INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

NOVEL PYRAZOLINES DERIVED FROM PIPERAZINE CHALCONES SYNTHESIS ANTIMICROBIAL STUDIES

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ARTICLE INFO

Article history
Received 15/12/2016
Available online
31/01/2017

Keywords
Chalcones,
Hydrazine Hydrate,
Pyrazolines,
Antimicrobial Activity.

ABSTRACT

In pursuit to synthesize the molecules of biological interest we reported here the synthesis of some novel pyrazolines from piperazine chalcones under basic condition using hydrazine hydrate. Ethanol is used as a solvent medium for the reaction. These newly synthesized pyrazolines are screened for antimicrobial studies and showed moderate to good activity.

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*Please cite this article in press as **Rajashree Markandewar** et al. Novel Pyrazolines Derived from Piperazine Chalcones Synthesis Antimicrobial Studies. Indo American Journal of Pharmaceutical Research.2017:7(01).*

INTRODUCTION

Pyrazolines are the five member heterocyclic compounds containing two nitrogen atoms. As all heterocycles are well known for their biological utilizations, pyrazolines also shows variety of biological applications such as antinflammatory[1-3], antimicrobial[4-6], cytotoxic[7], antimycobacterial[8-9], anticonvulsant[10] and others[11-12].

A variety of methods are available for the synthesis of pyrazolines especially 2- pyrazolines. However, the work of Fischer and Knoevenagel in 19th century became one of the popular methods which involve the reaction of α, β- unsaturated ketones with phenyl hydrazine in acetic acid by refluxing. Few other methods involve basic conditions[13]. Researchers utilize hydrazine hydrate[14], phenyl hydrazine hydrochloride[15], thiosemicarbazide[16] & other derivatives with α, β- unsaturated carbonyl compounds to form pyrazolines. Li et.al reported the synthesis of pyrazolines using ultrasound irradiation at room temperature[17].

One of the important feature need to explain here is the functioning of pyrazolines in immune system. It is known that immune system is balanced by the activities of anti-inflammatory mediators or cytokine and tumor necrosis factor- α (TNF- α). One can face disastrous inflammatory diseases when the activities of one of these mediators go abnormal. Pthalidomide is one of the small molecules TNF- α inhibitors. Hence use of pthalimide in synthesis of pyrazolines is appreciable so as to get effective anti-inflammatory agent[1].

Taking in to consideration such broad spectrum of utilities one cannot ignore the existence of pyrazolines in the field of synthesis. Therefore we reported here the synthesis of some novel pyrazolines for the first time using piperazine chalcones under basic condition in presence of ethanol as a solvent media. The reaction is carried out in refluxing condition.

MATERIALS AND METHODS

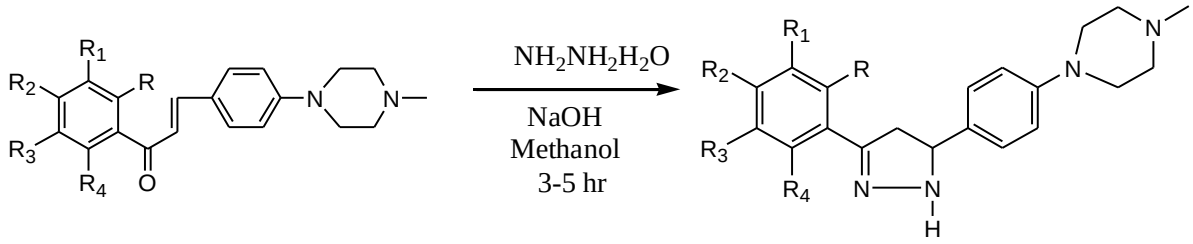
Experimental

All the melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on Perkin-Elmer 237 spectrometer. ^{1}HNMR spectra on a Bruker Avance DPX400 MHz spectrometer with $CDCl_3$ as a solvent and TMS internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet), t (triplet) and m (multiplate). Purity of the compounds is checked by TLC plates (Merck) using benzene and ethyl acetate as an eluent in the ratio of (9:1 v/v).

General Procedure for synthesis of pyrazolines:

To a mixture of chalcone (2 mmol) and hydrazine hydrate (2 mmol) in ethanol (15 ml) was added sodium hydroxide (2.5 mmol). The reaction mixture was then refluxed for 3-5 hrs. After completion of reaction (monitored by TLC) the reaction mixture was distilled to remove the excess solvent then it is poured into crushed ice. The solid obtained washed with water and recrystalised from ethanol

Physical data of all the synthesized compounds is mentioned in **table-1**.



Scheme I : Synthesis of Pyrazolines **(I-XVI)**

Entry	R	R_1	R_2	R_3	R_4
I	H	H	H	H	H
II	H	Br	H	H	H
III	H	H	Br	H	H
IV	H	H	OCH_3	H	H
V	H	F	OCH_3	H	H
VI	OCH_3	H	H	OCH_3	H
VII	H	H	OH	H	H
VIII	OH	H	H	H	H
IX	OH	H	CH_3	H	H
X	OH	Cl	H	H	H
XI	OH	H	H	Cl	H
XII	OH	I	H	Cl	H
XIII	OH	H	H	CH_3	H
XIV	OH	Br	H	CH_3	H
XV	OH	H	CH_3	Cl	H
XVI	OH	Cl	H	Cl	H

RESULTS AND DISCUSSION

A series of novel pyrazolines were synthesized by refluxing piperazine chalcone and hydrazine hydrate in presence of alkali. The reaction is completed within few hours as monitored by TLC providing good to excellent yield.

All the newly synthesized pyrazolines were subjected to antimicrobial studies and exhibited moderate to good activity.

1-Methyl-4-[4-(5-phenyl-3,4-dihydro-2H-pyrazol-3-yl)-phenyl]-piperazine(I):

IR(KBr): 1611cm^{-1}(C=N), 3341 cm^{-1}(N-H), 1245cm^{-1}(C-N); ^{1}HNMR($CDCl_3$):

δ 2.2 (s,3H,CH_3), δ 2.4 (t,4H,CH_2), δ 2.8(dd, 1H, H_a), δ 3.1 (t,4H,CH_2), δ 3.35(dd, 1H, H_b), δ 4.65 (dd, 1H ,H_x), δ 6.5 (s, 1H ,NH), δ 7.1-7.6 (m, 9H ,Ar-H), M.S. (m/z): m+1= 321.

1-{4-[5-(4-Bromo-phenyl)-3,4-dihydro-2H-pyrazol-3-yl]-phenyl}-4-methyl-piperazine (III):

IR(KBr): 1615cm^{-1}(C=N), 3361 cm^{-1}(N-H), 1222cm^{-1}(C-N); ^{1}HNMR($CDCl_3$):

δ 2.2 (s,3H,CH_3), δ 2.4 (t,4H,CH_2), δ 2.9(dd, 1H, H_a), δ 3.1 (t,4H,CH_2), δ 3.4(dd, 1H, H_b), δ 4.7 (dd, 1H ,H_x), δ 6.6 (s, 1H ,NH), δ 7.0-7.8 (m, 8H ,Ar-H), M.S. (m/z): m+1= 399.

1-{4-[5-(4-Methoxy-phenyl)-3,4-dihydro-2H-pyrazol-3-yl]-phenyl}-4-methyl-piperazine(IV):

IR(KBr): 1613cm^{-1}(C=N), 3355 cm^{-1}(N-H), 1235cm^{-1}(C-N); ^{1}HNMR($CDCl_3$):

δ 2.2 (s,3H,CH_3), δ 2.4 (t,4H,CH_2), δ 2.8(dd, 1H, H_a), δ 3.1 (t,4H,CH_2) δ 3.35(dd, 1H, H_b), δ 3.8 (s,3H,OCH_3), δ 4.65 (dd, 1H ,H_x), δ 6.5 (s, 1H ,NH), δ 6.9-7.7 (m, 8H ,Ar-H), M.S. (m/z): m+1= 351.

Table1. Physical data of synthesized compounds (I-XVI).

Entry	Molecular formula	Yield (%)	Melting point (°C)	
I	$C_{20}H_{24}N_4$	87	140	
II	$C_{20}H_{23}BrN_4$	92	175	
III	$C_{20}H_{23}BrN_4$	86	174	
IV	$C_{21}H_{26}N_4O$	78	119	
V	$C_{21}H_{25}FN_4O$	85	206	
VI	$C_{22}H_{28}N_4O_2$	89	168	
VII	$C_{20}H_{24}N_4O$	83	127	
VIII	$C_{20}H_{24}N_4O$	88	178	
IX	$C_{21}H_{26}N_4O$	88	177	
X	$C_{20}H_{23}ClN_4O$	92	197	
XI	$C_{20}H_{23}ClN_4O$	90	212	
XII	$C_{20}H_{22}ClIN_4O$	85	133	
XIII	$C_{21}H_{26}N_4O$	89	173	
XIV	$C_{21}H_{25}BrN_4O$	81	105	
XV	$C_{21}H_{25}ClN_4O$	93	170	
XVI	$C_{20}H_{22}Cl_2N_4O$	89	148	

Biological Screening

Antimicrobial screening was done by using cup plate method[18-19] at a concentration of 100µg/ml. All compounds were checked for their in vitro antimicrobial activity against different strains of bacterias and mentioned fungi as described in table 2. DMSO was used as solvent control. The obtained data of activity of all these tested compounds is as shown in table 2.

Table 2: Antimicrobial activity of synthesized compounds (I-XVII).

Products	Bacteria			Fungi				
	(Zone of Inhibition in mm)			(Zone of Inhibition in mm)				
A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	
I	12	16	12	---	---	17	---	14
II	11	12	13	---	---	14	16	17
III	12	18	21	---	14	---	16	---
IV	12	20	14	15	---	---	17	13
V	15	21	12	14	---	13	17	18
VI	12	16	13	---	---	---	15	17
VII	15	12	14	11	14	17	---	18
VIII	14	17	11	19	15	---	21	---
IX	14	11	21	10	---	13	---	14
X	11	11	14	18	12	---	17	---
XI	12	12	11	15	11	---	19	---
XII	10	10	13	09	25	13	---	15
XIII	11	14	12	14	14	---	27	---
XIV	13	12	11	14	---	---	17	14
XV	16	11	12	16	---	15	20	---
XVI	13	11	15	18	16	13	27	---
XVII	12	15	15	18	21	14	17	---

A= *Bacillus subtilis gr +ve*, B= *Pseudomonas aeruginosa gr –ve*,C= *Staphylococcus aureusgr +ve*,
D= *Escherichia coli gr –ve*, E= *Aspergillus niger*, F= *Aspergillus Flavus*, G= *Curvularia* H= *Alternaria*.

CONCLUSION

In conclusion, we have reported some novel pyrazolines using piperazine chalcones and hydrazine hydrate possessing good to moderate antimicrobial activity. In this study the molecules were tested for their antimicrobial activity, however the pharmacophoric possession of this pyrazoline moiety such as piperazine ring and bromo, chloro, flouro groups may provide us the fruitful results in biological and medicinal purposes.

ACKOWLEDGEMENT

The authors are thankful to Principal Yeshwant College Nanded and also to Director IICT Hyderabad for providing lab and spectral analysis facilities for the research work.

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