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Synthesis, anti-inflammatory and antimicrobial evaluation of novel 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole derivatives bearing urea, thiourea and sulfonamide moieties

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ABSTRACT

A series of novel 1-acetyl-3-(3,4-dimethoxypheny)-5-(4-(3-(arylureido/arylthioureido/arylsulfonamido) phenyl)-4,5-dihydropyrazole derivatives of biological interest have been prepared by sequential cyclization of 1-(4-nitrophenyl)-3-(3,4-dimethoxyphenyl)-pro-2-ene-1 with hydrazine hydrate, reduction followed by reaction of resulting amine with different arylisocyanates or arylisothiocyanates or arylsulfonyl chlorides. All the synthesized compounds (**1**–**32**) have been screened for their pro-inflammatory cytokines (TNF-α and IL-6) and antimicrobial activity (antibacterial and antifungal). Biological evaluation study showed, the compounds **4**, **5**, **9**, **11**, **14** and **16** found to have promising anti-inflammatory activity (up to 61–85% TNF-α and 76–93% IL-6 inhibitory activity) at concentration of 10 μM with reference to standard dexamethasone (76% TNF-α and 86% IL-6 inhibitory activity at 1 μM). Compounds **24**, **26**, **27**, **28** and **29** exhibited promising antimicrobial activity at MIC values ranging from 70 to 10 μg/mL against all the selected pathogenic bacteria and fungi.

The treatment of bacterial infections remains a challenging therapeutic disaster because of emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Despite of many antibiotics and chemotherapeutics available, the emergence of old and new antibiotic-resistant bacterial strains in the last decades lead to a substantial need for new classes of anti-microbial agents.

Several pyrazole derivatives possess important pharmacological activities therefore they are useful materials in drug research. The changes in their structure offered a high degree of diversity which is useful for the development of new therapeutic agents. Among the existing various pyrazole type derivatives '1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole' have been identified as one of the most promising scaffold in medicinal chemistry, which have been previously reported to exhibit a variety of biological activities such as inhibitors of monoamine oxidases, swine kidney oxidase and bovine serum amine oxidases,[1,2] antibacterial activity,[3–5] analgesic/anti-inflammatory/ulcerogenic/antipyretic,[6–8] anti-helicobactor pylori,[9] antiviral,[10] antimicrobial/antitubercular,[11–13] kinesin spindle protein (KSP) inhibitors,[14] xanthine oxidase inhibitors,[15] anticancer.[16–18] In addition, pyrazole derivatives enclose urea, thiourea and sulfonamide moieties have been reported as potent anticancer agents,[19,20] antiplatelet agents,[21] inhibitors of p38 MAP kinase[22] and also inhibit a growth of gram-positive bacteria.[23]

Moreover, the potential of 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole derivatives bearing urea, thiourea and sulfonamide moieties as their anti-inflammatory activity against the pro-inflammatory cytokines (TNF-α and IL-6) hitherto remained untested.

Non-steroidal anti-inflammatory drugs (NSAIDs) are therapeutically important in the treatment of rheumatoid 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 of new target which required the design and development of novel anti-inflammatory agents as an alternative to NSAIDs. Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are the two important multifunctional pro-inflammatory cytokines involved in the pathogenesis of autoimmune, inflammatory, cardiovascular, neurodegenerative and cancer diseases through a series of cytokine signaling pathways.[24,25] 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 it has not received the desired attention in drug discovery.[26] TNF-α and IL-6 are thus pharmaceutically important molecular targets for the treatment of the above-mentioned diseases.

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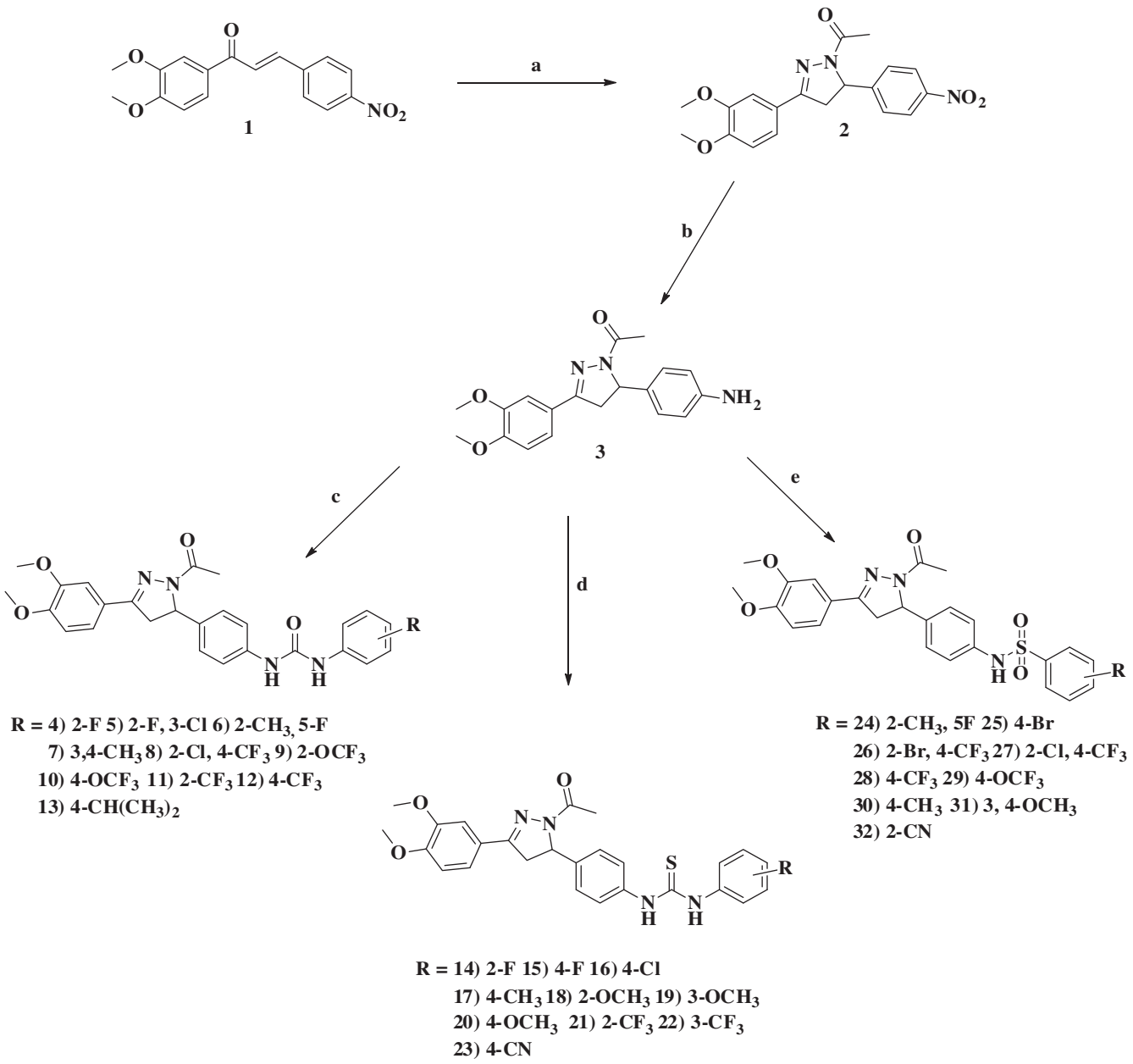
Motivated by the afore-mentioned literature and in persistence of our earlier work on different heterocyclic derivatives bearing urea, thiourea and sulfonamide moieties,[27–30] we envision our approach towards the design and synthesis of novel structurally diverse series of 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole derivatives bearing urea, thiourea and sulfonamide moieties for their anti-inflammatory and antimicrobial activity. Therefore, a single molecule containing more than one pharmacophore each with different mode of action could be beneficial for the treatment of inflammation and microbial diseases.

Our synthetic strategy for novel 1-acetyl-3-(3,4-dimethoxypheny)-5-(4-(3-(arylureido/arylthioureido/arylsulfonamido) phenyl))-4,5-dihydropyrazole derivatives is illustrated in Scheme 1. The reaction of **1** with hydrazine hydrate in acetic acid at 120 °C for 12 h afforded 1-acetyl-3-(3,4-dimetoxypheny)-5-(4-nitropheny)-pyrazole **2** in 65% yield. The desired amino analog **3** to be used in subsequent nucleophlic addition reaction was achieved by reduction of **2** using $SnCl_2 \cdot H_2O$ in ethyl acetate at room temperature in 70% yield. Next the 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole derivatives bearing urea (**4**–**13**), thiourea (**14**–**23**) and sulfonamide (**24**–**32**) moieties have been synthesized in good to high yields by reacting **3** with appropriate arylisocyanate, arylisothiocyanate and sulfonyl chloride respectively at room temperature under mild conditions. The purity of compounds checked by TLC and HPLC.



Scheme 1. Synthesis of 1-acetyl-3-(3,4-dimethoxypheny)-5-(4-(3-(arylureido/arylthioureido/arylsulfonamido) phenyl)-4,5-dihydropyrazole derivatives.

Spectral data ^{1}H NMR, ^{13}C NMR, IR HRMS and MS of the newly synthesized compounds **1**–**32** were in full agreement with their proposed structures.

The synthesized compounds **1**–**32** have been evaluated for invitro anti-inflammatory activity against the pro-inflammatory cytokines (TNF-α and IL-6) by TNF-α and IL-6 inhibition assay[31] and antimicrobial activity against various gram-positive, gram-negative bacteria and fungal strains by using an agar well diffusion method with little modifications.[32]

SAR of 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole derivatives for their anti-inflammatory, antibacterial and antifungal activity have been presented in Tables 1–3. Some interesting trend was observed since the lipophilicity as well as nature and position of the substituent presents on benzene ring of urea, thiourea and sulfonamide terminus affecting the biological activity of the synthesized analogues.

As from Table 1, compound **4** and **14** exhibited the good TNF-α (85% and 78%) and IL-6 (93% and 84%) inhibitory activity as compared to the standard dexamethasone but at higher concentration (10 μM) and found to be moderately potent anti-inflammatory agents while compounds **5**, **9**, **11**, **16** and **21** exhibited moderate inhibitory activity (68–40% TNF-α and 80–65% IL-6) and other compounds exhibited low or no activity at the same level of concentration (10 μM). It is to be noted that all these active compounds viz **4**, **5**, **9**, **11**, **14** and **16** are either urea or thiourea derivatives, unfortunately only compound **27** from sulfonamide derivatives having Cl at ortho and CF_3 at para position on the benzene ring of sulfonamide terminus was found to be moderately effective against TNF-α (38%) or IL-6 (55%) and rest are almost very low to no active. This finding implicates that the presence of special chemical space viz urea or thiourea in the novel 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole scaffold is of immense importance in order to have potent anti-inflammatory agent.

It can be seen that anti-inflammatory activity can be attributed to the presence of urea or thiourea functionality in pyrazole scaffold as the most potent compounds **4**, **5**, **9**, **11**, **14**, **16** and **21** are the pyrazole derivatives bearing either urea or thiourea moiety and similarly as our previously reported work[27] here also none of the members from the corresponding sulfonamide series (compounds **24**–**32**) was found to be a potent anti-inflammatory agent. It is to be noted that the nature of the substituent present on benzene ring of urea or thiourea terminus found to have strong influence to the activity and which can be confirmed by the fact that the presence of lipophilic H-bond acceptor type functionalities like F, CF_3 or OCF_3 at ortho position and Cl at para position leading to the moderately potent anti-inflammatory compounds **4**, **5**, **9**, **11**, **14** and **16**. Also the position of the substituent on the urea or thiourea terminal ring has dramatic effect on the said activity. Accordingly the compound **9** with OCF_3 and **11** with CF_3 at ortho position on benzene ring of urea terminus exhibited 58–61% TNF-α and 75–80% IL-6 inhibitory activity and proved to be a moderately potent anti-inflammatory agent, while the presence of same substituent at para position on benzene ring of urea terminus leading to compound **10** and **12** found to have very low TNF-α/IL-6 inhibitory activity. Similarly in thiourea series the compound **14** with F at ortho position on benzene ring of thiourea terminus exhibited 78% TNF-α and 84% IL-6 inhibitory activity and proved to be a moderately potent anti-inflammatory agent, while the presence of same substituent at para position on benzene ring of thiourea

Table 1
Anti-inflammatory activity of novel 1-acetyl-3-(3,4-dimethoxypheny)-5-(4-(3-(arylureido/arylthioureido/arylsulfonamido) phenyl)-4,5-dihydropyrazole derivatives

Compounds	% Inhibition at 10 μM	
	TNF-α	IL-6
1	0	0
2	0	0
3	0	0
4	85	93
5	61	76
6	28	31
7	18	30
8	3	8
9	58	75
10	8	11
11	61	80
12	3	21
13	11	16
14	78	84
15	3	10
16	68	76
17	0	3
18	0	0
19	11	26
20	3	10
21	40	65
22	0	8
23	0	21
24	0	0
25	0	0
26	0	8
27	38	55
28	0	0
29	8	30
30	0	0
31	0	0
32	10	31
Dexamethasone (1 μM)	76	84

Table 2
Antibacterial activity of novel 1-acetyl-3-(3,4-dimethoxypheny)-5-(4-(3-(arylureido/arylthioureido/arylsulfonamido) phenyl)-4,5-dihydropyrazole derivatives. (MIC[a] values μg/mL)

Compounds	Gram-positive		Gram-negative	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Salmonella typhimurium*
1	–	90	80	90
2	90	50	65	90
3	–	–	90	–
4	60	80	45	80
5	90	90	90	90
6	–	–	90	–
7	–	–	–	–
8	35	60	45	80
9	55	40	40	60
10	30	20	25	45
11	75	90	60	90
12	25	25	15	40
13	30	40	30	55
14	80	80	55	90
15	80	–	80	–
16	–	90	–	–
17	–	–	–	–
18	–	–	90	–
19	55	90	70	90
20	45	65	20	35
21	–	–	95	–
22	–	–	–	–
23	60	35	30	45
24	55	20	20	40
25	30	65	30	30
26	10	15	10	10
27	15	10	10	15
28	70	55	35	25
29	20	45	15	65
30	90	90	75	90
31	–	90	90	90
32	80	65	90	90
Ciprofloxacin	20	15	15	20

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

Table 3
Antifungal activity of novel 1-acetyl-3-(3,4-dimethoxypheny)-5-(4-(3-(arylureido/arylthioureido/arylsulfonamido) phenyl)-4,5-dihydropyrazole derivatives. (MIC[a] values μg/mL)

Compounds	*Candida albicans*	*Aspergillus niger*	*Fusarium solani*	*Aspergillus flavus*
1	90	—	—	—
2	90	90	—	90
3	—	—	—	—
4	80	80	90	80
5	90	—	—	—
6	—	—	—	—
7	90	—	90	90
8	55	35	20	20
9	40	75	60	30
10	25	35	20	20
11	80	90	75	80
12	15	25	15	15
13	20	40	20	20
14	80	—	90	90
15	—	—	90	—
16	90	—	90	90
17	—	—	—	—
18	90	—	75	—
19	80	95	0	95
20	90	—	90	90
21	—	—	—	—
22	—	—	—	—
23	55	20	20	35
24	30	60	20	20
25	25	15	15	40
26	20	10	10	10
27	40	15	10	15
28	35	20	10	10
29	45	25	35	20
30	70	90	65	90
31	—	—	90	—
32	65	40	80	70
Miconazole	20	15	15	20

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

terminus leading to compound **15** found to have very low TNF-α/IL-6 inhibitory activity. Until now, though we have not a concrete evidence in hand in support of the actual role of urea or thiourea moieties on this activity, we can at least speculate that the H-bond donor ability of the urea or thiourea (not present in sulfonamide framework) along with the lipophilicity and electronic effect of ortho or para substituent might be responsible for their anti-inflammatory activity.

The antimicrobial activity data is represented in Tables 2 and 3. As shown in our results, some analogues of this series were found to have even more potency than the standard drugs while some of them have comparable potency.

As can be seen the antibacterial activity data represented in Table 2, the compounds **26** and **27** from sulfonamide series exhibited higher antibacterial activities against each strain tested while compounds **10**, **12**, **24** and **29** showed moderate or comparable antibacterial activities than ciprofloxacin according to the strain tested. Other compounds (**13**, **23** and **25**) exhibited lower activities and rest are inactive. Compound **26** bearing Br at ortho and CF_3 at para position on benzene ring of sulfonamide terminus is twofold more potent against *Staphylococcus aureus and Salmonella typhimurium* while 1.5-fold more potent against *Escherichia coli* and comparable against *Bacillus subtilis* while compound **27** bearing Cl at ortho and CF_3 at para position on benzene ring of sulfonamide terminus is 1.5-fold more potent against *Bacillus subtilis and Escherichia coli* while 1.3-fold more potent against *Staphylococcus aureus and Salmonella typhimurium*. Compounds **29** bearing OCF_3 at para position on benzene ring of sulfonamide terminus showed comparable activities against *Staphylococcus aureus* and *Escherichia Coli*. Surprisingly compound **12** bearing CF_3 at para position on benzene ring of urea terminus found to be comparable active against *Escherichia coli* while moderately active against other tested strains.

Concerning the antifungal activity data represented in Table 3, compounds **26**, **27** and **28** from sulfonamide series exhibited comparable or higher activities while compounds **10**, **12**, **13** and **25** showed moderate or comparable antibacterial activities than miconazole according to the strain tested. Other compounds (**23**, **24** and **29**) exhibited lower activities and rest are inactive. Compound **26** is 1.5-fold more potent against *Aspergillus niger and Fusarium solani* and twofold more potent against *Aspergillus flavus* while comparable against *Candida albicans* while compound **27** is 1.5- to 1.3-fold more potent against *Aspergillus flavus and Fusarium solani* respectively while comparable against *Aspergillus niger*. Compound **28** bearing CF_3 at para position on benzene ring of sulfonamide terminus is 1.5- to 2-fold more potent against *Fusarium solani and Aspergillus flavus* respectively. Surprisingly compound **12** bearing CF_3 at para position on benzene ring of urea terminus found to be 1.3-fold more potent against *Candida albicans* and *Aspergillus flavus* while comparable against *Fusarium solani*.

From the above activity data we bring to a close that, the compounds **26** and **27** are the most potent antimicrobial agents. The high potency or comparable activity of compounds **25**, **26**, **27**, **28** and **29** may be attributed to the presence of lipophilic H-bond acceptor type group's like Br, Cl, CF_3, and OCF_3 at ortho or para position on benzene ring of sulfonamide functionality. This is further supported by the fact that the presence of group's like Cl, CF_3, OCF_3 or OCH_3 at ortho or para position on benzene ring of urea and thiourea terminus leading to compounds **8**, **10**, **12**, **13** and **20** showed moderate to comparable antimicrobial activity. No activity was observed in rest of the compounds up to concentration of 200 μg/mL.

It is clear from results (Tables 2 and 3) that the antibacterial activity SAR of 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazole derivatives strongly correlates with their antifungal activity SAR. To our surprise, none of the most active anti-inflammatory agents **4**, **5**, **9**, **11**, **14** and **16** was found to be active antibacterial or antifungal agent screened but importantly which indicates the low toxicity associate with them and should be considered as ideal anti-inflammatory agents.

In conclusion, we have synthesized and evaluated the anti-inflammatory and antimicrobial activity for structurally diverse 1-acetyl-3-(3,4-dimethoxypheny)-5-(4-(3-(arylureido/arylthioureido/arylsulfonamido) phenyl)-4, 5-dihydropyrazole derivatives. The compounds **4**, **5**, **9**, **11**, **14** and **16** having functionalities like F, CF_3 or OCF_3 at ortho position and Cl at para position on the benzene ring of urea or thiourea terminus found to be favorable for the anti-inflammatory activity while compounds **24**, **26**, **27**, **28** and **29** having functionalities like F, Cl, Br, CF_3, and OCF_3 at ortho or para position on benzene ring of sulfonamide terminus found to be effective antimicrobial agents**.** The lipophilicity as well as nature and position of the substituent present on benzene ring of urea, thiourea and sulfonamide terminus affecting the biological activity of the synthesized analogues.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.08.118.

References and notes

1. Manna, F.; Chimenti, F.; Bolasco, A.; Secci, D.; Bizzarri, B.; Befani, O.; Turini, P.; Mondovi, B.; Alcaro, S.; Tafi, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3629.
2. Chimenti, F.; Bolasco, A.; Manna, F.; Secci, D.; Chimenti, P.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B.; Cirilli, R.; Torre, F. *J. Med. Chem.* **2004**, *47*, 2071.
3. Holla, B. S.; Akberali, P. M.; Shivananda, M. K. *IL Farmaco* **2000**, *55*, 256.
4. Lv, P. C.; Sun, J.; Luo, Y.; Yang, Y.; Zhu, H. L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4657.
5. Liu, X.; Cui, P.; Song, B.; Bhadury, P. S.; Zhua, H.; Wang, S. *Bioorg. Med. Chem.* **2008**, *16*, 4075.
6. Bansal, E.; Srivatsava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2001**, *36*, 81.
7. Girisha, K. S.; Kalluraya, B.; Narayana, V.; Padamshree, P. *Eur. J. Med. Chem.* **2010**, *45*, 4640.
8. Manna, F.; Chimenti, F.; Bolasco, A.; Cenicolaz, M.; Amico, M. D.; Parrillo, C.; Rossi, F.; Marmo, E. *Eur. J. Med. Chem.* **1992**, *27*, 633.
9. Chimenti, F.; Bizzarri, B.; Manna, F.; Bolasco, A.; Secci, D.; Chimenti, P.; Granese, A.; Rivanera, D.; Lilli, D.; Scaltrito, M. M.; Brenciaglia, M. I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 603.
10. El-Sabbagh, O. I.; Baraka, M. M.; Ibrahim, S. M.; Pannnecouque, C.; Andrei, G.; Snoeck, R.; Balzarini, J.; Rashad, A. A. *Eur. J. Med. Chem.* **2009**, *44*, 3746.
11. Patel, P. S.; Shah, R. A.; Trivedi, D. K.; Vyas, P. J. *Der Pharma Chemica* **2010**, *2*, 168.
12. Azarifar, D.; Shaebanzadeh, M. *Molecules* **2002**, *7*, 885.
13. Chovatia, P. T.; Akabari, J. D.; Kachhadia, P. K.; Zalavadia, P. D.; Joshi, H. S. *J. Serb. Chem. Soc.* **2007**, *71*, 713.
14. Cox, C. D.; Breslin, M. J.; Mariano, B. J.; Coleman, P. J.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Huber, H. E.; Kohl, N. E.; Torrent, M.; Yan, Y.; Kuod, L. C.; Hartmana, G. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2041.
15. Nepali, K.; Singh, G.; Turan, A.; Agarwal, A.; Sapra, S.; Kumar, R.; Banerjee, U.; Verma, P. K.; Satti, N. K.; Gupta, M. K.; Suri, O. P.; Dhar, K. L. *Bioorg. Med. Chem.* **2011**, *19*, 1950.
16. Manna, F.; Chimenti, F.; Fioravanti, R.; Bolasco, A.; Secci, D.; Chimenti, P.; Ferlini, C.; Scambia, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4632.
17. Congiu, C.; Onnis, V.; Vesci, L.; Castorina, M.; Pisano, C. *Bioorg. Med. Chem.* **2010**, *18*, 6238.
18. Lv, P.; Li, H.; Sun, J.; Zhou, Y.; Zhu, H. *Bioorg. Med. Chem.* **2010**, *18*, 4606.
19. Rostom, S. A. F. *Bioorg. Med. Chem.* **2006**, *14*, 6475.
20. Faidallah, H. M.; Al-Saadi, M. S.; Rostom, S. A.; Fahmy, H. T. *Med. Chem. Res.* **2007**, *16*, 300.
21. Dosa, P. I.; Strah-Pleynet, S.; Jayakumar, H.; Casper, M.; Decaire, M.; Xiong, Y.; Lehmann, J.; Choi, K.; Elwell, K.; Wong, A.; Webb, R. R.; Adams, J. W.; Ramirez, J.; Richman, J. G.; Thomsen, W.; Semple, G.; Teegarden, B. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5486.
22. Dumas, J.; Hatoum-Mokdad, H.; Sibley, R.; Riedl, B.; Scott, W. J.; Monahan, M. K.; Lowinger, T. B.; Brennan, C.; Natero, R.; Turner, T.; Johnson, J. S.; Schoenleber, R.; Bhargava, A.; Wilhelm, S. M.; Housley, T. J.; Ranges, G. E.; Shrikhande, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2051.
23. Kane, J. L.; Hirth, B. H.; Liang, B.; Gourlie, B. B.; Nahill, S.; Barsomian, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4463.
24. Papadakis, K. A.; Targan, S. R. *Inflamm. Bowel Dis.* **2000**, *6*, 303.
25. Krishnamoorthy, S.; Honn, K. V. *Cancer Metastasis Rev.* **2006**, *25*, 481.
26. Dominic, S. C.; Raj, M. D. *Semin. Arthritis Rheum.* **2009**, *38*, 382.
27. Keche, A. P.; Hatnapure, G. D.; Tale, R. H.; Rodge, A. H.; Birajdar, S. S.; Kamble, V. M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3445.
28. Tale, R. H.; Rodge, A. H.; Hatnapure, G. D.; Keche, A. P. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4648.
29. Tale, R. H.; Rodge, A. H.; Hatnapure, G. D.; Keche, A. P.; Patil, K. P.; Pawar, R. P. *Med. Chem. Res.* **2011**. http://dx.doi.org/10.1007/s00044-011-9943-3.
30. Tale, R. H.; Rodge, A. H.; Hatnapure, G. D.; Keche, A. P.; Patil, K. P.; Pawar, R. P. *Med. Chem. Res.* **2012**. http://dx.doi.org/10.1007/s00044-012-0109-8.
31. Hwang, C.; Gatanaga, M.; Granger, G. A.; Gatanaga, T. *J. Immunol.* **1993**, *151*, 5631.
32. Sridhar, R.; Perumal, P. T.; Etti, S.; Shanmugam, G.; Ponnuswamy, M. N.; Prabavathyc, V. R.; Mathivanan, N. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6035.