2-Substituted-isoindoles: a novel synthetic route and a study of the Diels–Alder and Michael reactions

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A novel one-step procedure for the synthesis of 2-substituted-isoindoles and 1-aryl-2-substituted-isoindoles is described. The procedure is based on the reaction of 2-(bromomethyl)benzaldehyde or 2-(bromomethyl)benzophenone derivatives with primary aromatic or aliphatic amines. Reactions of 1,2-diarylisoindoles with *N*-phenylmaleimide were studied. Refluxing the reactants in *i*-PrOH in the presence of triethylamine leads to the formation of Diels–Alder *endo*-adducts; whilst refluxing in AcOH in the presence of AcONa affords Michael adducts. The structure of the latter was confirmed by X-ray diffraction.

Keywords: isoindoles, maleimides, cycloadditions, benzophenone, Diels–Alder and Michael reactions

The chemistry of isoindole and its derivatives is a rather young field in the chemistry of heterocyclic compounds.[1] At the same time, the amount of published papers devoted to research in this sphere is constantly growing. The cause of the high interest by researchers is not only due to the peculiar structure and properties of these compounds, but also their availability for practical applications. Thus, various heat-resistant and current-conductive polymers,[2] dyes[3,4] and materials with non-linear optical properties based on isoindole derivatives have been synthesised.[5] The derivatives of isoindole have a wide spectrum of biological activity.[6–8] 2-Substituted-isoindoles possess valuable properties as CNS-stimulants, as antidepressants and hypotensive agents, but, especially 1-aryl-2-substituted-isoindoles, are quite difficult to obtain.

Several methods for the synthesis of 1-aryl-2-substituted-isoindoles have been developed and reported that include, the action of organometallic compounds on phthalimidine[9,10] and reduction of fused isoindoles with lithium aluminum hydride.[11,12]

Results and discussion

In elaboration of our studies of isoindole chemistry,[13] we have developed a convenient one-step method for the synthesis of 2-substituted-isoindoles and 1-aryl-2-substituted-isoindoles, based on the reaction of the derivatives of 2-(bromomethyl)benzaldehyde[14] **1a** and 2-(bromomethyl)benzophenone[15] **1b** with primary aromatic and aliphatic amines (Table 1).

2-(Bromomethyl)benzaldehyde **1a** and 2-(bromomethyl)benzophenone **1b** have been known for a long time, but have not been used extensively in heterocyclisations due to their relative inaccessibility and instability. However, improved procedures to access **1a** and **1b** are available.[14,15] The reactivity of these bifunctional systems towards amines was therefore investigated.

The reaction of the 2-(bromomethyl)benzaldehyde **1a** with benzylamine or *p*-phenetidine proceeded smoothly and resulted in the formation of the 2-substituted-2*H*-isoindoles **3a** and **3b** respectively in high yields (73 and 88%). The best results were obtained under an inert atmosphere in 95% ethanol at room temperature with a twofold excess of the amine. Melting points and spectral properties of the obtained isoindole **3a** conform with the literature.[16,17] The reaction of the 2-(bromomethyl)benzophenone **1b** with amines required heating for 3 hours at 50 °C, and the reaction can also be carried out without an inert atmosphere.

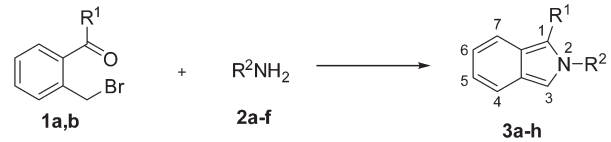
The structure of the compounds **3a–h** was determined by elemental analysis and spectral data. The chemical shift of the H-3 proton in the ^{1}H NMR spectra of the compounds **3a–h** depends on the nature of the substituent at N(2). Thus, when R^1 = alkyl, δ H-3 (H-3 and H-1 for **3a**) = 7.3–7.4 ppm. However, when R^1 = aryl, the signal was deshielded δ H-3 (H-3 and H-1 for **3b**) = 7.4–7.6 ppm. Signals for the protons H-4–H-7 appeared as two multiplets within the ranges 7.32–7.54 ppm and 6.81–6.93 ppm.

In the UV spectra of the 1,2-diarylisoindoles **3c-f** three distinct absorption bands are observed at λ = 220–260, 270–310 and 320–370 nm, while the 1-aryl-2-alkyl-isoindoles **3g,h** have only two bands at λ = 210–250 and 320–370 nm. The presence of the long-wave absorption band at 320–370 nm is a characteristic peculiarity of isoindole derivatives and is caused by the presence of the *o*-quinonoid chromophore.[18] Thus, the UV spectral data confirms the structure of compounds **3a–h** as derivatives of isoindole.

The presence of the diene fragment in the structure of the isoindoles enables [4+2]-cycloaddition reactions to be carried out. *N*-Phenylmaleimide was chosen as the active dienophile.

The outcome of the reaction of the 1,2-diarylisoindoles **3c**,**3e** and **3f** with *N*-phenylmaleimide **4** depends on the reaction conditions. In the first case the reaction mixture was kept under reflux in isopropanol during 5 hours (Scheme 2). Under these conditions the major product was the Diels–Alder adducts **5c**, **5e** and **5f**. The products were all obtained as the *endo*-isomers, which was confirmed by ^{1}H NMR spectral data, using criteria described in literature.[19,20] The signals of the

Table 1 Synthesis of 2-substituted-isoindoles and 1-aryl-2-substituted-isoindoles



1a,b **2a-f** **3a-h**

R^1 = H (**a**), 4-ClC_6H_4 (**b**)

Entry	R^1	R^2	2	3	Yield/%
1	H	Bn	**2a**	**3a**	88
2	H	4-$EtOC_6H_4$	**2b**	**3b**	73
3	4-ClC_6H_4	4-$EtOC_6H_4$	**2b**	**3c**	68
4	4-ClC_6H_4	3,4-$(MeO)_2C_6H_3$	**2c**	**3d**	64
5	4-ClC_6H_4	4-BrC_6H_4	**2d**	**3e**	55
6	4-ClC_6H_4	4-FC_6H_4	**2e**	**3f**	64
7	4-ClC_6H_4	Cy	**2f**	**3g**	67
8	4-ClC_6H_4	Bn	**2a**	**3h**	41

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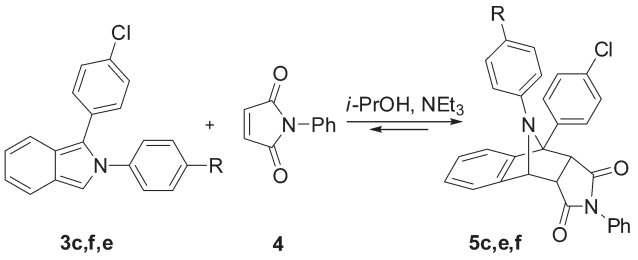


Scheme 1 The Diels–Alder reaction of 1,2-diarylisoindoles **3c,e,f** with *N*-phenylmaleimide.

aliphatic protons, that form the AMX spin system in the ^{1}H NMR spectra appeared within the range 3.80–5.80 ppm (Table 2).

All attempts to obtain the *exo*-isomer of **5**, which is thermodynamically more stable, turned out to be unsuccessful. Upon heating in high-boiling solvents, a retro-Diels–Alder reaction occurred and the *endo*-adduct decomposed with the formation of the parent isoindole and *N*-phenylmaleimide.

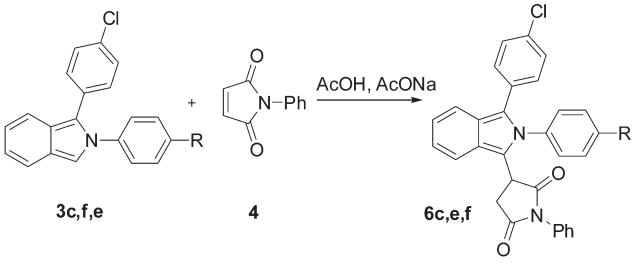
When a mixture of **3c**, **3e** or **3f** and *N*-phenylmaleimide was heated under reflux in acetic acid with a catalytic amount of sodium acetate during 5 hours (Scheme 3). The products from this procedure were the Michael adducts **6c**, **6e** and **6f**. In this case, the aliphatic proton signals appeared as typical ABX spin systems in their ^{1}H NMR spectra that absorbed within the range 2.90–4.70 ppm (Table 3).

The diene fragment is also present in compounds **6c**, **6e** and **6f**, but we failed to isolate any of the Diels–Alder adduct with one more molecule of *N*-phenylmaleimide, this failure is probably caused by steric hindrance.

The structure of the product **6f** was identified not only by spectral methods but also by X-ray diffraction analysis (Fig. 1).

Table 2 The characteristic ^{1}H NMR signals of Diels–Alder adducts **5c, 5e** and **5f**. The chemical shifts of **5e** and **5f** are reported in the experimental section

Compound	δ/ppm	*J*/Hz
5c	Ha 3.85 dd	J_{HaHm} = 8.2 Hz, J_{HaHx} = 7.3 Hz
	Hm 4.50 d	J_{HaHm} = 8.2 Hz
	Hx 5.64 d	J_{HaHx} = 7.3 Hz



Scheme 2 The Michael reaction of 1,2-diarylisoindoles **3c**, **3e** and **3f** with *N*-phenylmaleimide.

Table 3 The characteristic proton signals of Michael adducts **6c**, **6e**, and **6f** in ^{1}H NMR spectra. The chemical shifts of **6e,f** are reported in the experimental section

Compound	δ/ppm	*J*/Hz
6c	Ha 2.97 dd	J_{HaHb} = 17.0 Hz, J_{HaHx} = 8.0 Hz
	Hb 3.26 dd	J_{HaHb} = 17.0 Hz, J_{HbHx} = 10.0 Hz
	Hx 4.67 dd	J_{HaHx} = 8.0 Hz, J_{HbHx} = 10.0 Hz

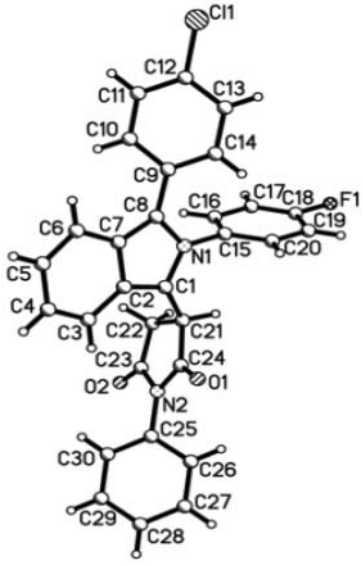


Fig. 1 The molecular structure of the molecule **6f** with atomic numbering used in structural analysis.

According to the X-ray diffraction study, the bicyclic fragment of the molecule **6f** is planar within 0.01 Å. The presence of bulky vicinal substituents causes significant steric strain in the molecule (shortened intramolecular contacts H3…C24 2.76 Å and H21…C15 2.56 Å, van der Waals radii sum[21] 2.87 Å). This leads to deviation of the substituent at the C1 atom from the plane of the bicyclic fragment [the C21–C1–C2–C3 torsion angle is 10.7(8)°] and non-coplanarity of the π-system of substituents at the C8 and N1 atoms and bicyclic fragment [the C7–C8–C9–C10 and C1–N1–C15–C16 torsion angles are –49.5(6)° and 94.9(5)°, respectively]. The pyrrolidinedione ring adopts an envelope conformation with deviation of the C21 atom by 0.13 Å from the mean plane of the remaining ring atoms and is turned in such way that the C21–C22 bond has +*sc*–orientation relative to the C2–C1 bond of the bicyclic fragment [the C2–C1–C21–C22 torsion angle is 72.7(6)°]. The phenyl substituent is twisted relative to the pyrrolidinedione ring (the C24–N2–C25–C26 torsion angle is –47.7(6)°).

In conclusion, the reaction of 2-(bromomethyl)benzaldehyde or 2-(bromomethyl)benzophenone with primary amines leads to the formation of 2-substituted-2*H*-isoindoles. It is demonstrated that the reaction of 1,2-diarylisoindoles with *N*-phenylmaleimide can result in the formation of either Diels–Alder of Michael adducts, depending on the reaction conditions.

Experimental

IR spectra were obtained with a Perkin-Elmer Spectrum BX spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 (400 and 100 MHz, respectively) spectrometer using tetramethylsilane as the internal standard. UV absorption spectra were recorded with a UV-Vis Spectrometer Lambda 20. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were carried out with a Vario MICRO Cube elemental analyser.2-(Bromomethyl)benzaldehyde **1a**[14] and 2-(bromomethyl) phenyl](4-chlorophenyl)methanone **1b**[15] were prepared as described previously in the literature.

*2-Benzyl-2*H*-isoindole* (**3a**): To the solution of benzylamine (1.07 g, 10.0 mmol) in ethanol (10 mL) under an inert atmosphere with intensive stirring was added dropwise a solution of 2-(bromomethyl) benzaldehyde **1a** (1.0 g, 5.0 mmol) in ethanol (4 mL). The reaction mixture was stirred for 2 h at r.t. and the precipitate formed was filtered and washed with the minimal quantity of cold ethanol. Yield 0.91 g (88%); pale yellow solid; m.p. 113–116 °C (lit.[16] m.p.

111–118 °C). IR (KBr) (ν_{max}, cm^{-1}): 3106, 3028, 1713, 1602, 1494, 1455, 1432, 1362, 1323, 1152, 1137, 763, 747 . ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 5.42 (s, 2 H, CH_2), 6.81 (m, 2 H, 5-H, 6-H), 7.22–7.38 (m, 7 H, ArH), 7.45 (m, 2 H, 4-H, 7-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 53.7, 110.9, 119.4, 119.9, 123.9, 127.3, 127.5, 128.4, 138.0 ppm. UV (MeOH): λ_{max} (log ε) = 224 (4.47), 327 (3.49) nm. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.67; H, 6.36; N, 6.81%.

*2-(4-Ethoxyphenyl)-2*H-*isoindole* **(3b)**: Prepared according to the procedure outline for **3a** with the use of 4-ethoxyaniline **2b**, (1.37 g, 10.0 mmol) and 2-(bromomethyl)benzaldehyde (**1a**, 1.0 g, 5.0 mmol). Yield 0.87 g (73%); white solid; m.p. 168–170 °C. IR (KBr) (ν_{max}, cm^{-1}): 3121, 3054, 2980, 2930, 1517, 1476, 1396, 1251, 1184, 1117, 1052, 923, 825, 758. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 1.40 (t, J = 7.2 Hz, 3 H, CH_3), 4.08 (q, J = 7.2 Hz, 2 H, CH_2), 6.85 (m, 2 H, 5-H, 6-H), 7.04 (d, J = 9.0 Hz, 2 H, 3′-H, 5′-H), 7.49 (m, 2 H, 4-H, 7-H), 7.61 (m, 4 H, 1-H, 3-H, 2′-H, 6′-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 14.7, 63.3, 109.4, 115.2, 119.6, 120.7, 122.5, 124.7, 133.3, 157.3 ppm. UV (MeOH): λ_{max} (log ε) = 214 (4.41), 247 (4.37), 297 (4.02), 331 (3.60) nm. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.76; H, 6.39; N, 5.88%.

Synthesis of 1-aryl-2-substituted-2H-isoindoles **3c–h***; general procedure*

To a solution of the appropriate amine **2a–f** (6.46 mmol) in isopropanol (15 mL) was added 2-bromomethyl-4′-chlorobenzophenone **1b** (1.0 g, 3.23 mmol). The reaction mixture was heated for 3 hours at 50 °C, and after cooling the precipitate formed was filtered and washed with isopropanol.

*1-(4-Chlorophenyl)-2-(4-ethoxyphenyl)-2*H-*isoindole* **(3c)**: Yield 0.76 g (68%); white solid; m.p. 162–164 °C. IR (KBr) (ν_{max}, cm^{-1}): 3109, 2980, 2919, 1589, 1513, 1494, 1471, 1245, 1091, 1041, 836, 820, 758, 750. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4)[22]: δ = 1.41 (t, J = 7.2 Hz, 3 H, CH_3), 4.05 (q, J = 7.2 Hz, 2 H, CH_2), 6.92 (m, 4 H, 5-H, 6-H, 3″-H, 5″-H), 7.18 (m, 4 H, 3′-H, 5′-H, 2″-H, 6″-H), 7.29 (d, J = 8.0 Hz, 2 H, 2′-H, 6′-H), 7.41 (s, 1 H, H-3), 7.54 (m, 2 H, 4-H, 7-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 15.0, 63.6, 114.9, 115.1, 119.2, 120.2, 121.2, 121.8, 122.4, 123.6, 124.4, 127.5, 128.6, 130.9, 131.3, 132.7, 158.3 ppm. UV (MeOH): λ_{max} (log ε) = 226 (4.49), 290 (4.15), 360 (3.92) nm. Anal. Calcd for $C_{22}H_{18}ClNO$: C, 75.97; H, 5.22; N, 4.03. Found: C, 75.89; H, 5.18; N, 4.06%.

*1-(4-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-2*H-*isoindole* **(3d)**: Yield 0.75 g (64%); white solid; m.p. 158–160 °C. IR (KBr) (ν_{max}, cm^{-1}): 3075, 2941, 2835, 1597, 1519, 1494, 1443, 1256, 1236, 1169, 1130, 1080, 1021, 831, 811, 747. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 3.65 (s, 3 H, 4″-OCH_3), 3.80 (s, 3 H, 3″-OCH_3), 6.75 (d, J = 8.0 Hz, 1 H, 6″-H), 6.86–6.94 (m, 4 H, 5-H, 6-H, 2″-H, 5″-H), 7.19 (d, J = 8.0 Hz, 2 H, 3′-H, 5′-H), 7.30 (d, J = 8.0 Hz, 2 H, 2′-H, 6′-H), 7.46 (s, 1 H, 3-H), 7.53 (m, 2 H, 4-H, 7-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 56.1, 56.2, 110.9, 112.0, 115.2, 118.6, 119.5, 120.4, 121.4, 122.1, 122.7, 123.9, 124.6, 128.9, 131.2, 131.3, 131.6, 133.2, 149.0, 149.5 ppm. UV (MeOH): λ_{max} (log ε) = 232 (4.49), 298 (4.16), 360 (3.91) nm. Anal. Calcd for $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.99; N, 3.85. Found: C, 72.97; H, 5.04; N 3.79%.

*2-(4-Bromophenyl)-1-(4-chlorophenyl)-2*H-*isoindole* **(3e)**: Yield 0.68 g (55%); slightly yellow solid; m.p. 153–155 °C. IR (KBr) (ν_{max}, cm^{-1}): 3064, 1491, 1399, 1348, 1320, 1194, 1088, 1066, 1013, 834, 755. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 6.93 (m, 2 H, 5-H, 6-H), 7.12–7.24 (m, 4 H, 2″-H, 6″-H, 3′-H, 5′-H), 7.30 (d, J = 8.0 Hz, 2 H, 2′-H, 6′-H), 7.46 (s, 1 H, 3-H), 7.54 (m, 4 H, 4-H, 7-H, 3″-H, 5″-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 114.8, 119.3, 120.3, 121.1, 121.3, 122.2, 122.8, 124.1, 124.7, 128.3, 128.8, 130.4, 131.0, 131.7, 132.5, 139.2 ppm. UV (MeOH): λ_{max} (log ε) = 241 (4.48), 280 (4.17), 357 (3.97) nm. Anal. Calcd for $C_{20}H_{13}BrClN$: C, 62.77; H, 3.42; N, 3.66. Found: C, 63.15; H, 3.51; N, 3.59%.

*1-(4-Chlorophenyl)-2-(4-fluorophenyl)-2*H-*isoindole* **(3f)**: Yield 0.67 g (64%); white solid; m.p. 121–123 °C. IR (KBr) (ν_{max}, cm^{-1}): 3070, 1510, 1494, 1214, 1197, 1088, 839, 822, 755. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 6.93 (m, 2 H, 5-H, 6-H), 7.10–7.22 (m, 4 H, 3′-H, 5′-H, 3″-H, 5″-H), 7.28 (m, 4 H, 2′-H, 6′-H, 2″-H, 6″-H), 7.45 (s, 1 H, 3-H), 7.54 (m, 2 H, 4-H, 7-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 115.2, 116.7 (d, J = 22 Hz), 119.5, 120.5, 121.6, 122.3, 122.9, 124.1, 124.8, 128.7 (d, J = 9 Hz), 129.0, 130.8, 131.3, 131.9, 136.5, 161.9 (d, J = 245 Hz) ppm. UV (MeOH): λ_{max} (log ε) = 244 (4.50), 288 (4.16), 360 (4.03) nm. Anal. Calcd for $C_{20}H_{13}ClFN$: C, 74.65; H, 4.07; N, 4.35. Found: C, 74.83; H, 4.08; N, 4.30%.

*1-(4-Chlorophenyl)-2-cyclohexyl-2*H-*isoindole* **(3g)**: Yield 0.67 g (67%); white solid; m.p. 112–114 °C. IR (KBr) (ν_{max}, cm^{-1}): 3053, 2924, 2852, 1524, 1491, 1446, 1337, 1155, 1085, 1013, 825, 747. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 1.32 (m, 3 H, Alk-H), 1.69 (m, 1 H, Alk-H), 1.84 (m, 4 H, Alk-H), 2.00 (m, 2 H, Alk-H), 4.23 (m, 1 H, NC*H*(CH_2-)$_2$), 6.81 (m, 2 H, 5-H, 6-H), 7.32 (d, J = 8.0 Hz, 1 H, 4(7)-H), 7.36–7.46 (m, 4 H, 3-H, 7(4)-H, 3′-H, 5′-H), 7.48 (d, J = 8.0 Hz, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 25.3, 25.9, 35.1, 56.4, 108.9, 119.0, 119.9, 120.7, 120.9, 121.2, 122.7, 123.9, 129.2, 130.9, 131.6, 132.2 ppm. UV (MeOH): λ_{max} (log ε) = 236 (4.46), 356 (3.85) nm. Anal. Calcd for $C_{20}H_{20}ClN$: C, 77.53; H, 6.51; N, 4.52. Found: C, 77.59; H, 6.48; N, 4.57%.

*2-Benzyl-1-(4-chlorophenyl)-2*H-*isoindole* **(3h)**: Yield 0.42 g (41%); yellow solid; m.p. 101–103 °C. IR (KBr) (ν_{max}, cm^{-1}): 3048, 1522, 1494, 1449, 1415, 1357, 1340, 1214, 1161, 1088, 1010, 831, 750. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 5.45 (s, 2 H, CH_2), 6.85 (m, 2 H, 5-H, 6-H), 6.92 (d, J = 7.2 Hz , 2 H, 2″-H, 6″-H), 7.15–7.24 (m, 3 H, 3″-H, 4″-H, 5″-H), 7.33 (s, 1 H, 3-H), 7.35-7.47 (m, 6 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 51.7, 113.5, 119.2, 120.0, 121.3, 121.6, 121.7, 123.4, 123.9, 126.8, 127.7, 128.9, 129.0, 130.7, 131.4, 132.3, 138.3 ppm. UV (MeOH): λ_{max} (log ε) = 220 (4.45), 358 (3.88) nm. Anal. Calcd for $C_{21}H_{16}ClN$: C, 79.36; H, 5.07; N, 4.41. Found: C, 79.03; H, 5.15; N 4.39%.

Synthesis of Diels–Alder adducts **5c,5e** *and* **5f***; general procedure*

A mixture of the isoindole **3c, 3e** or 3**f** (0.5 mmol) and *N*-phenylmaleimide **4** (86.5 mg, 0.5 mmol) was kept under reflux for 5 hours in isopropanol (10 mL) containing triethylamine (1 mL). After cooling the precipitate was filtered and washed with isopropanol.

Diels–Alder adduct **(5c)**: Yield 0.15 g (57%); light yellow solid; m.p. 169–170 °C. IR (KBr) (ν_{max}, cm^{-1}): 3060, 3032, 2968, 2900, 2866, 1694, 1494, 1372, 1226, 1172, 1042, 822, 744. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 1.33 (t, J = 7.2 Hz, 3 H), 3.85 (dd, J = 7.3, 8.2 Hz, 1 H), 3.91 (q, J = 7.2 Hz, 2 H), 4.50 (d, J = 8.2 Hz, 1 H), 5.64 (d, J = 7.3 Hz, 1 H), 6.41 (m, 2 H), 6.66 (m, 5 H), 7.25–7.35 (m, 5 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 2 H), 7.84 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 15.2, 49.5, 49.8, 63.5, 68.3, 79.0, 115.2, 121.4, 121.5, 121.9, 127.1, 128.0, 128.2, 128.8, 129.1, 129.4, 131.0, 132.1, 133.5, 136.0, 138.3, 140.1, 146.2, 154.1, 174.5, 175.0 ppm. Anal. Calcd for $C_{32}H_{25}ClN_2O_3$: C, 73.77; H, 4.84; N, 5.38. Found: C, 73.52; H, 4.77; N, 5.39%.

Diels–Alder adduct **(5e)**: Yield 0.20 g (72%); light yellow solid; m.p. 175–176 °C. IR (KBr) (ν_{max}, cm^{-1}): 3058, 3042, 2998, 2956, 1700, 1472, 1364, 1166, 758, 740. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 3.85 (dd, J = 7.3, 8.2 Hz, 1 H), 4.50 (d, J = 8.2 Hz, 1 H), 5.80 (d, J = 7.3 Hz, 1 H), 6.39 (m, 2 H), 6.61 (d, J = 7.6 Hz, 1 H), 6.72 (d, J = 8.8 Hz, 2 H), 7.22–7.27 (m, 6 H), 7.31 (t, J = 7.2 Hz, 1 H), 7.41 (d, J = 7.2 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 2 H), 7.84 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 49.0, 49.9, 67.8, 78.8, 114.3, 121.5, 121.9, 122.1, 127.1, 128.2, 128.3, 128.9, 129.1, 129.6, 130.9, 132.0, 132.1, 133.7, 135.6, 139.6, 144.6, 146.1, 174.2, 174.7 ppm. Anal. Calcd for $C_{30}H_{20}BrClN_2O_2$: C, 64.82; H, 3.63; N, 5.04. Found: C, 65.12; H, 3.57; N 5.13%.

Diels–Alder adduct **(5f)**: Yield 0.16 g (65%); light yellow solid; m.p. 148–149 °C. IR (KBr) (ν_{max}, cm^{-1}): 3056, 2962, 1700, 1492, 1360, 1208, 1162, 832, 740. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 3.85 (dd, J = 7.3, 8.2 Hz, 1 H), 4.50 (d, J = 8.2 Hz, 1 H), 5.73 (d, J = 7.3 Hz, 1 H), 6.40 (m, 2 H), 6.64 (d, J = 7.2 Hz, 1 H), 6.77 (m, 2 H), 6.89 (t, J = 8.4 Hz, 2 H), 7.26 (m, 4 H), 7.33 (t, J = 7.2 Hz, 1 H), 7.41 (d, J = 7.2 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 2 H), 7.83 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 49.3, 49.8, 68.2, 79.0, 115.9 (d, J = 22 Hz), 121.6, 121.7 (d, J = 9 Hz), 121.9, 127.1, 128.1, 128.3, 128.8, 129.1, 129.5, 130.9, 132.0, 133.7, 135.7, 139.9, 141.6, 146.0, 157.9 (d, J = 245 Hz), 174.3, 174.8 ppm. Anal. Calcd for $C_{30}H_{20}ClFN_2O_2$: C, 72.80; H, 4.07; N, 5.66. Found: C, 72.73; H, 4.15; N, 5.51%.

Synthesis of Michael adducts **6c, 6e** *and* **6f***: general procedure*

A mixture of of isoindole **3c, 3e** or **3f** (0.5 mmol) and *N*-phenylmaleimide **4** (86.5 mg, 0.5 mmol) was kept under reflux for 5 hours in acetic acid (10 mL) containing anhydrous sodium acetate (1 mg). After cooling the precipitate was filtered and washed with isopropanol.

Michael adduct **(6c)**: Yield 0.19 g (73%); red solid; m.p. 253–254 °C. IR (KBr) (ν_{max}, cm^{-1}): 3062, 2982, 2940, 2888, 1708, 1512, 1498, 1386, 1248, 1180, 754, 698. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 1.41 (t, *J* = 7.2 Hz, 3 H), 2.97 (dd, *J* = 8.0, 17.0 Hz, 1 H), 3.26 (dd, *J* = 10.0, 17.0 Hz, 1 H), 4.03 (q, *J* = 7.2 Hz, 2 H), 4.67 (dd, *J* = 8.0, 10.0 Hz, 1 H), 6.93–7.00 (m, 4 H), 7.19 (m, 5 H), 7.26 (d, *J* = 7.2 Hz, 2 H), 7.41–7.48 (m, 5 H), 7.56 (d, *J* = 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 15.2, 37.0, 38.7, 63.5, 117.7, 120.0, 120.7, 122.2, 122.7, 122.9, 123.2, 123.3, 127.5, 128.9, 129.1, 129.4, 130.6, 131.5, 131.7, 132.8, 132.9, 133.2, 140.1, 175.2, 176.5 ppm. Anal. Calcd for $C_{32}H_{25}ClN_2O_3$: C, 73.77; H, 4.84; N, 5.38. Found: C, 74.03; H, 4.72; N, 5.41%.

Michael adduct **(6e)**: Yield 0.23 g (82%); red solid; m.p. 250–251 °C. IR (KBr) (ν_{max}, cm^{-1}): 3064, 2924, 1712, 1496, 1380, 1184, 1012, 752, 692. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 3.03 (dd, *J* = 8.0, 17.0 Hz, 1 H), 3.29 (dd, *J* = 10.0, 17.0 Hz, 1 H), 4.63 (dd, *J* = 8.0, 10.0 Hz, 1 H), 6.99 (m, 2 H), 7.01–7.70 (m, 15 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 37.1, 38.7, 118.8, 119.8, 120.6, 122.2, 122.8, 122.9, 123.1, 123.2, 127.4, 128.9, 129.0, 129.4, 130.5, 131.6, 131.8, 132.8, 132.9, 133.0, 136.9, 175.2, 176.5 ppm. Anal. Calcd for $C_{30}H_{20}BrClN_2O_2$: C, 64.82; H, 3.63; N, 5.04. Found: C, 64.93; H, 3.54; N, 5.13%.

Michael adduct **(6f)**: Yield 0.19 g (77%); red solid; m.p. 254–255 °C. IR (KBr) (ν_{max}, cm^{-1}): 3060, 2968, 2916, 2840, 1704, 1496, 1364, 1212, 1168, 1076, 860, 748, 736, 696. ^{1}H NMR (400 MHz, DMSO-d_6/CCl_4): δ = 3.00 (dd, *J* = 8.0, 17.0 Hz, 1 H), 3.27 (dd, *J* = 10.0, 17.0 Hz, 1 H), 4.62 (dd, *J* = 8.0, 10.0 Hz, 1 H), 6.99 (m, 2 H), 7.00–7.57 (m, 15 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/CCl_4): δ = 37.0, 38.7, 116.8 (d, *J* = 22 Hz), 118.8, 119.8, 120.7, 122.2, 122.7, 123.1, 123.4, 127.4, 129.0, 129.4, 130.6, 131.6, 131.8 (d, *J* = 9 Hz), 132.9, 133.9, 162.5 (d, *J* = 245 Hz), 175.2, 176.6 ppm. Anal. Calcd for $C_{30}H_{20}ClFN_2O_2$: C, 72.80; H, 4.07; N, 5.66. Found: C, 72.54; H, 4.03; N, 5.51%.

X-ray crystal structure analysis of **6f**: The crystals of **6f** ($C_{30}H_{20}N_2O_2ClF$) are orthorhombic. At 293 K *a* = 23.480(2), *b* = 9.3059(8), *c* = 11.296(1) Å, V = 2468.2(4) Å^3, Mr = 494.93, Z = 4, space group $Pca2_1$, d_{calc} = 1.332 g cm^{-3}, $\mu(MoK_\alpha)$ = 0.193 mm^{-1}, F(000) = 1024. Intensities of 18624 reflections (4248 independent, Rint = 0.121) were measured on the "Xcalibur-3" diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, 2θmax = 50°). The structure was solved by a direct method using the SHELXTL package.[23] Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with U_{iso} = 1.2U_{eq} of the carrier atom. Full-matrix least-squares refinement against F2 in anisotropic approximation for non-hydrogen atoms using 4217 reflections was converged to wR^2 = 0.085 (R^1 = 0.053 for 2158 reflections with F>4σ(F), S = 0.880). The final atomic coordinates, and crystallographic data for molecule **6f** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC. CCDC-821341 (for **6f**) contains the supplementary crystallographic data for this paper.

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