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ORIGINAL RESEARCH ARTICLE

Newer Azitidinoyl Thiazolidinoyl And Formazan-1, 3 Thiazolyl Pyridines And Their Biological Activities

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ABSTRACT

A series of 2-(2′-substitutedarylidenylimino-1′,3′-thiazol-4′-yl)aminopyridines (**3a-3d**), 2-[2′-(3′′-chloro-2′′-oxo-4′′-substitutedaryl-1′′-azetidinyl)-1′,3′-thiazol-4′-yl] amino pyridines (**4a-4d**), 2-[2′-(2′′-substitutedaryl-4′′-thiazolidinon-3′′-yl)-1′,3′-thiazol-4′-yl] aminopyridines (**5a-5d**) and 2-[2′-(1′′-phenyl-3′′-substituted aryl-formazan-4′′-yl)-1′,3′-thiazol-4′-yl]aminopyrid-ines (**6a-6d**) were prepared in present study. The structure of all these newly synthesized compounds was confirmed on the basis of spectral (IR, ^{1}HNMR and mass) and analytical data. Out of four azetidinone derivatives, 2-[2′-(3′′-chloro-2′′-oxo-4′′-*o*-hydroxyphenyl-1′′-azetidinyl)-1′,3′-thiazol-4′-yl]aminopyridine (**4c**) was found to be the most potent compound of this series. This compound exhibited maximal insecticidal activity in comparison to standard, parathion at three tested concentrations. Furthermore, this compound also possessed comparable antifungal activity with fluconazo.

Keywords: Azetidinone, Thiazolidinone & Formazons Derivatives Insecticidal, Antifungal & Antibacterial Activity.

INTRODUCTION

Pyridine, heterocyclic nuclei, possessed a pivotal role in the development of different medicinal agents and in the field of agriculture. In the past years, by considering the novel insecticides belonging to the group, neonicotinoids like imidacloprid, acetamiprid[1-2] derivatives of pyridine have been utilized. From the recent literature, it has been found that pyridine congeners are associated with different biological properties like pesticidal[3-4], insecticidal[5], fungicidal[6], antimicrobial[7] etc. Furthermore, substituted derivatives of thiazole[8-10], azetidinone[11-12] and thiazolidinone[13] exhibited pesticidal, insecticidal and antimicrobial activities. In view of these findings, it was contemplated to synthesize some new pyridine derivatives bearing thiazole, thiazolidinone/azetidinone moieties at its 2-position and examined for their insecticidal, antifungal and antibacterial properties.

Biological Study

Various compounds have been synthesized and evaluated for insecticidal activity against male or female cockroaches (*Periplaneta americana*). These compounds were also assayed *in vitro* for their antifungal and antibacterial activities.

Insecticidal Activity

The insecticidal activity was determined by the method of Joshi and Tholia (1973). The cockroaches of either sex were divided in groups having five cockroaches each. An acetone solution (0.02 mL of 5 g/L) of standard insecticide, parathion, and different test compounds were injected on the ventral side of the insect, between the fourth and fifth abdominal segments with the help of a micrometer syringe. Insects receiving 0.02 mL of acetone by the same route served as control.

The treated cockroaches were kept under observation to record the time taken until 100 % mortality. During this period, no food was given. In an other set of experiment, most active compound of each *Series* at two graded doses i.e. 0.2 ml of 10 g/l and 20 g/l were also injected to groups of insects with identical doses of parathion. The statistical significance of the difference between the data of standard and test compounds was calculated by employing student's'‘t’ test (A 1).

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Antifungal Activity

The standard agar disc diffusion method (Pai and Platt, 1995) was performed to evaluate the antifungal property of test compounds and standard fluconazole.

Aspergillus fumigatus, Candida albicans ATCC 2091, Candida albicans ATCC 10231, Candida Krusei GO3 and *Candida glabrata HO5* were used in this study. All cultures were routinely maintained on SDA (A 2) and incubated at 30 ºC. In order to prepare homogeneous suspensions of these fungi for disc assays, they were grown overnight in sabouraud broth, centrifuged to collect the pellet and re-suspended in sterile phosphate buffered saline. The fungal pellet was homogenized in a sterile hand–held homogenizer. This suspension was then plated onto SDA using a bacterial spreader to obtain an even growth field. Sterile 6 mm what man filter paper discs (A 3) were impregnated with 250 µg/mL concentration of various test compounds and standard drug, fluconazole. These discs were then placed in the centre of each quadrant of an SDA plate. Each plate had one control disc impregnated with 10% DMSO in methanol. The plates were incubated at 30 ºC. After 48 hours, the plates were removed and the radius of the zone of inhibition (in mm) was measured.

Antibacterial Activity

The antibacterial activity of test compounds and standard chloramphenicol was done by filter paper disc method (Gould and Bowie, 1952) against *Staphyloccous aureus 209 p* and *Eschericia coli ESS 2231*, at a concentration of 250 µg/mL. Media with 10% DMSO in methanol was set up as control. The presence of methanol caused no visible change in the bacterial growth. The Whatman filter paper discs of standard size (7 mm) were prepared. These discs were put into 1 oz screw capped wide-mouthed containers. These bottles are then sterilised in hot-air oven at 150 ºC. Solution is then added to each bottle. Before use, the bottles should be shaken to distribute the discs around the walls of the container and this allows them to be picked up more easily with the forceps. The discs are transferred to the inoculated plates with a pair of fine pointed tweezers. The tweezers may be kept with their tips immersed in 70 % alcohol, which is flamed off before use to prevent contamination.

The test organisms were grown on nutrient agar (A 4) and, before use, were subcultured in nutrient broth at 37 ºC for 18-20 hours. Each disc was applied carefully to the surface of the agar without lateral movement once the surface had been touched; where necessary they were flattened down with the points of the forceps. The plates were then incubated for 24 hours at 37 ºC, and the resulting zones of inhibition (in mm) were measured.

EXPERIMENTAL

General

All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in oven-dried glassware. Melting points were determined with an electrothermal melting point apparatus, and are uncorrected.

The homogeneity of all newly synthesized compounds was checked by thin layer chromatography *(*TLC) on silica gel-G coated plates. Eluent was a mixture of different solvents in different proportions, and spots were visualized under iodine chamber. Elemental analysis (C, H, N) of all the compounds was performed on Carlo Erba-1108 elemental analyzer, and results were found within the $\pm$ 0.4% of theoretical values.Infrared (IR) spectra (KBr) were recorded on Brucker–IFS–66 FTIR instrument and wave number (ν) was recorded in cm^{-1}.^{1}H-NMR spectra were recorded JEOL, GSX-400 FTNMR instrument at 400 MHz in $CDCl_3$ or DMSO-d_6 unless otherwise specified, and chemical shifts (δ) are reported in ppm. relative to tetramethylsilane as an internal standard Mass spectra were determined from Mass Finniganmat 8230 MS.

Synthesis of 2-(chloroacetyl)aminopyridine (1).

2-aminopyridine (0.02 mole) was dissolved in dry benzene (80 mL) at 0-5 ºC temperature. To the clear solution chloroacetylchloride (0.04 mole) was added droped wise with continous stirring during 35 minutes. This resultant solution was futher stirred for 4 hours at room temperature, and refluxed for 6 hours on water bath. After removal of the solvant by distillation, the separated solid was washed with petroleum ether (40-60 ºC) and kept in refrigerator overnight, then recrystallized from benzene.

Compound **1**: M. P. 203 ºC; Yield 72 %; Molecular Formula $C_7H_7N_2ClO$. Calcd % C 49.27, H 4.11, N 16.42, Found % C 48.69, H 4.38, N 16.26.IR (KBr) ν_{max} in cm^{-1}: 3370 (N-H), 3010 (C-H aromatic), 2930 (C-H aliphatic), 1680 (C=O), 1580 (C=C of aromatic ring), 1140 (C-N), 690 (C-Cl).^{1}H-NMR ($CDCl_3$) δ in ppm: 8.40 (brs, 1H, N*H*CO, exchangeable with D_2O), 8.28 (d, *J* = 2.0 Hz, 1H, C_1 of pyridine), 7.62 (dd, *J* = 8.2/2.2 Hz, 1H, C_2 of pyridine), 7.41 (d, *J* = 8.0 Hz, 1H,

C_3 of pyridine), 7.30 (dd, *J* = 8.4/2.2 Hz, 1H, C_4 of pyridine), 4.42 (s, 2H, C*H*$_2$). MS: $[M]^+$ at m/z 170.

Synthesis of 2-(2′-amino-1′,3′-thiazol-4′-yl) aminopyridine (2).

A mixture of 2-(chloroacetyl) aminopyridine **1** (0.02 mole) and thiourea (0.01 mole) in absolute acetone (90 mL) was refluxed for 12 hours. Progress of the reaction was monitored by TLC. After refluxing, excess of solvent was evaporated, and thus the solid obtained was poured into ice-cold water, and then filtered. Now this solid was washed with 2 % sodium carbonate solution followed by water to liberate the base completely, finally dried with anhydrous sodium sulphate recrystallization from ethanol.

Compound **2** M. P. 130 ºC; Yield 65 %; Molecular Formula $C_8H_8N_4S$. Calcd % C 50.00, H 4.17, N 29.17, Found % C 49.85, H 4.30, N 28.90.IR (KBr) ν_{max} in cm^{-1}: 3385 (N-H), 3020 (C-H aromatic), 1610 (C=N), 1575 (C═C of aromatic ring), 1155 (C-N), 660 (C-S-C). ^{1}H-NMR ($CDCl_3$) δ in ppm: 8.30 (d, *J* = 2.1 Hz, 1H, C_1 of pyridine), 7.60 (dd, *J* = 8.2/2.1 Hz, 1H, C_2 of pyridine), 7.42 (d, *J* = 8.1 Hz, 1H, C_3 of pyridine), 7.28 (dd, *J* = 8.4/2.2 Hz, 1H, C_4 of pyridine), 7.15 (s, 1H, C*H* of thiazole ring) 6.25 (s, 2H, N*H*$_2$, exchangeable with D_2O), 5.90 (s, 1H, N*H*, exchangeable with D_2O). MS: $[M]^+$ at m/z 192.

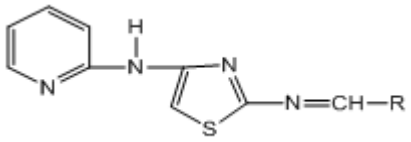
Synthesis of 2-(2′-*o*-hydroxyarylidenylimino-1′, 3′-thiazol-4′-yl)aminopyridine (3c).

A solution of compound **2** (0.01 mole) in ethanol (60 mL) and salicyldeyde (0.01 mole) along with few drops of glacial acetic acid was refluxed for 10 hours. After refluxing, reaction mixture was concentrated, cooled, poured over crushed ice and filtered. The isolated product was recrystallized from methanol.

Compound **3c**: M. P. 82 ºC; Yield 55 %; Molecular Formula $C_{15}H_{12}N_4OS$. Calcd % C 60.81, H 4.05, N 18.92, Found % C 61.10, H 4.33, N 18.75. IR (KBr) ν_{max} in cm^{-1}: 3535 (O-H), 3385 (N-H), 3065 (C-H aromatic), 2920 (C-H aliphatic), 1600 (C=N), 1540 (C═C of aromatic ring), 1155 (C-N), 750 (C-S-C). ^{1}H-NMR ($CDCl_3$) δ in ppm: 11.25 (ss, 1H, O*H*, exchangeable with D_2O), 8.40 (s, 1H, C*H*-Ar), 8.29 (d, *J* = 2.2 Hz, 1H, C_1 of pyridine), 7.62 (dd, *J* = 8.2/2.1 Hz, 1H, C_2 of pyridine), 7.44 (d, *J* = 8.1 Hz, 1H, C_4 of pyridine), 7.30 (dd, *J* = 8.6/2.2 Hz, 1H, C_3 of pyridine), 7.16 (s, 1H, C*H* of thiazole ring), 6.80-7.05 (m, 4H, Ar-*H*), 5.92 (s, 1H, N*H*, exchangeable with D_2O). MS: $[M]^+$ at m/z 296.

A number of 2-(2′-substitutedarylidenylimino-1′,3′-thiazol-4′-yl)aminopyridines (**3a, 3b**, and **3d**) have been prepared by following the similar method; and the physical and analytical data of these compounds are depicted in (**Table I**).

Table-I: Physical and analytical data of 2-(2'-substitutedarylidenylimino-1',3'-thiazol-4'-yl)aminopyridines (3a–3d).



Compd No.	R	M.P. (^{0}C)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental analysis					
						% C		% H		% N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	C_6H_5	150	62	Acetone	$C_{15}H_{12}N_4S$	64.29	64.38	4.29	4.05	20.0	20.10
3b	3-OCH_3, 4-OH C_6H_3	138	52	Ethanol	$C_{16}H_{14}N_4O_2S$	58.90	58.55	4.29	4.06	17.18	17.32
3c	2-OHC_6H_4	82	55	Methanol	$C_{15}H_{12}N_4OS$	60.81	61.10	4.05	4.33	18.92	18.75
3d	4-$OCH_3C_6H_4$	146	50	acetic acid	$C_{16}H_{14}N_4OS$	61.94	61.69	4.52	4.70	18.06	18.29

Synthesis of 2-[2′-(3′′-chloro-2′′-oxo-4′′-*o*-hydroxyphenyl-1′′-azetidinyl)-1′, 3′-thiazol-4′-yl] amino-pyridine (4c).

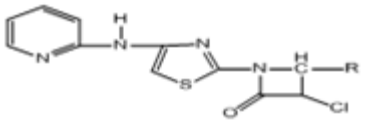
To a solution of compound **3c** (0.01 mole) in benzene (50 mL), chloroacetyl chloride (0.02 mole) and triethylamine (0.02 mole) were added drop wise with constant stirring. The reaction mixture was refluxed for 6 hours and excess of benzene was removed by distillation. This mixture was poured into ice cold water, filtered and the solid separated out was recrystallized from ethanol.

Compound **4c**: M. P. 116 ºC; Yield 48 %; Molecular Formula $C_{17}H_{13}N_4O_2SCl$. Calcd % C 54.77, H 3.49, N 15.03, Found % C 54.58, H 3.22, N 15.21.IR (KBr) ν_{max} in cm^{-1}: 3540 (O-H), 3360 (N-H), 3035 (C-H aromatic), 1730 (C=O), 1625 (C=N), 1575 (C═C of aromatic ring), 1175 (C-N),

710 (C-Cl), 680 (C-S-C).^{1}H-NMR (DMSO-d_6) δ in ppm: 11.22 (s, 1H, O*H*, exchangeable with D_2O), 8.32 (d, *J* = 2.2 Hz, 1H, C_1 of pyridine), 7.63 (dd, *J* = 8.1/2.1 Hz, 1H, C_2 of pyridine), 7.40 (d, *J* = 8.3 Hz, 1H, C_4 of pyridine), 7.32 (dd, *J* = 8.6/2.2 Hz, 1H, C_3 of pyridine), 7.18 (s, 1H, C*H* of thiazole ring), 6.82-7.06 (m, 4H, Ar-*H*), 5.85 (s, 1H, N*H*, exchangeable with D_2O), 5.05 (d, *J* = 6.7 Hz, 1H, C*H*-Cl), 4.83 (d, *J* = 5.6 Hz 1H, C*H*-Ar).MS: $[M]^+$ at m/z 372.

Several 2-[2′-(3′′-chloro-2′′-oxo-4′′-substitutedaryl-1′′-azetidinyl)-1′,3′-thiazol-4′-yl)am-inopyridines (**4a, 4b,** and **4d**) were prepared by aforementioned method and their physical and analytical data are given in (**Table.2**).

Table-2: Physical and analytical data of 2-[2′-(3′′-chloro-2′′-oxo-4′′-substitutedaryl-1′′-azetidinyl)-1′,3′-thiazol-4′-yl]aminopyridines (4a–4d).



Comp No.	R	M.P. (^{0}C)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental analysis					
						% C		% H		% N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	C_6H_5	142	40	DMF	$C_{17}H_{13}N_4OSCl$	57.22	57.02	3.65	3.87	15.71	15.55
4b	3-OCH_3, 4-OH C_6H_3	122	42	Methanol	$C_{18}H_{15}N_4O_3SCl$	53.66	53.28	3.73	3.94	13.91	13.66
4c	2-OHC_6H_4	116	48	Ethanol	$C_{17}H_{13}N_4O_2SCl$	54.77	54.58	3.49	3.22	15.03	15.21
4d	4-$OCH_3C_6H_4$	120	40	Ethanol	$C_{18}H_{15}N_4O_2SCl$	55.89	56.10	3.88	3.61	14.49	14.23

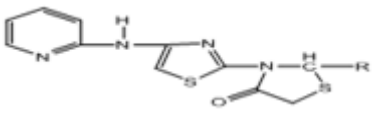
Synthesis of 2-[2′-(2′′-*o*-hydroxyphenyl-4′′-thiazolidinon-3′′-yl)-1′,3′-thiazol-4′-yl]aminopyridine (5c).

A solution of compound **3c** (0.01 mole), thioglycolic acid (0.01 mole) and anhydrous zinc chloride (2 g) in absolute ethanol (60 mL) was refluxed for 8 hours. The reaction mixture was concentrated by evaporation, cooled, poured into ice water. Further, by filtration, the product was isolated, which was recrystallized from acetone to give compound **5c**, while purity of the product was checked by TLC.

Compound **5c**: M. P. 135 ºC; Yield 52 %; Molecular Formula $C_{17}H_{14}N_4O_2S_2$. Calcd % C 55.14, H 3.78, N 15.14, Found % C 55.29, H 3.95, N 14.92. IR (KBr) ν_{max} in cm^{-1}: 3515 (O-H), 3345 (N-H), 3025 (C-H aromatic), 1695 (C=O), 1596 (C=N), 1570 (C⎓C of aromatic ring), 1170 (C-N).^{1}H-NMR ($CDCl_3$) δ in ppm: 11.18 (s, 1H, O*H*, exchangeable with D_2O), 8.31 (d, *J* = 2.2 Hz, 1H, C_1 of pyridine), 7.66 (dd, *J* = 8.1/2.1 Hz, 1H, C_2 of pyridine), 7.45 (d, *J* = 8.3 Hz, 1H, C_4 of pyridine), 7.32 (dd, *J* = 8.6/2.2 Hz, 1H, C_3 of pyridine), 7.16 (s, 1H, C*H* of thiazole ring), 6.85-7.10 (m, 4H, Ar-*H*), 5.88 (s, 1H, N*H*, exchangeable with D_2O), 5.02 (s, 1H, C*H*-Ar), 4.18 (s, 2H, CH_2 of thiazolidinone ring). MS: $[M]^+$ at m/z 370.

Different 2-[2′-(2′′-substitutedaryl-4′′-thiazolidinon-3′′-yl)-1′,3′-thiazol-4′-yl)amino-pyridines (**5a**, **5b** and **5d**) have been procured by above said method and their physical and analytical data are shown in (**Table.3**).

Table.3: Physical and analytical data of 2-[2’-(2’’-substitutedaryl-4’’-thiazolidinon-3’’-yl)-1’,3’-thiazol-4’-yl] aminopyridines (5a-5d).



Comp No.	R	M.P. (^{0}C)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental analysis					
						% C		% H		% N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
5a	C_6H_5	126	49	Ethanol	$C_{17}H_{14}N_4OS_2$	57.63	57.85	3.95	3.73	15.82	15.62
5b	3-OCH_3, 4-OH C_6H_3	102	45	Ethanol	$C_{18}H_{16}N_4O_3S_2$	54.00	53.88	4.00	4.24	14.00	14.16
5c	2-OHC_6H_4	135	52	Acetone	$C_{17}H_{14}N_4O_2S_2$	55.14	55.29	3.78	3.95	15.14	14.32
5d	4-$OCH_3C_6H_4$	109	42	Methanol	$C_{18}H_{16}N_4O_2S_2$	56.25	56.38	4.17	4.27	14.58	14.91

Synthesis of 2-[2′-(1′′-phenyl-3′′-o-hydroxyphenyl-formazan-4′′-yl)-1′,3′-thiazol-4′-yl]amino pyridine (6c).

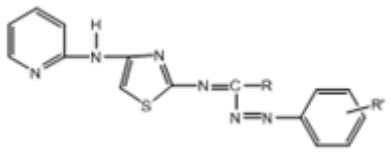
To a solution of aniline (0.01 mole) in glacial acetic acid (10 mL), concentrated HCl (3 mL) was added at 0-5 ^{0}C temperature. Then, solution of sodium nitrite (1g in 5 mL of water) was added to the above said solution. The diazonium salt solution thus prepared was added drop by drop to a solution of compound **3c** (0.01 mole) in methanol (40 mL) with constant stirring at 0 ^{0}C temperature. Now, the reaction mixture was kept at room temperature for one day, then poured into a mixture of ice. The resulting solid was washed with water and finally recrystallized from ethanol.

Compound **6c**: M. P. 102 ºC; Yield 46 %; Molecular Formula $C_{21}H_{16}N_6OS$. Calcd % C 63.00, H 4.00, N 21.00, Found % C 62.83, H 4.27, N 21.16. IR (KBr) ν_{max} in cm^{-1}: 3510 (O-H), 3340 (N-H), 3020 (C-H aromatic), 1600 (C=N), 1180 (C-N), 680 (C-S-C). ^{1}H-NMR ($CDCl_3$) δ in ppm: 11.21 (ss, 1H, O*H*, exchangeable with D_2O), 8.33 (d, *J* = 2.2 Hz, 1H, C_1 of pyridine), 7.65 (dd, *J* = 8.1/2.1 Hz, 1H, C_2 of pyridine), 7.43 (d, *J* = 8.3 Hz, 1H, C_4 of pyridine), 7.33 (dd, *J* = 8.6/2.2 Hz, 1H, C_3 of pyridine), 7.22 (s, 1H, C*H* of thiazole ring), 6.86-7.19 (m, 9H, Ar-*H*), 5.85 (s, 1H, N*H*, exchangeable with D_2O).

MS: $[M]^+$ at m/z 400.

Various 2-[2′-(1′′-phenyl-3′′-substitutedaryl-formazan-4′′-yl)-1′,3′-thiazol-4′-yl]-aminopyridines (**6a, 6b** and **6d**) have been synthesized by following the procedure for synthesis of compound **6c**. Their physical and analytical data are shown in (**Table.4**).

Table.4: Physical and analytical data of 2-[2′-(1′′-phenyl-3′′-substitutedaryl-formazan-4′′-yl)-1′,3′-thiazol-4′-yl]aminopyridines (6a-6d).



Comp. No.	R'	R	M.P. (^{0}C)	Yield (%)	Recrystallization Solvent	Molecular Formula	Elemental analysis					
							% C		% H		% N	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
6a	H	C_6H_5	158	40	Ethanol	$C_{21}H_{16}N_6S$	65.63	65.38	4.17	3.98	21.88	21.66
6b	H	3-OCH_3, 4-OH C_6H_3	165	45	DMF	$C_{22}H_{18}N_6O_2S$	61.40	61.62	4.19	4.31	19.53	19.67
6c	H	2-OHC_6H_4	102	46	Ethanol	$C_{21}H_{16}N_6OS$	63.00	62.83	4.00	4.27	21.00	21.16
6d	H	4-$OCH_3C_6H_4$	142	38	acetic acid	$C_{22}H_{18}N_6OS$	63.77	64.05	4.35	4.58	20.29	20.43

RESULTS& DISCUSSION

Compounds **3a–3d, 4a–4d, 5a–5d** and **6a–6d** and the standard parathion were assessed for insecticidal activity against *periplaneta americana* at a concentration of 5 g/L. All the tested compounds exhibited more potent activity than the standard (**Table.5**). Among these, compound **4c** was found to be the most active, that's why it was further evaluated at two different concentrations i.e. 10 g/L and 20 g/L and the results obtained (**Table 5**) reveal that increase in concentration increases the activity, which shows that dose dependent activity. Sixteen compounds **3a–3d, 4a–4d, 5a–5d** and **6a–6d** were assayed for antifungal activity against *A. funigatus, C. albicans 2091, C. albicans ATCC 10231, C. krusei GO3 and C. glabrata H05* at a concentration of 250 μg/mL. All compounds except **3b**, **6a**, and **6d** exhibited antifungal activity (**Table.6**). None of the compound possessed better activity than the fluconazole.

The newly synthesized compounds have also been screened for *in vitro* antibacterial activity. The data indicated that compounds **3a-3d** and **6c**, **6d** have shown no inhibition against both the strains of bacteria, while rest of the compounds exhibited antibacterial activity (Table VI) than the standard. Compound **4c** showed comparable activity with chloramphenicol.

The biological results (Table 5, 6) for compounds **3a-3d**, **4a-4d**, **5a-5d** and **6a-6d** show that

substitution pattern on 2-position of 2-aminopyridinylthiazole moiety appears to be vital for broad-spectrum activities. Substituted benzylidene congeners (**3a-3e**) exhibited promising insecticidal activity. Compounds **3a**, **3c** and **3d** possessed inhibitory zone against all strains of fungi. Interestingly, it was observed that compounds **3a** and **3c** inhibited the growth of *A. fumigatus*, while standard drug, fluconazole, was found to be inactive against same fungus. Cyclization of compounds **3a-3d** into their corresponding azetidinones (**4a-4d**) enhanced the insecticidal and antifungal activity and introduced antibacterial property. Besides this, conversion of compounds **3a-3d** into thiazolidinones (**5a-5d**) has no remarkable change on their insecticidal activity. However, enhancement regarding the antimicrobial activities of compounds **5a-5d** has been noticed. It is clear from the results that azetidinones possessed better biological activities than thiazolidinones. It is important to note from the biological data that compounds **3c**, **4c**, **5c** and **6c** having *o*-hydroxyphenyl group as a substituent showed maximal ainsecticidal and antifungal activity. Whereas substitution with *p*-methoxyphenyl group as found in compounds **3d**, **4d**, **5d** and **6d** exhibited remarkable activities. Other substitution i.e. *p*-hydroxy,*m*-methoxyphenyl in compounds **3b**, **4b**, **5b** and **6b** displayed less but still adequate activity.Out of four azetidinone derivatives, 2-[2′-(3′′-chloro-2′′-oxo-4′′-*o*-hydroxyphenyl-1′′-azetidinyl)-1′,3′-thiazol-4′-yl]aminopyridine (**4c**) was found to be the most potent compound of this series. This compound exhibited maximal insecticidal activity in comparison to standard, parathion at three tested concentrations. Furthermore, this compound also possessed comparable antifungal activity with fluconazole.

Table 5. Insecticidal activity of compounds 3a-3d, 4a-4d, 5a-5d and 6a-6d against cockroaches (*periplaneta americana*).

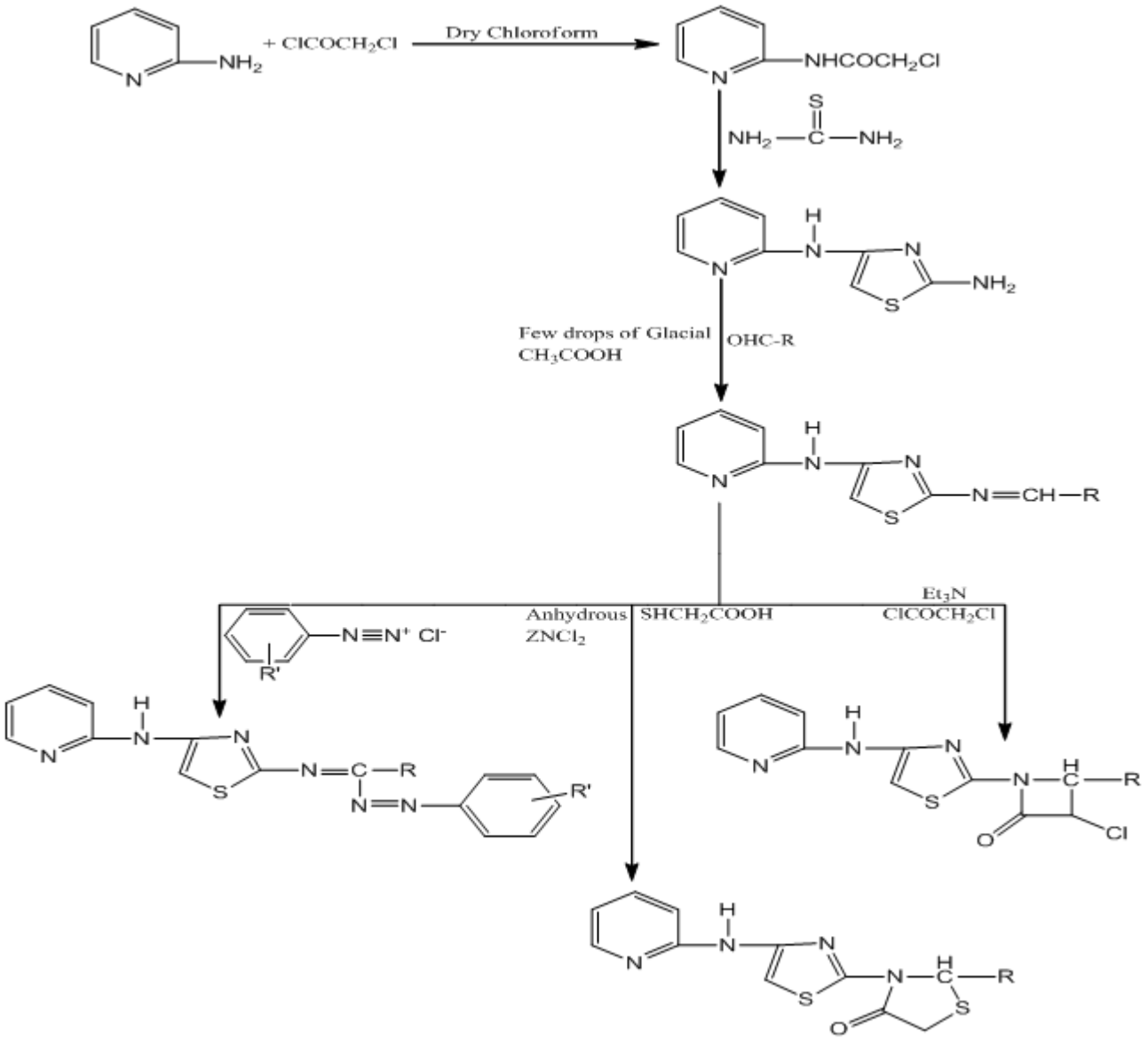
Compounds	R'	R	Concentration	Mean killing time (minutes) ± S.E.M.
[@]Control			0.02 mL	720 ± 10.29
Parathion			5 g/L	280 ± 11.74$^{\Delta\Delta\Delta}$
			10 g/L	247 ± 9.29 $^{\Delta\Delta\Delta}$
			20 g/L	231 ± 13.75$^{\Delta\Delta\Delta}$
3a	-	C_6H_5	5 g/L	163.4 ± 4.72***
3b	-	3-OCH_3, 4-OH C_6H_3	5 g/L	202 ± 11.38**
3c	-	2-OHC_6H_4	5 g/L	142 ± 7.61***
3d	-	4-$OCH_3C_6H_4$	5 g/L	156.2 ± 4.07***
4a	-	C_6H_5	5g/L	117 ± 10.32***
4b	-	3-OCH_3, 4-OH C_6H_3	5g/L	139.2 ± 5.62***
4c	-	2-OHC_6H_4	5g/L	105 ± 5.72***
			10g/L	80 ± 14.57***
			20g/L	43 ± 4.03***
4d	-	4-$OCH_3C_6H_4$	5 g/L	112 ± 4.63***
5a	-	C_6H_5	5 g/L	198.6 ± 10.73**
5b	-	3-OCH_3, 4-OH C_6H_3	5 g/L	212 ± 8.31**
5c	-	2-OHC_6H_4	5 g/L	194 ± 4.30***
5d	-	4-$OCH_3C_6H_4$	5 g/L	230 ± 9.63*
6a	H	C_6H_5	5 g/L	250 ± 7.65**
6b	H	3-OCH_3, 4-OH C_6H_3	5 g/L	268 ± 6.81
6c	H	2-OHC_6H_4	5 g/L	212 ± 7.65**
6d	H	4-$OCH_3C_6H_4$	5 g/L	222.8 ± 12.14*

n = 5 in each group; $^{\Delta}P < 0.05$, $^{\Delta\Delta}P < 0.01$, $^{\Delta\Delta\Delta}P < 0.001$ in comparison to control; *P < 0.05, **P < 0.01, ***P < 0.001 in comparison to standard; [@]acetone.

Table 6. Antifungal and antibacterial activities of compounds 3a-3d, 4a-4d, 5a-5d and 6a-6d by agar diffusion and filter paper disc methods, respectively.

Compounds	Antifungal activity[#] [Diameter of the inhibition zone (mm)]					Antibacterial activity[#] [Diameter of the inhibition zone (mm)]	
	Aspergillus fumigatus	*Candida albicans ATCC 2091*	*Candida albicans ATCC 10231*	*Candida krusei G03*	*Candida glabrata H05*	*Staphyloc-occus aureus 209 p*	*Eschericia coli ESS 2231*
[@]Control	0	0	0	0	0	0	0
Fluconazole	0	29	25	19	15	—	—
Chloramp-henicol	—	—	—	—	—	20	20
3a	09	10	10	0	11	0	0
3b	0	0	0	0	0	0	0
3c	13	10	12	0	13	0	0
3d	0	10	10	09	0	0	0
4a	10	15	11	10	0	15	11
4b	11	17	14	0	11	10	13
4c	15	23	20	16	14	19	22
4d	0	14	10	0	10	13	13
5a	08	13	10	0	0	11	10
5b	10	14	12	0	08	08	10
5c	12	18	15	0	09	12	15
5d	10	13	10	0	10	10	0
6a	0	0	0	0	0	08	0
6b	10	08	10	0	0	10	0
6c	0	12	11	0	09	0	0
6d	0	0	0	0	0	0	0

[#]Concentration was 250μg /mL.
[@] 10 % DMSO in methanol
—: No activity done.
0: No inhibition zone.



SCHEME-III

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