

Electronic Supplementary Information

**New MCR based on intramolecular Heck reaction under aerobic condition: A direct access
to cytotoxic fused *N*-heterocycles**

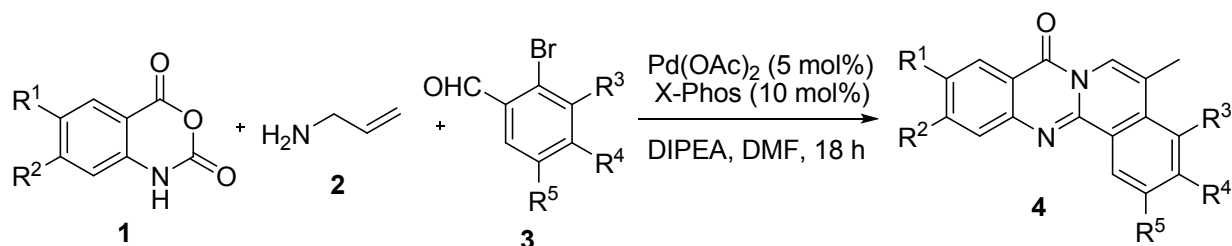
Raju Adepu,^a Bagineni Prasad,^a Mohd Ashraf Ashfaq,^a Nasreen Z. Ehtesham,^a and Manojit Pal^{a,*}

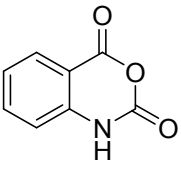
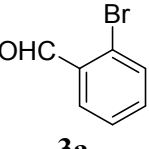
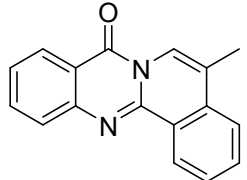
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Hyderabad 500 046, India*

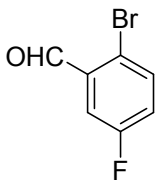
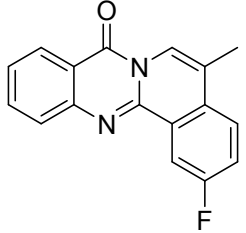
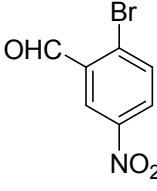
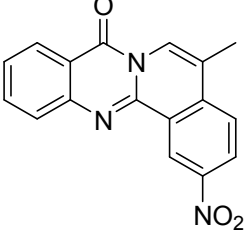
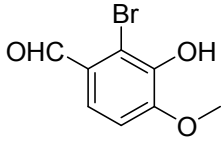
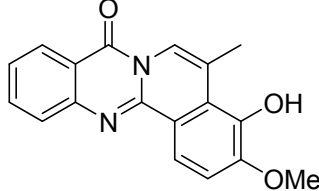
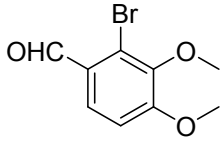
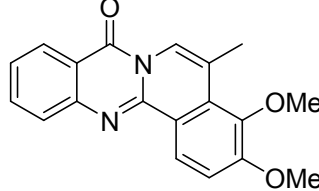
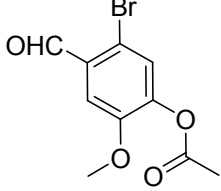
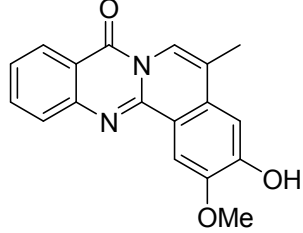
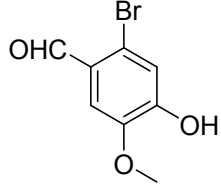
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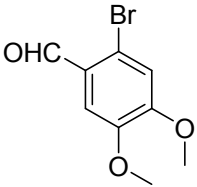
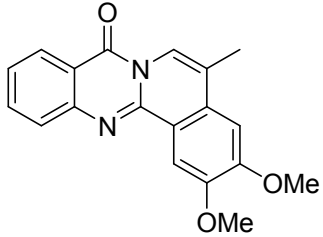
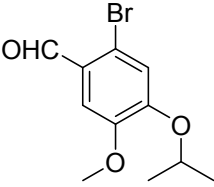
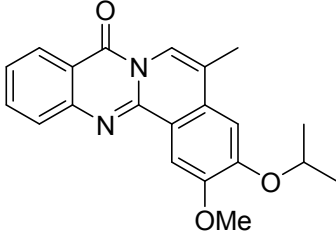
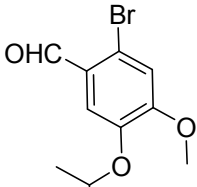
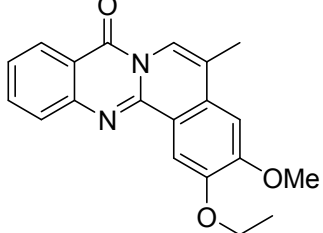
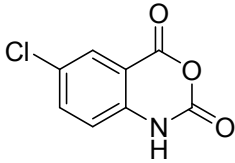
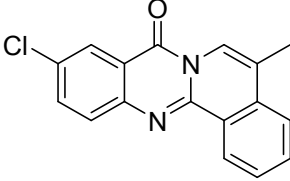
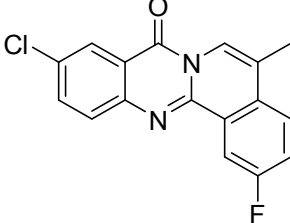
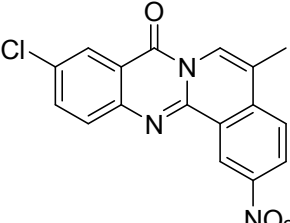
General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate, dichloromethane. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 or $\text{DMSO}-d_6$ solution by using a 400 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) q (quartet) and m (multiplet) as well as bs (broad). Coupling constants (J) are given in hertz. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. 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 time.

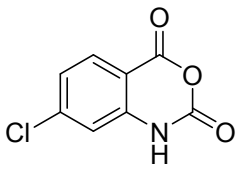
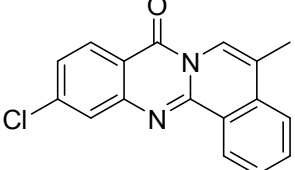
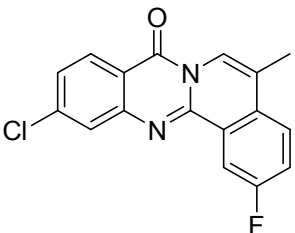
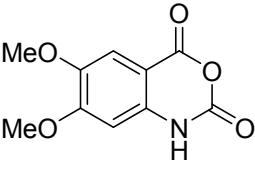
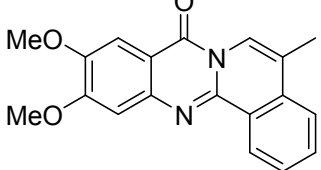
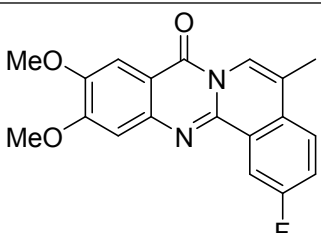
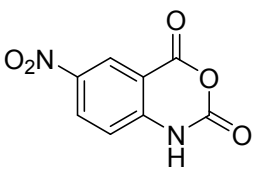
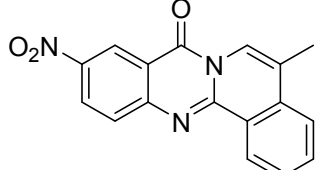
Table S-1: Synthesis of isoquinolino[1,2-*b*]quinazolinone derivatives (**4**) via new MCR



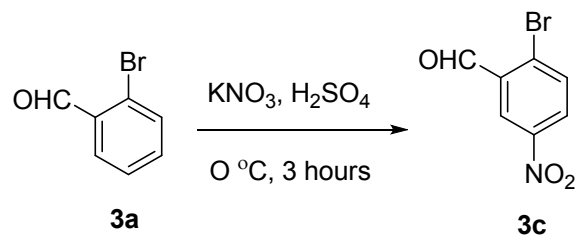
S. No	Isatoic anhydride (1)	Aldehyde (3)	Product (4)	Yield
1	 1a	 3a	 4a	78

2	1a	 <p>3b</p>	 <p>4b</p>	69
3	1a	 <p>3c</p>	 <p>4c</p>	65
4	1a	 <p>3d</p>	 <p>4d</p>	70
5	1a	 <p>3e</p>	 <p>4e</p>	71
6	1a	 <p>3f</p>	 <p>4f</p>	62 ^c
7	1a	 <p>3g</p>	<p>4f</p>	65

8	1a	 <p>3h</p>	 <p>4g</p>	70
9	1a	 <p>3i</p>	 <p>4h</p>	73
10	1a	 <p>3j</p>	 <p>4i</p>	72
11	 <p>1b</p>	3a	 <p>4j</p>	79
12	1b	3b	 <p>4k</p>	64
13	1b	3c	 <p>4l</p>	64

14	 1c	3a	 4m	75
15	1c	3b	 4n	62
16	 1d	3a	 4o	66
17	1d	3b	 4p	60
18	 1e	3a	 4q	45

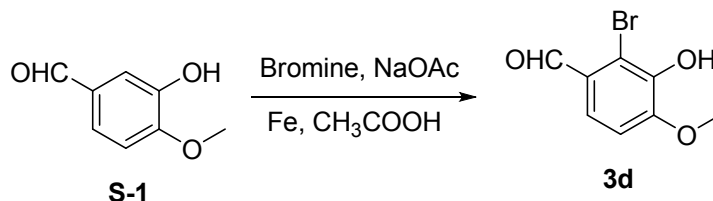
Preparation of 2-bromo-5-nitrobenzaldehyde¹ (3c)



Potassium nitrate (330 mg, 3.27 mmol) was slowly added to a stirred and chilled (ice bath) solution of 2-bromobenzaldehyde (0.5 g, 2.73 mmol) in sulfuric acid (6 mL) over 10 minutes. Then the reaction mixture was stirred at 0 °C for 3 h. After completion of the reaction the mixture was poured into ice water. The solid separated was filtered, washed with water and dried to give the desired product **3c**.

Yield: 52% (325 mg); light yellow solid; mp: 102-104 (lit² 105-107 °C); ¹H NMR (400 MHz, CDCl₃) δ: 10.41 (s, 1H), 8.73 (d, *J* = 2.1 Hz, 1H), 8.34 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H).

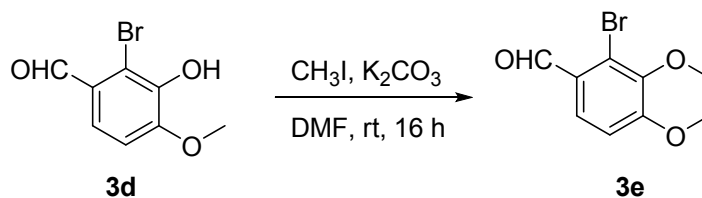
Synthesis of 2-bromo-3-hydroxy-4-methoxybenzaldehyde³ (**3d**)



Isovanillin (**S-1**) (2 g, 13.15 mmol) was dissolved in glacial acetic acid (10 ml). To this was added anhydrous sodium acetate (2.15 g, 26.23 mmol), followed by powdered iron (0.05 g) and then, a solution of bromine (0.7 mL, 14.46 mmol) in glacial acetic acid (10 ml) over a period of 15 min under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 45 min. After completion of the reaction the mixture was poured into aqueous 5% sodium bisulfite (50 mL) and stirred for 10 min. The precipitate was filtered, washed with water (50 mL), and dried to give the desired product **3d**.

Yield: 60% (1.8 g); white solid; mp: 195-197 °C (lit³ 200-202 °C); ¹H NMR (400 MHz, CDCl₃) δ: 10.26 (s, 1H), 7.58 (d, *J* = 8.55 Hz, 1H), 6.93 (d, *J* = 8.56 Hz, 1H), 6.10 (s, 1H), 4.01 (s, 3H).

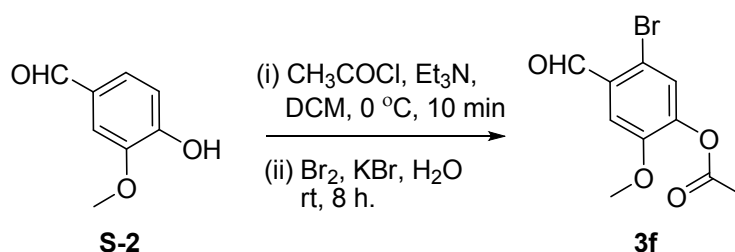
Synthesis of 2-bromo-3,4-dimethoxybenzaldehyde (**3e**)



A mixture of compound **3d** (200 mg, 0.87 mmol), methyl iodide (0.06 mL, 1.04 mmol) and potassium carbonate (180 mg, 1.30 mmol) in DMF (5 mL) was stirred at room temperature for 16 h. Upon completion of the reaction, the mixture was diluted with water (15 mL) and extracted with ethyl acetate (2 x 10 mL). The organic layers were collected, combined, washed with brine solution (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane to give the desired product **3e**.

Yield: 78% (165 mg); white solid; mp: 81-83 °C (lit⁴ 83-84 °C); ¹H NMR (400 MHz, CDCl₃) δ: 10.26 (s, 1H), 7.75 (d, *J* = 8.67 Hz, 1H), 6.96 (d, *J* = 8.69 Hz, 1H), 3.99 (s, 4H), 3.89 (s, 3H).

Synthesis of 5-bromo-4-formyl-2-methoxyphenyl acetate⁵ (**3f**)



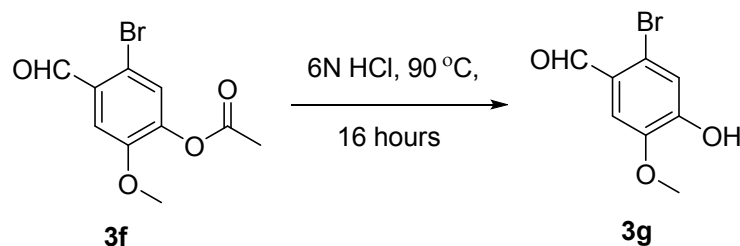
Step 1: To a mixture of vanillin (3 g, 19.73 mmol) and triethylamine (3.5 mL, 25.65 mmol) in DCM (50 mL), was added acetyl chloride (1.8 mL, 25.65 mmol) drop wise at 0 °C. The reaction mixture was stirred at 0 °C for 20 minutes, and then filtered. The solid separated was washed with methylene chloride (2 x 20 mL). The combined filtrate was washed with water (50 mL) followed by brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give vanillin acetate as a yellow solid.

Yield: quantitative; mp: 72 – 74 °C (lit⁶ 74-76 °C); ¹H NMR (400 MHz, CDCl₃) δ: 9.94 (s, 1H), 7.52-7.45 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 3.92 (s, 3H), 2.36 (s, 3H).

Step 2: To a solution of potassium bromide (5.5 g, 46.38 mmol) in water was added vanillin acetate (3 g, 15.46 mmol) and bromine (0.8 mL, 15.46 mmol), and the mixture was stirred at room temperature for 8 h. The precipitate was filtered, washed with water and dried under vacuum to give the desired compound **3f**.

Yield: 72% (3 g); white solid; mp 162-164 °C (lit⁷ 164-165 °C); ¹H NMR (400 MHz, CDCl₃) δ: 10.28 (s, 1H), 7.50 (s, 1H), 7.36 (s, 1H), 3.90 (s, 3H), 2.35 (s, 3H).

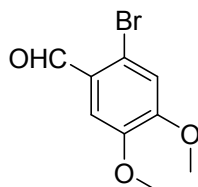
Synthesis of 2-bromo-4-hydroxy-5-methoxybenzaldehyde⁸ (**3g**)



To the compound **3f** (2.7 g, 10 mmol), 6 N hydrochloric acid (50 mL) was added, and the mixture was stirred at 90 °C for 16 hr. The precipitate was collected by filtration, and washed with saturated aqueous sodium hydrogen carbonate (50 mL) and water (50 mL). The obtained solid was dried to give the title compound **3g**.

Yield: 65% (1.4 g); white solid; mp: 176-178 °C (lit⁹ 174-175 °C); ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 10.02 (s, 1H), 7.35 (s, 1H), 7.11 (s, 1H), 3.83 (s, 3H).

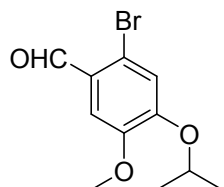
2-Bromo-4,5-dimethoxybenzaldehyde (**3h**)



Compound **3h** was synthesized by reacting **3g** with methyl iodide following a procedure similar to that of compound **3e**.

Yield: 65% (136 mg); white solid; mp: 145-147 °C (lit¹⁰ 144-145 °C); ¹H NMR (CDCl₃, 400 MHz) δ: 10.18 (s, 1H), 7.40 (s, 1H), 7.05 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H).

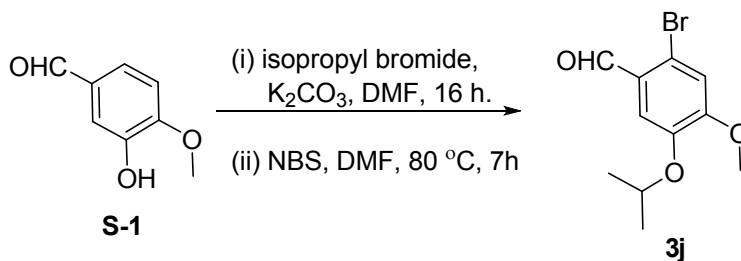
2-Bromo-4-isopropoxy-5-methoxybenzaldehyde (**3i**)



Compound **3i** was synthesized by reacting **3g** with isopropyl bromide following a procedure similar to that of compound **3e**.

Yield: 71% (167 mg); white solid; mp: 102-104 °C (lit¹¹ 105-107 °C); ¹H NMR (CDCl₃, 400 MHz) δ: 10.17 (s, 1H), 7.41 (s, 1H), 7.04 (s, 1H), 4.68-4.62 (m, 1H), 3.93 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 6H).

Synthesis of 2-bromo-5-isopropoxy-4-methoxybenzaldehyde^{12,13} (**3j**)



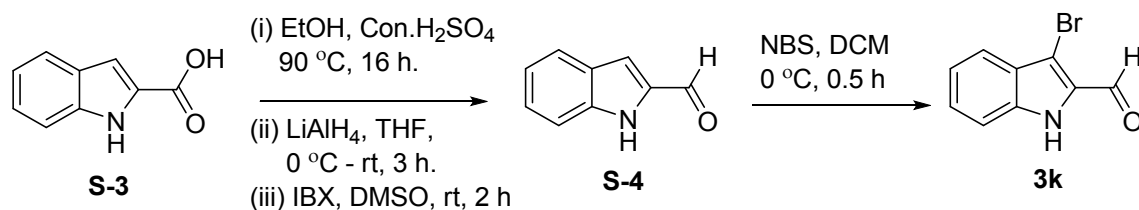
Step 1: A solution of isovanillin (500 mg, 3.28 mmol) in DMF (10 mL) was treated with K₂CO₃ (678 mg, 4.92 mmol) and isopropyl bromide (0.37 mL, 3.93 mmol). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 16 h. After completion of the reaction, the mixture was poured into H₂O (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane to give 3-isopropoxy-4-methoxybenzaldehyde.

Yield: 82% (520 mg); light yellow solid; ¹H NMR (CDCl₃, 400 MHz) δ: 9.83 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 4.66-4.62 (m, 1H), 3.93 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 6H).

Step 2: NBS (330 mg, 1.85 mmol) was added to a solution of 3-isopropoxy-4-methoxybenzaldehyde (300 mg, 1.54 mmol) in DMF (10 mL) at room temperature, and heated to 80 °C. After 7 h, the solution was cooled to room temperature, diluted with ethyl acetate (25 mL), washed with 10% Na₂S₂O₅ solution (30 mL), water (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane to give the desired product **3j**.

Yield: 62% (260 mg); white solid; mp: 79-81 °C (lit¹³ 78-79 °C); ¹H NMR (CDCl₃, 400 MHz) δ: 10.12 (s, 1H), 7.42 (s, 1H), 7.04 (s, 1H), 4.63-4.60 (m, 1H), 3.93 (s, 3H), 1.38 (d, *J* = 6.0 Hz, 6H).

Synthesis of 3-bromo-1H-indole-2-carbaldehyde^{14,15} (3k)



Step 1: To the solution of indole 2-carboxylic acid (**S-3**) (500 mg, 3.10 mmol) in EtOH (5 mL), was added con. H₂SO₄ (0.5 mL), and the mixture was stirred at 90 °C for 16 h. After completion of the reaction, the mixture was cooled to room temperature and the obtained solid was filtered, washed with water and dried under vacuum to give ethyl indole 2-carboxylate as a light brown solid (550 mg, 95%).

Step 2: In dry THF (10 mL), LiAlH₄ (200 mg, 5.29 mmol) was added slowly at 0 °C. To this was added a solution of ethyl indole-2-carboxylate (500 mg, 2.65 mmol) in THF (10 mL) drop wise. The reaction mixture was stirred at the same temperature for 1 h. Then the reaction mixture was quenched with H₂O (2 mL), 10% NaOH solution (2 mL), H₂O (3 mL) successively and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with water (20 mL) followed by brine solution (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the (1H-indol-2-yl)methanol as a light brown solid (342 mg, 88%).

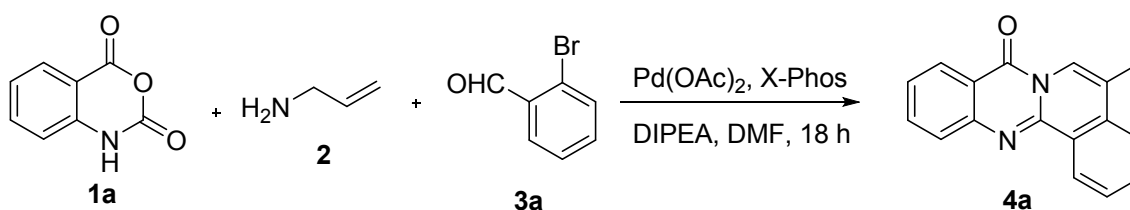
Step 3: The obtained alcohol (340 mg, 2.31 mmol) was dissolved in DMSO (4 mL), and then IBX (971 mg, 3.46 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, diluted with water (20 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane to give the desired product **S-4**.

Yield: 62% (207 mg); white solid; mp: 136-138 °C (lit¹⁶ 138-140 °C); ¹H NMR (CDCl₃, 400 MHz) δ: 9.89 (s, 1H), 9.68 (bs, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.49-7.50 (m, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.29 (s, 1H), 7.16-7.19 (m, 1H).

Step 4: To the solution of 1*H*-indole-2-carbaldehyde (**S-4**) (200 mg, 1.37 mmol) in DCM (10 mL), was added *N*-bromo succinimide (294 mg, 1.65 mmol) portion wise for about 10 min at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction the mixture was diluted with water (20 mL) and extracted with DCM (2 x 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane to give the desired product **3k**.

Yield: 55% (165 mg); white solid; mp: 172-174 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 10.00 (s, 1H), 9.30 (bs, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.49-7.42 (m, 2H), 7.30-7.21 (m, 1H).

Typical procedure for the preparation of 5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4a)

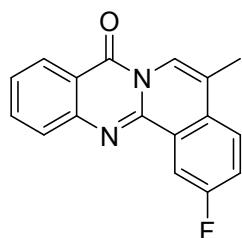


A mixture of isatoic anhydride (**1a**) (30 mg, 0.18 mmol), allyl amine (**2**) (10 mg, 0.18 mmol), 2-bromo benzaldehyde (**3a**) (33 mg, 0.18 mmol), DIPEA (0.94 mL, 0.54 mmol), Pd(OAc)₂ (2 mg, 0.009 mmol) and X-Phos (8 mg, 0.018 mmol) in DMF (2 mL) was stirred at room temp for 5 min (the effervescence of CO₂ was observed) and then slowly increased the temp to 130 °C under anhydrous conditions. The mixture was stirred at this temp for 18 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and passed through the celite. The resulting filtrate was washed with water (2 x 15 mL) followed by brine solution (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane to give the desired product **4a**.

Yield: 78% (36 mg); white solid; mp: 203-205 °C; *R_f* = 0.4 (10% EtOAc/ *n*-hexane); ¹H NMR (400 MHz, CDCl₃) δ: 9.19 (d, *J* = 7.9 Hz, 1H), 8.53 (d, *J* = 1.2 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.82-7.74 (m, 2H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 2.53 (d, *J* = 1.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 159.1,

146.1, 134.7, 133.9, 132.2, 128.2, 127.5, 127.2, 127.2 (2C), 125.6, 123.3 (2C), 119.7, 119.3, 117.6, 16.4; MS (ES mass): 260.6 (M+1); HPLC: 98.2%, column: X-Terra RP18 250 x 4.6 mm 5.0 μ m, mobile phase A: 0.1 % TFA in water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 280 nm, retention time 14.2 min.

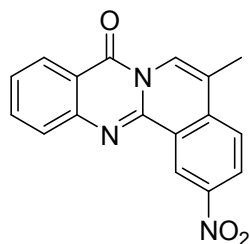
2-Fluoro-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4b)



Compound **4b** was synthesized by the reaction of **1a** with 2-bromo-5-fluorobenzaldehyde (**3b**) following a procedure similar to that of compound **4a**.

Yield: 69% (34 mg); light brown solid; mp: 196-198 °C; R_f = 0.4 (10% EtOAc/ *n*-hexane); ¹H NMR (400 MHz, CDCl₃) δ : 8.81 (dd, J = 9.2, 2.5 Hz, 1H), 8.48-8.46 (m, 2H), 7.94-7.83 (m, 2H), 7.76 (dd, J = 8.4, 5.2 Hz, 1H), 7.56-7.49 (m, 2H), 2.52 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 163.3 (C-F J = 235.6 Hz), 159.1, 147.2, 134.7, 130.4, 129.4, 127.5 (C-F J = 39.0 Hz), 125.9, 125.6 (C-F J = 8.3 Hz), 120.5 (C-F J = 23.2 Hz), 118.9, 118.8 (2C), 117.8, 113.2 (C-F J = 24.2 Hz), 109.9, 16.4; MS (ES mass): 279.0 (M+1); HPLC: 95.1%, column: X-Terra RP18 250 x 4.6 mm 5.0 μ m, mobile phase A: 0.1 % TFA in water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 235 nm, retention time 15.2 min.

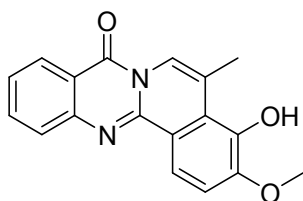
5-Methyl-2-nitro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4c)



Compound **4c** was synthesized by the reaction of **1a** with 2-bromo-5-nitrobenzaldehyde (**3c**) following a procedure similar to that of compound **4a**.

Yield: 65% (35 mg); brown solid; mp: 224-226 °C; $R_f = 0.3$ (10% EtOAc/ *n*-hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 9.96 (d, $J = 2.2$ Hz, 1H), 8.63 (s, 1H), 8.56 (dd, $J = 8.6, 2.2$ Hz, 1H), 8.47 (d, $J = 8.0$ Hz, 1H), 7.98-7.88 (m, 3H), 7.58 (t, $J = 7.6$ Hz, 1H), 2.56 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 158.8, 146.9, 144.7, 138.4, 137.2, 135.2, 128.3, 127.8, 127.3, 126.6, 126.0, 124.8, 123.3, 122.9, 118.2, 118.0, 16.4; MS (ES mass): 305.9 (M+1); HPLC: 91.2%, column: Symmetry C-18 75 x 4.6 mm 3.5 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 1/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.65 min.

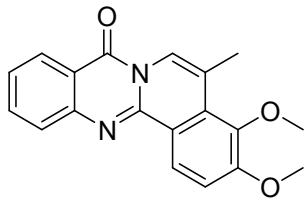
4-Hydroxy-3-methoxy-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**4d**)



Compound **4d** was synthesized by the reaction of **1a** with 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**3d**) following a procedure similar to that of compound **4a**.

Yield: 70% (38 mg); white solid; mp: 251-253 °C; $R_f = 0.4$ (15% EtOAc/ *n*-hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.78 (d, $J = 8.5$ Hz, 1H), 8.43 (d, $J = 8.1$ Hz, 1H), 8.30 (s, 1H), 7.84-7.78 (m, 2H), 7.45 (tb, $J = 8.3, 2.0$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 6.19 (s, 1H), 4.07 (s, 3H), 2.74 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 159.1, 153.8, 148.7, 147.8, 146.0, 142.2, 139.7, 134.4, 127.5, 127.2, 125.1, 121.7, 119.9 (2C), 118.9, 110.9, 56.5, 20.9; MS (ES mass): 307.0 (M+1); HPLC: 97.9%, column: Symmetry C-18 75 x 4.6 mm 3.5 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 1/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 315 nm, retention time 4.97 min.

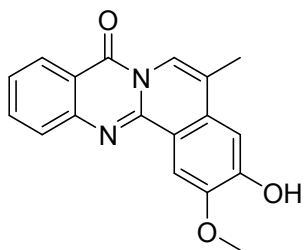
3,4-Dimethoxy-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**4e**)



Compound **4e** was synthesized by the reaction of **1a** with 2-bromo-3,4-dimethoxybenzaldehyde (**3e**) following a procedure similar to that of compound **4a**.

Yield: 71% (40 mg); light brown solid; mp: 176-178 °C; $R_f = 0.1$ (10% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 9.00 (d, $J = 8.5$ Hz, 1H), 8.44 (d, $J = 7.9$ Hz, 1H), 8.36 (s, 1H), 7.88-7.79 (m, 2H), 7.51-7.45 (m, 1H), 7.30 (d, $J = 8.6$ Hz, 1H), 4.06 (s, 3H), 3.94 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.0, 156.1, 147.8, 145.9, 145.0, 134.5, 128.4, 127.2, 125.1, 124.6, 121.5, 120.4, 119.1, 117.4, 112.9, 109.9, 61.4, 56.1, 20.5; MS (ES mass): 321.0 (M+1); HPLC: 99.3%, column: X-Terra RP18 250 x 4.6 mm 5.0 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 290 nm, retention time 14.0 min.

3-Hydroxy-2-methoxy-5-methyl-8H-isoquinolino[1,2-*b*]quinazolin-8-one (**4f**)

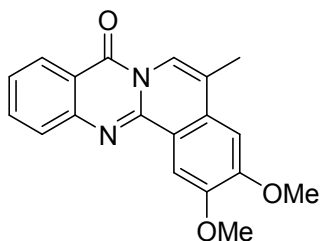


Compound **4f** was synthesized by the reaction of **1a** with 2-bromo-4-hydroxy-5-methoxybenzaldehyde (**3g**) following a procedure similar to that of compound **4a**.

Yield: 65% (35 mg); white solid; mp: 205-207 °C; $R_f = 0.4$ (15% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 8.58 (s, 1H), 8.49 (d, $J = 1.1$ Hz, 1H), 8.45 (d, $J = 7.8$ Hz, 1H), 7.89-7.80 (m, 2H), 7.46 (td, $J = 8.0, 1.1$ Hz, 1H), 7.26 (s, 1H), 6.27 (s, 1H), 4.19 (s, 3H), 2.47 (d, $J = 1.0$ Hz, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ : 158.8, 152.2, 149.3, 147.6, 145.6, 135.1, 129.4, 127.2, 127.0, 125.1, 119.6, 119.3, 117.7, 116.6, 108.8, 108.0, 56.1, 16.4; MS (ES mass): 307.0 (M+1); HPLC: 96.3%, column: X-Terra RP18 250 x 4.6 mm 5.0 μm , mobile phase A: 0.1 % TFA

in water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 280 nm, retention time 11.0 min.

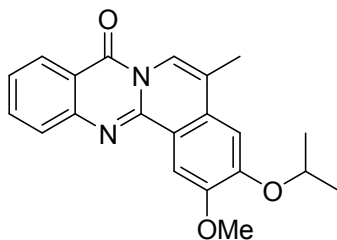
2,3-Dimethoxy-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4g)



Compound **4g** was synthesized by the reaction of **1a** with 2-bromo-4,5-dimethoxybenzaldehyde (**3h**) following a procedure similar to that of compound **4a**.

Yield: 70% (40 mg); light yellow solid; mp: 246-248 °C; *R_f* = 0.1 (10% EtOAc/ *n*-hexane); ¹H NMR (400 MHz, CDCl₃) δ: 8.57 (s, 1H), 8.52 (s, 1H), 8.46 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.84 (t, *J* = 7.1 Hz, 1H), 7.47 (t, *J* = 7.0 Hz, 1H), 7.10 (s, 1H), 4.17 (s, 3H), 4.08 (s, 3H), 2.52 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 159.3, 153.1, 149.7, 147.7, 145.6, 134.4, 129.2, 127.2, 127.0, 124.8, 121.0, 119.2, 118.3, 116.9, 107.8, 103.8, 56.3, 56.1, 16.6; MS (ES mass): 321.0 (M+1); HPLC: 95.3%, column: X-Terra RP18 250 x 4.6 mm 5.0μm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 275 nm, retention time 12.0 min.

3-Isopropoxy-2-methoxy-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4h)

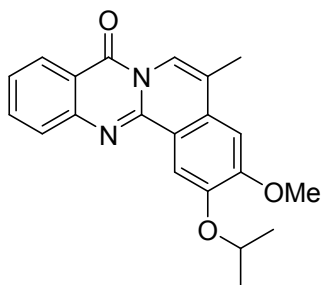


Compound **4h** was synthesized by the reaction of **1a** with 2-bromo-4-isopropoxy-5-methoxybenzaldehyde (**3i**) following a procedure similar to that of compound **4a**.

Yield: 73% (45 mg); light brown solid; mp: 196-198 °C; *R_f* = 0.5 (15% EtOAc/ *n*-hexane); ¹H NMR (400 MHz, CDCl₃) δ: 8.55 (s, 1H), 8.49 (s, 1H), 8.45 (d, *J* = 7.90 Hz, 1H), 7.88 (t, *J* = 8.08 Hz, 1H), 7.86-7.79 (m, 1H), 7.45 (tb, *J* = 8.0, 1.2 Hz, 1H), 7.12 (s, 1H), 4.85-4.79 (m, 1H),

4.14 (s, 3H), 2.49 (s, 3H), 1.50 (d, $J = 6.0$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.4, 151.6, 150.7, 147.8, 145.7, 134.4, 129.1, 127.2, 127.0, 124.8, 120.8, 119.2, 118.2, 116.9, 108.2, 106.7, 71.4, 56.3, 21.9 (2C), 16.6; MS (ES mass): 349.0 (M+1); HPLC: 97.6%, column: X-Terra RP18 250 x 4.6 mm 5.0 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 280 nm, retention time 12.9 min.

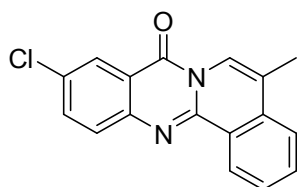
2-Isopropoxy-3-methoxy-5-methyl-8H-isoquinolino[1,2-b]quinazolin-8-one (4i)



Compound **4i** was synthesized by the reaction of **1a** with 2-bromo-5-isopropoxy-4-methoxybenzaldehyde (**3j**) following a procedure similar to that of compound **4a**.

Yield: 72% (45 mg); light yellow solid; mp: 177-179 $^{\circ}\text{C}$; $R_f = 0.5$ (15% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 8.60 (s, 1H), 8.50 (s, 1H), 8.45 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 7.9$ Hz, 1H), 7.82 (td, $J = 7.4, 1.8$ Hz, 1H), 7.45 (t, $J = 7.9$ Hz, 1H), 7.10 (s, 1H), 5.01-4.95 (m, 1H), 4.06 (s, 3H), 2.52 (s, 3H), 1.52 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.4, 154.2, 148.1, 147.8, 145.7, 134.4, 128.9, 127.2, 127.1, 124.8, 121.0, 119.2, 118.2, 116.9, 110.7, 104.3, 71.4, 56.1, 21.9 (2C), 16.6; MS (ES mass): 349.0 (M+1); HPLC: 94.3%, column: X-Terra RP18 250 x 4.6 mm 5.0 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 280 nm, retention time 13.1 min.

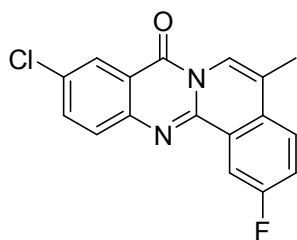
10-Chloro-5-methyl-8H-isoquinolino[1,2-b]quinazolin-8-one (4j)



Compound **4j** was synthesized by the reaction of 5-chloro isatoic anhydride (**1b**) with **3a** following a procedure similar to that of compound **4a**.

Yield: 79% (35 mg); light yellow solid; mp: 217-219 °C; $R_f = 0.5$ (10% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 9.13 (d, $J = 8.2$ Hz, 1H), 8.51 (s, 1H), 8.43 (d, $J = 2.3$ Hz, 1H), 7.87-7.75 (m, 4H), 7.70 (tb, $J = 8.4, 1.8$ Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.3, 148.3, 145.9, 135.1, 133.8, 132.3, 131.1, 129.1, 128.3, 127.5, 127.0, 126.3, 123.4, 120.2, 119.2, 118.5, 16.4; MS (ES mass): 294.9 (M+1); HPLC: 91.3%, column: Symmetry C-18 75 x 4.6 mm 3.5 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 1/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 285 nm, retention time 6.73 min.

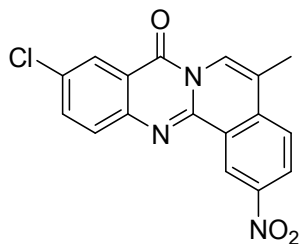
10-Chloro-2-fluoro-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**4k**)



Compound **4k** was synthesized by the reaction of **1b** with **3b** following a procedure similar to that of compound **4a**.

Yield: 64% (30 mg); white solid; mp: 224-226 °C; $R_f = 0.5$ (10% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 8.78 (dd, $J = 8.8, 2.5$ Hz, 1H), 8.47 (d, $J = 0.9$ Hz, 1H), 8.43 (d, $J = 2.4$ Hz, 1H), 7.85 (d, $J = 8.3$ Hz, 1H), 7.81-7.75 (m, 2H), 7.53 (tb, $J = 8.1, 2.5$ Hz, 1H), 2.53 (d, $J = 1.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.5 (C-F $J = 247.9$ Hz), 158.1, 145.7, 135.2, 131.5, 130.4, 129.2, 126.3, 125.8 (C-F $J = 8.2$ Hz), 123.4, 120.7 (C-F $J = 23.1$ Hz), 119.5, 118.7 (C-F $J = 13.5$ Hz), 118.7, 113.3 (C-F $J = 24.3$ Hz), 111.0, 16.5; MS (ES mass): 312.9 (M+1); HPLC: 92.1%, column: Symmetry C-18 75 x 4.6 mm 3.5 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 1/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 285 nm, retention time 6.86 min.

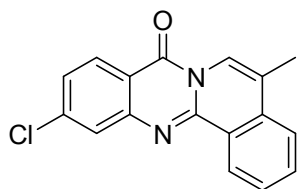
10-Chloro-5-methyl-2-nitro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**4l**)



Compound **4l** was synthesized by the reaction of **1b** with **3c** following a procedure similar to that of compound **4a**.

Yield: 64% (32 mg); yellow solid; mp: 279-281 °C; $R_f = 0.5$ (10% EtOAc/ *n*-hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 9.93 (d, $J = 2.3$ Hz, 1H), 8.62 (s, 1H), 8.59 (dd, $J = 8.2, 2.2$ Hz, 1H), 8.44 (d, $J = 2.2$ Hz, 1H), 7.92 (dd, $J = 8.0, 1.8$ Hz, 2H), 7.85 (dd, $J = 8.4, 2.2$ Hz, 1H), 2.58 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 157.9, 147.2, 145.5, 139.3, 138.3, 135.7, 132.3, 129.5, 128.1, 126.5, 126.3, 124.9, 123.3, 122.8, 118.9, 118.8, 16.4; MS (ES mass): 339.9 (M+1); HPLC: 92.2%, column: Symmetry C-18 75 x 4.6 mm 3.5 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 1/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.16 min.

11-Chloro-5-methyl-8H-isoquinolino[1,2-b]quinazolin-8-one (**4m**)

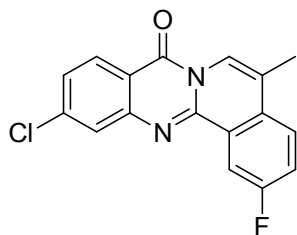


Compound **4m** was synthesized by the reaction of 4-chloro isatoic anhydride (**1c**) with **3a** following a procedure similar to that of compound **4a**.

Yield: 75% (33 mg); white solid; mp: 186-188 °C; $R_f = 0.5$ (10% EtOAc/ *n*-hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 9.09 (d, $J = 8.1$ Hz, 1H), 8.48 (s, 1H), 8.36 (d, $J = 8.6$ Hz, 1H), 7.86 (d, $J = 1.7$ Hz, 1H), 7.83-7.74 (m, 2H), 7.68 (t, $J = 7.6$ Hz, 1H), 7.42 (dd, $J = 8.4, 1.8$ Hz, 1H), 2.52 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 158.7, 148.3, 147.0, 140.8, 133.9, 132.5, 128.7, 128.3, 127.6, 126.9, 126.7, 126.2, 123.3, 120.1, 119.2, 116.0, 16.4; MS (ES mass): 294.9 (M+1); HPLC: 95.6%, column: X-Terra RP18 250 x 4.6 mm 5.0 μm , mobile phase A: 0.1 % TFA in

water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 275 nm, retention time 15.6 min.

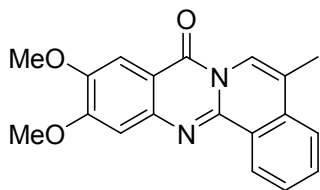
11-Chloro-2-fluoro-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4n)



Compound **4n** was synthesized by the reaction of **1c** with **3b** following a procedure similar to that of compound **4a**.

Yield: 62% (29 mg); white solid; mp: 221-223 °C; $R_f = 0.5$ (10% EtOAc/ *n*-hexane); ¹H NMR (400 MHz, CDCl₃) δ : 8.69 (dd, $J = 9.2, 2.1$ Hz, 1H), 8.40 (s, 1H), 8.34 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 1.2$ Hz, 1H), 7.73 (dd, $J = 8.4, 5.1$ Hz, 1H), 7.50 (td, $J = 8.4, 2.2$ Hz, 1H), 7.42 (dd, $J = 8.4, 1.4$ Hz, 1H), 2.49 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 163.4 (C-F $J = 246.9$ Hz), 158.5, 148.0, 146.2, 140.9, 130.6, 129.1 (C-F $J = 5.8$ Hz), 128.7, 126.8 (C-F $J = 27.0$ Hz), 125.7, 125.6, 120.9 (C-F $J = 23.3$ Hz), 119.4, 118.7, 116.1, 113.3 (C-F $J = 23.7$ Hz), 16.5; MS (ES mass): 312.9 (M+1); HPLC: 99.5%, column: X-Terra RP18 250 x 4.6 mm 5.0 μ m, mobile phase A: 0.1 % TFA in water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 285 nm, retention time 15.8 min.

10,11-Dimethoxy-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4o)

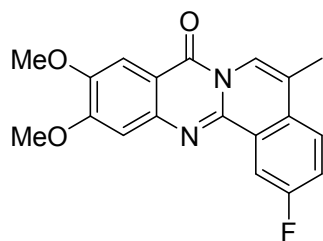


Compound **4o** was synthesized by the reaction of 4,5-dimethoxy isatoic anhydride (**1d**) with **3a** following a procedure similar to that of compound **4a**.

Yield: 66% (28 mg); light brown solid; mp: 184-186 °C; $R_f = 0.1$ (10% EtOAc/ *n*-hexane); ¹H NMR (400 MHz, CDCl₃) δ : 9.11 (d, $J = 7.8$ Hz, 1H), 8.56 (s, 1H), 7.80-7.78 (m, 2H), 7.76 (s, 1H), 7.72-7.65 (m, 1H), 7.30 (s, 1H), 4.09 (s, 3H), 4.06 (s, 3H), 2.54 (s, 3H); ¹³C NMR (100

MHz, CDCl₃) δ : 158.3, 155.7, 148.7, 145.2, 144.2, 133.5, 131.7, 128.1, 127.2, 126.9, 123.3, 119.5, 119.4, 111.2, 107.3, 105.5, 56.4 (2C), 16.4; MS (ES mass): 321.0 (M+1); HPLC: 99.1%, column: X-Terra RP18 250 x 4.6 mm 5.0 μ m, mobile phase A: 0.1 % TFA in water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 285 nm, retention time 13.4 min.

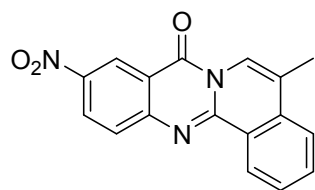
2-Fluoro-10,11-dimethoxy-5-methyl-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4p)



Compound **4p** was synthesized by the reaction of **1d** with **3b** following a procedure similar to that of compound **4a**.

Yield: 60% (27 mg); light brown solid; mp: 209-211 °C; R_f = 0.3 (15% EtOAc/ *n*-hexane); ¹H NMR (400 MHz, CDCl₃) δ : 8.73 (dd, J = 8.6, 2.5 Hz, 1H), 8.50 (s, 1H), 7.77-7.74 (m, 1H), 7.73 (s, 1H), 7.48 (tb, J = 8.0, 2.4 Hz, 1H), 7.27 (s, 1H), 4.09 (s, 3H), 4.06 (s, 3H), 2.52 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 163.4 (C-F J = 246.7 Hz), 158.0, 155.7, 148.9, 143.9, 130.1, 130.0, 129.3, 125.6 (C-F J = 8.1 Hz), 120.0 (C-F J = 23.2 Hz), 118.9 (C-F J = 27.0 Hz), 118.9, 112.7 (C-F J = 24.1 Hz), 111.3, 107.3, 105.4, 56.4, 56.3, 16.5; MS (ES mass): 339.0 (M+1); HPLC: 97.9%, column: X-Terra RP18 250 x 4.6 mm 5.0 μ m, mobile phase A: 0.1 % TFA in water, mobile phase B: CH₃CN, gradient (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 280 nm, retention time 14.1 min.

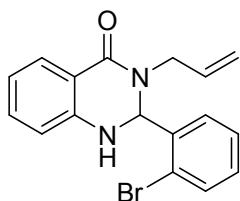
5-Methyl-10-nitro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (4q)



Compound **4q** was synthesized by the reaction of 5-nitro isatoic anhydride (**1e**) with **3a** following a procedure similar to that of compound **4a**.

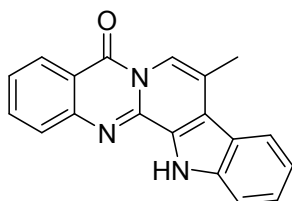
Yield: 45% (20 mg); brown solid; mp: 253-255 °C; $R_f = 0.4$ (10% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 9.35 (d, $J = 2.3$ Hz, 1H), 9.20 (d, $J = 8.4$ Hz, 1H), 8.59 (dd, $J = 8.6, 2.1$ Hz, 1H), 8.56 (d, $J = 0.9$ Hz, 1H), 7.96 (d, $J = 8.7$ Hz, 1H), 7.90-7.84 (m, 2H), 7.76 (td, $J = 8.1, 1.5$ Hz, 1H), 2.58 (d, $J = 1.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.5, 151.3, 144.2, 134.6, 133.4, 128.9, 128.7, 128.4, 128.1, 126.7, 124.6, 123.6, 121.4, 119.1, 116.9, 115.4, 16.4; MS (ES mass): 306.0 (M+1); HPLC: 94.1%, column: Symmetry C-18 75 x 4.6 mm 3.5 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 1/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.82 min.

3-Allyl-2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (5)



Colorless semi solid; $R_f = 0.1$ (10% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 7.98 (d, $J = 7.8$ Hz, 1H), 7.59 (dd, $J = 7.4, 1.0$ Hz, 1H), 7.26-7.16 (m, 4H), 6.83 (t, $J = 7.5$ Hz, 1H), 6.51 (d, $J = 7.8$ Hz, 1H), 6.04 (d, $J = 2.2$ Hz, 1H), 5.91-5.81 (m, 1H), 5.32-5.22 (m, 2H), 5.12 (s, 1H), 5.03-4.95 (m, 1H), 3.21 (dd, $J = 15.2, 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.2, 144.3, 137.6, 133.7, 133.5, 132.3, 130.4, 128.5, 127.9, 127.4, 121.9, 119.3, 118.2, 115.7, 114.6, 69.2, 46.7; MS (ES mass): 343.0 (M+1).

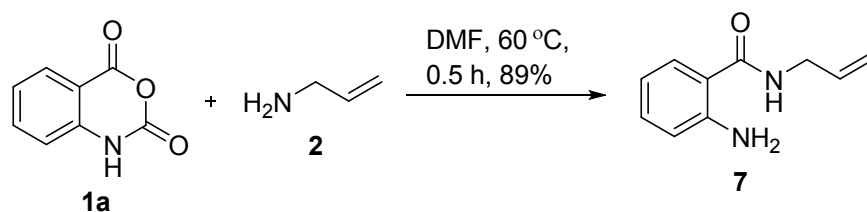
8-Methyl 7,8-dehydrorutaecarpine (6)



Compound **6** was synthesized by the reaction of **1a** with 3-bromo-1*H*-indole-2-carbaldehyde (**3k**) following a procedure similar to that of compound **4a**.

Yield: 40% (21 mg); light brown solid; mp: 285-287 °C; $R_f = 0.2$ (15% EtOAc/ *n*-hexane); ^1H NMR (400 MHz, CDCl_3) δ : 10.07 (bs, 1H), 8.56-8.48 (m, 2H), 8.17 (d, $J = 8.2$ Hz, 1H), 7.84-7.79 (m, 2H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.49-7.43 (m, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 2.85 (d, $J = 1.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.0, 141.2, 134.6, 134.5, 132.9, 129.0, 127.6, 126.9, 124.5, 122.3, 121.7, 121.2, 120.0, 119.9, 119.6, 115.9, 112.2, 105.3, 17.8; MS (ES mass): 300.0 (M+1); HPLC: 94.1%, column: Symmetry C-18 75 x 4.6 mm 3.5 μm , mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN , gradient (T/%B): 0/20, 1/20, 6/98, 10/98, 12/20, 15/20; flow rate: 1.0 mL/min; UV 250 nm, retention time 6.08 min.

Synthesis of *N*-allyl-2-aminobenzamide¹⁷ (**7**)



A solution of isatoic anhydride, **1a** (100 mg, 0.61 mmol) and allyl amine, **2** (34 mg, 0.61 mmol) in DMF (2 mL) was heated to 50-55 °C for 30 min. After completion of the reaction the mixture was cooled to room temperature, diluted with water (10 mL), and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine solution (15 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane to give the desired product **7**.

Yield: 89% (95 mg); white solid; mp: 84-86 °C (lit¹⁷ 83-84 °C); ^1H NMR (CDCl_3 , 400 MHz) δ : 7.35 (d, $J = 7.8$ Hz, 1H), 7.24 (td, $J = 8.0, 1.0$ Hz, 1H), 6.70-6.64 (m, 2H), 6.12 (bs, 1H), 5.99-5.90 (m, 1H), 5.40 (bs, 2H), 5.28 (dd, $J = 17.1, 1.3$ Hz, 1H), 5.20 (dd, $J = 10.2, 1.2$ Hz, 1H), 4.11-4.02 (m, 2H).

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SRB Assay

The principle: The anti-proliferative activity and cancer cell selectivity of the synthesized compounds on cancer cells was evaluated using the SRB (Sulforhodamine B) cell proliferation assay. This assay was chosen because of its sensitivity, large dynamic range and the ability to measure cell proliferation over three days with normalization to initial cell number as well as to vehicle-treated cells. Further, this assay is the standardized assay of choice for screening of anticancer compounds at the National Cancer Institute (NIH). The SRB assay provides a colorimetric readout which can be spectrophotometrically measured and does not involve antibodies or toxic reagents. The assay is based on detection of total protein content of cells, which increases or decreases in proportion with cell number.

The methodology: Cancer cells (around 5000 in number) were seeded in 96-well plates and incubated overnight. The optimum cell number to be seeded was determined by a growth curve analysis for the cell line. Compounds (dissolved in 100% DMSO to a stock concentration of

200mM) were added to the adhered cells at a final concentration of 10 μ M. After 72h of treatment, the cells were washed with phosphate-buffered saline and ice-cold 10% trichloroacetic acid was added to the cells to precipitate the proteins. It was incubated for 1h at 4 $^{\circ}$ C. The cells were then washed with water and air-dried. Cellular proteins were then stained using 0.4% SRB solution in 1% acetic acid for 30 min at room temperature. The unbound dye was washed away by destaining with 1% acetic acid and bound dye was solubilized with 10mM Tris solution (pH 10.5). Absorbance of solubilized dye was measured at a wavelength of 590 nm. Percentage growth was determined by the formula

$$[(At-A0/Ac-A0)] \times 100$$

where At=absorbance after 72h of test compound treatment,

A0=Absorbance at time 0,

Ac=Absorbance after 72h without treatment.

The known cytotoxic agent, gemcitabine was used as a positive control in the assay.