ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

SYNTHESIS AND EVALUATION OF ANTI-BACTERIAL ACTIVITY OF DIHYDROPYRIMIDINONE DERIVATIVES

Suresh kumar.P*, Navaneetha Krishnan.S, Azra Sultana.M, Vinupama.G, Shishira Reddy.P, Shaji.G
Browns College of Pharmacy, Khammam, Andhra Pradesh, India.
Email: surae81@gmail.com

Received on 29-10-2011 *Accepted on 15-11-2011*

Abstract

The aim of the present work is to synthesise pyrimidinone &dihydro pyrimidinethione derivatives by reacting ethylacetoacetate with various aromatic aldehydes, urea or thiourea respectively.Here the reaction of dihydropyrimidinone with sodium hypochlorite and ammonium hydroxide results in the formation of chloramino pyrimidine(C)&cyclization of this with sodium acetate&benzoyl chloride results in the formation of oxadiazolopyrimidine derivatives.and the reaction of dihydropyrimidine thione with the same reagent mentioned above result in the formation of sulfaminopyrimidine &thiadiazolopyrimidine derivatives. All these compounds were evaluated for their antibacterial activity using cup-plate diffusion method by using ciprofloxacin as a standard drug.

Key words; Pyrimidinone,Dihydro pyrimidinethione, antibacterial activity, ciprofloxacin.

Introduction

Dihydropyrimidinones, the products of the Biginelli reaction, are widely used in the pharmaceutical industry as calcium channel blockers[1], antihypertensive agents, and alpha-1-a-antagonists[2]. Dihydropyrimidinones and their derivatives are very important class of bioactive compounds because of their pharmacological properties. They are known to exhibit wide range of biological activity such as calcium channel blockers, antihypertensive agents, α-adrenergic antagonists and neuropeptide y antagonists. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the molecules[3]. Dihydropyrimidinones

and their derivatives were found to exhibit the anti viral, anti inflammatory, anticancer, anti hypertensive, coronary artery dilator and also used to treat the benign prostatic hyperplasia[4].The aim of the present work is to synthesize dihydropyrimidinones using a multi-component one pot condensation reaction, and to prepare its derivatives using suitable chemical reactions and to analyze their antibacterial activity.

Experimental Methods

General procedure for the synthesis of 3, 4-dihydropyrimidinone (a)

A 50 cm^3 round-bottom flask was charged with 3.6 m mole of urea or Thiourea, 3.0 m mole of aldehyde, 3.0 m mole of ethyl acetoacetate, 0.6 m mole of $Sncl_2.2H_2O$ and 4.0 cm^3 of ethanol (or acetonitrile). The mixture was heated to reflux for 6hrs period under magnetic stirrer. The solution was cooled to room temperature and 10 cm^3 of cold water was added, the mixture was additionally stirred for 15min. The resulting solid was filtered under suction, washed with cold ethanol (3 cm^3) and recrystallized from hot ethanol to afford the product.

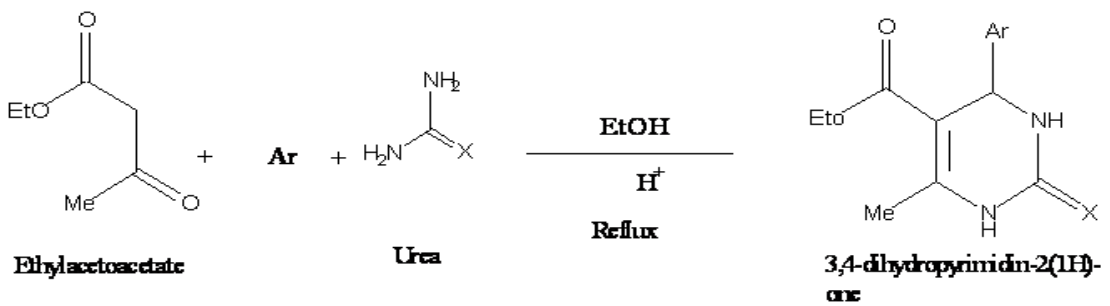
Synthesis of 5- ethyl 6-methyl-4-phenyl-2-oxamido pyrimidine-5-carboxylate (b), (c)

Aqueous solution of sodium hypochlorite (5% v/v, 90 ml) was added dropwise over a period of 30 min to a stirred solution of pyrimidine(0.02 moles) in a mixture of aqueous ammonium hydroxide (30% v/v, 90 ml) and aqueous sodium hydroxide (3.3% w/v, 90 ml) at room temperature. The precipitated solid was collected, washed with water and methanol and then crystallized from ethanol to give compound 3 as colourless crystals.

Synthesis of oxadiazolo pyrimidine derivative (d)

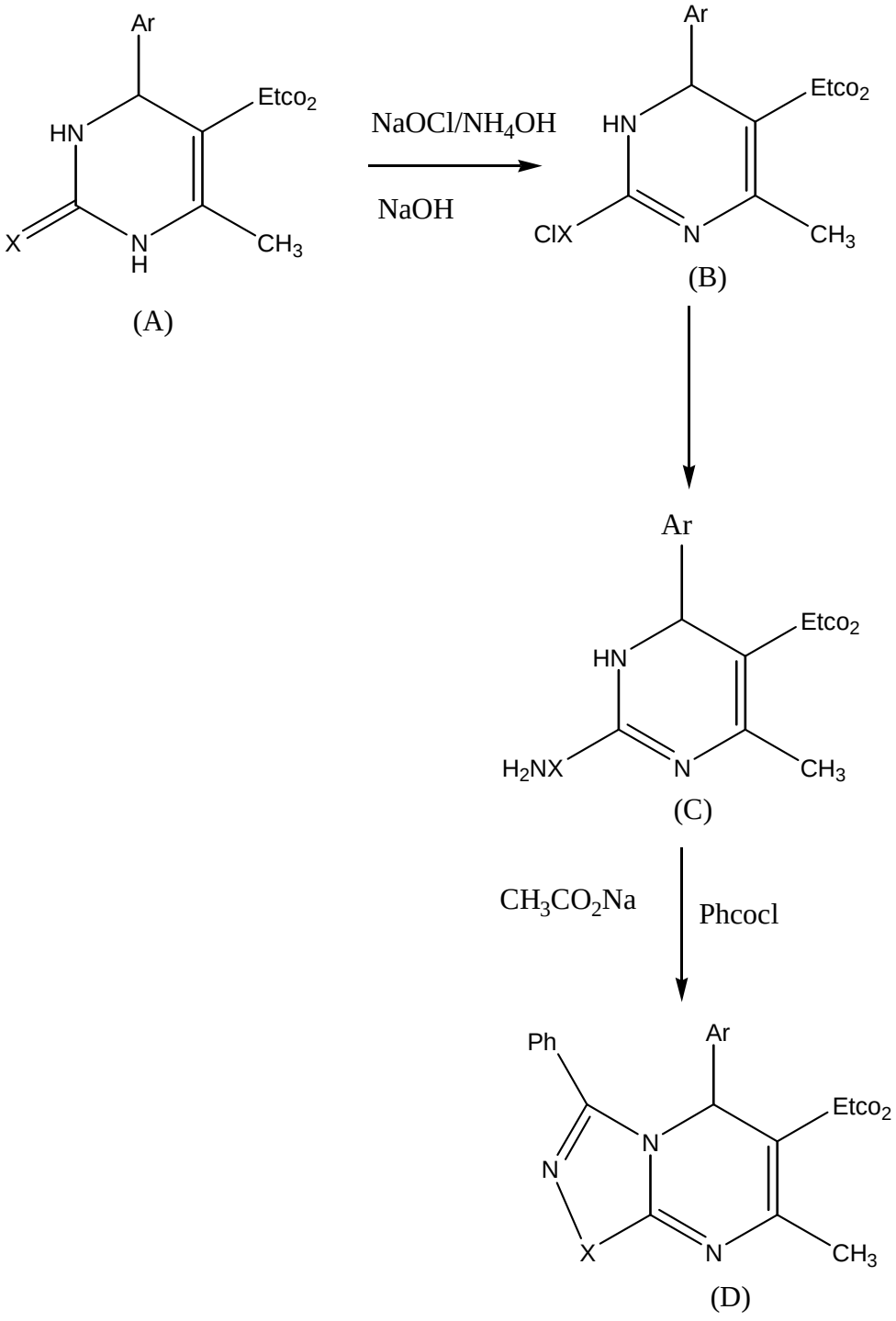
A mixture of compound 3(0.01 mole), benzoyl chloride (0.01) sodium acetate (2g) were fused at 160°c for 30 min. The solid mass obtained was crystallized from acetic acid to give as colourless crystals.

Scheme-I

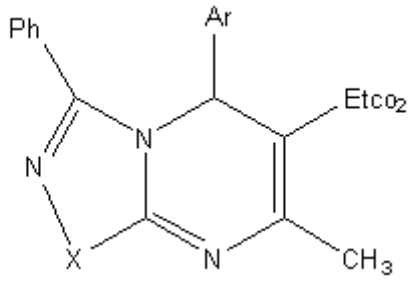


Ethylacetoacetate Urea 3,4-dihydropyrimidin-2(1H)-one

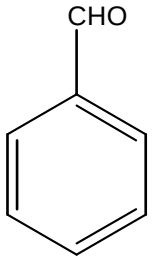
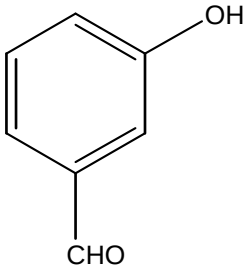
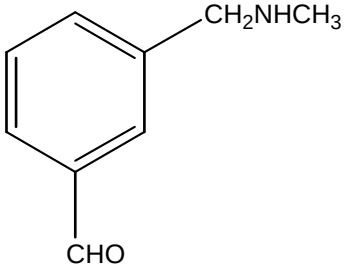
Scheme II


Ar
Etco2
HN
X
N
H
CH3
(A)
NaOCl/NH4OH
NaOH
Ar
Etco2
HN
ClX
N
CH3
(B)
Ar
Etco2
HN
H2NX
N
CH3
(C)
CH3CO2Na
Phcocl
Ph
Ar
Etco2
N
N
X
N
CH3
(D)

C) 5 Ethyl 6- methyl-4-phenyl-2-Oxamidopyrimidine-5-carboxylate, (D)-Oxadiazolopyrimidine derivative



(D)-Oxadiazolopyrimidine derivative

S.NO	ALDEHYDE(Ar)	STRUCTURE	(X)
1	BENZALDEHYDE		O/S
2	SALICYLALDEHYDE		O/S
3	PARA DIMETHYL AMINO BENZALDEHYDE		O/S

Evaluation of Anti-Bacterial Activity

Cup plate method

Inoculate a previously liquefied medium appropriate to the assay with the required quantity of suspension of the micro-organism, add the suspension to the medium at a temperature between 40°c and 50°c and immediately pour into the inoculated medium into Petri dishes. Using the appropriate buffer solutions prepare solutions of known concentration of the standard preparation and solutions of the corresponding assumed concentrations of the antibiotic to be examined.

Apply the solutions to the surface of the solid medium in sterile cylinders or in cavities prepared in the agar. The volume of solution is added to each cylinder. When Petri-dishes are used, arrange the solutions of the standard preparation and the antibiotic to be examined on each dish so that they alternate around the dish and so that the highest concentrations of standard and test preparations are not adjacent.Leave the dishes or plates standing for 1 to 4hrs at room temperature or at 4°, as appropriate as a period of pre-incubation diffusion to minimize the effects of variation in time between the applications of the different solutions. Incubate them for about 18hrs at given temperature. Accurately measure the diameter or area of the circular inhibition zones and calculate the results [5-6]

Result and Discussion

Standard drug of ciprofloxacin has shown zone of inhibition 5.5 cm and 4.5 cm against E.coli and Bacillus subtilis respectively.All the compounds have shown zone of inhibition against both Gram positive (Bacillus subtilis) and Gram negative(E.coli) organisms.Compound obtained with salicylaldehyde has shown more activity against both Gram positive and Gram negative organisms when compared to others.Accordingly as the concentration is increased the Zone of inhibition also increased and the salicylaldehyde-thiourea compound obtained showed a maximum zone of inhibition at 30µg/ml i.e 2.1 cm

Conclusion

The compilation of literature on dihydropyrimidinone and its derivatives has been done effectively. In conclusion, even though extensive work has been done on the dihydropyrimidines, still vast scope remains in this area of

research due to the unlimited pharmacological and therapeutic efficacy of drugs containing these moieties.At the same time it is also important to identify new targets which can be used for the design of novel anti-bacterial agents.

Table: Evaluation of Derivatives Stock Solution: **1mg in 1ml.**

S.No	Compound	Concentration (µg/ml)	Zone Of Inhibition(Cm)	
			Escherichia Coli (Gram –Ve)	**Bacillus Subtilis (Gram +Ve)**
1.	Ethylacetoacetate-Benzaldeyde-urea	10	1.2	0.9
		20	1.3	1.0
		30	1.5	1.3
2.	Ethylacetoacetate-Benzaldehyde-thiourea	10	1.4	1.1
		20	1.6	1.5
		30	1.7	1.6
3.	Ethylacetoacetate-Salicylaldehyde-urea	10	1.3	1.0
		20	1.5	1.2
		30	1.8	1.6
4.	Ethylacetoacetate-Salicylaldehyde-thiourea	10	1.7	1.3
		20	2.0	1.8
		30	2.1	2.0
5.	Ethylacetoacetate-Para-dimethyl aminobenzaldehyde-urea	10	0.6	0.1
		20	0.9	0.2
		30	1.1	0.3
6.	Ethylacetoacetate-Para-dimethyl aminobenzaldehyde-thiourea	10	1.0	0.4
		20	1.1	0.6
		30	1.3	0.9
		10	3.1	2.7

7.	Ciprofloxacin (standard drug)	20	4.3	3.9
		30	5.5	4.8

References

1. Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* 1992, *35*, 3254-3263.
2. http://en.wikipedia.org/wiki/Biginelli_reaction (accessed on Aug 2011)
3. Jieping zhu, Hugues Bienayme. Multicomponent reaction.1st edition, Springer publication, 2005, 96-99.
4. Maksim A. Kolosov et al ; A chemical placebo: NaCl as an effective, cheapest, non- acidic and greener catalyst for Biginelli-type 3,4-dihydropyrimidin-2(1*H*)-ones (-thiones) synthesis.Mol Divers 13, 5-25, (2009)
5. Indian pharmacopoeia (I.P), 1996, vol II, A-105.

Correspondence Author:

P.Suresh kumar*

Browns College of Pharmacy,

Ammapalem, Khammam-507305

Andhra Pradesh.

Email: *surae81@gmail.com*