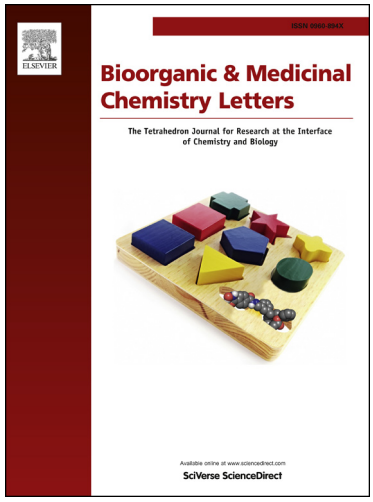


Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation

Srikantamurthy Ningaiah, Umesha K. Bhadraiah, Shridevi D. Doddaramappa, Shubakara Keshavamurthy, Chethan Javarasetty

PII: S0960-894X(13)01308-5
DOI: http://dx.doi.org/10.1016/j.bmcl.2013.11.029
Reference: BMCL 21056

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 14 September 2013
Revised Date: 4 November 2013
Accepted Date: 12 November 2013

Please cite this article as: Ningaiah, S., Bhadraiah, U.K., Doddaramappa, S.D., Keshavamurthy, S., Javarasetty, C., Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation, *Bioorganic & Medicinal Chemistry Letters* (2013), doi: http://dx.doi.org/10.1016/j.bmcl.2013.11.029

Graphical Abstract

Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation

Leave this area blank for abstract info.

Srikantamurthy Ningaiah[a], Umesha K. Bhadraiah[a,*], Shridevi D. Doddaramappa[b], Shubakara Keshavamurthy[a] and Chethan Javarasetty[c]

[a]*Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore570005,*
[b]*Department of Studies in Chemistry, Manasagangotri, University of Mysore,*
[c]*Department of Biotechnology, Manasagangotri, University of Mysore, Mysore-570 006. India*

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation

Srikantamurthy Ningaiah[a], Umesha K. Bhadraiah[a,*], Shridevi D. Doddaramappa[b], Shubakara Keshavamurthy[a] and Chethan Javarasetty[c]

[a] *Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore-570 005.*
[b]*Department of Studies in Chemistry, Manasagangotri, University of Mysore,*
[c]*Department of Biotechnology, Manasagangotri, University of Mysore, Mysore-570 006. India.*

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Pyrazole
1,3,4-oxadiazoles
Chloramine-T
Antimicrobial activity
Minimum inhibitory concentration (MIC)

ABSTRACT

A novel series of 2-(5-methyl-1,3-diphenyl-1*H*-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazoles **7(a-m)** were synthesized either by cyclization of *N'*-benzoyl-5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide **4a** using $POCl_3$ at 120 °C or by oxidative cyclization of hydrazones derived from various arylaldehyde and (E)-*N'*-benzylidene-5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide **5(a-d)** using chloramine-T as oxidant. Newly synthesized compounds were characterized by analytical and spectral (IR, ^{1}H NMR, ^{13}C NMR and LC–MS) methods. The synthesized compounds were evaluated for their antimicrobial activity and were compared with standard drugs. The compounds demonstrated potent to weak antimicrobial activity. Among the synthesized compounds, compound **7m** emerged as an effective antimicrobial agent, while compounds **7d**, **7f**, **7i** and **7l** showed good to moderate activity. The minimum inhibitory concentration of the compounds was in the range of 20–50µg mL^{-1} against bacteria and 25–55µg mL^{-1} against fungi. The title compounds represent a novel class of potent antimicrobial agents.

Pyrazole ring is a ubiquitous motif in biologically active compounds and therefore represents an interesting template for combinatorial[1,2] as well as medicinal chemistry.[3-5] Among the pyrazole derivatives some compounds are broadly used as insecticides (Fipronil-MB46030), selective COX-2 inhibitor (Celecoxib-M01AH01), phosphodiesterase inhibitor (Sildenafil-G04BE03), anorectic antiobesity drug (Rimonabant-A08AX01) and non-steroidal anti-inflammatory drug (Lonazolac-M01AB09).[6-11]

1,3,4-Oxadiazoles are an important class of heterocyclic compounds[12] with a wide range of biological activities such as antimicrobial,[13] anticancer,[14] antiviral,[15] antineoplastic,[16] CNS depressant[17] and tyrosinase inhibitory activity.[18] Further, 1,3,4-oxadiazole heterocycles are very good bioisostere of amide and ester functionalities with substantial improvement in biological activity by participating in hydrogen bonding interactions with different receptors.[19,20] In addition to pharmacophores pyrazole or 1,3,4-oxadiazole, there are other factors which influences the biological activity of the molecules. For instance, presence of electron releasing or withdrawing substituents, H-bond accepting or donating groups and presence of lipophilic groups etc.

The incidence of microbial infections has increased dramatically in recent years.[21] Resistance to antimicrobial agents has resulted in morbidity and mortality from treatment failures and increased health care costs.[22] Thus, intense efforts in antimicrobial drug discovery are still needed to develop more promising, economical, and effective drugs for use in the clinical arena.[23]

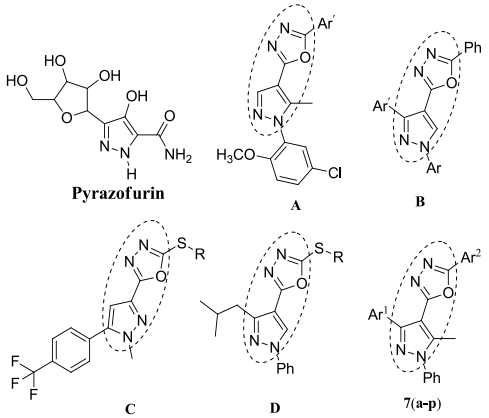


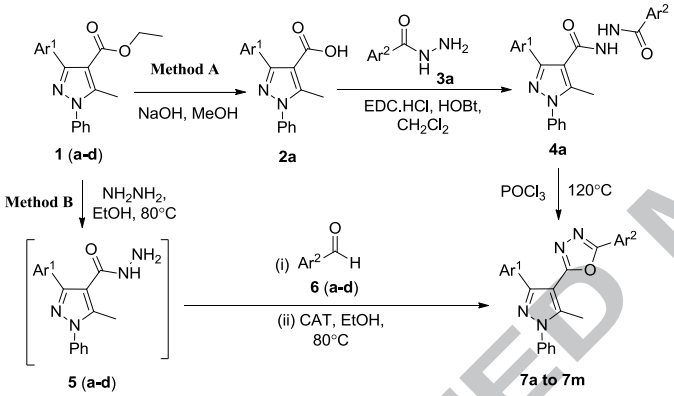
Fig. 1 Structures of Pyrazofurin and reported active pyrazolyl-1,3,4-oxadiazoles **A**, **B**, **C**, **D** and **7(a-p)**

Identification of novel structure leads that may be of use in designing new, potent and broad spectrum antimicrobial agents

* Corresponding author Tel.: +91 0821-2420398 E-mail address: kbu68umesha@rediffmail.com (U.K.B).

remains a major challenge for medicinal chemistry researchers. In this view, the discovery of the natural 4-hydroxypyrazole C-glycoside antibiotic pyrazofurin (Fig. 1); has provided a basis for more rationale design and synthesis of new pyrazoles as potential antimicrobial.[24-26] Consequently, several pyrazole derivatives that exhibited antimicrobial activity were reported.[27-29] However, a survey of the literature revealed that linked biheterocyclic compounds containing pyrazole to possess biological activity are often reported. Recently pyrazole incorporated thiazole,[30] thiadiazole,[31] 1,2,4-oxadiazole,[32] 1,2,4-triazoles and benzoxazoles,[33] were synthesized and observed in the enhancement of pharmacological effect. Also several biologically active pyrazolyl-1,3,4-oxadiazole analogues have been reported (Figure 1; **A**, **B**, **C** and **D**).[34-40]

Encouraged by these observations and in continuation of our research work on the synthesis of heterocyclic compounds containing multi-structure for biological activity,[41] we thought of synthesizing a new class of heterocycles, wherein potent 1,3,4-oxadiazole moiety is linked to pyrazole moiety at C-4 position to see the additive effect of these rings towards the antimicrobial activity, which is the current passion being accomplished in most of the drug discoveries.



Scheme 1 Synthesis of pyrazole integrated 1,3,4-oxadiazoles

The synthesis of our desired pyrazole integrated 1,3,4-oxadiazole derivatives began with ethyl 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylate[42] **1**(**a-d**) as starting material. The two reactions sequence (method A & B) of preparing the biheterocycle 2-(5-methyl-1,3-diphenyl-1*H*-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazoles **7**(**a-m**) are depicted in Scheme 1. The key intermediates 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid **2a** and 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazides **5**(**a-d**) were synthesized by simple procedure that involves reacting ethyl 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylate **1**(**a-d**) with 10% NaOH solution in refluxing MeOH for 4h followed by acidification with dilute hydrochloric acid and by treating **1**(**a-d**) with hydrazine hydrate in refluxing EtOH for 2h respectively. Finally the products **7**(**a-m**) were achieved either by sequential transformation that involves reaction of **2a** with benzohydrazide **3a** in presence of peptide coupling reagent EDC.HCl in dichloromethane resulted *N'*-benzoyl-5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide **4a** which, when heated with phosphorousoxychloride at 120°C, gave the respective title compound **7a** in moderate yield. On the other hand, condensing the hydrazides **5**(**a-d**) with a variety of aryl aldehydes **6**(**a-d**) followed by oxidative cyclization in presence of chloramine-T yielded the corresponding **7**(**a-m**) in good quality and yield.

The structures of newly synthesized compounds **2a**, **4a**, **5**(**a-d**) and **7**(**a-m**) were confirmed by their analytical and other spectral data. The IR spectra of the compounds **4a** and **5**(**a-d**) exhibited characteristic absorption band at 1640 cm^{-1} and 3217 cm^{-1} due to carbonyl and NH functional groups, respectively. The IR spectra of all other synthesized compounds showed characteristic signals at 1640-1595 cm^{-1} for (C═N), 1570-1460 cm^{-1} for (C═C), 1260-1285 cm^{-1} for (C–N), and 1240-1230 cm^{-1} for (C–O).

The ^{1}H NMR spectra of the compound **2a** showed singlet due to –OH of pyrazole-4-carboxylic acid at δ 12.44 and also disappearance of peaks at δ 1.15 (3H, t), and 4.13 (2H, q) due to $–CH_2CH_3$ and $–OCH_2–$ protons respectively confirms the formation of product **2a**. Similarly the disappearance of broad singlet due to –NH at δ 9.69 and due to $–NH_2$ proton at δ 9.72 of compounds **4** and **5** confirms the formation of cyclised biheterocycle **7**(**a-m**). In ^{13}C NMR spectra, absence of peak at δ 166.2 and 168.4 due to carbonyl group (C═O) of **4** and **5** substantiated the formation of compounds **7**(**a-m**). The mass spectrum of all the compounds showed molecular ion peak at M+1 corresponding to its molecular formula, which confirmed its chemical structure.

Initially we have followed method A for the synthesis of **7a** where, the pyrazole acid **2a** formed was treated with benzohydrazide **3a** in presence of coupling reagent EDC.HCl and HOBt in dichloromethane at 0-25°C for 8 to 12h to get *N'*-benzoyl-5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carbohydrazide **4a** in 72% yield after chromatographic separation. Then **4a** was heated to 120°C in presence of $POCl_3$ yielded 2-(5-methyl-1,3-diphenyl-1*H*-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazole **7a** in 64% yield. With this procedure the overall yield of the reaction was 46%. The low yield observed with method A was improved using method B where, the compounds **1**(**a-d**) were treated with NH2NH2 in refluxing EtOH for about 2 to 4h. After the reaction goes to completion (monitored through thin layer chromatography), the compounds **5**(**a-d**) thus obtained were taken for the next step without isolation. In the next step the compounds **5**(**a-d**) were treated with various aryl aldehydes **6**(**a-d**) followed by oxidative cyclization in presence of chloramine-T in refluxing EtOH for 2h yielded the corresponding **7**(**a-m**) in good to excellent yield. Good yield was accompanied with the shorter reaction time and was attributed to the single chemical transformation.

All the synthesized compounds **2a**, **4a**, **5a** and **7**(**a-m**) were tested *in vitro* for their antimicrobial activity against *Bacillus cereus* (MTCC 8372), *Staphylococcus aureus* (MTCC 96), (gram-positive bacteria), *Escheria coli* (MTCC 724), *Klebsiella pneumonia* (MTCC 3384), (gram-negative bacteria) and four fungi *Aspergillus flavus* (MTCC 873), *Aspergillus niger* (MTCC 281), *Fusarium oxysporum* (MTCC 284), *Fusarium monaliforme* (MTCC 156) by disc diffusion[43] and microdilution method.[44] The antibiotic Tetracycline and Nystatin are used as reference antibacterial and antifungal substances, respectively for comparison. In all the determinations tests were performed in six replicate and the results were taken as a mean of at least three determinations.

The results are summarized in Table 1-3. The results revealed that, compounds **7d**, **7f, 7i** and **7l** exhibited good to potent antimicrobial activity. Of the five tested bacterial strains, gram-positive bacteria were inhibited mostly by compounds **7d**, **7l** and **7f** which contains $–NO_2$ and $–OCH_3$ group on the phenyl ring, which in turn is linked to C3 of the pyrazole moiety. While the gram-negative bacteria were inhibited by compound **7j** which contains $–OCH_3$ group on the phenyl ring, which in turn is linked to C5 of the oxadiazole moiety. Compound **7m** showed excellent antimicrobial activity against all the tested strains of microbes this may be due to the presence of $–OCH_3$ group on the phenyl ring of both the pyrazole as well as oxadiazole moieties. In

comparison to the **7m**, the compound **7l** inspite of the presence of $-NO_2$ group on the phenyl ring of both the pyrazole as well as oxadiazole moieties, it inhibits only gram positive bacteria which is approximately same as the one exhibited by **7d**. This may be supported by the fact that, the compound **7i** which contains $-NO_2$ group on the phenyl ring of the oxadiazole moiety do not contribute much to the antimicrobial activity against both the strains. With these above findings we conclude that the presence of $-NO_2$ group on phenyl ring of the oxadiazole moiety is less effective. The compounds **7b**, **7g** and **7k** containing –Cl group were less active against bacterial strains but they possess good antifungal activity. While the compounds **7e** and **7f** showed moderate activity. Except the compound **7k**, the remaining compounds showed less activity against *Fusarium monaliforme*. Out of curiosity the intermediates **2a**, **4a** and **5a** were also tested for their antimicrobial activity. Surprisingly the compound **4a** showed comparable activity with standards but less when compare to 7 as shown in Table 1-3.

In conclusion, we have achieved the synthesis of novel pyrazole integrated 1,3,4-oxadiazoles 7(**a-m**) through an efficient single chemical transformation. All the synthesized compounds **2a**, **4a**, and **5**(**a-d**) have been investigated for their *In vitro* antimicrobial activity. Accordingly, these novel classes of pyrazolyl-1,3,4-oxadiazole analogues presented in our laboratory emerged as a potent antibacterial and antifungal agents. Among the synthesized compounds, compound **7m** showed excellent antimicrobial activity in comparison with standard drug. Hence, it could be a promising drug candidate for microbial infections. The other biological evaluation may render some other important applications. Currently, investigations are underway to understand the mechanism and the results will be reported in due course.

Acknowledgments

Authors are thankful to Dr. K. Yeshoda Nanjappa Assistant Professor in English, Yuvaraja's College, UOM, Mysore for proof reading the manuscript and the Principal, Yuvaraja's College, UOM, Mysore for providing necessary facilities and constant encouragement.

Supplementary Material

Supplementary data (Experimental details, NMR, MS and elementary analysis) associated with this article can be found, in the online version, at

References and notes

1. Tietze, L. F.; Steinmetz, A.; Balkenhohl, F. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303.
2. Grosche, P.; Holtzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis*. **1961**, 1999.
3. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, 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. *J. Med. Chem.* **1997**, *40*, 1347.
4. Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tang, L.; Torcellini, C. *J. Med. Chem.* **2002**, *45*, 2994.
5. Pevarello, P.; Brasca, M. G.; Amici, R.; Orsini, P.; Traquandi, G.; Corti, L.; Piutti, C.; Sansonna, P.; Villa, M.; Pierce, B. S.; Pulici, M.; Giordano, P.; Martina, K.; Fritzen, E. L.; Nugent, R. A.; Casale, E.; Cameron, A.; Ciomei, M.; Roletto, F.; Isacchi, A.; Fogliatto, G.; Pesenti, E.; Pastori, W.; Marsiglio, A.; Leach, K. L.; Clare, P. M.; Fiorentini, F.; Varasi, M.; Vulpetti, A.; Warpehoski, M. A. *J. Med. Chem.* **2004**, *47*, 3367.
6. Hansong, C.; Zhengming, Li.; Yufeng H. *J. Agric. Food Chem.* **2000**, *48*, 5312.
7. Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824.
8. Gang, S.; Pengfei, L.; and Yu Rao. *Org. Lett.* **2011**, *13*, 1746.
9. Strecker, A.; *Justus Liebigs Ann. Chem.* **1850**, *75*, 27.
10. Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
11. Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.
12. Benoit, R.; Daniel, C. *J. Heterocycl. Chem.* **1985**, *22*, 287.
13. Gaonkar, S. L.; Rai, K. M. L.; Prabhuswamy, B. *Eur. J. Med. Chem.* **2006**, *41*, 841.
14. Bhatt, J. J.; Shah, B. R.; Shah, H. P.; Trivedi, P. B. Undavia, N. K.; Desai, N. C. *J. Indian Chem.* **1994**, *33B*, 189.
15. Tan, T. M.; Chen, Y.; Kong, K. H.; Bai, J.; Li, Y.; Lim, S. G.; Ang, T. H.; Lam, Y. *Antivir. Res.* **2006**, *71*, 7.
16. Aboraia, A. S.; Rahman, H. M. A.; Mahfouz, N. M.; Gendy, M. A. *Bioorg. Med. Chem.Lett.* **2006**, *14*, 1236.
17. Namita Soni, J. P.; Barthwal, A. K.; Saxena, K. P.; Bhargava, S. S. *J. Heterocycl. Chem.* **2009**, *19*, 29.
18. Khan, M. T. H.; Choudhary, M. I.; Khan, K. M.; Rani, M.; Atta-ur- Rahman. *Bioorg. Med. Chem.* **2005**, *13*, 3385.
19. Guimaraes, C. R.W.; Boger, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2005**, *127*, 17377.
20. Rahman, V. P. M.; Mukhtar, S.; Ansari, W. H.; Lemiere, G. *Eur. J. Med. Chem.* **2005**, *40*, 173.
21. Peara, S.; Patterson, T. F. *Clin. Infect. Dis.* **2002**, *35*, 1073.
22. Giulia, M.; Luisa, M.; Paola, F.; Silvia, S.; Angelo, R.; Luisa, M.; Francesco, B.; Roberta, L.; Chiara, M.; Valeria, M.; Paolo, L. C.; Elena, T. *Bioorg. Med. Chem.* **2004**, *12*, 5465.
23. Vincent, T. A.; *J. Antimicrob. Chemother.* **1999**, *44*, 151.
24. Aiello, E.; Aiello, S.; Mingoia, F.; Bacchi, A.; Pelizzi, G.; Musiu, C.; Setzu, M. G.; Pani, A.; La Colla, P.; Marongiu, M. E. *Bioorg. Med. Chem.* **2000**, *8*, 2719.
25. El-Gaby, M. S. A.; Atalla, A. A.; Gaber, A. M.; Abd Al-Wahab, K. A. *Farmaco*. **2000**, *55*, 596.
26. Kaymakcioglu, B. K.; Rollas, S. *Farmaco*. **2002**, *57*, 595.
27. Tanitame, A.; Oyamada, Y.; Ofuji, K.; Kyoya, Y.; Suziki, K.; Ito, H.; Kawasaki, M.; Nagai, K.; Wachi, M.; Yamagishi, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2857.
28. Tanitame, A.; Oyamada, Y.; Ofuji, K.; Suziki, K.; Ito, H.; Kawasaki, M.; Wachi, M.; Yamagishi, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2863.
29. Tanitame, A.; Oyamada, Y.; Ofuji, K.; Fujimoto, M. Iwai, N. Hiyama, Y. Suziki, K. Ito, H. Terauchi, H. Kawasaki, M. Nagai, K. Wachi, M. Yamagishi, J. *J. Med. Chem.* **2004**, *47*, 3693.
30. Venkat Ragavan, R.; Vijayakumar, V.; Suchetha Kumari. N. Eur. J. Med. Chem. 2010, 45, 1173.
31. Bekhit, A. A.; Ashour, H. M. A.; Ghany, Y. S. A.; Bekhit, A. E. D. A.; Baraka. A. *Eur. J. Med. Chem.* **2008**, *43*, 456.
32. Ines, V.; Andrea, P. R.; Kata, M. M.; Karmen, B.; Branimir, B. *Bioorg. Med. Chem*, **2012**, *20*, 2101.
33. Vijesh, A. M.; Isloor, A. M.; Shetty, P.; Sundershan, S.; Fun, H. K. *Eur. J. Med. Chem*. **2013**, *62*, 410.
34. Rai, N. P.; Narayanaswamy, V. K., Shashikanth, S.; Arunachalam, P. N. *Eur. J. Med. Chem.* **2009**, *44*, 4522.
35. Prakash, O.; Kumar, M.; Kumar, R.; Sharma, C.; Aneja. K. R.; *Eur. J. Med. Chem.* **2010**, *45*, 4252.
36. Puthiyapurayil, P.; Poojary, B.; Chikkanna, C.; Buridipad. S. K. *Eur. J. Med. Chem.* **2012**, *53*, 203.
37. Abu-Zaied, M. A.; El-Telbani, E. M.; Elgemeie, G. H.; Nawwar. G. A. M. *Eur. J. Med. Chem.* **2011**, *46*, 229.
38. Hong-Shui L.; Bao-Xiang, Z.; Ji-Kun, L.; Young, X.; Song, L.; Wei-Young, L.; Zhong-Liang, G. *Dyes and Pigments*. **2010**, *86*, 25.
39. Hong-Shui, L.; Yong-Sheng, X.; Wei-Yong, L.; Zhong-Liang, Gong.; Bao-Xiang, Zhao.; *J Fluoresc.* **2011**, 21, 1797.
40. Horrocks, P.; Pickard, M. R.; Parekh, H.; Patel, S. P.; Ravindra, B.P. *Org. Biomol. Chem.*, **2013**, *11*, 4891.
41. Ningaiah, S.; Bhadraiah, U. K.; Keshavamurthy, S.; Javarasetty, C. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4532.
42. Umesha, K. B.; Rai, K. M. L.; *Bulg. Chem. Commun*, **2010**, *42*,11.
43. Andrews, J. M.; BSAC Working Party on Susceptibility Testing *J. Antimicrob. Chemother*. **2008**, *62*, 256.
44. Zgoda, J. R.; Porter, J. R.; *Pharmaceutical Biology*. **2001**, *39*, 221.

Tables

Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation

Srikantamurthy Ningaiah[a], Umesha K. Bhadraiah[a,*], Shridevi D. Doddaramappa[b], Shubakara Keshavamurthy[a] and Chethan Javarasetty[c]

[a] *Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore-570 005.*
[b]*Department of Studies in Chemistry, Manasagangotri, University of Mysore,*
[c]*Department of Biotechnology, Manasagangotri, University of Mysore, Mysore-570 006. India.*

Table 1. Inhibitory zone (diameter) mm of synthesized compounds against tested bacterial strains

Compounds	Ar^1	Ar^2	Antibacterial activity							
			Gram positive				Gram negative			
			B. cereus		*S. aureus*		*E. coli*		*K. pneumonia*	
			50 µg/ml ± SD	**100** µg/ml ± SD	**50** µg/ml ± SD	**100** µg/ml ± SD	**50** µg/ml ± SD	**100** µg/ml ± SD	**50** µg/ml ± SD	**100** µg/ml ± SD
2a	C_6H_5	C_6H_5	04 ± 0.11	08 ± 0.23	02 ± 0.03	08 ± 0.26	03 ± 0.05	08 ± 0.18	04± 0.11	06 ± 0.09
4a	C_6H_5	C_6H_5	08 ± 0.16	16 ± 0.17	06 ± 0.18	18 ± 0.11	13 ± 0.15	18 ± 0.10	08± 0.21	14 ± 0.03
5a	C_6H_5	C_6H_5	04 ± 0.12	06 ± 0.20	02 ± 0.12	09 ± 0.15	09 ± 0.13	11 ± 0.11	05± 0.09	08 ± 0.08
7a	C_6H_5	C_6H_5	05 ± 0.03	09 ± 0.20	06 ± 0.11	07 ± 0.13	05 ± 0.04	06 ± 0.10	06 ± 0.30	14 ± 0.18
7b	4–Cl–C_6H_4	C_6H_5	06 ± 0.11	10 ± 0.11	05 ± 0.16	10 ± 0.13	11 ± 0.11	18 ± 0.23	05± 0.10	09 ± 0.13
7c	4–OCH_3–C_6H_4	C_6H_5	04 ± 0.09	09 ± 0.25	04 ± 0.17	08 ± 0.24	08 ± 0.25	14 ± 0.12	04 ± 0.11	09 ± 0.19
7d	4–NO_2–C_6H_4	C_6H_5	14 ± 0.10	20 ± 0.21	10 ± 0.13	18 ± 0.06	09 ± 0.23	18 ± 0.09	09 ± 0.52	12 ± 0.18
7e	3,4–$(OCH_3)_2$–C_6H_3	C_6H_5	08 ± 0.15	16 ± 0.11	06 ± 0.22	13 ± 0.17	14 ± 0.11	20 ± 0.12	06 ± 0.18	09 ± 0.15
7f	3,4,5–$(OCH_3)_3$–C_6H_2	C_6H_5	11 ± 0.03	22 ± 0.10	10 ± 0.04	26 ± 0.10	12 ± 0.15	17 ± 0.12	06 ± 0.11	10 ± 0.12
7g	C_6H_5	4–Cl–C_6H_4	04 ± 0.11	08 ± 0.13	05 ± 0.45	10 ± 0.10	10 ± 0.11	12 ± 0.12	06 ± 0.10	12 ± 0.21
7h	C_6H_5	4–OCH_3–C_6H_4	05 ± 0.15	12 ± 0.19	06 ± 0.26	12 ± 0.20	08 ± 0.32	12 ± 0.13	09 ± 0.12	11 ± 0.22
7i	C_6H_5	4–NO_2–C_6H_4	06 ± 0.18	14 ± 0.08	05± 0.12	10 ± 0.22	11 ± 0.18	20 ± 0.17	07 ± 0.22	10 ± 0.11
7j	C_6H_5	3,4,5–$(OCH_3)_3$–C_6H_2	04 ± 0.11	13 ± 0.22	05 ± 0.19	12 ± 0.14	20± 0.22	32 ± 0.19	10 ± 0.25	20 ± 0.18
7k	4–Cl–C_6H_4	4–Cl–C_6H_4	06 ± 0.06	10 ± 0.10	06 ± 0.35	12 ± 0.10	10 ± 0.20	16 ± 0.11	08 ± 0.31	11 ± 0.11

* Corresponding author Tel.: +91 0821-2420398 E-mail address: kbu68umesha@rediffmail.com (U.K.B).

7l	4–NO_2–C_6H_4	4–NO_2–C_6H_4	14 ± 0.18	22 ± 0.08	12 ± 0.12	20 ± 0.22	12 ± 0.15	22 ± 0.17	08 ± 0.40	16 ± 0.16
7m	3,4,5–$(OCH_3)_3$–C_6H_2	3,4,5–$(OCH_3)_3$–C_6H_2	12 ± 0.08	23 ± 0.06	10 ± 0.10	24 ± 0.11	21 ± 0.11	36 ± 0.12	11 ± 0.17	21 ± 0.21
Tetracycline			10 ± 0.07	21± 0.11	09 ± 0.11	20 ± 0.10	18 ± 0.14	30 ± 0.16	12 ± 0.12	20 ± 0.19

[a] Zone of inhibition (Mean six replicate ± standard deviation).

Table 2. Inhibitory zone (diameter) mm of synthesized compounds against tested fungal strains

Compounds	**Antifungal activity**							
	A. flavus		***A. niger***		***F oxysporum***		***F monaliforme***	
	50 µg/ml ± SD	**100** µg/ml ± SD	**50** µg/ml ± SD	**100** µg/ml ± SD	**50** µg/ml ± SD	**100** µg/ml ± SD	**50** µg/ml ± SD	**100** µg/ml ± SD
2a	05± 0.12	08 ± 0.13	04 ± 0.15	06± 0.18	03 ± 0.11	05 ± 0.13	06± 0.20	05 ± 0.13
4a	10 ± 0.11	12 ± 0.21	08 ± 0.16	14 ± 0.13	08 ± 0.18	10 ± 0.16	06± 0.28	09 ± 0.09
5a	02 ± 0.17	06 ± 0.22	02 ± 0.18	08 ± 0.16	03 ± 0.15	08 ± 0.12	04± 0.22	06 ± 0.38
7a	04 ± 0.13	08 ± 0.27	05 ± 0.13	08 ± 0.16	03 ± 0.16	08 ± 0.17	04± 0.22	06 ± 0.08
7b	06 ± 0.11	10 ± 0.12	08 ± 0.16	10 ± 0.17	14 ± 0.17	22 ± 0.23	05± 0.17	08 ± 0.11
7c	02 ± 0.19	08 ± 0.25	02 ± 0.11	06 ± 0.28	04 ± 0.21	06 ± 0.22	03 ± 0.13	06 ± 0.19
7d	06 ± 0.12	14 ± 0.21	08 ± 0.13	12 ± 0.16	08 ± 0.23	10 ± 0.09	05 ± 0.51	14 ± 0.18
7e	05 ± 0.05	08 ± 0.18	03 ± 0.22	11 ± 0.17	15 ± 0.17	24 ± 0.11	06 ± 0.15	08 ± 0.13
7f	06 ± 0.09	12 ± 0.12	10 ± 0.04	20 ± 0.19	08 ± 0.15	10 ± 0.14	05 ± 0.13	10 ± 0.12
7g	14 ± 0.11	16 ± 0.13	09 ± 0.42	24 ± 0.10	04 ± 0.11	08 ± 0.18	06 ± 0.10	08 ± 0.23
7h	08 ± 0.12	14 ± 0.12	06 ± 0.35	12 ± 0.20	08 ± 0.20	12 ± 0.13	09 ± 0.18	11 ± 0.26
7i	03 ± 0.18	12 ± 0.17	02 ± 0.52	11 ± 0.41	06 ± 0.18	08 ± 0.28	06 ± 0.33	08 ± 0.22
7j	04 ± 0.15	13 ± 0.21	05 ± 0.19	12 ± 0.12	08 ± 0.22	10 ± 0.12	07 ± 0.25	10 ± 0.13
7k	14 ± 0.06	18 ± 0.21	14 ± 0.35	26 ± 0.10	15 ± 0.20	28 ± 0.11	10 ± 0.33	19 ± 0.11
7l	08 ± 0.08	11 ± 0.14	06 ± 0.22	14 ± 0.16	08 ± 0.15	16 ± 0.12	08 ± 0.40	18 ± 0.16
7m	18 ± 0.13	23 ± 0.02	11 ± 0.45	25 ± 0.14	14 ± 0.11	21 ± 0.12	12 ± 0.17	22 ± 0.21
Nystatin	16 ± 0.07	20 ± 0.10	10 ± 0.05	25 ± 0.12	16 ± 0.04	30 ± 0.06	12 ± 0.18	28 ± 0.09

[a] Zone of inhibition (Mean six replicate ± standard deviation).

Table 3. The minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and minimal fungicidal concentration (MFC) in µg/mL of synthesized compounds against tested strains

Compounds	Antibacterial activity								Antifungal activity							
	Gram positive				Gram negative											
	B. cereus		*S. aureus*		*E. coli*		*K. pneumonia*		*A. flavus*		*A. niger*		*F. oxysporum*		*F. monaliforme*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
2a	30	250	40	250	35	280	30	240	55	300	50	280	55	295	45	270
4a	25	180	25	200	25	190	25	200	50	275	30	215	40	260	50	260
5a	40	260	40	250	35	240	35	230	40	275	45	260	45	270	50	280
7a	35	230	35	240	40	260	30	220	40	280	45	270	50	275	55	290
7b	40	240	50	250	40	250	50	250	50	275	50	275	30	215	40	270
7c	50	240	40	240	35	240	35	260	50	270	45	275	40	280	40	290
7d	20	150	20	150	25	190	25	180	50	290	40	290	40	280	45	275
7e	35	230	40	235	35	220	35	250	45	275	40	275	25	220	55	290
7f	20	160	20	155	25	170	25	175	45	275	30	220	40	290	55	300
7g	40	240	45	250	35	235	30	220	30	230	25	215	40	275	55	300
7h	35	220	35	225	45	235	45	240	45	270	45	275	50	280	50	290
7i	25	200	25	190	25	180	25	185	55	290	45	280	40	275	50	290
7j	35	230	40	250	20	150	20	160	45	275	40	275	40	275	55	300
7k	40	260	40	250	45	245	50	250	25	210	30	220	30	215	25	215
7l	20	160	20	155	25	175	25	170	40	275	45	275	50	280	55	290
7m	20	160	20	150	20	150	20	155	30	215	25	225	25	220	25	225
Tetracycline	4	120	10	120	12	120	8	120	---	---	---	---	---	---	---	---
Nystatin	---	---	---	---	---	---	---	---	08	100	10	100	15	100	12	100

[a] (Mean six replicate ± standard deviation).

Figure and Scheme

Synthesis, characterization and antimicrobial evaluation of novel pyrazole integrated 1,3,4-oxadiazoles

Ningaiah Srikantamurthy[a], Kumbarandoddi B. Umesha[a,*], Keshavamurthy Shubakara[a] and Javarasetty Chethan[b]

[a] *Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore-570 005.*

[b]*Department of Biotechnology, Manasagangotri, University of Mysore, Mysore-570 005. India.*

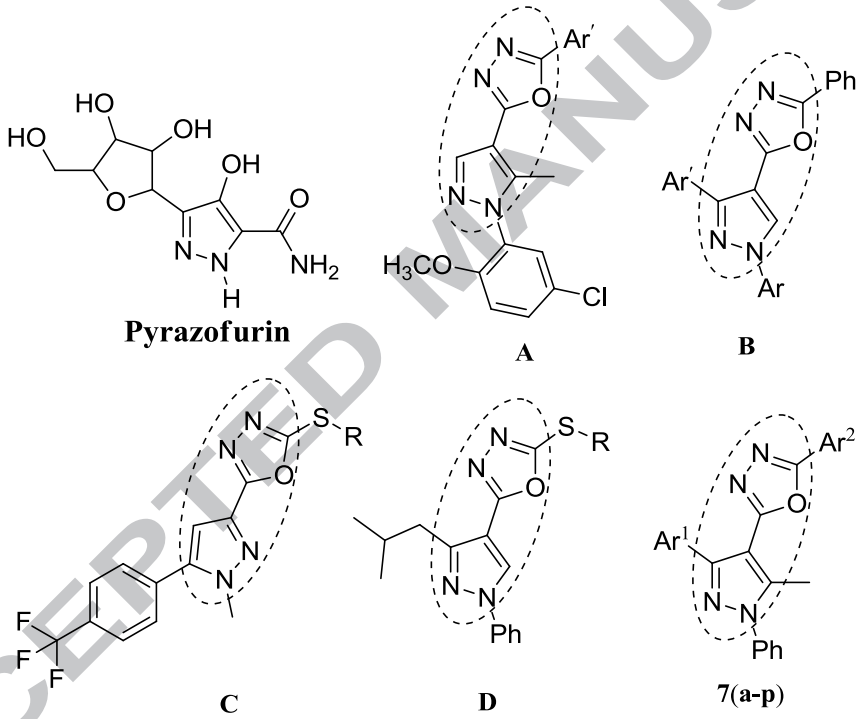
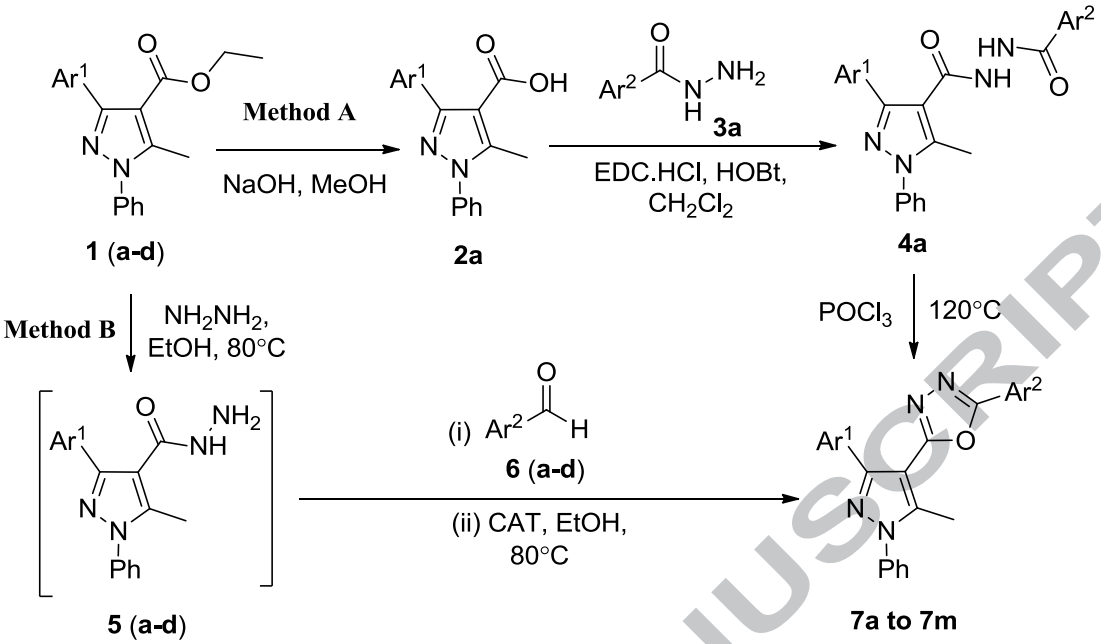


Fig. 1 Structures of Pyrazofurin and reported active pyrazolyl-1,3,4-oxadiazoles **A**, **B**, **C, D** and **7(a-p)**

* Corresponding author. Tel.: +91 9480477620; fax: +91-821- 2419292; e-mail: kbu68umesha@rediffmail.com (KBU), orgchemsri@gmail.com (NS).



Scheme 1 Synthesis of pyrazole integrated 1,3,4-oxadiazoles

Graphical Abstract

Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation

Leave this area blank for abstract info.

Srikantamurthy Ningaiah[a], Umesha K. Bhadraiah[a,*], Shridevi D. Doddaramappa[b], Shubakara Keshavamurthy[a] and Chethan Javarasetty[c]

[a]*Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore570005,*
[b]*Department of Studies in Chemistry, Manasagangotri, University of Mysore,*
[c]*Department of Biotechnology, Manasagangotri, University of Mysore, Mysore-570 006. India*