World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

Synthesis, and biological evaluation of new pyrimidine derivatives as potential anti-inflammatory agents

Vudumula Kotireddy*[1], K. Venkata Ramana[1] and Venkata Rao Vutla[2]

[1]Department of Pharmaceutical Chemistry, A.S.N Pharmacy College, Burripalem road, Tenali.
[2]Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, lam, Guntur, Andhra Pradesh, India

Received: 30-02-2017 / Revised: 06-04-2017 / Accepted: 21-04-2017 / Published: 26-04-2017

ABSTRACT

Pyrimidine is the parent substance of a large group of heterocyclic compounds and plays a vital role in many biological processes, as found in nucleic acids, several vitamins, co-enzymes and purines**.** Keeping this in mind new pyrimidines are synthesised by conventional method and the structures were confirmed by spectral evidence. Synthesised compounds were screened for their anti-inflammatory activity. Among the synthesized compounds compound **B_5P_5** and **B_6P_6** possessed maximum activity.

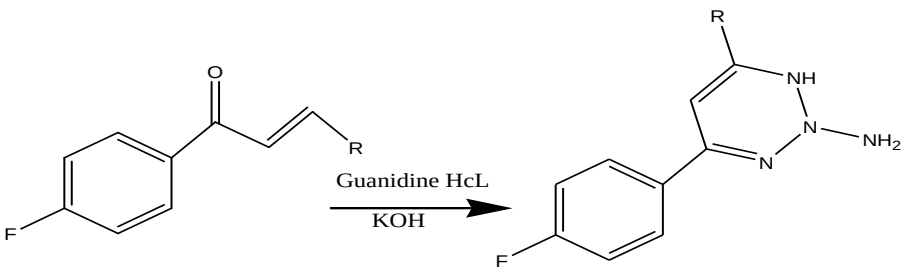
Keywords: Pyrimidine, phenylhydrazine and anti-inflammatory activity.

INTRODUCTION

Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six- member ring shows wide range of biological activities. Pyrimidine possess wide spectrum of biological activities like including anti-tubercular, anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, Anti-malarial activity, anti-cancer and anti-neoplastic activity. Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six- member ring shows wide range of biological activities. Pyrimidine possess wide spectrum of biological activities like including anti-tubercular, anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, Anti-malarial activity, anti-cancer and anti-neoplastic activity, anti-hiv activity

EXPERIMENTAL:

General procedure for synthesis of Synthesis of 2-amino-4-(4'-Fluorophenyl)-6-(3",4",5"-trimethoxyphenyl) pyrimidine **(B_1P_1)**:1-(4'-Fluorophenyl)-3-(3",4",5"-trimethoxyphenyl)-2-propen-1-one (B_1) (0.001 mol) was condensed with guanidine hydrochloride (0.001 mol) in the presence of potassium hydroxide (0.002 mol) in absolute ethanol (5 ml) at reflux temperature on a water bath for 3 hrs. The solvent was evaporated *in vacuo* and crushed ice was added to the residue while mixing thoroughly, whereupon a bright yellow solid separated out. This solid was filtered under vacuum, dried and purified by column chromatography to give pure pale yellow solid.physical characterization and spectral data are given below table 1-3.



***Corresponding Author Address:** Mr. Vudumula Kotireddy, Department of Pharmaceutical Chemistry, A.S.N Pharmacy College, Tenali, Andhra Pradesh, India; Mail ID: vkotireddy9@gmail.com*

Table- 1: Physical characterization data of 2,4,6-trisubstituted pyrimidines(B_1P_1-$B_{10}P_{10}$)

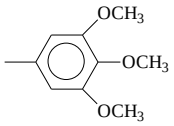
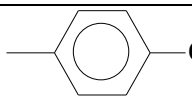
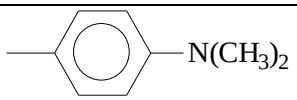
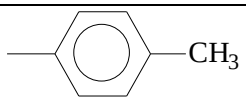
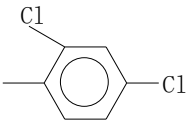
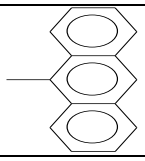
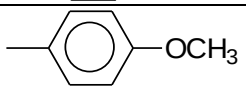
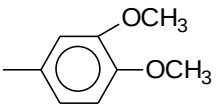
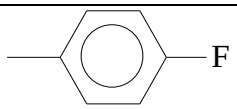
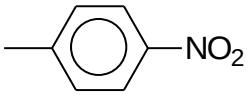
Compound	Ar	Molecular Formula	Relative Molecular Mass(RMM)	Melting Point (^oC)	Yield %
B_1P_1		$C_{19}H_{16}FN_3O_3$	352	315-319	53
B_2P_2		$C_{16}H_9ClFN_3O$	312	250-254	65
B_3P_3		$C_{18}H_{15}FN_4$	322	178-182	58
B_4P_4		$C_{17}H_{12}FN_3$	299	148-150	46
B_5P_5		$C_{16}H_8FCl_2N_3$	367	143-147	58
B_6P_6		$C_{24}H_{14}FN_3$	379	238-240	61
B_7P_7		$C_{17}H_{12}FN_3O$	309	313-317	63
B_8P_8		$C_{18}H_{14}FN_3O_2$	349	223-225	66
B_9P_9		$C_{16}H_9F_2N_3$	297	241-243	48
$B_{10}P_{10}$		$C_{16}H_9FN_4O_2$	324	264-268	63

Table- 2: IR spectral data (KBr disc) of 2,4,6-trisubstituted pyrimidines (B_1P_1-$B_{10}P_{10}$)

Compound	Position of absoption band (cm^{-1})
B_1P_1	3414, 3380 (NH_2), 1591 (C=N), 1503 (C=C), 1387(C-N),1228 (C-O-C), 1178 (O-CH_3)
B_2P_2	3405, 3346 (NH_2), 1636 (C=N), 1578 (C=C),1383 (C-N), 858 (C-Cl)
B_3P_3	3410, 3332 (NH_2), 1610 (C=N), 1570 (C=C), 1391 (C-N),1178 (-N(CH_3)$_2$)
B_4P_4	3412, 3335 (NH_2), 1597 (C=N), 1520 (C=C), 1365 (C-N)
B_5P_5	,3410, 3326 (NH_2), 1605 (C=N), 1525 (C=C),1372 (C-N),892 (C-Cl)
B_6P_6	3413, 3328 (NH_2), 1632 (C=N), 1515 (C=C), 1375 (C-N)
B_7P_7	3414 (NH_2), 1598 (C=N), 1503 (C=C), 1366 (C-N),1225 (C-O-C)
B_8P_8	3320, 3187 (NH_2), 1597 (C=N), 1556 (C=C), 1354 (C-N), 1261(C-O-C)
B_9P_9	3468, 3318(NH_2), 1599 (C=N), 1510 (C=C), 1350(C-N), 1219 (C-F)
$B_{10}P_{10}$	3370 (NH_2), 1645 (C=N), 1557 (N=O, asymmetric), 1406 (C-N), 1350 (N=O, symmetric)

Table-3: ^{1}H NMR spectral data (400MHz) of 2,4,6-trisubstituted pyrimidines (B_1P_1 – $B_{10}P_{10}$)

Compound	Chemical shift (δ) in ppm
B_1P_1	3.75-4.0 (9H, s, 3xOCH_3), 5.15 (2H, s, -NH_2), 6.45-6.60 (1H, m, C-4'-H) 7.38 (1H, d, J=6.0Hz, C-5'-H), 7.0 (1H, S ,C-5-H) 6.40 (2H, S , C-2"-H and C-6"-H), 7.28 (1H, d, J=6.0Hz C-3'-H
B_2P_2	5.45 (2H, s, -NH_2), 6.60 (1H, m , C-4'-H)8.03 (2H, d , J=8.0Hz, C-3"-H and C-5"-H) 7.48 (2H, d, J=8.0Hz, C-2"-H and C-6"-H)7.62 (1H, d C-5'-H) 7.30 (1H, d, J=6.5Hz and C-3'-H), 7.40 (1H, S, C-5-H)
B_3P_3	3.10 (6H, s, -$N(CH_3)_2$), 5.20 (1H, s , -NH_2),6.61 (1H, m , C-4'-H), 7.36 (1H, s , C-5-H)8.12 (2H, d , J=8.5Hz, C-3"-H and C-5"-H) 6.78 (2H, d , J=8.5Hz, C-2"-H and C-6"-H)7.67 (2H, d, J=6.0Hz, C-3'-H and C-5'-H)
B_4P_4	2.46 (3H, s, Ar-CH_3), 5.25 (2H, s, -NH_2), 6.67 (1H, m, C-4'-H) 7.45 (1H, s, C-5-H), 8.06 (2H, d, J=8.0Hz, C-3"-H and C-5"-H) 7.36 (2H, d, J=8.0Hz, C-2"-H and C-6"-H) 7.71(1H, d, J=6.0Hz, C-5'),7.60 (1H, d, J=6.0Hz, C-3'H)
B_5P_5	5.78 (2H, s, -NH_2), 6.62 (1H, m, C-4'-H),7.62 (1H, s , -C-3"-H) 7.64 (1H, d, J=6.5Hz, C-5'-H), 7.54 (1H, d, J=8.5Hz, C-5"-H) 7.41 (1H, d, J=8.5Hz, C-6"-H), 7.39 (1H, d, J=6.5Hz, C-3'-H)7.35 (1H, s, C-5-H)
B_6P_6	5.85 (2H,s, -NH_2), 6.61 (1H,m, C-4'-H), 7.60 (1H,s, C-5-H) 8.06 (1H, d, J=6.0Hz, C-5'-H), 7.78 (1H, d, J=6.0Hz, C-3'-H) 7.22-7.55(9H, m, Ar-H)
B_7P_7	3.87 (3H, s, C-4"-OCH_3), 5.11 (2H, s, C-2-NH_2), 6.56 (2H, d, J=6.0 Hz, C-3' and 5'-H), 7.07 (2H, d, J=8.5 Hz, C-3"and 5"-H), 7.37 (1H, s, C-5-H), 7.58 (1H, s, C-2'-H), 8.05 (2H, d, J=8.5 Hz, C-2" and 6"-H)
B_8P_8	5.63 (2H, s, C-4'-NH_2), 5.21 (2H, s, C-2-NH_2), 6.64 (2H, d, J=6.5 Hz, C-3'), 7.19 (2H, dd, J=8.5 Hz, C-2" and 6"-H), 7.37 (1H, s, C-5-H),8.084 (2H, dd, J=8.5 Hz, J=8.5 Hz, C-3" and 5"-H)
B_9P_9	5.63 (2H, s, C-4'-NH_2), 5.21 (2H, s, C-2-NH_2), 6.64 (2H, d, J=6.5 Hz, C-3'), 7.19 (2H, dd, J=8.5 Hz, C-2" and 6"-H), 7.37 (1H, s, C-5-H), 8.084 (2H, dd, J=8.5 Hz, J=8.5 Hz, C-3" and 5"-H)
$B_{10}P_{10}$	5.22 (1H, s, C-2-NH_2), 6.64-6.65 (1H, t, C-4'-H)7.62-7.58 (2H, m, C-3'), 7.79 (2H, d, J=8.0Hz, C-2″ , 6″-H)7.88 (1H, d ,J=16Hz, -CO-CH=) 8.24 (1H, d, J=15.6Hz, Ar-CH=)8.34 (2H, d, J=8.0Hz, C-3″and 5″-H)

ANTI-INFLAMMATORY ACTIVITY:

Experimental Procedure: 0.05 mL of 1 % carrageenan suspension was slowly injected subcutaneously into the subplantar region of the left hind paw to produce inflammation in all the groups. Groups III to XVII were treated with chalcones B_1-B_{15} (10 mg/kg). Group I used as carrageenan treated control was given only 1 % sodium CMC gel (1 mL/kg) whereas group II received aceclofenac (2 mg/kg). All these doses were administered orally and the induced paw oedema in each group was measured to assess the anti-inflammatory activity. The results and statistical analysis of anti-inflammatory activity of aceclofenac and the compounds tested are shown in Table 4.

Table4: Anti-inflammatory activity of tri-substituted pyrimidines (B_1P_1- $B_{10}P_{10}$).

Compound	**Ar**	**% inhibition ± SEM at various time intervals**					
		0.5 h	**1.0 h**	**2.0 h**	**3.0 h**	**4.0 h**	**6.0 h**
B_1P_1	4″-methylphenyl	21 ± 2	34 ± 1	39 ± 2	64 ± 1	74 ± 2	85 ± 2
B_2P_1	4″-fluorophenyl	26 ± 1*	38 ± 1*	59 ± 1*	78 ± 1*	88 ± 2	95 ± 1
B_3P_3	4″-chlorophenyl	25 ± 1	37 ± 1*	53 ± 1*	72 ± 2	82 ± 2	93 ± 2
B_4P_4	2″-chlorophenyl	24 ± 2*	37 ± 1	42 ± 1*	68 ± 1*	78 ± 1	82 ± 2
B_5P_5	2″,4″-difluorophenyl	28 ± 1*	39 ± 1*	60 ± 1	79 ± 2*	90 ± 2	98 ± 3
B_6P_6	2″,4″-dichlorophenyl	27 ± 1*	38 ± 1*	57 ± 2	78 ± 2	86 ± 2	95 ± 2
B_7P_7	3″-nitrophenyl	23 ± 2	36 ± 2*	41 ± 2	67 ± 2	77 ± 1	81 ± 2
B_8P_8	3″,4″,5″-trimethoxyphenyl	19 ± 1	30 ± 1*	35 ± 1	59 ± 1	70 ± 2	79 ± 2
B_9P_9	3″-nitro-4″-methylphenyl	22 ± 1	35 ± 1	40 ± 1*	66 ± 1	75 ± 1	80 ± 2
$B_{10}P_{10}$	5″-bromofuryl	20 ± 2	33 ± 1	38 ± 1*	60 ± 1*	71 ± 2	80 ± 2
Aceclofenac (standard)		28 ± 2	45 ± 2	65 ± 2	80 ± 2	97 ± 1	99 ± 2

DISCUSSIONS

From the above results it is evident that all the pyrimidines synthesized, showed anti-inflammatory activity with different paw oaedema values, but not comparable with that of the standard. Among the compounds tested compound **B_5P_5** and **B_6P_6** possessed maximum activity and this may be due to the presence of two fluorine substituents in the first case and two chlorine substituents in the later. However, the activity was not much higher with electron releasing substituents present on the phenyl ring.

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