Electronic Supplementary Information

A Pd-catalyzed direct entry to 11-substituted 6*H*-isoindolo[2,1-*a*]indol-6-one derivatives as potential anticancer agents

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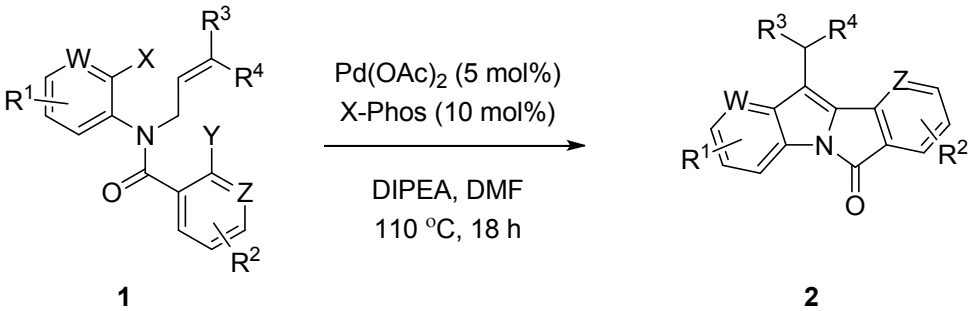
Experimental

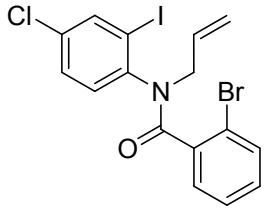
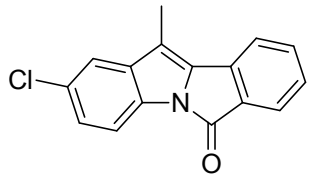
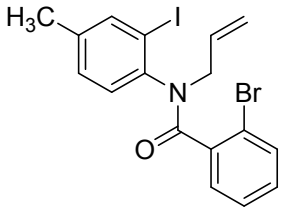
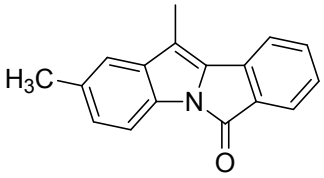
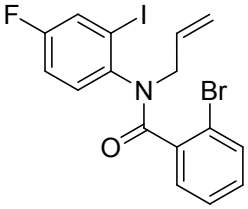
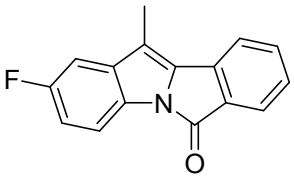
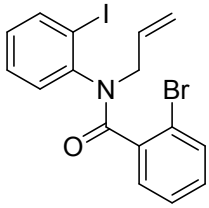
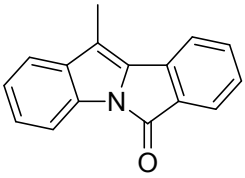
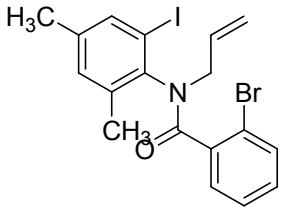
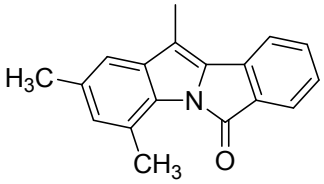
Chemistry

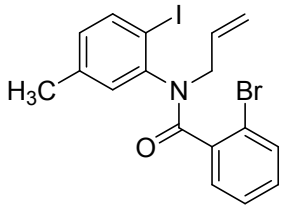
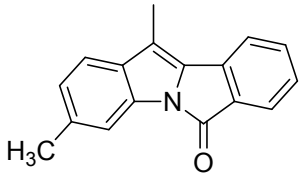
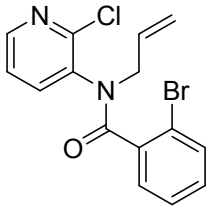
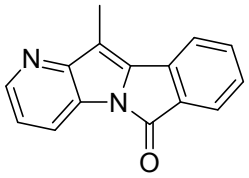
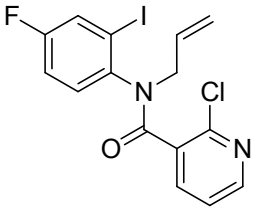
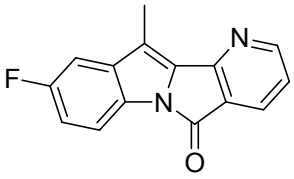
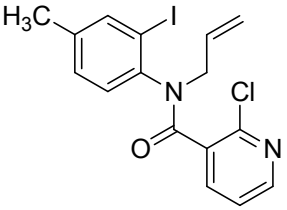
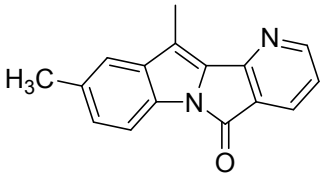
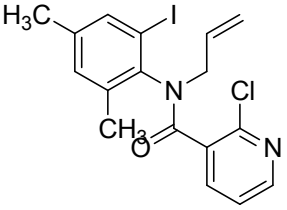
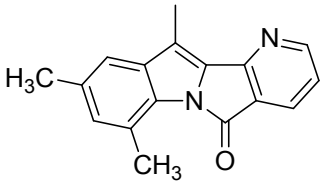
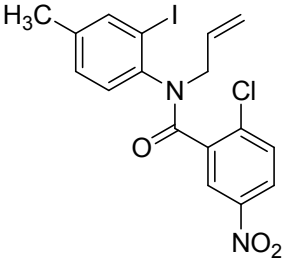
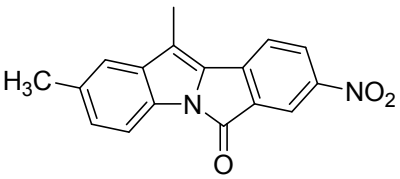
General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on 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.

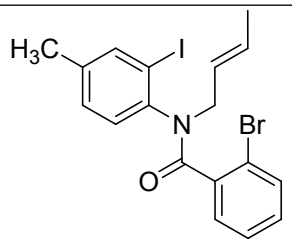
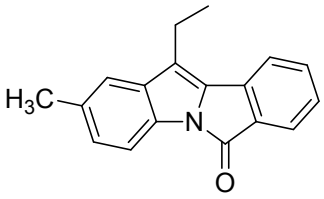
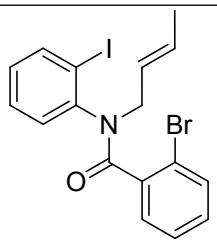
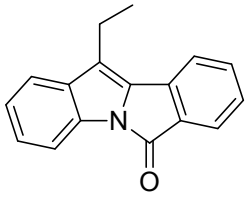
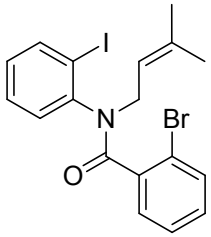
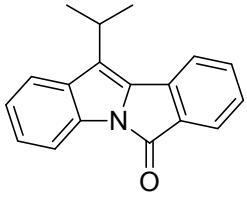
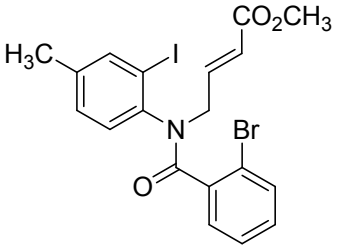
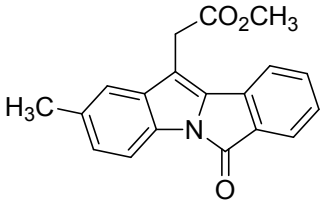
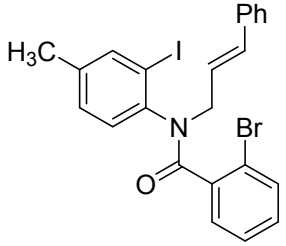
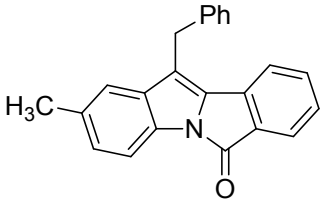
Table S-1: Pd catalyzed synthesis of 11-alkyl-6*H*-isoindolo[2,1-*a*]indol-6-one[a] (**2**)

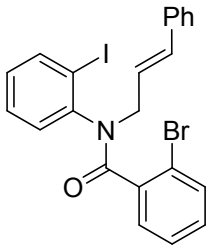
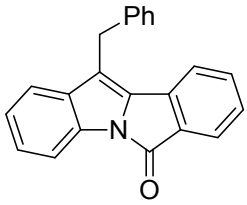
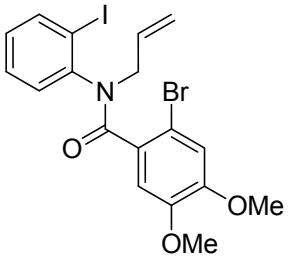
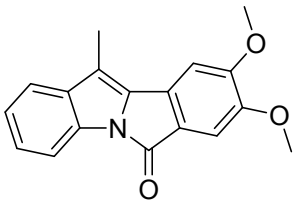


1 **2**

Entry	Allyl compound (**1**)	Product (**2**)	Yield (%)[b]
1	 **1a**	 **2a**	71
2	 **1b**	 **2b**	72
3	 **1c**	 **2c**	67
4	 **1d**	 **2d**	70
5	 **1e**	 **2e**	62

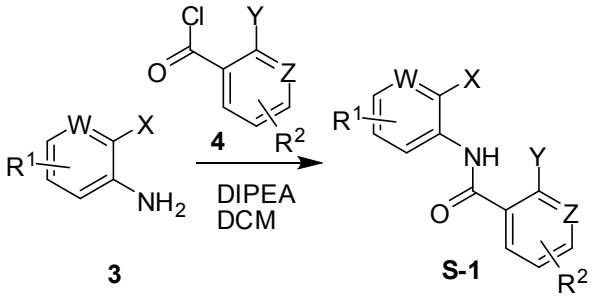
6	 **1f**	 **2f**	67
7	 **1g**	 **2g**	64
8	 **1h**	 **2h**	62
9	 **1i**	 **2i**	66
10	 **1j**	 **2j**	60
11	 **1k**	 **2k**	64

	1k		
12	 **1l**	 **2l**	66
13	 **1m**	 **2m**	64
14	 **1n**	 **2n**	61
15	 **1o**	 **2o**	62
16	 **1p**	 **2p**	60

17	 **1q**	 **2q**	59
18	 **1r**	 **2r**	64

[a]All the reactions were carried out using **1** (1 mmol), 5 mol% $Pd(OAc)_2$, 10 mol% X-Phos and DIPEA (3 mmol) in DMF (2 mL) at 110 ºC for 18 h. [b]Isolated yield.

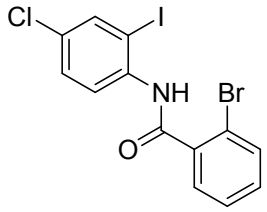
General procedure for the preparation of compound S-1



To a solution of compound 2-halo anilines[1] **3** (1.0 mmol) in DCM (20 mL), DIPEA (1.5 mmol) was added at 0 ºC under nitrogen atmosphere. To this was added slowly the corresponding acid chloride[1] (1.2 mmol) and the reaction mixture was stirred at room temperature for 6-9 h.. After completion of reaction (monitored by TLC), the mixture was diluted with DCM (25 mL), washed with saturated $NaHCO_3$ solution (2 x 30 mL), and water (30 mL) followed by brine solution (30 mL). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated

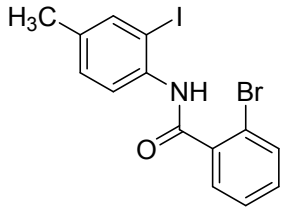
under reduced pressure. The residue was purified by column chromatography using ethyl acetate – hexane to give desired compound **S-1**.

2-Bromo-*N*-(4-chloro-2-iodophenyl)benzamide (S-1a)



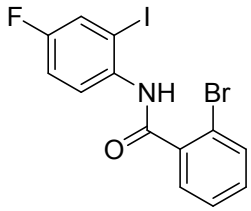
Yield: 75%; White solid; mp: 97-99 °C; R_f = 0.33 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (d, *J* = 8.7 Hz, 1H), 7.93 (s, 1H), 7.85-7.76 (m, 1H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.49-7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 138.0, 137.2, 136.8, 133.8, 132.0, 130.4, 129.5, 129.3, 127.8, 122.5, 119.3, 89.8; MS (ES mass): 437.9 (M+1).

2-Bromo-*N*-(2-iodo-4-methylphenyl)benzamide (S-1b)



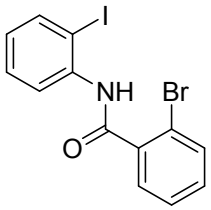
Yield: 83%; White solid; mp: 146-148 °C; R_f = 0.40 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 8.3 Hz, 1H), 7.84 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 3H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.39-7.31 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 139.2, 137.6, 136.6, 135.5, 133.7, 131.7, 129.9, 129.4, 127.7, 122.1, 119.4, 90.3, 20.4; MS (ES mass): 417.8 (M+1).

2-Bromo-*N*-(4-fluoro-2-iodophenyl)benzamide (S-1c)



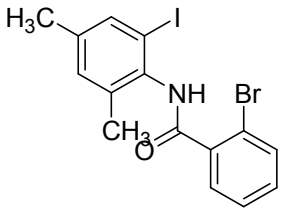
Yield: 72%; White solid; mp: 137-139 °C; R_f = 0.23 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.84 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.38 (td, *J* = 7.7, 1.4 Hz, 1H), 7.23-7.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 160.1 (C-F *J* = 248.1 Hz), 137.3, 134.5 (C-F *J* = 3.7 Hz), 133.7, 131.8, 129.4, 127.7 (C-F *J* = 24.8 Hz), 125.4, 123.4 (C-F *J* = 8.2 Hz), 119.3, 116.1 (C-F *J* = 21.6 Hz), 115.9, 89.9 (C-F *J* = 8.4 Hz); MS (ES mass): 421.7 (M+1).

2-Bromo-*N*-(2-iodophenyl)benzamide[2] (S-1d)



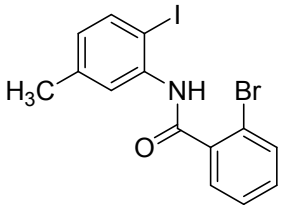
Yield: 81%; White solid; mp: 153-155 °C; R_f = 0.26 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.83 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.47-7.32 (m, 3H), 6.91 (td, *J* = 7.8, 1.4 Hz, 1H).

2-Bromo-*N*-(2-iodo-4,6-dimethylphenyl)benzamide (S-1e)



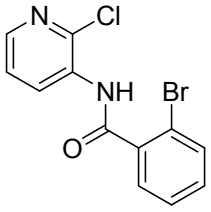
Yield: 78%; White solid; mp: 142-144 °C; R_f = 0.30 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81-7.75 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.56 (s, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 6.8 Hz, 2H), 7.07 (s, 1H), 2.43 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.6, 139.5, 137.6, 137.5, 137.1, 133.7, 133.5, 131.9, 131.5, 129.5, 127.5, 119.4, 99.2, 20.4, 20.0; MS (ES mass): 429.9 (M+1).

2-Bromo-*N*-(2-iodo-5-methylphenyl)benzamide (S-1f)



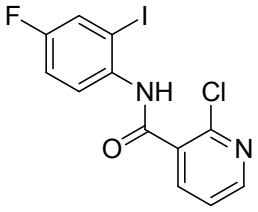
Yield: 74%; Off white solid; mp: 132-134 °C; R_f = 0.30 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.87 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 3H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.35 (td, *J* = 7.7, 1.4 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 139.6, 138.4, 137.6, 137.5, 133.6, 131.6, 129.2, 127.6, 127.5, 122.8, 119.4, 86.0, 21.2; MS (ES mass): 417.8 (M+1).

2-Bromo-*N*-(2-chloropyridin-3-yl)benzamide (S-1g)



Yield: 62%; White solid; mp: 109-111 °C; R_f = 0.40 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (d, *J* = 7.8 Hz, 1H), 8.31 (s, 1H), 8.18 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.70-7.67 (m, 2H), 7.50-7.42 (m, 1H), 7.42-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.7, 144.3, 140.2, 136.6, 133.8, 132.3, 131.7, 130.0, 129.2, 127.9, 123.3, 119.2; MS (ES mass): 312.8 (M+1).

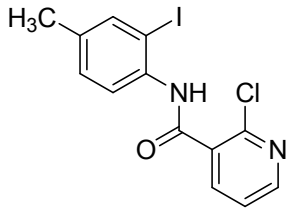
2-Chloro-*N*-(4-fluoro-2-iodophenyl)nicotinamide (S-1h)



Yield: 68%; White solid; mp: 195-197 °C; R_f = 0.23 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.38 (s, 1H), 8.29-8.21 (m, 2H), 7.57 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.43 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.16 (td, *J* = 8.8, 2.7 Hz, 1H); ^{13}C NMR (100

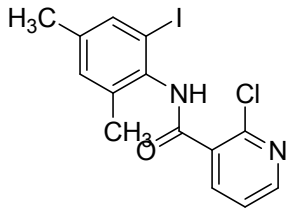
MHz, $CDCl_3$) δ: 162.7, 160.3 (C-F *J* = 249.0 Hz), 151.6, 147.0, 140.1, 134.4 (C-F *J* = 3.3 Hz), 130.8, 125.9 (C-F *J* = 24.8 Hz), 123.7 (C-F *J* = 7.7 Hz), 122.9, 116.2 (C-F *J* = 21.8 Hz), 90.0 (C-F *J* = 8.3 Hz); MS (ES mass): 376.8 (M+1).

2-Chloro-*N*-(2-iodo-4-methylphenyl)nicotinamide (S-1i)



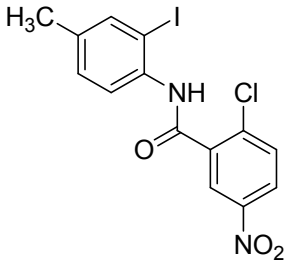
Yield: 67%; White solid; mp: 134-136 °C; R_f = 0.24 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 3.1 Hz, 1H), 8.34 (s, 1H), 8.24-8.13 (m, 2H), 7.66 (s, 1H), 7.41 (dd, *J* = 7.4, 4.8 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.7, 151.4, 147.1, 139.9, 139.3, 137.0, 135.3, 131.2, 129.9, 122.8, 122.4, 90.4, 20.4; MS (ES mass): 372.1 (M+1).

2-Chloro-*N*-(2-iodo-4,6-dimethylphenyl)nicotinamide (S-1j)



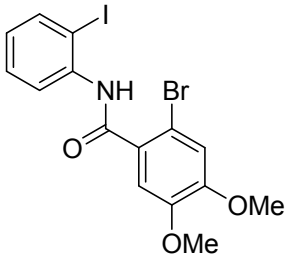
Yield: 66%; White solid; mp: 204-206 °C; R_f = 0.16 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.26 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 7.41 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.09 (s, 1H), 2.39 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9, 151.2, 147.3, 139.8, 139.7, 137.4, 137.3, 133.5, 131.9, 131.2, 122.7, 99.0, 20.4, 19.7; MS (ES mass): 386.8 (M+1).

2-Chloro-*N*-(2-iodo-4-methylphenyl)-5-nitrobenzamide (S-1k)



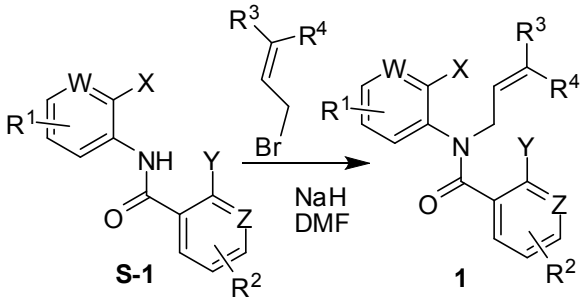
Yield: 59%; White solid; mp: 150-152 °C; R_f = 0.57 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (d, *J* = 2.5 Hz, 1H), 8.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.08 (s, 1H), 7.68-7.64 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.1, 146.6, 139.3, 137.6, 137.3, 136.2, 135.0, 131.7, 130.0, 126.1, 125.4, 122.5, 90.6, 20.4; MS (ES mass): 415.0 (M-1).

2-Bromo-*N*-(2-iodophenyl)-4,5-dimethoxybenzamide (S-1l)



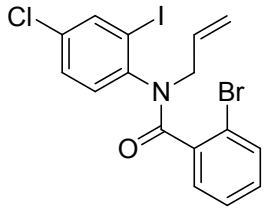
Yield: 65%; White solid; mp: 144-146 °C; R_f = 0.40 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (d, *J* = 7.5 Hz, 1H), 8.19 (s, 1H), 7.83 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28 (s, 1H), 7.08 (s, 1H), 6.90 (td, *J* = 7.8, 1.4 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 151.2, 148.5, 139.0, 138.2, 129.9, 128.9, 126.3, 122.1, 116.0, 112.7, 110.1, 89.9, 56.3, 56.2; MS (ES mass): 462.0 (M+1).

General procedure for preparation of *N*-allyl amide (1)



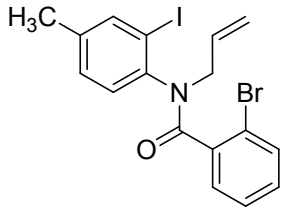
To a solution of compound **S-1** (1.0 mmol) in DMF (5 mL), was added NaH (2.0 mmol) at 0 ºC under nitrogen atmosphere. To this mixture was added the appropriate allyl bromide (1.4 mmol) slowly at 0 ºC and the reaction mixture was stirred at room temperature for 6 h. After completion of reaction, the mixture was quenched and diluted with cold water (25 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was collected, washed with brine solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate – hexane to give the desired compound **1**.

***N*-Allyl-2-bromo-*N*-(4-chloro-2-iodophenyl)benzamide (1a)**



Yield: 80%; Light yellow solid; mp: 95-97 °C; R_f = 0.27 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 2.3 Hz, 1H), 7.42 (dd, *J* = 7.8, 2.3 Hz, 1H), 7.36 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.14-7.03 (m, 3H), 6.08-5.94 (m, 1H), 5.24-5.12 (m, 3H), 3.64 (dd, *J* = 14.5, 8.2 Hz, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 141.9, 139.1, 137.6, 134.4, 132.7, 131.5, 131.3, 130.3, 129.0, 127.0, 126.6, 119.7, 119.6, 100.1, 51.2; MS (ES mass): 478.0 (M+1).

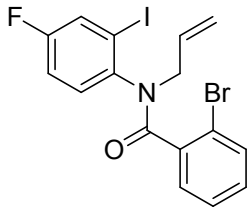
***N*-Allyl-2-bromo-*N*-(2-iodo-4-methylphenyl)benzamide (1b)**



Yield: 86%; White solid; mp: 84-86 °C; R_f = 0.30 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 1.0 Hz, 1H), 7.41-7.38 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.09-7.00 (m, 2H), 6.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.06-5.96 (m, 1H), 5.20-5.14 (m, 3H), 3.67 (dd, *J* = 14.7, 8.2 Hz, 1H), 2.18 (s, 3H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2,

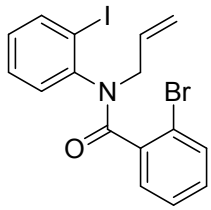
140.6, 140.2, 139.9, 138.0, 132.5, 131.9, 130.3, 130.0, 129.5, 126.8, 126.7, 119.9, 119.0, 99.4, 51.3, 20.4; MS (ES mass): 458.0 (M+1).

_N_-Allyl-2-bromo-_N_-(4-fluoro-2-iodophenyl)benzamide (1c)



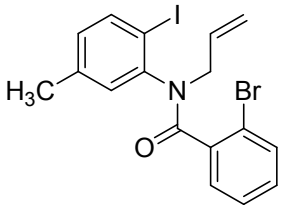
Yield: 85%; Yellow liquid; R_f = 0.42 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.44-7.37 (m, 2H), 7.33-7.29 (m, 1H), 7.11-7.02 (m, 2H), 6.88-6.81 (m, 1H), 6.08-5.96 (m, 1H), 5.22-5.14 (m, 3H), 3.65 (dd, *J* = 14.5, 8.2 Hz, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 162.1 (C-F *J* = 252.7 Hz), 139.6 (C-F *J* = 3.4 Hz), 137.7, 132.6, 131.6, 131.5 (C-F *J* = 8.7 Hz), 130.2, 126.9, 126.7 (C-F *J* = 24.6 Hz), 126.5, 119.7, 119.5, 115.8 (C-F *J* = 21.8 Hz), 99.8 (C-F *J* = 8.7 Hz), 51.2; MS (ES mass): 462.0 (M+1).

_N_-Allyl-2-bromo-_N_-(2-iodophenyl)benzamide (1d)



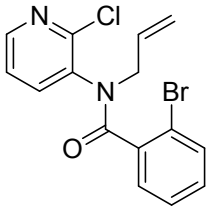
Yield: 81%; White solid; mp: 89-91 °C; R_f = 0.52 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 7.9 Hz, 1H), 7.41-7.37 (m, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.16-6.97 (m, 3H), 6.85 (t, *J* = 7.8 Hz, 1H), 6.10-5.97 (m, 1H), 5.26-5.13 (m, 3H), 3.70 (dd, *J* = 14.5, 8.2 Hz, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 143.2, 139.8, 137.9, 132.5, 131.8, 130.9, 130.5, 130.1, 129.6, 128.8, 126.7, 119.9, 119.2, 99.7, 51.2; MS (ES mass): 441.8 (M+1).

_N_-Allyl-2-bromo-_N_-(2-iodo-5-methylphenyl)benzamide (1f)



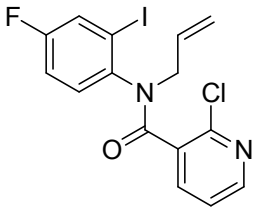
Yield: 78%; White solid; mp: 120-122 °C; R_f = 0.34 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.0 Hz, 1H), 7.41-7.36 (m, 2H), 7.16 (d, *J* = 1.1 Hz, 1H), 7.09-6.97 (m, 2H), 6.70-6.63 (m, 1H), 6.09-5.96 (m, 1H), 5.23-5.12 (m, 3H), 3.70 (dd, *J* = 14.8, 8.3 Hz, 1H), 2.13 (s, 3H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 142.9, 139.3, 139.1, 138.0, 132.4, 131.9, 131.6, 130.6, 130.0, 126.9, 126.7, 119.9, 119.0, 95.3, 51.2, 20.5; MS (ES mass): 456.0 (M+1).

_N_-Allyl-2-bromo-_N_-(2-chloropyridin-3-yl)benzamide (1g)



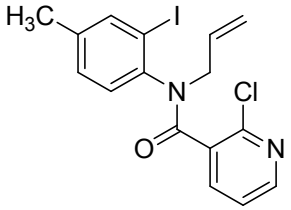
Yield: 72%; Off white solid; mp: 88-91 °C; R_f = 0.24 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.68 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.43-7.36 (m, 1H), 7.30-7.23 (m, 1H), 7.13-7.01 (m, 3H), 6.01-5.91 (m, 1H), 5.22-5.11 (m, 3H), 3.82 (dd, *J* = 14.8, 8.2 Hz, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 149.9, 149.0, 139.4, 137.4, 135.5, 132.6, 131.5, 130.6, 127.2, 126.7, 122.7, 119.7, 119.4, 50.3; MS (ES mass): 352.1 (M+1).

_N_-Allyl-2-chloro-_N_-(4-fluoro-2-iodophenyl)nicotinamide (1h)



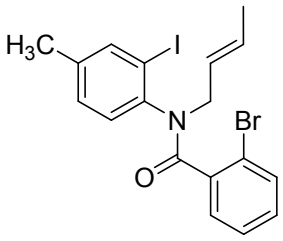
Yield: 72%; Light yellow solid; mp: 91-93 °C; R_f = 0.27 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.79 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.48 (dd, *J* = 7.5, 2.7 Hz, 1H), 7.34 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.08 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.90 (td, *J* = 8.7, 2.8 Hz, 1H), 6.06-5.93 (m, 1H), 5.27-5.13 (m, 3H), 3.66 (dd, *J* = 14.5, 8.2 Hz, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.6, 162.4 (C-F *J* = 253.6 Hz), 149.9, 147.1, 139.1 (C-F *J* = 3.6 Hz), 135.4, 132.3, 131.3 (C-F *J* = 8.7 Hz), 131.1, 126.9 (C-F *J* = 24.6 Hz), 121.8, 119.9, 116.3 (C-F *J* = 22.0 Hz), 99.9 (C-F *J* = 8.6 Hz), 51.4; MS (ES mass): 417.0 (M+1).

_N_-Allyl-2-chloro-_N_-(2-iodo-4-methylphenyl)nicotinamide (1i)



Yield: 69%; White solid; mp: 104-106 °C; R_f = 0.40 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.58 (d, *J* = 0.9 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.04-5.93 (m, 1H), 5.22-5.11 (m, 3H), 3.68 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.18 (s, 3H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.7, 149.6, 147.3, 140.5, 140.3, 140.0, 135.5, 132.6, 131.4, 130.0, 129.9, 121.7, 119.4, 99.4, 51.4, 20.4; MS (ES mass): 412.9 (M+1).

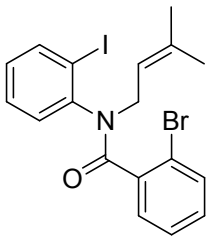
(*E*)-2-Bromo-*N*-(but-2-en-1-yl)-*N*-(2-iodo-4-methylphenyl)benzamide (1l)



Yield: 80%; White solid; mp: 74-76 °C; R_f = 0.44 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (s, 1H), 7.43-7.35 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.10-6.96 (m, 2H), 6.93-6.85 (m, 1H), 5.70-5.60 (m, 1H), 5.57-5.50 (m, 1H), 5.11-5.06 (m, 1H), 3.61 (dd, *J* = 14.2, 8.2 Hz,

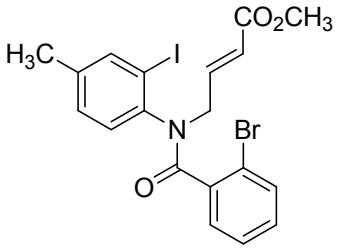
1H), 2.16 (d, *J* = 2.5 Hz, 3H), 1.64 (d, *J* = 6.2 Hz, 2H), 1.48-1.40 (m, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 140.6, 140.1, 139.7, 138.2, 132.5, 130.5, 130.3, 130.3, 129.9, 129.5, 129.4, 129.0, 126.7, 124.6, 123.8, 119.8, 99.6, 50.5, 44.4, 20.4, 17.7, 12.8 (extra carbons due to rotamers); MS (ES mass): 469.9 (M+1).

2-Bromo-*N*-(2-iodophenyl)-*N*-(3-methylbut-2-en-1-yl)benzamide (1n)



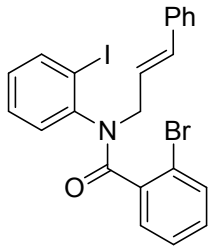
Yield: 80%; White solid; mp: 86-88 °C; R_f = 0.32 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.42-7.36 (m, 2H), 7.31-7.27 (m, 1H), 7.13-6.98 (m, 3H), 6.84 (td, *J* = 7.7, 1.5 Hz, 1H), 5.40-5.36 (m, 1H), 5.06 (dd, *J* = 14.5, 5.9 Hz, 1H), 3.88 (dd, *J* = 14.5, 8.7 Hz, 1H), 1.68 (s, 3H), 1.40 (s, 3H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 143.2, 139.6, 138.1, 137.6, 132.5, 131.0, 129.9, 129.4, 128.6, 126.8, 126.7, 119.9, 117.9, 99.8, 45.5, 25.6, 17.7; MS (ES mass): 472.0 (M+1).

(*E*)-Methyl 4-(2-bromo-*N*-(2-iodo-4-methylphenyl)benzamido)but-2-enoate (1o)



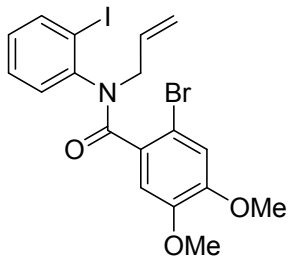
Yield: 82%; Light yellow semisolid; R_f = 0.34 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (s, 1H), 7.44-7.36 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.09-7.00 (m, 3H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.04 (d, *J* = 15.7 Hz, 1H), 5.28-5.23 (m, 1H), 3.87 (dd, *J* = 16.3, 7.5 Hz, 1H), 3.72 (s, 3H), 2.17 (s, 3H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 166.2, 141.5, 140.4, 140.3, 137.5, 132.6, 130.2, 129.9, 129.9, 128.4, 126.8, 126.8, 123.8, 119.8, 99.1, 51.6, 49.5, 20.4; MS (ES mass): 516.0 (M+1).

2-Bromo-*N*-cinnamyl-*N*-(2-iodophenyl)benzamide (1q)



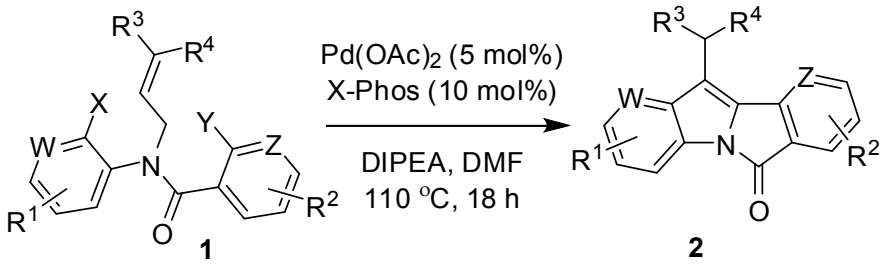
Yield: 69%; Light yellow liquid; R_f = 0.28 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 7.8 Hz, 1H), 7.45-7.38 (m, 2H), 7.35-7.28 (m, 6H), 7.25 (d, *J* = 7.3 Hz, 2H), 7.10-6.99 (m, 3H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.45 (s, 2H), 5.40-5.29 (m, 1H), 3.92-3.81 (m, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 143.2, 139.8, 137.8, 136.6, 134.3, 132.6, 130.9, 130.1, 129.7, 128.9, 128.5, 127.7, 126.8, 126.5, 123.0, 119.9, 99.9, 50.8; MS (ES mass): 518.0 (M+1).

***N*-Allyl-2-bromo-*N*-(2-iodophenyl)-4,5-dimethoxybenzamide (1r)**



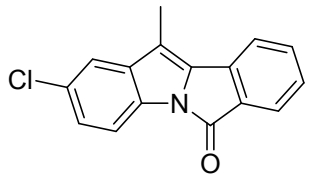
Yield: 75%; White solid; mp: 125-127 °C; R_f = 0.36 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 7.9 Hz, 1H), 7.27 (s, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.94-6.83 (m, 3H), 6.10-5.96 (m, 1H), 5.18-5.14 (m 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.69 (dd, *J* = 15.2, 8.3 Hz, 1H) (extra protons due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 149.4, 147.5, 143.5, 139.7, 131.8, 131.2, 129.8, 129.6, 129.0, 119.1, 115.0, 110.5, 109.8, 99.6, 56.1, 56.0, 51.3; MS (ES mass): 502.0 (M+1).

General procedure for the preparation of isoindolo[2,1-*a*]indol-6-one (2)



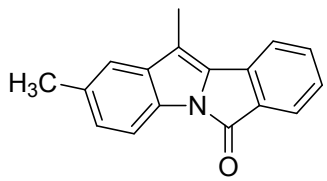
A mixture of allyl compound **1** (1.0 mmol), DIPEA (3.0 mmol), $Pd(OAc)_2$ (5 mol%) and X-Phos (10 mol%) in DMF (2 mL) was heated to 110 °C in a sealed tube for 18 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and washed with water (2 x 15 mL) followed by brine solution (15 mL). The organic layer was collected, 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 **2**.

2-Chloro-11-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2a)



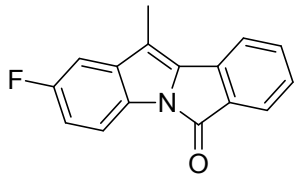
Yield: 71%;Yellow solid; mp: 166-168 °C; R_f = 0.45 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78-7.75 (m, 2H), 7.59-7.51 (m, 2H), 7.37-7.30 (m, 2H), 7.24-7.22 (dd, *J* = 7.8, 1.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.9, 137.0, 134.6, 133.6, 133.2, 131.7, 129.1, 128.7, 127.6, 126.3, 125.3, 124.5, 120.0, 118.3, 113.9, 9.5; MS (ES mass): 268.1 (M+1); HPLC: 96.4%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.76 min.

2,11-Dimethyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2b)



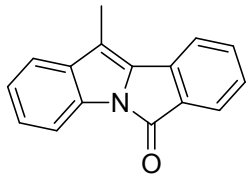
Yield: 72%; Yellow solid; mp: 148-150 °C; R_f = 0.52 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75-7.72 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.52-7.45 (m, 1H), 7.29 (td, *J* = 7.5, 1.1 Hz, 1H), 7.17 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.0, 135.9, 135.0, 134.7, 133.2, 133.1, 131.6, 127.8, 127.5, 125.1, 120.9, 120.3, 115.2, 112.8, 21.4, 9.4; MS (ES mass): 248.1 (M+1); HPLC: 99.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.54 min.

2-Fluoro-11-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2c)



Yield: 67%; Yellow solid; mp: 188-190 °C; R_f = 0.50 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78-7.69 (m, 2H), 7.53-7.46 (m, 2H), 7.30 (td, *J* = 7.3, 1.3 Hz, 1H), 7.04-6.92 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.8, 161.0 (C-F *J* = 239.2 Hz), 136.8 (C-F *J* = 9.2 Hz), 136.0, 134.6, 133.7, 133.4, 129.7, 128.3, 125.2, 121.1, 114.7 (C-F *J* = 4.0 Hz), 113.8 (C-F *J* = 33.7 Hz), 113.7, 106.5 (C-F *J* = 24.2 Hz), 9.3; MS (ES mass): 252.0 (M+1); HPLC: 99.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.25 min.

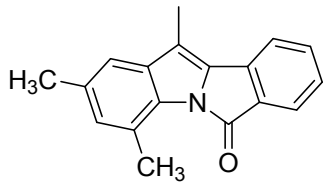
11-Methyl-6*H*-isoindolo[2,1-*a*]indol-6-one[3] (2d)



Yield: 70%;Yellow solid; mp: 166-168 °C (lit[3]: 173-175 °C); R_f = 0.47 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.53-7.46 (m, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.34-7.27 (m, 2H), 7.16 (t, *J* = 7.5 Hz,

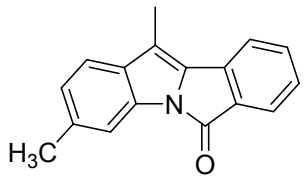
1H), 2.43 (s, 3H); MS (ES mass): 234.0 (M+1); HPLC: 99.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.32 min.

2,4,11-Trimethyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2e)



Yield: 62%; Yellow solid; mp: 116-118 °C; R_f = 0.55 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 7.5 Hz, 1H), 7.57-7.46 (m, 2H), 7.30-7.27 (dm, 1H), 6.96 (s, 1H), 6.87 (s, 1H), 2.84 (s, 3H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.8, 136.7, 134.6, 133.4, 133.2, 130.2, 129.5, 127.7, 127.4, 125.1, 124.4, 120.5, 117.3, 116.5, 115.2, 21.0, 20.9, 9.3; MS (ES mass): 262.1 (M+1); HPLC: 97.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.41 min.

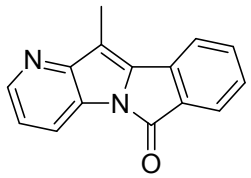
3,11-Dimethyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2f)



Yield: 67%; Yellow solid; mp: 118-120 °C; R_f = 0.48 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 7.5 Hz, 1H), 7.70 (s, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.49 (td, *J* = 7.5, 0.9 Hz, 1H), 7.30 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2, 137.0, 135.1, 133.8, 133.8, 133.4, 133.3, 131.3, 127.7, 125.2, 124.8, 120.9, 119.7, 115.5, 113.7, 21.7, 9.4; MS (ES mass): 248.2 (M+1); HPLC: 98.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase

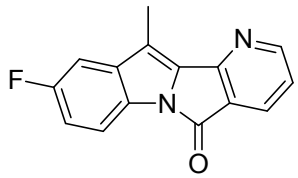
A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.52 min.

11-Methyl-6*H*-pyrido[2',3':4,5]pyrrolo[2,1-*a*]isoindol-6-one (2g)



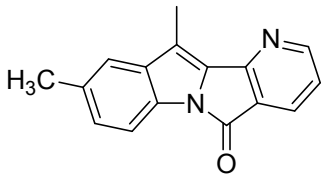
Yield: 64%; Yellow solid; mp: 144-146 °C; R_f = 0.30 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (d, *J* = 4.3 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.52-7.42 (m, 3H), 7.34-7.26 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4, 146.4, 145.5, 134.0, 133.2, 131.9, 129.0, 128.8, 127.7, 126.3, 125.4, 121.9, 120.4, 119.7, 8.6; MS (ES mass): 235.1 (M+1); HPLC: 98.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 2.76 min.

9-Fluoro-11-methyl-5*H*-pyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one (2h)



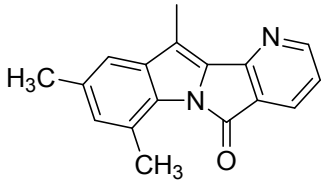
Yield: 62%; Yellow solid; mp: 210-212 °C; R_f = 0.42 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.99 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.82 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.21 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.07 (td, *J* = 8.5, 2.4 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.2 (C-F *J* = 239.9 Hz), 159.9, 155.7, 153.8, 136.8, 135.1 (C-F *J* = 4.5 Hz), 132.5, 128.6, 122.3, 118.1 (C-F *J* = 4.0 Hz), 115.0, 114.7 (C-F *J* = 9.2 Hz), 107.2 (C-F *J* = 24.4 Hz), 9.4; MS (ES mass): 253.1 (M+1); HPLC: 99.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 215 nm, retention time 3.93 min.

9,11-Dimethyl-5*H*-pyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one (2i)



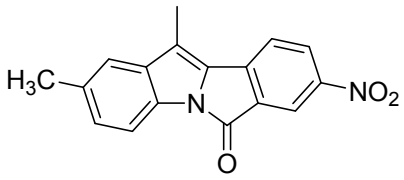
Yield: 66%; Yellow solid; mp: 136-138 °C; R_f = 0.36 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, *J* = 4.0 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.26-7.25 (m, 1H), 7.17 (t, *J* = 6.6 Hz, 2H), 2.55 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 153.5, 147.7, 137.6, 133.7, 132.3, 128.6, 122.6, 122.4, 121.9, 121.1, 119.8, 119.1, 113.3, 21.5, 9.6; MS (ES mass): 249.1 (M+1); HPLC: 95.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.86 min.

7,9,11-Trimethyl-5*H*-pyrido[2',3':3,4]pyrrolo[1,2-*a*]indol-5-one (2j)



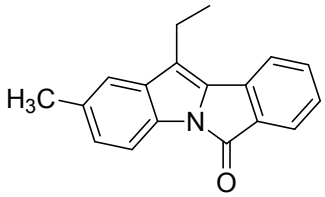
Yield: 60%; Yellow solid; mp: 123-125 °C; R_f = 0.53 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.95 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.17 (dd, *J* = 7.6, 5.0 Hz, 1H), 7.04 (s, 1H), 6.94 (s, 1H), 2.84 (s, 3H), 2.55 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 155.4, 150.4, 140.4, 136.6, 134.0, 132.3, 129.3, 128.4, 126.0, 121.9, 118.2, 116.5, 114.3, 21.1, 21.0, 9.7; MS (ES mass): 263.2 (M+1); HPLC: 93.0%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 200 nm, retention time 3.31 min.

2,11-Dimethyl-8-nitro-6*H*-isoindolo[2,1-*a*]indol-6-one (2k)



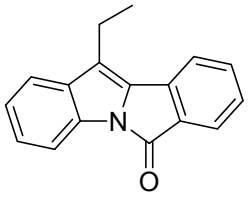
Yield: 64%; Yellow solid; mp: 217-219 °C; R_f = 0.50 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (d, *J* = 1.8 Hz, 1H), 8.38 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6, 147.2, 139.9, 135.5, 134.8, 134.2, 132.8, 132.1, 129.2, 128.7, 121.1, 121.0, 113.3, 109.9, 21.5, 9.8; MS (ES mass): 293.0 (M+1); HPLC: 99.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 225 nm, retention time 5.28 min.

11-Ethyl-2-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2l)



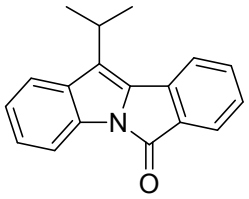
Yield: 66%; Yellow solid; mp: 124-126 °C; R_f = 0.50 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 8.0 Hz, 2H), 7.56-7.46 (m, 2H), 7.33-7.27 (m, 1H), 7.21 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 2.87 (q, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 1.35 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.1, 135.0, 134.9, 134.0, 133.3, 133.1, 131.8, 128.7, 127.9, 127.4, 125.1, 121.9, 121.0, 120.5, 113.0, 21.5, 18.0, 14.4; MS (ES mass): 262.2 (M+1); HPLC: 99.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.81 min.

11-Ethyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2m)



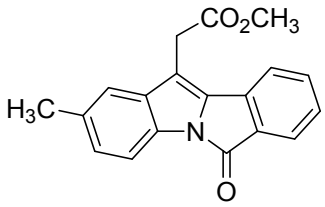
Yield: 64%; Yellow solid; mp: 111-113 °C; R_f = 0.50 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.0 Hz, 1H), 7.56-7.50 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.33-7.28 (m, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 2.90 (q, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 133.4, 133.1, 131.5, 128.7, 128.0, 127.6, 126.4, 125.3, 123.5, 121.2, 120.3, 119.6, 119.0, 113.4, 18.1, 14.4; MS (ES mass): 248.1 (M+1); HPLC: 96.5%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.47 min.

11-Isopropyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2n)



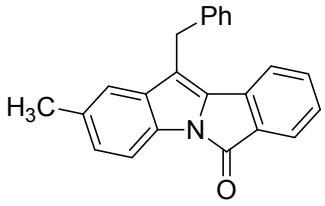
Yield: 61%; Off white solid; mp: 113-115 °C; R_f = 0.56 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83-8.15 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.49-7.45 (m, 2H), 7.44-7.38 (m, 1H), 7.36-7.31 (m, 1H), 6.88-6.47 (m, 1H), 3.13-3.03 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 137.2, 136.0, 133.2, 131.5, 130.8, 130.6, 128.7, 127.6, 125.1, 123.9, 121.0, 119.6, 119.4, 25.2, 22.4; MS (ES mass): 262.2 (M+1); HPLC: 99.8%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 245 nm, retention time 4.48 min.

Methyl 2-(2-methyl-6-oxo-6*H*-isoindolo[2,1-*a*]indol-11-yl)acetate (2o)



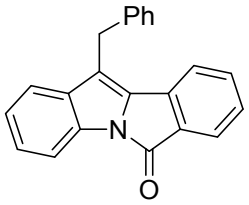
Yield: 62%; Yellow solid; mp: 176-178 °C; R_f = 0.47 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.25-7.24 (m, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 3.85 (s, 2H), 3.72 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 166.1, 136.9, 133.6, 131.6, 130.9, 128.5, 127.8, 126.8, 125.3, 125.1, 121.5, 120.3, 119.0, 115.4, 110.9, 52.1, 22.6, 21.5; MS (ES mass): 306.1 (M+1); HPLC: 98.7%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.87 min.

11-Benzyl-2-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2p)



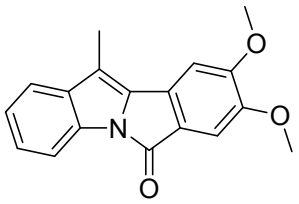
Yield: 60%; Yellow solid; mp: 139-141 °C; R_f = 0.42 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79-7.73 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.33-7.27 (m, 6H), 7.24 (d, *J* = 6.9 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 2H), 4.21 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2, 138.6, 135.4, 135.2, 134.7, 134.0, 133.4, 133.3, 131.7, 128.7, 128.3, 128.2, 127.6, 126.5, 125.2, 121.2, 120.7, 118.1, 112.9, 30.6, 21.5; MS (ES mass): 324.1 (M+1); HPLC: 98.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.81 min.

11-Benzyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2q)



Yield: 59%; Yellow solid; mp: 139-141 °C; R_f = 0.42 (10% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.34-7.27 (m, 8H), 7.25-7.20 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 4.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 138.6, 135.2, 134.9, 134.7, 133.9, 133.6, 133.5, 128.7, 128.4, 128.3, 126.6, 126.5, 125.3, 123.7, 121.3, 120.7, 118.2, 113.3, 30.7; MS (ES mass): 310.1 (M+1); HPLC: 98.2%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.52 min.

9,10-Dimethoxy-11-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (2r)



Yield: 64%; Yellow solid; mp: 199-201 °C; R_f = 0.48 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.25-7.24 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 153.7, 149.4, 135.7, 133.8, 129.3, 126.3, 126.2, 123.1, 119.9, 114.0, 112.7, 107.5, 103.7, 56.3, 56.2, 9.5; MS (ES mass): 294.1 (M+1); HPLC: 99.9%, column: Symmetry C-18 75 x 4.6 mm 3.5µm, mobile phase A: 0.1 % TFA in water, mobile phase B: CH_3CN, gradient (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min; UV 245 nm, retention time 3.93 min.

References:

1. R. Adepu, A. Rajitha, D. Ahuja, A. K. Sharma, B. Ramudu, R. Kapavarapu, K. V. L. Parsa, and M. Pal, *Org. Biomol. Chem*., 2014, **12**, 2514.

2. S. J. Balkrishna, and S. Kumar, *Synthesis*, 2012, **44**, 1417.
3. R. Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam, and T. Worakun, *Tetrahedron*, 1990, **46**, 4003.

Biology

Sulphorhodamine B (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 10μM. 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 ^{0}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)] X 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.