ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Synthesis of Pyrazolyl Pyrrolidines by 1, 3-Dipolar Cycloaddition using Azomethine Ylide

Manickam. Pramesh[1]*, Paramasivam. T. Perumal[2] and Bathey. R. Venkatraman[3]

1. Department of Chemistry, A.V.V.M. Sri Pushpam College, Poondi -613 503 India
2. Organic Chemistry Division, CLRI, Adayar, Chennai – 600 020 India
3. Department of Chemistry, Periyar EVR College, Tiruchirappalli-620 023 India

Manuscript Info

Manuscript History:

Received: 25 March 2014
Final Accepted: 26 April 2014
Published Online: May 2014

Key words:
1, 3-Dipolar cycloaddition, Ylides, Pyrrolidines Diastereoselectivity

Corresponding Author

Manickam. Pramesh

Abstract

1, 3-Dipolar cycloaddition is a fundamental tool for the synthesis of a number of five membered heterocyclic compounds. In this paper, a series of pyrazolyl pyrrolidine derivatives have been synthesized by reacting substituted pyrazole aldehydes with benzyl ethyl glycinate followed by azomethine cycloaddition. Synthesized compounds were characterized by using various spectroscopic techniques.

1. Introduction

1,3-Dipolar cycloaddition is one of the most important methods for the synthesis of five-membered heterocycles. The high regio and stereo selectivity typical of these reactions make them an indispensable tool for synthesizing natural products with a few chiral centers.[1] In particular, dipolar cycloaddition of azomethine ylide has been used in many instances for the diastereoselective synthesis of various pyrrolidine based alkaloids that were found application as chiral building blocks and as chiral catalysts in organic synthesis.[2-4] Highly substituted pyrrolidines are well known for their glucosidase inhibitory activity in addition to potent antiviral, antibacterial, antidiabetic and anticancer activities.[5]

Pyrazole-derivatives are important from the viewpoint of their pharmacological properties. They have been known to display antianxiety, antipyretic, analgesic, PDE-4, antimicrobial, and antiinflammatory activities.[6] They are also employed as agrochemicals.[7] As a consequence, there has been continued interest to develop methodologies for the synthesis of a variety of pyrazole-based compounds.[8] Recently S. Batra *et.al* synthesized pyrazole derived heterocyclic compounds.[9] Spirocyclic pyrrole derivatives are studied for their antibacterial activity[10] and pyrazolyl pyrrolidine derivatives are reported for expected biological activity[11]. We intend to synthesize novel pyrazolyl pyrrolidine derivatives starting from glycine ester.

2. Material and Methods

2.1 Chemicals and reagents

All chemicals were purchased from Sigma-Aldrich U.S.A. Analytical TLC was performed on precoated aluminium sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck, Germany). Column chromatography was performed on silica gel (100-200 mesh, Merck, India).

2.2 Equipments and analytical instruments

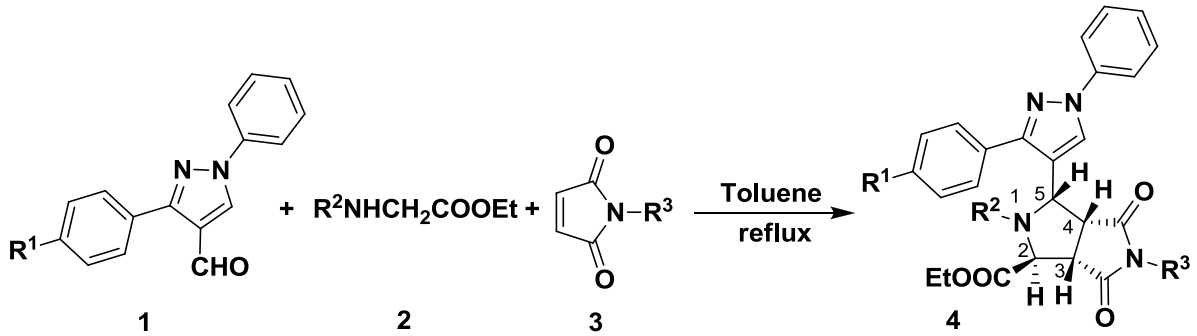
Melting points were obtained on a Cambridge Instruments Galen III hot stage apparatus. IR spectra were recorded on a Perkin–Elmer FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz respectively. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX 6000 ESI spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA1112 CHN analyzer.

2.3 Typical procedure for synthesis of comounds 4a-4g:

A mixture of pyrazole aldehyde (0.3 g), sacorsine (0.177 g) and maleimide (0.158 g) was refluxed in toluene (15 ml) until completion of the reaction as evidenced by TLC analysis. The solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel [Merck, 100–200 mesh, ethylacetate–petroleum ether (10:90)] to afford pure pyrazolyl pyrrolidine

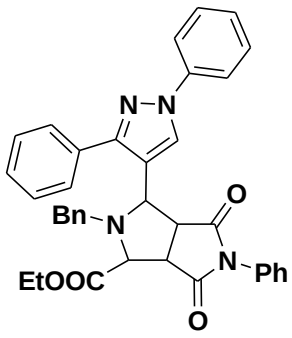
3. Result and Discussion

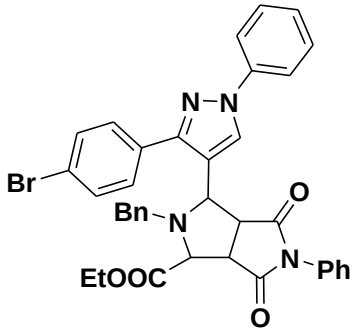
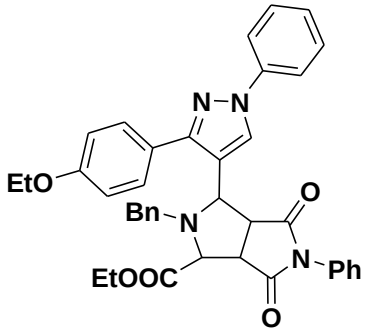
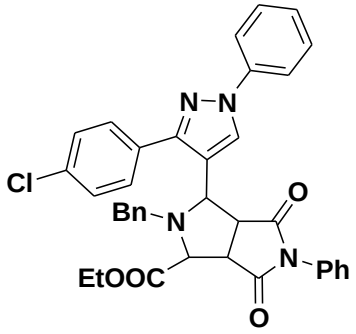
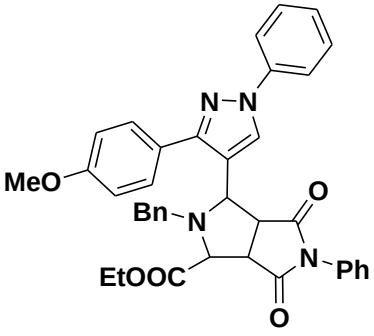
In continuation of our interest in the 1,3-dipolar cycloaddition reactions[12], here we developed a methodology for the synthesis of substituted pyrazolyl pyrrolidines. Reaction of substituted pyrazole aldehyde with glycine ester produced azomethine ylides, which were subsequently reacted in-situ with maleimides in toluene under refluxing conditions to produce highly substituted pyrazolyl pyrrolidines in good to excellent yields (Scheme 1,Table 1).These products were thoroughly characterized with various spectroscopic techniques.

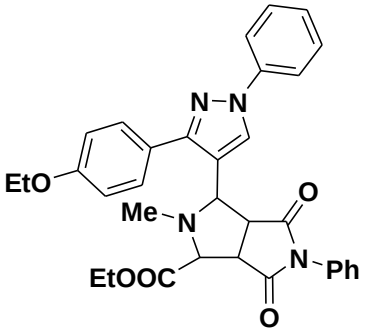
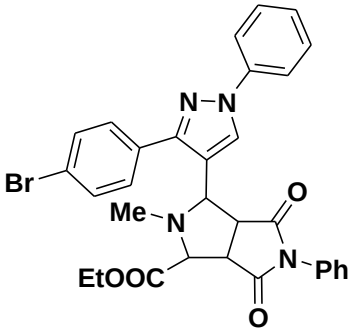


Scheme 1. Synthesis of Pyrazolyl Pyrrolidines (4a-g).

Table 1. Synthesis of Pyrazolyl Pyrrolidines (4a-4g)

Entry	R^1	R^2	R^3	Cycloadduct 4[a]	Time(h)	Yield[b] (%)
1	H	CH_2Ph	Ph	 4a	3.5	95

2	Br	CH_2Ph	Ph	 **4b**	4.5	93
3	OEt	CH_2Ph	Ph	 **4c**	6	96
4	Cl	CH_2Ph	Ph	 **4d**	5	92
5	OMe	CH_2Ph	Ph	 **4e**	4	98

6	OEt	Me	Ph	 **4f**	8	96
7	Br	Me	Ph	 **4g**	5	94

[a]All products were characterized by IR, [1]HNMR, [13]CNMR and mass spectroscopy
[b]Isolated yield after column chromatography.

In the [1]H NMR spectrum of compound **4g**, a singlet at δ 4.4 ppm was attributed to C2-H. The doublet at 3.52 ppm (J = 7.6 Hz), dd at 3.82 ppm (J = 7.6 and 9.2 Hz) and doublet at δ 4.65 ppm (J = 9.1 Hz) were assigned to protons at C5, C4, C3 carbons respectively. In [13]C NMR spectrum, the peaks at δ 170.7, 174.6 and 175.9 ppm were attributed to one ester and two imide carbonyl carbons respectively. The mass spectrum revealed the molecular ion peak $(M+H)^+$ at *m/z* 599.

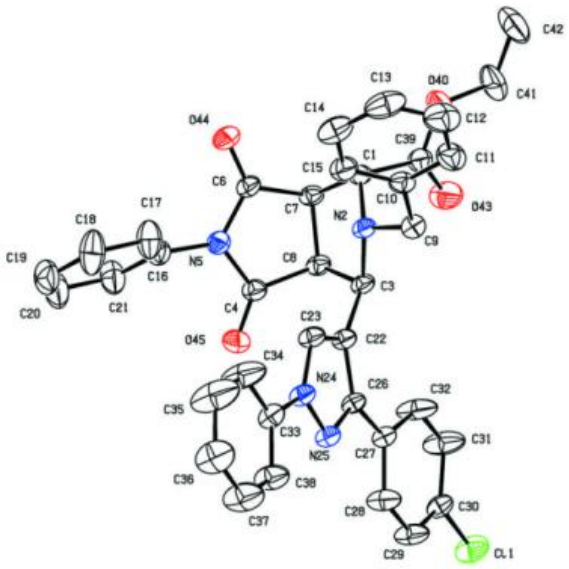


Figure 1. ORTEP diagram of compound 4d.

The stereochemistry of the compound was assigned by ^{1}H NMR spectrum, the hydrogen at C2 carbon appeared as singlet and trans relationship with proton at C5 carbon. The protons in the maleimide ring always in the *cis* relationship. The proton at C3 appeared as doublet with coupling constant (*J* = 9.9 Hz) and *cis* relationship with proton at C4 carbon (**Fig.2**). The stereochemistry was further confirmed by single crystal X-ray diffraction studies (CCDC 801528, ORTEP diagram **Fig.1**),[13] from this conclusion the formed product was a *exo* diastereoisomer due to the maleimide carbonyl carbon and ester carbonyl in the azomethine ylide are *trans* relationship.

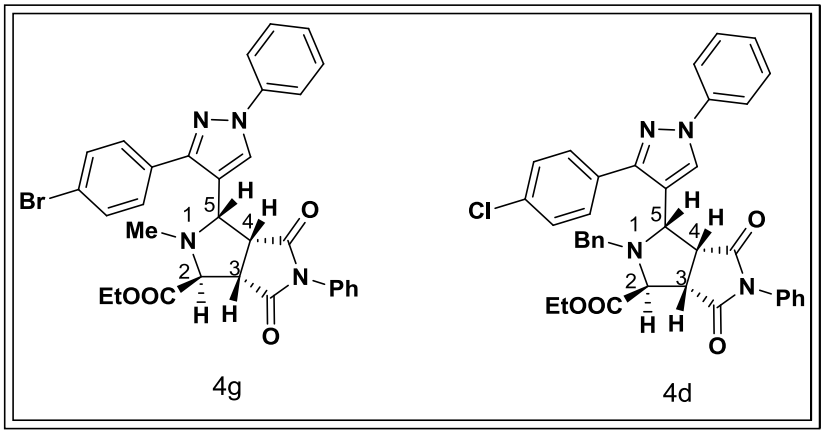


Figure 2.Structural diagram of compound 4g and 4d

Characterization of compound 4a-4g

Compound **4a**: Ethyl2-benzyl-octahydro-4,6-dioxo-5-phenyl-3-(1,3-diphenyl-1*H*-pyrazol-4 yl)pyrrolo[3,4-*c*]pyrrole-1-carboxylate, Yellow solid; Rf= 0.41 (50% EAPE) mp 164-172 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.27 (t, 3H, *J*=3.05Hz), 3.53 (d, 1H, *J*=7.65Hz), 3.60 (d, 1H, *J*=13.75Hz), 3.91 (t, 1H, *J*=9.9Hz), 4.0 (d, 1H, *J*=13.75Hz), 4.16-4.22 (m, 2H), 4.39(S,1H), 5.04 (d, 1H, *J*=9.95), 7.19 (t,4H, *J*=6.9Hz), 7.22-7.34 (m, 8H), 7.40 (t, 2H, *J*=8.40Hz), 7.51 (t, 2H, *J*=7.65Hz), 7.59 (d, 2H, *J*=7.65Hz), 7.81 (d, 2H, *J*=6.85Hz), 7.86 (S, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ = 14.4, 49.0, 49.5, 52.3, 60.2, 61.1, 63.1, 119.1, 125.6, 126.1, 126.7, 127.5, 127.9, 128.4, 128.5, 128.6, 128.8, 129.2, 129.5, 137.8, 139.8, 153.3, 163.0, 171.0, 174.6, 175.8; IR ν_{max}/KBr/cm^{-1}: 3425, 2974, 2864, 1721, 1595, 1540; MS *m/z* 596 $(M+H)^+$; Anal. Calcd for $C_{37}H_{32}N_4O_4$ C, 74.48; H, 5.41; N, 9.39; O, 10.73; Found C, 74.55; H, 5.53; N, 10.62.O, 10.42.

Compound **4b**: Ethyl 2-benzyl-3-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-octahydro-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate, Pale yellow solid; Rf= 0.48 (50% EtOAc:Pet.ether); mp 166-168 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.28 (t, 3H, *J*=6.9 Hz), 3.53 (d, 1H, *J*=7.6 Hz), 3.61 (d, 1H, *J*=13.7 Hz), 3.88 (q, 1H, *J*=7.6 Hz), 3.98 (d, 1H, *J*=13.7 Hz), 4.17-4.24 (m, 2H,), 4.39 (S, 1H), 5.00 (d, 1H, *J*=9.2 Hz), 7.17 (t, 4H, *J*=6.9 Hz), 7.24-7.34 (m, 8H), 7.40 (t, 2H, *J*=7.6 Hz), 7.57 (d, 2H, *J*=7.6 Hz), 7.63 (d, 2H, *J*=8.4 Hz), 7.69 (d, 1H, *J*=8.4 Hz), 7.85 (S, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ = 14.3, 49.0, 49.5, 52.4, 60.2, 61.2, 63.1, 119.0, 122.7, 125.6, 126.8, 127.9, 128.6, 128.8, 129.2, 129.5, 130.1, 131.9, 137.7, 139.7, 152.1, 171.0, 174.6, 175.7; IR ν_{max}/KBr/cm^{-1}: 3436, 3062, 2978, 2376, 1718, 1596, 1498; MS *m/z* 675 $(M+H)^+$; Anal. Calcd for $C_{37}H_{31}BrN_4O_4$ C, 65.78, H, 4.63; Br, 11.83; N, 8.29; O, 9.47; Found C, 65.60; H, 4.51; Br, 11.70; N, 8.20; O, 9.40.

Compound **4c**: Ethyl 2-benzyl-3-(3-(4-ethoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-octahydro-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate, Yellow solid; Rf= 0.44 (50% EAPE) mp 92-98 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.27 (t, 3H, *J*=6.85Hz), 1.44 (t, 3H, *J*=9.2Hz), 3.53 (d,1H, *J*=7.6Hz), 3.59 (d, 1H, *J*=14.55Hz), 3.89 (t, 1H, *J*= 7.6Hz), 3.99 (d, 1H, *J*=13.75Hz), 4.08-4.22 (m, 4H), 4.38 (S, 1H), 5.0 (d, 1H, *J*=9.9Hz), 7.02 (d, 2H, *J*=8.4Hz), 7.18 (d, 4H, *J*=7.65Hz), 7.25 (q, 3H, *J*=8.4Hz), 7.28-7.34 (m, 5H), 7.39 (t, 2H, *J*=8.4Hz), 7.58 (d, 1H, *J*=7.65Hz), 7.71 (d, 2H, *J*=8.4Hz), 7.83(S, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ = 14.4, 14.9, 27.0, 49.0, 49.5, 52.3, 60.2, 61.1, 63.0,63.6, 114.7, 118.8, 125.5, 125.6, 125.9, 126.5, 127.5, 127.9, 128.5, 128.7, 129.2, 129.4, 129.7,

131.8, 137.8, 139.9, 159.2, 171.0, 174.6, 175.8; IR ν_{max}/KBr/cm^{-1}: 3755, 3444, 2926, 2376, 1719, 1602, 1498; MS *m/z* 641 $(M+H)^+$; Anal. Calcd for $C_{39}H_{36}N_4O_5$ C, 73.11; H, 5.66; N, 8.74; O, 12.49; Found C, 73.20; H, 5.57; N, 8.62; O, 12.56.

Compound **4d**: Ethyl 2-benzyl-3-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-octahydro-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate Colourless solid; Rf= 0.52 (50% EAPE) mp 168-174 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.28 (t, 3H, *J*=6.85Hz),3.53 (d, 1H, *J*=7.65Hz), 3.6 (d, 1H, *J*=13.75Hz), 3.87 (t,1H, *J*=7.65Hz), 3.98 (d, 1H, *J*=13.75), 4.2 (q, 2H, *J*=6.85Hz), 4.38 (S, 1H), 5.0 (d, 1H, *J*=9.9Hz), 7.17 (t, 4H, *J*=6.1Hz), 7.22-7.34 (m, 7H), 7.40 (t, 2H, *J*= 7.65Hz), 7.48 (d, 2H, *J*=8.4Hz), 7.57 (d, 2H, *J*=7.65Hz),7.74 (d, 2H, *J*=8.4Hz), 7.85 (S,1H); ^{13}C NMR (125 MHz $CDCl_3$) δ = 14.4, 49.0, 49.5, 52.4, 60.2, 61.2, 63.1, 119.0, 119.2, 125.6, 127.6, 127.9, 128.6, 128.8, 128.9, 129.2, 129.5, 129.8, 134.4, 137.7, 139.7, 152.1, 163.1, 171.1, 174.6, 175.5; IR ν_{max}/KBr/cm^{-1}: 3757, 3432, 2925, 2856, 2373, 1719, 1599, 1494; MS *m/z* 631 $(M+H)^+$. Anal. Calcd for $C_{37}H_{31}ClN_4O_4$ C, 70.41; H, 4.95; Cl, 5.62; N, 8.88; O, 10.14; Found C, 70.52; H, 4.83; Cl, 5.53; N, 8.76; O, 10.22.

Compound **4e**: Ethyl 2-benzyl-octahydro-3-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate, Yellow solid; Rf= 0.34 (50% EAPE) mp 96-101 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.27 (t, 3H, *J*=7.65Hz), 3.52 (d, 1H, *J*=7.6Hz), 3.58 (d, 1H, *J*=14.5Hz), 3.88 (q, 4H, *J*=5.35Hz), 3.99 (d, 1H, *J*=14.5Hz), 4.19 (q, 2H, *J*=6.9Hz), 4.38 (S,1H), 5.01 (d, 1H, *J*=9.2Hz), 7.03 (d, 2H, *J*=8.4Hz), 7.17 (d, 3H, *J*=7.65Hz), 7.23-7.35 (m, 8H), 7.39 (t, 2H, *J*=6.85Hz), 7.58 (d, 2H, *J*=7.65Hz), 7.73 (d, 2H, *J*=8.4Hz), 7.83 (S, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ = 14.4, 49.0, 49.5, 52.3, 55.5, 60.3, 61.1, 63.1, 114.2, 118.9, 125.6, 126.5, 127.5, 127.9, 128.5, 128.7, 129.2, 129.5, 129.7, 137.8, 139.9, 153.1, 159.8, 171.1, 174.6, 175.8; IR ν_{max}/KBr/cm^{-1}: 3756, 3430, 2925, 2856, 2376, 2339, 1719, 1599, 1500; MS *m/z* 627 $(M+H)^+$; Anal. Calcd for $C_{38}H_{34}N_4O_5$ C, 72.83; H, 5.47; N, 8.97; O, 12.76; Found C, 72.71; H, 5.36; N, 8.86; O, 12.63.

Compound**4f**: Ethyl 3-(3-(4-ethoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-octahydro-2-methyl-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate, Colourless solid; Rf= 0.34 (50% EAPE) mp 170-178 °C. ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.32(t, 3H, *J*=6.9Hz), 1.44(t, 3H, *J*=6.9Hz), 2.36 (3H,S), 3.52(d, 1H, *J*=8.45Hz), 3.84(t, 1H, *J*=8.45Hz), 4.08(q, 2H, *J*=6.85Hz), 4.23(q, 2H, *J*=6.9Hz), 4.4(S, 1H), 4.66(d, 1H, *J*=9.95Hz), 7.0(d, 2H, *J*=8.4Hz), 7.16(d, 2H, *J*=7.65Hz), 7.22-7.25(m, 1H), 7.28-7.32(m, 3H), 7.40(t, 2H, *J*=8.4Hz), 7.64(d, 2H, *J*=7.6Hz), 7.68(d, 2H, *J*=9.1Hz), 7.80(S, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ = 14.5, 14.9, 35.8, 48.8, 49.9, 61.1, 61.2, 63.6, 67.3, 114.7, 118.7, 118.9, 125.6, 125.8, 126.1, 126.3, 128.5, 129.1, 129.4, 129.6, 131.8, 139.9, 152.8, 159.1, 170.7, 174.6, 176.1; IR ν_{max}/KBr/cm^{-1}: 3440, 3064, 2978, 2793, 2373, 1717, 1603, 1501; MS *m/z* 565 $(M+H)^+$; Anal. Calcd for $C_{33}H_{32}N_4O_5$ C, 70.20; H, 5.71; N, 9.92; O, 14.17; Found C, 70.33; H, 5.60; N, 9.81; O, 14.25.

Compound **4g**: Ethyl 3-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-octahydro-2-methyl-4,6-dioxo-5-phenylpyrrolo[3,4-*c*]pyrrole-1-carboxylate, Pale yellow solid; Rf= 0.59 (50%EAPE) mp 218-226 °C; ^{1}H NMR (500 MHz $CDCl_3$) δ = 1.32(t, 3H, *J*=6.8Hz), 2.37(S,3H), 3.52(d, 1H, *J*=7.6Hz), 3.82(dd, 1H, *J*=7.6, 9.2Hz), 4.24(q, 2H, *J*=6.9Hz), 4.40(S,1H), 4.65(d, 1H, *J*=9.1Hz), 7.13(d, 2H, *J*=7.6Hz), 7.25-7.32(m, 4H), 7.41(t, 2H, *J*=7.6Hz), 7.60(d, 2H, *J*=8.4Hz), 7.63-7.66(m, 4H), 7.82(S,1H); ^{13}C NMR (125 MHz $CDCl_3$) δ = 14.5, 35.8, 48.7, 49.9, 61.1, 61.2, 67.2, 118.8, 122.5, 125.7, 126.4, 126.6, 128.5, 129.1, 129.5, 129.9, 131.7, 131.8, 132.1, 139.7, 151.8, 170.7, 174.6, 175.9; IR ν_{max}/KBr/cm^{-1}: 3166, 3017, 2815, 1715, 1625, 1592, 1498; MS *m/z* 599 $(M+H)^+$; Anal. Calcd for $C_{31}H_{27}BrN_4O_4$ C, 62.11; H, 4.54; Br, 13.33; N, 9.35; O, 10.68; Found C, 62.20; H, 4.62; Br, 13.24; N, 9.47; O, 10.56.

4. Conclusions

In summary, the synthesis of some novel highly substituted pyrazolyl pyrrolidines is reported for the first time. The adducts were obtained using high regio and diastereoselective 1,3-dipolar cycloaddition strategy. The reactions showed an *exo*-diastereoselectivity as against the *endo*-diastereoselectivity observed in other similar reported reactions. Based on the inherent biological activity of the pyrazole unit we anticipate that these novel pyrazolyl containing pyrrolidines may display enhanced activity. Antibacterial activity together with low or no cytotoxicity to normal cells will be our ongoing interests.

Acknowledgments

MP thanks the CLRI, Chennai for providing lab facilities and all the spectroscopic and analytical data acquisition

References

1. A. Padwa, W. H. Pearson, Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; Wiley: New York, NY, **2002.**

2. (a) G. Pandey, J. K. Laha, G. Lakshmaiah, *Tetrahedron*, **2002,** 58, 3525; (b) T. Onishi, P. R Sebahar, R. M. Williams, *Tetrahedron*, **2004**, 60, 9503; (c) G.Pandey, P.Banerjee, R,Kumar ,V.G.Puranik,Org. Lett. 2005, 7, 3713; (d) G.Pandey, P.Banerjee, S. R.Gadre, *Chem. Rev*. **2006**, 106, 4484; (e) I.Coldham, R.Hufton, *Chem. Rev*. **2005**, 105, 2765; (f) H.Pellissier, *Tetrahedron*, **2007**, 63, 3235.

3. (a) K.Kawashima, A.Kakehi, M.Noguchi, *Tetrahedron*, **2007**, 63, 1630. (a) X. Yan, Q. Peng, K. Zhang, W. Hong, X. Hou, Y. Wu, *Angew. Chem*. **2006**, 118, 2013; (b) D. J. Aldous, M. G. B. Drew, W.N.Draffin, E. Hamelin, L. M. Harwood, S. Thurairatnam, *Synthesis*, **2005,** 19, 3271; (c) I. Coldham, K. M. Crapnell, J. D. Moseley,R. Rabot, *J. Chem. Soc*. Perkin Trans. **2001,** 1758.

4. (a) J. Jayashankaran, R. S. M. Rathina Durga, R. Raghunathan, *Synthesis*, **2006,** 1028; (b) M. Boruah, D. Konwar, S. D. Sharma, *Tetrahedron Lett*. **2007,** 48, 4535; (c) R. Grigg, V. Sridharan, M. Thornton-Pett, J. Wang, J. Xu, J. Zhang, *Tetrahedron*, **2002,** 58, 2627; (d) H. A. Dondas, C. W. G. Fishwick, R. Grigg, C. Kilner, *Tetrahedron*, **2004**, 60, 3473; (e) A. Dondoni, A. Marra, *Tetrahedron Lett*. **2002,** 43, 1649.

5. (a) A. D. Elbein, R. J. Molyneux, In Iminosugars as Glycosidase Inhibitors; Nojirimycin and Beyond; A. E. Stütz, Ed.; Wiley-VCH: Weinheim, **1999**; pp 216–251; (b) N. Asano, R. J. Nash, R. J. Molyneux, G.W. J. Fleet, G. *Tetrahedron: Asymmetry*, **2000,** 11, 1645; (c) P. Greimel, J. Spreitz, A. E. Stutz, T.M.Wrodnigg, *Curr. Top. Med. Chem.* **2003,** 11, 513 (d) H. Fiaux, F. Popowycz, S. Favre, C. Schütz, P. Vogel, S. Gerber-Lemaire, L. Juillerat-Jeanneret, *J. Med. Chem*. **2005,** 48, 4237; (e) Pharmaceuticals; J. L. McGuire, Ed.; Wiley-VCH: Weinheim, **2000**; Vol. 1–4.

6. A few examples only: (a) L.-L. Xu, C.-J. Zheng, L.-P. Sun, J. Miao, H.-R. Piao,Eur. *J. Med. Chem*. **2012**, 48, 174e178; (b) T. S .Reddy, K. S. Kumar, C. L. T. Meda, A. Kandale. D. Rambabu, G. Rama Krishna, C. Hariprasad, V. V. Rao, S. Venkataiah, C. M. Reddy, A. Naidu, P. K. Dubey, K. V. L. Parsa, M. Pal, *Bioorg. Med. Chem. Lett*. **2012,** 22, 3248e3255; (c) B. A. Thaher, M. Arnsmann, F. Totzke, J. E. Ehlert, M. H. G. Kubbutat, C. Schachtele, M. O. Zimmermann, P. Koch, F. M. Bockler, S. A. Laufer, *Eur. J. Med. Chem*. **2012,** 55, 961e965; (d) I. Vujasinovic, A. Paravic-Radicevic, K. Mlinaric-Majerski, K. Brajsa, B. Bertosa, *Bioorg. Med. Chem.* **2012**, 20, 2101e2110; (e) C. Alıs¸ B. kan, S. Luderer, Y. Ozkan, O. Werz, E. Banoglu, *Eur. J. Med. Chem*. **2011,** 46, 5021e5033; (f) M. H. El-Dakdouki, N. Adamski, L. Foster, M. Hacker, P. W. Erhardt, *J. Med. Chem.* **2011**, 54, 8224e8227; (g) J. S. M. Pasin, A. P. O. Ferreira, A. L. L. Saraiva, V. Ratzlaff, R. Andrighetto, P. Machado, S. Marchesan, R. A. Zanette, H. G. Bonacorso, N.Z anatta, M. A. P. Martins, J. Ferreira, C. F. Mello, Braz, *J. Med. Biol. Res.* **2010,** 43, 1193e1202; (h) J. Elguero, P. Goya, N. Jagerovic, A. M. S. Silva, Pyrazoles as Drugs: Facts and Fantasies O.A.Attanasi, D.Spinelli, Eds.. Targets in Heterocyclic Systems; Italian Society of Chemistry: Roma, Italy, **2002;** Vol. 6, pp 52e98; (i) Y.Xia, S. Chackalamannil, M. Czarniecki, H. Tsai, H. Vaccaro, R. Cleven, J. Cook, A. Fawzi, R. Watkins, H. Zhang, *J. Med. Chem*. **1997,** 40, 4372e4377.

7. (a) G. Theodoridis, In Modern Crop Protection Compounds; W.Kramer, U.Schirmer, Eds.; Wiley-VCH: Weinheim, Germany, **2007**; Vol. 1, pp 153e186; (b) Y. Shiga, I. Okada, Y. Ikeda, E. Takizawa, T. J. Fukuchi, Pestic. Sci. **2003,** 28, 313e314; (c) S. D. Lindell, B. A. Moloney, B. D. Hewitt, C. G. Earnshaw, P. J. Dunfield J. E. Dancer, *Bioorg. Med. Chem. Lett*. **1999,** 9, 1985e1990; (d) C. B. Vicentini, C. Romagnoli, E. Andreotti D.J.Mares, Agric. Food Chem. **2007,** 55, 10331e10338; (e) S. Fustero, R. Roman, J. F. Sanz-Cervera, A. Simon-Fuentes, J. Bueno, S. Villanova, *J. Org. Chem*. **2008**, 73, 8545e8552; (f) G. A. Dutra, B. C. Hamper, D. A. Mitschke, K. Moedritzer, K. D. Rogers, PCT Int. Appl., WO 9206962, **1992**. Chem. Abstr.**1992,** 117, 69859.

8. (a) Y. L. Janin, *Chem. Rev*. **2012,** 112, 3924e3958 and references cited therein; (b) S. Fustero, M. Sanchez-Rosello, P. Barrio, A. Simon-Fuentes, *Chem. Rev*. **2011**,111, 6984e7034 and references cited therein; (c) S. Guillou, F. J. Bonhomme, M. S. Ermolenko, Y. L. Janin, *Tetrahedron*, **2011,** 67, 8451e8457; (d) G. Vilkauskaite, A. Sackus, W. Holzer, *Eur. J. Org. Chem.***2011,** 5123e5133; (e) S. Guillou, Y. L. Janin, *Chem. Eur. J.* **2010,** 16, 4669e4677; (f) L.Yet, Five-Membered Ring Systems: With More than One N Atom, G. W. Gribble, J. A. Joule, Eds.. Progress in Heterocyclic Chemistry; Elsevier: **2009,** Vol. 21, pp 224e260; (g) L.Yet, In Comprehensive Heterocyclic Chemistry; A. R. Katrizky, C. A. Ramsden, E. F. V. Scriven, T. J. K. Taylor, Eds.; Pergamon: London, UK**, 2008;** Vol. 4, 4.01, pp 1e141; and references cited therein; (i) M. Schnurch, R. Flasik, A. F. Khan, M. Spina, M. D. Mihovilovic, P. Stanetty, *Eur. J. Org. Chem*. **2006,** 3283e3307.

9. (a) S. Nag, M. Nayak, S. Batra, *Adv. Synth. Catal*. **2009**, 351, 2715-2723 and references cited therein; (b). M. Nayak, S. Batra, *RSC Adv*. **2012,** 2, 3367e3373; (c). M. Nayak, S. Batra, *Adv. Synth. Catal*. **2010,** 352, 3431e3437; (d) M. Nayak, N .Rastogi, S.Batra, *Eur. J. Org. Chem*. **2012**, 1360e1366; (e). M. Nayak, S. Batra, *Eur. J. Org. Chem*. **2012,** 3677e3683; (f). M. Nayak, H. Batchu, S. Batra, *Tetrahedron Lett.* **2012**, 53, 4206e4208.

10. Y. Yu. Xiang, John finn, M.J ason, Hill, G.Zhong Wang, Dennis Keith Jared Silverman and N. Oliver. *Bioorg. Med. Chem. Lett*.**2004**, 14, 1339-1342.

11. J. Quiroga, J. Gálvez , A. Pérez , A. Valencia, R. A. Braulio Insuasty. *Tetrahedron Lett.*, **2011**,52, 5471–5473.

12. (a) K. Karthikeyan, P. T. Perumal, S. Etti, G. Shanmugam, *Tetrahedron*, **2007**, 63, 10581; (b) K. Karthikeyan, T. V. Seelan, K. G. Lalitha, P. T. Perumal, *Bioorg. Med. Chem. Lett*. **2009**, 19, 3370; (c) K. Karthikeyan, P. M. Sivakumar, M. Doble, P. T. Perumal, *Eur. J. Med. Chem*, **2010**, 45, 3446-3452; (d) K. Ramachandiran, K. Karthikeyan, T. Nandhakumar, D. Muralidharan, P. T. Perumal, *Synthesis*, **2011**, 3277-3286; (e) K. Karthikeyan, N. Saranya, A.Kalaivani, P. T. Perumal, *Synlett*. **2010**, 2751-2754. K. Ramachandiran, K. Karthikeyan, D. Muralidharan, P. T. Perumal, *Tetrahedron Lett.* **2010,** 51, 3006-3009.

13. P. Kamatchi, G. Jagadeesan, M. Pramesh, P. T. Perumal, and S. Aravindhan, *Acta Cryst*. **2012**, E68, o552.