Supporting information

Synthesis and bioactivities evaluation of novel *N*-pyridylpyrazole derivatives with 1,2,3-triazole and quinazolin-4(3*H*)-one substructures

Wei Wei [c], Liangliang Zhu [a], Yunyun Zhou [a, *], Zhengming Li [b, *]

[a] *State Key Laboratory of Molecular Engineering of Polymers, Department of Macromolecular Science, Fudan University, Songhu Road No. 2005, Shanghai, 200433, China*

[b] *State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, No. 94, Weijin Road, Nankai District, Tianjin 300071, China*

[c] *WuXi AppTec (Tian Jin) Co., Ltd., 168 Nan Hai Road, Tianjin, 300457, China*

***** Corresponding author. E-mail: nkzml@vip.163.com; zhouyunyun@fudan.edu.cn.

General procedures

(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)methanol (**2**). The $LiAlH_4$ (5 mmol) was added gradually to a solution of **1** (5 mmol) in THF at 0 °C. The reaction was stirred at room temperature until the starting materials disappeared according to TLC. $Na_2SO_4 \cdot 10H_2O$ was added to quench the reaction. After stirred for 30 min, the mixture was filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v=3/1) to afford **2** as white solid. Yield, 65 %, mp 109–111 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (dd, J =4.8 Hz, J =1.6 Hz, 1H, pyridyl-H), 8.01 (dd, J =8.2 Hz, J =1.4 Hz, 1H, pyridyl-H), 7.39 (dd, J =4.8 Hz, J =8.0 Hz, 1H, pyridyl-H), 6.49 (s, 1H, pyrazolyl-H), 4.51 (d, J =6.8 Hz, 2H, CH_2), 4.29 (t, J =6.8 Hz, 1H, OH).

2-(3-bromo-5-(chloromethyl)-1*H*-pyrazol-1-yl)-3-chloropyridine (**3**). The methanesulfonyl chloride (5 mmol) was added dropwised to a solution of **2** (5 mmol) in 1, 2-dichloroethane, after that the mixture was heated to reflux for 1 h. The reaction was monitored by TLC, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v=10/1) to afford **3** as green solid. Yield, 91 %, mp 71–72 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 4.5 Hz, 1H, pyridyl-H), 7.96 (d, J = 8.0 Hz, 1H, pyridyl-H), 7.46 – 7.38 (m, 1H, pyridyl-H), 6.54 (s, 1H, pyrazolyl-H), 4.65 (s, 2H, CH_2).

2-(5-(azidomethyl)-3-bromo-1*H*-pyrazol-1-yl)-3-chloropyridine (**4**). The NaN_3 (15 mmol) was added to a solution of **3** (5 mmol) in DMF, after that the mixture was heated to reflux for 8 h. After completion, the mixture was poured into water, then extracted with ethyl acetate (3 × 20 ml). The organic layer was combine and dried with anhydrous sodium sulfate, filtered and concentrated to obtained **4** as oil. Yield, 82 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 – 8.44 (m, 1H, pyridyl-H), 7.95 (dd, J = 8.0, 1.5 Hz, 1H, pyridyl-H), 7.41 (dd, J = 8.0, 4.7 Hz, 1H, pyridyl-H), 6.51 (s, 1H, pyrazolyl-H), 4.43 (s, 2H, CH_2).

General synthetic procedure for compounds 5a–h. Different substituted phenol (2 mmol) and K_2CO_3 (2 mmol) were added to acetone (20 ml), 30 min later, 3-bromopropyne (2 mmol) was added, after that the mixture was heated to reflux for10 h. The reaction was monitored by TLC, after completion, the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v=8/1) to afford **5a–h**.

2-(prop-2-yn-1-yloxy)benzonitrile (**5a**) white solid, yield 92 %, mp 71-72 ºC. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.61 – 7.57 (m, 1H, Ar-H), 7.57 – 7.53 (m, 1H, Ar-H), 7.15 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.07 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-H), 4.84 (d, *J* = 2.4 Hz, 2H, CH_2), 2.57 (t, *J* = 2.4 Hz, 1H, C≡CH).

1-nitro-2-(prop-2-yn-1-yloxy)benzene (**5b**) white solid, yield 94 %, mp 77-78 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.26 (t, *J* = 4.2 Hz, 1H, Ar-H), 7.10 (t, *J* = 7.7 Hz, 1H, Ar-H), 4.86 (d, *J* = 2.3 Hz, 2H, CH_2), 2.58 (t, *J* = 2.3 Hz, 1H, C≡CH).

1,3-dichloro-5-(prop-2-yn-1-yloxy)benzene (**5c**) white solid, yield 93 %, mp 47-48 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (t, *J* = 1.7 Hz, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 4.67 (d, *J* = 2.4 Hz, 2H, CH_2), 2.57 (t, *J* = 2.4 Hz, 1H, C≡CH).

2-methoxy-4-methyl-1-(prop-2-yn-1-yloxy)benzene (**5d**) oil, yield 89 %, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 6.69 (d, *J* = 9.7 Hz, 1H, Ar-H), 4.73 (d, *J* = 2.4 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 2.49 (t, *J* = 2.4 Hz, 1H, C≡CH), 2.31 (s, 3H, Ar-CH_3).

3-(prop-2-yn-1-yloxy)phenol (**5e**) oil, yield 30 %, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.56 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.49 (d, *J* = 7.0 Hz, 2H, Ar-H), 5.81 (s, 1H, OH), 4.65 (d, *J* = 0.6 Hz, 2H, CH_2), 2.53 (s, 1H, C≡CH).

1,3-bis(prop-2-yn-1-yloxy)benzene (**5f**) oil, yield 32 %, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 10.8, 6.6 Hz, 1H, Ar-H), 6.63 (d, *J* = 6.2 Hz, 3H, Ar-H), 4.67 (d, *J* = 1.9 Hz, 4H, CH_2), 2.53 (s, 2H, C≡CH).

7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one (**5g**) white solid, yield 87 %, mp 120-121 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 9.5 Hz, 1H, Ar-H), 7.40 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.95 – 6.89 (m, 2H, Ar-H), 6.28 (d, *J* = 9.5 Hz, 1H, Ar-H), 4.76 (d, *J* = 2.3 Hz, 2H, CH_2), 2.58 (t, *J* = 2.3 Hz, 1H, C≡CH).

7-(prop-2-yn-1-yloxy)-2H-chromen-2-one (**5h**) white solid, yield 88 %, mp 86-87 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 1.4 Hz, 1H, Ar-H), 7.70 – 7.65 (m, 1H, Ar-H), 7.63 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.52 (dd, *J* = 8.7, 1.9 Hz, 1H, Ar-H), 7.21 (dq, *J* = 5.3, 2.5 Hz, 2H, Ar-H), 4.81 (d, *J* = 2.4 Hz, 2H, CH_2), 2.56 (t, *J* = 2.4 Hz, 1H, C≡CH).

General synthetic procedure for compounds 7a–g. The compounds **6a-g** (1 mmol) was added to the solution of acetic anhydride (5 mL), the mixture was heated at 150 ℃ for 4 h. The reaction was monitored by TLC. After completion, the mixture was added to the ice water and extracted with ethyl acetate (3 × 10 mL), the organic phase was washed by sat. $NaHCO_3$ and brine successively.

The solvent was removed under reduced pressure and the residue was using directly without further purification. 25 mL ethanol was added to the residue followed by addition of $NH_2NH_2 \cdot H_2O$ (80%, 50 mmol) and the reaction was furtherly stirred at room temperature for 2 h. After the solvent was removed *in vacuo*, ethyl acetate (60 mL) was added to dissolve the materials. The organic phase was washed by 1M HCl, sat. $NaHCO_3$ and brine successively. The ethyl acetate was removed after drying over $MgSO_4$ and the residue was purified by column chromatography (100% ethyl acetate) to afford **7a-g**.

3-amino-2,8-dimethylquinazolin-4(3*H*)-one (**7a**) white solid, yield 82 %, mp 70-71 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.0 Hz, 1H, Ar-H), 7.57 (d, J = 7.2 Hz, 1H, Ar-H), 7.32 (t, J = 7.6 Hz, 1H, Ar-H), 4.89 (s, 2H, NH_2), 2.71 (s, 3H, Ar-CH_3), 2.60 (s, 3H, CH_3).

3-amino-7-chloro-2-methylquinazolin-4(3*H*)-one (**7b**) white solid, yield 76 %, mp 77-78 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.6 Hz, 1H, Ar-H), 7.63 (d, J = 1.6 Hz, 1H, Ar-H), 7.39 (dd, J = 8.6, 1.7 Hz, 1H, Ar-H), 4.87 (s, 2H, NH_2), 2.70 (s, 3H, CH_3).

3-amino-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (**7c**) white solid, yield 88 %, mp 236-237 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.1 Hz, 1H, Ar-H), 8.12 (d, J = 2.1 Hz, 1H, Ar-H), 4.90 (s, 2H, NH_2), 2.75 (s, 3H, CH_3).

3-amino-6-chloro-2,8-dimethylquinazolin-4(3*H*)-one (**7d**) white solid, yield 85 %, mp 214-216 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 2.4 Hz, 1H, Ar-H), 7.51 (d, J = 1.8 Hz, 1H, Ar-H), 4.89 (s, 2H, NH_2), 2.70 (s, 3H, Ar-CH_3), 2.56 (s, 3H, CH_3).

3-amino-6-bromo-2,8-dimethylquinazolin-4(3*H*)-one (**7e**) white solid, yield 76 %, mp 98-99 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 2.2 Hz, 1H, Ar-H), 7.66 (d, J = 1.4 Hz, 1H, Ar-H), 4.88 (s, 2H, NH_2), 2.69 (s, 3H, Ar-CH_3), 2.56 (s, 3H, CH_3).

3-amino-2,8-dimethyl-4-oxo-3,4-dihydroquinazoline-6-carbonitrile (**7f**) white solid, yield 77 %, mp 58-59 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 1.6 Hz, 1H, Ar-H), 7.74 (d, J = 0.9 Hz, 1H, Ar-H), 4.91 (s, 2H, NH_2), 2.75 (s, 3H, Ar-CH_3), 2.60 (s, 3H, CH_3).

3-amino-2,8-dimethyl-6-nitroquinazolin-4(3*H*)-one (**7g**) white solid, yield 80 %, mp 92-93 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 4.93 (s, 2H, NH_2), 2.77 (s, 3H, Ar-CH_3), 2.66 (s, 3H, CH_3).

General synthetic procedure for compounds Ia–h. compound **5a-h** (1 mmol), 2-(5-(azidomethyl)-3-bromo-1*H*-pyrazol-1-yl)-3-chloropyridine (**4**) and CuI (0.1 mmol) were added to a

mixture of THF/H_2O (v/v = 1/1), then refluxed for 5 h. The reaction was monitored by TLC, after completion, the mixture was poured into water, then extracted with ethyl acetate (3 × 20 ml). The organic layer was combine and dried with anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v = 2/1) to afford **Ia–h**.

2-((1-((3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzonitrile (**Ia**) white solid, yield 89 %, mp 108-109 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, *J* = 4.6 Hz, 1H, pyridyl-H), 7.86 (d, *J* = 8.0 Hz, 1H, pyridyl-H), 7.72 (s, 1H, triazole-CH), 7.54 (dd, *J* = 19.3, 8.0 Hz, 2H, Ar-H), 7.40 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.16 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.04 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.50 (s, 1H, pyrazolyl-H), 5.66 (s, 2H, CH_2), 5.28 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 146.9, 146.9, 143.6, 140.5, 139.3, 134.4, 133.8, 128.5, 128.3, 125.9, 123.1, 121.4, 116.3, 112.8, 111.3, 102.3, 62.8, 44.6. $C_{19}H_{13}BrClN_7O$. Calculated, %: C 48.48, H 2.78, N 20.83; Found, %: C 48.56, H 2.71, N 20.90. HRMS *m/z*: $[M + H]^+$ calcd for $C_{19}H_{14}BrClN_7O^+$, 470.0126; found, 470.0133.

2-(3-bromo-5-((4-((2-nitrophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-pyrazol-1-yl)-3-chloropyridine (**Ib**) white solid, yield 91 %, mp 108-109 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 4.6 Hz, 1H, pyridyl-H), 7.84 (dd, *J* = 12.8, 8.1 Hz, 2H, pyridyl-H and Ar-H), 7.71 (s, 1H, triazole-CH), 7.52 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.39 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.24 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.05 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.47 (s, 1H, pyrazolyl-H), 5.64 (s, 2H, CH_2), 5.28 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 146.9, 146.9, 143.6, 140.5, 139.4, 134.6, 134.3, 128.5, 128.3, 125.9, 125.6, 123.3, 121.1, 115.2, 111.2, 63.5, 44.5. $C_{18}H_{13}BrClN_7O_3$. Calculated, %: C 44.06, H 2.67, N 19.98; Found, %: C 44.15, H 2.71, N 20.06. HRMS *m/z*: $[M + H]^+$ calcd for $C_{18}H_{14}BrClN_7O_3^+$, 490.0025; found, 490.0033.

2-(3-bromo-5-((4-((3,5-dichlorophenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-pyrazol-1-yl)-3-chloropyridine (**Ic**) white solid, yield 88 %, mp 162-163 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 4.6 Hz, 1H, pyridyl-H), 7.87 (d, *J* = 8.1 Hz, 1H, pyridyl-H), 7.61 (s, 1H, triazole-CH), 7.40 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 6.98 (d, *J* = 1.3 Hz, 1H, Ar-H), 6.86 (s, 2H, Ar-H), 6.49 (s, 1H, pyrazolyl-H), 5.67 (s, 2H, CH_2), 5.12 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 146.8, 143.5, 140.4, 139.3, 135.6, 135.4, 128.5, 128.3, 125.8, 122.8, 121.6, 113.9, 113.4, 111.2, 110.7, 62.1, 44.6. $C_{18}H_{12}BrCl_3N_6O$. Calculated, %: C 42.01, H 2.35, N 16.33; Found, %: C 42.14, H 2.29, N

16.43. HRMS *m/z*: $[M + H]^+$ calcd for $C_{18}H_{13}BrCl_3N_6O^+$, 512.9394; found, 512.9404.

2-(3-bromo-5-((4-((2-methoxy-4-methylphenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-pyrazol-1-yl)-3-chloropyridine (**Id**) oil, yield 92 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (dd, *J* = 4.6, 1.2 Hz, 1H, pyridyl-H), 7.81 (dd, *J* = 8.0, 1.2 Hz, 1H, pyridyl-H), 7.60 (s, 1H, triazole-CH), 7.34 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 6.84 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 6.64 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.39 (s, 1H, pyrazolyl-H), 5.60 (s, 2H, CH_2), 5.17 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 2.28 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 146.9, 146.7, 145.1, 145.0, 140.4, 139.6, 131.7, 128.4, 128.3, 125.7, 122.9, 120.9, 114.6, 112.8, 111.0, 63.1, 55.7, 44.6, 21.0. $C_{20}H_{18}BrClN_6O_2$. Calculated, %: C 49.05, H 3.70, N 17.16; Found, %: C 49.14, H 3.59, N 17.21. HRMS *m/z*: $[M + H]^+$ calcd for $C_{20}H_{19}BrClN_6O_2^+$, 489.0436; found, 489.0438.

3-((1-((3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenol (**Ie**) oil, yield 90 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (dd, *J* = 4.7, 1.4 Hz, 1H, pyridyl-H), 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H, pyridyl-H), 7.60 (s, 1H, OH), 7.57 (s, 1H, triazole-CH), 7.31 (dd, *J* = 8.1, 4.7 Hz, 1H, pyridyl-H), 7.06 (dd, *J* = 10.2, 6.4 Hz, 1H, Ar-H), 6.49 – 6.40 (m, 4H, Ar-H, pyrazole-H and pyridyl-H), 5.60 (s, 2H, CH_2), 5.03 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 157.5, 146.8, 146.7, 144.5, 140.5, 139.3, 130.2, 128.6, 128.3, 126.0, 123.1, 111.3, 108.8, 106.5, 102.5, 61.2, 44.6. $C_{18}H_{14}BrClN_6O_2$. Calculated, %: C 46.83, H 3.06, N 18.20; Found, %: C 46.88, H 3.11, N 17.99. HRMS *m/z*: $[M + H]^+$ calcd for $C_{18}H_{15}BrClN_6O_2^+$, 461.0123; found, 461.0022.

2-(3-bromo-5-((4-((3-(prop-2-yn-1-yloxy)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-pyrazol-1-yl)-3-chloropyridine (**If**) white solid, yield 90 %, mp 123-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 4.6 Hz, 1H, pyridyl-H), 7.85 (d, *J* = 8.1 Hz, 1H, pyridyl-H), 7.58 (s, 1H, triazole-CH), 7.37 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.19 (t, *J* = 7.9 Hz, 1H, Ar-H), 6.60 (d, *J* = 8.8 Hz, 3H, Ar-H), 6.46 (s, 1H, pyrazolyl-H), 5.64 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 4.66 (d, *J* = 2.2 Hz, 2H, $\underline{CH_2}$C≡CH), 2.52 (s, 1H, C≡CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 158.7, 146.9, 146.8, 144.4, 140.4, 139.5, 130.0, 128.4, 128.3, 125.8, 122.8, 111.1, 107.8, 107.6, 102.2, 78.4, 75.7, 61.7, 55.8, 44.6. $C_{21}H_{16}BrClN_6O_2$. Calculated, %: C 50.47, H 3.23, N 16.82; Found, %: C 50.41, H 3.28, N 16.86. HRMS *m/z*: $[M + H]^+$ calcd for $C_{21}H_{17}BrClN_6O_2^+$, 499.0279; found, 499.0264.

7-((1-((3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one (**Ig**) white solid, yield 89 %, mp 89-90 ºC. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 8.44 (d, J = 4.6 Hz, 1H, pyridyl-H), 7.89 (d, J = 8.1 Hz, 1H, pyridyl-H), 7.68 (s, 1H, triazole-CH), 7.63 (d, J = 9.5 Hz, 1H, Ar-H), 7.40 (dd, J = 7.9, 4.6 Hz, 1H, pyridyl-H), 7.38 (d, J = 8.2 Hz, 1H, Ar-H), 6.90 (d, J = 9.7 Hz, 2H, Ar-H), 6.48 (s, 1H, pyrazolyl-H), 6.26 (d, J = 9.5 Hz, 1H, Ar-H), 5.67 (s, 2H, CH_2), 5.20 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 161.0, 155.7, 146.9, 146.8, 143.5, 143.3, 140.5, 139.3, 128.9, 128.5, 128.4, 125.8, 122.9, 113.5, 113.0, 112.8, 111.2, 102.0, 62.1, 44.6. $C_{21}H_{14}BrClN_6O_3$. Calculated, %: C 49.10, H 2.75, N 16.36; Found, %: C 49.02, H 2.69, N 16.41. HRMS *m/z*: $[M + H]^+$ calcd for $C_{21}H_{15}BrClN_6O_3^+$, 513.0072; found, 513.0079.

2-(3-bromo-5-((4-(((6-bromonaphthalen-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-1*H*-pyrazol-1-yl)-3-chloropyridine (**Ih**) oil, yield 92 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 4.6 Hz, 1H, pyridyl-H), 7.90 (s, 1H, triazole-CH), 7.74 (d, J = 8.0 Hz, 1H, pyridyl-H), 7.63 (d, J = 7.8 Hz, 2H, Ar-H), 7.57 (d, J = 8.8 Hz, 1H, Ar-H), 7.48 (dd, J = 8.7, 1.4 Hz, 1H, Ar-H), 7.29 (dd, J = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.19 – 7.13 (m, 2H, Ar-H), 6.45 (s, 1H, pyrazolyl-H), 5.64 (s, 2H, CH_2), 5.23 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 146.9, 146.7, 144.3, 140.4, 139.4, 132.8, 130.1, 129.7, 129.6, 128.6, 128.5, 128.4, 128.3, 125.7, 122.8, 119.8, 117.4, 111.2, 107.2, 61.8, 44.6. $C_{22}H_{15}Br_2ClN_6O$. Calculated, %: C 45.98, H 2.63, N 14.62; Found, %: C 46.11, H 2.68, N 14.58. HRMS *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}Br_2ClN_6O^+$, 574.9415; found, 574.9399.

General synthetic procedure for compounds IIa–h. Oxalyl chloride (3 mmol) was added to the suspension of 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (0.5 mmol) in 10 ml CH_2Cl_2, followed by one drop of DMF. After stirred at room temperature for 4 h, the solvent was evaporated and the residue was resolved in 10 ml toluene. The solution was added to a mixture of compound **7a-g** (0.5 mmol), Et_3N (0.7 mmol) and toluene (10 ml) in an ice bath. After refluxed for 2 h, the solvent was evaporated and the residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v = 2/1) to afford **IIa–h**.

3-bromo-1-(3-chloropyridin-2-yl)-N-(2,8-dimethyl-4-oxoquinazolin-3(4*H*)-yl)-1*H*-pyrazole-5-carboxamide (**IIa**) white solid, yield 59 %, mp 225-226 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H, NH), 8.45 (dd, J = 4.7, 1.4 Hz, 1H, pyridyl-H), 7.94 (d, J = 7.8 Hz, 1H, Ar-H), 7.86 (dd, J = 8.0, 1.4 Hz, 1H, pyridyl-H), 7.54 (d, J = 7.2 Hz, 1H, Ar-H), 7.38 (dd, J = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.29 (t, J = 7.7 Hz, 1H, Ar-H), 7.19 (s, 1H, pyrazolyl-H), 2.50 (s, 3H, Ar-CH_3), 2.48 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 157.4, 153.3, 148.4, 146.9, 145.5, 139.3, 136.0, 135.9, 129.0,

128.5, 126.5, 126.0, 124.3, 120.1, 114.9, 111.7, 21.4, 17.3. $C_{19}H_{14}BrClN_6O_2$. Calculated, %: C 48.17, H 2.98, N 17.74; Found, %: C 48.34, H 2.88, N 17.54. HRMS *m/z*: $[M + H]^+$ calcd for $C_{19}H_{15}BrClN_6O_2^+$, 473.0123; found, 473.0110.

3-bromo-N-(7-chloro-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**IIb**) white solid, yield 64 %, mp 135-136 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H, NH), 8.47 (d, *J* = 4.7 Hz, 1H, pyridyl-H), 8.07 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.91 (d, *J* = 8.0 Hz, 1H, pyridyl-H), 7.61 (s, 1H, Ar-H), 7.42 (dd, *J* = 8.6, 5.4 Hz, 1H, pyridyl-H), 7.38 (s, 1H, Ar-H), 7.12 (s, 1H, pyrazolyl-H), 2.50 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.1, 157.2, 156.3, 147.9, 147.4, 147.3, 139.9, 139.6, 136.1, 128.5, 127.8, 127.3, 127.2, 127.0, 126.2, 119.2, 111.6, 21.0. $C_{18}H_{11}BrCl_2N_6O_2$. Calculated, %: C 43.75, H 2.24, N 17.01; Found, %: C 43.65, H 2.30, N 17.10. HRMS *m/z*: $[M + H]^+$ calcd for $C_{18}H_{12}BrCl_2N_6O_2^+$, 492.9577; found, 492.9581.

3-bromo-1-(3-chloropyridin-2-yl)-N-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-1*H*-pyrazole-5-carboxamide (**IIc**) white solid, yield 62 %, mp 130-131 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H, NH), 8.45 (dd, *J* = 4.7, 1.4 Hz, 1H, pyridyl-H), 8.16 (d, *J* = 2.1 Hz, 1H, Ar-H), 8.10 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.91 (dd, *J* = 8.0, 1.3 Hz, 1H, pyridyl-H), 7.42 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.03 (s, 1H, pyrazolyl-H), 2.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.3, 157.1, 156.3, 147.8, 147.3, 143.1, 140.4, 139.6, 136.1, 128.4, 127.8, 127.3, 127.0, 123.1, 122.9, 119.2, 111.7, 21.4. $C_{18}H_{10}Br_3ClN_6O_2$. Calculated, %: C 35.01, H 1.63, N 13.61; Found, %: C 35.23, H 1.56, N 13.54. HRMS *m/z*: $[M + H]^+$ calcd for $C_{18}H_{11}Br_3ClN_6O_2^+$, 616.8156; found, 616.8168.

3-chloro-1-(3-chloropyridin-2-yl)-N-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-1*H*-pyrazole-5-carboxamide (**IId**) white solid, yield 58 %, mp 238-239 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H, NH), 8.46 (dd, *J* = 4.7, 1.5 Hz, 1H, pyridyl-H), 8.23 (d, *J* = 2.2 Hz, 1H, Ar-H), 8.12 (d, *J* = 2.2 Hz, 1H, Ar-H), 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H, pyridyl-H), 7.43 (dd, *J* = 8.1, 4.7 Hz, 1H, pyridyl-H), 7.03 (s, 1H, pyrazolyl-H), 2.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.2, 157.1, 156.4, 147.8, 147.3, 143.1, 140.4, 140.1, 139.6, 136.0, 128.4, 127.8, 127.0, 123.1, 122.9, 119.2, 108.4, 21.4. $C_{18}H_{10}Br_2Cl_2N_6O_2$. Calculated, %: C 37.73, H 1.76, N 14.67; Found, %: C 37.64, H 1.82, N 14.60. HRMS *m/z*: $[M + H]^+$ calcd for $C_{18}H_{11}Br_2Cl_2N_6O_2^+$, 572.8661; found, 572.8667.

3-bromo-N-(6-chloro-2,8-dimethyl-4-oxoquinazolin-3(4*H*)-yl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**IIe**) white solid, yield 67 %, mp 172-173 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H, NH), 8.50 – 8.41 (m, 1H, pyridyl-H), 7.92 – 7.87 (m, 1H, Ar-H), 7.84 (d, *J* = 2.0 Hz,

1H, Ar-H), 7.49 (d, *J* = 8.3 Hz, 1H, pyridyl-H), 7.39 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.15 (s, 1H, pyrazolyl-H), 2.49 (s, 3H, Ar-CH_3), 2.48 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 157.4, 153.8, 148.3, 146.9, 144.1, 139.4, 138.4, 135.9, 135.6, 131.9, 128.9, 128.5, 126.1, 123.3, 121.2, 111.8, 21.4, 17.3. $C_{19}H_{13}BrCl_2N_6O_2$. Calculated, %: C 44.91, H 2.58, N 16.54; Found, %: C 44.88, H 2.62, N 16.34. HRMS *m/z*: $[M + H]^+$ calcd for $C_{19}H_{14}BrCl_2N_6O_2^+$, 506.9733; found, 506.9742.

3-bromo-N-(6-bromo-2,8-dimethyl-4-oxoquinazolin-3(4*H*)-yl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**IIf**) white solid, yield 63 %, mp 117-119 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H, NH), 8.46 (dd, *J* = 4.7, 1.4 Hz, 1H, pyridyl-H), 8.09 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.90 (dd, *J* = 8.0, 1.4 Hz, 1H, pyridyl-H), 7.67 (s, 1H, Ar-H), 7.41 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.10 (s, 1H, pyrazolyl-H), 2.52 (s, 3H, Ar-CH_3), 2.49 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 157.4, 153.9, 148.3, 146.8, 144.4, 139.5, 138.5, 135.8, 131.0, 128.8, 126.6, 126.1, 121.5, 119.9, 114.9, 111.7, 21.4, 17.3. $C_{19}H_{13}Br_2ClN_6O_2$. Calculated, %: C 41.30, H 2.37, N 15.21; Found, %: C 41.22, H 2.33, N 15.33. HRMS *m/z*: $[M + H]^+$ calcd for $C_{19}H_{14}Br_2ClN_6O_2^+$, 552.9208; found, 552.9212.

3-bromo-1-(3-chloropyridin-2-yl)-N-(6-cyano-2,8-dimethyl-4-oxoquinazolin-3(4*H*)-yl)-1*H*-pyrazole-5-carboxamide (**IIg**) white solid, yield 50 %, mp 144-145 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H, NH), 8.46 (dd, *J* = 4.7, 1.5 Hz, 1H, pyridyl-H), 8.28 (d, *J* = 1.5 Hz, 1H, Ar-H), 7.91 (dd, *J* = 8.1, 1.5 Hz, 1H, pyridyl-H), 7.74 (d, *J* = 0.8 Hz, 1H, Ar-H), 7.42 (dd, *J* = 8.1, 4.7 Hz, 1H, pyridyl-H), 7.13 (s, 1H, pyrazolyl-H), 2.56 (s, 3H, Ar-CH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 157.5, 156.9, 148.1, 148.1, 146.8, 139.5, 138.3, 136.8, 135.7, 129.7, 129.0, 128.4, 126.2, 120.8, 118.0, 111.9, 109.6, 21.7, 17.3. $C_{20}H_{13}BrClN_7O_2$. Calculated, %: C 48.17, H 2.63, N 19.66; Found, %: C 48.34, H 2.72, N 19.54. HRMS *m/z*: $[M + H]^+$ calcd for $C_{20}H_{14}BrClN_7O_2^+$, 498.0075; found, 498.0083.

3-bromo-1-(3-chloropyridin-2-yl)-N-(2,8-dimethyl-6-nitro-4-oxoquinazolin-3(4*H*)-yl)-1*H*-pyrazole-5-carboxamide (**IIh**) white solid, yield 45 %, mp 172-173 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H, NH), 8.78 (d, *J* = 2.4 Hz, 1H, pyridyl-H), 8.47 (d, *J* = 4.7 Hz, 1H, Ar-H), 8.34 (s, 1H, pyridyl-H), 7.93 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.43 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.15 (s, 1H, pyrazolyl-H), 2.61 (s, 3H, Ar-CH_3), 2.59 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.0, 158.6, 156.7, 149.5, 148.3, 147.8, 144.9, 140.0, 138.7, 136.5, 129.1, 128.2, 127.8, 127.5, 120.9,

120.5, 112.2, 22.1, 17.6. $C_{19}H_{13}BrClN_7O_4$. Calculated, %: C 43.99, H 2.53, N 18.90; Found, %: C 44.15, H 2.63, N 18.72. HRMS *m/z*: $[M + H]^+$ calcd for $C_{19}H_{14}BrClN_7O_4^+$, 517.9974; found, 517.9979.

3-bromo-N-(6-chloro-2,8-dimethyl-7-nitro-4-oxoquinazolin-3(4*H*)-yl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**IIi**) The compound **IIe** (0.5 mmol) was dissolved in 5 ml H_2SO_4 in an ice bath, after 10 min, nitrosonitric acid (0.2 ml) was added dropwise. After stirred at room temperature for 1 h, the mixture was poured into ice water, the precipitate was collected and dried under vacuum to afford **IIi**. white solid, yield 80 %, mp 174-175 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H, NH), 8.45 (d, *J* = 3.3 Hz, 1H, pyridyl-H), 7.87 (d, *J* = 8.0 Hz, 1H, pyridyl-H), 7.66 (s, 1H, Ar-H), 7.39 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 7.23 (s, 1H, pyrazolyl-H), 2.59 (s, 3H, Ar-CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 157.1, 156.8, 148.2, 146.9, 144.8, 143.9, 140.8, 139.3, 136.0, 135.2, 128.9, 128.8, 125.9, 123.3, 112.7, 112.5, 21.3, 17.7. $C_{19}H_{12}BrCl_2N_7O_4$. Calculated, %: C 41.25, H 2.19, N 17.73; Found, %: C 41.08, H 2.23, N 17.88. HRMS *m/z*: $[M + H]^+$ calcd for $C_{19}H_{13}BrCl_2N_7O_4^+$, 551.9584; found, 551.9589.

3-amino-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-8-methylquinazolin-4(3*H*)-one (**IIj**) 2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-8-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one was prepared according to the procedure reported by Mao *et al*.[1] and the compound (1 mmol) was dissolved in 10 ml ethanol, followed by addition of $NH_2NH_2{\cdot}H_2O$ (80%, 3 mmol) and the reaction was refluxed for 4 h. After cooling to room temperature, the precipitate was formed and then filtered. The solid was washed by ethanol (2 × 2 ml) and dried to obtain **IIj**. white solid, yield 86 %, mp 64-65 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 4.6, 1.2 Hz, 1H, pyridyl-H), 8.05 (d, *J* = 2.3 Hz, 1H, Ar-H), 7.86 (dd, *J* = 8.0, 1.3 Hz, 1H, pyridyl-H), 7.43 (d, *J* = 1.9 Hz, 1H, Ar-H), 7.37 (s, 1H, pyrazolyl-H), 7.33 (dd, *J* = 8.0, 4.7 Hz, 1H, pyridyl-H), 5.07 (s, 2H, NH_2), 1.93 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 149.2, 147.6, 144.8, 143.3, 140.4, 138.8, 138.4, 135.0, 132.0, 127.9, 127.1, 126.6, 123.0, 121.4, 115.5, 16.3. $C_{17}H_{11}BrCl_2N_6O$. Calculated, %: C 43.80, H 2.38, N 18.03; Found, %: C 43.66, H 2.42, N 18.11. HRMS *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}BrCl_2N_6O^+$, 464.9628; found, 464.9631.

[1] M.-Z. Mao, Y.-X. Li, Y.-Y. Zhou, X.-L. Zhang, Q.-X. Liu, F.-J. Di, H.-B. Song, L.-X. Xiong, Y.-Q. Li, Z.-M. Li, J Agr. Food Chem. 62 (2014) 1536-1542.