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Research Article

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Synthesis and biological evaluation of novel benzoxazole derivatives as potent TNF-α and IL-6 inhibitor and antimicrobial agents

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ABSTRACT

*A new series of 2-(3-Arylureido)benzoxazole **(5a-j)** derivatives were synthesized via sequential oxidative cyclisation, reduction followed by the reaction of resulting amine with different arylisocynates. All the synthesized compounds were screened for their in-vitro pro-inflammatory cytokines TNF-α and IL-6 inhibition and antimicrobial activity (antibacterial and antifungal). Among all the compounds screened, the compounds **5e** found to be potent TNF-α and IL-6 inhibitor as compared to the standard dexamethasone but at the MIC of 10 µM, while the compounds **5f** found to be moderately active as compared to standard dexamethasone. The remaining compounds were found to have low, very low or no activity at the MIC of 10 µM. The antimicrobial data revealed that compounds **5b, 5f, 5h and 5i** found to be potent antibacterial and antifungal agents. Notably, the compounds **5b, 5h** and **5i** exhibited 1.5-2.5 fold antibacterial and antifungal activity to that of control drugs Micanazole and flucanazole almost against all the gram positive and gram negative bacteria and fungi and thus found to be more potent that the standard control drug.*

Keywords: Benzoxazoles, Anti-inflammatory, Cytokines, Antimicrobial, Antifungal

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INTRODUCTION

The concept of "privileged medicinal structures or scaffolds," originally introduced by Merck researchers in the course of their work on benzodiazepines, has recently emerged as one of the guiding principles of modern drug discovery[1,2]. It involves the utilization of molecular frameworks with inherent potential for biological activity. Through appropriate functional group modifications, these scaffolds are capable of providing ligands for a number of functionally and structurally discrete biological receptors. In addition, compound libraries designed on the basis of such frameworks exhibit enhanced drug like properties and result in high-quality leads.

Biologically active benzoxazole derivatives have been known for long time, since they are the isosteres of naturally occurring cyclic nucleotides and they may easily interact with the biopolymers of the organisms[3]. Literature survey revealed that benzoxazole possess most remarkable and a wide range of biological activities [4]. The substituted benzoxazoles have been shown to exhibit antitumor[5], antihistaminic, antiparasitic, herbicidal, antiallergic, antihelmintic[6], COX-2inhibitory [7], antifungal, anti-inflammatory (fig 1.), antibacterial, anticancer, antitubercular, anticonvulsant [8], diarrhea-predominant irritable bowel syndrome [9], hypoglycaemic [10], HIV-1 reverse transcriptase inhibitor [11] & insecticidal [3] activities. It has also been shown to have binding affinity to Aβ42 fibrils [12].

Non-steroidal anti-inflammatory drugs (NSADs) are therapeutically important in the treatment of rheumatic arthritis and in various types of inflammatory conditions, but their therapeutic utility has been limited due to their frequently observed gastrointestinal side effects. Thus, there is an urgent need for new targets that are required for the design and development of novel anti-inflammatory agents as an alternative to NSAIDs.[13] (Tumor_necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), the two important multifunctional proinflammatory cytokines that are involved in

the pathogenesis of autoimmune, inflammatory, cardiovascular, neurodegenerative and cancer diseases through a series of cytokine signaling pathways.[14-15] IL-6 contributes to the initiation and extension of the inflammatory process and considered as a central mediator in a range of inflammatory diseases but has not received the desired attention in drug discovery.[16] TNF-α and IL-6 are thus pharmaceutically important molecular targets for the treatment of the above-mentioned diseases.

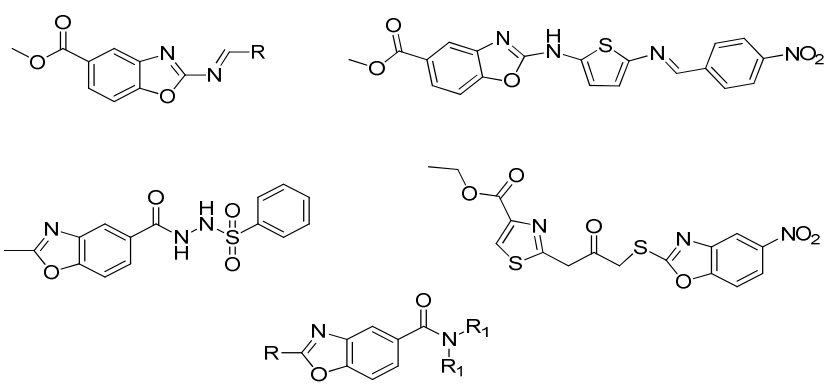


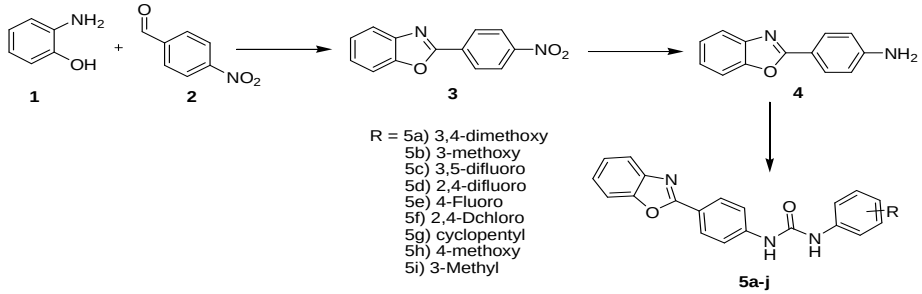
Figure 9. Srinivas *et al* benzoxazole moiety with some substitutions shows promosing anti inflammatory activity (Ref - J. Chem. Pharm. Res., 2010, 2(2), 213-219.)

However, there are few reports on the anti-inflammatory activity of oxazole derivatives. Most importantly, the potential of ureiodo-oxazole [2-(3-Arylureido) benzoxazoles] hybrid scaffold as to their anti-inflammatory activity against the pro-inflammatory cytokines (TNF-α and IL-6) hitherto remained untested.

In recent years, we have been engaged in design, synthersis and discovery of novel ureides as potent TNF-α and IL-6 inhibitor and antimicrobial agents. Prompted by our earlier efforts [17] and in order to further expand the scope of ureiodo appended heterocyclic as privileged medicinal scaffold, herein, we disclose our results on the design synthesis, and biological evaluation of novel ureido benzoxazoles as TNF-α and IL-6 inhibitor and antibacterial and antifungal agents.

Chemistry

Our synthetic strategy for the novel ureiodbenzoxazole **(5a-j)** derivatives is depicted in scheme **1.** The 2-(4-nitrophenyl)benzoxazole **3** constitute the key precursors for the present synthesis. The 2-(4-nitrophenyl)benzoxazole **3** was readily obtained by oxidative cyclisation of *o*-aminnophenol **1** and 4-nitrobenzaldehyde **2** catalyzed by molecular iodine in toluene at 70 ^{0}C. The reduction of **3** using $SnCl_2$ yielded the amine **4** in high yields which on further reaction with different arylisocyanates afforded the corresponding ureiodbenzoxazoles (**5a-j)** in good to high yields under mild conditions. The purity of the newly synthesized compounds was checked by TLC and HPLC. The ^{1}HNMR and Mass spectral data was found to be consistent with structures of the newly synthesized benzoxazole derivatives.



Reaction conditions: a) A mixture of 2-aminophenol, 4-nitrobenzaldehyde, 10mol % of iodine in toluene at 70^0 (b) $SnCl_2$, EtOAc, rt, 4 h; (c) different substituted isocynates, THF, rt, 6 h.

Biological Evaluation

1. Anti-inflammatory activity

Having secured a series of structurally diverse 2-(3-Arylureido) benzoxazole derivatives (5a-j), next their anti-inflammatory and antimicrobial activity was evaluated. The results of the anti-inflammatory, antibacterial and antifungal activity are collected in table 1, 2 and 3 respectively. As shown in table 1, among various

ureiodobenoxaazole derivatives screened the compounds 5e found to exhibit promising TNF-α and IL-6 inhibitory activity.

Table 1 – Anti-inflammatory activity data of novel benzoxazole derivatives

Compounds	% Inhibition at 10 µM **TNF-α**	IL-6
3	0	0
4	0	0
5a	0	0
5b	18	24
5c	08	12
5d	21	28
5e	55	62
5f	41	45
5g	31	41
5h	28	30
5i	11	16
5j	0	0
Dexamethasone (1µM)	74	81

The compounds 5g and 5h found to exhibited moderate TNF-α and IL-6 inhibitory activity but at MIC of 10µM. The remaining compounds from this series found to have low, very low or no activity at all against TNF-α and IL-6 with reference to the standard dexamethasone at the MIC of 10 µM.

2 Antibacterial and antifungal activity.

We also screened all the synthesized compounds for their antimicrobial activity. For antibacterial and antifungal activity study, the minimum inhibitory concentration (MIC) assay was conducted against the bacterial starins such as Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhimurium and fungi such as Candida albicans, Aspergillus niger, Fusarium solani.

The antimicrobial activity data of the compounds and control drug as MIC (µg/mL) values are given in Table 2 and 3.

Table 2 - Antibacterial activity data of novel oxazole derivatives

Compounds	*Gram-positive Staphylococcus aureus*	*Bacillus subtilis*	*Gram-negative Escherichia coli*	*Salmonella typhimurium*
3	-	-	90	-
4	-	-	-	-
5a	65	60	40	55
5b	20	15	10	25
5c	70	90	60	90
5d	90	-	90	90
5e	85	-	90	-
5f	15	15	10	15
5g	15	25	15	35
5h	20	35	25	25
5i	45	35	40	25
5j	-	-	90	90
Ciprofloxacin	20	25	20	25

Table 3 - Antifungal activity data of novel oxazole derivative

Compounds	*Candida albicans*	*Aspergillus niger*	*Fusarium solani*	*Aspergillus flavus*
3	-	90	90	90
4	-	-	-	-
5a	50	45	40	60
5b	15	15	10	10
5c	70	75	45	80
5d	90	-	-	-
5e	90	-	-	-
5f	15	10	10	20
5g	20	15	15	25
5h	20	20	15	20
5i	30	45	20	45
5j	90	90	-	90
Miconazole	25	20	15	20

As can be seen from our results, the compounds 5f, 5h and 5i were found to be potent antibacterial and antifungal agents against all the tested bacterial and fungal strain with the minimum inhibitory concentration (MIC) ranging over 10-25 μg/ml. Its worth mentioning here that the compound **5f, 5h** and **5i** exhibited 1.5-2.5 fold antibacterial and antifungal activity to that of standard drugs almost against all the gram positive and gram negative bacterial and fungal strains and thus found to be more potent even than the standard drug Micanazole and flucanazole. The compounds **3, 5a, 5c, 5e**, and **5g,** however**,** were found to have moderate anti-bacterial and anti-fungal activity with the MIC values ranging over 40-90 μg/ml. Thus the biological evaluation of novel ureiodbenzoxazoles lead to the discovery of novel TNFα and IL-6 inhibitor and highly potent antimicrobial agents which can be readily accessed via sequential oxidative condensation, reduction and nucleophilic addition strategy at great ease.

Structure activity relationship (SAR)

The structure activity relationship of the benzoxazole urea derivatives has been described herewith. It was found that the nature and the position of the substituents on the terminal benzene ring of the ureido moiety has crucial effect on the TNF-α and IL-6 inhibitory as well as anti-microbial activity. Regarding the anti-inflammatory activity, the OMe- and F- substituents on the terminal ring of the ureido moiety were found to be the preferred substituents for the promising TNF-α and IL-6 inhibition. The 4-position of the terminal ring found to be the suitable site for the favourable effect on this activity. Thus the compound **5e** bearing either 4-OMe- or 4-F at 4 proved to the most active member from the novel ureiobenzoxazol series. The urea derivatives bearing halides and halogenated alkyl and alkoxy groups found to be moderately active or having very low activity (**5a, 5b, 5g, 5h** and **5i**). In addition, presence of the substituents such as OMe-, F-, Cl- etc. at more than one position were found to have detrimental effect on the TNF-α and IL-6 inhibition (table-2, compare entries 5g-h with 5a-c).

Regarding antibacterial and antifungal activity, the compounds bearing halide and, fluorinated alkyl and alkoxy substituents (Cl-, F-,CF_3- etc.) were found to be the most potent antibacterial and antifungal agents while those with OMe-, 3,4-$(OMe)_2$ etc. were found to have moderate activity. This is in contrast to the trend observed for anti-inflammatory activity. Most striking feature regarding antimicrobial activity is that the compounds possessing multiple F- atoms found to retained the antibacterial and anti-fungal activity, while the presence of multiple Cl- atoms has resulted into dramatic decline in these activities (table 2&3, compound **5g** vs. **5a** and **5f** vs. **5b**). Another important finding is that the potent TNF-α and IL-6 inhibitors, compound **5e** from these novel compounds were found to be moderately active or inactive as antibacterial and antifungal agents.

All these findings lead us to speculate that the electronic effect of the substituent affect the anti-inflammatory and antimicrobial activity of these novel ureides in opposite fashion.

CONCLUSION

In conclusion, we have synthesized structurally diverse novel ureidobenzoxazoles and screened for their TNF-α and IL-6 inhibitory, antibacterial and antifungal activity. Thus the biological evaluation of novel ureiodbenzoxazoles resulted into the discovery of novel TNFα and IL-6 inhibitor such as compound **5e** and potent antimicrobial agents viz. **5f, 5h** and **5i** using simple and convenient synthetic strategy. In view of the simple, practical and diversity oriented synthetic approach coupled with their TNF-α and IL-6 inhibitory and antimicrobial activity, the present study could be potentially useful for design and discovery novel lead compounds for anti-inflammatory drugs and antibiotics.

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