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Synthesis, characterization and biological studies of some triazolothiadiazines and triazolothiadiazoles containing 6-chloropyridin-3-yl methyl moiety

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4-Amino-5-(6-chloropyridin-3-yl methyl)-4*H*-1,2,4-triazole-3-thiol has been synthesized and was converted into 3-(6-chloropyridin-3-yl methyl)-6-(4-substituted-phenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and (6-chloropyridin-3-yl-methyl)-6-(4-substituted-phenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles. The newly synthesized compounds are characterized on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data. Some of the compounds are screened for their antibacterial and insecticidal activities.

Key words: Triazolothiadiazines, triazolothiadiazoles, 6-chloropyridin-3-yl methyl moiety, antibacterial activity, insecticidal activity

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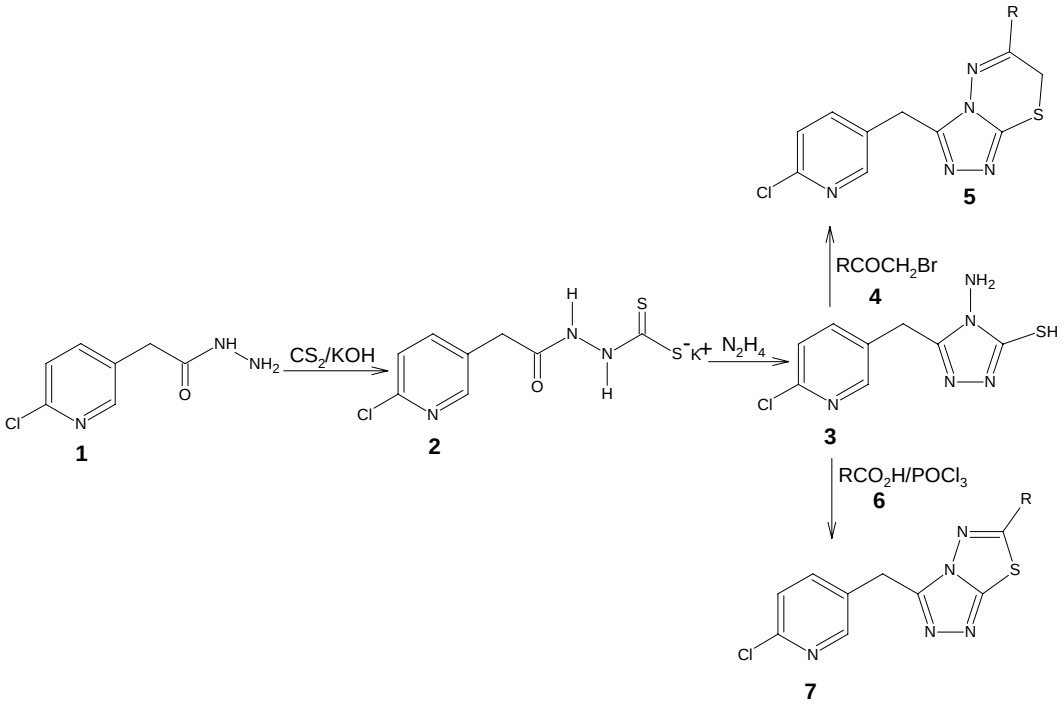
A number of 1,2,4–triazoles have been known as potential biologically active compounds[1-3]. 1, 2, 4-Triazolo[3,4-*b*]-1,3,4-thiadiazines and 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles are the interesting fused systems derived from 4-amino-5-substituted-1,2,4-triazole-3-thiols[4,5]. These two fused systems are reported to possess significant antibacterial, antifungal, CNS depressant, herbicidal, diuretic and anthelmintic activities[6-11]. On the other hand, 6-chloro-3-substituted pyridines are very important class of heterocycles and have been widely used in pharmaceutical and agrochemical industry[12-14]. Prompted by these findings and in continuation of our studies on 6-chloro-3-substituted pyridine derivatives[15,16], it was contemplated to synthesize 4-amino-5-(6-chloropyridin-3-yl methyl)-4*H*-1,2,4-triazole-3-thiol **3** and its fused derivatives, 3-(6-chloropyridin-3-yl methyl)-6-(4-substituted-phenyl)-7*H*-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines **5**, and 3-(6-chloropyridin-3-yl methyl)-6-(4-substituted phenyl)-7*H*-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles **7**. The newly synthesized compounds are screened for their antibacterial and insecticidal activity. Results of such studies are discussed in this paper.

The triazole **3** was reacted with 4-substituted phenacyl bromides **4** to yield 3-(6-chloropyridin-3-yl methyl)-6-(4-substituted phenyl)-7*H*-1, 2, 4-triazolo-[3,4-*b*]-1,3,4-thiadiazines **5**. Further, the reaction of this triazole with 4-substituted benzoic acids **6** in the presence of phosphorus oxychloride resulted in the formation of 3-(6-chloropyridin-3-yl methyl)-6-(4-substituted phenyl)-7*H*-1, 2, 4-triazolo[3,4-*b*]-1, 3, 4-thiadiazoles **7** (**Scheme I**). The characterization data of these newly synthesized compounds are given in **Table I**. The structures of these newly synthesized compounds **3**, **5** and **7** were confirmed on the basis of IR, ^{1}H NMR and mass spectral data **(Table II)**.

In the IR spectrum of triazole **3**, absorption bands appearing in the region 3296-3151 cm^{-1} were attributed to the $-NH_2$ and NH/SH stretching frequencies. The absorption band due to –C=O stretching frequency of the starting hydrazide **1** was absent in this spectrum, thus confirming the formation of the triazole ring. In the ^{1}H NMR spectrum signal due to –NH/SH proton appeared as a singlet at δ 13.47. Another singlet seen at δ 5.04 was assigned to $-NH_2$ protons of triazole ring. The absence of signals due to the protons of $NHNH_2$ group of hydrazide **1** at δ 9.3 and δ 4.3 in this spectrum confirmed triazole ring formation. The signals pertaining to 6-chloropyridin-3-ylmethyl moiety of this compound were seen at δ 4.06, 7.30, 7.67 and 8.36. In the mass



5a: R=C_6H_5; **5b**: R=4-Cl-C_6H_4; **5c**: R=4-F-C_6H_4; **5d**: R=4-CH_3O-C_6H_4; **5e**: R= 4-CH_3-C_6H_4
7a: R=C_6H_5; **7b**: R=4-Cl-C_6H_4; **7c**: R=4-F-C_6H_4; **7d**: R=4-CH_3O-C_6H_4; **7e**: R= 4-CH_3-C_6H_4

Scheme I

spectrum, the molecular ion peak (M^+), which is also the base peak, appeared at m/z 241 which was in confirmity with the molecular formula $C_8H_8ClN_5S$. The loss of chlorine radical from this molecular ion resulted in an ion at m/z 206. The peak corresponding to (6-chloropyridin-3-yl) acetonitrile radical cation was seen at m/z 152.

In the IR spectra of compounds **5** and **7**, the $–NH_2$ stretching frequencies of the starting triazole **3** were absent. These observations gave a clear evidence for the formation of fused ring system. In the ^{1}H NMR spectrum of triazolothiadiazine **5c**, signals due to protons of 6-chloropyridin-3-yl methyl moiety were seen as two doublets, a doublet of doublet and a singlet at δ 8.39 (J = 2.4 Hz), 7.28 (J = 8.1 Hz), 7.70 (J = 2.4 Hz and J = 8.1 Hz) and 4.31. A singlet appearing at δ 3.97 was assigned to $–SCH_2$ protons of thiadiazine ring. The protons of 4-fluorophenyl ring resonated as two doublet of doublets centered at δ 7.85 and 7.21, each integrating for two protons. Signals due to the protons of –NH/SH and $–NH_2$ groups of triazole ring were absent, thus confirming the formation of fused triazolothiadiazine ring. Similarly, in the ^{1}H NMR spectrum of triazolothiadiazole **7c**, signals due to the protons of –NH/SH and $–NH_2$ groups of triazole ring were absent. Protons of 4-fluorophenyl ring resonated as two doublet of doublets at δ 8.02 and 7.48 each integrating for two protons. In addition to these peaks, characteristic peaks pertaining to 6-chloropyridin-3-yl methyl moiety were also observed. In the mass spectrum of triazolothiadiazine **5c** and triazolothiadiazole **7c**, the molecular ion peaks (M^+) appeared at m/z 359 and 345, respectively. A peak seen at m/z 121 was attributed to 4-fluorobenzonitrile radical cation in both the cases.

Experimental Section

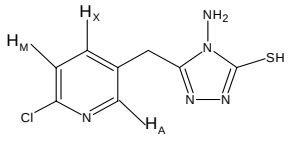
The melting points were determined by open capillary method and are uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer 882 IR spectrophotometer. ^{1}H NMR spectra were recorded (in DMSO-d_6/$CDCl_3$ or a mixture of them) on a Bruker AC-300F/amx 400 (300/400 MH_z) or Varian EM-360L (90 MHz) NMR spectrometer using TMS as internal standard. The mass spectra were recorded on a VG-Micromass or Hewlett-Packard 6890-GC mass spectrometer operating at 70 eV. Progresses of

Table I — Characterization data of compounds **3**, **5** and **7**

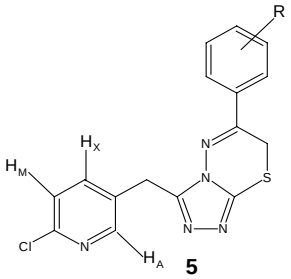
Compd. No.	R	m.p. (ºC)	Yield (%)	Solvent for recrystallisation	Purity* (a/a%)	R.T. (Mins)	Nature of the compd.	Mol. Formula	Calcd (Found) (%) C	H	N
3	--	170-72	67.5	Methanol	99.8	2.98	White crystals	$C_8H_8ClN_5S$	39.75	3.31	28.98
									(39.28	3.23	28.38)
5a	H	163-04	76.1	Methanol	98.9	4.36	Yellow powder	$C_8H_8ClN_5S$	56.22	3.54	20.49
									(56.68	3.66	20.68)
5b	Cl	190-91	59.8	Methanol	99.2	5.35	Yellow powder	$C_8H_8ClN_5S$	51.07	2.95	18.61
									(50.78	3.05	18.88)
5c	F	180-82	62.4	Methanol	98.3	4.41	Yellow crystals	$C_8H_8ClN_5S$	53.41	3.08	19.46
									(54.92	3.17	19.21)
5d	OCH_3	195-97	73.5	Methanol	97.9	4.35	Yellow powder	$C_8H_8ClN_5S$	54.91	3.79	18.83
									(55.55	3.85	18.54)
5e	CH_3	167-68	70.3	Methanol	98.6	5.07	Yellow crystals	$C_8H_8ClN_5S$	57.38	3.97	19.68
									(56.98	3.76	19.42)
7a	H	193-95	84.1	Ethyl acetate	97.8	4.64	Yellow powder	$C_8H_8ClN_5S$	54.96	3.07	21.36
									(55.18	2.96	21.08)
7b	Cl	206-08	74.8	Acetonitrile	98.3	5.87	Yellow powder	$C_8H_8ClN_5S$	49.74	2.50	19.73
									(50.06	2.66	19.87)
7c	F	186-88	82.6	Ethyl acetate	99.0	4.69	Yellow crystals	$C_8H_8ClN_5S$	52.10	2.62	20.25
									(52.44	2.76	20.53)
7d	OCH_3	208-10	79.3	Ethyl acetate	98.5	4.71	Yellow powder	$C_8H_8ClN_5S$	53.71	3.38	19.57
									(54.01	3.46	19.79)
7e	CH_3	200-01	81.2	Ethyl acetate	98.3	5.68	Yellow crystals	$C_8H_8ClN_5S$	56.22	3.54	20.49
									(56.58	3.71	20.74)

*HPLC: Shimadzu LC 10 AVP; Column: Intersil ODS: C_{18}: 250×4.5 mm; Detector: UV spectrometric; Solvent: CH_3CN:H_2O::70:30 v/v; λ = 254; Solvent flow: imL/min.

Table II — Spectral data of compounds **3**, **5** and **7**



3



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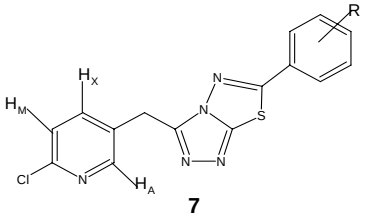

7

Compd No.	IR(KBr)	^{1}H NMR(300/400 MHz, DMSO-d_6)	Mass (m/z, %)
3	3296-3152 (N-H str), 3030 (C-H str), 1630-1468 (C=N, C=C str), 1435 (CH_2 bend), 831 (Py-H bend), 732 cm^{-1} (C-Cl str).	δ 4.06 (s, 2H, CH_2), 5.04 (s, 2H, NH_2), 7.30 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.67 (dd, 1H, Py-H_M, *J*=2.4 Hz and 8.2 Hz), 8.36 (d, 1H, Py-H_A, *J*=2.4 Hz).	241(M^+, 100), 243 (M^++2, 30), 206 (M^+-Cl, 30), 152 ($ClC_6H_3NCH_2N^+$, 18), 126 ($ClC_6H_3NCH_2^+$, 17).
5a	3058-2924 (C-H str), 1591-1468 (C=N, C=C str), 1428 (CH_2 bend), 898 (Ar-H bend), 829 (Py-H bend), 764 cm^{-1} (C-Cl str).	δ 4.35 (s, 2H, CH_2), 4.45 (s, 2H, -CH_2-Py), 7.38 (d, 1H, Py-H_X, *J*=8.3 Hz), 7.41-7.73 (m, 5H, Ar-H), 7.95 (dd, 1H, Py-H_M, *J*=2.4 Hz and 8.3 Hz), 8.55 (d, 1H, Py-H_A, *J*=2.4 Hz).	

Contd

Table II — Spectral data of compounds **3**, **5** and **7**—*Contd*

Compd No.	IR (KBr)	^{1}H NMR (300/400 MHz, DMSO-d_6)	Mass (m/z, %)
5b	3061-2915 (C-H str), 1593-1467 (C=N, C=C str), 1424 (CH_2 bend), 854 (Ar-H bend), 829 (Py-H bend), 778 cm^{-1} (C-Cl str).	δ 3.97 (s, 2H, CH_2), 4.41 (s, 2H, -CH_2-Py), 7.49 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.67 (d, 2H, Ar-H, *J*=8.5 Hz), 7.83 (dd, 1H, Py-H_M, *J*=2.4 Hz and 8.3 Hz), 8.04 (d, 2H, Ar-H, *J*=8.5 Hz), 8.43 (d, 1H, Py-H_A, *J*=2.4 Hz).	
5c	3059-2917 (C-H str), 1606-1469 (C=N, C=C str), 1427 (CH_2 bend), 846 (Ar-H bend), 839 (Py-H bend), 786 cm^{-1} (C-Cl str).	δ 3.97 (s, 2H, CH_2), 4.31 (s, 2H, -CH_2-Py), 7.21-7.25 (m, 2H, Ar-H), 7.28 (d, 1H, Py-H_X, *J*=8.1 Hz), 7.70 (dd, 1H, Py-H_M, *J*=2.5 Hz and 8.1 Hz), 7.75-7.85 (m, 2H, Ar-H), 8.39 (d, 1H, Py-H_A, *J*=2.5 Hz).	359 (M^+, 100), 361 (M^++2, 40), 238((M-$FC_6H_4CN)^+$, 74), 152 (ClC_6H_3N-CH_2N^+, 18), 126 ($ClC_6H_3NCH_2^+$, 36), 121 ($FC_6H_4CN^+$, 74), 95 ($FC_6H_4^+$, 87).
5d	3049-2915 (C-H str), 1594-1467 (C=N, C=C str), 1414 (CH_2 bend), 859 (Ar-H bend), 834 (Py-H bend), 773 cm^{-1} (C-Cl str).	δ 3.9 (s, 3H, OCH_3), 4.44 (s, 2H, CH_2), 4.55 (s, 2H, -CH_2-Py), 7.15 (d, 2H, Ar-H, *J*=8.5 Hz), 7.5 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.85 (d, 2H, Ar-H, *J*=8.5 Hz), 7.9 (dd, 1H, Py-H_M, *J*=2.4 Hz and 8.2 Hz), 8.45 (d, 1H, Py-H_A, *J*=2.4 Hz).	
5e	3051-2919 (C-H str), 1592-1468 (C=N, C=C str), 1427 (CH_2 bend), 834 (Ar-H bend), 821 (Py-H bend), 779 cm^{-1} (C-Cl str).	δ 2.5 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 4.35 (s, 2H, -CH_2-Py), 7.22 (d, 2H, Ar-H, *J*=8.1 Hz), 7.3 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.75 (dd, 1H, Py-H_M, *J*=2.2 Hz and 8.2 Hz), 7.91(d, 2H, Ar-H, *J*=8.1 Hz), 8.45 (d, 1H, Py-H_A, *J*=2.2 Hz).	
7a	3050-2930 (C-H str), 1594-1469 (C=N, C=C str), 1440 (CH_2 bend), 869 (Ar-H bend), 818 (Py-H bend), 739 cm^{-1} (C-Cl str).	δ 4.39 (s, 2H, CH_2), 7.39 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.43-7.76 (m, 5H, Ar-H), 8.01 (dd, 1H, Py-H_M, *J*=2.4 Hz and 8.2 Hz), 8.45 (d, 1H, Py-H_A, *J*=2.4 Hz).	
7b	3080-2931 (C-H str), 1599-1474 (C=N, C=C str), 1410 (CH_2 bend), 860 (Ar-H bend), 840 (Py-H bend), 774 cm^{-1} (C-Cl str).	δ 4.44 (s, 2H, CH_2), 7.51 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.7 (d, 2H, Ar-H, *J*=8.6 Hz), 7.85 (dd, 1H, Py-H_M, *J*=2.2 Hz and 8.2 Hz), 8.14 (d, 2H, Ar-H, *J*=8.6 Hz), 8.45 (d, 1H, Py-H_A, *J*=2.4 Hz).	
7c	3060-2928 (C-H str), 1606-1478 (C=N, C=C str), 1421 (CH_2 bend), 850 (Ar-H bend), 840 (Py-H bend), 763 cm^{-1} (C-Cl str).	δ 4.54 (s, 2H, CH_2), 7.48-7.55 (m, 2H, Ar-H), 7.6 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.89 (dd, 1H, Py-H_M, *J*=2.4 Hz and 8.2 Hz), 7.95-8.15 (m, 2H, Ar-H), 8.57 (d, 1H, Py-H_A, *J*=2.4 Hz).	345 (M^+, 40), 345 (M^++2, 15), 238 (M^+-$FC_6H_4CN^+$, 100), 152 ($ClC_5H_3NCH_2CN^+$, 18), 126 $ClC_5H_3NCH_2^+$, 22).
7d	3062-2928 (C-H str), 1606-1478 (C=N, C=C str), 1421 (CH_2 bend), 889 (Ar-H bend), 846 (Py-H bend), 769 cm^{-1} (C-Cl str).	δ 3.87 (s, 3H, OCH_3), 4.53 (s, 2H, CH_2), 7.17 (d, 2H, Ar-H, *J*=8.6 Hz), 7.52 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.86 (d, 2H, Ar-H, *J*=8.6 Hz), 7.91 (dd, 1H, Py-H_M, *J*=2.4 Hz and 8.2 Hz), 8.5 (d, 1H, Py-H_A, *J*=2.4 Hz).	
7e	3065-2924 (C-H str), 1595-1468 (C=N, C=C str), 1427 (CH_2 bend), 890 (Ar-H bend), 826 (Py-H bend), 760 cm^{-1} (C-Cl str).	δ 2.48 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 7.20 (d, 2H, Ar-H, *J*=8.2 Hz), 7.28 (d, 1H, Py-H_X, *J*=8.2 Hz), 7.72 (dd, 1H, Py-H_M, *J*=2.2 Hz and 8.2 Hz), 7.82 (d, 2H, Ar-H, *J*=8.2 Hz), 8.5 (d, 1H, Py-H_A, *J*=2.2 Hz).	

the reactions and purity of the product were monitored by TLC using ethyl acetate as eluent and UV/iodine as visualizer. 6-Chloropyridin-3-yl acetic acid hydrazide **1** was prepared from 6-chloro-3-chloromethyl pyridine according to the method reported by our group[15]. 4-Substituted phenacyl bromides **4** were synthesized by the bromination of 4-substituted acetophenones with bromine in acetic acid at low temperature[17]. 4-Substituted acetophenones and 4-substituted benzoic acids **6** were procured commercially and used after purification. 4-Amino-5-(6-chloropyridin-3-ylmethyl)-4*H*-1,2,4-triazole-3-thiol **3** was prepared from (6-chlorpyridin-3-yl) acetic acid hydrazide **1** through potassium dithiocarbazinate intermediate **2** using carbon disulphide**,** potassium hydroxide and hydrazine hydrate.

Preparation of 4-amino-5-(6-chloropyridin-3-yl methyl)-4*H*-1,2,4-triazole-3-thiol 3. To a continuously stirred solution of potassium hydroxide (8.4 g, 0.15 moles) and (6-chloropyridin-3-yl) acetic acid hydrazide (18.5 g, 0.1mole) in absolute ethanol (100 mL), carbon disulphide (11.2 g, 0.15 moles) was added dropwise. After the complete addition, the mixture was diluted with absolute ethanol (75 mL) and agitated for 16 hr. It was then diluted with dry ether (100 mL) and the precipitated solid was collected by filtration, washed with ether and dried at 65ºC under vacuum to obtain crude suspension of potassium dithiocarbazinate. To the above suspension, hydrazine hydrate (10 mL, 0.2 mole) was added and the mixture was refluxed for about an hour. The colour of the reaction mixture changed to green with the evolution of hydrogen sulphide and a homogeneous mass was obtained. It was then cooled and diluted with cold water (100 mL). The cold mixture was acidified with concentrated hydrochloric acid. The solid separated was filtered, washed with water, dried and recrystallized from methanol.

Procedure for the synthesis of 3-(6-chloropyridin-3-yl methyl)-6-(4-substituted-phenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines 5. A mixture of 4-amino-5-(6-chloropyridin-3-yl methyl)-4*H*-triazole-3-thiol **3** (0.01 mole), substituted phenacyl bromide (0.01 mole) and anhydrous sodium acetate (0.01 mole) in absolute ethanol (30 mL) was refluxed on a water-bath for 4 hr. The reaction mixture was cooled and the precipitated solid was filtered, dried and recrystallized from appropriate solvent.

Procedure for the preparation of 3-(6-chloropyridin-3-yl methyl)-6-(4-substituted-phenyl)-7*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles 7. A mixture of 4-amino-5-(6-chloropyridin-3-ylmethyl)-4*H*-1,2,4-trioazole-3-thiol **3** (0.01 mole), substituted benzoic acid (0.01 mole) and phosphorus oxychloride (10 mL) was refluxed for 6 hr on a water bath. Excess of phosphorus oxychloride was removed under vacuum. The thick mass obtained was treated with water and left overnight. Solid thus obtained was filtered, washed with 2% sodium bicarbonate solution, then with water, dried and recrystallized from appropriate solvent.

Antibacterial activity

All the newly synthesized compounds were initially screened for their *in vitro* antibactirial activities against *Escherischia coli, Pseudomonas areuginosa, Staphylococcus aureus* and *Bacillus subtilis* by serial dilution method[18]. The compounds were tested at a concentration of 200μg/mL in dimethylformamide against all the organisms. Furacin was used as standard drug for comparison of antibacterial activity and solvent control was kept. The minimum inhibitory concentrations (MIC values) of the above compounds were determined. The results of antibacterial screening studies are reported in **Table III**. A stock solution of concentration 100 μg/mL was prepared by dissolving 5 mg of the test compound in 50 mL of dimethylformamide. One loopful of an 18 hr broth culture was inoculated into 5 mL of nutrient broth and this was incubated at 37ºC for 4 hr. An assay was prepared by diluting 4-hr subculture in 1/1000 in nutrient broth.

Nutrient broth (0.5 mL) was taken in tubes with labeled numbers 1-11 and 0.5 mL of the solution of the test compound (100 μg/mL) was added to the first tube no.2. This process was repeated serially to obtain the quantities indicated in each of the test tubes. The eleventh tube was taken as control. Drop of diluted broth culture of the test organization (approximately 0.05 mL) was added to all the tubes using a sterilized Pasteur pipette. The solutions were mixed gently and the incubation was carried out at 37ºC for 16-18 hr. Furacin was dissolved in dimethylformamide and was used as a standard drug for comparison. The minimum concentration at which there was no turbidity was taken as the minimum inhibitory concentration (MIC value).

The antibacterial screening results indicate that all the tested compounds were found to possess lesser degree of activity against all the tested organisms

Table III—Antibacterial activity data of the newly synthesized compounds

Compd. No.	*Minimum Inhibition Concentration (μg/mL)			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*
3	10	20	20	<10
5a	100	-	-	100
5b	100	-	100	100
5c	-	-	-	-
5d	100	-	-	100
5e	10	20	10	10
7a	10	20	10	10
7b	10	20	10	10
7c	100	-	100	100
7d	20	50	50	20
7e	100	200	50	100
Furacin	6	12.5	12.5	12.5

*Index for antibacterial activity

Diameter of the disc	5 mm
Amount of the sample	100 μg/mL
Control (Solvent)	Dimethyl formamide

compared to the standard. Results of these studies are given in **Table III**.

Insecticidal activity

Laboratory reared three day old adult mosquitoes namely *Culex quinquefasciatus* were used in the experiments. The new molecules were tested at 10 mL and 20 mL per litre of water, against the above said insects in comparison with standard Lambda-cyhalothrin 5% EC at 0.5 mL per litre of water. Glass plates measuring (30cm × 30cm) were treated with 2 mL of the test time solution. Treated glass plates were allowed to dry for one hr. Later, mosquitoes were released on the treated surface and confined their movement by covering with glass petriplates. Observations were recorded for time taken for 50% knockdown (KT_{50}) and 100% knockdown (KT_{100}).

The results of the screening studies revealed that none of the new molecules showed insecticidal activity against adult mosquitoes even at test dosage of 20 mL per litre of water compared to positive control, Lambda-cyhalothrin 5% EC at 0.5 mL per litre of water, which showed 50% knockdown (KT_{50}) in 8 min 30 sec and 100% knockdown (KT_{100}) in 60 min 30 sec.

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