Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2013, 5 (1):340-354
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

The synthetic development of pyrazole nucleus: From reflux to microwave

Harish K. Arora[1*], Sandeep Jain[1]

[1]Drug Design and Research Laboratory, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology Hisar, Haryana, India.

ABSTRACT

Pyrazole belongs to the "diazole" class of heterocycles and is the most important moiety found in a large number of pharmaceutical agents. One of the earliest methods of pyrazole synthesis is refluxing the contents over hot water bath for few hours with constant stirring leading to the synthesis of a single compound in a particular yield. Overcoming the disadvantages of reflux method, newer technologies like one pot multicomponent synthesis, solution free synthesis, solid support synthesis, microwave and ultrasound synthetic technologies along with solution phase and solid phase combinatorial synthetic procedures are being adopted with the advantages of getting compounds in high yields in a lesser time duration. In the present review, an attempt has been made to describe the various development stages in the synthesis of pyrazole analogues.

Keywords: Pyrazole, 1,2-diazoles, Synthesis, Combinatorial chemistry, Solid phase synthesis.

INTRODUCTION

Pyrazoles owing to the presence of two neighbourhood nitrogen atoms, are also known as 1,2-diazoles. It has been the topic of medicinal research for the millions of researchers all over the world because of its large number of pharmacological activities. Some of the pyrazole possessing drugs like *celecoxib* [1], *antipyrine, analgin, allopurinol, butazoline, phenylbutazone, oxyphenbutazone, novalgin* [2], *pyrazofurin* [3], *ramifenazone* [4], *indisteron* [5], *apixaban, fipronil, rimonabant* [6] and many more are already in market. Structures of some of these drugs have been shown in Fig. **1**.

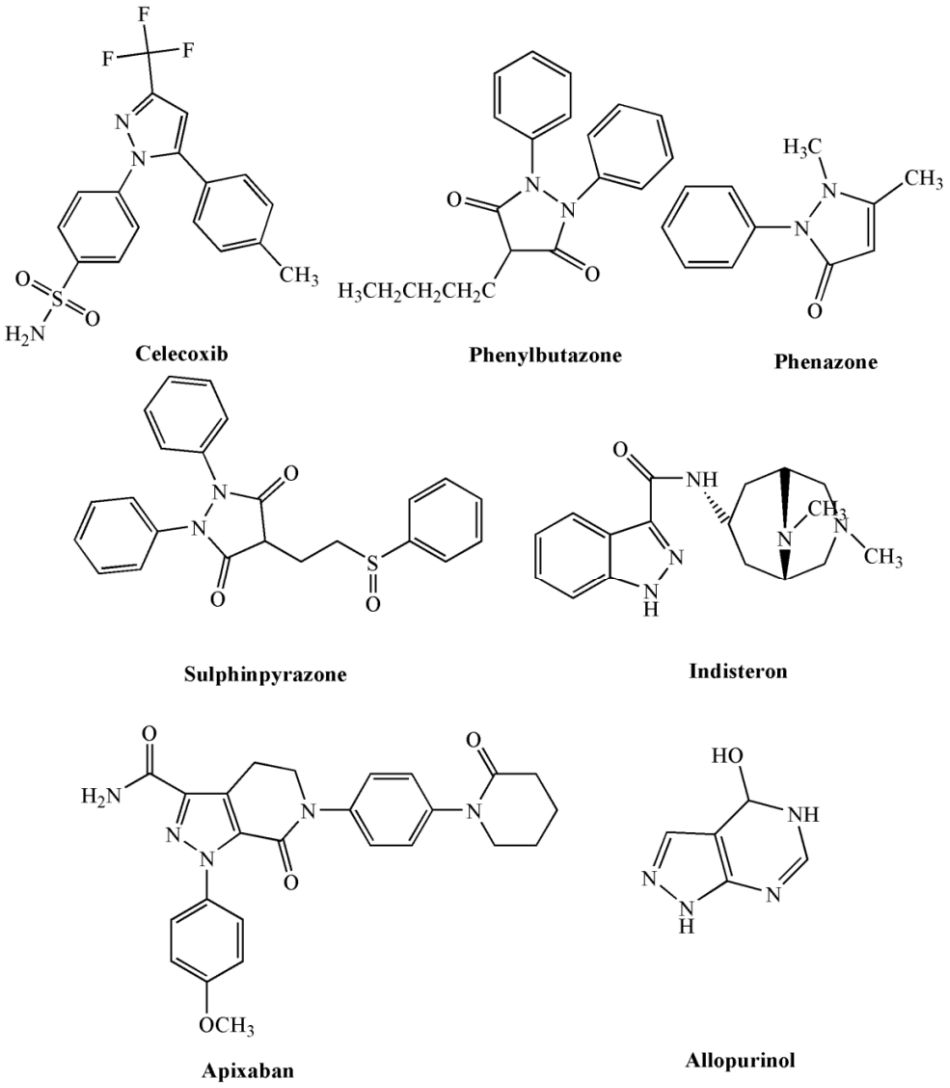
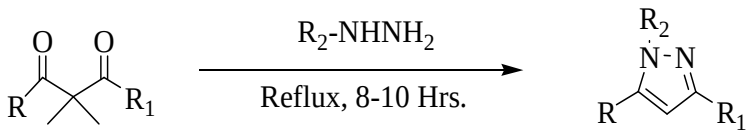


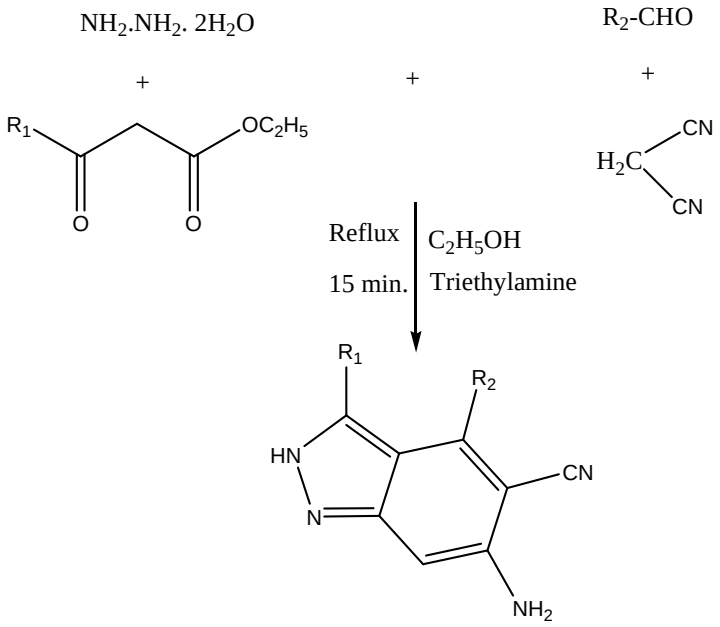
Figure 1. Few pyrazole based drugs available in the market.

1. Reflux Method: One of the oldest, common and mostly acceptable procedure for synthesis of pyrazole is reflux method where the reaction is performed between 1,3-diketo compound e.g diethyl malonate or ethylacetoacetate with hydrazine hydrate **(**Scheme **1)** in ethanol or hydrazine halides [7].



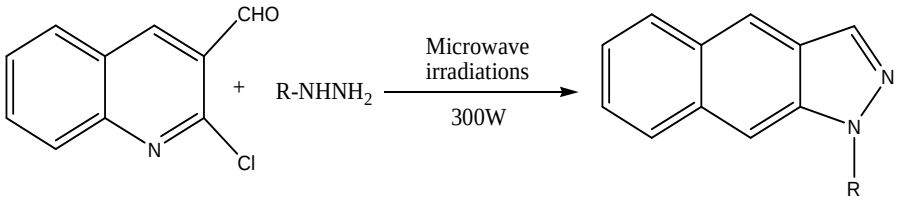
Scheme 1.

2. One pot multicomponent synthesis: In 2009, Shestopalov *et al*. reported a new method for the synthesis of 6-Amino-2,4-dihydropyrano[2,3-*c*]pyrazol-5-carbonitrile by reacting all four reactants in a single pot i.e β-ketoesters, aromatic aldehydes, hydrazine hydrate, malononitrile for 10-15 minutes taking triethylamine as base **(**Scheme **2)**. It was interesting to see that the method not only reduced the reaction time between substrates but also produced the target compounds in high yields [8].



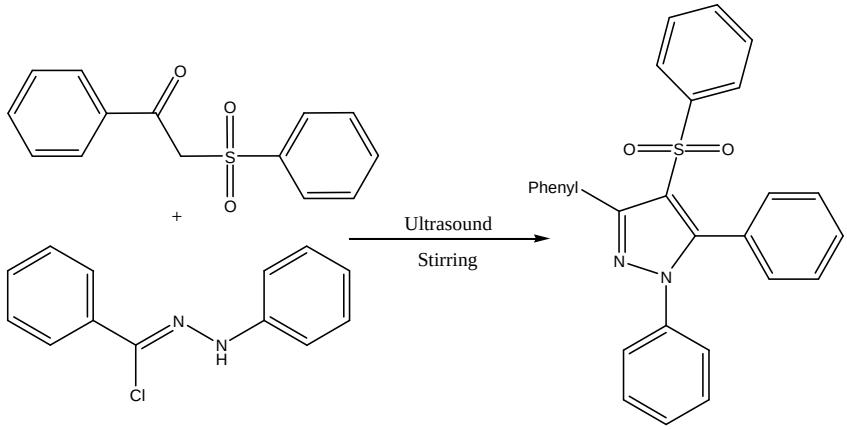
Scheme 2.

3. Microwave assisted solvent free synthesis: Gupta *et al.* in 2001, synthesized fused pyrazoles or pyrazolo[3,4-c]quinoline derivatives under microwave irradiation taking β-chlorovinylaldehyde and hydrazine hydrate (Scheme **3**) as reactants [9].



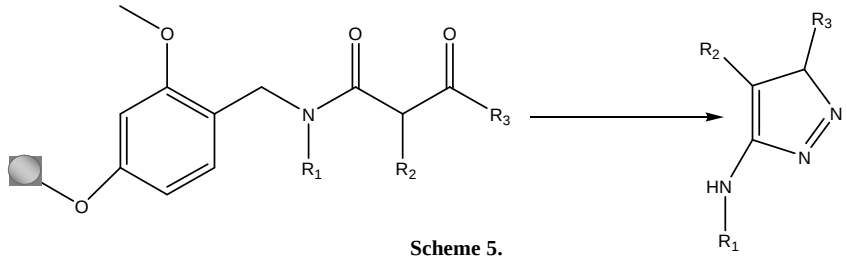
Scheme 3.

4. Ultrasound promoted synthesis: Ultrasound machines are now a days not limited to hospitals. The statement was proved by Rahman *et al.* in 2009, when he reported a new method of pyrazole synthesis using ultrasound radiations condensing together in a reaction vessel N-phenylbenzenecarbohydrazonoyl chloride and an alcoholic solution of 1-aryl-2-(phenylsulphonyl)ethanone at room temperature (Scheme **4**) under ultrasonic irradiations with constant stirring [10].



Scheme 4.

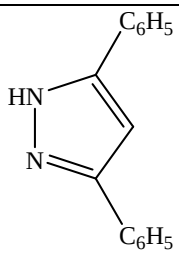
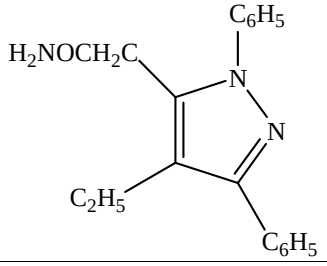
5. Solid phase combinatorial synthesis: Dodd *et al*. described an effective resin bound solid support synthetic method, synthesizing 5-N-arylamino and 5-N-alkylamino pyrazoles. Immobilized γ-ketoamide was taken as the starting material which was then reacted at 50-55°C with immobilized resin bound alkylhydazine and lawesson's reagent in a vessel containing THF solution (Scheme **5**). After the completion of the reaction, resin-bound 5-aminopyrazoles were generated and further purified and tested for their analytical profile [11].

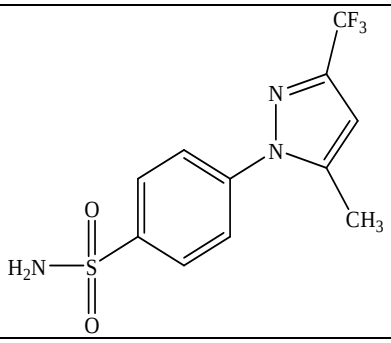
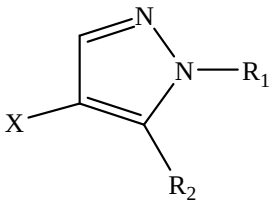
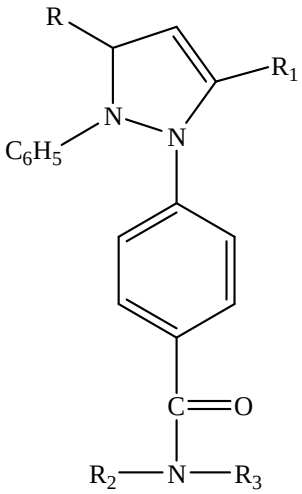
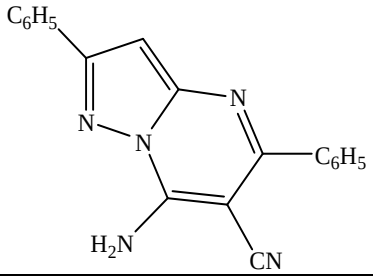
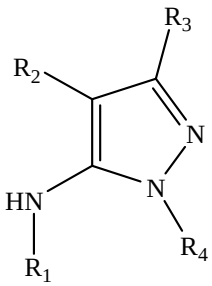


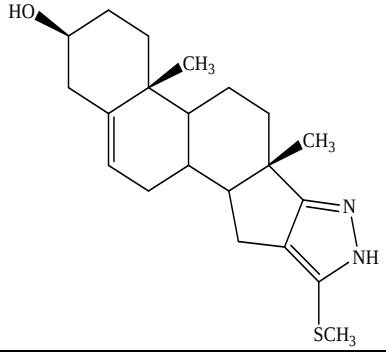
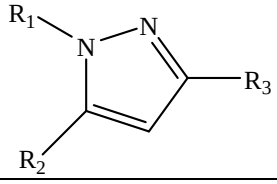
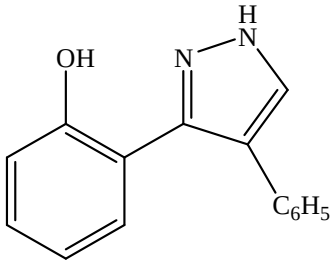
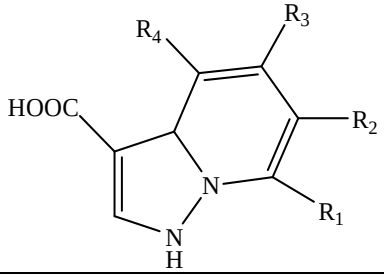
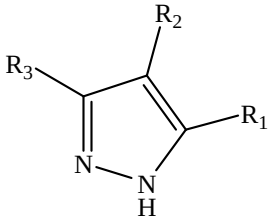
Scheme 5.

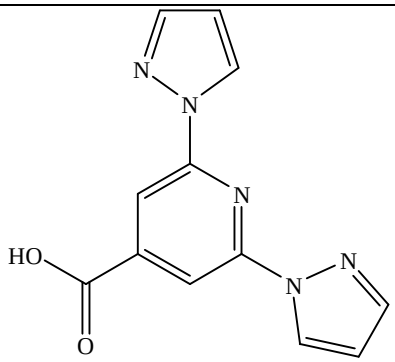
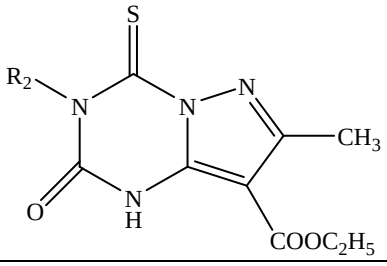
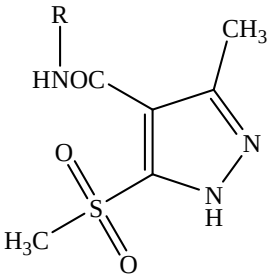
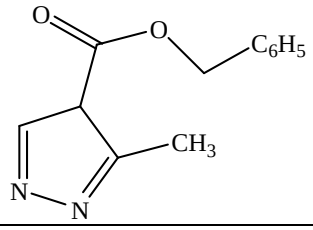
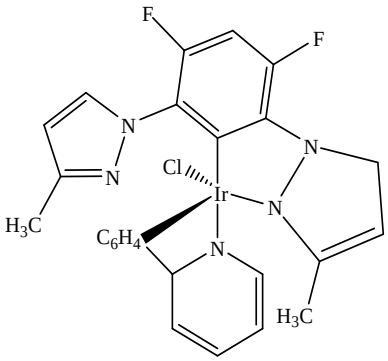
Below is some work done for the synthesis of pyrazoles by different techniques (Table **1**).

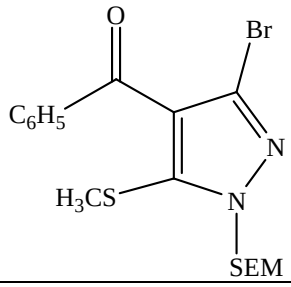
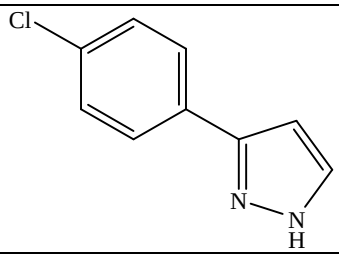
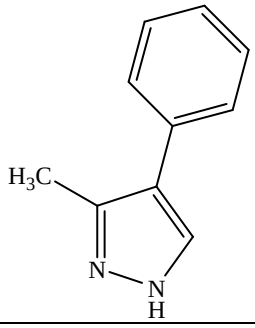
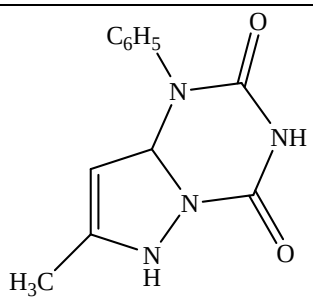
Table 1. Work done for the synthesis of pyrazole by different techniques.

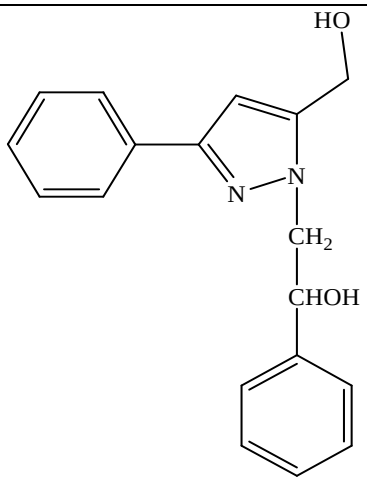
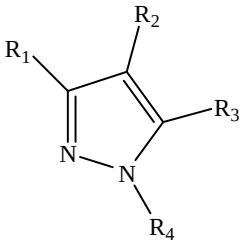
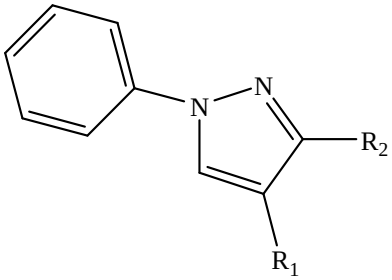
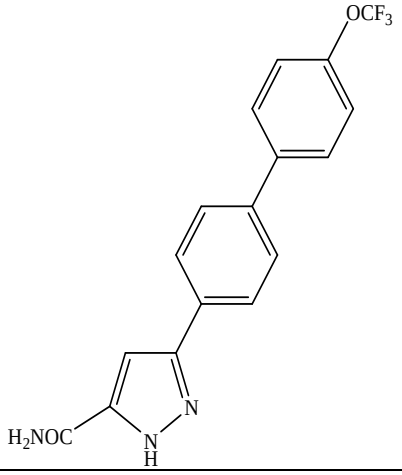
Sr. No	Work Done	Structure	Reference
1.	New "green" approaches to the synthesis of pyrazole derivatives		[12]
2.	Solid phase synthesis of variably substituted pyrazoles		[13]

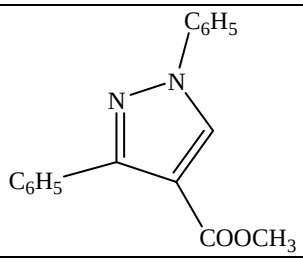
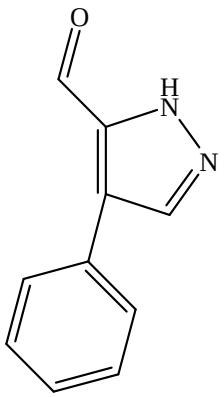
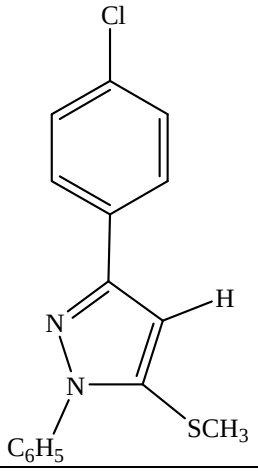
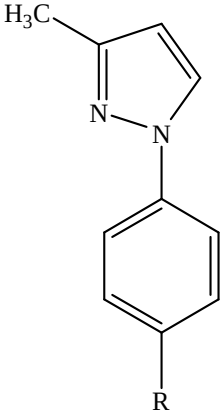
3.	Ultrasound promoted synthesis of substituted pyrazoles		[14]
4.	Greener and rapid access to bio-active heterocycles: room temperature synthesis of pyrazoles and diazepines in aqueous medium		[15]
5.	Fully automated polymer-assisted synthesis of 1,5-biaryl pyrazoles		[16]
6.	Green one pot solvent free synthesis of pyrano[2,3-c] pyrazoles and pyrazol[1,5-a] pyrimidines		[17]
7.	Solid phase synthesis of 5-substituted amino pyrazoles		[18]

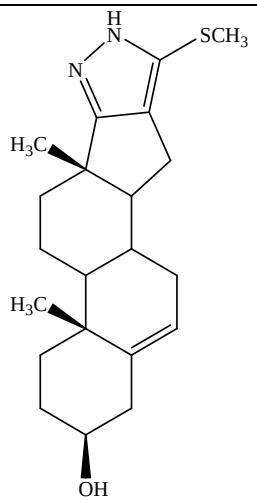
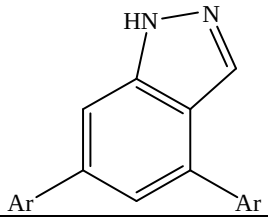
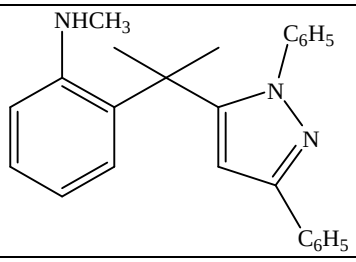
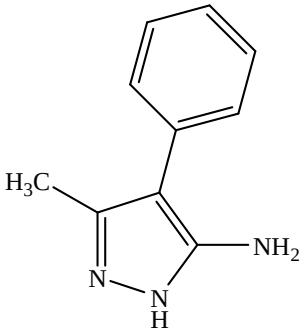
8.	Microwave assisted one-pot synthesis of pyrazolone derivatives under solvent-free conditions		[19]
9.	Microwave Assisted Synthesis of N-Azacyclo alkanes, Isoindole, Pyrazole, Pyrazolidine, and Phthalazine Derivatives		[20]
10.	Three-component, one pot reaction for the combinatorial synthesis of 1,3,4-substituted pyrazoles		[21]
11.	Solid phase synthesis of pyrazolo-pyridines from polymer-bound alkyne and azomethine imines		[22]
12.	Solid phase synthesis of amino acid derived N-unsubstituted pyrazoles via sydnones		[23]

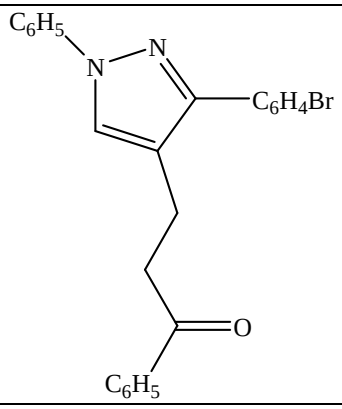
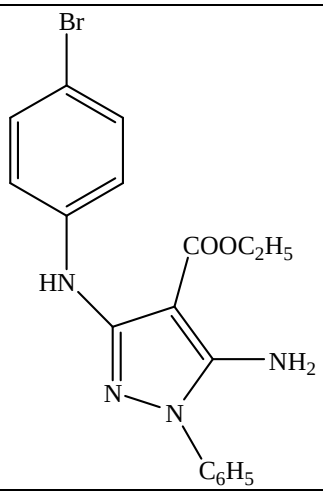
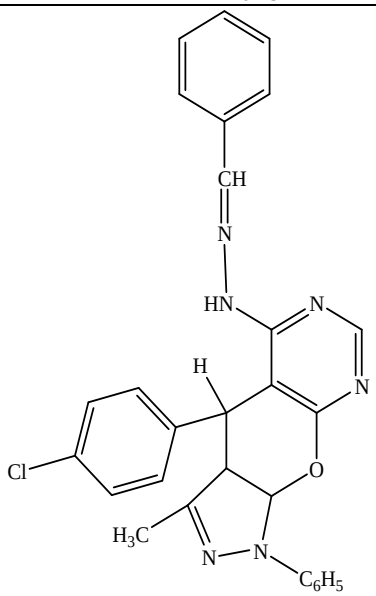
13.	Convenient synthesis of tridentate 2,6-di(pyrazol-1-yl)-4-carboxy pyridine and tetradentate 6,6'-di (pyrazol-1-yl) -4,4'-dicarboxy-2,2'-bipyridine ligands		[24]
14.	Solid phase synthesis of novel 7,8-functionalized pyrazolo [1,5-a] [1,3,5]-2-oxo-4-thioxotriazine derivatives via cyclization reactions of dithiocarboxy resin bound pyrazoles		[25]
15.	Water mediated construction of trisubstituted pyrazoles/ isoxazoles library using ketene dithioacetals		[26]
16.	Cellulose beads: a new versatile solid support for microwave-assisted synthesis. Preparation of pyrazole and isoxazole libraries		[27]
17.	Synthesis and phosphorescent properties of blue emissive iridium complexes with tridentate pyrazolyl ligands		[28]

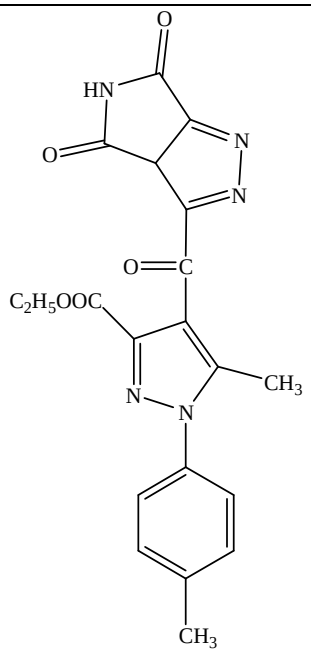
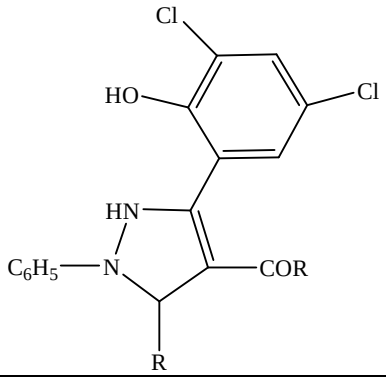
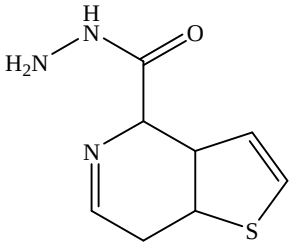
18.	Synthesis of fully substituted pyrazoles via regio and chemo-selective metalations		[29]
19.	Cyclization of 3-diazoalkenes to pyrazoles		[30]
20.	Reactions of diazo compounds with nitro olefins-the preparation of pyrazoles		[31]
21.	Synthesis of pyrazole derivatives and their evaluation as photosynthetic electron transport inhibitors		[32]

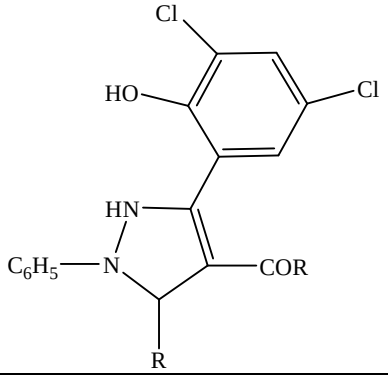
22.	Synthesis, crystal structure and biological evaluation of novel 2-(5-(hydroxyl methyl)-3-phenyl -1*H*-pyrazol-1-yl 1-phenyl ethanol derivatives		[33]
23.	Regioselective synthesis of 1,3,5- and 1,3,4,5-substituted pyrazoles via acylation of N-Boc-N-substituted hydrazones		[34]
24.	Pd-catalyzed Negishi coupling of pyrazole triflates with alkyl zinc halides		[35]
25.	Substituted biaryl pyrazoles as sodium channel blockers		[36]

26.	Expeditious synthesis of 1,3,4-trisubstituted pyrazoles from Baylis-Hillman adducts		[37]
27.	Synthesis of 3- and 5-formyl-4-phenyl-1*H*-pyrazoles: promising head units for the generation of asymmetric imine ligands and mixed metal polynuclear complexes		[38]
28.	Regioselective synthesis of 1-aryl-3,4-substituted /annulated-5-(methyl thio) pyrazoles and 1-aryl-3-(methylthio)-4,5 substituted/ annulated pyrazoles		[39]
29.	Zinc-catalyzed synthesis of pyrazolines and pyrazoles via hydro hydrazination		[40]

30.	Synthesis of new pyrazole and pyrimidine steroidal derivatives		[41]
31.	Synthesis of some fused pyrazoles		[42]
32.	A novel synthesis of 1,3,5-trisubstituted pyrazoles through a spiropyrazoline intermediate via a tandem 1,3-dipolar cycloaddition/ elimination		[43]
33.	Synthesis of 3-amino 1*H*-pyrazoles catalyzed by p-toluene sulphonic acid using polyethylene glycol-400 as an efficient and recyclable reaction medium		[44]

34.	Synthesis of new class of pyrazole based diaryl heterocycles		[45]
35.	Synthesis and pharmacological activity of substituted pyrazoles		[46]
36.	Synthesis of novel fused heterocycles based on pyrano[2,3-c] pyrazole		[47]

37.	Synthesis of some new pyrrolidino [3,4-c] pyrazolines, pyrazoles and pyrazolo [3,4-d] pyridazines		[48]
38.	Synthesis of some novel pyrazoles		[49]
39.	Synthesis, spectral investigation and biological evaluation of novel noncytotoxic tetrahydrothieno[3, 2-c] pyridine hydrazide derivatives		[50]

40.	Synthesis and study of chlorosubstituted 4-aroyl/alkoyl pyrazoles and isoxazoles and their impact on phytotic growth of some vegetable crop plants		[51]

CONCLUSION

This study presents some newer approaches useful for the synthesis of pyrazole nucleus. Huge collection of research articles cited in this review describes the different stages of developments in the synthesis of pyrazole moiety. Novel methods of pyrazole synthesis like solid phase synthesis, solution free synthesis, water mediated synthesis, one pot multicomponent synthesis, microwave and ultrasound mediated synthetic procedures are preferred now a days due to their several advantages over the longer duration reflux method which is also inferior in case of product yield. This article can serve as a better tool for the researchers and can provide fresh ideas in the minds of several medicinal chemists to develop new molecules possessing pyrazole scaffold.

Acknowledgement
The author(s) would like to express their sincere thanks to Priti Girotra for helping in the preparation of manuscript and critically reviewing it.

REFERENCES

[1] R.R. Ranatunge, D.S. Garvey, D.R. Janero, L.G. Letts, A.M. Martino, M.G. Murty, S.K. Richardson, D.V. Young, I.S. Zemetseva, *Bioorganic & Medicinal Chemistry*, **2004**, 12, 1357-1366.
[2] H. Singh, V.K Kapoor, *Medicinal and Pharmaceutical Chemistry*, Vallabh Prakashan, **1996**, 278-282.
[3] A.A. Bekhit, H.M.A. Ashour, Y.S. Abdel Ghany, A.E.-D.A. Bekhit, A. Baraka, *European Journal of Medicinal Chemistry*, **2008**, 43, 456-463.
[4] R. Fioravanti, A. Bolasco, F. Manna, F. Rossi, F. Orallo, F. Ortuso, S. Alcaro, R. Cirilli, *European Journal of Medicinal Chemistry*, **2010**, 45, 6135-6138.
[5] B.H. Lee, I.S. Choi, H. Rhim, K. Choi, S.Y. Nah, Nam, *Bullerian korean chemical society*, **2009**, 30 (11), 2707-2712.
[6] R. Deprez-Poulain, N. Cousaert, P. Toto, N. Willand, B. Deprez, *European Journal of Medicinal Chemistry*, **2011**, 46, 3867-3876.
[7] D.J. Wang, C.Y. Zheng, L. Fan, *Journal of Molecular Structure*, **2009**, 938, 311-315.
[8] Y.M. Litvinov, A.A. Shestopalov, L.A. Rodinovskaya, A.M. Shestopalov, *Journal of Combinatorial Chemistry*, **2009**, 11, 914-919.
[9] S. Paul, M. Gupta, R. Gupta, A. Loupy, *Tetrahedron Letters*, **2001**, 42, 3827-3829.
[10] T.S. Saleh, N.M. Abd El-Rahman, *Ultrasonics Sonochemistry*, **2009**, 16, 237-242.
[11] D.S. Dodd, R.L. Martinez, M. Kamau, Z. Ruan, K. Van Kirk, C.B. Cooper, M.A. Hermsmeier, S.C. Traeger, M.A. Poss, *Journal of Combinatorial Chemistry*, **2005**, 7, 584-588.
[12] A. Corradi, C. Leonelli, A. Rizzuti, R. Rosa, P. Veronesi, R. Grandi, S. Baldassari, C. Villa, *Molecules*, **2007**, 12, 1482-1495.
[13] A. Marzinzik, E. Felder, *Molecules*, **1997**, 2, 17-30.
[14] T.S. Saleh, N.M. Abd El-Rahman, *Ultrasonics Sonochemistry*, **2009**, 16, 237-242.
[15] V. Polshettiwar, R.S. Varma, *Tetrahedron Letters*, **2008**, 49, 397-400.

[16] E. Vickerstaffe, B.H. Warrington, M. Ladlow, S.V. Ley, *Journal of Combinatorial Chemistry*, **2004**, 6, 332-339.
[17] H.M. Al-Matar, K.D. Khalil, A.Y. Adam, M.H. Elnagdi, *Molecules*, **2010**, 15, 6619-6629.
[18] D.S. Dodd, R.L. Martinez, M. Kamau, Z. Ruan, K. Van Kirk, C.B. Cooper, M.A. Hermsmeier, S.C. Traeger, M.A. Poss, *Journal of Combinatorial Chemistry*, **2005**, 7, 584-588.
[19] R. Ma, J. Zhu, J. Liu, L. Chen, X. Shen, H. Jiang, J. Li, *Molecules*, **2010**, 15, 3593-3601.
[20] Y. Ju, R.S. Varma, *Journal of Organic Chemistry*, **2005**, 71, 135-141.
[21] F. Xie, G. Cheng, Y. Hu, *Journal of Combinatorial Chemistry*, **2006**, 8, 286-288.
[22] K. Harju, I. Kylanlahti, T. Paananen, M. Polamo, J. Nielsen, J. Yli Kauhaluoma, *Journal of Combinatorial Chemistry*, **2006**, 8, 344-349.
[23] K. Harju, J. Vesterinen, J. Yli Kauhaluoma, *Organic Letters*, **2009**, 11, 2219-2221.
[24] C. Klein, E. Baranoff, M. Gratzel, M.K. Nazeeruddin, *Tetrahedron Letters*, **2011**, *52*, 584-587.
[25] Y.D. Gong, I.A. Ryu, *Journal of Combinatorial Chemistry*, **2009**, 11, 626-630.
[26] M.M. Savant, A.M. Pansuriya, C.V. Bhuva, N. Kapuriya, A.S. Patel, V.B. Audichya, P.V. Pipaliya, Y.T. Naliapara, *Journal of Combinatorial Chemistry*, **2009**, 12, 176-180.
[27] L. De Luca, G. Giacomelli, A. Porcheddu, M. Salaris, M. Taddei, *Journal of Combinatorial Chemistry*, **2003**, 5, 465-471.
[28] L. Yang, F. Okuda, K. Kobayashi, K. Nozaki, Y. Tanabe, Y. Ishii, M.A Haga, *Inorganic Chemistry*, ***2008,*** 47, 7154-7165.
[29] C. Despotopoulou, L. Klier, P. Knochel, *Organic Letters*, **2009**, 11, 3326-3329.
[30] J.L. Brewbaker, H. Hart, *Journal of the American Chemical Society*, **1969**, 91, 711-715.
[31] W.E. Parham, J.L. Bleasdale, *Journal of the American Chemical Society*, **1950**, 72, 3843-3846.
[32] C.B. Vicentini, D. Mares, A. Tartari, M. Manfrini, G. Forlani, *Journal of Agricultural and Food Chemistry*, **2004**, 52, 1898-1906.
[33] L.W. Zheng, J. Zhu, B.X. Zhao, Y.H. Huang, J. Ding, J.-Y. Miao, *European Journal of Medicinal Chemistry*, **2010**, 45, 5792-5799.
[34] A. Tinarelli, P. Righi, G. Rosini, D. Andreotti, R. Profeta, S. Spada, *Tetrahedron*, **2011**, 67, 612-617.
[35] T. Zhang, X. Gao, H.B. Wood, *Tetrahedron Letters*, **2011**, 52, 311-313.
[36] S. Tyagarajan, P.K. Chakravarty, B. Zhou, B. Taylor, M.H. Fisher, M.J. Wyvratt, K. Lyons, T. Klatt, X. Li, S. Kumar, B. Williams, J. Felix, B.T. Priest, R.M. Brochu, V. Warren, M. Smith, M. Garcia, G.J. Kaczorowski, W.J. Martin, C. Abbadie, E. McGowan, N. Jochnowitz, W.H. Parsons, *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20, 5480-5483.
[37] H.S. Kim, S.H. Kim, J.N. Kim, *Bullerian korean chemical society*, **2007**, 28(10), 1841-1843.
[38] J. Olguin, S. Brooker, *New Journal of Chemistry*, **2011**, 35, 1242-1253.
[39] S. Peruncheralathan, T.A. Khan, H. Ila, H. Junjappa, *Journal of Organic Chemistry*, **2005**, 70, 10030-10035.
[40] K. Alex, A. Tillack, N. Schwarz, M. Beller, *Organic Letters*, **2008**, 10, 2377-2379.
[41] D. Rivera, K. Peseke, I. Jomarron, A. Montero, R. Molina, F. Coll, *Molecules*, **2003**, 8, 444-452.
[42] V. Padmavathi, B. Reddy, A. Balaiah, K. Reddy, D. Reddy, *Molecules*, **2000**, 5, 1281-1286.
[43] S. Dadiboyena, E.J. Valente, A.T. Hamme II, *Tetrahedron Letters*, **2009**, 50, 291-294.
[44] N. Suryakiran, D. Ramesh, Y. Venkateswarlu, *Green Chemistry Letters and Reviews*, **2007**, 1, 73-78.
[45] G.J Reddy, K. Pallavi, R.S. Reddy, K.S. Reddy, *Indian Journal of Chemistry*, **2005**, 44B, 812-814.
[46] B. Suresh, G.V.S. Rama Sarma, T. Sosamma Mani, Y.S.R. Reddy, *Indian Journal of Pharmaceutical Sciences*, **1999**, 61, 25-28.
[47] M. Zaki, *Molecules*, **1998**, 3, 71-79.
[48] A. Abdelhamid, H. Zohdi, M. Sallam, N. Ahmed, *Molecules*, **2000,** 5, 967-973.
[49] P. Priyadarsinia, B. Ujwalaa, C. Venkata Raob, V. Madhava Rao, *Der Pharmacia Lettre*, **2012**, 4 (4), 1123-1128.
[50] Visha P. Modi, Paresh N. Patel and Hasmukh S. Patel, *Der Pharmacia Lettre*, **2011**, 3 (4), 120-133.
[51] C. L. Deotalu, P. R. Rajput, *Der Pharma Chemica*, **2011**, 3 (5), 318-32.