Electronic Supplementary Information

Vinylic amino group activation: a new and general strategy leading to functionalized fused heteroaromatics

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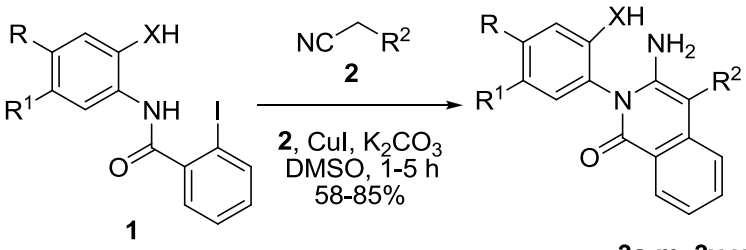
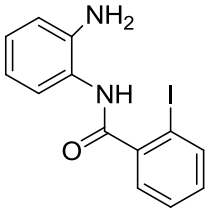
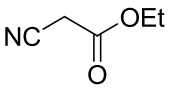
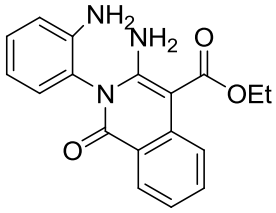
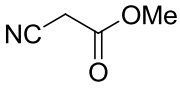
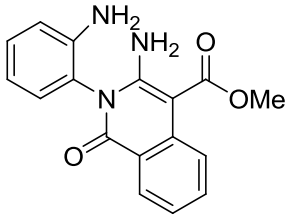
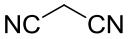
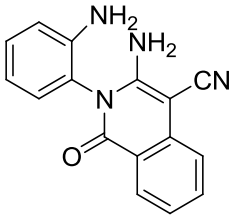
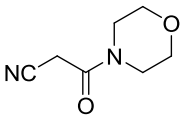
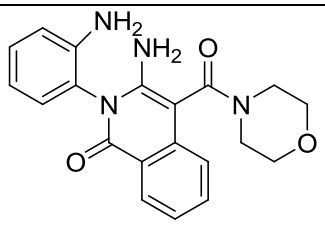
Table S-1: Synthesis of 3-amino-2-aryl-1-oxo-1,2-dihydroisoquinoline (**3**).[a]

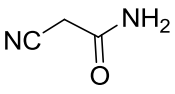
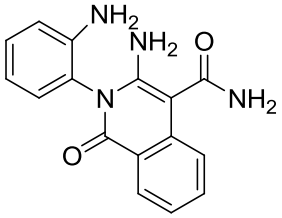
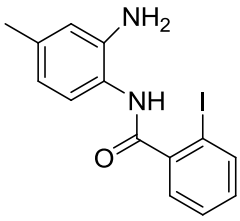
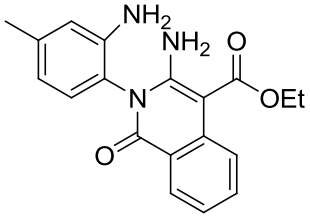
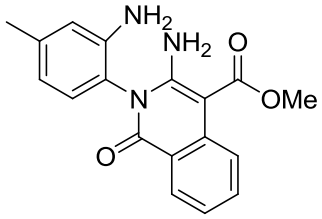
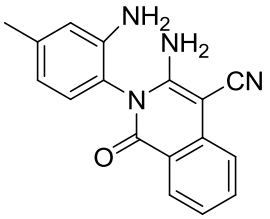
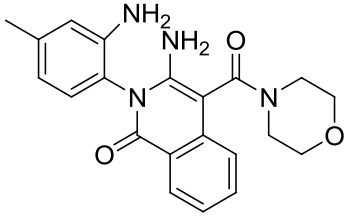
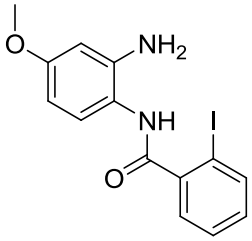
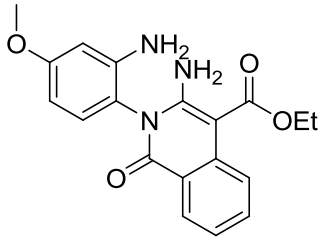


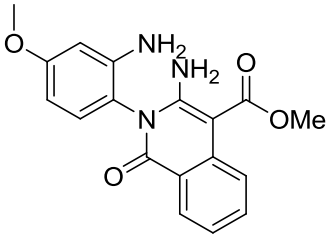
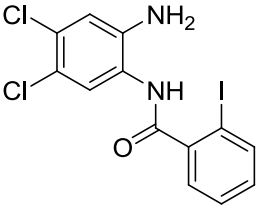
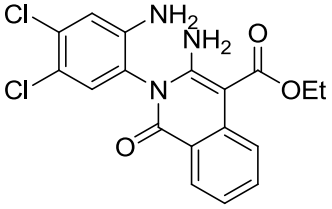
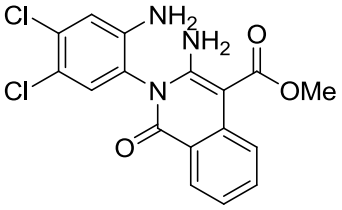
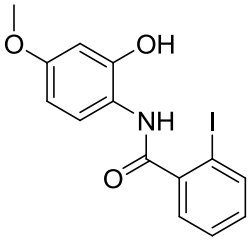
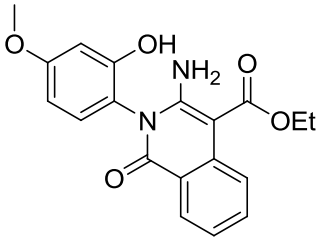
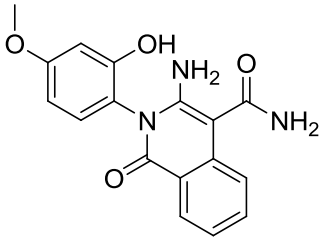
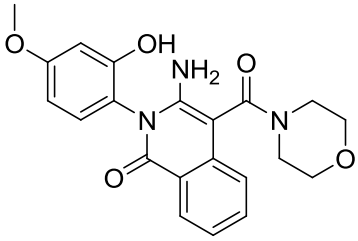
X = NH, O

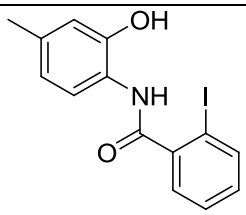
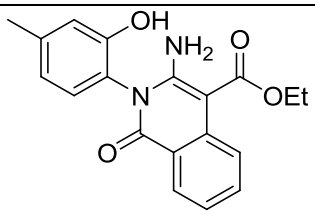
R = H, CH_3, OCH_3, Cl
R^1 = H, Cl

R^2 = CO_2Et, CO_2Me, CN, $CONH_2$, $CON(CH_2)_2(CH_2)_2O$

Entry	Substrate (**1**)	Substrate (**2**)	Time/ h	Product (**3**)	Yield[b] (%)
1	 **1a**	 **2a**	1.0	 **3a**	72
2	**1a**	 **2b**	1.0	 **3b**	69
3	**1a**	 **2c**	4.0	 **3c**	67
4	**1a**	 **2d**	3.0	 **3d**	58

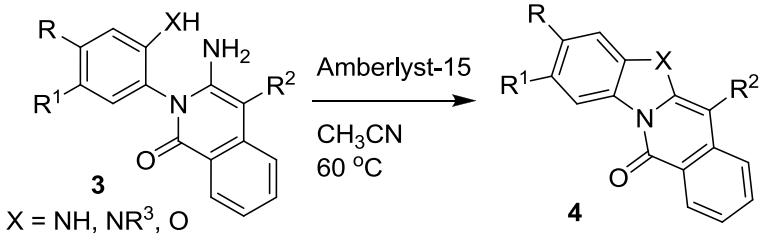
5	**1a**	 **2e**	3.0	 **3e**	64
6	 **1b**	**2a**	1.0	 **3f**	65
7	**1b**	**2b**	1.0	 **3g**	64
8	**1b**	**2c**	4.0	 **3h**	68
9	**1b**	**2d**	3.0	 **3i**	64
10	 **1c**	**2a**	3.0	 **3j**	83

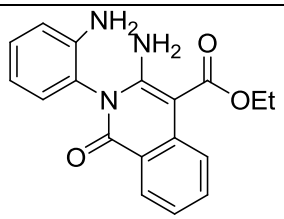
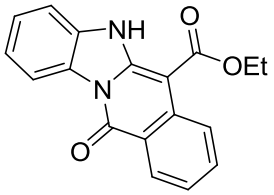
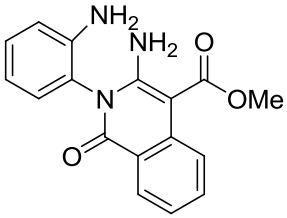
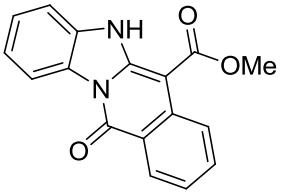
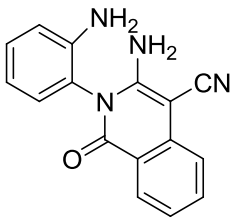
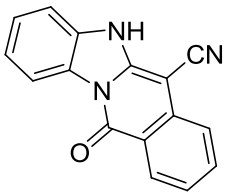
11	**1c**	**2b**	4.0	 **3k**	83
12	 **1d**	**2a**	1.0	 **3l**	85
13	**1d**	**2b**	1.0	 **3m**	84
14	 **1e**	**2a**	3.0	 **3v**	68
15	**1e**	**2e**	5.0	 **3w**	63
16	**1e**	**2d**	5.0	 **3x**	60

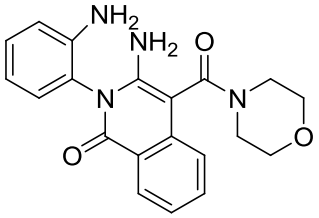
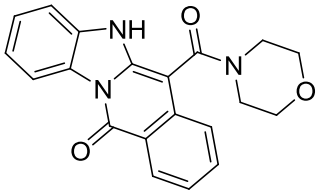
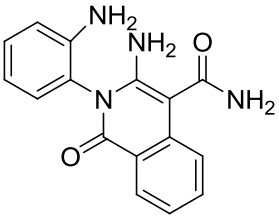
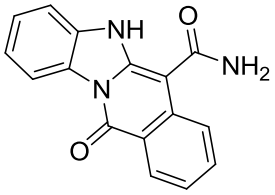
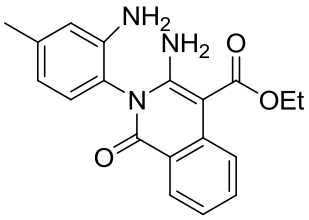
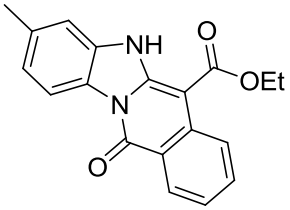
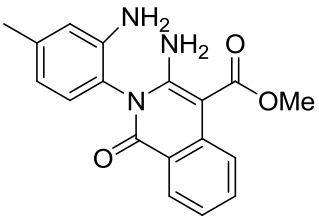
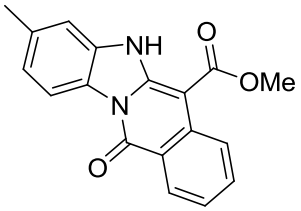
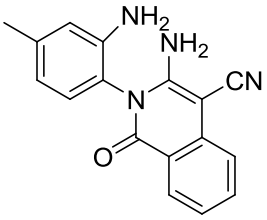
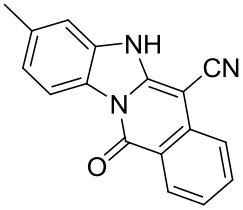
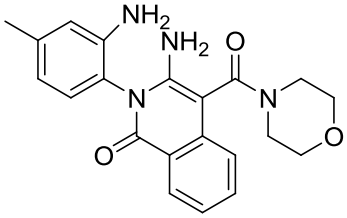
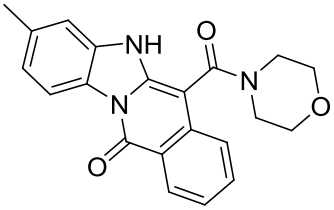
17	 **1f**	**2a**	3.0	 **3y**	65

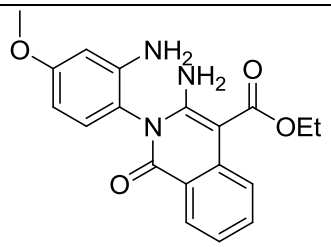
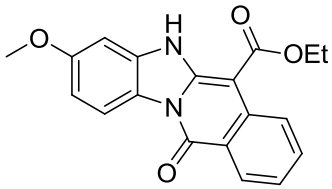
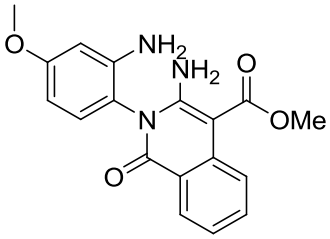
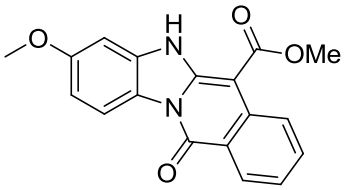
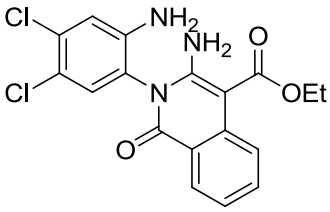
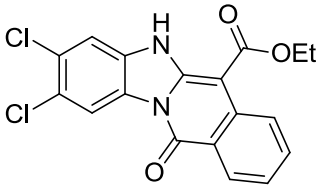
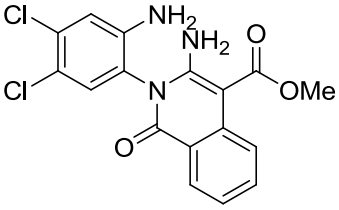
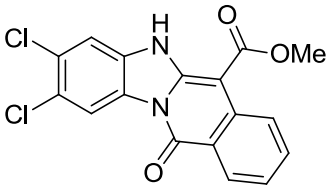
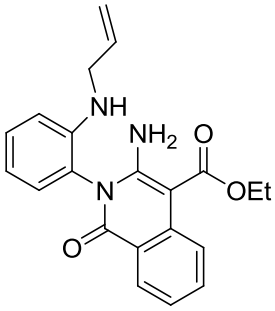
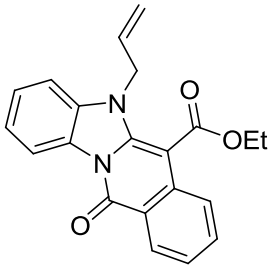
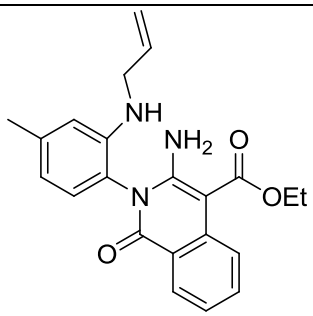
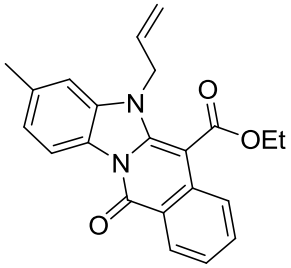
[a]All the reactions are carried out using compound **1** (1 mmol), **2** (1.2 mmol), K_2CO_3 (2.0 mmol) and 10 mol% CuI in DMSO (5 mL) at 85 °C under anhydrous conditions.
[b]Isolated yield.

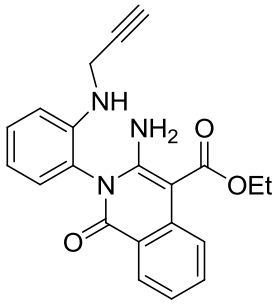
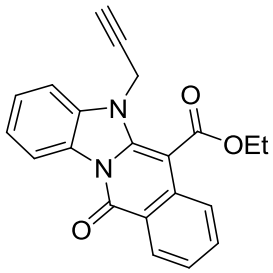
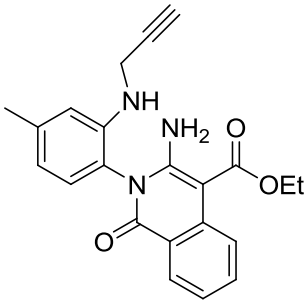
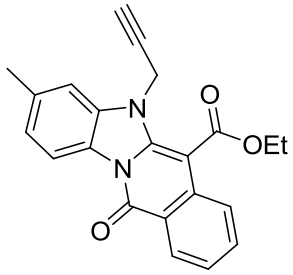
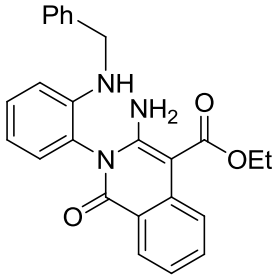
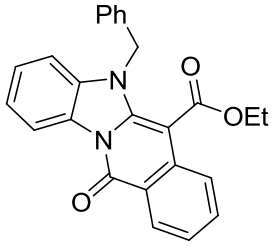
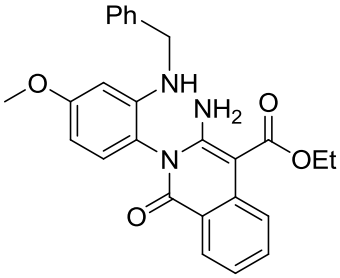
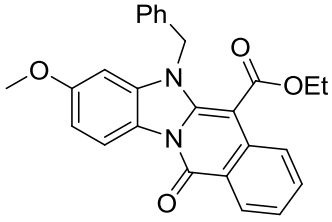
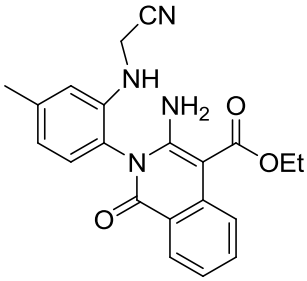
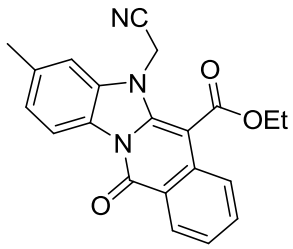
Table S-2: Amberlyst-15 mediated synthesis of benzimidazo[1,2-*b*]isoquinolin-11-ones / benzoxazolo[3,2-*b*]isoquinolin-11-ones (**4**).

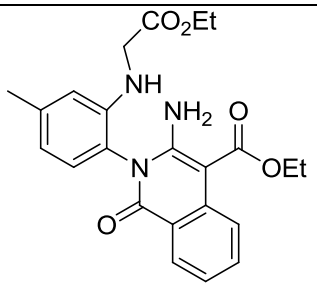
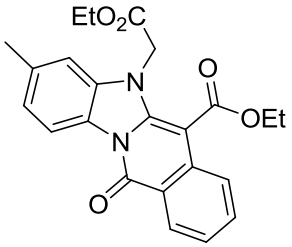
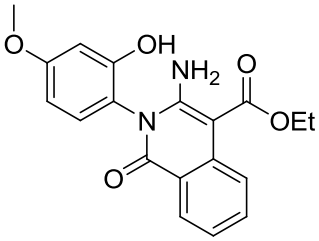
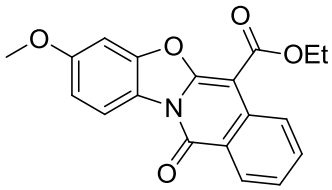
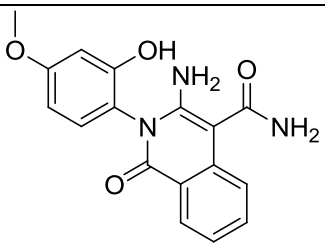
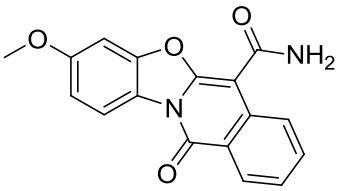
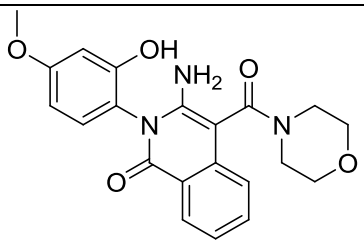
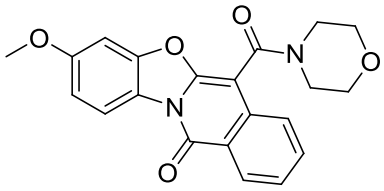
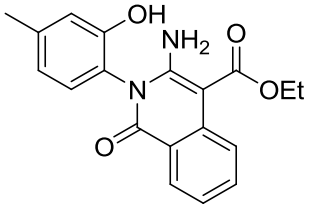
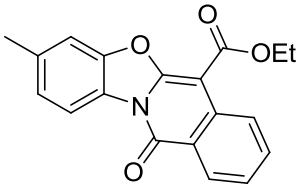


Entry	Substrate (**3**)	Time/h	Product (**4**)	Yield[b] (%)
1	 **3a**	1.5	 **4a**	98
2	 **3b**	2.0	 **4b**	87
3	 **3c**	7.0	 **4c**	71

4	 **3d**	11.5	 **4d**	63
5	 **3e**	8.5	 **4e**	65
6	 **3f**	1.5	 **4f**	91
7	 **3g**	2.0	 **4g**	83
8	 **3h**	7.0	 **4h**	75
9	 **3i**	12.0	 **4i**	61

10	 **3j**	1.5	 **4j**	92
11	 **3k**	2.0	 **4k**	91
12	 **3l**	2.0	 **4l**	93
13	 **3m**	2.0	 **4m**	90
14	 **3n**	3.5	 **4n**	89
15		3.5	 **4o**	91

	3o			
16	 **3p**	3.0	 **4p**	89
17	 **3q**	3.0	 **4q**	86
18	 **3r**	4.5	 **4r**	95
19	 **3s**	4.0	 **4s**	95
20	 **3t**	5.0	 **4t**	96

21	 **3u**	6.0	 **4u**	91
22	 **3v**	5.0	 **4v**	90
23	 **3w**	8.0	 **4w**	85
24	 **3x**	8.0	 **4x**	72
25	 **3y**	5.0	 **4y**	93

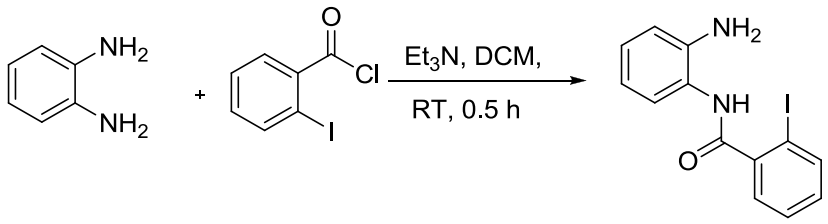
Experimental

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 NMR and ^{13}C NMR spectra were recodred in $CDCl_3$ or DMSO-d_6 solution by using 400 or 100 MHz spectrometers, respectively. 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 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.

Typical procedure for preparation of *N*-(2-aminophenyl)-2-iodobenzamide (1a)



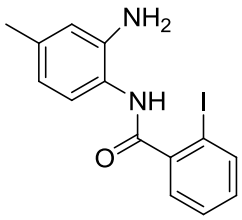
1a

To a solution of compound benzene-1,2-diamine (100 mg, 0.92 mmol) in dry DCM (5 mL), triethylamine (0.11 mL, 1.10 mmol) was added at 0 ºC under nitrogen atmosphere. To this 2-iodo benzoyl chloride (0.13 mL, 0.92 mmol) was slowly added and the reaction mixture stirred at room temperature for 0.5 h. After completion of reaction, the reaction mixture diluted with DCM (10 mL), washed with saturated $NaHCO_3$ solution (15 mL), followed by brine solution (10 mL), 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 **1a**.

Yield: 89% (275 mg); light yellow solid; mp: 130-132 °C; R_f = 0.2 (50% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3436, 3352, 3262, 3035, 1644; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.46-7.38 (m, 3H), 7.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.11-7.09

(m, 1H), 6.86 (dd, *J* = 8.8, 1.2 Hz, 2H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.7, 141.8, 140.8, 139.9, 131.4, 128.5, 128.3, 127.6, 125.3, 123.4, 119.5, 118.1, 92.4; MS (ES mass): 338.9 (M+1); HPLC: 95.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.74 min.

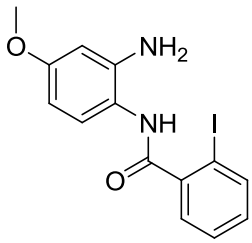
***N*-(2-Amino-4-methylphenyl)-2-iodobenzamide (1b)**



Compound **1b** was synthesized from 4-methylbenzene-1,2-diamine following a procedure similar to that of compound **1a.**

Yield: 95% (270 mg); white solid; mp: 140-142 °C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3426, 3312, 3139, 3028, 1642; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.17-7.13 (m, 1H), 6.66-6.64 (m, 2H), 3.91 (bs, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 142.0, 140.9, 139.9, 137.7, 131.4, 128.5, 128.3, 125.4, 120.7, 120.3, 118.5, 92.4, 21.0; MS (ES mass): 352.9 (M+1); HPLC: 96.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.01 min.

***N*-(2-Amino-4-methoxyphenyl)-2-iodobenzamide (1c)**

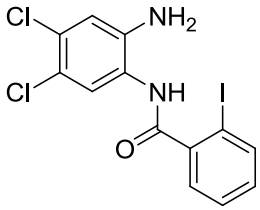


Compound **1c** was synthesized from 4-methoxybenzene-1,2-diamine following a procedure similar to that of compound **1a.**

Yield: 63% (168 mg); white solid; mp: 182-184 °C; R_f = 0.4 (50% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3439, 3356, 3265, 3043, 1638; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.52 (s, 1H), 7.93 (t, *J*

= 6.7 Hz, 1H), 7.54 (td, *J* = 7.2, 1.8 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.21 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.19 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.96 (bs, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.3, 158.6, 144.4, 143.6, 139.3, 131.2, 128.6, 128.4, 127.5, 116.3, 102.3, 101.0, 94.1, 55.3; MS (ES mass): 369.0 (M+1); HPLC: 93.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 1.0/50, 9/98, 16/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.47 min.

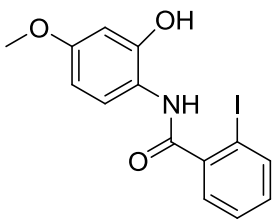
***N*-(2-Amino-4,5-dichlorophenyl)-2-iodobenzamide (1d)**



Compound **1d** was synthesized from 4,5-dichlorobenzene-1,2-diamine following a procedure similar to that of compound **1a.**

Yield: 73% (168 mg); light red solid; mp: 220-222 °C; R_f = 0.3 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3393, 3318, 3220, 3037, 1650; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.77 (bs, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.61 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.95 (s, 1H), 5.42 (bs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.5, 142.9 (2C), 139.3, 131.5, 128.7, 128.5, 128.2, 126.5, 122.9, 116.4, 116.3, 94.2; MS (ES mass): 406.9 (M+1); HPLC: 92.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.66 min.

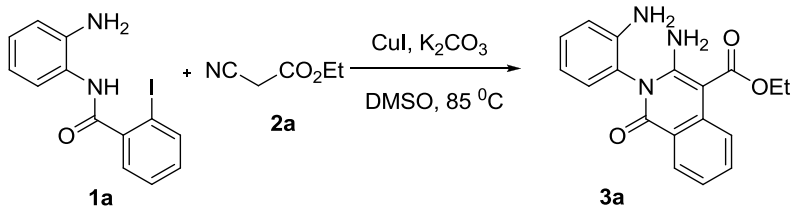
***N*-(2-Hydroxy-4-methoxyphenyl)-2-iodobenzamide (1e)**



Compound **1e** was synthesized from 2-amino-5-methoxyphenol following a procedure similar to that of compound **1a.**

Yield: 87% (230 mg); brown solid; mp: 176-178 °C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3563, 3277, 2953, 1515; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (s, 1H), 7.94-7.92 (m, 2H), 7.62-7.56 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.25-7.15 (m, 1H), 7.01 (dd, *J* = 9.2, 2.8 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 153.5, 141.9, 140.7, 140.1, 131.9, 128.8, 128.3, 125.7, 119.6, 112.5, 107.4, 92.4, 55.8; MS (ES mass): 369.9 (M+1); HPLC: 95.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.22 min.

Typical procedure for preparation of ethyl 3-amino-2-(2-aminophenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3a)

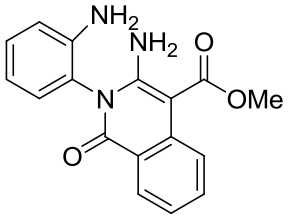


A mixture of compound **1a** (100 mg, 0.29 mmol), K_2CO_3 (80 mg, 0.58 mmol), ethyl cyano acetate (**2a**) (0.03 mL, 0.34 mmol) and CuI (5.5 mg, 0.029 mmol) in DMSO (2 mL) was heated to 85 °C under anhydrous conditions ($CaCl_2$ filled guard tube) for 1h. After completion of the reaction, reaction mixture was cooled to RT, diluted with ethyl acetate (15 mL) and passed through celite. The resulting solution was washed with water (3 x 15 mL) followed by brine solution (25 mL), 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 **3a**.

Yield: 72% (69 mg); white solid; mp: 150-152 °C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3460, 3322, 3227, 2986, 1645, 1590; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 8.6 Hz, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 5.7 Hz, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.09-7.07 (m, 1H), 6.99 (bs, 1H), 6.95-6.91 (m, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3,

161.5, 153.2, 136.7, 133.4, 131.1, 129.4, 128.4 (2C), 124.6 (2C), 123.0, 120.0, 119.9, 117.6, 84.0, 60.5, 14.5; MS (ES mass): 324.1 (M+1); HPLC: 99.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.46 min.

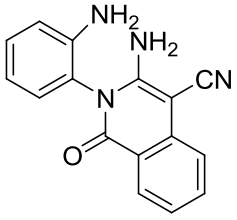
Methyl-3-amino-2-(2-aminophenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3b)



Compound **3b** was synthesized from **1a** and methylcyanoacetate (**2b**) following a procedure similar to that of compound **3a.**

Yield: 69% (63 mg); yellow solid; mp: 168-170 °C; R_f = 0.2 (50% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3445, 3356, 3202, 2931, 1636, 1573; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.45 (d, *J* = 8.8 Hz, 1H), 8.35-8.27 (m, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.37-7.29 (m, 1H), 7.23-7.21 (m, 1H), 7.18-7.00 (m, 3H), 6.95-6.92 (m, 2H), 3.96 (s, 3H), 3.71 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 161.5, 153.3, 143.6, 136.5, 133.5, 131.1, 129.4, 128.4, 124.6, 123.0, 119.9 (2C), 119.8, 117.6, 83.9, 51.3; MS (ES mass): 310.1 (M+1); HPLC: 99.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.17 min.

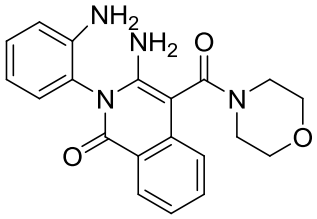
3-Amino-2-(2-aminophenyl)-1-oxo-1,2-dihydroisoquinoline-4-carbonitrile (3c)



Compound **3c** was synthesized from **1a** and malononitrile (**2c**) following a procedure similar to that of compound **3a.**

Yield: 67% (54 mg); light yellow solid; mp: 134-137 °C; R_f = 0.2 (40% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3463, 3340, 3213, 2968, 2204, 1656, 1566; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.03-7.96 (m, 2H), 7.72-7.66 (m, 2H), 7.45-7.40 (m, 1H), 6.97-6.89 (m, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 5.71 (bs, 2H), 5.25 (bs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.1, 152.7, 143.8, 135.9, 134.1, 131.2, 129.1, 128.4, 123.7, 121.6, 119.5, 119.1, 119.0, 117.5, 112.0, 80.3; MS (ES mass): 277.1 (M+1); HPLC: 95.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 3.72 min.

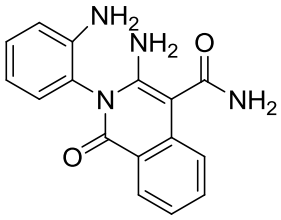
3-Amino-2-(2-aminophenyl)-4-(morpholine-4-carbonyl)isoquinolin-1(2H)-one (3d)



Compound **3d** was synthesized from **1a** and 3-morpholino-3-oxopropanenitrile (**2d**) following a procedure similar to that of compound **3a.**

Yield: 58% (62 mg); brown solid; mp: 115-117 °C; R_f = 0.2 (90% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3457, 3341, 3213, 2916, 1652, 1611; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.01 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.22-7.08 (m, 4H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.65 (t, *J* = 7.2 Hz, 1H), 5.10 (s, 2H), 3.66-3.44 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.7, 162.7, 161.4, 145.9, 144.4, 137.3, 133.1, 130.3, 130.0, 128.1, 121.8, 119.7, 119.6, 116.9, 116.4, 88.9, 66.9, 66.7, 47.0, 45.2; MS (ES mass): 365.0 (M+1); HPLC: 89.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 1/10, 5/95, 10/95, 10.5/10, 12/10; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.15 min.

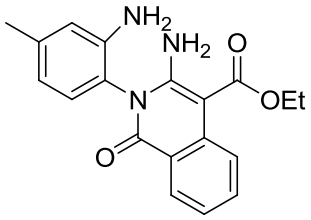
3-Amino-2-(2-aminophenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide (3e)



Compound **3e** was synthesized from **1a** and 2-cyanoacetamide (**2e**) following a procedure similar to that of compound **3a.**

Yield: 64% (54 mg); dark brown solid; mp: 122-124 °C; R_f = 0.2 (80% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3457, 3334, 3216, 2924, 1653, 1595; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.10 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.43 (bs, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.99-6.94 (m, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.31 (s, 2H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.2, 161.2, 148.7, 145.7, 137.5, 133.0, 130.3, 130.0, 128.1, 123.1, 121.8, 119.8 (2C), 117.2, 116.7, 88.7; MS (ES mass): 294.9 (M+1); HPLC: 91.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/10, 1/10, 5/95, 10/95, 10.5/10, 12/10; flow rate: 1.0 mL/min; UV 235 nm, retention time 3.96 min.

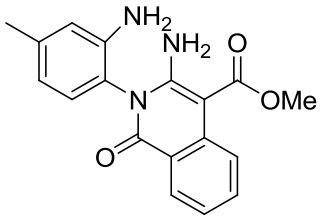
Ethyl-3-amino-2-(2-amino-4-methylphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3f)



Compound **3f** was synthesized from **1b** and ethyl 2-cyanoacetate (**2a**) following a procedure similar to that of compound **3a.**

Yield: 65% (62 mg); brown solid; mp: 114-116 °C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3462, 3325, 3229, 2983, 1649, 1595; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 8.8 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.62-7.57 (m, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.15 (bs, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 6.8 Hz, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.63 (bs, 2H), 2.33 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 161.7, 153.4, 143.2, 141.4, 136.7, 133.4, 129.0, 128.4, 124.5, 122.9, 121.1, 119.9, 118.1, 117.3, 83.9, 60.4, 21.3, 14.5; MS (ES mass): 338.1 (M+1); HPLC: 96.3%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.69 min.

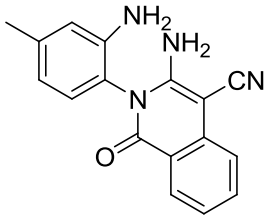
Methyl-3-amino-2-(2-amino-4-methylphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3g)



Compound **3g** was synthesized from **1b** and methyl 2-cyanoacetate (**2b**) following a procedure similar to that of compound **3a.**

Yield: 64% (58 mg); white solid; mp: 173-176 °C; R_f = 0.2 (40% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3441, 3337, 3218, 2948, 1641, 1575; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (d, *J* = 9.6 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.12 (t, *J* =7.6 Hz, 1H), 6.95 (s, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.83 (bs, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 161.7, 153.4, 142.2, 141.5, 136.5, 133.5, 129.0, 128.4, 124.5, 123.0, 121.8, 119.8, 118.8, 117.9, 84.0, 51.3, 21.3; MS (ES mass): 324.1 (M+1); HPLC: 98.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.41 min.

3-Amino-2-(2-amino-4-methylphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carbonitrile (3h)

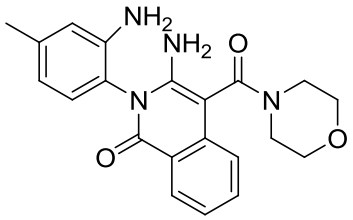


Compound **3h** was synthesized from **1b** and malononitrile (**2c**) following a procedure similar to that of compound **3a.**

Yield: 68% (56 mg); white solid; mp: 228-231 °C; R_f = 0.2 (60% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3447, 3350, 3208, 2958, 2209, 1666, 1558; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.24 (d, *J* = 7.9 Hz, 1H), 7.71-7.65 (m, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.98-6.95 (m, 1H), 6.77 (d, *J* = 2.9 Hz, 2H), 4.97 (s, 2H), 3.64 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.1, 152.4, 143.1, 141.9, 135.5, 134.3, 128.8, 128.7, 124.2, 121.9, 121.2, 119.4,

118.3, 117.1, 116.7, 67.5, 21.3; MS (ES mass): 291.0 (M+1); HPLC: 97.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 3.72 min.

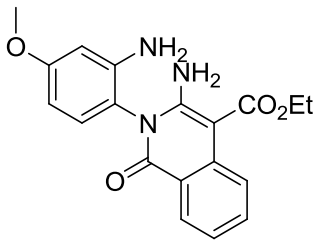
3-Amino-2-(2-amino-4-methylphenyl)-4-(morpholine-4-carbonyl)isoquinolin-1(2*H*)-one (3i)



Compound **3i** was synthesized from **1b** and 3-morpholino-3-oxopropanenitrile (**2d**) following a procedure similar to that of compound **3a.**

Yield: 64% (68 mg); brown solid; mp: 136-139 °C; R_f = 0.2 (70% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3451, 3341, 3224, 2957, 1654, 1610; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.99 (d, *J* = 8.0 Hz, 1H), 7.57-7.49 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.14-7.05 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.4Hz, 1H), 6.66-6.61 (m, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 5.12 (s, 2H), 3.47 (bs, 8H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.7, 164.1, 161.5, 145.5, 144.6, 139.5, 137.2, 133.0, 129.7, 128.1, 128.0, 121.7, 119.7, 118.0, 116.8, 88.8, 66.9, 66.5, 47.0, 42.3, 21.5; MS (ES mass): 379.2 (M+1); HPLC: 92.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.27 min.

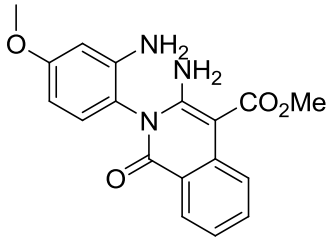
Ethyl-3-amino-2-(2-amino-4-methoxyphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3j)



Compound **3j** was synthesized from **1c** and ethyl 2-cyanoacetate (**2a**) following a procedure similar to that of compound **3a.**

Yield: 83% (79 mg); light red solid; mp: 170-172 °C; R_f = 0.5 (40% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3444, 3339, 3175, 2986, 1642, 1588; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 8.3 Hz, 1H), 8.31 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.60 (td, *J* = 7.4, 1.4 Hz, 1H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.18 (bs, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.50 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 4.44 (q, *J* = 7.12 Hz, 2H), 3.81 (s, 3H), 3.70 (bs, 2H), 1.47 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 161.9, 161.6, 153.6, 144.6, 136.7, 133.4, 130.2, 128.4, 124.5, 122.9, 119.9, 112.6, 106.1, 102.3, 83.9, 60.5, 55.4, 14.5; MS (ES mass): 354.1 (M+1); HPLC: 95.4%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 2.92 min.

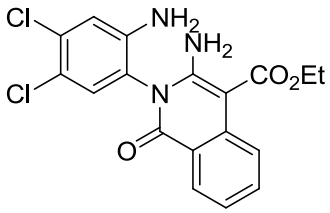
Methyl-3-amino-2-(2-amino-4-methoxyphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3k)



Compound **3k** was synthesized from **1c** and methyl 2-cyanoacetate (**2b**) following a procedure similar to that of compound **3a.**

Yield: 83% (76 mg); light red solid; mp: 237-239 °C; R_f = 0.5 (40% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3441, 3341, 3209, 2948, 1644, 1578; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.37 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.56 (tb, *J* = 7.4, 1.4 Hz, 1H), 7.40 (bs, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.25 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.20 (bs, 2H), 3.83 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.3, 161.6, 161.0, 154.8, 146.9, 137.1, 133.2, 130.8, 128.0, 124.6, 122.4, 120.3, 112.1, 103.6, 100.8, 82.5, 55.3, 51.4; MS (ES mass): 340.1 (M+1); HPLC: 94.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 2.29 min.

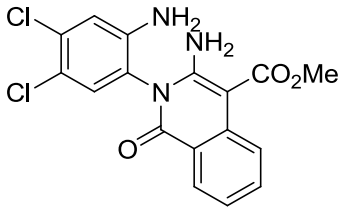
Ethyl-3-amino-2-(2-amino-4,5-dichlorophenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3l)



Compound **3l** was synthesized from **1d** and ethyl 2-cyanoacetate (**2a**) following a procedure similar to that of compound **3a.**

Yield: 85% (82 mg); light red solid; mp: 162-165 °C; R_f = 0.5 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3459, 3348, 3218, 2982, 1634, 1580; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (d, *J* = 8.4 Hz, 1H), 8.28 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.62 (td, *J* = 8.4, 1.4 Hz, 1H), 7.26-7.23 (m, 1H), 7.22 (s, 1H), 7.05 (s, 1H), 6.99 (bs, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.82 (bs, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1, 161.3, 152.4, 143.3, 136.6, 135.1, 133.8, 130.9, 128.4, 124.7, 123.3, 122.2, 119.6, 118.9, 118.4, 84.4, 60.7, 14.5; MS (ES mass): 392.0 (M+1); HPLC: 98.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.96 min.

Methyl-3-amino-2-(2-amino-4,5-dichlorophenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3m)

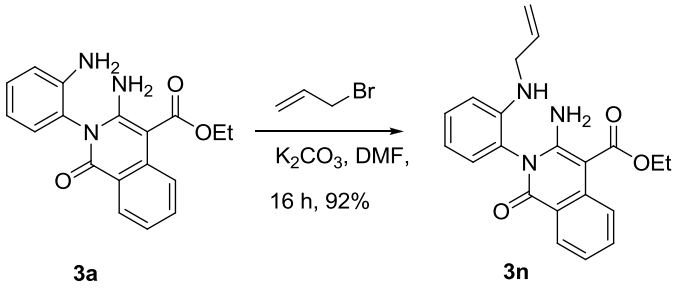


Compound **3l** was synthesized from **1d** and methyl 2-cyanoacetate (**2b**) following a procedure similar to that of compound **3a.**

Yield: 84% (78 mg); light red solid; mp: 276-278 °C; R_f = 0.5 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3448, 3342, 3218, 2990, 1645, 1595; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.38 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.70 (bs, 2H), 7.58 (td, *J* = 7.8, 1.1 Hz, 1H), 7.34 (s, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 5.72 (bs, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.4, 161.3, 154.4, 146.5, 137.3, 133.4, 132.7, 131.8, 128.0, 124.6, 122.4, 120.1, 118.8, 116.9, 116.7, 82.7, 51.4; MS (ES mass): 378.0 (M+1); HPLC: 92.2%, column: Symmetry C-18 75 x 4.6

mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.54 min.

Typical procedure for preparation of Ethyl 2-(2-(allylamino)phenyl)-3-amino-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3n)

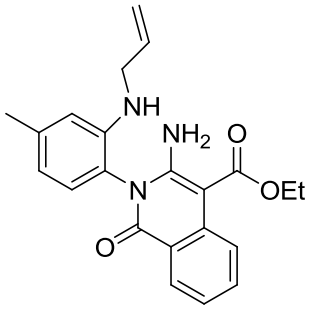


3a **3n**

A mixture of compound **3a** (100 mg, 0.30 mmol), K_2CO_3 (64 mg, 0.46 mmol), and allyl bromide (0.07 mL, 0.61 mmol) in DMF (2 mL) was stirred at room temperature for 16 h. After completion of the reaction, reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL). The organic layer was washed with brine solution (10 mL), 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 **3n.**

Yield: 92% (103 mg); white solid; mp: 124-125 °C; R_f = 0.5 (50% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3468, 3388, 3289, 2979, 1663, 1592; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.25-7.21 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.95 (bs, 1H), 6.89-6.83 (m, 2H), 5.90-5.76 (m, 1H), 5.22 (d, *J* = 17.6 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.87-3.73 (m, 3H), 1.47 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 161.6, 153.3, 144.1, 136.7, 134.2, 133.5, 131.2, 129.3, 128.5, 124.5, 123.0, 120.0, 119.3, 118.2, 116.4, 112.9, 83.9, 60.5, 45.4, 14.0; MS (ES mass): 364.1 (M+1); HPLC: 99.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.26 min.

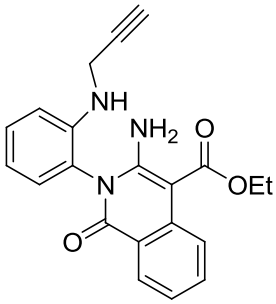
Ethyl-2-(2-(allylamino)-4-methylphenyl)-3-amino-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3o)



Compound **3o** was synthesized from **3f** and allyl bromide following a procedure similar to that of compound **3n.**

Yield: 89% (99 mg); white solid; mp: 136-138 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3465, 3378, 3287, 2976, 1669, 1594; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 8.8 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 8.4 Hz, 1H), 7.25-7.20 (m, 1H), 7.15 (bs, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.65 (s, 1H), 5.85-5.77 (m, 1H), 5.21 (d, *J* = 16.8 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 2.4 Hz, 3H), 2.37 (s, 3H), 1.47 (t, *J* = 7.10 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 161.7, 153.5, 143.7, 141.7, 136.6, 134.3, 133.4, 129.4, 128.9, 128.5, 124.5 (2C), 122.9, 119.2, 116.3, 113.5, 83.8, 60.5, 45.4, 21.8, 14.5; MS (ES mass): 378.2 (M+1); HPLC: 93.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.23 min.

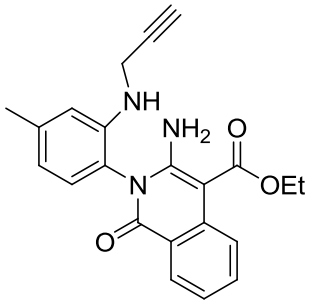
Ethyl-3-amino-1-oxo-2-(2-(prop-2-ynylamino)phenyl)-1,2-dihydroisoquinoline-4-carboxylate (3p)



Compound **3p** was synthesized from **3a** and propargyl bromide following a procedure similar to that of compound **3n.**

Yield: 93% (103 mg); white solid; mp: 245-247 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3452, 3376, 3277, 2971, 2114, 1664, 1595; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 8.8 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.63-7.59 (m, 1H), 7.46 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.97 (t, *J* = 7.6 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.99-3.86 (m, 3H), 2.18 (s, 1H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 161.6, 153.2, 143.3, 136.7, 133.5, 131.2, 129.4, 128.5, 124.6, 123.0, 120.2, 119.9, 119.5, 113.4, 84.0, 80.1, 71.7, 60.5, 33.0, 14.5; MS (ES mass): 362.1 (M+1); HPLC: 94.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 3/95, 10/95, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 236 nm, retention time 3.36 min.

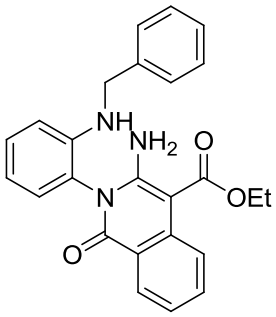
Ethyl-3-amino-2-(4-methyl-2-(prop-2-ynylamino)phenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3q)



Compound **3q** was synthesized from **3f** and propargyl bromide following a procedure similar to that of compound **3n.**

Yield: 82% (91 mg); white solid; mp: 115-117 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3464, 3387, 3289, 2972, 2374, 1649, 1592; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.00 Hz, 1H), 7.62-7.58 (m, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.10-7.01 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.81 (s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.97-3.83 (m, 3H), 2.41 (s, 3H), 2.30 (s, 1H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 161.7, 153.4, 143.0, 141.5, 136.7, 133.4, 129.1, 128.5, 128.4, 124.5, 122.9, 120.4, 119.9, 117.7, 83.9, 80.2, 71.6, 60.5, 33.0, 21.8, 14.5; MS (ES mass): 376.2 (M+1); HPLC: 95.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 3/95, 10/95, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.61 min.

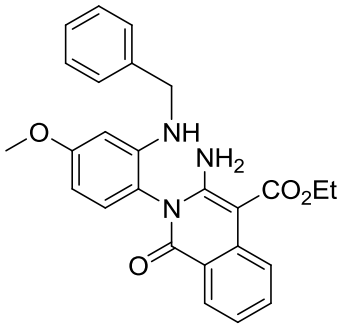
Ethyl-3-amino-2-(2-(benzylamino)phenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3r)



Compound **3r** was synthesized from **3a** and benzyl bromide following a procedure similar to that of compound **3n.**

Yield: 92% (113 mg); white solid; mp: 141-143 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3434, 3262, 3064, 2976, 1670, 1640; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 8.8 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7. 6 Hz, 1H), 7.31-7.29 (m, 4H), 7.26-7.22 (m, 3H), 7.17 (bs, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 4.55(q, *J* = 6.8 Hz, 2H), 4.39 (s, 2H), 4.24 (bs, 1H), 1.49 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 161.6, 153.4, 144.1, 138.4, 137.2, 136.7, 133.4, 131.2, 129.3, 128.6, 128.5, 128.0, 127.1, 126.8, 124.6, 123.0, 120.0, 119.4, 118.3, 113.0, 84.0, 60.5, 47.0, 14.5; MS (ES mass): 414.1 (M+1); HPLC: 99.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.99 min.

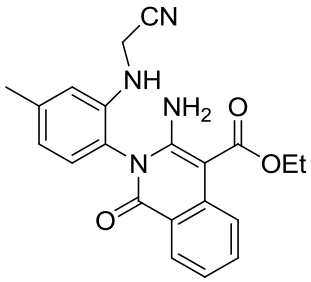
Ethyl-3-amino-2-(2-(benzylamino)-4,5-dichlorophenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3s)



Compound **3s** was synthesized from **3j** and benzyl bromide following a procedure similar to that of compound **3n.**

Yield: 87% (109 mg); white solid; mp: 139-142 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3381, 3265, 3163, 2976, 1672, 1625; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 8.4 Hz, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 7.60 (tb, *J* = 8.2, 1.1 Hz, 1H), 7.33-7.27 (m, 4H), 7.26-7.21 (m, 2H), 7.22 (bs, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.41 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.36-4.32 (m, 2H), 4.15 (t, *J* = 4.8 Hz, 1H), 3.75 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 161.9, 161.8, 153.8, 145.1, 138.3, 136.6, 133.4, 130.1, 128.7 (2C), 128.5, 127.2, 126.8 (2C), 124.5, 122.9, 120.0, 112.4, 103.3, 99.2, 83.9, 60.5, 55.3, 47.2, 14.5; MS (ES mass): 444.2 (M+1); HPLC: 92.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.41 min.

Ethyl-3-amino-2-(2-(cyanomethylamino)-4-methylphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3t)

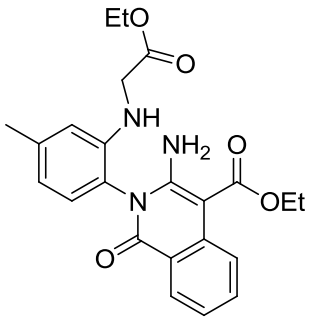


Compound **3t** was synthesized from **3f** and 2-bromo acetonitrile following a procedure similar to that of compound **3n.**

Yield: 90% (100 mg); white solid; mp: 216-219 °C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3427, 3344, 3301, 2915, 2338, 1644, 1524; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 8.8 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 4.43 (q, *J* = 7.6 Hz, 2H), 4.09-4.03 (m, 3H), 2.45 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2, 161.7, 153.1, 142.1, 141.4, 136.6, 133.6, 129.5, 128.3, 124.6, 123.1, 121.9, 119.7, 118.3, 116.3, 113.7, 84.2, 60.6, 32.0, 21.8, 14.4; MS (ES mass): 377.1 (M+1); HPLC: 93.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient

(T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.20 min.

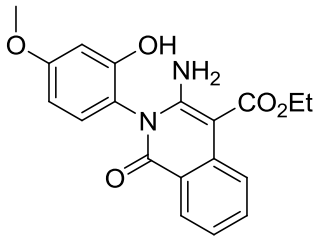
Ethyl-3-amino-2-(2-(2-ethoxy-2-oxoethylamino)-4-methylphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3u)



Compound **3u** was synthesized from **3f** and ethyl 2-bromoacetate following a procedure similar to that of compound **3n.**

Yield: 88% (110 mg); white solid; mp: 105-112 °C; R_f = 0.4 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3459, 3263, 2966, 1740, 1677, 1592; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.61-7.57 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.11 (s, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 4.42 (q, *J* = 6.8 Hz, 2H), 4.20-4.12 (m, 3H), 3.94 (d, *J* = 6.8 Hz, 1H), 3.86-3.83 (m, 1H), 2.37 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 169.3, 161.8, 153.7, 143.2, 141.1, 136.7, 133.2, 129.2, 128.4, 124.6, 122.8, 119.9 (2C), 117.4, 113.1, 83.8, 61.2, 60.3, 44.9, 21.8, 14.4, 14.0; MS (ES mass): 423.5 (M+1); HPLC: 96.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.08 min.

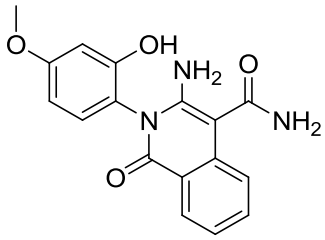
Ethyl-3-amino-2-(2-hydroxy-4-methoxyphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (3v)



Compound **3v** was synthesized from **1e** and ethyl cyanoacetate (**2a**) following a procedure similar to that of compound **3a.**

Yield: 68% (66 mg); white solid; mp: 167-169 °C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3639, 3398, 3196, 2923, 1639, 1604; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.01 (bs, 2H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.80-6.73 (m, 1H), 6.65 (s, 1H), 4.41 (q, *J* = 6.4 Hz, 2H), 3.70 (s, 3H), 1.45 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2, 162.7, 153.8, 153.1, 146.9, 137.0, 133.6, 128.2, 124.6, 123.0, 121.2, 119.5, 119.4, 117.7, 113.4, 84.6, 60.5, 55.8, 14.4; MS (ES mass): 355.1 (M+1); HPLC: 95.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.32 min.

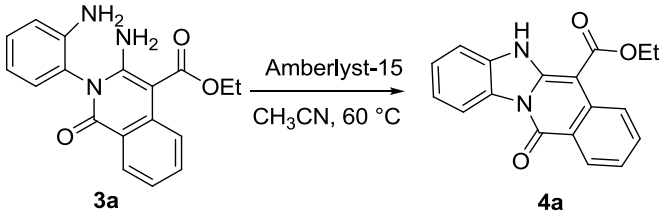
3-Amino-2-(2-hydroxy-4-methoxyphenyl)-1-oxo-1,2-dihydroisoquinoline-4-carboxamide (3w)



Compound **3w** was synthesized from **1e** and 2-cyanoacetamide (**2e**) following a procedure similar to that of compound **3a.**

Yield: 63% (55 mg); light yellow solid; mp: 174-177°C; R_f = 0.2 (60% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3647, 3427, 3370, 3300, 3188, 2944, 1645, 1602; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.48 (bs, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.40 (s, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.94 (s, 2H), 6.73 (s, 1H), 6.38 (bs, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.3, 161.2, 152.9, 149.1, 147.7, 137.4, 133.0, 127.9, 123.1, 122.7, 121.8, 119.5, 117.9, 116.8, 115.3, 88.1, 55.9; MS (ES mass): 326.1 (M+1); HPLC: 91.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 2.74 min.

Typical procedure for preparation of 11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid ethyl ester (4a)

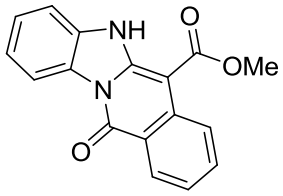


3a **4a**

To a solution of **3a (**100 mg, 0.30 mmol**)** in acetonitrile (5 mL), amberlyst-15 (10%, w/w) was added and the reaction mixture was allowed to stir at 60 ºC for 1 h. Upon completion of the reaction, the formed solid was filtered and washed with acetonitrile (5 mL) to give desired compound **4a**.

Yield: 98% (92 mg); white solid; mp: 321-323 °C (lit[1] 317-319 ºC); R_f = 0.6 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3317, 2973, 1643, 1601; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.20 (bs, 1H), 8.82 (d, *J* = 8.2 Hz, 1H), 8.61 (d, *J* = 7.9 Hz, 1H), 8.36 (d, *J* = 7.7 Hz, 1H), 7.72 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.34 (m, 2H), 4.47 (q, *J* = 6.9 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 159.9, 146.7, 135.3, 133.2, 130.9, 128.1, 127.3, 126.3, 124.3, 123.1, 122.6, 119.3, 117.0, 109.9, 82.4, 60.8, 14.6; MS (ES mass): 306.9 (M+1); HPLC: 99.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.45 min.

11-Oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid methyl ester (4b)[1]

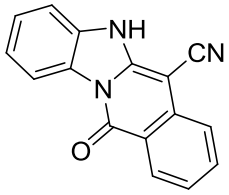


Compound **4b** was synthesized from **3b** following a procedure similar to that of compound **4a.**

Yield: 87% (78 mg); white fluffy solid; mp: 335-337 °C (lit[1] 330-333 ºC); R_f = 0.2 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3320, 2948, 1649, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.21 (s, 1H), 8.76 (d, *J* = 8.0 Hz, 1H), 8.71 (d, *J* = 8.8 Hz, 1H), 8.54 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.73-7.66

(m, 1H), 7.48-7.43 (m, 1H), 7.41-7.32 (m, 3H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 159.9, 146.7, 135.2, 133.3, 130.8, 128.1, 127.8, 126.4, 124.4, 123.2, 122.7, 119.3, 117.0, 109.9, 82.3, 51.6; MS (ES mass): 293.1 (M+1); HPLC: 99.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.13 min.

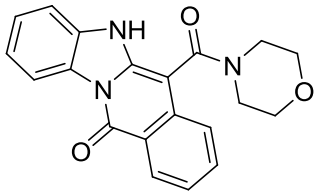
11-Oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carbonitrile (4c)[1]



Compound **4c** was synthesized from **3c** following a procedure similar to that of compound **4a** and purification done by column chromatography.

Yield: 72% (57 mg); white solid; mp: 290-292 °C (lit[1] 284-287 ºC); R_f = 0.2 (50% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3376, 2921, 2203, 1695, 1619; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.4 (bs, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.54-7.48 (m, 2H), 7.45-7.36 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.4, 146.8, 136.2, 135.6, 134.5, 130.4, 128.2, 127.8, 127.2, 123.9, 122.7, 122.1, 118.3, 116.4, 111.3, 61.7; MS (ES mass): 258.8 (M-1); HPLC: 95.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.99 min.

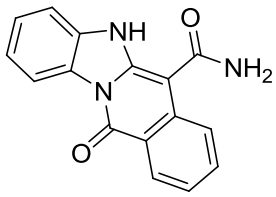
11-Oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-(2'-morpholino)carbamide (4d)



Compound **4d** was synthesized from **3d** following a procedure similar to that of compound **4a** and purification done by column chromatography.

Yield: 63% (67 mg); light yellow solid; mp: 245-248 °C; R_f = 0.2 (80% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3343, 2961, 1671, 1613; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.88 (s, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.44-7.42 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.28-7.24 (m, 1H), 3.67-3.48 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.4, 159.1, 140.0, 135.7, 133.5, 133.1, 128.0, 127.7, 126.6, 122.6, 122.4, 121.2, 117.9, 116.2, 110.3, 87.1, 66.8, 66.0, 47.7, 47.4; MS (ES mass): 348.2 (M+1); HPLC: 93.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.17 min.

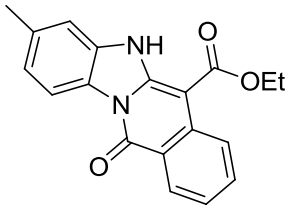
11-Oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carbamide (4e)



Compound **4e** was synthesized from **3e** following a procedure similar to that of compound **4a** and purification done by column chromatography.

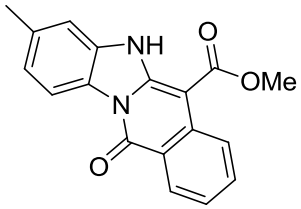
Yield: 65% (55 mg); white solid; mp: 266-269 °C; R_f = 0.2 (70% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3362, 2925, 1662, 1557; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.9 (bs, 1H), 8.62 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.73-7.69 (m, 1H), 7.62 (bs, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.1, 159.2, 142.3, 135.9, 133.2, 132.9, 127.6 (2C), 126.6, 123.7, 122.4, 121.3, 117.9, 116.2, 111.1, 88.5; MS (ES mass): 277.7 (M+1); HPLC: 99.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.23 min.

3-Methyl-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid ethyl ester (4f)[1]



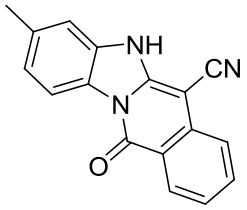
Compound **4f** was synthesized from **3f** following a procedure similar to that of compound **4a.** Yield: 91% (86 mg); white solid; mp: 199-201 °C (lit[1] 202-204 ºC); R_f = 0.2 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3304, 2920, 1672, 1612; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.24 (s, 1H), 8.81 (d, *J* = 8.4 Hz, 1H), 8.65-8.63 (m, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.41-7.37 (m, 1H), 7.21-7.18 (m, 2H), 4.56 (q, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 1.56 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 159.8, 146.8, 136.8, 135.4, 133.2, 131.1, 128.0, 125.7, 124.3, 123.6, 123.0, 119.3, 116.5, 110.2, 82.5, 60.7, 21.7, 14.6; MS (ES mass): 321.0 (M+1); HPLC: 99.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.76 min.

3-Methyl-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid methyl ester (4g)[1]



Compound **4g** was synthesized from **3g** following a procedure similar to that of compound **4a.** Yield: 83% (75 mg); light yellow solid; mp: 219-221 °C (lit[1] 213-215 ºC); R_f = 0.6 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3443, 2924, 1642, 1582; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.2 (bs, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.46-7.28 (m, 2H), 7.24-7.21 (m, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.3, 154.5, 145.4, 139.8, 137.2, 133.1, 132.5, 129.6, 128.0, 124.6, 122.4, 120.3, 118.3, 117.1, 116.6, 82.3, 51.3, 21.5; MS (ES mass): 307.0 (M+1); HPLC: 90.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.41 min.

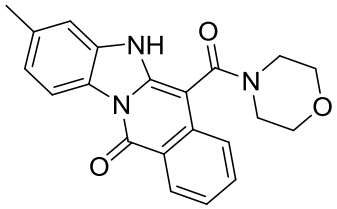
3-Methyl-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carbonitrile (4h)[1]



Compound **4h** was synthesized from **3h** following a procedure similar to that of compound **4a** and purification done by column chromatography.

Yield: 75% (60 mg); white solid; mp: 358-361 °C; R_f = 0.2 (40% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3261, 2923, 2208, 1687, 1627; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.21 (bs, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.35-8.29 (m, 1H), 7.86 (t, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.44-7.37 (m, 1H), 7.31 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.9, 146.5, 136.9, 135.9, 134.1, 132.7, 128.0, 126.0, 123.3, 121.9, 118.0, 117.2, 115.7, 111.1, 109.9, 62.7, 21.6; MS (ES mass): 274.0 (M+1); HPLC: 97.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.87 min.

3-Methyl-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-(2'-morpholino) carbamide (4i)

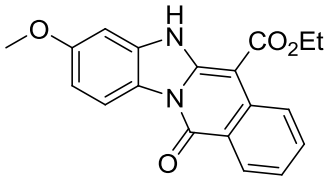


Compound **4i** was synthesized from **3i** following a procedure similar to that of compound **4a** and purification done by column chromatography.

Yield: 67% (71 mg); light green solid; mp: 264-267 °C; R_f = 0.2 (80% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3271, 2957, 1757, 1663; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.79 (bs, 1H), 8.44 (d, *J* = 7.6 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 3.69-3.43 (m, 8H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.1, 159.0, 142.3, 136.3, 135.8, 133.4, 132.7, 127.6, 125.6,

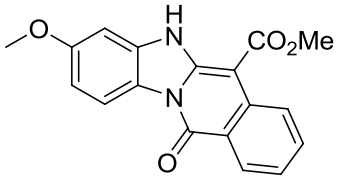
123.7, 122.3, 122.2, 117.9, 115.8, 111.2, 88.5, 66.7, 66.4, 47.9, 47.4, 21.8; MS (ES mass): 359.9 (M-1); HPLC: 91.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 3.84 min.

3-Methoxy-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid ethyl ester (4j)



Compound **4j** was synthesized from **3j** following a procedure similar to that of compound **4a.** Yield: 92% (87 mg); white solid; mp: 242-245°C; R_f = 0.6 (35% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3343, 2982, 1630, 1601; ^1H NMR (400 MHz, DMSO-d_6) δ: 12.09 (bs, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 7.73 (tb, *J* = 8.4, 1.0 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 1.41 (t, *J* = 7.07 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.4, 159.3, 158.5, 146.2, 135.9, 133.7, 133.4, 127.6, 124.5, 123.2, 121.6, 118.6, 117.0, 109.2, 97.0, 82.4, 60.4, 56.0, 15.1; MS (ES mass): 337.1 (M+1); HPLC: 96.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.61 min.

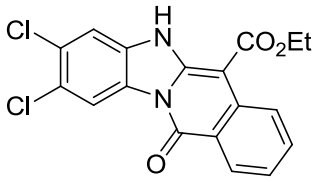
3-Methoxy-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid methyl ester (4k)



Compound **4k** was synthesized from **3k** following a procedure similar to that of compound **4a.** Yield: 91% (83 mg); white solid; mp: 245-247 °C; R_f = 0.6 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3326, 2948, 1638, 1605; ^1H NMR (400 MHz, DMSO-d_6) δ: 12.00 (bs, 1H), 8.86 (d, *J* =

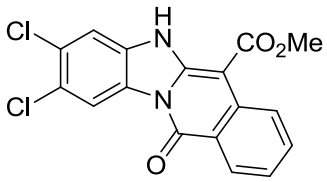
8.4 Hz, 1H), 8.44 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.17 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.3, 159.2, 158.5, 145.9, 136.0, 133.7, 133.3, 127.5, 124.3, 123.1, 121.6, 118.6, 116.9, 109.1, 96.7, 82.1, 55.9, 51.6; MS (ES mass): 323.0 (M+1); HPLC: 94.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.04 min.

2,3-Dichloro-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid ethyl ester (4l)



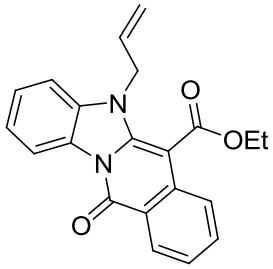
Compound **4l** was synthesized from **3l** following a procedure similar to that of compound **4a.** Yield: 93% (88 mg); white solid; mp: 162-164 °C; R_f = 0.5 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3316, 2980, 1677, 1640; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.27 (bs, 1H), 8.90 (s, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 7.74 (tb, *J* = 8.4, 1.1 Hz, 1H), 7.47 (s, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.53 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 159.3, 146.7, 135.0, 133.6, 130.4, 130.2, 128.0, 126.8, 126.3, 124.5, 123.6, 119.1, 118.2, 111.1, 83.2, 61.1, 14.5; MS (ES mass): 374.9 (M+1); HPLC: 96.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.98 min.

2,3-Dichloro-11-oxo-5,11-dihydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6-carboxylic acid methyl ester (4m)



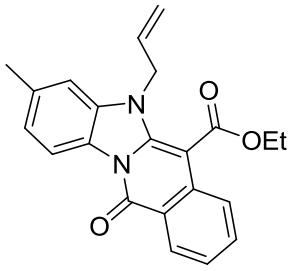
Compound **4m** was synthesized from **3m** following a procedure similar to that of compound **4a.** Yield: 90% (82 mg); light brown solid; mp: 278-280 °C; R_f = 0.6 (40% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3302, 2952, 1678, 1643; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.17 (s, 1H), 8.81 (d, *J* = 8.4 Hz, 1H), 8.62 (s, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 7.77-7.74 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.1, 159.2, 146.0, 135.9, 133.8, 132.4, 128.8, 127.6, 127.2, 124.4, 124.0, 123.5, 118.6, 117.1, 112.7, 82.7, 51.1; MS (ES mass): 360.9 (M+1); HPLC: 96.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.78 min.

11-Oxo-5-allyl-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4n)



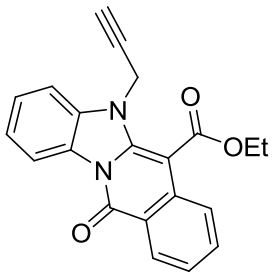
Compound **4n** was synthesized from **3n** following a procedure similar to that of compound **4a.** Yield: 89% (84 mg); white solid; mp: 244-247 °C; R_f = 0.5 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3315, 2926, 1759, 1670, 1597; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (d, *J* = 8.0 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.69-7.65 (m, 1H), 7.48-7.31 (m, 4H), 5.99-5.90 (m, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 5.26 (d, *J* = 17.6 Hz, 1H), 4.77 (dd, *J* = 3.6, 2.1 Hz, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 159.9, 135.6, 134.4, 132.9, 131.1, 127.9, 127.7, 126.0, 124.4, 123.2, 122.6, 122.4, 118.7, 118.4, 117.1, 108.4, 87.2, 61.3, 48.3, 14.3; MS (ES mass): 347.1 (M+1); HPLC: 92.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 3/95, 10/95, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.18 min.

3-Methyl-11-oxo-5-allyl-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4o)



Compound **4o** was synthesized from **3o** following a procedure similar to that of compound **4a**. Yield: 91% (86 mg); yellow solid; mp: 170-173 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3317, 2936, 1761, 1677, 1595; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (d, *J* = 8.4 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.68-7.64 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.04 (s, 1H), 5.97-5.89 (m, 1H), 5.31 (d, *J* = 10.4 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 4.77-4.73 (m, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.51 (d, *J* = 7.9 Hz, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.9, 159.7, 141.4, 136.4, 135.5, 134.6, 132.7, 131.1, 127.7, 125.7, 123.2, 123.1, 122.6, 118.6, 118.2, 116.6, 108.8, 87.2, 61.3, 48.1, 21.8, 14.3; MS (ES mass): 361.1 (M+1); HPLC: 99.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 245 nm, retention time 5.68 min.

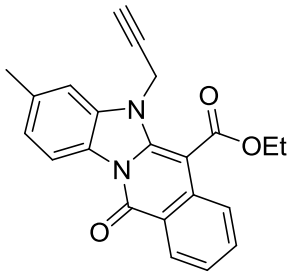
11-Oxo-5-propargyl-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4p)



Compound **4p** was synthesized from **3p** following a procedure similar to that of compound **4a.** Yield:89% (84 mg); white solid; mp: 280-282 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3215, 2983, 2112, 1789, 1674, 1609; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (d, *J* = 8.0 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.71-7.67 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.41-7.35 (m, 3H), 4.94 (d, *J* = 2.4 Hz, 2H), 4.58 (q, *J* = 7. 2 Hz, 2H), 2.36-2.35 (m, 1H), 1.47 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 159.8, 141.6, 135.4, 133.8, 133.0, 127.9, 127.7, 126.1, 123.6, 123.2, 122.8, 119.1, 117.2, 109.9, 108.2, 87.6, 74.3, 61.4, 36.0,

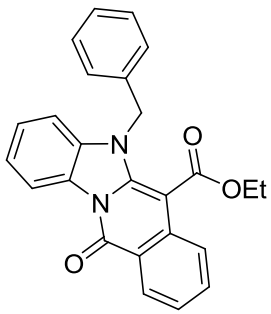
14.4; MS (ES mass): 345.1 (M+1); HPLC: 99.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 3/95, 10/95, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 250 nm, retention time 3.85 min.

3-Methyl-11-oxo-5-propargyl-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4q)



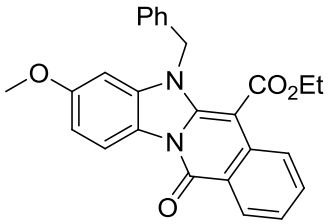
Compound **4q** was synthesized from **3q** following a procedure similar to that of compound **4a.** Yield: 86% (82 mg); white solid; mp: 293-295 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3218, 2986, 2385, 1693, 1668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (d, *J* = 8.8 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.69 (t, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 6.8 Hz, 2H), 4.94 (d, *J* = 2.2 Hz, 2H), 4.58 (q, *J* = 7.2 Hz, 2H), 2.54 (s, 3H), 2.35 (s, 1H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 159.7, 141.6, 136.5, 135.4, 134.0, 132.9, 127.7, 125.8, 123.7, 123.5, 123.1, 119.1, 116.8, 108.6, 87.6, 70.2, 74.2, 61.4, 35.9, 21.9, 14.4; MS (ES mass): 359.1 (M+1); HPLC: 94.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 3/95, 10/95, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 250 nm, retention time 4.15 min.

11-Oxo-5-benzyl-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4r)



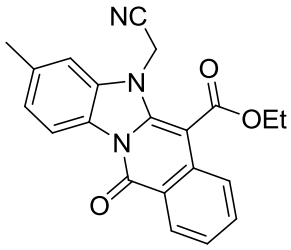
Compound **4r** was synthesized from **3r** following a procedure similar to that of compound **4a.** Yield: 95% (91 mg); white solid; mp: 186-189 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3069, 2981, 1663, 1608; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (d, *J* = 7.6 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 8.4 Hz, 1H), 7.41-7.28 (m, 6H), 7.15 (d, *J* = 6.8 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 5.40 (s, 2H), 4.05 (q, *J* = 7.6 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 159.9, 153.9, 141.2, 135.5, 134.8, 134.7, 132.9, 128.8 (2C), 127.7 (2C), 126.1, 126.0, 123.3, 122.6, 122.5, 118.7, 117.1, 109.9, 108.4, 87.6, 61.3, 49.1, 13.8; MS (ES mass): 397.1 (M+1); HPLC: 95.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 245 nm, retention time 5.66 min.

3-Methoxy-11-oxo-5-benzyl-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4s)



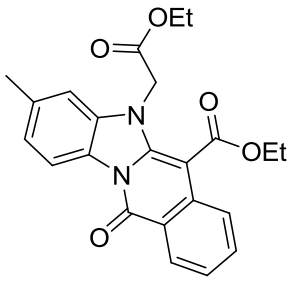
Compound **4s** was synthesized from **3s** following a procedure similar to that of compound **4a.** Yield: 95% (91 mg); light yellow solid; mp: 281-284 °C; R_f = 0.4 (20% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3084, 2985, 1669, 1645; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (d, *J* = 8.4 Hz, 1H), 8.55 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.64 (tb, *J* = 8.4, 1.0 Hz, 1H), 7.39-7.27 (m, 4H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.87 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.63 (d, *J* = 2.2 Hz, 1H), 5.36 (s, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 159.5, 158.6, 141.3, 136.0, 135.3, 134.7, 132.6, 128.8 (2C), 127.7, 127.5, 126.0 (2C), 123.3, 122.6, 121.9, 118.7, 117.7, 107.7, 95.0, 88.0, 61.3, 55.8, 49.1, 13.8; MS (ES mass): 427.2 (M+1); HPLC: 97.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.42 min.

3-Methyl-11-oxo-5-cyanomethyl-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4t)



Compound **4t** was synthesized from **3t** following a procedure similar to that of compound **4a.** Yield: 96% (91 mg); white solid; mp: 240-242 °C; R_f = 0.2 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3066, 2923, 2338, 1658, 1610; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (d, *J* = 8.0 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.35 (t, *J* = 8.4 Hz, 1H), 7.76-7.72 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H), 5.09 (s, 2H), 4.63 (q, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 1.54 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2, 161.7, 153.1, 142.1, 141.4, 136.6, 133.6, 129.5, 128.3, 124.6, 123.1, 121.9, 119.7, 118.3, 116.3, 113.7, 84.2, 60.6, 32.0, 21.8, 14.4; MS (ES mass): 360.1 (M+1); HPLC: 93.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.20 min.

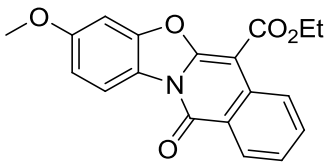
3-Methyl-11-oxo-5-(2'-ethoxy-2-oxoethyl)-11-hydro-benzo[4,5]imidazo[1,2-*b*]isoquinoline-6(5*H*)-carboxylic acid ethyl ester (4u)



Compound **4u** was synthesized from **3u** following a procedure similar to that of compound **4a.** Yield: 91% (88mg); yellow solid; mp: 169-172 °C; R_f = 0.6 (30% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3379, 2979, 1756, 1683, 1603; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (d, *J* = 8.0 Hz, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.16-8.11 (m, 1H), 7.67 (t, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 4.81 (s, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 4.29 (q, *J* = 7.2 Hz,

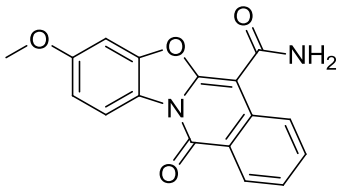
2H), 2.50 (s, 3H), 1.47 (t, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4, 167.4, 166.6, 159.4, 142.6, 136.5, 134.5, 132.7, 127.6, 123.6, 123.3, 123.1, 119.0, 117.3, 116.4, 108.3, 87.0, 61.9, 61.4, 47.9, 21.6, 14.3, 14.0; MS (ES mass): 406.5 (M+1); HPLC: 99.1%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.35 min.

3-Methoxy-11-oxo-11-hydro-benzo[4,5]oxazolo[3,2-*b*]isoquinoline-6-carboxylic acid ethyl ester (4v)



Compound **4v** was synthesized from **3v** following a procedure similar to that of compound **4a.** Yield: 92% (87 mg); white solid; mp: 185-188 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3352, 2981, 1689, 1609; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (d, *J* = 8.8 Hz, 1H), 8.52 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 2.4 Hz, 1H), 7.78 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.49 (t, *J* = 7. 6 Hz, 1H), 7.41(d, *J* = 8.8 Hz, 1H), 7.00-6.97 (m, 1H), 4.53 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.4, 159.1, 157.1, 141.0, 135.1, 133.7 (2C), 127.6, 127.5, 125.1, 125.0, 120.9, 113.5, 110.7, 101.5, 87.8, 60.9, 56.2, 14.4; MS (ES mass): 338.0 (M+1); HPLC: 94.6%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.45 min.

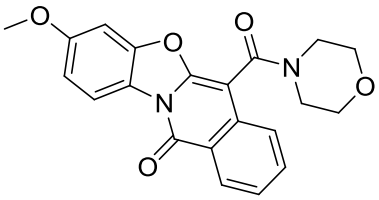
3-Methoxy-11-oxo-11-hydro-benzo[4,5]oxazolo[3,2-*b*]isoquinoline-6-carbamide (4w)



Compound **4w** was synthesized from **3w** following a procedure similar to that of compound **4a** and purification done by column chromatography.

Yield: 85% (73 mg); white solid; mp: 226-229 °C; R_f = 0.4 (80% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3395, 3315, 2922, 1658, 1610; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.35 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.81-7.79 (m, 2H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.50 (t, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.8, 158.4, 156.7, 141.2, 135.6, 133.6, 131.3, 128.0, 127.5, 125.1, 125.0, 120.9, 112.5, 111.4, 101.8, 79.5, 56.4; MS (ES mass): 309.0 (M+1); HPLC: 97.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µ, mobile phase A: 0.1 % Formic Acid in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 5.20 min.

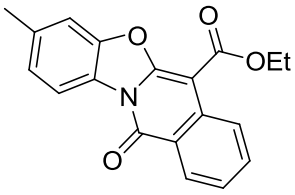
3-Methoxy-11-oxo-11-hydro-benzo[4,5]oxazolo[3,2-*b*]isoquinoline-6-(2'-morpholino) carbamide (4x)



Compound **4x** was synthesized from **3x** following a procedure similar to that of compound **4a** and purification done by column chromatography.

Yield: 72% (69 mg); light green solid; R_f = 0.2 (80% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 3392, 3315, 2929, 1651, 1614; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.54 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 2.8 Hz, 1H), 7.80-7.69 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 9.2 Hz, 1H), 6.97 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.07-3.97 (m, 2H), 3.94 (s, 3H), 3.92-3.83 (m, 2H), 3.77-3.67 (m, 1H), 3.65-3.58 (m, 1H), 3.56-3.49 (m, 1H), 3.49-3.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.2, 158.7, 157.0, 141.0, 134.8, 133.6, 128.1, 127.9, 125.1, 123.5, 121.3, 113.0, 110.4, 109.9, 101.7, 90.1, 67.1, 66.9, 56.2, 47.6, 47.6; MS (ES mass): 378.6 (M+1).

3-Methyl-11-oxo-11-hydro-benzo[4,5]oxazolo[3,2-*b*]isoquinoline-6-carboxylic acid ethyl ester (4y)



Compound **4y** was synthesized from **3y** following a procedure similar to that of compound **4a.** Yield: 93% (88 mg); white solid; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR (KBr, cm^{-1}): 2987, 1685, 1602; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 7.6 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* =7.2 Hz, 1H), 7.52 (t, *J* =7.2 Hz, 1H), 7.37 (s, 1H), 7.25 (s, 1H), 4.55 (q, *J* = 7.2 Hz, 2H), 2.54 (s, 3H), 1.52 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.6, 162.2, 158.6, 147.2, 137.3, 135.1, 133.5, 127.6, 125.5, 125.1, 125.0, 121.2, 116.1, 110.8, 109.9, 87.8, 60.8, 21.7, 14.4; MS (ES mass): 322.1 (M+1).

References:

1. J. Lu, X. Gong, H. Yang, H. Fu, *Chem. Commun.*, **2010**, *46*, 4172.

Pharmacology

PDE4B protein production and purification

PDE4B1 cDNA was sub-cloned into pFAST Bac HTB vector (Invitrogen) and transformed into DH10Bac (Invitrogen) competent cells. Recombinant bacmids were tested for integration by PCR analysis. Sf9 cells were transfected with bacmid using Lipofectamine 2000 (Invitrogen) according to manufacturer's instructions. Subsequently, P3 viral titer was amplified, cells were infected and 48 h post infection cells were lysed in lysis buffer (50 mM Tris-HCl pH 8.5, 10 mM 2-mercaptoethanol, 1 % protease inhibitor cocktail (Roche), 1 % NP40). Recombinant His-tagged PDE4B protein was purified as previously described elsewhere.[19a] Briefly, lysate was centrifuged at 10,000 rpm for 10 min at 4 ºC and supernatant was collected. Supernatant was mixed with Ni-NTA resin (GE Life Sciences) in a ratio of 4:1 (v/v) and equilibrated with binding buffer (20 mM Tris-HCl pH 8.0, 500 mM-KCl, 5 mM imidazole, 10 mM 2-mercaptoethanol and 10 % glycerol) in a ratio of 2:1 (v/v) and mixed gently on rotary shaker for 1 hour at 4 ºC. After incubation, lysate-Ni-NTA mixture was centrifuged at 4,500 rpm for 5 min at 4 ºC and the supernatant was collected as the flow-through fraction. Resin was washed twice with wash buffer (20 mM Tris-HCl pH 8.5, 1 M KCl, 10 mM 2-mercaptoethanol and 10% glycerol). Protein was eluted sequentially twice using elution buffers (Buffer I: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 250 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol, Buffer II: 20 mM Tris-HCl pH 8.5, 100

mM KCl, 500 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol). Eluates were collected in four fractions and analyzed by SDS-PAGE. Eluates containing PDE4B protein were pooled and stored at -80 ºC in 50% glycerol until further use.

PDE4 enzymatic assay

The inhibition of PDE4 enzyme was measured using PDElight HTS cAMP phosphodiesterase assay kit (Lonza) according to manufacturer's recommendations. Briefly, 10 ng of in house purified PDE4B1 or 0.5 ng commercially procured PDE4D2 enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 µM) for 1 hour. The reaction was halted with stop solution and reaction mix was incubated with detection reagent for 10 minutes in dark. Dose response studies were performed at 13 different concentrations ranging from 200 µM to 0.001 µM. Luminescence values (RLUs) were measured by a Multilabel Plate Reader (PerklinElmer 1420 Multilabel Counter). The percentage of inhibition was calculated using the following formula and the IC_{50} values were determined by a nonlinear regression analysis from dose response curve using Graphpad Prism software (San Diego, U.S.A). IC_{50} values are presented as mean ± SD.

$$\%\ inhibition = \frac{(RLU\ of\ vehicle\ control - RLU\ of\ inhibitior)}{RLU\ of\ vehicle\ control} X\ 100$$

Some of the synthesized compounds were tested for their PDE4B inhibitory potential *in vitro* at 30 μM using PDE4B enzyme[1] and rolipram as a reference compound.

Reference

1. P. Wang, J. G. Myers, P. Wu, B. Cheewatrakoolpong, R. W. Egan and M. M. Billah, *Biochem. Biophys. Res. Commun* 1997, **234**, 320

Table S-3: In vitro PDE4B inhibition by compound **4**

S. No.	Compounds	% PDE4B Inhibition @ 30 µM[a]
1	**4a**	62.16
2	**4b**	25.80
3	**4f**	53.46
4	**4g**	56.56
5	**4d**	48.25
6	**4p**	37.25
7	**4j**	27.99
8	**4n**	85.44
9	**4o**	39.66
10	**4e**	59.32

[a]Results are average of three experiments.

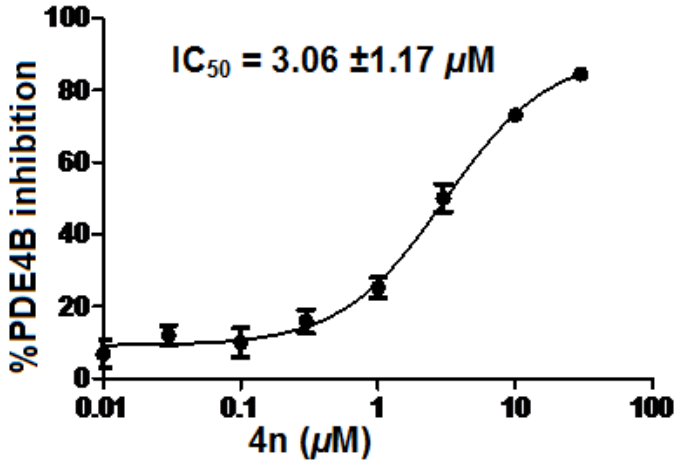


Fig.S-1. Dose dependent inhibition of PDE4B by **4n**.

Molecular Modeling Studies

The following molecular docking Simulation was done with Chemical Computing Group's Molecular Operating Environment (MOE) software 2008.10 Version, "DOCK" application Module. The compound **4a** and rolipram were docked in the PDE4B protein and their respective Docking scores and interactions were observed.

The following Dock scores were obtained after docking with PDE4B protein:-

MOE Dock score(K.cal/mol)	
Molecule	PDE4B
Rolipram	-22.94
4a	-22.07

The purpose of the Dock application is to search for favorable binding configurations in macromolecular target, which is usually a protein. For each ligand, a number of configurations called *poses* are generated and scored in an effort to determine favorable binding modes.

The Dock workflow involves Conformational Analysis, Placement, scoring, and Force field method of Refinement.

Docking Method: The PDE4B protein in complex with Rolipram (PDB code-1XMY) was used as the receptor for docking. The original PDB file containing crystallized Zn and Mn metal ions were retrieved from PDB database and Protonated (Addition of Hydrogen atoms) with Protonation 3D application in MOE, Connolly Molecular surface was generated around the ligand site of the protein, Gasteiger Partial charges was added to the protein and finally energy minimized to relieve bad crystallographic contacts. "Active site finder" function of the MOE software was used to denote potential docking pockets within the Protein crystal structure. The **4a** molecule was placed in the Active site pocket of the protein by the "Triangle Matcher" Method, which generated poses by aligning the ligand triplet of atoms with the triplet of alpha spheres in cavities of tight atomic packing. Dock scoring was done with London dG method after retaining and scoring the best 10 poses of molecules. The Preparation of the Ligands for Docking Simulation involves the Energy minimization with Molecular Mechanics Force-field MMFF94x (Merck Molecular Force Field 94×) and then molecules were subjected to conformational search in MOE using the Conformational Stochastic search module to find the lowest Energy Conformers.

The docking results appeared as Docking Score in which the docking poses were ranked by the Molecular Mechanics and Generalized Born solvation model (MM/GBVI) binding free energy. For all scoring functions, lower scores indicate more favorable binding poses. The unit for all scoring functions is k.cal/mol. The final energy was calculated using the Generalized Born solvation model. Poses for each ligand were scored based on complementarity with binding pocket.

The London dG scoring function estimates the free energy of binding of the ligand from a given pose. The functional form is a sum of terms:

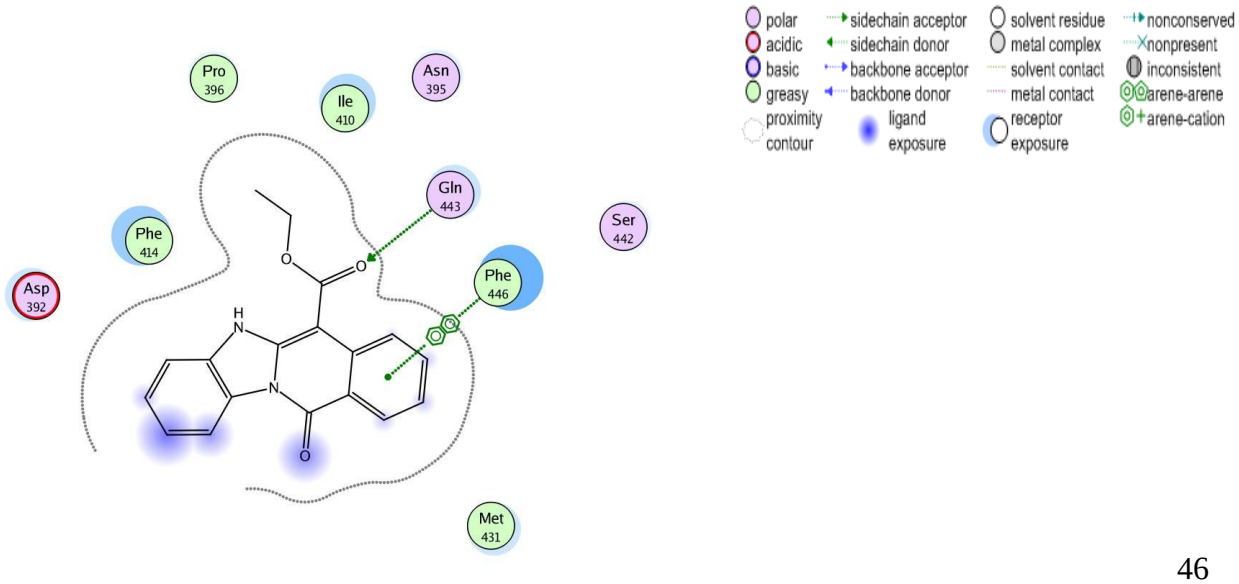
$$\Delta G = c + E_{flex} + \sum_{h-bonds} c_{HB} f_{HB} + \sum_{m-lig} c_M f_M + \sum_{atoms\ i} \Delta D_i$$

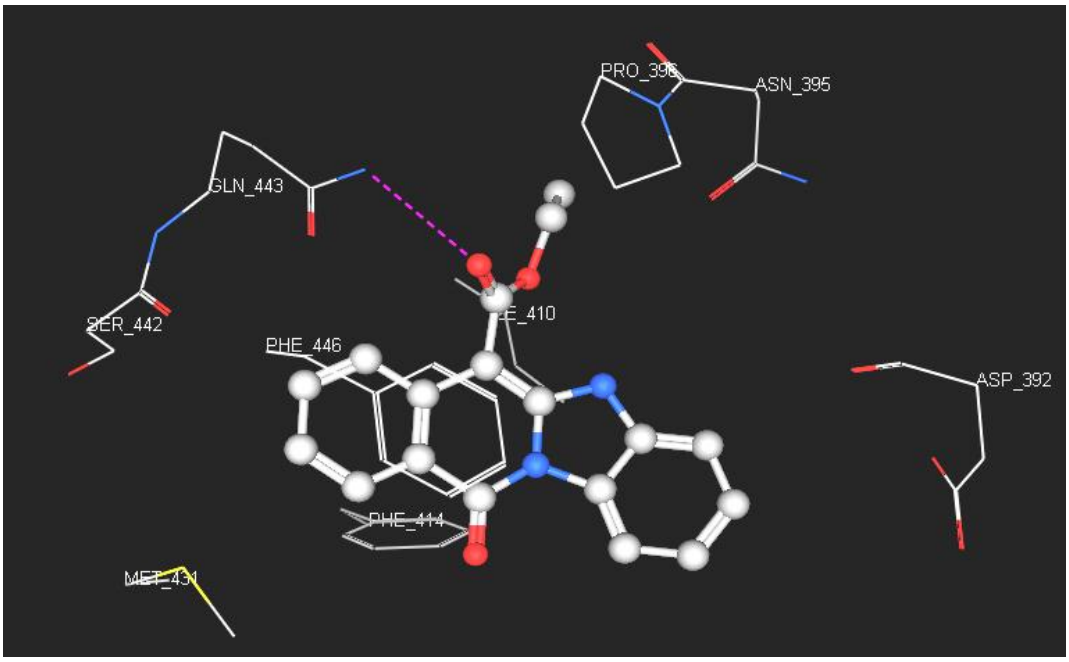
where c represents the average gain/loss of rotational and translational entropy; E_{flex} is the energy due to the loss of flexibility of the ligand (calculated from ligand topology only); f_{HB} measures geometric imperfections of hydrogen bonds and takes a value in [0,1]; c_{HB} is the energy of an ideal hydrogen bond; f_M measures geometric imperfections of metal ligations and takes a value in [0,1]; c_M is the energy of an ideal metal ligation; and D_i is the desolvation energy of atom i.

To validate the Docking accuracy of the program used, the native co-crystallized Rolipram ligand was docked back into its binding site of PDE4B Protein.

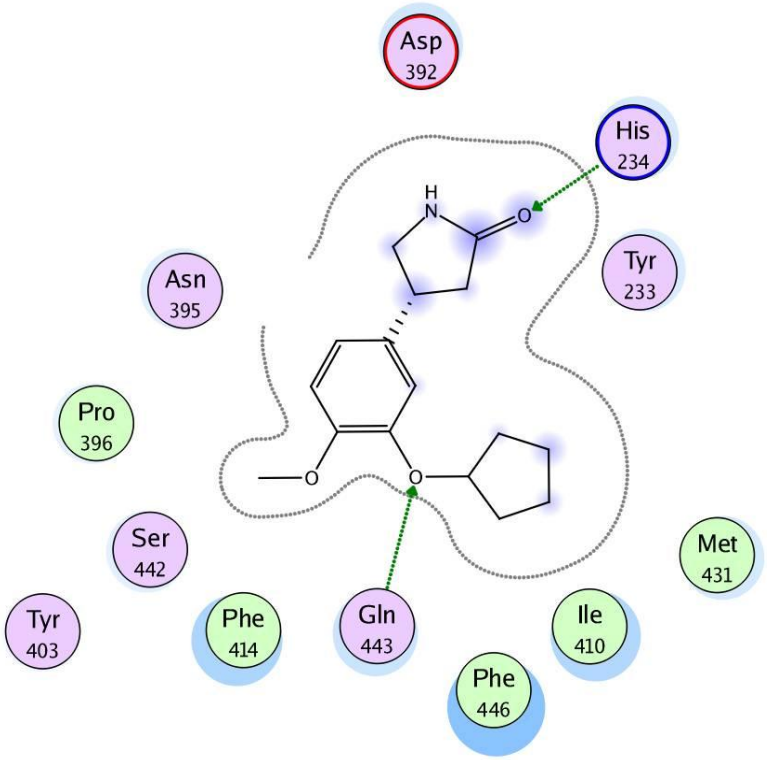
Protein-Molecular Interactions in Docking Pose

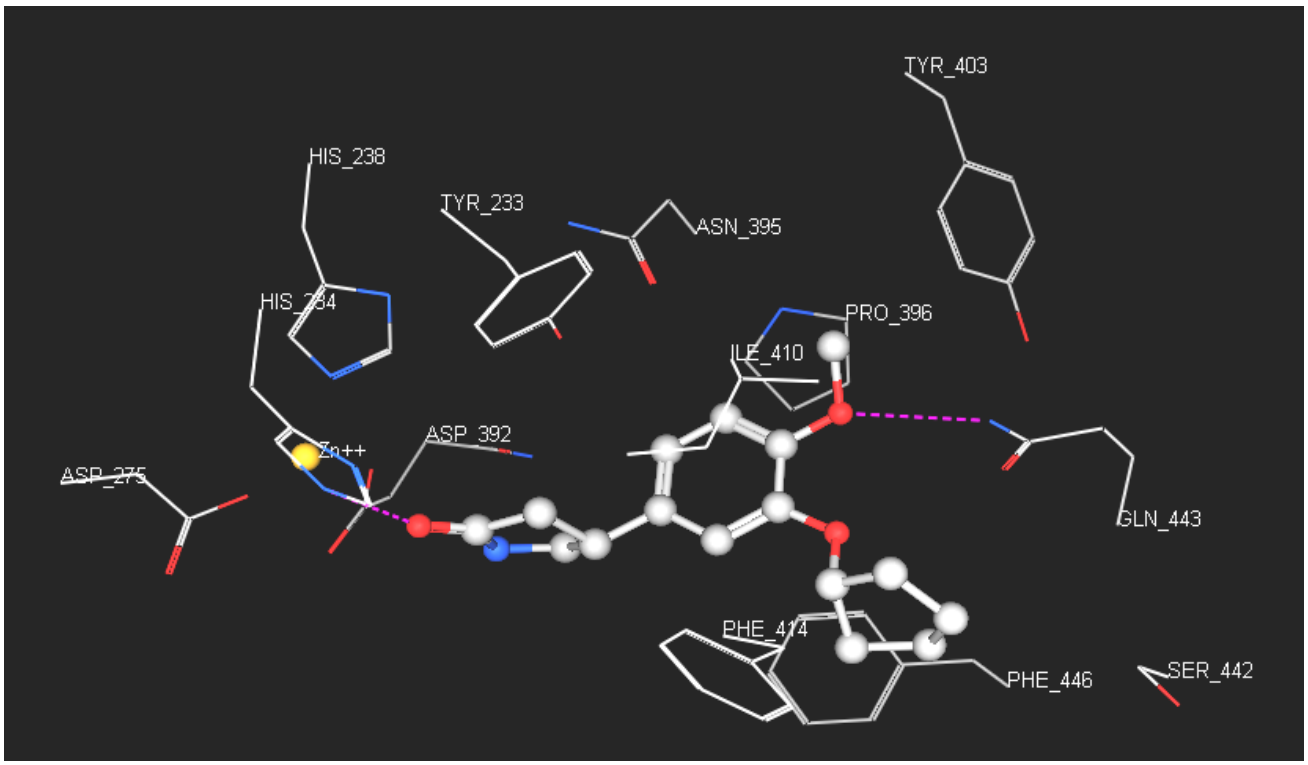
Docking of 4a into PDE4B:-





Docking of Rolipram into PDE4B:-





Molecular interactions Summary of top-ranked docking poses of 4a and rolipram

H-bond interactions	
Compounds	**PDE4B**
Rolipram	His234, Gln443
4a	Gln 443

References

1. Orly Dym, Ioannis Xenarios, Hengming Ke and John Colicelli, Molecular Docking of Competitive Phosphodiesterase Inhibitors, Mol Pharmacol 61:20–25, 2002.
2. Fernanda G. Oliveira, Carlos M. R. Sant'Anna, Ernesto R. Caffarena, Laurent E. Dardenne and Eliezer J. Barreiro, Molecular docking study and development of an empirical binding free energy model for Phosphodiesterase 4 inhibitors, Bioorganic & Medicinal Chemistry 14 (2006) 6001–6011.
3. Annalisa Tait, Amedeo Luppi, Armin Hatzelmann, Paola Fossa and Luisa Mosti, Synthesis, biological evaluation and molecular modelling studies on benzothiadiazine derivatives as PDE4 selective inhibitors, Bioorganic & Medicinal Chemistry (2004).
4. Chidochangu P. Mpamhanga, Beining Chen,Iain M. McLay, Daniel L. Ormsby, And Mika K. Lindvall, Retrospective Docking Study of PDE4B Ligands and an Analysis of the Behavior of Selected Scoring Functions, J. Chem. Inf. Model.2005,45,1061-1074.