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DESIGN, SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF PYRIMIDINE DERIVATIVES

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ABSTRACT

A series of 2-(3-(4-substitutedphenyl)-8-phenylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-10-yl)phenol (6-10) were synthesized by the reaction of 2-(4-hyrazinyl-7-phenylpyrido[2,3-d]pyrimidin-5-yl)phenol (5) with substituted benzaldehyde in glacial acetic acid. The starting material for the compounds was 2-hydroxybenzaldehyde. All the newly synthesized compounds were evaluated for their anti-inflammatory activity. The newly synthesized compounds have been characterized by elemental (C, H, N) and spectral (IR, and ^{1}HNMR) analysis.

KEYWORDS: Pyrimidine, Triazole, phenyl butazone, Anti-inflammatory activity.

INTRODUCTION

Heterocyclic compounds represents an important class of biological molecules. The heterocyclic molecules which posses pyrimidine and triazole moiety exhibit wide range of biological activities. Pyrimidines are one of the most important alkaloids molecules found extensively in biological system, which play vital role in many of the biochemical process. Pyrimidine derivatives found to posses high biological activities such as analgesic[1], anti-inflammatory[2-4], antimicrobial[5-6], antibacterial[7] etc. Moreover triazole is alternative vital pharmacodynamic heterocyclic nuclei that once in corporate in several heterocyclic templates have currently been possess wide spectrum of activities like antimicrobial[8-9], anticancer[10], antitubercular[11], anticonvulsant[12] and anti-inflammatory[13] etc. Encouraged by these derivatives, we synthesized novel pyrimidine derivatives with triazole moiety and evaluated their anti-inflammatory activity.

MATERIALS AND METHODS

Chemistry

All reagents and solvents were of analytical grade and used directly. The melting points were determined in open glass capillaries tubes. The homogeneity of all newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel G plates and spots were located by using iodine chamber. Elemental analysis (C, H, N) of all the synthesized compounds were determined by perkin-Elmer 2400 elemental analyzer. The IR spectra were recorded on a Beckman Acculab-10 spectrometer (ν□ max in cm^{-1}) and the ^{1}H NMR spectra were recorded by Brucker DPX-300 MHz using $CDCl_3$ as solvent. The animal research study was approved by the animal ethical committee (CPCSEA). The synthesis of the target compounds was accomplished according to the reaction sequence illustrated in Scheme 1.

Anti-inflammatory activity

Preliminary study at all the three tested dose (25, 50, 100 mg/kg) were compared with standard drug, phenyl butazone. These compounds were administered either by oral or intraperitoneal route. Rats of either sex weighing 60-130 were divided into groups of 6 animals each. A freshly prepared suspension of carrageenin (1.0% in 0.9% saline) 0.05 ml, was injected under the planter aponeurosis of right paw of the rat by the method of Winter et al.[14]. One group was kept as control and the animals of other group were pretreated with the test drugs given orally 1 h before the carrageenin injection. The volume of foot was measured before one and 3 h after carrageenin treatment with the help of a Plethysmometer. The mean increase of paw volume in each group was measured and percentage anti-inflammatory activity was calculated according to the formula given below-

Percentage of inhibition of oedema = $(1-V_t/V_c) \times 100$

Where V_t and V_c are the volumes of oedema in drug treated and the control groups.

RESULTS AND DISCUSSION

All the newly synthesized compounds 1-10 were tested in vivo in order to evaluate their anti inflammatory activity. These compounds were screened for their anti-inflammatory activities at a dose of 50 mg/kg p.o. exhibited substantive anti-inflammatory activity of varying degree from 6.4-37.6 are given in table-1. The

characteristic feature of this series is substituted phenyl moiety at third position of triazole nucleus. It was observed that compound 10 showed maximum anti-inflammatory 37.6% inhibition of oedema. This compound showed better anti-inflammatory activities than standard drug phenyl butazone at the three graded doses of 25,50 and 100 mg/kg.

Table 1: Anti –inflammatory activity data of compounds 1-10.

Compound No.	Dose (mg/kg p.o.)	Anti-inflammatory activity % oedema inhibition relative to control.
1	50	6.4
2	50	10.7
3	50	12.9
4	50	14.2
5	50	15.7
6	50	20.3
7	50	25.4
8	50	29.6
9	50	34.2
10	25 50 100	18.1 37.6 68.5
Phenylbutazone	25 50 100	17.6 36.3 65.6

Synthesis of (E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (1)

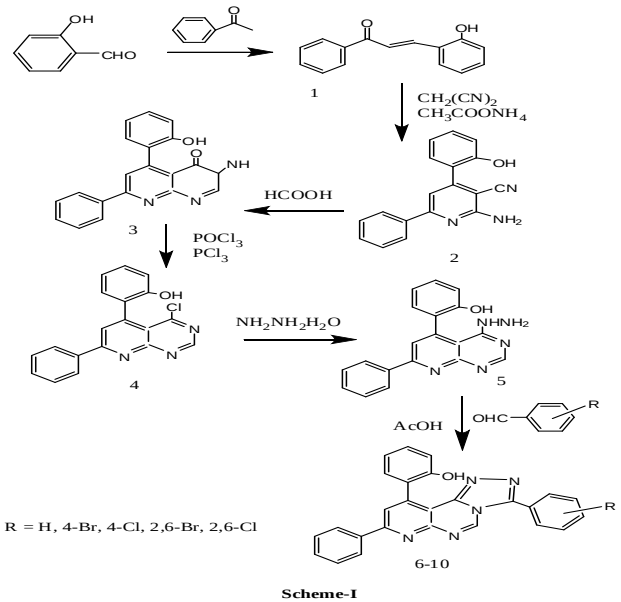
A solution of 2-hydroxy benzaldehyde (0.01 mol) and acetophenone (0.01 mol) in 20 ml of ethanol was treated with 20 ml of 60% KOH solution at 5-10^{0}C. The reaction mixture was stirred at room temperature for 4hr. It was then diluted with water (20 ml) and extracted with diethyl ether (20 ml). The aqueous solution was acidified with dilute HCl and the solid obtained was filtered, washed with water and dried. The crude product was purified by recrystallization from benzene to furnish compound 1. Yield (67), m.p > 156 ^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1540 (C-C aromatic ring), 1724 (-C=O), 3017 (C-H aromatic), 3425 (OH); ^{1}H-NMR (DMSO-d$_6$ δ ppm): 7.72-8.30 (m, 9H, ArH), 8.58 (s, 1H, =CHAr), 8.97 (s, 1H, CO-CH), 12.35 (s, 1H, OH exchangeable); Anal. Calcd. For $C_{15}H_{12}O_2$: C, 80.34; H, 5.39: Found: C, 80.36; H, 5.35%.

Synthesis of 2-amino-4-(2-hydroxyphenyl)-6-phenylnicotinonitrile (2)

To a solution of compound 1 (0.01 mol) in acetic acid (10 ml), malononitrile (0.01 mol) and ammonium acetate (0.01 mol) were added and the reaction mixture was refluxed for 5hr. The reaction mixture was cooled to room temperature and decomposed in ice cold water (50 ml). The solid separated was filtered, dried and purified in ethanol to furnish compound 2. Yield (56), m.p > 168^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1298 (C-N), 1545 (C-C aromatic ring), 1574 (-N=CH), 3010 (C-H aromatic), 3422 (-OH); ^{1}H-NMR (DMSO-d$_6$ δ ppm): 4.63 (hump, 2H, NH$_2$ exchangeable), 7.70-8.32 (m, 9H, ArH), 8.78 (s.1H, CH of pyridine ring), 12.27 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63: Found: C, 75.28; H, 4.54; N, 14.63%.

Synthesis of 5-(2-hydroxyphenyl)-7-phenylpyrido[2,3-d]pyrimidin-4(3H)-one (3)

A solution of compound 2 (2.09 g, 0.01 mol) in formic acid (80%) (10ml) was refluxed for 10h. The solvent was evaporated under reduced pressure and the obtained residue was triturated with ethanol, the solid formed was filtered off, dried and crystallized to give compound 3. Yield (52), m.p > 176^{0}C; IR (KBr) $_{max}$ in cm^{-1} 1293 (C-N), 1542 (C-C aromatic ring), 1575 (-N=CH), 1728 (-C=O), 3011 (C-H aromatic), 3320 (-C-NH); ^{1}H-NMR (DMSO-d$_6$ δ ppm): 7.48 (br, 1H, NH exchangeable), 7.71-8.31 (m, 9H, ArH), 8.77 (s.2x1H, CH of pyropyrimidine ring), 12.24 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33: Found: C, 72.38; H, 4.14; N, 13.36%.



Scheme-I

Synthesis of 2-(4-chloro-7-phenylpyrido[2,3-d]pyrimidin-5-yl)phenol (4)

A mixture of compound 3 (2.37g, 0.01 mol), phosphorus pentachloride (2.05g, 0.03 mol) and phosphorus oxychloride (20 ml) was heated under reflux for 2h. The reaction mixture was cooled and poured into ice, the resulting precipitate was filtered off, dried and crystallized to give compound 4. Yield (48), m.p: > 172^0C; IR (KBr) $_{max}$ in cm^{-1} 1290 (C-N), 1545 (C-C aromatic ring), 1579 (-N=CH), 1722 (-C=O), 3015 (C-H aromatic), 3326 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 7.70-8.30 (m, 9H, ArH), 8.76 (s.2x1H, CH of pyropyrimidine ring), 12.26 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{19}H_{12}ClN_3O$: C, 68.37; H, 3.62; N, 12.59: Found: C, 68.34; H, 3.65; N, 12.56%.

Synthesis of 2-(4-hyrazinyl-7-phenylpyrido[2,3-d]pyrimidin-5-yl)phenol (5)

A mixture of compound 4 (0.01 mol) and hydrazine hydrate (3 ml) in absolute ethanol (20 ml) was refluxed for 1h. After cooling, the formed precipitate was filtered off, dried and crystallized to give compound 5. Yield (45), m.p > 180^0C; IR (KBr) $_{max}$ in cm^{-1} 1295 (C-N), 1538 (C-C aromatic ring), 1570 (-N=CH), 1729 (-C=O), 3016 (C-H aromatic), 3328 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 4.62 (hump, 2H, NH_2 exchangeable), 7.43 (br, 1H, NH exchangeable), 7.70-8.33 (m, 9H, ArH), 8.75 (s.2x1H, CH of pyropyrimidine ring), 12.29 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{19}H_{15}N_5O$: C, 69.29; H, 4.59; N, 21.26: Found: C, 69.27; H, 4.55; N, 21.24%.

Synthesis of 2-(3-(4-substitutedphenyl)-8-phenylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-10-yl)phenol (6-10)

A mixture of compound 5 (2.50g, 0.01 mol) and substituted benzaldehyde (1.50g, 0.01 mol) in glacial acetic acid (50 ml) was heated under reflux for 6h. After cooling the obtained solid was collected by filtration, dried and crystallized to give compounds 6-10. The physical and spectral data of compounds 6-10 were given below.

2-(3,8-diphenylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-10-yl)phenol (6)

Yield (42), m.p > 178^0C; IR (KBr) $_{max}$ in cm^{-1} 1292 (C-N), 1543 (C-C aromatic ring), 1571 (-N=CH), 1722 (-C=O), 3010 (C-H aromatic), 3321 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 8.78 (s.2x1H, CH of pyropyrimidine ring), 7.70-8.31 (m, 14H, ArH), 12.27 (s, 1H, OH exchangeable);; Anal. Calcd. for $C_{26}H_{17}N_5O$: C, 75.17; H, 4.12; N, 16.86: Found: C, 75.19; H, 4.15; N, 16.84%.

2-(3-(4-Bromophenyl)-8-phenylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-10-yl)phenol (7)

Yield (39), m.p > 182^0C; IR (KBr) $_{max}$ in cm^{-1} 1295 (C-N), 1540 (C-C aromatic ring), 1573 (-N=CH), 1729 (-C=O), 3015 (C-H aromatic), 3327 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 8.76 (s.2x1H, CH of pyropyrimidine ring), 7.71-8.33 (m, 13H, ArH), 12.23 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{26}H_{16}BrN_5O$: C, 63.17; H, 3.26; N, 14.17: Found: C, 63.14; H, 3.25; N, 14.14%.

2-(3-(4-chlorophenyl)-8-phenylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-10-yl)phenol (8)

Yield (41), m.p > 169^0C; IR (KBr) $_{max}$ in cm^{-1} 1290 (C-N), 1548 (C-C aromatic ring), 1572 (-N=CH), 1726 (-C=O), 3013 (C-H aromatic), 3329 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 8.73 (s.2x1H, CH of pyropyrimidine ring), 7.72-8.32 (m, 13H, ArH), 12.21 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{26}H_{16}ClN_5O$: C, 69.41; H, 3.58; N, 15.57: Found: C, 69.44; H, 3.55; N, 15.54%.

2-(3-(2,6-dibromophenyl)-8-phenylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-10-yl)phenol (9)

Yield (36), m.p > 188^0C; IR (KBr) $_{max}$ in cm^{-1} 1297 (C-N), 1545 (C-C aromatic ring), 1576 (-N=CH), 1725 (-C=O), 3012 (C-H aromatic), 3324 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 8.74 (s.2x1H, CH of pyropyrimidine ring), 7.71-8.30 (m, 12H, ArH), 12.27 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{26}H_{15}Br_2N_5O$: C, 54.48; H, 2.64; N, 12.22: Found: C, 54.45; H, 2.67; N, 12.24%.

2-(3-(2,6-dichlorophenyl)-8-phenylpyrido[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-10-yl)phenol (10)

Yield (38), m.p > 185^0C; IR (KBr) $_{max}$ in cm^{-1} 1295 (C-N), 1543 (C-C aromatic ring), 1573 (-N=CH), 1724 (-C=O), 3015 (C-H aromatic), 3322 (-C-NH); ^{1}H-NMR (DMSO-d_6 δ ppm): 8.78 (s.2x1H, CH of pyropyrimidine ring), 7.70-8.31 (m, 12H, ArH), 12.25 (s, 1H, OH exchangeable); Anal. Calcd. for $C_{26}H_{15}Cl_2N_5O$: C, 64.48; H, 3.12; N, 14.46: Found: C, 64.44; H, 3.15; N, 14.44%.

CONCLUSION

Anti-inflammatory activity results indicated that all the derivatives of pyrimidine derivatives showed this activity. Moreover, compound 10 (having 2,6-dichlorophenyl ring) showed more potent anti-inflammatory activity which was more effective than standard drug phenyl butazone.

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