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Research Article

SYNTHESIS, CHARACTRISATION AND ANTIBACTERIAL ACTIVITY OF MERCAPTO 1,2,4-TRIAZOLE, 1,3,4-THIADIAZOLES, MERCAPTO BENZHYDRAZONES AND THIAZOLIDINONE DERIVATIVES OF 4-HYDROXYBENZHYDRAZIDE

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ABSTRACT

4-hydroxy benzhydrazide was converted to 4-amino-3-(4-hydroxy phenyl)-5-mercapto 1,2,4-triazole **1**. This mercapto 1,2,4-triazole on condensation with substituted aromatic aldehyde in methanol with a trace of glacial acetic acid furnished mercaptobenzaldehyde hydrazones **2**. This benzaldehyde hydrazones on condensation with thioglycollic acid in 1,4 -dioxane with pinch of $ZnCl_2$ furnished thiazolidinon **3**. Similarly this mercapto 1,2,4-triazole on treatment with substituted aromatic carboxylic acid in $POCl_3$ underwent ring closer and furnished 1,3,4-triazoles **4**. All the mercapto benzaldehyde hydrazones and 1,3,4-triazoles were screened for antibacterial activity.

Keywords: Mercapto 1,2,4 triazole, Mercaptobenzaldehydehydrazones, Thiazolidinones, 1,3,4- triazole

INTRODUCTION

The pharmacologically important heterocyclic compounds with nitrogen bridge derived from 1,2,4-triazole paved the way towards active research in triazole chemistry. As a result a variety of new improved compounds where being added to this field every years. In the last few decades the chemistry of 1,2,4-triazoles and their fused heterocyclic derivative has received considerable attention using their synthetic and biological importance for example a large number of 1,2,4-triazole containing ring system have been in corporated into a wide variety of therapeutically interesting drugs candidates including anti-inflammatory, CNS stimultants, sedatives, antianxiety, antimicrobial agents[1,2] and antimycotic activity such as fluconazole, intraconazole, variconazole[3,4]. Also, there are known drug containing the 1,2,4-triazole group eg. Triazolam[5], Alprazolam[6], Etizolam[7] and furacyclin[8]. More over sulphur containing heterocycles, the mercapto and thione substituted 1,2,4-triazole ring system have been well studied and so far a variety of biological activities have been reported for a large number of derivative such as antibacterial[9-12], antifungal[13,14], antitubercular[15], antimycobacterial[16], anticancer[17,18], diuretic[19,20] and hypoglycermic[21] properties. In addition to these important biological application mercapto-1,2,4-triazole are also of grate utility in preparative organic chemistry. For example in the preparation of various reagents, undergo different type of reaction to yield other heterocyclic compounds such as thiazolotriazoles, triazolothiadiazoles, triazolothiazines, triazolothiazines, triazolothiazepines trizolothiadiazines.

RESULT AND DISCUSSION

Mercaptotriazoles are important class of compounds due to presence of functional groups at C_1 and C_2 serve as intermediate for large number of heterocyclic compound having wide range of biological properties. 1-Amino-2-mercapto-5-(4-hydroxy phenyl)-1,3,4-triazole was prepared from 4-hydroxy methybenzoate[22] by the treatment with hydrazine hydrate to get 4-hydroxy phenol hydrazide which was then converted to potassium salt by stirring with carbon disulfide and potassium hydroxide at room temperature finally 1-amino-2-mercapto-5-(4-hydroxy phenyl)[23] was obtained by refluxing potassium salt with hydrazine hydrate in ethanol for 6 hrs. as shown in scheme-I. The condensation of triazole 1 with aromatic aldehyde in refluxing methanol with a trace of glacial acetic acid furnished mercapto benzhydrazones 2a-d with thioglycollic acid afforded compounds 3a-d scheme-II.

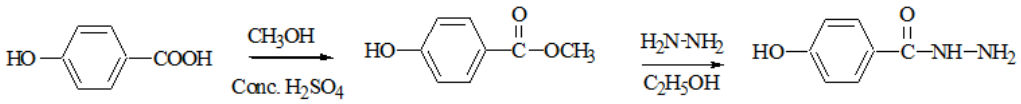
On the other hand the mercapto 1,2,4-triazole on treatment with substituted aromatic carboxylic acids ho $POCl_3$ underwent ring closer are furnished 1,3,4-triazoles 4a-g scheme-III. All the products were characterized on the basis of their spectral data I. R., NMR and elemental analysis.

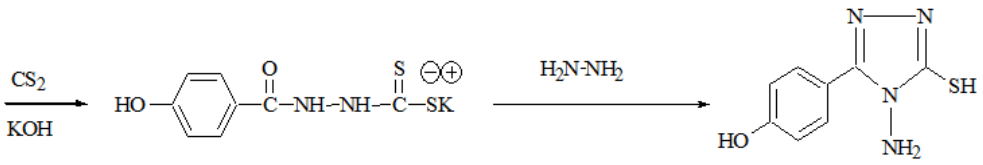
Biological testing of compounds

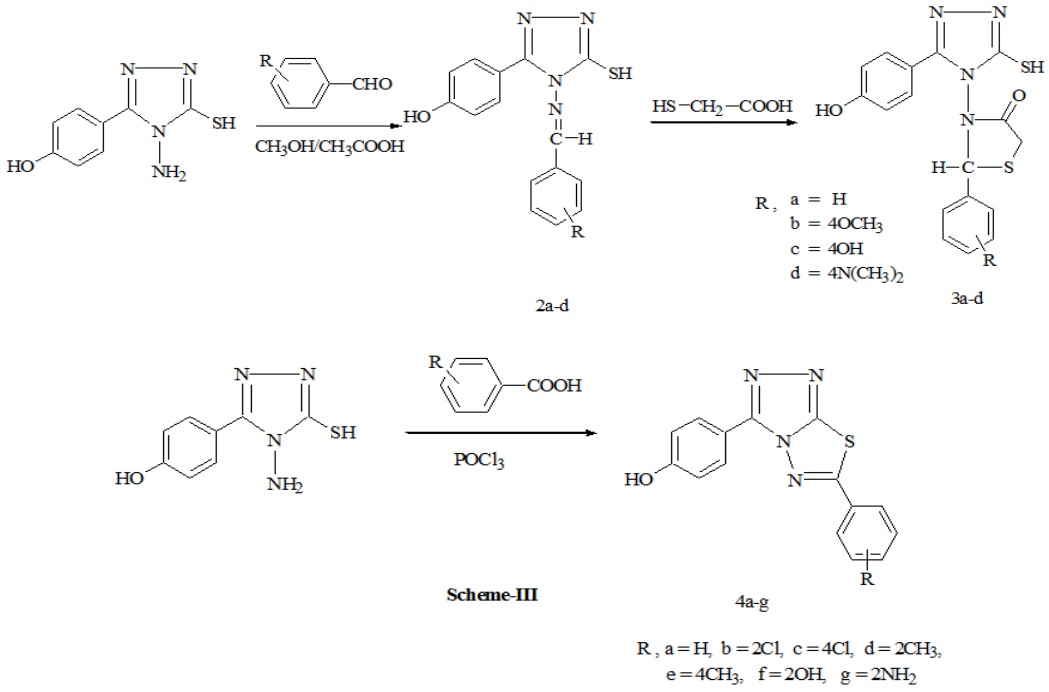
The synthesized compounds 2a-d and 4a-g were evaluated in-vitro for antimicrobial activity against *Escherichia coli, Pseudomas aeruginasa, Bacillus sabtilis, Staphylococus aureus, Aspergillus niger* and *Candida albicans* at the concentration 1mg/ml by paper disk diffusion method using DMF as solvent and nutrient agar was employed as culture media, the results were obtained in the form of clearing zone and were noted after the period of incubation (at 37^{0}C for 24-48 hrs). The zones of inhibitions were measured in mm and the data is presented in table-I.

RESULT

Most of the compounds were found to be active against *Escherichia coli* and *Pseudomas aeraginasa*.







Scheme-III

Table I: Antimicrobial activities of compounds 2_{a-d} and 4_{a-}

Zone of inhibition (mm)						
Compound	***Escherichia coli***	***Pseudomas aeruginasa***	***Bacillus sabtilis***	***Staphylococus aureus***	***Aspergillus niger***	***Candida albicans***
2a	-	8.60	-	-	-	-
2b	8.20	9.67	-	-	-	-
2c	8.23	7.78	-	-	13.70	15.70
2d	9.11	8.34	-	-	-	-
4a	7.34	8.30	13.20	12.40	15.60	14.50
4b	9.23	9.23	-	-	-	-
4c	7.67	9.67	13.50	12.45	-	-
4d	8.23	8.45	-	-	-	-
4e	8.23	-	-	-	-	-
4f	-	9.12	12.90	13.34	-	-
4g	-	8.23	-	-	-	-
NY Statin (100v/disk)	-	-	-	-	20.50	22.10
Chloramphnicol (100mg/disk)	30.10	25.20	30.10	33.10	NA	NA

Experimental section

All the melting points were determined by open capillary method and are uncorrected. The IR spectra were measured as potassium bromide pellets on Shimanzu 8400-S FT-IR spectrophotometer. The wave numbers are given in cm^{-1}. The ^{1}H-NMR spectra were taken in DMSO-d6 solution on Bruker ARX-300 spectrometer. Chemical shift were recorded as δ values in part per millions (ppm). The reactions were monitored by TLC. Elemental analysis were carried out on Carlo Erba 1108 model analyzer.

General procedure for the synthesis of 1-Amino-2-mercapto-5-(4-hydroxy phenyl)-1,3,4 triazole

The 4-hydroxy benzhydrazide (0.01 mole) was added to absolute alcohol (50 ml) containing KOH (1.9 g) at room temperature. Carbon disulphide was added (2.3 g, 0.013 mole) and the mixture stirred at room temperature for 10 hrs. The mixture was diluted with ether (30 ml) and stirred for further 1 hr. The potassium salt was used for the next stage without further purification. Hydrazine hydrate (99 %, 0.02 moles) was gradually added to the above potassium salt (0.01mole) dissolved in water (20 ml) with stirring and the mixture changed to deep green. It was then cooled at 5 ^{0}C and acidified with conc. HCl to pH 1.00. A white solid separated out which was filtered, wash with water and purified by recrystalization from ethanol to afforded the triazole 1. Yield 70 %, m.p. 264-266 ^{0}C IR (KBr): 3306 (OH), 3120 (NH), 2591 (SH), 1614 (C=N), 1515-1442 (Ar) ^{1}H-NMR(DMSO-d_6): δ, 5.7 (2H,s,-NH_2), 13.7 (1H,s,SH), 9.9 (1H,s,OH), 7.8-7.6(4H,m, Ar) MS: m/z (m^+):209.0. Anal. calculated for $C_8H_8N_4OS$: C,46.14; H,3.87; N,26.90 Found : C,45.80; H, 3.65; N, 26.15.

General procedure for preparation of schiff bases 2a-d.

A mixture of triazole 1 (0.01 mole) and the corresponding aldehydes (0.01 mole) in methanol (25 ml) containing a drop of glacial acetic acid was refluxed for 2 hrs. The reaction mixture on cooling was filtered and purified by recrystallization from ethanol to give 2a-d.

4-[4-(Benzylidine-amino)-5-mercapto-4H[1,2,4]-triazol-3-yl]-phenol (2a)

Yield 64 %, m.p. 196-198 ^{0}C. IR (KBr): 3306 (OH), 2560 (SH), 1611 (C=N), 1513-1436 (Ar). ^{1}H-NMR(DMSO-d_6): δ, 13.6 (1H,s,SH), 9.6 (1H,s,OH), 7.8-7.6(4H,m,Ar), 7.5-6.9(4H,m,Ar), 2.4 (1H,s,CH). Anal. calculated for $C_{15}H_{12}N_4OS$: C,60.81; H,4.05; N,18.91 Found : C,59.84; H,3.85; N,18.00.

4-{5-mercapto-4-[(4-methoxy-benzylidine)-amino]-4H[1,2,4]-triazol-3-yl}-phenol (2b)

Yield 72 %, m.p. 236-238 ^{0}C. IR (KBr): 3306 (OH), 2592 (SH), 1612 (C=N), 1530-1483 (Ar). ^{1}H-NMR(DMSO-d_6): δ, 13.7 (1H,s,SH), 9.4 (1H,s,OH), 7.8-7.6(4H,m,Ar), 7.1-6.8 (4H,m,Ar), 2.4 (1H,s,CH), 3.3 (3H,s,OCH_3). Anal. calculated for $C_{16}H_{14}N_4O_2S$: C,58.89; H,4.29; N,17.17 Found : C,58.20; H,3.92; N,16.90.

4-{4-[(4-hydroxy-benzylidine)-amino]-5-mercapto-4H-[1,2,4]-triazol-3-yl}-phenol (2c)

Yield 74 %, m.p. 210-212 ^{0}C. IR (KBr): 3206 (OH), 2598 (SH), 1611 (C=N), 1517-1487 (Ar). ^{1}H-NMR(DMSO-d_6): δ, 13.7 (1H,s,SH), 9.3 (1H,s,OH), 7.8-7.6 (4H,m,Ar), 6.9-6.8 (4H,m,Ar), 2.4 (1H,s,CH). Anal. calculated for $C_{15}H_{12}N_4O2S$: C,57.69; H,3.84; N,17.94 Found: C,57.00; H,3.01; N,17.0.

4-{4-[(4-Dimethoxyamino-benzylidine)-amino]-5-mercapto-4H-[1,2,4]-triazol-3-yl}-phenol (2d)

Yield 68 %, m.p. 216-218 ^{0}C. IR (KBr): 3341 (OH), 2566 (SH), 1613 (C=N), 1535-1445 (Ar). ^{1}H-NMR(DMSO-d_6): δ, 13.8 (1H,s,SH), 9.1 (1H,s,OH), 7.7-7.6 (4H,m,Ar), 6.8-6.7 (4H,m,Ar), 2.4 (1H,s,CH), 3.01 (3H,s,N-CH). Anal. calculated for $C_{17}H_{17}N_5OS$: C,60.57; H,5.01; N,20.64 Found: C,59.85; H,4.87; N,19.70.

General procedure for preparation of thiazolidinon 3a-d:

The schiff bases 2a-d (0.01 mole) were refluxed with thioglycollic acid (0.01 mole) in the presence me catalytic amount of anhydrous $ZnCl_2$ in 1,4-dioxane (30 ml) for 7 hrs. The mixture was then cooled and poured into crushed ice and water. The product separated was filtered, dried and recrystallized from ethanol to give 3a-d.

3-[3-(4-hydroxy-phynyl)-5-mercapto-[1,2,4]-triazol-4-yl]-2-phynyl-thiazolidine-4-one (3a)

Yield 54 %, m.p. 282-282 ^{0}C. IR (KBr): 3210 (OH), 2591 (SH), 1726 (C=O), 732 (C-S-C). ^{1}H-NMR(DMSO-d_6): δ, 13.6 (1H,s,SH), 9.8 (1H,s,OH), 8.0-6.8 (4H,m,Ar), 3.5 (2H,s,CH_2), 3.01 (1H,s,N-CH). Anal. calculated for $C_{17}H_{14}N_4O_2S_2$: C,55.12; H,3.81; N,15.12

Found: C,55.00; H,3.60; N,14.85.

3-[3-(4-hydroxy-phynyl)-5-mercapto-[1,2,4]-triazol-4-yl]-2-(4-methyoxy-phynyl)-thiazolidine-4-one (3b)

Yield 58 %, m.p. 330-332 ^{0}C IR (KBr): 3317 (OH), 2590 (SH), 1711 (C=O), 736 (C-S-C). Anal. calculated for $C_{18}H_{16}N_4O_3S_2$: C,53.58; H,4.03; N,13.99 Found : C,53.40; H,3.90; N,13.55.

2-(4-hydroxy-phynyl)-3-[3-(4-hydroxy-phynyl)-5-mercapto-[1,2,4]-triazol-4-yl]-2-phynyl-thiazolidine-4-one (3c)

Yield 60 %, m.p. 276-278 ^{0}C. IR (KBr): 3194 (OH), 2568 (SH), 1715 (C=O), 733 (C-S-C). ^{1}H-NMR(DMSO-d_6): δ, 13.8 (1H,s,SH), 9.9 (1H,s,OH), 8.04-6.6 (4H,m,Ar), 3.3 (2H,s,CH_2), 2.9 (1H,s,N-CH). Anal. calculated for $C_{17}H_{14}N_4O_3S_2$: C,52.84; H,3.65; N,14.50 Found: C,52.10; H,3.40; N,14.10.

2-(4-Dimethyl amino-phynyl)-3-[3-(4-hydroxy-phynyl)-5-mercapto-[1,2,4]-triazol-4-yl]-2-phynyl-thiazolidine-4-one (3d)

Yield 62 %, m.p. 289-291 ^{0}C. IR (KBr): 3202 (OH), 2566 (SH), 1715 (C=O), 736 (C-S-C). ^{1}H-NMR(DMSO-d_6): δ, 13.5 (1H,s,SH), 9.9 (1H,s,OH), 8.04-6.7 (4H,m,Ar), 3.3 (2H,s,CH_2), 2.9 (1H,s,N-CH), 1.2 (3H,s,N-CH_3). Anal. calculated for $C_{19}H_{19}N_5O_2S_2$: C,55.9; H,4.63; N,16.94 Found: C,55.00; H,4.15; N,16.23.

General procedure for preparation of 1,3,4 thiadiazoles 4a-g:

A mixture of triazole 1 (0.01 mole) substituted benzoic acid (0.01 mole) and phosphorus oxychloride (10 ml) was refluxed for 6 hrs on a water bath. Excess of phosphorus oxychloride was removed under vacuum. The remaining reaction mixture poured in ice water. Wid solution was made alkali by adding KOH the deposited solid filtered and crystallized from ethanol.

4-[6-phynyl-[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazol-3-yl]-phenol (4a)

Yield 72 %, m.p. 182-185 ^{0}C. IR (KBr): 3062 (OH), 1608 (C=N), 1538-1475 (Ar), 687 (C-S-C). ^{1}H-NMR(DMSO-d_6): δ, 8.4 (1H,s,OH), 7.7-7.5 (5H,m,Ar), 7.4-6.9 (4H,m,Ar). Anal. calculated for $C_{15}H_{10}N_4OS$: C,61.22; H,3.40; N,19.40 Found : C,61.00; H,3.21; N,18.84.

4-[6-(2-chlorophynyl)-[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazol-3-yl]-phenol (4b). Yield

78 %, m.p. 218-220 ^{0}C. IR (KBr): 3070 (OH), 1608 (C=N), 1590-1480 (Ar). ^{1}H-NMR(DMSO-d_6): δ, 8.3 (1H,s,OH), 7.7-7.6 (4H,m,Ar), 7.3-6.9 (4H,m,Ar). Anal. calculated for $C_{15}H_9N_4OSCl$: C,54.80; H,2.74; N,17.04 Found: C,54.80; H,2.52; N,16.92.

4-[6-(4-chlorophynyl)-[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazol-3-yl]-phenol (4c). Yield

71 %, m.p. 210-212 ^{0}C

4-[6-o-Tolyl-[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazol-3-yl]-phenol (4d)

Yield 72 %, m.p. 190-192 ^{0}C.

4-[6-p-Tolyl-[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazol-3-yl]-phenol (4e)

Yield 68 %, m.p. 188-190 ^{0}C. IR (KBr): 3028 (OH), 1609 (C=N), 1535-1476 (Ar), 630 (C-S-C). ^{1}H-NMR(DMSO-d_6): δ, 8.3(1H,s,OH), 7.9-7.8(4H,m,Ar), 7.5-6.3(4H,m,Ar), 1.2(3H,s,CH_3).

Anal. calculated for $C_{16}H_{12}N_4OS$: C,62.33; H,3.89; N,18.89Found: C,61.82; H,3.25; N,17.81.

4-[6-(2-hydroxy-phynyl)-[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazol-3-yl]-phenol (4f)

Yield 64 %, m.p. 228-230 ^{0}C. IR (KBr): 3079 (OH), 1606 (C=N), 1504-1462 (Ar), 656 (C-S-C).

^{1}H-NMR(DMSO-d_6): δ, 8.4(1H,s,OH), 7.5-7.3(4H,m,Ar), 7.2-6.9(4H,m,Ar). Anal. calculated for $C_{15}H_{10}N_4OS$: C,58.06; H,3.22; N,18.06 Found : C,57.80; H,3.00; N,17.82.

4-[6-(2-amino-phynyl)-[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazol-3-yl]-phenol (4g). Yield

60 %, m.p. 222-223 ^{0}C

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