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Preparation, Characterisation and In-Vitro Evaluation of Mercapto Analogue of Dihydropyrimidone Derivatives for their Antimicrobial, Anti-Arthitic and Thrombolytic Activity

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Abstract: ***In the present paper, we wish to report the synthesis of mercapto- dihydropyrimidone derivatives starting from readily available reactants, reagents and catalysts. We have successfully carried out the cyclocondensation reaction of aromatic aldehydes, thiourea and ethyl cyanoacetate in presence of sodium carbonate. Yields of these derivatives are high and the crude products can be purified either by column chromatography or recrystallisation techniques. Finally they were characterised by IR, PMR and CMR spectroscopy. The mercapto- dihydropyrimidones were tested positive for their antimicrobial activity. They were also found to exhibit invitro-anti-arthtic and thrombolytic activity.***

Keywords: Mercapto-dihydropyrimidones, cyclocondensation, antimicrobial activity

1. Introduction

Heterocyclic compounds are abundant in nature and are of great significance to life because of their structural subunits exist in many natural products such as vitamins, hormones and antibiotics. They have attracted considerable attention in the design of biologically active molecules. Nitrogen and sulphur containing heterocyclic molecules have immense significance in the medicinal chemistry.

In the recent past, the pyrimidine and its derivatives have significant contribution in the field of medicines by the virtue of their pharmacological properties such as antibacterial, antiviral, expectorant, repairing urinary track infection, respiratory track disorder.

Pyrimidones and its derivateives can be prepared by using the Biginelli protocol involving three component one pot chemical reaction yielding dihydropyrimidine 2(1H)-ones. This reaction was first reported by Patterno Biginelli in 1893[1]. Recently the reaction has been modified by number of research groups to improve the yield of the desired product. The reaction can be catalysed by $InCl_3$ [2] and Lanthanide triflate[3]. Recently zeolite catalysed synthesis of dihydropyrimidin-2-(1H)- one was reported in the literature[4]. Dihydropyrimidine was also synthesised employing chloroacetic acid as a catalyst[5]. Titanium (IV) chloride[6], Ruthenium (III) chloride [7], $Yb(OTf)_3$ [8], ionic liquids[9], silver salt of heteropolyacid [10] and copper (II) trifluoroacetate [11] were used successfully for the synthesis of dihydropyrimidone derivatives. We have synthesised a new set of compounds using the Biginelli approach and the reaction is catalysed by sodium carbonate. We have also tried the reaction with ammonium acetate, but the reaction is sluggish and the conversion is poor.

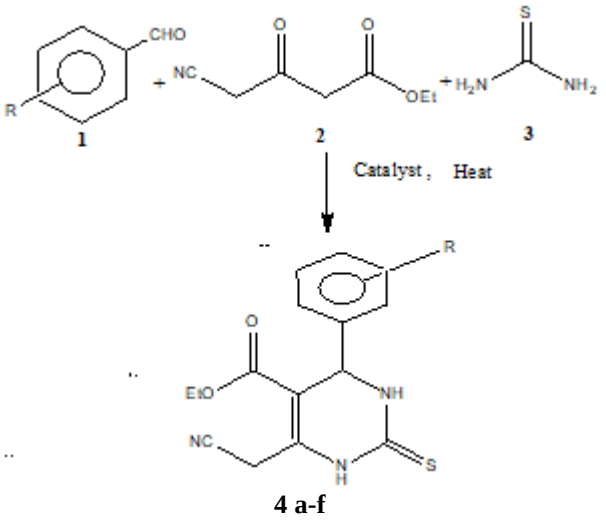
2. Experimental

Synthesis of 4 a

Procedure

A solution of indole-6-carboxaldehyde 0.2 gm (1.3 mmol.), thiourea 0.125 gm (1.6 mmol), ethyl cyanoacetate 0.22 ml (2.7 mmol) and potassium carbonate 0.570 gm (4.13 mmol) were dissolved in ethanol and the reaction mixture was refluxed for 5 hours as per the requirement. The reaction mixture was poured into ice cold water and the product was isolated by extraction with ethyl acetate. This ethyl acetate layer on acidification furnished the mercapto –derivate of dihydropyrimidine in 92% yield. The crude product was filtered, purified and was characterised by PMR, CMR and IR spectroscopy. Various derivatives of mercapto-pyrimidones were prepared by this method in excellent yield.

Scheme I



4 a-f

3. Results and Discussion

The cyclocondensation of three components to prepare the mercapto-dihydropyrimidones has been achieved successfully. The reaction was clean, efficient, high yielding and simple to perform. The different mercapto-dihydropyrimidones were prepared and their biological evaluation was carried out. Most of the samples showed substantial activity against different bacteria. The results are summarised in the form of result **Table 1**.

Table 1

Entry	Substrates	Catalyst	Reaction Time in Hrs	% Yield
4 a	Indole-6-carboxaldehyde	K_2CO_3	05	92
4 b	3-ethoxy-benzaldehyde	K_2CO_3	07	88
4 c	2-bromobenzaldehyde	K_2CO_3	05	62
4 d	O- tolualdehyde	K_2CO_3	03	71
4 e	1-methylimidazole-5-carboxaldehyde	K_2CO_3	03	70
4 f	Tetrahyrdopyran-3-carbaldehyde	K_2CO_3	14	66

Spectral Data of Compound - 4 c
M.P. 198^{o} C
IR cm $^{-1}$: 3308, 2217, 1581, 1682, 2600, 1600
PMR (δ) DMSO –D_6 10.7 (bs, 1H), 11.8 (s, 1H), 7.3-8.4 (m, 4H), 6.6 (s, 1H), 4.08 (s, 2H), 4.02 (q, 2H), 3.59 (s, 2H), 1.18 (t, 3H)
^{13} **C NMR** (δ) 172, 164, 116, 113-125, 75, 60, 56, 14

Biological evaluation
Antimicrobial activity
The derivatives were examined for their pharmacologically potent antimicrobial activity at100 µg/ml. The streptomycin was used as the standard and DMSO as the control. The derivatives showed moderate to good antibacterial activity against S. Aureus and E. Koli. They also exhibited anti-fungal activity against A. Niger. The anti-microbial activity results are summarised in result **Table-2**

Entry	Compound	Concentration in µg/ml	Antibacterial activity against S. Aureus Zone of inhibition	Antibacterial activity against E.Koli Zone of inhibition	Anti-fungal activity against A. Niger Zone of inhibition
1	a	100	17 mm	14 mm	23.5
2	b	100	12 mm	-	27.5 mm
3	c	100	29 mm	20 mm	22.5
4	d	100	17 mm	19.5 mm	8.5 mm
5	e	100	09 mm	06 mm	-
6	f	100	07 mm	06 mm	-
7	Streptomycin	100	23 mm	17mm	-
8	Fluconazole	100	-	-	22 mm

In-vitro-anti-arthitic activity
For the evaluation of this activity, the inhibition of protein denaturation was carried out employing dichlorofenoc sodium as a standard. The test solution was prepared by taking 0.45 ml of bovine serum albumin (5%w/v in water) and 0.05 ml of test solution with 100 µg/ml concentration. The test control solution was made from 0.45 ml of bovine serum albumin (5% in water) and 0.05 ml of distilled water. Product control was prepared from 0.45 ml of distilled water and 0.05 ml of test solution. All the samples were adjusted to pH 6.3 using 1N HCl. The standard solution was made from 0.45 ml of bovine serum albumin and 0.05 ml diclofenac sodium. The samples were incubated at 37 ^{0} C for 20 minutes and at 57^{o} C for 3 minutes. The solutions were cooled and 2.5 ml of phosphate buffer was added. The absorbance was measured at 416 nm with the help of uv-

visible spectrophotometer. The control showed 100% denaturation.

In-vitro thrombolytic test

The dried compound was dissolved in dimethyl sulphoxide to obtain 100 µg/ml concentration. Aliquotes (5ml) of venous blood drawn from healthy volunteers. This blood was equally distributed in 5 centrifujes and were incubated at 37^{o} C for 45 minutes. The serum was removed carefully and the weight of the clot was recorded. As a positive control 100 µl of streptokinase and for the negative control 100 µl of water was added to the control tube. All the tubes were incubated at 37^{o} C for 90 minutes and monitored the breaking down of the clot. The released fluid was removed and the tubes were weighed again. The differences in weights taken before and after clot lyses were expressed as a % clot lyses.

4. Conclusion

Simple, efficient protocols for the synthesis of mercapto-pyrimidinones have been synthesised using readily available substrates, reagents and catalysts. The present method is simple, efficient and requires shorter reaction time. The catalyst is cheap and easily available. The products are formed in high yields and showing antibacterial activity against various strains of bacteria. They were also screened for their anti-fungal, anti-arthitic and in –vitro-thrombolytic test. Majority of the compounds have shown good results.

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