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Photochemical synthesis of indazolo[3,2-*b*]quinazolines and their redox-switching properties

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ABSTRACT

Several indazolo[3,2-*b*]quinazolines were synthesized in moderate to good yields by exposing 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinazolines to UV light (306 nm) in acetonitrile. The scope, limitation, and possible mechanism of this light-mediated reaction as well as the redox-switching properties of the target compounds were explored. Reduction of the colored indazolo[3,2-*b*]quinazoline with sodium borohydride resulted in a distinct change to colorless and a sharp increase in fluorescence intensity. The reduced product can be swiftly reverted to the original form by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidation. The reversible redox-switching between the indazolo[3,2-*b*]quinazoline and its reduced product utilizing chemical reduction and oxidation as two external stimuli with dual output properties; that is, color change and emission variation was reported.

1. Introduction

Indazoloquinazolines refer to a small family of indazole- and quinazoline-fused heterocycles, including indazolo[2,3-*a*]quinazolines [1], indazolo[2,3-*c*]quinazolines [2], and indazolo[3,2-*b*]quinazolines [3–6] (Fig. 1). The molecular scaffolds of indazoloquinazolines are rarely present in the natural products, but indazoloquinazoline-derived compounds have been reported to possess a wide range of biological activities. Some indazolo[2,3-*a*]quinazoline derivatives [7], for instance, were found to exhibit anti-bacterial activity against Gram-negative bacteria and anti-fungal activity against yeast, whereas indazolo[2,3-*c*]quinazoline-11-sulfonamide [2] was claimed to possess therapeutic activity against inflammation. Nevertheless, the biological and physical properties of indazolo[3,2-*b*]quinazoline derivatives have not yet been described. In light of the potential biological activity associated with the indazole/quinazoline-fused molecular structure, we envisage that an efficient preparation of the indazolo[3,2-*b*]quinazoline derivatives may facilitate the exploration of their properties.

Recently we reported [8] an efficient route for the preparation of indazolo[2,3-*a*]quinoline derivatives from 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinolines via visible light photoredox catalysis, as shown in Fig. 2. The successful formation of an indazole functionality via light-mediated cyclization of an *N*-(2-nitrobenzyl)aniline moiety prompted us to examine the possibility of extending this methodology to the preparation of indazoloquinazolines. Herein, we describe our efforts to the facile synthesis of indazolo[3,2-*b*]quinazoline derivatives by exposing 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinazolines to UV light in acetonitrile. The scope and limitation of this photochemical reaction as well as the properties of the target compounds were investigated.

2. Experimental

2.1. General

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. MS were performed on JEOL JMS-SX/SX 102A spectrometer. Single crystal structures were determined by a Bruker AXS SMART-1000 X-ray single-crystal diffractometer. IR spectra were obtained using a 1725XFT-IR spectrophotometer. Absorption spectra were recorded using an HP8453 spectrophotometer. Fluorescence spectra were measured with a Hitachi F-4500 fluorescence spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Varian VXR300 spectrometer as well as 600 and 150 MHz on a Varian Unity Inova 600 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal

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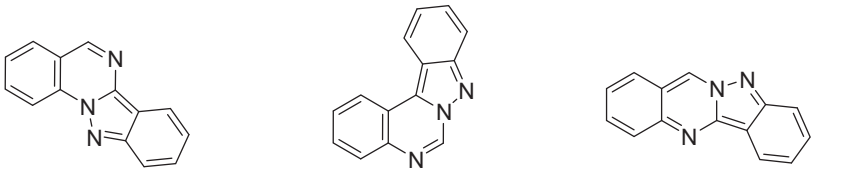


Fig. 1. Structures of indazoloquinazolines.

standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. The visible light irradiation reaction was performed with a 23 W household fluorescence lamp.

2.2. Calculation of fluorescence quantum yield

Quinine hemisulfate salt monohydrate (Φ_f = 0.546, λ_{max} = 455 nm in aqueous H_2SO_4) was used as an external standard for the measurement of fluorescence quantum yields of **1b** and **24**. Fluorescence quantum yields were measured by comparing the integrated area under the fluorescence curve for compounds **1b**, **24**, and quinine sulfate dihydrate at equal absorbance at the same excitation wavelength. The quantum yields were corrected for the refractive index of the solvent.

2.3. General procedure for the preparation of compounds ***4a–e***

To a solution of *o*-aminobenzylamine (**2**, 4.1 mmol) in ethanol (25 mL) was added *o*-nitrobenzaldehydes (**3**, 4.1 mmol) and a catalytic amount of ammonium chloride (0.04 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1–2 h. The precipitate was then filtered and washed with water and hexanes to afford the desired product.

2.3.1. 2-(2-Nitrophenyl)-1,2,3,4-tetrahydroquinazoline (***4a***)

Yellow solid; yield 95%; R_f = 0.4 (20% EtOAc/hexanes); mp 80–81 °C (lit.[9] 80–81 °C); IR ν_{max} (KBr) 3412, 3319, 1605, 1523, 1484, 1359, 1255, 1110, 1043, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (td, J = 8.1, 1.5 Hz, 2H), 7.57 (td, J = 7.8, 1.5 Hz, 1H), 7.45 (td, J = 7.8, 1.5 Hz, 1H), 7.07 (td, J = 7.5, 1.2 Hz, 1H), 6.91 (d, J = 6.9 Hz, 1H), 6.73 (td, J = 7.5, 1.2 Hz, 1H), 6.65 (dd, J = 8.1, 0.9 Hz, 1H), 5.89 (s, 1H), 4.34 (s, 1H), 4.04, 3.73 (ABq, J = 16.5 Hz, 1H each).

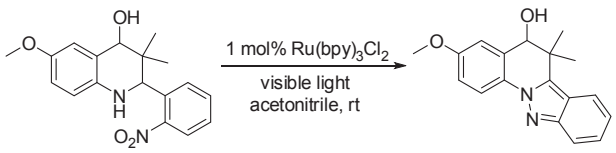


Fig. 2. Visible light-mediated preparation of indazolo[2,3-*a*]quinoline.

2.3.2. N,N-dimethyl-3-nitro-4-(1,2,3,4-tetrahydroquinazolin-2-yl) aniline (***4b***)

Yellow solid; yield 97%; R_f = 0.4 (40% EtOAc/hexanes); mp 115–116 °C; IR ν_{max} (KBr) 3400, 3332, 2871, 1605, 1531, 1483, 1266, 1071, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (d, J = 8.7 Hz, 1H), 7.02–7.11 (m, 2H), 6.91 (d, J = 7.2 Hz, 1H), 6.83 (dd, J = 9.0, 3.0 Hz, 1H), 6.71 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 5.66 (d, J = 1.8 Hz, 1H), 4.26 (s, 1H), 4.13, 3.85 (ABq, J = 16.5 Hz, 1H each), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.1, 150.0, 143.3, 129.1, 127.1, 126.1, 121.9, 121.3, 118.1, 115.4, 115.1, 106.9, 64.4, 45.5, 40.1; HRMS (EI) calcd for $C_{16}H_{18}N_4O_2$ [M$^+$] 298.1430, found 298.1435.

2.3.3. 2-(6-Nitrobenzo[d][1,3]dioxol-5-yl)-1,2,3,4-tetrahydroquinazoline (***4c***)

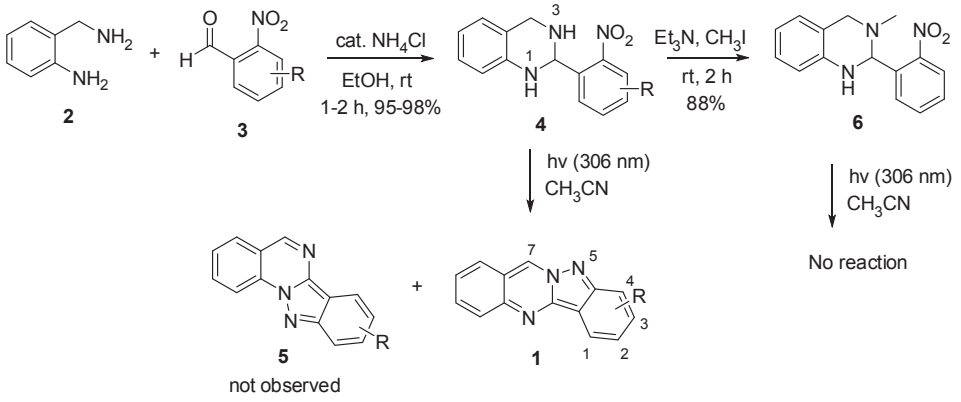
Yellow solid; yield 97%; R_f = 0.6 (40% EtOAc/hexanes); mp 104–105 °C; IR ν_{max} (KBr) 3332, 2779, 1716, 1612, 1501, 1478, 1328, 1251, 1036, 929, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 1H), 7.07 (t, J = 8.1 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.74 (td, J = 7.5, 1.2 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.12, 6.10 (ABq, J = 1.2 Hz, 1H each), 5.86 (s, 1H), 4.28 (s, 1H), 4.11, 3.82 (ABq, J = 16.5 Hz, 1H each); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4, 146.7, 143.4, 142.7, 133.1, 126.9, 125.8, 120.5, 116.3, 114.2, 108.0, 105.4, 103.2, 63.1, 43.5; HRMS (EI) calcd for $C_{15}H_{13}N_3O_4$ [M$^+$] 299.0906, found 299.0903.

2.3.4. 2-(4-Bromo-2-nitrophenyl)-1,2,3,4-tetrahydroquinazoline (***4d***)

Yellow solid; yield 98%; R_f = 0.4 (20% EtOAc/hexanes); mp 125–126 °C; IR ν_{max} (KBr) 3412, 3331, 1709, 1606, 1530, 1488, 1364, 1258, 1051, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (dd, J = 1.8, 0.9 Hz, 1H), 7.67 (d, J = 1.8 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 6.73 (td, J = 7.5, 1.8 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 5.90 (d, J = 3.3 Hz, 1H), 4.32 (s, 1H), 3.96, 3.63 (ABq, J = 16.8 Hz, 1H each); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4, 141.9, 135.3, 135.0, 130.5, 127.5, 127.4, 126.2, 121.9, 121.3, 118.5, 115.2, 63.9, 43.9; HRMS (EI) calcd for $C_{14}H_{12}BrN_3O_2$ [M$^+$] 333.0113, found 333.0117.

2.3.5. 2-(1-Nitronaphthalen-2-yl)-1,2,3,4-tetrahydroquinazoline (***4e***)

Yellow solid; yield 78%; R_f = 0.4 (20% EtOAc/hexanes); mp 121–122 °C; IR ν_{max} (KBr) 3414, 3326, 1710, 1609, 1528, 1489, 1263, 1116, 1066, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (d, J = 9.0 Hz, 1H), 7.92 (dd, J = 7.2, 2.4 Hz, 1H), 7.79–7.75 (m, 2H), 7.68–7.58 (m, 2H), 7.08 (t, J = 8.7 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.75 (td, J = 7.5, 1.2 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 5.62 (d, J = 1.8 Hz, 1H), 4.32 (bs, 1H), 4.16, 3.90 (ABq, J = 16.5 Hz, 1H each); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 147.0, 142.6, 133.6, 131.0, 130.5, 128.8, 128.0, 127.6, 127.4, 126.3, 124.4, 124.0, 121.8, 121.3, 118.7, 115.3, 65.5, 45.4; HRMS (EI) calcd for $C_{18}H_{15}N_3O_2$ [M$^+$] 305.1164, found 305.1160.



Scheme 1. Synthesis of the indazolo[3,2-*b*]quinazolines **1**.

2.4. General procedure for the preparation of compounds ***1a–e***, ***15***, ***17***

Photoreactions were performed in the Rayonet photochemical reactor equipped with 306 nm lamps (8 watts each × 8). To a solution of **4** (3×10^{-3} M) in acetonitrile (20 mL) was irradiated for 90 min. The solution was then concentrated *in vacuo* and the product was purified by column chromatography (5–20% EtOAc and benzene) to give the product.

2.4.1. Indazolo[3,2-b]quinazoline (*1a*)

Red solid; yield 86%; R_f = 0.4 (20% EtOAc/hexanes); mp 216–217 °C; IR ν_{max} (KBr) 3043, 1711, 1635, 1439, 1361, 1099, 906, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.66 (s, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.74–7.89 (m, 3H), 7.60 (t, J = 8.1 Hz, 1H), 7.37 (td, J = 8.1, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 144.9, 143.8, 131.4, 131.3, 128.4, 126.9, 125.7, 121.9, 119.9, 119.0, 115.1, 112.1; HRMS (EI) calcd for $C_{14}H_9N_3$ [M^+] 219.0796, found 219.0790.

2.4.2. N,N-dimethylindazolo[3,2-b]quinazolin-3-amine (*1b*)

Orange solid; yield 62%; R_f = 0.4 (40% EtOAc/hexanes); mp 200 °C (dec.); IR ν_{max} (KBr) 3047, 2900, 1715, 1634, 1435, 1121, 1098, 902, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.44 (s, 1H), 8.29 (d, J = 8.7 Hz, 1H), 9.00 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.72 (td, J = 8.1, 1.8 Hz, 1H), 7.48 (t, J = 8.1 Hz, 1H), 6.93 (dd, J = 9.0 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 3.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 153.5, 145.3, 143.7, 130.9, 129.8, 127.8, 125.8, 125.7, 122.4, 118.1, 109.9, 103.5, 92.6, 40.7; HRMS (EI) calcd for $C_{16}H_{14}N_4$ [M^+] 262.1218, found 262.1213.

2.4.3. [1,3]Dioxolo[4′,5′:5,6]indazolo[3,2-b]quinazoline (*1c*)

Red solid; yield 84%; R_f = 0.6 (40% EtOAc/hexanes); mp 256–257 °C; IR ν_{max} (KBr) 3050, 2910, 1708, 1649, 1492, 1449, 1365, 1301, 1188, 1108, 1042, 954 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (dd, J = 9.0, 0.9 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.72–7.78 (m, 2H), 7.51 (td, J = 7.8, 1.2 Hz, 1H), 7.18 (d, J = 0.6 Hz, 1H), 6.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.7, 151.8, 144.3, 144.1, 143.9, 131.3, 130.9, 128.1, 126.1, 125.8, 118.0, 105.7, 101.6, 97.8, 93.3; HRMS (EI) calcd for $C_{15}H_9N_3O_2$ [M^+] 263.0695, found 263.0698.

2.4.4. 3-Bromoindazolo[3,2-b]quinazoline (*1d*)

Orange solid; yield 65%; R_f = 0.4 (20% EtOAc/hexanes); mp 262–263 °C; IR ν_{max} (KBr) 3044, 1713, 1634, 1425, 1366, 1106, 1038, 918, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.64 (s, 1H), 8.36 (d, J = 8.7 Hz, 1H), 8.21 (d, J = 8.7 Hz, 1H), 8.01–7.98 (m, 2H), 7.85 (td, J = 7.8, 1.5 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.42 (dd, J = 8.7, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 144.7, 144.3, 131.9, 131.3, 128.4, 127.2, 125.91, 125.86, 123.4, 123.0, 119.1, 117.7, 110.9; HRMS (EI) calcd for $C_{14}H_8BrN_3$ [M^+] 296.9902, found 296.9908.

2.4.5. Benzo[6,7]indazolo[3,2-b]quinazoline (*1e*)

Red solid; yield 62%; R_f = 0.5 (20% EtOAc/hexanes); mp 264–265 °C; IR ν_{max} (KBr) 3033, 1711, 1614, 1422, 1395, 1325, 1110, 745 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 9.28 (d, J = 7.8 Hz, 1H), 8.80 (s, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.2 Hz, 1H), 7.18–7.10 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.86 (t, J = 6.6 Hz, 1H); ^{13}C NMR (C_6D_6, 150 MHz) δ 153.4, 145.2, 145.1, 135.6, 131.9, 131.0, 130.3, 128.9, 128.3, 126.4, 126.2, 125.3, 124.8, 123.9,

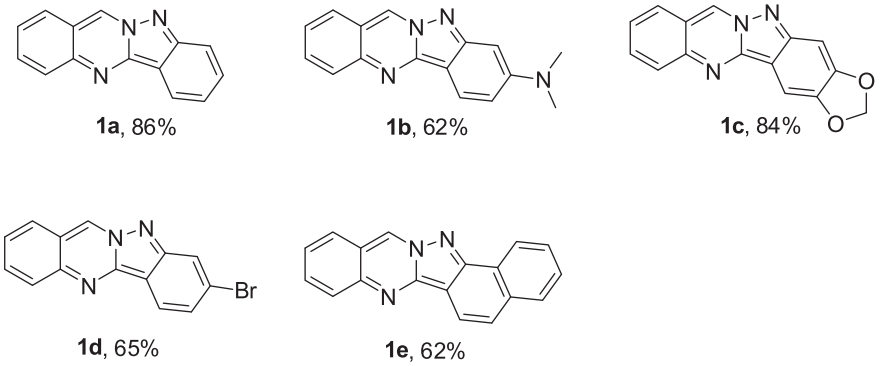


Fig. 3. Structures of the prepared **1a–e**.

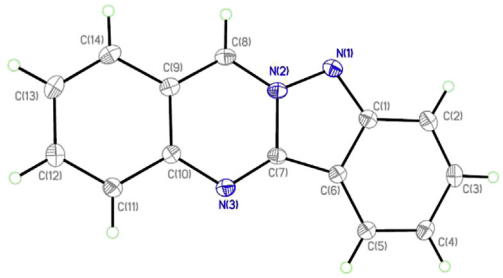


Fig. 4. X-ray crystal structure of **1a**.

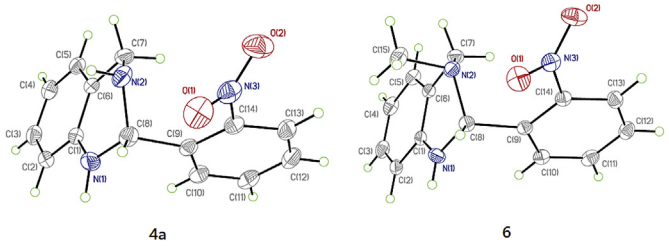


Fig. 5. X-ray crystal structures of **4a** and **6**.

121.6, 119.2, 118.0, 108.0; HRMS (EI) calcd for $C_{18}H_{11}N_3$ [M^+] 269.0953, found 269.0959.

*2.4.6. N-(2-carbamoylphenyl)-6-nitrosobenzo[d][1,3]dioxole-5-carboxamide (**15**)*

Dark green solid; yield 84%; $R_f = 0.6$ (40% EtOAc/hexanes); mp 162–163 °C; IR ν_{max} (KBr) 3249, 1694, 1583, 1465, 1364, 1281, 1090, 1021, 920, 769 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 13.00 (s, 1H), 8.19 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.87 (td, $J = 8.1$, 1.5 Hz, 1H), 7.75 (d, $J = 7.5$ Hz, 1H), 7.65 (s, 1H), 7.58 (td, $J = 8.1$, 1.2 Hz, 1H), 6.31 (s, 2H), 6.14 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 198.5, 191.6, 189.9, 187.6, 186.0, 176.4, 172.1, 165.0, 164.6, 163.3, 158.7, 147.1, 141.4, 124.6; HRMS (EI) calcd for $C_{15}H_{11}N_3O_5$ [M^+] 313.0699, found 313.0691.

*2.4.7. 3-Methyl-2-(6-nitrosobenzo[d][1,3]dioxol-5-yl)quinazolin-4(3H)-one (**17**)*

Light green solid; yield 85%; $R_f = 0.3$ (20% EtOAc/hexanes); mp 226–227 °C; IR ν_{max} (KBr) 1674, 1567, 1472, 1346, 1265, 1068, 1014, 921, 771 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.23 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.86 (ddd, $J = 8.7$, 7.2, 1.5 Hz, 1H), 7.70–7.65 (m, 3H), 7.60 (ddd, $J = 8.1$, 7.2, 1.2 Hz, 1H), 6.33 (s, 2H), 3.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 198.5, 198.4, 192.5, 191.3, 187.5, 184.3, 177.0, 172.0, 164.8, 164.6, 163.6, 158.0, 146.4, 141.6, 126.0, 70.7; HRMS (EI) calcd for $C_{16}H_{11}N_3O_4$ [M^+] 309.0750, found 309.0755.

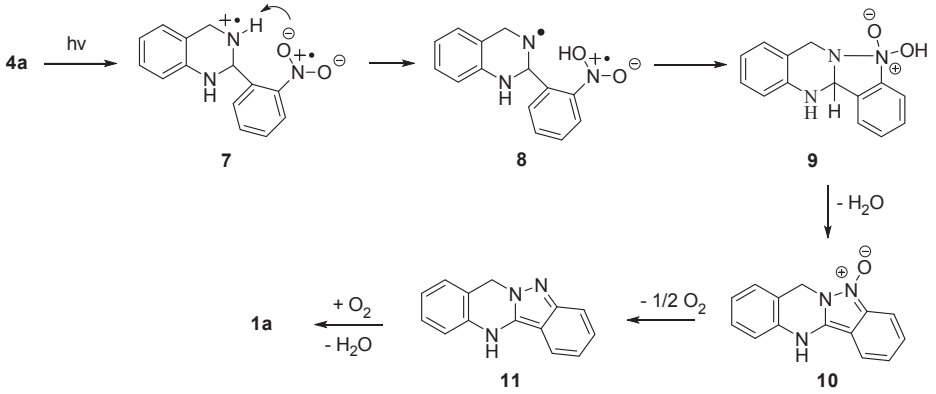
*2.5. Preparation of compounds **12**, **6**, **16**, **21**, **23**, **24***

*2.5.1. 2-(6-Nitrobenzo[d][1,3]dioxol-5-yl)-2,3-dihydroquinazolin-4(1H)-one (**12**)*

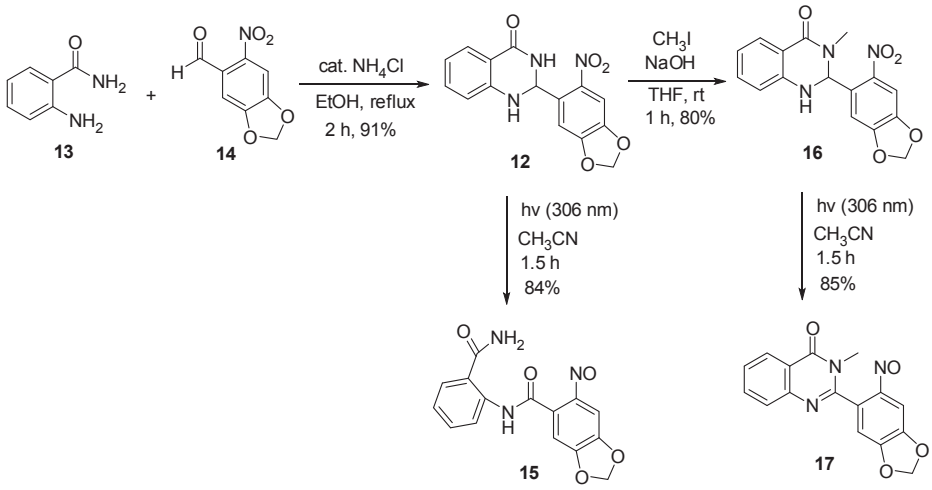
To a solution of 2-aminobenzamide (**13**, 500 mg, 3.67 mmol) in ethanol (25 mL) was added 6-nitrobenzo[*d*][1,3]dioxole-5-carbaldehyde (**14**, 716.5 mg, 3.67 mmol) and a catalytic amount of ammonium chloride (0.18 mmol) at room temperature. The resulting mixture was refluxed for 2 h. After cooled down to room temperature, the precipitate was filtered, and washed with water and hexanes to give a yellow solid; 91%, $R_f = 0.4$ (40% EtOAc/hexanes); mp 192–193 °C; IR ν_{max} (KBr) 3410, 3327, 2901, 1655, 1481, 1261, 1034, 879, 748 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.16 (s, 1H), 7.69 (s, 1H), 7.63 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.25 (td, $J = 8.1$, 1.5 Hz, 1H), 7.21 (s, 1H), 6.93 (s, 1H), 6.77 (d, $J = 7.5$ Hz, 1H), 6.71 (td, $J = 8.1$, 1.2 Hz, 1H), 6.30 (t, $J = 2.1$ Hz, 1H), 6.25, 6.22 (ABq, $J = 0.9$ Hz, 1H each); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 163.8, 152.2, 148.2, 147.7, 142.2, 134.0, 133.5, 127.7, 118.1, 115.2, 114.8, 107.6, 105.6, 104.1, 62.8; HRMS (EI) calcd for $C_{15}H_{11}N_3O_5$ [M^+] 313.0699, found 313.0694.

*2.5.2. 3-Methyl-2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinazoline (**6**)*

To a solution of **4a** (100 mg, 0.39 mmol) in methylene chloride (10 mL) was added triethylamine (39.4 mg, 0.39 mmol) and methyl iodide (111 mg, 0.47 mmol) at room temperature. The resulting mixture was stirred at that temperature for 2 h. After completion of the reaction, water (30 mL) was added to quench the reaction. The product was then extracted with methylene chloride (20 mL) twice, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to give a yellow solid; yield 88%; $R_f = 0.5$ (20% EtOAc/hexanes); mp 56–57 °C; IR ν_{max} (KBr) 3429, 2865, 1709, 1606, 1520, 1356, 1263, 1056, 834, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (dd, $J = 6.6$, 1.5 Hz, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.47 (td, $J = 7.5$, 1.5 Hz, 1H), 7.39 (td, $J = 7.2$, 1.5 Hz, 1H), 7.09 (t, $J = 8.4$ Hz, 1H), 8.85 (d, $J = 7.5$ Hz, 1H), 6.72–6.67 (m, 2H), 5.71 (d, $J = 4.2$ Hz, 1H), 4.38 (bs, 1H), 3.54, 3.37 (ABq, $J = 17.4$ Hz, 1H each), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 149.1, 140.8, 136.7, 132.0, 129.0, 128.5, 127.6, 127.5, 124.5, 118.4, 118.0, 113.8, 69.5, 49.7, 41.5; HRMS (EI) calcd for $C_{15}H_{15}N_3O_2$ [M^+] 269.1164, found 269.1159.



Scheme 2. Proposed mechanism of the formation of **1a** from **4a**.



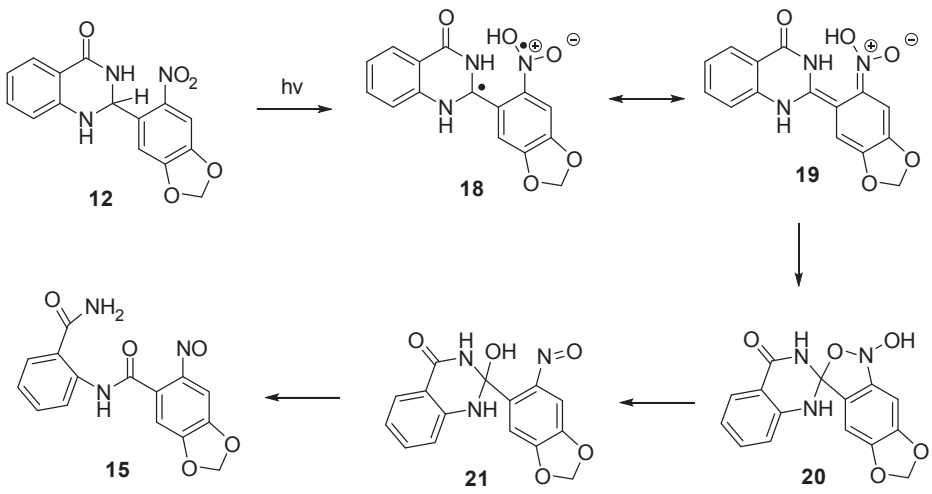
Scheme 3. Synthesis of **15** and **17**.

*2.5.3. 3-Methyl-2-(6-nitrobenzo[d][1,3]dioxol-5-yl)-2,3-dihydroquinazolin-4(1H)-one (**16**)*

To a solution of **12** (100 mg, 0.32 mmol) in THF (10 mL) was added sodium hydroxide (64 mg, 1.6 mmol) and methyl iodide (54 mg, 0.38 mmol) at room temperature. The resulting mixture was stirred at that temperature for 1 h. After completion of the reaction, the solution was concentrated and the residue was neutralized by hydrochloric acid to pH about 6. The product was then extracted with ethyl acetate (20 mL) twice, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to give a yellow solid; yield 80%; $R_f = 0.5$ (40% EtOAc/hexanes); mp 211–212 °C; IR ν_{max} (KBr) 3386, 2924, 1737, 1608, 1498, 1260, 1039, 883, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, $J = 7.8$ Hz, 1H), 7.61 (s, 1H), 7.26–7.22 (m, 2H), 6.82 (t, $J = 7.5$ Hz, 1H), 6.77 (s, 1H), 6.50 (d, $J = 8.1$ Hz, 1H), 6.27 (d, $J = 2.1$ Hz, 1H), 6.13, 6.07 (ABq, $J = 18.6$ Hz, 1H each), 5.39 (s, 1H), 3.01 (s, 3H) ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.6, 153.2, 148.3, 144.0, 141.8, 133.9, 132.7, 128.4, 119.0, 114.5, 114.3, 106.6, 106.5, 103.4, 69.4, 33.2; HRMS (EI) calcd for $C_{16}H_{13}N_3O_5$ [M^+] 327.0855, found 327.0849.

*2.5.4. 5-(2-Hydroxyethyl)-5H-indazolo[3,2-b]quinazolin-6-ium (**23**)*

To a solution of **1a** (100 mg, 0.46 mmol) in toluene (5 mL) was added 2-bromoethanol (85.7 mg, 0.69 mmol) at room temperature. The resulting mixture was refluxed for 2 days. After cooled down to room temperature, the precipitate was filtered, and washed with ethyl acetate and hexanes to give a pink solid. To this solid was added water (10 mL) and triethylamine to adjust the pH of the solution to 8. The crude product was then extracted with ethyl acetate (20 mL) twice, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to give a yellow solid; yield 45%; $R_f = 0.5$ (40% EtOAc/hexanes); mp 81–83 °C; IR ν_{max} (KBr) 3178, 2946, 2351, 1739, 1599, 1451, 1343, 1187, 893, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.10 (s, 1H), 9.98 (s, 1H), 8.32 (d, $J = 8.7$ Hz, 1H), 7.80 (dt, $J = 8.4$, 1.2 Hz, 1H), 7.64 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.57 (ddd, $J = 9.0$, 7.8, 1.8 Hz, 1H), 7.44 (ddd, $J = 8.7$, 6.6, 1.2 Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.16 (ddd, $J = 8.1$, 6.9, 1.2 Hz, 1H), 6.98 (td, $J = 7.8$, 0.9 Hz, 1H), 4.43 (t, $J = 5.1$ Hz, 2H), 4.14 (q, $J = 6.0$ Hz, 2H), 2.84 (t, $J = 6.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 194.9, 145.1, 143.0, 140.6, 136.3, 136.2, 127.7, 119.9, 119.7, 119.4, 118.5, 116.1, 116.0,



Scheme 4. Proposed mechanism for the formation of **15** from **12**.

108.7, 62.1, 50.3; HRMS (EI) calcd for $C_{16}H_{15}N_3O_2$ [M^+] 281.1164, found 281.1165.

*2.5.5. N,N-dimethyl-7,12-dihydroindazolo[3,2-b]quinazolin-3-amine (**24**)*

To a solution of **1b** (100 mg, 0.46 mmol) in methanol (10 mL) was added sodium borohydride (1.9 mg, 0.05 mmol) in one portion at room temperature. After completion of the reaction within 5 min, the solvent was concentrated *in vacuo*. This mixture was poured into water. The product was then extracted twice with methylene chloride to give a white solid, yield 99%; $R_f = 0.3$ (40% EtOAc/hexanes); mp 227–229 °C; IR ν_{max} (KBr) 2854, 1709, 1636, 1494, 1363, 1264, 1157, 873, 751 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 7.51 (dd, $J = 9.3$, 0.9 Hz, 1H), 7.24–7.19 (m, 2H), 6.99–6.93 (m, 2H), 6.70 (dd, $J = 9.0$, 2.1 Hz, 1H), 6.45 (d, $J = 2.1$ Hz, 1H), 5.44 (s, 2H), 2.95 (s, 6H); ^{13}C NMR (CD_3OD, 75 MHz) δ 151.52, 151.51, 136.7, 135.8, 129.3, 128.1, 122.2, 121.1, 115.9, 115.5, 112.1, 102.4, 94.6, 49.5, 41.6; HRMS (EI) calcd for $C_{16}H_{16}N_4$ [M^+] 264.1375, found 264.1369.

*2.6. DDQ oxidation of compound **24***

*2.6.1. N,N-dimethylindazolo[3,2-b]quinazolin-3-amine (**1b**)*

To a solution of **24** (66.0, 0.25 mmol) in methylene chloride (10 mL) was added DDQ (61.0, 0.27 mmol) in one portion at room temperature. After completion of the reaction within 30 min, the solvent was concentrated *in vacuo*. This mixture was poured into water. The product was then extracted twice with methylene chloride. The resulting solid was recrystallized from methylene chloride/hexane to give an orange red solid of **1b** quantitatively.

3. Results and discussion

Scheme 1 shows the two-step synthesis of the indazolo[3,2-*b*]quinazolines **1**. The sequence commenced with NH_4Cl-promoted condensation of *o*-aminobenzylamine (**2**) and *o*-nitrobenzaldehydes (**3**) to yield the tetrahydroquinazolines **4** [9–11]. The subsequent UV irradiation of **4** under aerobic conditions in acetonitrile afforded the target compounds **1**. Note that the formation of the indazolo[2,3-*a*]quinazolines **5** was not observed. Fig. 3 lists the structures and yields (from **4**) of the prepared compounds **1a**–**e**. The molecular structures of **1a**–**e** were verified by ^1H and ^{13}C NMR spectroscopy. Among all proton NMR spectra, a characteristic singlet absorption peak appearing at chemical shift of 9.66–9.44 ppm was observed and assigned to the C-7 hydrogen of the indazolo[3,2-*b*]quinazoline moiety (see **1** in Scheme 1 for atom-numbering). The structure of **1a** (R = H, CCDC-980236) was further confirmed by single-crystal X-ray diffraction analysis as shown in Fig. 4, explicitly revealing an indazole/quinazoline-fused molecular skeleton.

Scheme 2 depicts the proposed mechanism of the formation of **1a** from **4a** via UV irradiation (306 nm). Presumably, it begins with photoinduced intramolecular electron transfer from the benzylamine nitrogen atom to the *o*-nitrophenyl group of **4a** to yield the biradical species **7**. Compound **7** further undergoes intramolecular proton transfer from the amine hydrogen atom to the adjacent *ortho* nitro oxygen to give the nitrene **8**. The subsequent *N*–*N* bond formation between nitrene nitrogen and nitrogen atom of the protonated nitro group of **8** furnishes the *N*-oxide **9** which is then dehydrated to the aromatized indazole *N*-oxide **10** via 1,4-elimination. Final light-mediated deoxygenation of **10** affords the 7,12-dihydroindazolo[3,2-*b*]quinazoline (**11**) which is then oxidized *in situ* by molecular oxygen to give the target compound **1a**.

Fig. 5 shows the X-ray crystal structures of **4a** (CCDC-980238) and **6** (CCDC-980239). The former reveals that the 1,2,3,4-tetrahydropyrimidine moiety adopted the envelope-like conformation with the benzylamine nitrogen (*N*-3) atom protruding from the plane. The *o*-nitrophenyl group of **4a** was found to be situated at the axial position of the envelope-like ring with the nitro group *anti* to the aniline nitrogen (*N*-1) and *syn* to the benzylamine nitrogen (*N*-3). This observation might explain the exclusive formation of **1** in preference to **5** upon UV irradiation of **4** since the benzylamine nitrogen atom is closer to the *o*-nitro group to facilitate the photoinduced electron transfer (the distance between the two nitrogen atoms was measured to be only 2.928 Å). Conversely, no photogenerated product was observed upon UV irradiation of the *N*-3-methylated **6** (Scheme 1), indicating that **6** is insensitive to the applied irradiation conditions. Apparently, the extra methyl group attached to the *N*-3 nitrogen blocks the indazole formation between the benzylamine and nitro group but fails to facilitate the indazole formation between *N*-1 nitrogen and nitro group, presumably due to the fact that the distance between the *N*-1 nitrogen and the *o*-nitrophenyl group remain the same after *N*-3 methylation (Fig. 5). Therefore, no photochemical reaction of **6** was observed.

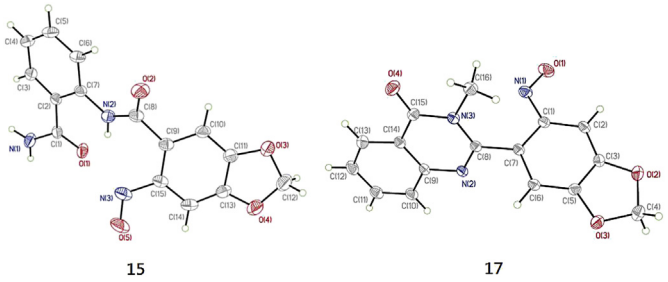
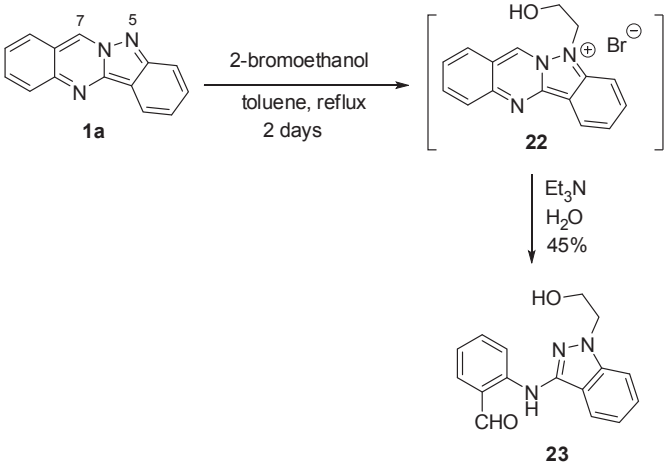


Fig. 6. X-ray crystal structures of **15** and **17**.

To further explore the scope and limitation of this photoreaction, compound **12** with a carbonyl group incorporated at the 4-position of the quinazoline ring was prepared and subsequently subjected to UV irradiation. Scheme 3 shows the synthesis of **12**, which was prepared by condensation of 2-aminobenzamide (**13**) and 6-nitrobenzo[*d*][1,3]dioxole-5-carbaldehyde (**14**) in the presence of NH_4Cl in ethanol under conditions [12]. Upon irradiation of **12** in acetonitrile, the major product isolated was the unexpected *o*-nitrosobenzamide **15**, rather than the desired indazolo[3,2-*b*]quinazolin-7(12*H*)-one. Scheme 4 depicts the proposed mechanism for



Scheme 5. Synthesis of compound **23**.

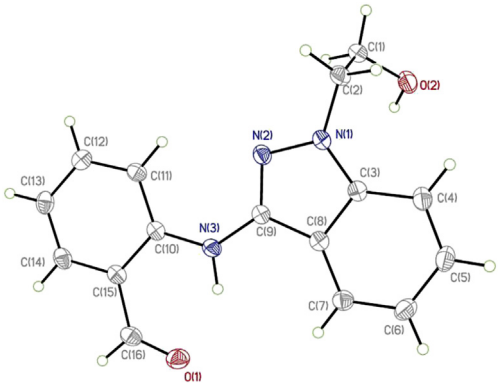
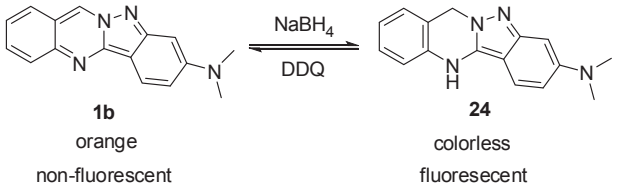


Fig. 7. X-ray crystal structure of **23**.

the formation of the *o*-nitrosobenzamide **15** from **12**. It presumably begins with light-induced hydrogen transfer from the benzylic hydrogen to nitro group to give the biradical species **18**, which may undergo electron delocalization to the structure **19**. The nucleophilic attack from the nitro oxygen to the benzylic carbon of **19** yields the benzo[*c*]isoxazol-1(3*H*)-ol **20**. The subsequent ring opening of the isoxazolidine ring of **20** gives the 2-hydroxy-2,3-dihydroquinazolin-4(1*H*)-one **21**. Final ring opening of 2-hydroxy-2,3-dihydroquinazolin-4(1*H*)-one moiety of **21** to expel the amide leaving group affords the product *o*-nitrosobenzamide **15**. A similar photoconversion of *o*-nitrophenyl imine to the corresponding *o*-nitrosobenzamide has been previously reported [13]. Interestingly, when the amide nitrogen of **12** was selectively methylated by methyl iodide in the presence of NaOH as a base in THF (Scheme 3), the resulting *N*-methylated **16** was converted to the nitrosophenyl imine **17** rather than undergoing ring opening reaction upon irradiation. The molecular structures of both **15** (CCDC-980240) and **17** (CCDC-980241) were confirmed by the X-ray crystal crystallography as presented in Fig. 6.

With the availability of compounds **1a**–**e**, we then focused our attention on their chemical properties. Upon alkylation of the *N*-5 position of **1a** by 2-bromoethanol in toluene under reflux, the resulting proposed *N*-5 alkylated **22** was found to be highly susceptible to base-mediated hydrolysis to afford the ring-opened 1*H*-indazol-3-amine **23** (Scheme 5). The structure of **23** (CCDC-980242)



Scheme 6. Redox switch between **1b** and **24**.

was confirmed by single-crystal X-ray diffraction analysis as presented in Fig. 7.

The formation of the hydrolyzed **23** implies that **1a**, in the presence of a suitable nucleophile, is susceptible to 1,4-addition at the C-7 position of the indazolo[3,2-*b*]quinazoline moiety. Indeed, when treated with $NaBH_4$ in methanol, the orange **1b** was instantly converted to the colorless **24**. The reduced **24** can be reverted back to **1b** upon 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation. Fig. 8 shows the UV–vis absorption spectra of **1b** prior to and after $NaBH_4$ reduction in methanol. It displays two intense bands at 252 and 346 nm, and two shoulder bands at 295 and 334 nm, along with a long wavelength broad absorption with maximum at 465 nm before reduction. Presumably, the broad band at 465 nm is attributed to the increased π delocalization of the chromophore. The reduction of **1b** to the indazole **24** resulted in the complete disappearance of the long-wavelength absorbance (465 nm) and the appearance of a short-wavelength band at around 326 nm, which resembles the absorption behavior of *N*,*N*-dimethylamino substituted indazole moiety.

Scheme 6 depicts the proposed redox switch between *N*,*N*-dimethylindazolo[3,2-*b*]quinazolin-3-amine (**1b**) and 7,12-dihydroindazolo[3,2-*b*]quinazoline (**24**). In addition to color change, compound **1b** also exhibited a variation in emission as a second output property upon reduction. Fig. 9 shows the emission spectra of **1b** prior to and after $NaBH_4$ reduction. While compound **1b** was essentially non-fluorescent in acetonitrile ($\Phi_f = 0.007$), the fluorescence intensity at 455 nm increased substantially after reduction, presumably due to the *N*,*N*-dimethylamino substituted indazole fluorophore of **24**. The reduced **24** is highly fluorescent in acetonitrile ($\Phi_f = 0.64$) with up to a 91-fold increase in fluorescence quantum yield after reduction.

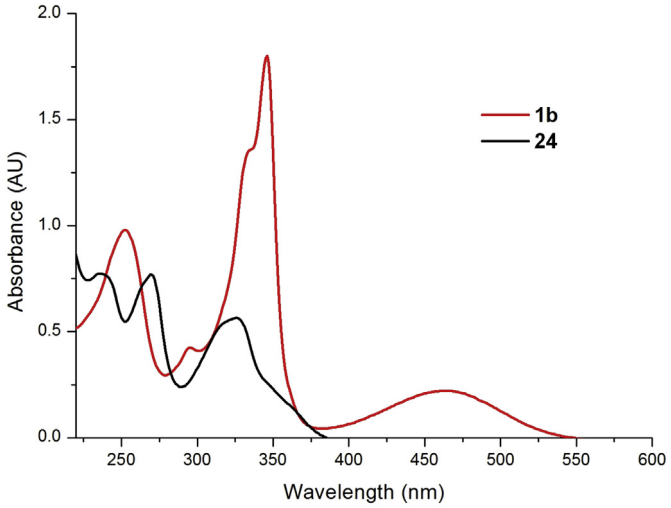


Fig. 8. UV–vis spectra of **1b** (3.0×10^{-5} M in MeOH) prior to and after $NaBH_4$ reduction.

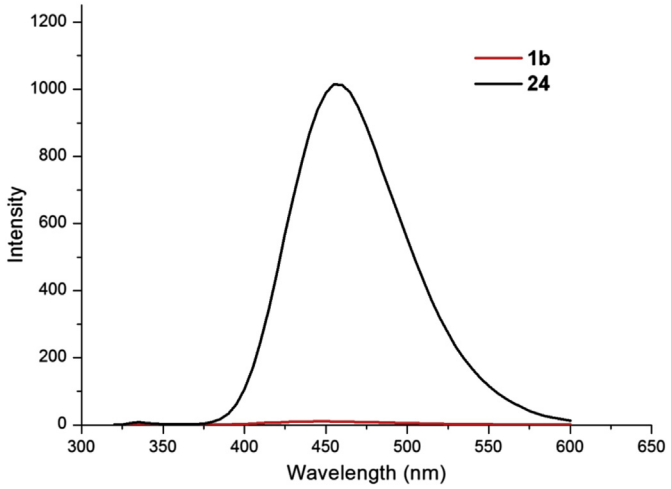


Fig. 9. Emission spectra of **1b** (3.0×10^{-5} M in MeOH) prior to and after $NaBH_4$ reduction.

4. Conclusions

In summary, we have developed an efficient route for the construction of indazolo[3,2-*b*]quinazoline skeleton by exposing readily available 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinazolines to UV light. The prepared compounds were shown to exhibit redox-switching behavior with color change and emission variation as two easily detectable output properties. Further evaluation of their potential to function as materials for organic thin film transistors is currently in progress.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dyepig.2014.11.020.

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