Accepted Manuscript

1*H*-1,2,3-Triazolyl-substituted 1,3,4-oxadiazole derivatives containing structural features of ibuprofen / naproxen: their synthesis and antibacterial evaluation

Papigani Neeraja, Suryapeta Srinivas, Khagga Mukkanti, Pramod Kumar Dubey, Sarbani Pal

PII: S0960-894X(16)31008-3
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.09.059
Reference: BMCL 24283

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 14 August 2016
Revised Date: 21 September 2016
Accepted Date: 24 September 2016

Please cite this article as: Neeraja, P., Srinivas, S., Mukkanti, K., Dubey, P.K., Pal, S., 1*H*-1,2,3-Triazolyl-substituted 1,3,4-oxadiazole derivatives containing structural features of ibuprofen / naproxen: their synthesis and antibacterial evaluation, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.09.059

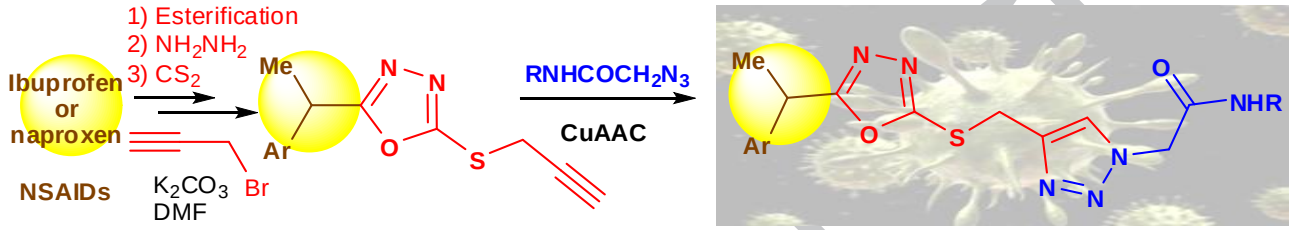
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

1*H*-1,2,3-Triazolyl-substituted 1,3,4-oxadiazole derivatives containing structural features of ibuprofen / naproxen: their synthesis and antibacterial evaluation

Leave this area blank for abstract info.

Papigani Neeraja, Suryapeta Srinivas, Khagga Mukkanti, Pramod Kumar Dubey, and Sarbani Pal*



20 examples, 60-85% yields

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

1*H*-1,2,3-Triazolyl-substituted 1,3,4-oxadiazole derivatives containing structural features of ibuprofen / naproxen: their synthesis and antibacterial evaluation

Papigani Neeraja,[a] Suryapeta Srinivas,[b] Khagga Mukkanti,[c] Pramod Kumar Dubey,[d] and Sarbani Pal[e,*]

[a]*Department of Chemistry, DVR College of Engineering & Technology, Kashipur village, Medak District, Telangana- 502285, India*
[b]*BIOCON LTD, Plot No 213, 214 & 215, IDA phase-2 , Pashamylaram, Medak(dist),Telangana-502307, India*
[c]*Centre for Chemical Sciences and Technology, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500085, India*
[d]*Department of Medicinal Chemistry, NIPER, Hyderabad- 500037, India*
[e]*Department of Chemistry, MNR Degree & PG College, Kukatpally, Hyderabad-500085, India*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Ibuprofen
Naproxen
1,2,3-Triazole
Azide
Alkyne
Antibacterial activity

ABSTRACT

1*H*-1,2,3-Triazolyl-substituted 1,3,4-oxadiazole derivatives containing structural features of ibuprofen / naproxen were synthesized for the first time using a Cu catalyzed azide–alkyne cycloaddition (CuAAC) strategy. An optimized reaction condition was established for this purpose and twenty new compounds were synthesized using this methodology. Several of these compounds showed good to reasonable antibacterial activities when tested against three gram-positive and three gram-negative species. The compound **4m** i.e. *N*-(2-chlorophenyl)-2-(4-((5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazol-2-ylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide showed promising activities across both the species.

Various life-threatening diseases related to bacterial infections have reached an alarming level in many countries around the world and therefore there is a pressing need for the discovery of new drugs. In this context, the earlier reports on the role of microorganisms in arthritis[1-5] and suggested administration of antibiotics to patients suffering from rheumatoid arthritis[6-11] attracted our particular attention. Additionally, studies indicated that some of the commonly used NSAIDs that fight pain, fever, and inflammation may have the ability to kill bacteria as well.[12,13] In light of all these reports we wondered if the incorporation of structural features of some of the well known NSAIDs (nonsteroidal anti-inflammatory drugs) into NCEs (new chemical entities) designed as antibacterial agents would be beneficial for the potential treatment of rheumatoid arthritis. We therefore designed and synthesized a series of novel substances possessing this type of hybrid chemical structures for their initial evaluation as new antibacterial agents.

Combining the 1,2,3-triazole moiety with substituted 1,3,4-oxadiazole[14] in a single molecule leading to the identification of interesting antibacterial agents is known in the literature.[15] Indeed, most of these compounds (e.g. **A**, Fig. 1) were found to

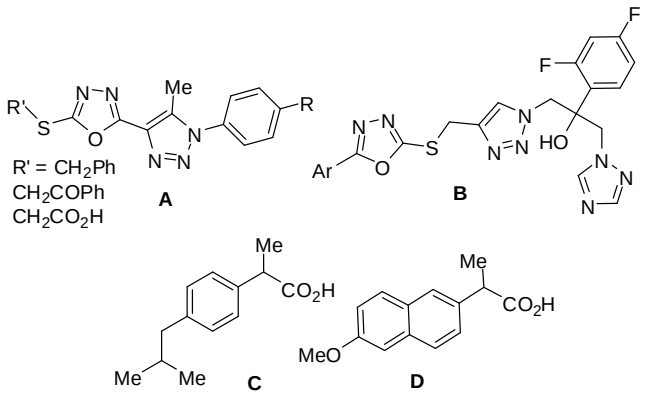


Fig. 1. Known 1,2,3-triazolyl oxadiazoles (**A** and **B**), ibuprofen (**C**) and naproxen (**D**).

be effective against *E. coli*, *P. aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus* in primary antibacterial activity tests. Additionally, the fluconazole analogues bearing 1,3,4-oxadiazole moiety (e.g. **B**, Fig. 1) have been reported as potent antifungal agents.[16] The antimicrobial activity of ibuprofen (**C**, Fig. 1) on the other hand is also known in the literature.[13] The study indicated that ibuprofen may be responsible for the broad spectrum of antimicrobial activity as inhibition zones were obtained for *B. subtilis*, *S. aureus*, *Candida albicans*, and *Aspergillus brasiliensis* in the disk diffusion assay. The

* Corresponding author: Tel.: +91 40 23041488; fax: -----

E-mail address: sarbani277@yahoo.com (S. Pal)

antimicrobial activity of other NSAIDs has also been reported[17] most of which including naproxen (**D**, Fig. 1) showing activity against *S. aureus*, one of the important microorganisms in infections.[18] The commonality in antibacterial activities of **A** with **C** particularly against *B. subtilis* and *S. aureus* prompted us to design a template (**E**, Fig. 2) integrating the structural features of **A** and **C** into a single molecular entity. The design of **E** was further encouraged by the similar structural features of **B** that also contains a 2-[(1,2,3-triazol-4-yl)methylthio]-1,3,4-oxadiazole moiety as the key framework.

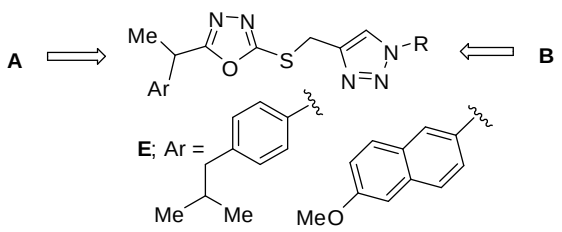
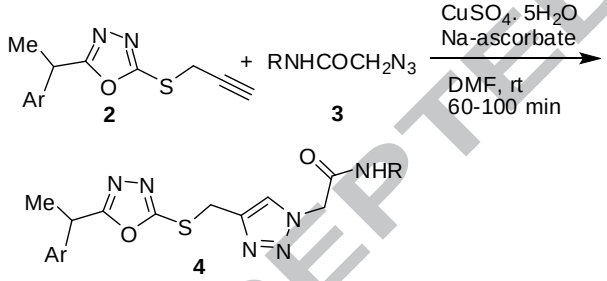


Fig.2. New template (**E**) for the generation of potential antimicrobial agents.

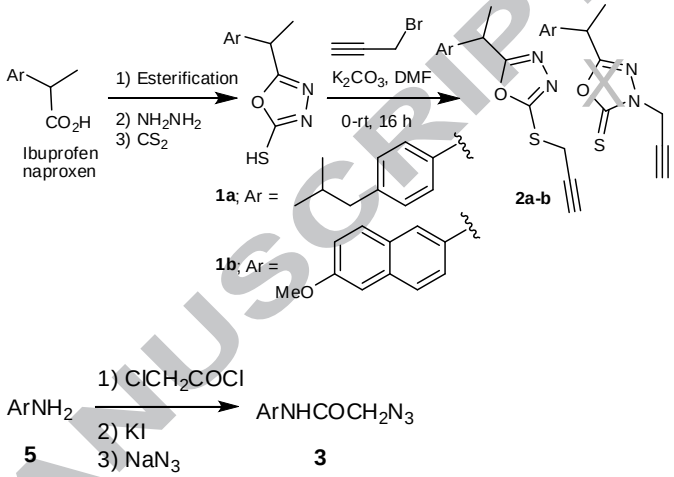
The structural features of **D** were also considered in the present design to introduce further diversity into the template **E** (Fig. 2). The new template **E** was used to generate a library of molecules that were evaluated for their antibacterial activities *in vitro*. Herein, we report our preliminary results of this study. Our objective was not only to achieve a rapid synthesis of compounds based on **D** but also to establish mild and environmentally benign reaction conditions leading to these 1,2,3-triazolyl oxadiazoles. Thus Cu(I)-catalyzed alkyne-azide click reaction (CuAAC) of **2** with **3** was explored for this purpose which finally afforded the desired product **D** (or **4**, Scheme 1).



Scheme 1. Preparation of compound **4** *via* CuAAC of **2** with **3**.

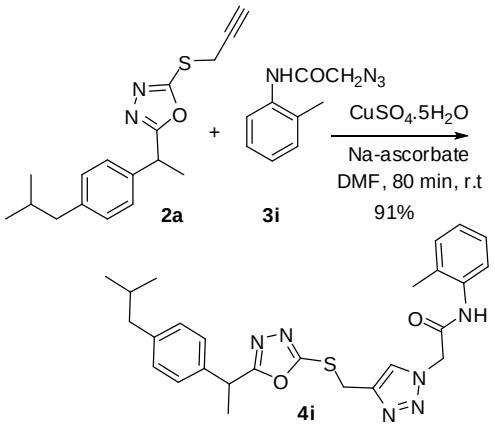
The Cu(I)-catalyzed alkyne-azide click reaction (CuAAC) has been widely accepted as the most efficient method for the preparation of 1,2,3-triazole derivatives. Initially the 1,3-dipolar cycloaddition reaction of azides and alkynes was studied by Huisgen and co-workers.[19,20] The uncatalyzed reaction was found to afford mixtures of 1,4- and 1,5-triazole regioisomers and use of high temperature was necessary. Later, the CuAAC reported at the same time by Meldal et al[21] as well as Fokin and Sharpless afforded 1,4-disubstituted 1,2,3-triazoles exclusively.[22a] Termed as "click chemistry" the CuAAC was established as a functional group tolerant and powerful method in organic synthesis.[22b-25] The reaction generally involves *in situ* generation of the required Cu(I) catalyst *via* the reduction of a Cu(II) salt with Na-ascorbate. We adopted this methodology[26-28] for the preparation of our target compounds based on **D** (or **4**, Scheme 1).

The synthesis of both the starting compounds i.e. alkyne **2** and azide **3** was undertaken following a multi-step sequence as shown in Scheme 2. The esterification of commercially available racemic ibuprofen or (*S*)-naproxen followed by acid hydrazide formation and finally reaction with CS_2 and KOH afforded the corresponding oxadiazole (**1a,b**).[29] The reaction of **1a,b** with propargyl bromide gave the corresponding *S*-propargylated products **2a,b**. Notably the propargylation step was found to be highly regioselective for *S*-propargylation as no *N*-propargylated product was formed during the reaction (Scheme 2). This was supported by the fact that the -CH_2- group of **2a** and **2b** appeared at δ 4.4 and 20.4 in ^{1}H and ^{13}C NMR spectra respectively (a higher value was expected for the –NCH_2- group). The other starting compound i.e. azide **3** was synthesized from the corresponding aromatic amines (**5**) *via* the reaction with 2-chloroacetyl chloride followed by treatment with KI finally with sodium azide (Scheme 2) according to the literature procedure.[30]



Scheme 2. Preparation of alkyne **2** and azide **3**

Initially, the feasibility of CuAAC leading to the target compound was examined using a model reaction of **2a** with **3i**. The compound **2a** (1 mmol) was treated with the azide **3i** (1 mmol) in dry DMF (3 mL) at room temperature in presence of the pre-catalytic system $CuSO_4$•$5H_2O$ (0.25 mmol) and Na-ascorbate (0.25 mmol). The reaction proceeded well under this condition to afford target compound **4i** (Scheme 3) in 91% yield. The compound **4i** was characterized by NMR, Mass and IR spectra. The appearance of a singlet at δ 5.11 in ^{1}H NMR spectrum (Fig. 3) was due to the –CH_2- group attached to the triazole nitrogen whereas the –SCH_2- moiety appeared at δ 4.47. The C-5 proton of triazole ring appeared at δ 7.19. The presence of three –CH_2- (aliphatic) groups was further supported by the appearance of three ^{13}C signals at 51.5, 44.1, and 36.9 ppm. The presence of amidic carbonyl carbon atoms was supported by the ^{13}C signal at 170.1 ppm in the corresponding spectra. Having prepared **4i** in good yield we then focused on optimizing the amount of catalyst used. Accordingly, the above reaction was performed using a particular concentration of alkyne **2a** and azide **3i** i.e. 1 mmol each in DMF with the varying amount of $CuSO_4$•$5H_2O$ and Na-ascorbate (Table 1). It is evident from Table 1 that conditions of entry 4 and 5 were more attractive compared to others. Indeed, the use of lower quantity of $CuSO_4$•$5H_2O$ and Na-ascorbate (less than 0.20 mmol each) not only increased the reaction time considerably but also did not allow the reaction to reach completion within this time period (entries 6 and 7, Table 1). The yield of **4i** was also decreased with the further decrease of catalyst quantity (entry 8, Table 1). While all these reactions were performed in dry DMF the use of aqueous DMF or PEG 400 was found to be less effective. Nevertheless, on balance we preferred entry 5 over 4 as lower quantity of catalyst was used in this case. Thus the preferred condition involved the use of azide: $CuSO_4$•$5H_2O$: Na-ascorbate in the ratio of 1: 0.20: 0.20 and was used for the synthesis of other analogues of **4i**.



Scheme 3. CuAAC of alkyne **2a** with azide **3i** leading to product **4i**

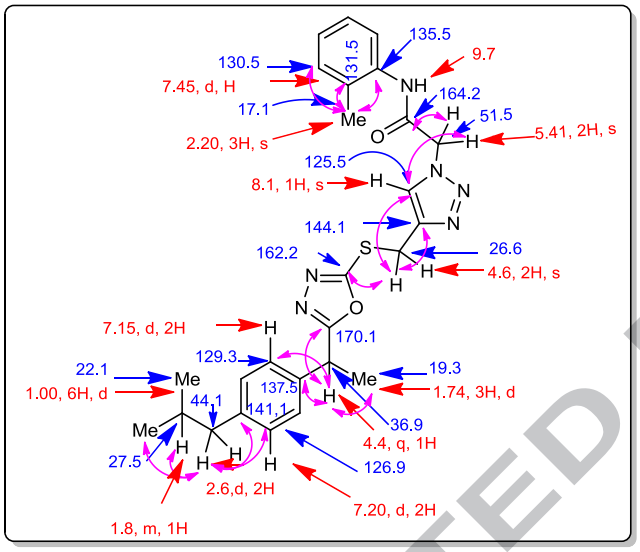


Fig. 3. [1]HNMR (red), [13]CNMR (blue) signals and HMBC cross peaks (pink arrows) observed in the 1D & 2D NMR spectra of **4i**.

Table 1: The effect of varying concentrations of CuSO4•5H2O and Na-ascorbate on the reaction of **2a** (1 mmol) with **3i** (1 mmol).[a]

Entry	$CuSO_4.5H_2O$ (mmol)	Na-ascorbate (mmol)	Time (min)	Yield (%)[b]
1	1	1	60	92
2	0.5	0.5	60	90
3	0.4	0.4	70	92
4	0.25	0.25	80	91
5	0.20	0.20	90	90
6	0.15	0.15	240[c]	77
7	0.10	0.10	240[c]	61
8	0.05	0.05	240[c,d]	39

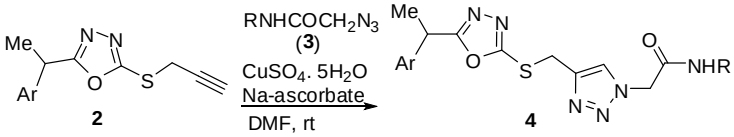
[a]Reaction conditions: the reactions were carried out using the alkyne **2a** (1.0 mmol), azide **3i** (1.0 mmol), $CuSO_4$•$5H_2O$, and Na-ascorbate in DMF (3 mL) at room temp.

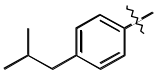
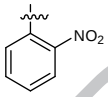
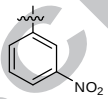
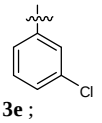
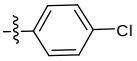
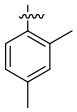
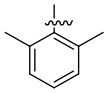
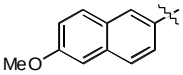
[b]Isolated yield.

[c]The reaction was not completed.

[d]Formation of two regioisomeric products observed after 25 min.

Table 2: Synthesis of compound **4** *via* CuAAC of **2** with **3**.[a]



Entry	2; Ar =	3; R =	Time (min)	Product (4)	Yield[b] (%)
1	**2a;** 	**3a;** 	60	**4a**	85
2	**2a**	**3b;** 	90	**4b**	80
3	**2a**	**3c;** 	100	**4c**	83
4	**2a**	**3d;** 	90	**4d**	65
5	**2a**	**3e ;** 	90	**4e**	70
6	**2a**	**3f;** 	60	**4f**	75
7	**2a**	**3g;** 	70	**4g**	73
8	**2a**	**3h**; Ph	90	**4h**	85
9	**2a**	**3i;** 	60	**4i**	90
10	**2a**	**3j**[c]	90	**4j**	85
11	**2b** 	**3a**	60	**4k**	85
12	**2b**	**3b**	90	**4l**	85
13	**2b**	**3c**	90	**4m**	75
14	**2b**	**3d**	60	**4n**	70
15	**2b**	**3e**	60	**4o**	80
16	**2b**	**3f**	60	**4p**	80
17	**2b**	**3g**	90	**4q**	65
18	**2b**	**3h**	80	**4r**	70
19	**2b**	**3i**	60	**4s**	85
20	**2b**	**3j**[c]	90	**4t**	60

[a]Reaction conditions: the reactions were carried out using the alkyne **2** (1.0 mmol), the azide **3** (1.0 mmol), $CuSO_4$•$5H_2O$ (0.20 mmol), Na-ascorbate (0.20 mmol), in DMF (3 mL) at room temp.

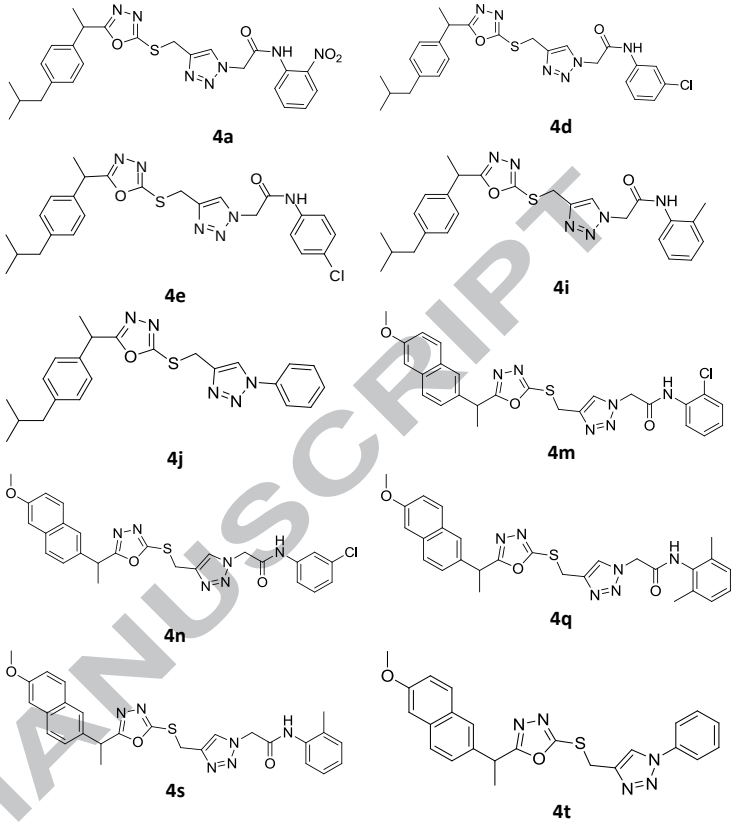
[b]Isolated yield (average of three repeated reactions).

[c]PhN_3(**3j**) was used in place of $RNHCOCH_2N_3$

A range of compounds were prepared by using the optimized reaction conditions (Table 2, see also Table S-1 in Supp data file). While alkynes e.g. **2a** and **2b** obtained from both ibuprofen and naproxen were used for this purpose a wide verity of azides e.g. **3a-j** were employed in these reactions. The reaction proceeded well in all these cases affording the corresponding desired products in good yields (yields presented are the average of three repeated reactions). It appeared that electron donating groups at *o*- and *p*- position of benzene ring attached to the amide side chain facilitated the reaction with shorter reaction time (entry 5, 6, 7, 9, 13, 15, 16, 17 and 19 of Table 2). However, yields were not affected greatly by the nature and position of the substitutional group(s) attached to the basic framework of product **4**, i.e. the 2-[(1,2,3-triazol-4-yl)methylthio]-1,3,4-oxadiazole moiety. Notably, the lowest yield (65%) of product was obtained in case of entry 4 and 17 (Table 2) where a *m*-chlorophenyl and *o*,*o*-dimethylphenyl group was attached to the amide side chain, respectively. Nevertheless, all the synthesized compounds, found to be completely soluble in DMSO and EtOH but sparingly soluble in water were characterized by NMR, IR and Mass spectra.[31]

The reported role of microorganisms in arthritis and suggested administration of antibiotics to patients suffering from rheumatoid arthritis prompted us to devise a new strategy for the design of novel antibacterial agents. Accordingly, oxadiazole substituted 1,2,3-triazole derivatives containing structural features of ibuprofen / naproxen, were designed and synthesized. All these compounds were then evaluated for their antibacterial properties against six strains of bacterial microorganisms including three gram-positive e.g. *Staphylococcus aureus*, *B. Subtilis* and *Staphylococcus epidermidis*, and three gram-negative species e.g. *Pseudomonas Aeruginosa*, *K. pneumonia* and *Escherichia coli*. An agar-well diffusion method was employed for the evaluation of antibacterial activity of test compounds.[32,33] Amikacin, a broad spectrum antibiotic that is active against several gram positive and gram negative bacteria was used at a concentration of 0.05 mg/50 µL as a positive reference to determine the sensitivity of microorganisms tested. DMSO was used as a negative control. After overnight incubation at 37 ºC the diameter of inhibition zone (DIZ) around each well caused by the 50 µL of test sample (0.5 mg / 50 µL concentration of test compound) was measured in mm to determine the activity of that compound and compared with the reference compound. The results obtained for active compounds are summarized in Table 3, 4 and Fig 4. While most of the compounds showed moderate to reasonable activities against all strains, compounds **4d**, **4e**, **4m** and **4t** against *S. aureus* (gram positive species), **4e, 4m, 4n** and **4q** against *B. Subtilis*, **4e, 4m, 4s** and **4t** against *Staphylococcus epidermidis*, **4d, 4e, 4i, 4m** and **4s** against *P. Aeruginosa*, **4e** against *E. coli* and **4e** and **4m** against *K. pneumonia* were found to be notable. Indeed, the compound **4m** was identified as the most interesting among these compounds as it showed activities against almost all the species. In general, the present class of oxadiazole substituted 1,2,3-triazole derivatives containing structural features of ibuprofen / naproxen appeared to be effective against both gram positive and gram negative bacteria and therefore are of further medicinal interest.

Table 3. Antibacterial activities of compound **4** against Gram positive bacteria



Compound	Zone of inhibition (mm)		
	S. aureus	*B. subtilis*	*Staphylococcus epidermidis*
4a	11±0.2	10±0.4	10±0.1
4d	14±0.4	12±0.3	13±0.3
4e	11±0.2	16±0.3	15±0.3
4i	13±0.1	11±0.3	13±0.1
4j	10±0.3	11±0.1	09±0.3
4m	15±0.1	15±0.4	16±0.3
4n	12±0.4	14±0.2	11±0.1
4q	13±0.4	15±0.3	12±0.3
4s	13±0.3	12±0.3	15±0.2
4t	14±0.1	14±0.4	15±0.3
Control (DMSO)	00	00	00
Amikacin	23	ND	ND

ND = not determined.

Table 4. Antibacterial activities of compound **4** against Gram negative bacteria

Compound	Zone of inhibition (mm)		
	P. aeruginosa	*E. coli*	*K. pneumonia*
4a	09±0.3	11±0.1	09±0.1
4d	15±0.1	12±0.3	11±0.2
4e	14±0.2	15±0.4	15±0.3
4i	14±0.3	13±0.3	13±0.1
4j	11±0.4	10±0.2	10±0.3
4m	14±0.3	13±0.3	14±0.4
4n	13±0.1	12±0.3	10±0.3
4q	11±0.3	11±0.3	09±0.3
4s	14±0.2	10±0.1	13±0.3
4t	12±0.3	13±0.2	12±0.3

Control (DMSO)	00	00	00
Amikacin	22	20	23

ND = not determined.

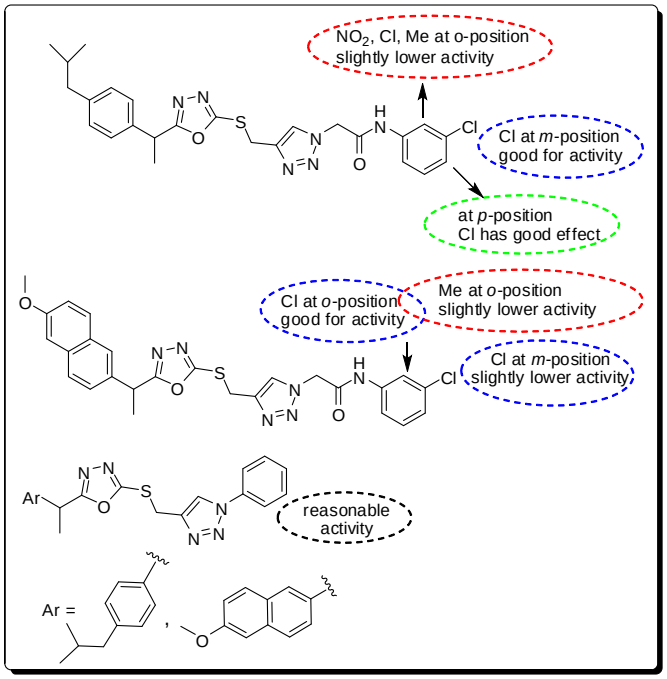


Fig 4. SAR summary of compound **4** tested.

In conclusion, novel 1*H*-1,2,3-triazolyl-substituted 1,3,4-oxadiazole derivatives containing structural features of ibuprofen / naproxen were designed and synthesized as potential antibacterial agents. The design of this class of compounds was prompted by the reported role of microorganisms in arthritis and suggested administration of antibiotics to patients suffering from rheumatoid arthritis. These compounds were prepared for the first time using a Cu catalyzed azide–alkyne cycloaddition (CuAAC) strategy. Well known NSAIDs e.g. ibuprofen and naproxen were used to prepare the respective alkyne required for the CuAAC with an appropriate azide. An optimized reaction condition was established for this step and twenty new compounds were synthesized using this methodology. Several of these compounds showed good to reasonable antibacterial activities when tested against three gram-positive e.g. *Staphylococcus aureus*, *B. Subtilis* and *Staphylococcus epidermidis*, and three gram-negative species e.g. *Pseudomonas Aeruginosa*, *K. pneumonia* and *Escherichia coli*. The compound **4m** i.e. 2-(4-((5-(1-(4-isobutylphenyl)ethyl)-1,3,4-oxadiazol-2-ylthio)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-nitrophenyl)acetamide was found to be promising among them. Thus the present strategy on identification of new antibacterial agents *via* incorporating the structural features of NSAIDs appeared to be unique and may pave the way for discovery of new and potential drugs targeting rheumatoid arthritis.

Acknowledgements

SP thanks Mr. M. N. Raju, the chairman of M. N. R. Educational Trust for his constant encouragement and CFRD, Osmania University, Hyderabad for recording spectra.

.

References and notes

1. Midtvedt, T., *Scand. J. Rheumatol. Suppl.* **1987**, *64*, 49.
2. Aoki, S., Yoshikawa, K., Yokoyama, T., Nonogaki, T., Iwasaki, S., Mitsui, T., Niwa, S., *Ann. Rheum. Dis.* **1996**, *55*, 363.
3. Krause, A., Karadt, T., Burmester, G.R., *Curr. Opin. Rheumatol.* **1996**, *8*, 203.
4. Stephenson, J., *J. Am. Med. Assoc.* **1997**, *278*, 2051.
5. Haier, J., Nasralla, M., Franco, A.R., Nicolson, G.L., *Br. J. Rheumatol.* **1999**, *38*, 504.
6. Greenwald, R.A., Golub, L.M., Lavietes, B., Ramamurthy, N.S., Gruber, B., Laskin, R.S. McNamara, T.F., *J. Rheumatol*, **1987**, *14*, 28.
7. Kloppenburg, M., Breedveld, F.C., Mitenburg, A.M.M., Dijkmans, B.A.C., *Clin. Exp. Rheumatol.* **1993**, *11*, Suppl.8, S113.
8. Brandt, K.D., *J. Rheumatol.* **1995**, Suppl. 43, 149.
9. Tilley, B.C., Alarcon, G.S., Heyse, S.P., Ann. Intern. Med. **1995**, *122*, 81.
10. Trentham, D.E., Trentham, R.A.D., *Rheum. Dis. Clin. North Am.* **1995**, *21*, 817.
11. Caruso, I., *J. Int. Med. Res.* **1997**, *25*, 307.
12. Yin, Z., Wang, Y., Whittell, L. R., Jergic, S., Liu, M., Harry, E., Dixon, N. E., Kelso, M. J., Beck, J. L., Oakley, A. J., *Cell Chem. Biol.*, **2014**, *21*, 481.
13. Obad, J., Šušković, J., Kos, B., *Eur. J. Pharm. Sci.* **2015**, *71*, 93.
14. Piccionello, A. P., Musumeci, R., Cocuzza, C., Fortuna, C. G.,Guarcello, A., Pierro, P., Pace, A., *Eur. J. Med. Chem.*, **2012**, *50*, 441.
15. Zhang, Y., Qiao, R.-Z., Xu, P.-F., Zhang, Z.-Y., Wang, Q., Mao, L.-M., Yu, K.-B., *J. Chin. Chem. Soc.* **2002**, *49*, 369; doi: 10.1002/jccs.200200057
16. Liao, J.; Yang, F.; Zhang, L.; Chai, X.; Zhao, Q.; Yu, S.; Zou, Y.; Meng, Q.; Wu, Q., *Arch. Pharm. Res.* **2014**, DOI: 10.1007/s12272-014-0378-5.
17. Kruszewska, H., Zareba, T., Tyski, S., *Acta Pol. Pharm.* **2002**, *59*, 436.
18. Hugo, W.B., Russell, A.D., 1995. Pharmaceutical Microbiology, fifth edition, Blackwell Science London, UK.
19. Huisgen, R., 1984. 1,3-Dipolar Cycloaddition Chemistry; A. Padwa, Ed.; Wiley: New York, NY, USA, Volume 1, pp. 1–176.
20. Padwa, A., 1991. Intermolecular 1,3-dipolar cycloaddition. In Comprehensive Organic Synthesis; B. M. Trost, Ed.; Pergamon: Oxford, UK, Volume 4, pp. 1069–1109.
21. Tornøe, C.W., Christensen, C., Meldal, M., *J. Org. Chem.* **2002**, *67*, 3057.
22. (a) Kolb, H.C., Finn, M.G., Sharpless, K.B., *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; (b) Rostovtsev, V.V., Green, L.G., Fokin, V.V., Sharpless, K.B., *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
23. Hein, J. E., Fokin, V. V., *Chem. Soc. Rev.*, **2010**, *39*, 1302.
24. Díez-González, S., *Catal. Sci. Technol.*, **2011**, *1*, 166.
25. Alzahrani, A. A., 2014. Copper-Catalyzed Azide Alkyne Cycloaddition Polymer Networks, Ph.D. thesis, University of Colorado at Boulder, Publication Number: AAT 3682662; ISBN: 9781321563825; Source: Dissertation Abstracts International, Volume: 76-07(E), Section: B.; 153 p.
26. Praveena, K.S.S., Durgaprasad, S., Babu, N.S., Akkenapally, A., Kumar, C.G., Deora, G.S., Murthy, N.Y.S., Mukkanti, K., Pal, S., *Bioorg. Chem.* **2014**, *53*, 8.
27. Mareddy, J., Nallapati, S.B., Anireddy, J., Devi, Y.P., Mangamoori, L.N., Kapavarapu, R., Pal, S., Bioorg. Med. Chem. Lett. **2013**, *23*, 6721.
28. Praveena, K.S.S., Ramarao, E.V.V.S., Murthy, N.Y.S., Akkenapally, S., Kumar, C.G., Kapavarapu, R., Pal, S., *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1063.
29. Kumar, R., Yar, M.S., Rai, A.K., Chaturvedi, S., *Der Pharmacia Lettre*, **2013**, *5*, 366.
30. Kuntala, N., Telu, J.R., Banothu, V., Nallapati, S.B., Anireddy, J.S., Pal, S., *Med. Chem. Commun.* **2015**, *6*, 1612.
31. Since racemic ibuprofen was used for the preparation of compounds **4a-j** hence all these compounds are racemic mixtures, whereas (*S*)-naproxen was used for the synthesis of compounds **4k-t** hence all these compounds are single enantiomers.
32. Kavanagh, F., Analytical Microbiology, F. Kavana (ED), vol II, Academic press, New York and London, 1972, pp 11- 23.
33. Miles, A.A., Misra, S.S., *J. Hyg.* **1938**, *38*, 732.