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Article

Synthesis, Antibacterial, Anthelmintic and Anti-Inflammatory Studies of Novel Methylpyrimidine Sulfonyl Piperazine Derivatives

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Uma síntese estratégica de novas piperazinas sulfonil metilpirimidina envolvendo acoplamento Suzuki foi desenvolvida e as atividades farmacológicas dos compostos foram avaliadas. As reações foram realizadas pelo método convencional e apresentaram boas transformações dos grupos funcionais e elevados rendimentos. As estruturas dos novos compostos sintetizados foram estabelecidas por espectroscopia no infravermelho (IR), ressonância magnética nuclear (NMR) de ^{1}H e de ^{13}C, e cromatografia líquida-espectrometria de massas (LC-MS) e análise elementar. Os compostos foram testados quanto à atividade antibacteriana *in vitro* contra as cepas bacterianas *Escherichia coli* e *Staphylococcus aureus*, à atividade antihelmíntica utilizando *Pheretima posthuma* e à atividade anti-inflamatória envolvendo o modelo de edema de pata de rato induzido pela carragena. Provou-se que alguns compostos são farmacóforos potentes.

A strategic synthesis of novel methylpyrimidine sulfonyl piperazines involving Suzuki coupling was designed and pharmacological activities of the compounds were evaluated. Reactions were carried out under conventional method and show good functional group transformations and high yields. Structures of the newly synthesized compounds were established by infrared spectroscopy (IR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and liquid chromatography-mass spectrometry (LC-MS) and elemental analysis. The compounds were tested for *in vitro* antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* bacterial strains, anthelmintic activity using *Pheretima posthuma* and anti-inflammatory activity involving carrageenan induced rat paw edema model. Some compounds were proven to be potent pharmacophores.

Keywords: carbon-carbon bond formation, pharmacology, propylphosphonic anhydride, sulfonyl chlorides, antimicrobial, anti-inflammatory

Introduction

Suzuki-Miyaura coupling involves the cross coupling of organic halides and organic boron compounds, it is a strong synthetic tool for carbon-carbon bond formation via borylation.[1] This coupling procedure is used to synthesize different varieties of biologically necessary intermediates. Delicate and effective amidation of carboxyl acids with amines is the most elementary and necessary reaction in organic synthesis. In nature, amide bond is one of the most important functional group that constitutes the backbone of the biologically important peptides and is found in several natural products and also in the majority of pharmaceutically fascinating compounds containing amide bond.[2,3] Pyrimidine, piperazine and sulfonamide derivatives represent a category of pharmacologically interesting compounds having diverse biological activities. Intensive research has been carried out on the synthesis and analysis of pharmacological activities of these derivatives. Substituted sulfonamide derivatives are important category of pharmacophores that have a wide spectrum of pharmaceutical accomplishments: as antimalarial,[4] anti-microbial,[5] anti-bacterial,[6,7] anti-cancer,[8] anti-fungal,[9] anti-helmintic,[9] anti-oxidant,[10] anti-HIV,[11] anti-tumor,[11] antiplasmodial,[12] anti-neoplastic,[13] anti-proliferative,[14] activities and additionally known to act as 5-HT$_6$, 5-HT$_7$ receptor antagonists,[15,16] A2B and CXCR3

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antagonists,[17,18] 11β-HSD,[19] histone deacetylase (HDAC) inhibitors,[20] β-secretase (BACE1) inhibitors[21] and dual PI3K/mTOR inhibitors.[22]

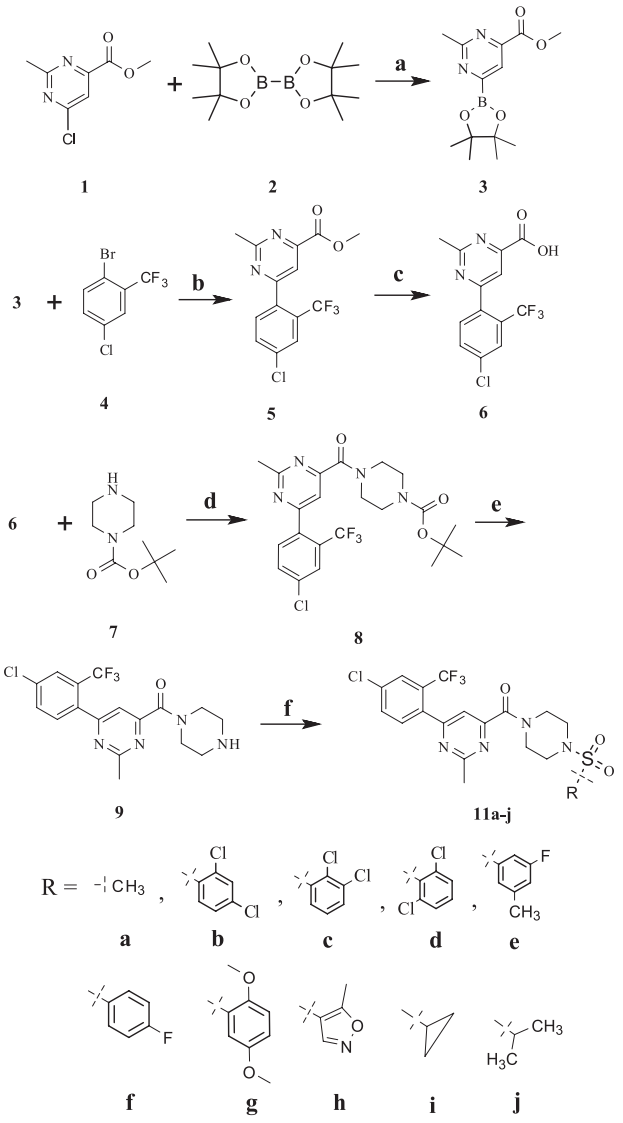
Owing to our interest in developing new biologically active pyrimidine sulfonyl piperazines, our group has previously reported the new series of substituted methylpyrimidine piperazine methanones and their biological activities.[23] In this article, we are intended to report the synthesis of methylpyrimidine sulfonyl piperazines. Literature survey revealed the paucity of information on these functionalities incorporated in one molecule and their collective biological significance. Prompted by these facts, it was designed and synthesized a new series of molecules having all the three nuclei in a single molecule as shown in Scheme 1 and studied their communal pharmacological impact as potent antibacterial, anthelmintic and anti-inflammatory agents.

Experimental

Melting points (mp) reported were determined in open capillary and are uncorrected. Purification of the newly synthesized sulfonyl piperazine methanone derivatives was made by column chromatography using silica gel 60-120 mesh size and petroleum ether/ethyl acetate (7:3) as solvent system. Reactions were monitored by thin layer chromatography (TLC), visualization was done using UV light (254 nm) chamber. Characterization was done by Fourier transform infrared (FTIR) spectra recorded on a Jasco FT-IR spectrometer. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 and 100 MHz, respectively, on a JEOL ECX NMR spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS), respectively, as internal standard. Liquid chromatogram with mass spectrometry detection (LC-MS) was obtained on a Waters Alliance 2795 separation module and Waters Micromass LCT mass detector and elemental analysis (C, H, N and S) was performed on an Elementarvario Micro cube analyzer.

Synthesis of methyl 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-4-carboxylate (**3**)

A mixture of bis(pinacolato)diboron (98 mmol) (**2**), dioxane and water (2:1) (183 mL) was stirred at room temperature under nitrogen atmosphere. To this reaction mixture, potassium acetate (245 mmol), $Pd(dppf)Cl_2$ in CH_2Cl_2 (49 mmol) and methyl-6-chloro-2-methylpyrimidine-4-carboxylate (**1**) (9.8 mmol) were added and stirred at 80 °C for 18 h. Reaction mixture was then cooled to room temperature, diluted with ethyl acetate, filtered over celite, washed with ethyl acetate followed by one water wash. Resulting organic layer was separated, dried over sodium sulfate concentrated under reduced pressure to get crude compound (**3**) which was further purified by column chromatography using petroleum ether: ethyl acetate (7:3) as eluent to get pure ethyl-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-4-carboxylate (**3**) as white crystalline solid; mp 177-178 °C; IR ν_{max}/cm^{-1} 1589.2 (CO); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 8.60 (s, 1H, Ar-H), 3.97 (s, 3H, O–CH_3), 2.89 (s, 3H, Ar-CH_3), 1.37 (s, 12H, (–CH_3)$_4$); yield 65%.



Scheme 1. Reagents and conditions: (a) $PdCl_2(dppf)$, KOAc/1,4-dioxane and H_2O, 80 °C, 18 h; (b) K_2CO_3, dikis, dioxane/H_2O, Δ, 6 h; (c) NaOH/THF: H_2O, rt, stirred, 7 h; (d) T_3P, Et_3N/EDC, stirred, Δ, 3 h; (e) TFA/EDC, stirred, Δ, 6 h; and (f) different substituted sulfonyl chloride, Et_3N/EDC, Δ, 3 h.

Synthesis of methyl 6-(4-chloro-2-(trifluoromethyl) phenyl)-2-methylpyrimidine-4-carboxylate (**5**)

A solution of methyl 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxa borolan-2-yl)pyrimidine-4-carboxylate (**3**)

(89 mmol), dioxane and water (2:1) (183 mL) was stirred at room temperature under nitrogen atmosphere. To this reaction mixture, potassium acetate (252 mmol), bis(triphenylphosphine)palladium(II) dichloride (dikis) (35 mmol) and 1-bromo-4-chloro-2-(trifluoro methyl) benzene (**4**) (89.9 mmol) were added and stirred under heating for 6 h. Reaction mixture was then cooled to room temperature, diluted with ethyl acetate, filtered over celite, washed with ethyl acetate followed with water. Resulting organic layer was separated, dried over sodium sulfate concentrated under reduced pressure to get crude compound (**5**) which was further purified by column chromatography using petroleum ether: ethyl acetate (7:3) as eluent to get pure methyl-6-(4-chloro-2-(trifluoro methyl)phenyl)-2-methyl pyrimidine-4-carboxylate (**5**) as white crystalline solid; mp 199-200 °C; IR ν_{max}/cm^{-1} 1673.2 (CO); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 8.06 (s, 1H, Ar-H), 7.83 (d, 1H, *J* 1.5, Ar-H), 7.69 (dd, 1H, *J* 8.3, 1.5, Ar-H), 7.50 (d, 1H, *J* 8.3, Ar-H), 3.79 (s, 3H, –O–CH_3), 2.81(s, 3H, Ar-CH_3); yield 60%.

Synthesis of 6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carboxylic acid (**6**)

A mixture of methyl 6-(4-chloro-2-(trifluoromethyl) phenyl)-2-methyl pyrimidine-4-carboxylate (**5**) (45 mmol) in aqueous tetrahydrofuran was stirred at room temperature for 7 h resulting in base hydrolysis. Reaction mixture was then acidified with 1.5 mol L^{-1} HCl to precipitate compound (**6**). Compound 6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methyl pyrimidine-4-carboxylic acid (**6**) was filtered and dried to get pure colorless solid; mp 221-222 °C; ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 8.06 (s, 1H, Ar-H), 7.83 (d, 1H, *J* 1.5, Ar-H), 7.69 (dd, 1H, *J* 8.3, 1.5, Ar-H), 7.50 (d, 1H, *J* 8.3, Ar-H), 2.81(s, 3H, Ar-CH_3); LC-MS (M + 1) 317.12; yield 90%.

Synthesis of *tert*-butyl 4-(6-(4-chloro-2-(trifluoromethyl) phenyl)-2-methylpyrimidine-4-carbonyl)piperazine-1-carboxylate (**8**)

A equimolar mixture of 6-(4-chloro-2-(trifluoromethyl) phenyl)-2-methylpyrimidine-4-carboxylic acid (**6**) (59 mmol) and *tert*-butyl piperazine-1-carboxylate (**7**) (59 mmol) along with propylphosphonic anhydride ($T_3P^®$) (240 mmol), triethylamine (Et_3N) (180 mmol) in ethylene dichloride (200 mL) was refluxed under nitrogen atmosphere for 3 h. Reaction mixture was washed with water, organic layer separated, dried and concentrated under vacuum to obtain crude compound (**8**) which was further purified by column chromatography using petroleum ether:ethyl acetate (7:3) as eluent to obtain pure 4-(6-(4-chloro-2-(trifluoromethyl) phenyl)-2-methylpyrimidine-4-carbonyl)piperazine-1-carboxylate (**8**) as colorless solid; mp 241-243 °C; ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 7.79 (d, 1H, *J* 1.9, Ar-H), 7.66 (dd, 1H, *J* 7.9, 1.9, Ar-H), 7.50 (d, 2H, *J* 8.7, Ar-H), 3.79 (t, 2H, *J* 4.3, NCH_2), 3.58-3.52 (m, 6H, NCH_2, H_2C–N–CH_2), 2.81 (s, 3H, Ar-CH_3), 1.48 (s, 9H, –CH_3); LC-MS (M + 1) 485.12; yield 88%.

Synthesis of (6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(piperazin-1-yl)methanone (**9**)

A mixture of 4-(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carbonyl) piperazine-1-carboxylate (**8**) (12 mmol) along with trifluroacetic acid (6 mL) in ethylene dichloride (60 mL) was refluxed for about 6 h. Reaction mixture was cooled to room temperature and concentrated to get deprotected crude 6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methyl pyrimidin-4-yl) (piperazin-1-yl)methanone (**9**) as pale yellow solid which was taken for next step directly without purification; mp 221-222 °C; ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 9.75 (s, 1H, NH), 7.80 (d, 1H, *J* 1.9, Ar-H), 7.67 (dd, 1H, *J* 7.9, 1.9, Ar-H), 7.61 (s, 1H, Ar-H), 7.50 (d, 1H, *J* 8.3, Ar-H), 4.11 (t, 4H, *J* 21.9, H_2C–N–CH_2), 3.34 (t, 4H, *J* 7.9, H_2C–N–CH_2), 2.81 (s, 3H, Ar-CH_3); LC-MS (M + 1) 385.12; yield 80%.

General procedure for the synthesis of {6-[4-chloro-2-(trifluoromethyl)phenyl]-2-methylpyrimidin-4-yl} [4-(substitutedsulfonyl) piperazin-1-yl]methanone (**11a-j**)

Equimolar mixture of 6-(4-chloro-2-(trifluoromethyl) phenyl)-2-methylpyrimidin-4-yl)(piperazin-1-yl) methanone (**9**) (1 mmol) and substituted sulfonyl chlorides (**10a**-**j**) (1 mmol) along with triethylamine (Et_3N) (0.003 mmol) in ethylene dichloride (5 mL) was refluxed for 3 h. Reaction mixture was then cooled to room temperature, washed with water; organic layer was separated and dried using sodium sulfate, organic layer on further concentration yielded pale yellow solid (**11a**-**j**). Crude compound obtained was further purified by column chromatography using petroleum ether: ethyl acetate (7:3) as eluent to get the pure {6-[4-chloro-2-(trifluoromethyl) phenyl]-2-methylpyrimidin-4-yl}[4-(substitutedsulfonyl) piperazine-1-yl]methanone (**11a**-**j**) in good yield.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methyl-pyrimidin-4-yl)(4(methylsulfonyl) piperazin-1-yl) methanone (**11a**): IR ν_{max}/cm^{-1} C=O 1651.8, S=O 1320.6 (asymmetric), 1168.7 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 7.80 (d, 1H, *J* 1.9, Ar-H), 7.67 (dd, 1H, *J* 8.3, 1.9, Ar-H),

7.52 (d, 1H, *J* 3.9, Ar-H), 7.49 (s, 1H, Ar-H), 3.93 (t, 2H, *J* 9.9, N-CH_2), 3.73 (t, 2H, *J* 4.7, N-CH_2), 3.46 (t, 2H, *J* 5.1, N–CH_2), 3.41 (t, 2H, *J* 5.1 Hz, N–CH_2), 3.91 (s, 3H, –SO_2–CH_3), 2.82 (s, 3H, –CH_3); CHNS (calculated, found) C% 46.71 (46.62), H% 3.92 (3.90), N% 12.10 (12.11), S% 6.93 (6.92); LC-MS (M + 1) 463.8.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-((2,4-dichlorophenyl) sulfonyl) piperazin-1-yl)methanone (**11b**): IR ν_{max}/cm^{-1} C=O 1650.8, S=O 1300.6 (asymmetric), 1164.7 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 8.04 (dd, 1H, *J* 5.5, 1.5, Ar-H); 7.79 (d, 1H, *J* 1.5, Ar-H); 7.72 (dd, 1H, *J* 7.9, 1.5, Ar-H); 7.66 (dd, 1H, *J* 8.3, 1.9, Ar-H); 7.49 (d, 2H, *J* 9.1, Ar-H); 7.40 (d, 1H, *J* 7.9, Ar-H); 3.89 (t, 2H, *J* 4.7, N–CH_2); 3.71 (t, 2H, *J* 4.3, N–CH_2), 3.49 (t, *J* 4.7, 4H, N–CH_2), 2.80 (s, 3H, –CH_3); CHNS (calculated, found) C% 46.52 (46.54), H% 3.06 (3.07), N% 9.43 (9.42), S% 5.40 (5.39); LC-MS (M + 1) 594.8.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-((2,3-dichlorophenyl)sulfonyl) piperazin-1-yl)methanone (**11c**): IR ν_{max}/cm^{-1} C=O 1649.8, S=O 1304.6 (asymmetric), 1166.7 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 8.04 (dd, 1H, *J* 5.5, 1.5, Ar-H), 7.79 (d, 1H, *J* 1.5, Ar-H), 7.72 (dd, 1H, *J* 7.9, 1.5, Ar-H), 7.66 (dd, 1H, *J* 8.3, 1.9, Ar-H), 7.49 (d, 2H, *J* 9.1, Ar-H), 7.40 (t, 1H, *J* 7.9, Ar-H), 3.89 (t, 2H, *J* 4.7, N–CH_2), 3.71 (t, 2H, *J* 4.3, N–CH_2), 3.49 (t, 4H, *J* 4.7, N-CH_2), 2.80 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.70, 165.80, 165.37, 160.40, 138.10, 136.07, 135.34, 134.75, 132.48, 132.11, 130.58, 130.58, 130.33, 129.80, 127.30, 127.08, 124.25, 121.52, 116.75, 46.98, 45.89, 45.37, 42.20, 26.04; CHNS (calculated, found) C% 46.52 (46.57), H% 3.06 (3.09), N% 9.43(9.46), S% 5.40 (5.45); LC-MS (M + 1) 594.8.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-((2,6-dichlorophenyl) sulfonyl) piperazin-1-yl)methanone (**11d**): IR ν_{max}/cm^{-1} C=O 1633.8, S=O 1310.6 (asymmetric), 1162.7 (symmetric), ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 8.04 (dd, 1H, *J* 5.5, 1.5, Ar-H), 7.79 (d, 1H, *J* 1.59, Ar-H), 7.72 (dd, 1H, *J* 7.9, 1.5, Ar-H), 7.66 (dd, 1H, *J* 8.3, 1.9, Ar-H), 7.49 (d, 2H, *J* 9.1, Ar-H), 7.40 (t, 1H, *J* 7.9, Ar-H), 3.89 (t, *J* 4.7, 2H, N–CH_2), 3.71 (t, 2H, *J* 4.3, N–CH_2), 3.49 (t, 4H, *J* 4.7, N–CH_2), 2.80 (s, 3H, –CH_3); CHNS (calculated, found) C% 46.52 (46.54), H% 3.06 (3.04), N% 9.43 (9.40), S% 5.40 (5.43); LC-MS (M + 1) 594.8.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-((3-fluoro-4-methyl phenyl)sulfonyl) piperazin-1-yl)methanone (**11e**): IR ν_{max}/cm^{-1} C=O 1623.7, S=O 1308.4 (asymmetric), 1165.6 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* 1.9, Ar-H), 7.65 (dd, 1H, *J* 8.3, 1.9 Hz, Ar-H), 7.58-7.56 (m, 2H, Ar-H), 7.49-7.45 (m, 2H, Ar-H), 7.38-7.33 (m, 1H, Ar-H), 3.92 (t, 2H, *J* 5.1, N–CH_2), 3.75 (t, 2H, *J* 4.7, N–CH_2), 3.21 (t, *J* 5.1, 2H, N–CH_2), 3.15 (t, 2H, *J* 5.1, N–CH_2), 2.80 (s, 3H, –CH_3), 2.41 (s, 3H, Ar-CH_3); CHNS (calculated, found) C% 51.76 (51.75), H% 3.80 (3.85), N% 10.06 (10.37), S% 5.76 (5.75); LC-MS (M + 1) 557.9.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-((4-fluorophenyl) sulfonyl)piperazin-1-yl) methanone (**11f**): IR ν_{max}/cm^{-1} C=O 1639.2, S=O 1302.68 (asymmetric), 1166.72 cm^{-1}(symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* 1.9, Ar-H), 7.65 (dd, 1H, *J* 8.3, 1.9, Ar-H), 7.58-7.56 (m, 2H, Ar-H), 7.49-7.45 (m, 3H, Ar-H), 7.38-7.33 (m, 1H, Ar-H), 3.92 (t, 2H, *J* 5.1, N–CH_2), 3.75 (t, 2H, *J* 4.7, N–CH_2), 3.21 (t, 2H, *J* 5.1, N–CH_2), 3.15 (t, 2H, *J* 5.1, N-CH_2), 2.80 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.74, 165.83, 165.29, 163.77, 161.25, 160.29, 137.50, 136.13, 132.50, 132.14, 131.19, 127.12, 123.35, 120.64, 120.42, 116.70, 115.08, 114.84, 46.37, 46.12, 45.60, 41.65, 26.06; CHNS (calculated, found) C% 50.88 (50.90), H% 3.53 (3.55), N% 10.32 (10.36), S% 5.91 (5.98); LC-MS (M + 1) 543.9.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-((2,5-dimethoxyphenyl) sulfonyl) piperazin-1-yl)methanone (**11g**): IR ν_{max}/cm^{-1} C=O 1632.45, S=O 1303.64 (asymmetric), 1154.19 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* 1.9, Ar-H), 7.66 (dd, 1H, *J* 8.3, 1.9, Ar-H), 7.49-7.43 (m, 3H, Ar-H), 7.10 (dd, 1H, *J* 9.1, 3.1, Ar-H), 6.9 (d, 1H, *J* 8.7, Ar-H), 3.89 (s, 3H, O–CH_3), 3.80 (s, 3H, O–CH_3), 3.65 (t, 4H, *J* 4.7, CH_2–N–CH_2), 3.42 (t, 4H, *J* 4.7 Hz, CH_2–N–CH_2), 2.79 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.79, 165.68, 165.40, 160.62, 153.07, 150.88, 136.07, 135.36, 132.51, 132.14, 127.01, 126.46, 124.28, 121.54, 120.55, 116.59, 116.02, 114.01, 56.59, 55.96, 47.04, 46.08, 45.60, 42.29, 26.06; CHNS (calculated, found) C% 51.33 (51.35), H% 4.14 (4.17), N% 9.58 (9.60), S% 5.48 (5.50); LC-MS (M + 1) 585.9.

(6-(4-Cloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-((5-methylisoxazol-4-yl)sulfonyl) piperazin-1-yl)methanone (**11h**): IR ν_{max}/cm^{-1} C=O 1635.85, S=O 1308.94 (asymmetric), 1164.49 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 8.30 (s, 1H, isoxazole proton), 8.06 (s, 1H, Ar-H), 7.83 (d, 1H, *J* 1.5, Ar-H), 7.69 (dd, 1H, *J* 8.3, 1.5, Ar-H), 7.50 (d, 1H, *J* 8.3, Ar-H), 2.88 (s, 3H, isoxazole –CH_3), 2.81(s, 3H, Ar-CH_3); CHNS (calculated, found) C% 47.60 (47.65), H% 3.61 (3.63), N% 13.22 (13.24), S% 6.05 (6.09); LC-MS (M + 1) 530.9.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methyl-pyrimidin-4-yl)(4-(cyclopropylsulfonyl) piperazin-1-yl) methanone (**11i**): IR ν_{max}/cm^{-1} C=O 1653.66, S=O 1306.54 (asymmetric), 1165.76 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 7.80 (d, 1H, *J* 1.9, Ar-H), 7.67 (dd, 1H, *J* 8.3, 1.9, Ar-H), 7.52 (d, 1H, *J* 3.9, Ar-H), 7.49 (s, 1H, Ar-H), 3.93 (t, 2H, *J* 9.9, N–CH_2), 3.73 (t, 2H, *J* 4.7, N–CH_2), 3.46 (t, 2H, *J* 5.1, N–CH_2), 3.41 (t, 2H, *J* 5.1, N–CH_2), 2.82 (s, 3H, –CH_3), 2.32-2.26 (m, 1H, junction proton), 1.21-1.01 (m, 4H, (–CH_2–)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.77, 165.81, 165.41, 160.49, 136.11, 135.36, 132.51, 132.15, 127.16, 124.28, 121.55, 116.76, 46.80, 46.25, 45.75, 42.04, 26.08, 25.71, 4.40, 4.40; CHNS (calculated, found) C% 49.13 (49.16), H% 4.12 (4.16), N% 11.46 (11.50), S% 6.56 (6.60); LC-MS (M + 1) 489.8.

(6-(4-Chloro-2-(trifluoromethyl)phenyl)-2-methyl-pyrimidin-4-yl)(4-(isopropylsulfonyl) piperazin-1-yl) methanone (**11j**): IR ν_{max}/cm^{-1} C=O 1655.67, S=O 1305.56 (asymmetric), 1166.78 (symmetric); ^{1}H NMR (399.6 MHz, $CDCl_3$) δ 7.80 (d, 1H, *J* 1.9, Ar-H); 7.67 (dd, 1H, *J* 8.3, 1.9, Ar-H), 7.52 (d, 1H, *J* 3.9, Ar-H), 7.49 (s, 1H, Ar-H), 3.93 (t, 2H, *J* 9.9, N–CH_2), 3.73 (t, 2H, *J* 4.7, N–CH_2), 3.46 (t, 2H, *J* 5.1, N–CH_2), 3.41 (t, 2H, *J* 5.1, N–CH_2), 2.82 (s, 3H, –CH_3), 2.32-2.26 (m, 1H, junction proton), 1.4 (d, *J* 1.9, 4H, (–CH_3)$_2$); CHNS (calculated, found) C% 48.93 (48.92), H% 4.52 (4.53), N% 11.41 (11.43), S% 6.53 (6.53); LC-MS (M + 1) 491.9.

Biological evaluation

Antibacterial activity

In vitro antibacterial activity of the sulfonyl piperazine methanone derivatives (**11a**-**j**) was studied against Gram positive *Staphylococcus aureus* (NCIM-5022) and Gram negative *Escherichia coli* (NCIM-5051) bacterial strains. All the bacterial strains were procured form CSIR-National Chemical Laboratory (NCL) (Pune, India). Agar well diffusion method was incorporated for the study,[24] broth cultures of bacterial strains were incubated for 24 h and were uniformly smeared on sterile nutrient agar medium in each petri plates using sterile L-shaped glass rod. Five uniform wells with 6 mm diameter were bored using cork borer to accommodate 50 µL of solution in each well. Samples were dissolved in dimethylsulfoxide (DMSO), a negative control which showed no zone of inhibition and ciprofloxacin (10 µg 50 µL^{-1}) was taken as standard drug, a positive control was purchased from Himedia (Mumbai, India). Concentrations of 2.5, 5, 10 and 20 µg 50 µL^{-1} were used to assess the dose dependent activity of test samples. Sterile micropipette tips were used to load the wells with appropriate amount of sample, control and standard. Then, the plates were incubated at 37 °C for 36 h. After the incubation period, the diameter of the zone of inhibition of each well was measured in mm; the experiment was performed in triplicates.

Anthelmintic activity

Anthelmintic activity of compounds (**11a**-**j**) was done using *P. posthuma* (Indian Earthworm), worms were maintained under normal vermicomposting medium with adequate supply of nourishment and water for about 3 weeks. Adult earthworms of approximately 4 cm in length and 0.2-0.3 cm in width were chosen for experiment. Different concentrations 50 and 100 mg of samples were evaluated as *per* the standard method reported.[25] Five groups, each with six earth worms, were taken. Each *P. posthuma* was washed separately with normal saline before the initiation of experimental procedure and was placed into a 20 mL of normal saline. Group I earthworms were placed in 20 mL saline in a clean petri plate and group II earthworms were placed in 20 mL saline containing standard drug piperazine citrate (50 mg mL^{-1}). Similarly, group III to XXII earthworms were placed in a 20 mL saline containing 50 and 100 mg mL^{-1} of test samples, respectively. Observation was done keeping time taken for paralysis and the time taken for death as objective and was documented in minutes. Paralysis time was analyzed based on behavior of the worms with no revival body state in normal saline medium. Death was concluded based on total loss of motility with faded body color.[26]

Anti-inflammatory activity

Effect of compounds (**11a**-**e**) on carrageenan induced paw edema was studied on albino Wistar rats of either sex which were obtained from Sree Venkateshwara Enterprises Bangalore. The animals were acclimatized, maintained under standard laboratory condition for a week. Given free access to UV purified and filtered water and standard pelleted feed procured from M/S Pranava Agro Industries Sangli, Maharastra, *ad libitum*. All the studies conducted were approved by the Institutional Animal Ethics Committee (IAEC) of Sree Siddaganga College of Pharmacy, Tumkur (Ref No. SSCPT/IAEC.Clear/141/2012-13). The standard was indomethacin from Research Lab Fine Chem Industries, (B. No. 99550509, Mfg date: May 2009, exp. date: May 2014). Test compounds (100 mg kg^{-1} body weight) and indomethacin (10 mg kg^{-1} body weight). The dose selected in the present study is done on the previously published literature which dealt with pyrimidine, piperazine and

sulfonamide as moieties in molecules exhibiting anti-inflammatory activity.[27,28] Test compounds were made it into suspension by using 1% carboxy methyl cellulose (vehicle) and administered through oral route.

Carrageenan induced rat paw edema[29] experiment was carried out on test system (albino Wistar rats) weighing between 150-180 g randomly divided into seven groups of six animals each and was fasted overnight. Group I served as carrageenan inducer (control) and received vehicle, group II standard indomethacin (10 mg kg^{-1} body weight) through oral route. Group III to group VII were administrated with test compounds (**11a-e**) in the dose of (100 mg kg^{-1} body weight) and after administering samples/ indomethacin/vehicle, test systems were kept under clinical sign observation for 30 min and suspension of carrageenan (0.1 mL of 1% kg m^{-3}) was injected into the sub-plantar region of right hind paw of each test system. The paw volume was measured by using digital plethysmometer (IITc Life science, USA), immediately after injection, again at 30, 60, 120 and 180 min intervals.

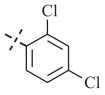
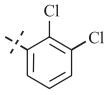
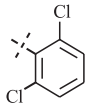
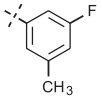
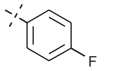
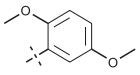
Statistical analysis

The data of antibacterial and anthelmintic were expressed as mean ± standard error (SE) of triplicates and six *Pheretima posthuma* in each group. The difference in values at $p \leq 0.01$ was considered as statistically significant. The analysis of variance (ANOVA) was performed using ezANOVA (version 0.98) software to determine the mean and standard error of the inhibition zone in antibacterial activity and standard error of paralysis and death time of earthworms. Anti-inflammatory data were expressed as mean ± standard error of the mean (SEM) of seven groups of six albino Wistar rats in each group, the difference in values at $p < 0.05$, $p < 0.01$ and $p < 0.001$ when compared with carrageenan control using ANOVA followed by Dunnett multiple comparison test on Graph Pad Prism 5.

Results and Discussion

The synthetic pathway for the synthesis of compounds (**11a-j**) is illustrated in Scheme 1. Initial borylation of (**1**) with (**2**), in presence of $Pd(dppf)Cl_2$, methylene chloride, potassium acetate and 1,4-dioxane and water afforded (**3**). Treatment of (**3**) with (**4**) in 1,4-dioxane:water using potassium carbonate and catalytic quantity of dikis, underwent Suzuki coupling to give (**5**). Upon hydrolysis of (**5**), it gave (**6**) and it was further condensed with (**7**) in presence of triethylamine and dehydrating agent T3P® to get (**8**) a key intermediate. Deprotection of *N*-boc group from (**8**) was done by using trifluroacetic acid to get (**9**) a pre-final product. Compound (**9**) revealed to be the important intermediate which was reacted with appropriate substituted aryl/alkyl/hetro-substituted sulfonyl chlorides to get pyrimidine sulfonyl piperazine derivatives (**11a-j**) in good yield as reported in Table 1.

Table 1. Physical and analytical data of methylpyrimidine sulfonyl piperazine derivatives **11a-j**

R	Molecular formula	Molecular weight	mp / °C	Yield / %
	$C_{18}H_{18}ClF_3N_4O_3S$	462	187-189	92
	$C_{23}H_{18}Cl_3F_3N_4O_3S$	593	219-221	91
	$C_{23}H_{18}Cl_3F_3N_4O_3S$	593	220-222	90
	$C_{23}H_{18}Cl_3F_3N_4O_3S$	593	218-220	92
	$C_{24}H_{21}ClF_4N_4O_3S$	556	237-239	95
	$C_{23}H_{19}ClF_4N_4O_3S$	542	244-246	96
	$C_{25}H_{24}ClF_3N_4O_5S$	584	249-251	93
	$C_{21}H_{19}ClF_3N_5O_4S$	529	248-250	91
	$C_{20}H_{20}ClF_3N_4O_3S$	488	224-226	94
	$C_{20}H_{22}ClF_3N_4O_3S$	490	217-219	92

Initial investigation of the antibacterial screening data revealed that all tested compounds (**11a-j**) showed activity against *E. coli* and *P. aeruginosa*, data given in Table 2. Test samples upon detailed investigation for activity at different concentrations of 2.5, 5, 10 and 20 µg 50 μL^{-1} against *E. coli* and *P. aeruginosa*, respectively, given in Table 3. Minimum inhibitory concentrations (MIC) obtained by micro dilution method were observed to be 10 µg 50 μL^{-1}. Data reveal that the tested samples are active at and above the concentration level 10 µg 50 μL^{-1} which is the minimum inhibitory concentration. Further the compounds were screened at 10 and 20 µg 50 μL^{-1} against *E. coli* and *P. aeruginosa*, respectively and it is evident that all the tested compounds showed activity against tested strains.

Table 2. Antibacterial activity of methylpyrimidine sulfonyl piperazine derivatives **11a-j**

Code	Concentration / (μg 50 μL^{-1})	Zone of inhibition / mm	
		E. coli (mean ± SE)	*P. aeruginosa* (mean ± SE)
CIPRO	10	13.00 ± 0.58	14.17 ± 0.17
11a	10	4.67 ± 0.33^b	2.17 ± 0.17^b
	20	5.67 ± 0.33^b	2.83 ± 0.44^b
11b	10	6.50 ± 0.29^b	2.50 ± 0.29^b
	20	7.17 ± 0.17^b	2.83 ± 0.60^b
11c	10	6.17 ± 0.22^b	2.33 ± 0.33^b
	20	7.17 ± 0.38^b	3.50 ± 0.29^b
11d	10	4.50 ± 0.29^b	2.83 ± 0.44^b
	20	5.50 ± 0.29^b	3.50 ± 0.29^b
11e	10	3.50 ± 0.29^b	3.33 ± 0.44^b
	20	4.50 ± 0.29^b	4.33 ± 0.33^b
11f	10	5.50 ± 0.29^b	3.67 ± 0.33^b
	20	6.57 ± 0.30^b	4.50 ± 0.29^b
11g	10	5.83 ± 0.44^b	2.67 ± 0.17^b
	20	6.97 ± 0.03^b	3.17 ± 0.44^b
11h	10	3.83 ± 0.17^b	4.50 ± 0.29^b
	20	4.83 ± 0.70^b	5.67 ± 0.33^b
11i	10	5.50 ± 0.29^b	3.67 ± 0.17^b
	20	4.17 ± 0.44^b	4.67 ± 0.33^b
11j	10	6.67 ± 0.33^b	3.50 ± 0.58^b
	20	4.17 ± 0.44^b	4.17 ± 0.33^b

CIPRO: standard drug ciprofloxacin; $^a p < 0.05$, $^b p < 0.01$ and $^c p < 0.001$; SE: standard error.

Table 3. Antibacterial activity minimum inhibitory concentration (MIC) values of methylpyrimidine sulfonyl piperazine derivatives **11a-j**

Bacterial stain	Code	Concentration / (μg 50 μL^{-1})	Growth
E. coli	**11a-j**	2.5	+
		5.0	+
		10	–
		20	–
P. aeruginosa	**11a-j**	2.5	+
		5.0	+
		10	–
		20	–

+: presence of growth; –: absence of growth.

Evaluation of anthelmintic activity using *P. posthuma* showed comparably moderate results with that of standard drug piperazine citrate, given in Table 4. Earthworms belonging to control group showed paralysis time at 142.67 ± 1.45 min and death time at 168.00 ± 1.53 min. For the sample tests (**11a-j**) upon detailed anthelmintic activity study at different concentrations 15, 25, 35 and 50 mg mL^{-1}, shown in Table 5, it was observed activity at concentration of 50 mg mL^{-1} and above. Further testing of samples at 50 mg mL^{-1} and 100 mg mL^{-1} concentrations showed the time (in min) of paralysis and death as reported. Investigation of anthelmintic activity revealed that methylpyrimidine sulfonyl piperazines were potent anthelmintic agents.

Table 4. Anthelmintic activity of methylpyrimidine sulfonyl piperazine derivatives **11a-j**

Code	Concentration / (mg mL^{-1})	Time taken for paralysis / min	Time taken for death / min
Control	–	142.33 ± 0.49	165.33 ± 1.58
PC	50	39.17 ± 0.48^b	57.67 ± 0.88^b
11a	50	74.33 ± 0.42^b	102.67 ± 0.56^b
	100	37.50 ± 0.62^a	53.83 ± 0.79^b
11b	50	72.67 ± 0.71^b	96.00 ± 1.12^b
	100	40.83 ± 0.48^b	53.00 ± 0.58^b
11c	50	69.00 ± 0.73^b	97.33 ± 1.12^b
	100	41.17 ± 0.70^b	53.00 ± 1.29^b
11d	50	70.83 ± 0.60^b	98.67 ± 0.76^b
	100	38.67 ± 0.56^b	54.17 ± 0.75^b
11e	50	61.33 ± 0.71^b	104.33 ± 0.71^b
	100	41.33 ± 0.49^b	55.50 ± 1.09
11f	50	64.17 ± 0.48^b	102.83 ± 1.19^b
	100	42.67 ± 0.71^b	57.00 ± 0.86
11g	50	59.17 ± 0.48^b	110.50 ± 0.67^b
	100	33.17 ± 0.48^b	59.67 ± 0.42^a
11h	50	72.00 ± 0.97^b	103.00 ± 0.89^b
	100	41.50 ± 0.43^b	54.67 ± 0.49^b
11i	50	68.17 ± 0.60^b	105.33 ± 0.61^b
	100	41.50 ± 0.43^b	54.67 ± 0.49^b
11j	50	71.83 ± 0.65^b	107.23 ± 0.51^b
	100	38.67 ± 0.56^b	53.83 ± 0.79^b

PC: standard drug piperazine citrate; $^a p < 0.05$, $^b p < 0.01$ and $^c p < 0.001$.

Table 5. Anthelmintic activity values of methylpyrimidine sulfonyl piperazine derivatives **11a-j**

Test model	Code	Concentration / (mg mL^{-1})	Activity
P. posthuma	**11a-j**	15	IA
		25	IA
		35	IA
		50	AC

AC: active; IA: inactive.

Increase in paw volume was observed in all time intervals after the administration of carrageenan (1%, 0.1 mL). Samples (**11a-e**) were administered orally to test

systems at dose of 100 mg kg^{-1} body weight, significantly ($p < 0.05$, $p < 0.01$ and $p < 0.001$) inhibited the carrageenan (control) induced paw edema. Treatment with standard drug indomethacin also significantly ($p < 0.001$) inhibited the carrageenan induced paw edema. At 30 min interval, no significance was observed for all the tested compounds against carrageenan induced paw edema. At 60 min interval, for compounds **11a**, **11b**, **11d** and **11e**, it was moderately significance ($p < 0.01$), in addition at 120 min interval for compounds **11a** and **11c**, it was also showed moderate significance ($p < 0.01$). Finally, results obtained at 180 min interval were comparably significance ($p < 0.001$) to standard drug indomethacin (Figure 1).

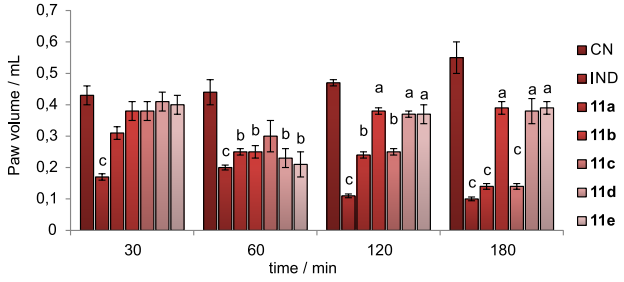


Figure 1. Effect of **11a-e** on carrageenan induced paw edema in rats; CN: carrageenan and IND: indomethacin; $^{a}p < 0.05$, $^{b}p < 0.01$ and $^{c}p < 0.001$.

Values are expressed in mean ± SEM for five animals in each group. ANOVA followed by Dunnett multiple comparison tests. Values are statistically $p < 0.05$, $p < 0.01$ and $p < 0.001$ when compared with carrageenan control.

Successful design and synthesis of methylpyrimidine sulfonyl piperazines with different R group (alkyl, cycloalkyl, substituted hetero and aromatic rings) in the final molecule in search of better antibacterial, anthelmintic and antifungal agents were achieved. Further evaluation of the antibacterial activity against *E. coli* and *P. aeruginosa* bacterial strains, anthelmintic activity against *P. posthuma* model and anti-inflammatory activity studied on carrageenan induced rat paw edema model was successfully carried out. The results show new group of sulfonamides with a promising activity.

Conclusion

Synthesis of pyrimidine sulfonyl piperazine derivatives resulted in potent antibacterial, anthelmintic and anti-inflammatory agents. Compounds **11b**, **11c**, **11f**, **11g**, **11h**, **11i** and **11j** were proven to be good antibacterial and anthelmintic agents. Compounds **11a** and **11c** were proven to be good anti-inflammatory agents. Further studies for better therapeutic activities can be observed by functional group modifications and detailed toxicity studies will be taken up in future.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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