

# Novel Pyrazolines Derived From Piperazine Chalcones Synthesis Antimicrobial Studies

Rajashree Markandewar<sup>1</sup>, Hanfi Mohd. Ziauddin<sup>2</sup>, M.A.Baseer<sup>3</sup>

Assistant Professor Department of Chemistry, Rashtrapita Mahatma Gandhi Mahavidlaya, Saoli, Dist.  
Chandrapur, India.<sup>1</sup>

DGM, Chemspech Chemicals Pvt Ltd, India<sup>2</sup>

Associate Professor, P.G. Department of Chemistry, Yeshwant College Nanded, India<sup>3</sup>

**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.

**KEYWORDS:** Chalcones, Hydrazine hydrate, Pyrazolines, Antimicrobial activity.

## I. 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 anti-inflammatory<sup>1-3</sup>, antimicrobial<sup>4-6</sup>, cytotoxic<sup>7</sup>, antimycobacterial<sup>8-9</sup>, anticonvulsant<sup>10</sup> and others<sup>11-12</sup>.

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

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-  $\alpha$  (TNF-  $\alpha$ ). One can face disastrous inflammatory diseases when the activities of one of these mediators go abnormal. Pthalidomide is one of the small molecules TNF-  $\alpha$  inhibitors. Hence use of pthalimide in synthesis of pyrazolines is appreciable so as to get effective anti-inflammatory agent<sup>1</sup>.

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

## II. 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. <sup>1</sup>HNMR spectra on a Bruker Avance DPX400 MHz spectrometer with CDCl<sub>3</sub> 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 (multiplet).

## International Journal of Innovative Research in Science, Engineering and Technology

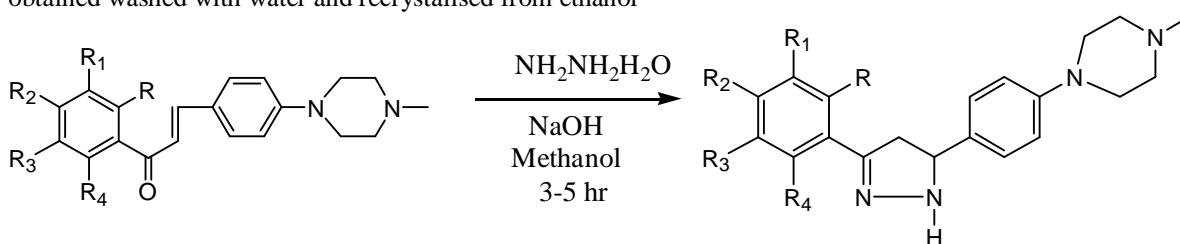
(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

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 recrystallised from ethanol



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

Table-1

Entry	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
<b>I</b>	H	H	H	H	H
<b>II</b>	H	Br	H	H	H
<b>III</b>	H	H	Br	H	H
<b>IV</b>	H	H	OCH <sub>3</sub>	H	H
<b>V</b>	H	F	OCH <sub>3</sub>	H	H
<b>VI</b>	OCH <sub>3</sub>	H	H	OCH <sub>3</sub>	H
<b>VII</b>	H	H	OH	H	H
<b>VIII</b>	OH	H	H	H	H
<b>IX</b>	OH	H	CH <sub>3</sub>	H	H
<b>X</b>	OH	Cl	H	H	H
<b>XI</b>	OH	H	H	Cl	H
<b>XII</b>	OH	I	H	Cl	H

# International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

<b>XIII</b>	OH	H	H	CH <sub>3</sub>	H
<b>XIV</b>	OH	Br	H	CH <sub>3</sub>	H
<b>XV</b>	OH	H	CH <sub>3</sub>	Cl	H
<b>XVI</b>	OH	Cl	H	Cl	H

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

### III. 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<sup>-1</sup>(C=N), 3341 cm<sup>-1</sup>(N-H), 1245cm<sup>-1</sup>(C-N); **<sup>1</sup>HNMR(CDCl<sub>3</sub>):** δ 2.2 (s,3H,CH<sub>3</sub>), δ 2.4 (t,4H,CH<sub>2</sub>), δ 2.8(dd, 1H, H<sub>a</sub>), δ 3.1 (t,4H,CH<sub>2</sub>), δ 3.35(dd, 1H, H<sub>b</sub>), δ 4.65 (dd, 1H ,H<sub>x</sub>), 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<sup>-1</sup>(C=N), 3361 cm<sup>-1</sup>(N-H), 1222cm<sup>-1</sup>(C-N); **<sup>1</sup>HNMR(CDCl<sub>3</sub>):** δ 2.2 (s,3H,CH<sub>3</sub>), δ 2.4 (t,4H,CH<sub>2</sub>), δ 2.9(dd, 1H, H<sub>a</sub>), δ 3.1 (t,4H,CH<sub>2</sub>), δ 3.4(dd, 1H, H<sub>b</sub>), δ 4.7 (dd, 1H ,H<sub>x</sub>), 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<sup>-1</sup>(C=N), 3355 cm<sup>-1</sup>(N-H), 1235cm<sup>-1</sup>(C-N); **<sup>1</sup>HNMR(CDCl<sub>3</sub>):** δ 2.2 (s,3H,CH<sub>3</sub>), δ 2.4 (t,4H,CH<sub>2</sub>), δ 2.8(dd, 1H, H<sub>a</sub>), δ 3.1 (t,4H,CH<sub>2</sub>) δ 3.35(dd, 1H, H<sub>b</sub>), δ 3.8 (s,3H,OCH<sub>3</sub>), δ 4.65 (dd, 1H ,H<sub>x</sub>), δ 6.5 (s, 1H ,NH), δ 6.9-7.7 (m, 8H ,Ar-H), **M.S. (m/z):** m+1= 351.

**Table 2**

Entry	Molecular formula	Yield (%)	Melting point (°C)
<b>I</b>	C <sub>20</sub> H <sub>24</sub> N <sub>4</sub>	87	140
<b>II</b>	C <sub>20</sub> H <sub>23</sub> BrN <sub>4</sub>	92	175
<b>III</b>	C <sub>20</sub> H <sub>23</sub> BrN <sub>4</sub>	86	174
<b>IV</b>	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O	78	119
<b>V</b>	C <sub>21</sub> H <sub>25</sub> FN <sub>4</sub> O	85	206
<b>VI</b>	C <sub>22</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub>	89	168
<b>VII</b>	C <sub>20</sub> H <sub>24</sub> N <sub>4</sub> O	83	127

## International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

<b>VIII</b>	$C_{20}H_{24}N_4O$	88	178
<b>IX</b>	$C_{21}H_{26}N_4O$	88	177
<b>X</b>	$C_{20}H_{23}ClN_4O$	92	197
<b>XI</b>	$C_{20}H_{23}ClN_4O$	90	212
<b>XII</b>	$C_{20}H_{22}ClN_4O$	85	133
<b>XIII</b>	$C_{21}H_{26}N_4O$	89	173
<b>XIV</b>	$C_{21}H_{25}BrN_4O$	81	105
<b>XV</b>	$C_{21}H_{25}ClN_4O$	93	170
<b>XVI</b>	$C_{20}H_{22}Cl_2N_4O$	89	148

**Table 2. Physical data of synthesized compounds ( I-XVI)**

### Biological Screening

Antimicrobial screening was done by using cup plate method<sup>18-19</sup> at a concentration of 100µg/ml. All compounds were checked for their in vitro antimicrobial activity against different strains of bacteria 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**.

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	---

# International Journal of Innovative Research in Science, Engineering and Technology

(An ISO 3297: 2007 Certified Organization)

Vol. 5, Issue 12, December 2016

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	---

**Table 3: Antimicrobial activity of synthesized compounds (I-XVII)**

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

## IV. 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, fluoro groups may provide us the fruitful results in biological and medicinal purposes.

## V. ACKNOWLEDGEMENT

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

## REFERENCES

- [1] Rasika A. Pophale, Meenakshi N. Deodhar. Synthesis and evaluation of novel phthalimide derivatives as analgesic and anti-inflammatory agents. *Der Pharma Chemica*; 2(1): 185-193,2010.
- [2] Pankaj Malhotra, Shashikant Pattan, Anna Pratima Nikalje. Microwave assisted synthesis and anti-inflammatory activity of 3,5-diaryl substituted 2-pyrazolines. *International Journal of Pharmacy and Pharmaceutical Sciences*; 2(2): 21-26, 2010.
- [3] Ramesh B and Sumana T, Synthesis and Anti-Inflammatory Activity of Pyrazolines. *E-Journal of Chemistry*; 7(2): 514-516, 2010.
- [4] Revanasiddappa BC, Nagendra Rao R, Subrahmanyam EVS and Satyanarayana D, Synthesis and Biological Evaluation of Some Novel 1, 3, 5-Trisubstituted Pyrazolines. *E-Journal of Chemistry*; 7(1): 295-298, 2010
- [5] Rakesh N Mistry and Desai KR. Studies on Synthesis of Some Novel Heterocyclic Chalcone, Pyrazoline, Pyrimidine - 2 - One, Pyrimidine -2 - Thione, para-Acetanilide Sulphonyl and Benzoyl Derivatives and their Antimicrobial Activity. *E-Journal of Chemistry*; 2(6): 30-41,
- [6] Jadhav SB, Shastri RA, Gaikwad KV and Gaikwad SV. Synthesis and Antimicrobial Studies of Some Novel Pyrazoline and Isoxazoline Derivatives. *E-Journal of Chemistry*; 6(S1): S183-S188, 2009
- [7] Mohammad Shahar Yar, Anees Ahmad Siddiqui, Mohamed Ashraf Ali, Vedigounder Murugan and Raghu Chandrashekhar. Synthesis and cytotoxic activity of novel pyrazoline derivatives against human lung tumor cell line (A549). *Journal of the Chinese Chemical Society*; 54: 81-86, 2007
- [8] M. Shahar Yar, A. Ahmad Siddiqui and M. Ashraf Ali, Synthesis and antimycobacterial activity of novel heterocycles, *J. Serb. Chem. Soc.*; 72(1): 5-11, 2007
- [9] Ahmet ozdemir, Gulhan turan-zitouni, Zafer Asim kaplancikli. Novel Analogues of 2-Pyrazoline: Synthesis, Characterization, and Antimycobacterial Evaluation, *Turk J Chem.*; 32: 529 – 538, 2008
- [10] Anees A Siddiqui, Md. Azizur Rahman, Md. Shaharyar, Ravinesh Mishra, Synthesis And Anticonvulsant Activity Of Some Substituted 3,5-Diphenyl-2-Pyrazoline-1-Carboxamide Derivatives, *Chemical Sciences Journal*; CSJ-8, 2010
- [11] Shyam S. Mogle, Archana Y. Vibhute, Sandeep V. Khansole, Sainath B. Zangade and Yeshwant B. Vibhute, Synthesis, characterization and antibacterial activity of some new 2-pyrazolines using triethanolamine as reaction solvent, *RJPBCS*; 1(3): 631,2010
- [11] Rahaman SA, Raghendra Prasad Y, Bhuvaneshwari K, Phani Kumar. Synthesis and antihistaminic activity of novel pyrazoline derivatives. *Int.J. Chem Tech Res*; 2(1): 2010
- [12] Dawane BS, Konda SG, Shaikh BM, Chobe SS, Khandare NT, Kamble VT and Bhosale RB. Synthesis and invitro antimicrobial activity of some new 1-thiazolyl-2-pyrazoline derivatives. *International Journal of Pharmaceutical Sciences Review and Research* ; 1(2) 2010
- [13] Powers DG, Casebier DS, Fokas D, Ryan WJ. Automated parallel synthesis of chalcone-based screening libraries. *Tetrahedron*; 54: 4085, 1998
- [14] Ozan Ruhoglu, Zuhail Ozdemir, Unsal Calis, Bulusent Gumusel and Abdullah Altan Bilgin. Synthesis of and Pharmacological Studies on The Antidepressant and Anticonvulsant Activities of Some 1,3,5-Trisubstituted Pyrazolines. *Arzneim-Forsch Drug Res*; 55(8): 431-436, 2005.
- [15] Li JT, Zhang XH and Lin ZP. An improved synthesis of 1,3,5-triaryl-2-pyrazolines in acetic acid aqueous solution under ultrasound irradiation. *Beilstein Journal of Organic Chemistry* 2007; 3(13).
- [16] Seely HW and Van Demark PJ. *Microbes in Action: A Laboratory Manual of Microbiology* DB Taraporewala Sons and Co. Bombay; 55, 1975
- [17] Bantay AL. *The Antimicrobial Susceptibility Test: Principle and Practice* Ed. by Illus Lea and Febiger (Philadelphia, PA, USA); 180, 1976