, 2H, -C*H*$_2$(CH$_2$)$_3$OAr), 1.44 (m, 2H, -C*H*$_2$(CH$_2$)$_2$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 165.2, 157.3, 149.1, 146.1, 134.3, 133.0, 126.2, 125.2, 124.0, 115.7, 112.6, 101.2, 69.5, 51.2, 51.0, 46.0, 45.2, 32.9, 29.6, 25.8, 24.7; HRMS (ESI): m/z calcd for $C_{25}H_{29}N_5O_6Na^+$ (M + Na^+): 518.2010, found: 518.2033.



N-(8-((6-(hydroxyamino)-6-oxohexyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-methylbenzamide (**12i**)

Compound **12i** was synthesized as a white solid (67 mg, 46 %) by treatment of compound **11i** (150 mg, 0.31 mmol), hydroxyamine hydrochloride (212 mg, 3.05

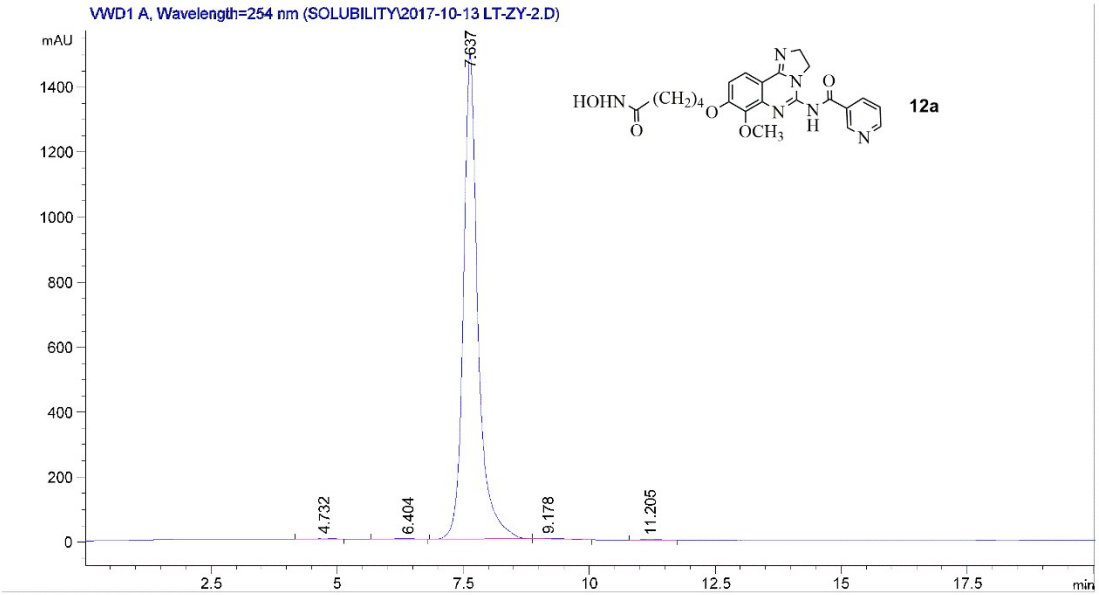
mmol) and KOH (257 mg, 4.58 mmol) according to above-mentioned general procedure; mp: 230~231℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.92 (s, 1H, -N*H*CO-), 10.35 (s, 1H, *H*ONH-), 8.62 (s, 1H, HON*H*-), 7.95 (m, 2H, *H*-Ar), 7.57 (m, 1H, *H*-Ar), 7.33 (m, 2H, *H*-Ar), 7.04 (m, 1H, *H*-Ar), 4.11 (m, 2H, =NCH_2CH$_2$NH-), 4.09 (m, 2H, =NCH$_2$CH_2NH-), 4.04 (m, 2H, -CH_2OAr), 3.93 (s, 3H, -OCH_3), 2.36 (s, 3H, ArCH_3), 1.99 (t, 2H, *J* = 7.0 Hz, HONHCOCH_2-), 1.79 (m, 2H, -CH_2CH$_2$OAr), 1.58 (m, 2H, -CH_2(CH$_2$)$_3$OAr), 1.44 (m, 2H, -CH_2(CH$_2$)$_2$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 157.3, 149.1, 146.1, 139.6, 134.9, 134.3, 133.5, 133.0, 132.3, 129.8, 125.4, 124.0, 112.6, 101.2, 69.5, 51.2, 46.0, 45.2, 32.9, 29.6, 25.8, 24.7, 22.8; HRMS (ESI): m/z calcd for $C_{25}H_{29}N_5O_5Na^+$ (M + Na^+): 502.2061, found: 502.2090.



N-(8-((6-(hydroxyamino)-6-oxohexyl)oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-methyl-1H-imidazole-2-carboxamide (**12j**)

Compound **12j** was synthesized as a white solid (74 mg, 51 %) by treatment of compound **11j** (150 mg, 0.31 mmol), hydroxyamine hydrochloride (216 mg, 3.11 mmol) and KOH (262 mg, 4.66 mmol) according to above-mentioned general procedure; mp: 237~239℃; ^{1}H-NMR (300M, DMSO-d_6) δ (ppm): 12.58 (s, 1H, -N*H*CO-), 10.33 (s, 1H, *H*ONH-), 8.67 (s, 1H, HON*H*-), 7.74 (s, 1H, *H*-imidazole), 7.62 (s, 1H, *H*-imidazole), 7.57 (m, 1H, *H*-Ar), 7.02 (m, 1H, *H*-Ar), 4.12 (m, 2H, =NCH_2CH$_2$NH-), 4.09 (m, 2H, =NCH$_2$CH_2NH-), 4.03 (m, 2H, -CH_2OAr), 3.92 (s, 3H, -OCH_3), 3.90 (s, 3H, ArCH_3), 1.99 (t, 2H, *J* = 7.0 Hz, HONHCOCH_2-), 1.79 (m, 2H, -CH_2CH$_2$OAr), 1.58 (m, 2H, -CH_2(CH$_2$)$_3$OAr), 1.44 (m, 2H, -CH_2(CH$_2$)$_2$OAr); ^{13}C-NMR (300M, DMSO-d_6) δ (ppm): 177.2, 176.1, 157.3, 155.4 149.1, 146.1, 134.3, 133.0, 132.5, 131.9, 124.0, 112.6, 101.2, 69.5, 51.2, 46.0, 45.2, 35.6, 32.9, 29.6, 25.8, 24.7; HRMS (ESI): m/z calcd for $C_{22}H_{27}N_7O_5Na^+$ (M + Na^+): 492.1966, found: 492.1985.

HPLC Spectra for Compound Purity



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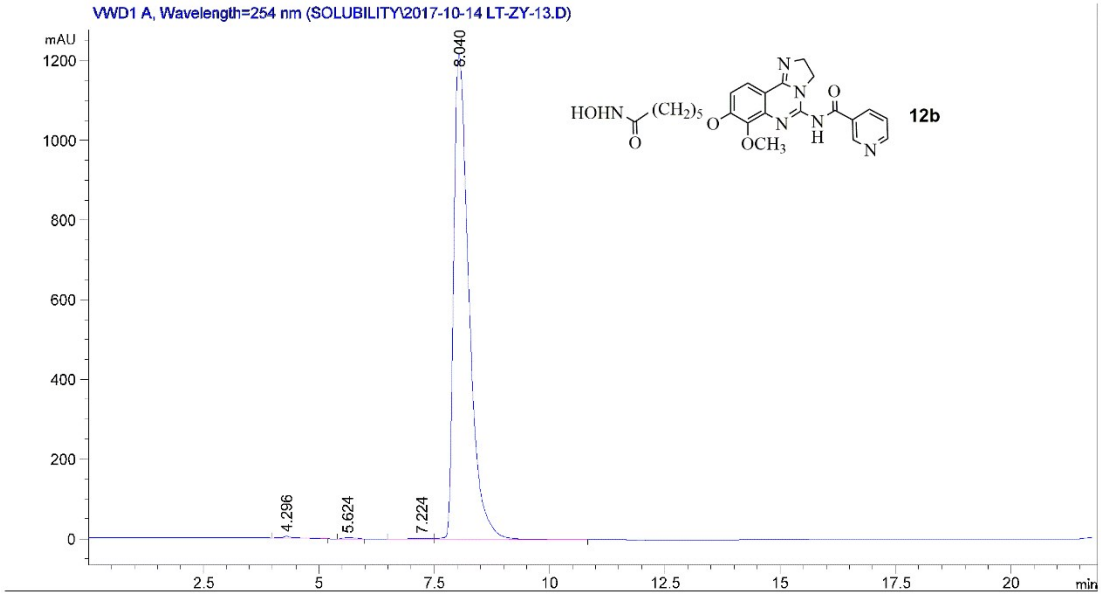
2	6.404	BB	0.3820	94.09118	3.22815	0.3111
3	7.637	BB	0.2944	2.99543e4	1491.13513	99.0346
4	9.178	BB	0.6351	76.17569	1.76302	0.2519
5	11.205	BB	0.3600	66.44173	2.85016	0.2197



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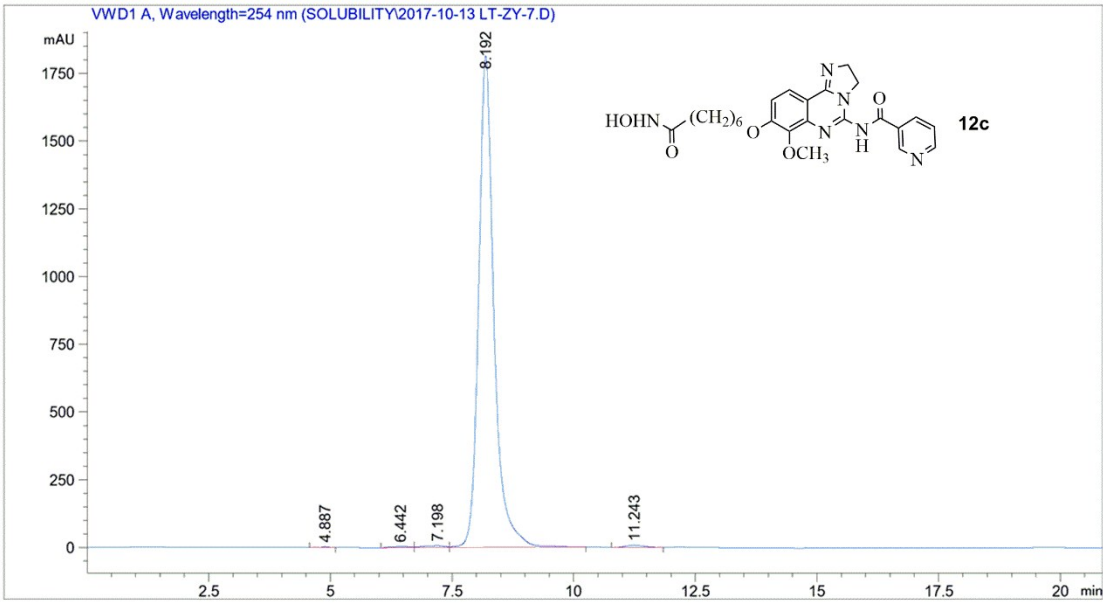
2	5.624	BV	0.2388	58.91901	3.27656	0.2081
3	7.224	BV	0.4073	57.47442	2.00003	0.2030
4	8.040	VB	0.3533	2.81329e4	1218.82629	99.3425



Peak #	Ret.Tim [min]	Typ	Width [min]	Area [mAu*S]	Height [mAu]	Area %
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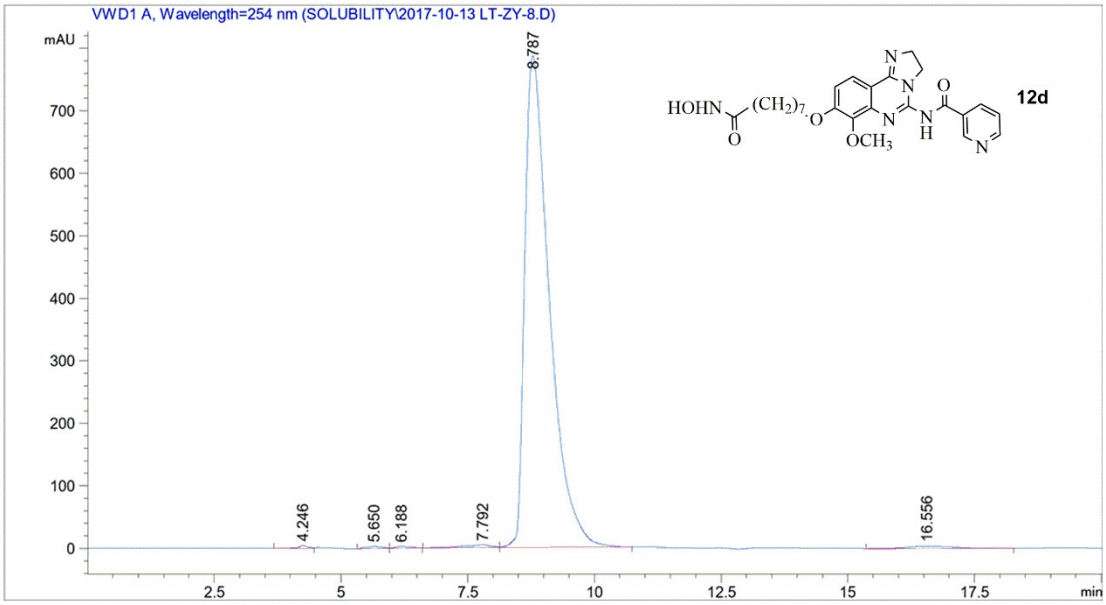
2	6.442	BV	0.4404	109.66405	3.86052	0.2723
3	7.198	VV	0.3931	198.54131	6.82978	0.4931
4	8.192	VB	0.3244	3.97271e4	1815.08704	98.6596
5	11.243	BB	0.4155	205.13512	7.75684	0.5094



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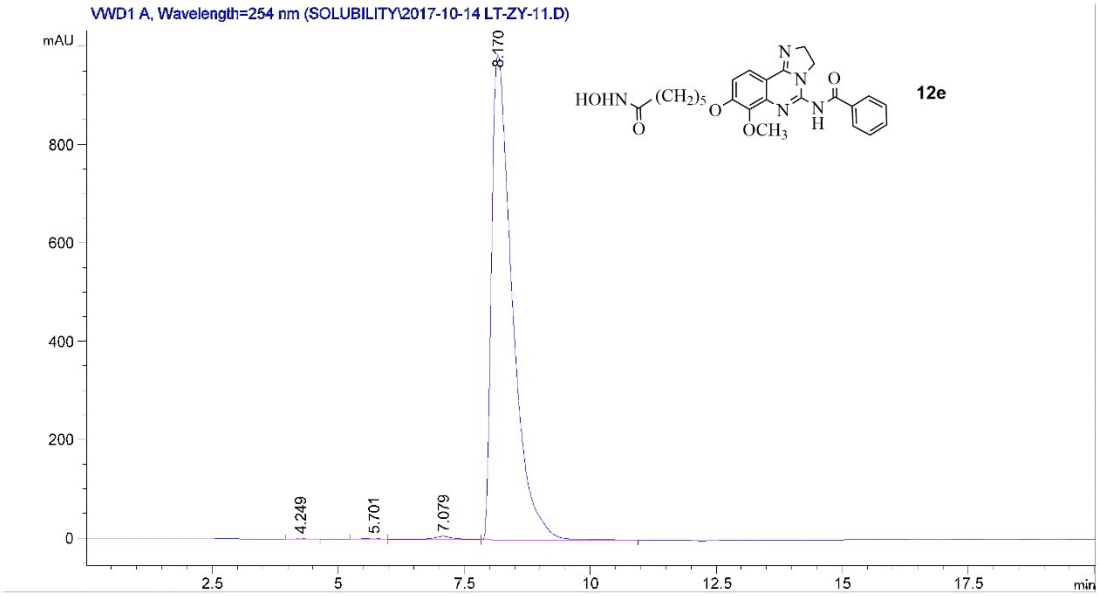
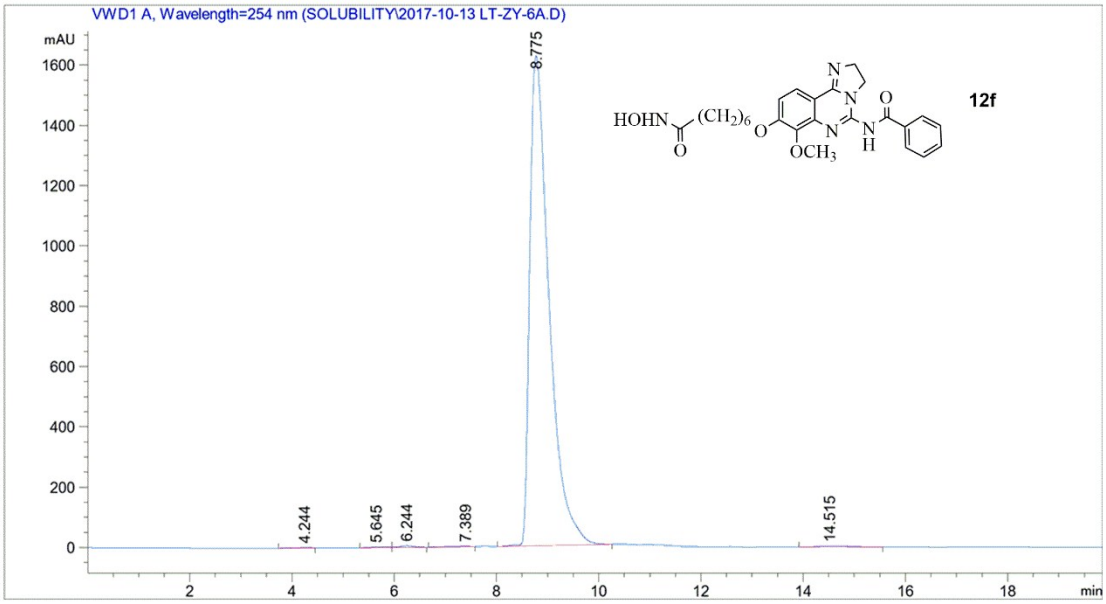
1	4.246	BV	0.1809	53.18676	4.22265	0.1958
2	5.650	BV	0.2838	67.62865	3.08424	0.2490
3	6.188	VB	0.2942	54.22522	2.60091	0.1997
4	7.792	BV	0.5257	167.58337	4.23484	0.6170
5	8.787	VB	0.5093	2.65838e4	786.58221	97.8791
6	16.556	BB	0.8734	233.40318	3.69768	0.8594



Peak #	Ret.Tim [min]	Typ	Width [min]	Area [mAu*S]	Height [mAu]	Area %
1	4.249	BB	0.1466	30.80868	3.05733	0.1082
2	5.701	BV	0.3341	69.87434	2.91066	0.2453
3	7.079	VV	0.4974	259.56967	7.05229	0.9113
4	8.170	VB	0.4253	2.81235e4	987.23633	98.7352



Peak #	Ret.Tim [min]	Typ	Width [min]	Area [mAu*S]	Height [mAu]	Area %
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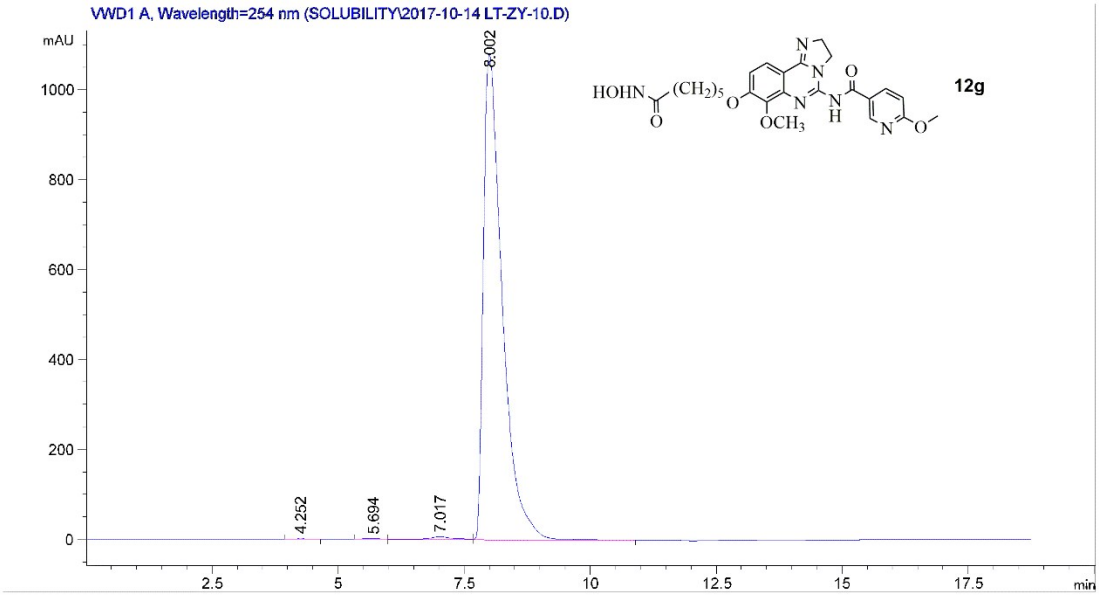
2	5.645	BV	0.2967	73.59514	3.20795	0.1707
3	6.244	VB	0.2717	102.62791	5.55030	0.2381
4	7.389	BV	0.3418	64.35471	2.61755	0.1493
5	8.775	BB	0.3951	4.26463e4	1625.21814	98.9437
6	14.515	BB	0.6016	176.55275	4.18146	0.4096



Peak #	Ret.Tim [min]	Typ	Width [min]	Area [mAu*S]	Height [mAu]	Area %
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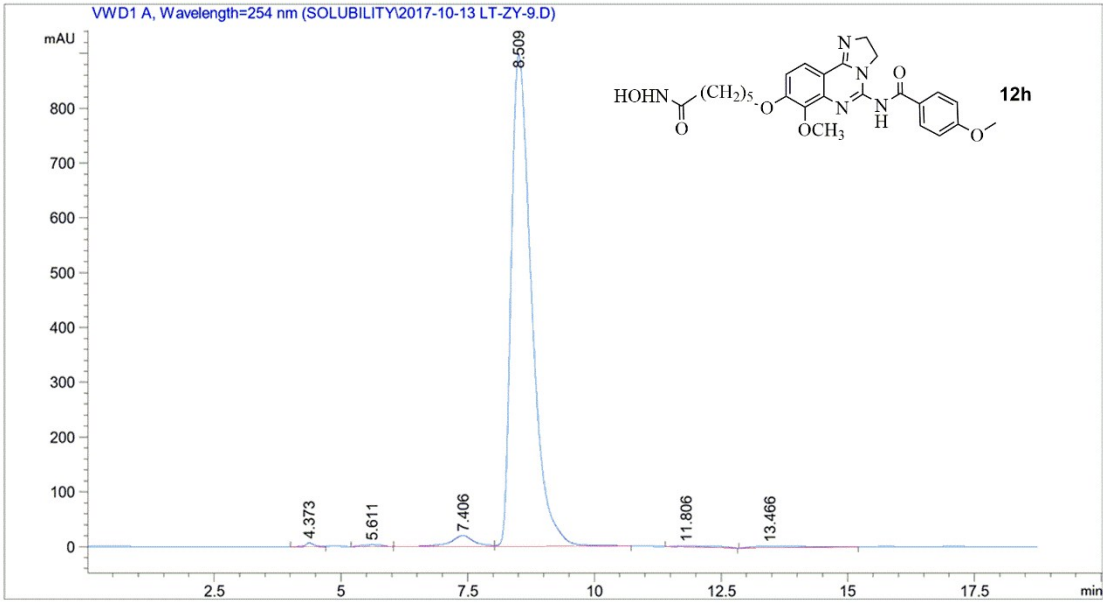
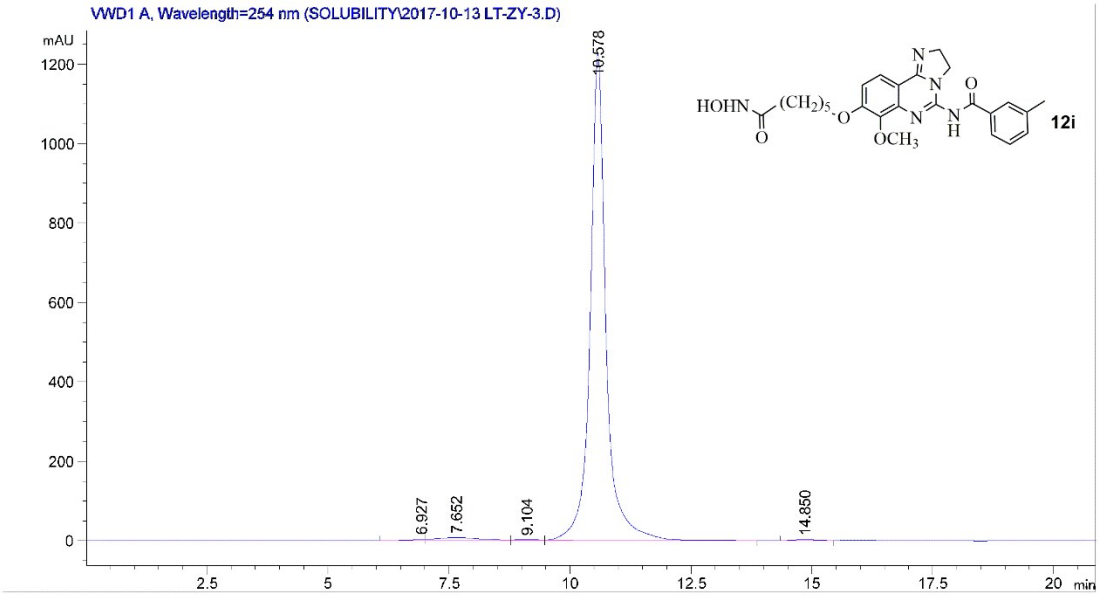
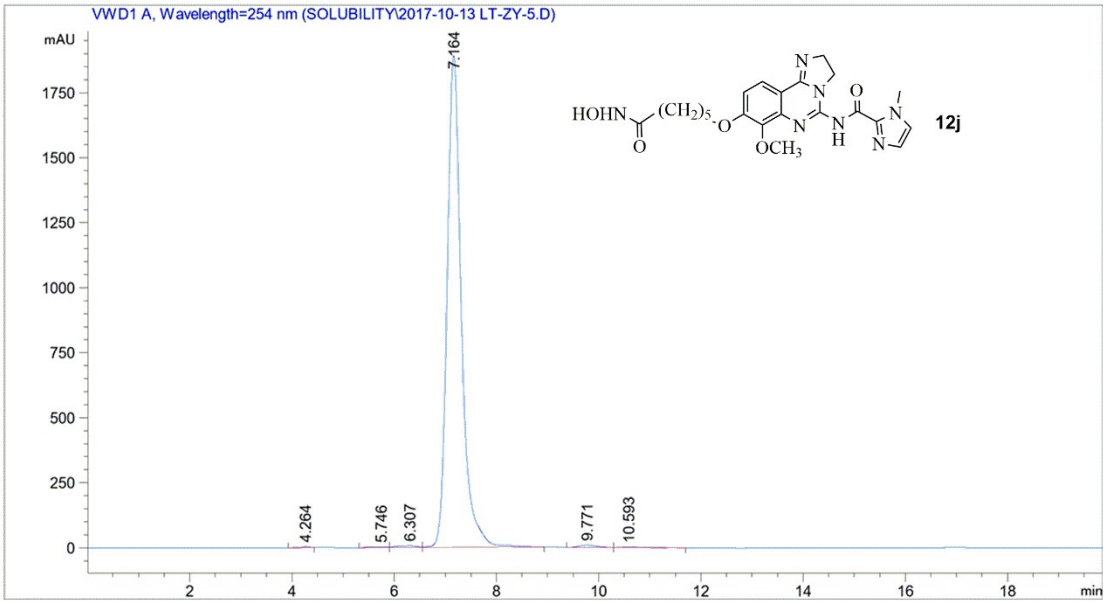
2	5.694	BV	0.3542	67.14887	2.81580	0.2356
3	7.017	VV	0.5236	288.29681	7.33462	1.0116
4	8.002	VB	0.3906	2.81055e4	1079.92395	98.6172



Peak #	Ret.Tim [min]	Typ	Width [min]	Area [mAu*S]	Height [mAu]	Area %
1	4.373	BV	0.1745	88.97709	7.33456	0.3396
2	5.611	BB	0.3427	95.57246	3.65921	0.3647
3	7.406	BV	0.4627	638.52753	19.98843	2.4369
4	8.509	VB	0.4278	2.50505e4	896.95276	95.6038
5	11.806	BB	0.8710	121.95226	1.83100	0.4654
6	13.466	BB	1.0061	206.87315	2.89015	0.7895



Peak #	Ret.Tim [min]	Typ	Width [min]	Area [mAu*S]	Height [mAu]	Area %
1	6.927	BV	0.2496	69.57221	4.08734	0.2426
2	7.652	VB	0.8726	484.20282	7.88281	1.6885
3	9.104	BV	0.3599	51.12120	1.87037	0.1783
4	10.578	VB	0.3310	2.80125e4	1223.81970	97.6857
5	14.850	BB	0.3927	58.76385	2.31103	0.2049



Peak #	Ret.Tim [min]	Typ	Width [min]	Area [mAu*S]	Height [mAu]	Area %
1	4.264	BV	0.1485	37.98119	3.77077	0.1025
2	5.746	BV	0.3369	93.25212	3.54489	0.2516
3	6.307	VV	0.3549	187.71327	7.16003	0.5064
4	7.164	VB	0.2900	3.64685e4	1890.82239	98.3890
5	9.771	BV	0.3832	208.25964	8.42956	0.5619
6	10.593	VB	0.5382	69.92619	1.80415	0.1887