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Synthesis of fluorinated 3-hydrazino-1,2,4-triazino[5,6-*b*] indoles as novel herbicidal systems

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A few fluorinated 3-hydrazino-1,2,4-triazino[5,6-b] indoles (**5-8**) have been synthesized and screened for their herbicidal effect. Treatment of 3-hydrazino-8*H*/8-fluoro-1,2,4-triazino[5,6-b] indoles (**3** and **4**) with fluorinated acyl derivatives (**A** and **B**) yielded the rich fluorine 1,2,4-triazino indole. Structure of the products have been established by elemental analysis and spectral measurements. The presence and position of fluorine atoms have been deduced from ^{19}F NMR. The novel fluorinated hydrazino-1,2,4-triazino[5,6-b] indoles have been tested for post-emergent herbicidal activity against grass weed species and broadleaf weed species.

Keywords: Synthesis, 1,2,4-triazino indole, herbicidal, fluorinated hydrazine-1,2,4-triazino indole

3-Functionaly-1,2,4-triazino[5,6-*b*] indoles are utilized as a carrier for diverse functional groups in the development of antiviral drugs[1,2]. Analogous3-hydrazino triazino indoles were proven to show the efficacy of such systems in the production of antibacterial[3], antifungal[4], inhibitors of blood platelet aggregation, anti-hypertensive agents and thromboxane synthetase inhibitors[5]. On the other hand, fused heteropolycyclic nitrogen systems were obtained from the interaction between 3-hydrazino-1,2,4-triazino [5,6-*b*] indoles with π-acceptors[6] as well as a large number of Nucleosides and Nucleotides isolated from condensation of 3-hydrazino-triazino indoles with various monosaccharides[7]. Recently, introduction of CF_3, CF_2 and/or CF to heterocyclic nitrogen systems, especially 1,2,4-triazine compounds, often enhance and improve their physical, chemical and bio-cidalproperties[8-10]. Based upon our observations, and due to the importance and scarcity research of this area and to add more, thus the present work reports the fluoro-acylation of fluoro-3-hydrazino-1,2,4-triazino[5,6-*b*] indole in view of their herbicidal evaluation.

Results and Discussion

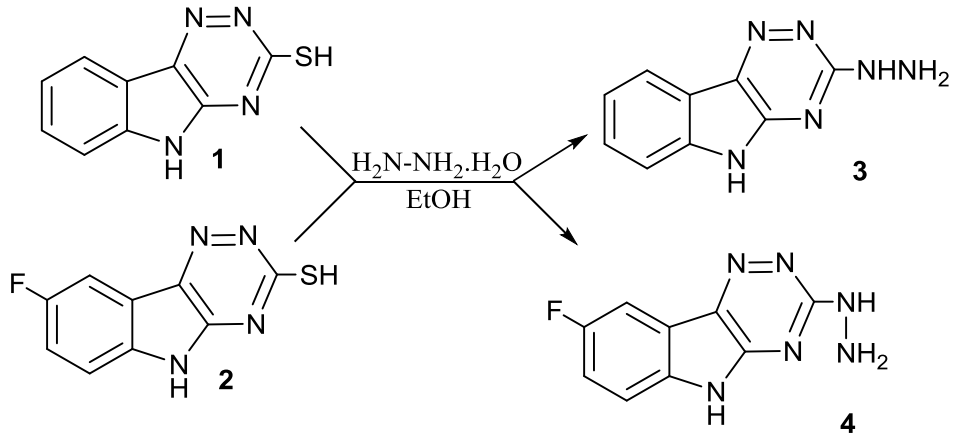
3-Hydrazino-1,2,4-triazine derivatives, use as starting materials to obtain a various isolated and/or fused heteropolycyclic nitrogen system, which mainly have an strong nucleophilic centers[11]. But, a little work done on the full acylation of these triazines[12] 3-hydrazino-5*H*-1,2,4-triazino[5,6-b] indole (**3**) and 3-hydrazino-8-fluoro-1,2,4-triazino[5,6-b] indole (**4**) were obtained according the reported methods from hydrazinolysis of the corresponding 3-mercapto-1,2,4-triazino[5,6-*b*] indoles (Scheme I)[13].

Based upon these observations, the reflux of 3-hydrazino-1,2,4-triazino[5,6-b] indole (**3**) and/or 3-hydrazino-8-fluoro-1,2,4-triazino[5,6-b] indole (**4**) with excess tri-fluoroacetic anhydride and/or pentafluoropropinic anhydride in THF, afforded the full fluorinated acyl hydrazino-8-fluoro-1,2,4-triazino [5,6-*b*] indoles (**7** and **8**) respectively (Scheme II). Formation of **8** from **4** may be as shown in Figure 1.

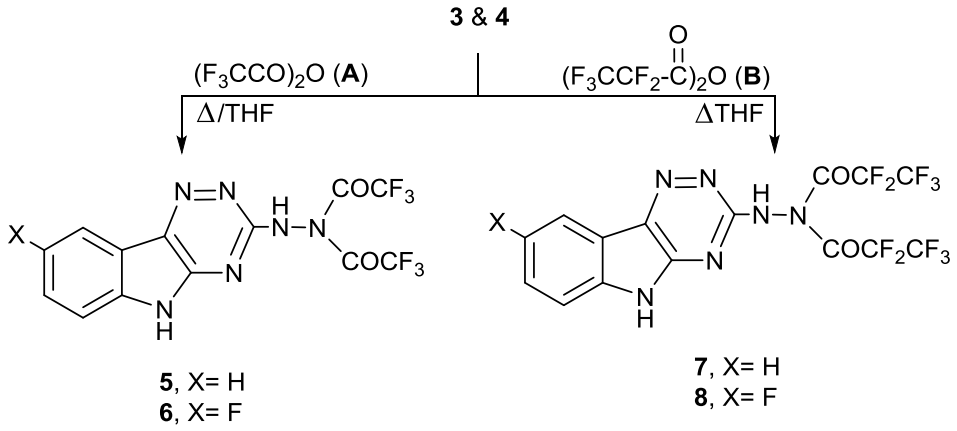
3-Hydrazino-1,2,4-triazino[5,6-*b*] indoles displaying high activity as inhibitors, in addition as biocidal agents as well as use as starting materials for building of various isolated and/or fused heteropolycyclic nitrogen systems. On the other hand, introduction of CF_3 group or CF_2 and CF functional to heterocyclic nitrogen systems, improve that properties. Thus, the present work tends to obtain fluorinated 3-hydrazino-1,2,4-triazino[5,6-*b*] indoles in view of their herbicidal activity.

Structures of the new compounds prepared were deduced upon their correct elemental analysis and spectral measurements.

IR spectra of all the compounds **5-8** showed the important bands at ν 1720, 1680 and 1250 cm^{-1} attributed to 2(C=O) and C-F functional groups. It is



Scheme I — Synthesis of 1,2,4-riazino[5,6-*b*]indole from hydrazinolysis



Scheme II — Synthesis of full fluorinated acyl hydrazino-8-fluoro-1,2,4-triazino[5,6-*b*] indoles (**7** and **8**)

interest that, presence of ν at 3364 and 3150 cm^{-1} for NH of 1,2,4-triazine and NH of indole.

NMR spectral study of compounds **5-8** showed a two δ at 14.01 and 11.51 for NH of 1,2,4-triazine and NH of indole. With presence of δ at 7.9-7.8, 7.15-7.13 as d,d for adjacent two protons to C-F, in addition δ at 6.99-6.83 for indole proton.

^{13}C NMR spectra of compounds **5-8** recorded at δ 179.08 (C=O), 149.12 (C-F), 143 (C=N), 135.55, 131.8 (aromatic carbons), 123.01, 121.83 (indole carbons), 117.67, 112.94 (C-N of 1,2,4-triazines).

Presence and positions of fluorine atoms of the compounds **5-8** were deduced from ^{19}F NMR. Thus, fluorine atom adjacent to an indole ring observed as doublet at δ -115.150 and -115.50 (*J* HF= 25 Hz), while the CF_3 group as singlet at -59.63, -65.04 and -74.33. Finally, mass fragmentation pattern of the fluorinated **6** and **8** showed the molecular ions peak with a base peak at m/e 134 attribute to 5-fluoroindole ion (Figure 1).

The starting herbicidal studies on the fluorinated alkyl 1,2,4-triazino[5,6-*b*] indoles was reported by Mizutani *et al*.[14] The results obtained before tends to desperately need to search for new full fluorinated 3-hydrazino-1,2,4-triazino[5,6-*b*] indoles in view of use as new herbicide drugs by use the Known method[15].

Thus, the compounds, **5-8** were tested for postemergent herbicidal activity against one grass weed species and also one broadleaf weed species. The results obtained reported in the Table I.

It is clear that, the full fluorinated compounds which contain $COCF_2CF_3$ greatly enhance the herbicidal activity followed the contain $COCF_3$ groups (**8**>**6**>**5**>**7**).On the other hand, lower fluorinated of indole nucleus, activity decreased (**5** and **7**).

In addition, higher concentration of $COCF_2CF_3$ compounds showed higher activity than the other low concentration (Table I).

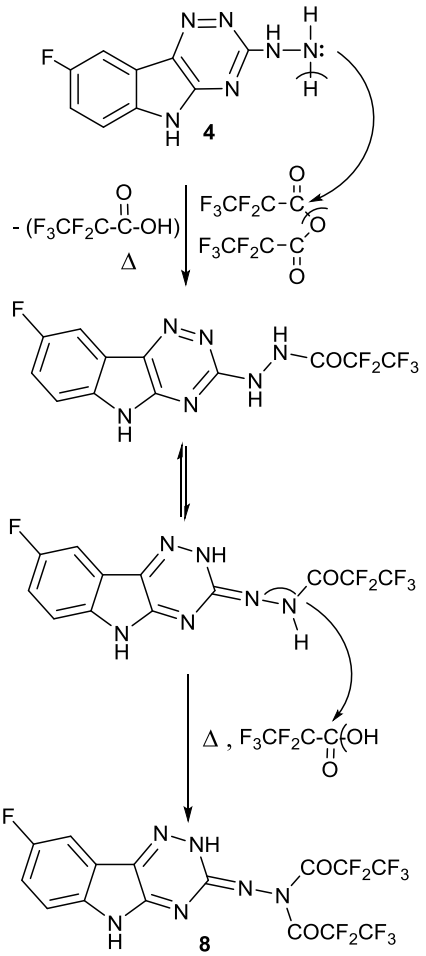


Figure 1 — Formation of compound **8** from **4**

Table I — Herbicidal activity of synthesized compounds

Compd	Rate (g/a)	Herbicidal activity*	
		Grasses (wiedoats)	Broadleaves (velet-leaf)
5	2.5	2	1
	1.25	0	0
6	2.5	3	4
	1.25	2	2
7	2.5	3	5
	1.25	2	4
8	2.5	4	4
	1.25	5	5

Herbicidal ratings: 0= no effect, 5= completely killed, Reference= 5

Experimental Section

Microanalysis (CHNF) carried out with a Perkin-Elmer 240Q elemental analyzer. All the chemical shifts are given relative to TMS and recorded on a Varian 700 spectrometer (DMSO, δ, ppm). Compounds **1**, **2** and **3**, **4** have been obtained according the reported methods[13].

3-[1,1-Di(trifluoroacetyl)] hydrazino-5-*H*-1,2,4-triazino[5,6-*b*] indole, 5

A mixture of **3** and excess of trifluoroacetic anhydride (A) in THF (100 mL) refluxed 2 h, cooled, then filtered. The solid obtained crystallized from THF to give **5**, yield 58%. m.p.277-79°C. Anal. Calcd for $C_{13}H_6N_6F_6O_2$ (Mol. Wt. 392): C, 39.79; H, 1.53; N, 21.42; F, 29.08. Found: C, 39.29; H, 1.44; N, 21.18; F, 28.88%. IR: 3248, 3081 (2NH), 1737, 1695 (2C=O), 1562, 1550 (C=N), 1316 (cyclic), 1210 (C-F), 904, 827 (substituted phenyl), 703 cm^{-1} (C-F); ^{1}H NMR (DMSO-d_6): δ 14.01 (*s*, 1H, NH, 1,2,4-triazine), 11.51 (*s*, 1H, NH of indole), 7.48-6.95 (m, 4H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 163.0, 159.63 (2C=O), 142.83 (C-F), 139.84 (C=N), 120.08-119.62 (aromatic carbons), 119.62, 116.82 (C-N), 109.24, 108.99 (C_5 & C_6 1,2,4-triazine); ^{19}F NMR (DMSO-d_6): δ −74.69 (*s*, C-F of side chain), −119.76 (d, C-F of indole *J*= 25).

3-[1,1-Di(trifluoroacetyl)] hydrazino-5*H*-8-fluoro-1,2,4-triazino[5,6-*b*] indole, 6

A mixture of **4** and excess of pentafluoropropionic anhydride in THF (100 mL) was refluxed 2 h and then cooled. The solid product was crystallized from dioxin to give **6**, yield 62%. m.p.318-20°C. Anal. Calcd for $C_{13}H_5N_6F_7O_2$ (Mol. Wt. 410): C, 38.04; H, 1.21; N, 20.48; F, 37.54. Found: C, 37.88; H, 1.21; N, 20.48; F, 32.42%. IR: 3253, 3079 (2NH), 1748, 1720 (2C=O), 1596, 1543 (C=N), 1316 (cyclicN-CN-N), 1224 (C-F), 903, 888 (substituted ph), 758 cm^{-1} (C-F); ^{1}H NMR (DMSO-d_6): δ 14.18, 11.52 (each *s*, 2H, indole and 1,2,4-triazine), 7.48-7.45, 7.33-7.27, 6.98-6.95 (each *s*, 3H, aromatic H); ^{13}C NMR (DMSO-d_6): δ 163.1, 159.63 (2C=O), 143.26 (C-F), 139.97 (C=N), 120.0-118.87 (aromatic carbons), 116.01, 112.02 (C-N), 109.31, 109.06 (C_5,C_6 1,2,4-triazine); ^{19}F NMR (DMSO-d_6): δ −123.16, −119.76 (d, F of indole), −82.24 (*s*, F of side chain).

3-[1,1-Di(pentafluoroethyl carbonyl)] hydrazino-5-*H*-1,2,4-triazino[5,6-*b*] indole, 7

A mixture of **3** and excess pentafluoropropionic anhydride in THF (100 mL), refluxed 2 h and then cooled. The solid product was filtered off and crystallized from ethylbenzene to give **7**, yield 55%. m.p.317-20°C. Anal. Calcd for $C_{15}H_6N_6F_{10}O_2$ (Mol. Wt. 492): C, 36.58; H, 1.21; N, 17.07; F, 38.61. Found: C, 36.33; H, 1.11; N, 16.97; F, 38.41%. IR: 3300-3036 (b, bonded NH), 1729 (C=O), 1611, 1589

(C=N), 1310 (cyclic NCN), 1210 (C-F), 860, 824 (substituted ph), 749 cm^{-1} (C-F); ^{1}H NMR (DMSO-d_6): δ 14.56, 12.39 (each *s*, 2NH), 8.01-7.33 (m, 4H, aromatic protons); ^{13}C NMR (DMSO-d_6): δ 179 (C=O), 149.12 (C-F), 143.05 (C=N), 135.55, 131.80 (C-N), 123.01-121.80 (aromatic carbons), 117.67, 112.94 (C_5-C_6 1,2,4-triazine); ^{19}F NMR (DMSO-d_6): δ −74.33, −73.90, −65.04, −64.71, −64.61, −62, −90, −59.63 (F of side chains).

3-[1,1-Di(pentafluoroethyl carbonyl)] hydrazine -1,2,4-triazino[5,6-*b*] indole, 8

A mixture of **4** and pentafluoropropionic anhydride in THF (100 mL) was refluxed 2 h and then cooled. The solid obtained was filtered off and crystallized from ethylbenzene to give **8**, yield 62%. m.p.308-10°C. Anal. Calcd for $C_{15}H_5N_6F_{11}O_2$ (Mol. Wt. 510): C, 32.29; H, 0.98; N, 16.47; F, 40.9. Found: C, 32.10; H, 0.75; N, 16.29; F, 40.71%. IR: 3300-3080 (b, bonded NH), 1741, 1681 (2C=O), 1614 (C=N), 1557, 1516 (C-N), 1320 (NCN), 1275 (C-F), 903,842 (substituted ph), 746 cm^{-1} (C-F); ^{1}H NMR (DMSO-d_6): δ 14.56, 12.39 (each *s*, 2H, NH), 8.01-7.99, 7.63-7.61, 7.45-7.32 (aromatic protons); ^{13}C NMR (DMSO-d_6): δ 179.0 (C=O), 149.12 (C-F), 43.06 (C=N), 115.55, 131.81 (C-N), 123.02-121.84 (aromatic carbons), 117.68, 112.94 (C_5-C_6 1,2,4-triazine); ^{19}F NMR (DMSO-d_6): δ −115.15, −115.50 (*J* HF= 25 Hz), −74.33, −65.04, −59.63; MS: *m/z* (656, 1.11), 187 (23.5), 134 (100%, C_8H_5NF).

Conclusion

A new full fluorinated acyl 3-hydrazino-1,2,4-triazino[5,6-*b*] indoles has been developed as herbicidal agents to kill some grass weed species and broadleaf weed species. The preparation efficiency of the simple methodology and its very pure and high yield with low cost present series. Most of the novel fluorinated systems obtained were found active, but the full fluorinated derivative is highly active agent as herbicidal biocidal probe. These compounds may be use as chemotherapeutic agents in the future.

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