

Synthesis and Antiinflammatory Evaluation of some more New 1,2,4-Triazolo[3,4-b]Thiadiazoles as an Antimicrobial agent:Part-I

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Abstract: Some of the new 1,2,4-triazolothiadiazole derivatives (2-9) have been synthesized starting from the interaction between 4-amino-3-(pyrid-4yl)-5- mercapto-1,2,4-triazole(1) and α , α,β -bifunctional compounds, such as tri ethylphosphite, trifluoroacetamide, cyanamide, isothiocyanate, carbon disulfide and /or fluorinated aromatic aldehydes in different conditions. The new semi-drugs 5-substituted amino-4-amino-3-(pyrid-4y)1,2,4-triazoles(10a,10b) were also obtained from treatment of compound1 with 4-fluoroaniline and sulfa-drug as sulfathiazole. Structure of the products have been established on the basis of their elemental analysis and spectral (UV, IR, ^1H NAR, ^{13}C nmr and mass) data. The novel molecules synthesized were evaluated for their anti-inflammatory and antimicrobial behavior in comparison with Indomethacin (Anti-inflammatory), Nalidexic acid (bacteria) and Nystain (fungi) as antibiotics, Where the compounds 3,7b and 9exhibited higher activities .

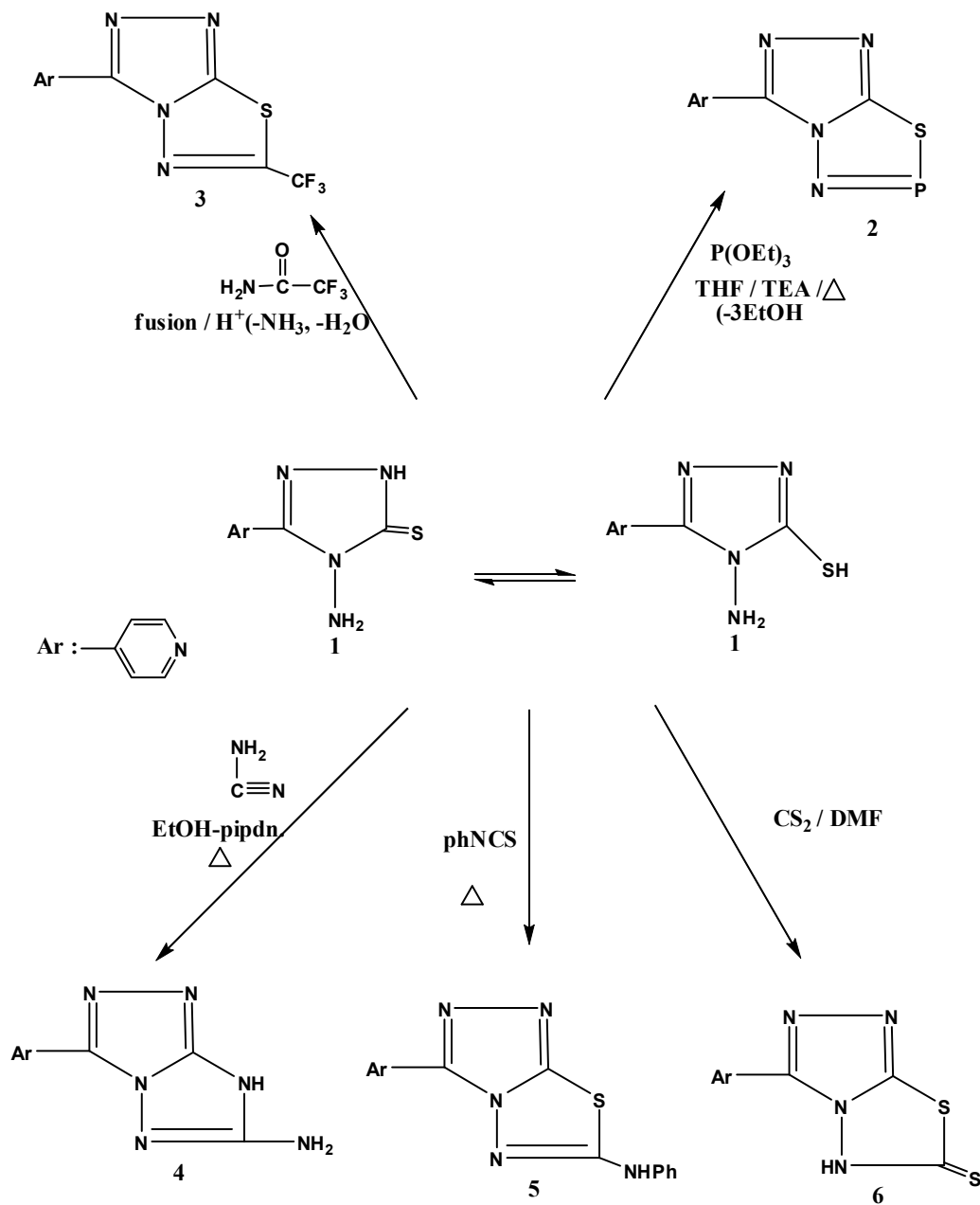
Key Words: Synthesis, Fused Triazolothiadiazoles, pharmacological properties.

Intoduction:

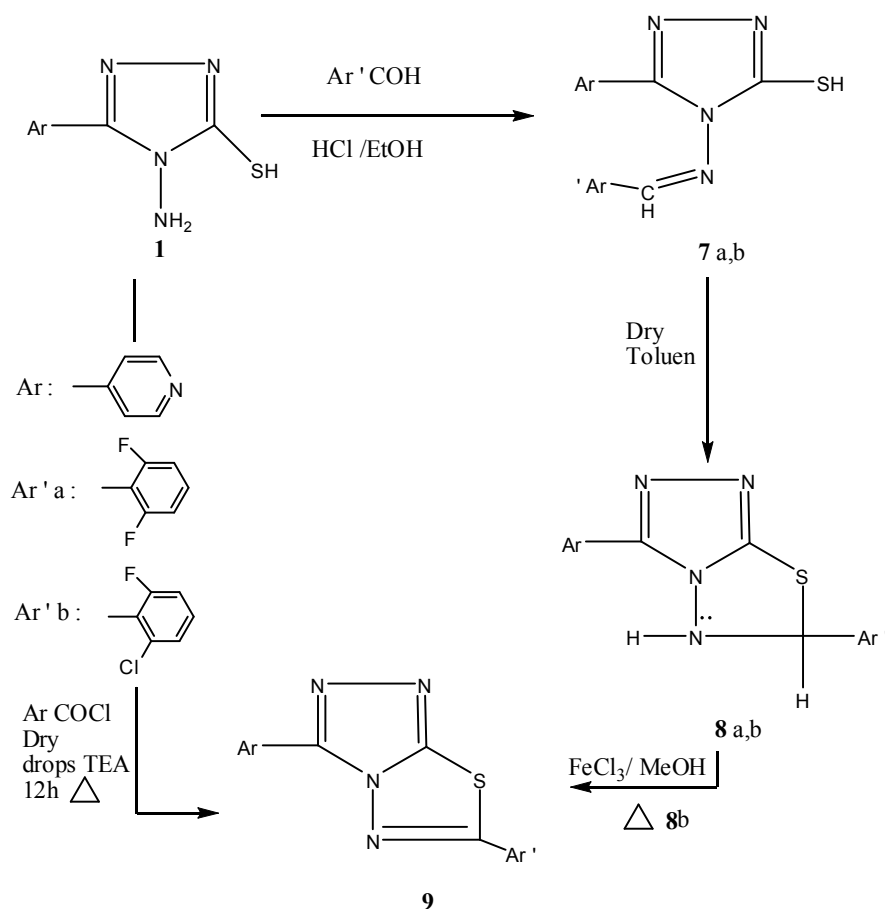
Recently, a large number of heterocyclic systems containing 1,2,4-triazoles and 1,3,4-thiazoles have been synthesized as selective cytotoxicity with effects on immunocompetent cells¹. Some fused 1,2,4-triazoles derivatives has shown showed pharmacological properties as lipophilicity, anticancer and antimicrobial agents².

Currently available non-steroidal anti-inflammatory drugs like ibuprofen, when connected with fused triazole thiadiazines, showed a wide spectrum of pharmacological activities as anti-inflammatory, analgesic, ulcergoenic, lipid peroxidation, antibacterial and antifungal agents³. 1,2,4-triazolothiadiazines containing 6-chloropyridin-3-yl methyl moiety exhibited an insecticidal activity⁴. Similarly As well as Triazolothiadiazoles were used as competitive inhibitors of urease enzymes⁵. In addition, bis-triazolothiadiazoles have been reported to possess anticancer activity against a panel of 60 cell lines derived from seven cancer types namely, lung, colon, melanoma, renal, ovarian, CNC and leukemia⁶. Prompted by these observations and in continuation of our search for bio-active heterocyclic⁷⁻¹⁰, we

designed the synthesis novel fused 1,2,4-triazolothiadiazole derivatives starting from 4-amino-3-(pyrid-4yl)-5-mercapto-1,2,4-triazole (**1**). The synthesis, characterization and the results of anti-inflammatory and / or antimicrobial activities screening studies of the newly synthesized compounds are have seen presented in this paper [Schemes 1-2].



Scheme 1



Scheme 2

Materials and Methods:

Melting points were determined in an electrothermal Bibby Stuart Scientific melting point SMP (US). The IR spectra recorded for KBr discs on a Perkin Lemer Spectrum RXI FT-IR systems No. 55529. ¹H/¹³C-NMR were determined for solution in deaterated DMSO with a Bruker NMR Advance DPX 400 MH using

TMS as an internal standard solvent. Mass spectra were measured on a GCMS-Q 1000 Ex spectrometer. Electronic absorption spectra were recorded in DMF on Shimadzu UV and visible 3101 PC spectrophotomer. Microanalyses (C. H. N. S elemental) were performed by the Microanalyses center of Cairo University, Egypt. The anti-inflammatory and antimicrobial evaluation were carried out in Department of pharmaceutical Microbiology.National Center for Radiation Research and Technology. Nasr City, Egypt.

Compound 1 was prepared according to the reported method¹¹ by direct hydrazinolysis of 4-C₅H₄N-CONHNHCS₂K.

(1)UV (λ_{\max}): 317 nm , IR: 3000-2342 and 2000-1720 cm⁻¹ (each b. superimposed NH₂ with SH), 1560 (C=N). 1330 (NCS), 1120 (C-S), 820, 790 cm⁻¹ (pyridine CH); m/z (Int.): 193 [M-46 (H₂CS, 147 (100)], 106 (57.1), 91 (45-10), 78 (70.0),64(31.15),51(65.0),44(100),40(18.61).

Synthesis of 3-(pyrid-4-yl)-1,2,4-triazolo[3,4-c] [1,2,4,5]thiadiazaphosphole (2)

Equimolar mixture of compound 1 and triethylphosphite in THF (20 mL) with drops of TEA was refluxed for 2h. cooled. The formed solid was filtered off and crystallized to give 2 (Table 1).

UV (λ_{\max}): 374 nm IR: 3010 cm⁻¹ , 1399 cm⁻¹ (aromatic CH and P=N), 1588, 1520 cm⁻¹ (C=N), 900,

850 cm^{-1} (pyridine CH) m/z (Int.%): 221(M^+ , 1.1%), 207(8.5), 192(32.8), 146(62.11), 104(20.11), 106(68), 78(95), 44(100), 40 (16.79).

Synthesis of 3-(pyrid-4-yl)-6-trifluoromethyl-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole (3)

Equimolar amounts of compound **1** and trifluoroacetamide were fused at 100-120°C for 30 min. and treated with methanol. The yielded solid was filtered off and crystallized to give **3** (Table 1).

UV (λ_{max}): 382 & 316 nm IR: 1601, 1552 (C=N of thiazole & C=N of triazole), 1206 (C-S), 1146, 1030 and 731 cm^{-1} (3C-F) m/z (Int.): 240(M^+ -32, 10.11), 227(5.0), 202(2.00), 146(2.15), 119(10.10), 78(1.2), 44(100), 40(16.35).

Synthetic of 3-(pyrid-4-yl) 6-amino-7H-1,2,4-triazolo[4,3-b][1,2,4]triazole (4)

A mixture of compound **1** (0.01 mol) and cyanamide (0.01 mol) in absolute ethanol (50 mL) with a few drops of piperidine (0.5 mL) were refluxed for 8h, cooled. The Produced solid was filtered off and crystallized to give **4** (Table 1).

IR: 3445 and 3157 cm^{-1} (NH_2 & NH), 1604, 1569 (2C=N), 1214 (C-N), and 824, 734 cm^{-1} (p-substituted pyridine) $^1\text{H NMR}(\delta)$: 5.87(τ , 2H, NH_2), 7.81, 8.03 (each τ , 2H, CH-3 & 5 pyridine), 8.77, 8.81 (each τ , 2H, CH-2, 6 pyridine) and at 13.64 ppm (τ , 1H, NH of 1,2,4-triazole). $^{13}\text{C nmr}(\delta)$: 167.68 (NH-C-NH₂), 150.84 (C₂-1,2,4-triazole), 148 (C₃-1,2,4-triazole), 135 (C₄ of pyridine), 121.16 (C₃, C₅ of pyridine), 150.11, 147.39 (C₂, C₆ of pyridine).

Synthesis of 3-(pyrid-4-yl)-6-phenylamino-1,2,4-triazolo[4,3-b][1,3,4] thiadiazole(5)

Equimolar mixture of compound **1** and phenyl isothiocyanate in DMF (50 mL) was refluxed for 4h, cooled, and then poured onto ice. The resultant solid was filtered off and crystallized to give **5** (Table 1).

UV (λ_{max}): 266 nm, IR: 3010-2700 cm^{-1} (the interaction between the sulfur atom and NH of thiadiazole), 1620, 1550 (2C=N), 1350 (cyclic NCS), 1150 (C-S), and 800, 740 cm^{-1} (aromatic CH). $^1\text{H NMR}(\delta)$: 13.98(τ , 1H, NH-Ph), 8.83, 8.77(τ , 2H of pyridine), 7.95, 7.85(τ , 2H of pyridine), 7.39-6.94(m, 4H, aromatic protons) m/z (Int.%) at 298(281.8, 18.00%), 238(4.50), 207(40.2), 203(2.1), 167(5.0), 78(2.2), 44(100), 40(18.91).

Synthetic of 6-thioxo-3-(pyridin-4-yl)-5H-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole (6)

A mixture of compound **1** (0.01 mol) and CS₂ (0.02 mol) in DMF (100 mL) was refluxed for 6h then it was cooled, and then poured onto ice. The yielded solid was filtered off and crystallized to give **6** (Table 1).

UV (λ_{max}): 318 nm IR: 2788 cm^{-1} (SH), 1555 (C=N), 1320 (cyclic NCS), 1239 (C=S), 1028 (C-S), and 828, 744 cm^{-1} (pyridine CH)

Preparation of Schiff's base 7a,b

Equimolar mixture of compound **1** and 2,6-difluorobenzaldehyde and/or 2-chloro-6-fluorobenzaldehyde in ethanol (100 mL) with a few drops conc. HCl (0.05 mL) was Refluxed for 1h, cooled, The produced solid was filtered off and crystallized to give **7a** and/or **7b** respectively (Table 1).

7b: λ_{max} 350 and 277 nm IR: 3010 and 2890 cm^{-1} (aromatic & aliphatic CH), 2600- 2450 cm^{-1} (**b**, S-H) with 1597.94 (C=N), 1484, 1426 (deformation of CH=N), 1251 (C-F), 1207 (C-S) and 830, 780 cm^{-1} (aromatic CH) and 720.81, 695.38 cm^{-1} (C-Cl, C-F) $^1\text{H NMR}(\delta)$: 10.47(τ , 1H, SH), 8.71(τ , 1H, CH=N), 7.91, 7.65, 7.56, 7.53(m, 4H, of pyridine), 7.52, 7.47, 7.45 (m, 3H, of aryl protons) m/z (Int.%) : 333(1.50), 281(20.1), 253(2.01), 207(50.88), 162(15.15), 142(3.12), 78(32.13), 44(100), 40(30.80).

Internal cyclization of 7 –Formation of 6,7-dihydro-3-(pyrid-4-yl)-6-aryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole(8a,b)

Compounds **7a** and/or **7b** (0.2 g) in dry toluene (50 mL) was refluxed for 12h, cooled after that addition petroleum ether (60-80) The yielded solid was filtered off and crystallized to give **8a** and/or **8b** respectively (Table 1).

8b: λ_{\max} 354nm, $^1\text{H NMR}(\delta)$: 10.60(τ , 1H, NH, disappeared in D_2O exchange), 8.73(τ , 1H, CH=N), 7.93 (δ , 2H, pyridine), 7.66, 7.50(τ , 2H, pyridine), 7.55, 7.47 and 7.46 ppm (each τ , 3H, of aromatic aryl protons) m/z (Int.%) : 333(2.15), 287(4.0), 253(5.90), 207(34.1), 129(5.4), 78(1.1), 44(100), 40(24.94).

Oxidation of 8b- Formation of triazolothiazole 9

Compound **8b** (0.2 g) and FeCl_3 (0.25 g) in methanol (50 mL) were refluxed 4h, filtered while hot. The filtered obtained was concentrated. The obtained solid was filtered off and crystallized to give **9** (Table 1).

UV (λ_{\max}): 285 nm IR: 1602, 1554(2C=N), 1362(cyclic NCS), 1216(C-F), 933, 823(aromatic CH) and 732.92, 686.41 cm^{-1} (C-Cl, C-F) $^1\text{H NMR}(\delta)$: 8.8, 8.78, 8.5, and 8.3(pyridine protons), 7.65, 7.51 and 7.45 ppm (aromatic protons), ^{13}C nmr (δ): 172.01(C_1 -F), 115.98(C_2 -benzen), 121.6(C_3 -benzene), 118.54(C_4 -benzen), 135.23(C_5 -Cl), 126.64(C_6 -benzen), 50(C_7 thiadiazol-5-yl), 149.92(C_3 -triazole) 146.72(C_5 -triazole), 121.88, 121.15(C_2 & C_6 of pyridine), 150.22, 150.43(C_3 & C_5 of pyridine) m/z (Int.%) : 331(2.0), 287(1.2), 242(100), 215(20.0), 138(5.5), 78(1.15), 44(27.80), 40(6.58).

Heterocyclization of 1- Formation of 9

A mixture of compound **1** (0.01 mol) and 2,6-difluorobenzoyl chloride (0.01 mol) in dry benzene with a few drops of TEA, was refluxed for 12h, and then cooled. The solid was filtered off and crystallized. The Melting point and mixed melting point gave no depression.

Formation semi-drug 4-amino-5-arylamino-3-(pyrid-4-yl)-1,2,4-triazoles (10a,b)

Equimolar mixture of compound **1** and 4-fluoroaniline or sulfathiazole in DMF- ethanol (1:1, 100 ml), was refluxed for 4h, cooled, and then poured onto ice. The produced solid was filtered off and crystallized to give **10a** and /or **10b** respectively (Table 1).

10a: UV (λ_{\max}): 374 nm IR: 3250, 3130 cm^{-1} (NH_2 , NH), 16010, 1585(C=N), 1250(C-F), 830, 780(aromatic CH, pyridine CH) and 705 cm^{-1} (C-F) $^1\text{H NMR}(\delta)$: 5.87(τ , 2H, NH_2), 7.2, 7.4(each τ , 4H, aromatic protons), 7.82, 8.041(each τ , 2H of pyridine), 8.77, 8.81(each τ , 2H of pyridine), and at 14.22 ppm (NH aryl protons)

^{13}C nm(δ): 158(C_1 of C-F), 115.13, 114.99(C_2 & C_3 of aryl), 119.58, 119.99(C_4 & C_5 of aryl), 132.99(C_6 of aryl), 147.36(C_3 & C_5 of triazole), 129.75, 121.63, 150.82, 150.04 ppm (carbons of pyridine) m/z (Int.%) at : 270(5.5), 253(5.21), 226(4.21), 207(37.71), 165(5.8), 103(4.85), 78(2.11), 44(100), 40(12.18).

Biocidal Evaluation:

Recently, much attention has been focused on fused heterobicyclic nitrogen systems especially containing 1,2,4-triazole and 1,3,4-thiadiazle moieties¹⁻¹¹. In view of these facts, the aim of this work is to obtain the new

fluorine compounds containing these systems it is an attempt to enhance the antimicrobial and anti-inflammatory activities.

A- Antimicrobial activity: The newly prepared compounds were screened for their antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* (-ve) bacteria: *Staphylococcus aureus* as (+ve) bacterial, in addition, *Candida albicans* as fungi by applied standard method¹² DMF was used as solvent and Nalidexic acid and Nystatin were used as reference drugs for bacteria and fungi. The inhibition zone and MIC of the screening reported in Table 2.

B- Anti-inflammatory activity: The compounds tested were evaluated via carrageenan-induced paw edema method^{13, 14} with reference to drug indomethacin as a suspension in 2% tween 80s using method of Winkes et al.^{13, 14}. The percentage inhibition of inflammation was calculated according to the following equation below –

$$\% \text{ inhibition} = \frac{\text{wt. of paw edema of control} - \text{wt. of paw edema}}{\text{wt. of paw edema of control.}}$$

Table -1- physical properties of new synthetic compounds 1-10

Compd. No.	Solvent	M.P(oC)	Mol.Formula	M.wt M+	Elemental Analysis (%)							
					C		H		N		S	
					Found	Calcd	Found	Calcd.	Found	Calcd	Found	Calcd
2	THF	238	C ₄ H ₄ N ₂ SP	221	37.82	38.9	1.78	1.80	31.47	31.67	14.38	14.47
3	THF	205	C ₉ H ₄ N ₂ SF ₃	271	39.57	39.85	1.40	1.47	25.57	25.83	11.68	11.80
4	EtOH	195	C ₈ H ₇ N ₇	201	47.28	47.76	3.44	3.48	48.26	48.75	-	-
5	EtOH	250	C ₁₄ H ₁₀ N ₆ S	294	56.28	57.14	3.35	3.40	27.99	28.57	10.66	10.88
6	AcOH	213	C ₈ H ₅ N ₅ S ₂	235	40.03	40.85	2.07	2.12	29.18	29.78	26.41	27.23
7a	EtOH	238	C ₁₄ H ₉ N ₅ SF ₂	317	51.93	52.99	2.08	2.83	21.63	22.08	11.62	10.09
7b	EtOH	248	C ₁₄ H ₉ N ₅ SFCl	333	49.54	50.45	2.64	2.70	20.38	21.02	9.31	9.60
8a	C ₆ H ₆	260	C ₁₄ H ₉ N ₅ SF ₂	317	52.46	52.99	2.80	2.83	21.36	22.08	11.68	10.09
8b	C ₆ H ₆	252	C ₁₄ H ₉ N ₅ SFCl	333	49.48	50.45	2.48	2.70	20.38	21.02	9.32	9.60
9	THF	180	C ₁₄ H ₇ N ₅ SFCl	331	49.79	50.75	2.06	2.11	20.50	21.14	9.37	9.66
10a	Dioxan	220	C ₁₃ H ₁₁ N ₆ F	270	56.90	57.77	3.98	4.07	30.17	31.11	-	-
10b	DMF	210	C ₁₆ H ₁₄ N ₈ S ₂ O ₂	414	45.44	46.37	3.31	3.38	26.45	27.05	15.06	15.45

Yield (%): between 55-85%

Table 2. The antimicrobial Activity Screening of New Synthesized compounds

MIC	inhibition Zone (mm)*											
	Bacteria									Fungi		
	<i>E. Coli</i>			<i>P.aeruginosa</i>			<i>S. aureus</i>			<i>C. albicans</i>		
Conc.	100	50	25	100	50	25	100	50	25	100	50	25
Compd.NO.												
2	13	-	-	19	-	-	30	15	-	11	-	-
3	18	-	-	19	-	-	20	13	-	12	-	-
5	13	-	-	19	-	-	19	13	-	11	-	-
4	15	-	-	20	-	-	29	18	-	12	-	-
6	17	-	-	23	11	-	20	13	-	12	-	-
7a	11	-	-	28	17	-	20	15	-	13	11	-
7b	22	13	-	30	18	-	23	13	-	13	-	-
9	30	20	-	32	20	-	18	-	-	13	-	-

*Concentration: 100,50 and 25 µg /disc .

Highly active : IZ \geq 12

Moderately active : IZ= 9-12

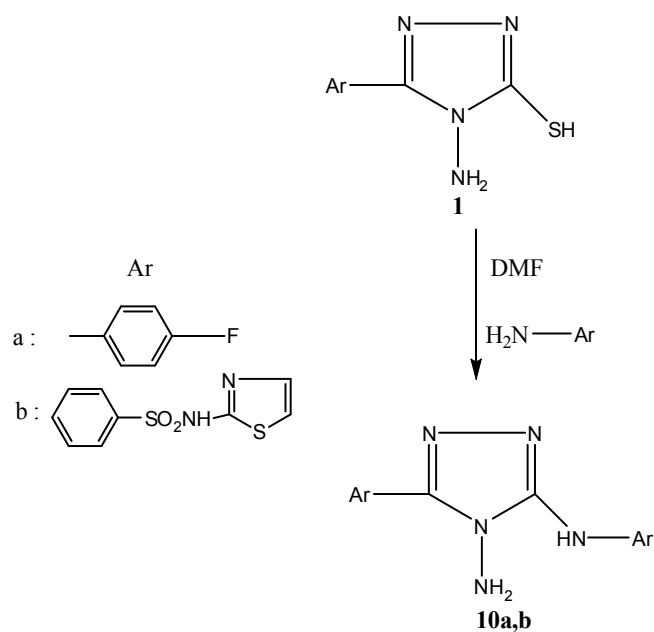
Slightly active : IZ= 6-9

Not sensitive : IZ< 6 mm

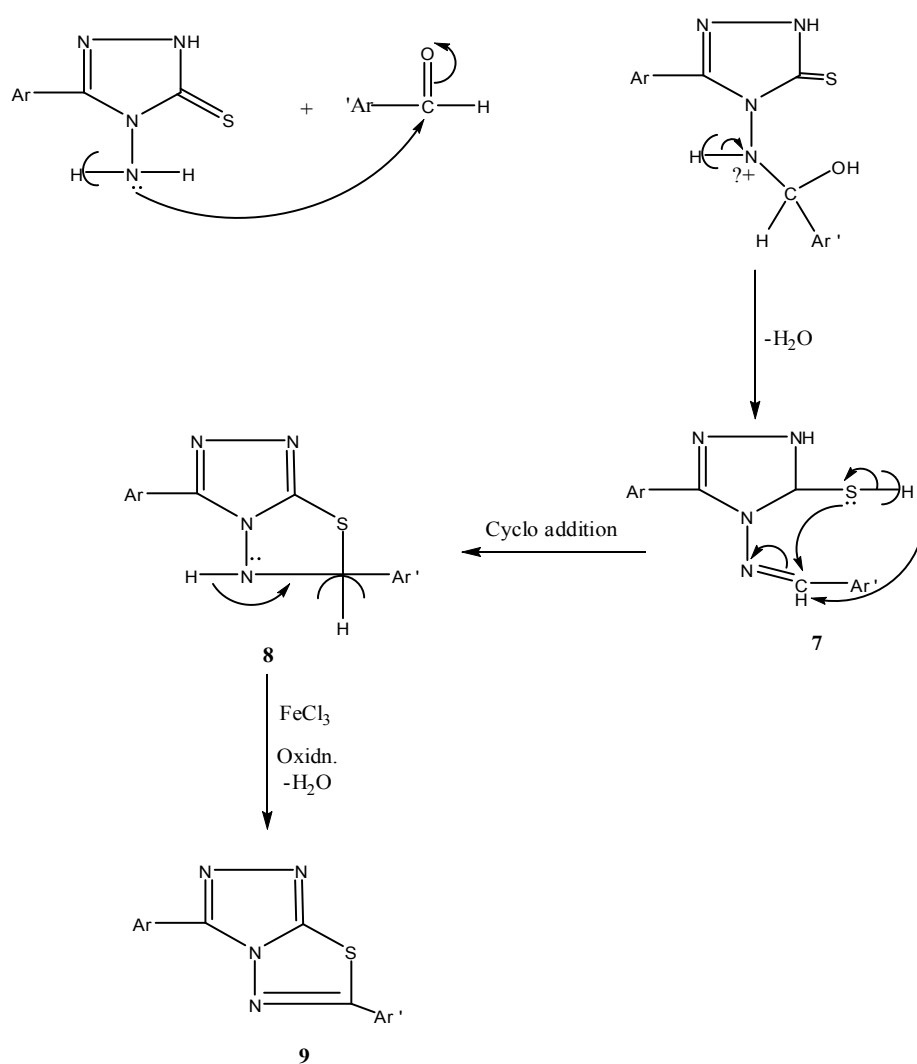
Table 3. The anti-inflammatory of highly active new compounds.

Compd.No.	Dose Mg /Kg	Paw edema(g)* ± S.E.	%inhibition
3	25	0.40±0.03	39.25
	5	0.35±0.05	44.44
7b	25	0.10 ± 0.01	84.84
	5	0.31 ± 0.05	53.03
9	25	0.21 ± 0.02	68.16
	5	0.32 ± 0.05	51.51
Control	0	0.66±0.05	0
Indomethacin	5	0.32±0.02	51.51

*S.E. : Standard Control at value p< 0.05



Scheme 3



Scheme 4- Formation of compound 9 from 1.



Scheme 5. Mass Fragmentation pattern of compound 9.

Results and Discussion:

Some more new N-bridgehead heterocycles such as 1,2,4-triazolo-1,3,4-thiadiazoles have been synthesized starting from 4-amino-3-(pyrid-4yl)-5-mercapto-1,2,4-triazole (**1**). These fused heterobicyclic systems were also evaluated as antimicrobial and anti-inflammatory agents.

Thus, treatment of compound **1** with triethyl phosphate and trifluoroacetamide-Produced 3-(pyrid-4yl)-1,2,4-triazoleo[3,4-c][1,2,4,5] thiadiazaphosphole (**2**) and or 3-(pyrid-4yl)-6-trifluoromethyl-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole (**3**) respectively [Scheme 1].

Structures of **2** and **3** were deduced from UV spectra which recorded λ_{\max} 374nm (**2**) and 382nm (**3**) while that of compound **1** exhibited λ_{\max} 317 nm. Also, IR spectra showed the absence of both the NH_2 and SH absorption bands.

^1H NMR spectrum of **2** and **3** recorded only the pyridine protons at δ 8.2-7.9 ppm.

On the other hand, the interaction between compound **1** and cyanamide via a double nucleophilic attack of amino group of compound **1** to carbonitrile group followed by attack of amino group of cyanamide to thioxo group of **1**, yielded 3-(pyrid-4-yl)-6-amino-3H-1,2,4-triazolo[4,3-b][1,2,4]triazole (**4**) [Scheme 1]. Similarly, 6-phenylamino-3-(pyrid-4yl)-1,2,4-triazolo [4,3-b] [1,3,4] thiadiazole (**5**) was obtained from refluxing compound **1** with phenyl isothiolanate in DMF ¹⁶[Scheme 1].

Both structures of **4** and **5** were established from their IR spectra were compound **4** exhibited absorption band at 3445, 3157 and 1604, 1569 cm^{-1} attributed to NH_2NH and $\text{C}=\text{N}$ functional groups, while that of **5** recorded only absorption bands at 3010 -2700 cm^{-1} (NH interaction with SH). ^1H NMR spectra also gave us a good Confirmation, for compound **4**, which showed resonated signals at 5.87, 13.64 ppm due to NH_2 and NH of 1,2,4-triazole protons, while that of **5** showed only δ at 13.98 ppm for NHph, in addition to pyridine and phenyl protons between 8.77-785 ppm and 7.39-6.94 ppm.

^{13}C nmr of compound **4** refer to the presence of $\text{NH}-\text{C}-\text{NH}_2$ at 167.68 ppm with various carbons of pyridine and triazole. M/s of **5** gave a molecular ion at 281.8(18.00) with a base peak at 44(100) which that support structure.

Novel 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles containing thiol group were Synthesized were reported as very good antimicrobial agents ¹⁷. Thus, addition of CS_2 to 4-amino-5-mercapto1,2,4-triazole derivative **1** in boiling DMF ¹⁷ produced 6- thioxo-3-(pyrid-4yl)-5H-1,2,4-triazolo[3,4-b][1,3,4-] thiadiazole (**6**) (Scheme 1).

Structure of **6** was elucidated from spectral studies.

UV absorption spectrum of **6** recorded λ_{\max} 318 similar to compound **1**, while IR spectrum showed a lacks of NH_2 absorptions bands. In addition the presence of characteristic γ at 2788, 1239 and 1028 cm^{-1} attributed to SH, NCS, $\text{C}=\text{S}$ and $\text{C}-\text{S}$ functional groups.

Fluorinated compounds are of growing importance so far as their applications in medicine is concerned also, fluorine substitution has profound effects on the properties of organic compounds. The very high electro negativity of fluorine can modify the electronic distribution in the molecule, effecting its absorption, distribution and metabolism as well as antimicrobial activities ^{18,19}.

Thus, condensation of compound **1** with fluorinated aromatic aldehydes as 2,6-difluorobenzaldehyde and /or 2-chloro-6-fluorobenzaldehyde in boiling ethanol with a few drops ²⁰ of Conc. HCl yielded the schiff's base **7a,b**. Self cyclization of **7** via refluxing with dry toluene afforded the 6,7-dihydro-3-(pyridine-4-yl)-6-aryl-

1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (**8a,b**). More over, careful oxidation of **8b** by warming with FeCl_3 -methanol ²¹ led to the direct formation of triazolothiadiazole **9**[Scheme 2]. Formation of **9** may take place via cycloaddition reaction of SH on $\text{C}=\text{N}$ center of triazole, follow by careful oxidation (Scheme 4). Compound **9** was also was obtained from refluxing **1** with 2,6-difluorobenzoyl chloride in dry benzene- TEA. Melting point and mixed melting point gave no depreation (Scheme 2).

The structure difference between the compounds **7-9** were deduced from: UV absorption spectrum of **7** exhibited λ_{\max} at 350 nm while that of compound **9** recorded λ_{\max} at 285 nm ^1H NMR spectrum of **7** showed mainly resonated signals at δ 10.47 and 7.91 ppm afforded SH and HC=N protons, while that of **8** exhibited δ 10.60, 8.73 ppm for NH and CH=N protons. The compound **9** showed δ only of pyridine and aromatic protons between 8.8-8.3 and 7.65-7.45 ppm. M/s of **7** showed an molecular ion at m/z 333(1.50) with a base peak at 44 and for **9**, 331(2.00) with a base peak at m/s 242 (Scheme 5). ^{13}C nmr of compound **9** give us a good evidence that the structure recorded mainly a resonated signals at δ 172 (C-F), 135.23(C-Cl), in addition to the resonated carbons of pyridine, triazole and thiadiazole nucleus.

Directed nucleophilic displacement of the sulfur atoms by a nitrogen atoms or other strong nucleophilic can easily occur at thiocarbonyl carbon center is well possible ²².

Thus, a nucleophilic attack of mercapto group of compound **1** was takes place via refluxing with *p*-fluoroaniline and/or sulfathiazole as strong nucleophilic nitrogen types in DMF or isopropyl alcohol produced the 4-amino-5-arylamino-3-(pyrid-4-yl)-1,2,4-triazoles(**10a,b**). Structures of compound **10** were deduced from their UV absorption spectrum **10a**, which recorded λ_{\max} 374nm, while it's IR showed the characteristic bands at γ 3250, 3130(NH₂,NH), 1610,1585(C=N) and 1250 cm^{-1} (C-F). Also ^1H NMR spectrum of **10a** showed δ at 5.87 ppm for NH₂ and 14.22 ppm for NH, In addition to pyridine and aromatic protons. ^{13}C nmr spectrum of **10a** showed mainly resonated carbons at 158(C-F), with pyridine and aryl carbons. Finally M/S recorded molecular ions at m/z 270 (5.50) due to the presence of a molecular ion with a base peak at m/e 44.

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