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Synthesis of Some New Fluorinated 3-Substituted Amino-*5H*-8-fluoro-1,2,4-triazino[5,6-*b*]indoles and 3-Substituted Amino-*9H*-7-fluoroimidazo[3,2-b][1,2,4]triazino[5,6-*b*]indoles as Anti-inflammatory Agents

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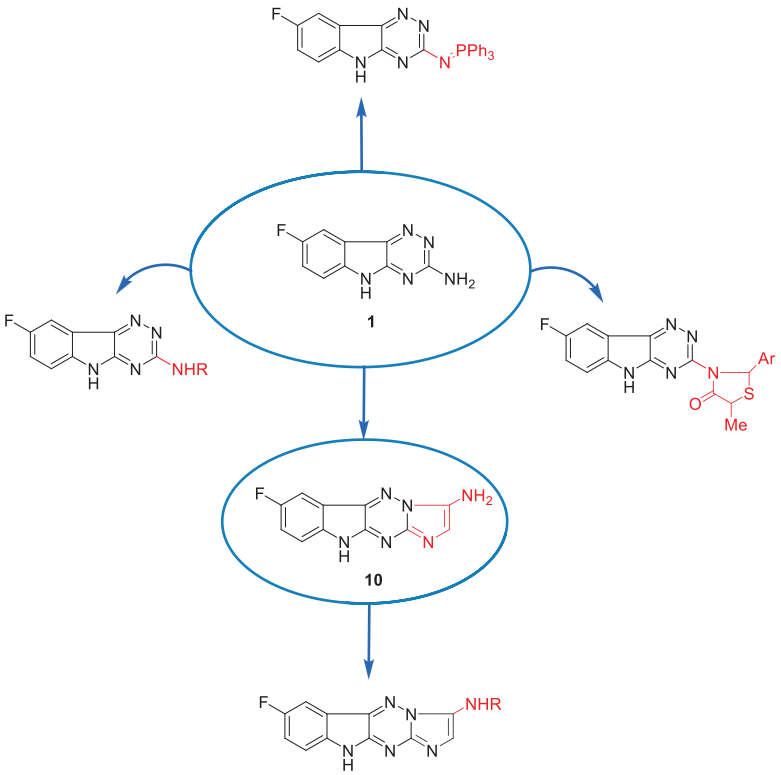
ABSTRACT Some new fluorinated 3-substituted amino-1,2,4-triazino[5,6-*b*]indoles (**2-9**) and 3-substituted amino-imidazo[3,2-*b*][1,2,4]triazino[5,6-*b*]indoles (**11-14**) have been obtained from the reactions of 3-amino-5H-8-fluoro-1,2,4-triazine (**1**) with alkyl/acyl compounds, and/or the treatment of 3-amino-imidazo[3,2-*b*][1,2,4]triazino[5,6-*b*]indole (**10**) with the various reagents under the various conditions. Structures of the new compounds were established from elemental analyses and spectral measurements. The fluorinated compounds were evaluated for their anti-inflammatory properties and the compounds **9 >3 >12 >5** exhibited a high activity.



KEYWORDS Synthesis, Fluorinated 3-Substituted amino-1,2,4-triazino[5,6-b]indoles, Anti-inflammatory.

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INTRODUCTION

Joshi *et al*.[1] reported the synthesis of new fluorine-containing 3-dialkyl amino-ethylthio-5-morpholino-methyl-1,2,4-triazino[5,6-*b*]indoles as antibacterial, antifungal, and antiviral activities.[1] Abdel-Rahman *et al*.[2] synthesized new fluorine substituted 3-amino-1,2,4-triazino[5,6-*b*]indoles as photochemical probes for the inhibition of vitiligo disease. Furthermore, novel herbicidal 3-dimethylamino-*4H*-1,2,4-triazino[5,6-b]indoles were obtained by Mizutani *et al*.[3] [**Figure 1**].[4] Makki *et al*.[5] obtained full fluorinated 3,5-diamino-6-aryl-1,2,4-triazine as lamotrigine drugs as long as anti-inflammatory probes [**Figure 1**].

Based on these observations, the present work tends to obtain some more new fluorine substituted 3-amino-1,2,4-triazino[5,6-*b*]indoles and/or 3-amino-imidazo[3,2-*b*][1,2,4]triazino[5,6-*b*]indoles through acylation, aroylation, condensation, and/or alkylation reaction, in view of their anti-inflammatory properties.

RESULTS AND DISCUSSION

Chemical synthesis

3-Amino-8-fluoro-*5H*-1,2,4-triazino[5,6-*b*]indole **1**[6] was used to obtain various new fluorinated substituted amino-1,2,4-triazino[5,6-*b*]indoles (**2–9**) through treatment with different electrophilic reagents. Thus, acylation of **1** by warming with acetic acid for short time yielded 3-acetamido-8-fluoro-*5H*-1,2,4-triazino[5,6-*b*]indole (**2**), while that on treatment with 3,5-dinitrobenzoyl chloride in warming dimethylformamide (DMF) produced 3-arcylamino-8-fluoro-*5H*-1,2,4-triazino[5,6-*b*]indole (**3**). The presence of amino group of **1** was deduced from refluxing with $P(Ph)_3$ in tetrahydrofuran (THF)-piperidine or CH_3CN similar as Wittig reaction[6] to give 3-(triphenylphosphinimino)-8-fluoro-*5H*-1,2,4-triazino[5,6-*b*]indole (**4**), respectively [**Scheme 1**].

Most of the *N*-alkylamino derivatives exhibited a wide spectrum of biological activities.[4c]

Similarly, the treatment of compound **1** with MeI in aq. KOH by stirring for 12 h at room temperature produced 3-methylamino-8-fluoro-*1H*-1,2,4-triazino[5,6-*b*]indole (**5**), while that on refluxing with monochloroacetic acid in DMF yielded substituted α-aminoacetic acid **6**. Decarboxylation of compound **6** on refluxing with aq. K_2CO_3 for 1 h afforded the corresponding 3-methylamino derivative **5** [**Scheme 2**].

The interaction between 3-amino-triazino[5,6-*b*]indole (**1**) and chloroacetonitrile in warming DMF furnished 3-(cyanomethyl)amino-8-fluoro-*5H*-1,2,4-triazino[5,6-*b*]indole (**7**). Acidic hydrolysis of compound **7** by refluxing with aq. HCl for 1 h led to the formation of compound **5**. Melting point and mixed melting of **5** from different pathways showed no depression [**Scheme 2**].

Thiazolidin-4-one derivatives exhibit an important biological, pharmacological, and medical properties.[7]

Similarly, condensation of 3-amino-8-fluoro-*5H*-1,2,4-triazino[5,6-*b*]indole (**1**) with aromatic aldehyde in refluxing with glacial acetic acid yielded the Schiff base (**8**) which upon cycloaddition with thiolactic acid in non-polar

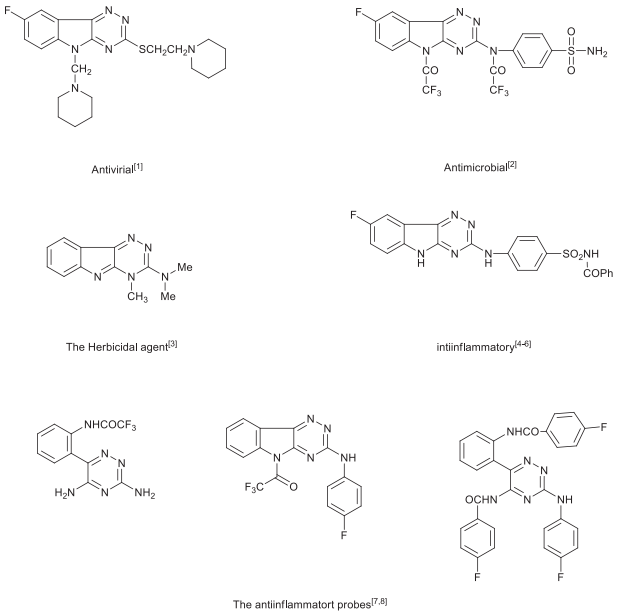
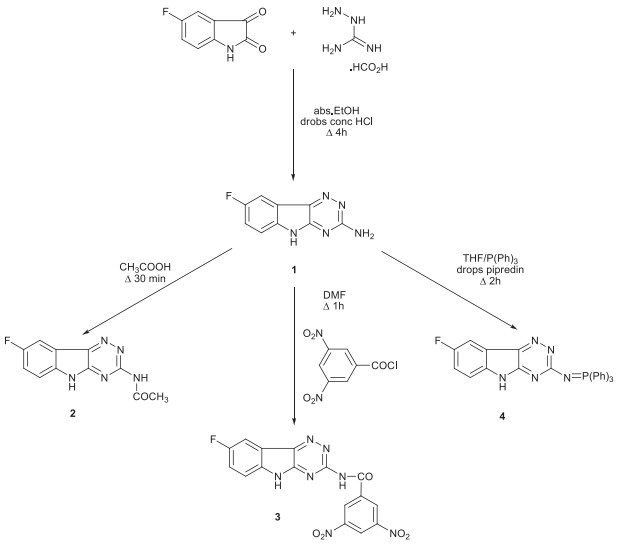
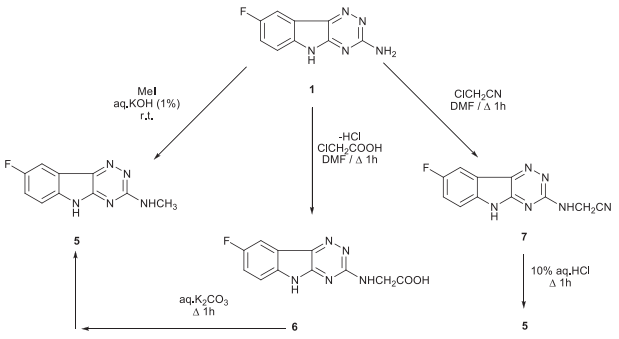


Figure 1: Some bioactive fluorine substituted amino-1,2,4-triazino[5,6-*b*]indoles



Scheme 1: Formation of compounds 2, 3, and 4



Scheme 2: Formation of compounds 5, 6, and 7

solvent, 1,4-dioxane, afforded 3-(2'-aryl-5'-methyl-5'H-4'-oxothiazol-3'yl)-8-fluoro-5*H*-1,2,4-triazino[5,6-*b*] indole (**9**) [**Scheme 3**]. Formation of compound **9** may be as shown in **Figure 2**. M/S study supported the structure **9a** containing five-membered ring rather than **9b** containing seven-membered ring.

It is of interest that, reaction of 3-amino-8-fluoro-5H-1,2,4-triazino[5,6-*b*]indole (**1**) with chloroacetonitrile in DMF[8] gave 3-amino-7-fluoro-10H-imidazo[3,2-*b*][1,2,4] triazino[5,6-*b*]indole (**10**), produced via cycloaddition reaction [**Scheme 4**].

Similarly, acylation, aroylation, and/or alkylation of amino group bearing 1,2,4-triazinoindole moiety were deduced. Thus, compound **10** on warming with glacial acetic acid afforded the acetamido **11**, while that on warming with 3,5-dinitrobenzoyl chloride in DMF yielded the corresponding aroylamino derivative **12** [**Scheme 4**].

In addition, treatment of **10** with MeI in aq. 1% KOH at room temperature produced 3-(methyl)amino-7-fluoro-*10H*-imidazo[3,2-*b*][1,2,4]triazino[5,6-*b*]indole (**13**). Substituted α-aminoacetic acid **14** isolated from refluxing compound **10** with monochloroacetic acid in DMF. Decarboxylation of compound **14** by warming with aq. K_2CO_3 gave the compound **13** [**Scheme 5**].

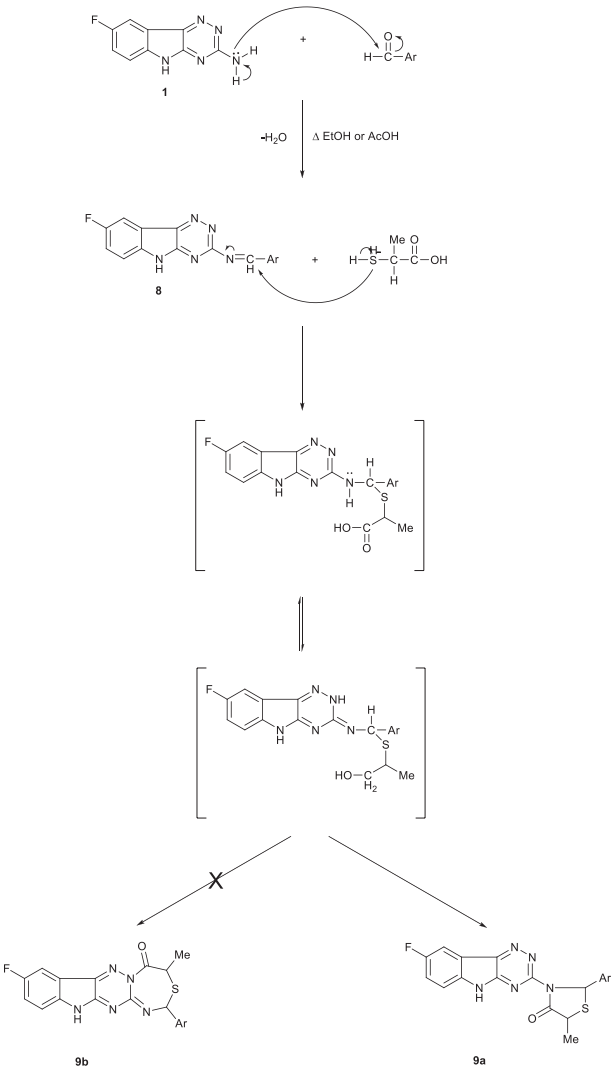
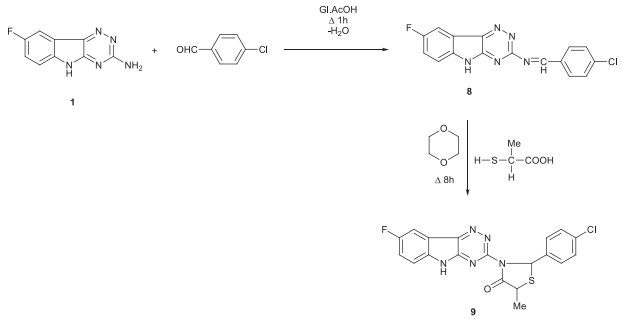


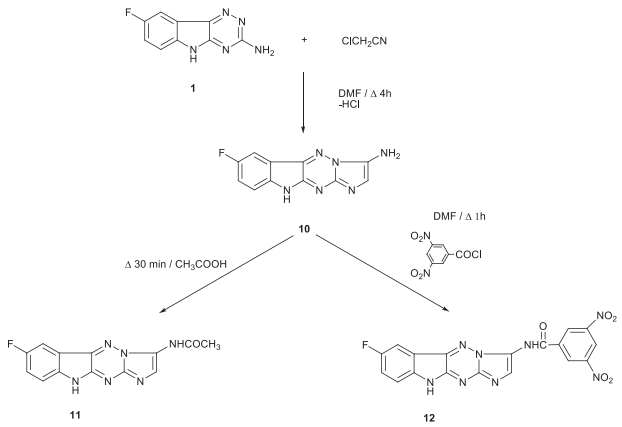
Figure 2: Formation of 9 from 1

Spectroscopic studies

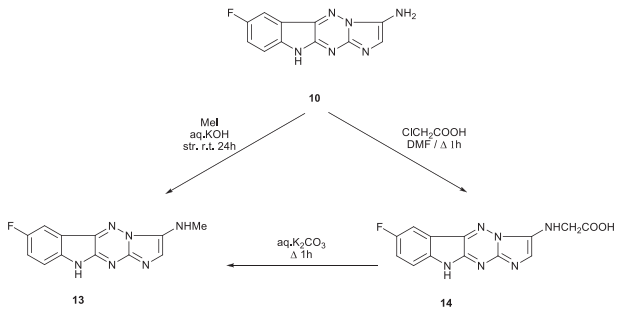
Structures of the new products were established by the help of correct elemental analysis and their various spectral data. Infrared (IR) absorption spectra of compounds **1, 2, 3, 4, 5, 6, and 7** showed γ at 3300–3100 for NH, in addition of N^5H of indole. Furthermore, IR spectra of **10, 11, 12, 13, and 14** recorded γ at 3150 cm^{-1} for NH group, with other NH of indole. On the other hand, compounds **2, 3, 6, 9, 11, 12, and 14** exhibited γ at 1720–1660 for C=O of CONH, COOH. All the synthesized compounds recorded γ at 1250 and 700 attribute to C-F group. Only the compounds **4** and **7** showed γ at 1200 and 2207 cm^{-1} for the presence of N=P and CN functional groups. ^1H nuclear magnetic resonance (NMR) spectra showed signals at δ 12~11 and 10.5 ppm



Scheme 3: Formation of compounds 8 and 9



Scheme 4: Formation of compounds 11 and 12 from 10



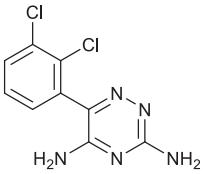
Scheme 5: Formation of compounds 13 and 14 from 10

for NHR and NHCO protons. The compounds **2, 5, 6, 7, 9**, and **11, 13,** and **14** showed a signal at 4~2 for aliphatic protons. Only the compounds **6** and **14** exhibit δ at 10.55 ppm attribute to COOH protons. All the synthesized new compounds showed δ at 7.88~6.99 ppm for the various aromatic protons. ^{1}H-NMR spectra of the starting materials **1** and **10** recorded δ at 8.55 and 3.5 attribute to NH and NH_2 protons. ^{13}C-NMR spectra of synthesized compounds give us a good indication about their structure, where the compounds **2, 3, 6, 9, 11, 12,** and **14** showed δ at 168–164 for C=O and the compounds **2, 5, 6, 7, 9**, **11, 13,** and **14** recorded δ at 60, 40, and 39 attribute to aliphatic carbons. All the new targets showed δ at 130–120 for aromatic carbons and at 145–140 for C-F carbons.

^{19}F-NMR spectra recorded δ at −120 ppm, while ^{1}H-NMR showed a coupling constant ^{1}J = 8.66 H_2 and ^{3}J = 6.55 Hz for the adjacent protons in aromatic ring of indole. Finally, mass fragmentation pattern of some compounds recorded the molecular ion peak with a base peak which differs according to a type of conjugation systems of the fused heteropolycyclic formed. A highly, molecular fragment refers to a degree of stability of the fluorinated compounds synthesized [**Figures 3 and 4**].

Anti-inflammatory evaluation

Lamotrigine is one of the important antiepileptic and mood-stabilizing drugs was detected in waste water, ground water, surface water, and drinking water.



Lamotrigine drug

Anti-inflammatory drug

Furthermore, lamotrigine drug used as a resistant to direct photodegradation as carbamazepine, is a frequently detected pharmaceutical in surface waters.[9]

Carrageenan-induced paw edema method in mice, adult albino male and female rats (weight 150 ~200 g) was used. Each rat was orally hydrated by 3 ml of water on the dry of an experiment to reduce the variability of edema responses.[10]

Indomethacin was used as a reference drug and the evaluated compounds were prepared as a suspension in 2% Tween 80 and a dose of 5 and 25 mg/kg were used for each tested compound. The method of carrageenan-induced paw edema of Winter *et al*[10a] was used. Each group consists of six animals administered intraperitoneally (i.p.). The induction of inflammation in the right kind paw was performed after 1 h of the drug administration by subcutaneous injection of 50 ml of one dose. After 3 h of inflammation induction, the rats sacrificed the two types of paws of each rat cut and weighted. The difference between

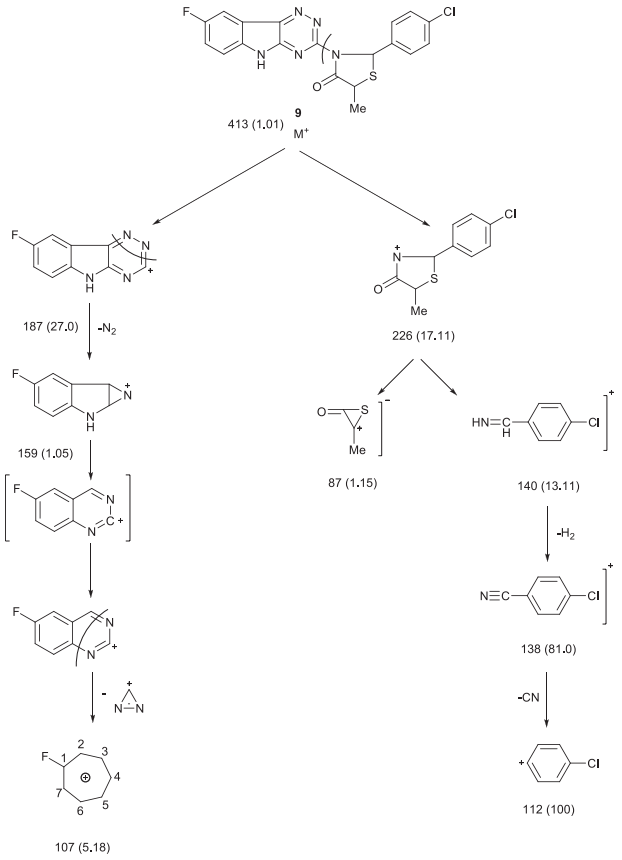


Figure 3: Mass fragmentation pattern of compound 9

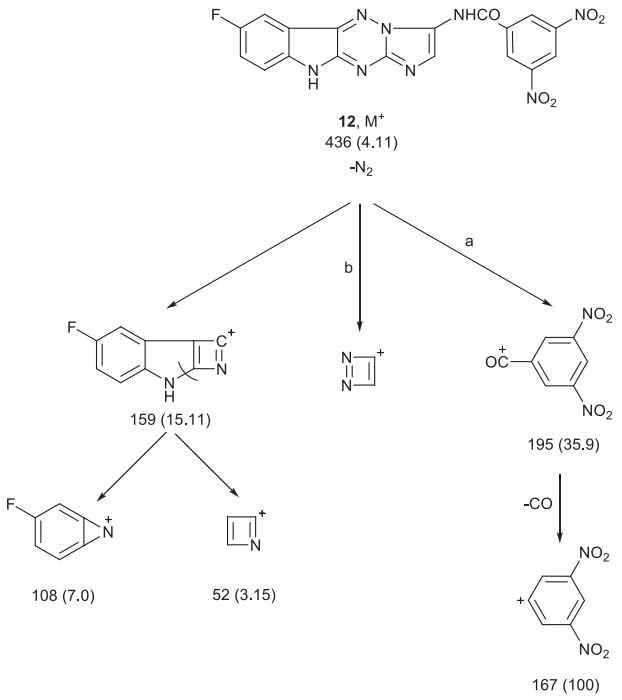


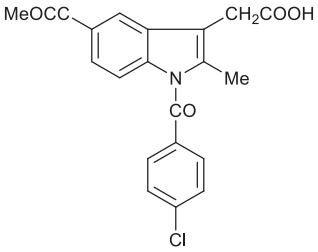
Figure 4: Mass fragmentation pattern of compound 12

the left and right kind of paw was taken as a measure of edema. The percentage of inflammation is calculated[11] according to the relation:

$$Inhibition = \frac{A - B}{A}$$

Where, A is the weight of paw edema of control.
B is the weight of paw edema of treated.

The effect of new fluorinated lamotrigine synthesized on carrageenan-induced[12] paw edema in rates anti-inflammatory activity, is shown in **Table 1**.



The standard Indomethacin drug used

From the results obtained [**Table 1**], we can conclude that:

1. Most of the tested compounds synthesized exhibit a high degree of anti-inflammatory activity which may be due to the presence of fluorine atom bonded to fused conjugated heteropolycyclic system.
2. Both the compounds **1 and 10** which contain fluorine atoms and an amino group form a type of bioconjugated systems, thereby increasing the electronegativities over all the systems which enhance both hydrophobic and distribution properties. This, highly affects the biological process.
3. The higher activity was in the order of **9 >1 >3 >12 >5 >13 >10 >4** at a lower concentrations (with different molecular weight) may be due to the presence a highly bioactive thiazolidin-4-one (**9**); NH_2 (**1**), 3,5-dinitrobenzoyl (**3**), (**2**), α-amino acetic acid (**5**) and methyl amine **13** bonded to 1,2,4-triazino[5,6-*b*]indoles and/or imidazo-1,2,4-triazino[5,6-*b*]indoles
4. A higher activity of compound **9** may be a type of combination between the thiazolidin-4-one and fluorine bonded to 1,2,4-triazino[5,6-b]indole, presence of thiazolidin-4-one enhances the biodynamic effect of 1,2,4-triazinoindole
5. Furthermore, both the compounds **3** and **12** exhibit a good degree of activity, may be the presence of arylnitro moiety bonded a fluorinated 1,2,4-triazino[5,6-*b*]indole moiety
6. A lower to the activity of compound **4** may induce to the activity role of P – atom through the stable P=N systems.

A good degree of activity for tested systems, in comparison with the standard used, may be caused by the electron-withdrawing fluorine atoms which have a higher degree of activity effects.[4b,4c,11-13]

Quantitative structure–activity relationship

The higher biological activities depend not only on the site of fluorination and the geometry of the conjugate carbanion found but also on the totally net electronegativity present over all the heterocyclic centers.

EXPERIMENTAL

The melting point recorded on Stuart scientific SMP3 (Bibby, UK) melting point apparatus and reported as uncorrected. A PerkinElmer (Lambda EZ-2101) double-beam spectrophotometer (190–1100 nm) used for recording the electronic spectra. A PerkinElmer model RXI-FT-IR 55,529 cm^{-1} used for recording the IR spectra. A Bruker Avance DPX 400 MHz using TMS as an internal standard for recording the $^{1}H/^{13}C/^{19}F$-NMR spectra in deuterated

Table 1: Effect of new fluorinated functionalized 1,2,4-triazino[5,6-*b*]indoles synthesized on carrageenan-induced paw edema in rats – anti-inflammatory activity

Compound no.	Dose µg/kg	Paw edema (g)±S.E.*	% inhibition
Control	0	0.66±0.05	0
Indomethacin	5	0.32±0.02	51.51
1	5	0.30±0.01	54.50
	25	0.2±0.01	60.01
3	5	0.30±0.05	50.51
	25	0.15±0.03	70.20
5	5	0.40±0.05	38.39
	25	0.32±0.05	50.51
9	5	0.31±0.05	80.05
	25	0.10±0.01	41.45
10	5	0.30±0.01	44.40
	25	0.20±0.01	54.51
12	5	0.21±0.02	51.50
	25	0.12±0.02	68.16
13	5	0.50±0.03	24.14
	25	0.36±0.03	45.45

*S.E.=Standard control±significant difference from the control values at $P < 0.05$

dimethyl sulfoxide (δ in ppm). AGC-MS-QP 1000 Ex model used for recording the mass spectra. Elemental analysis performed on Microanalytical Center of National Institute Center-Dokki, Cairo, Egypt.

3-AMINO-8-FLUORO-5H-1,2,4-TRIAZINO[5,6-B] INDOLE (1)[6]

A mixture of 5-fluoroisatin (0.01 mol) and aminoguanidine bicarbonate (0.01 mol) in abs. ElOH (100 ml) with a few of conc. HCl was refluxed for 4 h cooled. The solid obtained was filtered off, and crystallized for EtOH to give **1**, yield 70% m.p. >350°C. IR (γ cm^{-1}) = 3272, 3300, 3174 (NH, NH, NH_2), 3064 (aromatic CH), 1621 (deformation NH_2), 1594 (C=N), 1257 (C-F), 880, 810 (phenyl) 688 (C-F). ^{1}HNMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 8.38, 8.17 (d, d, 1H, C_9), 7,42 (d, 1H, C_7), 6.93 (s, 1H, C_6), 11.50 (s, 1H, N^5H), 3.57 (s, 2H, NH_2). ^{13}C-NMR (δ ppm), 162 (C_3-N), 147.8 (C_{4a}), 139.60 (C_{5a}), 110.8 (C_6), 120.11 (C_7), 132 (C_8-F), 122.3 (C_9), 118 (C_{9a}), 140.9 (C_{9b}). ^{1}F-NMR (δ ppm) −121. Analytical data calcd.: C, 53.20; H, 2.98; N, 34.47; F, 9.35% for $C_9H_6N_5F$ (203). Found: C, 53.01; H, 2.88; N, 34.39; F, 9.31%.

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

A mixture of **1** (0.01 mol) and glacial acetic acid (10 ml) was refluxed 30 min, cooled, and then poured onto ice. The produced solid was filtered off and crystallized from EtOH to give **2**, yield 77% m.p. 220–222°C. IR (γ cm^{-1}) = 3310, 3310, 3190 (NH, NH), 3060 (aromatic CH), 2880, 2718 (aliphatic CH), 1659 (C=O), 1611 (C=N) 1470 (deformation CH_3) 1388 (cyclic NCN), 1242 (C-F), 692 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 10.4 (s, 1H, NH), 8.88 (s, 1H, NH), 8.4–8.2 (d, d, 1H, C_9), 7.44 (d, 1H, C_7), 6.95 (s, 1H, C_6), 2.23 (s, 3H, CH_3). ^{13}C-NMR (δ ppm), 166 (C=O), 162 (C_3) 148 (C_{4a}), 140 (C_{5a}), 111 (C_6), 121 (C_7), 132 (C_8), 123 (C_9), 118.9 (C_{9a}), 140.8 (C_{9b}), 39.8 (CH_3). ^{1}F-NMR (δ ppm) −118. Analytical data calcd.: C, 53.88; H, 3.29; N, 28.56; F, 7.75% for $C_{11}H_8N_5FO$ (245). Found: C, 53.79; H, 3.19; N, 28.50; F, 7.71%.

3-(3',5'-Dinitrobenzoyl)amino-8-fluoro-5H-1,2,4-triazino[5,6-*b*]indole (3)

Equimolar amounts of **1** and 3,5-dinitrobenzoyl chloride in DMF (20 ml) was warmed 1 h, cooled, and then poured onto ice. The yielded solid was filtered off and crystallized from MeOH to give **3**. Yield 66 % m.p. 150–152°C. IR (γ cm^{-1}) = 3320, 3150 (NH, NH), 3059 (aromatic CH), 1690 (C=O), 1566 (C=N) 1530, 1350 (asymmetric and symmetric NO_2), 1243 (C-F), 916, 867 (Ph), 691 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 11.65 (s, 1H, N^5H), 10.55 (s, 1H, NHCO), 9.2–9.1 (d, d, 2H, aryl), 8.7–8.4 (d, d, 1H, C_9), 7.8–7.66 (s, 1H, C_8), 7.2–7.01 (s, 1H, C_6). ^{13}C-NMR (δ ppm), 164 (C=O), 156 (C=O), 148.7 (C_3), 140 (C_8-F), 138 (C_5), 111 (C_6), 121.39 (C_7), 127.59 (C_9), 119.92 (C_{9a}), 136 (C_{9b}), 132–127 (aromatic carbons). ^{1}F-NMR (δ ppm) −120 ppm. M/S (Int. %): 398 (M^{+1}, 1.09), 195 (13.5), 174 (18.1), 167 (100), 134 (73.10). Analytical data calcd.: C, 48.37; H, 2.03; N, 24.68; F, 4.78% for $C_{16}H_8N_7FO_5$ (397.28). Found: C, 48.17; H, 2.00; N, 24.53; F, 4.69%.

3-(Triphenylphosphinimino)-8-fluoro-5H-1,2,4-triazino[5,6-b]indole (4)

A mixture of **1** (0.01 mol) and triphenylphosphine (0.01 mol) in THF (50 ml) with few drops of piperidine was refluxed 2 h, cooled, and then poured onto ice. The resulted solid was filtered off and crystallized from THF to give **4**, yield 72% m.p. 265–267°C. IR (γ cm^{-1}) = 3067 (NH), 3051 (aromatic CH), 158 (C=N), 1333 (cyclic NCN), 1257 (C-F), 1142 (P=N), 925, 889, 820, 782, 752 (aromatic rings). 669 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 12.88 (s, 1H, N^5H), 7.01 (s, 1H, C_6), 7.66 (s, 1H, C_7), 8.41–8.2 (d, d, 1H, C_9). 7.2–7.6 (m,15H of PPh_3). ^{13}C-NMR (δ ppm), 166.70 (C_3), 162 (C_{4a}), 138.29 (C_{5a}), 112 (C_6), 121 (C_7), 132 (C_8), 122 (C_9), 118 (C_{9a}), 142 (C_{9b}), 141 (C-F). ^{1}F-NMR (δ ppm) −120 ppm. Analytical data calcd.: C, 69.97; H, 4.13; N, 15.11; F, 4.13% for $C_{27}H_{19}N_5FP$ (463). Found: C, 69.79; H, 4.11; N, 15.01; F, 4.01%.

3-(Methyl)amino-8-fluoro-5H-1,2,4-triazino [5,6-*b*] indole (5)

A mixture of **1** (0.01 mol) and MeI (0.01 mol) in aq. KOH (1%, 100 ml) was stirred at room temperature for 24 h then acidified with aq. HCl. The solid obtained was filtered off, and crystallized from EtOH to give **5**, yield 66%, m.p. >350°C. IR (γ cm^{-1}) = 3312, 3170 (NH), 3030 (aromatic CH), 2920 (aliphatic CH), 1590 (C=N), 1465 (deformation CH_3). 1370 (cyclic NCN), 1253 (C-F), 853, 805 (Ph), 679 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 12.11 (s, 1H, N^5H), 6.99 (s, 1H, C_6), 7.66 (s, 1H, C_7), 8.5–8.2 (d, d, 1H, C_9). 2.5 (s, 3H, NH), 1.5 (s, 3H, CH_3). ^{13}C-NMR (δ ppm), 161.91 (C_3), 148 (C_4), 139 (C_{5a}), 111 (C_6), 121 (C_7), 141 (C_8), 122.55 (C_9), 118.5 (C_{9a}), 139 (C_{9b}), 39.70 (Me). ^{1}F-NMR (δ ppm) −121 ppm. Analytical data calcd.: C, 55.30; H, 3.71; N, 32.24; F, 8.75% for $C_{10}H_8N_5F$ (217). Found: C, 55.21; H, 3.55; N, 32.14; F, 8.69%.

3-(Carboxymethyl)amino-8-fluoro-5H-1,2,4-triazino[5,6-*b*]indole (6)

A mixture of **1** (0.01 mol) and monochloroacetic acid (0.01 mol) in DMF (20 ml) was refluxed 1 h, cooled, and then poured onto ice. The solid produced was filtered off and crystallized from EtOH to give **6**, yield 62%, m.p. 215–216°C. IR (γ cm^{-1}) = 3500, 2890 (OH, NH, aromatic, aliphatic CH), 1691 (C=O), 1583 (C=N), 1478 (deformation CH_2), 1382 (cyclic NCN), 1250 (C-F), 904, 870 (Ph), 685 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 12.5 (s, 1H, N^5H), 11.3 (s, 1H, NH), 10.96 (s, 1H, OH), 6.99 (s, 1H, C_6), 7.55 (s, 1H, C_7), 8.5–8.2 (d, d, 1H, C_9). 4.55 (s, 2H, CH_2). ^{13}C-NMR (δ ppm), 164.19 (C=O), 161.81 (C_3), 149 (C_4), 140.1 (C_5), 111.56 (C_6), 121.01 (C_7), 139.9 (C-8), 122 (C_9), 119.29 (C_{9a}), 138.47 (C_{9b}), 40.0 (CH_2). ^{1}F-NMR (δ ppm) −120 ppm. Analytical data calcd.: C, 50.58; H, 3.09; N, 26.81; F, 7.27% for $C_{11}H_8N_5FO_2$ (261). Found: C, 50.39; H, 3.01; N, 26.69; F, 7.18%.

Decarboxylation of 6-formation of 5

A mixture of **6** (0.5 g) and aq. K_2CO_3 (10%, 50 ml) was warmed 1 h, cooled, and then neutralized by dil. HCl. The solid obtained was filtered off, and crystallized from EtOH to give **5**. Melting point and mixed melting gave >350°C.

3-(Cyanomethyl)amino-8-fluoro-5H-1,2,4-triazino [5,6-*b*]indole (7)

Equimolar amounts of **1** and chloroacetonitrile in DMF (20 ml) was warmed for 1 h, cooled, and then poured onto ice. The solid obtained was filtered off, and crystallized from dioxan to give **7**, yield 60 %, m.p. 290–292°C. IR (γ cm^{-1}) = 3200 (NH), 3171 (NH), 3050 (aromatic CH), 2980, 2880 (aliphatic CH), 2207 (C≡N), 1619 (C=N), 1479 (deformation CH_2), 1251 (C-F), 869, 813 (Ph). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 10.77 (s, 1H, N^5H), 7.45 (s, 1H, C_6), 8.3–8.1 (d, d, 1H, C_9). 3.55 (s, 1H, NH), 2.77 (s, 2H, CH_2). ^{13}C-NMR (δ ppm), 166 (C_3), 156 (C_4), 150 (C_5), 109.65 (C_6), 111.45 (C_7), 136.62 (C_8), 126.1 (C_9), 119.35 (C_{9a}), 135.41 (C_{9b}), 105.45 (CN), 40.12 (CH_3). ^{1}F-NMR (δ ppm) −121 ppm. Analytical data calcd.: C, 54.55; H, 2.91; N, 34.70; F, 7.84% for $C_{11}H_7N_6F$ (242). Found: C, 54.51; H, 2.80; N, 34.60; F, 7.79%.

Acidic hydrolysis of 7-formation of 5

A mixture of **7** (0.5 g) and dil. HCl (10%, 50 ml) was refluxed 1 h, cooled, and then neutralized with aq. K_2CO_3. The solid produced was filtered off, and crystallized from EtOH to give **5**, melting point and mixed melting point >350°C.

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

A mixture of **1** (0.01 mol) and 4-chlorobenzaldehyde (0.01 mol) in acetic acid (50 ml) refluxed 1 h, cooled, and then poured onto ice. The solid obtained, filtered off, and crystallized from EtOH to give **8**, yield 80% m.p. 215–217°C. IR (γ cm^{-1}) = 3190 (NH), 1616 (exo C=N), 1574 (endo C=N), 1481 (deformation CH=), 1242 (C-F), 693 (C-F), 645 (C-Cl). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 10.49 (s, 1H, N^5H), 8.3 (s, 1H, CH=), 8.7–8.66 (d, d, 2H, C-Cl), 8.2–8.1 (d, d, 1H, C_9), 6.89 (H, C_6), 7.42 (H, C_7), 6.8, 6.7 (2H, aromatic). ^{13}C-NMR (δ ppm), 164.23 (C_3), 140 (C_4), 133 (C_5), 109.34 (C_6), 119.49 (C_7), 136.66 (C_8), 119.33 (C_9), 119.43 (C_{9a}), 131.13 (C_{9b}), 133.64 (CH=N), 133 (C-Cl), 126 (aromatic). ^{1}F-NMR (δ ppm) −119 ppm. Analytical data calcd.: C, 59.07; H, 2.76; N, 21.50; F, 5.83; Cl, 10.88% for $C_{16}H_9N_5FCl$ (325). Found: C, 58.79; H, 2.70; N, 21.41; F, 5.75; Cl, 10.80%.

3-[2'-(4"Chlorophenyl)-4'-oxo-5'-methyl-5'H-thiazol-3'3yl]-8-fluoro-5H-1,2,4-triazino[5,6-*b*]indole (9)

A mixture of **8** (0.01 mol) and thiolactic acid (0.02 mol) in dioxin (100 ml) was refluxed 8 h, cooled, and then treated with aq. K_2CO_3 (10%). The solid produced was filtered off, and crystallized from dioxan to give **9**, yield 60%, m.p. 125–127°C. IR (γ cm^{-1}) = 3492 (OH), 3165 (NH), 3044 (aromatic CH), 1692 (C=O), 1615 (C=C), 1585 (C=N), 1453 (deformation Me), 1256 (C-F), 924, 889, 820 (aromatic ring) 761 (C-F), 690 (C-Cl), 668 (C-S-C). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 10.33 (s, 1H, N^5H), 6.88 (H, C_6), 7.42 (1H, C_7), 8.4–8.2 (d, d, 1H, C_9), 7.01–6.99 (d, d, 1H, C-Cl), 6.66 (2H, aromatic), 3.65 (N-CH-S), 3.55 (COCHS), 1.22 (s, 3H, Me). ^{13}C-NMR (δ ppm), 166.82 (C=O), 164.25 (C_3), 136.24 (C_4), 135.74 (C_5), 109.66 (C_6), 119.42 (C_7), 156.32 (C_8-F), 125.72 (C_9), 119.13 (C_{9a}), 136.65 (C_{9b}), 131.56 (C-Cl), 125.75 (C aromatic), 122.72 (NCH-Ar), 66 (N-CH-Ar), 65 (COCH-S), 39.45 (Me). ^{1}F-NMR (δ ppm) −119 ppm. M/S (Int. %): 413 (1.01), 226 (17.11), 187 (27.0), 159 (1.05), 140 (13.11), 138 (81.0), 112 (100), 107 (5.18). Analytical data calcd.: C, 55.14; H, 3.17; N, 16.92; F, 4.59; Cl, 8.57; S, 7.74% for $C_{19}H_{13}N_5FClSO$ (413). Found: C, 55.01; H, 3.12; N, 16.88; F, 4.39; Cl, 8.39; S, 7.63%.

3-Amino-7-fluoro-10H-imidazo[3,2-*b*][1,2,4] triazino[5,6-*b*]indole (10)

A mixture of **1** (0.01 mol) and chloroacetonitrile (0.01 mol) in DMF (50 ml), was refluxed 4–6 h, cooled, and then poured onto ice. The solid obtained was filtered off, and crystallized from dioxin to give **10**, yield 70%, m.p. 220–222°C. IR (γ cm^{-1}) = 3338, 3187 (NH, NH_2), 1628 (deformation NH_2), 1616 (C=N), 1250 (C-F), 889, 809 (Ph), 726 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 10.4 (s, 1H, N^5H), 6.93 (1H, C_6), 7.45 (1H, C_7), 8.4–8.2 (d, d, 1H, C_9), 5.5 (s, 1H, CH= imidazo), 3.5 (s, 2H, NH_2). ^{13}C-NMR (δ ppm), 164.24 (N-C-C imidazo), 164.44 (C_3), 148.54 (C_4), 136.67 (C_5), 111.82 (C_6), 116.90 (C_7), 134.76 (C_8-F), 123 (C_9), 116 (C_{9a}), 141.01 (C_{9b}). ^{1}F-NMR (δ ppm) −120 ppm. Analytical data calcd.: C, 54.55; H, 2.91; N, 34.70; F, 7.48% for $C_{11}H_7N_6F$ (242). Found: C, 54.39; H, 2.88; N, 34.65; F, 7.40%.

3-(Acetomido)-7-fluoro-*10H*-imidazo[3,2-*b*][1,2,4] triazino[5,6-*b*]indole (11)

A mixture of **10** (0.01 mol) and acetic acid (10 ml) was warmed 30 min, cooled, and then poured onto ice. The produced solid was filtered off and crystallized from EtOH to give **11**, yield 55%, m.p. <350°C. IR (γ cm^{-1}) = 3200 (NH), 3150 (NH), 1734 (C=O), 1605 (C=N), 1476 1 (deformation CH_3), 1366 (cyclic NCN), 1216 (C-F), 889, 814 (Ph), 726 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 11.55 (s, 1H, N^5H), 8.4–8.2 (d, d, 1H, C_9), 6.95 (1H, C_6), 7.48 (1H, C_7), 5.88 (CH imidazo), 5.5 (s, 1H, NHCO), 2.55 (s, 3H, CH_3CO). ^{13}C-NMR (δ ppm), 166.1 (C=O), 148 (CH=N imidazo) 166.5 (C_3), 147.8 (C_4), 139.11 (C_5), 110.66 (C_6), 126 (C_7), 138.55 (C_8-F), 122.3 (C_9), 118.8 (C_{9a}), 141.8 (C_{9b}), 39.48 (CH_3). ^{1}F-NMR (δ ppm) −120 ppm. Analytical data calcd.: C, 54.93; H, 3.19; N, 29.57; F, 6.68% for $C_{13}H_9N_6FO$ (284). Found: C, 54.89; H, 3.11; N, 29.45; F, 6.55%.

3-[3',5'-Dinitrobenzoyl]amino-7-fluoro-10H-imidazo[3,2-*b*][1,2,4]triazino[5,6-*b*]indole (12)

A mixture of **10** (0.01 mol) and 3,5-dinitrobenzoyl chloride (0.01 mol) in DMF (10 ml) was warmed 1 h, cooled, and then poured onto ice. The solid resulted was

filtered off, and crystallized from MeOH to give **12**, yield 70%; m.p. 150–152°C. IR (γ cm^{-1}) = 3300 (NH), 3096 (NH), 1722 (C=O), 1616 (C=N), 1590 (C=N), 1540, 1344 (deformation asymmetric and symmetric NO_2), 1265 (C-F), 908, 816 (Ph), 724 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 11.35 (s, 1H, N^5H), 6.95 (s, 1H, C_6), 7.40 (1H, C_7), 8.3–8.2 (d, d, 1H, C_9), 9.2–9.1 (d, d, 1H, CH-NO_2), 6.988, 6.985 (2H, aromatic), 5.88 (s, CH = imidazo), 5.5 (s, 1H, NHCO). ^{13}C-NMR (δ ppm), 164.43 (C=O), 162.11 (N-CH_2 = imidazo), 164.11 (C_3), 161.60 (C_4), 134.77 (C_5), 118.05 (C_6), 122.11 (C_7), 148.33 (C_8), 121.65 (C_9), 117 (C_{9a}), 135.29 (C_{9b}), 148.24 (N-C=NH imidazol), 128.81 (C-NO_2), 115.42, 111.91 (aromatic). ^{1}F-NMR (δ ppm) −120 ppm. M/S (Int. %.): M^+ 436 (4.11), 195 (35.9), 167(100), 159 (15.11), 108 (7.0), 52 (3.15). Analytical data calcd.: C, 49.55; H, 2.08; N, 25.68; F, 4.35% for $C_{18}H_9N_8FO_5$ (436). Found: C, 49.49; H, 2.00; N, 25.53; F, 4.25%.

3-Methylamino-7-fluoro-10H-imidazo[3,2-*b*][1,2,4] triazino[5,6-*b*]indole (13)

A mixture of **10** (0.01 mol) and MeI (0.01 mol) in aq. KOH (1%, 100 ml) was stirred at room temperature for 24 h, then acidified with aq. HCl. The yielded solid was filtered off and crystallized from MeOH to give **13**, yielded 60%, m.p.< 350°C. IR (γ cm^{-1}) = 3300, 3181 (NH, NH), 2928 (aliphatic 1H), 1595 (C=N), 1472 (deformation CH_3), 1262 (C-F), 918, 873, 811 (Ph). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 11.11 (s, 1H, N^5H), 8.3–8.13 (d, d, 1H, C_9), 8.00 (s, 1H, NH-Me), 7.21 (1H, C_6), 7.99 (1H, C_7), 5.66 (CH= imidazo), 3.5 (s, 3H, MeN). ^{13}C-NMR (δ ppm), 162.11 (C_3), 161.1 (C_5), 133.88 (C_6), 120.11 (C_7), 146.55 (C_8), 121.16 (C_9), 118.3 (C_{9a}), 135.89 (C_{9b}), 148.11 (C_{10} imidazo), 162.11 (N-CH = imidazo), 39.44 (Me). ^{1}F-NMR (δ ppm) −120 ppm. Analytical data calcd.: C, 52.25; H, 3.54; N, 32.80; F, 7.41% for $C_{12}H_9N_6F$ (256). Found: C, 52.11; H, 3.50; N, 32.70; F, 7.31%.

3-(Carboxymethyl)amino-7-fluoro-*10H*-imidazo[3,2-b][1,2,4]triazino[5,6-*b*]indole (14)

Equimolar amounts of **10** and monochloroacetic acid in DMF (20 ml) refluxed 1 h, cooled, and then poured onto ice. The solid yielded, filtered off, and crystallized from EtOH to give **14**, yield 58% m.p.< 350°C. IR (γ cm^{-1}) = 3480 (OH) 3300, 3180 (NH), 3040 (aromatic CH), 2970, 2880 (aliphatic CH), 1710 (C=O), 1610, 1580 (C=N)m 1480, 1440 (deformation CH_2), 1330 (cyclic NCN), 1250 (C-F), 880, 840, 810 (aromatic ring). 710 (C-F). ^{1}H-NMR (δ ppm) = d, d 8.66 (^{3}J of H-C_α-F), 6.55 (^{1}J of H-C_β-F), 12.11 (s, 1H, N^5H), 10.88 (s, 1H, OH), 8.55 (s, 1H, NH), 8.3–8.11 (d, d, 1H, C_9), 7.72 (1H, C_6), 7.9 (1H, C_7), 5.66 (s, 1H, C = imidazo), 3.56 (s, 2H, CH_2). ^{13}C-NMR (δ ppm), 162.88 (C=O), 162.11 (N-CH= imidazo), 161.8 (C_3), 149.5 (C_4), 136.15 (C_5), 120.11 (C_6), 132.9 (C_7), 142.18 (C_8), 122.11 (C_9), 118.55 (C_{9a}), 141.01 (C_{9b}), 1485 (N-C-N imidazo), 39.27 (CH_2). ^{1}F-NMR (δ ppm) −120 ppm. Analytical data calcd.: C, 52.0; H, 3.0; N, 27.29; F, 6.33% for $C_{13}H_9N_6FO_2$ (300). Found: C, 51.89; H, 2.85; N, 27.12; F, 6.28%.

Decarboxylation of 14-formation 13

Compound **14** (0.5 g) and aq. K_2CO_3 (10%, 50 ml) warmed 1 h, cooled, and then treated with dil. HCl. The produced solid filtered off and crystallized from EtOH to give **13**. Melting point and mixed melting point gave > 350°C.

CONCLUSION

The present work reports the synthesis of new fluorine compounds bonded 1,2,4-triazino[5,6-b]indole, bearing and/or containing other heterocyclic nitrogen moieties with various functional groups. The results obtained indicate that the presence of both F, NH_2, NO_2, and thiazolidin-4-one enhances the anti-inflammatory effect in comparison with indomethacin as standard drug. This work led to highly control on the paw edema effect in the future.

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REFERENCES

[1] Joshi, K., Pathak, V., Jain, S. *Fluorine-containing Bioactive Heterocycles: Part I. Synthesis and Antibacterial, Fungicidal and Antiviral Activities of Some New Fluorine-containing 3-Dialkylaminoethylthio-5-Morpholinomethyl (1, 2, 4) Triazino (5, 6-b) Indoles and 3-(2-(5-Benzylidene-4-Thiazolidinone) Diazo) Indol-2-Ones*, Vol. 12. Chemischer Informationsdienst, Bruxelles, **1981**.

[2] Abdel-Rahman, R.M., Makki, M.S.I., Bawazir, W.A.M. Synthesis of fluorine heterocyclic nitrogen systems derived from sulfa drugs as photochemical probe agents for inhibition of vitiligo disease-part II, *J. Chem.*, **2010**, *7*, S93–S102.

[3] Mizutani, M., Yoshida, R., Sanemitsu, Y. Effects of diets on the concentration of fructose-2, 6-bisphosphate in rat liver, *Agric. Biol. Chem*., **1987**, *51*, 3177–3178.

[4] a) Makki, M., Bakhotmah, D.A., Abdel-Rahman, R.M., Aqlan, F.M. New route to synthesize fluorine substituted lamotrigine drug analogues as an anti-inflammatory, *Agent Curr. Org. Synth.*, **2018**, *15*, 116–125; b) Makki, M.S., Abdel-Rahman, R.M., Alharbi, A.S. Synthetic approach for novel fluorine substituted α-aminophosphonic acids containing 1, 2, 4-triazin-5-one moiety as antioxidant agents, *Int. J. Org. Chem.*, **2018**, *8*, 1; c) Mohammed, S.T.M., Reda, M.A.R., Salim, A.A. Synthesis and anti-inflammatory effect of some more new fluorinated 3-substituted amino/3,5-diamino-1,2,4-triazine derivatives as lamotrigine analogs, *Curr. Org. Synth.*, **2019**, *16*, 165–172.

[5] a) Makki, M.S., Abdel-Rahman, R.M., Alharbi, A.S. Synthesis and anti-inflammatory effect of some more new fluorinated 3- substituted amino/3,5-diamino-1,2,4-triazine derivatives as lamotrigine analogs,

Curr. Org. Synth., **2019**, *16*, 165–172; b) Makki, M., Bakhotmah, D.A., Abdel-Rahman, R.M., Aqlan, F.M. New route to synthesize fluorine substituted lamotrigine drug analogues as an anti-inflammatory agent. *Curr. Org. Synth.*, **2018**, *15*, 116-125.

[6] Al-Romaizan, A.N., Makki, M.S., Abdel-Rahman, R.M. Synthesis of new fluorine/phosphorus substituted 6-(2'-amino phenyl)-3-thioxo-1,2,4-triazin-5(2H, 4H)one and their related alkylated systems as molluscicidal agent as against the snails responsible for bilharziasis diseases, *Int. J. Org. Chem*., **2014**, *4*, 154–168.

[7] Abdel-Rahman, R. Chemoselective heterocyclization and pharmacological activities of new heterocycles--a review. Part V-Synthesis of biocidal 4-thiazolidinones derivatives, *Boll. Chim. Farm.*, **2001**, *140*, 401–410.

[8] Tomchin, A.B., Uryupov, O.Y., Smirnov, A. Thiourea and thiosemicarbazide derivatives: Structure, transformations, and pharmacological activity. Part III. Antihypoxic and antiinflammatory activity of 1,2,4-triazino[6,5-b]indole derivatives, *Pharm. Chem. J*., **1997**, *31*, 632–637.

[9] Rees, R.W., Russell, P.B., Foell, T.J., Bright, R.E. Antimalarial activities of some 3, 5-diamino-as-triazine derivatives, *J. Med. Chem.*, **1972**, *15*, 859–861.

[10] a) Winter, C.A., Risley, E.A., Nuss, G.W. Anti-inflammatory and antipyretic activities of indomethacin, 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, *J. Pharmacol. Exp. Ther*., **1963**, *141*, 369–376; b) Hitchings, G., Maggiolo, A., Russell, P., Werff, H.V., Rollo, I. Diamino-AS-triazines as inhibitors of lactic acid bacteria and plasmodia, *J. Am. Chem. Soc*., **1952**, *74*, 3200–3201.

[11] Dalvi, V.H., Rossky, P.J. Molecular origins of fluorocarbon hydrophobicity, *Proc. Natl. Acad. Sci*., **2010**, *107*, 13603–13607.

[12] Dolain, C., Patwa, A., Godeau, G., Barthélémy, P. Nucleic acid based fluorinated derivatives: New tools for biomedical applications, *Appl. Sci*., **2012**, *2*, 245–259.

[13] Abdel-Rahman, R.M., Al-Footy, K.O., Aqlan, F. Synthesis and antiinflammatory evaluation of some more new 1,2,4-triazolo[3,4-b] thiadiazoles as an antimicrobial agent-part-I, *Int. J. Chem. Tech. Res*., **2011**, *3*, 423–434.

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