The photochemistry of 1-alkenyl-substituted-1,2,3-benzotriazoles leading to formation of indole and fused indole derivatives

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Abstract

Under photolysis conditions involving irradiation with a 16 W low pressure mercury arc-lamp (254 nm) or sunlight, functionally substituted 1-vinylbenzotriazoles react efficiently to produce 2-acylindoles, 2-benzotriazol-1-yl-4-methylquinolin-3-ol, isatin, indolo[2,1-*b*]quinazoline-6,12-dione (tryptanthrin) and dihydropyrazolo[4,3-*b*]indole.

Keywords: Photolysis, 1-vinylbenzotriazoles, 2-acylindoles, 3-quinolinol, isatin, tryptanthrin, pyrazolo[4,3-*b*]indole

Introduction

It is generally known that 3-substituted indoles can be readily generated via reactions of indoles with electrophilic reagents and that 2-substituted indoles are better produced by using Nenitzescu, Madelung and Gassman ring synthesis methodologies.[1] Earlier, we described a protocol for the synthesis of 3-acylindoles,[2] in which difficultly obtained C-2 substituted indoles could be prepared.

Previous studies have shown that thermolytic and/or photolytic reactions of 1-substituted benzotriazole derivatives take place with elimination of N_2 followed by subsequent ring closure of the resulting biradical intermediates to form heterocyclic products (Figure 1).[3-8] These efficient processes have been described by Katritzky and his coworkers.[9] In a follow up to our earlier efforts in which syntheses of the benzotriazole derivatives **1a-c, 10** and **15** were developed,[10a-d] we gained have explored the photochemistry of these substances, postulating that the reactions would afford 2-substituted indoles in good yields. Below, we report the results of this investigations aimed at the synthesis of substances of 2-substituted indoles through photochemical reactions of benzotriazoles **1a-c, 10** and **15.**

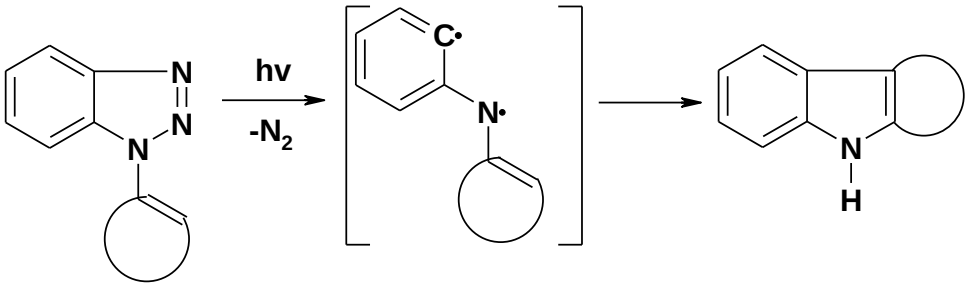
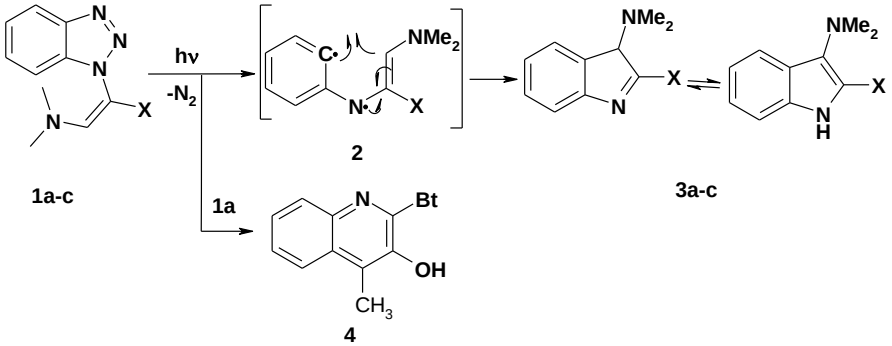


Figure 1

Results and Discussion

The 1-substituted benzotriazole derivatives **1a-c**, **10** and **15**, required in this study, were prepared following the procedures described by us earlier.[10a-d] These substances were fully characterized by using spectroscopic techniques. The UV spectra of these compounds display absorption maxima in the 248-296 nm wavelength regions (Table 1).

In Scheme 1 are summarized the results of reactions promoted by irradiation of acetonitrile solutions of **1a-c** in quartz glass tubes with a 16 W low pressure mercury arc-lamp (254 nm) under a nitrogen atmosphere for 24 h at room temperature. Upon irradiation, benzotriazole **1a** reacts to give 2-acetyl-3-dimethylaminoindole **3a** (58%) and 2-benzotriazolyl-4-methylquinolin-3-ol **4** (15%). The structure of **4** is well defined by its complete ^{1}H NMR, ^{13}C NMR, and mass spectrometric data, as well as by x-ray crystallographic analysis (Figure 4). In a similar manner, **1b** and **1c** undergo photochemical reactions to form only the 2-benzoyl- and 2-cyano-3-dimethylaminoindole derivatives **3b** and **3c**, respectively, in respective yields of 62% and 73% (Table 1). Products **3a-c** can also be generated in 10-18% yields by irradiation of acetonitrile solutions of **1a-c** in Pyrex glass tubes using sunlight for 15 days (Table 1).



a, X = CH_3CO; b, X = PhCO; c, X = CN; Bt = 1-benzotriazolyl

Scheme 1. Photolysis of **1a-c.**

T**able 1**. Photoproducts formed by irradiation of **1a-c**, **10** and **15**

Entry	Substrate	λ_{max}	Condition	Product (Yield)
1	**1a**	286	A	**3a** (58%)
				4 (15%)
2	**1a**		B	**3a** (18%)
3	**1b**	296	A	**3b** (62%)
4	**1b**		B	**3b** (10%)
5	**1c**	278	A	**3c** (73%)
6	**1c**		B	**3c** (16%)
7	**10**	274	A	**12** (41%)
				14 (38%)
8	**15**	248	A	**16** (68%)

A: Irradiation using a low pressure mercury arc-lamp (254 nm); B: Irradiation using sunlight

The structures of all new compounds were assigned by using spectroscopic and analytical methods. The structure of **3a** is readily assigned based on 2D NMR results. The ^{1}H and ^{13}C signal assignments and the H-C correlations from the HMBC 2-D experiments are displayed in Figure 2. The important HMBC results include the observations that H-4 at 7.83 ppm correlates with C-2a, C-6 at 135.2 ppm, 126.1 ppm; H-7 at 7.25 ppm correlates with C-3a, C-5 at 124.3 ppm, 119.6 ppm; H-6 at 7.21 ppm correlates with C-2a, C-4 at 135.2 ppm, 122.9 ppm; H-5 at 6.99 ppm correlates with C-3a, C-7 at 124.3 ppm, 112.6 ppm; H-9 at 2.66 ppm correlates with C-8, C-2 at 190.5 ppm, 128.7 ppm; H-10 at 2.98 ppm correlates with C-3 at 137.8 ppm. Finally, single crystal X-ray structure analysis (Figures 3 and 4) confirmed the structures of the new compounds **3c** and **4**.

2-Acetyl-3-dimethylamino-1*H*-indole

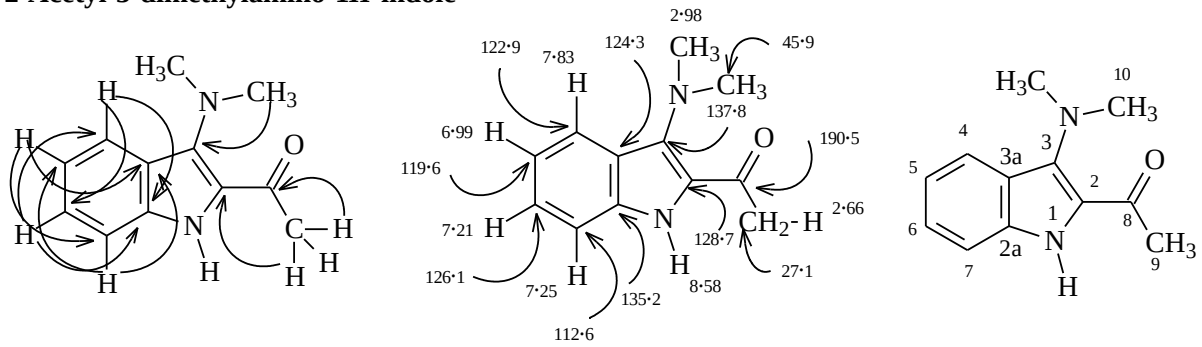


Figure 2. Important HMBC, H-C correlation of compound **3a.**

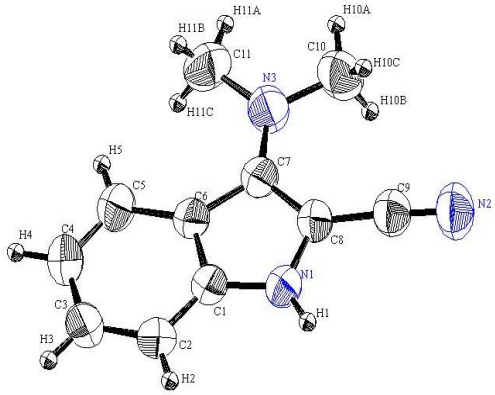


Figure 3. ORTEP drawing of **3c**.

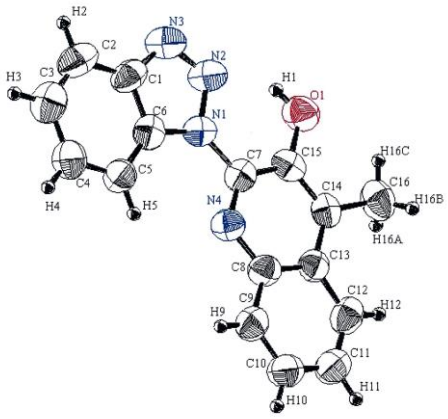
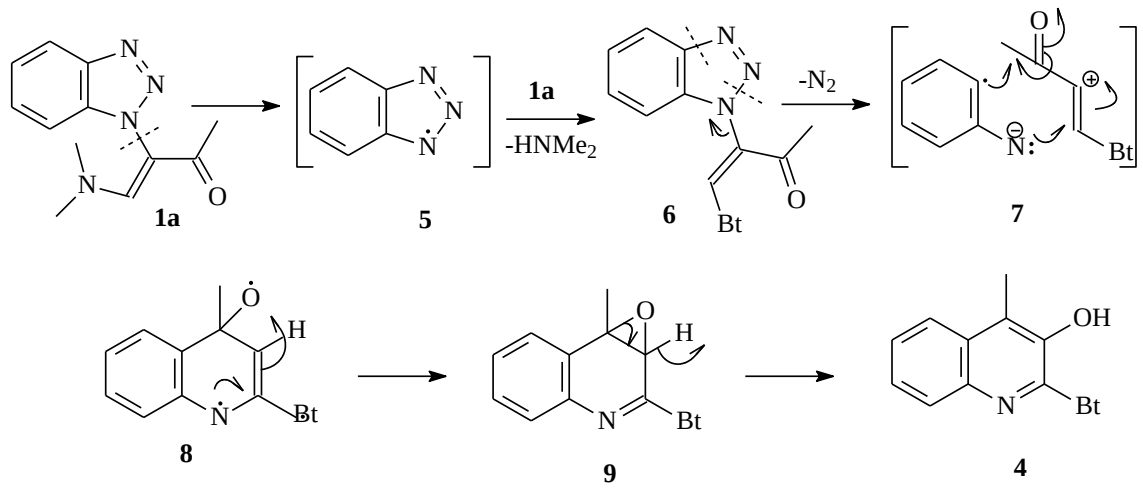


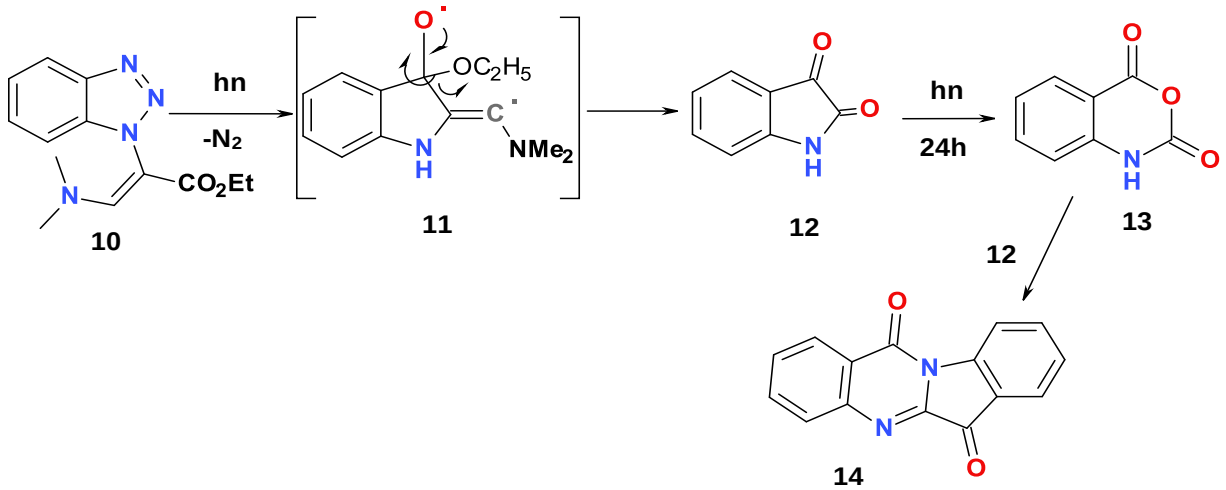
Figure 4. ORTEP drawing of **4**.

The formation of **3a-c** in these processes can be readily explained by a mechanism involving initial photo-extrusion of N_2 to form the corresponding diradical intermediates **2**, which then cyclize followed by a 1,3-H shift to yield the indole derivatives. On the other hand, formation of 2-benzotriazolyl-4-methylquinolin-3-ol **4** from **1a** is likely a result of initial excited state N1-C bond cleavage to give radical **5**, which then reacts with another molecule of **1a** to form **6**. The latter intermediate then loses N_2 and rearranges to give radicals **7, 8** and **9** sequentially and finally **4** (Scheme 2).



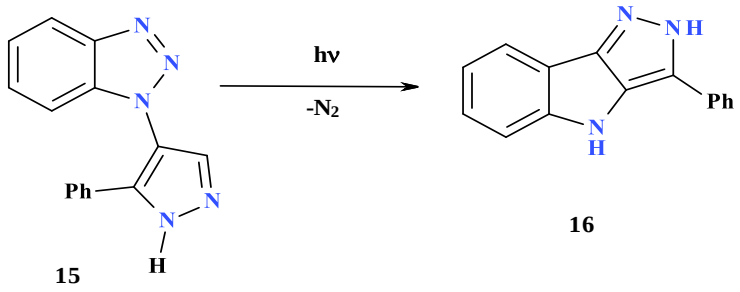
Scheme 2. Possible mechanism for the formation of **4.**

Photochemical reaction of ethyl 2-benzotriazol-1-yl-3-dimethylaminoacrylate **10** gives isatin **12** (41%) and indolo[2,1-*b*]quinazoline-6,12-dione (tryptanthrin) **14** (39%) (Scheme 3, Table 1). A plausible route for formation of isatin involves the intermediacy of biradical **11.** A similar pathway has been previously described.[11] On the other hand, the tetracyclic product **14** is most likely formed by secondary photochemical reaction of **12** giving isatoic anhydride **13** that relies on the presence of traces of water in the reaction mixture. This assumption was probed by carrying out photoreaction of **12**, which after a 24 h irradiation period gave **13** in quantitative yield. It has been previously reported that under basic conditions anhydride **13** reacts with **12** to produce **14**.[12a] It should be noted that the present method serves as a direct route for the preparation of tryptanthrin **14**, a well known and biologically interesting natural product.[12b]



Scheme 3. Photolysis products of compound **10.**

The current studies were extended to include the exploration of the photochemistry of 1-(5-phenyl-1*H*-pyrazol-4-yl)-1*H*-benzotriazole **15**, which was observed to undergo irradiation promoted N_2 elimination to generate a biradical intermediate that cyclizes to yield the corresponding 3-phenyl-1,4-dihydropyrazolo[4,3-*b*]indole **16** in 68% yield (Scheme 4).



Scheme 4. Photolysis of **15.**

Conclusion

The investigation described above has resulted in an efficient direct photochemical methodology for the preparation of new indole derivatives, some of which are difficult to obtain using other procedures. Also, a new interesting photochemical route for synthesis of the biologically active natural product tryptanthrin as well as other biologically and pharmaceutically interesting indole and condensed indole derivatives have been developed.[13-15]

Experimental Section

General. Melting points were recorded on a Gallenkamp apparatus. IR spectra were recorded using KBr pellets on a Perkin-Elmer 2000 FT-IR spectrophotometer. ^{1}H- and ^{13}C- NMR spectra were recorded on a Bruker DPX 400 MHz, Avance^{II} 600 MHz super-conducting NMR spectrometer with proton spectra measured at 400 MHz and carbon spectra at 100 and 150 MHz. All chemical shifts are reported in ppm relative to tetramethylsilane (TMS) for ^{1}H or $CHCl_3$ for ^{13}C. IR data are reported in cm^{-1}. Mass spectra were measured on a VG Auto-spec-Q (high resolution, high performance, tri-sector GC/MS/MS) and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalysis were performed on a LECO CH NS-932 Elemental Analyzer. The UV/VIS absorption spectra were recorded using a Varian Cary 5 instrument. X-Ray analysis were performed using a Rigaku Rapid II diffractometer.

Starting materials. Starting compounds **1a-c, 10** and **15** were prepared using previously reported procedures.[10a-d]

Preparation of (15). A mixture of **1b** (2.92 g, 10 mmol) and hydrazine hydrate (99%, 3 mL) in ethanol (25 mL) was stirred at reflux for 3-4 h. Concentration of the mixture *in vacuo* gave a residue which was subjected to crystallization from ethanol.

1-(5-Phenyl-1*H*-pyrazol-4-yl)-1*H*-benzotriazole (15). Yield 2.0 g (76%) from ethanol, mp 168-170 ºC. UV/VIS ($CHCl_3$): λ_{max} = 248 nm. ^{1}H NMR (400 MHz, DMSO-d_6): 13.58 (br, 1H, NH), 8.36 (s, 1H), 8.17 (d, 1H, *J* 8.4 Hz), 7.53 (t, 1H, *J* 8.4 Hz), 7.47 (t, 1H, *J* 8.4 Hz), 7.40 (d, 1H, *J* 8.4 Hz), 7.27 (m, 3H), 7.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 145.3, 144.9, 134.3, 131.3, 129.2, 128.7, 128.5, 128.2, 126.1, 124.5, 119.5, 114.8, 110.4. MS: *m/z* (%) 261 (M^+, 40), 233 (100), 205 (50). Anal. Calc. for $C_{15}H_{11}N_5$ (261.3): C 68.95; H 4.24; N 26.80. Found: C 68.90; H 4.19; N 26.77%.

Photochemistry

Method A. **Irradiation using a low pressure mercury arc-lamp**. Each of the substrates **1a-c, 10** and **15** (1.0 mmol) was dissolved in acetonitrile (25 mL) in a quartz tube and purged with nitrogen while being irradiated for 24 h at room temperature (RT). The progress of each reaction was monitored by using TLC. The solvent was removed *in vacuo* and the resulting residue was subjected to column chromatography on silica gel using ethyl acetate/ petroleum (b.p. 60-80 ºC) as the eluent to give the corresponding products (Table 1).

Method B. Irradiation using sunlight. Each of the substrates **1a-c** (0.5 g) was dissolved in acetonitrile (150 mL) in a Pyrex tube, purged with nitrogen, and exposed to direct sunlight for 15 days in (July 1-15) at RT. The progress of each reaction was monitored by using TLC and LCMS. The solvent was removed *in vacuo* and the resulting residue was subjected to column chromatography on silica gel using ethyl acetate/ petroleum (b.p. 60-80 ºC) as eluent to give the products **3a-c** in 10-18% yields (Table 1).

2-Acetyl-3-dimethylamino-1*H*-indole (3a). Yellow crystals from ethanol, mp 145-146 ºC, yield 58% (method A), 18% (method B), (R_f 0.48, EtOAc: petroleum b.p. 40-60 ºC: 1:8v/v). IR: 3337, 3064, 2974, 1639, 1571, 1527, 1452, 1332, 1249, 1192, 975, 927, 744, 712. ^{1}H NMR (400 MHz, $CDCl_3$): 8.58 (br, 1H, NH), 7.83 (d, 1H, *J* 8.0 Hz), 7.25 (d, 1H, *J* 8.0 Hz), 7.21 (t, 1H, *J* 7.8 Hz), 6.99 (t, 1H, *J* 7.8 Hz), 2.98 (s, 6H, $2CH_3$), 2.66 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 190.5, 137.8, 135.2, 128.7, 126.1, 124.3, 122.9, 119.6, 112.6, 45.9 (2C), 27.1. LCMS: *m/z* = 203 (M + 1). MS: *m/z* (%) 202 (M^+, 100), 158 (75), 105 (100). Anal. Calc. for $C_{12}H_{14}N_2O$ (202.3): C 71.26; H 6.98; N 13.85. Found: C 71.20; H 6.90; N 13.79%.

2-Benzotriazol-1-yl-4-methylquinolin-3-ol (4). Yield 15 %, (method A). Yellow crystals from ethanol: mp 174-176 ºC. (R_f 0.68, EtOAc: petroleum b.p. 40-60 ºC, 1:5). IR: 3181, 3065, 2955, 2860, 1728, 1451, 1379, 1272, 1122, 1072, 747cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): 10.69 (s, 1H, OH), 9.13 (d, 1H, *J* 8.4 Hz), 8.25 (d, 1H, *J* 8.4 Hz), 8.12 (dd, 1H, *J* 8.0, 1,4 Hz), 8.00 (dd, 1H, *J* 8.0, 1.4 Hz), 7.79 (t, 1H, *J* 8.0 Hz), 7.68-7.59 (m, 3H), 2.78 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): 145.1, 140.6, 140.5, 139.0, 132.0, 130.4, 129.8, 128.9, 128.4, 127.2, 126.9, 126.1, 123.2, 120.1, 116.4, 11.0. LCMS: *m/z* = 277 (M + 1). MS: *m/z* (%) 276 (M^+, 20), 248 (45), 219

(100). Anal. Calc. for $C_{16}H_{12}N_4O$ (276.3): C 69.55; H 4.38; N 20.28. Found: C 69.49; H 4.34; N 20.27%. HRMS = 276.1005, requires $C_{16}H_{12}N_4O$ 276.1005.

2-Benzoyl-3-dimethylamino-1*H*-indole (3b). Yellow crystals from ethanol: mp 197-198 ºC, yield 62% (method A), 10% (method B), (R_f 0.47, EtOAc: petroleum b.p. 40-60 ºC: 3:7). IR: 3337, 3064, 2974, 1639, 1571, 1527, 1452, 1332, 1249, 1192, 975, 927, 744, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 8.08 (d, 1H, *J* 8.4 Hz), 7.68 (d, 1H, *J* 8.0 Hz), 7.55 (d, 2H, *J* 8.0 Hz), 7.40-7.33 (m, 3H), 7.26 (t, 2H, *J* 7.8 Hz), 7.03 (t, 1H, *J* 8.0 Hz), 3.28 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 190.6, 151.7, 138.5, 134.4, 130.0, 128.1, 127.9, 127.7, 127.3, 125.9, 123.6, 119.2, 108.4, 43.0 (2C). LCMS: *m/z* = 265 (M+1). MS: *m/z* (%) 264 (M^+, 20), 208 (65), 105 (50), 77 (100). (HRMS = 264.1258, requires $C_{17}H_{16}N_2O$ 264.1257).

3-Dimethylamino-1*H*-indole 2-carbonitrile (3c). Colorless crystals, mp 91-92 ºC, yield 73% (method A), 16 % (method B), (R_f 0.57, EtOAc: petroleum bp 40-60 ºC: 1:9). IR: 3305, 3067, 2924, 2202, 1571, 1549, 1455, 1339, 1219, 1137, 915, 744. ^1H NMR (600 MHz, $CDCl_3$): 7.73 (d, 1H, *J* 8.4 Hz), 7.71 (br, 1H, NH), 7.33 (dt, 1H, *J* 8.4, 1.2 Hz), 7.26 (d, 1H, *J* 8.4 Hz), 7.10 (dt, 1H, *J* 8.0, 1.2 Hz), 3.18 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 142.6, 137.2, 126.6, 121.6, 120.7, 120.0, 116.8, 111.9, 91.9, 43.8 (2C). MS: *m/z* (%) 185 (M^+, 100), 170 (60), 142 (50). Anal. Calc. for $C_{11}H_{11}N_3$ (185.2): C 71.33; H 5.99; N 22.69. Found: C 71.23; H 5.90; N 22.63%. (HRMS = 185.0948, requires $C_{11}H_{11}N_3$ 185.0947).

1*H*-Indol-2,3-dione (Isatin) (12). Red brown crystals, mp 196-197 ºC (lit.[16] 195-197 ºC).

Isatoic anhydride (13). Colorless crystals from ethanol, mp 243-45 ºC (lit.[12a] 243-47 ºC).

Indolo[2,1-*b*]quinazoline-6,12-dione (Tryptanthrin) (14). Greenish yellow needles, mp 265-267 ºC (lit.[12b] mp 266-267 ºC). IR: 3020, 2938, 1732, 1691, 1585, 1462, 1314, 1194, 1110, 1036, 916, 751. ^1H NMR (600 MHz, $CDCl_3$): 8.65 (d, 1H, *J* 8.0 Hz), 8.47 (dd, 1H, *J* 8.0, 1.2 Hz), 8.06 (dd, 1H, *J* 8.0, 1.2 Hz), 7.94 (dd, 1H, *J* 7.8, 1.0 Hz), 7.88 (dt, 1H, *J* 7.8, 1.2 Hz), 7.80 (dt, 1H, *J* 7.8, 1.2 Hz), 7.71 (t, 1H, *J* 8.0 Hz), 7.46 (t, 1H, *J* 7.8 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): 182.6, 158.1, 146.7, 146.4, 144.4, 138.3, 135.1, 130.8, 130.3, 127.6, 127.2, 125.4, 123.8, 121.9, 118.0. MS: *m/z* (%) 248 (M^+, 100), 220 (30), 192 (15). Anal. Calc. for $C_{15}H_8N_2O_2$ (248.28): C 72.58; H 3.25; N 11.28. Found: C 72.50; H 3.24; N 11.19%.

3-phenyl-1,4-dihydropyrazolo[4,3-*b*]indole (16). Colorless crystal from ethanol, mp 195-197 ºC, yield 68% (method A), (R_f 0.47, EtOAc: petroleum, bp 40-60°: 1 : 5). IR: 3020, 2938, 1732, 1691, 1595, 1462, 1314, 1194, 1110, 1036, 916, 751. ^1H NMR (400 MHz, DMSO-d_6): 12.98 (br, 1H, NH), 10.97 (br, 1H, NH), 7.98 (d, 2H, *J* 7.8 Hz), 7.77 (d, 1H, *J* 7.8 Hz), 7.50 (d, 1H, *J* 7.8 Hz), 7.46 (t, 2H, *J* 7.8 Hz), 7.29 (m, 2H), 7.09 (t, 1H, *J* 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 145.3, 131.7, 130.9, 129.1, 128.7, 127.9, 127.7, 125.5, 125.4, 119.9, 119.7, 114.7, 112.5. MS: *m/z* (%) 233 (M^+ 100), 205 (10), 103 (25). Anal. Calc. for $C_{15}H_{11}N_3$ (233.3): C 77.23; H 4.75; N 18.01. Found: C 77.20; H 4.68; N 18.07.

Acknowledgements

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17. Crystallographic data of for the structures (excluding structure factors) in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 836134 **3c** and CCDC 836135 **4**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK).

