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Efficient Synthesis of Novel Thiazole Substituted Pyrrolidine Derivatives and their Antimicrobial Evaluation

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A series of new molecules containing pyrrolidine and thiazole moiety (**4a-l**) were designed and synthesized. The structures of the synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral data. All the synthesized compounds were screened for their antibacterial activity against strains of bacteria as well as antifungal activity against fungal strains. Minimum inhibitory concentrations (MICs) of all the synthesized compounds were determined. The screening of title compounds revealed that most of the tested compounds showed moderate to good microbial inhibitions.

Keywords: Pyrrolidine, Thiazole, Antimicrobial activity.

INTRODUCTION

There are many types of nitrogen-containing heterocyclic compounds, which are commonly found in drug molecules and natural products. Among them, pyrrolidine is a five-membered heterocyclic compound containing nitrogen, which has the characteristics of small ring tension and high stability [1,2] and also constitutes a very important class of natural alkaloids [3]. It is imperative in pharmacologically active molecules and widely used. The pyrrolidine ring is one of the important moiety in medicinal chemistry [4], as this compound is present in the molecular structure of many drugs [5] and alkaloids [6]. The compounds containing a pyrrolidine ring exhibit various significant pharmacological activities such as antimycobacterial and antibacterial [7-10], antiamnesic [11], anticonvulsant [12], urinary incontinence [13], anticancer [14] and other pharmacological activities such as antidiabetic [15] and potent neuraminidase inhibitors [16].

Chiral pyrrolidines are an important unit of many natural alkaloids and pharmaceutical active molecules. Some molecules containing pyrrolidine structures have therapeutic values such as antibiotics, dipeptidyl peptidase IV inhibitor and for treatment of ulcerative colitis and Crohn′s disease [17], *etc*., which makes them more and more demand in the market. Therefore, the synthesis of chiral pyrrolidine compounds has attracted widespread attention from researchers.

Thiazole is one of the most-studied medicinally active moiety in recent years. Thiazoles are nitrogen and sulfur-containing heterocyclic compounds. It is present in the structure of many biologically important synthetic or natural products [18]. Hydrazones containing azomethine (-NH-N=C) constitute an important class of compounds for new drug development [19]. It is known that thiazole derivatives which exhibits antibacterial activity [20,21], antitubercular [22], anticonvulsant [23], anticancer [24,25] as well as a wide range of other pharmacological activities such as antiviral [26], antimalarial [27], antitumor [28,29] and P13 kinase inhibitor [30].

The structural diversity and biological importance of pyrrolidine and thiazoles have made them attractive targets for synthesis. Pyrrolidine and thiazole ring present in the same molecule could be convenient models for investigation of their biological activity. The literature revealed many routes for synthesis of

such thiazolylpyrrolidine, which include condensation of thiosemicarbazone with phenacyl bromide or condensation of hydrazino thiazoles with aromatic aldehyde or acetophenone.

EXPERIMENTAL

All the chemicals used for reactions were purchased from Sigma-Aldrich and solvents were distilled before use. Reaction progress was monitored by thin-layer chromatography using Merck silica gel 60 F_{254} plates. Melting points are uncorrected. ^{1}H NMR (300 MHz) spectra were recorded on Varian mercury spectrometer (300). The solvents used for NMR spectra were $CDCl_3$ and DMSO-d_6. Infrared spectra were recorded on Shimadzu FTIR-8400S using KBr pellets. The mass spectra were recorded on Agilent 1100 mass spectrometer with an ionization potential of 70 eV.

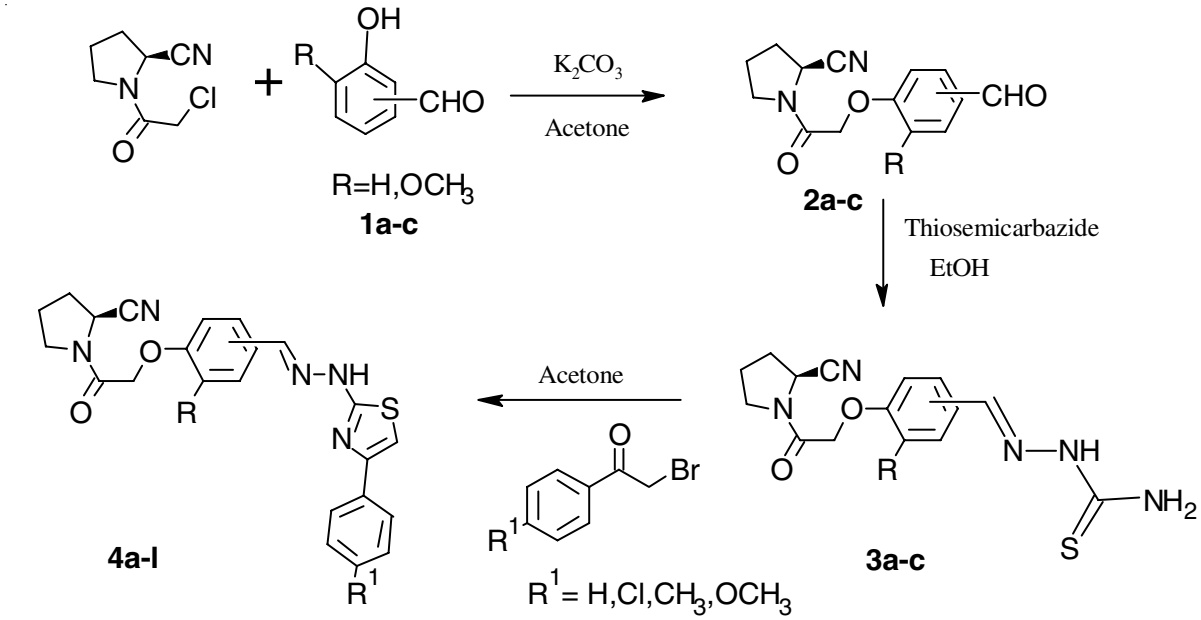
(2*S*)-1-Chloroacetyl-2-cyanopyrolidine was synthesized using L-prolinamide, chloroacetyl chloride and subsequent dehydration using $POCl_3$ in MDC as solvent by literature procedure [31].

Synthesis of (2*S*)-1-[formyl substituted aryl)acetyl]-pyrrolidine-2-carbonitrile (2a-c): A mixture of substituted hydroxybenzaldehyde (**1a-c**, 1 mmol), 1-chloroacetyl-2-cyanopyrrolidine (1 mmol) and K_2CO_3 (1 mmol) in acetone (20 mL) was refluxed for overnight. After the completion of the reaction, the reaction mixture was filtered. The filtrate concentrated under vacuum and poured ice-cold water. The product separated was filtered, washed with water and recrystallized from ethanol (**Scheme-I**).

1-[2-(2-Formylphenoxy)acetyl]pyrrolidine-2-carbonitrile (2a): Off-white solid; m.p: 74-80 ºC ; yield: 88% , IR (KBr, ν_{max}, cm^{-1}): 2962 (C-H *str*., aliph.), 2800 (C-H, aldehyde), 2242 (C≡N, nitrile), 1660 (C=O, amide), 1190 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.05 (m, 2H, -CH_2), 2.16 (m, 2H, -CH_2), 3.52 (m, 1H), 3.68 (t, 1H), 4.79 (q, 1H, -CHCN), 5.06 (s, 2H, -CH_2O), 7.11 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.18 (d, 1H, *J* = 9 Hz, Ar-H), 7.63 (m, 1H, Ar-H), 7.72 (dd, 1H, Ar-H), 10.47 (s, 1H, -CHO); ESI-MS (*m/z*): 259 $[M+H]^+$, 281 $[M+Na]^+$.

1-[2-(4-Formylphenoxy)acetyl]pyrrolidine-2-carbonitrile (2b): Light yellow solid; m.p: 96-100 ºC; yield: 89%, IR (KBr, ν_{max}, cm^{-1}): 2965 (C-H *str*., aliph.), 2804 (C-H, aldehyde), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1191(C-O, *str*.); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.06 (m, 2H, -CH_2), 2.17 (m, 2H, -CH_2), 3.52 (m, 1H), 3.68 (t, 1H), 4.79 (q, 1H, -CHCN), 4.99 (s, 2H, -CH_2O), 7.13 (dd, 2H, J_1 = 8.5 Hz, J_2 = 2.8 Hz, Ar-H), 7.86 (dd, 2H, *J* = 9 Hz, Ar-H), 9.88 (s, 1H, -CHO); ESI-MS (*m/z*): 259 $[M+H]^+$, 281 $[M+Na]^+$.

1-[2-(4-Formyl-2-methoxyphenoxy)acetyl]pyrrolidine-2-carbonitrile (2c): Off white solid; m.p: 80-85 ºC; yield: 88%, IR (KBr, ν_{max}, cm^{-1}): 2965 (C-H *str*., aliph.), 2804 (C-H, aldehyde), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1191 (C-O, *str*.); ^{1}H NMR (DMSO-d_6) δ (ppm): 2.04 (m, 2H, -CH_2), 2.16 (m, 2H, -CH_2), 3.52 (m, 1H), 3.68 (t, 1H), 3.86 (s, 3H, -OCH_3), 4.79 (q, 1H, -CHCN), 4.98 (s, 2H, -CH_2O), 7.09 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.43 (d, 1H, *J* = 2.1 Hz, Ar-H), 7.51 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.1Hz), 9.85 (s, 1H, -CHO); ESI-MS (*m/z*): 289 $[M+H]^+$.



Compound	Ar- CHO	Ar^{1}COCH$_2$Br
4a	2-OH	H
4b	2-OH	4-Cl
4c	2-OH	4-CH_3
4d	2-OH	4-OCH_3
4e	4-OH	H
4f	4-OH	4-Cl
4g	4-OH	4-CH_3
4h	4-OH	4-OCH_3
4i	2-OCH_3,4-OH	H
4j	2-OCH_3,4-OH	4-Cl
4k	2-OCH_3,4-OH	4-CH_3
4l	2-OCH_3,4-OH	4-OCH_3

Scheme-I: Synthetic route of compounds **4a-l**

Synthesis of (2*S*) {[2-(2-cyanopyrrolidin-1-yl)-2-oxoethoxy]-substituted arylidine}thiosemicarbazide (3a-c): A mixture of (2*S*)-1-[formyl substituted aryl)acetyl]pyrrolidine-2-carbonitrile (**2a-c**) (1 mmol) and thiosemicarbazide (1 mmol) in absolute ethanol (20 mL) was refluxed for overnight. After completion of reaction, cooled mixture to room temperature. The product separated out was filtered, washed with ethanol, dried and recrystallized from ethanol (**Scheme-I**).

(*E*)-{2-[2-(2-cyanopyrrolidin-1-yl)-2-oxoethoxy]-benzylidene}thiosemicarbazide (3a): Light off white; m.p: 142-148 ºC; yield: 78%; IR (KBr, ν_{max}, cm^{-1}): 3309 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N),1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.05 (m, 2H, -CH_2), 2.16 (m, 2H, -CH_2), 3.52 (m, 1H), 3.68 (t, 1H), 4.79 (q, 1H, -CHCN), 5.06 (s, 2H, -CH_2O), 7.11 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.18 (d, 1H, *J* = 9 Hz, Ar-H), 7.63 (m, 1H, Ar-H), 7.72 (dd, 1H, Ar-H), 7.89 (s, 1H, -CH=N), 8.0 & 8.1 (2bs, 2H, -NH_2), 11.3 (1H, -NH); ESI-MS (*m/z*): 332 $[M+H]^+$, 354 $[M+Na]^+$.

(*E*)-({4-[2-(2-Cyanopyrrolidin-1-yl)-2-oxoethoxy]-benzylidene}thiosemicarbazide (3b): Light yellow solid; m.p: 155-160 ºC; yield: 80%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S)1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.17 (m, 2H, -CH_2), 3.51 (m, 1H), 3.68 (t, 1H), 4.79 (q, 1H, -CHCN), 4.88 (s, 2H, -CH_2O), 6.96 (dd, 2H, J_1 = 8.5 Hz, J_2 = 2.8 Hz, Ar-H), 7.73 (dd, 2H, *J* = 9 Hz, Ar-H), 7.92 & 8.11 (2bs, 2H, -NH_2), 7.99 (s, 1H, -CH=N), 11.32 (s, 1H, -NH); ESI-MS (*m/z*): 332 $[M+H]^+$, 354 $[M+Na]^+$.

{4-[2-(2-Cyanopyrrolidin-1-yl)-2-oxoethoxy]-3-methoxy-benzylidene}thiosemicarbazide (3c): Light yellow solid; m.p: 116-122 ºC; yield: 85%, IR (KBr, ν_{max}, cm^{-1}): 3287 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.04 (m, 2H,-CH_2), 2.16 (m, 2H, -CH_2), 3.51 (m, 1H), 3.68 (t, 1H), 3.86 (s, 3H, -OCH_3), 4.76 (q, 1H, -CHCN), 4.85 (s, 2H,-CH_2O), 6.89 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.11 (d, 1H, *J* = 2.1 Hz, Ar-H), 7.54 (dd, 1H , J_1 = 8.3 Hz, J_2 = 2.1 Hz), 7.96 (s, 1H, -CH=N), 8.02 & 8.16 (2bs, 2H, -NH_2), 11.33 (s, 1H, -NH); ESI-MS (*m/z*): 362 $[M+H]^+$, 384 $[M+Na]^+$.

Synthesis of 1-(2-(substituted-((2-(4-aryl thiazol-2-yl)-hydrazono)methyl)phenoxy)acetyl)pyrrolidine-2-carbonitrile (4a-l): A mixture of {[2-(2-cyanopyrrolidin-1-yl)-2-oxoethoxy]-substituted arylidine}thiosemicarbazide and substituted phenacyl bromide refluxed in acetone for 7-8 h. After completion of reaction, cooled reaction mixture to room temperature. The product separated out was filtered, dried and recrystallized from ethanol (**Scheme-I**).

(*S*,*E*)-1-(2-{2-[(4-Phenyl thiazol-2-yl)hydrazonomethyl]-phenoxy}acetyl)pyrrolidine-2-carbonitrile (4a): Light brown solid; m.p: 130-136 ºC; yield:74%, IR (KBr, ν_{max}, cm^{-1}): 3287 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.01 (m, 2H, -CH_2), 2.18 (m, 2H, -CH_2), 3.54 (m, 1H), 3.7 (t, 1H), 4.80 (q, 1H, -CHCN), 4.97 (s, 2H, -CH_2O), 7.0-7.83 (10H, Ar-H & thiazole-H) , 8.46 (s, 1H, N=C-H), 12.26 (s, 1H, -NH); ESI-MS (*m/z*): 432 $[M+H]^+$, 454 $[M+Na]^+$.

(*S*,*E*)1-[2-(2-{[4-(4-Chlorophenyl)thiazol-2-yl]hydrazonomethyl}phenoxy)acetyl]pyrrolidine-2-carbonitrile (4b): Light brown solid; m.p: 110-116 ºC; yield: 70%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.18 (m, 2H, -CH_2), 3.53 (m, 1H), 3.70 (t, 1H), 4.79 (q, 1H, -CHCN), 5.01 (s, 2H, -CH_2O), 6.99-7.87 (9H, Ar-H & thiazole H), 8.45 (s, 1H, N=C-H), 12.22 (s, 1H, -NH); ESI-MS (*m/z*): 466 $[M+H]^+$, 488 $[M+Na]^+$.

(*S*,*E*)-1-(2-{2-[(4-*p*-Tolyl-thiazol-2-yl)-hydrazono-methyl]phenoxy}acetyl)pyrrolidine-2-carbonitrile (4c): Light brown solid; m.p: 124-128 ºC; yield: 70%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.18 (m, 2H, -CH_2), 2.32 (s, 3H, Ar-CH_3), 3.53 (m, 1H), 3.70 (t, 1H), 4.79 (q, 1H, -CHCN), 5.01 (s, 2H, -CH_2O), 6.99-7.98 (9H, Ar-H & thiazol-H), 8.24 (s, 1H, N=C-H), 12.01 (s, 1H, -NH); ESI-MS (*m/z*): 446 $[M+H]^+$, 468 $[M+Na]^+$.

(*S*,*E*)-1-[2-(2-{[4-(4-Methoxyphenyl)thiazol-2-yl]-hydrazonomethyl}phenoxy)acetyl]pyrrolidine-2-carbonitrile (4d): Light brown solid; m.p: 130-136 ºC; yield: 78%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.18 (m, 2H, -CH_2), 2.4 (s, 3H, Ar-OCH_3), 3.53 (m, 1H), 3.70 (t, 1H), 4.79 (q, 1H, -CHCN), 5.01 (s, 2H, -CH_2O), 7.01-7.98 (9H, Ar-H & thiazole H), 8.26 (s, 1H, N=C-H), 12.18 (s, 1H, -NH); ESI-MS (*m/z*): 462 $[M+H]^+$, 484 $[M+Na]^+$.

(*S*,*E*)-1-(2-{4-[(4-Phenylthiazol-2-yl)hydrazonomethyl]-phenoxy}acetyl)pyrrolidine-2-carbonitrile (4e): Brown solid; m.p: 185-190 ºC; yield: 78%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H stret.), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.17 (m, 2H, -CH_2), 3.51 (m, 1H), 3.68 (t, 1H), 4.79 (q, 1H, -CHCN), 4.88 (s, 2H, -CH_2O), 7.0-7.83 (10H, Ar-H & thiazole-H), 8.46 (s, 1H, N=C-H), 12.26 (s, 1H, -NH); ESI-MS (*m/z*): 432 $[M+H]^+$, 454 $[M+Na]^+$.

(*S*,*E*)-1-[2-(4-{[4-(4-Chlorophenyl)thiazol-2-yl]hydrazonomethyl}phenoxy)acetyl]pyrrolidine-2-carbonitrile (4f): Light brown solid; m.p: 200-206 ºC; yield: 70%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.18 (m, 2H, -CH_2), 3.53 (m, 1H), 3.70 (t, 1H), 4.79 (q, 1H, -CHCN), 5.01 (s, 2H, -CH_2O), 6.99-7.87 (9H, Ar-H & thiazole-H), 8.45 (s, 1H, N=C-H), 12.22 (s, 1H, -NH); ESI-MS (*m/z*): 466 $[M+H]^+$, 488 $[M+Na]^+$.

(*S*,*E*)-1-(2-{4-[(4-*p*-Tolyl-thiazol-2-yl)-hydrazono-methyl]phenoxy}acetyl)pyrrolidine-2-carbonitrile (4g): Light brown solid; m.p: 145-150 ºC; yield: 70%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243(C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.18

(m, 2H, -CH_2), 2.32 (s, 3H, Ar-CH_3), 3.53 (m, 1H), 3.70 (t, 1H), 4.79 (q, 1H, -CHCN), 5.01 (s, 2H, -CH_2O), 6.99-7.98 (9H, Ar-H & thiazole-H), 8.24 (s, 1H, N=C-H), 12.01 (s, 1H, -NH); ESI-MS(*m/z*): 446 $[M+H]^+$, 468 $[M+Na]^+$.

(*S,E*)-1-[2-(4-{[4-(4-Methoxyphenyl)thiazol-2-yl]hydrazonomethyl}phenoxy)acetyl]pyrrolidine-2-carbonitrile (4h): Light brown solid; m.p: 160-166 ºC; yield: 78%; IR (KBr, ν_{max}, cm^{-1}): 3285 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (m, 2H, -CH_2), 2.18 (m, 2H, -CH_2), 3.4 (s, 3H, Ar-OCH_3), 3.53 (m, 1H), 3.70 (t, 1H), 4.79 (q, 1H, -CHCN), 5.01 (s, 2H, -CH_2O), 7.01-7.98 (9H, Ar-H & thiazole-H), 8.26 (s, 1H, N=C-H), 12.18 (s, 1H, -NH); ESI-MS (*m/z*): 462 $[M+H]^+$, 484 $[M+Na]^+$.

(*S,E*)-1-(2-{2-Methoxy-4-[(4-phenylthiazol-2-yl)-hydrazonomethyl]phenoxy}acetyl)pyrrolidine-2-carbonitrile (4i): Light brown solid; m.p: 158-164 ºC; yield: 85%, IR (KBr, ν_{max}, cm^{-1}): 3287 (N-H *str.*), 2965 (C-H str., aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.04 (m, 2H,-CH_2), 2.16 (m, 2H, -CH_2), 3.51 (m, 1H), 3.68 (t, 1H), 3.86 (s, 3H, -OCH_3), 4.76 (q, 1H, -CHCN), 4.85 (s, 2H, -CH_2O), 6.99-7.98 (9H, Ar-H & thiazole-H), 8.20 (s, 1H, N=C-H), 12.03 (s, 1H, -NH); ESI-MS (*m/z*): 462 $[M+H]^+$, 484 $[M+Na]^+$.

(*S,E*)-1-[2-(4-{[4-(4-Chlorophenyl)thiazol-2-yl]hydrazonomethyl}-2-methoxyphenoxy)acetyl]pyrrolidine-2-carbonitrile (4j): Light yellow solid; m.p: 205-210 ºC; yield: 85%, IR (KBr, ν_{max}, cm^{-1}): 3287 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.04 (m, 2H, -CH_2), 2.16 (m, 2H, -CH_2), 3.51 (m, 1H), 3.68 (t, 1H), 3.86 (s, 3H, -OCH_3), 4.76 (q, 1H, -CHCN), 4.85 (s, 2H, -CH_2O), 6.99-7.98 (8H, Ar-H & thiazole-H), 8.24 (s, 1H, N=C-H), 12.05 (s, 1H, -NH); ESI-MS (*m/z*): 497$[M+H]^+$, 519 $[M+Na]^+$.

(*S,E*)-1-(2-{2-Methoxy-4-[(4-*p*-tolylthiazol-2-yl)-hydrazonomethyl]phenoxy}acetyl)pyrrolidine-2-carbonitrile (4k): Light yellow solid; m.p: 185-190 ºC; yield: 85%, IR (KBr, ν_{max}, cm^{-1}): 3287(N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.04 (m, 2H, -CH_2), 2.16 (m, 2H, -CH_2), 2.35 (s, 3H, CH_3), 3.51 (m, 1H), 3.68 (t, 1H), 3.86 (s, 3H, -OCH_3), 4.76 (q, 1H, -CHCN), 4.85 (s, 2H, -CH_2O), 6.99-7.98 (8H, Ar-H & thiazole-H), 8.23 (s, 1H, N=C-H), 12.07 (s, 1H, -NH); ESI-MS (*m/z*): 476 $[M+H]^+$, 498 $[M+Na]^+$.

(*S,E*)-1-[2-(2-Methoxy-4-{[4-(4-methoxyphenyl)thiazol-2-yl]hydrazonomethyl}phenoxy)acetyl]pyrrolidine-2-carbonitrile (4l): Light yellow solid; m.p: 210-215 ºC; yield: 85%, IR (KBr, ν_{max}, cm^{-1}): 3287 (N-H *str.*), 2965 (C-H *str.*, aliph.), 2243 (C≡N, nitrile), 1662 (C=O, amide), 1608 (-C=N), 1269 (-C=S), 1191 (C-O, *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 2.04 (m, 2H, -CH_2), 2.16 (m, 2H, -CH_2), 3.51 (m, 1H), 3.68 (t, 1H), 3.86 (s, 3H, -OCH_3), 4.76 (q, 1H, -CHCN), 4.85 (s, 2H, -CH_2O), 6.99-7.98 (8H, Ar-H & thiazole-H), 8.21 (s, 1H, N=C-H), 12.04 (s, 1H, -NH); ESI-MS (*m/z*): 492 $[M+H]^+$, 514 $[M+Na]^+$.

Antimicrobial assay: All the synthesized compounds were evaluated for their antimicrobial activity by the agar-well diffusion technique. For the antimicrobial and antifungal medium study, Muller-Hinton agar and Czapek Dox broth were used respectively. The evaluation is done by using bacteria incubated for 24 h at 37 ºC and fungi were seeded by cooling at 25 ºC for 48 h. The pathogens strain was collected from the National Chemical Laboratory (NCIM), Pune, India. The compounds were diluted in DMSO for the required concentration for bioassay. DMSO was also loaded as control. To evaluate the potency of tested compounds under similar conditions streptomycin and griseofluvin were used as a standard drugs. The inhibition zone around each disc was measured from the center of the disc. The diameter of zone of inhibition was measured after incubation using a caliper. Each inhibition zone was measured thrice to get an average value.

RESULTS AND DISCUSSION

In the present work, 1-chloroacetyl -2-cyanopyrrolidine and substituted hydroxy benzaldehyde (**1a-c**) on reaction gives 1-[2-(substituted formyl aryl)acetyl]pyrrolidine-2-carbonitrile (**2a-c**). The substituted [2-(2-cyanopyrrolidn-1-yl)-2-oxoethoxy]-arylidines}thiosemicarbazide (**3a-c**) were synthesized by reacting 1-[2-(substituted formyl aryl)acetyl]pyrrolidine-2-carbonitrile (**2a-c**) with thiosemicarbazide using catalytic amount of acetic acid in ethanol as solvent. Compounds **3a-c** were condensed with substituted phenacyl bromide leads the formation of 1-(substituted {2-[(4-aryl thiazol-2-yl)hydrazonomethyl]-phenoxy}acetyl)pyrrolidine-2-carbonitrile (**4a-l**) as shown in **Scheme-I**. Structures of novel compounds were confirmed from analytical and spectral data (IR, ^{1}H NMR and EI-MS). The activity of thiocarbamoyl functional motif in thiosemicarbazone with phenacyl bromide was investigated. Literature discloses the use of pyridine, fused sodium acetate as a catalyst in absolute ethanol at room temperature for reaction of thiosemicarbazone with phenacyl bromide. Thiosemicarbazones **3a-c** with phenacyl bromide in acetone as solvent at reflux temperature for 5-6 h to give corresponding compounds in good yields without using a catalyst (**Scheme-I**).

The structure of intermediate **2a-c** was confirmed by IR, NMR and mass. IR spectra of compound **2** revealed in each case by absorption bands in the region of 2810-2800 and 1190-1180 cm^{-1} correspond to CHO and C-O stretching, respectively. In the NMR, compounds **2a-c** shows singlet between δ 9.8-10.5 ppm due to proton of -CHO group. The intermediates **3a-c** structure was also confirmed by using IR and ^{1}H NMR. In IR spectra, the absorption bands in the region 3395-3215, 1613-1604 and 1276-1275 cm^{-1} correspond to N-H, C=N and C=S, respectively, confirmed the structure of intermediate **3**. The structure of the title compounds has been confirmed by IR, ^{1}H NMR and MS. The IR spectra of these compounds showed a broad band at 3118-3104 cm^{-1} due to N-H group absorption. In the NMR, final compounds exhibited broad singlet between δ 12.06-11.90 ppm, due to N-H protons. The multiplet signal at δ 6.96-7.87 ppm was assigned to the aromatic protons and thiazole-H. In the NMR, compounds also exhibit singlet at δ 8.2-8.5 ppm due to presence of proton of N=C-H. In MS spectra, molecular ion peaks of all title compounds were obtained from EI-MS.

Biological activity: All the synthesized compounds **4a-l** were screened for their *in vitro* antibacterial activity against bacterial strains the standard strains *Staphylococcus aureus* (Gram-Positive), *Escherichia coli* (Gram-negative) and fungal strains *Aspergillus niger* and *Candida albicans* for their anti-fungal activity. Compound **4i** shows good activity against Gram-negative bacteria *E. coli* while compounds **4e** and **4f** show moderate activity. Compounds **4e**, **4f** and **4j** show moderate activity while compound **4i** shows good activity against S. aureus. For fungal strain *A. niger*, compound **4i** shows good while compounds **4f** and **4j** shows moderate activity. Compounds **4e** and **4f** showed a good antifungal activity against *C. albicans* while compound **4i** shows moderate activity (Table-1).

TABLE-1
in vitro ANTIMICROBIAL SCREENING OF SYNTHESIZED COMPOUNDS **4a-l** (ZONE DIAMETER OF GROWTH INHIBITION IN mm); THE MIC VALUES (µg/mL)

Compounds	*E. coli*	*S. aureus*	*A. niger*	*C. albicans*
4a	11.3 (10)	10.2 (10)	12.1 (10)	10.3 (10)
4b	11.1 (10)	10.4 (10)	11.5 (10)	10.1 (10)
4c	12.2 (10)	10.8 (10)	11.3 (10)	9.6 (10)
4d	12.7 (10)	10.9 (10)	11.1 (10)	10.7 (10)
4e	16.4 (10)	15.1 (10)	14.3 (10)	20.5 (10)
4f	16.4 (10)	15.3 (10)	15.7 (10)	21.6 (10)
4g	12.2 (10)	11.3 (10)	10.7 (10)	10.8 (10)
4h	13.4 (10)	11.6 (10)	12.3 (10)	11.2 (10)
4i	19.4 (10)	17.2 (10)	18.3 (10)	17.4 (10)
4j	12.2 (10)	15.6 (10)	15.7 (10)	13.5 (10)
4k	9.6 (10)	10.4 (10)	10.6 (10)	9.1 (10)
4l	9.6 (10)	10.2 (10)	10.3 (10)	11.3 (10)
Streptomycin	20.4 (3)	19.1 (3)	–	–
Griseofluvin	–	–	18.5 (3)	22.2 (3)

Conclusion

The synthesis and characterization of hydrazine-thiazole derivatives of pyrrolidine **4a-l** were synthesized from corresponding thiosemicarbazones and phenacyl bromide was reported. The present series of compounds were synthesized in excellent yield and most of the compounds exhibited good antimicrobial activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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