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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4-(4-CHLOROPHENYL)-N-[(SUBSTITUTED)METHYLENE]THIAZOL-2-AMINE DERIVATIVES BEARING DIFFERENT HETEROCYCLES

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Abstract
With the aim of developing potential antimicrobial active class of compounds, a series of novel 4-(4-chlorophenyl)-N-[(substituted)methylene]thiazol-2-amines (**3a-c**) and 3-[4-(4-chlorophenyl)thiazol-2-yl]-2-(substituted)thiazolidin-4-ones (**4a-c**) were synthesized using appropriate synthetic routes. These newly synthesized compounds were evaluated for their antimicrobial activity. Structures of these compounds have been deduced upon the basis of elemental analysis and spectral data. Antibacterial activity results revealed that, compound **4a** showed promising activity versus *B. Subtilus, E. Coli* and *S. Aureus*. Antifungal activity results indicated that, **3c** and **4b** exhibited promising activity against *A. Flavus,* whereas compounds **3a** and **4a** exhibited maximum zone of inhibition against *A. Niger*.

Key words Pyrazole, Quinoline, Salicyaldehyde, Thiazole, Thiazolidinone, Antimicrobial activity.

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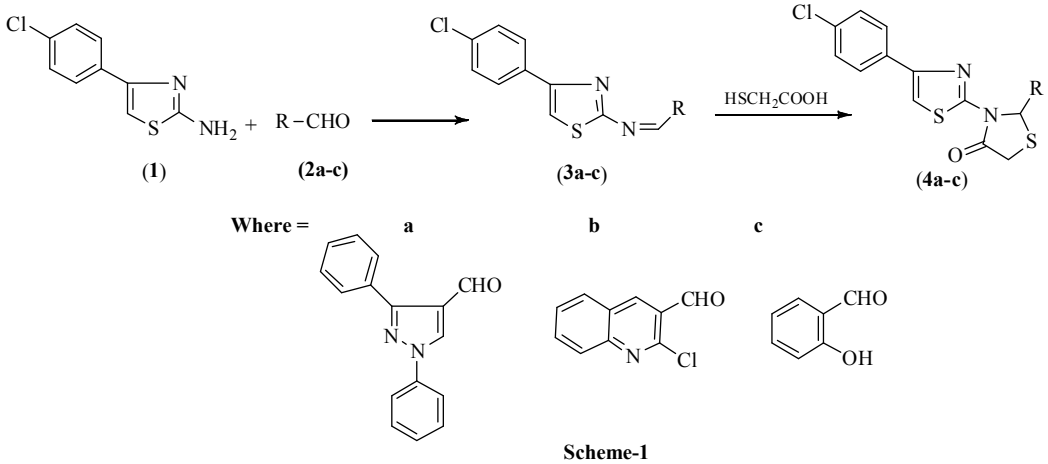
Introduction

Because of the rapid development of resistance to existing antimicrobial drugs, which posses a major threat to public health, there is a urgent need to develop new antimicrobial agents with potent activity against the resistant micro-organism. Nitrogen containing heterocyclic compounds, which are thought to be electron rich is one of the most fruitful and extensively developing fields of heterocyclic chemistry, plays an important role in diverse biological activities such as gastric ulcer, cancer[1, 2] etc. Thiazole compounds are of considerable interest from therapeutic point of view because of their utility as antimicobial,[3] anti-inflammatory,[4] analgesic,[5] antitubercular,[6] CNS stimulate,[7] anti-HIV[8] and algicidol[9] agents.

4-Thiazolidinone and their derivatives are an import class of compounds in organic and medicinal chemistry. The 4-thiazolidinone ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as, antitubercular,[10] antibacterial,[11] anti-HIV,[12] anti-inflammatory,[13] anti-mycobacterial,[14] anticonvulsant,[15] anti-histaminic,[16] anti-cancer,[17] anti-protocol,[18] analgesic[19] and antioxidant[20] activities. Based on above findings, in present communication we report the synthesis of title compounds and their antimicrobial activity.

Result and discussion

The titled compounds were synthesized as outlined in **Scheme-1**. The requisite starting materials such as 4-phenylthiazol-2-amine **(1)** were synthesized using reported procedure.[21] The precursor 4-(4-chlorophenyl)-N-[(substituted)methylene]thiazol-2-amines (**3a-c**) were synthesized by cyclocondensation of 2-amino-4-phenylthiazole (**1)** with carbaldehydes (**2a-c)**. Compounds (**3a-c**) on refluxing with thioglycolic acid in DMF afforded 3-[4-(4-chlorophenyl)thiazol-2-yl]-2-(substituted)thiazolidin-4-ones (**4a-c)**. The structures of all these previously unknown compounds were confirmed by their spectral studies and elemental analysis.



Scheme-1

4-arylthiazol-2-amine (**1**) on condensation with carboxaldehyde (**2a**) in methanol using catalytic amount of acetic acid under reflux conditions afforded 4-(4-chlorophenyl)-N-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]thiazol-2-amine (**3a**). The IR spectrum of **3a** exhibited characteristics absorption bands at 1609 and 1555 cm^{-1} due to C=N and N=CH functions, respectively. The ^1H NMR spectrums revealed characteristics signals at δ 8.80 singlet due to one proton of azomethine, the multiplet extending from 7.00-8.00 accounted for fourteen aromatic protons. Whereas singlet appeared at 6.00 and 5.00 integrating for one proton of

thiazole and pyrazole moieties, respectively. The mass spectrum of **3a** exhibited isotopic molecular ion peak at m/z 440 (M^+) and 442 (M^+ +2).

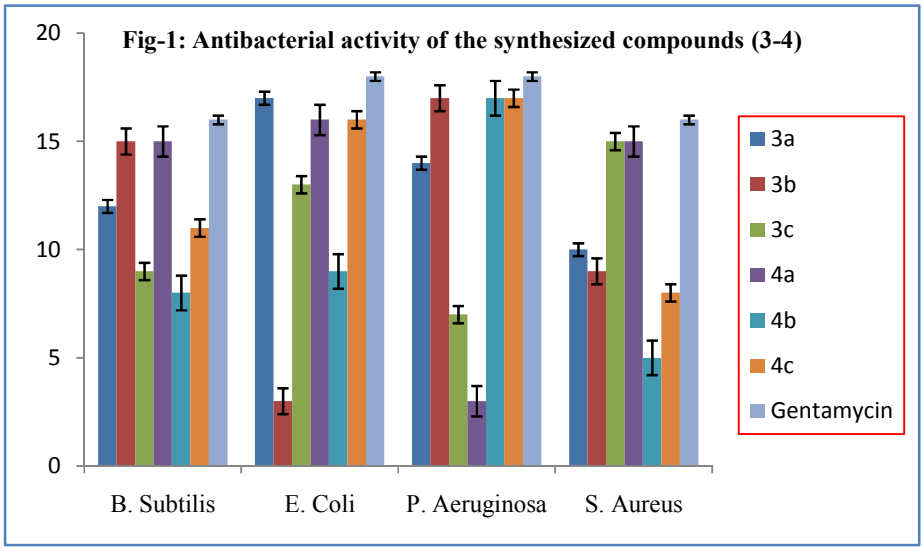
Compound **3a** on refluxing with thioglycolic acid in DMF afforded 3-[4-(4-chlorophenyl)thiazol-2-yl]-2-(1,3-diphenyl-1H-pyrazol-4-yl)thiazolidin-4-one (**4a).** The IR spectrum of **4a** exhibited characteristics absorption bands at 1720, 1605, 765 due to C=O, C=N, S-C-S, respectively. In its ^{1}H NMR spectrum, cluster of fourteen aromatic protons was resonated in the range of δ 7.10-8.05. Whereas singlet appeared at 6.20 and 5.80 integrating for one proton of thiazole and pyrazole system, respectively. A singlet resonated at 5.30 was accounted for the one protons of CH-N, whereas singlet appeared at 5.00 integrating for two protons was attributed to CH_2CO. The mass spectrum of **4a** exhibited isotopic molecular ion peaks at m/z 514 (M^+) and 516 (M^++2) confirming the chlorine substitution.

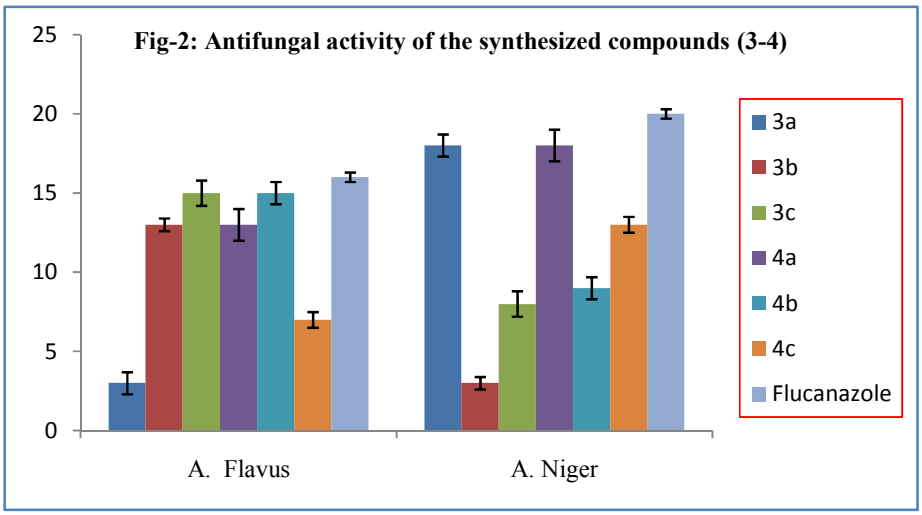
Antimicrobial activity

The newly synthesized compounds **(3-4)** were evaluated for their antibacterial activity against *B. Subtilis, E. Coli, P. Aerginosa* and *S. Aureus* and for antifungal activity against *A. Flavus* and *A. Niger* by cup-plate method at a concentration of 1mg/mL following reported procedure.[22] The zones of inhibition were compared with the standards Gentamycine and Flucanazole for antibacterial and antifungal activity, respectively. The results are reported in **Fig-1** and **2**.

The investigation of antibacterial screening revealed that, compounds **3b** and **4a** showed maximum zone of inhibition against *B. Subtilis.* Compounds **3a**, **4a** and **4c** showed maximum zone of inhibition against *E. Coli.* Whereas, compounds **3b**, **4b** and **4c** showed good zone of inhibition against *P. Aerginosa.* Compounds **3c** and **4a** exhibited the maximum zone of inhibitory against *S. Aureus.*

In case of antifungal screening, compounds **3c** and **4b** exhibited promising activity against *A. Flavus,* whereas compounds **3a** and **4a** exhibited maximum zone of inhibition against *A. Niger.* Remaining other compounds showed poor activity against all the bacterial and fungal strains.





Experimental Section

All the reagents were obtained commercially and used by further purification. Melting points were determined by an open capillary method and are uncorrected. Purity of the compounds was checked by thin layer chromatography using silica gel-G coated Al plates (Merck) and spots were visualized by exposing the dry plates in iodine vapors, using benzene/ethyl acetate and/or toluene/ethyl acetate. The IR (KBr pellet) spectra were recorded on a Perkin-Elmer (Spectrum ONE) FT-IR Spectrometer. The ^{1}H NMR (DMSO-d_6) spectra were recorded with a BRUKER NMR 500 MHz spectrometer, the chemical shift values are expressed in ppm (δ scale) using tetramethylsilane as an internal standard. The mass spectral measurements were carried out by Electron Impact method on JEOL GC mate spectrometer at 70 eV. Elemental analyses were performed on flash EA 1112 series elemental analyzer. All the compounds gave C, H and N analysis within ± 0.4 %.

General procedure for synthesis of 4-(4-chlorophenyl)thiazol-2-amine (1)

These compounds were prepared by following literature procedure.[21]

General procedure for synthesis of 1, 3-diphenyl-1*H*-pyrazole-4-carboxyaldehyde (2a)

5.4 ml of phenyl hydrazine (0.01 mol) and 6 mL of acetophenone (0.01 mol) are taken in a round bottom flask and heated for 15 min, add 20 mL of DMF and shake then prepare Vilsmeier reagent [i.e by mixing phosphorous oxychloride and dimethyl formamide (0.03 mol each) maintaining a temperature of 0-5 ^{0}C], add the reagents to the round bottom flask drop wise by cooling and reflux for 5 h. Basify the solution with 25 % ammonia, solid separated is filtered and washed with water, dried and recrystallized with hexane and ethyl acetate (1:1) to furnish **(2a).**

General procedure for synthesis of 2-chloroquinoline-3-carboxyaldehyde (2b)

Dimethylformamide (0.06 mol) was cooled to 0 ^{0}C in flask equipped with a drying tube and phosphorousoxychloride (0.06 mol) was added drop wise with constant stirring at room temperature. To this solution acetanilide (0.01 mol) was added in small portions and after 5 min, the reaction mixture was refluxed for 16 h on boiling water bath. The reaction mixture was decomposed in crushed ice and stirred for 30 min. The solid separated was filtered, washed with water, dried and recrystallized from ethyl acetate to furnish **(2b).**

General procedure for the synthesis of 4-(chlorophenyl)-N-[(substituted-yl)methylene]thiazol-2-amines (3a-c)

A mixture of compounds **1** (0.01 mol) and carboxaldehydes (**2a-c)** (0.01 mol) containing 4-5 drops of glacial acetic acid was refluxed in methanol (35 mL) on a water bath for 6 h. The reaction contents were cooled to room temperature and poured into ice-cold water. The resulting solid was filtered, washed with sodium bisulphate solution then with water, dried and recrystalized from ethanol (**3a-c**). Physical data and spectral data are tabulated in **Table-1** and **2.**

General procedure for the synthesis of 3-(4-(chlorodphenyl)thiazol-2-yl)-2-(substituted-yl)thiazolidin-4-ones (4a-c).

A mixture of compounds **3a-c** (0.01 mol) and thioglycolic acid (0.01 mol) containing a pinch of anhydrous zinc chloride in DMF (30 mL) was refluxed for 8 h. The mixture was then cooled to room temperature and poured into ice-cold water. The separated product was filtered, washed with saturated sodium carbonate solution to remove unreacted thioglycolic acid followed by cold-water, dried and recrystallized from ethanol to get pure (**4a-c)**. Physical and spectral data of compounds are tabulated in **Table-1** and **2.**

Conclusion

The present work reports the synthesis of novel 4-(4-chlorophenyl)-N-[(substituted) methylene]thiazol-2-amines and thiazolidinones in simple reaction conditions and evaluated for antimicrobial activity.

Table-1: Physical data of synthesized compounds (3-4)

Comp No	Substitution R	Molecular formula	Yield (%)	M. P. (°C)	Elemental Analysis. Calculated (found)		
					C	H	N
3a		$C_{25}H_{17}N_4ClS$	67	227-28	68.10 (68.07)	3.89 (3.86)	12.71 (12.72)
3b		$C_{19}H_{11}N_3SCl_2$	64	206-07	59.38 (59.35)	2.89 (2.88)	10.93 (10.91)
3c		$C_{16}H_{11}N_2OSCl$	70	218-19	61.05 (61.00)	3.52 (3.50)	8.90 (8.88)
4a		$C_{27}H_{19}N_4OS_2Cl$	61	250-51	62.96 (62.94)	3.72 (3.70)	10.88 (10.85)
4b		$C_{21}H_{13}N_3OS_2Cl_2$	60	225-26	55.02 (55.00)	2.86 (2.83)	9.17 (9.15)
4c		$C_{18}H_{13}N_2O_2S_2Cl$	63	232-33	55.59 (55.56)	3.37 (3.35)	7.20 (7.18)

Table No-2: Spectral data of synthesized compounds (3-4)

Comp No	IR(KBr) cm^{-1}	^1H NMR (DMSO) δ ppm	MS m/z $[M^+]$
3a	1609 (C=N), 1555 (N=CH)	8.80 (s, 1H, N=CH), 7.00-8.00 (m, 14H, Ar-H), 6.00 (s, 1H, thiazole-CH), 5.00 (s, 1H, pyrazole-CH)	440, 442
3b	1623 (C=N), 1583 (N=CH)	9.00 (s, 1H, N=CH), 7.00-8.00 (m, 9H, Ar-H), 6.00 (s, 1H, thiazole-CH)	383, 385
3c	3320 (OH), 1645 (C=N), 1600 (N=CH)	10.10 (s, 1H, OH), 9.05 (s, 1H, N=CH), 6.98-7.85 (m, 8H, Ar-H), 6.00 (s, 1H, thiazole-CH)	314, 316
4a	1720 (C=O), 1605 (C=N), 765 (C-S-C)	7.10-8.05 (m, 14H, Ar-H), 6.20 (s, 1H, thiazole-CH), 5.80 (s, 1H, pyrazole-CH), 5.30 (s, 1H, CHN), 5.00 (s, 2H, CH_2CO)	514, 516
4b	1715 (C=O), 1630 (C=N), 760 (C-S-C)	7.00-8.00 (m, 9H, Ar-H), 6.00 (s, 1H, thiazole-CH), 5.15 (s, 1H, CHN), 5.00 (s, 2H, CH_2CO)	456, 458
4c	3300 (OH), 1718 (C=O), 1625 (C=N), 768 (C-S-C)	10.00 (s, 1H, OH), 6.95-7.80 (m, 8H, Ar-H), 6.10 (s, 1H, thiazole-CH), 5.10 (s, 1H, CHN), 5.00 (s, 2H, CH_2CO)	388, 390

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