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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], 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

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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 be effective against *Escherichia coli*, *Pseudomonas 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 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.

* Corresponding author. Tel.: +91 40 23041488.
E-mail address: sarbani277@yahoo.com (S. Pal).

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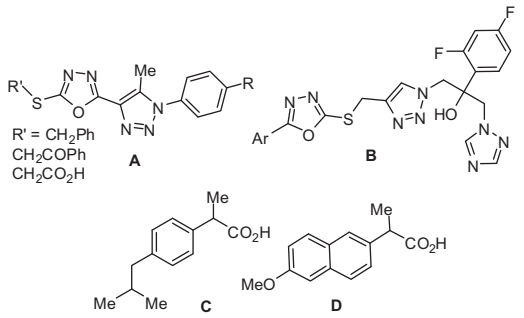


Figure 1. Known 1,2,3-triazolyl oxadiazoles (**A** and **B**), ibuprofen (**C**) and naproxen (**D**).

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).

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 ^1H 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

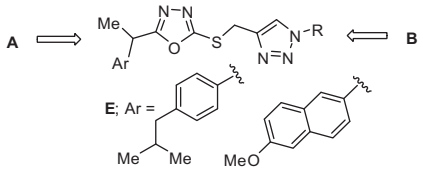
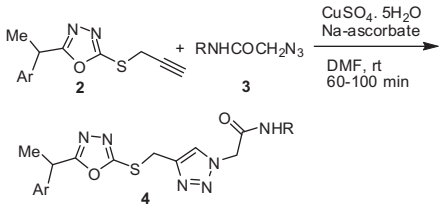
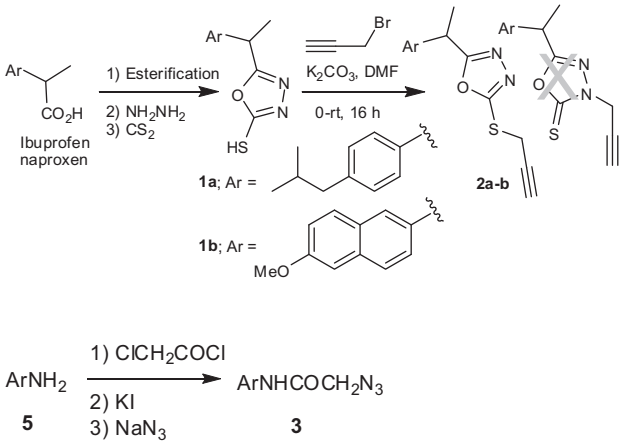


Figure 2. New template (**E**) for the generation of potential antimicrobial agents.



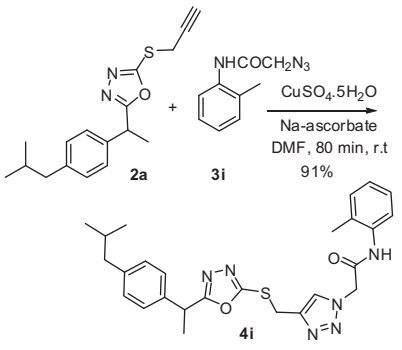
Scheme 1. Preparation of compound **4** via CuAAC of **2** with **3**.



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

the reaction with 2-chloroacetyl chloride followed by treatment with KI finally with sodium azide (Scheme 2) according to the literature procedure.[30]

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 $CuSO_4{\cdot}5H_2O$ (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 ^1H 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 opti-



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