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A REVIEW ON NOVEL PYRIMIDINES ANALOGUES AS POTENTIAL TREATMENT FOR INFLAMMATORY DISORDERS

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Abstract

Pyrimidines are the fused heterocyclic ring systems, biologically active molecules including synthetic and natural products are the area of interest of many researchers all over the world. Synthetic manipulations of pyrimidines and their derivatives are being investigated worldwide for the development of more potent and efficient drugs for the treatment of various diseases such as inflammation, cancer, diabetes, HIV, tuberculosis etc, therefore it is important to gather the earlier information to understand the present status of pyrimidines. The present review article mainly focuses on the anti-inflammatory activity of pyrimidines and their analogue.

Keywords: Pyrimidines derivatives, anti-inflammatory, heterocycles.

1. Introduction

Synthesis of new chemical compounds is an interesting and active area of research [1-3]. Heterocyclic compounds form a special class of compounds due to their diverse usefulness in synthetic applications, and pharmaceuticals and also a major component of the natural products *etc*., which exhibit enormous number of biological activities [4-7]. As the most of drugs contain a major part of heterocyclic rings in them, so synthetic analogues of new heterocyclic molecules [8-12] is one of the key factor used in the development and discovery of new drugs. Solvent phase synthesis, microwave assisted reactions [13, 14], development of new reagents [15, 16] for chemical synthesis and modern instrumental techniques [17, 18] have been reported in literature which is quite useful for rapid synthesis and identification of new heterocyclic compounds. A number of synthetic routes have been reported for synthesis of heterocyclic compounds and evaluated for biological activities [19-21], amoung them pyrimidine and their derivatives are very potent molecules which are very active to words various biological activities. Motivated by the various biological activities of pyrimidine and their derivatives, a report highlighting the synthesis and medicinal significance are included in this mini review article.

2. Pyrimidine and their derivatives As inflammation inhibitors

Inflammations are a protective mechanism of body to the foreign organisms, such as bacteria and viruses and bring the defense cell to the area of concern as well as destroy the external stimuli or repair the cell. Various types of inflammations pain, swelling and fever etc are promoted by prostaglandins (PGs) which is derived from arachidonic acid by the action of prostaglandin H. Cyclooxygenase (COX) exists in two isoforms COX-1 and COX-2 are expressed in most tissues, which is responsible for the production of prostaglandins. Cyclooxygenase-1 (COX-1) produces prostaglandins that mediate homeostatic functions and play an important role in Gastric mucosa, Kidney and Platelets where as cyclooxygenase-2 (COX-2) mediate inflammation, pain, and fever, which are induced mainly at sites of inflammation by cytokines enzyme and also control of cell growth. The production of cyclooxygenase (COX) is mainly inhibited due to action of nonsteroidal anti-inflammatory drugs (NSAIDs) which block the formation of prostaglandins (PGs) and result in inflammatory action of drugs. Various non specific non-steroidal anti-inflammatory drugs (NSAIDs) *i.e*. phenylbutazone, indomethacin, piroxicam, celecoxib, rofecoxib and valdecoxib are the COX inhibiter containing heterocyclic ring. Pyrimidine and their derivatives are very potent molecules which have very wide range of anti-inflammatory activities,

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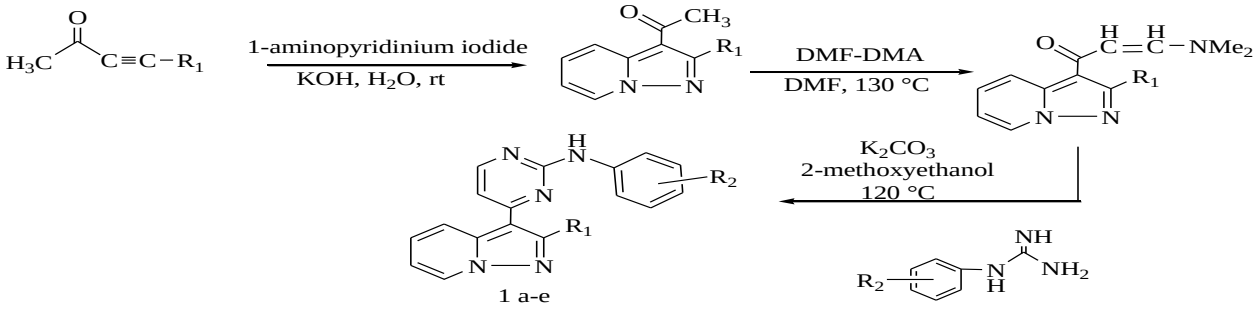
some of newly synthesized pyrimidine derivatives with their anti-inflammatory activities are discussed in this section.

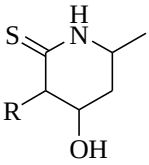
A number of pyrimidine derivatives **1a-e,** Figure 1; have been reported [22] and their following reaction scheme mentioned below and evaluated their anti-inflammatory activity. These compounds are expected to be useful for treatment of inflammation related diseases



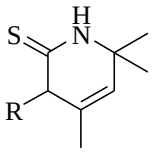
[a, R_2= H, R_1=H; b, R_2= 3-methoxy; R_1=H; c, R_2= 2-Me-5-Cl, R_1=H; d, R_2= H; , R_1=Ph; e, R_2= 3-methoxy; , R_1=Ph

Figure 1

Sondhi et al., [23] have been reported a series of wide variety of dihydropyrimidine derivatives Figure 2; and, these compounds were screened for anti- inflammatory activity at a dose of 50 mg/kg p.o. Compounds 5 and **14** exhibited good anti-inflammatory which is better than most



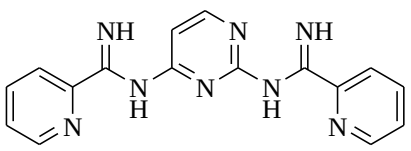
2 R= cyclopropyl
3 R= 2-thienyl methyl
4 R= thienyl ethyl
5 R= 2-furyl methyl
6 R= imidazol-4-ethyl
7 R= 2-pyridyl methyl
8 R= 2-nitro-4-methoxy phenyl



9 R= cyclopropyl
10 R= 2-acetamido-4-ethoxyphenyl
11 R= 2-thienyl methyl
12 R= 2-thienyl ethyl
13 R= 2-pyridyl amino
14 R= 2-hydroxy-1-naphthyl

Figure 2

Commonly used standard drug Ibuprofen. Pyrimidine derivatives, Figure 3; synthesized by Sondhi et. al., [24] exhibited promising anti-inflammatory activity at a dose of 50 mg/kg p.o. and



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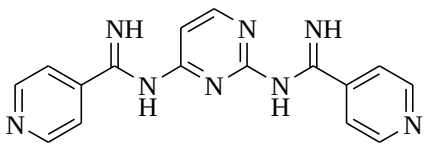

15b

Figure 3

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exhibited moderate activity. Synthesis and biological evaluation of thieno [20,30:4,5]pyrimido[1,2-b] [1,2,4]triazines and thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidines have been reported by Ashour et. al., [25], Figure 4; and some of the compounds exhibited

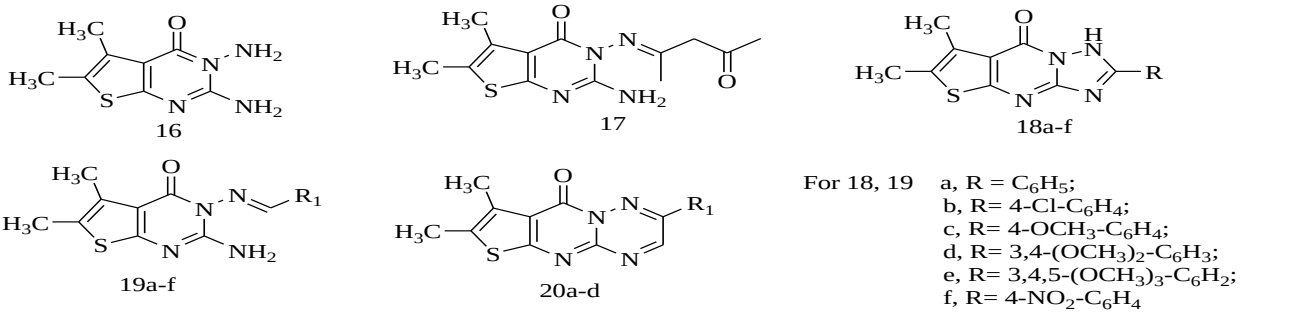

Figure 4

excellent anti-inflammatory activity up to 47% whereas standard drug diclofenac Na 33%. Synthesis and anti-inflammatory evaluation of pyrimidine derivatives, Figure 5; using the carrageenin induced paw oedema in albino rats has been reported by Sondhi et. at., [26] and compound **21c,** 2**3c and 24b** exhibit good anti-inflammatory whereas the remaining

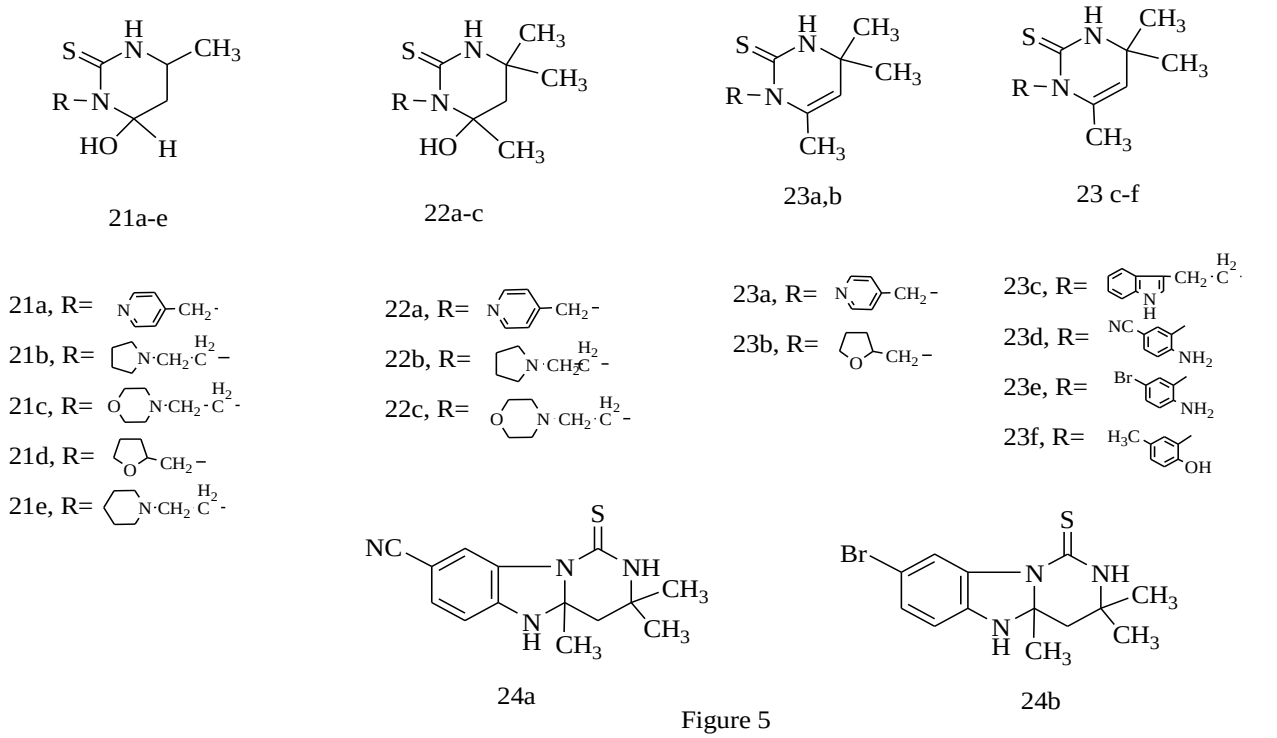

Figure 5

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compounds showed moderate activity. Chetan M. Bhalgat et. al., [27] have been reported a series of pyrimidine derivative and evaluated for anti-inflammatory activity, Figure 6.

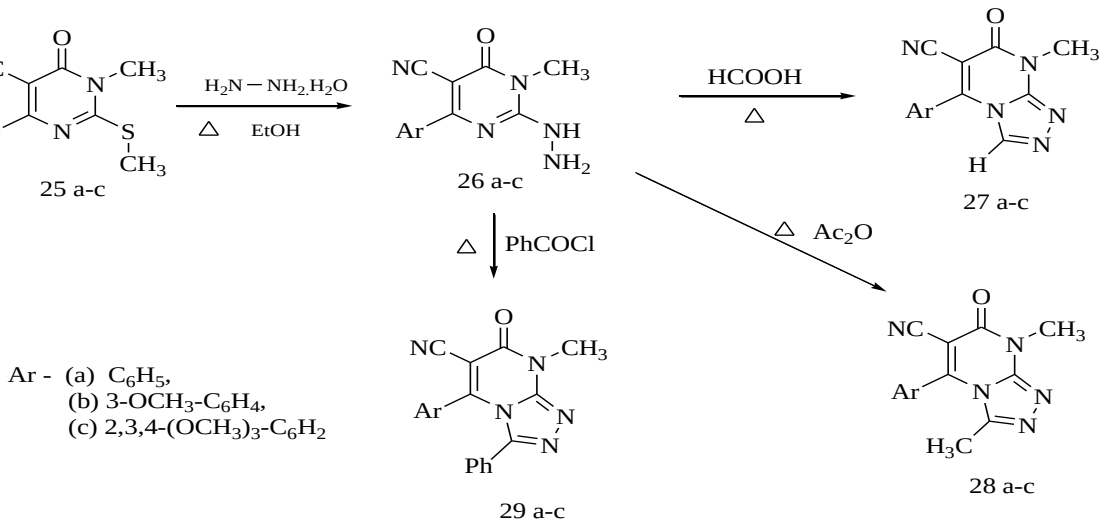
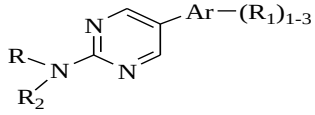


Figure 6

Among the tested compounds, **26b, 25b,** showed better anti-inflammatory activity. In an international patent [28], Figure 7; synthesis and usefulness in the treatment of irritable bowel

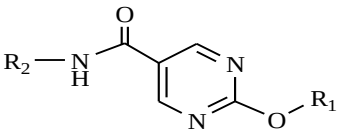


30

R = H, alkyl; R_1 = alkyl, alkenyl, alkynyl; R_2 = substituted 6-membered nitrogen heterocycle contg. up to 4 nitrogen atoms; Ar = (un)substituted (hetero)aryl, with provisions]

Figure 7

syndrome of pyrimidine derivatives. Several pyrimidine derivatives 31-34, Figure 8a, b; useful in the treatment of inflammatory diseases have been synthesized and reported in literature [29-32].



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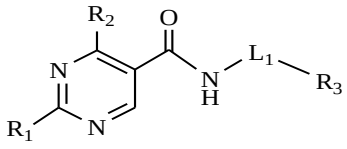
[R_1 = (un)substituted 5- or 6-membered unsatd. heterocyclyl or Ph; R_2 = unsatd. heterocyclyl contg. 1-3 heteroatom(s) selected from N, O, and S atoms contg. 0-2 no. of $R_3(CH_2)m$ group(s), Ph contg. $R_3(CH_2)m$ group(s) at one or both of 3- and 4-positions; m = 0-4; R_3 = halo, cyano, NO_2, (un)substituted and (un)satd. heterocyclyl, (un)substituted NH_2, COR_6, OR_7, SR_8; R_6 = H,HO, (un)substituted C_{1-6} alkoxy or NH_2; R_7 = H, (un)substituted C_{1-6} alkyl, C_{2-6} alkenyl, (un)substituted carbonyl; R_8 = H, (un)substituted C_{1-6} alkyl]



32

[wherein R_1 = (un)substituted (hetero)aryl or cycloalkyl; R_2 = H or alkyl; R_3 = -P(=O)(alkoxy)$_2$, Y_1Y_1N-SO_2-, aryl, etc.; Y_1, Y_2 = independently H or alkyl; L_1 = a bond or (un)substituted alkylene; and hydrates, solvates or N-oxides thereof, or pharmaceutically acceptable salts thereof]

Figure 8a

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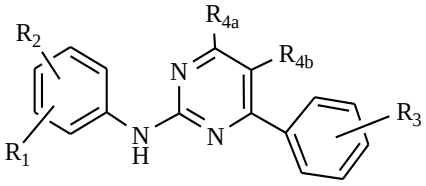
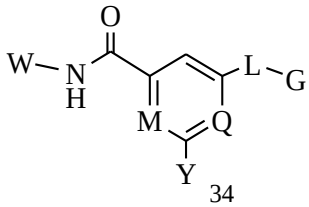


33

[R_1 = $-XSO_2NR_5R_6$ or $-XSO_2R_8$; X = alkylene, wherein alkylene can be bound to R_5 or R_6 to form a 5- or 6-membered heterocycle; R_5 and R_6 independently = H, alkyl, hydroxy-alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl etc.; or NR_5R_6 = (un)substituted 5- to 8-membered heterocycloalkyl; R_8 = (un)substituted alkyl, hydroxy-alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl or heterocycloalkyl-alkyl; R_2 = halo or H; R_3 independently = H, halo, OH, alkyl, cycloalkyl, alkylcycloalkyl, etc.; R_{4a} and R_{4b} independently = H, alkyl or NR_aR_b, wherein R_a and R_b independently = H or alkyl]

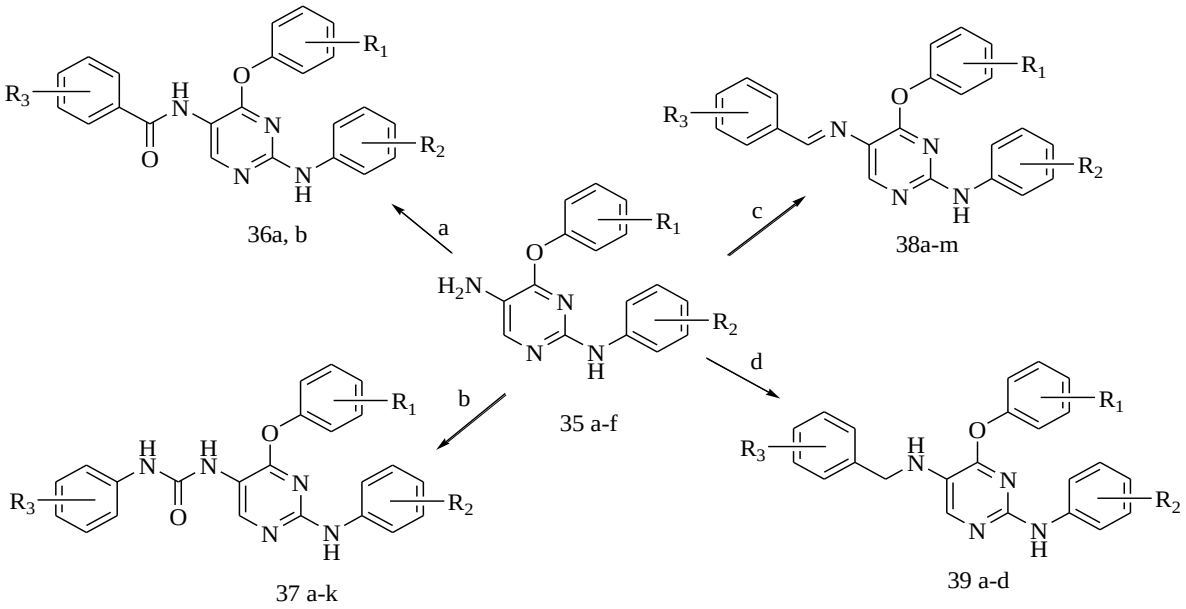


34

[G = alkylene-R_0, R_0 (wherein R_0 = alkyl, 3-7 membered heterocycloalkyl, 3-8 membered cycloalkyl); M = N or CR_1; Q = N or CR_2, provided that if Q = CR_2, then M = N; W = Ph-alkylenyl, pyridyl-alkylenyl, heteroaryl-alkylenyl; Y = alkyl, haloalkyl, hydroxyalkyl; L = 5-membered heteroaryl; R_1, R_2 = H or alkyl]

Figure 8b

Synthesis of novel Novel LCK/FMS inhibitors based on phenoxypyrimidine have been synthesized by Farag et. at., [33] and scheme described below, Figure 9; Table 1. The



Scheme 1. Synthesis of compounds 36a,b, 37a–k, 38a–m and 39a–d. Reagents and conditions: (a) appropriate benzoyl chloride derivatives, DCM, 0–50 °C, 12 h; (b) appropriate phenyl isocyanate reagent, DCM, 0–50 °C, 12 h; (c) appropriate benzaldehyde derivative, anhydrous IPA, TFA, 80 °C, 6–12 h; (d): (i) appropriate benzaldehyde derivative, IPA, TFA, 80 °C, 6–12 h; (ii) $NaBH_3CN$, rt, 12 h.

Figure 9

Where compound	R_1	R_2	R_3
36a	2-methoxy-4-methyl	3,5-dimethoxy	3,5-dimethoxy
36b	2-methoxy-4-methyl	4-morpholino	3,5-dimethoxy
37a	2-methoxy-4-methyl	3,5-dimethoxy	3,5-dimethoxy
37c	2-methoxy-4-methyl	3,5-dimethoxy	4-methoxy
37d	2-methoxy-4-methyl	3,5-dimethoxy	2,6-dichloro
37e	2-methoxy-4-methyl	4-morpholino	2,6-dichloro
37f	2-methoxy-4-methyl	4-morpholino	3,5-dichloro
37g	2-methoxy-4-methyl	4-morpholino	2-methoxy
37h	3-methoxy	4-morpholino	3,5-dimethoxy
37i	4-trifluoromethyl	4-morpholino	3,5-dimethoxy
37j	4-fluoro	4-morpholino	3,5-dimethoxy
37k	2-methoxy-4-methyl	4-morpholino	3,5-bis(trifluoromethyl)
38a	2-methoxy-4-methyl	4-morpholino	2,5-dimethoxy
38b	2-methoxy-4-methyl	4-morpholino	3,5-dimethoxy
38c	3-methoxy	4-morpholino	3,5-dimethoxy
38d	2-methoxy-4-methyl	4-morpholino	2-chloro
38e	2-methoxy-4-methyl	4-morpholino	3-chloro
38f	4-trifluoromethyl	4-morpholino	3,5-dimethoxy
38g	4-methoxy	4-morpholino	3,5-dimethoxy
38h	2-methoxy-4-methyl	4-morpholino	4-chloro
38i	4-fluoro	4-morpholino	3,5-dimethoxy
38j	2-methoxy-4-methyl	4-morpholino	3,5-dichloro
38k	2-methoxy-4-methyl	4-morpholino	3-triflouromethoxy
38l	2-methoxy-4-methyl	4-morpholino	3-isopropoxy
38m	2-methoxy-4-methyl	4-morpholino	3,5-bis(trifluoromethyl)
39a	2-methoxy-4-methyl	4-morpholino	3,5-bis(trifluoromethyl)
39b	2-methoxy-4-methyl	4-morpholino	3-triflouromethoxy
39c	2-methoxy-4-methyl	4-morpholino	4-triflouromethoxy
39d	2-methoxy-4-methyl	4-morpholino	4-chloro

Table 1

compounds **7g** showed excellent selectivity profile and also selectively potent over FMS kinase (IC50 value of 4.6 nM). Swarbrick *et. al* [34] have been synthesized a wide verity of [4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidinyl] amines and ethers (**40-44),** Figure 10 and screened them for COX-2 inhibition and selectivity. Among them compound **44** was found to be a potent and selective inhibitor with a favourable pharmacokinetic profile, high brain penetration and good efficacy in rat models of hypersensitivity. A number of

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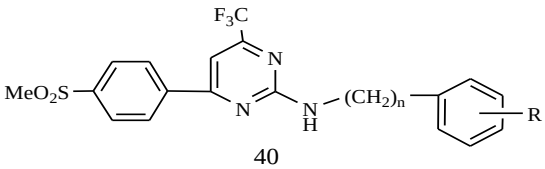

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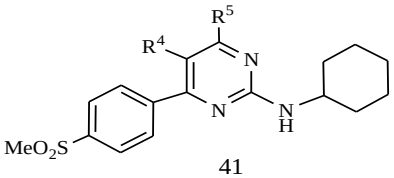

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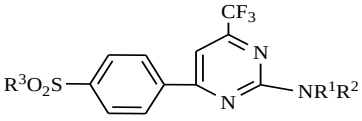

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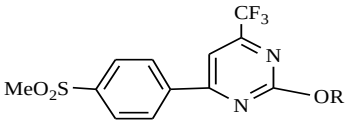

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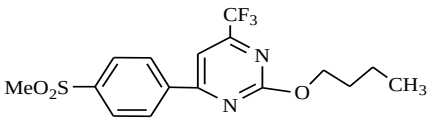
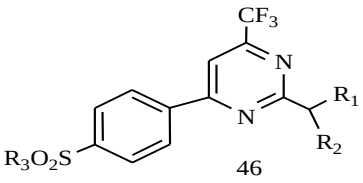


44

Where R_1, R_2, R_3, R_4, R_5 and n are various substituents

Figure 10

trisubstituted pyrimidine derivatives **46-49,** Figure 11; which are selective COX-2 inhibitors and hence useful in the treatment of inflammation have been synthesized and



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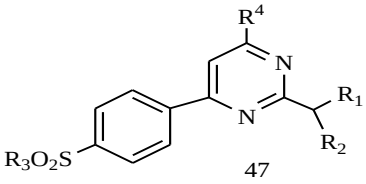
[R_1 = H, alkyl; R_2 = tetrahydropyranyl, tetrahydrofuran-3-yl, etc.; R_3 = alkyl, NH_2]



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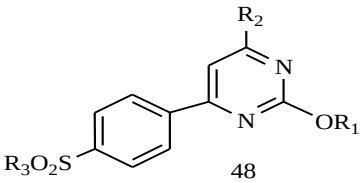
[R_1, R_2 = H, alkyl, alkenyl, etc.; R_3 = alkyl, NH_2, R_5CONH; R_4 = CH_2F, CHF_2, CF_3CH_2, CF_3CHF and CF_3CF_2; R_5 = H, alkyl, alkoxy, etc.]



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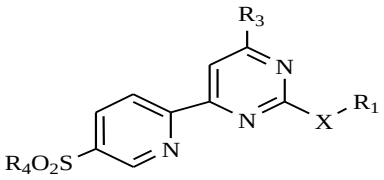
[R_1 = H, alkyl, alkyl substituted by 1-5 fluorine atoms, alkenyl, etc.; R_2 = alkyl substituted by 1-5 fluorine atoms; R_3 = alkyl, NH_2, R_7CONH; R_7 = H, alkyl, alkoxy, etc.]



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[X = O, NR_2; R_1 = H, alkyl, fluoroalkyl, etc.; R_2 = H, alkyl; R_3 = C_{1-2} alkyl substituted by 0-5 fluorine atoms; R_4 = alkyl, NH_2, $NHCOR_8$; R_8 = H, alkyl, alkoxy, etc.]

Figure 11;

disclosed in international patents [35-38]. 5-Ethoxycarbonyl-6-isopropylamino-4-(substituted phenyl)amino pyrimidine derivatives **50a-e** & **51** have been synthesized [39] by following reaction scheme mentioned below, Figure 12. On screening for anti-inflammatory and analgesic activities, compounds **50b, c** and **50 e** showed potent anti-inflammatory activity with very low

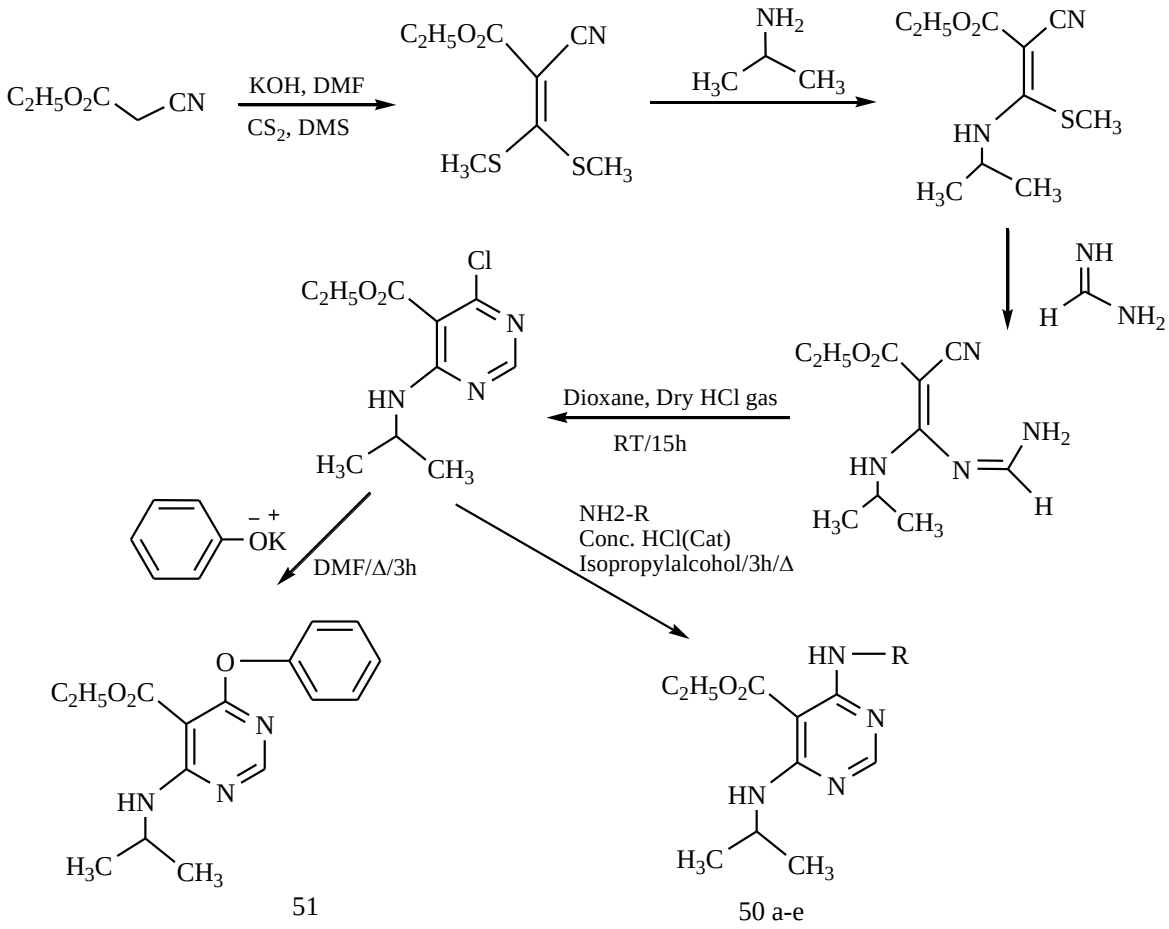
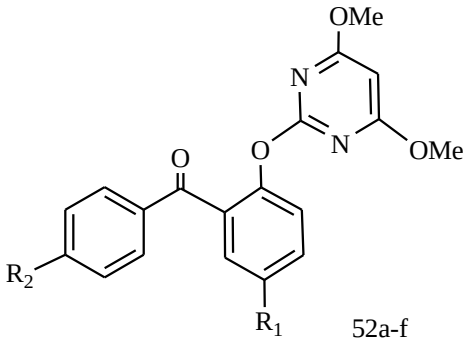


Figure 12

ulcerogenic potential when compared with that of celecoxib and dichlofenac sodium respectively. However ulcerogenic activity was more than celecoxib. Compound **50d** exhibited better analgesic activity than dichlofenac sodium (a standard drug). Several 2-(2-aroylaroxy)-4,6-dimethoxy pyrimidine derivatives **52a-f,** Figure 13; have been synthesized and screened for anti-inflammatory activity [40]. Compound **52e** exhibited anti-inflammatory activity better than

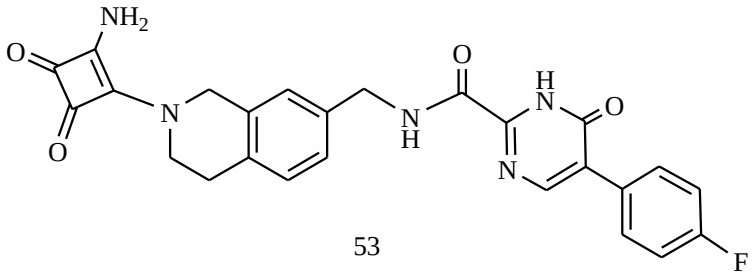


52a-f

[a, R_1= CH_3, R_2 = CH_3; b, R_1= CH_3, R_2= Cl; c, R_1= Cl, R_2= Cl; d, R_1= F, R_2= CH_3; e, R_1=F, R_2= Cl; f, R_1= Br, R_2= Cl]

Figure 13;

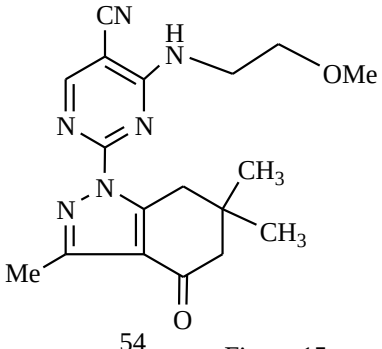
Figure 14;standard drugs *i.e.* aspirin and phenylbutazone. Gege *et.al.*, [41] synthesized amino cyclobutenedione-pyrimidine derivative **53,** Figure 14; which exhibited metalloprotease



53

Figure 14

inhibitory activity and hence is useful in the treatment of inflammation. In an international patent [42], Figure 15; synthesis of pyrimidine derivative 54 which exhibited HSP-90 inhibitory activity and hence useful in the treatment of proliferative diseases such as cancer, inflammation,



54

Figure 15

arthritis *etc*, is described. Synthesis of pyrimidine derivatives **55,** Figure 16; which are p38α kinase inhibitors and hence useful for treating immune or inflammatory disorders is reported in

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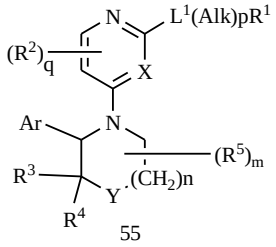
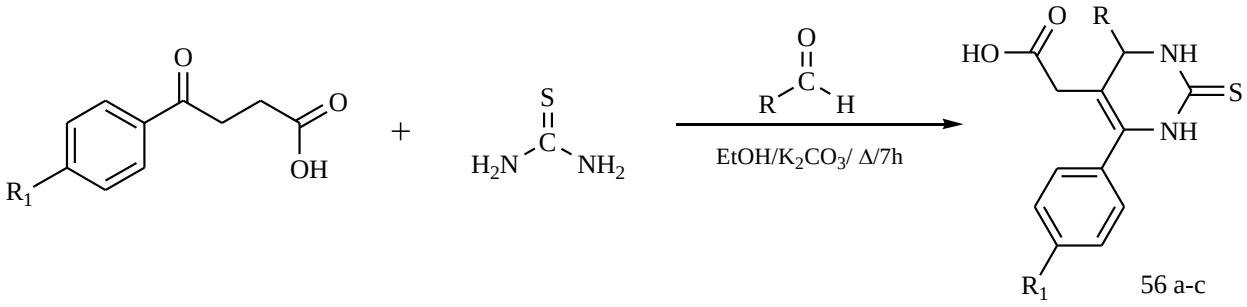


55

[X = N, (un)substituted CH; Y = O, S, S(O), SO_2, (un)substituted CH_2, NH; when R_3R_4 = O, S, Y = (un)substituted CH_2, NH; L1 = covalent bond, linker atom or group; Alk = (un)substituted aliph., heteroaliph.; p = 0, 1; n = 0-3; when n = 0, Y = (un)substituted CH_2; Ar = (un)substituted arom., heteroarom.; m = 0-3; q = 0-2; R_1 = H, halogen, CN, NO_2, (un)substituted cycloaliph., polycycloaliph., heterocycloaliph., arom., heteroarom; when L_1 = bond and p = 0, R_1 ? H, halogen, CN, NO_2; R_2 = H, halogen, CN, (un)substituted alkyl, OH, SH, CO_2H; R_3, R_4 = H, R_5; R_3R_4 = O, S; R_5 = H, O, S, (un)substituted alkyl, OH, SH, CN,CO_2H]

Figure 16

literature [43]. Bahekar *et. al* [44] synthesized [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid derivatives **56a-c** by following reaction scheme, Figure 17; mentioned below. Out of eighteen compounds screened for anti-inflammatory activity compound **56b** (R_1=Cl; R=OCH_3) exhibited good anti-inflammatory activity.



56 a-c

Figure 17

[R= aryl, R_1= H, Cl, CH_3]

3. Conclusion

Pyrimidines are not only excellent molecules for synthetic manipulations but also possess a large number of multiple biological and medicinal properties among them anti-inflammatory activity is one of good application of pyrimidines and their derivatives. Most of the clinical studies reveal the excellent bioavailability and maximum tolerance in the human body. Therefore from last few decade main focus of researcher are on the synthesis of different pyrimidines analogues in seek of novel and more potent drugs. The present review article mainly compiles the pyrimidines analogues have largely been targeted for their anti-inflammatory activity not only for multiple biological but also for design of novel pyrimidines molecules with enhanced medicinal properties.

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