Electronic Supplementary Information

Ligand free MCR for linking quinoxaline framework with benzimidazole nucleus: A new strategy for the identification of novel hybrid molecules as potential inducers of apoptosis

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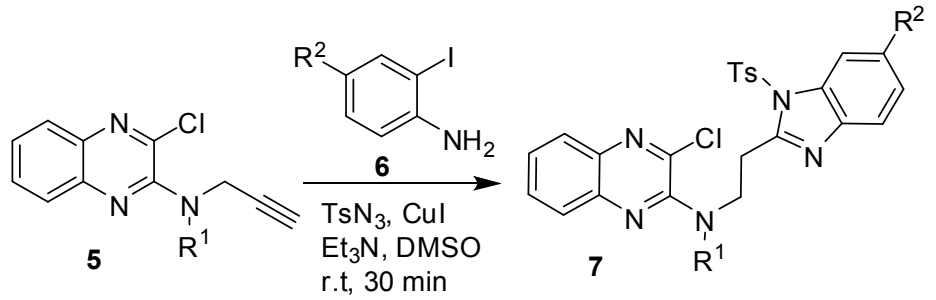
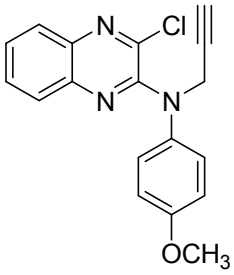
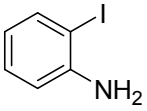
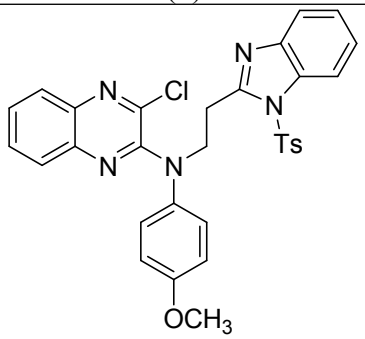
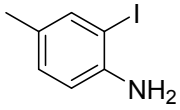
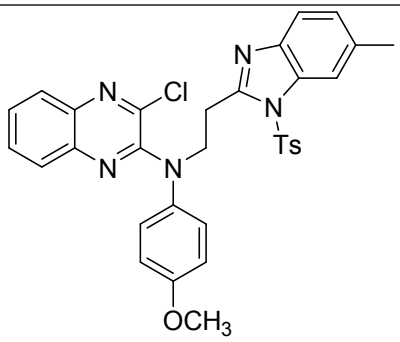
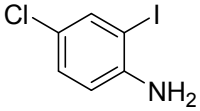
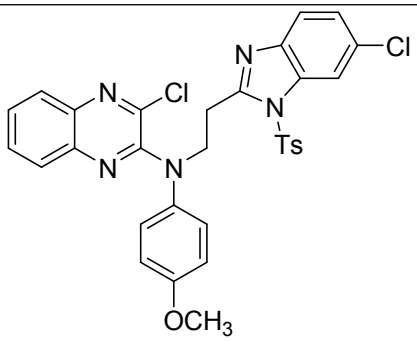
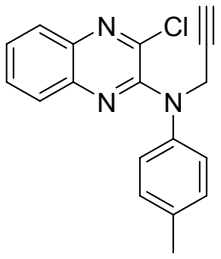
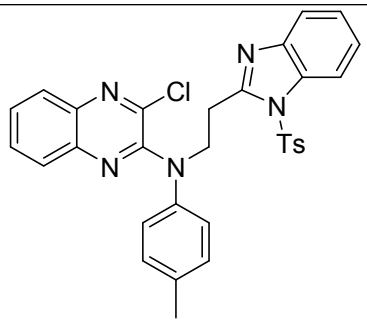
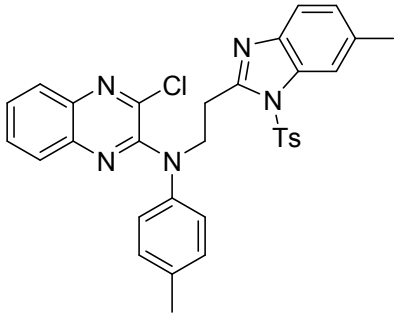
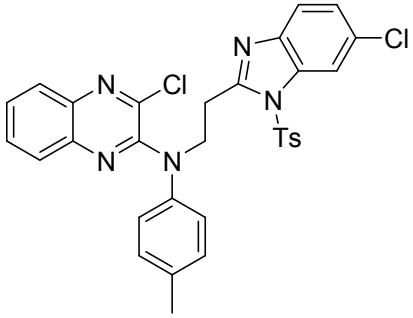
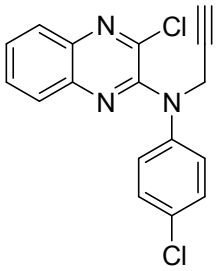
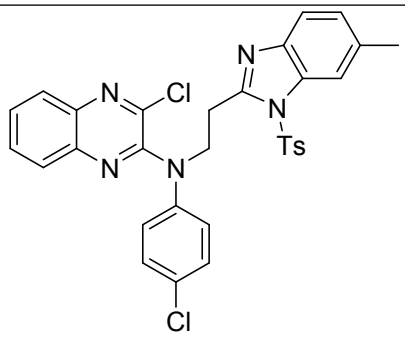
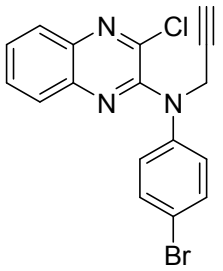
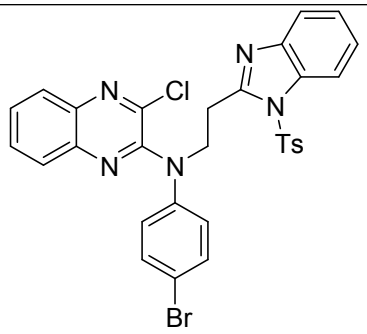
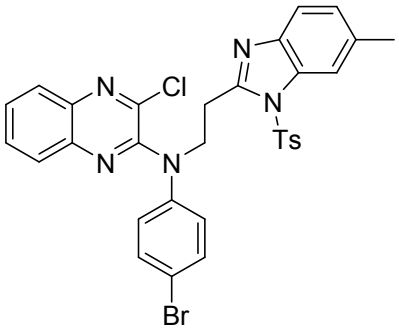
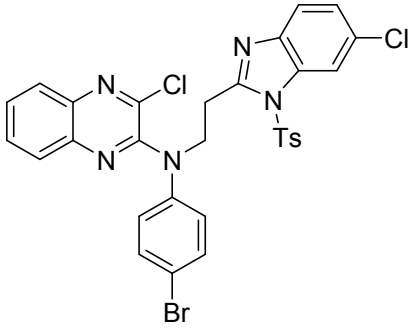
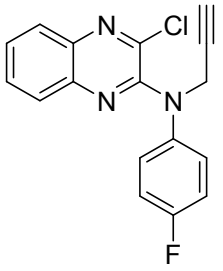
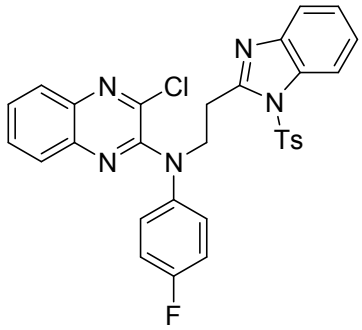
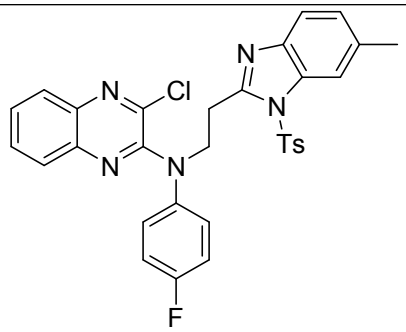
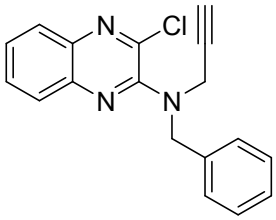
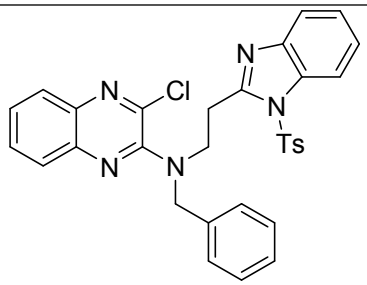
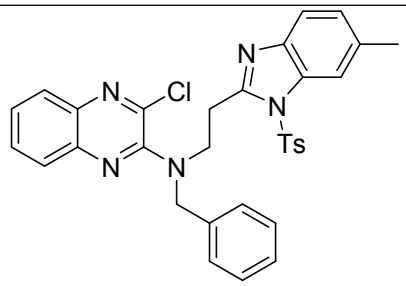
Table S-1: Synthesis of *N*-substituted 3-chloro-*N*-(2-(1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)ethyl)quinoxalin-2-amines (**7**).



Entry	Alkyne (**5**)	Iodo Aniline (**6**)	Product (**7**)	Yield (%)
1	 **5a**	 **6a**	 **7a**	94
2	**5a**	 **6b**	 **7b**	89
3	**5a**	 **6c**	 **7c**	90

4	 **5b**	**6a**	 **7d**	92
5	**5b**	**6b**	 **7e**	86
6	**5b**	**6c**	 **7f**	90
7	 **5c**	**6b**	 **7g**	89

8	 **5d**	**6a**	 **7h**	95
9	**5d**	**6b**	 **7i**	91
10	**5d**	**6c**	 **7j**	89
11	 **5e**	**6a**	 **7k**	93

12	**5e**	**6b**	 **7l**	86
13	 **5f**	**6a**	 **7m**	73
14	**5f**	**6b**	 **7n**	81

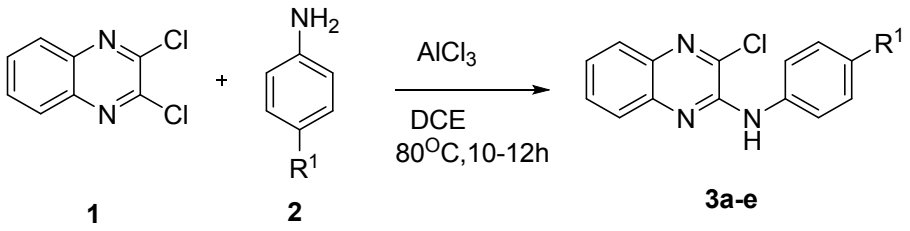
Experimental

Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate. ^{1}H and ^{13}C NMR spectra were recodred in $CDCl_3$ or DMSO-d_6 solution by using a 400 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of

doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. MS spectra were obtained on a Agilent 6430 series Triple Quard LC-MS / MS spectrometer. Melting points (mp) were determined by using Buchi B-540 melting point appratus and are uncorrected. Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times.

1. General Procedure for the preparation of 3-Chloro-N-aryl quinoxalin-2-amine (3a-e)[1]

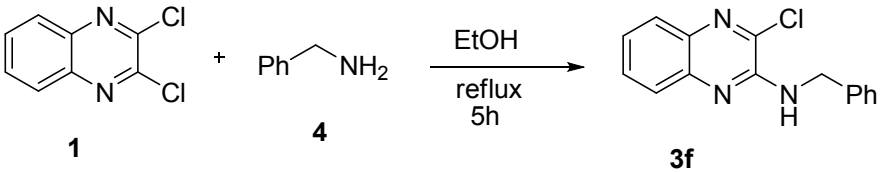


1 **2** **3a-e**

R^1=OCH_3, CH_3, F, Cl, Br

A mixture of 2,3-dichloroquinoxaline **1** (1.0 mmol), an appropriate amine **2** (1.0 mmol) and $AlCl_3$ (1.25 mmol) in 1,2-dichloroethane (5mL) was stirred at 80°C for 10-12 h under a nitrogen atmosphere. After completion of the reaction, the mixture was cooled to room temperature, poured into ice-cold water (15 mL), stirred for 10 min and then extracted with ethylacetate (3 × 10 mL). The combined organic layers were washed with cold water (2 × 10 mL), brine (4mL) and dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue obtained was purified by column chromatography on silica gel (230-400 mesh) using ethylacetate/hexane to give the desired product **3a-e**.

2. Preparation of N-benzyl-3-chloroquinoxalin-2-amine (3f)

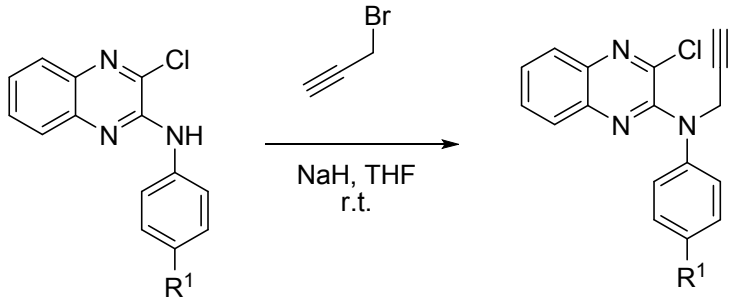


1 **4** **3f**

A mixture of 2,3-dichloroquinoxaline **1** (0.01 mmol) and benzylamine **4** (0.015 mmol) in

EtOH (5 mL) was heated under reflux for 5 h. After completion of the reaction, the reaction mass was cooled to room temperature and ethanol was removed under reduced pressure. The resulting solid was washed with water and dried to afford the desired products **3f**.

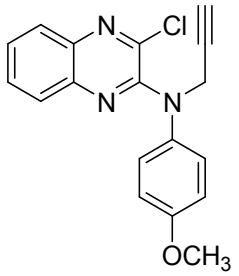
3. General procedure for the preparation of 3-chloro-N-aryl-N-(prop-2-ynyl)quinoxalin-2-amine (5a-f)



3a-f **5a-f**

Proparyl bromide (3 mmol) was added to a solution of N-substituted quinoxaline-2-amine derivatives **3a-f** (1 mmol) and sodium hydride in THF (10 mL) under nitrogen atmosphere. The reaction mixture was then stirred for 2h at room temperature. After completion of the reaction (confirmed by TLC), the mixture was diluted with ice water (3 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel using ethylacetate/ hexane as eluent to afford the N-propallylated quinoxaline-2-amine derivatives **5a-f**.

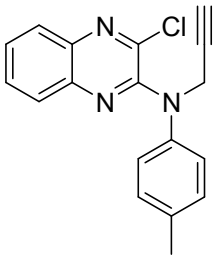
3.1. Preparation of 3-chloro-N-(4-methoxyphenyl)-N-(prop-2-ynyl)quinoxalin-2-amine (5a)



Yield: 92%; Light yellow; R_f = 0.2 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3265.7, 3057.5, 3008.2, 2964.3, 2926.0, 2849.3, 1512.3, 1435.6, 1402.7, 1221.9, 1084.9; ^1H NMR (400 MHz,

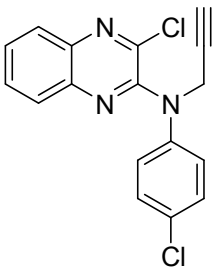
$CDCl_3$) δ: 7.95-7.90 (m, 1H), 7.90-7.85 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.71-7.64 (m, 1H), 7.59-7.51 (m, 1H), 7.09 (m, 2H), 6.93-6.85 (m, 2H), 4.69 (d, *J* = 2.3 Hz, 2H), 3.82 (s, 3H), 2.19 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 158.0, 149.4, 141.0, 139.8, 138.3, 138.2, 130.1 (2C), 127.6, 127.2, 127.1, 127.0, 114.5 (2C), 79.8, 72.2, 55.4, 43.7; MS (ES mass): 323.8 (M+1); HPLC: 85.8%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN (T/%B): 0/50, 2/50, 10/98, 15/98, 18/50, 20/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 215.5 nm, retention time 7.0 min.

3.2. Preparation of 3-chloro-N-(prop-2-ynyl)-N- tolylquinoxalin-p- 2-amine (5b)



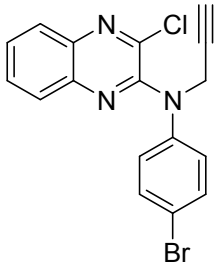
Yield: 94%; Yellow solid; R_f = 0.2 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3265.7, 1545.2, 1512.3, 1457.5, 1397.2, 1227.4, 1084.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.72-7.66 (m, 1H), 7.58-7.54 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 4.73 (d, *J* = 2.4 Hz, 2H), 2.37 (s, 3H), 2.19 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.3, 142.9, 141.3, 139.9, 138.3, 136.0, 130.1, 130.0, 129.4, 127.6, 127.4, 127.1, 125.1, 109.9, 79.8, 72.1, 43.5, 21.1; MS (ES mass): 307.9 (M+1); HPLC: 92.6%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN (T/%B): 0/50, 2/50, 10/98, 15/98, 18/50, 20/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 7.9 min.

3.3. Preparation of 3-chloro-N-(4-chlorophenyl)-N-(prop-2-ynyl)quinoxalin-2-amine (5c)



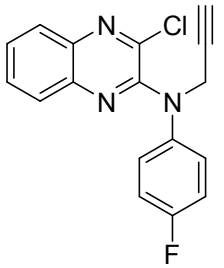
Yield: 90%; White solid; R_f = 0.2 (5% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3275.3, 1541.6, 1490.3, 1362.3, 1225.9, 1073.2; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.94 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.91 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.73-7.68 (m, 1H), 7.62-7.57 (m, 1H), 7.36-7.31 (m, 2H), 7.09-7.04 (m, 2H), 4.74 (d, *J* = 2.4 Hz, 2H), 2.21 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.9, 144.0, 141.2, 139.8, 138.6, 131.4, 130.3, 129.5(2C), 127.9, 127.7, 127.2, 126.1(2C), 79.4, 72.6, 43.3; MS (ES mass): 328.0 (M+1); HPLC: 99.1%, Column: Symmetry C-18 250 * 4.6 mm, 5µm, mobile phase A: 5mm Ammonium Acetate in water, mobile phase B: CH_3CN (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20,30/20; flow rate: 1.0 mL/min; Diluent: ACN: WATER (50:50); UV 210.4 nm, retention time 14.4 min.

3.4. Preparation of N-(4-bromophenyl)-3-chloro-N-(prop-2-ynyl)quinoxalin-2-amine (5d)



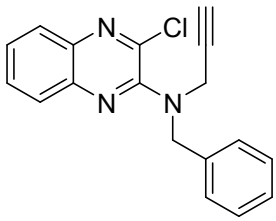
Yield: 89%; Light yellow solid; R_f = 0.2 (5% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3276.7, 1545.2, 1495.8, 1364.3, 1221.9, 1073.9; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 8.4 Hz, 1H), 7.92 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.74-7.69 (m, 1H), 7.64-7.58 (m, 1H), 7.50-7.47 (m, 2H), 7.02-7.00 (m, 2H), 4.75 (d, *J* = 2.4 Hz, 2H), 2.22 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.9, 144.5, 141.3, 139.8, 138.6, 132.5, 131.8, 130.3, 128.0, 127.7, 127.2, 126.3 (2C), 119.2, 79.3, 72.6, 43.3; MS (ES mass): 372.5 (M+1); HPLC: 98.3%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 6.2 min.

3.5. Preparation of 3-chloro-N-(4-fluorophenyl)-N-(prop-2-ynyl)quinoxalin-2-amine (5e)



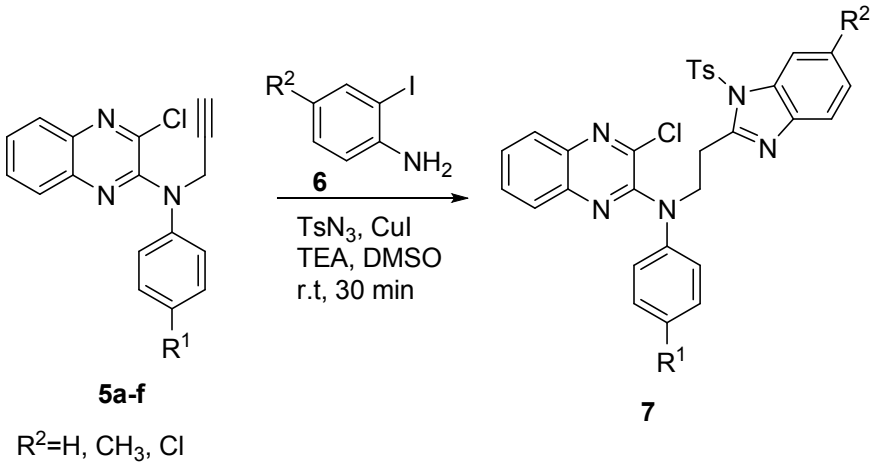
Yield: 90%; Yellow solid; R_f = 0.2 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3274.4, 1535.1, 1486.8, 1334.3, 1218.9, 1072.9; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71-7.67 (m, 1H), 7.60-7.56 (m, 1H), 7.14-7.11 (m, 2H), 7.08-7.04 (m, 2H), 4.71 (d, *J* = 2.3 Hz, 2H), 2.21 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.1 (C-F *J* = 244.8 Hz), 159.6, 149.2, 141.4 (2C), 140.9, 139.8, 138.4, 130.2, 127.6, 127.2 (2 C), 127.1 (C-F *J* = 8.5 Hz), 116.4 (2C), 116.1 (C-F *J* = 22.5 Hz), 109.9, 79.4, 72.5, 43.6; MS (ES mass): 311.8 (M+1); HPLC: 98.9%, Column: X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: Formic acid in water B: CH_3CN (T/%B): 0/40, 2/40, 9/98, 14/98, 16/40, 18/40; flow rate: 1.0 mL/min; Diluent: ACN: WATER (80:20); UV 215.4 nm, retention time 9.5 min.

3.6. Preparation of N-benzyl-3-chloro-N-(prop-2-ynyl)quinoxalin-2-amine (5f)



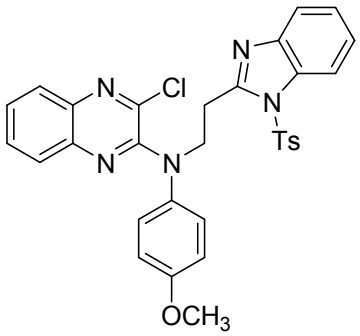
Yield: 91%; Yellow solid; R_f = 0.2 (5% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3274.7, 1535.3, 1497.3, 1367.2, 1231.9, 1063.7; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.92-7.88 (m, 2H), 7.69-7.65 (m, 1H), 7.59-7.57 (m, 1H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 4.86 (s, 2H), 4.24 (d, *J* = 2.3 Hz, 2H), 2.25 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.5, 141.0, 139.9, 138.4, 136.8, 130.2 (2C), 128.5 (2C), 128.4, 127.6 (2), 127.5, 127.2, 79.1, 72.8, 53.2, 39.1; MS (ES mass): 307.9 (M+1); HPLC: 88.3%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: NH_4OAc in water B: CH_3CN (T/%B): 0/20, 2/20, 7/98, 11/98, 12/20, 15/20; flow rate: 1.0 mL/min; Diluent: ACN: WATER (80:20); UV 210.4 nm, retention time 8.3 min.

4. General procedure for preparation of 3-chloro-*N*-(4-aryl)-*N*-(2-(1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)ethyl)quinoxalin-2-amine (7)



To a solution of sulfonyl azide (0.36 mmol), alkynes (0.30 mmol), 2-iodoanline (0.34 mmol), and CuI (0.03 mmol) in DMSO (2mL) was added TEA (0.36 mmol) slowly via syringe. The reaction solution was stirred at room temperature under N_2 for 30min. After completion of the reaction, the reaction mixture was partitioned between ethyl acetate and saturated NH_4Cl, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane to give desired compound **7**.

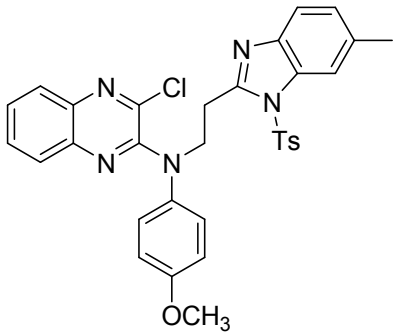
4.1. Preparation of 3-chloro-N-(4-methoxyphenyl)-N-(2-(1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7a)



Yield: 94%; Yellow solid; mp: 164-166 °C ; R_f = 0.4 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3409.3, 2936.6, 2832.5, 2719.7, 1604.9, 1539.1, 1369.2, 1303.4; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.08-8.05 (m, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.71-7.63 (m, 4H), 7.56-

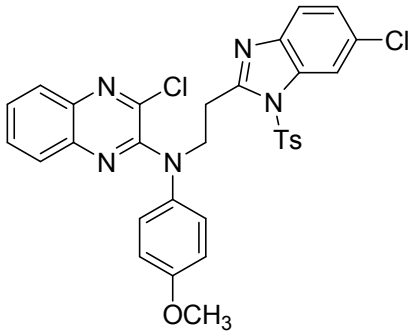
7.52 (m, 1H), 7.41-7.31 (m, 2H), 7.11 (dd, *J* = 14.5, 8.5 Hz, 4H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.58 (t, *J* = 7.3 Hz, 2H), 3.84 (s, 3H), 3.70 (dd, *J* = 9.39, 5.14 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 152.8, 149.6, 145.7, 141.9, 141.2, 140.9, 140.0, 138.7, 137.8, 135.2, 132.9, 130.0 (2C), 129.9, 127.5, 126.7 (2C), 126.6 (2C), 126.5, 124.7, 124.5, 119.7, 114.6 (2C), 113.4, 55.4, 52.0, 27.1, 21.6; MS (ES mass): 584.1 (M+1); HPLC: 99.1%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/40, 1/40, 6/98, 10/98, 12/40, 15/40; flow rate: 1.0 mL/min; Diluent: ACN: WATER (80:20); UV 210 nm, retention time 7.6 min.

4.2. Preparation of 3-chloro-N-(4-methoxyphenyl)-N-(2-(6-methyl-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7b)



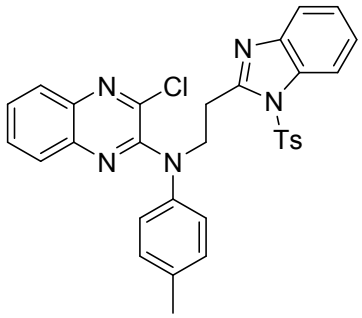
Yield: 89%; Yellow solid; m.p.170-175 ^{0}C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3381.3, 3302.2, 2928.0, 2831.6, 2718.7, 1626.0, 1597.1, 1353.1, 1307.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.68-7.59 (m, 3H), 7.52 (m, 2H), 7.18-7.03 (m, 5H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.54 (t, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.63 (t, *J* = 7.3 Hz, 2H), 2.51 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 152.0, 149.5, 145.5, 141.1, 139.9, 139.8, 138.7, 137.7, 135.3, 134.9, 133.1, 129.9 (2C), 129.8, 127.4, 126.7, 126.6 (2C), 126.5, 126.4 (2C), 125.8, 119.0, 114.5 (2C), 113.4, 55.3, 51.9, 27.0, 21.8, 21.5; MS (ES mass): 598 (M+1); HPLC: 97.9%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 7.5 min.

4.3. Preparation of 3-chloro-N-(2-(6-chloro-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)-N-(4-methoxyphenyl)quinoxalin-2-amine (7c)



Yield: 90%; Yellow solid; m.p.174-175 ^{0}C; R_f = 0.4 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3409.3, 2955.0, 2848.0, 2719.7, 1626.0, 1596.1, 1383.0, 1352.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.70-7.60 (m, 3H), 7.52 (t, *J* = 6.92 Hz, 2H), 7.30 (d, *J* = 1.89 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.54 (t, *J* = 6.8Hz, 2H), 3.82 (s, 3H), 3.63 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 153.4, 149.5, 146.0, 141.1, 140.4, 139.8, 138.5, 137.7, 134.8, 133.4, 130.5, 130.1 (2C), 129.8, 127.4, 126.7, 126.6 (2C), 126.6 (2C), 126.5, 125.1, 120.3, 114.5 (2C), 113.6, 55.3, 51.8, 27.0, 21.5; MS (ES mass): 617.9 (M+1); HPLC: 98.8%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 7.9 min.

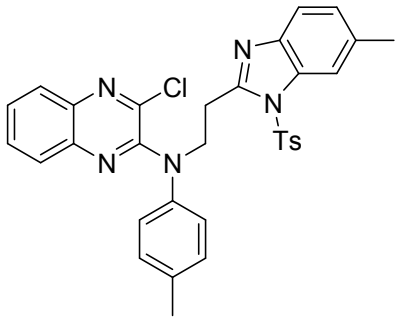
4.4. Preparation of 3-chloro-N-p-tolyl-N-(2-(1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2 amine (7d)



Yield: 92%; Yellow solid; m.p.162-167 ^{0}C; R_f = 0.4 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2958.5, 2925.6, 2848.9, 1741.9, 1593.9, 1544.6, 1511.2, 1374.7, 1265.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07-8.01 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.67-6.63 (m, 4H), 7.56-7.50 (m, 1H), 7.36-7.29 (m, 2H), 7.13 (dd, *J* = 8.4, 8.0 Hz, 4H), 7.01 (d, *J* = 8.4 Hz,

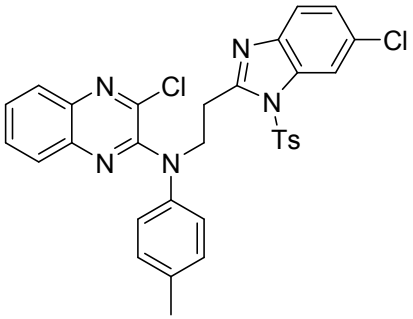
2H), 4.59 (t, *J* = 7.2 Hz, 2H), 3.69-3.65 (m, 2H), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.7, 149.6, 145.7, 143.1, 141.8, 141.5, 140.0, 138.0, 135.3, 135.2, 132.9, 130.1, 130.0 (2C), 129.8, 127.5, 126.9, 126.8, 126.6 (2C), 124.9 (2C), 124.7, 124.5, 119.7, 113.4, 109.9, 51.8, 27.2, 21.6, 20.9; MS (ES mass): 568 (M+1); HPLC: 97.5%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 7.7 min.

4.5. Preparation of 3-chloro-N-(2-(6-methyl-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)-N-p-tolylquinoxalin-2-amine (7e)



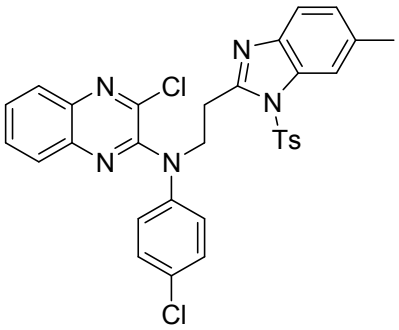
Yield: 86%; Yellow solid; m.p.160-162 ^{0}C; R_f = 0.2 (40% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3024.3, 2914.7, 2859.9, 1741.9, 1604.9, 1544.6, 1511.7, 1380.2, 1265.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91-7.83 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.66-7.61 (m, 3H), 7.55-7.49 (m, 2H), 7.15-7.09 (m, 5H), 7.01 (d, *J* = 8.2 Hz, 2H), 4.57 (t, *J* = 7.3 Hz, 2H), 3.63 (t, *J* = 7.3 Hz, 2H), 2.51 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.1, 149.6, 145.6, 143.2, 141.6, 140.0, 139.9, 138.0, 135.4, 135.3, 134.9, 133.1, 130.0 (2C), 129.8, 127.5, 126.8 (2C), 126.5 (2C), 125.9 (2C), 124.8 (2C), 119.1, 113.4, 109.9, 51.8, 27.2, 21.9, 21.6, 20.9; MS (ES mass): 582 (M+1); HPLC: 99.3%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 8.0 min.

4.6. Preparation of 3-chloro-N-(2-(6-chloro-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)-N-p-tolylquinoxalin-2-amine (7f)



Yield: 90%; Yellow solid; m.p.170-173 ^{0}C; R_f = 0.4 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2953.0, 2926.6, 2854.4, 1747.3, 1599.4, 1544.6, 1506.2, 1380.2, 1265.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.70-7.61 (m, 3H), 7.54 (t, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.14 (dd, *J* = 7.6, 5.4 Hz, 4H), 6.99 (d, *J* = 8.3 Hz, 2H), 4.57 (t, *J* = 7.2 Hz, 2H), 3.63 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.4, 149.6, 146.1, 143.1, 141.5, 140.4, 139.9, 138.0, 135.4, 134.9, 133.5, 130.6, 130.2 (2C), 130.0, 129.9, 127.5, 127.0, 126.8, 126.7 (2C), 126.7, 125.1, 124.8 (2C), 120.4, 113.7, 51.7, 27.3, 21.6, 21.0; MS (ES mass): 601.9 (M+1); HPLC: 95.5%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 230.5 nm, retention time 8.4 min.

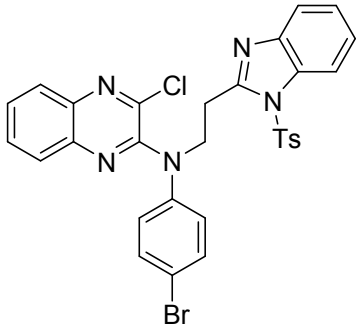
4.7. Preparation of 3-chloro-N-(4-chlorophenyl)-N-(2-(6-methyl-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7g)



Yield: 89%; Yellow solid; m.p.162-166 ^{0}C; R_f = 0.4 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2947.6, 2920.2, 1599.4, 1539.1, 1495.2, 1374.7, 1265.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 8.07 Hz, 1H), 7.86-7.79 (m, 2H), 7.71-7.55 (m, 4H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.12 (t, *J* = 9.3 Hz, 3H), 7.04 (d, *J* = 8.6 Hz, 2H), 4.59 (t, *J* = 6.9 Hz, 2H), 3.61 (t, *J*

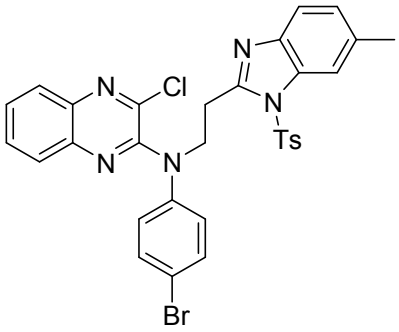
= 7.1 Hz, 2H), 2.50 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.6, 149.1, 145.7, 144.4, 141.4, 139.8, 139.7, 138.2, 135.2, 135.0, 133.1, 130.5, 130.0 (2C), 129.9, 129.4 (2C), 127.5, 127.4 (2C), 126.9, 126.4, 125.9, 125.6 (2C), 119.0, 113.4, 51.7, 27.5, 21.8, 21.5; MS (ES mass): 601.9 (M+1); HPLC: 99.4%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 7.9 min.

4.8. Preparation of N-(4-bromophenyl)-3-chloro-N-(2-(1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7h)



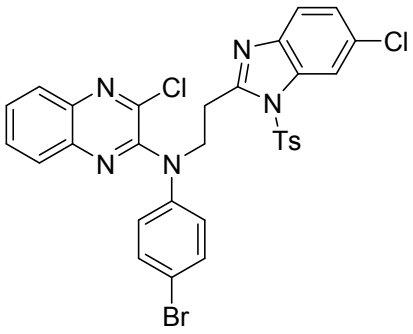
Yield: 95%; Light yellow solid; m.p.145-150 ^{0}C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3035.2, 2931.1, 2859.9, 1621.3, 1599.4, 1544.6, 1374.7, 1193.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07-8.00 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.71-7.55 (m, 5H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.37-7.30 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.62 (dd, *J* = 9.4, 4.9 Hz, 2H), 3.65 (t, *J* = 7.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.9, 152.4, 149.2, 145.9, 144.9, 141.8, 141.5, 139.9, 138.3, 135.2, 132.9, 132.5 (2C), 130.1 (2C), 127.6, 127.0, 126.5 (2C), 126.0 (2C), 125.9, 124.9, 124.6, 119.7, 118.4, 113.5, 51.7, 27.5, 21.6; MS (ES mass): 633.9 (M+1); HPLC: 99.2%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 7.9 min.

4.9. Preparation of N-(4-bromophenyl)-3-chloro-N-(2-(6-methyl-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7i)



Yield: 91%; Brown solid; m.p.165-169 ^{0}C; R_f = 0.4 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3783.5, 3433.4, 3407.4, 2926.1, 2828.7, 1595.2, 1492.2, 1437.9, 1354.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 8.0 Hz, 1H), 7.86-7.80 (m, 2H), 7.71-7.56 (m, 4H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.12 (t, *J* = 8.3 Hz, 3H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.60 (t, *J* = 7.10 Hz, 2H), 3.62 (t, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:151.7, 149.2, 145.8, 145.0, 141.6 (2C), 139.9, 139.8, 138.3,135.3, 135.1, 132.4, 130.1, 130.0, 127.6, 127.5, 127.1, 126.5, 126.0, 125.9 (2C), 125.8, 125.7, 119.1, 118.3, 113.5 (2C), 51.7, 27.6, 21.9, 21.6; MS (ES mass): 647.8 (M+1); HPLC: 98.8%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 210.5 nm, retention time 8.0 min.

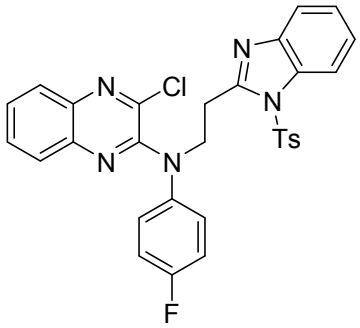
4.10. Preparation of N-(4-bromophenyl)-3-chloro-N-(2-(6-chloro-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7j)



Yield: 89%; Brown solid; m.p.190-193 ^{0}C; R_f = 0.4 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3786.4, 3432.4, 3383.2, 2958.9, 2830.6, 2719.7, 1595.2 , 1486.2, 1443.7, 1380.1, 1353.; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.91-7.88 (m, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.69-7.56 (m, 4H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.45 (t, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.13

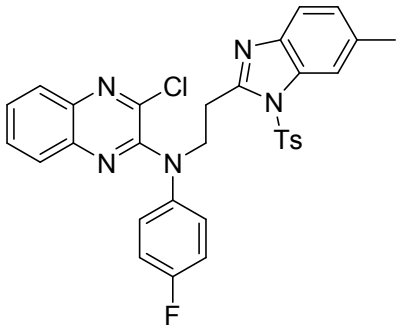
(d, *J* = 8.1 Hz, 2H), 6.98 (t, *J* = 8.8 Hz, 2H), 4.59 (t, *J* = 7.1 Hz, 2H), 3.61 (t, *J* = 7.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.1, 149.1, 146.3, 144.9, 141.5, 140.4, 139.9, 138.3, 134.9, 133.5, 132.5 (2C), 130.7, 130.2 (2C), 130.1, 127.6, 127.0, 126.6, 126.5, 126.0, 125.9, 125.3, 120.4, 118.4, 113.7, 109.9, 51.6, 27.6, 21.6; MS (ES mass): 667.8 (M+1); HPLC: 88.8%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN (T/%B): 0/50, 2/50, 10/98, 15/98, 18/50, 20/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 225.5 nm, retention time 7.9 min.

4.11. Preparation of 3-chloro-N-(4-fluorophenyl)-N-(2-(1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7k)



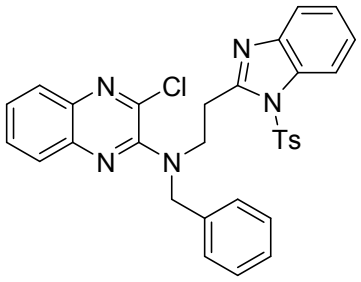
Yield: 93%; Brown solid; m.p.141-142.9 ^{0}C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3057.2, 2953.0, 2920.2, 1599.4, 1539.7, 1473.3, 1418.5, 1369.2, 1226; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.64-7.61 (m, 4H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.36-7.28 (m, 2H), 7.10 (t, *J* = 6.9 Hz, 4H), 7.02 (t, *J* = 8.4 Hz, 2H), 4.58 (t, *J* = 7.2 Hz, 2H), 3.65 (t, *J* = 7.2 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6 (C-F *J* = 244.1 Hz), 159.1, 152.5, 149.4, 145.8, 142.0, 141.9, 141.8, 141.2, 139.9, 138.0, 135.2, 132.9 (2C), 130.0, 129.2, 127.5, 127.2, 126.9, 126.7 (C-F *J* = 8.3 Hz), 126.7, 126.5, 124.8, 124.6, 119.7, 116.3 (C-F *J* = 22.6 Hz), 116.1, 113.4 (2C), 109.9, 52.0, 27.3, 21.5; MS (ES mass): 572 (M+1); HPLC: 98.6%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (80:20); UV 210 nm, retention time 7.4 min.

4.12. Preparation of 3-chloro-N-(4-fluorophenyl)-N-(2-(6-methyl-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7l)



Yield: 86%; White solid; m.p.141-142.9 ^{0}C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3799.0, 3714.0, 3461.4, 3293.5, 2927.1, 2833.5, 2719.7, 1597.1, 1486.2, 1358.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91-7.83 (m, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.70-7.61 (m, 3H), 7.60-7.53 (m, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.17-7.07 (m, 5H), 7.03 (t, *J* = 8.5 Hz, 2H), 4.57 (t, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 7.2 Hz, 2H), 2.51 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.6 (C-F *J* = 244.3 Hz), 159.1, 152.5, 149.4, 145.8, 142.0, 141.9, 141.8, 141.2, 139.9, 138.0, 135.3, 135.0, 133.1, 129.9 (2C) , 127.5, 127.1, 126.8, 126.8, 126.6 (C-F *J* = 8.4 Hz), 126.5 (2C), 126.4 (2C), 125.9, 119.0, 116.2 (C-F *J* = 22.7 Hz), 116.0 (2C), 113.4, 52.0, 27.3, 21.8, 21.5; MS (ES mass): 586 (M+1); HPLC: 98.8%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (80:20); UV 210 nm, retention time 7.6 min.

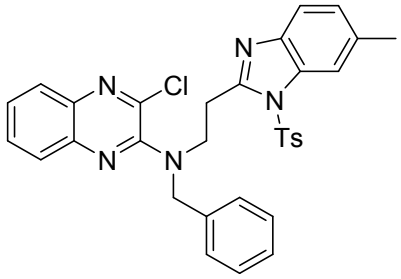
4.14. Preparation of N-benzyl-3-chloro-N-(2-(1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7m)



Yield: 73%; White solid; m.p.125-130 ^{0}C; R_f = 0.3 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3431.5, 3412.2, 2966.6, 2827.7, 2720.7, 1594.2, 1380.1, 1353.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04-7.96 (m, 1H), 7.91-7.84 (m, 1H), 7.71-7.62 (m, 3H), 7.60-1,56 (m, 2H), 7.55-7.47 (m, 1H),

7.46-7.37 (m, 2H), 7.29 (d, *J* = 7.18 Hz, 5H), 7.13 (d, *J* = 7.6 Hz, 2H), 4.87 (s, 2H), 4.13 (s, 2H), 3.57 (d, *J* = 0.49 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5, 151.5, 145.8, 141.8, 140.7, 139.8, 137.8, 137.6 (2C), 135.2, 132.9, 130.2, 130.1, 130.0, 128.4, 127.6, 127.2, 126.9, 126.8, 126.6, 124.8, 124.6, 121.9, 119.7, 113.5 (2C), 109.9, 54.9, 47.9, 27.9, 21.6; MS (ES mass): 568 (M+1); HPLC: 98.6%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 250 nm, retention time 7.5 min

4.13. Preparation of N-benzyl-3-chloro-N-(2-(6-methyl-1-tosyl-1H-benzo[d]imidazol-2-yl)ethyl)quinoxalin-2-amine (7n)



Yield: 81%; Light green solid; m.p.174-175 ^{0}C; R_f = 0.3 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3433.4, 3407.4, 3383.2, 2927.1, 2829.6, 2720.7, 1594.2, 1590.3, 1492.9, 1443.7, 1381.0, 1354.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.65-7.58 (m, 3H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.44-7.40 (m, 3H), 7.30 (t, *J* = 7.08 Hz, 3H), 7.15-7.08 (m, 3H), 4.86 (s, 2H), 4.12 (t, *J* = 7.3 Hz, 2H), 3.53 (t, *J* = 7.3 Hz, 2H), 2.49 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.8, 151.5, 145.7, 140.7, 139.8, 137.8, 135.4, 135.0, 133.1, 130.1 (2C), 129.9, 128.4 (2C), 127.8 (2C), 127.5, 127.2, 126.9, 126.8, 126.5 (2C), 125.9, 119.1 (2C), 113.5 (2C), 54.8, 48.0, 27.9, 21.9, 21.6; MS (ES mass): 582 (M+1); HPLC: 99%, Column: Symmetry C-18 75 * 4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN (T/%B): 0/50, 1/50, 6/98, 12/98, 13/50, 15/50; flow rate: 1.0 mL/min; Diluent: ACN: WATER (90:10); UV 250 nm, retention time 7.8 min.

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Pharmacology

Zebrafish embryo studies:

Husbandry:

Zebrafish obtained from a local vendor were maintained in in-house built recirculatory system under 14-10hrs light dark cycle and 28˚C temperature as described in (Banote et al., 2013). Breeding was carried out using females and males in ratio of 2:3 and the embryos obtained were collected in petridishes and maintained at 28^0C. (Westerfield et al., 2000, Nakhi et al.,2013).

Apoptosis Assay:

24hpf embryos were de-chorinated manually. 6 embryos were distributed as two sets in each well of 24 well plate with 250 µl of 0.1% DMSO. The working stock solutions were prepared by serial dilution as described earlier. Each well was added with 250µl of respective concentration to obtain final working concentration. Embryos were incubated at 28˚C for 24hrs and 48hrs.

Check apoptotic effect at 24hrs and 48hrs by washing drug exposed embryos thrice with E3 medium. Acridine orange (2µg/ml) solution of dye in E3 medium was added and incubated for 30mins. The embryos were rinsed thoroughly twice in fresh E3 medium to wash the acridine orange solution. Stained embryos were anesthetized with tricaine and photographed under UV illumination using Zeiss AxioCamMR camera attached to a Zeiss florescence microscope (GFP filter set : excitation 473,emission 520) under 5X magnification. The Images were taken and analyzed using Image J software.

Teratogenicity assay:

Zebrafish appeal of rapid organogenesis and transparency of developing embryos made it as a promising model for teratogenicity assay. In this assay, 1dpf embryos at same developmental stage were sorted out and dechorionated using protease K. Test compounds stock solutions were prepared by dissolving in 100% DMSO. By serial dilution from stock solutions various concentrations were prepared and the final concentration of DMSO becomes 0.1%. The embryos were distributed in 24 well plate (3/well) and concentrations of test compounds starting from 1µM to 30µM compound was added to each well accordingly where n=6.The plate was incubated at 28˚C until 5dpf. The embryos were washed with PBS and anesthetized using tricaine (0.008%). Morphological scoring was done based on the procedure previously described (Panzica-Kelly et al, 2010).

Table S-2: Results of zebrafish embryo toxicity study with toxicological indices and major organs/systems affected in positive control and at MTC of test compounds (- no effect, x- slightly toxic, xx-moderately toxic, xxx-severely toxic).

	Compound 7k	**Compound 7e**	**Compound 7i**	**Phenobarbital**
Test Concentrations (µM)	1, 3, 10, 30	1, 3, 10, 30	1, 3, 10, 30	3000
Statistically Significant Toxic Concentration (µM)	-	-	10 &30	Positive Control
No Observed Adverse Effect Level (NOAEL) (µM)	30	10	3	
Parameters of toxicity at MTC (Maximum Tolerable Concentration)				
Body Shape	-	-	xx	xxx
Somites	-	-	xx	xxx
Notochord	-	-	xxx	xxx
Tail	-	-	xx	xxx
Fins	-	-	xxx	xxx
Brain	-	-	xxx	xxx
Upper jaw	-	-	xx	xxx
Heart	-	xx	xx	xx
Intestine	-	xx	xx	xxx
Lower jaw	-	-	xxx	xx
Liver	-	xx	xx	xxx
Swim Bladder	-	xx	xx	xxx

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