Synthesis of fused heteropolycyclic systems containing an indole moiety

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New fused heterocyclic systems containing the indole moiety with 1,3,4–thiadiazolo-, 1,3,4-thiadiazino-, 1,2,4-triazino-, pyridazino-, pyrimido-, imidazo-, 1,3-thiazolo- and pyrazolo-fusion have been synthesised starting from reactions of isatin-3-thiohydrazone, 1-(*N*-phenylbenzimidoyl)isatin and isatin-3-cyanoacetic acid hydrazone with α,β-bifunctional oxygen, halogen and nitrogen reagents.

Keywords: isatins, fused 1,3,4-thiadiazoles, pyrimidines, 1,2,4-triazines, 1,3,4-thiadiazines, indoles

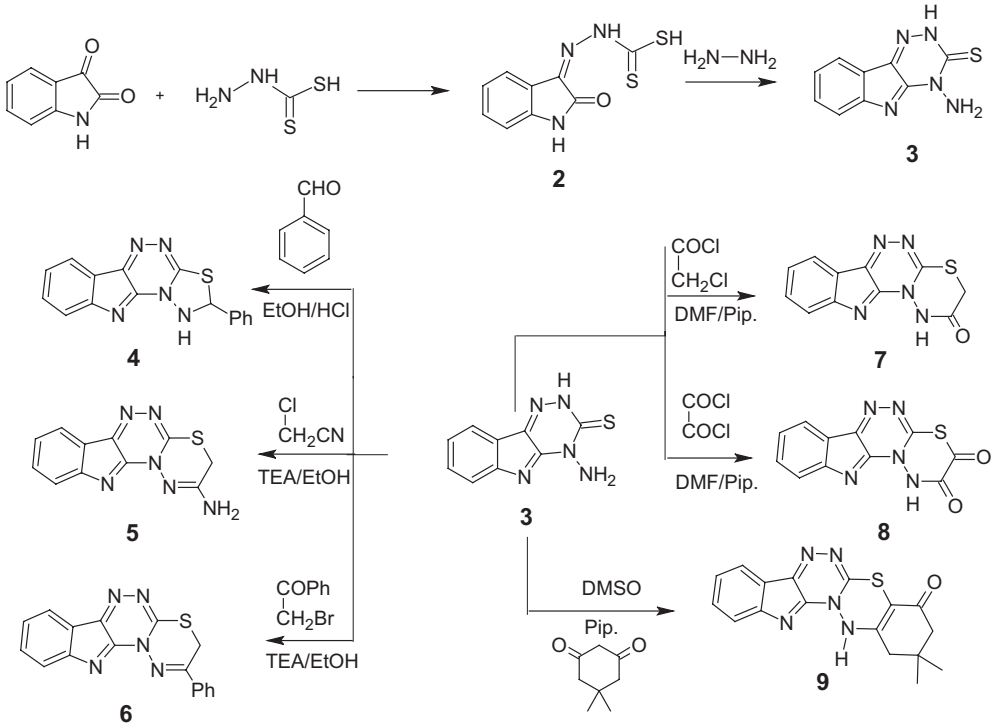
Isatin has been used in a colourimetric screening test for human serum hyperprolinemia,[1] in a colourimetric assay of HIV-1 proteinase,[2] and for the estimation of the age of bones in criminal investigations.[3] In a similar manner, isatin-3-hydrazone has been studied for the colourimetric determination of steroids[4] and in steroid analysis, as well as a colour marker in the Sephadex LH-20 chromatographic separation of steroidal blood components.[5] Further, isatin has been used for the synthesis of fused indole derivatives, such as indolothiazoles,[6] thiadiazinoindoles,[7] pyrazinoindoles,[8] trisindolobenzenes,[9] indoloquinazolines,[10] and 1,2,4-triazinoindole derivatives.[11-15]

Isatin derivatives can suffer nucleophilic attack at positions C-2 and/or C-3. The chemoselectivity of these reactions depends upon the nature of the nucleophile and on that of the substituents attached to the isatin nucleus and especially of those bonded to the nitrogen atom, as well as upon the solvent and temperature employed. The initial products obtained undergo further reaction in the presence of a second nucleophilic group to give cyclisation products.[16] In this project we have been concerned with preparation of fused heterocyclic systems containing an indole moiety, in continuation of an earlier publication[17] in which we prepared fused heterocyclic systems containing phenazone derivatives.

Results and discussion

In the present work, we combine indole with other heterocyclic moieties through heterocyclisation of isatin, isatin-3-thiohydrazone, 1-(*N*-phenylbenzimidoyl)isatin, and isatin-3-(cyanoacetyl)hydrazone with α,β-bifunctional oxygen, halogen and nitrogen compounds in different media. Tomchin and Ioffe[18] obtained 4-amino-2,4-dihydro-3*H*-[1,2,4]triazino[5,6-*b*]indole-3-thione (**3**) through cyclisation of the β-thiocarbohydrazone of isatin in the presence of base. In the present work, we prepared compound **3** via refluxing N'-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)dithiocarbohydrazide **2** with hydrazine hydrate in isopropanol (Scheme 1). Because of the discrepancy in the m.p. of compound **3** from that reported,[18] the structure of **3** was confirmed by IR, ^{1}H, ^{13}C NMR and microanalysis. The ^{1}H and ^{13}C NMR spectra of our **3** show δ 2.30, 6.82 ppm for NH_2 and NH groups and δ 186.2 ppm characteristic for the C=S group. Compound **3** was used as starting material for the construction of fused heteropolycyclic systems containing an indole moiety.

Thus, cyclocondensation of compound **3** with benzaldehyde in boiling ethanol/HCl[19] gave 2-phenyl-1,2-dihydro[1,3,4]-thiadiazolo[2',3': 3,4][1,2,4]triazino[5,6-*b*]indole (**4**). The IR spectrum of **4** indicates the presence of NH group at 3218 cm^{-1}



Scheme 1 Condensation products of triazino-indole **3**.

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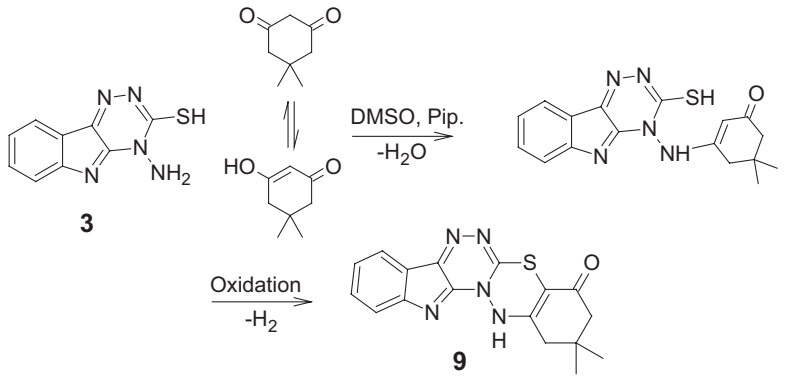


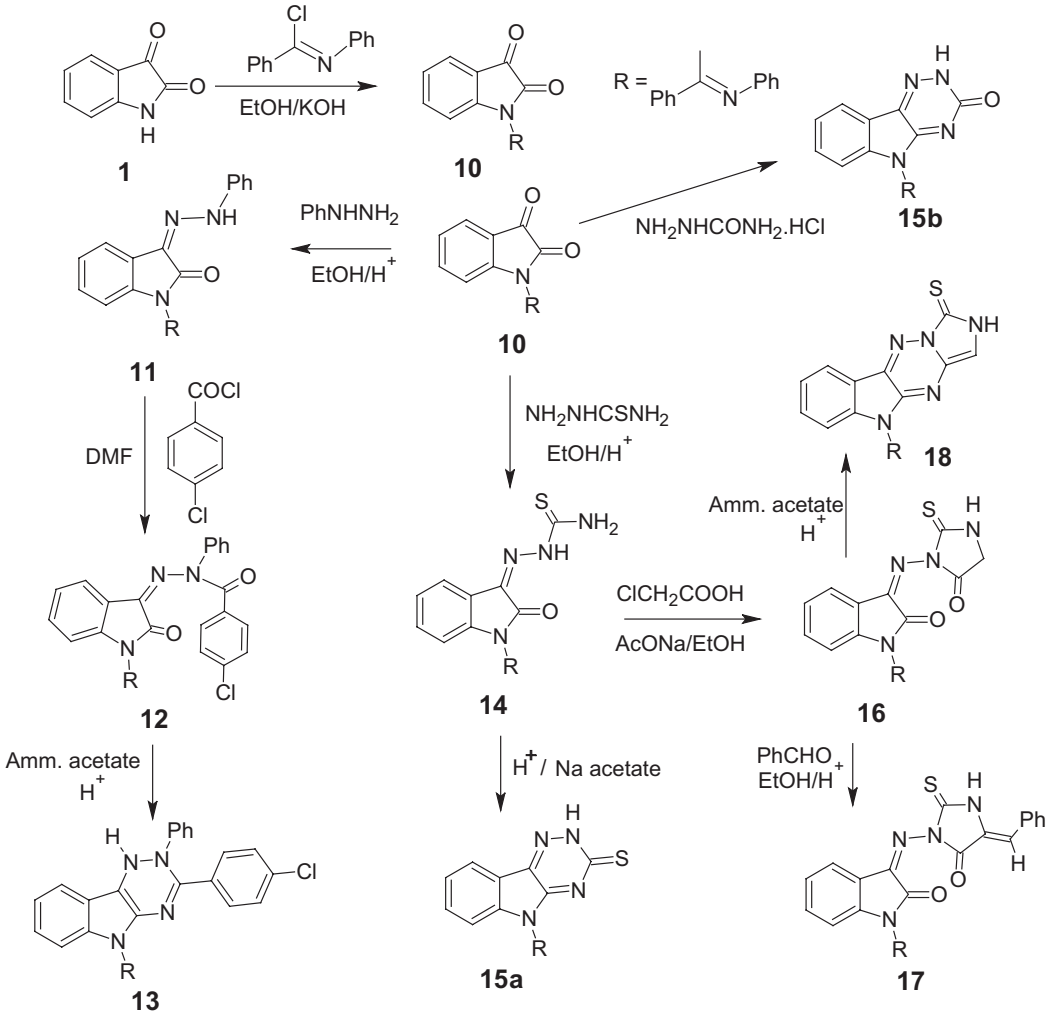
Scheme 2 Formation of fused compound **9**.

and the ^{1}H and ^{13}C NMR spectra showed signals at δ 4.80 ppm for (N–C<u>H</u>–S) and at δ 62.5 ppm for (N–<u>C</u>–S) atoms.

The synthesis of heterocyclic systems containing the thiadiazine moiety has gained much attention because of their effects on various diseases.[20,21] So, a facile route to the synthesis of the [1,3,4]thiadiazino[2',3': 3,4][1,2,4]triazino[5,6-*b*]indoles **5–8** was produced by refluxing compound **3** with chloroacetonitrile, phenacyl bromide, chloroacetyl chloride, and oxalyl chloride, in basic media. The ^{1}H, ^{13}C NMR spectra of compounds **5–8** are reported in the Experimental section.

Structure **9**, 10,10-dimethyl-10,11-dihydro-9*H*-indolo[2',3': 5,6][1,2,4]triazino[3,4-*b*][1,3,4]benzothiadiazin-8(12*H*)-one, was formed by cycloaddition of compound **3** with dimedone in boiling DMSO with a few drops of piperidine (Scheme 1). A related reaction is reported.[22] The ^{1}H NMR spectra showed a signal at δ 1.11 ppm for $2CH_3$, 1.88 and 2.86 ppm for CH_2 and CH_2CO groups, and the ^{13}C NMR indicated signals at δ 17.8 <u>C</u>$(CH_3)_2$, 26.4 ($2CH_3$) and 45.2 and 50.3 ppm for CH_2 and CH_2CO groups. The formation of compound **9** from **3** can be explained as in Scheme 2.

Reaction of isatin with *N*-phenylbenzimidoyl chloride[23] in boiling ethanol/KOH mixture furnished 1-(*N*-phenylbenzimidoyl)isatin **10** (Scheme 3). The dicarbonyl compound **10** was used as starting material for synthesis of heteropolycyclic systems. Thus, condensation of compound **10** with



Scheme 3 1-(*N*-Phenylbenzimidoyl)isatin derivatives.

phenylhydrazine in boiling ethanol/acetic acid yielded the hydrazone **11.** The IR spectrum of compound **11** gave two strong bands at 3240 and 1685 cm^{-1} for NH and C=O groups. Aroylation of compound **11** using *p*-chlorobenzoyl chloride in boiling DMF produced the *N*-aroyl derivative **12**. The IR spectrum of **12** showed the presence of two carbonyl groups at 1695 and 1680 cm^{-1}. Heterocyclisation of **12** by fusion with ammonium acetate in a few drops of acetic acid led directly to 3-chlorophenyl-2-phenyl-5-[phenyl(phenylimino)methyl]-2,5-dihydro-1*H*-[1,2,4]triazino[5,6-*b*]indole **13**. The IR, ^{1}H, ^{13}C NMR spectra and microanalysis details of **13** are given in the Experimental section.

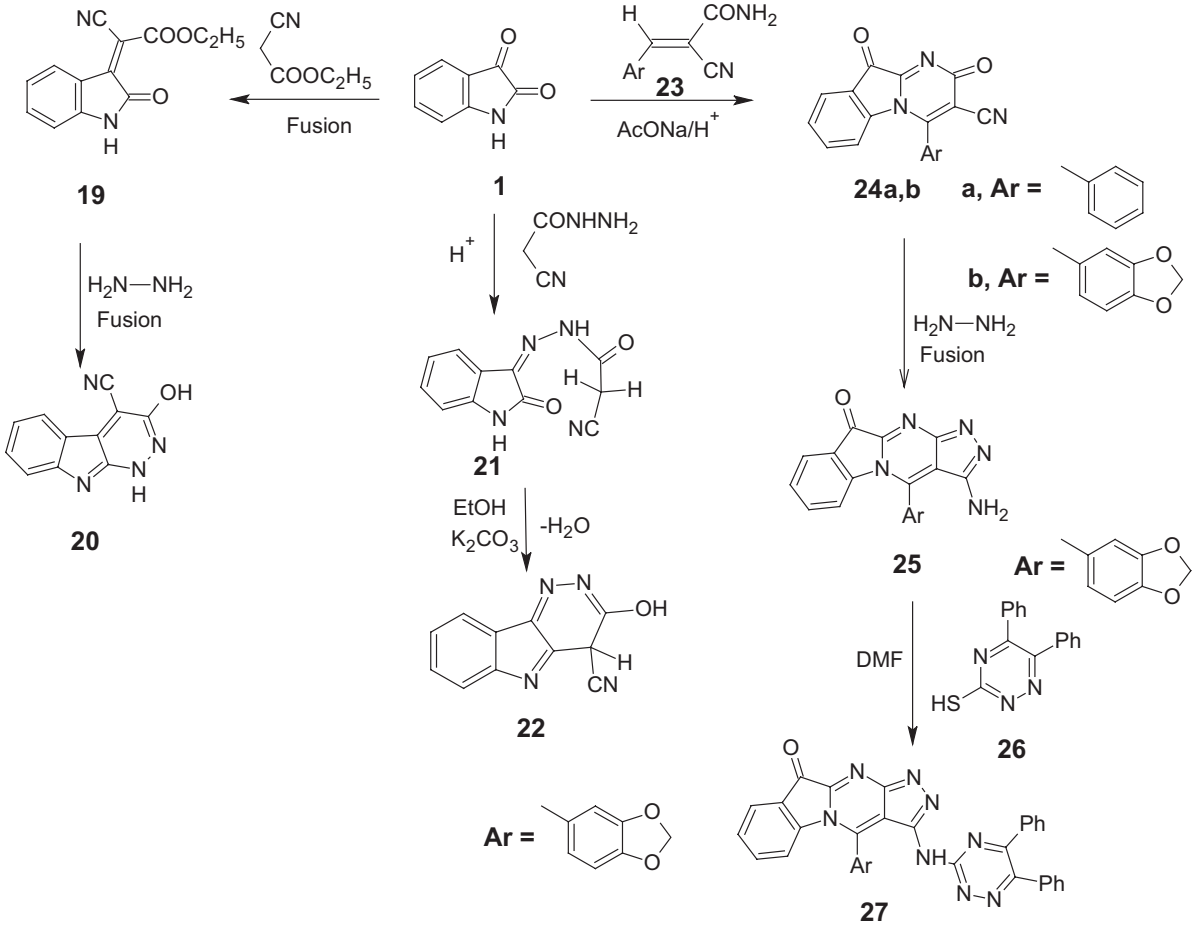
Many synthetic methodologies have been described for the conversion of isatin-3-thiosemicarbazones into other heterocyclic systems.[24,25] Direct nucleophilic displacement of the C=S and C=O groups by nitrogen and/or active methylene can easily occur, more readily at C=S than C=O. Thus condensation of 1-(*N*-phenylbenzimidoyl)isatin (**10**) with thiosemicarbazide in boiling ethanol/acetic acid produced the 3-thiosemicarbazone **14**. The IR spectrum of **14** contained characteristic bands at 3420, 3220, 1685 and 1130 cm^{-1} for NH_2, NH, C=O and C=S groups. Ring closure of compound **14** on reflux with anhydrous sodium acetate in acetic acid yielded 5-[phenyl(phenylimino) methyl]-2,5-dihydro-3*H*-[1,2,4]triazino[5,6-*b*]indole-3-thione (**15a**). The analogous compound **15b** was obtained under the same conditions using semicarbazide hydrochloride. The spectral details of compounds **15a** and **15b** are shown in the Experimental section.

Alkylation of compound **14** using monochloroacetic acid in ethanol/sodium acetate produced the 5-oxo-2-thioxo-imidazoline derivative **16**. The structure of **16** was established chemically by condensation with aromatic aldehydes in boiling acetic acid to give the arylmethylene products **17** and by fusion with ammonium acetate/acetic acid to give 5-[phenyl(phenylimino)methyl]-2,5-dihydro-1*H*-imidazo[3',4':2,3][1,2,4]triazino[5,6-*b*]indole-1-thione (**18**) (Scheme 3). The IR spectrum showed the presence of bands at 1175 and 3210 cm^{-1} characteristic of C=S and NH groups and the ^{1}H NMR spectrum gave signals at δ 2.50 and 5.33 ppm for NH and C<u>H</u>= of the imidazole ring (Scheme 3).

The reactivity of isatin derivatives towards active methylene groups has been the subject of a number of reports and some of these are quite intriguing. Thus, isatin itself failed to yield Knoevenagel condensation products with malonic acid,[26] while an important issue with respect to the Knoevenagel condensation is that the products obtained from the reaction of isatin or 1-methylisatin with ethyl cyanoacetate exist as mixtures of *E* and *Z* isomers, and that the *E* isomers exist in equilibrium between two conformers *trans*-s-*cis* and *trans*-s-*trans*.[27]

Fusion of compound **1** with ethyl cyanoacetate produced ethyl cyano-(2-oxo-1,2-dihydroindol-3-ylidene)acetate (**19**) which upon fusion with hydrazine hydrate afforded 3-hydroxy-1*H*-pyridazino[3,4-*b*]indole-4-carbonitrile (**20**). The IR spectrum of **20** indicated the absence of a C=O group and the presence of NH at 3215 cm^{-1} and OH at 3380 cm^{-1} beside the presence of CN at 2250 cm^{-1} (Scheme 4).

Compound 3-hydroxy-4*H*-pyridazino[4,3-*b*]indole-4-carbonitrile **22** was obtained from condensation of isatin with cyanoacetic acid hydrazide[28] in ethanol/acetic acid followed by intramolecular condensation and enolisation of **21** using ethanol/K_2CO_3 (Scheme 4). The IR spectrum of compound **22**



Scheme 4 Further heterocyclisations from isatin.

showed an OH band at 3410 cm^{-1} and the absence of a C=O group. Also the ^1H NMR spectrum gave a signal at δ 3.41 ppm for (NC–C<u>H</u>–C) and the ^{13}C NMR spectrum showed a signal at 23.6 ppm for (NC–<u>C</u>–C) group. The addition of isatin **1** to the arylidine **23** in acetic acid/sodium acetate led to the direct formation of the 2,10-dioxo-4-aryl-2*H*,10*H*-pyrimido[1,2-*a*] indole-3-carbonitriles **24a** and **24b**.

The heterocyclisation of compound **24b** by refluxing with hydrazine hydrate in ethanol with a few drops of piperidine afforded **25**. The presence of an NH_2 group in **25** was deduced from heteroarylation using 3-mercapto-5,6-diphenyl-1,2,4-triazine[29] **26** in boiling DMF to give 3-heteroarylamino-5,6-diphenyl-1,2,4-triazine **27** (Scheme 4). The formation of **24** from **1** and **23** may be as outlined in Scheme 5.

Experimental

All experiments were carried out using anhydrous solvents. IR (KBr) spectra were obtained on a Perkin–Elmer FTIR 1600 spectrometre. ^1H and ^{13}C NMR spectra were determined with a JEOL-JNM-LA 400 spectrometre. The chemical shifts are expressed on the δ (ppm) scale using TMS as standard.

N'-(2-Oxo-1,2-dihydro-3H-indol-3-ylidene)dithiocarbohydrazide (**2**): A mixture of isatin (**1**, 10 mmol) and dithiocarbonic acid hydrazide (10 mmol) in acetic acid (10 ml) was boiled under reflux for 6 h. It was then cooled and poured into ice-water to give a pale yellow precipitate which was collected by filtration, dried and recrystallised from EtOH (10 ml) to afford a pale yellow powder (yield 75 %), m.p. 210–212 °C. IR (KBr): 1120 (C=S), 1680 (CO), 2250 (SH) and 3280 (NH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.52 (s, 1H, SH), 6.81 (s, 2H, 2 NH), 7.00–7.62 (m, 4H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 120.5, 123.1, 124.7, 129.3, 131.1, 138.7 (Ar–C), 155.2, 161.4 and 192.2 (C=N, C=O and C=S). Calcd for $C_9H_7N_3OS_2$ (237.3): C, 45.55; H, 2.97; N, 17.71. Found: C, 45.38; H, 2.99; N, 17.58 %.

4-Amino-2,4-dihydro-3H-[1,2,4]triazino[5,6-b]indole-3-thione (**3**): Hydrazine hydrate (15 mmol) in isopropanol (10 ml) was added dropwise to a solution of **2** (10 mmol) in isopropanol (10 ml). The mixture was heated under reflux for 4 h, then concentrated, and the reaction mixture was left to cool. A yellow precipitate was collected and recrystallised from ethanol to give yellow needles (yield 82 %); m.p. 295–297 °C (lit.[18] m.p. >300 °C). IR (KBr): 1090 (C=S), 1620 (C=N), 3150 (NH) and 3340–3240 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.30 (s, 2H, NH_2), 6.82 (s, 1H, NH), 7.30–7.62 (m, 4H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 122.1, 124.7, 127.1, 130.3, 132.1, 149.5, 155.0, 163.2 (Ar–C and 2 C=N) and 186.2 (C=S). Calcd for $C_9H_7N_5S$ (217.3): C, 49.76; H, 3.25; N, 32.24. Found: C, 49.86; H, 3.32; N,32.20 %.

1,2-Dihydro-2-phenyl[1,3,4]thiadiazolo[2',3': 3,4][1,2,4]triazino [5,6-b]indole (**4**): An equimolar mixture of **3** (10 mmol) and benzaldehyde (10 mmol) in ethanol–HCl (20 ml)[3: 1] was boiled under reflux for 10 h, cool, then poured into ice-water and neutralised with sodium bicarbonate solution. The precipitate was collected and recrystallised from ethanol/DMF (15 ml) to give a pale brown powder (yield 65 %); m.p. 275–276 °C. IR (KBr): 3218 (NH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.10 (s, 1H, NH), 4.80 (s, 1H, NH–C<u>H</u>–S), 7.00–7.65 (m, 9H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 62.5 (N–<u>C</u>–S), 102.1, 111.2, 119.6, 120.5, 121.7, 124.1, 126.9, 127.9, 128.5, 135.5, 155.2, 161.3, 163.1, (Ar–C and 3 C=N). Calcd for $C_{16}H_{11}N_5S$ (305.4): C, 62.93; H, 3.63; N, 22.93. Found: C, 62.90; H, 3.66; N, 22.90 %.

2-Amino-3H-[1,3,4]thiadiazino[2',3': 3,4][1,2,4]triazino[5,6-b]indole (**5**): A mixture of **3** (10 mmol) and chloroacetonitrile (10 mmol) in ethanol (20 ml) with a few drops of triethylamine was boiled under reflux for 6 h, and the reaction mixture was then cooled. The precipitate was recrystallised from DMF (15 ml) to afford **5** as a brown powder (yield 68 %); m.p. 260–262 °C. IR (KBr): 3280–3370 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.23 (s, 2H, NH_2), 2.93 (s, 2H, CH_2), 7.03–7.69 (m, 4H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 27.5 (CH_2), 122.1, 124.7, 127.1, 130.3, 132.1, 149.5, 155.2, 163.4, 163.5, 164.2, (Ar–C and 4 C=N). Calcd for $C_{11}H_8N_6S$ (256.3): C, 51.55; H, 3.15; N, 32.79. Found: C, 51.58; H, 3.18; N, 23.80 %.

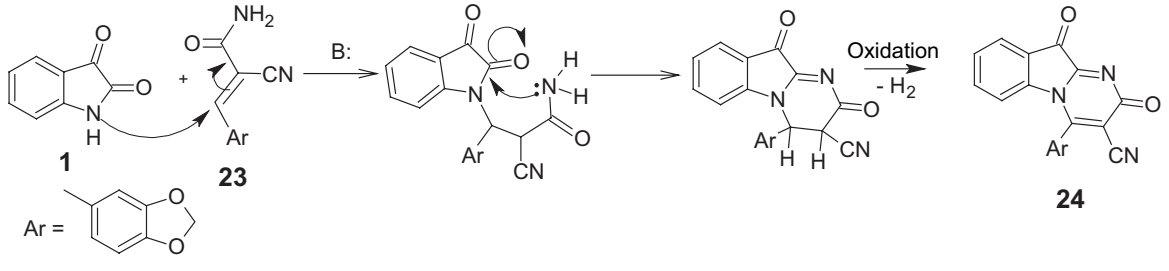
2-Phenyl-3H-[1,3,4]thiadiazino[2',3': 3,4][1,2,4]triazino[5,6-b] indole (**6**): Phenacyl bromide (10 mmol) in ethanol (10 ml) was added dropwise to a solution of **3** (10 mmol) and 3 drops of triethylamine in ethanol (10 ml). The mixture was heated under reflux for 6 h, and then cooled. The precipitate was collected and recrystallised from DMF (20 ml) to afford a brown powder of **6** (yield 80 %); m.p. 270–272 °C. IR (KBr): 1618 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.93 (s, 2H, CH_2), 7.32–7.83 (m, 9H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 25.5 (CH_2), 122.1, 124.7, 127.1, 128.6, 129.2, 130.3, 130.8, 131.2, 132.1, 149.5 (Ar–C), 155.6, 163.3, 163.5, 164.2 (4 C=N). Calcd for $C_{17}H_{11}N_5S$ (317.4): C, 64.34; H, 3.49; N, 22.07. Found: C, 64.50; H, 3.29; N, 22.12 %.

1H-[1,3,4]Thiadiazino[2',3': 3,4][1,2,4]triazino[5,6-b]indol-2(3H)-one (**7**): A mixture of **3** (10 mmol) and chloroacetyl chloride (10 mmol) in DMF (15 ml) and few drops of piperidine was heated under reflux for 8 h, and then cooled and poured into ice-water. The precipitate obtained recrystallised from DMF/ethanol (20 ml) to afford pure product **7** (yield 60 %); m.p. 240–242 °C. IR (KBr): 1620 (C=N), 1685 (C=O) and 3225 (NH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.76 (s, 2H, CH_2), 7.25–7.68 (m, 4H, Ar–H), 8.21 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 34.9 (CH_2), 122.1, 124.8, 127.2, 130.3, 132.1, 149.5, 163.1, 163.4, 164.2 (Ar–C and 3 C=N), 170.3 (C=O). Calcd for $C_{11}H_7N_5OS$ (257.3): C, 51.35; H, 2.74; N, 27.22. Found: C, 51.30; H, 2.77; N, 27.23 %.

1H-[1,3,4]Thiadiazino[2',3': 3,4][1,2,4]triazino[5,6-b]indole-2,3-dione (**8**): The experimental method was as for compound **7,** but using oxalyl chloride in place of chloroacetyl chloride; (yield 60 %) m.p. 258–260 °C. IR (KBr): 1618 (C=N), 1690, 1710 (2 C=O) and 3210 (NH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.00–7.70 (m, 4H, Ar–H), 8.52 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 122.1, 124.7, 127.1, 130.3, 132.1, 149.5 (Ar–C).163.2, 163.5, 164.2 (3 C=N) and 169.6, 177.3, (2 C=O). Calcd for $C_{11}H_5N_5O_2S$ (271.3): C, 48.71; H, 1.86; N, 25.82. Found: C, 48.89; H, 2.01; N, 25.91 %.

10,10-Dimethyl-10,11-dihydro-9H-indolo[2',3': 5,6][1,2,4]triazolo [3,4-b][1,3,4]benzothiadiazin-8(12H)-one (**9**): A solution of **3** (10 mmol) and dimedone (10 mmol) in DMSO (20 ml) and few drops of piperidine was heated under reflux for 24 h, the reaction mixture was cooled, then poured into ice-cold aqueous HCl. The precipitate was collected and recrystallised from DMF/ethanol (20 ml) to afford a brown powder of **9** (yield 77 %); m.p. 326–328 °C. IR (KBr): 1625 (C=N), 1718 (C=O) and 3220 (NH) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.12 (s, 6H, 2 CH_3), 1.88 (s, 2H, CH_2), 2.20 (s, 1H, NH), 2.86 (s, 2H, C<u>H</u>$_2$CO), 7.30–7.68 (m, 4H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 17.8 (<u>C</u>Me$_2$), 26.4 (2 CH_3), 45.2 (CH_2), 50.3 (<u>C</u>H$_2$CO), 115.1, 122.1, 124.7, 127.1, 130.3, 132.2, 149.5, 150.3 (Ar–C), 163.2, 163.4, 164.3 (3 C=N) and 179.6 (C=O). $C_{17}H_{15}N_5OS$ (337.4): C, 60.52; H, 4.48; N, 20.76. Found: C, 60.80; H, 4.52; N, 20.79 %.

1-[Phenyl(phenylimino)methyl]-1H-indole-2,3-dione (**10**): A mixture of **1** (10 mmol) and *N*-phenylbenzimidoyl chloride[23] (10 mmol) in ethanol (20 ml) and KOH (1.0 g) was heated under reflux for 2 h. The reaction mixture cooled and poured into ice-water. Recrystallisation of the precipitate from ethanol gave an orange powder (88 %); m.p. 143–145 °C. IR (KBr): 1615 (C=N) and 1685, 1718 (2 C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.94 (d, J = 8.8 Hz, 1H, Ar–H), 7.00–7.61 (m, 11H, Ar–H), 7.81 (dd, J = 8.9, 7.0 Hz, 1H, Ar–H), 7.98 (d, J = 7.00 Hz, 1H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 120.9, 122.0, 124.6,



Scheme 5 Formation of the pyrimido-indoledione **24.**

125.9, 127.1, 128.6, 128.9, 129.8, 129.9, 130.1, 132.9, 134.5, 139.4, 153.2 (Ar–C) and 158.3, 164.1, 187.2 (C=N and 2 C=O). Calcd for $C_{21}H_{14}N_2O_2$ (326.3): C, 77.29; H, 4.32; N, 8.58. Found: C, 77.39; H, 4.42; N, 8.45 %.

3-(Phenylhydrazono)-1-[phenyl(phenylimino)methyl]-1,3-dihydro-2H-indol-2-one (**11**): To a solution of **10** (10 mmol) in ethanol (10 ml) and few drops of acetic acid, phenylhydrazine (10 mmol) was added. The reaction mixture was heated under reflux for 6 h, and then cooled. The product was filtered, and recrystallised from ethanol to give a yellow powder (80 %), m.p. 168–170 °C. IR (KBr): 1612 (C=N), 1685 (C=O) and 3240 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6) δ 6.46 (S, 1H, NH), 6.62–7.62 (m, 19H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 115.1, 118.5, 120.5, 122.1, 123.1, 124.2, 125.9, 127.1, 128.6, 129.2, 129.4, 129.8, 129.9, 131.0, 132.9, 138.7, 146.7, 153.2 (Ar), 155.0, 161.2, 164.2 (2 C=N and (C=O). Calcd for $C_{27}H_{20}N_4O$ (416.5): C, 77.87; H, 4.84; N, 13.45. Found: C, 78.00; H, 4.89; N, 13.56 %.

4-Chloro-N-phenyl-N′-[2-oxo-1-[phenyl(phenylimino)methyl]-1,2-dihydroindol-3-ylidene]benzohydrazide (**12**): A mixture of **11** (10 mmol) and 4-chlorobenzoyl chloride (10 mmol) in DMF (20 ml) was refluxed for 8 h. The reaction mixture was cooled and poured into ice-water. The precipitate is collected by filtration, then recrystallised from ethanol (75 % yield), m.p. 185–187 °C. IR (KBr): 1620 (C=N), 1682, 1695 cm^{-1} (2 C=O). ^{1}H NMR (DMSO-d_6): δ = 7.00–7.89 (m, 23H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 120.4, 120.6, 122.0, 123.1, 124.1, 124.2, 125.9, 127.0, 128.6, 128.7, 128.9, 129.0, 129.2, 129.8, 129.9, 131.0, 131.6, 132.9, 137.2, 138.2, 138.7, 153.2 (Ar), 155.0, 161.2, 164.3, 165.2 (2 C=N and 2 C=O). Calcd for $C_{34}H_{23}ClN_4O_2$ (555.0): C, 73.58; H, 4.18; N, 10.09. Found: C, 73.70; H, 4.20; N, 10.12 %.

3-(4-Chlorophenyl)-2-phenyl-5-[phenyl(phenylimino)methyl]-2,5-dihydro-1H-[1,2,4]triazino[5,6-b]indole (**13**): The aroylhydrazone **12** (10 mmol) was boiled under reflux for 4 h in acetic acid (10 ml) with NH_4OAc (15 mmol). After cooling, the mixture was poured into ice-water. The precipitated solid was isolated by filtration and washed with aqueous $NaHCO_3$ and then with H_2O. Recrystallisation from ethanol afforded a pale brown powder (65 % yield), m.p. 224–226 °C. IR (KBr): 1612 (C=N), 3185 (NH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 1H, NH), 6.52–7.62 (m, 23H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 112.1, 114.9, 118.3, 118.9, 122.0, 125.9, 127.0, 127.3, 127.9, 128.5, 128.6, 128.7, 129.0, 129.3, 129.8, 129.9, 131.8, 132.9, 140.5, 142.2, 145.3, 146.0, 153.2, 162.2 (Ar) and 164.2, 167.1 (2 C=N). Calcd for $C_{34}H_{24}ClN_5$ (538.0): C, 75.90; H, 4.50; N, 13.02. Found: C, 75.88; H, 4.47; N, 13.00 %.

1-[Phenyl(phenylimino)methyl]indole-2,3-dione 3-thiosemicarbazone (**14**): to a solution of **10** (10 mmol) in anhydrous ethanol (10 ml)and few drops of acetic acid thiosemicarbazide (10 mmol) in ethanol (10 ml) was added. The reaction mixture was boiled under reflux for 4 h, then cooled and poured into ice-water. The precipitate was recrystallised from ethanol (20 ml) to give pure product (85 % yield), m.p. 238–240 °C. IR(KBr): 1130 (C=S), 1612 (C=N), 1685 (C=O), 3220 (NH) and 3310–3420 cm^{-1} (NH_2). ^{1}H NMR (DMSO-d_6) δ 2.01 (br, 2H, NH_2), 6.92 (s, 1H, NH), 7.00–7.69 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 120.5, 122.0, 123.1, 124.2, 125.9, 127.0, 128.6, 129.2, 129.8, 129.9, 131.0, 132.9, 138.7, 153.2 (Ar), 155.2, 161.0, 164.3 (2 C=N and C=O), 186.0 (C=S). Calcd for $C_{22}H_{17}N_5OS$ (399.5): C, 66.15; H, 4.29; N, 17.53. Found: C, 66.33; H, 4.20; N, 17.52 %.

2,5-Dihydro-5-[phenyl(phenylimino)methyl]-3H-[1,2,4]triazino[5,6-b]indole-3-thione (**15a**): Compound **14** (10 mmol) was heated under reflux in acetic acid (10 ml) with sodium acetate (4.0 g) for 4 h, then cooled and poured into ice-water. The solid obtained was filtered off and recrystallised from ethanol (20 ml) to give a pale yellow powder (80 % yield), m.p. 306–308 °C. IR (KBr): 1080 (C=S), 1620 (C=N) and 3180 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6): δ 6.52 (S, 1H, NH), 6.70–7.62 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 115.2, 117.8, 118.6, 122.0, 125.9, 127.0, 128.6, 129.6, 129.8, 129.9, 131.6, 132.9, 147.2, 153.2 (Ar), 155.0, 163.2, 164.3 (3 C=N) and 190.3 (C=S). Calcd for $C_{22}H_{15}N_5S$ (381.5): C, 69.27; H, 3.96; N, 18.36. Found: C, 69.30; H, 3.90; N, 18.30 %.

2,5-Dihydro-5-[phenyl(phenylimino)methyl]-3H-[1,2,4]triazino[5,6-b]indol-3-one (**15b**): Compound **10** (10 mmol), semicarbazide hydrochloride (10 mmol) and a few drops of gl. acetic acid were boiled together in ethanol (20 ml) under reflux for 6 h. After cooling and pouring into ice-water, the product which separated was recrystallised from ethanol (76 % yield), m.p. 290–292 °C. IR (KBr): 1618 (C=N), 1678 (C=O) and 3215 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6): δ 6.53 (s, 1H, NH), 6.75–7.68 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 115.4, 117.8, 118.7, 122.0, 125.9, 127.0, 128.6, 129.6, 129.8, 129.9, 131.6, 132.9, 147.2, 153.2, (Ar), 155.0, 163.2, 164.3 (3 C=N) and 165.6 (C=O). Calcd for $C_{22}H_{15}N_5O$ (365.4): C, 72.32; H, 4.14; N, 19.17. Found: C, 72.50; H, 4.18; N, 19.28 %.

1,3-Dihydro-3-(5-oxo-2-thioxoimidazolidin-1-ylimino)-1-[phenyl(phenylimino)methyl]-2H-indol-2-one (**16**): The thiosemicarbazone **14** (10 mmol), chloroacetic acid (10 mmol) and anhydrous NaOAc (3.0 g) in ethanol (20 ml) were refluxed for 4 h, then cooled and poured into ice-water. The solid obtained was filtered off and recrystallised from ethanol to give a colourless powder (80 % yield), m.p. 196–198 °C. IR (KBr): 1110 (C=S), 1618 (C=N), 1685, 1695 (2 C=O) and 3250 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 1H, NH), 4.34 (s, 2H, CH_2), 7.00–7.87 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 56.3 (CH_2), 120.5, 122.0, 123.1, 124.2, 125.9, 127.0, 128.6, 129.2, 129.8, 129.9, 131.0, 132.9, 138.7, 153.3 (Ar), 155.0, 161.2, 164.3, 172.7 (2 C=N and 2 C=O) and 183.4 (C=S). Calcd for $C_{24}H_{17}N_5O_2S$ (439.5): C, 65.59; H, 3.90; N, 15.94. Found: C, 65.69; H, 3.98; N, 15.98 %.

3-(4-Benzylidene-5-oxo-2-thioxoimidazolidin-1-ylimino)-1,3-dihydro-1-[phenyl(phenylimino)methyl]-2H-indol-2-one (**17**): Compound **16** (10 mmol), benzaldehyde (10 mmol) and a few drops of acetic acid were refluxed in ethanol (20 ml) for 1 h. After cooling the precipitated solid was filtered off and recrystallised from ethanol to give a pale brown powder (58 % yield), m.p. 182–184 °C. IR (KBr): 1115 (C=S), 1680, 1695 (2 C=O) and 3280 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 1H, NH), 7.00–7.69 (m, 20H, Ar–H and olefinic C<u>H</u>). ^{13}C NMR (DMSO-d_6): δ 113.6 (<u>CH=</u>), 120.5, 122.0, 123.1, 124.2, 125.9, 126.2, 127.0, 127.7, 128.4, 128.6, 129.2, 129.8, 129.9, 131.0, 132.9, 134.9, 138.7, 140.8, 153.2 (Ar), 155.2, 161.2, 164.3, 168.4 (2 C=N and 2 C=O) and 183.5 (C=S). Calcd for $C_{31}H_{21}N_5O_2S$ (527.6): C, 70.57; H, 4.01; N, 13.27. Found: C, 70.82; H, 4.23; N, 13.50 %.

2,5-Dihydro-5-[phenyl(phenylimino)methyl]-1H-imidazo[3′,4′:2,3][1,2,4]triazino[5,6-b]indole-1-thione (**18**): Compound **16** (10 mmol) and NH_4OAc (15 mmol) in acetic acid (15 ml) were boiled under reflux for 4 h. After cooling, the mixture was poured into ice-water. The precipitated solid was filtered off and washed with aq. solution of $NaHCO_3$ and then with water. Recrystallisation from ethanol afforded a pale brown powder (65 % yield), m.p. 265–267 °C. IR (KBr): 1175 (C=S), 1618 (C=N) and 3210 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 1H, NH), 5.33 (s, 1H, CH=) and 6.70–7.62 (m, 14H, Ar–H), ^{13}C NMR (DMSO-d_6): δ 107.1, 115.2, 117.8, 118.6, 122.0, 125.9, 127.0, 128.6, 129.8, 129.9, 130.1, 131.2, 131.6, 132.9, 147.2, 153.2 (Ar), 155.4, 163.2, 164.3 (3 C=N) and 178.2 (C=S). Calcd for $C_{24}H_{16}N_6S$ (420.5): C, 68.55; H, 3.84; N, 19.99. Found: C, 68.75; H, 3.89; N, 20.20 %.

Ethyl cyano-(2-oxo-1,2-dihydroindol-3-ylidene)acetate (**19**): Isatin (**1**) (10 mmol) with ethyl cyanoacetate (10 mmol) above its melting point for 1 h. After cooling, the solid was treated with methanol and recrystallised from ethanol to give a pale brown powder (85 % yield); m.p. 160–162°C. IR (KBr): 1130 (C–O), 1620 (C=N), 1680, 1730 (2 C=O) and 2240 cm^{-1} (CN). ^{1}H NMR (DMSO-d_6): δ 1.30 (t, J = 7.1 Hz, 3H, CH_3), 4.19 (q, J = 7.1 Hz, 2H, CH_2O), 6.95–7.59 (m, 4H, Ar–H) and 8.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 13.7, 59.1 (CH_3, CH_2), 106.3, 117.2, 120.3, 124.0, 126.4, 126.8, 127.9, 135.9, 163.8, 164.5, 165.2 (Ar, C≡N and 2 C=O). Calcd for $C_{13}H_{10}N_2O_3$ (242.2): C, 64.46; H, 4.16; N, 11.56. Found: C, 64.62; H, 4.25; N, 11.58 %.

3-Hydroxy-1H-pyridazino[3,4-b]indole-4-carbonitrile (**20**): Compound **19** (10 mmol) was fused with hydrazine hydrate (10 mmol) for 2 h, cooled, then triturated with methanol and the precipitate crystallised from ethanol to give a pale brown powder (75 % yield), m.p. 250–252 °C. IR (KBr): 2250 (CN), 3215 (NH) and 3380 cm^{-1} (OH). ^{1}H NMR (DMSO-d_6): δ 2.01 (s, 1H, OH), 6.80 (S, 1H, NH), 7.20–7.70 (m, 4H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 102.2, 117.2, 121.9, 126.9, 127.5, 128.4, 129.0, 146.7, 155.0, 164.2, 165.9 (Ar, CN and C=N). Calcd for $C_{11}H_6N_4O$ (210.2): C, 62.86; H, 2.88; N, 26.66. Found: C, 63.00; H, 2.89; N, 26.78 %.

Cyano-N′-(2-oxo-1,2-dihydroindol-3-ylidene)acetohydrazide (**21**): Cyanoacetohydrazide (10 mmol) in gl. acetic acid (10 ml) was added to isatin (**1**) (10 mmol) in gl. acetic acid (10 ml). The reaction mixture was boiled under reflux for 6 h, cooled, poured into ice-water. The precipitate was collected and recrystallised from ethanol to give a pale yellow powder (80 % yield), m.p. 224–226 °C. IR (KBr): 1612 (C=N), 1680, 1695(2 C=O), 2235 (CN) and 3218 cm^{-1} (NH). ^{1}H NMR (DMSO-d_6): δ 3.30 (s, 2H, CH_2), 6.82 (s, 1H, NH), 7.00–7.62 (m, 4H, Ar–H), 8.10 (s, 1H, NH for indole). ^{13}C NMR (DMSO-d_6): δ 24.3 (CH_2), 114.9, 120.5, 123.1, 124.2, 129.2, 131.0, 138.7 (Ar and CN), 155.2 (C=N), 161.2, 173.1 (2 C=O). Calcd for $C_{11}H_8N_4O_2$ (228.2): C, 57.89; H, 3.53; N, 24.55. Found: C, 57.88; H, 3.58; N, 24.58 %.

3-Hydroxy-4H-pyridazino[4,3-b]indole-4-carbonitrile (**22**): Compound **21** (10 mmol) was heated under reflux in ethanol (10 ml) with anh. potassium carbonate (3.0 g) for 8 h, cooled and poured into ice-water. The solid obtained crystallised from ethanol (85 % yield); m.p. 253–255 °C. IR (KBr): 2250 (CN), 3410 cm^{-1} (OH). ^1H NMR (DMSO-d_6): δ 2.20 (s, 1H, OH), 3.41 (s, 1H, C<u>H</u>), 7.30–7.60 (m, 4H, Ar). ^{13}C NMR (DMSO-d_6): δ 23.6 (CH), 114.9, 122.1, 124.7, 127.1, 130.3, 132.1, 149.5, (Ar and CN) 164.2, 164.5, 164.7 (3 C=N). Calcd for $C_{11}H_6N_4O$ (210.2): C, 62.86; H, 2.88; N, 26.66. Found: C, 62.89; H, 2.87; N, 26.70 %.

2,10-Dioxo-4-phenylpyrimido[1,2-a]indole-3-carbonitrile (**24a**): Isatin (**1**) (10 mmol), NaOAc (15 mmol), and benzylidenecyanoacetamide (10 mmol) were boiled under reflux in acetic acid (20 ml) for 12 h. After cooling, the mixture was poured into ice-water. The precipitate was collected and washed with aqueous $NaHCO_3$ and then with water. Crystallisation from ethanol afforded a pale brown powder (70 % yield), m.p. 320–322 °C. IR (KBr): 1612 (C=N), 1680, 1710 (2 C=O) 2258 cm^{-1} (CN). ^1H NMR (DMSO-d_6): δ 6.65–7.50 (m, 9H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 82.5 (=C–CN), 115.6, 117.2, 119.0, 123.3, 126.2, 127.7, 128.4, 130.5, 134.9, 135.1, 147.9, 163.0, 180.9, 189.8, 190.1 (Ar, CN, C=N and 2 C=O). Calcd for $C_{18}H_9N_3O_2$ (299.3): C, 72.24; H, 3.03; N, 14.04. Found: C, 72.35; H, 3.14; N, 14.32 %.

4-(1,3-Benzodioxol-5-yl)-2,10-dioxopyrimido[1,2-a]indole-3-carbonitrile (**24b**): The experimental method was as for compound **24a**, using the appropriate substituted reagent **23**. Yield 75 %, m.p. 318–320 °C. IR (KBr): 1618 (C=N), 1690, 1715 (2 C=O) and 2280 cm^{-1} (CN). ^1H NMR (DMSO-d_6): δ 5.90 (s, 2H, CH_2), 6.65–7.56 (m, 7H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 82.6 (=C–CN), 91.3 (O–C<u>H</u>$_2$–O), 112.8, 115.0, 115.6, 117.2, 119.2, 119.5, 123.3, 128.2, 130.5, 135.1, 146.8, 147.5, 147.9, 163.2, 180.9, 189.9, 190.0 (Ar, CN, C=N and 2 C=O). Calcd for $C_{19}H_9N_3O_4$ (343.3): C, 66.47; H, 2.64; N, 12.24. Found: C, 66.50; H, 2.70; N, 12.28 %.

3-Amino-4-(1,3-benzodioxol-5-yl)-10H-pyrazolo[3',4':4,5]pyrimido[1,2-a]indol-10-one (**25**): A mixture of **24** (10 mmol), hydrazine hydrate (15 mmol) and a few drops of piperidine was boiled under reflux in ethanol (10 ml) for 10 h, then cooled and poured into ice/dil. HCl. The precipitate crystallised from ethanol/DMF to afford a brown powder (60 % yield), m.p. 310–312 °C. IR (KBr): 1620 (C=N), 1718 (C=O) and 3315–3410 cm^{-1} (NH_2). ^1H NMR (DMSO-d_6): δ 4.10 (br, 2H, NH_2), 5.90 (s, 2H, CH_2), 6.72–7.80 (m, 7H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 91.3 (O–C<u>H</u>$_2$–O), 91.5, 113.6, 115.6, 120.3, 129.1, 129.3, 129.8, 130.2, 130.3, 132.0, 133.1, 147.6, 148.1, 154.0, 161.5, 162.9, 187.0 (Ar, 3 C=N and C=O). Calcd for $C_{19}H_{11}N_5O_3$ (357.3): C, 63.86; H, 3.10; N, 19.60. Found: C, 63.98; H, 3.13; N, 19.80 %.

4-(1,3-Benzodioxol-5-yl)-3-[(5,6-diphenyl-1,2,4-triazin-3-yl)amino]-10H-pyrazolo[3',4':4,5]pyrimido[1,2-a]indol-10-one (**27**): A mixture of **25** (10 mmol) and **26** (10 mmol)in DMF (20 ml) was boiled under reflux for 10 h. The reaction mixture was concentrated and poured into ice-water. The precipitate formed was recrystallised from ethanol/DMF to give a brown powder (55 % yield); m.p. 338–340 °C. IR (KBr): 1620 (C=N), 1715 (C=O) and 3215 cm^{-1} (NH). ^1H NMR (DMSO-d_6): δ 4.10 (s, 1H, NH), 5.90 (s, 2H, CH_2), 6.72–7.88 (m, 17H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 91.3 (O–C<u>H</u>$_2$–O), 91.5, 113.6, 115.5, 120.3, 127.0, 128.5, 129.0, 129.2, 129.4, 129.8, 130.0, 130.2, 132.0, 132.2, 132.4, 132.5, 133.0, 136.5, 147.6, 148.1, 154.0, 155.4, 161.5, 162.9, 187.0 (Ar, 4 C=N and C=O). Calcd for $C_{34}H_{20}N_8O_3$ (588.6): C, 69.38; H, 3.43; N, 19.04. Found: C, 69.42; H, 3.58; N, 19.28 %.

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