Supplementary data

Design, synthesis and antiproliferative activity studies of 1,2,3-triazole-chalcones

Dong-Jun Fu¹a, Sai-Yang Zhang¹a, Ying-Chao Liu³a, Xiao-Xin Yue⁵b, Jun-Ju Liu³a, Jian Song³a, Ruo-Han Zhao³a, Feng Li³a, Hui-Hui Sun³a, Yan-Bing Zhang⁵a, and Hong-Min Liu³a

¹Collaborative Innovation Center of New Drug Research and Safety Evaluation, School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, PR China
²Henan Medical College, Zhengzhou 450001, PR, China
³These authors contributed equally

1. General Experimental

The reaction process was monitored by TLC with silica gel plates (thickness 250μm, Indicator F-254). The target analogues were purified by column chromatography with silica gel (300 meshes). Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. The novel structures of target analogues were characterized by NMR (400 and 100 MHz) in Acetone-d₆, DMSO-d₆ or CDCl₃ with TMS as an internal standard and HRMS. The purity of all biologically evaluated compounds was determined to be >95% by reverse phase high performance liquid chromatography (HPLC) analysis. HPLC measurement was performed with a Phenomenex column (C₁₈, 5.0 μm, 4.60 mm × 250 mm) on Dionex UltiMate 3000 UHPLC instrument from Thermo-Fisher. The signal was monitored at 254 nm with a UV detector. A flow rate of 0.5 ml/min was used with mobile phase of MeOH in H₂O (60:40, v/v).

2. Experimental Procedures and Analytical Data

General Procedure for the Synthesis of Compounds 5a-e

To a magnetically stirred solution of aryl bromides (3 mmol) in CH₃CN (15 mL), sodium azide (9 mmol) and tetrabutylammonium bromide (1 mmol) were added carefully and the reaction mixture was refluxed for 10 h. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc (30 mL) and washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford compounds 5a-e, which were used in the next reaction without further purification (yield:
87.4%~92.6%.

**General Procedure for the Synthesis of Compounds 6a-c**

*p*-aminoacetophenone (1 mmol), substituted aromatic aldehyde (1 mmol) and NaOH (1 mmol) were dissolved in ethanol (10 ml). The mixture was allowed to stir for 3 h at room temperature. Upon completion, the precipitated product was filtered off and washed with ethanol to afford the crude product (yield: 80.4%~86.9%).

**General Procedure for the Synthesis of Compounds 9a-g**

Propargyl bromide (1 mmol), *p*-acetylphenol (1 mmol), K$_2$CO$_3$ (1 mmol) were dissolved in acetone (10 ml) and the reaction mixture was refluxed for 8 h. Upon completion, the precipitated product was filtered off and washed with ethylacetate to afford the crude product 7. Compound 7 (1.05 mmol), 5a (1 mmol), CuSO$_4$.5H$_2$O (0.2 mmol) and sodium ascorbate (0.1 mmol) were dissolved in THF/H$_2$O (5 ml/5 ml) to stir for 7 h at room temperature. Upon completion, the precipitated product was filtered off and washed with ethanol to afford the crude product 8. Compound 8 (1 mmol), substituted aromatic aldehyde (1 mmol) and NaOH (1 mmol) were dissolved in ethanol (10 ml) to stir at room temperature. The reaction was monitored by TLC till the reaction was finished. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc and washed with water, brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to afford 9a-g which were purified with column chromatography (total yield: 62.2%~71.3%).

**General Procedure for the Synthesis of Compounds 12a-n**

Propargyl bromide (1 mmol), *p*-aminoacetophenone (1 mmol), K$_2$CO$_3$ (1 mmol) were dissolved in acetone (10 ml) and the reaction mixture was refluxed for 8 h. Upon completion, the precipitated product was filtered off and washed with ethylacetate to afford the crude product 10. Compound 10 (1.05 mmol), azide derivatives (1 mmol), CuSO$_4$.5H$_2$O (0.2 mmol) and sodium ascorbate (0.1 mmol) were dissolved in THF/H$_2$O (5 ml/5 ml) to stir for 7 h at room temperature. Upon completion, the precipitated product was filtered off and washed with ethanol to afford the crude product 11a-e. Compound 11a-e (1 mmol), substituted aromatic aldehyde (1 mmol) and NaOH (1 mmol) were dissolved in ethanol (10 ml) to stir at room temperature. The reaction was monitored by TLC till the reaction was finished.
Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc and washed with water, brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to afford compounds 12a-n which were purified with column chromatography (68.9%–77.5%).

**1H, 13C NMR and HRMS Spectra for all new compounds**

(E)-1-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(2-fluorophenyl)prop-2-en-1-one (9a)

![Chemical Structure](image)

White solid, yield: 85%, m.p: 249.6~253.2 °C. purity: 98.23 %.

**1H NMR (400 MHz, CDCl$_3$)** δ 8.03 (d, $J$ = 8.9 Hz, 2H), 7.88 (d, $J$ = 15.9 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.56 (s, 1H), 7.38 (dt, $J$ = 7.0, 2.2 Hz, 4H), 7.28 (dd, $J$ = 7.2, 2.1 Hz, 2H), 7.23 – 7.10 (m, 2H), 7.06 (d, $J$ = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H).

**13C NMR (100 MHz, CDCl$_3$)** δ 188.71, 162.04, 143.88, 136.90, 134.34, 131.71, 131.62, 131.42, 130.92, 129.85, 129.21, 128.92, 128.17, 124.50, 123.10, 122.77, 116.41, 116.19, 114.67, 62.16, 54.35. HRMS (ESI) calcd for C$_{25}$H$_{20}$FN$_3$O$_2$ [M+H]$^+$: 414.1618, found: 414.1616.
(E)-1-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (9b)
White solid, yield: 86%, m.p: 182.3~184.4 °C, purity: 98.04 %.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, $J$ = 8.9 Hz, 2H), 7.74 (d, $J$ = 15.6 Hz, 1H), 7.57 (d, $J$ = 8.7 Hz, 3H), 7.50 (d, $J$ = 15.6 Hz, 1H), 7.39 (dd, $J$ = 7.9, 1.9 Hz, 5H), 7.28 (dd, $J$ = 7.2, 2.2 Hz, 2H), 7.06 (d, $J$ = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 188.42, 162.07, 143.84, 142.63, 136.26, 134.33, 133.54, 131.41, 130.85, 129.53, 129.23, 129.22, 128.93, 128.17, 122.77, 122.23, 114.69, 62.16, 54.35.
(E)-1-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (9c)

White solid, yield: 75%, m.p: 156.6~158.2 °C. purity: 99.13 %.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 7.2$ Hz, 2H), 7.71 (d, $J = 15.8$ Hz, 1H), 7.56 (s, 1H), 7.40 (d, $J = 16.0$ Hz, 4H), 7.31 – 7.25 (m, 2H), 7.07 (d, $J = 7.2$ Hz, 2H), 6.86 (s, 2H), 5.55 (s, 2H), 5.27 (s, 2H), 3.92 (dd, $J = 9.4$, 1.4 Hz, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 188.71, 161.93, 153.49, 144.32, 143.87, 140.33, 134.33, 131.62, 130.81, 130.53, 129.21, 128.92, 128.17, 122.79, 121.16, 114.65, 105.60, 62.13, 61.02, 56.24, 54.35. HRMS (ESI) calcd for C$_{28}$H$_{27}$N$_{3}$O$_{5}$ [M+H]+: 486.2029, found: 486.2028.
(E)-1-((4-(1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(2,4-dichlorophenyl)prop-2-en-1-one (9d)
White solid, yield:  84%, m.p:  145.6~147.2 °C. purity: 97.17 %.  \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.08 (d, \(J = 15.7\) Hz, 1H), 8.01 (d, \(J = 8.9\) Hz, 2H), 7.68 (d, \(J = 8.5\) Hz, 1H), 7.56 (s, 1H), 7.47 (dd, \(J = 8.9, 6.8\) Hz, 2H), 7.42 – 7.35 (m, 3H), 7.29 (ddd, \(J = 6.7, 4.9, 2.0\) Hz, 3H), 7.06 (d, \(J = 8.9\) Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 188.28, 162.17, 143.81, 138.67, 136.30, 135.99, 134.32, 132.02, 131.17, 130.97, 130.13, 129.22, 128.93, 128.50, 128.17, 127.54, 124.87, 122.77, 114.73, 62.17, 54.35. HRMS (ESI) calcd for C\(_{25}\)H\(_{19}\)Cl\(_2\)N\(_3\)O\(_2\) [M+H]+: 464.0933, found: 464.0938.
(E)-1-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (9e)

White solid, yield: 75%, m.p: 130.6~132.4 °C. purity: 98.65 %. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 15.8$ Hz, 1H), 8.02 (d, $J = 8.7$ Hz, 2H), 7.67 – 7.58 (m, 2H), 7.55 (s, 1H), 7.38 (d, $J = 6.5$ Hz, 4H), 7.28 (d, $J = 5.5$ Hz, 2H), 7.05 (d, $J = 8.7$ Hz, 2H), 6.99 (t, $J = 7.5$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 5.55 (s, 2H), 5.27 (s, 2H), 3.92 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 189.36, 161.76, 161.27, 158.79, 139.75, 134.36, 131.93, 131.57, 130.82, 129.27, 129.21, 128.91, 128.17, 127.50, 124.10, 122.68, 120.74, 114.56, 111.23, 62.16, 55.56, 54.34. HRMS (ESI) calcd for C$_{26}$H$_{23}$N$_3$O$_3$ [M+H]+: 426.1818, found: 426.1819.
(E)-1-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (9f)
White solid, yield: 89%, m.p: 203.6~205.4 °C. purity: 98.93 %. ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 2H), 8.09 – 8.00 (m, 2H), 7.79 (dd, J = 12.0, 9.9 Hz, 3H), 7.64 (d, J = 15.7 Hz, 1H), 7.56 (s, 1H), 7.38 (dt, J = 4.5, 2.4 Hz, 3H), 7.32 – 7.27 (m, 2H), 7.09 (d, J = 8.9 Hz, 2H), 5.55 (s, 2H), 5.28 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 187.79, 162.40, 148.48, 143.72, 141.24, 140.85, 134.30, 130.99, 130.95, 129.22, 128.94, 128.86, 128.18, 125.18, 124.22, 122.79, 114.84, 62.18, 54.36. HRMS (ESI) calcd for C₂₅H₂₀N₄O₄ [M+H]⁺: 441.1563, found: 441.1567.
(E)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)prop-2-en-1-one (9g)

White solid, yield: 71%, m.p.: 163.4~165.9 °C. purity: 96.38 %. 1H NMR (400 MHz, CDCl3) δ 8.01 (d, J = 8.9 Hz, 2H), 7.71 (d, J = 15.5 Hz, 1H), 7.55 (s, 1H), 7.42 – 7.35 (m, 4H), 7.35 – 7.27 (m, 4H), 7.05 (d, J = 8.9 Hz, 2H), 6.93 (t, J = 8.8 Hz, 1H), 5.55 (s, 2H), 5.27 (s, 2H), 3.31 – 3.16 (m, 4H), 2.64 (d, J = 4.4 Hz, 4H), 2.38 (s, 3H).

13C NMR (100 MHz, CDCl3) δ 188.43, 161.87, 156.37, 153.92, 143.90, 142.94, 141.92, 134.34, 131.70, 130.73, 129.20, 128.91, 128.16, 125.92, 122.72, 120.26, 118.64, 114.95, 114.60, 62.16, 54.90, 54.33, 49.86, 45.95. HRMS (ESI) calcd for C30H30FN5O2 [M+H]+: 512.2462, found: 512.2463.
(E)-1-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(3-chlorophenyl)prop-2-en-1-one (9h)
White solid, yield: 68%, m.p: 151.4~153.4 °C. purity: 97.62 %. 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 (d, $J$ = 8.9 Hz, 2H), 7.72 (d, $J$ = 15.7 Hz, 1H), 7.62 (s, 1H), 7.56 (s, 1H), 7.52 (d, $J$ = 15.7 Hz, 1H), 7.48 (s, 1H), 7.37 (dt, $J$ = 10.3, 4.6 Hz, 5H), 7.28 (dd, $J$ = 7.1, 2.1 Hz, 2H), 7.06 (d, $J$ = 8.9 Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). 

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 188.28, 162.14, 143.82, 142.38, 136.89, 134.95, 134.34, 131.30, 130.99, 130.90, 130.20, 129.21, 128.92, 128.17, 127.83, 126.76, 123.01, 122.78, 114.71, 62.17, 54.35. HRMS (ESI) calcd for C$_{25}$H$_{20}$ClN$_3$O$_2$ [M+H$^+$]: 430.1322, found: 430.1324.
(E)-1-(4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3-(pyridin-4-yl)prop-2-en-1-one (9i)

White solid, yield: 65%, m.p.: 126.6~128.4 °C. purity: 98.74%. ¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, J = 5.9 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.68 (s, 2H), 7.56 (s, 1H), 7.47 (d, J = 6.0 Hz, 2H), 7.40 – 7.37 (m, 3H), 7.32 – 7.27 (m, 2H), 7.08 (d, J = 8.9 Hz, 2H), 5.55 (s, 2H), 5.28 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 187.94, 162.38, 150.55, 143.72, 142.32, 140.82, 134.31, 131.00, 130.91, 129.21, 128.93, 128.17, 125.93, 122.79, 122.02, 114.82, 62.17, 54.35. HRMS (ESI) calcd for C₂₄H₂₀N₄O₂ [M+H]+: 397.1665, found: 397.1666.
(E)-1-(4-((1-benzyl-1H-1,2,3-tetrazol-4-yl)methoxy)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (9j)
White solid, yield: 79%, m.p: 168.3~170.4 °C. purity: 98.57 %. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.86 (d, \(J = 1.5\) Hz, 1H), 8.67 – 8.58 (m, 1H), 8.11 – 7.99 (m, 2H), 7.95 (dt, \(J = 7.9, 1.8\) Hz, 1H), 7.78 (d, \(J = 15.7\) Hz, 1H), 7.60 (d, \(J = 15.8\) Hz, 1H), 7.57 (s, 1H), 7.46 – 7.33 (m, 4H), 7.29 (dd, \(J = 7.2, 2.3\) Hz, 2H), 7.08 (d, \(J = 8.9\) Hz, 2H), 5.55 (s, 2H), 5.27 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 187.99, 162.21, 150.94, 149.88, 143.77, 140.21, 134.59, 134.32, 131.12, 130.92, 130.83, 129.20, 128.92, 128.16, 123.79, 123.65, 122.78, 114.75, 62.16, 54.34. HRMS (ESI) calcd for C\(_{24}\)H\(_{20}\)N\(_4\)O\(_2\) [M+H]+: 397.1665, found: 397.1665.
(E)-1-(4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(3-chlorophenyl)prop-2-en-1-one (12a)

White solid, yield: 80%, m.p: 177.5~179.4 °C. purity: 96.90 %. \( ^1 \)H NMR (400 MHz, DMSO) \( \delta \) 8.15 – 7.94 (m, 5H), 7.78 (d, \( J = 3.0 \) Hz, 1H), 7.60 (d, \( J = 15.6 \) Hz, 1H), 7.47 (d, \( J = 4.7 \) Hz, 2H), 7.34 (dt, \( J = 17.4, 7.1 \) Hz, 5H), 7.21 (t, \( J = 5.6 \) Hz, 1H, D\(_2\)O exchangeable), 6.74 (d, \( J = 8.7 \) Hz, 2H), 5.58 (s, 2H), 4.44 (d, \( J = 5.6 \) Hz, 2H). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 189.36, 161.76, 158.79, 143.99, 139.75, 134.36, 131.93, 131.57, 130.82, 129.27, 129.21, 128.91, 128.17, 124.10, 122.73, 122.68, 120.74, 114.56, 111.23, 62.16, 54.34. HRMS (ESI) calcd for C\(_{25}\)H\(_{21}\)ClN\(_4\)O [M+H]+: 429.1482, found: 429.1485.
$(E)$-1-(4-(((1-benzyl-1$H$-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(pyridin-4-yl)prop-2-en-1-one (12b)
White solid, yield: 71%, m.p: 164.0~166.2 °C. purity: 99.14 %. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.65 (d, $J = 5.5$ Hz, 2H), 8.17 – 8.06 (m, 2H), 8.01 (d, $J = 8.7$ Hz, 2H), 7.81 (d, $J = 5.8$ Hz, 2H), 7.57 (d, $J = 15.6$ Hz, 1H), 7.40 – 7.28 (m, 5H), 7.26 (t, $J = 5.7$ Hz, 1H, D$_2$O exchangeable), 6.75 (d, $J = 8.8$ Hz, 2H), 5.59 (s, 2H), 4.44 (d, $J = 5.7$ Hz, 2H). $^{13}$C NMR (100 MHz, DMSO) $\delta$ 186.13, 153.42, 150.74, 145.48, 142.77, 139.13, 136.60, 131.66, 129.20, 128.57, 128.38, 127.25, 125.80, 123.57, 122.82, 111.93, 53.21, 38.35. HRMS (ESI) calcd for C$_{22}$H$_{21}$N$_5$O [M+H]+: 396.1824, found: 396.1825.
(E)-1-(4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (12c)

White solid, yield: 78%, m.p: 178.9~181.2 °C. purity: 98.92 %. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.85 (d, $J = 1.7$ Hz, 1H), 8.60 (dd, $J = 4.8, 1.3$ Hz, 1H), 7.93 (dd, $J = 11.6, 5.3$ Hz, 3H), 7.75 (d, $J = 15.7$ Hz, 1H), 7.60 (d, $J = 15.7$ Hz, 1H), 7.46 – 7.31 (m, 5H), 7.25 (d, $J = 1.9$ Hz, 2H), 6.67 (d, $J = 8.8$ Hz, 2H), 5.52 (s, 2H), 4.91 (t, $J = 5.2$ Hz, 1H, D$_2$O exchangeable), 4.52 (d, $J = 5.3$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 187.18, 151.68, 150.67, 149.78, 145.29, 139.09, 134.50, 134.45, 131.15, 129.22, 129.18, 128.88, 128.06, 127.54, 123.91, 123.72, 121.43, 112.07, 54.29, 39.24.
\[(E)-1-(4-(((1\text{-benzyl}-1H-1,2,3\text{-triazol-4-yl})\text{methyl})\text{amino})\text{phenyl})-3-(3,5\text{-dichlorophenyl})\text{prop-2-en-1-one} \quad (12d)\]
White solid, yield: 69%, m.p: 189.4~190.3 °C. purity: 98.84 %. \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.96 (d, \( J = 8.7 \) Hz, 2H), 7.63 (d, \( J = 15.6 \) Hz, 1H), 7.54 (d, \( J = 15.6 \) Hz, 1H), 7.50 (d, \( J = 1.7 \) Hz, 2H), 7.46 – 7.35 (m, 5H), 7.29 (s, 2H), 6.69 (d, \( J = 8.8 \) Hz, 2H), 5.54 (s, 2H), 4.93 (t, \( J = 5.5 \) Hz, 1H, D\(_2\)O exchangeable), 4.53 (d, \( J = 5.5 \) Hz, 2H). \( ^{13}\)C NMR (100 MHz, DMSO) \( \delta \) 186.07, 153.34, 145.51, 139.45, 138.90, 136.60, 135.03, 131.65, 129.29, 129.19, 128.56, 128.37, 127.42, 125.96, 125.89, 123.55, 111.87, 53.21, 38.37. HRMS (ESI) calcd for \( \text{C}_{25}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O} \) [M+H]+: 463.1092, found: 463.1093.
(E)-1-(4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(3,5-difluorophenyl)prop-2-en-1-one (12e)

White solid, yield: 82%, m.p: 172.6~174.4°C. purity: 97.45%. ¹H NMR (400 MHz, DMSO) δ 8.08 (s, 1H), 8.02 (dd, J = 12.1, 3.2 Hz, 3H), 7.69 (d, J = 6.9 Hz, 2H), 7.60 (d, J = 15.5 Hz, 1H), 7.41 – 7.25 (m, 6H), 7.23 (t, J = 5.6 Hz, 1H, D₂O exchangeable), 6.75 (d, J = 8.8 Hz, 2H), 5.59 (s, 2H), 4.44 (d, J = 5.6 Hz, 2H). ¹³C NMR (100 MHz, DMSO) δ 186.13, 164.41, 164.28, 162.00, 161.84, 153.33, 145.51, 136.60, 131.61, 129.19, 128.56, 128.37, 125.95, 125.64, 123.56, 118.87, 105.29, 53.21, 38.35. HRMS (ESI) calcd for C₂₅H₂₀F₂N₄O [M+H]+: 431.1683, found: 431.1684.
(E)-1-((4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one (12f)
White solid, yield: 73%, m.p.: 182.3~184.4 °C. purity: 99.13%. $^1$H NMR (400 MHz, DMSO) δ 8.07 (s, 1H), 8.00 (d, $J = 15.7$ Hz, 1H), 7.86 (d, $J = 15.7$ Hz, 1H), 7.81 (d, $J = 8.6$ Hz, 2H), 7.54 - 7.20 (m, 5H), 7.08 (t, $J = 5.6$ Hz, 1H, D$_2$O exchangeable), 6.72 (d, $J = 8.7$ Hz, 2H), 6.32 (s, 2H), 5.58 (s, 2H), 4.41 (d, $J = 5.6$ Hz, 2H), 3.92 (s, 6H), 3.86 (s, 3H). $^{13}$C NMR (100 MHz, DMSO) δ 187.63, 163.15, 161.52, 152.63, 145.67, 136.63, 133.31, 130.70, 129.18, 128.55, 128.37, 126.95, 123.55, 121.21, 111.90, 105.84, 91.46, 56.49, 55.97, 53.19, 38.42. HRMS (ESI) calcd for C$_{28}$H$_{28}$N$_4$O$_4$ [M+H]$^+$: 485.2189, found: 485.2188.
(E)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (12g)

White solid, yield: 72%, m.p: 165.3~167.4 °C. purity: 97.98%. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.08 (s, 1H), 7.99 (d, $J = 8.5$ Hz, 2H), 7.97 – 7.90 (m, 2H), 7.87 (d, $J = 15.5$ Hz, 1H), 7.63 (d, $J = 15.5$ Hz, 1H), 7.44 – 7.23 (m, 7H), 7.17 (t, $J = 5.3$ Hz, 1H, D$_2$O exchangeable), 6.74 (d, $J = 8.5$ Hz, 2H), 5.59 (s, 2H), 4.43 (d, $J = 5.3$ Hz, 2H). $^{13}$C NMR (100 MHz, DMSO) $\delta$ 186.39, 164.77, 162.31, 153.12, 145.57, 140.79, 136.61, 132.31, 131.39, 129.19, 128.56, 128.37, 126.19, 123.55, 122.74, 116.40, 111.86, 53.20, 38.38. HRMS (ESI) calcd for C$_{25}$H$_{21}$FN$_4$O [M+H]+: 413.1778, found: 413.1779.
(E)-1-((4-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(furan-2-yl)prop-2-en-1-one (12h)
White solid, yield: 48%, m.p: 165.4~167.0 °C. purity: 97.99 %. ¹H NMR (400 MHz, DMSO) δ 8.08 (s, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 15.2 Hz, 1H), 7.73 (d, J = 4.9 Hz, 1H), 7.62 (d, J = 3.3 Hz, 1H), 7.53 (d, J = 15.3 Hz, 1H), 7.33 (ddd, J = 12.0, 10.9, 6.6 Hz, 5H), 7.23 – 7.12 (m, 2H), 6.73 (d, J = 8.8 Hz, 2H), 5.58 (s, 2H), 4.42 (d, J = 5.7 Hz, 2H). ¹³C NMR (100 MHz, DMSO) δ 185.90, 153.08, 145.54, 140.66, 136.61, 134.84, 132.22, 131.20, 129.85, 129.19, 129.04, 128.56, 128.37, 126.04, 123.56, 121.21, 111.91, 53.20, 38.37. HRMS (ESI) calcd for C₂₃H₂₀N₄O₂ [M+H]+: 385.1665, found: 385.1667.
(E)-1-(4-(((1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(thiophen-2-yl)prop-2-en-1-one (12i)

White solid, yield: 69%, m.p: 159~160 °C. purity: 98.05 %. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.92 (dd, $J = 11.7$, 8.0 Hz, 3H), 7.50 – 7.29 (m, 6H), 7.20 (d, $J = 8.2$ Hz, 2H), 7.15 – 7.03 (m, 1H), 6.67 (d, $J = 8.5$ Hz, 2H), 5.48 (s, 2H), 4.94 (t, $J = 5.4$ Hz, 1H, D$_2$O exchangeable), 4.53 (d, $J = 5.4$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.63, 157.82, 150.37, 145.41, 140.37, 139.61, 138.03, 137.01, 135.96, 135.07, 134.61, 133.94, 133.79, 130.79, 128.37, 125.93, 116.65, 57.13, 43.10. HRMS (ESI) calcd for C$_{23}$H$_{19}$ClN$_4$OS [M+H]$: 435.1046$, found: $435.1044$. 
\((E)-3-(4\text{-chlorophenyl})-1-(4-(((1-(3\text{-methoxybenzyl})-1H-1,2,3\text{-triazol-4-yl})\text{methyl})\text{amino})\text{phenyl})\text{prop-2-en-1-one (12j)}\)
White solid, yield: 51%, m.p.: 145.7~147.3 °C. purity: 97.83 %. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.95 (d, \(J = 8.1\) Hz, 2H), 7.73 (d, \(J = 15.6\) Hz, 1H), 7.55 (t, \(J = 14.4\) Hz, 3H), 7.47 – 7.34 (m, 3H), 7.29 (d, \(J = 2.4\) Hz, 1H), 6.87 (dd, \(J = 19.0, 7.5\) Hz, 2H), 6.78 (s, 1H), 6.67 (d, \(J = 8.1\) Hz, 2H), 5.49 (s, 2H), 4.95 (s, 1H, D\(_2\)O exchangeable), 4.52 (d, \(J = 4.7\) Hz, 2H), 3.78 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 187.59, 160.11, 151.57, 145.39, 141.49, 135.92, 135.87, 133.83, 131.07, 130.27, 129.43, 129.15, 127.73, 122.40, 121.56, 120.21, 114.17, 113.72, 112.04, 55.33, 54.20, 39.23.
(E)-1-(4-(((1-(3-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl) amino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (12k)

yellow liquid, yield: 50%. m.p: 179.7~180.3 °C purity: 99.03 %.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.85 (s, 1H), 8.61 (s, 1H), 7.95 (d, $J$ = 8.7 Hz, 3H), 7.75 (d, $J$ = 15.8 Hz, 1H), 7.61 (d, $J$ = 15.7 Hz, 1H), 7.43 (s, 1H), 7.36 (dd, $J$ = 7.7, 4.9 Hz, 1H), 7.29 (t, $J$ = 7.9 Hz, 1H), 6.89 (dd, $J$ = 8.2, 2.0 Hz, 1H), 6.84 (d, $J$ = 7.5 Hz, 1H), 6.77 (s, 1H), 6.68 (d, $J$ = 8.7 Hz, 2H), 5.48 (s, 2H), 5.06 (s, 1H), 4.52 (d, $J$ = 2.6 Hz, 2H), 3.77 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 187.18, 160.08, 151.79, 150.60, 149.73, 145.36, 139.03, 135.91, 134.57, 131.17, 130.31, 130.26, 127.35, 123.90, 123.80, 121.62, 120.20, 114.13, 113.73, 112.05, 55.31, 54.18, 39.16. HRMS (ESI) calcd for C$_{25}$H$_{23}$N$_5$O$_2$ [M+H]+: 426.1930, found: 426.1931.
(E)-3-(pyridin-3-yl)-1-(4-(((1-(2-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)prop-2-en-1-one (12l)
Yellow solid, yield: 67%, m.p.: 189.6~191.4 °C. Purity: 98.03 %.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.85 (s, 1H), 8.61 (s, 1H), 7.96 (d, $J = 7.0$ Hz, 3H), 7.75 (d, $J = 15.3$ Hz, 2H), 7.62 (d, $J = 15.6$ Hz, 1H), 7.57 – 7.41 (m, 3H), 7.32 (d, $J = 28.6$ Hz, 1H), 7.19 (d, $J = 6.5$ Hz, 1H), 6.69 (d, $J = 7.6$ Hz, 2H), 5.73 (s, 2H), 5.07 (s, 1H, D$_2$O exchangeable), 4.55 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 187.18, 151.71, 150.66, 149.78, 145.51, 139.09, 134.52, 132.94, 132.75, 131.15, 130.11, 128.88, 127.79, 127.50, 126.31, 123.88, 123.75, 122.71, 122.04, 112.09, 50.27, 39.18.
(E)-3-(pyridin-3-yl)-1-(4-(((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)prop-2-en-1-one (12m)

White solid, yield: 68%, m.p: 181.7~182.4°C, purity: 97.99%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.85 (s, 1H), 8.61 (s, 1H), 7.94 (d, $J$ = 8.0 Hz, 3H), 7.74 (d, $J$ = 15.6 Hz, 1H), 7.68 – 7.54 (m, 3H), 7.47 (s, 1H), 7.35 (d, $J$ = 7.4 Hz, 3H), 6.68 (d, $J$ = 8.3 Hz, 2H), 5.58 (s, 2H), 5.04 (s, 1H, D$_2$O exchangeable), 4.54 (d, $J$ = 4.7 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 187.19, 151.61, 150.66, 149.75, 145.76, 139.20, 138.42, 134.51, 131.62, 131.16, 130.98, 128.20, 127.63, 126.19, 126.16, 123.84, 121.62, 112.10, 111.98, 53.59, 39.21. HRMS (ESI) calcd for C$_{25}$H$_{20}$F$_3$N$_5$O [M+H]$^+$: 464.1698, found: 464.1699.
(E)-1-(4-(((1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (12n)
White solid, yield: 76%, m.p: 115.6~116.2 °C. purity: 98.40 %. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.85 (s, 1H), 8.61 (d, \(J = 4.4\) Hz, 1H), 7.94 (t, \(J = 8.4\) Hz, 3H), 7.75 (d, \(J = 15.7\) Hz, 1H), 7.61 (d, \(J = 15.7\) Hz, 1H), 7.40 (s, 1H), 7.35 (d, \(J = 8.1\) Hz, 3H), 7.20 (d, \(J = 8.2\) Hz, 2H), 6.68 (d, \(J = 8.5\) Hz, 2H), 5.49 (s, 2H), 4.91 (t, \(J = 5.4\) Hz, 1H, D\(_2\)O exchangeable), 4.53 (d, \(J = 5.4\) Hz, 2H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 187.19, 151.69, 150.67, 149.77, 145.57, 139.14, 134.92, 134.56, 132.96, 131.17, 131.11, 129.39, 127.49, 123.84, 123.77, 123.72, 121.49, 112.08, 53.52, 39.18. HRMS (ESI) calcd for C\(_{24}\)H\(_{20}\)ClN\(_5\)O [M+H]+: 430.1435, found: 430.1434.