Amino acid Catalysed Reactions. A facile route to some heteroarylbispyrazoles

Faryal Chaudhry[1,2], Sadia Naureen[1], Fatima Ijaz[1], Munawar Ali Munawar[1], Misbahul Ain Khan[1,3]

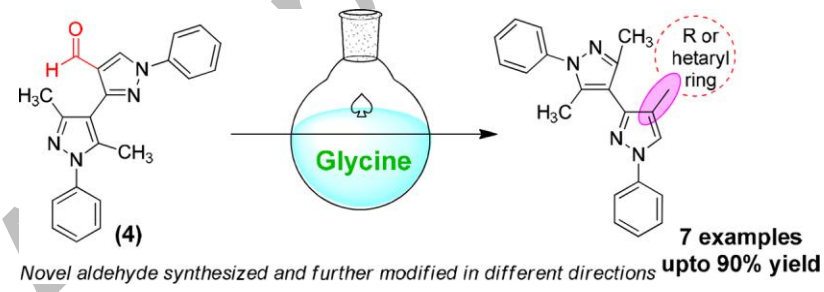
[1]Institute of Chemistry, University of the Punjab, Lahore, Pakistan,[2]Department of Chemistry, Kinnaird College for Women, Lahore, Pakistan,[3]Department of Chemistry, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

Faryal Chaudhry, Institute of Chemistry, University of the Punjab, Lahore 54590, Pakistan.E-mail: frylchaudhry@yahoo.com

Abstract

This newly designed route assembled a pyrazole ring with an aldehydic functionality over another pyrazole moiety. Further, formyl group was exploited in different routes such as condensation reactions, imidazole and pyrimidone/thione synthesis. The present reactions were carried out with glycine, a facile catalyst, and the results compared well with those of conventional methods.

GRAPHICAL ABSTRACT



KEYWORDS: Bispyrazoles; Knoevenagel condensation; Arylidenes; Imidazoles; Biginelli reaction

INTRODUCTION

Syntheses of pyrazoles have grabbed substantial attention of researchers on account of their comprehensive pharmacological and industrial properties.[1,2] Besides some clinical candidates: Crizotinib[3] and Mepirizole[4] which have been introduced as anti-cancer and NSAID drugs, other pyrazole moiety containing anti-inflammatory,[5] COX-1 inhibitor,[6] anti-leishmanial,[7] anti-hypertensive,[8] anti-malarial,[9] anti-parkinsonian,[10] anti-Alzheimer,[11] anti-microbial,[12] anti-hyperglycemic[13] and anti-tubercular[14] agents have also been exhibited promising results. Among these, diverse C-C linked hetarylpyrazoles are presented as potentially active pharmacophores (**Fig. 1**).

Pyrazole being a valuable scaffold, different synthetic methods have been employed to build this nucleus and these have their own pros and cons. Mostly, these are documented with conventional β-diketones and hydrazines. This methodology resulted in regioisomers which is a major disadvantage indeed.[15] Other methods like ring opening, arylation or cycloaddition reactions are found much expensive or sometimes tedious ones to deal with.[16,17] However, Vilsmeier-Haack formylation is generally an open ended practice where not only cyclisation takes place while a new formyl group could be used for building yet another pyrazole or providing an opportunity to use this functionality in several directions.[18]

In search of enhanced, multi-functional and more effective scaffolds, the exploitation of core structure meets the demand of building targeted molecules. Therefore, clean, facile and expeditious access to such type of derivatives is always a matter of concern. The

significant nature of pyrazoles was the basis of current study. Therefore, in the present preliminary communication we would like to report the synthesis of novel pyrazolylpyrazole aldehyde by exploring this route and its utilization, with the help of amino acid catalysis, in some pioneering reactions for preparing hetarylbipyazoles containing additional pyrazoles, imidazoles and pyrimidine rings to demonstrate the versatility of this aldehydic intermediate.

RESULTS AND DISCUSSION

The **Scheme 1** was adopted to synthesize a novel bispyrazolic derivative which was further manipulated in different dimensions. At first, the Grandberg's acylation[19] approach was somewhat modified and solid supported acid SSA (SiO_2-*conc.* H_2SO_4) was introduced as an active catalyst. The acidic silica helped in the completion of acylation reaction in short time and produced desired product in good yield. Afterwards, this acetylpyrazole was transformed into its phenylhydrazone. The IR spectrum possessed two new N-H bands (stretching and bending) around 3320 cm^{-1} and 1551 cm^{-1} whereas C=O absorption band had disappeared. Unfortunately, this product was not very stable therefore was immediately used for the formylation step to build up a new ring with an aldehydic group.

The most significant ^{1}H NMR signals included the two singlets: one was of H-5 of new pyrazole ring (9.32 ppm) while other was of O=C-H (9.86 ppm). Similarly ^{13}C NMR has two important signals appearing at 111.10 ppm and 184.79 ppm for C'-4 of new pyrazole ring and O=C-H respectively. The mass peaks of this newly formed molecule were

observed at m/z 342.1 (M^+), m/z 341.0 (oxonium ion, M^+-H), m/z 325.1 (M^+-H_2O) and m/z 313.0 (M^+-CHO). The IR spectrum and elemental analysis also supported the expected structure. To explore the feasibility of aldehydic functionality and to construct five or six member heterocyclic rings; these reactions were carried out with conventional method **(Method A**) and also with the aid of easily accessible glycine (**Method B**). As in previous experiments, glycine was screened out as a best choice of a catalyst thus invariably **Method B** resulted in better yields **Table 1**. The role of the catalyst as well as the suggested mechanism has previously been discussed.[20]

A white solid was obtained by the reaction of new aldehyde with malonic acid. The IR spectrum of compound **5a** (two C=O bands: 1699 cm^{-1} and 1643 cm^{-1}; broad O-H band: 3368-3168 cm^{-1}) has indicated the presence of two carboxyl groups. The ^{1}H NMR has a prominent singlet of olefinic proton (=C-H) at 7.23 ppm which confirmed the condensation process. However, due to the intramolecular hydrogen bonding the acidic protons were highly deshielded and not observable in typical span of NMR.

Two significant ^{13}C NMR signals (165.67 ppm and 167.80 ppm for two C=O), mass spectrum and elemental compositions supported the retention of two carboxylic groups in a molecule. Another condensation reaction was carried out with ethyl cyanoacetate. The IR absorption band of nitrile found at 2216 cm^{-1} and that of C=O appeared at 1717 cm^{-1}. In ^{1}H NMR, an olefinic proton (=C-H) emerged at 8.03 ppm while the corresponding carbon recorded at 149.34 ppm. Similarly, ^{1}H NMR has a pronounced triplet at 1.37 ppm and a quartet at 4.34 ppm (with J = 7.1 Hz) which specified the presence of an ester

group. An orange solid arylidene was also obtained by the reaction of aldehyde with a pyrazolone with glycine as catalyst. Besides other spectroscopic data, the most promising ^{1}H NMR signal was of olefinic proton which appeared as a singlet at 7.31 ppm. Here, H-5 of pyrazole has shifted downfield and was spotted at 10.21 ppm. The pyrazolone C=O was detected at 162.50 ppm.

The tri/tetrasubstituted imidazole rings are also successfully constructed with an aldehyde, benzil, ammonium acetate and aniline. This Debus-Radiszewski imidazole synthesis was carried out conventionally in acetic acid and also with glycine as catalyst in ethanol. The IR spectrum of compound **6a** has N-H stretching band at 3220 cm^{-1}. In ^{1}H NMR, aromatic protons appeared as multiplets in the aromatic region. A singlet of H-5 of pyrazole was found at 8.91 ppm. Perhaps, the extensive hydrogen bonding prevented the detection of the N-H proton. The prominent carbon signal at 148.70 ppm was of C-2 of imidazole ring. The HRMS results and CHN data also confirmed the $C_{35}H_{28}N_6$ as the molecular formula. The imidazole formation with N-substitution in confirmed through IR spectrum, mass and elemental analysis.

Biginelli reaction is another way to exploit the aldehydic group. A pyrimidone/thione ring was created with the help of aldehyde, ethyl acetoacetate and urea/thiourea. The IR spectra of both derivatives possessed N-H band around 3250 cm^{-1} whereas C=O of ester appeared around 1700 cm^{-1} and that of pyrimidone at 1645 cm^{-1}. The compound **7a** has most promising ^{1}H NMR signals of ester group and of NH-CH which actually splitted into a doublet at 5.32 ppm (J = 2.5 Hz) due to the coupling with vicinal NH proton. A

carbon signal recorded at 46.33 ppm was assigned to CH-4 of pyrimidone confirmed the cyclisation with partial aromatization. Similar spectral data of compound **7b** also helped in establishing the structure successfully.

CONCLUSION

Starting with 4-acetyl-3,5-dimethyl-1-phenylpyrazole, a phenylhydrazone was prepared which by Vilsimeier-Haack formylation provided the useful intermediate **4** which was shown to provide diverse hetaryl(3,4´)bipyrazoles **5-7** by appropriate reactions. An alternate method using glycine as a catalyst gave better yields in an eco-friendly medium. Thus compound **4** opens up possibilities for the synthesis of other hetaryl(3,4´)bipyrazoles.

EXPERIMENTAL

The chemicals were purchased from the Sigma-Aldrich and Merck in pure form. The melting points of new compounds were uncorrected. FTIR spectra were carried out in Agilent Technologies Cary 630 FTIR. The ^{1}H NMR spectra were obtained on Bruker DPX-400 or 500 MHz Spectrometer in $CDCl_3$. The MAT312 or JEOL MS Route was used for MS spectra. The Perkin-Elmer 2400 Series II CHN/S Analyzer was used for elemental analyses. The compounds **1-4** were prepared by the slight alteration of literature protocols.[18-20]

General Procedures For The Synthesis Of Compounds 5(A-C)

Method A.

To the ethanolic solution of compound **4** (1.46 mmol, 1.0 equiv) and active methylene (1.46 mmol, 1.0 equiv), pyridine (5 drops) and piperidine (3 drops) were added and refluxed till reaction completion. The reaction flask was cooled and poured over crushed ice to obtain the product (**5a-5c**).[21]

Method B:

In 5 mL of DMSO, a mixture of 1.46 mmol of compound **4**, active methylene (1.46 mmol, 1.0 equiv) and glycine (0.02 g, 20 mol%, 0.29 mmol, 0.2 equiv) were stirred at room temperature for specified time (**Table-1**) and quenched with crushed ice. The crude product (**5a-5c**) was recrystallized with ethanol.[20]

(*E*)-Ethyl 2-Cyano-3-(3',5'-Dimethyl-1,1'-Diphenyl-1*H*,1'*H*-[3,4'-Bipyrazol]-4-Yl)Acrylate (5b)

White solid; m.p. 115 ºC; Yield: **Method A**: 0.46 g; 72%; **Method B**: 0.56 g; 88%; IR (ν_{max}-cm^{-1}; neat): 3055-2911 (C-H), 2216 (C≡N), 1717 (C=O), 1590 (C=N), 1225 & 1096 (C-O-C); ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.37 (t, 3H, *J* = 7.1 Hz; CH_2-CH_3), 2.29 (s, 3H; CH_3-3' Py'), 2.33 (s, 3H; CH_3-5' Py'), 4.34 (q, 2H, *J* = 7.1 Hz; CH_2-CH_3), 7.39-7.41 (m, 2H; Ar-1H & Ar'-1H), 7.49-7.53 (m, 7H; Ar-3H & Ar'-4H), 7.81 (d, 2H, *J* = 8.0 Hz; Ar-2H), 8.03 (s, 1H; =C-H), 9.14 (s, 1H; H-5 Py); ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 11.50 (CH_3-5' Py'), 12.34 (CH_3-3' Py'), 13.96 (CH_2-CH_3), 62.15 (CH_2-CH_3), 99.17 (C'-4 Py'), 109.87 (-C-C≡N), 115.51 (C-4 Py), 115.91, 119.65 (2C), 124.63 (2C), 127.79, 128.12, 129.23 (2C & C-4 Py), 129.87 (2C), 138.51, 138.87, 139.11, 145.52, 147.22, 149.34 (=C-

H), 161.99 (C=O); MS (EI+): m/z (%) 437.2 (M^+, 16.9); Anal. Calcd. For $C_{26}H_{23}N_5O_2$: C, 71.38; H, 5.30; N, 16.01%. Found: C, 71.25; H, 5.22; N, 16.12%.

General Procedures For The Synthesis Of Compounds 6(A,B)

Method A.

In 10 mL of AcOH, a mixture of **4** (1.46 mmol, 1.0 equiv), benzil (1.46 mmol, 1.0 equiv) and ammonium acetate (2.92 mmol, 2.0 equiv) or ammonium acetate : *p*-chloroaniline (1.46 mmol, 1 equiv : 1.46 mmol, 1.0 equiv) was refluxed to get crude product **6(a,b)** which was further purified with EtOH.

Method B:

By the replacement of acetic acid in **Method A** with glycine (0.02 g, 20 mol%, 0.29 mmol, 0.20 equiv) and EtOH (10 mL), reaction was completed in half an hour.

4-(4,5-Diphenyl-1*H*-Imidazol-2-Yl)-3',5'-Dimethyl-1,1'-Diphenyl-1*H*,1'*H*-3,4'-Bipyrazole (6a)

White solid; m.p. 155 ºC; Yield: **Method A**: 0.60 g; 78%; **Method B**: 0.70 g; 90%; IR (ν_{max}-cm^{-1}; neat): 3220-2927 (-NH & C-H), 1598 (C=N), 1565 (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 2.30 (s, 3H; CH_3-3' Py'), 2.32 (s, 3H; CH_3-5' Py'), 7.27-7.29 (m, 1H; Ar^1-1H), 7.30-7.32 (m, 1H; Ar^2-1H), 7.33-7.36 (m, 5H; $Ar^{'}$-1H, Ar^1-2H & Ar^2-2H), 7.40-7.46 (m, 5H; Ar-H, Ar^1-2H & Ar^2-2H), 7.48-7.52 (m, 6H; Ar-2H & $Ar^{'}$-4H), 7.83 (d, 2H, *J* = 7.9 Hz; Ar-2H), 8.91 (s, 1H; H-5 Py); ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 11.78 (CH_3-5' Py'), 12.60 (CH_3-3' Py'), 111.94 (C-4 Py), 113.81 (C'-4 Py'), 119.15, 125.07, 127.17, 127.27,

127.67, 127.84, 128.15, 128.89, 129.15, 129.38, 129.71, 130.03, 132.09, 139.56, 139.64, 140.20, 142.93, 148.70 (C-2 Im); MS (ESI): m/z (%) 533.2 ($[M+H]^+$, 100), 555.2 ($[M+Na]^+$, 25.4); HRMS (ESI) Calcd. For $C_{35}H_{29}N_6$ $[M+H]^+$: 533.2454 Found: 533.2446; Anal. Calcd. For $C_{35}H_{28}N_6$: C, 78.92; H, 5.30; N, 15.78%. Found: C, 78.81; H, 5.33; N, 15.65%.

General Procedures For The Synthesis Of Compounds 7(A,B)

Method A.

A mixture of of reactant **4** (1.46 mmol; 1.0 equiv), ethyl acetoacetate (1.46 mmol, 1.0 equiv), urea (2.04 mmol, 1.4 equiv) or thiourea (2.04 mmol, 1.4 equiv) and *conc.* HCl (two drops) in 10 mL of ethanol was refluxed for 6-8 hrs. After treating with ice water, the crude product **7(a,b)** was precipitated out.

Method B:

Here the glycine (0.02 g, 20 mol%, 0.29 mmol, 0.20 equiv) was added in place of *conc.* HCl to obtain product in short time **7(a,b)**.

Ethyl 4-(3',5'-Dimethyl-1,1'-Diphenyl-1*H*,1'*H*-[3,4'-Bipyrazol]-4-Yl)-6-Methyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5-Carboxylate (7a)

From urea (0.12 g), compound **4** (0.5 g) and ethyl acetoacetate (0.19 g/0.19 mL), **7a** was obtained as white solid; m.p. 190 ºC; Yield: Method A: 0.48 g; 66%; Method B: 0.60 g; 83%; IR (ν_{max}-cm^{-1}; neat): 3235-2927 (-NH & C-H), 1697 (C=O), 1645 (C=O), 1596 (C=N), 1228 & 1088 (C-O-C); ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.07 (t, 3H, J = 7.0

Hz; CH_2-CH_3), 1.99 (s, 3H; CH_3-3' Py'), 2.04 (s, 3H; CH_3 Pyrimidine), 2.07 (s, 3H; CH_3-5' Py'), 3.97 (q, 2H, *J* = 7.0 Hz; CH_2-CH_3), 5.32 (d, 1H, *J* = 2.5 Hz; NH-CH Pyrimidine), 7.29 (t, 1H, *J* = 7.3 Hz; Ar'-1H'), 7.41 (t, 1H, *J* = 8.0 Hz; Ar-1H), 7.47-7.50 (m, 3H; Ar'-2H' & NH-3 Pyrimidine), 7.52-7.55 (m, 2H; Ar-2H), 7.58-7.59 (m, 2H; Ar'-2H'), 7.85 (d, 2H, *J* = 8.0 Hz; Ar-2H), 8.40 (s, 1H; H-5 Py), 8.77 (s, 1H; NH-1 Pyrimidine); ^{13}C NMR (DMSO-d_6, 125 MHz), δ: 11.25 (CH_3-5' Py'), 11.94 (CH_3-3' Py'), 14.15 (CH_2-CH_3), 17.58 (CH_3 Pyrimidine), 46.33 (CH-4 Pyrimidine), 58.92 (CH_2-CH_3), 97.05 (C-5 Pyrimidine), 112.34 (C'-4 Py'), 117.74 (C-4 Py), 124.66, 125.99, 126.61, 127.14, 127.23, 128.96, 129.57, 138.21, 139.45, 139.79, 144.19, 147.49, 148.04 (C-6 Pyrimidine), 151.26 (O=C-2 Pyrimidine), 165.28 (O=C-O-CH_2-CH_3); MS (ESI): m/z (%) 497.2 ($[M+H]^+$, 100), 519.2 ($[M+Na]^+$, 15.2); HRMS (ESI) Calcd. For $C_{28}H_{29}N_6O_3$ $[M+H]^+$: 497.2301 Found: 497.2293; Anal. Calcd. For $C_{28}H_{28}N_6O_3$: C, 67.73; H, 5.68; N, 16.92%. Found: C, 67.54; H, 5.59; N, 16.81%.

FUNDING

We thank Higher Education Commission (HEC), Pakistan, for the award of Indigenous and IRSIP fellowships (to F.C., S.N. and F.I.).

SUPPLEMENTAL MATERIAL

The experimental details, characterization data and spectral data for this article can be accessed on the publisher's website.

REFERENCES

[1] Khan, M. F.; Alam, M. M.; Verma, G.; Akhtar, W.; Akhtar, M.; Shaquiquzzaman, M. *Eur. J. Med. Chem.* **2016**, *120*, 701-201.

[2] Kucukguzel, S. G.; Senkardes, S. *Eur. J. Med. Chem.* **2015**, *97*, 786-815.

[3] Sun, H. Y.; Ji, F. Q. *Res. Comm.* **2012**, *423*, 319-324.

[4] Garcia-Lozano, J.; Server-Carrioa, J.; Escrivaa, E.; Folgadoa, J-V.; Mollaa, C.; Lezamab, L. *Polyhedron.* **1997**, *16*, 939-944.

[5] Bekhit, A. A.; Abdel-Aziem, T. *Bioorg. Med. Chem*. **2004**, *12*, 1935-1945.

[6] Calvello, R.; Panaro, M. A.; Carbone, M. L.; Cianciulli, A.; Perrone, M. G.; Vitale, P.; Malerba, P.; Scilimati, A. *Pharmacol. Res.* **2012**, *65*, 137-148.

[7] Faria, J. V.; Dos Santos, M. S.; Bernardino, A. M.; Becker, K.M.; Machado, G. M. Rodrigues, R. F.; Canto-Cavalheiro, M. M.; Leon, L. L. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6310-6312.

[8] Hasui, T.; Ohyabu, N.; Ohra, T.; Fuji, K.; Sugimoto, T.; Fujimoto, J.; Asano, K.; Oosawa, M.; Shiotani, S.; Nishigaki, N.; Kusumoto, K.; Matsui, H.; Mizukami, A.; Habuka, N.; Sogabe, S.; Endo, S.; Ono, M.; Siedem, C. S.; Tang, T. P.; Gauthier, C.; De, L. A.; Meese,; Boyd, S. A.; Fukumoto, S. *Bioorg. Med. Chem.* **2014**, *22*, 5428-5445.

[9] Bekhit, A. A.; Hassan, A. M.; Abd El Razik, H. A.; El-Miligy, M. M.; El-Agroudy, E. J.; Bekhit Ael, D. *Eur. J. Med. Chem.* **2015**, *94*, 30-44.

[10] Estrada, A. A.; Chan, B. K.; Baker-Glenn, C.; Beresford, A.; Burdick, D. J.; Chambers, M.; Chen, H.; Dominguez, S. L.; Dotson, J.; Drummond, J.; Flagella, M.; Fuji, R.; Gill, A.; Halladay, J.; Harris, S. F.; Heffron, T. P.; Kleinheinz, T.; Lee, D. W.; Le Pichon, C. E.; Liu, X.; Lyssikatos, J. P.; Medhurst, A. D.; Moffat, J. G.; Nash, K.;

Scearce-Levie, K.; Sheng, Z.; Shore, D. G.; Wong, S.; Zhang, S.; Zhang, X.; Zhu, H.; Sweeney, Z. K. *J. Med. Chem.* **2014**, *57*, 921-936.

[11] La Pietra, V.; La Regina, G.; Coluccia, A.; Famiglini, V.; Pelliccia, S.; Plotkin, B.; Eldar-Finkelman, H.; Brancale, A.; Ballatore, C.; Crowe, A.; Brunden, K. R.; Marinelli, L.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2013**, *56*, 10066-10078.

[12] Taggi, A. E.; Stevenson, T. M.; Bereznak, J. F.; Sharpe, P. L.; Gutteridge, S.; Forman, R.; Bisaha, J. J.; Cordova, D.; Crompton, M.; Geist, L.; Kovacs, P.; Marshall, E.; Sheth, R.; Stavis, C.; Tseng, C-P. *Bioorg. Med. Chem.* **2016**, *24*, 435-443.

[13] Doddaramappa, S. D.; Rai, K. M. L.; Srikantamurthy, N.; Chandra; Chethan, J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3671-3675.

[14] Kalaria, P. N.; Satasia, S. P.; Raval, D. K. *Eur. J. Med. Chem.* **2014**, *78*, 207-216.

[15] Shkineva, T. K.; Dalinger, I. L.; Shevelev, S. A. *Chem. Het. Compds.* **1995**, *31*, 509-529.

[16] Abdel-Wahab, B. F.; Dawood, K. M. *ARKIVOC*. **2012**, *ii*, 491-545.

[17] Sera, M.; Mizufune, H.; Tawada, H. *Tetrahedron*. **2015**, *71*, 2833-2838.

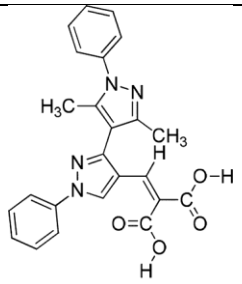
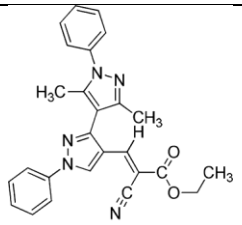
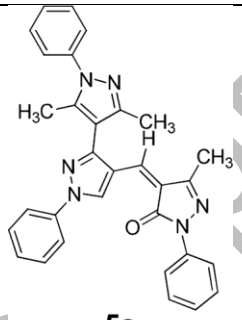
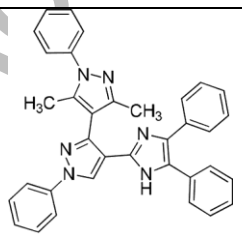
[18] Abdel-Wahab, B. F.; Khidre, R. E.; Farahat, A. A. *ARKIVOC*. **2011**, *i*, 196-245.

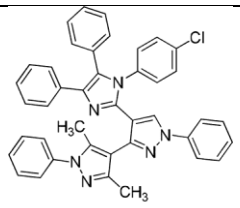
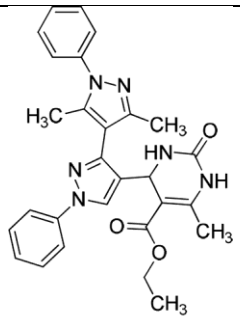
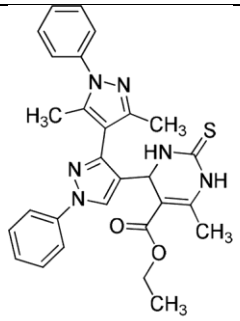
[19] Grandberg, I. I.; Tabak, S. V.; Bobrova, N. I.; Kost, A. N.; Vasina, L. G. *Khim. Geterotsikl. Soedin.* **1965**, *1*, 407-411.

[20] Chaudhry, F.; Asif, N.; Shafqat, S. S.; Khan, A. A.; Munawar, M. A.; Khan, M. A. *Synth. Commun*. **2016**, *46*, 701-709.

[21] Chaudhry, F.; Asif, N.; Khan, M. N.; Ribeiro, J.; Ather, A. Q.; Hina, S.; Munawar, M. A.; Nasrullah., M.; Ain, A. T.; Suhail, F.; Khan, M. A. *Asian J. Chem.* **2013**, *25*, 7879-7882.

Table 1. Some Hetaryl(3,4')bipyrazoles.

Entry	Product	M.P. °C	Method A		Method B	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	 **5a**	201	1	68	6.5	84
2	 **5b**	115	0.5	72	10	88
3	 **5c**	188	2	76	15	80
4	 **6a**	155	4	78	0.5	90

5	 **6b**	120	6	75	0.5	87
6	 **7a**	190	6	66	2	83
7	 **7b**	264	8	65	2	84

Scheme 1. Synthesis of bispyrazolic derivatives **(4-7)**. Reaction conditions: **a.** Active methylenes/1-Phenyl-3-methylpyrazolone, pyridine, piperidine, ethanol, reflux; **b.** Active methylenes/1-Phenyl-3-methylpyrazolone, glycine, DMSO, stirring at r. temp.; **c.** Benzil, ammonium acetate/*p*-chloroaniline, acetic acid, reflux; **d.** Benzil, ammonium acetate/*p*-chloroaniline, glycine, ethanol, reflux; **e.** Ethyl acetoacetate, urea/thiourea, *conc*. HCl, ethanol, reflux; **f.** Ethyl acetoacetate, urea/thiourea, glycine, ethanol, reflux.

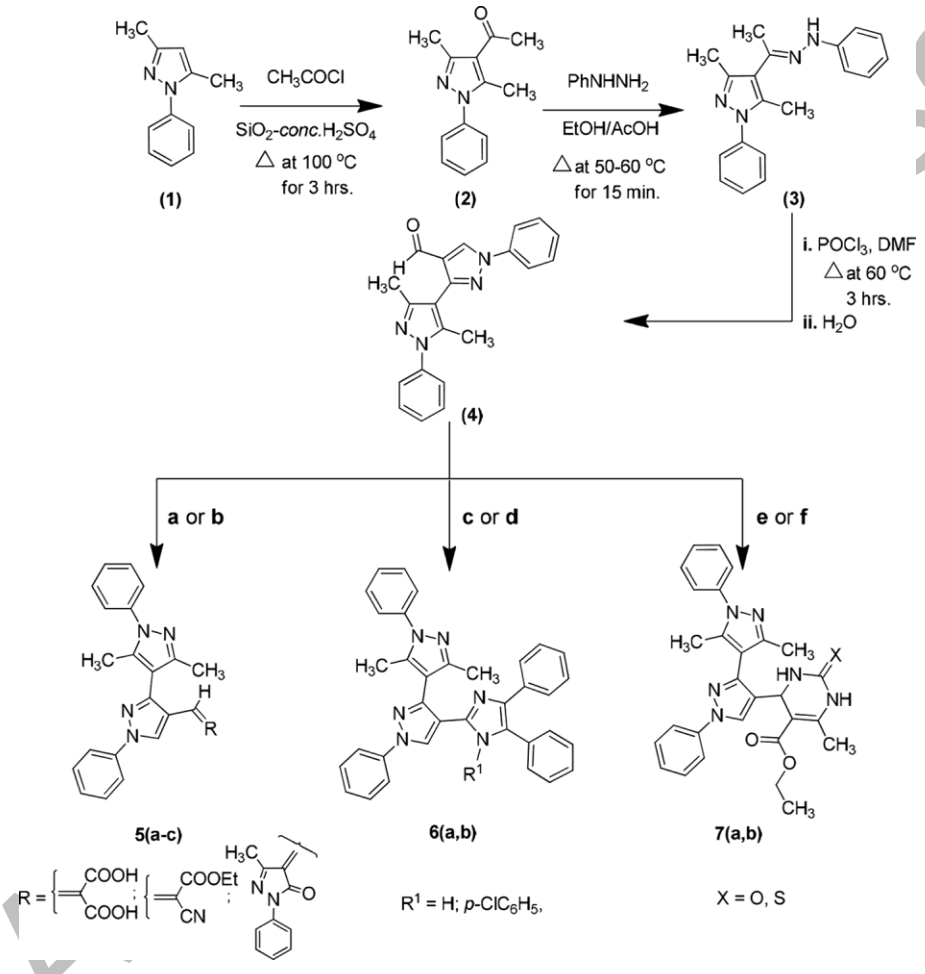


Figure 1. Biologically active hetarylpyrazoles.