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Polyethylene glycol mediated catalyst-free synthesis of 5,9b-dihydro-1*H*-[1,2,4] triazino[5,6-b]indole-3-ols/thioles

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ABSTRACT

An efficient one pot environmentally benign chemical synthesis of 5,9b-dihydro-1H-[1,2,4] triazino [5,6-b] indole-3-ols and 5,9b-dihydro-1H-[1,2,4] triazino [5,6-b] indole-3-thiols is carried out in PEG as a recycle reaction medium under neutral conditions by using isatin, and semicarbazide/thiosemicarbazide. No additional base or solvents are utilized.

Keywords: Isatin, Semicarbazide, thiosemicarbazide, PEG-400 (Poly Ethylene Glycol).

INTRODUCTION

Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs. [1] In the family of heterocyclic compounds nitrogen-containing heterocycles are an important class of compounds in the medicinal chemistry and also contribute to the society from biological and industrial point, which helps to understand life processes. [2] Among nitrogen containing heterocycles, indole represents a pharmaceutically important class of compounds because of its diverse biological activities like antibacterial, antifungal, antiplasmodial and anti HIV. [3] Further triazine derivatives have also received considerable attention due to their potent bioactivity such as antiprotozoal, anticancer, estrogen receptor modulators, antiviral and antimalarials. [4] The [1,2,4] triazino [5,6-*b*] indole derivatives have considerable interest as a result of their broad spectrum of antimicrobial, [5-9] antiviral, [10] antihypertensive, [10,11] blood-platelet aggregation inhibitory,[11,12] and analgesic[13] activities. Irachtchenko et al. reported the synthesis of 5*H*-[1,2,4] triazino [5,6-*b*] indole-3-thiol mediated by base followed by acid. [14] The reaction is generally carried out in the presence of large amount of base, which is harmful and toxic.

Recently Ramesh et al. reported the synthesis of 5,9b-dihydro-1*H*-[1,2,4] triazino [5,6-*b*] indole-3-ols/5,9b-dihydro-1*H*-[1,2,4] triazino [5,6-*b*] indole-3-thiols mediated by β-Cyclodextrin in H_2O.[15]

Presently, organic reactions in PEG have attracted the attention of researchers because of the ability of PEG to act as phase transfer catalyst and its eco-friendly nature when compared to other “neoteric solvents” such as ionic liquids, super-critical fluids and micellar systems. [16] PEG has hydrophilic nature and some benign characteristic properties with respect to environment and chemical industry such as non-toxic, inexpensive, easy to handle, thermally stable, reduced flammability and moreover it can be an interesting recyclable solvent in synthetic chemistry for various

organic transformations [17] with unique properties such as thermal stability, commercial availability and immiscibility with a number of organic solvents.

MATERIALS AND METHODS

All chemicals were purchased from *Sigma Aldrich* and *S.D. Fine Chemicals* with purity not less than 99.9%. Analytical Thin Layer Chromatography (TLC) was carried out by using silica gel 60 F_{254} pre-coated plates. Visualization was accomplished with UV lamp of I_2 stain. All products were characterized by their NMR and Mass spectra. ^{1}H NMR and ^{13}C NMR recorded on 200 or 300 MHz, in $CDCl_3$/DMSO using TMS as the internal standard and chemical shifts were reported in parts per million (ppm, δ) downfield from the tetramethylsilane.

Typical Experimental Procedure

A mixture of isatin (1.0 mmol) and semicarbazide hydrochloride (1.0 mmol) was taken in 5ml of Polyethylene glycol (PEG 400), and stirred at 70^{o}C for 6hr. The completion of reaction was monitored by TLC. Then the reaction mixture was cooled to precipate PEG and extracted with ether. Concentrated the ether layer under vacuum and diluted with ice-cold water and stirred at 0^{o}C for 15 min. Solid was collected by filtration (Table 1). The recovered PEG was washed with ether and reused for further reactions. The product obtained was characterized by its spectral and analytical data.

Spectral data:

5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 1); Light yellow solid. M.p. 242-243 ^{O}C; IR ν_{max} (KBr): 3465, 3305, 3233, 3130, 2924, 2822, 1708, 1621, 1573, 1465, 1390, 1346, 1303, 1212 cm^{-1}; ^{1}H-NMR (300MHz,DMSO,TMS) δ = 10.34 (s, 1H, -OH), 7.27-7.19 (m, 1H), 7.00 (d, 1H, *J* = 7.3 Hz), 6.69 (s, 1H), 6.45 (t, 1H), 6.35 (d, 1H, *J* = 7.7 Hz), 6.1 (s, 2H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 162.70, 154.96, 141.68, 131.04, 130.26, 122.03, 120.31, 120.08, 110.83; Mass (ESI-MS): m/z 189 $(M+H)^+$; Anal calcd for : ($C_9H_8N_4O$) C: 57.42, H: 4.31, N: 29.68; found C: 57.45, H: 4.28, N: 29.7.

8-methyl-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 2); Yellow solid. M.p. 297-299 ^{O}C; IR ν_{max} (KBr): 3388, 3310, 3210, 2952, 2681, 1695, 1610, 1508, 1485, 1393, 1218, 1148 cm^{-1}; ^{1}H-NMR (300MHz, DMSO,TMS) δ = 10.92 (s, 1H, -OH), 8.0 (s, 1H), 7.53 (s, 1H), 7.19 (d, 1H, *J* = 7.9 Hz), 6.92 (t, 3H), 2.71 (s, 3H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 160.99, 153.29, 137.46, 129.37, 129.16, 128.75, 118.75, 118.49, 108.63; Mass (ESI-MS): m/z 225 $(M+Na)^+$; Anal calcd for : ($C_{10}H_{10}N_4O$) C: 59.40, H: 4.98, N: 27.71; found C: 59.38, H: 4.95, N: 27.69.

8-methoxy-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 3); Reddish solid. M.p. 292-293 ^{O}C; IR ν_{max} (KBr): 3385, 3282, 3182, 1722, 1693, 1647, 1582, 1518, 1483, 1344, 1204, 1155 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$,TMS) δ = 11.72 (s, 1H, -OH), 10.80 (s, 1H), 7.20 (s, 1H), 6.99 (s, 2H), 6.78 (t, 2H), 3.74 (s, 3H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 162.77, 155.14, 154.97, ,1365.01, 131.14, 121.13, 116.42, 111.48, 104.52, 55.32 ; Mass (ESI-MS): m/z 219 $(M+H)^+$; Anal calcd for : ($C_{10}H_{10}N_4O_2$) C: 55.04, H: 4.62, N: 25.68; found C: 55.02, H: 4.59, N: 25.65.

8-fluoro-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 4); Reddish orange solid. M.p. 253-254 ^{O}C; IR ν_{max} (KBr): 3467, 3381, 3222, 1724, 1573, 1481, 1380, 1304, 1162 cm^{-1}; ^{1}H-NMR (300MHz, DMSO,TMS) δ = 11.25 (s, 1H, -OH), 10.32 (s, 1H), 6.75 (s, 1H), 6.43-6.20 (m, 4H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 161.11, 155.1, 153.31, 135.89, 128.83, 119.99, 119.87, 114.79, 114.47, 109.98, 109.87, 105.75, 105.41; Mass (ESI-MS): m/z 229 $(M+Na)^+$; Anal calcd for : ($C_9H_7FN_4O$) C: 52.43, H: 3.42, N: 27.17; found C: 52.38, H: 3.40, N: 27.14.

8-chloro-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 5); Yellow solid. M.p. 272-274 ^{O}C; IR ν_{max} (KBr): 3470, 3237, 2976, 2819, 1717, 1624, 1574, 1458, 1384, 1309, 1167 cm^{-1}; ^{1}H-NMR (300MHz, DMSO,TMS) δ = 11.05 (s, 1H, -OH), 10.41 (s, 1H), 6.98 (s, 1H), 6.56 (d, 1H, *J* = 8.3 Hz), 6.24 (t, 3H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 161.20, 153.77, 138.63, 128.76, 128.07, 125.41, 120.55, 118.72, 110.52; Mass (ESI-MS): m/z 245 $(M+Na)^+$; Anal calcd for : ($C_9H_7ClN_4O$) C: 48.55, H: 3.17, N: 25.17; found C: 48.51, H: 3.12, N: 25.13.

8-bromo-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 6); Yellow solid. M.p. 291-293 ^{O}C; IR ν_{max} (KBr): 3467, 3243, 2972, 2818, 1720, 1621, 1575, 1458, 1383, 1309, 1166 cm^{-1}; ^{1}H-NMR (300MHz, DMSO,TMS) δ = 10.46 (s, 1H, -OH), 7.19-7.16 (m, 1H), 6.84-6.81 (m, 1H), 6.50-6.29 (m, 2H), 6.17 (s, 2H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 160.37, 152.96, 138.51, 130.39, 127.67, 120.84, 120.62, 112.21, 110.75; Mass (ESI-MS): m/z 268 $(M+H)^{+}$; Anal calcd for : ($C_9H_7BrN_4O$) C: 40.47, H: 2.64, N: 20.98; found C: 40.43, H: 2.62, N: 20.95.

6-chloro-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 7); Yellow solid. M.p. 293-295 ^{O}C; IR ν_{max} (KBr): 3451, 3240, 3155, 2790, 1719, 1620, 1583, 1461, 1393, 1337, 1166 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$, TMS) δ = 11.77 (s, 1H, -OH), 11.28 (s, 1H), 7.86 (s, 1H), 7.48 (d, 1H, *J* = 7.3 Hz), 7.28 (d, 1H, *J* = 7.9 Hz), 6.95 (t, 1H), 6.79 (s, 1H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 160.91, 153.01, 136.97, 127.84, 121.26, 120.49, 116.77, 113.47; Mass (ESI-MS): m/z 245 $(M+Na)^{+}$; Anal calcd for : ($C_9H_7ClN_4O$) C: 48.55, H: 3.17, N: 25.17; found C: 48.49, H: 3.14, N: 25.12.

5-methyl-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 8); Yellow solid. M.p. 229-231 ^{O}C; IR ν_{max} (KBr): 3397, 3312, 3193, 2924, 2661, 1690, 1607, 1500, 1464, 1380, 1216, 1123 cm^{-1}; ^{1}H-NMR (300MHz, DMSO,TMS) δ = 11.42 (s, 2H), 10.49 (s, 1H), 10.10-8.83 (m, 4H), 5.04 (s, 3H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 156.66, 157.5, 143.9, 126.9, 126.5, 126.3, 115.9, 109.00, 65.2, 41.2; Mass (ESI-MS): m/z 225 $(M+Na)^{+}$; Anal calcd for : ($C_{10}H_{10}N_4O$) C: 59.40, H: 4.98, N: 27.71; found C: 59.35, H: 4.91, N: 27.65.

5-phenyl-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 9); Yellow solid. M.p. 214-216 ^{O}C; IR ν_{max} (KBr): 3464, 3287, 3195, 2924, 2855, 1717, 1686, 1595, 1462, 1372, 1306, 1177, 1143 cm^{-1}; ^{1}HNMR (300MHz, DMSO,TMS) δ = 9.35-9.45 (m, 12H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 158.19, 152.97, 140.50, 131.17, 128.15, 127.65, 126.37, 124.48, 118.41, 118.00, 107.80; Mass (ESI-MS): m/z 265 $(M+H)^{+}$; Anal calcd for : ($C_{15}H_{12}N_4O$) C: 68.17, H: 4.58, N: 21.20; found C: 68.15, H: 4.54, N: 21.16.

5-benzyl-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 10); Yellow solid. M.p. 223-225 ^{O}C; IR ν_{max} (KBr): 3406, 3204, 2924, 2854, 1664, 1606, 1464, 1353, 1164, 1107 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$,TMS) δ = 8.75-8.25 (m, 12H), 4.06 (s, 2H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 160.73, 154.83, 141.60, 135.80, 130.09, 129.85, 128.61, 127.48, 127.27, 122.77, 119.98, 119.73, 109.99, 42.36; Mass (ESI-MS): m/z 301 $(M+Na)^{+}$; Anal calcd for : ($C_{16}H_{14}N_4O$) C: 69.05, H: 5.07, N: 20.13; found C: 69.01, H: 5.02, N: 20.08.

8-nitro-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indol-3-ol (Table 1, Entry 11); Yellow solid. M.p. 296-298 ^{O}C; IR ν_{max} (KBr): 3409, 2969, 2828, 1745, 1655, 1587, 1468, 1398, 1168 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$,TMS) δ = 10.88 (s, 1H, -OH), 10.63 (s, 1H), 7.60 (s, 1H), 7.34-7.30 (m, 1H), 6.19 (d, 3H, *J* = 8.6 Hz), 6.95 (t, 1H), 6.79 (s, 1H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 162.86, 154.72, 146.53, 142.56, 128.95, 126.11, 121.17, 115.60, 110.91; Mass (ESI-MS): m/z 234 $(M+H)^{+}$; Anal calcd for : ($C_9H_7N_5O_3$) C: 46.36, H: 3.03, N: 30.03; found C: 46.29, H: 3.02, N: 29.98.

5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 1); Orenge solid. M.p. 206-208 ^{O}C; IR ν_{max} (KBr): 3420, 3263, 3155, 2360, 1697, 1621, 1591, 1495, 1464, 1346, 1276, 1205, 1129, 1058 cm^{-1}; ^{1}H-NMR (300MHz,$CDCl_3$+DMSO, TMS) δ = 12.59 (s, 1H, -SH), 11.04 (s, 1H), 8.84 (s, 1H), 8.29 (s, 1H), 7.60 (d, 1H, *J* = 7.9 Hz), 7.26 (s, 1H), 7.00 (t, 1H), 6.88 (d, 1H, *J* = 7.9 Hz); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 176.85, 160.70, 140.42, 129.95, 129.10, 120.32, 119.01, 118.05, 109.06; Mass (ESI-MS): m/z 227 $(M+Na)^{+}$; Anal calcd for : ($C_9H_8N_4S$) C: 52.92, H: 3.95, N: 27.43; found C: 52.86, H: 3.92, N: 27.37.

8-chloro-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 2); Yellow solid. M.p. 246-250 ^{O}C; IR ν_{max} (KBr): 3410, 3233, 3142, 2371, 1685, 1611, 1571, 1455, 1424, 1316, 1256, 1215, 1152 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$+DMSO) δ 3.10 (s, 1H), 6.76 (d, 1H, *J* = 8.3 Hz), 7.13 (d, 1H, *J* = 8.1 Hz), 7.55 (s, 1H), 8.01 (s, 1H), 8.65 (s, 1H), 11.00 (s, 1H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 177.37, 160.72, 139.19, 128.87, 128.48, 125.38, 119.17, 110.59; Mass (ESI-MS): m/z 261 $(M+Na)^{+}$; Anal calcd for : ($C_9H_7ClN_4S$) C: 45.29, H: 2.96, N: 23.47; found C: 45.24, H: 2.92, N: 23.43.

8-bromo-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 3); Light yellow solid. M.p. 257-260 ^{O}C; IR ν_{max} (KBr): 3462, 3280, 3141, 2385, 1678, 1641, 1594, 1499, 1481, 1355, 1279, 1129, 1025 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$+DMSO) δ 6.77 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 7.9 Hz), 7.76 (s, 1H), 8.31 (s, 1H), 8.76

(s, 1H), 11.07 (s, 1H), 12.37 (s, 1H); ^{13}C-NMR (75MHz, DMSO, TMS) δ= 176.90, 160.23, 139.32, 131.08, 128.44, 121.59, 120.26, 111.01; Mass (ESI-MS): m/z 284 $(M+H)^+$; Anal calcd for : ($C_9H_7BrN_4S$) C: 38.18, H: 2.49, N: 19.28; found C: 38.16, H: 2.42, N: 19.20.

8-methyl-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 4); Orenge solid. M.p. 247-250 ^{O}C; IR ν_{max} (KBr): 3415, 3344, 3164, 2381, 16865, 1615, 1551, 1458, 1435, 1321, 1260, 1255, 1158 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.26 (s, 3H), 6.71 (d, 1H, *J* = 7.9 Hz), 6.98 (d, 1H, *J* = 7.9 Hz), 7.30 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H), 8.52 (s, 1H). 10.75 (s, 1H); ^{13}C-NMR (75MHz, DMSO, TMS) δ= 176.83, 160.76, 138.19, 130.11, 129.61, 119.42, 118.03, 108.82; Mass (ESI-MS): m/z 219 $(M+H)^+$; Anal calcd for : ($C_{10}H_{10}N_4S$) C: 55.02, H: 4.62, N: 25.67; found C: 54.94, H: 4.57, N: 25.60.

8-methoxy-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 5); Reddish orenge solid. M.p. 221-223 ^{O}C; IR ν_{max} (KBr): 3423, 3373, 3144, 2358, 1698, 16261 1593, 1496, 1464, 1361, 1285, 1210, 1155 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$+DMSO) δ 3.78 (s, 3H), 6.79 (s, 2H), 7.18 (s, 1H), 8.04 (s, 1H), 8.69 (s, 1H) 10.77 (s, 1H), 12.62 (s, 1H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 177.43, 161.25, 153.86, 134.58, 130.70, 119.19, 115.64, 110.10, 104.53; Mass (ESI-MS): m/z 257 $(M+Na)^+$; Anal calcd for : ($C_{10}H_{10}N_4OS$) C: 51.27, H: 4.30, N: 23.91; found C: 51.24, H: 4.23, N: 23.85.

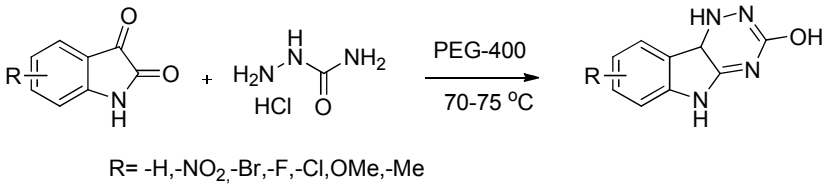
5-methyl-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 6); Yellow solid. M.p. 244-246 ^{O}C; IR ν_{max} (KBr): 3450, 3283, 3175, 2372, 1687, 1628, 1585, 1481, 1465, 1346, 1278, 1135, 1060 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$+DMSO) δ 3.22 (s, 3H), 7.04 (t, 2H, *J* = 7.5 Hz), 7.32 (t, 1H, *J* = 7.7 Hz), 7.61 (d, 1H, *J* = 7.5 Hz), 8.01 (s, 1H), 8.84 (s, 1H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 177.11, 129.13, 128.99, 121.02, 118.92, 117.56, 107.55; Mass (ESI-MS): m/z 219 $(M+H)^+$; Anal calcd for : ($C_{10}H_{10}N_4S$) C: 55.02, H: 4.62, N: 25.67; found C: 54.97, H: 4.59, N: 25.62.

5-benzyl-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 7); Yellow solid. M.p. 247-249 ^{O}C; IR ν_{max} (KBr): 3442, 3354, 3153, 2361, 1699, 1618, 1593, 1427, 1354, 1278, 1215, 1132 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 6.91-7.34 (m, 8H), 8.50 (s, 2H), 8.98 (s, 1H), 12.42 (s, 1H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 176.95, 158.86, 140.56, 133.64, 128.97, 128.70, 126.72, 125.66, 125.48, 121.05, 118.99, 117.63, 108.25; Mass (ESI-MS): m/z 295 $(M+H)^+$; Anal calcd for : ($C_{16}H_{14}N_4S$) C: 65.28, H: 4.79, N: 19.03; found C: 65.22, H: 4.71, N: 19.01.

8-nitro-5,9b-dihydro-1H-[1,2,4]triazino[5,6-b]indole-3-thiol (Table 2, Entry 8); Yellow solid. M.p. 268-270 ^{O}C; IR ν_{max} (KBr):3416, 3383, 3148, 2385, 1692, 1626, 1569, 1424, 1352, 1259, 1225, 1141 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 5.78 (s, 1H), 6.86-7.48 (m, 3H), 8.26 (s, 1H), 8.39 (s, 1H), 10.88 (s, 1H); ^{13}C-NMR (75MHz, DMSO,TMS) δ= 178.69, 162.64, 147.06, 142.66, 129.41, 126.48, 120.76, 116.36, 110.93; Mass (ESI-MS): m/z 250 $(M+H)^+$; Anal calcd for : ($C_9H_7N_5O_2S$) C: 43.37, H: 2.83, N: 28.10; found C: 43.32, H: 2.77, N: 28.03.

RESULTS AND DISCUSSION

Herein we report a one pot tandem synthesis of 5,9b-dihydro-1*H*-[1,2,4] triazino [5,6-*b*] indole-3-ols and 5,9b-dihydro-1*H*-[1,2,4] triazino [5,6-*b*] indole-3-thiols by the reaction of derivatives of isatin with semicarbazide/thiosemicarbazide at 70-75 ^{o}C for 6-9 h under catalyst free conditions by using an environmentally benign and recyclable medium PEG.



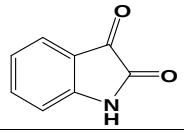
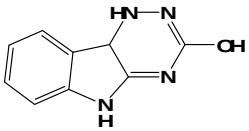
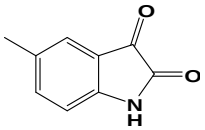
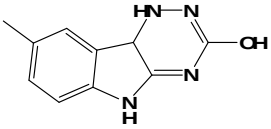
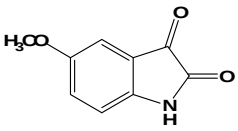
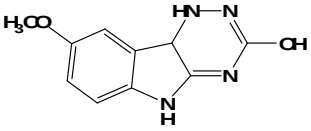
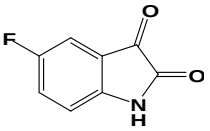
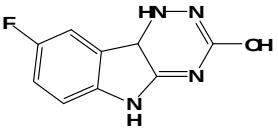
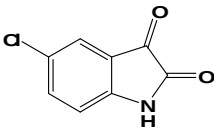
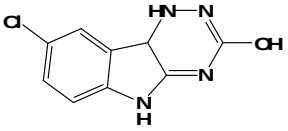
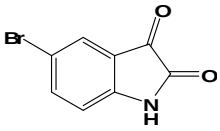
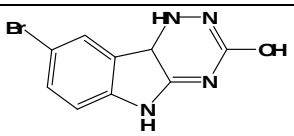
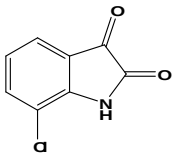
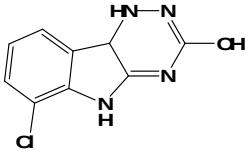
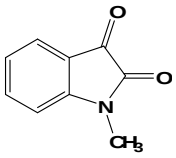
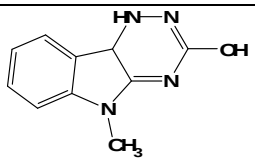
R= -H,-NO_2,-Br,-F,-Cl,OMe,-Me

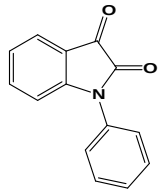
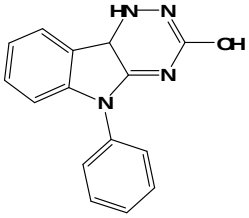
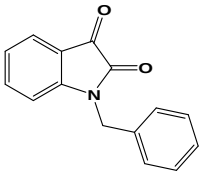
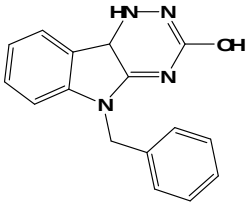
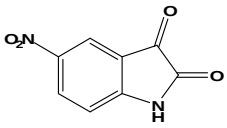
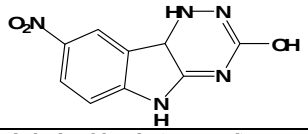
Scheme 1. Synthesis of 5,9b-dihydro-1H-[1,2,4]triazino [5, 6-b] indole-3-ols

Initially, the reaction was carried out using Isatin with semicarbazide hydrochloride in PEG at room emperature for 24 h, but no expected product was obtained. The starting materials are recovered. When the same reaction mixture

was heated at 70-75^{o}C, surprisingly, a significant improvement was observed and the yield of product was dramatically increased to 96% after 6 h (Scheme 1). With this promising result in hand, as shown in Table 1, a variety of substituted isatins, bearing either electron-donating or electron-withdrawing substituents, afforded the products in excellent yields.

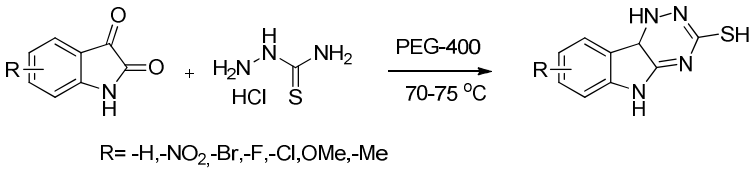
Table-1: Synthesis of 5,9b-dihydro-1H-[1,2,4]triazino [5, 6-b] indole-3-ols

Entry	(1)	Product (2)	Time(h)	Yield(%)b
1			6	96
2			8	92
3			9	88
4			9.5	89
5			8.5	89
6			8	90
7			8	90
8			7	90

9			6.5	88
10			7	87
11			8.5	88

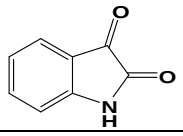
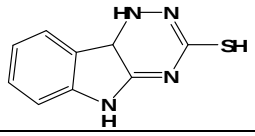
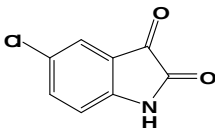
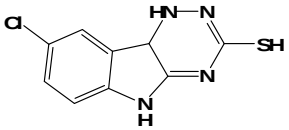
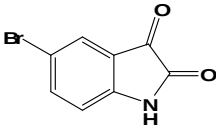
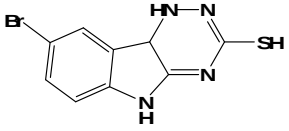
[a]*Reaction conditions: Substituted isatin (1.0 mmol), semicarbazide hydrochloride (1.0 mmol), PEG-400 (5 ml), 70 °C, 6 h.* [b]*Isolated yield.*

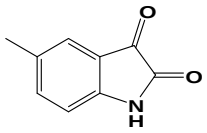
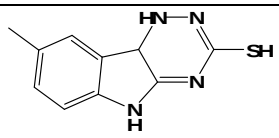
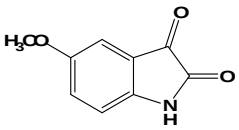
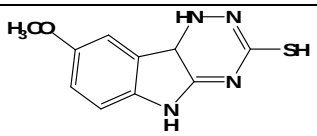
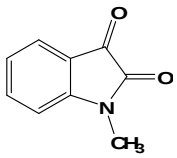
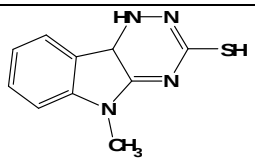
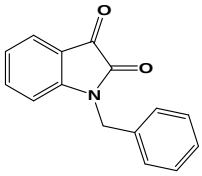
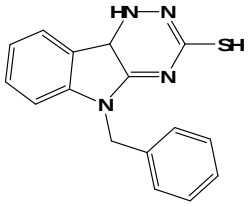
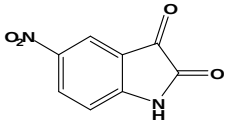
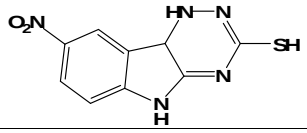
After these encouraging results, we further tested this protocol with various substituted isatins and thiosemicarbazide (Scheme 2) under same reaction conditions to offered various 9b-dihydro-1*H*-[1,2,4] triazino [5,6-*b*] indole-3-thiols (Table 2). The synthesized derivatives were characterized by their melting points; the structures of the compounds were elucidated by NMR, IR and Mass spectroscopy.



Scheme 2. Synthesis of 5,9b-dihydro-1H-[1,2,4]triazino [5, 6-b] indole-3thiols

Table-2 : *Synthesis of 5,9b-dihydro-1H-[1,2,4]triazino [5, 6-b] indole-3thiols*

Entry	(1)	Product (2)	Time(h)	Yield(%)b
1			8	86
2			6.5	88
3			6.5	93

4			7	91
5			9	86
6			9	85
7			9	84
8			9.5	85

[a]*Reactionconditions: Substituted isatin (1.0 mmol), thiosemicarbazide Hydrochloride (1.0 mmol), PEG-400 (5 ml), 70 °C, 6 h.* [b]*Isolated yield.*

CONCLUSION

In conclusion we have developed an efficient and facile method for the synthesis of 5,9b-dihydro-1*H*-[1,2,4] triazino [5,6-*b*] indole-3-ol and 5,9b-dihydro-1*H*-[1,2,4] triazino [5,6-*b*] indole-3-thiols by using an environmentally benign solvent PEG-400 under catalyst free conditions. PEG-400 mediated reactions are very use full in both economical and environmental point of view, the mild reaction conditions, eco-friendly reaction medium, reaction simplicity are advantages of this protocol.

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