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SYNTHESIS OF NOVEL FUSED 1, 2, 4-TRIAZINO (5, 6-b) INDOLE SYSTEMS AND THEIR FLRUORINE CONTAINING ANALOGUES OF BIOLOGICAL INTEREST

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ABSTRACT

A series of novel fluorine containing fused indole system were synthesized the reaction of 3-hydrazino-1,2,4 triazino (5,6-b) indole with indole-2,3-diones followed by cyclization in $POCl_3$*. Considering the clinical efficacy of triazino indole derivatives, we have synthesized some novel fused systems, where indole, triazine and triazole nuclei are fused together in different ways, in anticipation of better pharmacological properties. The interesting feature of these syntheses is that fusion of two heterocyclic nuclei resulted in formation of a new system having ring junction nitrogen.*

Keywords : Heterocycle, Indole, Triazole, Triazine

I. INTRODUCTION

Innovation, discovery and synthesis of new compounds of biological interest is the hall mark of recent developments in the field of heterocyclic chemistry. The synthesis requires rational and mechanistically based design of process. It is well known that fusion of the biologically active nuclei enhance the pharmacological properties [1]. The fusion of triazine ring with biologically active indole system has aroused considerable interest for synthetic organic chemists, because many members of the family exhibit potent biological activities.
Among the various biologically active fused heterocyclic systems, the most important are those containing ring junction nitrogen, i.e. where nitrogen is common to both rings [2]. The vast majority of these systems do not occur naturally but they have been subject of many studies from theoretical view point, for the preparation of potentially biologically active analogues and for other industrial uses. Some of the naturally occurring alkaloids, Reserpine [3] used for treatment of hypertension and lupine [4] used as tranquillizer contain quinolizine moiety. Amongst synthetic compounds, tetrabenazine [5] and benzquinamide [6] used as tranquilizers cite the example of heterocyclic compound containing ring junction nitrogen. The key intermediate for the synthesis was identified as 3-hydrazino-1, 2, 4-triazino (5, 6-b) indole. Interest in this compound was not only because of its biological importance but also due to its asymmetric triazine ring. Which can undergo cyclisation reaction with

different reagents using its hydrazino functionality to give two possible products involving cyclisation at N-4 and N-2.[7] 3-hydrazino-1, 2, 4-triazino (5, 6-b) indole is reported to undergo condensation with various aldehydes, ketones, diketone and enolizable ketone to form corresponding hydrazones [8,9]. These hydrazones are well known for their biological activities. However, its hydrazones with indole-2, 3-diones (isatins) have not been studied so far, of course hydrazones of isatin with 2-hydrazino-3-phenyl-1,8-naphthyridines are reported as antibacterial agents [10] We have earlier discussed the biological activities of indole-2,3-dione. It contains two different types of carbonyl functionalities, one as amidic carbonyl at C-2 position and other as free carbonyl at C-3 position. So one could be used in preference to other in condensation with hydrazines as these two differ markedly in their reactivities.

II. RESULTS AND DISCUSSION

In our comprehensive plan for developing new fluorine containing bioactive compounds, a series of novel fluorine containing fused indole system compounds **8(a-d)** have been synthesized by the reaction of compound **5** with indole-2,3-diones resulting in formation of hydrazones **7** followed by cyclization. Substructures **5** were synthesized by the reaction of indole-2,3-diones with thiosemicabarzide in weakly alkaline medium resulting in the formation of compound **4(a-d)** via intermediate **3**, followed by their reaction with hydrazine hydrate **(Scheme 1).** The formation of these compounds was confirmed by IR and ^{1}HNMR spectral studies. In IR spectra, characteristic absorption bands were observed in the region 3200-3050(>NH), 1650-1630(C=N), and 1260(>C=S) cm^{-1}.In ^{1}HNMR Spectra, signals at δ6.9-7.6(m, Ar-H) and 8.8(s, NH) ppm were observed.

A mixture of substituted indole-2,3-dione, thiosemicarbazide and K_2CO_3 in water gave the substituted adduct 3-thioxo-1,2,4-triazino (5,6-b) indole **4(a-d) (Table1)** in good yield, which in turn reacted with hydrazine hydrate to give the compounds **5(a-d) (Table1)**. Conversion of thioxo compounds into hydrazine derivative was confirmed by the IR spectra as the absorption band due to C=S disappeared and NH_2 was observed in the region 3450-3320cm^{-1} in ^{1}HNMR spectra, broad signal was observed at δ8.4-8.6ppm. Due to NH and protonated NH_3.

These compounds **(5a-d)** and substituted indole 2,3- diones were refluxed in absolute ethanol in the presence of catalytic amount of glacial acetic acid under anhydrous conditions **(Scheme 2).**

Table 1:

Compound	R_1	Time (h)	Yield (%)
4a	-H	7	82
4b	5-F	7.5	85
4c	6-F	8	83
4d	4-CF3	8	70
5a	-H	4.5	82
5b	5-F	4	70
5c	6-F	5	82
5d	4-CF3	4.5	92

On cooling the reaction mixture, bright orange coloured crystalline compound were separated labeled as **7(a-e) (Table-2).** The structural assignment of these compounds were based on their spectral data. The IR spectra of **7** exhibited strong absorption band around 3100-3250(>NH), 1685(>C=O) and 1620 cm^{-1} (>C=N). The disappearance of absorption band corresponding to free >C=O of indole 2-3 dione and appearance of >C=N absorption indicated the formation of hydrazones. The ^{1}HNMR spectrum (DMSO-d_6+$CDCl_3$) displayed three broad signals at δ 9.1, 10.3 and 13.3 (NH) . Aromatic protons appeared as multiplet at δ 6.8-7.8. These hydrazones **7** on cyclization with $POCl_3$ afforded dark green colored compounds **8(a-d) (Table-2)**, which were Indolo (3’,2’:5,6)-1,2,4 triazino(4,3-c) 1,2,4-triazino (5,6-b)indoles. In the IR spectra of these compounds, absorption bands corresponding to hydrazones NH and >C=O stretching disappeared, indicating the cyclization. The 1HNMR spectra showed multiplet at δ 6.9-7.6 ppm (8H, Ar-H) and a broad band at 9.1 ppm (triazino indole NH). The mass spectrum of **8A** exhibited weak molecular ion peak at m/z 311 (6%), indicating cyclization by loss of H2O from hydrazone, and corresponding to expected molecular weight. Cyclization of **7** can afford either angular product **8** involving cyclization at N-4 or **8A** by cyclization at N-2. However, in this case the spectral data could not convincingly decide if the product was angular or linear. The mode of cyclization will be governed by the stability of the product formed [14,15].

Similar reports in the literature favour the formation of a more benzenoid structure [16] Thus in the present case, formation of angular product involving cyclization at N-4 should be preferred as depicted by mechanism **(Fig.2)**. In this structure, the 10π electron system, i.e. aromatic character of indole ring is preserved and is stabilized by the high resonance energy. The preferential formation of angular product could result from the equilibrium**. (Fig.1)**

Table 2:

Compound	R_1	R'_1	Time (h)	Yield (%)
7a	H	H	6	70
7b	H	5-F	6	75
7c	H	6-F	6	60
7d	H	4-CF_3	6	65
7e	5-F	H	6	60
7f	6-F	H	6	65
7g	6-F	5-F	6	72
7h	5-F	5-F	6	75
8a	H	H	5	60
8b	H	5-F	5	52
8c	H	6-F	5	55
8d	H	4-CF_3	5	52
8e	5-F	H	5	50
8f	6-F	H	5	52
8g	6-F	5-F	5	58
8h	5-F	5-F	5	56

Compound **5** **(Fig.1)** will have the structure **5A** rather than **5B** because in **5A** the double bond in the triazine rings are in conjugation with the indole ring. Whereas in **5B** this conjugation is disturbed. Thus in compound **5**, N-4 being more nucleophelic than N-2, as N-2 is attached to N-1, will attach at indole-2 carbon, which undergoes prototropic changes followed by loss of H_2O to give **8.** In view of these considerations the cyclized product has been tentatively identified as **8** **(Scheme 3).**

III. CONCLUSION

A series of novel fluorine containing fused indole system have been synthesized which are of considerable biological interest as mentioned in introduction section. Their novelty also lies in that indole, triazine and triazole nuclei are fused together in different ways, which may result in much improved biological activity of these compounds. The interesting feature of these syntheses is that fusion of two heterocyclic nuclei have resulted in formation of a new system having ring junction which is an interesting aspect of heterocyclic synthesis.

IV. ACKNOWLEDGEMENTS

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V. EXPERIMENTAL SECTION

5.1 General methods, reagents and materials

Characterization of synthesized compounds has been done on the basis of IR, ^{1}HNMR, ^{13}CNMR and mass spectral studies. Infrared spectra were recored on shimadzu model 435 spectrophotometer as thin film of using KBr discs and important absorption bands are quoted in cm$^{-1.}$ Proton nuclear magnetic resonance (^{1}HNMR) spectra were recorded on Perkin-Elmer (400MHz) spectrometer with reference to TMS as internal standard. The chemical shifts are expressed in δ values. The Mass spectra were recorded on a Goel GC-MS Japan instrument by using electron ionization (EL) at 70ev and only major peaks are quoted.

All melting points are in centigrade scale, uncorrected and taken in sulphuric acid bath. All organic solvents petrol, benzene, ethyl acetate, ethanol, methanol, chloroform were dried. Petrol and benzene were distilled over phosphorus pentaoxide while ethanol was dried and distilled over anhydrous calcium oxide and finally over magnesium cake. All ethereal extracts were dried over anhydrous sodium sulphate. Column chromatography was carried out using silica gel (60-120mesh) as an adsorbent. The column was eluted with different organic solvents in order of increasing polarity and homogeneity of fractions was tested on TLC plates. R_f value were recorded for TLC carried out on glass plates coated with 0.2mm layer of silica gel-G, developed in iodine atmosphere.

5.2 Procedure for the synthesis of 8-fluoro-2*H-[1,2,4]* triazino[5,6-*b*] indole-3(5*H*)-thione 4(b)

A mixture of 5-fluoro indole-2, 3-dione (0.05mol, 8.25gm), thiosemicarbazide (0.055mol, 5.005gm) and K_2CO_3 (0.075 mol, 10.35 gm) in water was refluxed for 7-8 h. The reaction mixture was then filtered and acidified with glacial acetic acid to give the desired compound in 85% yield (11gm), which was recrystallized from ethanol. The other thioxo derivatives have been synthesized following a similar procedure and are given in Table-1.

5.2.1. 2H-[1,2,4]triazino[5,6-b]indole-3(5H)-thione. Yield 82%, m.p. >300°C, Anal. Calcd for $C_9H_5FN_4S$: C, 53.45; H, 2.99; N, 27.70; S, 15.86.. Found: C, 53.41; H, 2.89; N, 27.65, S, 15.80, IR (KBr)$^{\acute{\upsilon}}$max 3080.50 (>NH), 1637.12(>C=N), 1608.10 (C=C), 1549.08, 1430.00, 1360.50, 1260.00(>C=S), 1140.17, 1090, 980, 910, 840cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21(1H,s, NH), 7.65(1H,d), 7.43(1H, t), 7.35(1H, d), 7.20 (1H, t), 4.5 (1H, s, NH), ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.23, 160.15, 152.28, 143.58, 128.80, 125.95, 115.24, 113.29, ms (ES$^+$) m/z 202.03, (M$^+$+1).

5.2.2. 8-fluoro-2H-[1,2,4]triazino[5,6-b]indole-3(5H)-thione. Yield 85%, m.p. 304-305°C (Lit [7] mp>350°C), Anal. Calcd for $C_9H_6N_4S$: C, 49.08; H, 2.29; N, 25.44; S, 14.56. Found: C, 49.07; H, 2.26; N, 25.41, S, 14.53, IR (KBr)$^{\acute{\upsilon}}$max 3090.15 (>NH), 1635.00(>C=N), 1611.20 (C=C), 1540.12, 1420.08, 1360.50, 1270.50(>C=S), 1145.22, 1095cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30(1H, s, NH), 7.52(1H, d), 7.33(1H, d), 7.22(1H, m), 4.4(1H, s, NH), ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.88, 161.24, 154.14, 152.83, 143.32, 119.46, 118.39, 118.25, ms (ES$^+$) m/z 220.02, (M$^+$+1).

5.2.3. 7-fluoro-2H-[1,2,4]triazino[5,6-b]indole-3(5H)-thione. Yield 83%, m.p. 304-306°C, Anal. Calcd for $C_9H_6N_4S$: C, 49.08; H, 2.29; N, 25.44; S, 14.56. Found: C, 49.06; H, 2.25; N, 25.42, S, 14.52, IR (KBr)$^{\acute{\upsilon}}$max 3092.27 (>NH), 1641.25(>C=N), 1605.22, 1543.25, 1422, 1265.(>C=S), 1142, 1070cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25(1H, s, NH), 7.58(1H, d), 7.28(1H, m), 7.20(1H, m), 4.35(1H,s, NH), ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.20, 162.20, 161.47, 153.89, 144.16, 126.42, 108.75, 107.95, ms (ES$^+$) m/z 220.02, (M$^+$+1).

5.2.4. 9-(trifluoromethyl)-2H-[1,2,4]triazino[5,6-b]indole-3(5H)-thione. Yield 70%, m.p. 308-310°C , Anal. Calcd for $C_{10}H_5F_3N_4S$: C, 44.45; H, 1.86; N, 20.73; S, 11.87. Found: C, 44.41; H, 1.83; N, 20.75, S, 11.82, IR (KBr)$^{\acute{\upsilon}}$max 3087.28 (>NH), 1635.42(>C=N), 1605.68 , 1540, 1262 (>C=S), 1048, 969cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28(1H, s, NH), 7.12 -7.30 (3H, m), 4.35(1H, s, NH), ^{13}C NMR (100 MHz, $CDCl_3$): δ

188.62, 162.07, 154.29, 144.87, 126.42, 128.79, 127.92, 119.13, 118.89(CF$_3$), 113.01; ms (ES$^+$) m/z 270.01, (M$^+$+1).

5.3 Procedure for the synthesis of 8-fluoro-3-hydrazinyl-5*H*-[1,2,4]triazino[5,6-*b*]indole 5(b)

It was prepared following the method of joshi et al [7]. 8-Fluoro-3-thioxo-1, 2, 4-triazino (5, 6-b) (0.05mol, 11gm) indole was refluxed with hydrazine hydrate (30-40 ml) for 4-5 h. The reaction mixture was cooled and filtered. The precipitate was washed with water(100ml) and recrystallized from ethanol to give the desired compound in 70% yield (10.9gm). The other hydrazine derivatives have been synthesized following a similar procedure and are given in Table-1.

5.3.1. 3-hydrazinyl-5H-[1,2,4]triazino[5,6-b]indole. Yield 82%, m.p. 280-282°C, Anal. Calcd for $C_9H_8N_6$: C, 53.99; H, 4.03; N, 41.98; Found: C, 53.98; H, 4.00; N, 41.94, IR (KBr)$^{\acute{\upsilon}}$max 3435.05-3315.71 (NH2)(>NH), 1627.37(>C=N), 1056; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.62 (1H, d), 7.45 (1H,d), 7.15-7.28 (2H, m), 5.1(1H, s), 2.6 (2H, s), ^{13}C NMR (100 MHz, CDCl$_3$): δ 139.69, 129.48, 126.11, 124.23, 123.37, 122.82, 120.65, 113.41, 104.91; ms (ES$^+$) m/z 200.08, (M$^+$+1).

5.3.2. 8-fluoro-3-hydrazinyl-5H-[1,2,4]triazino[5,6-b]indole. Yield 70%, m.p. 295-297°C, Anal. Calcd for $C_9H_7FN_6$: C, 49.54; H, 3.23; N, 38.52; Found: C, 49.51; H, 3.21; N, 38.47, IR (KBr)$^{\acute{\upsilon}}$max 3427.89-3325.25 (NH2)(>NH), 1629.89(>C=N), 1148, 1051; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.5 (1H, s), 7.42 (1H, d), 7.33 (1H,d), 7.10 (1H, m), 4.9 (1H, s), 2.8 (2H, s); ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.43, 136.15, 131.59, 127.29, 114.21, 109.63, 107.19; ms (ES$^+$) m/z 218.07, (M$^+$+1).

5.3.3. 7-fluoro-3-hydrazinyl-5H-[1,2,4]triazino[5,6-b]indole. Yield 82%, m.p. 278-280°C, Anal. Calcd for $C_9H_7FN_6$: C, 49.54; H, 3.23; N, 38.52; Found: C, 49.50; H, 3.21; N, 38.47, IR (KBr)$^{\acute{\upsilon}}$max 3415.92-3324.27 (NH2)(>NH), 1631.21(>C=N), 1146, 1052; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.9 (1H, s), 7.60 (1H,d), 7.29 (1H, s), 7.10 (1H,m), 4.7 (1H, s), 2.6 (2H, s); ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.84, 138.26, 130.95, 127.34, 124.19, 109.49, 101.14; ms (ES$^+$) m/z 218.07, (M$^+$+1).

5.3.4. 3-hydrazinyl-9-(trifluoromethyl)-5H-[1,2,4]triazino[5,6-b]indole. Yield 92%, m.p. 230-232°C, Anal. Calcd for $C_{10}H_7F_3N_6$: C, 44.78; H, 2.63; N, 31.34; Found: C, 44.73; H, 2.60; N, 31.29, IR (KBr)$^{\acute{\upsilon}}$max 3419.15-3305.19 (NH2)(>NH), 1630.47(>C=N), 1181, 1062; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.5 (1H, s), 7.52 (1H, d), 7.34 (1H, d), 7.21 (1H, m), 4.92 (1H, s), 2.76 (2H, s); ^{13}C NMR (100 MHz, CDCl$_3$): δ 137.91, 127.26, 127.11, 125.33, 121.05, 120.75, 117.21, 115.88; ms (ES$^+$) m/z 268.06, (M$^+$+1).

5.4 Procedure for the synthesis of 3-(2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl) hydrazono) indolin-2-one -7(a)

A mixture of 3-hydrazino-5H-1, 2, 4-triazino (5,6-b) indol (5a)(0.01mol, 2.0 gm) and indole 2,3- dione (0.01mol, 1.47 gm) was refluxed in absolute ethanol (30ml) in the presence of a catalytic amount of glacial acetic acid under anhydrous condition for 6 h. On cooling, the reaction mixture bright red coloured crystalline compound was separated which was filtered, washed with cold ethanol and recrystallized with DMF to give the desired product in 70% yield (3.29gm). The other compounds 7a-7h mentioned in Table-2 were synthesized following a similar procedure.

5.4.1. 3-(2-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)indolin-2-one. Yield 70%, m.p. 306-308°C, Anal. Calcd for $C_{17}H_{11}N_7O$: C, 62.00; H, 3.37; N, 29.77; Found: C, 61.95; H, 3.36; N, 29.72, IR (KBr)$^{\upsilon}$max 3115.23 (>NH), 1683.11 (>C=O), 1623.49(>C=N), 1460.25, 1380.19, 1316.82, 1272.32, 1182.11, 1099.04, 976.08, 744.03; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.3 (1H, s, NH), 10.2 (1H, s, NH), 8.8 (1H, s, NH), 7.75-7.45 (4H, m), 7.25-7.32 (4H, m), ^{13}C NMR (100 MHz, $CDCl_3$): δ 168(C=O)amidic, 158(C=N), 139, 137, 130,129, 126, 125, 123, 120, 118, 110 ; ms (ES$^+$) m/z 329.10, (M$^+$+1).

5.4.2. 3-(2-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)-5-fluoroindolin-2-one. Yield 75%, m.p. 310-312°C, Anal. Calcd for $C_{17}H_{10}FN_7O$: C, 58.79; H, 2.90; N, 28.23; Found: C, 58.74; H, 2.87; N, 28.19, IR (KBr)$^{\upsilon}$max 3145.82 (>NH), 1679.82 (>C=O), 1627.22(>C=N), 1468.36, 1384.29, 1145.44; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.2 (1H, s, NH), 10.3 (1H, s, NH), 8.9 (1H, s, NH), 7.78-7.43 (4H, m), 7.29-7.18 (3H, m), ^{13}C NMR (100 MHz, $CDCl_3$): δ 167(C=O)amidic, 159(C=N), 138, 137, 131,129, 127, 125, 122, 120, 119, 111; ms (ES$^+$) m/z 347.09, (M$^+$+1).

5.4.3. 3-(2-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)-6-fluoroindolin-2-one. Yield 60%, m.p. 309-311°C, Anal. Calcd for $C_{17}H_{10}FN_7O$: C, 58.79; H, 2.90; N, 28.23; Found: C, 58.75; H, 2.85; N, 28.20, IR (KBr)$^{\upsilon}$max 3127.32 (>NH), 1683.49 (>C=O), 1624.84 (>C=N), 1462.72, 1364.23, 1141.92; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.1 (1H, s, NH), 10.4 (1H, s, NH), 8.6 (1H, s, NH), 7.68-7.40 (4H, m), 7.35-7.20 (3H, m), ^{13}C NMR (100 MHz, $CDCl_3$): δ 168(C=O)amidic, 158(C=N), 139, 137, 130,129, 126, 125, 123, 121, 118, 111; ms (ES$^+$) m/z 347.09, (M$^+$+1).

5.4.4. 3-(2-(5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)-4-(trifluoromethyl)indolin-2-one. Yield 65%, m.p. 313-315°C, Anal. Calcd for $C_{18}H_{10}F_3N_7O$: C, 54.41; H, 2.54; N, 24.68; Found: C, 54.35; H, 2.52; N, 24.53, IR (KBr)$^{\upsilon}$max 3138.42 (>NH), 1684.21 (>C=O), 1624.95 (>C=N), 1382.64, 1275.49, 1146.28; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.4 (1H, s, NH), 10.2 (1H, s, NH), 8.95 (1H, s, NH), 7.62-7.39 (3H, m), 7.15-7.26 (4H, m), ^{13}C NMR (100 MHz, $CDCl_3$): δ 168(C=O)amidic, 157.5(C=N), 138, 136.8, 130,129, 127, 125, 122, 119, 113, 111; ms (ES$^+$) m/z 397.09, (M$^+$+1).

5.4.5. 3-(2-(8-fluoro-5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)indolin-2-one. Yield 60%, m.p. 306-308°C, Anal. Calcd for $C_{17}H_{10}FN_7O$: C, 58.79; H, 2.90; N, 28.23; Found: C, 58.73; H, 2.89; N, 28.18, IR (KBr)$^{\upsilon}$max 3142.72 (>NH), 1625.13 (>C=O), 1625.13 (>C=N), 1381.59, 1269.29, 1141.21; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.1 (1H, s, NH), 10.4 (1H, s, NH), 9.1 (1H, s, NH), 7.62 (1H, d), 7.50(1H, d), 7.42-7.20 (4H, m), 6.91 (1H, d), ^{13}C NMR (100 MHz, $CDCl_3$): δ 169(C=O)amidic, 158(C=N), 157(C-F), 138, 136, 131,129, 127, 125, 122, 119, 112, 108, 107; ms (ES$^+$) m/z 347.09, (M$^+$+1).

5.4.6. 3-(2-(7-fluoro-5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)indolin-2-one. Yield 65%, m.p. 306-307°C, Anal. Calcd for $C_{17}H_{10}FN_7O$: C, 58.79; H, 2.90; N, 28.23; Found: C, 58.76; H, 2.85; N, 28.20, IR (KBr)$^{\upsilon}$max 3140.39 (>NH), 1684.75 (>C=O), 1627.55 (>C=N), 1380.65, 1265, 1140.19; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.35 (1H, s, NH), 10.31 (1H, s, NH), 9.08 (1H, s, NH), 7.64 (1H, d), 7.54 (2H, m), 7.35-7.22 (3H, m), 6.85 (1H, d), ^{13}C NMR (100 MHz, $CDCl_3$): δ 165(C=O)amidic, 158(C=N), 158(C-F), 139, 137, 130, 129, 128, 126, 122, 121, 118, 112, 102; ms (ES^+) m/z 347.09, (M^++1).

5.4.7. 5-fluoro-3-(2-(7-fluoro-5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)indolin-2-one. Yield 72%, m.p. 312°C, Anal. Calcd for $C_{17}H_9F2N_7O$: C, 55.89; H, 2.48; N, 28.84; Found: C, 55.82; H, 2.44; N, 28.81, IR (KBr)$^{\acute{\upsilon}}$max 3130.94 (>NH), 1675.69 (>C=O), 1625.98 (>C=N), 1350, 1240, 1155; ^1H NMR (400 MHz, $CDCl_3$): δ 12.24 (1H, s, NH), 10.29 (1H, s, NH), 8.84 (1H, s, NH), 7.62 (1H, d), 7.55(1H, d), 7.32-7.18 (3H, m), 6.92 (1H, d), ^{13}C NMR (100 MHz, $CDCl_3$): δ 166(C=O)amidic, 158(C=N), 157(C-F), 154, 139, 136, 129, 127, 124, 110, 102; ms (ES^+) m/z 365.08, (M^++1).

5.4.8. 5-fluoro-3-(2-(8-fluoro-5H-[1,2,4]triazino[5,6-b]indol-3-yl)hydrazono)indolin-2-one. Yield 75%, m.p. 314°C, Anal. Calcd for $C_{17}H_9F2N_7O$: C, 55.89; H, 2.48; N, 28.84; Found: C, 55.84; H, 2.46; N, 28.79, IR (KBr)$^{\acute{\upsilon}}$max 3148.10 (>NH), 1680.25 (>C=O), 1621.43 (>C=N), 1389.94, 1265, 1151; ^1H NMR (400 MHz, $CDCl_3$): δ 12.35 (1H, s, NH), 10.14 (1H, s, NH), 8.95 (1H, s, NH), 7.60 (1H, d), 7.55(1H, d), 7.35-7.22 (4H, m), 6.90 (1H, d), ^{13}C NMR (100 MHz, $CDCl_3$): δ 166(C=O)amidic, 158(C=N), 157(C-F), 155, 137, 132, 128, 123, 120, 117, 113, 108, 106; ms (ES^+) m/z 365.08, (M^++1).

5.5 Procedure for the synthesis of Indolo (3' 2':5, 6)-1, 2, 4 triazino (4, 3-*c*) 1, 2, 4- triazino (5, 6-*b*) indoles -8(a)

A mixture of 3- (1, 2, 4-Triazino (5, 6-b) indole-3-yl hydrazono)-2-indolinone (7a) (0.01 mol, 3.29 gm) and $POCl_3$ (15ml) was refluxed in an oil bath of 130^0C for 5 h. the reaction mixture was cooled to room temperature, poured on to crushed ice and neutralized with Na_2CO_3. The solid thus obtained, was filtered, washed with water and purified by column chromatography using silica gel as an adsorbent. The desired compound was obtained in 60% yield (3.10gm). The other compounds 8a-8h were synthesized following a similar procedure and are mentioned in table 2

5.5.1 Yield 60%, m.p. 292-294°C, IR (KBr)$^{\acute{\upsilon}}$max 3090.41, 1598, 1464, 1316, 1193, 1096, 926, 756; ^1H NMR (400 MHz, $CDCl_3$): δ 9.4 (1H, s, NH), 7.66 (2H, d), 7.46 (1H, d), 7.38-7.20 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166, 164, 163, 147.5, 135, 132.1, 130, 128, 126, 124.7, 123, 122.1, 122, 121, 120, 110,102 ; ms (ES^+) m/z 311.09, (M^++1). Anal. Calcd for $C_{17}H_9N_7$: C, 65.59; H, 2.91; N, 31.50; Found: C, 65.51; H, 2.87; N, 31.44.

5.5.2 Yield 52%, m.p. 282-284°C, IR (KBr)$^{\acute{\upsilon}}$max 3088.41, 1590, 1450, 1323, 1146, 1082, 945; ^1H NMR (400 MHz, $CDCl_3$): δ 9.6 (1H, s, NH), 7.64 (1H, d), 7.42 (1H, d), 7.39-7.22 (3H, m); 7.28-7.20 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164, 163, 162, 160, 144, 135, 127, 124, 123, 122, 121, 120, 119, 117, 111, 102 ; ms (ES^+) m/z 329.08, (M^++1). Anal. Calcd for $C_{17}H_8FN_7$: C, 62.01; H, 2.45; N, 29.78; Found: C, 61.95; H, 2.45; N, 29.73.

5.5.3 Yield 55%, m.p. 280-282°C, IR (KBr)$^{\acute{\upsilon}}$max 3095, 1588, 1462, 1343, 1142, 1096, 923; ^1H NMR (400 MHz, $CDCl_3$): δ 9.45 (1H, s, NH), 7.66-7.63 (2H, d), 7.45 (1H, d), 7.30-7.20 (4H, m); 7.28-7.20 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166, 164, 163, 150, 135, 131, 130, 126, 124, 123, 122, 121, 120, 115, 111, 102 ; ms

(ES$^+$) m/z 329.08, (M$^+$+1). Anal. Calcd for $C_{17}H_8FN_7$: C, 62.01; H, 2.45; N, 29.78; Found: C, 61.97; H, 2.41; N, 29.72.

5.5.4 Yield 52%, m.p. 265-268°C, IR (KBr)$^{\upsilon}$max 3075, 1591, 1455, 1343, 1155, 1092, 840; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (1H, s, NH), 7.66 (1H, d), 7.55 (1H, d), 7.41 (1H, d), 7.32-7.19 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165, 164, 163, 150, 137, 132.8, 132.4, 128, 125.3, 124.5, 124, 122, 121.5, 121, 112.9, 111, 101 ; ms (ES$^+$) m/z 379.07, (M$^+$+1). Anal. Calcd for $C_{18}H_8F_3N_7$: C, 57.00; H, 2.15; N, 25.85; Found: C, 56.92; H, 2. 13; N, 25.79

5.5.5 Yield 50%, m.p. 278-280°C, IR (KBr)$^{\upsilon}$max 3098, 1578, 1469, 1330, 1146, 1055, 940, 819; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.2 (1H, s, NH), 7.68-7.62 (2H, d), 7.34-7.25 (4H, m), 6.94 (1H, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166, 164, 163, 150, 148, 137, 131, 130, 126, 124, 123, 122.2, 122, 121, 108, 104, 100 ; ms (ES$^+$) m/z 329.08, (M$^+$+1). Anal. Calcd for $C_{17}H_8FN_7$: C, 62.01; H, 2.45; N, 29.78; Found: C, 61.90; H, 2.39; N, 29.70

5.5.6 Yield 52%, m.p. 277-280°C, IR (KBr)$^{\upsilon}$max 3098, 1584, 1473, 1313, 1145, 1085, 940, 823; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (1H, s, NH), 7.65 (1H, d), 7.46 (1H, d), 7.36-7.28 (4H, m), 6.95 (1H, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164, 163, 162, 154, 150, 132.2, 131, 130.4, 128, 127.1, 124, 123, 122, 112, 109, 108, 104 ; ms (ES$^+$) m/z 329.08, (M$^+$+1). Anal. Calcd for $C_{17}H_8FN_7$: C, 62.01; H, 2.45; N, 29.78; Found: C, 61.93; H, 2.40; N, 29.73

5.5.7 Yield 58%, m.p. 286-288°C, IR (KBr)$^{\upsilon}$max 3094, 1581, 1485, 1343, 1150, 1075, 935, 824; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (1H, s, NH), 7.58 (1H, d), 7.32-7.24 (3H, m), 7.09-6.98 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165, 164, 163, 160.7, 155, 144.1, 138, 127, 124, 123, 122, 121, 119.3, 116.5, 109, 104, 102 ; ms (ES$^+$) m/z 347.07, (M$^+$+1). Anal. Calcd for $C_{17}H_7F_2N_7$: C, 58.79; H, 2.03; N, 28.25; Found: C, 58.71; H, 1.99; N, 28.23

5.5.8 Yield 56%, m.p. 285-287°C, IR (KBr)$^{\upsilon}$max 3087, 1578, 1479, 1349, 1148, 1081, 941, 820; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (1H, s, NH), 7.44 (1H, d), 7.32-7.20 (3H, m), 7.05-6.95 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168, 167, 164, 160.8, 156, 145.4, 134, 131, 130, 126.3, 124.7, 120, 118, 115, 109, 107, 102 ; ms (ES$^+$) m/z 347.07, (M$^+$+1). Anal. Calcd for $C_{17}H_7F_2N_7$: C, 58.79; H, 2.03; N, 28.23; Found: C, 58.69; H, 2.00; N, 28.20

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