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Synthesis of diheteroarylmethanes from activated nitriles†

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Novel procedures for the synthesis of diheteroarylmethanes **3-7** have been developed from the base-catalysed condensation-cyclization reactions of (indol-3-yl)methylmalononitrile **2** with amidine, dicyandiamide, hydroxylamine, hydrazine and thioglycolic acid separately. The acid catalysed reaction of **1** and **9** with thiosemicarbazide separately affords **8** and **10**. The latter on reaction with phenacyl bromide yield **11**. Base-catalysed reaction of **9** with dicyandiamide gives symmetrical triazine **14**.

Diverse pharmacological activities such as analgesic[1], antiulcer[1], antiinflammatory[2], antihypertensive[3], dopamine autoreceptor stimulant[4], thromboxane synthetase inhibitor[5] and blood platelet anti-aggregating agents[6] are associated with polysubstituted arylindoles which enthused us to develop new routes for the synthesis of highly functionalized heteroalkylindoles. Various functionalized azoles and azines are also known to display antimalarial[7], antimicrobial[8] and antiviral[8] activities. Presuming that the association of azoles and azines with functionalized indole moiety at position 3 will result compounds with broad spectrum biodynamic properties from easily accessible precursors, several diheteroarylmethanes were synthesized.

In view of our continued interest in the chemistry of malononitrile, (indol-3-yl)methylmalononitrile **2** used as a precursor for the synthesis of various heterocycles obtained by sodium borohydride reduction of 2-cyano-3-(indol-3-yl)acrylonitriles **1** and transformed into 2, 4, 6-triamino- and (4, 6-diaminopyrimidin-5-yl) (indol-3-yl)methane **3** by refluxing a mixture of **2** with guanidine or amidines in sodium ethoxide solution. Similarly, (2-cyanoamino-4, 6-diaminopyrimidin-5-yl)(indol-3-yl)methanes **4** were obtained[9] by the reaction of **2** with dicyandiamide in isopropanol under basic conditions. 3, 5-Diaminoisoxazoles **5** and 3, 5-diaminopyrazole **6** were synthesized by the reaction of **2** with hydroxylamine hydrochloride and hydrazine hydrate respectively. On heating, an equimolar mixture of **2** and thioglycolic acid in pyridine afforded heterocycles **7**. The various syntheses of 2-amino-5-substituted-1, 3, 4-thiadiazoles are reported by the acid-catalysed cyclization of aroylthiosemicarbazides[10], arylthiosemicarbazide[11] or direct condensation-cyclization of carboxylic acid or carbonitrile with thiosemicarbazide[12]. In the present paper the synthesis of 2-(5-amino-1, 3, 4-thiadiazol-2-yl)-3-(indol-3-yl)acrylonitriles **8** by TFA-catalysed condensation-cyclization of **1** with thiosemicarbazide has been reported (Scheme I).

Reaction of **9** with thiosemicarbazide in TFA led to the formation of (2-amino-1, 3, 4-thiadiazol-5-yl) (indol-3-yl) methane **10** which on reaction with phenacyl bromide provided [2-(4-chlorophenyl)imidazo[2, 1-*b*]-1, 3, 4-thiadiazol-6-yl]methane **11**. In order to synthesize bisthiadiazoles, compound **12** was prepared by alkylation of **9** with chloroacetonitrile which on acid-catalysed reaction with thiosemicarbazide gave **10** instead of bis-thiadiazole **13**. The base-catalysed reaction of **9** with dicyandiamide yielded (2, 4-diamino-1, 3, 5-triazin-6-yl)(indol-3-yl)methane **14** (Scheme II).

Experimental Section

Melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded in KBr discs on a Perkin-Elmer Ac-1 spectrometer (ν_{max} in cm^{-1}); ^1H NMR spectra on Perkin-Elmer (90 MHz), EM-360 (60 MHz) or a Brüker WM (400 MHz) NMR spectrometer using TMS as reference compound (chemical shifts in δ, ppm) and mass spectra on a Jeol JMS D-300 spectrometer. TLC was performed on precoated silica gel plastic plates (7 × 3 cm).

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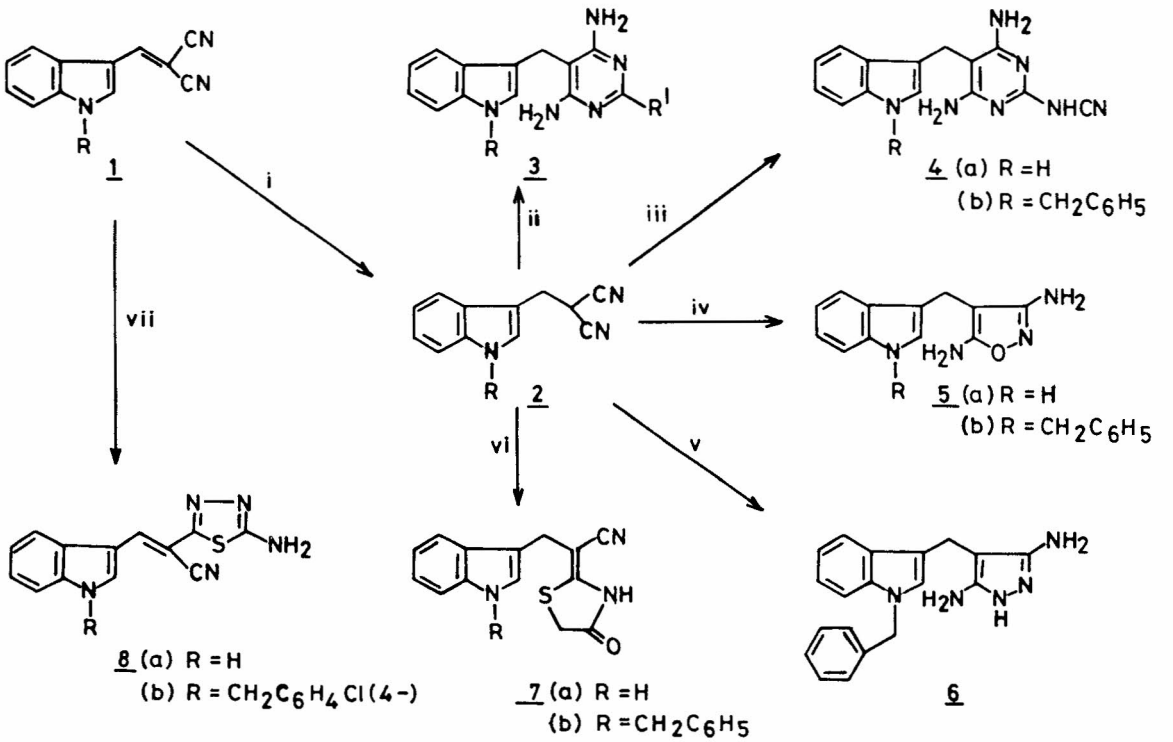
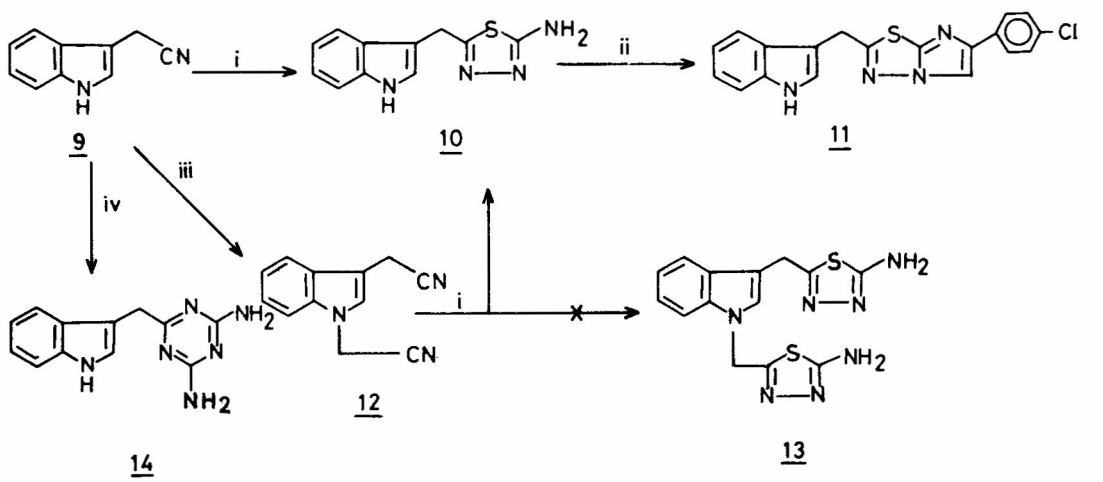


Reagents:- (i) $NaBH_4$/ Abs.; EtOH, (ii) Amidine/NaOEt, (iii) Dicyandiamide / $(CH_3)_2CHOH$/KOH-MeOH, (iv) $NH_2OH.HCl/Et_3N$/MeOH, (v) N_2H_4/ EtOH, (vi) $HSCH_2COOH$ (vii) Thiosemicarbazide/TFA.

Scheme I



Reagents:(i)Thiosemicarbazide / TFA ,(ii) 4-$ClC_6H_4COCH_2$ Br/ EtOH ,(iii) $ClCH_2CN$ / K_2CO_3/Acetone, (iv) Dicyandiamide / $(CH_3)_2CHOH$ / KOH–MeOH

Scheme II

(4, 6-Diaminopyrimidin-5-yl) (indol-3-yl) methane 3a. A mixture of (indol-3-yl) methylmalononitrile (3.9 g, 20 mmoles) and formamidine (3.22 g, 40 mmoles) in sodium methoxide solution (obtained by dissolving 1.38 g sodium in 40 mL dry methanol) was refluxed for 3 hr. The solvent was removed and the solid obtained was purified on column by using $CHCl_3$: hexane (3:1) as a solvent; yield 1.25 g (26.2%): m.p. 236°C; MS: m/z 239 (M^+), 223 ($M^+ - NH_2$), 117 (1H-indol-3-yl); IR (KBr): 3300, 3400 cm^{-1} (NH_2); ^1H NMR (Py-d_5): δ4.31 (s, 2H, CH_2), 6.80

(s, 4H, 2×NH_2), 7.18 (t, 1H, ArH), 7.22 (s, 1H, CH), 7.29 (t, 1H, ArH), 7.35 (s, 1H, CH-2), 7.56(d, 1H, ArH), 7.89 (d, 1H, ArH). (Found: C, 65.32; H, 5.41; N, 29.23. $C_{13}H_{13}N_5$ requires C, 65.25; H, 5.48; N, 29.27%).

Compounds **3b-g** were prepared similarly and their characterization data are given in Table I.

(2-Cyanoamino-4, 6-diaminopyrimidin-5-yl) (indol-3-yl)methane 4a: To a mixture of (indol-3-yl)methylmalononitrile (0.39 g, 2 mmoles) and dicyandiamide (0.34 g, 4 mmoles) in isopropanol (10 mL), was added a solution of KOH (0.11 g, 2 mmoles) in methanol (4 mL). The reaction mixture was refluxed for 8 hr. The solvent was removed and the residue treated with water. The solid obtained was filtered and crystallized from DMSO-water (1:1); yield 0.25 g (45.5%), m.p. 205°C; MS: m/z 279 (M^+), 130 (indol-3-ylmethyl), 117 (indol-3-yl); IR(KBr): 2200 (CN), 3400 cm^{-1} (NH_2); ^1H NMR (Acetone-d_6): δ 3.70 (s, 2H, CH_2), 6.18 (br, 4H, 2×NH_2), 6.95 (t, 1H, ArH), 7.04 (t, 1H, ArH), 7.18 (s, 1H, CH), 7.32 (d, 1H, ArH), 7.59 (d, 1H, ArH), 10.04 (brs, 1H, NH) (Found: C, 60.34; H, 4.47; N, 35.09. $C_{14}H_{13}N_7$ requires C, 60.20; H, 4.69; N, 35.11%).

(2-Cyanoamino-4, 6-diaminopyrimidin-5-yl) (1-benzylindol-3-yl)methane (4b). Compound **4b** was obtained by the reaction of (1-benzylindol-3-yl)methylmalononitrile (0.29 g, 1 mmole) and dicyandiamide (0.168 g, 2 mmoles) as described in the preceding experiment; yield 0.08 g (21%); m.p. 265°C; MS: m/z 369 (M^+); IR(KBr): 2160 (CN), 3200 (NH), 3340 cm^{-1} (NH_2) (Found: C, 68.21; H, 5.26; N, 26.19. $C_{21}H_{19}N_7$ requires C, 68.27; H, 5.18; N, 26.54%).

(3,5-Diaminoisoxazol-4-yl)(indol-3-yl)methane 5a. The title compound was prepared by stirring a mixture of hydroxylamine hydrochloride (0.695 g, 10 mmoles) and (indol-3-yl)methylmalononitrile (1.95 g, 10 mmoles) in methanol (60 mL), in the presence of triethylamine (1.01 g, 10 mmoles) at room temperature for two days. After removal of solvent, the residue was treated with cold water. The precipitate obtained was filtered and crystallized from acetone, yield 2.0 g (87.7%); m.p. 144°C; MS: m/z 228 (M^+); IR (KBr): 3180 (NH), 3440 cm^{-1} (NH_2); ^1H NMR (DMSO-d_6): δ 3.52 (s, 2H, CH_2), 4.72 (s, 2H, NH_2), 5.81 (s, 2H, NH_2), 6.85 (t, 1H, ArH), 6.94 (t, 1H, ArH), 7.04 (s, 1H, CH), 7.28 (d, 1H, ArH), 7.46 (d, 1H, ArH) (Found: C, 63.32; H, 5.44; N, 24.78). $C_{12}H_{12}N_4O$ requires C, 63.21; H, 5.26; N, 24.56%).

(3,5-Diaminoisoxazol-4-yl)(1-benzylindol-3-yl) methane 5b. It was synthesized from (1-benzylindol-3-yl)methylmalononitrile (2.85 g, 10 mmoles) and hydroxylamine hydrochloride (0.695 g, 10 mmoles) as described in the preceding experiment, yield 2.00 g (62.9%), m.p. 130°C; MS: m/z 318 (M^+); IR(KBr): 3300, 3440 cm^{-1} (NH_2); ^1H

Table I—Characterization data of the compounds **3b-g**

Compd	R	R^1	m.p. °C	Yield (%)	Mol. Formula* M^+	^1H NMR (δ, ppm)
3b	H	NH_2	217	54	$C_{13}H_{14}N_6$ (254)	(DMSO-d_6): 3.68 (s, 2H, CH_2), 5.20 (s, 2H, NH_2), 5.46 (s, 4H, 2×NH_2), 6.92 (t, 1H, ArH), 7.04 (t, 2H, ArH & –CH), 7.30 (d, 1H, ArH), 7.59 (d, 1H, ArH)
3c	H	CH_3	238	46	$C_{14}H_{15}N_5$ (253)	(DMSO-d_6): 2.05 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 5.75 (brs, 4H, 2×NH_2), 6.75-7.06(m, 3H, CH & ArH), 7.22 (d, 1H, ArH), 7.50(d, 1H, ArH)
3d	H	C_6H_5	157	49	$C_{19}H_{17}N_5$ (315)	(Acetone-d_6): 3.82 (s, 2H, CH_2), 5.39 (s, 4H, 2×NH_2), 6.81-7.0 (m, 3H, ArH), 7.12-7.32 (m, 4H, CH & ArH), 7.4-7.56 (m, 1H, ArH), 8.15-8.32 (m, 2H, ArH)
3e	H	4-Pyridyl	175	29	$C_{18}H_{16}N_6$ (316)	(DMSO-d_6): 3.72(s, 2H, CH_2), 6.15 (s, 4H, 2×NH_2), 6.92(t, 1H, ArH), 7.05 (t, 1H, ArH), 7.05 (t, 1H, ArH), 7.20 (s, 1H, CH), 7.31 (d, 1H, ArH), 7.62 (d, 1H, ArH), 8.08 (d, 2H, ArH), 8.63 (d, 2H, ArH), 10.75 (s, 1H, NH)
3f	H	Morpholino	159	54	$C_{17}H_{20}N_6O$ (324)	($CDCl_3$ + DMSO-d_6): 3.56 [s, 8H, $-N(CH_2)_2$ & $O(CH_2)_2$], 3.69 (s, 2H, CH_2), 4.52 (s, 4H, 2×NH_2), 6.76 (s, 1H, CH), 6.91-7.22 (m, 3H, ArH), 7.38-7.65 (m, 1H, ArH), 9.54 (br, 1H, NH).
3g	$CH_2C_6H_5$	NH_2	203	61	$C_{20}H_{20}N_6$ (344)	(DMSO-d_6): 3.24 (s, 2H, CH_2), 3.62 (s, 2H, CH_2), 5.12 (s, 2H, NH_2), 5.25(s, 2H, NH_2), 5.36 (s, 2H, NH_2), 7.04-7.25(m, 8H, ArH), 7.42-7.66 (m, 2H, ArH).

* Elemental analyses for C, H and N were found to be satisfactory (±0.5% of the calculated values).

NMR (DMSO-d_6): δ 3.49 (s, 2H, CH_2), 4.68 (s, 2H, CH_2), 5.25 (s, 2H, NH_2), 5.8 (s, 2H, NH_2), 6.82-6.98 (m, 2H, ArH), 7.05 (s, 1H, CH), 7.08-7.3 (m, 5H, ArH), 7.41-7.58 (m, 2H, ArH) (Found: C, 71.41; H, 5.70; N, 17.72. $C_{19}H_{18}N_4O$ requires C, 71.68; H, 5.69; N, 17.59%).

(3, 5-Diamino-1*H*-pyrazol-4-yl)(1-benzylindol-3-yl)methane 6. A mixture of (1-benzylindol-3-yl)methylmalononitrile (2.85 g, 10 mmoles) and hydrazine hydrate (0.501 g, 1 mmole) was refluxed with ethanol (20 mL) for 4 hr. Additional amount of hydrazine hydrate (0.25 g, 5 mmoles) was added and heating continued for another 4 hr. After removal of solvent, the residue obtained was purified from silica gel column by using 1% methanol in chloroform as eluent; yield 0.8 g (25%); m.p. 70°C; MS: m/z 317 (M^+); IR(KBr): 3400 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$): δ3.62 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 6.92-7.05 (m, 3H, ArH & CH), 7.08-7.14 (m, 2H, ArH), 7.16-7.25 (m, 4H, ArH), 7.51 (d, 1H, ArH). (Found: C, 72.11; H, 5.92; N, 22.31. $C_{19}H_{19}N_5$ requires C, 71.90; H, 6.03: N, 22.06%).

3 - (Indol-3-yl) -2-(4-oxothiazolidin-2-ylidene) propionitrile 7a. A mixture of (indol-3-yl)methylmalononitrile (0.195 g, 1 mmole) and thioglycolic acid (0.184 g, 2 mmoles) in pyridine (4 mL) was refluxed for 3hr. After completion of the reaction, it was poured into water and extracted from chloroform. The chloroform layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue obtained was purified from silica gel column using $CHCl_3$ as a solvent, yield 0.14 g (50%); m.p. 191°C; MS: m/z 269 (M^+); IR(KBr): 1710 (CO), 2180 (CN), 2800 (CH_2), 3150 cm^{-1} (NH); ^1H NMR (Acetone-d_6): δ3.58 (s, 2H, CH_2), 4.00 (s, 2H, CH_2), 7.01 (t, 1H, ArH), 7.10 (t, 1H, ArH), 7.30 (s, 1H, CH), 7.38 (d, 1H, ArH), 7.62 (d, 1H, ArH), 10.13 (brs, 1H, NH), 10.31 (brs, 1H, NH) (Found: C, 62.40; H, 4.14; N, 15.87. $C_{14}H_{11}N_3OS$ requires C, 62.43; H, 4.12; N, 15.60%).

3- (1-Benzylindol-3-yl) -2- (4-oxothiazolidin-2-yldene)propionitrile 7b. Compound **7b** was obtained from (1-benzylindol-3-yl)methylmalononitrile (0.28 g, 1 mmole) and thioglycolic acid (0.184 g, 2 mmoles) as described above, yield 0.12 g (33%); m.p. 198-200°C; MS: m/z 359 (M^+); IR(KBr): 1720 (CO), 2200 (CN), 3180 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ3.58 (s, 2H, CH_2), 3.88 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 7.07-7.11 (m, 2H, ArH & CH), 7.19 (t, 1H, ArH), 7.27-7.32 (m, 6H, ArH), 7.62 (d, 1H, ArH), 8.22 (brs, 1H, NH).

2-(2-Amino-1, 3, 4-thiadiazol-5-yl)-3-(indol-3-yl)acrylonitrile 8a. A mixture of 2-cyano-3-(indol-3-yl)acrylonitrile (0.193 g, 1 mmole) and thiosemicarbazide (0.14 g, 1.5 mmoles) in trifluoroacetic acid (3 mL) was heated while stirring at 60°C for 6 hr. The reaction mixture was worked-up following the literature procedure[9]. The crude product thus obtained was filtered and purified from column chromatography using $CHCl_3$:MeOH (100:1) as eluent, yield 0.1 g (37.4%); m.p. 225°C; MS: m/z 267 (M^+): R (KBr): 2220 (CN), 3300 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ6.34 (brs, 2H, NH_2), 7.20-7.31 (m, 2H, ArH), 7.50 (d, 1H, ArH), 7.78 (d, 1H, ArH), 8.06 (s, 1H, CH), 8.49 (s, 1H, CH), 11.4 (brs, 1H, NH) (Found: C, 58.59; H, 3.48; N, 26.29. $C_{13}H_9N_5S$ requires C, 58.41; H, 3.39; N, 26.19%).

2-(2-Amino-1, 3, 4-thiadiazol-5-yl)-3-[1-(4-chlorobenzyl)indol-3-yl]acrylonitrile 8b. It was prepared from 2-cyano-3-[1-(4-chlorobenzyl)-indol-3-yl]acrylonitrile (0.32 g, 1 mmole) and thiosemicarbazide (0.14 g, 1.5 mmole) as described in the preceding experiment, yield 0.27 g (69.2%); m.p. 80°C; MS: m/z 389 (M^+); IR(KBr): 2200 (CN), 3340 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ5.46 (brs, 2H, NH_2), 7.10-7.42 (m, 8H, ArH), 7.90 (s, 1H, CH), 8.44 (s, 1H, CH) (Found: C, 61.75; H, 3.42; N, 18.08. $C_{20}H_{12}ClN_5S$ requires C, 61.62; H, 3.10; N, 17.96%).

(2-Amino-1, 3, 4-thiadiazol-5-yl)(indol-3-yl)methane 10. It was synthesized from 3-indoleacetonitrile **9** (1.56 g, 10 mmoles) and thiosemicarbazide (1.36 g, 15 mmoles) as described in the preceding experiment, yield 1.51 g (66%); m.p. 198-200°C; MS: m/z 230 (M^+); IR(KBr): 3400 cm^{-1} (NH_2); ^1H NMR (TFA): δ 4.10 (s, 2H, CH_2), 6.90-7.09 (m, 2H, ArH), 7.11-7.30 (m, 3H, ArH & CH) (Found: C, 57.61; H, 4.18; N, 24.40. $C_{11}H_{10}N_4S$ requires C, 57.37; H, 4.38; N, 24.33%).

[6-(4-Chlorophenyl)imidazo[2, 1-*b*]-1, 3, 4-thiadiazol-2-yl) (indol-3-yl)methane 11: A mixture of **10** (0.23 g, 1 mmole) and ω-bromo-4-chloroacetophenone (0.23 g, 1 mmole) in ethanol (10 mL) was refluxed for 8 hr. On cooling the crystalline solid obtained was filtered and dried, yield 0.18 g (50%); m.p. 225°C: MS: m/z 364 (M^+); ^1H NMR (DMSO-d_6): δ4.5 (s, 2H, CH_2), 6.94 (t, 1H, ArH), 7.10 (t, 1H, ArH), 7.40 (d, 4H, ArH), 7.48 (d, 1H, ArH), 7.75 (d, 2H, ArH & CH), 8.48 (s, 1H, CH), 10.95 (brs, 1H, NH) (Found: C, 63.02; H, 3.63; N, 15.45. $C_{19}H_{13}ClN_4S$ requires C, 62.55; H, 3.59; N, 15.36%).

(2, 4-Diamino-1, 3, 5-triazin-6-yl)(indol-3-yl)methane (14). To a mixture of **9** (0.156 g, 1 mmole), dicyandiamide (0.084 g, 1 mmole) and isopropyl alcohol (5 mL), KOH (0.014 g, 0.25 mmoles) in methanol (1 mL) was added. The reaction mixture was refluxed for 16 hr. On cooling the solid obtained was filtered, washed with water and dried, yield 0.12 g (50%); m.p. 212°C; MS: m/z 240 (M^+); IR(KBr): 3320, 3400 cm^{-1} (NH_2); ^1H NMR (DMSO-d_6): δ 3.69 (s, 2H, CH_2), 6.52 (brs, 4H, $2 \times NH_2$), 6.79-6.88 (m, 2H, ArH), 7.08 (s, 1H, CH), 7.24 (d, 1H, ArH), 7.51 (d, 1H, ArH) (Found: C, 59.87; H, 5.19; N, 35.12. $C_{12}H_{12}N_6$ requires C, 59.98; H, 5.03; N, 34.98%).

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