Research Journal of Chemical Sciences ISSN 2231-606X
Vol. **4(9),** 16-21, September **(2014)** *Res. J. Chem. Sci.*

Simple Grinding, Catalyst-free, One-Pot, Three-Component Synthesis of Polysubstituted Amino Pyrazole

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Available online at: www.isca.in, www.isca.me
Received 13th August 2014, revised 2nd September 2014, accepted 11th September 2014

Abstract

An efficient, one-pot, three-component catalyst free synthesis of various biologically important heterocyclic compounds is described by simple grinding of aromatic aldehydes, malononitrile, and phenyl hydrazine.

Keywords: Multi-component reactions (MCRs), grinding, catalyst-free, Pyrazole, 5-amino pyrazole, green chemistry.

Introduction

Heterocyclic compounds containing nitrogen linkage have received considerable attention in recent times due to their wide applications. The cyclization reaction of suitable linear compounds is one of the most common and popular methods for preparing these heterocyclic compounds[1,2]. Between these aza containing heterocyclic compounds, pyrazoles have a long history of application in various agrochemical and pharmaceutical industries[3]. These compounds are known to display anti-tumor[4], anti-bacterial[5], anti-microbial[6], anti-fungal[7], anti-inflammatory[8], analgesic[9], anti-depressant[10], antimalarial[11], anti-tumor[12], and anti-viral activities[13]. It is well-known that the study of pyrazole derivatives is significant in pesticide chemistry, because of their herbicidal[14], and insecticidal activities[15]. A previous investigation revealed that 5- amino-4-cyanopyrazole derivatives have anti-bacterial activity[16]. The pyrazole moiety makes the core structure of blockbuster drugs such as Celebrex(R) [17] and Viagra(R)[18] that act as PDE-5 inhibitors (figure-1).

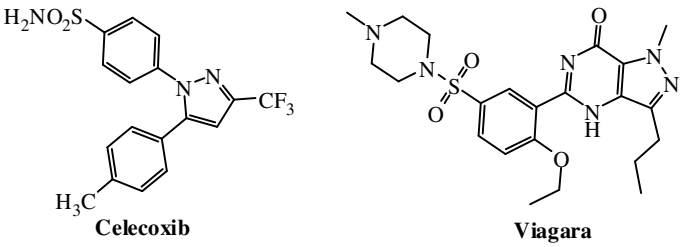
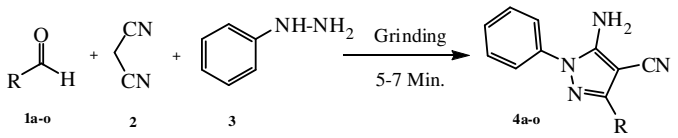


Figure-1
Biological active compounds based on pyrazole derivatives

Many synthetic methods are available for the synthesis of pyrazole derivatives[19-21]. The most popular methods for the preparation of 1,3,4,5-tetrasubstituted pyrazoles are the reactions between 1,3-dipolar cycloadditions of diazo compounds onto triple bonds[22].

A survey of the literature shows that the majority of the strategies involve either multistep sequences or expensive catalysts, inert atmosphere, anhydrous conditions, lengthy reaction times, and laborious workup.

It is well-known that nitriles are widely used as intermediates for a large number of heterocyclic compounds[23]. In continuation of our research interest in the synthesis of biologically important heterocyclic compounds, we have synthesized a series of new pyrazole derivatives by simple grinding of aromatic aldehydes, malanonitrile, and phenyl hydrazine (scheme-1).



Scheme-1
Synthesis of poly-substituted amino pyrazoles by simple grinding

Material and Methods

All chemicals were purchased from Merck or Fluka Chemical Companies and they were used as received. The 1 H NMR (500 MHz, 400 MHz) and 13 C NMR (125 MHz, 100 MHz) spectra were recorded on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Tetramethylsailane (TMS) was used as internal standard. The abbreviations used for NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

General procedure for the preparation of 5-Amino-1, 3-diaryl-1 *H*-pyrazole-4-carbonitriles derivatives: Phenyl hydrazine, (1 mmol) aromatic aldehyde (1 mmol), and malononitrile (1 mmol) were taken in mortar and the resulting mixture was grinded at room temperature for 5-7 min. After

completion of the reaction (as monitored by TLC), the product were isolated by adding ethanol to obtain pure products.

Representative spectral data of the products: 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (table 1, entry 1). White powder (85 %), M.P. = 160 – 161 ◦C, IR (KBr) 3485, 3341, 3083, 2359, 1599, 1412, 1253, 1126, 1100, 1075 cm−1. 1H NMR (CDCl3, 500 MHz): δ (ppm) 6.91 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.29– 7.35 (m, 3H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.64 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.72 (s, 1H). 13 C NMR (CDCl3, 125 MHz): δ (ppm) 112.80, 113.26, 120.58, 126.65, 128.9, 129.05, 129.75, 135.74, 137.81, 145.09, 150.41, 156.50. MS (*m*/*z*): 260 (M+). Anal.Calcd for C16H12N4: C, 73.83; H, 4.65; N, 21.52%. *Found*: C, 73.48; H, 4.86; N, 21.72%.

5-Amino-1-phenyl-3-p-tolyl-1H-pyrazole-4-carbonitrile (table 1, entry 2): Pink powder (76%), M.P. = 117–118 ◦C, IR (KBr) 3482, 3319, 3095, 2925, 2359, 1598, 1415, 1257, 1127, 1113, 1096 cm−1. 1H NMR (CDCl3, 500 MHz): δ (ppm) 2.41 (s, 3H), 6.91 (dd, *J* = 3.5 Hz and *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.76 Hz, 2H), 7.22 (d, *J*= 7.9 Hz, 2H), 7.29–7.33 (m, 2H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.70 (s, 2H). 13 C NMR (CDCl3, 125 MHz): δ (ppm) 21.90, 104.65, 113.22, 120.44, 126.62, 129.71, 129.77, 132.95, 138.14, 138.97, 145.20, 148.82, 153.20. Anal.Calcd for C17H14N4: C, 74.43; H, 5.14; N, 20.42%. *Found*: C, 74.88; H, 5.18; N, 20.12%.

5-Amino-3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4- carbonitrile (table 1, entry 3): Yellow powder (85 %), M.P. = 161–162 ◦C, IR (KBr) 3583, 3487, 3341, 3102, 2358, 2197, 1602, 1413, 1222, 1192, 1108, 1050 cm−1 .1H NMR (DMSO–d6, 500 MHz): δ (ppm) 6.76 (t, J = 7.3 Hz, 1H), 6.85–6.90 (m, 2H), 6.96 (d, J = 7.6 Hz, 2H), 7.14–7.18 (m, 1H), 7.24 (dd, J = 7.5 Hz and J = 8.3 Hz, 2H), 7.53 (dd, J = 1.5 Hz and J = 7.7 Hz, 1H), 8.14 (s, 1H), 10.38 (s, 1H), 10.52 (s, 1H).13 C NMR (DMSO–d6, 125 MHz): δ (ppm) 112.60, 116.80, 119.83, 120.25, 121.35, 125.45, 128.17, 130.05, 130.15, 138.13, 145.62, 150.55, 152.30, 156.51. Anal.Calcd for C16H12N4 O: C, 69.55; H, 4.38; N, 20.28%. Found: C, 69.48; H, 4.46; N, 20.35%.

5-Amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (table 1, entry 4): White powder (83 %), M.P. = 129–130 ◦C, IR (KBr) 3448, 3315, 3074, 2358, 1595, 1414, 1293, 1254, 1133, 1083cm−1. 1HNMR(CDCl3, 500 MHz): δ (ppm) 6.93 (t, J = 7.3Hz, 1H), 7.15 (d, J = 7.7 Hz, 2H), 7.29–7.34 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.67 (s, 2H).13 CNMR(CDCl3, 125 MHz): δ (ppm) 110.24, 113.29, 120.85, 127.71, 129.26, 129.77, 134.26, 134.44, 136.35, 144.78, 150.21, 155.45. Anal.Calcd for C16H11ClN4: C, 65.20; H, 3.76; N, 19.01%. Found: C, 65.37; H, 3.81; N, 18.95%.

5-Amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4- carbonitrile (table 1, entry 5): Red powder (86 %),M.P. = 164–165 ◦C, IR (KBr) 3467, 3350, 3102, 2359, 1600, 1415, 1457, 1344, 1256, 1123, 1107, 1095 cm−1. 1HNMR(CDCl3, 500 MHz): δ (ppm) 6.98 (s, 1H) 7.18 (d, J = 7.5 Hz, 2H), 7.29–7.34 (m, 2H), 7.73–7.79 (m, 3H), 8.05 (s, 1H), 8.24 (d, J = 7.6 Hz, 2H). MS (m/z): 305 (M+). Anal.Calcd for C16H11N5O2: C, 62.95; H, 3.63; N, 22.94%. Found: C, 63.05; H, 3.58; N, 23.03%.

5-Amino-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole-4- carbonitrile (table 1, entry 6): Orange powder (84 %), M.P. = 129–130 ◦C, IR (KBr) 3452, 3324, 3103, 2357, 1594, 1478, 1447, 1344, 1338, 1263, 1147, 1100, 1096 cm−1. 1HNMR(CDCl3, 500 MHz): δ (ppm) 6.97 (t, J =7.2 Hz, 1H), 7.18 (d, J =8.4 Hz, 2H), 7.35 (t, J =7.5 Hz, 2H), 7.56 (t, J =7.9 Hz, 1H), 7.74 (s, 1H), 7.89 (s, 1H), 8.01 (d, J =7.5 Hz, 1H), 8.14 (d, J =8.0 Hz, 1H), 8.48 (s, 1H). 13C NMR (CDCl3, 125 MHz): δ (ppm) 112.44, 113.42, 121.10, 121.38, 122.98, 129.85, 129.94, 131.80, 134.30, 137.72, 144.27,149.16, 156.41. Anal.Calcd for C16H11N5O2: C, 62.95; H, 3.63; N, 22.94%. Found: C, 62.78; H, 3.77; N, 22.90%.

5-Amino-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole-4- carbonitrile (table 1, entry 10): Yellow powder (75 %), M.P. = 140–141 ◦C, IR (KBr) 3412, 3325, 3092, 2357, 1600, 1478, 1298, 1264, 1138, 1069 cm−1. 1H NMR (CDCl3, 500 MHz): δ (ppm) 6.92 (t, J = 7.3 Hz, 1H), 7.05 (dd, J = 3.6 Hz and J = 4.9 Hz, 1H), 7.12 (d, J = 7.4 Hz, 3H), 7.31 (dd, J = 5.0 Hz and J = 14.1Hz, 3H), 7.56 (s, 1H), 7.84 (s, 1H). 13CNMR(CDCl3, 125 MHz): δ (ppm) 113.24, 114.21, 120.64, 122.44, 126.33, 126.89, 127.66, 129.76, 132.70, 140.91, 144.86, 155.22. Anal.Calcd for C14H10N4S: C, 63.14; H, 3.78; N, 21.04%. Found: C, 63.33; H, 3.82; N, 20.88%.

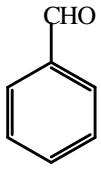
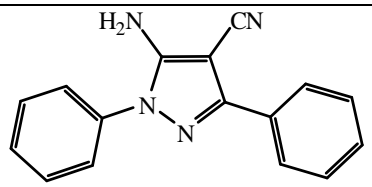
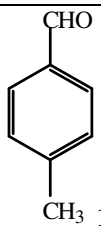
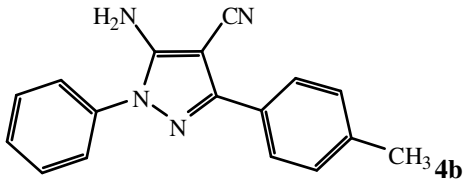
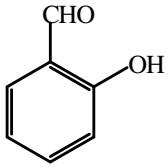
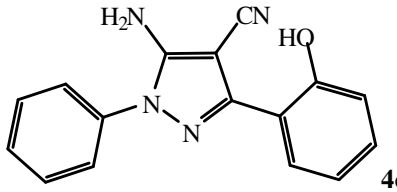
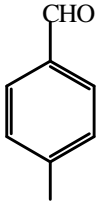
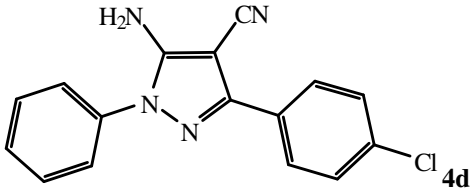
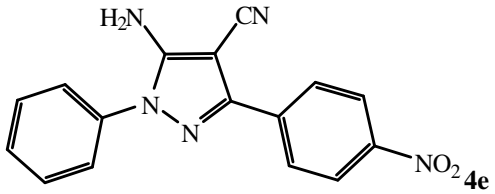
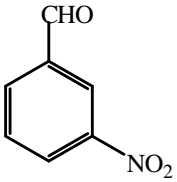
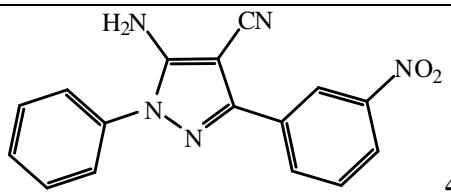
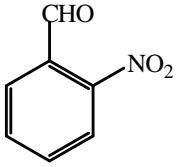
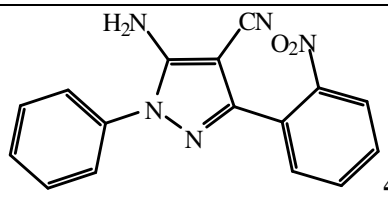
5-Amino-3-(5-methylthiophen-2-yl)-1-phenyl-1H-pyrazole- 4-carbonitrile (table 1, entry 11): Yellow powder (76 %), M.P. = 131–132 ◦C, IR (KBr) 3427, 3303, 3102, 2919, 2357, 1600, 1469, 1257, 1230, 1126, 1100, 1070 cm−1. 1H NMR (CDCl3 , 500 MHz): δ (ppm) 2.53 (s, 3H), 6.68–6.71 (m, 1H), 6.88–6.92 (m, 2H), 7.10 (d, J = 7.7 Hz, 2H), 7.28–7.32 (m, 2H), 7.46 (s, 1H), 7.76 (s, 1H). 13 C NMR (CDCl3, 125 MHz): δ (ppm) 16.08, 113.15, 114.13, 120.42, 125.86, 126.10, 127.16, 129.71, 133.18, 138.66, 141.38, 145.05, 156.73. Anal.Calcd for C15H12N4 S: C, 64.26; H, 4.31; N, 19.98%. Found: C, 64.37; H, 4.25; N, 20.05%.

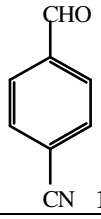
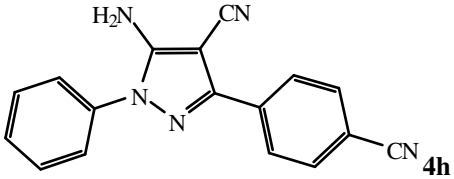
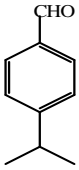
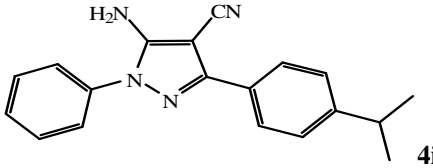
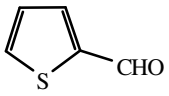
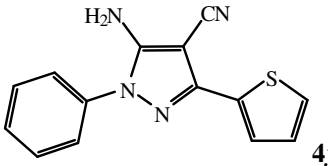
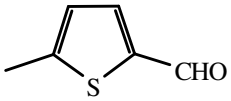
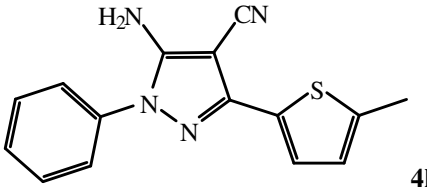
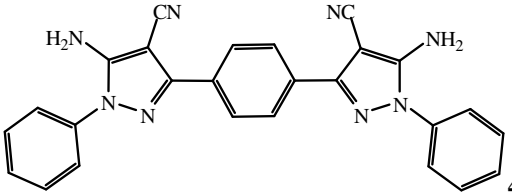
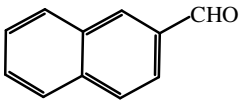
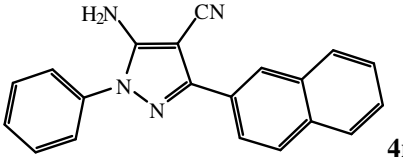
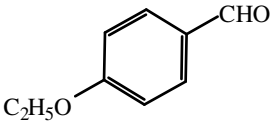
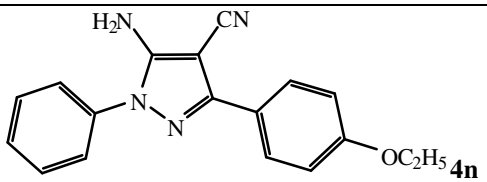
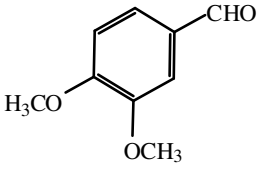
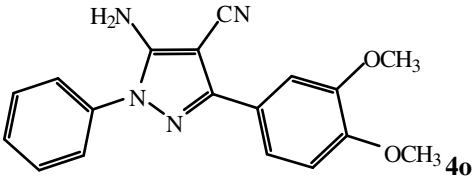
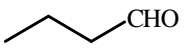
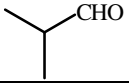
Results and Discussion

To find the optimized reaction conditions, we initiated a catalyst screening exercise employing benzaldehyde (1 mmol), malononitrile (1 mmol), and phenyl hydrazine (1 mmol) in the presence of various base catalysts such as Et_3N, DABCO, DBU, NaOH, and K_2CO_3 at room temperature. Screening of the reaction conditions established that the nature of the catalyst had no significant effect on the yield of pyrazole. Interestingly, in the absence of any base catalyst, this three-component coupling cyclization reaction proceeded smoothly to afford the desired 5-amino-4-cyano 1, 3 diphenyl pyrazole in excellent yield after 5-7 min by simple grinding method. Therefore, the phenyl hydrazine itself is acting as both a Brønsted base catalyst in this reaction and as a nucleophile. This is why the bases had no effect on the reaction yield. Hence, we monitored the effect of the amount of phenyl hydrazine on the yield of reaction. With a higher amount of phenyl hydrazine no increase in the yield of 5-

amino-4-cyano 1, 3 diphenyl pyrazole is observed. However, diminishing the amount of phenyl hydrazine resulted in incomplete conversion. With these optimized conditions in hand, this three component reaction can be readily diversified through a combination of a range of aryl aldehydes, malononitrile, and phenyl hydrazine.

Table-1
Substituted Synthesis Product with Yield

Entry	Aldehyde	Product	Yield[a] (%)
1	 **1a**	 **4a**	85
2	 **1b**	 **4b**	76
3	 **1c**	 **4c**	85
4	 **1d**	 **4d**	83
5	 **1e**	 **4e**	86
6	 **1f**	 **4f**	84
7	 **1g**	 **4g**	82
Entry	**Aldehyde**	**Product**	**Yield[a] (%)**

8	 **1h**	 **4h**	79
9	 **1i**	 **4i**	77
10	 **1j**	 **4j**	75
11	 **1k**	 **4k**	76
12	 **1l**	 **4l**	80
13	 **1m**	 **4m**	78
14	 **1n**	 **4n**	75
15	 **1o**	 **4o**	68
16		--	--
17		--	--

[a]Isolated yields

Similarly, dialdehydes were also successfully employed to give bis poly-substituted pyrazoles in excellent yields (table-1, entries 12).

To explore the generality of the reaction, aldehydes with electron-withdrawing substituents on aromatic ring were also employed (table 1, entries 5, 6, 7, 8). It is worth mentioning that sterically bulky aldehydes were readily converted into the desired products (table 1, entries 3, 7). To further expand the scope of the reaction, the use of heteroaryl aldehydes was investigated (table 1, entries 10, 11).

Some aliphatic aldehydes were also screened to carry out the three-component coupling by this method and the results are listed in table 1. However, no products were obtained when aliphatic aldehydes were involved in this one-pot catalyst-free reaction (table 1, entries 16, 17). The trend observed due chiefly to the lower reactivity of alyphatic aldehydes toward nucleophilic addition in comparison with aromatic aldehydes.

Thus, from a practical point of view, the newly developed protocol is a significant proof of the fact that nitrile is one of the most versatile functional groups as it can be readily transformed into various other functional groups. Significantly, the reaction occurred in a catalyst-free fashion with high selectivity and atom economy. To our knowledge, the use of catalyst-free reactions, namely Knoevenagel reaction, Michael-type reaction, ring closure, and subsequent aromatization, in one pot has not been previously reported.

Conclusion

In conclusion, we have disclosed a novel and convenient one-pot synthesis of polysubstituted amino pyrazole analogues *via* multi-component reactions. This catalyst-free reaction proceeded smoothly in good to excellent yields and offered several other advantages including short reaction time, simple experimental workup procedures, and no toxic by-products. The approach to pyrazole systems presented herein avoids the use of catalyst, toxic organic solvent. This protocol represents a promising green route for the synthesis of this class of compounds.

Acknowledgment

The authors are thankful to Principal, ASC College, Naldurg, Dist- Osmanabad, Maharashtra, India for providing laboratory facilities.

References

1. Hasaninejad A., Zare A. and Shekouhy M., Sulfuric acid modified PEG-6000 (PEG-OSO3H): an efficient, bio-degradable and reusable polymeric catalyst for the solvent-free synthesis of poly-substituted quinolines under microwave irradiation, *Green Chem*, **13,** 958–964 **(2011)**

2. Hasaninejad A., Zare A. and Shekouhy M., Catalyst-free one-pot four component synthesis of polysubstituted imidazoles in neutral. Ionic liquid 1-butyl-3-methylimidazolium bromide, *J Comb Chem,* **12,** 844–849 **(2010)**

3. Anzai K., Furuse M., Yoshida A., Matsuyama A., Moritake T., Tsuboi K. and Ikota N., In vivo radioprotection of mice by 3-methyl-1- phenyl-2-pyrazolin-5-one (Edaravone; Radicut), a clinical drug, *J Radiat Res.,* **45,** 319–323 **(2004)**

4. Daidone G., Maggio B., Plescia S., Raffa D., Musiu C., Milia C., Perra G. and Marongiu M.E., Antimicrobial and antineoplastic activities of new 4-diazopyrazole derivatives, *Eur J Med Chem.,* **33,** 375–382 **(1998)**

5. Tanitame A., Oyamada Y. and Ofuji K. Design, synthesis and structure-activity relationship studies of novel indazole analogues as DNA gyrase inhibitors with Gram-positive antibacterial activity, *Bioorg Med Chem Lett* **14,** 2857–2862 **(2004)**

6. Nauduri D. and Reddy G.B. Antibacterials and antimycotics: part 1: synthesis and activity of 2-pyrazoline derivatives, *Chem Pharm Bull.,* **46,** 1254–1260 **(1998)**

7. Hiyama Y., Suzuki K.M. and Yamagishi J., Synthesis and antibacterial activity of a novel series of potent DNA gyrase inhibitors, Pyrazole derivatives, *J Med Chem.,* **47,** 3693–3696 **(2004)**

8. Tewari A.K. and Mishra A., Synthesis and anti-inflammatory activities of N4,N5-disubstituted-3-methyl-1H-pyrazolo[3,4- c]pyridazines, *Bioorg Med Chem*, **9,** 715–718 **(2001)**

9. Gursoy S.A., Demirayak G. and Capan K., Synthesis and preliminary evaluation of new 5-pyrazolinone derivatives as analgesic agents, *Eur J Med Chem.,* **35,** 359–364 **(2000)**

10. Bailey D.M., Hansen P.E., Hlavac A.G., Baizman E.R., Pearl J., Defelice A.F., Feigenson M.E., 3,4-Diphenyl-1H-pyrazole-1- propanamine antidepressants, *J Med Chem,* **28,** 256–260 **(1985)**

11. Katiyar S.B., Srivastava K., Purib S.K. and Chauhana PMS, Synthesis of 2-[3,5-substituted pyrazol-1-yl]-4,6-trisubstituted triazine derivatives as antimalarial agents, *Bioorg Med Chem Lett.,* **15,** 4957–4960 **(2005)**

12. Farag A.M., Ali K.A., Mayhoub A.S., Abdalla T.M., Amr A.E., Abdel- Hafez N. and Abdalla M.M., Design, synthesis and structureactivity relationship study of novel pyrazole-based heterocycles as potential antitumor agents, *Eur J Med Chem,* **45,** 5887–5898 **(2010)**

13. Allen S.H., Johns B.A., Gudmundsson K.S. and Freeman G.A., Synthesis of C-6 substituted pyrazolo[1,5-*a*]pyridines with potent activity against herpesviruses, *Bioorg Med Chem.,* **14,** 944–954 **(2006)**

14. He F.Q., Liu X.H., Wang B.L. and Li Z.M., Synthesis and biological activities of novel bis-heterocyclic pyrrodiazole derivatives, *Heteroatom Chemistry,* **19,** 21–27 **(2008)**

15. Parlow J.J., Synthesis of pyrazolecarbonylaminopyridine carboxamides as herbicides, *J. Heterocycl Chem* **35,** 1493–1499 **(1998)**

16. Kumar V., Aggarwal R., Tyagi P. and Singh S.P., Synthesis and antibacterial activity of some new 1-heteroaryl-5-amino-4-phenyl- 3-trifluoromethylpyrazoles, *Eur J Med Chem.,* **40,** 922–927 **(2005)**

17. Penning T.D., Talley J.J., Bertenshaw S.R., Carter J.S., Collins P.W., Doctor S., Graneto M.J., Lee L.F., Malecha J.W., Miyashiro J.M., Rogers R.S., Rogier D.J., Yu S.S., Anderson G.D., Burton E.G., Cogburn J.N., Gregory S.A., Koboldt C.M., Perkins W.E., Seibert K., Veenhuizen A.W., Zhang Y.Y., Isakson P.C., Synthesis and biological evaluation of the 1, 5-diarylpyrazole class of cyclooxygenase-2 inhibitors:? identification of 4-[5-(4-methylphenyl)-3- (trifluoromethyl)-1*H*pyrazol- 1-yl]benzenesulfonamide (SC-58635, celecoxib), *J Med Chem,* **40,** 1347–1365 **(1997)**

18. Terrett NK, Bell AS, Brown D, Ellis P Sildenafil (VIAGRA*TM)*, a potent and selective inhibitor of type 5 cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction, *Bioorg Med Chem Lett***., 6**, 1819–1824 **(1996)**

19. Varvounis G, Fiamegos Y, Pilidis G Pyrazol-3-ones. Part II: reactions of the ring atoms, *Adv Heterocycl Chem.,* **87,** 141–272**(2004)**

20. Salaheldin A.M., Oliveira-Campos A.M.F., Rodrigues L.M., N-Bromosuccinimide assisted oxidation of 5-aminopyrazoles: formation of bis diazenylderivatives, *Tetrahedron Lett* **48,** 8819–8822 **(2007)**

21. Varvounis G., Fiamegos Y., PilidisGPyrazol-3-ones, Part III: reactivity of the ring substituents, Adv *Heterocycl, Chem.,* **95,** 27–141**(2007)**

22. Martin R., Rivero M.R., Buchwald S.L., Domino Cu-catalyzed C–Ncoupling/hydroamidation: a highly efficient synthesis of nitrogen heterocycles, *AngewChem Int Ed Engl,* **45,** 7079–7082 **(2006)**

23. Hasaninejad A., Shekouhy M., Golzar N., Zare A. and Doroodmand M.M., Silica bonded n -propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (SB-DABCO): a highly efficient, reusable and new heterogeneous catalyst for the synthesis of 4 H -benzo[b] pyran derivatives, *Appl Catal A: General,* **402,** 11–22 **(2011)**