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Synthesis of Some Novel Triazole Heterocyclic Derivatives as Antibacterial Agents

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ABSTRACT

4-(4′-chlorophenyl)-thiazol-2-carbohydrazide(**2**) obtained from Ethyl-4-(4′-chloro phenyl)-thiazol-2-carboxylate(**1**) by the treatment with hydrazine hydrate. The synthesis of Potassium-[4-(4′-chlorophenyl)-thiazol]-2-dithiocarbazinate(**3**) was performed from reaction of **2** with alcoholic potassium hydroxide and carbon disulphide. Moreover 4-amino-5-(4′-(4′′-chlorophenyl)thiazol-2′-yl)-3-mercapto-4H-1,2,4-triazole(**4**) were obtained by refluxed in the presence of compound **3** and hydrazine hydrate with water. The condensation of **4** with substituted aromatic aldehydes generated the corresponding different triazole Derivatives (***5a-m*).** The structures of the compounds were confirmed by elemental analysis and spectral analysis. Antibacterial activity of the synthesized compounds was evaluated by tube dilution method against two gram positive and two gram negative bacteria using ciprofloxacin as standard.

Keywords: Synthesis, Triazoles, Anti bacterial activity

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INTRODUCTION

It is well known that most of the present diseases are due to invasion by pathogenic microorganism like bacteria and fungi. Infections caused by these resistant microorganism is fail to respond to treatment and greater risk of death. To treat this disease various potent and broad spectrum antibiotics are discovered. In the current literature survey, it has been observed that drug designed by molecular modification is more rational and productive foundation of new drug, consequently the need of synthesize new molecule as potential medicinal agent is more relevant today.[1]

Incorporation of thiazole nucleus with triazole increase the biological activities and posses wide spectrum of activities including antibacterial[2], anticonvulsant[3], antituberculer[4], anti-inflammatory[5], anticancer[6], anticandida species agent[7], plant-growth regulators[8], antifungal[9], anticoagulant.[10]

In the current literature survey, the design of new bioactive agents, the development of hybrid molecules through the combination of different pharmacophores in the same structure may lead to compounds having more efficiency in biological activity. Systematic structural modifications of the amide-1,2,4-triazole leads to development of bioisosteric relationship in that molecule[11]. On the other hand, many authors reveal that the introduction of halogen atoms into the pharmacophore structure can be beneficial for antimicrobial activity in many cases.

Accordingly, we synthesized series of 4-[(N-substituted benzylidene)-imino]-5-[4′-(4″-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole derivatives (Scheme 1) with the aim to evaluate their antibacterial activity.

MATERIALS AND METHODS

Reagents and solvents used for synthesis were purchased from SDFCL LTD and MERCK. Melting points (mp) were determined on melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu spectrophotometer (FTIR). NMR spectra were recorded on a Bruker 400 MHz spectrometer at Indian Institute of Science, Bangalore and the chemical shifts are given in δ (ppm), coupling constants (*J*) are in Hertz (Hz). Chemical shifts are expressed relative to the chemical shifts of the remaining protons of DMSO-*d*6: 1H: δ 2.49 ppm. The ESI-MS were determined at department of chemistry, Saurastra University, Rajkot.

Method for synthesis of Ethyl-4-(4′-chlorophenyl)-thiazole-2-carboxylate (1)

A mixture of ethyl thio-oxamate (1 equivalent weight), p-chlorophenacyl bromide (1.1equivalent weight) and ethanol 10-15ml were taken, in a round bottom flask and the mixture was refluxed

for 4 hr, the ethanol was distilled off under vaccum and it was neutralized with sodium bicarbonate. The mixture was extracted with ethyl acetate and washed with water. The solvent was removed under vaccum. The crude product obtained was recrystallized from ethanol.

Method for synthesis of 4-(4′-chlorophenyl)-thiazol-2-carbohydrazide (2)

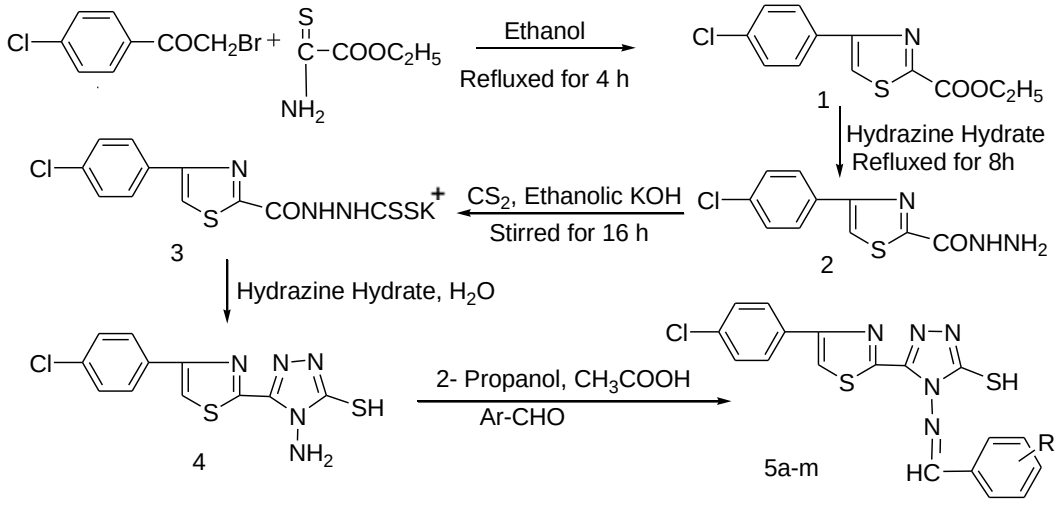
Mixtures of ethyl-4-(4′-chloro phenyl) thiazole-2-carboxylate (0.1 M), hydrazine hydrate (0.1 M), 20 ml of ethanol was taken in a round bottom flask, and the mixture was refluxed for 8hr. Excess ethanol was distilled off and the contents were allowed. The crystals formed were filtered, washed with water and dried under vacuum.

Method for synthesis of Potassium-[4-(4′-chlorophenyl)-thiazol]-2-dithiocarbazinate (3)

To a solution of potassium hydroxide (0.0067 mol) in ethanol (30ml), 4-(4′-chloro phenyl)-thiazol-2-carbohydrazide (0.003mol) was dissolved at 0-5ºC. After that carbon disulphide (0.006mol) was added drop wise and mixture was agitated for 16 hr at room temperature. To the resulting solution anhydrous ether was added and the precipitated potassium dithiocarbazinate was collected by filtration, washed with ether and dried under vacuum. The potassium salt was obtained in quantitative yield and was used for next step.

Method for synthesis of 4-amino-5-(4′-(4′′-chlorophenyl)thiazol-2′-yl)-3-mercapto-4H-1,2,4-triazole (4)

A suspension of the potassium dithiocarbazinate salt, hydrazine hydrate(0.003mol) and water (10ml) was refluxed for 8 hr. Hydrogen sulfide gas evolved and homogenous solution resulted which was diluted with 50ml water and subsequent acidification with dilute acetic acid gave white precipitate which was filtered and washed with water and crystallized with DMF.



Scheme 1: Synthesis of 4-[(N-substituted benzylidene)-imino]-5-[4′-(4′′-chloro phenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazoles (5a-m)

General method for synthesis of 4-[(N-substituted benzylidene)-imino]-5-[4′-(4′′-chloro phenyl)thiazol-2-yl]-3-mercapto-4H-1,2,4-triazoles [5(a-m)]

A mixture of 0.01 mol of 4-amino-5-(4′-(4′′-chlorophenyl)thiazol-2′-yl)-3-mercapto-4H-1,2,4-triazole (4), 0.01 mol of substituted aromatic aldehydes in 2-propanol along with catalytic amount of glacial acetic acid was heated under reflux for 3-4 hr. After completion of reaction excess of solvent was distilled off and the reaction mixture was cooled. The separated solid was filtered and crystallized from DMF: H_2O (5:2).

Antibacterial Activity

The newly synthesized compounds were screened against gram-positive bacteria: *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative bacteria: *Pseudomonas aeruginosa* , *Escherichia coli* by tube dilution method. Concentration used was 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250 and 500 (µg/mL). Ciprofloxacin was used as standard drug. The minimum inhibitory concentration values of synthesized compounds is given in Table 1.

Control: DMSO (Dimethyl sulfoxide).

Medium: Muller-Hinton broth.

RESULTS AND DISCUSSION

Triazole derivatives are known to exhibit an array of biological activities. In our laboratories various substituted thiazoles were synthesized and screened for antibacterial activity. Hence, we synthesized and screened some novel 4-[(N-substituted benzylidene)-imino]-5-[4′-(4′′-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazoles for antibacterial activity.

synthesis of Ethyl-4-(4′-chlorophenyl)-thiazole-2-carboxylate (1)

Yield 81.3%; mp 78-79 °C; IR cm^{-1}: 3087.62 (Ar-CH), 2920.16 (Ali-CH), 1728(C=O), 1601.16 (Ar C=C), 1178.93(O-C_2H_5), 1148.16 (C-N), 770.11 (C-S), 738.79 (C-Cl).

synthesis of 4-(4′-chlorophenyl)-thiazol-2-carbohydrazide (2)

Yield 79%; mp; 120-121 °C; IR cm-1: 3475.78(NH), 3286.32(NH_2), 3101.63(Ar-CH), 1522.70(Ar C=C), 1733.70 (C=O), 758(C-S), 708.49(C-Cl).

synthesis of 4-amino-5-(4′-(4′′-chlorophenyl)thiazol-2′-yl)-3-mercapto-4H-1,2,4-triazole (4)

Yield 85%; mp 200-201 °C; IR cm^{-1}: 3448.40 (NH_2 str of amine), 3273.63 (NH_2 str), 1617.62 (NH_2 bend), 2931.85 (Ar C=C str), 3206.84 (Ar C=C), 760.48 (C-S), 2363.59 (S-H), 669.38 (C-Cl), 1283.37(C-N), 1664.19 (C=N); ^{1}H NMR (DMSO-d_6) (chemical shift δ in ppm) : 7.39-7.43 (m, 4H, Ar-CH), 8.35 (s, 1H, CH, thiazole), 13.98 (s, 1H, SH), 3.58 (s, 2H, NH_2); m/z % : 311 (M^{+2} Cl^{37} 1), 309 (M^{+} Cl^{35} 2); Elemantal analysis for ($C_{10}H_8N_5ClS_2$): Found: C- 38.43%, H-

2.46% N- 2.20% (Calculated: C-38.83%, H – 2.58%, N- 2.26%).

4-[(4′′′-chlorobenzylidene)-imino]-5-[4′-(4′′-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole(5a)

Yield 84%; mp 242-244°C; IR cm^{-1}: 3328.16 (Ar CH), 1639.06 (C=N imine), 760.48 (C-S), 2345.29(S-H), 1090.55 (C-N), 669.38 (C-Cl); ^{1}H NMR (DMSO-d_6) (chemical shift δ in ppm) : 7.69-8.10 (m, 8H, ArCH), 9.94 (s, 1H, CH, thiazole), 14.53 (s, 1H, SH), 8.49 (s, 1H, CH, benzylidene); m/z % : 435(M^{+4} Cl^{37} 2),433 (M^{+2} Cl^{37} 2), 431 (M^{+} Cl^{35} 3); Elemantal analysis for ($C_{18}H_{11}N_5Cl_2S_2$): Found: C- 49.34%, H-2.45% N- 16.19% (Calculated: C- 50%, H – 2.54%, N- 16.20%) .

4-[(4′′′-hydroxybenzylidene)-imino]-5-[4′-(4′′-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole(5b)

Yield 81%; mp 233-235 °C; IR cm-1: 3060.57 (Ar CH), 1611.06 (C=N imine), 784.89 (C-S); 2345.0(S-H), 1319.01(C-N), 617.92 (C-Cl), 3423.2 (OH str); ^{1}H NMR (DMSO-d_6) (chemical shift δ in ppm) : 6.8-7.42 (m, 8H, ArCH), 9.4 (s, 1H, CH, thiazole), 14.13 (s, 1H, SH), 8.59 (s, 1H, CH, benzylidene), 5.0 (s, 1H, OH); Elemantal analysis for ($C_{18}H_{12}N_5OClS_2$): Found: C- 52.01%, H-2.78%, N- 16.72% (Calculated: C-52.17%, H – 2.89%, N- 16.76%) .

4-[(4′′′-methoxybenzylidene)-imino]-5-[4′-(4′′-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole(5c)

Yield 79%; mp 250-253°C; IR cm-1:3060.57 (ArCH), 1608.85 (C=N imine), 783.50(C-S), 2381.58 (S-H); 1415.86(C-N), 617.02 (C-Cl), 1277.55 (Ar OCH_3); ^{1}H NMR (DMSO-d_6) (chemical shift δ in ppm) :7.89-8.23 (m, 8H, ArCH), 10.1 (s, 1H, CH), 14.01 (s, 1H, SH), 8.61 (s, 1H, CH, benzylidene), 3.79 (s, 3H, OCH_3); Elemantal analysis for ($C_{19}H_{14}N_5OClS_2$): Found: C- 53.17%, H-3.21% N- 16.29% (Calculated: C-53.27%, H – 3.27%, N- 16.35%) .

4-[(3′′′,4′′′-dimethoxy benzylidene)-imino]-5-[4′-(4′′-chloro phenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole(5d)

Yield 58%; mp 231-233°C; IR cm^{-1}:3108.05 (Ar CH str), 1599.56 (C=N imine), 803.20(C-S), 2381.58 (S-H), 11137.69 (C-N), 697.88 (C-Cl), 1331.92 (Ar-OCH_3); ^{1}H NMR (DMSO-d_6) (chemical shift δ in ppm) : 7.60-7.99 (m, 7H, ArCH), 10.09 (s, 1H, CH, thiazole), 14.50 (s, 1H, SH), 8.59 (s, 1H, CH, benzylidene), 3.73(s, 6H, $2OCH_3$); Elemantal analysis for ($C_{20}H_{16}N_5O_2ClS_2$): Found: C- 52.32%, H-3.89% N- 15.21% (Calculated: C-52.40%, H – 3.93%, N- 15.28%) .

4-[(3′′′,4′′′,5′′′-trimethoxy benzylidene)-imino]-5-[4′-(4′′-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole(5e)

Yield 62%; mp 239-241°C; IR cm^{-1} : 3158.18 (Ar CH str), 1562.37 (C=N str) imine, 812.00(C-S), 2402.12 (S-H), 1185.00 (C-N), 775.80 (C-Cl), 1460.75 (Ar- OCH_3); ^1H NMR (DMSO-d_6) (chemical shift δ in ppm) : 7.56-7.71(m, 6H, ArCH), 10.14 (s, 1H, CH, thiazole), 14.43 (s, 1H, SH), 8.39 (s, 1H, CH, benzylidene), 3.70(s, 9H, $3OCH_3$); Elemantal analysis for ($C_{18}H_{11}N_5Cl_2S_2$): Found: C- 51.36%, H-3.64% N- 14.31% (Calculated: C-51.63%, H – 3.68%, N- 14.34%) .

4-[(2′′′-hydroxybenzylidene)-imino]-5-[4′-(4′′-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole(5f)

Yield 67%; mp 210-212°C; IR cm^{-1}: 3328.16 (Ar CH str), 1603.53 (C=N imine), 770.48 (C-S), 2345.29(S-H), 1266.11 (C-N), 668.35 (C-Cl); ^1H NMR (DMSO-d_6) (chemical shift δ in ppm) : 7.39-7.90 (m, 8H, ArCH), 9.74 (s, 1H, CH, thiazole), 14.73 (s, 1H, SH), 8.79 (s, 1H, CH, benzylidene), 5.25 (s, 1H, OH); Elemantal analysis for ($C_{18}H_{12}N_5OClS_2$): Found: C- 52.07%, H-2.80% N- 16.89% (Calculated: C-52.17%, H – 2.89%, N- 16.90%) .

4-[(4′′′-hydroxy-3′′′-methoxybenzylidene)-imino]-5-[4′-(4′′-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole(5g)

Yield 75%; mp 246-248°C; IR cm^{-1} : 3161.95 (Ar CH str); 1603.53 (C=N imine), 755.77(C-S), 2361.18 (S-H), 1288.91 (C-N), 699.89 (C-Cl), 3501.56 (O-H str.), 1403.87 (OCH_3); ^1H NMR (DMSO-d_6) (chemical shift δ in ppm) : 6.75-7.21 (m, 8H, ArCH), 14.01 (s, 1H, SH), 8.12 (s, 1H, CH, benzylidene), 5.01 (s, 1H, OH), 3.85 (s, 3H, OCH_3); Elemantal analysis for ($C_{19}H_{14}N_5O_2ClS_2$): Found: C- 37.76%, H-3.01% N- 15.74% (Calculated: C-37.83%, H – 3.15%, N- 18.96%) .

4-[(3′′′-nitrobenzylidene) -imino] -5-[4′-(4′′- chlorophenyl) -thiazol-2- yl]-3- mercapto-4H-1,2,4-triazole(5h)

Yield 65%; mp 225-227°C; IR cm^{-1} :3079.96 (Ar CH str), 1600.54 (C=N imine), 849.52(C-S), 2273.47(S-H), 1348.03 (C-N), 748.27 (C-Cl), 1527.71 (NO_2); ^1H NMR (DMSO-d_6) (chemical shift δ in ppm) :7.49-7.90 (m, 8H, ArCH), 10.04 (s, 1H, CH, thiazole), 14.75 (s, 1H, SH), 8.40 (s, 1H, CH, benzylidene); Elemantal analysis for ($C_{18}H_{11}N_6O_2ClS_2$): Found: C- 48.57%, H-2.41% N- 18.94% (Calculated: C-48.75%, H – 2.48%, N- 18.96%) .

4-[(4′′′-dimethylamino benzylidene) -imino] -5-[4′-(4′′- chloro phenyl)-thiazol- 2-yl]-3-mercapto-4H-1,2,4-triazole(5i)

Yield 58%; mp 228-230°C; IR cm^{-1} : 3081.68.16 (ArCH str), 1613.75 (C=N imine), 808.54 (C-S), 2362.52(S-H), 1176.98 (C-N), 740.92.38 (C-Cl), 1374.79 (CH_3 bend); ^1H NMR (DMSO-d_6) (chemical shift δ in ppm) :7.39-8.10 (m, 8H, ArCH), 10.34 (s, 1H, CH, thiazole), 14.43 (s, 1H,

SH), 8.19 (s, 1H, CH, benzylidene), 2.85 (s, 6H, $2CH_3$); Elemantal analysis for ($C_{20}H_{17}N_6ClS_2$): Found: C- 54.37%, H-3.79% N-19.01% (Calculated: C-54.42%, H – 3.85%, N- 19.04%) .

4-[(2′′′-nitrobenzylidene) -imino]-5-[4′-(4′′- chlorophenyl) –thiazol -2-yl] -3- mercapto- 4H-1,2,4-triazole(5j)

Yield 65%; mp 264-267°C; IR cm^{-1} :3079.96 (Ar CH str), 1600.54 (C=N imine), 849.52(C-S), 2273.47(S-H), 1348.03 (C-N), 748.27 (C-Cl), 1527.71 (NO_2); ^{1}H NMR (DMSO-d_6) (chemical shift δ in ppm) : 7.49-7.90 (m, 8H, ArCH), 10.04 (s, 1H, CH, thiazole), 14.75 (s, 1H, SH), 8.40 (s, 1H, CH, benzylidene); Elemantal analysis for ($C_{18}H_{11}N_6O_2ClS_2$): Found: C- 48.67%, H-2.43 % N- 18.89% (Calculated: C-48.75 %, H – 2.48%, N- 18.96%) .

Antibacterial Activity

The newly synthesized compounds were screened against gram-positive bacteria: *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative bacteria: *Pseudomonas aeruginosa* , *Escherichia coli* by tube dilution method. Concentration used was 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250 and 500 (µg/mL). Ciprofloxacin was used as standard drug. The minimum inhibitory concentration values of synthesized compounds is given in Table 1.

Control: DMSO (Dimethyl sulfoxide).

Medium: Muller-Hinton broth.

Table 1. MICs values of synthesized compounds 3, 4, 5a-m

Compound No.	Gram-positive organisms		Gram-negative organisms	
	Staphylococcus aureus	***Bacillus subtilis***	***Pseudomonas aeruginosa***	***Escherichia coli***
3	125	250	16	125
4	125	62.5	125	250
5a	62.5	125	31.25	125
5b	250	500	250	250
5c	31.25	8	31.25	8
5d	62.5	31.25	31.25	4
5e	250	250	125	250
5f	250	250	250	125
5g	31.25	8	62.5	62.5
5h	500	125	125	250
5i	250	125	250	125
5j	125	125	250	250
5k	62.5	250	125	500
5l	62.5	4	8	31.25
5m	250	125	500	31.25
Ciprofloxacin	4	4	8	4
DMSO	-	-	-	-

CONCLUSION

From the antibacterial activity results, it was observed that the electron donating groups (methoxy, methyl and hydroxyl) containing compounds influenced the activity. Among all the compounds tested, 5c [4-[(4‴-methoxybenzylidene)-imino]-5-[4′-(4″-chloro phenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole], 5d[4-[(3‴, 4‴-dimethoxy benzylidene) -imino] -5-[4′-(4″-chlorophenyl) –thiazol -2-yl]-3- mercapto -4H-1,2,4- triazole], 5g[4-[(4‴ -hydroxy -3‴-methoxybenzylidene) -imino]-5-[4′-(4″- chlorophenyl)- thiazol-2-yl]- 3-mercapto- 4H-1,2,4-triazole] and 5l [4-[(4‴-methyl benzylidene)-imino]-5-[4′-(4″-chlorophenyl)-thiazol-2-yl]-3-mercapto-4H-1,2,4-triazole] was found to be most active against both Gram-positive and Gram-negative bacteria among the series.

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