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To cite this Article Nami, Navabeh , Hosseinzadeh, Masoumeh , Nami, Nasrin and Haghdadi, Mina(2009) 'Synthesis of Substituted Pyrazino[5,6-b]pyrimidine and Some Indole Derivatives', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 184: 11, 2846 — 2855

To link to this Article: DOI: 10.1080/10426500802590228

URL: <http://dx.doi.org/10.1080/10426500802590228>

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Synthesis of Substituted Pyrazino[5,6-b]pyrimidine and Some Indole Derivatives

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Refluxing dimethyl acetylenedicarboxylate (DMAD) or 1,2-dibenzoylacetylene with isatin-3-thiosemicarbazone or isatin-3-thiocarbohydrazone in methanol produced 3-substituted oxindoles in good yields. Reaction of equimolecular amounts of 5,6-diamino-uracil-sulfate, trans-(1R,2R)-diaminocyclohexane, and 3,4-diamino-1,2,4-triazol-5-methyl hydrochlorid with isatin in ethanol (85%) afforded tetracyclic ring systems and ring-opened products in mild reaction conditions.

Keywords Indolo[2,3-b]-4a,5,6,7,8,8a-hexahydroquinoxaline; isatin-3-substituted; pyrazino[5,6-b]pyrimidine; triazolo [4,3:3',2']triazino[5, 6-b]indole

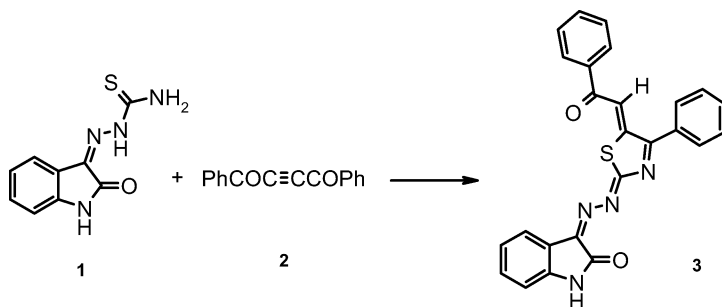
INTRODUCTION

Five and six membered ring of heterocyclic compounds have occupied a prominent place among various classes of organic compounds for their diverse biological activities.¹ Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, isatin(1H-indole-2,3-dione) derivatives have played an important role in medicinal chemistry.^{2–9} Isatins are synthetically versatile substrates, where they can be used for the synthesis of a large variety of compounds, such as indoles and quinolines, and as raw material for drug synthesis.^{10–11} Isatins have also been found in mammalian tissue.¹² In continuation of our work on the synthesis of heterocyclic

Received 3 March 2008; accepted 22 October 2008.

The authors are thankful to the Islamic Azad University of Ghaemshahr for their support.

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SCHEME 1

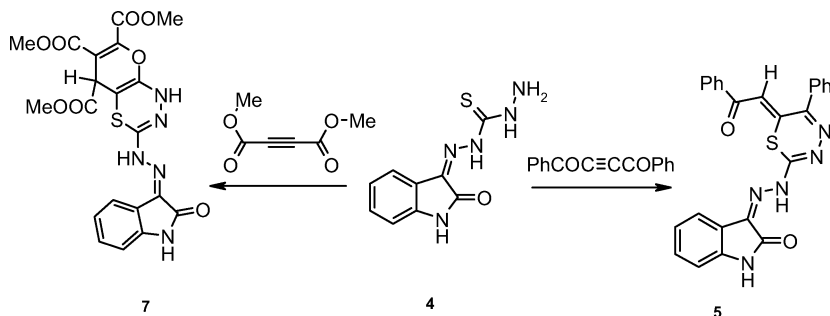
systems containing nitrogen and sulfur,¹³ we describe here the synthesis of new isatin derivatives with isatin-3-imines and tetracyclic ring systems.

RESULTS AND DISCUSSION

Reaction of isatin-3-thiosemicarbazone **1** with 1,2-dibenzoylacetylene **2**¹⁴ yielded 2-(2-oxo-1,2-dihydroindol-3-yliden)hydrazon-4-phenyl-1,3-thiazol-5-methylidenbenzoyl **3** (Scheme 1). The structure of compound **3** was deduced from its elemental analyses and its IR, ¹H, and ¹³C NMR spectrum. The ¹H NMR of compound **3** exhibited a broad resonance at δ 10.61 ppm arising from the NH proton along with a sharp singlet signal from the exomethylene proton C=CH in the region δ 7.38 ppm.

We can assume that in the reaction of **1** with **2**, the sulfur and nitrogen nucleophiles add to the activated triple bond (by Michael type addition) and C=O under cyclocondensation reaction. The reaction of isatin-3-thiocarbohydrazone **4** with 1,2-dibenzoylacetylene **2** and dimethyl acetylenedicarboxylate in methanol afforded 2-(2-oxo-1,2-dihydroindol-3-yliden)hydrazon-5-phenyl-1,3,4-thiadiazin-6-methylidenbenzoyl **5** and 2-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazon-4,8-dihydro-pyrano [2,3-e]-1,3,4-thiadiazin-6,7,8-trimethylcarboxylate **7**, respectively (Scheme 2). The ¹H NMR spectrum of compound **5** exhibited two broad peaks at δ 10.34 and 9.87 ppm arising from NH protons along with a sharp singlet from exomethylene proton C=CH in the region δ 7.14 ppm. The IR spectrum of the reaction product **5** showed NH stretching at 3428 and 3169 cm⁻¹, and two CO groups stretching at 1704 and 1693 cm⁻¹.

TLC and the NMR spectrum of compound **7** showed that only a single, pure compound was present. The ¹H NMR spectrum of compound **7** showed no CH stretching for C=CH exomethylene present in structure

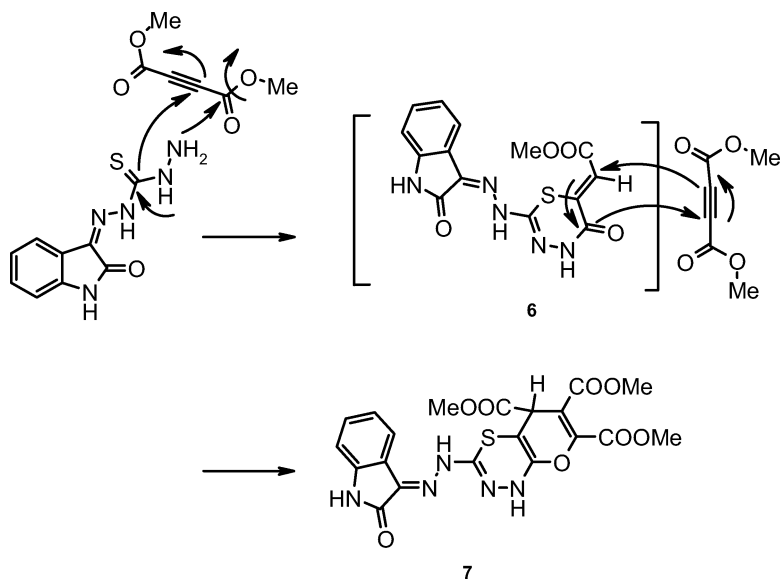


SCHEME 2

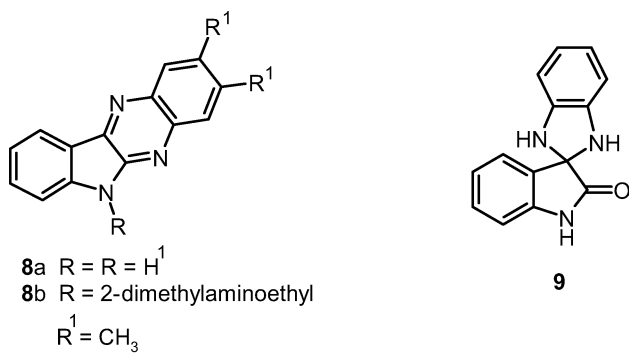
6, and the appearance of a sharp singlet at δ 3.65 ppm for one C-CH group also was indicative of the formation of **7**. The IR spectrum of this reaction product showed NH stretching at 3252–3326 cm^{-1} . The mass spectrum of this compound displayed a molecular ion peak at appropriate m/z 487. Any initial fragmentation involves loss from or complete loss of the side chain and section of the ring systems. These data indicated that a Michael type addition and Diels–Alder [4+2] cycloaddition reaction have occurred to afford **7**. The reaction took place via first addition of S and NH_2 groups of the isatin-3-thiocarbohydrazone to acetylene bond and C=O groups of DMAD by Michael type addition and water elimination. The reaction likely took place through the intermediate formation of **6** followed by Diels–Alder [4+2] cycloaddition reaction to give **7** (Scheme 3).

Several members of the tetracyclic ring system 6*H*-indolo[2,3-*b*]quinoxaline **8**, first synthesized¹⁵ in 1895 by Schunck and Marchlewski from isatin (indole-2,3-diones) **11** and *o*-phenylenediamine, have been intensely studied¹⁶ because some derivatives with basic side chains in the 6-position, such as 2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]quinoxaline **8b**, exhibit potent antiviral activity, against, e.g., HSV-1, CMV, and VZV.¹⁷ The condensation between isatin and *o*-phenylenediamine, depending on the solvent used, gives rise to three different products (**8a**, **9**, or **10**) (Scheme 4). In acidic solvents, such as acetic acid, the linear product **8a** is the dominating product. The spiro compound **9** reportedly has been obtained in a high yield when the reaction was performed in *N*-methyl-2-pyrrolidone, whereas the ring-opened quinoxalinone **10** was the major product when THF or benzene was used as solvent.^{18–20}

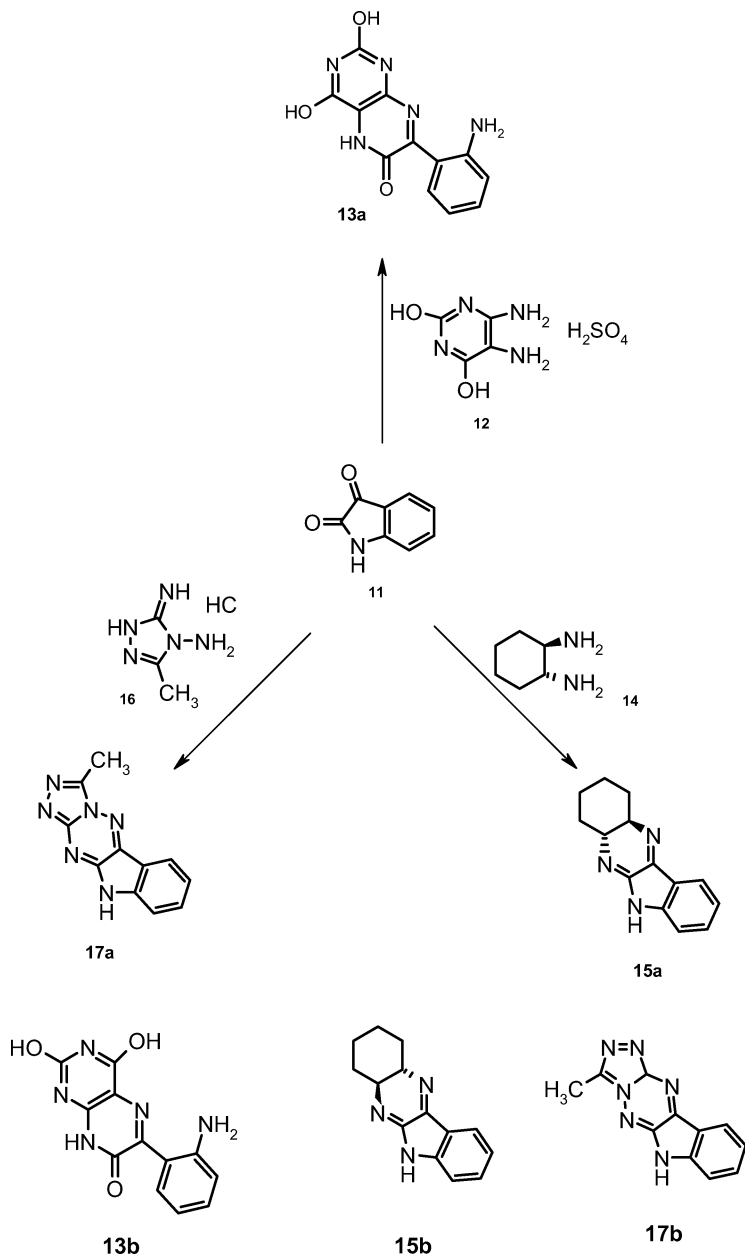
As indicated in Scheme 5, the reaction of isatin (1*H*-indole-2,3-dione) **11** with 5,6-diamino-uracil-sulfate **12**, *trans*-(1*R*,2*R*)-diaminocyclohexane (DACH) **14**, and 3,4-diamino-1,2,4-triazol-5-



SCHEME 3



SCHEME 4



SCHEME 5

methyl hydrochlorid **16** in ethanol 85% afforded 3-(2-aminophenyl)-6,8-dihydroxy-pyrazino[5,6-*b*]pyrimidine **13a**, 4*aR*,11*aR*-6*H*-indolo[2,3-*b*]-4*a*,5,6,7,8,8*a*-hexahydroquinoxaline **15a**, and 10*H*-3-methyl-1,2,4-triazolo[4,3-*3'*,2']-1,2,4-triazino[5,6-*b*]indole **17a**, respectively. The condensation of isatin with *o*-phenylenediamine in refluxing methanol has been reported¹⁸ to produce a mixture of **8a** (39%), **10** (30%), and only traces of the spiro compound **9**. Now, in a similar experiment in ethanol 85% using compounds **14** and **16** as partners to isatin, the linear compounds **15a** and **17a** (which can be considered as a higher homologue of **8**) were obtained as the sole products, while none of the possible spiro products or the ring-opened products was observed. The reaction of isatin and compound **12** in ethanol 86% gave ring-opened product **13a**. Two different nucleophilic groups in compounds **12**, **14**, and **16** offer the possibility of structures **13b**, **15b**, and **17b** (Scheme 5), but the spectroscopic data showed compounds **13a**, **15a**, and **17a**.

The IR spectrum of **13a** exhibits a characteristic carbonyl at 1710 cm^{-1} , OH at 3300–3490 cm^{-1} , NH_2 at 3185 cm^{-1} , and NH at 3398 cm^{-1} . The ^1H NMR spectrum features signals at 10.67 and 11.93 ppm from the OH groups and a signal at 10.57 ppm from the NH. The strong deshielding of the amide proton showed an intramolecular hydrogen bond $\text{NH}=\text{O}$ in compound **13a**. The mass spectrum of **13a** showed $m/z = 271$ (M^+) for $\text{C}_{12}\text{H}_9\text{N}_5\text{O}_3$. The IR and ^1H NMR spectrum of compound **15a** clearly indicated the NH group at 3438 cm^{-1} and δ 6.73 ppm, respectively. The mass spectrum of this compound displayed a molecular ion peak at 225 m/z value. The ^1H NMR spectrum of **17a** included a 3H singlet from the methyl group (2.74 ppm) and a broad signal (12.18 ppm) from the NH function.

CONCLUSIONS

In conclusion, a general and convenient synthesis of functionalized $\text{C}=\text{S}$ and NH_2 has been developed using a nucleophilic reaction. The main advantages of these reactions are mild reaction conditions. In this article, we have shown that simple indole-2,3-dione is reacted with 1,2-diamino compounds in ethanol (85%) resulting in conversion to tetracyclic compounds and a ring-opened product.

EXPERIMENTAL

Trans-(1*R*,2*R*)-DACH and 5,6-diamino-uracil-sulfate were purchased from Aldrich Chemical Company. The other chemicals and solvents were purchased from Merck Chemical Company. 1,2-Dibenzoylacetylene was prepared by the method in the literature.¹⁴ The

melting points were obtained using an Electrothermal IA 9100 Digital melting point apparatus. The IR spectra were recorded on a Bruker IFS-88 instrument (the samples as KBr disks for the range 4000–400 cm^{-1}). The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (^1H , 300.134 MHz; ^{13}C , 75.469 MHz) using TMS as an internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system. The C, H, and N analyses were performed by the microanalytical service of the NIOC Research Institute of Petroleum Industry.

General Procedure

A mixture of two reactants was heated to reflux in methanol (40 mL) for 2 h. The progress of the reaction was monitored by TLC, using *n*-hexane:ethylacetate (4:1). The solution was cooled and the separated solid was filtered. The crude product was purified by recrystallization from methanol.

2-(2-Oxo-1,2-dihydroindol-3-yliden)hydrazon-4-phenyl-1,3-thiazol-5-methylidenbenzoyl (3)

3 was obtained from the reaction of isatin-3-thiosemicarbazone (10 mmol, 2.24 g) **1** with 1,2-dibenzoylacetylene (10 mmol, 2.34 g) **2**, and this compound was obtained as an orange powder from methanol. Yield 77%, mp: 271–272°C; MS: m/z 436 (M^+); FT-IR: NH 3428, 3169, CO 1693 cm^{-1} ; ^1H NMR ($\text{DMSO-}d_6$) δ 10.61 (br, 1H, NH), 7.81 (d, J = 7.6 Hz, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 7.61 (d, J = 7.6 Hz, 1H, Ar-H), 7.49 (m, 5H, Ar-H), 7.38 (s, 1H, C = CH), 7.24 (m, 4H, Ar-H), 7.04 (m, 1H, Ar-H), 6.88 (s, 1H, Ar-H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 118.8 (C-Ar), 124.6 (CH = C), 121.4 (C-Ar), 123.8 (C-Ar), 125.3 (C-Ar), 126.1 (C-Ar), 127.9 (C-Ar), 128.7 (C-Ar), 130.4 (C-Ar), 131.6 (C-Ar), 131.9 (C-Ar), 132.4 (C-Ar), 134.0 (C-Ar), 136.1 (C-Ar), 137.1 (C-Ar), 145.7 (C = CH), 151.0 (NH-C = O), 154.2 (C = N-N =), 159.1 (C = N), 162.8 (C = N), 177.3 (C = O). *Anal.* Calcd. for $\text{C}_{25}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$: C, 68.81; H, 3.67; N, 12.84. Found: C, 68.78; H, 3.66; N, 12.83.

2-(2-Oxo-1,2-dihydroindol-3-yliden)hydrazon-5-phenyl-1,3,4-thiadiazin-6-methylidenbenzoyl (5)

5 was obtained from the reaction of isatin-3-thiocarbohydrazone (10 mmol, 2.35 g) **1** with 1,2-dibenzoylacetylene (10 mmol, 2.34 g) **2**, and this compound was obtained as yellow crystals from methanol. Yield 73%, mp: 187–188°C; MS: m/z 451 (M^+); FT-IR: NH 3428, 3169, CO 1704, 1693 cm^{-1} ; ^1H NMR ($\text{DMSO-}d_6$) δ 10.34 (br, 1H, NH), 9.87 (br, 1H, NH), 8.16 (m, 2H, Ar-H), 7.88 (m, 3H, Ar-H), 7.80 (d, J = 7.5 Hz, 1H,

Ar-H), 7.71 (t, $J = 7.6$ Hz, 1H, Ar-H), 7.49 (m, 5H, Ar-H), 7.14 (s, 1H, =CH), 7.19 (t, $J = 7.6$ Hz, 1H, Ar-H), 7.02 (d, $J = 7.5$ Hz, 1H, Ar-H); ^{13}C NMR (DMSO- d_6) δ 112.5 (C-Ar), 119.6 (CH = C), 122.4 (C-Ar), 122.8 (C-Ar), 126.3 (C-Ar), 127.1 (C-Ar), 128.9 (C-Ar), 129.5 (C-Ar), 129.7 (C-Ar), 130.4 (C-Ar), 131.8 (C-Ar), 132.6 (C-Ar), 136.4 (C-Ar), 137.0 (C-Ar), 138.1 (C-Ar), 144.2 (C = NNH-), 148.0 (C = CH), 152.0 (NH-C = O), 159.1 (C = N), 167.8 (HN-C = N), 176.0 (C = O). *Anal.* Calcd. for $\text{C}_{25}\text{H}_{17}\text{N}_5\text{O}_2\text{S}$: C, 66.52; H, 3.77; N, 15.52. Found: C, 66.49; H, 3.76; N, 15.55.

2-(2-Oxo-1,2-dihydroindol-3-ylidene)hydrazone-4,8-dihydro-pyrano[2,3-*e*]-1,3,4-thiadiazin-6,7,8-trimethylcarboxylate (7)

7 was obtained from the reaction of isatin-3-thiocarbohydrazone (10 mmol, 2.35 g) **4** with dimethyl acetylenedicarboxylate (10 mmol, 1.42 g), and this compound was obtained as orange crystals from methanol. Yield 89%, mp: 258–259°C; MS: m/z 487 (M^+); FT-IR: NH 3326, 3252, CO 1734, 1699 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 14.49 (br, 1H, NH), 12.26 (s, 1H, NH), 11.28 (s, 1H, NH), 7.67 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.36 (t, $J = 7.6$ Hz, 1H, Ar-H), 7.09 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.93 (d, $J = 7.5$ Hz, 1H, Ar-H), 3.77 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.65 (s, 1H, CH), 3.38 (s, 3H, OMe); ^{13}C NMR (DMSO- d_6) δ 35.9 (CH), 50.6 (OMe), 51.4 (OMe), 51.8 (OMe), 117.5 (C-Ar), 115.9 (S-C), 117.3 (C = C), 120.6 (C-Ar), 121.1 (C-Ar), 125.0 (C-Ar), 132.2 (C-Ar), 137.1 (O-C =), 138.3 (C-Ar), 142.8 (C = NNH), 144.7 (HN-C-O), 152.4 (HN-C = O), 159.3 (C = O), 164.5 (C = O), 164.8 (C = O), 165.0 (HN-C = N). *Anal.* Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_5\text{O}_8\text{S}$: C, 49.28; H, 3.49; N, 14.37. Found: C, 49.30; H, 3.51; N, 14.39.

3-(2-Aminophenyl)-6,8-dihydroxy-pyrazino[5,6-*b*]pyrimidine (13a)

13a was obtained from the reaction of isatin (1H-indole-2,3-dione) (10 mmol, 1.47 g) **6** with 5,6-diamino-uracil-sulfat (10 mmol, 2.40 g) **7**, and this compound was obtained as an orange powder from ethanol. Yield 78%, mp: > 300°C; MS: m/z 271 (M^+); FT-IR: OH 3300–3490, NH 3398, 3185, CO 1710 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 11.93 (s, 1H, OH), 10.67 (s, 1H, OH), 10.57 (s, 1H, NH), 7.26 (t, $J = 7.5$ Hz, 1H, Ar-H), 6.94 (m, 2H, Ar-H), 6.80 (d, $J = 7.6$ Hz, 1H, Ar-H), 6.73 (br, 2H, NH_2); ^{13}C NMR (DMSO- d_6) δ 116.8 (= C-NH), 117.2 (C-Ar), 118.5 (C-Ar), 120.7 (C-Ar), 123.4 (C-Ar), 126.8 (C-Ar), 128.6 (C-Ar), 152.7 (C = N), 153.4 (C = N), 156.1 (C-OH), 164.0 (N-C-N), 168.1 (C = O). *Anal.* Calcd. for $\text{C}_{12}\text{H}_9\text{N}_5\text{O}_3$: C, 53.13; H, 3.32; N, 25.83. Found: C, 53.10; H, 3.35; N, 25.81.

4aR, 11aR-6H-Indolo[2,3-b]-4a,5,6,7,8,8a-hexahydroquinoxaline (15a)

15a was obtained from the reaction of isatin (1*H*-indole-2,3-dione) (10 mmol, 1.47 g) **6** with *trans*-(1*R*,2*R*)-diaminocyclohexane (DACH) (10 mmol, 1.14 g) **9**. It was obtained as red crystals from ethanol. Yield: 81%, mp: 257–258°C; MS: *m/z* 225 (*M*⁺); FT-IR: NH 3438, C = N 1659 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 9.02 (br, 1H, NH), 7.46 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.27 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.85 (m, 2H, Ar-H), 3.17 (m, 2H, CH), 2.27 (m, 1H, CH), 1.99 (m, 1H, CH), 1.74 (m, 2H, CH₂), 1.43 (m, 2H, CH₂), 1.35 (m, 2H, CH₂); ¹³C NMR (DMSO-*d*₆) δ 20.1 (CH₂), 21.5 (CH₂), 30.4 (CH₂), 31.8 (CH₂), 59.8 (CH), 60.5 (CH), 115.4 (C-Ar), 117.2 (C-Ar), 123.0 (C-Ar), 124.8 (C-Ar), 129.1 (C-Ar), 138.4 (C = N), 140.3 (C-Ar), 148.9 (C = N). *Anal.* Calcd. for C₁₄H₁₅N₃: C, 74.67; H, 6.67; N, 18.67. Found: C, 74.64; H, 6.70; N, 18.66.

10H-3-Ethyl-1,2,4-triazolo[4,3:3',2']-1,2,4-triazino[5,6-b]indole (17a)

17a was obtained from the reaction of isatin (1*H*-indole-2,3-dione) (10 mmol, 1.47 g) **6** with 3,4-diamino-1,2,4-triazol-5-methyl hydrochloride (10 mmol, 181 g) **11**. It was obtained as orange crystals from ethanol. Yield 68%, mp: > 300°C; FT-IR: NH 3431, C = C 1615 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 12.18 (s, 1H, NH), 8.17 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.70 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.41 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.31 (t, *J* = 7.5 Hz, 1H, Ar-H), 2.74 (s, 3H, CH₃); ¹³C NMR (DMSO-*d*₆) δ 14.9 (CH₃), 118.4 (C-Ar), 120.2 (C-Ar), 124.8 (C-Ar), 126.7 (C-Ar), 129.1 (C-Ar), 138.4 (C-Ar), 147.8 (C = N), 150.2 (N = C-NH), 152.5 (C = N), 155.8 (N = C-N). *Anal.* Calcd. for C₁₁H₈N₆: C, 58.93; H, 3.57; N, 37.50. Found: C, 58.87; H, 3.59; N, 37.46.

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