WALAILAK JOURNAL
http://wjst.wu.ac.th Health Sciences

Novel Series of Pyrimidine Derivatives as Anti-inflammatory Agents

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Received: 16 January 2015, Revised: 21 August 2015, Accepted: 29 September 2015

Abstract

A series of compound 6-bromo-3-(6-substitutedphenyl)-2-(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one (**BT_1M-$BT_{10}M$**), 3(2-((piperidin-1-yl) methylamino)-6- (2-substitutedphenyl) pyrimidin-4-yl)-6-bromo-2*H*-chromen-2-one (**BT_1P-$BT_{10}P$**) has been synthesized from 3-(2-amino-6 -pyrimidin- 4-yl)-6- bromo- 2H-chromen-2-one (**T_1-T_{10}**). The structures of the synthesized compounds were elucidated by I.R., ^{1}HNMR, elemental analysis and mass spectroscopic techniques. The synthesized compounds were screened for *in-vivo* anti-inflammatory activity at a dose of 50 mg/kg body weight by a carrageenan-induced rat paw edema method. Among them, compounds **BT_8M**, **BT_4P**, **BT_5P**, and **BT_7P** exhibited significant anti-inflammatory activity. Compounds **BT_3M**, **BT_9M**, **$BT_{10}M$**, **BT_9P**, and **$BT_{10}P$** showed highly significant anti-inflammatory activity. The remaining compounds showed less anti-inflammatory activity, comparable to that of standard drug diclofenac sodium.

Keywords: Pyrimidine, anti-inflammatory activity, rat paw edema

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been among the most widely used therapeutics for decades, primarily for the treatment of pain and inflammation in arthritis. However, long-term clinical usage of NSAIDs is associated with significant side effects, such as gastrointestinal lesions, bleeding, and nephrotoxicity. Therefore, the discovery of new, safer, anti-inflammatory and analgesic drugs represents a challenging goal for such a research area [1].

Pyrimidines, being an integral part of DNA and RNA, possess diverse pharmacological properties as effective bactericide and fungicides [2]. Nitrogen containing heterocyclic rings, such as pyrimidine, is a promising structural moiety for drug design. Pyrimidine derivatives are found in a number of useful drugs, and are associated with many biological activities [3]. Condensed pyrimidine derivatives have been reported as being anti-microbial [4], analgesic, anti-viral, anti-inflammatory [5], anti-HIV, anti-tubercular [6], anti-tumor [7], anti-neoplastic [8], anti-malarial [9], diuretic [10], and cardiovascular agents [11]. Pyrimidine compounds are also used as hypnotic drugs for the nervous system [12], calcium-sensing receptor antagonists [13], and also as antagonists of the human A2A adenosine receptor [14]. Like pyrimidine, coumarin also exhibits diverse biological properties [15]. It was envisaged that these 2 active pharmacophores, if linked together, would generate novel molecular templates which are likely to exhibit interesting biological properties in animal models. The above-cited applications prompted us to synthesize a series of new compounds, reported in this article.

Owing to its importance, we here describe in this paper the synthesis of new pyrimidine derivatives from 3-acetyl-6-bromo-2H-chromen-2-one (3). The compounds were screened for their anti-inflammatory activity. Thus, we have created new avenues to explore the potent heterocyclic moieties for pharmacological activities in medicinal chemistry.

Materials and methods

Chemistry

All reagents and solvents were used as obtained from the supplier. The melting points of the products were determined by the open capillaries method and were uncorrected. I.R. Spectra (KBr) were recorded on a Fourier transform infrared (FTIR) Spectrophotometer (Shimadzu FTIR 84005, 4000 - 400 cm^{-1}). ^{1}H-nuclear magnetic resonance (NMR) spectra were recorded on a JEOL AL300 FTNMR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard, with ^{1}H resonance frequency of 300 MHz chemical shift values expressed in δ ppm. Mass spectra were recorded on a 70 eV EI-MS-QP 1000 EX (Schimadzu). The elemental analysis was carried out using a Heraus CHN rapid analyser. The homogeneity of the compounds was described by TLC on alumina silica gel using a solvent system "toluene: ethyl acetate: formic acid" (5:4:1) and "benzene: acetone" (9:1), detected by iodine vapours. The physical data of all these compounds are summarized in **Tables 1 - 4**.

General procedures for the preparation of compounds

Synthesis of 3-acetyl-6-bromo-2H-chromen-2-one (3):

A mixture of 5-bromosalicyldehyde (0.02 mol) and ethyl acetoacetate (2) (0.03 mol) in ethanol were placed in a round bottom flask. To this mixture, a few drops of piperidine were added and refluxed for 2-3 h. After completion of the reaction, the content was poured onto crushed ice. The solid separated was filtered, dried, and recrystallized from ethanol. Compound 3-acetyl-6-bromo- 2H-chromen-2-one can be explained on the basis of "Knoevenagel reaction". The purity of compound was established on the basis of TLC and melting point.

Synthesis of 3-acetyl-6-bromo- 2H-chromen-2-one: This was obtained from the reaction of 5-bromo salicyldehyde (1) with ethylacetoacetate in the presence of piperidine. M.P. 115 - 117 ºC; % Yield:75 %; molecular formula; $C_{11}H_7BrO_3$; molecular weight:267.08; IR (KBr, cm^{-1}): 1735.26 and 1675.61 (C=O), 1549.96 (C=C), 1232.96 (aryl ethers, C-O-C); ^{1}H NMR ($CDCl_3$-d_6, δ, ppm): 2.72 (s, 3H, CH_3), 7.25 - 7.78 (m, 3H, Ar-H), 8.40 (s, 1H, Ar-H).

Synthesis of compounds (BS_1-BS_{10}):

Equimolar quantities of 3-acetyl-6-bromo-2H-chromen-2-one and different quantities of substituted benzaldehyde were refluxed in absolute ethanol, using piperidine as a catalyst, for 8 - 10 h. The solution mixture was concentrated and poured onto crushed ice. The compound so obtained was filtered by a vacuum pump, dried, and recrystallized from ethanol to get pure crystalline solid. The formation of compounds (BS_1-BS_{10}) can be explained on the basis of "Claisen-Schmidt condensation".

Synthesis of 6-bromo-3-((E)-3-(2-chlorophenyl)-acryloyl)-2H-chromen-2-one (BS_1): This was obtained from the reaction of compound 3 with 2-Chlorobenzaldehyde. IR (KBr, cm^{-1}): 1629.74 and 1608.52 (C=O), 1585.38 (C=C), 1116.71 (C-O-C), 749.62 (C-Cl), 526.53(C-Br).

Synthesis of 6-bromo-3-((E)-3-(3-chlorophenyl)-acryloyl)-2H-chromen-2-one (BS_2): This was obtained from the reaction of compound 3 with 3-Chlorobenzaldehyde. IR (KBr, cm^{-1}): 1688.5 and 1635.52 (C=O), 1589.23 (C=C), 1141.78 (C-O-C), 694.33 (C-Cl), 576.68 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(4-chlorophenyl)-acryloyl)-2H-chromen-2-one (BS_3): This was obtained from the reaction of compound 3 with 4-Chlorobenzaldehyde. IR (KBr, cm^{-1}): 1772.74 and 1608.52 (C=O), 1571.88 (C=C), 1176.50 (C-O-C), 757.97 (C-Cl), 590.18 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(2-bromophenyl)-acryloyl)-2H-chromen-2-one (BS_4): This was obtained from the reaction of compound 3 with 2-Bromobenzaldehyde. IR (KBr, cm^{-1}): 1741.80 and 1614.03 (C=O), 1557.71 (C=C), 1159.41 (C-O-C), 638.67 (C-Cl), 523.31 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(3-bromophenyl)-acryloyl)-2H-chromen-2-one (BS_5): This was obtained from the reaction of compound 3 with 3-Bromobenzaldehyde. IR (KBr, cm^{-1}): 1637.45 and 1627.81 (C=O), 1585.38 (C=C), 1155.28 (C-O-C), 754.12 (C-Cl), 565.10 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(4-bromophenyl)-acryloyl)-2H-chromen-2-one (BS_6): This was obtained from the reaction of compound 3 with 4-Bromobenzaldehyde. IR (KBr, cm^{-1}): 1683.74 and 1635.22 (C=O), 1504.37 (C=C), 1128.28 (C-O-C), 698.18 (C-Cl), 594.03 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(2-methoxyphenyl)-acryloyl)-2H-chromen-2-one (BS_7): This was obtained from the reaction of compound (3) with 2-Methoxybenzaldehyde. IR (KBr, cm^{-1}): 1734.87 and 1675.83 (C=O), 1550.38 (C=C), 1069.87 (C-O-C), 659.77 (C-Cl), 559.43 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(3-methoxyphenyl)-acryloyl)-2H-chromen-2-one (BS_8): This was obtained from the reaction of compound 3 with 3-Methoxybenzaldehyde. IR (KBr, cm^{-1}): 2854.45 (C-H stretch of O-CH_3), 1670.24 and 1637.45 (C=O), 1585.38 (C=C), 1151.42 (C-O-C), 757.97 (C-Cl), 570.89 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(2, 4-dichlorophenyl)-acryloyl)-2H-chromen-2-one (BS_9): This was obtained from the reaction of compound 3 with 2, 4-dichlorobenzaldehyde. IR (KBr, cm^{-1}): 1691.46 and 1641.31 (C=O), 1577.66 (C=C), 1149.50 (C-O-C), 696.25 (C-Cl), 578.60 (C-Br).

Synthesis of 6-bromo-3-((E)-3-(2, 6-dichlorophenyl)-acryloyl)-2H-chromen-2-one (BS_{10}): This was obtained from the reaction of compound 3 with 2, 6-dichlorobenzaldehyde. IR (KBr, cm^{-1}): 1691.40 and 1639.38 (C=O), 1585.35 (C=C), 1155.28 (C-O-C), 692.40 (C-Cl), 588.25 (C-Br).

Synthesis of compounds (BT_1-BT_{10}):

A mixture of compounds (BS_1-BS_{10}) (0.01 mol) and guanidine HCl (0.02 mol) was refluxed in ethanol for 8 - 10 h. The content was evaporated to dryness, and so the product obtained was washed with water repeatedly and recrystallized from ethanol.

Synthesis of 3-(2-amino-6-(2-chlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_1): This was obtained from reacting BS_1 with guanidine HCl. IR (KBr, cm^{-1}): 3151.47 (N-H stretch), 1650.95 (C=O), 1596.95 & 1361.65 (C-N stretch), 1249.79 (C-O-C), 894.91 (C-N bend), 817.76 (C-Cl), 759.90 (NH_2 bend), 659.61 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.72 (s, 2H, NH_2), 6.72 - 7.25 (m, 9H, Ar-H).

Synthesis of 3-(2-amino-6-(3-chlorophenyl)-pyrimidin-4-yl)-6-bromo-2H–chromen-2-one (BT_2): This was obtained from reacting BS_2 with guanidine HCl. IR (KBr, cm^{-1}) 3294.19 (N-H stretch), 1654.81 (C=O), 1596.95 & 1253.64 (C-N stretch), 1234.36 (C-O-C), 871.76 (C-N bend), 817.76 (C-Cl), 763.76 (NH_2 bend), 659.61 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.88 (s, 2H, NH_2), 6.84 - 7.25 (m, 9H, Ar-H)

Synthesis of 3-(2-amino-6-(4-chlorophenyl)-pyrimidin-4-yl)-6-bromo-2H–chromen-2-one (BT_3): This was obtained from reacting BS_3 with guanidine HCl. IR (KBr, cm^{-1}): 3340.48 (N-H stretch), 1685.67 (C=O), 1593.09 & 1365.51 (C-N stretch), 1238.21 (C-O-C), 871.76 (C-N bend), 817.76 (C-Cl), 756.04 (NH_2 bend), 628.75 (C-Br) ; ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 4.88 (s, 2H, NH_2), 6.90 - 7.48 (m, 9H, Ar-H).

Synthesis of 3-(2-amino-6-(2-bromophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_4): This was obtained from reacting BS_4 with guanidine HCl. IR (KBr, cm^{-1}) 3355.91 (N-H stretch), 1654.81 (C=O), 1542.95 & 1365.51 (C-N stretch), 1238.21 (C-O-C), 875.62 (C-N bend), 779.19 (NH_2 bend), 628.75 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 3.51 (s, 2H, NH_2), 6.90 - 7.60 (m, 9H, Ar-H).

Synthesis of 3-(2-amino-6-(3-bromophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_5): This was obtained from reacting BS_5 with guanidine HCl. IR (KBr, cm^{-1}): 3355.91 (N-H stretch), 1654.81 (C=O), 1542.95 & 1373.22 (C-N stretch), 1269.07 (C-O-C), 871.76 (C-N bend), 779.19 (NH_2 bend), 628.75 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 3.94 (s, 2H, NH_2), 6.72 - 7.41 (m, 9H, Ar-H).

Synthesis of 3-(2-amino-6-(4-bromophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_6): This was obtained from reacting BS_6 with guanidine HCl. IR (KBr, cm^{-1}): 3417.63 (N-H stretch), 1666.38 (C=O), 1577.66 & 1384.79 (C-N stretch), 1234.36 (C-O-C), 871.76 (C-N bend), 759.90 (NH_2 bend), 628.75 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 3.51 (s, 2H, NH_2), 6.92 - 7.52 (m, 9H, Ar-H)

Synthesis of 3-(2-amino-6-(2-methoxyphenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_7): This was obtained from reacting BT_7 with guanidine HCl. IR (KBr, cm^{-1}) : 3382.91 (N-H stretch), 2835.16 (C-H stretch of O-CH_3), 1670.24 (C=O), 1550.66 & 1384.79 (C-N stretch), 1477.37 (CH_3 umbrella mode), 1245.93 (C-O-C), 871.76 (C-N bend), 756.04 (NH_2 bend), 628.75 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 3.88 (s, 3H, CH_3), 3.93 (s, 2H, NH_2), 6.90 - 7.60 (m, 9H, Ar-H).

Synthesis of 3-(2-amino-6-(3-methoxyphenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_8): This was obtained from reacting BS_8 with guanidine HCl. IR (KBr, cm^{-1}): 3367.48 (N-H stretch),

2935.46 (C-H stretch of O-CH_3), 1666.38 (C=O), 1577.66 & 1384.79 (C-N stretch), 1477.37 (CH_3 umbrella mode), 1265.22 (C-O-C), 871.76 (C-N bend), 783.05 (NH_2 bend), 628.75 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 3.882 (s, 3H, CH_3), 3.887 (s, 2H, NH_2), 6.92 - 7.73 (m, 9H, Ar-H)

Synthesis of 3-(2-amino-6-(2,4-dichlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_9): This was obtained from reacting BS_9 with guanidine HCl. IR (KBr, cm^{-1}): 3417.63 (N-H stretch), 1677.95 (C=O), 1589.23 and 1384.79 (C-N stretch), 1234.36 (C-O-C), 867.91 (C-N bend), 817.76 (C-Cl), 775.33 (NH_2 bend), 628.75 (C-Br); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 5.22 (s, 2H, NH_2), 6.93 - 7.42 (m, 7H, Ar-H), 7.97 (s, 1H, CH).

Synthesis of 3-(2-amino-6-(2,6-dichlorophenyl)-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_{10}): This was obtained from reacting BS_{10} with guanidine HCl. IR (KBr, cm^{-1}): 3425.34 (N-H stretch), 1604.66 (C=O), 1589.23 and 1384.79 (C-N stretch), 1265.22 (C-O-C), 871.76 (C-N bend), 817.76 (C-Cl), 775.33 (NH_2 bend), 628.75 (C-Br) ; ^{1}HNMR ($CDCl_3$-d_6, δ, ppm) : 5.18 (s, 2H, NH_2), 6.72 - 7.41 (m, 7H, Ar-H), 7.94 (s, 1H, CH).

Synthesis of compounds (BT_1M-BT_{10}M):

A mixture of compounds BT_1-BT_{10} (0.01 mol), morpholine (0.01 mol) and formaldehyde (0.02) was refluxed in ethanol for 6 - 10 h. The reaction mixture was reduced to half of its volume and poured onto crushed ice. The product so obtained was washed with water repeatedly, dried, and recrystallized from ethanol. The formation of compounds (BT_1M-BT_{10}M) can be explained on the basis of "Mannich reaction".

Synthesis of 6-bromo- 3-(6-(2-chlorophenyl)-2-(morpholinomethylamino)pyrimidin-4- yl) -2H-chromen-2-one (BT_1M): This was obtained from reacting BT_1 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3440.77 (N-H stretch), 1641.31 (C=O),1384.79 (C=N stretch),1629.74 (C=C),1116.71 (C-O-C); ^{1}HNMR ($CDCl_3$-d_6, δ, ppm): 1.253 (t,4H,2 x CH_2), 2.506(t,4H,2 x CH_2) , 3.737 (t,4H,2 x CH_2), 4.253 (s,2H, CH_2) 6.498 - 7.516 (m, 9H, Ar-H); MS m/z: 527.0, 410.9,303.1(100 %), 217.0, 151.1; elemental analysis ($C_{24}H_{20}N_4O_3ClBr$), found % (calculated %): C,54.61 (54.62); N,10.60 (10.61).

Synthesis of 6-bromo-3-(6-(3-chlorophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_2M): This was obtained from reacting BT_2 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3417.63 (N-H stretch), 1645.8 (C=O),1587.31 and 1382.87 (C=N stretch) ,1573.81 (C=C),1134.07 (C-O-C), 852.48 (C-N bend) , 688.18 (C-Cl); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.50 (s, 1H, NH), 2.093-2.28 (t, 4H, 2 x CH_2), 3.43 (t, 4H, 2 x CH_2), 4.459 (s, 2H, CH_2), 6.66 - 7.89 (m, 9H, Ar-H).

Synthesis of 6-bromo-3-(6-(4-chlorophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_3M): This was obtained from reacting -BT_3 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3452.34 (N-H stretch), 1660.60 (C=O),1604.66 and 1384.79 (C=N stretch) ,1575.73 (C=C),1153.35 (C-O-C), 746.40 (C-N bend) , 665.40 (C-Cl); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.514 (s, 1H, NH), 1.252 - 1.687 (t, 4H, 2 x CH_2), 3.729 (t, 4H, 2 x CH_2), 4.254 (s, 2H, CH_2), 6.907 - 7.256 (m, 9H, Ar-H); MS m/z: 527.8, 304.0, 222.93, 204.0, 163.0; elemental analysis ($C_{24}H_{20}N_4O_3ClBr$), found % (calculated %): C,54.60 (54.62);N, 10.60 (10.61).

Synthesis of 6-bromo-3-(6-(2-bromophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_4M): This was obtained from reacting BT_4 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3417.63 (N-H stretch), 1674.10 (C=O), 1612.38 and 1377.08 (C=N stretch), 1562.23 (C=C),1377.08 (C-O-C), 829.33 (C-N bend) , 540.03 (C-Br); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.514 (s, 1H, NH), 1.254 - 2.392 (t, 4H, 2 x CH_2), 3.740 (t, 4H, 2 x CH_2), 4.051 (s, 2H, CH_2), 7.260 - 8.668 (m, 9H, Ar-H); MS m/z: 517.0, 347.0, 206.9, 156.2,100.2 (100 %); elemental analysis ($C_{24}H_{20}N_4O_3Br_2$), found % (calculated %): C, 50.39 (50.37); N, 9.77 (9.79).

Synthesis of 6-bromo-3-(6-(3-bromophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_5M): This was obtained from reacting BT_5 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3421.48 (N-H Stretch), 1677.95 (C=O), 1612.38 and 1365.51 (C=N stretch) , 1558.38 (C=C), 1365.51 (C-O-C), 871.76 (C-N bend) , 551.60 (C-Br); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.305 (s, 1H, NH), 1.138 - 1.305 (t, 4H, 2 x CH_2), 3.583-3.856 (t, 4H, 2 x CH_2), 5.290 (s, 2H, CH_2), 6.980 - 7.181 (m, 9H, Ar-H).

Synthesis of 6-bromo-3-(6-(4-bromophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_6M): This was obtained from reacting BT_6 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3402.20 (N-H stretch), 1685.67 (C=O), 1604.66 and 1365.51 (C=N stretch) , 1558.38 (C=C), 1164.92 (C-O-C), 821.62 (C-N bend), 570.89 (C-Br).^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.331 (s, 1H, NH), 1.124 - 1.300 (t, 4H, 2 x CH_2), 3.353-3.908 (t, 4H, 2 x CH_2), 5.290 (s, 2H, CH_2), 6.629 - 7.786 (m, 9H, Ar-H).

Synthesis of 6-bromo-3-(6-(2-methoxyphenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_7M): This was obtained from reacting BT_7 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3261.40 (N-H stretch), 2835.16 (C-H stretch of O-CH_3), 1641.31 (C=O), 1629.74 and 1384.79 (C=N stretch),1596.95 (C=C),1114.78 (C-O-C); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.499 (s, 1H, NH), 1.154 - 1.714 (t, 4H, 2 x CH_2), 2.905 (t, 4H, 2 x CH_2), 3.696(s, 3H,OCH_3) 4.254 (s, 2H, CH_2), 6.944 - 7.293 (m, 9H, Ar-H) ;MS m/z: 523.1, 237.0 (100 %), 221.1, 205.1, 193.1;elemental analysis ($C_{25}H_{23}N_4O_3Br$), found % (calculated %): C,50.39 (57.37); N, 10.71 (10.70).

Synthesis of 6-bromo-3-(6-(3-methoxyphenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_8M): This was obtained from reacting -BT_8 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3440.77 (N-H stretch), 2854.45 (C-H stretch of O-CH_3), 1608.10 (C=O), 1608.52 and 1384.79 (C=N stretch), 1550.66 (C=C), 1137.92 (C-O-C), 894.91 (C-N, bend), 559.32 (C-Br); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.515 (s, 1H, NH), 1.253-1.277 (t, 4H, 2 x CH_2), 3.735-3.833 (t, 4H, 2 x CH_2), 3.833(s, 3H, OCH_3), 4.253 (s, 2H, CH_2), 6.772 - 7.258 (m, 9H, Ar-H).

Synthesis of 6bromo-3-(6-(2,4-dichlorophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one (BT_9M): This was obtained from reacting BT_9 with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3400.27 (N-H stretch), 1608.52 (C=O), 1614.31 (C=N stretch), 1556.45 (C=C); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.496 (s, 1H, NH), 1.125-2.496 (t, 4H, 2 x CH_2), 3.707-3.908 (t, 4H, 2 x CH_2), 4.283 (s, 2H, CH_2), 6.283 - 7.633 (m, 8H, Ar-H); MS m/z: 338, 301.0, 196.11, 100.2 (100 %); elemental analysis ($C_{24}H_{20}N_4O_3Br_2$), found % (calculated %): C, 50.39 (50.37); N, 9.77 (9.79).

Synthesis of 6-bromo-3-(6-(2,6-dichlorophenyl)-2-(morpholinomethylamino)pyrimidin-4-yl)-2H-chromen-2-one ($BT_{10}M$): This was obtained from reacting BT_{10} with morpholine and formaldehyde. IR (KBr, cm^{-1}): 3421.48 (N-H stretch),1608.52 (C=O),1356.08 (C=N stretch),754.88 (C-N, bend); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.80 (s, 1H, NH), 1.117-2.643 (t, 4H, 2 x CH_2), 3.323 - 3.838 (t, 4H, 2 x CH_2), 5.290 (s, 2H, CH_2), 6.910-7.645 (m, 8H, Ar-H).

Synthesis of compounds (BT_1P-$BT_{10}P$):

A mixture of compound BT_1-BT_{10} (0.01 mol), piperidine (0.01 mol) and formaldehyde (0.02) was refluxed in ethanol for 6 - 10 h. The reaction mixture was reduced to half of its volume and poured onto crushed ice. The product so obtained was washed with water repeatedly, dried, and recrystallized from ethanol. The formation of compounds (BT_1P-$BT_{10}P$) can be explained on the basis of "Mannich reaction".

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(2-chlorophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_1P): This was obtained from reacting BT_1 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3440.77 (N-H stretch), 1608.10 (C=O), 1608.52 and 1384.79 (C=N stretch), 1550.66 (C=C), 1137.92 (C-O-C), 894.91 (C-N, bend), 559.32 (C-Br); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.640 (s, 1H, NH), 1.213 - 2.390 (m, 10H, 5 x CH_2), 4.254 (s, 2H, CH_2), 6.406 - 7.635 (m, 9H, Ar-H); MS m/z: 526.3, 301.0, 285.0, 281.0 (100 %), 267.1, 208.2,163.0; elemental analysis ($C_{25}H_{22}N_4O_2Cl$ Br), found % (calculated %): C, 57.09 (57.10); N, 10.64 (10.65).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(3-chlorophenyl)pyrimidin-4-yl)-6-bromo-2H- chromen -2-one (BT_2P): This was obtained from reacting BT_2 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3458.20 (N-H stretch), 1637.45 (C=O), 1612.52 and 1384.79 (C=N stretch), 1581.52 (C=C), 1155.28 (C-O-C), 823.55 (C-N, bend); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.42(s, 1H, NH), 1.43 - 2.54 (m, 10H, 5 x CH_2), 4.45 (s, 2H, CH_2), 6.53 - 7.82 (m, 9H, Ar-H).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(4-chlorophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_3P): This was obtained from reacting (BT_3) with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3421.48 (N-H stretch), 1596.95 (C=O), 1384.79 (C=N stretch), 1460.01 (C=C), 1232.43

(C-O-C); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.62 (s, 1H, NH), 1.253 - 1.615 (m, 10H, 5 x CH_2), 4.25 (s, 2H, CH_2), 6.92 - 7.63 (m, 9H, Ar-H).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(2-bromophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_4P): This was obtained from reacting BT_4 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3440.77 (N-H stretch), 1608.10 (C=O), 1608.52 and 1384.79 (C=N stretch), 1550.66 (C=C), 1137.92 (C-O-C), 894.91 (C-N, bend), 559.32(C-Br); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.88 (s, 1H, NH), 1.007 - 2.389 (m, 10H, 5 x CH_2), 3.655 (s, 2H, CH_2), 6.904 - 7.509 (m, 9H, Ar-H); MS m/z: 570.9, 428.8, 275.0, 268.0, 258.9; elemental analysis ($C_{25}H_{22}N_4O_2Br$), found % (calculated %): C, 52.62 (52.65);N, 9.80 (9.82).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(3-bromophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_5P): This was obtained from reacting BT_5 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3427.27 (N-H stretch), 1670.24 (C=O), 1604.52 and 1384.79 (C=N stretch), 1550.66 (C=C), 1137.92 (C-O-C), 894.91(C-N, bend), 559.32 (C-Br); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 2.801 (s, 1H, NH), 1.17 - 2.76 (m, 10H, 5 x CH_2), 3.56 (s, 2H, CH_2), 6.75 - 7.58 (m, 9H, Ar-H)

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(4-bromophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_6P): This was obtained from reacting BT_6 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3398.34 (N-H stretch), 1685.67 (C=O), 1602.74 & 1384.79 (C=N stretch), 1226.64 (C-O-C),765.60 (C-N, bend); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.599(s, 1H, NH), 1.25 - 2.83 (m, 10H, 5 x CH_2), 4.34 (s, 2H, CH_2), 6.77 - 7.01 (m, 9H, Ar-H).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(2-methoxyphenyl)pyrimidin-4-yl)-6-bromo -2H- chromen-2-one (BT_7P): This was obtained from reacting BT_7 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3411.84 (N-H stretch), 2866.02 (C-H stretch of O-CH_3), 1596.95 (C=O), 1155.28 (C-O-C), 833.19 (C-N, bend), 555.46 (C-Br) ; ^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.89 (s, 1H, NH), 1.25 - 2.38 (m, 10H, 5 x CH_2),4.38 (s, 2H, CH_2), 3.66 (s, 3H, CH_3) 6.53 - 7.82 (m, 9H, Ar-H); MS m/z: 521.0, 408.0, 267.1, 226.9 (100 %), 209.1; elemental analysis ($C_{26}H_{25}N_4O_3Br$), found % (calculated %): C, 59.87 (59.89); N, 10.77 (10.75).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(3-methoxyphenyl)pyrimidin-4-yl)- 6-bromo-2H-chromen-2-one (BT_8P): This was obtained from reacting BT_8 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3442.70 (N-H stretch), 2871.81 (C-H stretch of O-CH_3), 1610.45 (C=O), 1265.22 (C-O-C), 754.12 (C-N, bend), 611.39 (C-Br) ;^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.67(s, 1H, NH), 1.18 - 2.88 (m, 10H, 5 x CH_2), 4.54 (s, 2H, CH_2), 3.36 (s, 3H, OCH_3), 6.53 - 7.82 (m, 9H, Ar-H).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(2,4-dichlorophenyl)pyrimidin-4-yl)-6-bromo-2H-chromen-2-one (BT_9P): This was obtained from reacting BT_9 with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3413.77 (N-H stretch), 1647.10 (C=O), 1591.16 (C=N stretch), 1577.60 (C=C), 1180.35 (C-O-C), 885.98 (C-N, bend), 663.47 (C-Cl), 586.32(C-Br); ^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.808 (s, 1H, NH), 1.11 - 2.77 (m, 10H, 5 x CH_2), 4.68 (s, 2H, CH_2), 6.90 - 7.82 (m, 8H, Ar-H).

Synthesis of 3-(2-((piperidin-1-yl)methylamino)-6-(2,6-dichlorophenyl) pyrimidin-4-yl)-6-bromo -2H-chromen-2-one ($BT_{10}P$): This was obtained from reacting BT_{10} with piperidine and formaldehyde. IR (KBr, cm^{-1}): 3421.48 (N-H stretch), 1608.52 (C=O), 1384.79 (C=N stretch) ; ^{1}HNMR ($CDCl_3$-d, δ, ppm): 3.94 (s, 1H, NH), 1.3 - 2.77 (m, 10H, 5 x CH_2), 4.01 (s, 2H, CH_2), 6.54 - 7.58 (m, 8H, Ar-H) ; MS m/z: 558.0, 510.9, 326.1 (100 %), 208.1, 149.1; elemental analysis ($C_{25}H_{21}N_4O_2Cl_2Br$), found % (calculated %): C, 53.57 (53.59); N, 9.99 (10.00).

Pharmacological screening

Swiss albino rats were used for studying *in-vivo* anti-inflammatory activity. Animals were maintained under standard laboratory conditions (24 ± 2 °C; relative humidity 60 - 70 %). The animals were kept in polypropylene cages and maintained on balanced rations with free access to clean drinking water. All experimental procedures were conducted in accordance with the guide for care and use of laboratory animals and in accordance with the local animal care and use committee.

Anti-inflammatory activity

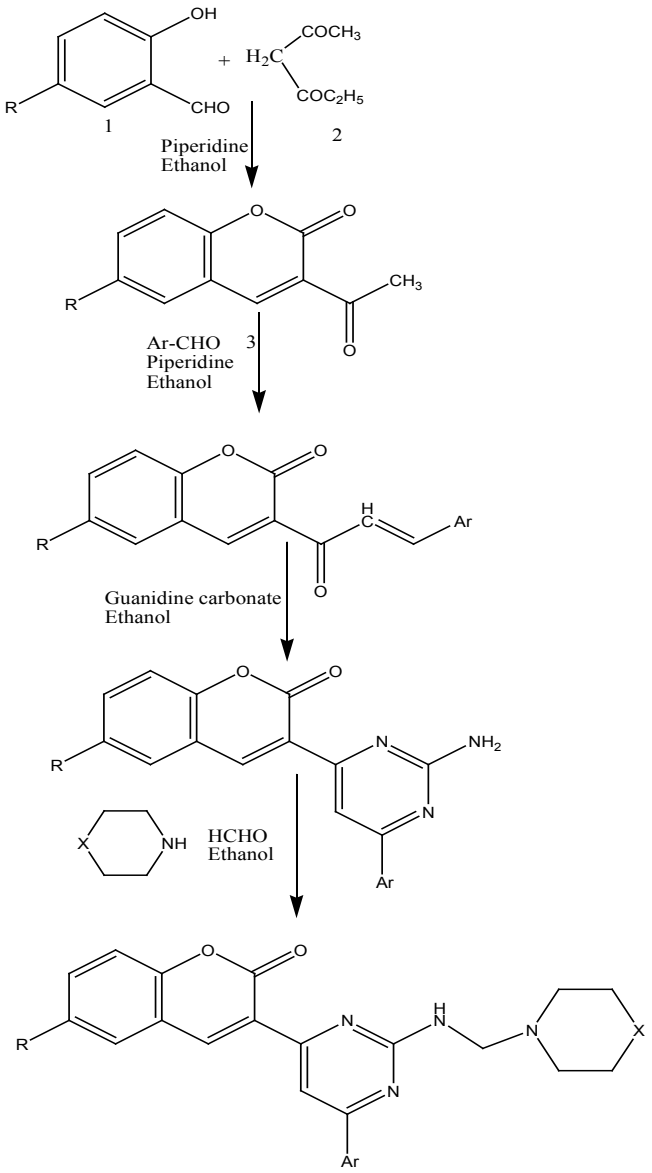
The activity of synthesized compounds was assessed using carrageenan-induced rat paw edema; briefly, rats were divided into 6 groups. Thirty minutes after oral administration of synthesized compound (50 mg/kg), 0.1 mL of 1 % carrageenan solution was injected, sub-plantar, to the left hind paw of each animal. Paw volumes were measured using standard fluid displacement procedures (a digital plethysmometer) by dipping the hind left paw in saline solution at 0.0, 0.5, 1, 2, 3, 4, and 6 h after the carragenan injection. The percentage change in paw volume relative to the base line measurement was taken as the criteria of comparison. Diclofenac sodium (50 mg/kg) was used as a standard anti-inflammatory agent.

Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Dunnett's t-test for multiple comparisons of all compounds in various pharmacological assays. Data are expressed as mean ± SEM.

Results and discussion

From these data, a preliminary SAR can be drawn for synthesized compounds. A novel series of compounds (BT_1M-$BT_{10}M$ and BT_1P-$BT_{10}P$) were synthesized and characterized. The synthesized compounds were screened for their *in-vivo* anti-inflammatory activity according to the paw edema method, using Swiss albino rats. All the compounds at doses, of 50 mg/kg each, exhibited significant anti-inflammatory activity in acute inflammatory models in the rats. Some of the synthesized compounds, viz., BT_8M, BT_4P, BT_5P, and BT_7P, exhibited significant anti-inflammatory activity, and compounds BT_3M, BT_9M, $BT_{10}M$, BT_9P, and $BT_{10}P$ showed highly significant activity. The remaining compounds showed less anti-inflammatory activity. The percentage change in paw volumes at 0, 0.5, 1, 2, 3, 4, and 6 h after drug administration were calculated. The most potent effects were produced by derivatives of $BT_{10}M$. Conversely, the weakest activity in this test was displayed by BT_1M, BT_2M, BT_5M, and BT_7M. The data for the compounds tested for anti-inflammatory activity are presented in **Table 5** and **Figure 1**. From the data presented, it follows that the most active substance in the carrageenan-induced rat paw edema method was [6-Bromo-3-(6-(2, 6-dichlorophenyl)-2(morpholinomethylamino) pyrimidin-4-yl)-2H-chromen-2-one] ($BT_{10}M$).

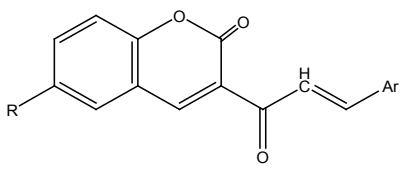


BT_1M-$BT_{10}M$,BT_1P-$BT_{10}P$

Ar =o-Chloro Benzaldehyde, m-Chloro Benzaldehyde,p-Chloro Benzaldehyde
o -Bromo Benzaldehyde,m -BromoBenzaldehyde,p -BromoBenzaldehyde
o -Methoxy Benzaldehyde,m -Methoxy Benzaldehyde
2,4 dichloro Benzaldehyde
2,6-dichloro Benzaldehyde
X= CH2, O
R=Br

Scheme 1 Schematic diagrams for the synthesis of pyrimidine derivatives (BT_1M-$BT_{10}M$, BT_1P-$BT_{10}P$).

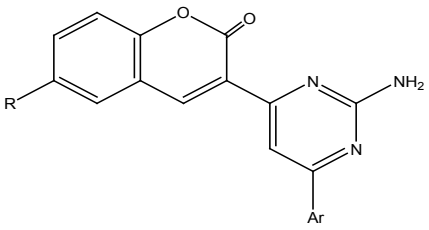
Table 1 Physical parameters of compounds (BS_1-BS_{10}).



Compound [a]	R	-Ar	Yield (%)[b]	m.p.(ºC) [c]	Rf value	Molecular formula
BS_1	Br		65	162 - 165	0.73	$C_{18}H_{10}BrClO_3$
BS_2	Br		70	165 - 167	0.75	$C_{18}H_{10}BrClO_3$
BS_3	Br		60	156 - 158	0.71	$C_{18}H_{10}BrClO_3$
BS_4	Br		70	190 - 192	0.77	$C_{18}H_{10}Br_2O_3$
BS_5	Br		75	185 - 187	0.76	$C_{18}H_{10}Br_2O_3$
BS_6	Br		*75*	185 - 188	0.69	$C_{18}H_{10}Br_2O_3$
BS_7	Br		65	180 - 182	0.64	$C_{19}H_{13}BrO_4$
BS_8	Br		65	173 - 175	0.69	$C_{19}H_{13}BrO_4$
BS_9	Br		70	175 - 177	0.71	$C_{18}H_9BrCl_2O_3$
BS_{10}	Br		68	180 - 183	0.79	$C_{18}H_9BrCl_2O_3$

[a]Products were characterized by IR, NMR. [b]synthesized yields. [c]m.p. are uncorrected.

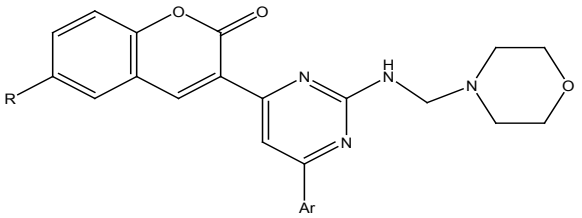
Table 2 Physical parameters of compounds (BT_1-BT_{10}).



Compound [a]	R	-Ar	Yield (%)[b]	m.p.(°C) [c]	Rf value	Molecular formula
BT_1	Br		65	162 - 165	0.62	$C_{19}H_{11}BrClN_3O_2$
BT_2	Br		60	165 - 167	0.74	$C_{19}H_{11}BrClN_3O_2$
BT_3	Br		70	156 - 158	0.70	$C_{19}H_{11}BrClN_3O_2$
BT_4	Br		65	190 - 192	0.75	$C_{19}H_{11}Br_2N_3O_2$

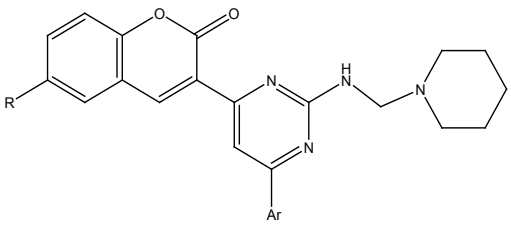
Compound [a]	R	-Ar	Yield (%)[b]	m.p.(°C) [c]	Rf value	Molecular formula
BT_5	Br		50	185 - 187	0.72	$C_{19}H_{11}Br_2N_3O_2$
BT_6	Br		60	185 - 188	0.68	$C_{19}H_{11}Br_2N_3O_2$
BT_7	Br		65	177 - 179	0.67	$C_{20}H_{14}BrN_3O_3$
BT_8	Br		65	173 - 175	0.65	$C_{20}H_{14}BrN_3O_3$
BT_9	Br		70	175 - 177	0.78	$C_{19}H_{10}BrCl_2N_3O_2$
BT_{10}	Br		68	180 - 183	0.70	$C_{19}H_{10}BrCl_2N_3O_2$

Table 3 Physical parameters of compounds (BT_1M-$BT_{10}M$).



Compound [a]	R	-Ar	Yield (%)[b]	m.p.(°C) [c]	Rf value	Molecular formula
BT_1M	Br		55.4	176 - 178	0.76	$C_{24}H_{20}BrClN_4O_3$
BT_2M	Br		60.9	175 - 177	0.74	$C_{24}H_{20}BrClN_4O_3$
BT_3M	Br		60.7	177 - 179	0.66	$C_{24}H_{20}BrClN_4O_3$
BT_4M	Br		65.1	180 - 182	0.73	$C_{24}H_{20}Br_2N_4O_3$
BT_5M	Br		50.9	175 - 178	0.72	$C_{24}H_{20}Br_2N_4O_3$
BT_6M	Br		60.5	178 - 180	0.68	$C_{24}H_{20}Br_2N_4O_3$
BT_7M	Br		65.3	177 - 179	0.67	$C_{25}H_{23}BrN_4O_4$
BT_8M	Br		65.5	173 - 175	0.65	$C_{25}H_{23}BrN_4O_4$
BT_9M	Br		60.3	175 - 177	0.71	$C_{24}H_{19}BrCl_2N_4O_3$
$BT_{10}M$	Br		55.1	171 - 173	0.66	$C_{24}H_{19}BrCl_2N_4O_3$

Table 4 Physical parameters of compounds (BT_1P-$BT_{10}P$).



Compound [a]	R	-Ar	Yield (%)[b]	m.p.(°C) [c]	Rf value	Molecular formula
BT_1P	Br		50.4	168 - 170	0.72	$C_{25}H_{22}BrClN_4O_2$
BT_2P	Br		60.7	170 - 172	0.73	$C_{25}H_{22}BrClN_4O_2$
BT_3P	Br		60.5	176 - 178	0.66	$C_{25}H_{22}BrClN_4O_2$
BT_4P	Br		65.3	172 - 174	0.73	$C_{25}H_{22}Br_2N_4O_2$
BT_5P	Br		50.7	175 - 178	0.72	$C_{25}H_{22}Br_2N_4O_2$
BT_6P	Br		60.5	178 - 180	0.68	$C_{25}H_{22}Br_2N_4O_2$
BT_7P	Br		65.3	177 - 179	0.67	$C_{26}H_{25}BrN_4O_3$
BT_8P	Br		65.8	173 - 175	0.65	$C_{26}H_{25}BrN_4O_3$
BT_9P	Br		60.9	169 - 171	0.71	$C_{25}H_{21}BrCl_2N_4O_2$
$BT_{10}P$	Br		55.6	187 - 189	0.66	$C_{25}H_{21}BrCl_2N_4O_2$

[a]Products were characterized by IR, NMR, [b]synthesized yields. [c]m.p. were uncorrected.

Table 5 Anti-inflammatory activity of compounds (BT_1M-$BT_{10}M$ and BT_1P-$BT_{10}P$) by carrageenan-induced paw edema model.

Anti- inflammatory activity by carrageenan-induced rat paw edema model (mean±SEM)							
Compound	**0.00 hrs**	**0.5 hrs**	**1.00 hrs**	**2.00 hrs**	**3.00 hrs**	**4.00 hrs**	**6.00 hrs**
Standard drug	3.39±0.14	2.72±0.15	2.33±0.09***	2.18±0.08	1.70±0.08	1.41±0.07*	1.33±0.51*
Control	3.65±0.14	3.33±0.04	3.38±0.048	3.44±0.03	3.57±0.021	3.61±0.026	3.47 ±0.33
BT_1M	3.19±0.06	2.97±0.30	2.75±0.024***	2.49±0.024***	2.52±0.076***	2.45±0.11**	1.95±0.17*
BT_2M	3.28±0.10	3.01± 0.05*	2.87±0.027***	2.73±0.023***	2.65±0.024***	2.46±0.023*	2.08±0.27***
BT_3M	3.23±0.06	3.03±0.05*	2.87±0.029***	2.74±0.015***	2.58±0.027***	2.39±0.026***	1.58±0.043***
BT_4M	3.22±0.04	2.95±0.02	2.78±0.014***	2.66±0.019***	2.58±0.027***	2.41±0.039*	1.59±0.67*
BT_5M	3.13±0.03	2.94±0.007	2.75±0.017***	2.56±0.027***	2.53±0.081***	2.23±0.12***	2.03±0.18***
BT_6M	3.14±0.02	2.95±0.017	2.73±0.012***	2.57±0.019***	2.43±0.156***	2.32±0.10***	1.92 ±0.71
BT_7M	3.52±0.10	3.25±0.07***	3.00±0.043***	2.8±0.04***	2.63±0.038***	2.47±0.075***	1.98±0.26**

Anti- inflammatory activity by carrageenan-induced rat paw edema model (mean±SEM)							
Compound	**0.00 hrs**	**0.5 hrs**	**1.00 hrs**	**2.00 hrs**	**3.00 hrs**	**4.00 hrs**	**6.00 hrs**
BT_8M	3.14± 0.04	2.93±0.02	2.72±0.016***	2.54±0.012***	2.51±0.10***	2.13±0.036***	1.74±0.06**
BT_9M	3.58±0.05	2.96±0.007	2.75±0.019***	2.54±0.012***	2.41±0.031***	2.04±0.051***	1.66±0.55
$BT_{10}M$	3.39±0.07	2.96±0.008	2.74±0.019***	2.51±0.09***	2.50±0.080***	2.08±0.023***	1.39±0.09***
BT_1P	3.46±0.096	2.95±0.014*	2.74±0.011***	2.61±0.009***	2.42±0.013***	2.23±0.057***	1.89±0.09***
BT_2P	3.2±0.030	2.92±0.013*	2.69±0.014***	2.59±0.017***	2.41±0.019***	2.17±0.066***	1.90 ±0.88
BT_3P	3.16±0.035	2.95±0.010*	2.71±0.009***	2.35±0.006***	2.34±0.012***	1.97±0.062***	1.93±0.55***
BT_4P	3.09±0.018*	2.96±0.009*	2.75±0.008***	2.56±0.023***	2.34±0.015***	1.99±0.038***	1.75±0.32
BT_5P	3.28±0.051	2.94±0.009	2.72±0.013***	2.52±0.007***	2.38±0.020***	2.21±0.018***	1.88 ±0.31
BT_6P	3.42±0.039	2.95±0.008*	2.73±0.011***	2.64±0.013***	2.43±0.012***	2.25±0.021***	1.90±0.55***
BT_7P	3.1±0.026	2.94±0.007	2.75±0.009***	2.61±0.05***	2.46±0.08***	2.16±0.029***	1.78 ±0.09
BT_8P	3.39±0.063	2.92±0.006	2.72±0.022***	2.47±0.023***	2.31±0.009***	2.05±0.045***	1.77±0.08***
BT_9P	3.16±0.027	2.92±0.027	2.72±0.027***	2.44±0.027***	2.24±0.027***	1.95±0.027***	1.65±0.22*
$BT_{10}P$	3.13±0.035	2.94±0.006*	2.69±0.011***	2.5±0.029***	2.28±0.057***	2.04±0.052***	1.54 ±0.13

Corresponding compounds were compared to control *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 6 Anti-inflammatory activity of compounds (BT_1M-$BT_{10}M$ and BT_1P-$BT_{10}P$) by carrageenan-induced paw edema model.

Percent inhibition against carrageenan-induced rat paw edema model							
Compound	**0.00 hrs**	**0.5 hrs**	**1.00 hrs**	**2.00 hrs**	**3.00 hrs**	**4.00 hrs**	**6.00 hrs**
Standard	7.12±3.97	18.19±4.52	31.08±2.82	36.72±2.49	52.40±1.92	60.98±1.98	61.67±1.28
BT_1M	12.37±1.55	10.99±0.91*	18.86±0.79**	27.66±0.69***	28.62±2.12	32.19±3.09	43.80±2.66
BT_2M	9.67±2.82	9.64±1.36	15.3±0.79**	20.78±0.67***	25.96±0.66**	32.01±0.60***	40.05 ±0.87***
BT_3M	11.55±1.66	9.15±1.53	15.27±0.86	20.34±0.41**	27.78±0.73**	33.85±0.73***	54.46±0.54***
BT_4M	11.78±1.02	11.49±0.46	17.88±0.39*	22.67±0.58**	27.87±0.75**	33.48±1.23***	54.7±1.12***
BT_5M	14.33±0.68	11.85±0.24	18.71±0.49	25.53±0.78**	29.23±2.28	38.41±3.33	41.40±3.09
BT_6M	13.88±0.43	11.64±0.51*	19.4±0.36*	25.38±0.58	31.93±0.43***	35.97±3.46	44.66±3.21
BT_7M	3.65±2.79	3.33±2.08	11.23±1.27	18.65±1.29	26.38±1.16***	31.78±2.07***	42.93±1.99***
BT_8M	14.1±0.97	12.15±0.61*	19.75±0.49*	26.16±0.34*	29.41±2.88	41.13±3.18	49.89±3.00*
BT_9M	6.19±1.43	11.25±0.22*	18.86±0.56**	26.3±0.35*	32.58±0.87**	43.52±1.40***	52.16±1.2**
$BT_{10}M$	7.08±2.04	11.29±0.26	19.06±0.57**	26.88±0.25*	29.97±2.24	42.65±0.64***	59.94±0.54***
BT_1P	5.21±2.62	11.49±0.42	19.01±0.33*	24.13±0.64**	32.31±1.57***	38.37±2.62	45.53±2.51
BT_2P	12.33±0.68	12.39±0.41	20.49±0.73	24.71±0.32*	32.59±1.19***	40.03±0.68**	45.24±0.66***
BT_3P	13.42±0.88	11.49±0.33	19.9±0.26*	31.63±0.17*	34.55±1.71	45.56±0.88***	44.38±0.56***
BT_4P	9.34±0.71	11.19±0.28*	18.72±0.46	25.58±0.67	34.55±1.20***	45.02±0.72	49.56±0.79***

Percent inhibition against carrageenan-induced rat paw edema model							
Compound	**0.00 hrs**	**0.5 hrs**	**1.00 hrs**	**2.00 hrs**	**3.00 hrs**	**4.00 hrs**	**6.00 hrs**
BT_5 P	10.14±1.39	11.79±0.28*	19.6±0.38	26.74±0.22**	33.43±0.51*	38.92±1.39*	45.82±1.33**
BT_6 P	6.3±1.09	11.49±0.26	19.31±0.34	23.26±0.49**	32.03±0.59*	37.82±1.09***	45.24±1.02**
BT_7 P	15.07±0.70	11.79±0.65**	18.72±0.28	24.13±1.44	31.19±0.80**	40.3±0.70**	48.70±0.59***
BT_8 P	7.12±1.73	12.39±0.29*	19.60±0.56	28.19±0.67	35.39±1.24***	43.34±1.73*	48.99±1.66**
BT_9 P	13.42±0.87	12.39±0.63	19.60±0.53	29.07±0.36	37.34±1.18***	46.11±1.18***	52.44±1.11**
BT_{10} P	14.25±0.96	11.79±0.86	20.49±0.57	27.33±0.59	36.22±0.72*	43.62±0.96*	55.61±1.00**

Corresponding compounds were compared to control *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

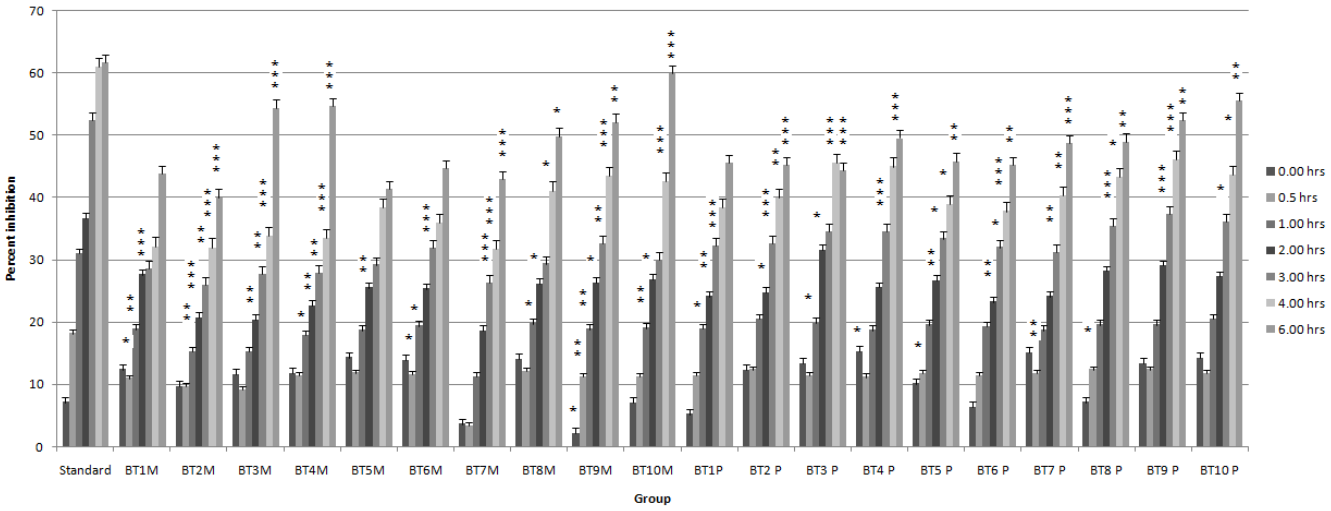


Figure 1 Anti-inflammatory activity of synthesized compounds (BT_1M-$BT_{10}M$, BT_1P-$BT_{10}P$).

Conclusions

A new series of compounds (**BT_1M-$BT_{10}M$ and BT_1P-$BT_{10}P$**), i.e., pyrimidine analogues, were synthesized by piperidine and morpholine and characterized by modern analytical techniques. The synthesized compounds were screened for their *in-vivo* anti-inflammatory activity. Some of the synthesized compounds, viz. **BT_1M, BT_3M, BT_8M, BT_2P, BT_3P, BT_5P**, and **BT_7P** exhibited significant anti-inflammatory activity, and compounds **BT_9M, $BT_{10}M$, BT_1P**, and **BT_9P** showed highly significant anti-inflammatory activity. The remaining compounds showed less anti-inflammatory and analgesic activity comparable to that of standard drug diclofenac sodium.

Acknowledgements

The authors are thankful to CDRI, Lucknow, India, for providing spectral data, and VIMS, Dadri, India, for providing all of the facilities used to carry out the present work.

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