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Synthesis, Characterization and Antimicrobial Activity of pyrimidothionyl - [Triazolo-thiadiazole] Fused Heterocycles

Pranay Shah, R. I. Patel, P. J. Vyas
Sheth M. N. Patel Science College, Patan, Gujarat, India

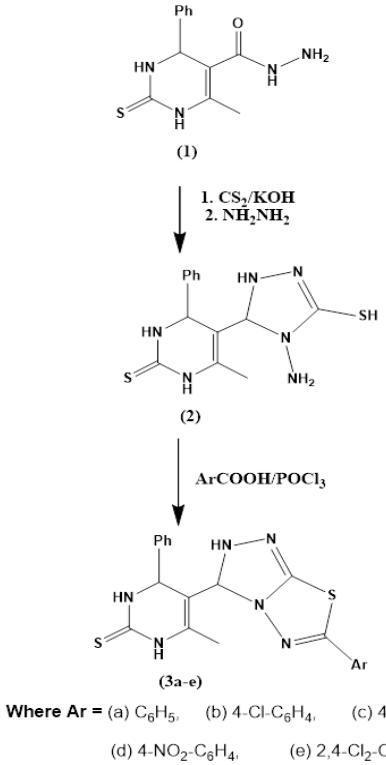
ABSTRACT

The reaction of 6-methyl-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidone carbo hydrazides (1) with CS2 in presence of KOH yielded 5-(4-amino-3-mercapto-4,5-dihydro-1H-1,2,4-triazol-5-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (2). The compound (2) on reaction with various aromatic acids afforded 5-[6-aryl-2,3-dihydro-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl]-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2(1H)-thiones (3a-e). The structures of fused heterocycles compounds were confirmed by elemental contents and spectral features. The antimicrobial activities of all compounds have also been monitored against plant pathogens.

Keywords: Pyrimidinthione, Triazole-Thiadiazole, Spectral Study, Antibacterial And Antifungal Activities.

I. INTRODUCTION

In recent year many researchers and scientists were attracted to synthesis nitrogen containing heterocyclic compounds due to their biological and pharmaceutical efficacy.[1,2] Among them triazoles and their fused heterocycles has got considerable attention due to their synthetic utility and broad spectrum biological activity. A number of triazole rings are found into a wide variety of pharmaceutical drugs including antitubercular [3], antimicrobial agents [4], antibacterial [5,6], antimycobacterial [7], antifungal [8], anticancer [9], anticonvulsants [10], anti-inflammatory and analgesic [11,12], antioxidant [13], antidepressant [14],etc. properties. Similarly another heterocyclic compounds i.e. 3,4-Dihydropyrimidin-2(1H)-one carboxylate and its derivatives were found to be anticancer, antimicrobial, antiviral agents[15-18]. The merged molecule of 3,4-Dihydropyrimidin-2(1H)-one and triazole has not been post reacted for fused heterocycles. Thus present authors initiated the work in this direction [19]. In continuous of this work the present communication comprises the synthesis and study of 5-[6-aryl-2,3-dihydro-[1,2,4]triazole-[3,4-b][1,3,4]thiadiazol-3-yl]-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2(1H)-thione (3a-e). The whole route of synthesis is given in scheme-1.



SCHEME 1

II. EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D FTIR spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (1) was prepared by reported method. [20]

Synthesis of 5-[4-amino-3-mercapto-4,5-dihydro-1H-1,2,4-triazol-5-yl]-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (2):– A mixture of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (1) (0.01mole) and solution of dropwise added CS_2 to KOH in ethanol (15ml) was stirred and cool in ice. The reaction mixture was stirred for 8 hrs and diluted with dry ether. Then this solid product was reflux 6-7 hrs with water and hydrazine hydrate (0.02 mole). The solution cooled and then acidified with CH_3COOH .The resultant solid was collected by filtration, dried and recrystallized from ethanol. yields- 74% and m.p.168°C. IR cm^{-1}:3127(NH),3200(NH_2),3020-3080(C-H,of Ar.),1650,1540(C=C),1430(C-N),1190,1120(C=S). ^{1}H NMR:7.2–7.3(m, 5H, Ar-H), 8.3-8.1 (s,3H,NH), 3.2(s,2H,NH_2),5.2-4.6(s,2H,CH),1.7(s,1H,SH),2.3 (s, 3H, CH_3). *Anal.* Calcd for $C_{13}H_{16}N_6S_2$ (321): C, 48.73; H, 5.03; N, 26.23;S,20.01.Found: C, 48.7; H, 5.0; N, 26.2;S,19.9.

Synthesis of 5-[6-aryl-2,3-dihydro-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-3-yl]- 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (3a-e):- A mixture of 5-(4-amino-3-mercapto-4,5-dihydro-1H-1,2,4-triazol-5-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidine-2 (1H) -thione (2) (0.01 mole) and aromatic acid (0.01mole) was dissolved in dry $POCl_3$. The resulted solution was further refluxed for 7-9 hrs. Excess $POCl_3$ was then distilled off and the mixture was gradually poured onto crushed ice with stirring. The mixture was kept aside for overnight. The solid separated out was filtered, washed thoroughly with cold water, 20% $NaHCO_3$ solution and recrystallised from a mixture of dioxane : ethanol (50:50v/v) mixture. The yields, melting points and other characterization data of these compounds are given in Table -1.

III. RESULTS AND DISCUSSION

It was observed that 5-[4-amino-3-mercapto-4,5-dihydro-1H-1,2,4-triazol-5-yl]-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (2) was synthesized from 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (1) and CS_2/KOH . The structure of (2) was confirmed by elemental analysis as well as spectral data.

5-(4-amino-3-mercapto-4,5-dihydro-1H-1,2,4-triazol-5-yl)-6-methyl-4-phenyl-3,4-dihydro pyrimidine-2(1H)-thione (2) undergoes facile condensation with aromatic acids to afford the corresponding 5-[6-aryl-2,3-dihydro-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-3-yl]- 6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (3a-e). The structures of (3a-e) were confirmed by elemental analysis and IR spectra showing an absorption band at IRcm^{-1}: 3127(NH), 3020-3080(C-H of Ar.),1650,1540(C=C),1430(C-N),1190,1120(C=S),735 (C-Cl),590 (C-Br) and 1550,1375(NO_2). ^{1}H NMR:7.2–7.8(m, 10H, Ar-H), 8.3-8.1 (s,3H,NH), 5.2-4.6(s,2H,CH),2.3 (s, 3H, CH_3). The C, H, N analysis data of all compounds are presented in Table -1.

Table:-1 Analytical Data and Elemental Analysis of Compounds (3a-e)

Compd.	Molecular formula (Mol. wt.)	M.P.* °C	Yield %	Elemental Analysis			
				%C	% H	%N	%S
				Calcd. Found	Calcd. Found	Calcd. Found	Calcd. Found
3a	$C_{20}H_{18}N_6S_2$ (406)	195-196	82	59.09 59.0	4.46 4.4	20.67 20.6	15.78 15.7
3b	$C_{20}H_{17}N_6S_2Cl$ (440)	182-184	76	54.47 54.4	3.89 3.8	19.06 19.0	14.54 14.5
3c	$C_{20}H_{17}N_6S_2Br$ (485)	203-204	80	49.49 49.4	3.53 3.5	17.31 17.2	13.21 13.2
3d	$C_{20}H_{17}N_7O_2S_2$ (451)	199-200	74	53.20 53.1	3.79 3.7	21.71 21.6	14.20 14.1
3e	$C_{20}H_{16}N_6S_2Cl_2$ (475)	204-205	72	50.53 50.5	3.39 3.3	17.68 17.6	13.49 13.4

***** Uncorrected LC-MS data 3a-415,3d-462

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The spectral data also direct for assignment of the predicted structure. LC-MS data of selected compounds shows the molecular ion peak, which is consistent with their corresponds molecular weight.

IV. ANTIBACTERIAL ACTIVITIES

The antibacterial activities of the series of compounds (3a-e) were studied against gram +Ve and Ve bacteria shown in Table-2. The activity was measured at a conc. 50µg/ml by agar-cup plate method.[19] Antimicrobial activity is calculated as relative percent inhibition (with reference to the standard). DMF was used as solvent control. Cotrimoxazole is used as standards for antibacterial. The percentage inhibition of growth of bacteria by the compounds is shown in Table-2.

The examination of antibacterial activity data reveals that all compounds toxic against microbes and the compounds 3b and 3e found more active against the gram-positive and gram-negative bacteria.

Table:-2 Antibacterial Activity of Compounds (3a-e)

Compounds	Zone of Inhibition(mm)			
	Gram +Ve		Gram Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
3a	15	15.5	15	15
3b	17	17.5	17	17
3c	16	16	16	16
3d	16	16.5	16	16
3e	18	18	18	18

V. ANTIFUNGAL ACTIVITIES

The antifungal activity of the series of compounds (3a-e) were measured at 1000ppm concentration in vitro Plant pathogen shown in Table-3 have been selected for study.[20,21] Antimicrobial activity is calculated as relative percent inhibition (with reference to the standard). DMF was used as solvent control. Flucanazole is used as standard for antifungal.

Table:-3 Antifungal Activity of Compounds (3a-e)

Zone of Inhibition at 1000 ppm (%)				
Compounds	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*	*Nigrospora Sp.*	*Fusarium oxyporium*
3a	74	76	72	75
3b	80	81	82	82
3c	78	80	85	80
3d	75	73	76	75
3e	85	89	90	90

VI. ACKNOWLEDGEMENT

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