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# The interaction of 4-hydroxymethyl isoindolines with dehydrobenzene. Synthesis of 3-phenylaminomethyldihydrobenzo[*c*]furanes

Alexey V. Varlamov [a], Natalia I. Guranova [a], Tatiana N. Borisova [a], Flavien A.A. Toze [b], Maxim V. Ovcharov [c], Sindi Kristancho [a], Leonid G. Voskressensky [a], *

[a] *Organic Chemistry Department of Peoples' Friendship University of Russia, 6, Miklukho-Maklaya St., Moscow 117198, Russia*
[b] *Department of Chemistry, University of Douala, Faculty of Sciences, PO Box 24157, Douala, Cameroon*
[c] *Bruker Ltd, 50/2-1 Pyatnitskaya St., Moscow 119017, Russia*

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ABSTRACT

2-Alkyl or 2-aryl-substituted 4-hydroxymethylisoindolines smoothly undergo intramolecular recyclization through reaction with arynes to give isobenzofurans with good yields.

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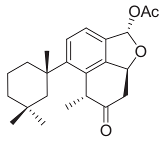
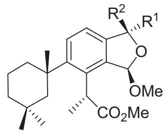
## 1. Introduction

Dehydrobenzenes or arynes, which were discovered in the middle of the twentieth century, nowadays represent a powerful tool for the creation of a wide range of heterocyclic compounds[1] that are hardly accessible via known methods. For arynes, the following types of reactions are known: pericyclic reactions, nucleophilic additions, insertion reactions, and transition-metal catalyzed reactions.[2] In this paper we describe the nucleophilic aryne-induced recyclization of 4-hydroxymethyl isoindolines leading to substituted isobenzofurans with preparative yields.

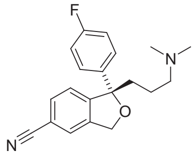
The 1,3-dihydroisobenzofuran motive is found in natural products such as Aplysulphurin isolated from marine sponge *Aplysilla sulphurea*,[3] Membranolide C, and Membranolide D—diterpenes, which were found in Antarctic sponge *Dendrilla membranosa*,[4] and show antibiotic activity against G-ve bacteria. The study of some microorganisms revealed phthalans as secondary metabolites.[5,6] In the last 20 years, isobenzofurans and derivatives thereof were studied for various types of biological activities including antimicrobial, antihistamine, antimycotic,[7] anti-HIV,[8] and anticancer[9] activities. Citalopram® and Talopram® are registered trademarks and are widely used in medicine as potent antidepressants.



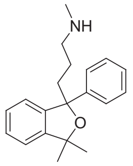
*Aplysulphurine*



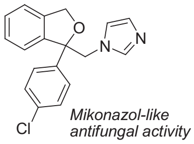
*Membranolide C:* R$^1$ = OMe, R$^2$ = H
*Membranolide D:* R$^1$ = H, R$^2$ = OMe



*Citalopram (Celexa)*



*Talopram*



*Mikonazol-like antifungal activity*

Despite the simple structure of phthalans, methods of synthesizing them are limited. Previously we presented a novel approach

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* Corresponding author. Tel./fax: +7495 9550779; e-mail address: lvoskressensky@sci.pfu.edu.ru (L.G. Voskressensky).

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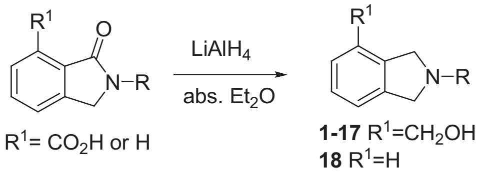
towards dihydroisobenzofurans through the action of activated alkynes such as DMAD, methyl propiolate, and acetyl acetylene on substituted isoindolines.[10] This route is a peculiar case of a general transformation of *N*-heterocycles under the action of electron-deficient alkynes.[11,12] Unfortunately, these reactions have some limitations and can be applied mostly for compounds with aliphatic substituents at nitrogen.

Arynes can also be considered as activated alkynes due to their high reactivity caused by the strain induced by the triple bond in the six-membered ring. In arynes the new π-bond is formed by side overlapping of sp$^2$-orbitals and is out of the aromatic ring plane. The HOMO of the side π-bond is considerably higher and the LUMO is significantly lower compared to frontier molecular orbitals of the π-bond in normal alkynes. The triple bond in arynes is significantly distorted and weak, especially in substituted arynes. These facts make dehydrobenzene and its derivatives highly reactive intermediates.

The present paper reports on unusual transformations of related dihydroisoindoles **1**–**18** under the action of dehydrobenzene.

## 2. Results and discussion

Isoindolines **1**–**18** required for the study were obtained by reduction of the corresponding isoindolone carboxylic acids,[13] or in the case of compound **18** *N*-(4-fluorophenyl) indolone with $LiAlH_4$ in dry $Et_2O$ (Scheme 1, Table 1).

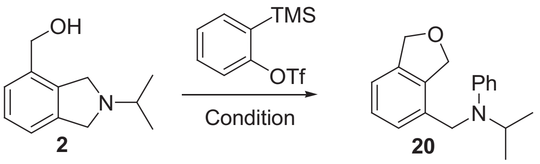


**Scheme 1.** Synthesis of starting material.

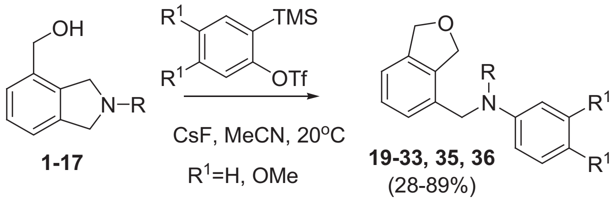
**Table 1**
Yields of 4-hydroxymethyl isoindolines **1**–**17** and **18**

| Product # | R | Yield % |
|---|---|---|
| 1 | Et | 61 |
| 2 | *i*-Pr | 64 |
| 3 | *n*-Pent | 67 |
| 4 | $(CH_2)_3OMe$ | 62 |
| 5 | *c*-$C_3H_5$ | 34 |
| 6 | *c*-$C_5H_9$ | 76 |
| 7 | Ph | 83 |
| 8 | 2-Me-$C_6H_4$ | 34 |
| 9 | 4-*i*-Pr-$C_6H_4$ | 61 |
| 10 | 4-OMe-$C_6H_4$ | 76 |
| 11 | 4-F-$C_6H_4$ | 70 |
| 12 | 3-$CF_3$-$C_6H_4$ | 87 |
| 13 | 2-Cl-$C_6H_4$ | 67 |
| 14 | Bn | 65 |
| 15 | 3,4-$(OMe)_2C_6H_3CH_2$ | 71 |
| 16 | 2,3-$(Cl)_2C_6H_3CH_2$ | 25 |
| 17 | $(CH_2)_2C_6H_4$ | 71 |
| 18 | 4-F-$C_6H_4$, $R^1$=H | 80 |

The model experiments with 4-hydroxymethyl isoindolines **2**–**4** and **11** showed that the reaction with dehydrobenzene proceeded smoothly at room temperature in dry acetonitrile in the presence of CsF as catalyst to give the corresponding phthalans **20**–**22** and **29** as the sole products in good yields (Scheme 3, Table 3). It is worth noting that N–Ar substituted isoindoline **11**, which was inert in reactions with activated alkynes, rapidly interacted with dehydrobenzene to form phthalan **29** with 67% yield.



**Scheme 2.** Optimization studies.



**Scheme 3.** Synthesis of phthalans.

**Table 2**
The yield of phthalan **20** under various reaction conditions

| Conditions | Reaction time | Yield % |
|---|---|---|
| CsF, MeCN, 5 °C | 5 days | 70 |
| CsF, MeCN, 20 °C | 1 h | 77 |
| CsF, MeCN, 65 °C | 30 min | 73 |
| CsF, MeCN, 65 °C, MW | 15 min | 75 |
| CsF, MeCN, 125 °C, MW | 5 min | 76 |
| KF, MeCN, 20 °C | 5 days | No reaction |
| TBAT, MeCN, 20 °C | 4 h | 70 |
| TBAF (1 M solution in THF), 20 °C | 5 days (not completed) | 52 |
| CsF, THF, 25–65 °C | 3 days at rt and 3 days at heat | 63 |

TBAT=tetrabutyl ammonium difluoro triphenyl silicate.

**Table 3**
Yields of phthalans **19**–**36**

| Product # | Starting material # | R | $R^1$ | Yield % |
|---|---|---|---|---|
| 19 | 1 | Et | H | 69 |
| 20 | 2 | *i*-Pr | H | 77 |
| 21 | 3 | *n*-Pent | H | 79 |
| 22 | 4 | $(CH_2)_3OMe$ | H | 62 |
| 23 | 5 | *c*-$C_3H_5$ | H | 85 |
| 24 | 6 | *c*-$C_5H_9$ | H | 69 |
| 25 | 7, 15[a] | Ph | H | 80, 28[a] |
| 26 | 8 | 2-Me-$C_6H_4$ | H | 78 |
| 27 | 9 | 4-*i*-Pr-$C_6H_4$ | H | 64 |
| 28 | 10 | 4-OMe-$C_6H_4$ | H | 72 |
| 29 | 11 | 4-F-$C_6H_4$ | H | 67 |
| 30 | 12 | 3-$CF_3$-$C_6H_4$ | H | 84 |
| 31 | 13 | 2-Cl-$C_6H_4$ | H | 73 |
| 32 | 14 | Bn | H | 64 |
| 33 | 14 | Bn | OMe | 89 |
| 34 | 15 | 3,4-$(OMe)_2C_6H_3CH_2$ | H | Not formed |
| 35 | 16 | 2,3-$(Cl)_2C_6H_3CH_2$ | H | 64 |
| 36 | 17 | $(CH_2)_2C_6H_4$ | H | 89 |

[a] Phthalan **25** was isolated from the reaction of compound **15** and benzyne with 28% yield.

In order to investigate the influence of solvents and fluorine source on reaction time and efficiency, we carried out some optimization studies to find the best reaction conditions (Table 2). The *N*-isopropyl substituted isoindoline **2** was chosen as a model starting material for these studies (Scheme 2).

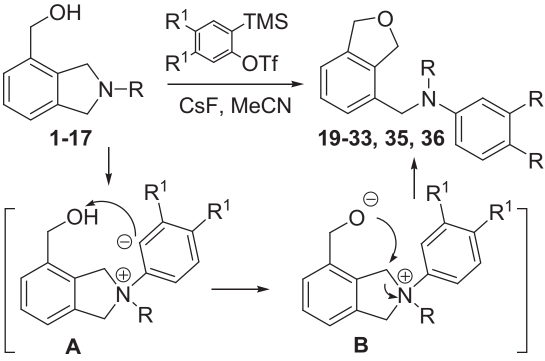
It was shown that variation of temperature from 5 to 65 °C did not significantly affect the reaction yield. The lower temperature dramatically increased the reaction time, while elevated temperature obviously resulted in its decrease. In order to evaluate the influence of microwave irradiation on the course of the reaction, the interaction was repeated in a microwave reactor from Anton

Paar. Although in this case the reaction time was minimized, the higher temperature caused self-condensation of benzyne and the formation of byproducts of unidentified structure that complicated the isolation of the desired product. Using TBAT as a fluorine source resulted in an increased reaction time, and it was very difficult to wash out from this catalyst. Changing the solvent to THF led to lower yields due to the fact that the reaction failed to be completed; even on heating at 65 °C with an excess of aryne precursor, the starting isoindoline still remained in the reaction mixture. As Table 2 shows, a better result was obtained with CsF in acetonitrile at room temperature. Therefore the rest of the experiments were carried out under these conditions.

To find the scope and limitation of the reaction, the interaction of 4-hydroxymethyl isoindolines **1**, **5**–**10**, and **12**–**17** with arynes was performed. The reaction proceeded smoothly at room temperature and finished within 0.5–5 h, giving the corresponding phthalan derivatives **19**–**33**, **35**, and **36** with preparative yields (Scheme 3, Table 3).

Surprisingly, isoindoline **15** did not give the corresponding product of pyrrolidine ring recyclization **34**, and the only product isolated after the column chromatography was phthalan **25**.

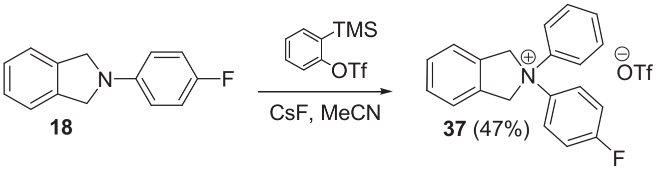
We presume that the reaction starts with the Michael addition of the aryne to the tertiary *N*-atom of the starting compound followed by abstraction of $H^+$ from the hydroxy group in intermediate **A**. The resulting zwitterion **B** undergoes intramolecular recyclization to yield the corresponding phthalan derivatives (Scheme 4).



**Scheme 4.** Proposed mechanism.

The formation of isobenzofuran **25** in the reaction of **15** with benzyne could presumably be explained by the elimination of the dimethoxybenzyl cation from the initially formed zwitterion **A**, and the obtained *O*-anion reacts further with the next molecule of aryne.

Non-substituted isoindoline **18**, which was also inert in the case of activated alkynes, gave quaternary salt **37** with moderate yield under these conditions (Scheme 5).



**Scheme 5.** Interaction of unsubstituted isoindoline with aryne.

## 3. Conclusion

We have reported a novel synthetic approach to 4-aminomethyl-substituted dihydroisobenzofuran derivatives, based on aryne-induced recyclization of easily available 4-hydroxymethyl isoindolines.

## 4. Experimental section

### 4.1. General information

The aryne precursors were purchased from Sigma–Aldrich and TCI and were used without additional purification. $^1H$ NMR and $^{13}C$ NMR were recorded on a Bruker AMX-400 (400 MHz for $^1H$ and 100.6 MHz for $^{13}C$) and a JEOL JNM ECA (600 MHz and 150.9 MHz, respectively). Proton chemical shifts are reported relative to the residual solvent peak ($CDCl_3$ at $\delta$ 7.26 ppm). Carbon chemical shifts are reported relative to $CDCl_3$ at $\delta$ 77.2 ppm. Mass spectra were recorded by Bruker Micro TOF-QII (Germany), ESI, collision-induced dissociation (argon, 17 eV), direct injection, and a Finnigan MAT 95 XL mass spectrometer (electron ionization, 70 eV). IR spectra were recorded on FT spectrometer Infralum FT-801. For the elemental analyses, a Carlo Erba 1106 was used. Melting points were measured on SMP 10 in open capillaries. TLC on Sorbfil plates was used for the monitoring of reactions. Kieselgel from Macherey–Nagel GmbH&Co (0.04–0.06 mm/230–400 mesh), 60 Å, was used for column chromatography. All solvents were dried according to standard procedures.[14]

### 4.2. General procedure for the synthesis of isoindolines (1–18)

To a suspension of $LiAlH_4$ (3 equiv) in absolute ether (150 mL), the corresponding isoindoline acid (1 equiv) [in the case of indoline **18**, the isoindolinone was used] was added in portions. The mixture was stirred at reflux for 3–4 h (TLC monitoring). After the reaction was completed, the mixture was cooled to room temperature, and then 25 mL of EtOAc (cooled with an ice-bath) was added dropwise. The resulting mixture was poured out into 200 mL of cold water and extracted with EtOAc (3*100 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The resulting powder was recrystallized from the mixture of hexane-EtOAc to give corresponding isoindoline.

The spectra of compounds **2**–**4**, **11**, **14**, and **15** correspond to literature data.[10]

*4.2.1. (2-Ethyl-2,3-dihydro-1H-isoindol-4-yl)methanol (**1**).* From *N*-ethyl isoindolone acid (1.0 g, 5 mmol). Yellow powder (523 mg, 61%); mp 75–76 °C; [Found: C, 74.38; H, 8.27; N, 8.10. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%]; $\nu_{max}$(KBr) 3142, 2974, 2809, 1451, 1389, 1077, 781 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.28 (1H, d, *J* 7.5 Hz, Ar), 7.20 (1H, t, *J* 7.5 Hz, Ar), 7.09 (1H, d, *J* 7.5 Hz, Ar), 4.23 (2H, s, $CH_2OH$), 3.89 (2H, s, 3-$CH_2$), 3.58 (2H, s, 1-$CH_2$), 2.75 (2H, q, *J* 6.7 Hz, $CH_2Me$), 1.21 (3H, t, *J* 7.2 Hz, $CH_2Me$); $\delta_C$ (100.6 MHz, $CDCl_3$) 139.3, 136.6, 136.3, 127.1, 124.1, 120.7, 61.4, 58.2, 56.2, 49.7, 13.4. *m*/*z* EI (70 eV), ($I_{rel}$,%): 177 (23) [$M^+$], 176 (71), 159 (74), 158 (100), 146 (21), 130 (28), 117 (47), 103 (25), 91 (49), 77 (40), 65 (19), 42 (18).

*4.2.2. (2-Cyclopropyl-2,3-dihydro-1H-isoindol-4-yl)methanol (**5**).* From *N*-cyclopropyl isoindolone acid (1.0 g, 5 mmol). Almost white powder (295 mg, 34%); mp 128–130 °C; [Found: C, 75.94; H, 7.83; N, 7.55. $C_{12}H_{15}NO$ requires C, 76.16; H, 7.99; N, 7.40%]; $\nu_{max}$(KBr) 3171, 2938, 2814, 1451, 1348, 1074, 774 $cm^{-1}$; $\delta_H$ (400 MHz, $CDC1_3$) 7.31–7.20 (2H, m, Ar), 7.14 (1H, d, *J* 6.9 Hz, Ar), 4.34 (2H, s, $CH_2OH$), 4.07 (2H, s, 3-$CH_2$), 3.86 (2H, s, 1-$CH_2$), 2.10–1.99 (1H, m, CH), 0.66–0.49 (4H, m, $CH_2$); $\delta_C$ (100.6 MHz, $CDCl_3$) 140.3, 137.6, 135.9, 127.3, 124.8, 121.5, 62.6, 58.8, 57.1, 35.7, 5.8 (2C); *m*/*z* EI (70 eV), ($I_{rel}$,%): 189 (26) [$M^+$], 174 (100), 156 (100), 144 (26), 117 (20), 103 (32), 91 (50), 77 (44), 65 (18), 51 (16), 41 (61), 39 (66).

*4.2.3. (2-Cyclopentyl-2,3-dihydro-1H-isoindol-4-yl)methanol (**6**).* From *N*-cyclopentyl isoindolone acid (2.0 g, 8 mmol). Light yellow powder (1.34 g, 76%); mp 142–143 °C; [Found: C, 77.23; H, 8.71; N, 6.68. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81; N, 6.45%]; $\nu_{max}$(KBr) 3140, 2955, 2801, 1453, 1347, 1078, 790 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.36 (1H, d, *J* 7.6 Hz, Ar), 7.24 (1H, t, *J* 7.6 Hz, Ar), 7.12 (1H, d, *J* 7.6 Hz, Ar), 4.09 (2H, s, C*H*$_2$OH), 3.92 (2H, s, 3-CH$_2$), 3.49 (2H, s, 1-CH$_2$), 2.93–2.81 (1H, m, CH), 1.94–1.76 (4H, m, CH$_2$), 1.71–1.53 (4H, m, CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 139.5, 137.0, 136.1, 127.1, 123.6, 120.6, 66.6, 61.0, 58.1, 55.9, 31.6 (2C), 23.9 (2C); *m*/*z* EI (70 eV), (I$_{rel}$,%): 217 (39) [M$^+$], 199 (14), 188 (59), 174 (69), 156 (54), 131 (16), 130 (72), 118 (40), 91 (51), 77 (38), 65 (19), 41 (100).

*4.2.4. (2-Phenyl-2,3-dihydro-1H-isoindol-4-yl)methanol (**7**).* From *N*-phenyl isoindolone acid (2.0 g, 8 mmol). Beige powder (1.48 g, 83%); mp 95–97 °C; [Found: C, 79.85; H, 6.51; N, 6.32. $C_{15}H_{15}NO$ requires C, 79.97; H, 6.71; N, 6.22%]; $\nu_{max}$(KBr) 3370, 2822, 1597, 1506, 1372, 743, 688 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.36–7.23 (5H, m, Ar), 6.76 (1H, t, *J* 7.6 Hz, Ar), 6.70 (2H,d, *J* 7.6 Hz, Ar), 4.72 (2H, s, CH$_2$OH), 4.66 (2H, br s, 3-CH$_2$), 4.62 (2H, br s, 1-CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 146.8, 138.1, 135.9, 135.2, 129.3 (2C), 127.6, 125.6, 121.7, 116.7, 111.9 (2C), 63.1, 53.9, 52.7; *m*/*z* EI (70 eV), (I$_{rel}$,%): 225 (42) [M$^+$], 207 (42), 206 (59), 194 (27), 165 (12), 130 (12), 104 (25), 91 (28), 77 (100), 65 (14), 51 (40).

*4.2.5. (2-(2-Methylphenyl)-2,3-dihydro-1H-isoindol-4-yl)methanol (**8**).* From *N*-(2-methyl)phenyl isoindolone acid (2.5 g, 9 mmol). Yellow powder (753 mg, 34%); mp 78–79 °C; [Found: C, 80.23; H, 7.11; N, 5.94. $C_{16}H_{17}NO$ requires C, 80.30; H, 7.16; N, 5.85%]; $\nu_{max}$(KBr) 3274, 2872, 2819, 1597, 1492, 1456, 759, 727 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.31–7.22 (3H, m, Ar), 7.21–7.16 (2H, m, Ar), 7.10 (1H, d, *J* 8.2 Hz, Ar), 6.95–6.91 (1H, m, Ar), 4.69 (2H, s, C*H*$_2$OH), 4.66 (2H, br s, 3-CH$_2$), 4.63 (2H, br s, 1-CH$_2$), 2.45 (3H, s, Me); $\delta_C$ (100.6 MHz, CDCl$_3$) 147.9, 139.2, 136.9, 134.9, 132.1, 129.4, 127.3, 126.7, 125.5, 121.4 (2C), 117.4, 63.1, 56.6, 55.3, 20.7; *m*/*z* EI (70 eV), (I$_{rel}$,%): 239 (43) [M$^+$], 238 (48), 220 (62), 218 (26), 208 (20), 204 (16), 178 (12), 130 (16), 118 (30), 103 (24), 91 (100), 77 (36), 65 (80), 63 (20), 39 (28).

*4.2.6. (2-(4-Isopropylphenyl)-2,3-dihydro-1H-isoindol-4-yl)methanol (**9**).* From *N*-(4-isopropyl)phenyl isoindolone acid (1.0 g, 3 mmol). Yellow powder (488 mg, 61%); mp 98–100 °C; [Found: C, 80.78; H, 8.13; N, 5.41. $C_{18}H_{21}NO$ requires C, 80.86; H, 7.92; N, 5.24%]; $\nu_{max}$(KBr) 3293, 2956, 2863, 1615, 1520, 1375, 812 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.33–7.26 (3H, m, Ar), 7.18 (2H, d, *J* 8.2 Hz, Ar), 6.66 (2H, d, *J* 8.2 Hz, Ar), 4.74 (2H, s, CH$_2$OH), 4.67 (2H, br s, 3-CH$_2$), 4.63 (2H, br s, 1-CH$_2$), 2.86 (1H, m, –C*H*Me$_2$), 1.25 (6H, d, *J* 6.9 Hz, –CH*Me*$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 145.2, 138.5, 136.6, 136.2, 135.2, 127.5, 127.2 (2C), 125.5, 121.7, 111.6 (2C), 63.1, 53.8, 52.5, 33.1, 24.2 (2C); *m*/*z* EI (70 eV), (I$_{rel}$,%): 267 (63) [M$^+$], 252 (100), 248 (28), 232 (23), 220 (19), 204 (12), 132 (14), 130 (24), 117 (42), 103 (57), 91 (64), 77 (64), 65 (20), 51 (15), 39 (22).

*4.2.7. (2-(4-Methoxyphenyl)-2,3-dihydro-1H-isoindol-4-yl)methanol (**10**).* From *N*-(4-methoxy)phenyl isoindolone acid (1.0 g, 3.5 mmol). Yellow powder (680 mg, 76%); mp 143–144 °C; [Found: C, 75.10; H, 6.80; N, 5.57. $C_{16}H_{17}NO_2$ requires C, 75.27; H, 6.71; N, 5.49%]; $\nu_{max}$(KBr) 3274, 2932, 2834, 1517, 1250, 1035, 816, 775 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.35–7.19 (3H, m, Ar), 6.90 (2H, d, *J* 8.9 Hz, Ar), 6.64 (2H, d, *J* 8.9 Hz, Ar), 4.71 (2H, s, C*H*$_2$OH), 4.61 (2H, br s, 3-CH$_2$), 4.58 (2H, br s, 1-CH$_2$), 3.77 (3H, s, OMe); $\delta_C$ (150.9 MHz, CDCl$_3$) 154.5, 145.1, 141.8, 139.5, 138.1, 130.5, 128.6, 124.7, 118.4 (2C), 115.5 (2C), 66.3, 58.9, 57.2, 56.0; *m*/*z* EI (70 eV), (I$_{rel}$,%): 255 (69) [M$^+$], 253 (100), 236 (54), 222 (41), 192 (22), 180 (44), 165 (33), 152 (32), 119 (28), 103 (28), 92 (36), 91 (51), 77 (76), 63 (54), 39 (29).

*4.2.8. (2-(3-(Trifluoromethyl)phenyl)-2,3-dihydro-1H-isoindol-4-yl) methanol (**12**).* From *N*-(3-trifluoromethyl)phenyl isoindolone acid (2.0 g, 6 mmol). Orange powder (1.53 g, 87%); mp 122–123 °C; [Found: C, 65.37; H, 4.67; N, 4.91. $C_{16}H_{14}F_3NO$ requires C, 65.52; H, 4.81; N, 4.78%]; $\nu_{max}$(KBr) 3319, 3233, 2864, 2828, 1613, 1507, 1457, 1389, 1311, 1161, 1103, 774, 693 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.36 (1H, t, *J* 7.6 Hz, Ar), 7.33–7.22 (3H, m, Ar), 6.98 (1H,d, *J* 7.6 Hz, Ar), 6.84 (1H, s, Ar), 6.79 (1H, d, *J* 8.2 Hz, Ar), 4.70 (2H, s, C*H*$_2$OH), 4.64 (2H, br s, 3-CH$_2$), 4.61 (2H, br s, 1-CH$_2$); $\delta_C$ (150.9 MHz, CDCl$_3$) 147.1, 138.0, 135.8, 135.3, 131.8, 131.6, 129.8, 128.0, 126.0, 122.1, 114.6, 112.6, 107.9, 63.5, 53.7, 52.6; *m*/*z* EI (70 eV), (I$_{rel}$,%): 293 (56) [M$^+$], 275 (100), 262 (32), 145 (100), 104 (26), 103 (50), 91 (60), 77 (71), 75 (34), 63 (33), 51 (30).

*4.2.9. (2-(2-Chlorophenyl)-2,3-dihydro-1H-isoindol-4-yl)methanol (**13**).* From *N*-(2-chlorophenyl) isoindolone acid (2.0 g, 7 mmol). Orange powder (1.2 g, 67%); mp 68–69 °C; [Found: C, 69.51; H, 5.63; N, 5.51. $C_{15}H_{14}ClNO$ requires C, 69.36; H, 5.43; N, 5.39%]; $\nu_{max}$(KBr) 3285, 2862, 1679, 1594, 1482, 1360, 1055, 1033, 747, 737 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.35 (1H, d, *J* 7.6 Hz, Ar), 7.31–7.23 (3H, m, Ar), 7.20 (1H, t, *J* 6.9 Hz, Ar), 7.06 (1H, d, *J* 7.6 Hz, Ar), 6.85 (1H, t, *J* 7.2 Hz, Ar), 4.85 (4H, br s, 3-CH$_2$,C*H*$_2$OH), 4.71 (2H, s, 1-CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 145.5, 138.6, 136.2, 134.8, 131.7, 127.5, 127.4, 125.5, 123.1, 121.4, 120.7, 118.0, 63.1, 56.0, 54.7; *m*/*z* EI (70 eV), (I$_{rel}$,%): 261 (13), 260 (16), 259 (40) [M$^+$], 258 (57), 241 (100), 240 (70), 228 (32), 192 (12), 178 (14), 165 (30), 138 (24), 116 (26), 111 (61), 91 (62), 77 (100), 75 (80), 63 (44), 51 (50).

*4.2.10. (2-(2,3-Dichlorobenzyl)-2,3-dihydro-1H-isoindol-4-yl)methanol (**16**).* From *N*-(2,3-dichlorobenzyl) isoindolone acid (2.0 g, 6 mmol). White powder (428 mg, 25%); mp 120–121 °C; [Found: C, 62.41; H, 5.01; N, 4.67. $C_{16}H_{15}Cl_2NO$ requires C, 62.35; H, 4.91; N, 4.54%]; $\nu_{max}$(KBr) 3149, 2850, 2800, 1450, 1421, 1072, 785, 771 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.48 (1H, d, *J* 7.6 Hz, Ar), 7.40 (1H, d, *J* 7.6 Hz, Ar), 7.22 (1H, t, *J* 7.6 Hz, Ar), 7.19–7.15 (2H, m, Ar), 7.12 (1H, d, *J* 6.9 Hz, Ar), 4.48 (2H, s, C*H*$_2$OH), 4.07 (2H, s, C*H*$_2$Ph), 4.02 (2H, s, 3-CH$_2$), 3.97 (2H, s, 1-CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 139.9, 138.5, 137.4, 135.4, 133.1, 132.1, 129.1, 128.6, 127.2, 127.1, 124.8, 121.3, 62.6, 58.8, 57.3, 57.2; *m*/*z* EI (70 eV), (I$_{rel}$,%): 308 (15) [M$^+$], 306 (20), 289 (22), 288 (13), 163 (12), 162 (20), 161 (100), 148 (21), 130 (84), 123 (38), 91 (55), 89 (64), 77 (38), 63 (28), 39 (18).

*4.2.11. (2-(2-Phenethyl)-2,3-dihydro-1H-isoindol-4-yl)methanol (**17**).* From *N*-(phenethyl) isoindolone acid (2.0 g, 7 mmol). White powder (1.27 g, 71%); mp 110–111 °C; [Found: C, 80.52; H, 7.41; N, 5.77. $C_{17}H_{19}NO$ requires C, 80.60; H, 7.56; N, 5.53%]; $\nu_{max}$(KBr) 3399, 3168, 2922, 2810, 1461, 1449, 1134, 1079, 778, 735, 700 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.33–7.29 (2H, m, Ar), 7.26 (3H, d, *J* 8.9 Hz, Ar), 7.22 (2H, t, *J* 7.6 Hz, Ar), 7.13 (1H, d, *J* 6.9 Hz, Ar), 4.40 (2H, s, C*H*$_2$OH), 3.99 (2H, s, 3-CH$_2$), 3.82 (2H, s, 1-CH$_2$), 3.05–2.81 (4H, m, (C*H*$_2$)$_2$Ph); $\delta_C$ (100.6 MHz, CDCl$_3$) 139.7, 139.5, 136.6, 136.4, 128.6 (2C), 128.4 (2C), 127.2, 126.2, 124.3, 120.9, 61.8, 58.7, 57.7, 56.8, 35.2; *m*/*z* EI (70 eV), (I$_{rel}$,%): 253 (<10) [M$^+$], 163 (11), 162 (100), 144 (12), 117 (14), 105 (15), 91 (54), 77 (18), 65 (16).

*4.2.12. (2-(4-Fluorophenyl)isoindoline (**18**).* From *N*-fluorophenyl isoindolone (4.3 g, 20 mmol). Beige powder (3.4 g, 80%). Mp 143–145°C. [Found: C, 78.94, H, 5.53, N, 6.65. $C_{14}H_{12}FN$ requires C, 78.85; H, 5.67; N, 6.57%]; $\nu_{max}$(KBr) 3429, 3055, 2843, 1519, 1374, 1233, 1220, 810, 743, 623 cm$^{-1}$; $\delta_H$ (600 MHz, CDCl$_3$) 7.20–7.07 (4H, m, Ar), 6.85 (2H, t, *J* 7.9 Hz, Ar), 6.43–6.40 (2H, m, Ar), 4.45 (4H, s, CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 162.4, 157.5, 149.1 (2C), 136.7 (2C), 128.7 (2C), 121.3 (2C), 117.8 (2C), 63.4 (2C). ESI MS 214 [M+H]. (213.25).

### 4.3. General procedure for the synthesis of phthalans (19–32, 35, 36)

To a suspension of CsF (3 equiv) in 5–7 mL of dry acetonitrile, the corresponding 4-hydroxymethyl isoindoline (1 equiv) was added, and after the dissolution of starting material 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (1.2 equiv) was added into the flask. The mixture was stirred at room temperature for 1–3 h with TLC monitoring. Upon completion, the solvent was removed under reduced pressure, 10 mL of $CHCl_3$ was added, the white precipitate of CsOTf was filtrated and washed 2 times with $CHCl_3$, the filtrate was evaporated, and the resulting crude oil was then purified by column chromatography (glass column, H=100 mm, *d*=15 mm, mobile phase: EtOAc-hexane, 1:5) to give the corresponding isobenzofurans (**19**–**32**, **35**, **36**).

*4.3.1. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-N-ethylaniline (**19**).* From isoindoline **1** (70 mg, 0.4 mmol). Light yellow viscous oil (68 mg, 67%); $R_f$ (EtOAc/Hexane, 1:3) 0.81; [Found: C, 80.51; H, 7.39; N, 5.71. $C_{17}H_{19}NO$ requires C, 80.60; H, 7.56; N, 5.53%]; $\nu_{max}$(liquid film) 3397, 2968–2853 (br), 1598, 1499, 1350, 1049, 904, 747, 691 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.29–7.20 (3H, m,Ar), 7.17 (2H, t, *J* 6.2 Hz, Ar), 6.78–6.66 (3H, m, Ar), 5.16 (2H, s, 1-$CH_2$), 5.14 (2H, br s, 3-$CH_2$), 4.43 (2H, s, $CH_2$), 3.50 (2H, q, *J* 6.9 Hz, $CH_2$Me), 1.23 (3H, t, *J* 7.2 Hz, $CH_2$*Me*); $\delta_C$ (100.6 MHz, $CDCl_3$) 148.2, 139.5, 136.5, 133.1, 129.2 (2C), 127.7, 125.3, 119.3, 116.6, 112.6 (2C), 73.4, 72.6, 52.2, 45.3, 11.7; ESI MS 254 [M+H] (253.34).

*4.3.2. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-N-isopropylaniline (**20**).* From isoindoline **2** (105 mg, 0.55 mmol). Colorless transparent viscous oil (108 mg, 77%); $R_f$ (EtOAc/Hexane, 1:5) 0.83; $\nu_{max}$(liquid film) 3397, 3318, 2970, 2856, 1598, 1499, 1390, 1046, 905, 746, 691 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.31–7.20 (4H, m, Ar), 7.15 (1H, d, *J* 6.9 Hz, Ar), 6.80–6.73 (3H, m, Ar), 5.22 (2H, br s, 1-$CH_2$), 5.19 (2H, s, 3-$CH_2$), 4.34–4.27 (3H, m, C*H*$Me_2$, $CH_2$), 1.27 (6H, d, *J* 6.2 Hz, CH*$Me_2$*); $\delta_C$ (100.6 MHz, $CDCl_3$)149.1, 139.1, 135.7, 134.3, 129.1 (2C), 127.7, 125.2, 118.9, 117.0, 113.9 (2C), 73.5, 72.5, 48.8, 46.3, 19.7 (2C); HRMS (ESI+): $[M+H]^+$, found 268.1695 $C_{18}H_{21}NO$ calcd 268.1995, MS2 (*m*/*z* 268.1695): *m*/*z* 133.0656, 120.0815, 105.0707.

*4.3.3. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-N-pentylaniline (**21**).* From isoindoline **3** (150 mg, 0.68 mmol). Yellow oil (160 mg, 79%); $R_f$ (EtOAc/Hexane, 1:5) 0.7; [Found: C, 81.25, H, 8.39, N, 4.86. $C_{20}H_{25}NO$ requires C, 81.31; H, 8.53; N, 4.74%]; $\nu_{max}$(liquid film) 3397, 2930, 2858, 1598, 1508, 1459, 1367, 1052, 905, 747, 691 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.29–7.19 (3H, m, Ar), 7.15 (2H, t, *J* 6.9 Hz, Ar), 6.79–6.62 (3H, m, Ar), 5.16 (2H, s, 1-$CH_2$), 5.13 (2H, s, 3-$CH_2$), 4.45 (2H, s, $CH_2$), 3.47–3.33 (2H, m, *N*-C*$H_2$*$(CH_2)_3$Me), 1.70 (2H, q, *J* 7.6 Hz, *N*-$CH_2$C*$H_2$*$(CH_2)_2$Me), 1.46–1.27 (4H, m, *N*-$(CH_2)_2$C*$H_2$*C*$H_2$*Me), 0.96 (3H, t, *J* 6.9 Hz, Me); $\delta_C$ (150.9 MHz, $CDCl_3$) 148.4, 139.7, 136.6, 133.1, 129.5 (2C), 128.1, 125.5, 119.5, 116.6, 112.6 (2C), 73.6, 72.8, 52.9, 51.6, 29.4, 26.6, 22.7,14.2; ESI MS 296 [M+H] (295.42).

*4.3.4. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-N-(3-methoxypropyl)aniline (**22**).* From isoindoline **4** (100 mg, 0.45 mmol). Orange oil (83 mg, 62%); $R_f$ (EtOAc/Hexane, 1:3) 0.58; [Found: C, 76.61, H, 7.73, N, 4.85. $C_{19}H_{23}NO_2$ requires C, 76.73; H, 7.80; N, 4.71%]; $\nu_{max}$(liquid film) 3397, 3000–2800 (br), 1598, 1351, 1049, 904, 748, 691 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.25–7.17 (3H, m, Ar), 7.14 (1H, d, *J* 7.6 Hz, Ar),7.10 (1H, d, *J* 7.6 Hz, Ar), 6.74–6.66 (3H, m, Ar), 5.13 (2H, s, 1-$CH_2$), 5.11 (2H, s, 3-$CH_2$), 4.44 (2H, s, $CH_2$), 3.54 (2H, t, *J* 7.2 Hz, *N*-$(CH_2)_2$$CH_2$OMe), 3.44 (2H, t, *J* 5.8 Hz, *N*-C*$H_2$*$(CH_2)_2$OMe), 3.35 (3H, s, OMe), 1.98–1.87 (2H, m, *N*-$CH_2$C*$H_2$*$CH_2$OMe); $\delta_C$ (150.9 MHz, $CDCl_3$) 151.2, 142.5, 139.5, 135.9 (2C), 132.3, 130.8, 128.2, 122.3, 119.5, 115.4, 76.5, 75.6, 73.1, 61.6 (2C), 55.6, 51.2, 30.2; ESI MS 298 [M+H] (297.39).

*4.3.5. N-Cyclopropyl-N-(1,3-dihydro-2-benzofuran-4-ylmethyl) aniline (**23**).* From isoindoline **5** (109 mg, 0.58 mmol). Light yellow powder (130 mg, 85%); mp 116–117 °C; $\nu_{max}$(KBr) 3500–3300 (br), 3081, 3005, 2849, 1599, 1504, 1362, 1335, 1257, 1041, 748, 692 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.25–7.17 (3H, m, Ar), 7.13 (1H, d, *J* 7.6, Ar), 7.03 (1H, d, *J* 7.6 Hz, Ar), 6.91 (2H, d, *J* 8.3 Hz, Ar), 6.79 (1H, t, *J* 7.2 Hz, Ar), 5.15 (2H, s, 1-$CH_2$), 5.11 (2H, s, 3-$CH_2$), 4.51 (2H, s, $CH_2$), 2.68–2.59 (1H, m, CH), 0.89–0.82 (2H, m, $CH_2$), 0.74–0.68 (2H, m, $CH_2$); $\delta_C$ (100.6 MHz, $CDCl_3$) 149.6, 139.4, 136.3, 129.0 (4C), 127.9, 125.3, 119.3, 118.2, 114.3, 73.7, 72.6, 54.7, 33.2, 8.9 (2C); HRMS (ESI+): $[M+H]^+$, found 266.1544 $C_{18}H_{19}NO$ calcd 266.1539., MS2 (*m*/*z* 266.1544): *m*/*z* 133.0683, 105.0707.

*4.3.6. N-Cyclopentyl-N-(1,3-dihydro-2-benzofuran-4-ylmethyl) aniline (**24**).* From isoindoline **6** (100 mg, 0.46 mmol). Almost white powder (94 mg, 69%); mp 121–123 °C; $\nu_{max}$(KBr) 3500–3300 (br), 3051, 2961, 2864, 1597, 1504, 1393, 1335, 194, 1046, 900, 777, 751, 700 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.32–7.07 (5H, m, Ar), 6.85–6.70 (3H, m, Ar), 5.19 (4H, s, 1-$CH_2$), 4.43–4.28 (3H, m, 3-$CH_2$, CH), 2.12–2.01 (2H, m, $CH_2$), 1.83–1.46 (6H, m, $CH_2$); $\delta_C$ (100.6 MHz, $CDCl_3$) 150.0, 139.2, 136.2, 135.6, 134.4, 129.0 (2C), 127.8, 125.1, 119.0, 117.1, 113.9, 73.5, 72.4, 59.8, 48.6, 29.4 (2C), 24.0 (2C); HRMS (ESI+): $[M+H]^+$, found 294.1858 $C_{20}H_{23}NO$ calcd 294.1852, MS2 (*m*/*z* 294.1858): *m*/*z* 226.1225, 208.1117, 161.1197, 133.0662, 105.0702.

*4.3.7. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-N-phenylaniline (**25**).* From isoindoline **7** (100 mg, 0.44 mmol). White powder (106 mg, 80%); From isoindoline **15** (200 mg, 0.67 mmol) as byproduct (55 mg, 28%); mp 121–122 °C; $\nu_{max}$(KBr) 3500–3300 (br), 3034, 2847, 1587, 1493, 1371, 1227, 1044, 899, 778, 748, 690, 592 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.30 (1H, d, *J* 7.6 Hz, Ar), 7.26–7.19 (5H, m, Ar), 7.11 (1H, d, *J* 7.6 Hz, Ar), 7.04 (4H, d, *J* 7.6 Hz, Ar), 6.95 (2H, t, *J* 7.2 Hz, Ar), 5.12 (4H, br s, 1-$CH_2$, 3-$CH_2$), 4.86 (2H, s, $CH_2$); $\delta_C$ (100.6 MHz, $CDCl_3$) 148.2, 139.5, 136.4, 132.9, 129.4 (4C), 127.9, 125.4, 121.8, 121.1, 120.9 (4C), 119.4, 117.9, 73.6, 72.7, 54.6; HRMS (ESI+): $[M+H]^+$, found 302.1534 $C_{21}H_{19}NO$ calcd 302.1539, MS2 (*m*/*z* 302.1534): *m*/*z* 284.1421, 169.0880, 133.0654, 105.0702.

*4.3.8. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-2-methyl-N-phenylaniline (**26**).* From isoindoline **8** (100 mg, 0.42 mmol). Orange powder (103 mg, 78%); mp 90 °C; [Found: C, 83.63, H, 6.57, N, 4.60. $C_{22}H_{21}NO$ requires C, 83.78; H, 6.71; N, 4.44%]; $\nu_{max}$(KBr) 3500–3300 (br), 3064, 3021, 2847, 1595, 1499, 1373, 1229, 1045, 774, 748, 691 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.44 (1H, d, *J* 7.6 Hz, Ar), 7.34 (1H, d, *J* 6.2 Hz, Ar), 7.31–7.22 (4H, m, Ar), 7.21–7.12 (3H, m, Ar), 6.77 (1H, t, *J* 7.2 Hz, Ar), 6.56 (2H, d, *J* 8.2 Hz, Ar), 5.17 (2H, s, 1-$CH_2$), 5.13 (2H, s, 3-$CH_2$), 4.75 (2H, s, $CH_2$), 2.20 (3H, s, Me); $\delta_C$ (100.6 MHz, $CDCl_3$) 148.4, 145.9, 139.2, 136.8, 136.3, 132.5, 131.7, 129.0 (2C), 128.9, 127.8, 127.5, 126.7, 125.6, 119.3, 117.6, 113.7 (2C), 73.6, 72.4, 53.8, 18.4; ESI MS 316 [M+H] (315.41).

*4.3.9. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-4-isopropyl-N-phenylaniline (**27**).* From isoindoline **9** (108 mg, 0.40 mmol). Light yellow oil (88 mg, 64%); $R_f$ (EtOAc/Hexane, 1:5) 0.77; $\nu_{max}$(liquid film) 3397, 2958, 2865, 1596, 1510, 1365, 1049, 905, 837, 752, 697, 613 $cm^{-1}$; $\delta_H$ (600 MHz, $CDC1_3$) 7.33 (1H, d, *J* 7.6 Hz, Ar), 7.24–7.18 (3H, m, Ar), 7.15 (2H, d, *J* 8.9 Hz, Ar), 7.12 (1H, d, *J* 7.6 Hz, Ar), 7.06 (2H, d, *J* 8.9 Hz, Ar), 6.96 (2H,d, *J* 8.2 Hz, Ar), 6.88 (1H, t, *J* 7.2 Hz, Ar), 5.13 (2H, m, 1-$CH_2$), 5.12 (2H, s, 3-$CH_2$), 4.85 (2H, s, $CH_2$), 2.96–2.80 (1H, m, C*H*$Me_2$), 1.30–1.20 (6H, d, *J* 6.9 Hz, CH*$Me_2$*); $\delta_C$ (150.9 MHz, $CDCl_3$) 148.4, 145.9, 143.3, 139.5, 136.4, 135.2, 129.2 (2C), 127.9, 127.4, 125.4, 122.4 (2C), 120.5, 119.4, 119.1 (2C), 117.2, 73.6, 72.7, 54.8, 33.5, 24.2 (2C); HRMS (ESI+): $[M+H]^+$, found 344.2009 $C_{24}H_{25}NO$ calcd 344.2009, MS2 (*m*/*z* 344.2009): *m*/*z* 211.1354, 196.1124, 133.0651, 105.0703.

*4.3.10. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-4-methoxy-N-phenylaniline (**28**).* From isoindoline **10** (200 mg, 0.78 mmol). White powder (187 mg, 72%); mp 94–96 °C; $\nu_{max}$(KBr) 3500–3300, 3004, 2850, 1595, 1503, 1344, 1220, 1045, 751 cm$^{-1}$; $\delta_H$ (600 MHz, CDC1$_3$) 7.32 (1H, d, *J* 7.6 Hz, Ar), 7.23 (1H, t, *J* 7.6 Hz, Ar), 7.20–7.08 (5H, m, Ar), 6.88 (2H, d, *J* 8.9 Hz, Ar), 6.83–6.75 (3H, m, Ar), 5.13 (4H, s, 1-CH$_2$, 3-CH$_2$), 4.80 (2H, s, CH$_2$), 3.81 (3H, s, OMe); $\delta_C$ (100.6 MHz, CDCl$_3$) 156.5, 149.1, 141.2, 139.5, 136.5, 133.1, 129.1 (2C), 127.9, 126.5 (2C), 125.6, 119.4, 119.1, 116.6 (2C), 115.0 (2C), 73.7, 72.7, 55.6, 55.0; HRMS (ESI+): [M+H]$^+$, found 332.1636 $C_{22}H_{21}NO$ calcd 332.1645, MS2 (*m*/*z* 332.1636): *m*/*z* 330.1632, 199.0987, 184.0755.

*4.3.11. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-4-fluoro-N-phenylaniline (**29**).* From isoindoline **11** (150 mg, 0.62 mmol). Red powder (132 mg, 67%); mp 63–64 °C; $\nu_{max}$(KBr) 3500–3300 (br), 3066, 2845, 1593, 1504, 1211, 1045, 750, 691 cm$^{-1}$; $\delta_H$ (600 MHz, CDC1$_3$) 7.30–7.26 (1H, d, *J* 7.6 Hz, Ar), 7.24–7.19 (3H, m, Ar), 7.13 (1H, d, *J* 6.9 Hz, Ar), 7.08 (2H, m, Ar), 6.97 (2H, m, Ar), 6.93–6.87 (3H, m, Ar), 5.12 (4H, s, 3-CH$_2$, 1-CH$_2$), 4.81 (2H, s, CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 160.1, 157.7, 148.5, 144.2, 141.1, 139.6, 136.5, 132.7, 129.3, 128.0, 125.5, 124.4, 124.5, 120.8, 119.6, 118.8, 116.3, 116.1, 73.6, 72.7, 54.9; HRMS (ESI+): [M+H]$^+$, found 320.1445 $C_{21}H_{18}FNO$ calcd 320.1445, MS2 (*m*/*z* 320.1433): *m*/*z* 302.1354, 200.0872, 187.0784, 133.0652, 105.0703.

*4.3.12. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-N-phenyl-3-(trifluoromethyl)aniline (**30**).* From isoindoline **12** (200 mg, 0.68 mmol). Yellow powder (212 mg, 84%); mp 75–76 °C; $\nu_{max}$(KBr) 3500–3300 (br), 2853, 1612, 1499, 1457, 1383, 1326, 1123, 1073, 791, 701 cm$^{-1}$; $\delta_H$ (600 MHz, CDC1$_3$) 7.33 (2H, t, *J* 7.2 Hz,Ar), 7.30–7.25 (2H, m, Ar), 7.23 (1H, t, *J* 7.2 Hz, Ar), 7.17 (3H, d, *J* 7.6 Hz, Ar), 7.14 (1H, d, *J* 7.6 Hz, Ar), 7.11 (2H, t, *J* 6.5 Hz, Ar), 7.05 (1H, dd, *J* 8.3, 2.1 Hz, Ar), 5.12 (4H, s, 3-CH$_2$, 1-CH$_2$), 4.88 (2H, s, CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 148.6, 147.3, 139.8, 136.5, 132.1, 131.5, 129.9 (2C), 129.7, 128.1, 125.3, 124.1, 123.5 (2C), 121.2, 120.5, 119.7, q 116.8–116.7 (*J* 12.6 Hz), q 114.7–114.6 (*J* 12.6 Hz), 73.6, 72.6, 54.6; HRMS (ESI+): [M+H]$^+$, found 370.1409 $C_{22}H_{18}F_3NO$ calcd 370.1413, MS2 (*m*/*z* 370.1409): *m*/*z* 352.1321, 133.0650, 105.0705.

*4.3.13. (2-Chlorophenyl)(1,3-dihydro-2-benzofuran-4-ylmethyl)-N-phenylaniline (**31**).* From isoindoline **13** (105 mg, 0.38 mmol). Yellow oil (93 mg, 73%); R$_f$ (EtOAc/Hexane, 1:3) 0.63; $\nu_{max}$(liquid film) 3600–3400 (br), 3057, 2857, 1580, 1495, 1478, 1365, 1190, 1054, 758, 749, 698 cm$^{-1}$; $\delta_H$ (600 MHz, CDC1$_3$) 7.52 (1H, dd, *J* 7.6, 1.4 Hz, Ar), 7.46 (1H, d, *J* 6.9 Hz, Ar), 7.37 (1H, dd, *J* 8.2, 1.4 Hz, Ar), 7.30 (1H, td, *J* 7.6, 1.4 Hz, Ar), 7.28–7.22 (2H, m, Ar), 7.21–7.13 (3H, m, Ar), 6.81 (1H, t, *J* 7.2 Hz, Ar), 6.58 (2H, d, *J* 8.2 Hz, Ar), 5.15 (4H, s, 3-CH$_2$, 1-CH$_2$), 4.78 (2H, s, CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 147.9, 144.1, 139.2, 136.3, 133.7, 132.2, 131.1, 130.8, 128.9 (2C), 128.1, 127.8, 127.6, 125.6, 119.4, 118.5, 114.3 (2C), 73.6, 72.4, 53.7; HRMS (ESI+): [M+H]$^+$, found 336.1141 $C_{21}H_{18}ClNO$ calcd 336.1149, MS2 (*m*/*z* 336.1121): *m*/*z* 318.1025, 203.0495, 133.0651, 105.0706.

*4.3.14. N-Benzyl-N-(1,3-dihydro-2-benzofuran-4-ylmethyl)aniline (**32**).* From isoindoline **14** (100 mg, 0.42 mmol).White powder (84 mg, 64%); mp 64–65 °C; $\nu_{max}$(KBr) 3500–3300 (br), 2922, 2852, 1598, 1506, 1359, 1233, 1046, 750, 694 cm$^{-1}$; $\delta_H$ (600 MHz, CDC1$_3$) 7.34 (2H, t, *J* 7.6 Hz, Ar), 7.30–7.22 (3H, m, Ar), 7.22–7.14 (4H, m, Ar), 7.06 (1H, d, *J* 8.2 Hz, Ar), 6.74 (3H, d, *J* 6.9 Hz, Ar), 5.14 (2H, br s, 1-CH$_2$), 5.06 (2H, br s, 3-CH$_2$), 4.66 (2H, s, CH$_2$), 4.53 (2H, s, CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 147.7, 139.6, 136.6, 134.7, 130.6, 129.2 (2C), 128.6 (2C), 127.8 (2C), 126.9, 126.8, 125.2, 121.6, 120.6, 119.4, 112.9, 73.4, 72.5, 54.4, 52.4; HRMS (ESI+): [M+H]$^+$, found 316.1718 $C_{22}H_{21}NO$ calcd 316.1695, MS2 (*m*/*z* 316.1703): *m*/*z* 298.1590, 224.1069, 196.1118, 183.1036, 133.0654, 105.0706, 91.0545.

*4.3.15. N-Benzyl-N-((1,3-dihydro-2-benzofuran-4-yl)methyl)-3,4-dimethoxybenzenamine (**33**).* From isoindoline **14** (200 mg, 0.84 mmol), CsF (362 mg, 2.4 mmol), 7 mL of dry acetonitrile, and 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (300 mg, 0.84 mmol). White powder (228 mg, 76%); mp 68–69 °C; $\nu_{max}$(KBr) 3600–3300 (br), 2916, 2854, 1521, 1240, 1021, 776 cm$^{-1}$; $\delta_H$ (600 MHz, CDC1$_3$) 7.34–7.27 (2H, m, Ar), 7.26–7.19 (4H, m, Ar), 7.17 (1H, d, *J* 7.6 Hz, Ar), 7.13 (1H, d, *J* 7.6 Hz, Ar), 6.71 (1H, d, *J* 8.3 Hz, Ar), 6.36 (1H, br s, Ar), 6.26 (1H, d, *J* 8.3 Hz, Ar), 5.10 (2H, s, 1-CH$_2$), 5.05 (2H, br s, 3-CH$_2$), 4.52 (2H, s, CH$_2$), 4.40 (2H, s, CH$_2$), 3.78 (3H, s, OMe), 3.69 (3H, s, OMe); $\delta_C$ (150.9 MHz, CDCl$_3$) 149.8, 144.2, 141.9, 139.8, 138.6, 137.1, 132.9, 128.7 (2C), 127.9 (2C), 127.3, 127.1, 125.9, 119.6, 113.0, 105.9, 100.4, 73.6, 72.9, 56.6, 55.9, 55.8, 53.7; HRMS (ESI+): [M+H]$^+$, found 376.1909 $C_{24}H_{25}NO_3$ calcd 376.1907, MS2 (*m*/*z* 376.1909): *m*/*z* 285.1358, 243.1256, 228.1021, 153.0783, 132.0576.

*4.3.16. N-(2,3-Dichlorobenzyl)-N-(1,3-dihydro-2-benzofuran-4-ylmethyl)-aniline (**35**).* From isoindoline **16** (100 mg, 0.34 mmol). Pale yellow powder (83 mg, 64%); mp 178–180 °C; $\nu_{max}$(KBr) 3600–3300 (br), 3058, 2847, 1599, 1507, 1420, 1349, 1236, 1192, 1047, 749 cm$^{-1}$; $\delta_H$ (600 MHz, CDC1$_3$) 7.39 (1H, d, *J* 7.6 Hz, Ar), 7.28–7.23 (1H, m, Ar), 7.21–7.13 (5H, m, Ar), 7.12–7.09 (1H, m, Ar), 6.75 (1H, t, *J* 7.2 Hz, Ar), 6.62 (2H, d, *J* 8.2 Hz, Ar), 5.14 (2H, s, 1-CH$_2$), 5.09 (2H, s, 3-CH$_2$), 4.70 (2H, s, CH$_2$), 4.56 (2H, s, CH$_2$); $\delta_C$ (150.9 MHz, CDCl$_3$) 148.1, 139.9, 137.7, 136.6, 133.5, 131.9, 131.1, 129.5 (2C), 129.1, 128.2, 127.5, 125.8, 125.0, 119.7, 117.6, 112.4 (2C), 73.7, 72.6, 53.4, 52.7; HRMS (ESI+): [M+H]$^+$, found 384.0914 $C_{22}H_{19}Cl_2NO$ calcd 385.0994, MS2 (*m*/*z* 384.0914): *m*/*z* 250.0187, 133.0650, 105.0701.

*4.3.17. N-(1,3-Dihydro-2-benzofuran-4-ylmethyl)-N-(2-phenylethyl) aniline (**36**).* From isoindoline **17** (100 mg, 0.39 mmol). Colorless transparent oil (118 mg, 89%); R$_f$(EtOAc/Hexane, 1:5) 0.75; $\nu_{max}$(liquid film) 3600–3400 (br), 3024, 2852, 1603, 1505, 1350, 1046, 904, 743, 700, 689 cm$^{-1}$; $\delta_H$ (400 MHz CDC1$_3$) 7.38–7.31 (2H, m, Ar), 7.31–7.20 (6H, m, Ar), 7.16 (1H, d, *J* 7.3 Hz, Ar), 7.11 (1H, d, *J* 7.3 Hz, Ar), 6.84–6.74 (3H, m, Ar), 5.15 (2H, s, 3-CH$_2$), 5.07 (2H, s, 1-CH$_2$), 4.37 (2H, s, CH$_2$), 3.67 (2H, t, *J* 7.6 Hz, CH$_2$), 2.97 (2H, t, *J* 7.6 Hz, CH$_2$); $\delta_C$ (100.6 MHz, CDCl$_3$) 147.8, 139.5, 139.4, 136.6, 132.7, 129.3 (2C), 128.7 (2C), 128.5 (2C), 127.8, 126.3, 125.2, 119.3, 116.8, 112.5 (2C), 73.4, 72.5, 53.0, 52.8, 33.2; HRMS (ESI+): [M+H]$^+$, found 330.1870 $C_{23}H_{23}NO$ calcd 330.1852, MS2 (*m*/*z* 330.1870): *m*/*z* 196.1119, 133.0653, 105.0707.

*4.3.18. 2-(4-Fluorophenyl)-2-phenylisoindolinium trifluoromethanesulfonate (**37**).* From isoindoline **18** (108 mg, 0.51 mmol). The reaction was heated at 50 °C during 1.5 h. Yellow powder (105 mg, 47%); mp 185–186 °C; [Found: C, 57.36; H, 3.71; N, 3.21. $C_{21}H_{17}F_4NO_3S$ requires C, 57.40; H, 3.90; N, 3.19%]; $\nu_{max}$(KBr) 2962, 1667, 1446, 1386, 1260, 1172, 1074, 759; $\delta_H$ (400 MHz, DMSO-*d*$_6$) 6.09 (4H, s, 1-CH$_2$, 3-CH$_2$), 7.50–7.40 (4H, m, Ar), 7.56–7.50 (3H, m, Ar), 7.59 (2H, t, *J* 7.9 Hz, Ar), 7.82 (2H, d, *J* 8.3 Hz, Ar), 7.90 (2H, dd, *J* 9.5, 4.4 Hz, Ar); $\delta_C$ (100.6 MHz, CDCl$_3$) 192.3, 162.8 (d, *J* 253.1 Hz), 147.3, 142.9, 132.3, 131.0 (3C), 130.7, 130.2 (3C), 124.7 (d, *J* 9.0 Hz), 123.6 (3C), 122.1 (3C), 117.8 (d, *J* 23.3 Hz), 72.6 (2C).

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.01.022.

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