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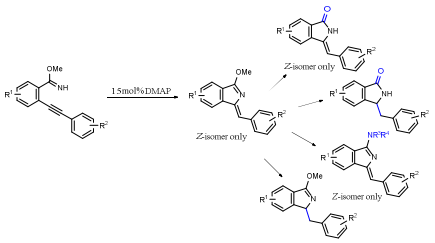

Highly Stereoselective Synthesis of (*Z*)-3-Methoxy-1-methyleneisoindoles via DMAP Catalyzed Cyclization of Methyl 2-Alkynylbenzimidates

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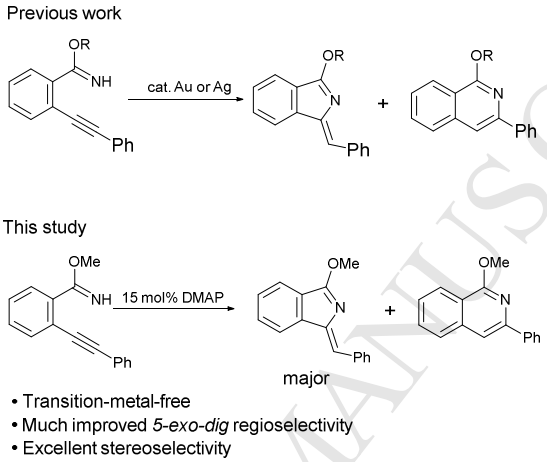
Abstract: A DMAP (4-dimethylaminopyridine) catalyzed cyclization of methyl 2-alkynylbenzimidates has been developed, which affords 3-methoxy-1-methyleneisoindoles with excellent *Z*-stereoselectivity under mild and transition-metal-free conditions. The (*Z*)-3-methoxy-1-methyleneisoindole products can be converted to corresponding 3-amino-1-methyleneisoindoles, 3-methoxy-isoindoles, 3-methyleneisoindolinones and isoindolinones with high efficiency.

Key words: cyclization; metal-free; 2-alkynylbenzimidates; 3-methoxy-1-methyleneisoindoles

1. Introduction

Intramolecular cyclization of alkynes containing proximate nucleophilic centers represents one of the most efficient methods to synthesize heterocyclic molecules [1]. Intramolecular hydroamination of alkynes using nitrogen-containing internal nucleophiles such as imines [2] and amides [3], has been well explored. These cyclizations were achieved in the presence of excess base, or catalysts such as transition metal or base. However, imidates, which are more nucleophilic and chemoselective than amides, were underdeveloped. The cyclization of *in situ* generated imidates from 2-alkynylbenzonitriles has been investigated, in which excess methoxide or ethoxide was applied [4]. Recently, synthesis of 2-alkoxyisoquinolines [5] and 3-methoxy-1-methylene-1*H*-isoindoles [6] via transition-metal-catalyzed cyclization of 2-alkynylbenzimidates have been reported (Scheme 1). To date, no transition-metal-free cyclization of 2-alkynylbenzimidates using base as the catalyst which fulfils the requirements of green chemistry, has been reported.

Our research interest in intramolecular cyclization of alkynes [7] promoted us to investigate base mediated cyclization of methyl 2-alkynylbenzimidates, Herein, we report the successful DMAP catalyzed cyclization of methyl 2-alkynylbenzimidates which shows much improved regioselectivity comparing with corresponding silver catalyzed cyclization and preferentially forms (*Z*)-3-methoxy-1-methyleneisoindoles with excellent stereoselectivity.



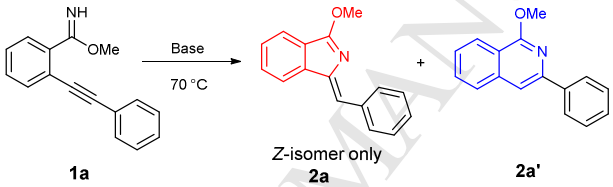
Scheme 1. Intramolecular cyclization of 2-alkynylbenzimidates

2. Results and discussion

We initiated our investigation by examing the reaction of methyl 2-(phenylethynyl)benzimidate (**1a)** in MeCN. In the presence of 3.0 equiv of K_2CO_3, a mixture of 1-benzylidene-3-methoxyisoindole (**2a**) and 1-methoxy-3-phenylisoquinoline (**2a'**) was obtained in a 55% total yield with a moderate 3.3:1 regioselectivity (*5-exo-dig* vs 6-*endo-dig*) (Table 1, entry 1). The reaction shows excellent stereoselectivity (*Z*-5-exo vs *E*-5-exo) and only the *Z*-isomer of **2a** was obtained. Encouraged by this promising result, we first investigated the effect of bases on the reaction. A little bit lower yield and similar regioselectivity were obtained when using Na_2CO_3 as the base (Table 1, entry 2). However, using Cs_2CO_3 as the base only provided 8% of the cyclized products (Table 1, entry 3). A weaker base such as NaOAc led to better regioselectivity, albeit in a lower 45% yield (Table 1, entry 4). Interestingly, *t*-BuOK which was successfully applied in the cyclization of *o*-alkynylbenzamides, did not provide any cyclization product (Table 1, entry 5). When pyridine was employed, a lower yield was observed with a

similar regioselectivity (Table 1, entry 6). 4-Dimethylaminopyridine (DMAP) which is a stronger base than pyridine, afforded a better 61% yield with similar regioselectivity (Table 1, entry 7). Using *p*rotic solvents which can readily protonate alkenyl anion intermediates generated in the cyclization, dramatically improved the regioselectivity (Table 1. entries 9-12) and *i*PrOH outperformed in both yield and regioselectivity. The yield and selectivity can be further improved by employing catalytic 15 mol % of DMAP (Table 1, entry 13). In the absence of DMAP, a much lower 51% yield of **2a** was obtained and 15% of **1a** was recovered under otherwise same conditions (Table 1, entry 14). In addition, prolonging reaction time would not make the reaction complete. The optimized conditions were thus selected on the basis of these results.

Table 1. Optimization of reaction[a]



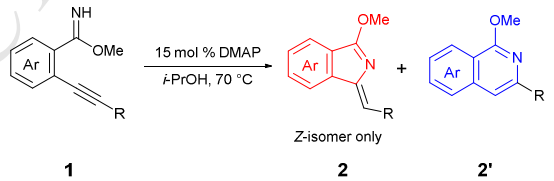
Entry	Solvent	Base	Yield (%)[b]	Ratio (**2a** : **2a'**)
1	MeCN	K_2CO_3 (3.0 eq.)	55	3.3 : 1
2	MeCN	Na_2CO_3 (3.0 eq.)	49	4.0 : 1
3	MeCN	Cs_2CO_3 (3.0 eq.)	8	4.3 : 1
4	MeCN	NaOAc (3.0 eq.)	45	4.8 : 1
5	MeCN	*t*-BuOK (3.0 eq.)	0	
6	MeCN	pyridine (1.0 eq.)	39	3.2 : 1
7	MeCN	DMAP (1.0 eq.)	61	4.0 : 1
9	MeOH	DMAP (1.0 eq.)	50	7.8 : 1
10	EtOH	DMAP (1.0 eq.)	61	8.4 : 1
11	*i*PrOH	DMAP (1.0 eq.)	72	8.0 : 1
12	*t*BuOH	DMAP (1.0 eq.)	71	7.5 : 1
13	*i*PrOH	DMAP (0.15 eq.)	75	10 : 1
14[c]	*i*PrOH	-	51	6 : 1

[a]Reaction conditions: **1a** (0.2 mmol), base, solvent (1.5 mL), 70 °C, 24 h, air. [b]Isolated yield. [c]15% of **1a** was recovered.

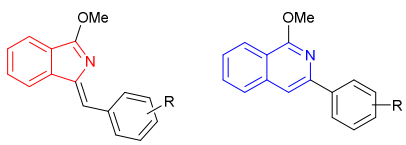
With the optimized conditions in hand (Table 1, entry 13), the scope of this cyclization was examined (Table 2). This DMAP-catalyzed cyclization was found to be completely

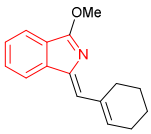
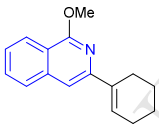
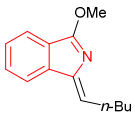
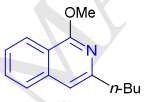
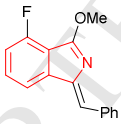
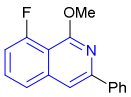
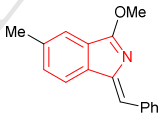
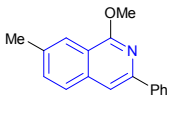
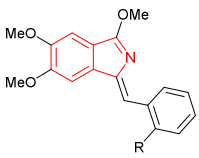
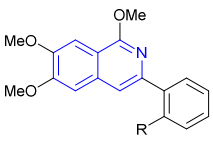
stereoselective and only *Z*-isomer of **2** was obtained in all cases. When phenyl on the remote end of the alkyne moiety was substituted with a strong electron-withdrawing-group on the *para* position, only the desired products **2b**-**e** were isolated (Table 2, entries 2-5). An electron-donating *para* methoxy substitution led to an incomplete reaction because the carbon–carbon triple bond is not sufficiently polarized and produced isomers **2g** and **2g'** in 36% and 16% yields, respectively (Table 2, entry 7). Phenyl and phenyl substituted with a halide or an alkyl group afforded the desired 1-methylene-3-methoxyisoindoles **2a, 2f, 2h** and **2i** in 60-68% yields and 0-8% yields of the isomeric 1-methoxyisoquinolines (Table 2, entries 1, 6, 8 and 9). All these results are consistent with an intramolecular anion cyclization mechanism [9]. Alkyl and alkenyl substituted alkynes afforded 1-methoxyisoquinolines **2j'** and **2k'** as the major products (Table 2, entries 10 and 11). The effect of substitution on the aromatic ring bearing imidate group has also been examined. Halide, alkyl, methoxy and CF_3 group are all well tolerated (Table 1, entries 12-18). The existing of a substitution on the 6-positon of methyl 2-alkynylbenzimidate enhanced the selectivity and afforded predominantly **2p** (Table 2. entry 16). Methyl 2-naphthimidate **1s** produced isomers **2s** and **2s'** in 57% and 15% yields, respectively, favoring the desired product **2s** (Table 2. entry 19). The structure of **2s** was confirmed by single-crystal X-ray diffraction [10]. It is worth noting that, although the isomeric 1-methoxy isoquinolines were isolated as undesired products in this chemistry, they are still medicinally important hetereocycles.

Table 2. DMAP-catalyzed cyclization of methyl 2-alkynylbenzimidates[a]

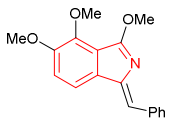
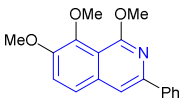
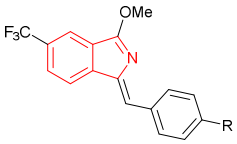
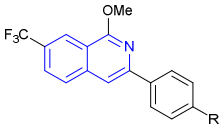
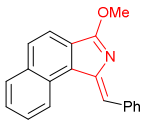
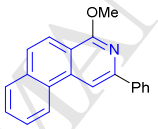
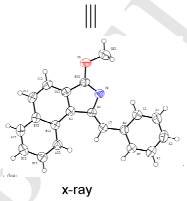


Entry	Product (s)	% Isolated Yield(s)



	R			
1	H	**2a**	**2a'**	68+7
2	*p*-CO_2Et	**2b**	**2b'**	74+0
3	*o*-CO_2Me	**2c**	**2c'**	66+0
4	*p*-CF_3	**2d**	**2d'**	62+0
5	*p*-CN	**2e**	**2e'**	48+0
6	*p*-F	**2f**	**2f'**	60+8
7[b]	*p*-OMe	**2g**	**2g'**	36+16
8[c]	*o*-Me	**2h**	**2h'**	63+5
9[d]	*o*-*i*-Pr	**2i**	**2i'**	63+0
10[e]		**2j**	 **2j'**	21+45
11		**2k**	 **2k'**	24+58
12		**2l**	 **2l'**	52+0
13		**2m**	 **2m'**	54+7
				

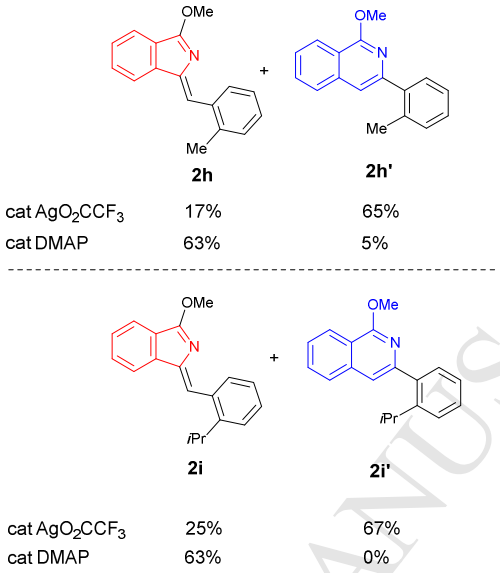
R

14	H	**2n**	**2n'**	47+12
15	CO_2Me	**2o**	**2o'**	61+0
16[f]				
		2p	**2p'**	50+0
				
	R			
17	H	**2q**	**2q'**	72+8
18	CO_2Et	**2r**	**2r'**	72+0
19				
		2s	**2s'**	57+15
	 x-ray			

[a]Reaction conditions: **1** (0.2 mmol), DMAP (0.15 eq.), *i*PrOH (1.5 mL), 70 °C, 24 h. [b]18% of SM recovered. [c]12% of SM recovered. [d]11% of SM recovered. [e]90 °C. [f]37% of SM recovered.

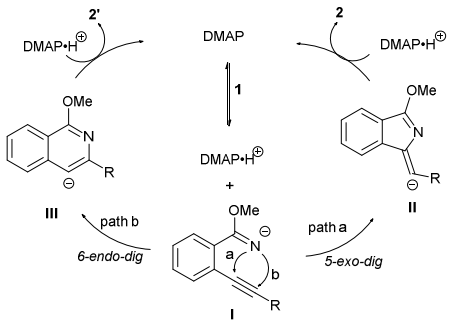
Comparing with silver catalyzed cyclization of methyl 2-alkynylbenzimidates, DMAP catalyzed cyclization showed much improved regioselectivity favoring *5-exo-dig* in all the cases. Although the same trend is followed by these two conditions in most cases, it should be noted that when phenyl on the remote end of the alkyne moiety has an *ortho* substitution, 6-*endo-dig* cyclization is disfavored in DAMP catalyzed cyclization because of the steric hindrance during cyclization, which led to formation of **2h** and **2i** as the major products (Table 2, entries 8 and 9). This is a

notable contrast to transition-metal-catalyzed cyclization of 2-alkynyl-benzimidates, in which 1-alkoxyisoquinoline **2h'** and **2i'** were the major products (Scheme 2) [7d].



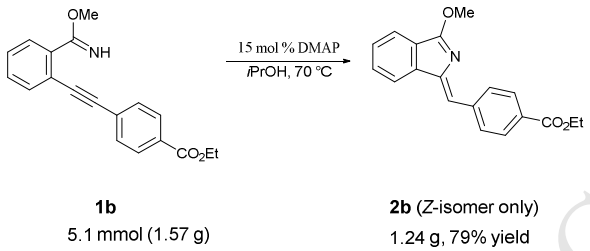
Scheme 2. Comparison of DMPA catalyzed cyclization with silver-catalyzed cyclization

The proposed mechanism for the DMAP catalyzed cyclization of methyl 2-alkynylbenzimidates is shown in Scheme 3. The benzimidate N-H was first deprotonated by DMAP to form imidate nitranion **I**. A *5-exo-dig* and *6-endo-dig* cyclization onto the triple bond could generate carboanion intermediate **II** and **III**, which could be protonated by $DMAP{\cdot}H^+$ to afford product **2** and **2'** and simultaneously regenerate the catalyst DMAP.



Scheme 3. Proposed mechanism

To demonstrated the synthetic utility of the present method, the DMAP catalyzed cyclization was amenable to scale-up to gram quantities, which proceeded with same efficiency as the milligram-scale reaction (Scheme 4).

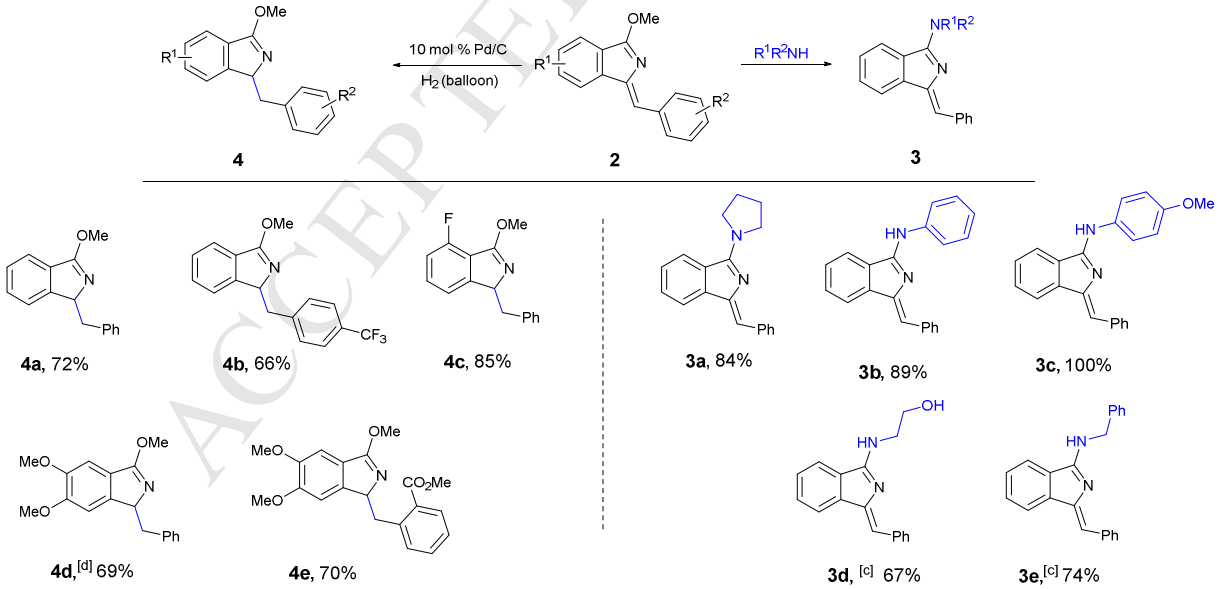


1b
5.1 mmol (1.57 g)

2b (Z-isomer only)
1.24 g, 79% yield

Scheme 4. Gram-scale synthesis of **2b**

The versatility of this cyclization chemistry was further demonstrated by elaboration of the 1-methylene-3-methoxyisoindole products **2**. 3-Amino-1-methyleneisoindoles **3** were prepared by reacting **2** with various amines such as primary amine, secondary amine and aniline (Scheme 5). 3-Methoxyisoindoles **4** were prepared by Pd/C-catalyzed hydrogenation. Demethylation of **2** afforded 3-methyleneisoindolin-1-ones **5**, which can be converted to 3-benzylisoindolin-1-ones **6** by Pd/C hydrogenation (Scheme 6).

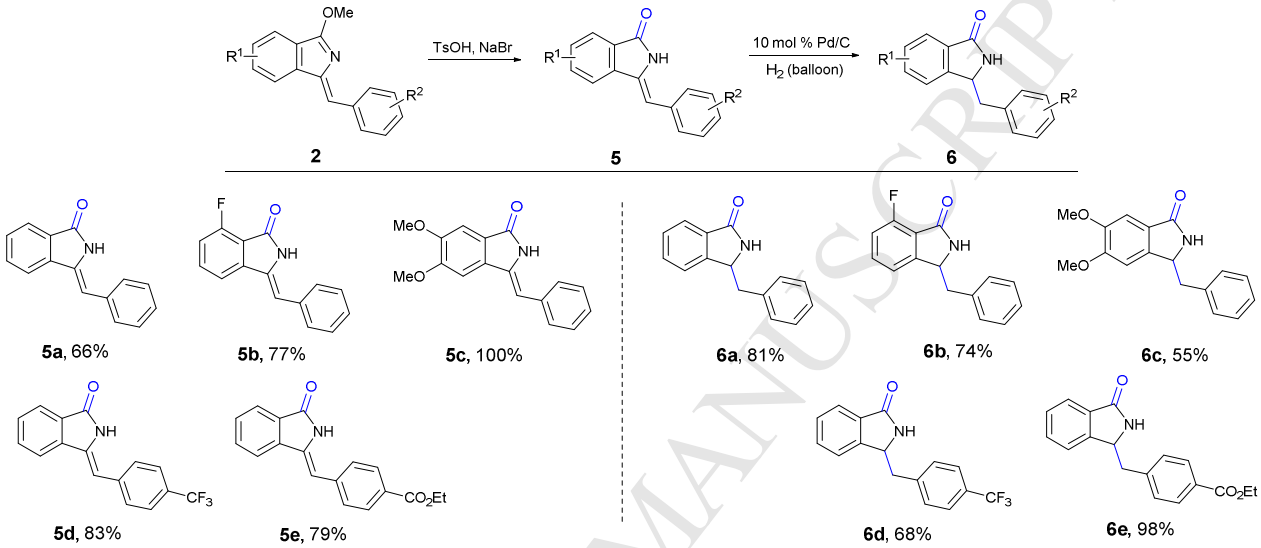


Scheme 5. Preparation of 3-amino-1-methyleneisoindoles (**3**)[a] and 1-benzyl-3-methoxyisoindoles (**4**)[b].

[a]Reaction conditions: **2a** (0.2 mmol) and amine (1.2 mmol) in MeOH (0.4 mL) at 50 °C for 24h.

[b]Reaction conditions: 2 (0.5 mmol), Pd/C (10 mol %) and H_2 (1 atm) in MeOH (15 mL) at RT for 12h.

[c]Amine (12 mmol) in *i*PrOH (1 mL) at 100 °C for 24h. [d]14% of SM was recovered.



Scheme 6. Preparation of 3-methyleneisoindolin-1-ones (**5**)[a] and 3-benzylisoindolin-1-ones (**6**)[b].
[a]Reaction conditions: **2** (0.5 mmol), TsOH (7.5 mmol) and NaBr (30 mmol) in MeOH (70 mL) at 50 °C for 2h.

[b]Reaction conditions: **5** (0.3 mmol), H_2 (1 atm) and Pd/C (10 mol %) in MeOH (10 mL) at RT for 7h.

3. Conclusions

In summary, we have developed an efficient, regio- and stereoselective synthesis of 1-methylene-3-methoxyisoindoles via DMAP-catalyzed cyclization of methyl 2-alkynyl-benzimidates. This method features mild reaction conditions, excellent *Z*-stereoselectivity, scalability and good functional group compatibility. Comparing with silver catalyzed cyclization of methyl 2-alkynylbenzimidates, DMAP catalyzed cyclization showed much improved regioselectivity favoring *5-exo-dig* in all the cases. The 3-methoxy-1-methyleneisoindole products can be efficiently converted to corresponding 3-

methyleneisoindolin-1-ones, isoindolin-1-ones, 3-methoxyisoindoles and 3-amino-1-methylene-isoindoles.

4. Experimental

4.1 *General information*

NMR spectra were recorded on a Bruker AM 400 or 600 MHz spectrometer and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ (^1H): δ = 7.26 ppm; $CDCl_3$ (^{13}C): δ = 77.16 ppm; DMSO-d6 (^1H): 2.50 ppm; DMSO-d_6 (^{13}C): 39.52 ppm). HPLC/MS analysis was carried out with gradient elution (5% CH_3CN to 100% CH_3CN) on an Agilent 1200 RRLC with a photodiode array UV detector and an Agilent 6224 TOF mass spectrometer (also used to produce high resolution mass spectra). Melting points were determined on a Stanford Research Systems OptiMelt apparatus. The infrared (IR) spectra were acquired as thin films using a universal ATR sampling accessory on a Bruker Vertex 80 FT-IR spectrometer and the absorption frequencies are reported in cm^{-1}. Flash chromatography separations were carried out using silica gel columns. The new compounds were characterized by ^1H NMR,^{13}C NMR, HRMS, and IR. The structure of known compounds were further confirmed by comparing their ^1H NMR and ^{13}C NMR data with those of literature. All reagents and solvents were used as received from commercial sources without further purification. 2-((4-(Trifluoromethyl)phenyl)ethynyl)benzamide [11], 2-(cyclohex-1-en-1-ylethynyl) benzamide [12], **1b** [7d], **1c** [7d], **1g** [7d], **1f**[7d], **1g**[7d], **1h**[7d], **1i**[7d], **1n**[7d], and **1p**[7d] were prepared according to literature procedure.

4.2. *Synthesis of 2-bromo-5-(trifluoromethyl)benzamide*.

A solution of 2-bromo-5-(trifluoromethyl)benzoic acid (2.67 g, 10.0 mmol, 1.0 equiv) in thionyl chloride (10 mL) was refluxed for 3h. After cooling down to room temperature, excess thionyl chloride was removed under reduced pressure. Aqueous ammonia (25 wt %, 10 mL) was added drop-wise and the reaction was stirred for 16h at room temperature. The precipitate was collected by filtration, washed with water and dried under air to afford desired product as a

white solid (2.63 g, 98%): m.p.: 163-164 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.06 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.78 (s, 1H), 7.75 – 7.66 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 167.8, 140.3, 134.0, 128.2 (q, *J* = 32.2 Hz), 127.2 (d, *J* = 3.3 Hz), 125.1 (q, *J* = 3.7 Hz), 123.7 (d, *J* = 272.7 Hz), 123.5 (d, *J* = 1.4 Hz). IR (neat) 3354, 1721, 1499, 1123 cm^{-1}. HRMS (ESI-TOF) m/z: [M+Na]$^{+}$ calcd for $C_8H_5BrF_3NNaO$ 289.9399; found 289.9394.

4.3. *General procedure for the synthesis of 2-alkynylbenzamides.*

To a solution of 2-halobenzamide (2.0 mmol, 1.0 equiv) in MeCN (13 mL) were added $PdCl_2(PPh_3)_2$ (0.05 equiv), terminal alkyne (1.2 equiv.), and Et_3N (3.0 equiv.). The resulting mixture was stirred at 80 °C under argon. The progress of the reaction was monitored by TLC analysis to establish completion. After cooling to room temperature, the reaction was diluted with ethyl acetate (30 mL), washed with water (30 mL) and brine (30 mL). The organic phase was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (Silica Gel, petroleum ether / ethyl acetate).

4.3.1. 2-((4-Cyanophenyl)ethynyl)benzamide [13]. This product was obtained as a yellow solid (0.399 g, 81%): m.p.: 172-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.96 (m, 1H), 7.67 – 7.57 (m, 5H), 7.52 – 7.47 (m, 2H), 6.91 (s, 1H), 6.25 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 135.9, 133.9, 132.4, 132.3, 131.2, 130.0, 129.8, 127.3, 119.5, 118.5, 112.6, 93.5, 91.8. IR (neat) 3297, 3183, 3051, 2223, 1647, 1499 cm^{-1}. HRMS (ESI-TOF) m/z: [M+H]$^{+}$ calcd for $C_{16}H_{11}N_2O$ 247.0866; found 247.0866.

4.3.2. 2-(Hex-1-yn-1-yl)benzamide. This product was obtained as a yellow solid (0.334 g, 83%) and the spectral data were consistent with literature [14]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 1H), 7.67 (s, 1H), 7.50 – 7.45 (m, 1H), 7.42 – 7.33 (m, 2H), 5.78 (s, 1H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.65 – 1.56 (m, 2H), 1.52 – 1.41 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

4.3.3. 2-Fluoro-6-(phenylethynyl)benzamide. This product was obtained as a pale yellow solid (0.391 g, 72%): m.p. 136-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.39 – 7.26 (m, 5H), 7.11 – 7.03 (m, 1H), 6.62 (s, 1H), 6.11 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 159.5 (d, *J* = 251.5 Hz), 132.0, 131.2 (d, *J* = 10.1 Hz), 129.1, 128.8 (d, *J* = 3.0 Hz), 128.6, 126.3 (d, *J* =

17.2 Hz), 123.3 (d, *J* = 5.1 Hz), 122.6, 116.3 (d, *J* = 22.2 Hz), 94.8, 86.0 (d, *J* = 4.0 Hz). IR (neat) 3841, 2210, 1650, 1493 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{10}FNNaO$ 262.0639; found 262.0639.

4.3.4. 5-Methyl-2-(phenylethynyl)benzamide. This product was obtained as a yellow solid (0.419 g, 89%) and the spectral data were consistent with literature [11]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.54 – 7.44 (m, 4H), 7.37 (d, *J* = 2.4 Hz, 2H), 7.36 (s, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 5.88 (s, 1H), 2.40 (s, 3H).

4.3.5. Methyl 2-((2-carbamoyl-4,5-dimethoxyphenyl)ethynyl)benzoate. This product was obtained as a pale yellow solid (0.658 g, 97%): m.p.: 148-151 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.68 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 6.96 (s, 1H), 6.47 (s, 1H), 3.851 (s, 3H), 3.845 (s, 3H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.2, 166.1, 150.7, 149.5, 134.5, 132.1, 130.6, 130.3, 128.4, 127.5, 123.3, 115.6, 113.1, 113.0, 93.4, 92.9, 56.1, 56.0, 52.4; IR (neat) 3825, 2925, 2847, 2374, 1723, 1657, 1591, 1514 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{18}NO_5$ 340.1179; found 340.1180.

4.3.5. 2-(Phenylethynyl)-5-(trifluoromethyl)benzamide. This product was obtained as a white solid (0.463 g, 80%): m.p.: 136-138 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.75 – 7.66 (m, 2H), 7.57 – 7.50 (m, 2H), 7.46 (s, 1H), 7.43 – 7.31 (m, 3H), 6.85 (s, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 135.5, 134.2, 131.9, 130.9 (q, *J* = 33.0 Hz), 130.0, 128.9, 127.7 (q, *J* = 3.6 Hz), 127.6, 124.0, 123.6(q, *J* = 272.9 Hz), 121.5, 98.5, 86.6 (one carbon missing due to overlap); IR (neat) 3378, 2220, 1650, 1615, 1496, 1120 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{11}F_3NO$ 290.0787; found 290.0790.

4.3.6. Ethyl 4-((2-carbamoyl-4-(trifluoromethyl)phenyl)ethynyl)-benzoate. This product was obtained as a white solid (0.412 g, 57%): m.p.: 155-156 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.75 – 7.68 (m, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.24 (s, 1H), 6.84 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.3, 165.9, 136.1, 134.3, 131.8, 131.4, 131.3 (d, *J* = 33.2 Hz), 129.9, 127.7 (d, *J* = 3.3 Hz), 127.4 (q, *J* = 3.6

Hz), 126.0, 123.55 (d, *J* = 272.9 Hz), 123.53, 97.1, 88.9, 61.6, 14.5; IR (neat) 3368, 2985, 2216, 1722, 1646, 1612, 1445, 1123 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{15}F_3NO_3$ 362.0999; found 362.1000.

4.3.7. 1-(Phenylethynyl)-2-naphthamide. This product was obtained as a white solid (0.532 g, 98%): m.p. 170-171 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.89 (t, *J* = 7.9 Hz, 2H), 7.71 – 7.54 (m, 4H), 7.50 (s, 1H), 7.46 – 7.38 (m, 3H), 6.22 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.2, 134.4, 133.9, 133.3, 131.8, 129.6, 129.2, 128.9, 128.5, 128.2, 127.8, 127.5, 126.2, 122.4, 118.5, 102.0, 85.9; IR (neat) 3362, 3050, 2913, 1792cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{14}NO$ 272.1070; found 272.1069.

*4.4. General Procedure for the Synthesis of methyl 2-alkynylbenzimidates **1**.*

To a solution of 2-alkynylbenzamide (0.5 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at 0°C, was added trimethyloxonium tetrafluoroborate (1.5 equiv.). The reaction mixture was warmed up to room temperature and stirred overnight. The completed reaction was quenched with methanol (1.5 mL) and concentrated under reduced pressure. The residue was purification by column chromatography (deactivated Silica Gel, DCM/MeOH) to afford methyl 2-alkynylbenzimidates **1**.

4.4.1. Methyl 2-((4-(trifluoromethyl)phenyl)ethynyl)benzimidate (**1d**). This product was obtained as a yellow oil (0.107 g, 70%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.77 – 7.71 (m, 1H), 7.66 - 7.57 (m, 5H), 7.42 – 7.38 (m, 2H), 3.94 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.2, 134.9, 133.9, 132.1, 130.7 (d, *J* = 32.3 Hz), 130.2, 129.2, 128.3, 126.5, 125.6 (q, *J* = 3.8 Hz), 124.0 (d, *J* = 273.7 Hz), 120.6, 93.9, 89.6, 53.7; IR (neat) 3037, 2940, 2308 1440 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}F_3NO$ 304.0944; found 304.0945.

4.4.2. Methyl 2-((4-cyanophenyl)ethynyl)benzimidate (**1e**). This product was obtained as a yellow oil (0.096 g, 74%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.1 Hz, 1H), 7.68 – 7.56 (m, 5H), 7.51 – 7.37 (m, 2H), 4.04 (s, 3H). This compound is not stable enough to obtain $^{13}C\{^1H\}$ NMR; IR (neat) 2929, 2677, 2219 1535, 1385 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$ 261.1022; found 261.1023.

4.4.3. Methyl 2-(cyclohex-1-en-1-ylethynyl)benzimidate (**1j**). This product was obtained as a yellow oil (0.073 g, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.36 – 7.25 (m, 2H), 6.26 (t, *J* = 6.0 Hz, 1H), 3.89 (s, 3H), 2.32 – 2.17 (m, 2H), 2.17 – 2.06 (m, 2H), 1.70 – 1.53 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7, 136.8, 133.6, 133.3, 130.0, 128.1, 128.0 121.8, 120.5, 98.0, 84.9, 53.5, 29.0, 26.0, 22.4, 21.6; IR (neat) 2932, 2858, 2198, 1544, 1436 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}NO$ 240.1383; found 240.1382.

4.4.4. Methyl 2-(hex-1-yn-1-yl)benzimidate (**1k**). This product was obtained as a yellow oil (0.080 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.74 – 7.69 (m, 1H), 7.49 – 7.43 (m, 1H), 7.34 – 7.25 (m, 2H), 3.89 (s, 3H), 2.45 (t, *J* = 7.1 Hz, 2H), 1.66 – 1.55 (m, 2H), 1.51 – 1.40 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 134.1 133.5, 123.0, 128.0, 127.8, 122.1, 97.7, 78.8, 53.4, 30.8, 22.3, 19.6, 13.8; IR (neat) 3454, 3337, 2934, 2867, 2225, 1573, 1486 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{16}NO$ 216.1383; found 216.1384.

4.4.5. Methyl 2-fluoro-6-(phenylethynyl)benzimidate (**1l**). This product was obtained as a yellow oil (0.084 g, 67%): ^{1}H NMR (400 MHz, CDCl3) δ 7.75 (s, 1H), 7.52 – 7.46 (m, 2H), 7.38 – 7.30 (m, 5H), 7.10 – 7.04 (m, 1H),3.96 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.9, 159.0 (d, *J* = 251.5 Hz), 131.9, 130.8 (d, *J* = 9.1 Hz), 129.1, 128.6, 128.3 (d, *J* = 4.0 Hz), 125.9 (d, *J* = 17.2 Hz), 123.4 (d, *J* = 3 Hz), 122.6, 116.3 (d, *J* = 22.2 Hz), 94.5, 86.0 (d, *J* = 4.0 Hz), 53.9; IR (neat) 2947, 2849, 2214, 1607, 1566, 1493 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}FNO$ 254.0976; found 254.0976.

4.4.6. Methyl 5-methyl-2-(phenylethynyl)benzimidate (**1m**). This product was obtained as a yellow oil (0.085 g, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.57 (s, 1H), 7.56 – 7.52 (m, 2H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.23 – 7.17 (m, 1H), 3.93 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 138.9, 134.0, 133.7, 131.8, 130.9, 128.9, 128.8, 128.6, 122.9, 118.3, 95.0, 87.5, 53.6, 21.6; IR (neat) 3293, 3038, 2309, 1502, 1543 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}NO$ 250.1226; found 250.1228.

4.4.7. Methyl 2-((2-(imino(methoxy)methyl)-4,5-dimethoxyphen-yl)ethynyl) benzoate (**1o**). This product was obtained as a yellow oil (0.076 g, 45%) and 56% of SM was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.28 (s, 1H), 7.05 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.87 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3, 166.0, 150.3, 149.2, 134.2, 132.0, 131.2, 130.7, 128.4, 126.0, 123.3, 115.9, 114.5, 110.9, 93.7, 92.0, 56.13, 56.10, 54.2, 52.5; IR (neat) 3433, 3326, 2925, 2854, 2202, 1721, 1590, 1450 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{20}NO_5$ 354.1336; found 354.1340.

4.4.8. Methyl 2-(phenylethynyl)-5-(trifluoromethyl)benzimidate (**1q**). This product was obtained as a yellow oil (0.071 g, 47%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.58-7.55 (m, 2H), 7.39-7.34 (m, 3H), 3.97 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.7, 134.4, 134.2, 132.1, 130.4 (q, *J* = 33.1 Hz), 129.7, 128.8, 126.7 (q, *J* = 3.5 Hz), 125.5 (q, *J* = 3.3 Hz), 125.1, 123.7 (q, *J* = 272.6 Hz), 122.0, 98.4, 86.2, 54.0; IR (neat) 3480, 2949, 2215, 1645, 1610, 1496, 1129 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}F_3NO$ 304.0944; found 304.0947.

4.4.9. Ethyl 4-((2-(imino(methoxy)methyl)-4-(trifluoromethyl)phen-yl)ethynyl)benzoate (**1r**). This product was obtained as a yellow oil (0.079 g, 42%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 – 8.01 (m, 3H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.65 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.0, 165.7, 134.8, 134.4, 131.9, 131.2, 130.9 (q, *J* = 33.7 Hz), 129.8, 126.8(q, *J* = 3.6 Hz), 126.4, 125.6 (q, *J* = 3.8 Hz), 124.5, 124.1 (q, *J* = 272.6 Hz), 97.1, 88.6, 61.5, 54.1, 14.5; IR (neat) 3668, 3337, 2941, 2214, 1720, 1645, 1606, 1442, 1127 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO_3$ 376.1155; found 376.1156.

4.4.10. Methyl 1-(phenylethynyl)-2-naphthimidate (**1s**). This product was obtained as a light green oil (0.096 g, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.3 Hz, 1H), 7.88 – 7.76 (m, 3H), 7.71 – 7.53 (m, 4H), 7.44 – 7.36 (m, 3H), 4.05 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.1, 133.8, 133.5, 132.9, 131.9, 129.3, 128.8, 128.7, 128.3, 127.9, 127.7, 127.3, 124.7, 122.8, 119.5,

101.6, 85.3, 54.3; IR (neat) 3058, 2929, 2582, 2204, 1642, 1437 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{16}NO$ 286.1226; found 286.1227.

4.5. General Procedure for the Cyclization of Methyl 2-alkynylbenzimidates.

A solution of compound **1** (0.2 mmol, 1.0 equiv) and 4-dimethylaminopyridine (15 mol %) in isopropanol (1.5 mL) was heated at 70 °C for 24h. After cooling to room temperature, the reaction mixture was diluted with brine (20 mL), and extracted with EtOAc (20 mL x 2). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Silica Gel, petroleum ether/EtOAc).

4.5.1. (*Z*)-1-Benzylidene-3-methoxy-1*H*-isoindole (**2a**). This product was obtained as a white solid (0.032 g, 68%): m.p. 93-94 °C; (lit. [7d] 94-96 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.19 (m, 2H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.47 – 7.38 (m, 3H), 7.35 (td, *J* = 7.4, 0.8 Hz, 1H), 7.32 – 7.26 (m, 1H), 6.90 (s, 1H), 4.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.4, 145.5, 143.2, 136.3, 131.4, 130.2, 129.5, 128.7, 128.3, 127.7, 120.4, 120.0, 119.7, 56.4.

4.5.2. 1-Methoxy-3-phenylisoquinoline (**2a'**). This product was obtained as a white solid (0.0033 g, 7%): m.p. 41-42 °C; (lit. [7d] 41-42 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.2 Hz, 1H), 8.17 (d, *J* = 7.4 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.68 (s, 1H), 7.66 – 7.60 (m, 1H), 7.53 – 7.44 (m, 3H), 7.38 (t, *J* = 7.3 Hz, 1H), 4.23 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.7, 148.1, 139.7, 139.0, 130.7, 128.8, 128.6, 126.9, 126.8, 126.6, 124.4, 119.2, 110.6, 53.8.

4.5.3. Ethyl (*Z*)-4-((3-methoxy-1*H*-isoindol-1-ylidene)methyl)benzo-ate (**2b**). This product was obtained as a white solid (0.0468 g, 74%): m.p. 92-93 °C; (lit. [7d] 94-96 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.44 (td, *J* = 7.5, 0.9 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.87 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.26 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}

NMR (101 MHz, $CDCl_3$) δ 174.1, 166.7, 147.4, 143.0, 140.8, 131.0, 130.5, 129.8, 129.4, 128.2, 120.6, 119.9, 118.5, 61.1, 56.6, 14.6 (one carbon missing due to overlap).

4.5.4. Methyl (*Z*)-2-((3-methoxy-1*H*-isoindol-1-ylidene)methyl)be-nzoate (**2c**). This product was obtained as a yellow solid (0.0384 g, 66%): m.p. 67-69 °C; (lit. [7d] 65-66 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 7.9 Hz, 1H), 7.94 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.60 – 7.52 (m, 2H), 7.45 (td, *J* = 7.5, 1.0 Hz, 1H), 7.38 – 7.30 (m, 2H), 4.22 (s, 3H), 3.90 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.0, 168.3, 146.6, 143.2, 136.8, 133.5, 131.8, 130.7, 130.4, 130.2, 129.7, 128.0, 127.5, 120.3, 120.2, 117.6, 56.4, 52.3.

4.5.5. (*Z*)-3-Methoxy-1-(4-(trifluoromethyl)benzylidene)-1*H*-isoindole (**2d**). This product was obtained as a white solid (0.037 g, 62%): m.p. 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 6.86 (s, 1H), 4.26 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.3, 147.5, 142.9, 139.8, 131.3, 130.5, 129.9, 129.4 (q, *J* = 32.4 Hz), 128.3, 125.5 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 272.7 Hz), 120.6, 120.0, 117.9, 56.6; IR (neat) 3046, 2918, 1577, 1445 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}F_3NO$ 304.0944; found 304.0944.

4.5.6. (*Z*)-4-((3-Methoxy-1*H*-isoindol-1-ylidene)methyl)benzo-nitrile (**2e**). This product was obtained as a white solid (0.025 g, 48%): m.p. 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 6.9 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 6.80 (s, 1H), 4.26 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.6, 148.4, 142.7, 140.9, 132.3, 131.4, 130.6, 130.0, 128.6, 120.8 120.0, 119.5, 117.3, 110.7, 56.7; IR (neat) 2941, 1643, 1596, 1534 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$ 261.1022; found 261.1024.

4.5.7. (*Z*)-1-(4-Fluorobenzylidene)-3-methoxy-1*H*-isoindole (**2f**). This product was obtained as a white solid (0.0294 g, 58%): m.p. 89-90 °C; (lit. [7d] 88-89 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.18 (m, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.44 (td, *J* = 7.5, 1.0 Hz, 1H), 7.35 (td, *J* = 7.4, 0.8 Hz, 1H), 7.11 – 7.05 (m,

2H), 6.85 (s, 1H), 4.25 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.5, 162.7 (d, *J* = 250.5 Hz), 145.0, 143.1, 133.1 (d, *J* = 8.0 Hz), 132.6 (d, *J* = 3.3 Hz), 130.2, 129.6, 127.8, 120.5, 119.6, 118.7, 115.7 (d, *J* = 21.6 Hz), 56.4.

4.5.8. 3-(4-Fluorophenyl)-1-methoxyisoquinoline (**2f'**). This product was obtained as a white solid (0.004 g, 8%): m.p. 79-81 °C; (lit. [7d] 81-83 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.3 Hz, 1H), 8.17 – 8.09 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.52 – 7.45 (m, 1H), 7.19 – 7.10 (m, 2H), 4.22 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ163.4 (d, *J* = 248.6 Hz), 160.7, 147.1, 139.0, 135.8, 130.8, 128.6, 128.5, 126.7 (d, *J* = 11.2 Hz), 124.4, 119.0, 115.7 (d, *J* = 21.5 Hz), 110.3, 53.8.

4.5.9. (Z)-3-methoxy-1-(4-methoxybenzylidene)-1*H*-isoindole (**2g**). This product was obtained as a yellow solid (0.0193 g, 36%) and 18% of SM was recovered. m.p. 142-143 °C (lit. [7d] 143-145 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.42 (td, *J* = 7.6, 0.9 Hz, 1H), 7.32 (t, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.87 (s, 1H), 4.25 (s, 3H), 3.84 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 172.7, 159.9, 143.6, 143.3, 132.9, 129.9, 129.3, 127.3, 120.3, 119.9, 119.5, 114.3, 56.3, 55.5 (one carbon missing due to overlap).

4.5.10. 1-Methoxy-3-(4-methoxyphenyl)isoquinoline (**2g'**). This product was obtained as a white solid (0.0083 g, 16%): m.p. 56-58 °C; (lit. [7d] 58-59 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 1H), 8.14 – 8.05 (m, 2H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.58 (s, 1H), 7.48 – 7.42 (m, 1H), 7.09 – 6.93 (m, 2H), 4.22 (s, 3H), 3.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 160.5, 160.2, 147.8, 139.2, 132.4, 130.7, 128.1, 126.6, 126.2, 124.3, 118.8, 114.2, 109.4, 55.6, 53.8.

4.5.11. (*Z*)-3-Methoxy-1-(2-methylbenzylidene)-1*H*-isoindole (**2h**). This product was obtained as a white solid (0.032 g, 64%) and 12% of SM was recovered. m.p. 73-74 °C (lit. [7d] 70-71 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.46 (td, *J* = 7.5, 1.0 Hz, 1H), 7.37 (td, *J* = 7.4, 0.7 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.23 – 7.19 (m, 2H), 7.16 (s, 1H), 4.26 (s, 3H), 2.52 (s, 3H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.5, 145.4, 143.2, 137.6, 134.5, 132.2, 130.4, 130.2, 129.4, 128.2, 127.7, 126.3, 120.3, 119.7, 117.0, 56.4, 20.5.

4.5.12. 1-Methoxy-3-(*o*-tolyl)isoquinoline (**2h'**). This product was obtained as colorless oil (0.0030 g, 6%). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.57 – 7.49 (m, 2H), 7.32 (s, 1H), 7.31 – 7.27 (m, 3H), 4.15 (s, 3H), 2.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 160.1, 151.0, 140.7, 138.7, 136.7, 131.1, 130.7, 130.1, 128.1, 126.63, 126.60, 126.0, 124.3, 118.6, 114.6, 54.0, 21.2.

4.5.13. (*Z*)-1-(2-Isopropylbenzylidene)-3-methoxy-1*H*-isoindole (**2i**). This product was obtained as a white solid (0.0349 g, 63%) and 11% of SM was recovered. The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 6.3, 2.9 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.36 – 7.26 (m, 4H), 4.24 (s, 3H), 3.47 (hept, *J* = 6.8 Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 173.5, 147.9, 145.6, 143.3, 133.3, 132.7, 130.3, 129.4, 128.5, 127.7, 125.9, 125.1, 120.3, 119.6, 117.0, 56.4, 29.7, 23.9.

4.5.14. (*Z*)-1-(Cyclohex-1-en-1-ylmethylene)-3-methoxy-1*H*-isoindole (**2j**). This product was obtained as a yellow oil (0.010 g, 21%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.54 (s, 1H), 6.30 (t, *J* = 4.4 Hz, 1H), 4.16 (s, 3H), 2.86 – 2.82 (m, 2H), 2.34 – 2.19 (m, 2H), 1.78 – 1.69 (m, 2H), 1.78 – 1.69 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.4, 143.4, 142.6, 137.1, 135.9, 129.8, 128.9, 127.1, 124.4, 120.0, 119.4, 56.0, 28.5, 27.1, 23.2, 22.3; IR (neat) 2937, 2862, 1583, 1442 cm^{-1} HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}NO$ 240.1383; found 240.1384.

4.5.15. 3-(Cyclohex-1-en-1-yl)-1-methoxyisoquinoline (**2j'**). This product was obtained as a yellow oil (0.021 g, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.18 – 7.11 (m, 2H), 4.14 (s, 3H), 2.59 – 2.48 (m, 2H), 2.34 – 2.30 (m, 2H), 1.89 – 1.77 (m, 2H), 1.76 – 1.65 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.7, 149.0, 139.0, 135.5, 130.5, 127.9, 126.7, 126.0, 124.3, 119.1, 108.6, 53.5, 26.2,

25.9, 23.1, 22.6; IR (neat) 2929, 2858, 1627, 1578, 1498, 1453, 832 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}NO$ 240.1383; found 240.1384.

4.5.16. (*Z*)-3-Methoxy-1-pentylidene-1*H*-isoindole (**2k**). This product was obtained as a yellow oil (0.0103 g, 24%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.18 (t, *J* = 7.6 Hz, 1H), 4.16 (s, 3H), 2.73 (q, *J* = 7.5 Hz, 2H), 1.55 – 1.50 (m, 2H), 1.47 – 1.37 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.5, 146.0, 141.8, 131.1, 129.3, 127.3, 125.3, 120.1, 119.4, 56.0, 31.9, 27.8, 22.7, 14.2; IR (neat) 2929, 2859, 1669, 1502, 1449 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{18}NO$ 216.1383; found 216.1385.

4.5.17. 3-Butyl-1-methoxyisoquinoline (**2k'**). This product was obtained as a yellow oil (0.025 g, 58%) The spectral data were consistent with literature [15]. ^1H NMR (400 MHz, CDCl3) δ 8.15 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 4.09 (s, 3H), 2.75 (t, *J* = 7.5 Hz, 2H), 1.81–1.69 (m, 2H), 1.45 – 1.33 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.4, 153.2, 138.8, 130.3, 125.8, 125.7, 124.2, 118.3, 111.9, 53.7, 37.8, 31.7, 22.7, 14.3; IR (neat) 2932, 2860, 1597, 1498 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{18}NO$ 216.1383; found 216.1386.

4.5.18. (*Z*)-1-Benzylidene-4-fluoro-3-methoxy-1*H*-isoindole (**2l**). This product was obtained as a white solid (0.026 g, 52%): m.p. 93-95 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.17 (m, 2H), 7.56 – 7.50 (m, 1H), 7.45 – 7.35 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 8.7 Hz, 1H), 6.91 (s, 1H), 4.28 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.9, 156.4 (d, *J* = 256.5 Hz), 146.7 (d, *J* = 3.0 Hz), 144.8, 135.9, 131.5, 131.4, 128.7, 128.7, 121.5, 117.2 (d, *J* = 15 Hz), 115.7 (d, *J* = 3.0 Hz), 114.6 (d, *J* = 20.2 Hz), 56.8; IR (neat) 3022, 2924, 2852, 1473, 1443 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}FNO$ 254.0976; found 254.0977.

4.5.19. (*Z*)-1-Benzylidene-3-methoxy-5-methyl-1*H*-isoindole (**2m**). This product was obtained as a white solid (0.028 g, 54%): m.p. 78-81 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.18 (m, 2H) 7.63 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.36 (s, 1H), 7.31 – 7.25 (m, 2H), 6.84 (s, 1H), 4.26 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.3, 145.4, 140.8, 137.9, 136.4, 131.2,

130.6, 130.5, 128.7, 128.1, 120.7, 119.5, 119.4, 56.3, 21.7; IR (neat) 3022, 2923, 2852, 1473, 1443 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}NO$ 250.1226; found 250.1227.

4.5.20. 1-Methoxy-7-methyl-3-phenylisoquinoline (**2m'**). This product was obtained as a white solid (0.004 g, 7%): m.p. 77-79 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.13 (m, 2H), 8.01 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.64 (s, 1H), 7.49 – 7.43 (m, 3H), 7.38 – 7.33 (m, 1H), 4.22 (s, 3H), 2.51 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.2, 147.1, 139.8, 137.1, 136.6, 132.8, 128.8, 128.4, 126.7, 123.4, 119.2, 110.5, 53.7, 22.0 (one carbon missing due to overlap); IR (neat) 3026, 2924, 2856, 1574, 1452 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}NO$ 250.1226; found 250.1228.

4.5.21. (*Z*)-1-Benzylidene-3,5,6-trimethoxy-1*H*-isoindole (**2n**). This product was obtained as a yellow solid (0.0277 g, 47%): m.p. 144-146 °C; (lit.[7d] 140-143 °C). The spectral data are consistent with literature [7d]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.22 (s, 1H), 7.01 (s, 1H), 6.76 (s, 1H), 4.24 (s, 3H), 3.99 (s, 3H), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.3, 151.4, 149.8, 145.6, 136.9, 136.4, 131.2, 128.7, 128.1, 123.1, 119.2, 102.5, 56.40, 56.38, 56.35(one carbon missing due to overlap).

4.5.22. 1,6,7-Trimethoxy-3-phenylisoquinoline (**2n'**). This product was obtained as a white solid (0.0069 g, 12%): m.p. 169-171 °C; (lit. [7d] 170-171 °C). The spectral data are consistent with literature [7d]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.3 Hz, 2H), 7.57 (s, 1H), 7.49 (s, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.06 (s, 1H), 4.21 (s, 3H), 4.01 (s, 3H), 4.00 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.6, 153.1, 149.7, 146.9, 139.9, 135.3, 128.8, 128.2, 126.6, 113.8, 109.9, 105.7, 103.1, 56.3, 56.2, 53.7.

4.5.23. Methyl (Z)-2-((3,5,6-trimethoxy-1*H*-isoindol-1-ylidene)meth-yl)benzoate (**2o**). This product was obtained as a yellow solid (0.042 g, 60%): m.p. 131-132 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.71 (s, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 6.99 (s, 1H), 4.18 (s, 3H), 3.99 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.9, 168.3, 151.4, 150.0, 146.7, 137.1, 136.8, 133.6, 131.8, 130.6, 129.8, 127.3, 123.3, 116.8, 102.9, 102.3, 56.5, 56.4, 52.3 (one carbon missing due to

overlap); IR (neat) 3001, 2947, 2838, 1716, 1597 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{20}NO_5$ 354.1336; found 354.1338.

4.5.24. (*Z*)-1-Benzylidene-3,4,5-trimethoxy-1*H*-isoindole (**2p**). This product was obtained as a yellow solid (0.030 g, 50%) and 37% of SM was recovered. m.p. 114-116 °C (lit. [7d] 116-118 °C). The spectral data are consistent with literature [7d]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.5 Hz, 2H), 7.45 – 7.34 (m, 3H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.75 (s, 1H), 4.27 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1, 152.8, 144.8, 144.0, 137.6, 136.5, 131.0, 128.6, 128.0, 123.2, 118.6, 115.3, 115.0, 62.4, 57.0, 56.8.

4.5.25. (*Z*)-1-Benzylidene-3-methoxy-5-(trifluoromethyl)-1*H*-isoindole (**2q**). This product was obtained as a white solid (0.044 g, 72%): m.p. 75-77 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.5 Hz, 2H), 7.84 - 7.80 (m, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 4.27 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 172.2, 146.1, 144.3, 135.7, 131.7, 130.3, 129.9 (q, *J* = 32.8 Hz), 129.0, 128.8, 126.4 (q, *J* = 3.3 Hz), 124.4 (q, *J* = 272.4 Hz), 122.4, 120.0, 117.8 (q, *J* = 3.9 Hz), 56.7; IR (neat) 3026, 2924, 1684, 1595, 1450, 1123 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}F_3NO$ 304.0944; found 304.0952.

4.5.26. 1-Methoxy-3-phenyl-7-(trifluoromethyl)isoquinoline (**2q'**). This product was obtained as a yellow oil (0.005 g, 8%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.19 – 8.13 (m, 2H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.79 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.70 (s, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 4.25 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 161.0, 150.5, 140.6, 139.0, 129.20 (q, *J* = 312.7 Hz), 129.21, 128.9, 128.1, 127.8, 127.0, 126.5 (q, *J* = 3.8 Hz), 122.6 (q, *J* = 4.2 Hz), 118.1, 110.0, 54.1; IR (neat) 2924, 2854, 1639, 1580, 1497, 1122 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{13}F_3NO$ 304.0944; found 304.0953.

4.5.27. Ethyl (*Z*)-4-((3-methoxy-5-(trifluoromethyl)-1*H*-isoindol-1-ylidene)methyl)benzoate (**2r**). This product was obtained as a white solid (0.054 g, 72%): m.p. 112-113 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.82 - 7.78 (m, 2H), 7.68 (d, *J* = 7.8 Hz, 1H), 6.92 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.26 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 172.7, 166.4, 145.9, 145.6, 139.8, 131.2, 130.4, 130.2 (d, *J* = 33.2 Hz), 130.0,

129.7, 126.5 (q, *J* = 3.3 Hz), 124.1 (q, *J* = 272.4 Hz), 120.6, 120.0, 117.7 (q, *J* = 3.8 Hz), 61.0, 56.6, 14.4; IR (neat) 2926, 2856, 1716, 1641, 1600, 1545, 1483, 1112 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO_3$ 376.1155; found 376.1155.

4.5.28. (*Z*)-1-Benzylidene-3-methoxy-1*H*-benzo[e]isoindole (**2s**). This product was obtained as a light green solid (0.033 g, 57%): m.p. 163-164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.33 (d, *J* = 7.5 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.59 (s, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 4.29 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.0, 147.7, 138.5, 136.9, 135.1, 132.3, 130.1, 129.4, 129.3, 128.7, 128.6, 127.8, 126.6, 126.4, 124.1, 117.9, 56.2 (one carbon missing due to overlap); IR (neat) 3053, 2925, 2856, 1584, 1448 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{16}NO$ 286.1226; found 286.1232.

4.5.29. 4-Methoxy-2-phenylbenzo[f]isoquinoline (**2s'**). This product was obtained as a white solid (0.0085 g, 15%): m.p. 133-135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.67 (m, 1H), 8.48 (s, 1H), 8.28 – 8.21 (m, 2H), 8.16 (d, *J* = 9.0 Hz, 1H), 7.95 – 7.88 (m, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.55 – 7.49 (m, 2H), 7.45 – 7.39 (m, 1H), 4.26 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.0, 149.8, 140.0, 137.7, 134.1, 129.1, 129.0, 128.9, 128.8, 128.4, 127.3, 127.1, 127.0, 123.7, 121.3, 116.2, 106.4, 54.0; IR (neat) 2924, 2852, 1482 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{16}NO$ 286.1226; found 286.1230.

*4.6. General Procedure for the Synthesis of 3-Amino-1-methyleneisoindoles (**3**).*

A solution of compound **2a** (0.2 mmol, 1.0 equiv) and amine (1.2 mmol, 6.0 equiv.) in MeOH (0.4 mL) was heated at 50 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with saturated $NaHCO_3$ (20 mL), and extracted with EtOAc (20 mL x 2). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (Silica Gel, petroleum ether/EtOAc) to afford compound **3a**.

4.6.1. (*Z*)-1-Benzylidene-3-(pyrrolidin-1-yl)-1*H*-isoindole (**3a**). This product was obtained as a yellow solid (0.046 g, 84%): m.p. 212-213 °C; (lit. [16] 210-212 °C). The spectral data were

consistent with literature [16]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.59 (s, 1H), 3.99 (br, 4H), 2.06 (br, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.9, 148.1, 145.0, 137.7, 132.0, 130.5, 128.7, 128.5, 127.1, 126.7, 122.4, 120.0, 112.6, 50.0, 48.4, 26.7, 24.5; IR (neat) 3041, 2917, 2862 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{19}N_2$ 275.1543; found 275.1543.

4.6.2. (*Z*)-1-Benzylidene-N-phenyl-1*H*-isoindol-3-amine **(3b**). This product was obtained as a yellow oil (0.053 g, 89%): ^{1}H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 8.28 (d, *J* = 7.6 Hz, 2H), 8.23– 8.14 (m, 3H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.58 – 7.40 (m, 6H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.99 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 161.0, 148.2, 141.5, 140.5, 136.9, 132.5, 130.2, 129.0, 128.8, 128.4, 127.3, 127.2, 122.6, 120.3, 119.8, 119.3, 115.3; IR (neat) 3281, 3053, 2953, 1597, 1493, 1447 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{17}N_2$ 297.1386; found 297.1386.

4.6.3. (*Z*)-1-Benzylidene-N-(4-methoxyphenyl)-1*H*-isoindol-3-amine (**3c**). This product was obtained as a yellow oil (0.0653 g, 100%): ^{1}H NMR (400 MHz, DMSO) δ 9.98 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 2H), 8.20 – 8.10 (m, 3H), 7.96 (d, *J* = 7.1 Hz, 1H), 7.57 – 7.38 (m, 4H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.93 (s, 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 160.7, 154.9, 141.5, 137.0, 133.6, 132.4, 130.1, 129.0, 128.4, 127.3, 127.0, 120.7, 120.3, 119.7, 114.3, 114.1, 55.2 (one carbon missing due to overlap); IR (neat) 3298, 3040, 2920, 1511 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}N_2O$ 327.1492; found 327.1492.

4.6.4. (*Z*)-2-((1-Benzylidene-1*H*-isoindol-3-yl)amino)ethan-1-ol (**3d**). 2-Aminoethan-1-ol (12 mmol) in isopropanol (1 mL) at 100 °C was applied. This product was obtained as a pale yellow solid (0.0354 g, 67%): m.p. 170-172 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.25 (s, 1H), 8.21 (d, *J* = 7.5 Hz, 2H), 7.93 – 7.84 (m, 2H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.70 (s, 1H), 5.12 (s, 1H), 3.78 – 3.73 (m, 2H), 3.73 – 3.66 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 164.9, 148.5, 142.9, 137.5, 131.7, 130.0, 128.9, 128.2, 127.2, 126.4, 120.1, 119.5, 111.7, 59.8, 45.1; IR (neat) 3660, 3298, 3046, 2919, 2855, 1518, 1571 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{17}N_2O$ 265.1335; found 265.1336.

4.6.5. (*Z*)-*N*-Benzyl-1-benzylidene-1*H*-isoindol-3-amine (**3e**). Phenylmethanamine (12 mmol) in isopropanol (1 mL) at 100 °C was applied. This product was obtained as a light green solid (0.046 g, 74%): m.p. 113-116 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.68 (t, *J* = 5.8 Hz, 1H), 8.23 (d, *J* = 7.5 Hz, 2H), 7.91 – 7.86 (m, 2H), 7.52 – 7.44 (m, 3H), 7.42 – 7.31 (m, 5H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.71 (s, 1H), 4.83 (d, *J* = 5.8 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 164.6, 148.7, 143.1, 139.6, 137.4, 131.7, 130.1, 128.8, 128.3, 128.1, 127.8, 127.1, 127.0, 126.4, 119.9, 119.5, 112.1, 45.7; IR (neat) 3268, 3058, 2924, 1670, 1453 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}N_2$ 311.1543; found 311.1541.

*4.7. General Procedure for the Synthesis of 3-Methoxyisoindoles (**4**).*

Compound **2** (0.5 mmol, 1.0 equiv) and Pd/C (5 wt %, 0.106 g, 0.05 mmol, 0.1 equiv.) were added to MeOH (15 mL). H_2 gas (1 atm) was introduced using a balloon and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Silica Gel, petroleum ether/EtOAc) to afford compound **4**.

4.7.1. Benzyl-3-methoxy-1*H*-isoindole (**4a**). This product was obtained as a yellow oil (0.086 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.0 Hz, 1H), 7.39 – 7.28 (m, 4H), 7.28 – 7.24 (m, 3H), 7.00 (d, *J* = 7.3 Hz, 1H), 4.97 (dd, *J* = 8.5, 5.8 Hz, 1H), 4.12 (s, 3H), 3.46 (dd, *J* = 13.4, 5.8 Hz, 1H), 2.80 (dd, *J* = 13.4, 8.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.6, 153.2, 138.4, 132.8, 129.8, 128.8, 128.2, 127.4, 126.5, 122.9, 120.7, 69.5, 55.4, 40.1; IR (neat) 2938, 2856, 1622, 1581, 1445 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}NO$ 238.1226; found 238.1226.

4.7.2. 3-Methoxy-1-(4-(trifluoromethyl)benzyl)-1*H*-isoindole (**4b**). This product was obtained as a yellow oil (0.101 g, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 3H), 7.35 – 7.25 (m, 4H), 7.20 – 7.03 (m, 1H), 4.91 (br, 1H), 4.05 (s, 3H), 3.29 (dd, *J* = 13.5, 6.1 Hz, 1H), 3.00 (dd, *J* = 13.5, 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.9, 152.8, 142.4, 132.9, 130.2, 129.2, 128.8 (d, *J* = 32.3 Hz), 127.8, 125.1 (q, *J* = 3.7 Hz), 124.5 (d, *J* = 273.0 Hz), 122.6, 120.9, 69.0, 55.5, 39.8; IR (neat) 2926, 2855, 1625, 1602, 1577 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{15}F_3NO$ 306.1100; found 306.1101.

4.7.3. 1-Benzyl-4-fluoro-3-methoxy-1*H*-isoindole (**4c**). This product was obtained as a yellow oil (0.109 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 6H), 7.00 (t, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 4.98 (dd, *J* = 7.8, 6.2 Hz, 1H), 4.13 (s, 3H), 3.41 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.86 (dd, *J* = 13.5, 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3 (d, *J* = 3.6 Hz), 156.9, 156.4 (d, *J* = 54.7 Hz), 137.85, 131.0 (d, *J* = 6.8 Hz), 129.79, 128.23, 126.63, 120.1 (d, *J* = 14.8 Hz), 118.9 (d, *J* = 3.7 Hz), 114.6 (d, *J* = 19.9 Hz), 69.8, 55.8, 39.9; IR (neat) 3028, 2946, 1611, 1453 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}FNO$ 256.1132; found 256.1133.

4.7.4. 1-Benzyl-3,5,6-trimethoxy-1H-isoindole (**4d**). This product was obtained as a red oil (0.103 g, 69%) and 14% of SM was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 3H), 7.28 – 7.25 (m, 2H), 6.98 (s, 1H), 6.26 (s, 1H), 4.83 (dd, *J* = 9.4, 5.6 Hz, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.70 (s, 3H), 3.53 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.59 (dd, *J* = 13.2, 9.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.6, 150.4, 149.2, 146.8, 138.7, 130.1, 128.3, 126.7, 125.0, 106.0, 102.7, 69.2, 56.2, 56.0, 55.5, 40.5; IR (neat) 2941, 2845, 1573, 1499 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{20}NO_3$ 298.1438; found 298.1438.

4.7.5. Methyl 2-((3,5,6-trimethoxy-1H-isoindol-1-yl)methyl)benzoa-te (**4e**). This product was obtained as a pink solid (0.124 g, 70%): m.p. 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.26 (m, 2H), 6.96 (s, 1H), 6.48 (s, 1H), 4.87 (br, 1H), 4.08 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.45 (br, 1H), 3.35 (dd, *J* = 12.9, 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 168.2, 150.6, 149.1, 147.0, 140.8, 133.1, 131.8, 130.9, 130.4, 126.7, 124.8, 105.8, 102.7, 68.9, 56.2, 56.1, 55.5, 52.1, 38.9; IR (neat) 2926, 2850, 1718, 1574, 1498 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{22}NO_5$ 356.1492; found 356.1494.

*4.8. General Procedure for the Synthesis of 3-Methylene-isoindolin-1-ones **5**.*

Compound **2** (0.5 mmol, 1.0 equiv), TsOH (7.5 mmol, 15 equiv) and NaBr (30 mmol, 60 equiv) were added to MeOH (7 mL). The suspension was heated at 50 °C for 2h. After cooling to room temperature, the reaction mixture was diluted with saturated $NaHCO_3$ (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were dried (anhydrous $MgSO_4$), filtered

and concentrated. The residue was purified by column chromatography (Silica Gel, petroleum ether/EtOAc) to afford compound **5**.

4.8.1. (Z)-3-Benzylideneisoindolin-1-one (**5a**). This product was obtained as a light green solid (0.073 g, 66%): m.p. 182-184 °C; (lit. [17] 182-183 °C). The spectral data were consistent with literature [17]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.37 (m, 5H), 7.29 (t, *J* = 7.1 Hz, 1H), 6.53 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 138.4, 135.1, 133.2, 132.4, 129.39, 129.36, 128.7, 127.9, 123.7, 120.0, 106.2 (one carbon missing due to overlap); IR (neat) 3860, 2922, 1704, 1455 cm^{-1}; HRMS(ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{12}NO$ 222.0913; found 222.0916.

4.8.2. (*Z*)-3-Benzylidene-7-fluoroisoindolin-1-one (**5b**). This product was obtained as a white solid (0.092 g, 77%): m.p. 245-246 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.77 – 7.68 (m, 1H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.26 (m, 2H), 6.84 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 166.3, 158.2 (d, *J* = 258.6 Hz), 141.9 (d, *J* = 2.9 Hz), 134.9 (d, *J* = 8.1 Hz), 134.5, 131.9, 129.3 (d, *J* = 34.1 Hz), 127.9, 117.0 (d, *J* = 3.5 Hz), 116.1 (d, *J* = 19.2 Hz), 115.2 (d, *J* = 14.2 Hz), 107.7, 79.3; IR (neat) 3213, 3050, 1702, 1488 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{11}FNO$ 240.0819; found 240.0819.

4.8.3. (*Z*)-3-Benzylidene-5,6-dimethoxyisoindolin-1-one (**5c**) [18]. This product was obtained as a pale pink solid (0.141 g, 100%): m.p. 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.44 – 7.35 (m, 4H), 7.31 – 7.24 (m, 2H), 7.16 (s, 1H), 6.39 (s, 1H), 4.00 (s, 3H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 153.5, 151.1, 135.3, 133.4, 132.3, 129.3, 128.5, 127.6, 121.7, 105.2, 104.8, 101.7, 56.5, 56.4; IR (neat) 3196, 3058, 2946, 1601, 1491 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}NO_3$ 282.1125; found 282.1124.

4.8.4. (*Z*)-3-(4-(Trifluoromethyl)benzylidene)isoindolin-1-one (**5d**). This product was obtained as a white solid (0.120 g, 83%): m.p. 250-252 °C; (lit. [17] 249-250 °C). The spectral data were consistent with literature [17]. ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.75 – 7.69 (m, 3H), 7.59 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 169.2, 138.8, 138.5, 134.6, 132.5, 129.7, 129.5, 128.4, 127.0 (d, *J* = 31.9 Hz),

125.4 (q, *J* = 3.6 Hz), 124.3 (d, *J* = 273.0 Hz), 122.8, 120.7, 104.0; IR (neat) 2957, 2922, 2850, 1704 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{11}FNO$ 290.0787; found 290.0785.

4.8.5. Ethyl (*Z*)-4-((3-oxoisoindolin-1-ylidene)methyl)benzoate (**5e**). This product was obtained as a white solid (0.116 g, 79%): m.p. 212-213 °C; ^1H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.80 – 7.68 (m, 4H), 7.58 (t, *J* = 7.4 Hz, 1H), 6.81 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 169.2, 165.5, 139.4, 138.6, 134.4, 132.5, 129.6, 129.4, 129.1, 128.3, 127.9, 122.8, 120.6, 104.5, 60.7, 14.2; IR (neat) 3049, 1838, 1596, 1515, 1465 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{16}NO_3$ 294.1125; found 294.1128.

*4.9. General Procedure for the Synthesis of 3-Benzylisoindolin-1-ones **6**.*

Compound **5** (0.3 mmol,1.0 equiv) and Pd/C (5 wt %, 0.064 g, 0.03 mmol, 0.1 equiv.) were added to MeOH (10 mL), H_2 gas (1 atm) was introduced using a balloon and the reaction mixture was stirred at room temperature for 7 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Silica Gel, petroleum ether/EtOAc) to afford compound **6**.

4.9.1. 3-Benzylisoindolin-1-one (**6a**). This product was obtained as a white solid (0.054 g, 81%): m.p. 135-137 °C; m.p. 131-133 °C; (lit. [19] 129.7-131.3 °C). The spectral data were consistent with literature [19]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.32 – 7.25 (m, 4H), 7.23 – 7.13 (m, 3H), 4.80 (dd, *J* = 8.0, 5.8 Hz, 1H), 3.16 (dd, *J* = 13.5, 4.4 Hz, 1H), 2.86 (dd, *J* = 13.4, 8.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.8, 147.0, 137.0, 132.1, 131.9, 129.5, 128.9, 128.5, 127.3, 124.0, 122.9, 58.2, 41.4; IR (neat) 3231, 3061, 2921, 1610, 1462 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{13}NNaO$ 246.0889; found 246.0888.

4.9.2. 3-Benzyl-7-fluoroisoindolin-1-one (**6b**). This product was obtained as a white solid (0.054 g, 74%): m.p. 156-157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 1H), 7.40 – 7.28 (m, 3H), 7.27 – 7.19 (m, 2H), 7.17 – 7.03 (m, 2H), 4.86 (br, 1H), 3.18 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.99 (dd, *J* = 13.5, 7.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.9, 159.3 (d, *J* = 261.2 Hz), 149.8 (d, *J* =

2.5 Hz), 136.5, 133.9 (d, *J* = 7.6 Hz), 129.5, 128.9, 127.4, 119.4 (d, *J* = 261.2 Hz), 119.0 (d, *J* = 3.9 Hz), 115.7 (d, *J* = 19.6 Hz), 58.1, 41.3; IR (neat) 3239, 3071, 2926, 1622, 1482 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{12}FNNaO$ 264.0795; found 264.0796.

4.9.3. 3-Benzyl-5,6-dimethoxyisoindolin-1-one (**6c**). This product was obtained as a white solid (0.047 g, 55%): m.p. 163-164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 4H), 7.28 – 7.21 (m, 2H), 7.03 (s, 1H), 6.59 (s, 1H), 4.74 (br, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.07 (br, 1H), 2.99 (br, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.0, 152.7, 150.0, 140.8, 137.2, 129.6, 128.9, 127.3, 124.2, 105.4, 105.2, 57.8, 56.4, 56.3, 41.7; IR (neat) 3300, 3040, 2926, 2843, 1682, 1610, 1500 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}NO_3$ 284.1281; found 284.1284.

4.9.4. 3-(4-(Trifluoromethyl)benzyl)isoindolin-1-one (**6d**). This product was obtained as a white solid (0.059 g, 68%): m.p. 166-168 °C; (lit. [20] 167-168 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.43 (m, 5H), 7.35 – 7.26 (m, 3H), 4.84 (dd, *J* = 7.3, 5.9 Hz, 1H), 3.25 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.97 (dd, *J* = 13.6, 7.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.9, 146.6, 140.9, 132.14, 132.10, 130.0, 129.6 (d, *J* = 32.7 Hz), 128.8, 125.8 (q, *J* = 3.7 Hz), 124.2, 122.84, 122.80 (d, *J* = 273.1 Hz), 57.8, 41.1; IR (neat) 3216, 3072, 2923, 2855, 1612, 1508 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}FNO$ 292.0944; found 292.0945.

4.9.5. Ethyl 4-((3-oxoisoindolin-1-yl)methyl)benzoate (**6e**). This product was obtained as a white solid (0.087 g, 98%): m.p. 156-159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.1 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 3H), 6.79 (s, 1H), 4.83 (br, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.25 (dd, *J* = 13.1, 3.7 Hz, 1H), 2.93 (dd, *J* = 13.0, 7.9 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.6, 166.5, 146.7, 142.1, 132.2, 132.0, 130.3, 129.7, 129.5, 128.8, 124.3, 122.9, 61.3, 57.9, 41.5, 14.5; IR (neat) 3223, 2931, 1610, 1466 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1281; found 296.1285.

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