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The novel 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives of N-aryl urea: Synthesis, anti-inflammatory, antibacterial and antifungal activity evaluation

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ABSTRACT

A series of novel 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives of biological interest were prepared by sequential Bigineli's reaction, reduction followed by reaction of resulting amines with different arylisocynates. All the synthesized (**1–23**) compounds were screened against the pro-inflammatory cytokines (TNF-α and IL-6) and antimicrobial activity (antibacterial and antifungal). Biological activity evaluation study reveled that among all the compounds screened, compounds **12** and **17** found to have promising anti-inflammatory activity (68–62% TNF-α and 92–86% IL-6 inhibitory activity at 10 μM). Interestingly compounds **3**, **4**, **5**, **6**, **15**, **22** and **23** revealed promising antimicrobial activity at MIC of 10–30 μg/mL against selected pathogenic bacteria and fungi.

Due to their broad range of pharmacological properties such as calcium channels blockers, antioxidant, anticancer, and anti-inflammatory activity of 3,4-dihydropyrimidin-2(1*H*)-one nucleus have increasingly attracted the attention of synthetic chemists.[1–5] Moreover, the dihydropyrimidine-5-carboxylate core has been found in several marine natural products which are potent HIV-gp-120-CD4 inhibitors.[6,7] In addition, antimicrobial activity of 3,4-dihydropyrimidone derivatives have been extensively studied and well established in the literature.[8–14] However, relatively there are very few reports on the anti-inflammatory activity of the 3,4-dihydropyrimidin-2(1*H*)-one derivatives,[5,15] and most importantly, the potential of 3,4-dihydropyrimidin-2(1*H*)-one nucleus as to their anti-inflammatory activity against the pro-inflammatory cytokines (TNF-α and IL-6) hitherto remained untested.

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.[16] Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), the two important multifunctional proinflammatory cytokines are involved in the pathogenesis of autoimmune, inflammatory, cardiovascular, neurodegenerative and cancer diseases through a series of cytokine signaling pathways.[17,18] 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.[19] TNF-α and IL-6 are thus pharmaceutically important molecular targets for the treatment of the above-mentioned diseases.

Biological importance of heterocyclic derivatives of aryl ureas have been reported in the literature. For example, *N*-2,4-pyrimidine-*N*,*N*-phenyl/alkyl ureas were reported to be inhibitor of tumor necrosis factor alpha (TNF-α),[20,21] SA13353, substituted urea derivatives is reported as a potent inhibitor of TNF-α production,[22] pyrido-quinazolone analogues reported as antifungal, antibacterial and anticancer agents.[23] However, to the best of our knowledge, there has been no report on synthesis and evaluation of biological activities of 3,4-dihydropyrimidinone urea derivatives despite of their easy synthetic access.

In present study, in order to further expand the scope of 3,4-dihydropyrimidone derivatives as antimicrobial agents and due to surprise lack of literature on their anti-inflammatory activity against TNF-α and IL-6, we report herein for the first time our results on anti-inflammatory activity study of novel 3,4-dihydropyrimidinone urea derivatives against for TNF-α and IL-6 along with antimicrobial activities.

In an attempt to design and develop new potential biological active compounds, we undertook the synthesis of some series of novel 3,4-dihydropyrimidin-2(1*H*)-ones derivatives viz. *N*-aryl-*N*′-[4-(3,4-dihydropyridin-2-(1*H*)-one] derivatives and evaluation of their anti-inflammatory and antimicrobial activities.

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Our synthetic strategy for 3,4-dihydropyrimidin-2(1*H*)-ones urea derivatives is illustrated in Scheme 1. A key intermediate ethyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1** for the proposed synthesis was synthesized by heating a mixture of *p*-nitrobenzaldehyde, ethyl acetoacetate and thiourea in ethanol at 80 °C for 8 h using catalytic amount of PTSA. Reduction of nitro group using $SnCl_2$ in ethyl acetate at room temperature followed by treatment of resulting amine with different substituted isocynates in THF afforded the structurally diverse 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives (**3**–**23**) in 70–90% yields.

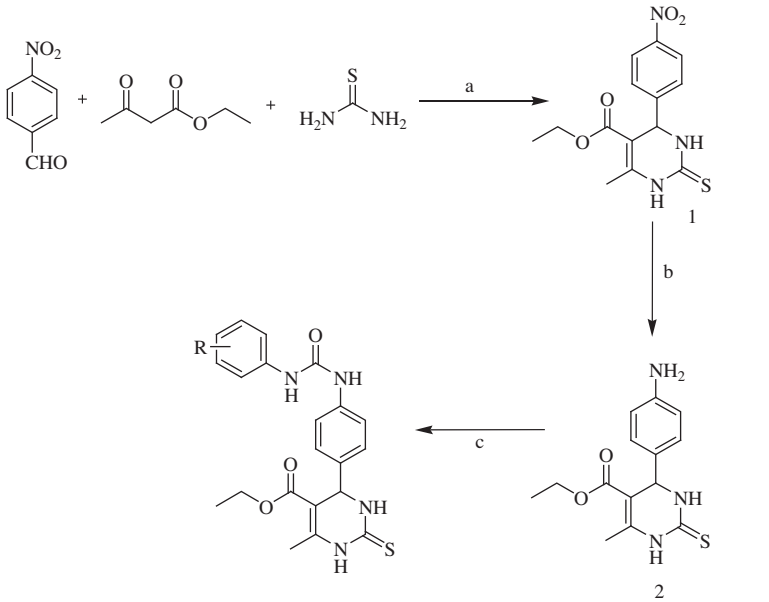
Having secured the series of the novel 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives of N-aryl urea, next in order to search for the potent compounds from these newly synthesized 3, 4-dihydropyrimidin-2(1*H*)-ones urea derivatives, compounds **1**–**23** were evaluated for in vitro anti-inflammatory, antibacterial and antifungal activity against various Gram-positive, Gram-negative bacteria and fungal strains using agar well diffusion method.

SAR of 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives has been presented in Tables 1–3 and some interesting trend was observed as to the effect of substituent present on terminal ring of urea moiety on various activities. It is found from our results (Tables 1–3) that the lipophilicity as well as nature of the substituent affecting the biological activity of the synthesized analogues. Thus, from the TNF-α and IL-6 inhibitory activity data (Table 1), it is observed that a majority of the analogues of this series found to be active as IL-6 inhibitor while very few exhibited TNF-α inhibitory activity. As can be seen from Table 1, compounds **12** and **17** exhibited the good (68% and 62%) TNF-α and IL-6 (92% and 86%) inhibitory activity as compared to the standard dexamethasone but at higher concentration (10 μM) and found to be moderately potent anti-inflammatory agents.

Table 1
Anti-inflammatory activity of 3,4-dihydropyrimidin-2(1*H*)-ones urea derivatives

Compound	% Inhibition at 10 μM	
	TNF-α	IL-6
1	0	8
2	0	3
3	0	40
4	0	43
5	10	27
6	20	60
7	0	36
8	0	6
9	0	27
10	2	11
11	0	39
12	68	92
13	16	73
14	0	36
15	0	11
16	3	40
17	62	86
18	0	2
19	0	16
20	30	65
21	0	10
22	3	55
23	0	42
Dexamethasone (1 μM)	71	84

Compounds **6**, **13**, **20** and **22** exhibited moderate activity (55–73% inhibition) while other compounds **8**, **10**, **15** and **18** exhibited low inhibitory activity at same level of concentration. It is also observed that the two-potent compounds in this series **12** and **17** present no or very low anti-microbial activity, which



3: 2-F
4: 2-Cl
5: 2-CF_3
6: 2-OCF_3
7: 2-OC_6H_5
8: 2-F, 6-CH3
9: 2-F, 6-CF_3
10: 2-Cl, 6-CH_3
11: 2-Cl, 6-CF_3
12: 2-Cl, 5-CF_3
13: 2-Cl, 4-CF_3
14: 2-Cl, 6-F
15: 3-CF_3
16: 3-Cl, 4-F
17: 3,5-F
18: 3,4-CH_3
19: 4-F, 3-CH_3
20: 4-isopropyl
21: 4-butyl
22: 4-CF_3
23: 4-OCH_3

Scheme 1. Synthesis of novel series of 3,4-dihydropyrimidin-2(1*H*)-ones urea derivatives. Reagents and conditions: (a) PTSA, EtOH, reflux, 8 h; (b) $SnCl_2$, EtOAc, rt, 4 h; (c) different substituted isocynates, THF, rt, 6 h.

Table 2
Antibacterial activity of 3,4-dihydropyrimidin-2(1*H*)-ones urea derivatives (MIC[a] values μg/mL)

Compound	Gram-positive		Gram-negative	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Salmonella typhimurium*
1	35	45	30	50
2	40	55	40	60
3	10	15	10	40
4	10	20	10	40
5	25	25	15	30
6	30	30	25	20
7	40	55	35	40
8	60	65	30	30
9	55	40	40	60
10	40	65	55	80
11	40	85	60	90
12	55	85	80	90
13	35	35	25	55
14	65	55	85	85
15	40	55	20	40
16	60	—	85	—
17	90	—	—	—
18	90	95	—	—
19	65	90	—	90
20	85	85	55	95
21	—	—	95	—
22	20	25	10	30
23	15	20	15	45
Ciprofloxacin	25	25	15	25

—: No activity was observed up to 200 μg/mL.
[a] Values are the average of three reading.

Table 3
Antifungal activity of 3,4-dihydropyrimidin-2(1*H*)-ones urea derivatives (MIC[a] values μg/mL)

Compound	*Candida albicans*	*Aspergillus niger*	*Fusarium solani*	*Aspergillus flavus*
1	30	50	60	60
2	55	40	45	60
3	10	10	15	10
4	10	15	15	30
5	25	40	30	30
6	15	20	15	15
7	40	60	30	30
8	50	35	40	40
9	55	30	60	60
10	40	55	40	40
11	60	65	80	55
12	60	80	85	90
13	35	40	60	35
14	40	60	80	90
15	25	20	15	15
16	80	—	95	—
17	95	—	—	—
18	95	—	—	—
19	80	95	—	95
20	90	90	80	95
21	—	—	—	—
22	15	15	10	25
23	10	25	30	30
Miconazole	25	20	15	20

—: No activity was observed up to 200 μ/mL.
[a] Values are the average of three reading.

could indicate low toxicity associated and should be considered as ideal anti-inflammatory agents.

It is observed that the position of the substituent on terminal benzene ring of urea moiety has profound effect on the activity. The 2- and 5-positions on the terminal benzene ring are the favourable site for the higher potency. Evidently, the compound **12** with Cl and CF_3 at 2- and 5-positions, respectively, exhibiting highest TNF-α and IL-6 inhibitory activity, while presence of Cl at 2-position and CF_3 group at 6-position **11** exhibits no TNF-α activity or low IL-6 inhibitory activity. The compound **17** with fluoro group at 3- and 5-position of terminal benzene ring showed better TNF-α (62% at 10 μM) and IL-6 (86% at 10 μM) inhibitory activity. Interestingly, the large bulky lipophilic group such as isopropyl at 4-position generated compound **20** that was found to be moderate TNF-α or IL-6 inhibitor. However, replacement of isopropyl group with *n*-butyl group at 4-position has detrimental effect on inhibition as it exhibits no TNF-α activity or very low IL-6 inhibitory activity.

The antibacterial activity data is represented in Table 2. As shown in our results, some analogues of this series were found to have even more potency than the standard drug ciprofloxacin while some of them have comparable potency. The compounds **3** and **4** bearing F, Cl group at 2-position are most potent followed by compounds **5**, **6**, **22** and **23** bearing CF_3, OCF_3 and OMe at 2- or 4-position. Thus compounds bearing substituent such as CF_3, OCF_3 and OMe at 2- or 4-position of the terminal benzene ring of urea part found to have higher potency than the compounds bearing such a group at 3- or 5-positions or at both. Explicitly, 2- or 4-position is the favourable site for high antibacterial activity. The high potency of **3**, **4**, **22**, and **23** may be attributed to the presence of lipophilic or H-bond acceptor type group's placement such as F, Cl, CF_3, OCF_3 and OCH_3 at 2- or 4-positions. This is further supported by the fact that the presence of nonpolar lipophilic groups such as isopropyl, *n*-butyl etc. at 4-position, compounds **20** and **21**, respectively, has no major effect on the activity. Rest of the compounds bearing substituent such as F, Cl, CF_3, OCF_3, OCH_3 and OPh at position 3 or 4 or both showed moderate or no activity with respect to standard drug against the test strains. No activity was observed in case of compounds **16**–**19** up to concentration of 200 μg/mL against some bacteria and fungi.

It is clear from our results (Table 2 vs Table 3) that the SAR of 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives for antibacterial activity strongly correlates with their SAR of antifungal activity. Again the position 2 and 4 of terminal benzene ring is favorable site for high activity. The compounds **3** and **4** found to be 2.5-fold more potent than the standard drug Micanazole while **22** and **23** exhibited comparable antifungal activity. Similar to the antibacterial activity trend, nonpolar lipophilic groups such as isopropyl or *n*-butyl at 4-position, compounds **20** and **21**, respectively, has no major effect on the antifungal activity also.

In conclusion, we have synthesized a novel series of 3, 4-dihydropyrimidin-2(1*H*)-one urea derivatives of N-aryl urea in convenient and atom economic and ecological manner and evaluated their anti-inflammatory and antimicrobial activity. It was found that amongst all the compounds screened, compounds **12** and **17** showed promising anti-inflammatory activity against TNF-α and IL-6. The antimicrobial evaluation study of the synthesized compounds shows moderate high activity against tested bacteria and fungi. Most importantly some of the compounds from this newly synthesised series of 3,4-dihydropyrimidin-2(1*H*)-one urea derivatives of N-aryl urea viz. compounds **3** and **4** found to be much more potent antibacterial and antifungal agents (1.5–2.5-fold more potent) than the standard drug Ciprofloxacin and Micanozole, respectively.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.03.062.

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