International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.3, No.1, pp 11-17, Jan-Mar 2011

Pyrazole: A Versatile Moiety

Alka Chauhan*, P. K. Sharma, Niranjan Kaushik

Pharmaceutical Chemistry Research Lab, Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, NH-58, By Pass Road, Meerut-250001,India

Corres.author: alka.chauhan86@gmail.com, Tel.: +91-1212439019, Fax: +91-1212439058

Abstract: The aim of this review is to provide an overview of diverse pharmacological activities of pyrazole moiety. This review highlighted recent reports of antimicrobial, anticancer, ACE inhibitory, antiviral as well as anti-inflammatory activities of pyrazole**.** The purpose of this review was to collate literature work reported by researchers on pyrazole for their varoius pharmacological activities and also reported recent efforts made on this moiety.
Keywords: Pyrazole Analogues, Pharmacological activity, *in vitro* & *in vivo assays* and potent compounds.

INTRODUCTION:

The term Pyrazole was given by Ludwig Knorr in 1883.

Pyrazole (Fig.1) refers to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons [1].

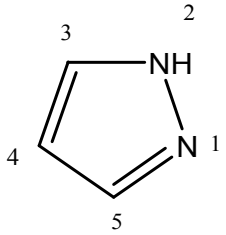


Figure 1

Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of
pyrazole COX-2 inhibitor has further highlighted the importance of these heterocyclic rings in medicinal chemistry. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacoactive agents play important role in medicinal chemistry**.** The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead [1].

LITERATURE REVIEW:

In the present review our main objective is to search the potent compounds for various pharmacological activities with lesser adverse effects. Pyrazole are well established in literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due to their widespread potential biological activities. Literature survey revealed that pyrazole derivatives possess diverse pharmacological activities:

(1) Antitumor Activity:

Peng-cheng LV ***et al,*** (2010) synthesized a series of pyrazole derivatives. The compound (Fig. 2) having R_1= 3, 4- $2CH_3$ and R_2=4-OCH_3 substitution own high antiproliferative activity against MCF-7 with IC_{50} 0.08 µM [2].

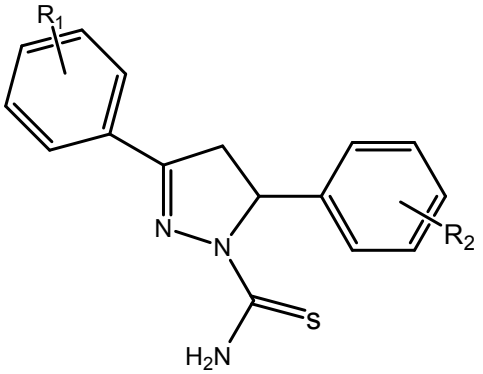


Figure 2

R_1	R_2
3, 4- $2CH_3$	4-OCH_3

Michael S. Christodoulo (2010) ***et al*** synthesized a new series of trisubtituted pyrazole derivatives and screened the compounds for anti-antiangiogenic activity. Compounds containing the fused pyrazole[4,3-c]quinololine motifs emerged as potent anti-angiogenic compounds, which also had the ability to inhibit the growth of human breast (MCF-7) and cervical (Hela) carcinoma cells *in vitro.* Compound **8b** (Fig. 3) were found to be active, eliciting 64% of inhibition ($p<0.01$) by chicken chlorioallantoic membrane (CAM) assay [3].

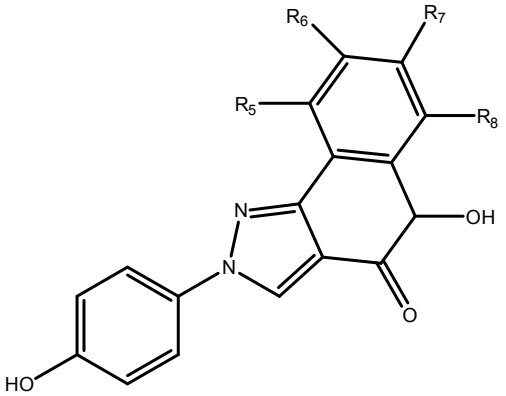


Figure 3

Compounds	R_5	R_6	R_7	R_8
8b	-H	-OH	-H	-H

Ronghui Lin ***et al*** (2007) synthesized 3, 4-disubstituted pyrazole derivatives. The analogues (Fig. 4 & 5) showed potent and selective cyclin-dependent kinase inhibitory activities & inhibited *in-vitro* cellular proliferation in various human cells [4].

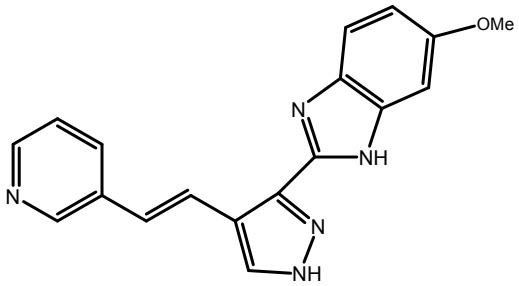


Figure 4

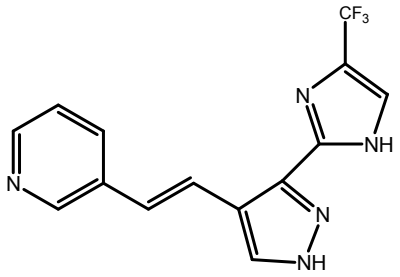


Figure 5

(2) ACE-Inhibitory Activity:

Macro Bonesi ***et al,*** (2010) synthesized a series of pyrazole derivatives (Fig. 5) and investigated their potential activity as Angiotensin-I-converting enzymes inhibitory activity by performing assay. This derivative of pyrazole (Fig. 6) showed effective ACE-inhibitory activity with 0.123 mM IC_{50} value [5].

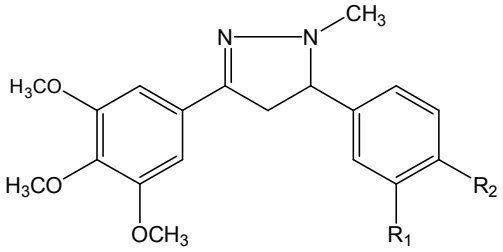


Figure 6

R_1	R_2
NO_2	OCH_3

(3) Antimicrobial Activity:

Samir Bondock ***et al,*** 2010 synthesized a series of substituted pyrazole derivatives. The given compound (Fig. 7) was found to exhibit the most potent *in-vitro* antifungal activity with MICs (6.25 µ/ml) against *A. fumigatus* & *F. Oxysporum* comparab;e with Chloroamphenicol [6].

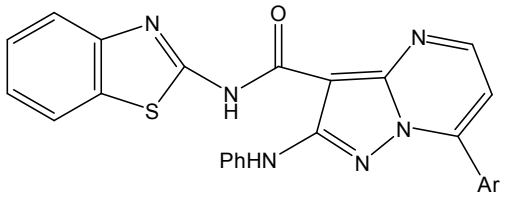


Figure 7

Smaail Radi ***et al, (***2010) synthesized novel pyrazole derivatives and these derivatives were evaluated for their antimicrobial activity determined by agar plate diffusion technique. Antibacterial activity: Against antibacterial strains *Escherichia coli* and determined by agar plate diffusion method. Antifungal activity: Against two fungal strains *Saccharomyces cerevisae* and *Fusarium oxysporum f. sp.ablicans*.
Streptomycin was used as reference compound in performing antimicrobial assay. These derivatives (Fig. 8) were found to be most potent [7].

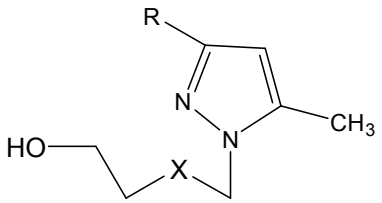


Figure 8

Compounds	R	X
9	CH_3	O
10	CH_3	CH_2
11	CO_2Et	O
12	CO_2Et	CH_2

S. K. Sahu ***et al*** (2008) synthesized novel pyrazoline derivatives. The derivatives **2c**, **2e** & **2f** (Fig.9) showed potent Antimicrobial activity: Antibacterial activity; by muller hinton agar (Hi-media) plates by agar diffusion cup-plate method for Staphylococcus aureus, salmonella typhi & E. coli. Antifungal activity; was tested on sabouraud dextrose agar plates by cup-plate method against Candida albicans & Aspergillus niger)
In both of these assays ciprofloxacin and cotrimazole was used as standard drugs.
Also the compounds 2 c & 2 e (Fig. 9) showed effective analgesic (by Tail flick method) and anti-inflammatory (by Carageenan induced rat paw edema method) [8].

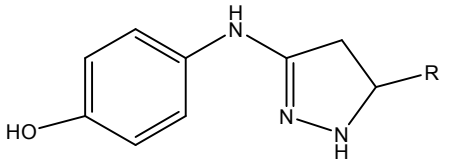
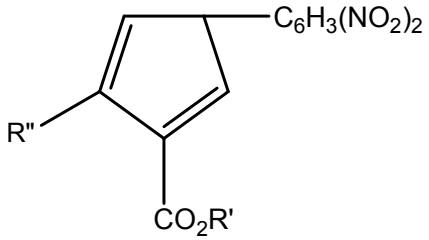


Figure 9

Compounds	R
2c	-4-NO_2-C_6H_4
2e	-2-OH-C_6H_4
2f	-4-Cl- C_6H_4

Radhakrishnan sridhar ***et al*** (2004) synthesized 1-H Pyrazole carboxylate derivatives and screened for antimicrobial activities: Antibacterial activity: Against four human pathogenic bacterias, *Escherichia coli*, *Pseudomonas aeuroginosa*, *Enterobacter facecalis* and *Staphylococcus aureus*. Antifungal activity: Against five pathogenic fungi such as, Against five pathogenic fungi such as, *Rhizochonia solani*, *Fusaricom oxysperum*, *Curuvularia lunata*, *Bipolaris oryzae* and *Alernarnia alternata*.
These derivatives (Fig. 10 & 11) showed significant antimicrobial activity [9].



(R' = C_2H_5, R" = CH_3)

Figure 10

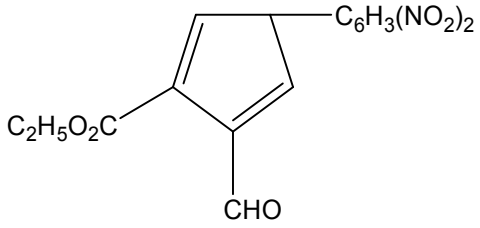
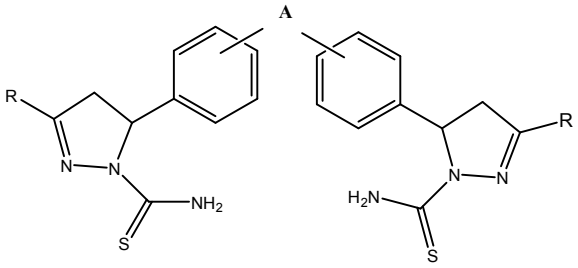


Figure 11

(4) Anti-Inflammatory Activity:
Flora F. Barsoum ***et al*** (2009) synthesized bis (3-aryl-4, 5-dihydro-1H Pyrazole-1-thio carboxamide derivatives. The derivative (Fig.12) with substitution, A = 4-O $(CH_2)_2O$-4' , R = Ph, showed potent anti-

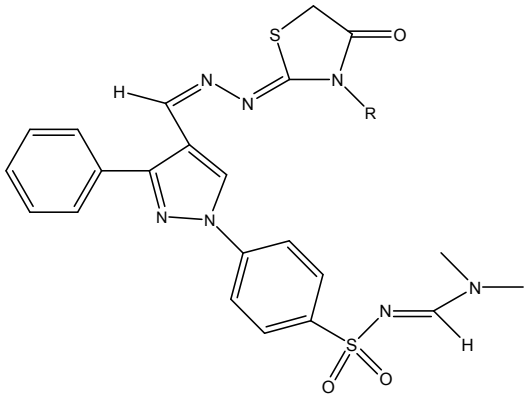
inflammatory activity against carrageenan-induced rat paw edema test [10].



(A = 4-O$(CH_2)_2$O-4' , R = Ph)

Figure 12

Adnan A. bechit *et* ***al*** (2008) synthesized thiazolyl and thaidiazolyl derivatives of 1H-Pyrazole. Potent derivative showed significant anti-inflammatory activity by the cotton pellet granuloma method of rat paw edema bioassay. Derivative **3 b** (Fig.13) has showed comparable antimicrobial activity to that of ampicillin against *E.coli* [11].



(3 b**;** R = 4-$CH_3C_6H_4$)

Figure 13

Asuncio´n Burguete *et* ***al*** (2007) Synthesized substituted pyrazole derivatives and evaluated them for their anti-inflammatory activities. These derivatives **5a**, **5b** & **5c** (Fig. 14) showed good anti-inflammatory activity against carrageenan induced rat paw edema test [12].

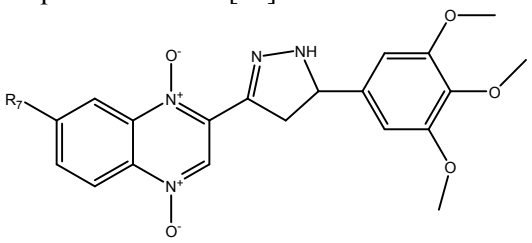
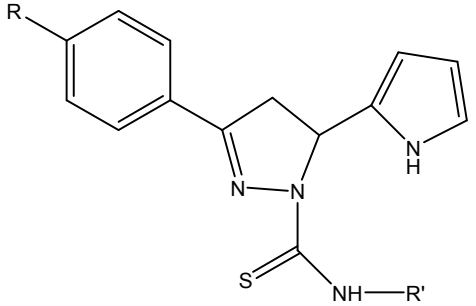


Figure 14

Compounds	R_7
5a	H
5b	F
5c	CH_3O

Nesrin Go¨khan-Kelekc ***et al*** (2007) synthesized novel pyrazole derivatives, compound **3k** (Fig.15) exhibited anti-inflammatory activity using carrageenan induced paw edema method and acetic-acid induced increased capillary permeability comparable to that of indomethacin with no ulcerogenic effect and compound **3k** also showed MAO-B inhibitor activity in mice [13].

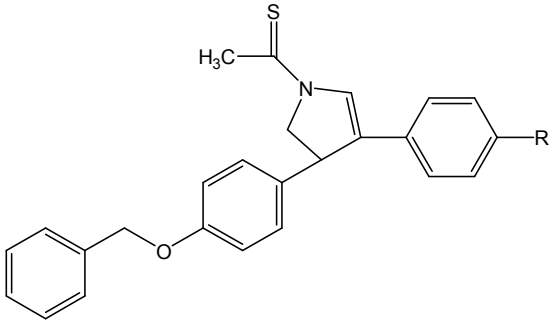


3 k; (R = OCH_3 , R' = C_3H_5)

Figure 15

(5) Antiviral Activity:

Osama I ***et al*** (2009) synthesized 4, 5-disubstituted pyrazole derivatives. The derivative containing R= Cl group (Fig. 16) showed the potent antiviral activity against a broad panel of viruses in different cell culture (HEL Cell cultures) [14].



(R = Cl)

Figure 16

Aymn E. Rashad ***et al*** (2008) synthesized substituted pyrazole derivatives (Fig 17). These derivatives showed promising antiviral activity against hepatitis A virus and Herpes Simplex virus type-1 using plaque infective assay [15].

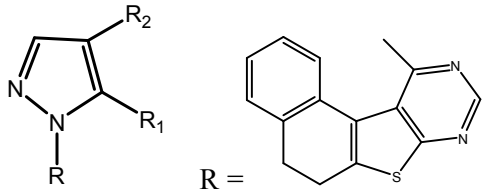


Figure 17

R_1	R_2
CN	NH_2
CN	NHCSNHCOPh
NH_2	COOEt

(6) ANTICONVULSANT AND ANTIDEPRESSANT ACTIVITY:

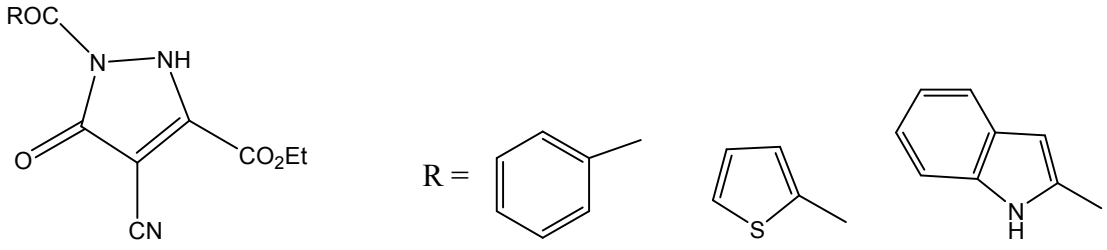
Mohamed Abdel Aziz ***et al,*** (2009) synthesized novel pyrazole derivatives and screened them for anticonvulsant and antidepressant activities. The derivatives **4a** and **4b** (Fig. 18) showed comparable antidepressant activity by using tail suspension behavioral despair test and anticonvulsant activity for derivatives **11a**, **11b** and **11d** (Fig. 19) by using PTZ induced seizures in mice [16].

RESULT AND DISCUSSION:

Pharmaceutical chemistry is devoted to the discovery and development of new agents for treating diseases. Inorganic compound continue to be important in therapy, for example, as antacids, mineral supplements and radiopharmaceuticals, but organic molecules with increasingly specific pharmacological activities are clearly dominant [17]. The objective of medicinal chemistry is design and production of compounds that can be use as medicine for the prevention, treatment and cure of humans or animal diseases. It is concerned with the invention, discovery, design, identification of biologically active compounds, the study of their metabolism, interpretation of their mode of action at the molecular level and the construction of structure activity relationship (SAR), the relationship between chemical structure and pharmacological activity for a series of compounds [18]. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and biological activity [19]. The intellectual goal of researchers are to know the mode of action of drugs at molecular level taken in the prospective sense [20].

4 a **4b**

Figure 18



11a **11b** **11d**

Figure 19

In the present review, interest is focused on the profile of various pharmacological activities pyrazole.
The five and six membered heterocyclic nitrogen containing systems such as pyrazole, imidazole, trizoles, thiozolidine, pyrazolidine, etc. are far by the most important in the ongoing research for more efficacious drugs in the fields such as antibacterials, fungicidal, anti-inflammatory, anticonvulsant, diuretics, and antihistaminic, etc.

CONCLUSION:
Pyrazole is a unique template that is associated with several biological activities. This article highlightened research work of many researchers reported in literature for different pharmacological activities on pyrazole compounds synthesized.
The review has presented comprehensive details of pyrazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of pyrazole for many diseases whose treatment are difficult in the medical sciences.

FUTURE PROSPECTIVE:
Several economical and social merits have been prospected for compounds with effects like anti-inflammation, antimicrobial and others. Pyrazoles are an important class of compounds for new drug development that attracted much attention. Several pyrazole derivatives have been synthesized as target structures and evaluated for their biological activities. The cytotoxicity of the reported compounds in the review indicate good safety associated with many of the pyrazole derivatives, however, the need for standardized method for cytotoxicity evaluation is required for better understanding of the compounds safety and the safety-structure relationships.

REFERNCES:

[1] Eicher T, Hauptmann, S, **(2003)**, Edition IInd, 'The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications', Wiley-VCH, ISBN 3527307206.

[2] Lv. Peng-Cheng, Zhu Hai-L , Li Huan-Qiu , Sun J, Zhou Y, **(2010)**, 'synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents' **,** Bioorg. Med. Chem., 18: 4606–4614.

[3] Lin R, Chiu G, Yu Y, Connolly P J, Li S, Lu Y, Mary Adams, Angel R. Fuentes-Pesquera, Stuart L. Emanuel and Lee M. Greenberger, **(2007)**, 'Design, synthesis, and evaluation of 3,4-disubstituted pyrazole analogues as anti-tumor CDK inhibitors' , Bioorg. Med. Chem. Lett, 17: 4557–4561

[4] Christodoulou M S, Sandra L, Kasiotis K M, Harotounian S A, **(2010) ,** 'Novel pyrazole derivatives: synthesis and evaluation of anti-angiogenic activity' Bioorg. Med. Chem., 18, 4338-4350.

[5] Bonesi M, Loizzo M R, Statti G A, Michel S, Tillequin F, Menichini, **(2010)** , ' The synthesis and ACE inhibitory activity of chalcones and their pyrazole derivatives' , Bioorg. Med. Chem. Lett, 20: 1990–1993.

[6] Sridhar R, Perumal P J, Etti S, Shanmugam G, Ponnuswamy M N, Prabavathy V R, Mathivanan N, **(2004)** , ' Design, synthesis and anti-microbial activity of 1*H*-prazole carboxylate' , Bioorg. Med. Chem. Lett. , 14; 6035–6040.

[7] Bondock S, Fadaly W, Metwally M A, **(2010)** , 'Synthesis and antimicrobial activity of some new thiazole, thiophene and pyrazole derivatives containing benzothiazole moiety' , Eur. J. Med. Chem., 1e: 10.

[8] Radi S, Salhi S, Radi A, **(2010)**, 'Synthesis and preliminary biological activity of some new pyrazole derivatives as acyclonucleoside analogues' , Letters in Drug Design & Discovery, Bentham Science Publishers Ltd, 7: 27-30.

[9] Bekhit A A, Ashour H M A, Ghany Y S A, El-Din A. Bekhit A, Baraka A, **(2008)** , 'Synthesis and biological evaluation of some thiazolyl and thiadiazolyl derivatives of 1H-pyrazoles as anti-inflammatoey antimicrobial agents' , Eur J. Med. Chem. , 43: 456-463.

[10] Burguete A, Pontiki E, Hadjipavlou-Litina D, Villar R, Vicente E, Solano B, Ancizu S, Pe´rez-Silanes S, Aldanaa I, Monge A, **(2007)** , 'Synthesis and anti-inflammatory/antioxidant activities of some new ring 3-phenyl-1-(1,4-di-*N*-oxide quinoxalin-2-yl)-2-propen-1-one derivatives and of their 4,5-dihydro-(1*H*)-pyrazole analogues' , Bioorg. Med. Chem. Lett. , 17; 6439–6443.

[11] Barsoum F F, Girgis A S, **(2009)** , **'**Facile synthesis of bis(4,5-dihydro-1*H*-pyrazole-1-carboxamides) and their thio-analogues of potential PGE_2 inhibitory properties' , Eur. J. Med. Chem. , 44: 2172–2177.

[12] Gokhan-Kelekc N, Yabanog˘lu S, Ku¨peli E, Salgın U, Ozgen O, Ucar G, Yesilada E, Kendi E, Yesiladaf Y, Altan Bilgin A, **(2007)** , 'Synthesis and biological evaluation of some thiazole and thiadiazolyl derivatives of 1*H*-pyrazole as anti-inflammatory antimicrobial' , Bioorg. Med. Chem. 15: 5775–5786.

[13] El-Sabbagh O I, Baraka M M, Ibrahim S M, Pannecouque P, Andrei G, Snoeck R, Balzarini J, Rashad A A, (**2009)** , 'Synthesis and antiviral activity of new pyrazole and thiazole derivatives' , Eur. J. Med. Chem. , 44; 3746–3753.

[14] Rashad A E, Hegab M I, Abdel-Megeid R E, Micky J A, Abdel-Megeid F M E, **(2008)**, Bioorg. Med. Chem., 16: 7102–7106.

[15] Abdel-Aziz M, El-Din A. Abuo-Rahma G, Hassan A A, **2009**, 'Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities' , Eur. J. Med. Chem. 44: 3480–3487.

[16] Sahu S K, Banerjee M, Samantray A, Behera C, Azam M A, **2008**, 'Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives' , Tropical J. Pharm. Research, 7 (2): 961-968.

[17] Block John H., "Wilson & Gisvold's Text Book of Organic Medicinal and Pharmaceutical Chemistry", 11th Edition, **2003**, 1-3.

[18] David A. Williams, Thomas L. Lemke, Foye"s principles of medicinal chemistry; sixth edition, **2008**.

[19] Remington, the science and practice of pharmacy, 20th edition, **2002**. 2, 458.

[20] Singh H., Kapoor V. K., Medicinal and pharmaceutical chemistry, II, 29, **2003**.

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