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Synthesis and Biological Evaluation of some new Azetidin-2-one and Thiazolidin-4-one Derivatives

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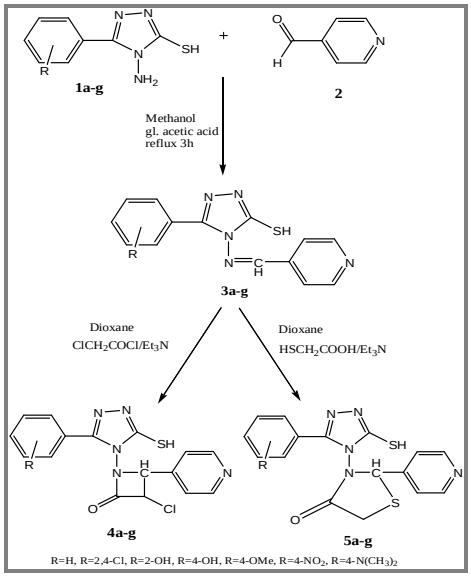
ABSTRACT

4-amino-5-substituted aryl-3-mercapto-1,2,4-triazole (3a-g) were used as key synthons for the preparation of 3-chloro-1-(3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl)-4-(pyridine-4-yl)azetidin-2-one (4a-g) and 3-(3-mercapto-5-phenyl-4H-1,2,4-triazol-4yl)-2-(pyridine-4-yl)thiazolidin-4-one (5a-g) was synthesized in order to determine their antimicrobial activity. The compounds were synthesized in good yield and the structures of newly synthesized compounds were established on the basis of their IR, ^{1}HNMR and elemental analysis. The synthesized compounds were tested in vitro antibacterial activity against B. subtilis, S. aureus, Enterobacter, K. pneumonia and antifungal activity against T. indica, Tricoderma, S. fuliginea and P.infestans by measuring the zone of inhibition in mm.

Graphical Abstract

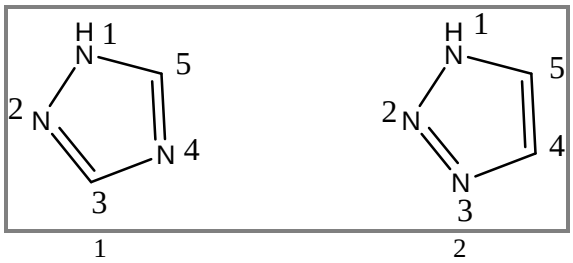


Synthesis of 4a-g and 5a-g.

Keywords: Substituted 1, 2, 4-Triazole, Pyridine Aldehyde, Schiff's base, Biological activity.

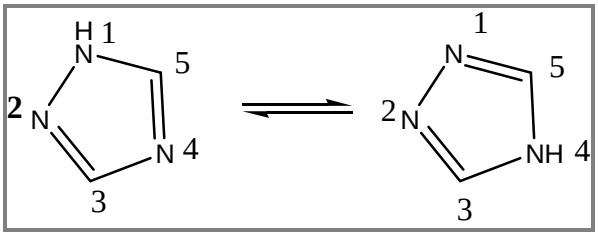
INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics and alkaloids, as well as in pharmaceuticals, herbicides, dyes, and many more compounds [**1**]. These heterocycles have great importance in drug discovery as the heteroatoms present in them make hydrogen bonds with the receptors present in the body and thus giving their significant pharmacological actions. Out of several heterocyclic compounds, those with Nitrogen atom in their structure give promising pharmacological activities**.** Triazole, also known as pyrrodiazole, is one of the classes of organic heterocyclic compounds containing a five membered di-unsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions having molecular formula $C_2H_3N_3$. Two isomers of triazole are 1, 2, 4-triazole (1) and 1, 2, 3-triazole (2):



Tautomers of 1, 2, 4-triazoles

1, 2, 4-triazoles exists in two tautomeric forms. 1*H* and 4*H*-1, 2, 4-triazole is considered to be pharmacologically important nucleus [**2**].



The synthesis of heterocyclic compound has always drawn the attention of chemist over the years mainly because of their important biological properties. Most of the researches up to early 90s focused on synthesis of azetidinones and thiazolidinone and study of their antibacterial property. In recent years, renewed interest has been focused on the synthesis and modification of azetidinones and thiazolidinone. Among the five member heterocyclic compounds, 1,2,4-trizoles has become an important synthon for the development new therapeutic agents. Compounds with 1,2,4-triazole core substantiate for broad spectrum of biological activities including antimicrobial [**3**], antifungal [**4**], anti-inflammatory [**5**], anticonvulsant [**6**], antioxidant, analgesic [**7**] and mutagenic activity [**8**]. Azetidin-2-ones are very important class of compounds possessing wide range of biological activities such as antimicrobial [**9, 10**], pesticidal [**11**], antitumor [**12**], antitubercular [**13**], anticancer [**14**], cytotoxic [**15-17**], enzyme inhibitors [**18**], elastase inhibitors [**19**] and cholesterol absorption inhibitors [**20**]. 4-thiazolidinones moiety is associated with variety of biological activities including antifungal [**21**], anti-inflammatory [**22**], anticonvulsant [**23**], antitubercular [**24**], antihistaminic [**25**].

2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among organic and medicinal chemists [**26**]. The activities of famous antibiotics penicillin's, aztreonam, and carbapenem are attributed to the presence of 2-azetidinone ring in their structure. Azetidinones are a very important class of compounds possessing a wide range of biological activities such as antimicrobial [**27**], antiviral [**28**], and others. Thiazolidin-4-one ring system is the core structure in a

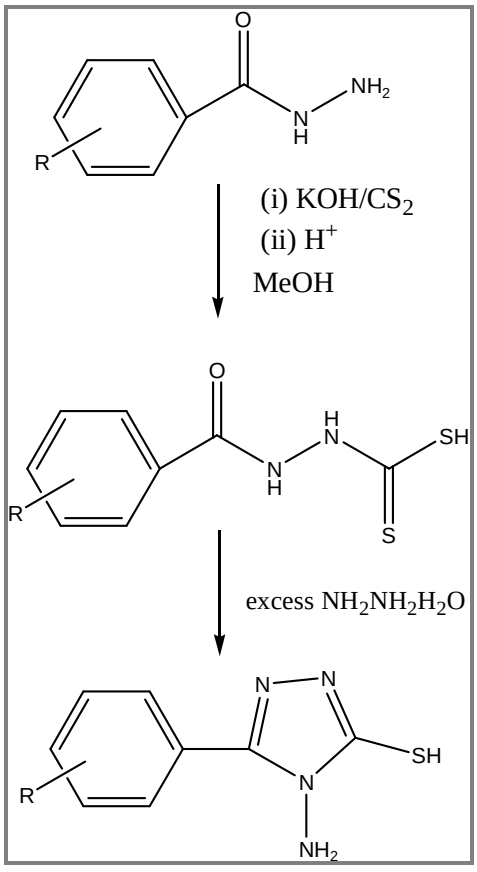
variety of synthetic pharmaceuticals with broad spectrum of biological activities, for example, antifungal [29], antitubercular [30], and others.

MATERIALS AND METHODS

Instrumentation: All chemicals were purchased from Aldrich Chemical Company (USA). They were used without further purification. All melting points that were measured with a capillary apparatus are uncorrected. All the compounds were checked by IR, ^{1}HNMR and elemental analysis. IR spectra were recorded in KBr on a Perkin-Elmer model 400 FTIR spectrometer. ^{1}HNMR spectra were recorded in DMSO at ambient temperature using a Bruker Avance II 400 NMR spectrometer. The following abbreviations were used to indicate the peak multiplicity s-singlet, d-doublet, t-triplet, m-multiplet. Column chromatography was performed on silica gel (Merck).

General procedure

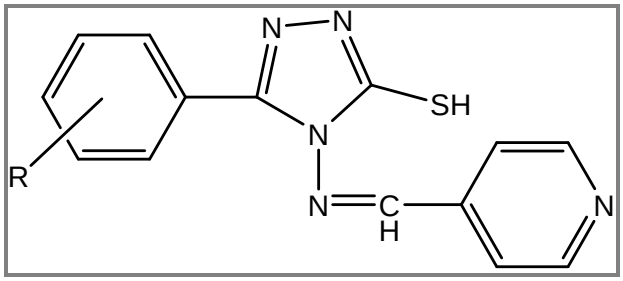
Synthesis of 4-Amino-5-substituted aryl-3-mercapto-[1,2,4]-triazoles: This compound has been prepared according to the method of E. Hoggrath *et al.*, to a methanolic solution of substituted benzohydrazide (eg. 2, 4-dichloro) (4.0 g, 0.02 M), KOH (1.5 g, 0.03 M), CS_2 (2.2 mL, 0.03 M) was added slowly with continuous shaking, after 2 h a solid mass was obtained. It was refluxed with excess oh hydrazine hydrate for 4 h. The reaction mixture was cooled, poured into cold water and neutralized with dil. HCl. Product thus obtained was filtered, washed well with water and recrystallized from aq. Ethanol. m.p. 169°C.



Synthesis of 4-amino-5-substituted aryl-3-mercapto-1, 2, 4-triazole.

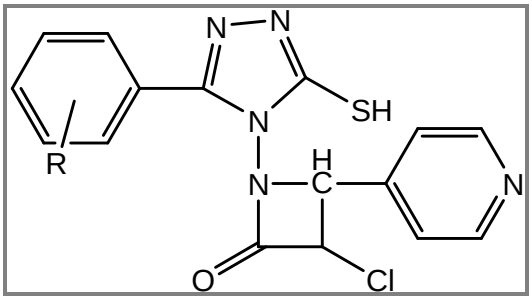
Preparation of Schiff base (3a-g): A mixture of equimolar amount (0.01) of 4-Amino-5-substituted aryl-3-mercapto-[1, 2, 4]-triazoles and pyridine aldehyde in methanol (30 mL) with 2 drops glacial

acetic acid was refluxed for 4 hrs on water bath. The reaction mixture was concentrated, cooled and poured in water; the solid obtained was filtered and recrystallized from ethanol to give Schiff base (3a-g). It was obtained in 80-85% yield.



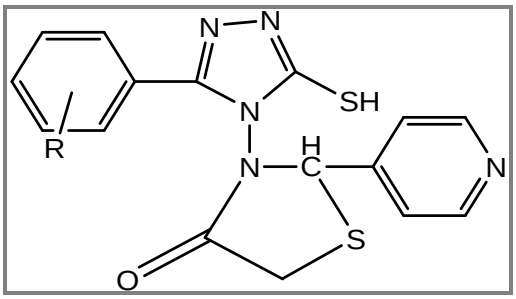
Structure of Schiff's base 3a-g.

Preparation of 2-Azetidionones (4a-g): A mixture of Schiff base (3a-g) (0.002 mol) and triethyl amine [TEA] (0.004 mol) was dissolved in 1, 4-dioxane (50 mL), cooled and stirred. To this well-stirred cooled solution chloro acetyl chloride (0.004 mmol) was added drop wise with in a period of 20 min. The reaction mixture was then stirred for an additional 3 h. Excess solvent was removed and then poured in to water, the solid mass thus obtained was filtered, washed with excess of water and then recrystallized from aq. Ethanol gave 2-azetidinones (4a-g), which were obtained in 80-85% yield.



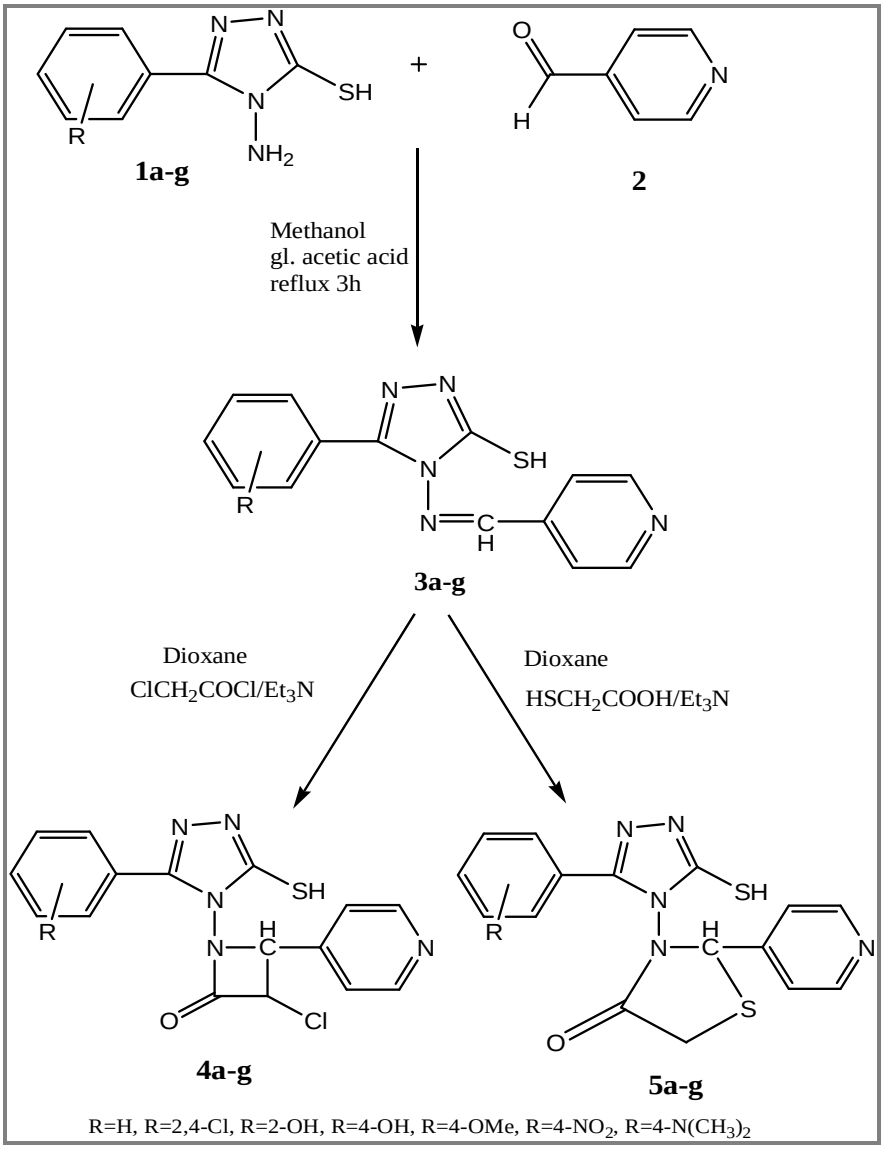
Structure of 2-azetidinone (4a-g).

Preparation of 4-Thiazolidinones (5a-g): A mixture of Schiff base (3a-g) (0.01 mmol) and triethyl amine [TEA] (0.004 mol) was dissolved in 1,4-dioxane (50 mL), cooled and stirred. To this well-stirred cooled solution mercapto acetic acid (0.004 mmol) was added drop wise with in a period of 20 min. The reaction mixture was then stirred for an additional 3 h. Excess solvent was removed and then poured in to water, the solid mass thus obtained was filtered, washed with excess of water and then recrystallized from aq. Ethanol gave 4-Thiazolidinones (5a-g), which were obtained in 80-85% yield.



Structure of 4-thiazolidinone (5a-g).

Synthetic route for the synthesis of targeted molecules



Scheme 1. Synthesis of 4a-g and 5a-g.

The analytical data of all the compounds 4a –g and 5a-g are given below;

[4a].3-chloro-1-(3-mecapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)-4-(pyridine-4-yl)azetidin-2-one: m.p. 135-138°C (yield 81%) IR (KBr)(cm^{-1}) 2462 (S-H), 1722 (C=O), 1679 (C=N), 1596 (C=C), 1452,1491,1546 (Py. ring), 1350 (C-N) 772 (C-Cl); ^{1}HNMR (DMSO-d_6) δ 13.79 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring) 7.50-8.05 (m, 5H, ArH) 5.08 (d, 1H, NCH), 4.50 (d, 1H, CHCl); Anal. calculated for $C_{16}H_{12}ClN_5OS$: C, 53.71; H, 3.38; N, 19.57; Found: C, 53.65; H, 3.32; N, 19.51.

[4b]. 3-chloro-1(3-(2,4-dichlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-4-(pyridine-4-yl) azetidin-2-one: m.p. 112-114°C (yield 84%) IR (KBr)(cm^{-1}) 2462 (S-H), 1722 (C=O), 1679 (C=N), 1596 (C=C), 1452,1491,1546 (Py. ring), 1350 (C-N) 770-772 (C-Cl); ^{1}HNMR (DMSO-d_6) δ 13.82 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring) 7.60 (s, 1H, ArH), 7.66-7.80(s, 2H, ArH), 5.06 (d, 1H, NCH), 4.52 (d, 1H, CHCl); Anal. calculated for $C_{16}H_{10}Cl_3N_5OS$: C, 45.05; H, 2.36; N, 16.41; Found: C, 45.00; H, 2.31; N, 16.35.

[4c]. 3-chloro-1(3-(2-hydroxyphenyl-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-(pyridine-4-yl) azetidin-2-one: m.p. 160-162°C (yield 84%) IR (KBr)(cm^{-1}) 3290 (Ph-OH str.), 2460 (S-H), 1725 (C=O), 1622 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1350 (C-N), 773(C-Cl); ^{1}HNMR (DMSO-d_6) δ 13.81 (br s, 1H, SH), 9.63 (s, 1H, OH), 7.35-8.55 (dd, 4H, Py. ring) 7.50-8.05 (m, 4H, ArH) 5.10 (d, 1H, NCH), 4.48 (d, 1H, CHCl); Anal. calculated for $C_{16}H_{12}ClN_5O_2S$: C, 51.41; H, 3.24; N, 18.74; Found: C, 51.34; H, 3.17; N, 18.67.

[4d]. 3-chloro-1(3-(4-hydroxyphenyl-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-(pyridine-4-yl)azetidin-2-one: m.p. 170-172°C (yield 85%) IR (KBr)(cm^{-1}) 3295 (Ph-OH str.), 2435 (S-H), 1725 (C=O), 1622 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1350 (C-N), 772 (C-Cl); ^{1}HNMR (DMSO-d_6) δ 13.79 (br s, 1H, SH), 9.72 (s, 1H, OH), 7.35-8.55 (dd, 4H, Py. ring), 6.62 (s, 2H, ArH), 7.05(s, 2H, ArH),5.06 (d, 1H, NCH), 4.50 (d, 1H, CHCl), Anal. calculated for $C_{16}H_{12}ClN_5O_2S$: C, 51.41; H, 3.24; N, 18.74; Found: C, 51.34; H, 3.17; N, 18.67.

[4e]. 3-chloro-1-(3-mercapto-5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-4-yl)-2-(pyridine-4-yl)azetidin-2-one: m.p. 150-152°C (yield 82%) IR (KBr)(cm^{-1}) 2463 (S-H), 1725 (C=O), 1620 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1350 (C-N), 772 (C-Cl); ^{1}HNMR (DMSO-d_6) δ 13.81 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring), 7.05 (s, 2H, ArH), 8.05 (s, 2H, ArH) 5.10 (d, 1H, NCH), 4.52 (d, 1H, CHCl); Anal. calculated for $C_{17}H_{14}ClN_5O_2S$: C, 47.71; H, 2.75; N, 20.86; Found: C, 47.65, H, 2.68, N, 20.80.

[4f]. 3-chloro-1(3-mercapto-5-(4-nitrophenyl)-4*H*-1, 2, 4-triazol-4-yl)-2-(pyridine-4-yl)azetidin-2-one: m.p. 220-222°C (yield 84%) IR (KBr)(cm^{-1}) 2444 (S-H), 1728 (C=O), 1628 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1530 (NO_2), 1352 (C-N), 773 (C-Cl); ^{1}HNMR (DMSO-d_6)) δ 12.98 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring), 8.04 (s, 2H, ArH), 8.27(s, 2H, ArH),5.07 (d, 1H, NCH), 4.51 (d, 1H, CHCl); Anal. calculated for $C_{16}H_{11}ClN_6O_3S$: C, 52.65; H, 3.64; N, 16.71; Found: C, 52.58; H, 3.57; N, 16.66.

[4g]. 3-chloro-1(3-(4-(dimethylamino)phenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-(pyridine-4-yl) azetidin-2-one: m.p. 178-180°C (yield 85%) IR (KBr)(cm^{-1}) 2460 (S-H), 1725 (C=O), 1624 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1352 (C-N), 773 (C-Cl); ^{1}HNMR (DMSO-d_6)) δ 13.87 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring), 6.64 (s, 2H, ArH), 7.05(s, 2H, ArH), 5.05 (d, 1H, NCH), 4.52 (d, 1H, CHCl), 3.02 (s, 6H, CH_3); Anal. calculated for $C_{18}H_{17}ClN_6OS$: C, 53.93; H, 4.27; N, 20.96; Found: C,53.85; H, 4.19, N, 20..88.

[5a]. 3-(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)-2-(pyridine-4-yl)thiazolidin-4-one: m.p. 140-141°C (yield 83%) IR (KBr)(cm^{-1}) 2456 (S-H), 1728 (C=O), 1680 (C=N), 1598 (C=C), 1452,1491,1546 (Py. ring), 1351 (C-N), 688 (C-S-C); ^{1}HNMR (DMSO-d_6) δ 13.79 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring) 7.50-8.05 (m, 5H, ArH) 5.08 (d, 1H, NCH), 4.50 (d, 1H, CHCl), 3.81 (s, 2H, thiazolidin-4-one); Anal. calculated for $C_{16}H_{13}N_5OS_2$: C, 53.71; H, 3.38; N, 19.57; Found: C, 53.65; H, 3.32; N, 19.51.

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[5c]. 3-(3-(2-hydroxyphenyl-5-mercapto--4*H*-1, 2, 4-triazol-4-yl)-2-(pyridine-4-yl)thiazolidin-4-one: m.p. 160-162°C (yield 84%) IR (KBr)(cm^{-1}) 3290 (Ph-OH str.), 2460 (S-H), 1725 (C=O), 1622 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1350 (C-N), 689 (C-S-C); ^{1}HNMR (DMSO-d_6) δ 13.81 (br s, 1H, SH), 9.63 (s, 1H, OH), 7.35-8.55 (dd, 4H, Py. ring) 7.50-8.05 (m, 4H, ArH) 5.10 (d,

1H, NCH), 4.48 (d, 1H, CHCl), 3.95 (s, 2H, thiazolidin-4-one); Anal. calculated for $C_{16}H_{13}N_5O_2S_2$: C, 51.74; H, 3.53; N, 18.86; Found: C, 51.65; H, 3.45; N, 18.79.

[5d]. 3-(3-(4-hydroxyphenyl-5-mercapto--4*H*-1, 2, 4-triazol-4-yl)-2-(pyridine-4-yl)thiazolidin-4-one: m.p. 170-172°C (yield 85%) IR (KBr)(cm^{-1}) 3295 (Ph-OH str.), 2435 (S-H), 1725 (C=O), 1622 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1350 (C-N), 709 (C-S-C); ^{1}HNMR (DMSO-d_6) δ 13.79 (br s, 1H, SH), 9.72 (s, 1H, OH), 7.35-8.55 (dd, 4H, Py. ring), 6.62 (s, 2H, ArH), 7.05(s, 2H, ArH),5.06 (d, 1H, NCH), 4.50 (d, 1H, CHCl), 3.92 (s, 2H, thiazolidin-4-one); Anal. calculated for $C_{16}H_{13}N_5O_2S$: C, 51.74; H, 3.53; N, 18.86; Found: C, 51.65; H, 3.45; N, 18.79.

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[5f]. 3-(3-mercapto-5-(4-nitrophenyl)-4*H*-1, 2, 4-triazol-4-yl)-2-(pyridine-4-yl)thiazolidin-4-one: m.p. 220-222°C (yield 84%) IR (KBr)(cm^{-1}) 2444 (S-H), 1728 (C=O), 1628 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1530 (NO_2), 1352 (C-N), 709 (C-S-C); ^{1}HNMR (DMSO-d_6) δ 12.98 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring), 8.04 (s, 2H, ArH), 8.27(s, 2H, ArH),5.07 (d, 1H, NCH), 4.51 (d, 1H, CHCl), 3.78 (s, 2H, thiazolidin-4-one); Anal. calculated for $C_{16}H_{12}N_6O_3S_2$: C, 47.99; H, 3.02; N, 20.99; Found: C, 47.90; H, 3.24; N, 16.57.

[5g]. 3-(3-(4-(dimethylamino)phenyl)-5-mercapto-4*H*-1,2, 4-triazol-4-yl)-2-(pyridine-4-yl)thiazolidin-4-one: m.p. 178-180°C (yield 85%) IR (KBr)(cm^{-1}) 2460 (S-H), 1725 (C=O), 1624 (C=N), 1600 (C=C), 1452,1492,1540 (Py. ring), 1352 (C-N), 692 (C-S-C); ^{1}HNMR (DMSO-d_6) δ 13.87 (br s, 1H, SH), 7.35-8.55 (dd, 4H, Py. ring), 6.64 (s, 2H, ArH), 7.05(s, 2H, ArH), 5.05 (d, 1H, NCH), 4.52 (d, 1H, CHCl), 3.02 (s, 6H, CH_3), 3.91 (s, 2H, thiazolidin-4-one); Anal. calculated for $C_{18}H_{18}N_6OS_2$: C, 54.25; H, 4.55; N, 21.09; Found: C,54.18; H, 4.10, N, 20.00.

RESULTS AND DISCUSSION

It describes the synthesis and antibacterial, antifungal activity of some newly synthesized 2-azetidinones and 4-thiazolidinones moiety that were tested for in vitro antibacterial and antifungal activities. The synthesized compounds were studied by the disc-diffusion method and measured by halo zone test. The diameter of the zone of inhibition was measured in mm. It was found that all the compounds were screened for their antibacterial activity against a variety of Gram-positive and Gram-negative bacterial strains, such as *B. subtilis*, *S. aureus*, *Enterobacter* and *K.pneumonia*. The assaying of antifungal activity was against *T. indica*, *Tricoderma*, *S. fuliginea* and *P.infestans.* Looking at the structural activity relationship, compounds exhibit good activity as compared to standard known antibiotic, such as Ciprofloxacin that were used for comparison purposes. On the basis of the above observations, modification will be done to improve antibacterial activity, whereas the antifungal screening data showed good to moderate activity.

APPLICATION

Pharmacology: All the synthesized compounds of 2-azetidinones and 4-thiazolidinones derivatives were evaluated for antibacterial, antifungal activities by using disk diffusion method and the Minimum Inhibitory Concentration (MIC) are summarized in table 1and 2 respectively.

Antibacterial activity: The newly prepared compounds were screened for their antibacterial activity against *B. subtilis*, *S. aureus*, *Enterobacter* and *K.pneumonia* (Clinical isolate) bacterial strains by

disk diffusion method [31, 32]. The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition against *B. subtilis, S. aureus, Enterobacter* and *K.pneumonia* species. The structural activity study showed that antimicrobial activity depends on the nature of heterocyclic moieties.

Table 1. Antibacterial activity of 2-azetidinones and 4-thiazolidinones derivatives

Compound	Gram positive bacteria				Gram negative bacteria			
	B. subtilis		*S. aureus*		*Enterobacter*		*K. pneumonia*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
4b	70	100	40	100	40	50	NA	NA
4e	50	100	30	100	30	50	50	100
4f	100	200	50	100	50	100	40	100
4g	30	50	30	50	30	50	25	50
5b	50	100	40	100	25	50	NA	NA
5e	25	50	30	50	30	100	40	100
5f	60	100	50	100	50	100	40	100
5g	30	50	30	50	35	50	40	50
Ciprofloxacin	6.25	12.5	6025	12.5	10.25	25	6.25	25
DMSO	-	-	-	-	-	-	-	-

MIC (µg mL^{-1}), minimum inhibitory concentration i.e. the lowest concentration of the compound to inhibit growth of bacteria completely: MBC (µg mL^{-1}) minimum bacterial concentration i.e. the lowest concentration of the compound for killing bacteria completely; MBC/MIC ratio are against- *B. subtilis, S. aureus, Enterobacter* and *K. pneumonia,* NA-No activity detected.

Among the tested compounds, all the compounds showed more potent antibacterial activity (MIC 12.5 µg mL^{-1}) against all bacterial strains *B. subtilis, S. aureus, Enterobacter* and *K.pneumonia.* A comparative study also revealed that the compound 4b and 5b is less potent antibacterial agent against *K.pneumonia* and all the compounds showed effective inhibition (MIC 12.5-25 µg mL^{-1}). The minimum bactericidal concentration (MBC) of the compounds was two-, three- or Four-fold higher than the corresponding MIC results.

Antifungal activity: Antifungal activity was also done by disk diffusion method. For assaying antifungal activity *T. indica, Tricoderma, S. fuliginea* and *P.infestans* were re-cultured in DMSO by agar diffusion method [33, 34]. The investigation of antifungal screening data revealed that all the tested compounds showed moderate to good bacterial inhibition against *T. indica, Tricoderma, S. fuliginea* and *P.infestans* species. The structural activity study showed that antimicrobial activity depends on the nature of heterocyclic moieties.

Table 2. Antifungal activity of 2-azetidinones and 4-thiazolidinones derivatives

Compound	*T. indica*	*Tricoderma*	*S. fuliginea*	*P. infectans*
	MIC	MIC	MIC	MIC
4b	20	16	12	16
4e	18	14	14	14
4f	14	12	8	14
4g	16	18	12	12
5b	15	12	16	14
5e	17	10	12	18
5f	20	15	10	14
5g	12	16	10	13
Ciprofloxacin	6.25	120.25	10.25	6.25
DMSO	-	-	-	-

MIC (µg mL^{-1}), minimum inhibitory concentration i.e. the lowest concentration of the compound to inhibit the growth of fungi.

The antifungal screening data showed good to moderate activity. All compounds showed good fungicidal activity against *T. indica, Tricoderma, S. fuliginea* and *P.infestans* fungal strains. Among the tested compounds, 4b, 4e, 5e and 5f showed more potent fungicidal activity against all fungal strains (MIC 12.5 µg mL^{-1}). The compounds 4b, 4e, 5e and 5f showed maximum inhibition results against *T. indica,* and *Tricoderma.* The inhibition activity of the compound 4e, 5b and 5f (12.5 µg mL^{-1}) against *S. fuliginea* and *P.infestans* is significantly higher than the other tested compounds. The compounds 4f, 4g, 5b and 5g were moderately active against most of the fungal strains. The MFC of the compounds was found to be two-, three-or Four-fold higher than the corresponding MIC results. Thus, the nature of heterocycles and basic skeleton of molecules have significant influence on the extent of antibacterial and antifungal activities. A comparative study of the results (Table 1 and 2) with standard drugs (Ciprofloxacin) revealed that none of the compound exceeds the activity of commercial drugs.

CONCLUSION

In the present study, the antibacterial and antifungal activities of the 1, 2, 4-triazole derivatives were investigated. The compounds (4a-g and 5a-g) displayed good antibacterial activity and antifungal agents as compared to Ciprofloxacin. Thus, the newly synthesized compounds can be used as template for future development through modification and derivatives to design more potent and selective antimicrobial as well as antifungal agents.

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REFERENCES

[1]. A. A. Patel, A. G. Mehta, Synthesis and characterization of some pyrimidine-quinoline clubbed molecules and their microbicidal efficacy, *Journal of Saudi Chemical Society*, **2010**, 14, 203-208.

[2]. R. Singh, A. Chouhan, Important methods of synthesis and biological significance of 1, 2, 4-triazole derivatives, *World Journal of Pharmacy and Pharmaceutical Sciences*, **2014**, 3(8), 874- 906.

[3]. Rakesh R.Somani, Anuj G. Agrawal, Pushkar P. Kalantri, Pratibha S. Gavarkar and Erik De Clerq, Synthesis, characterization and biological evaluation of novel linked 1,3,4-oxadiazoles possessing azetidin-2-one, thiazolidin-4-one and tetrazoles moieties. *International Journal of Drug Design and Discovery*, **2011**, 2(1), 353-360.

[4]. PonnilavarasanIlangovan, Ayaluraja Sekaran, Sundaramoorthi, Chenniappan, BhalchandraKeshao Chaple, Synthesis, characterization and antimicrobial activity of 1,3,4-Oxadiazole derivatives, *Journal of Pharmacy Research*, **2011**, 4(6),1696-1698.

[5]. Rakesh Saini, Saurabh Chaturvedi, Achyut Narayan Kesari, Swatrantra Kushwaha, Synthesis of 2-(substituted)-5-(benzotriazomethyl)-1,3,4-oxadiazole for anti-fungal activity, *Der Pharma Chemica*, **2010**, 2(2), 297-302.

[6]. Mohd Amir, S A Javed, Harish Kumar, Synthesis of some 1,3,4-Oxadiazole derivatives as potential anti inflammatory agents, *Indian Journal of Chemistry*, **2007**, 46B, 1014-1019.

[7]. Poonam Singh and Pankaj K. Jangra, Oxadiazole- A novel class of anticonvulsant agents, *Der ChemicaSinica*, **2010**, 1(3), 118-123.

[8]. M VijeyAanandhi, Mohammed Hashim Mansoori, S Shanmugapriya, Shiny George, P Shanmugasundaram, *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, **2009**, 59, 223–233.

[9]. R. Dua, S. K. Srivastava, Synthesis of some Noval 2-Azetidinone derivatives of 2-methyl benzimidazole by conventional and microwave assisted and evaluation of their antimicrobial efficacy.*Int. J. Pharma. Bio Sci*., **2010**, 1, 1.
[10]. V. Kumar, S. Sharma, S. Singh, A. Kumar, S. Sharma, Synthesis of some new 1,3-thiazolyldiphenyl amine derivative and evaluation of their antibacterial effects, *Archiv der Pharmazie*, **2010**, 343, 98.
[11]. V. P. Singh, K. K.Saxsena, S. K. Bhati, A. Kumar, Azetidinone as an important biologically active agents. A review, *J. Global Pharma Tech*., **2010**, 2, 42.
[12]. G. Veinberg, I. Shestakova, M. Vorona, I. Kanepe, E. Lukevics, Synthesis of antitumor-6-alkylidene pencillanate sulfones and related 3-alkylidene-2-azetidinones, *Bioorg. Med. Chem. Lett*., **2004**, 14, 147.
[13]. A. S Narute., P. B. Khedekar, K. P. Bhusari, QSAR Studies on 4-thiazolidinones and 2-azetidinones bearing benzothiophene nucleus as potential antitubercular agents, *Ind. J. Chem*., **2008**, 47B, 586.
[14]. B. K. Banik, F. F. Beckerr, I. Banik, Synthesis of anticancer beta-lactams: mechanism of action, *Bioorg. Med. Chem*., **2004**, 12, 2523.
[15]. G. Veinberg, R. Bokaldere, K. Dikovskaya, M..Vorona, I. Kanepe, I. Shestakova, E. Yashchenko E. Lukevics, Synthesis of cytotoxic 1,3,4-trisubstituted 2-azetidinones, *Chem. Het. Comp*., **2003**, 39, 587.
[16]. G. Veinberg, K. Dikovskaya, M. Vorona, I. Turovskis, I. Shestakova, I. Kanepe, E. Lukevics, Synthesis of penicillin derivatives and study of their cytotoxic properties, *Chem. Het. Com*., **2005**, 41, 93.
[17]. D. P. Maia, D. V. Wilke, J. Mafezoli, J.N. Junior, M.O. Moraes, C. Pessoa, L. V. Costa-Studies on the cytotoxic activity of synthetic 2H-azirine-2-azetidinone compounds, *Chemico-Biological Interactions*, 180, **2009**, 220.
[18]. C. Beauve, M. Bouchet, R. Touillaux, J. Fastrez, J. Marchand-Brynaert, Synthesis and In-vitro antioxidant activity of substituted Pyridinyl-1,3,4-oxadiazole derivatives, *Cheminform*, **2000**, 31(4).
[19]. S. Gerard, G. Dive, B. Clamot, R. Touillaux, J. Marchand-Brynaert, Synthesis, hydrolysis, biochemical and theoretical evaluation of 1,4-bis(alkoxycarbonyl)azetidin-2-ones as potential elastase inhibitors, *Tetrahedron*, **2002**, 58, 2423.
[20]. Y. Wang, H. Zhang, W. Huang, J. Kong, J. Zhou, B. Zhang, 2-Azetidinone derivatives: Design, synthesis and evaluation of cholesterol absorption inhibitors, *Eur. J. Med. Chem*., **2009**, 44, 1638.
[21]. K. H. Patel, A. G. Mehta, Synthesis and antifungal activity of azetidinones and thiazolidinones derivative of 2-amino-6- (2-naphthalenyl) thiazolo [3,2-d] thiadiazole, *E J Chem.,* **2006**, 3, 267-73.
[22]. S. Cuzzocrea, B. Zingarelli, E. Gilard, P. Hake, A. L. Salzman., C. Szabo, Anti inflammatory effects of mercaptoethylguanidine a combined inhibitor of nitric oxide synthase and peroxynitrite scavenger, in carrageenan-induced models of inflammation, *Free Radical Biol. Med.,* **1998**, 24**,** 450.
[23]. A. Gursoy, N. Terzioglu, Synthesis and isolation of new regioisomeric 4-thiazolidinones and their anti-convulsant activity, *Turk J Chem.,* **2005**, 29, 247-54.
[24]. G. Turan-Zitouni, Z. A. Kaplancikli, A. Ozdemir, Synthesis and antituberculosis activity of some N-pyridyl-N'-thiazolylhydrazine derivatives, *Eur. J. Med. Chem*., **2010**, 45, 2085.
[25]. V. K. Agrawal, S. Sachan, P. V. Khadikar, QSAR studies on antihistaminic activity of some thiazolidin-4-ones, *Acta Pharm.,* **2000**, 50, 281.
[26]. G. S. Singh and B. J. Mmolotsi, Synthesis of 2- azetidinones from 2-diazo-1, 2-diarylethanones and *N*- (2-thienylidene)imines as possible antimicrobial agents, *IlFarmaco*, **2005**, 60(9), 727–730.
[27]. J. Anaya, D. S. Gero, H. Grande, J. Hermando, and N. M. Laso, D-glucosamine propanedithioacetal, an efficient chiral auxiliary in *β*-Lactam chemistry 1, *Bioorganic and Medicinal Chemistry*, **1999**, 7(5), 837–850.

[28]. E. E. Kucukguzel, S. Oruc Rollas, F. Sahin, A. Ozbek, Synthesis, characterization and biological activity of novel 4-thiazolidinones, 1,3,4-oxadiazoles and some related compounds, *European Journal of Medicinal Chemistry*, **2002**, 37(3), 197–206.
[29]. G. Capan, N. Ulusoy, N. Ergenc, and M. Kiraz, New 6- phenylimidazo[2,1-b]thiazole derivatives: synthesis and antifungal activity, *Monatsheftefür Chemie*, **1999**, 130(11), 1399–1407.
[30]. A. R. Bhat, S. Shetty, Synthesis of 4-thiazolidinones and azetidin-2-ones and their biological activities, *Indian Journal of Pharmaceutical Sciences*, 1987, 49(5), 194–197.
[31]. Shaik Khadar Yazdan, K. Renuka Sowjanya, Sai Avinash, M. Ratna Kumari, Synthesis of Pyrazoline Derivatives from Chalcones and their Antibacterial Activity, *J. Applicable Chem*., **2013**, 2(6), 1679-1682.
[32]. N. F. Ansari, A. K. Pandey, A. Kumar, K. P. Singh and I. R. Siddiqui, A Convenient and Efficient One-Pot Three Component Synthesis of 1, 3-Bis (2-Subsituted Aryl)-4, 5-Diphenyl Oxazol-3(2*H*-Yl)Thiourea as Potential Antimicrobial Agents, *J.Applicable Chemistry*, **2018**, 7(3), 488-495.
[33]. A. Kumar, A. K. Pandey, K. P. Singh, N. F. Ansari, S. Tiwari, M. K. Shrivash, PDB Moderated Synthesis of Some 2-Substituted Aryl-5-Phenyl-1,3,4-Oxadiazole/5-Substituted Aryl-2-(Furan-2-yl)-1,3,4-Oxadiazoleas Potential Pesticides, *J.Applicable Chemistry*, **2018**, 7(1), 33-44.
[34]. Vasu Namanil, B. Bharath Kumar Goud, Y. Bharathi Kumari and Ramesh Kumbham Synthesis and Biological Evaluation of N-(Benzo[D]Thiazol-2-yl)-6-Methoxy-5-(Phenylamine) Picolinamide Derivatives as Antimicrobial Agents, *J.Applicable Chemistry*, **2015**, 4(3), 840-846.