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Synthesis, characterization and biological activity of some new 5-halo-4, 6-dimethoxy-2-(alkoxy or aryloxy) pyrimidines

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ABSTRACT

*New 5-halo-4, 6-dimethoxy-2-(alkoxy or aryloxy) pyrimidines (**4a-r**) were prepared from 5-halo-4,6-dialkoxy,2-methylsulfonylpyrimidine. The structure of newly synthesized compounds was characterized by their spectral date. The newly synthesized compounds were evaluated for their anmicrobial and antifungal studies. Some of the compounds showed moderate to good activity.*

Keywords: 4,6-dimethoxy-2-methyl sulphonyl pyrimidine, chlorination, bromination, 4,6-dimethoxy-5-halo-2-methyl sulphonyl pyrimidines, antimicrobial activity.

INTRODUCTION

Heterocyclic compounds containing the pyrimidine nucleus possess a diversity of useful biological effects. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities [1]. The synthesis of substituted pyrimidine and many detailed reviews have been appeared [2]. Pyrimidines and their derivatives are considered to be important for drugs [3] and agricultural chemicals [4]. Pyrimidine derivatives possess several interesting biological activities such as antimicrobial [5], antitumor [6], antiviral [7], hypnotic sedative [8] and anticonvulsant activities [9]. Many Pyrimidine derivatives are used for thyroid drugs [10] and leukaemia [11]. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic [12] agents and have found wide clinical applications such as anti-inflammatory [13], diuretic [14], antimalarial [15] and cardiovascular [16].

The 2-alkoxy or aryloxy has low toxicity and active against the growth of various yeasts and bacteria. [17, 18, 19]. It is well known that the presence of halogenated groups in organic molecules often confer significant and useful changes in their chemical, physical and biological properties due the elevated electro negativity and lipophilic character of halogen atoms[20,21]. More over the introduction of electron-releasing substitution into any position of the pyrimidine ring makes the 5th position readily halogenatable [22]. However pyrimidines having amino, hydroxyl, or methoxy activating groups have been chlorinated under controlled conditions. Keeping in view of the importance of pyrimidine molecule and for their biological activity we report the synthesis and antimicrobial activity of 2-alkoxy (aryloxy)-4, 6-dimethoxy-5-halo-pyrimidines.

MATERIALS AND METHODS

All chemicals used for the synthesis were of reagent and procured form Sigma Aldrich, Bangalore, India. ^{1}H and ^{13}C NMR spectra were recorded on AS 400 MHz Varian NMR spectrometer using TMS as an internal standard. IR spectra were recorded by using PerkinElmer Spectrum 100 Series FT-IR spectrometer. Mass spectra were recorded on Agilent 1200 Series LC/MSD VL system. Melting points were determined by using Buchi melting point B-545 instrument and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC) using precoated silica 60 F_{254}, 0.25 mm aluminum plates (Merck). The crude compounds were purified using silica gel 100-200 column chromatography eluting with hexane: ethyl acetate as mobile phase.

Preparation of 5-halo-4,6-dimethoxy-2-(methylsulfonyl) pyrimidine (2a-b). To a solution of 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine (**1)** (1.0 g, 4.6 mmole), Con. HCl (2.0 mL) and water (2.0 mL) was added respective hypochlorite (10.0 mL) solution under stirring. The reaction mixture was stirred at 25-30 ^{o}C for 6 hours. After completion of reaction, filtered the precipitated product, water washed and dried in an air drier to afford **2a-b** as pure product**.**

5-Chloro-4,6-dimethoxy-2-(methylsulfonyl) pyrimidine (2a). White colored solid; Yield = 0.97 g (85%); M.P = 192-193 ^{o}C; IR (KBr): 3039, 3018, 2937, 1577, 1473, 1382, 1315 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.30 (s, 3H), 4.12 (s, *6*H); ^{13}C-NMR ($CDCl_3$) δ 34.5, 51.6, 98.3, 155.9, 161.8; ESI-MS: *m/z* 253^{+}. Analysis Calculated: C, 33.27; H, 3.59; Cl, 14.03; N, 11.09; O, 25.33; S, 12.69; Found C, 33.21; H, 3.62; Cl, 14.05; N, 11.07; O, 25.31; S, 12.67.

5-Bromo-4,6-dimethoxy-2-(methylsulfonyl) pyrimidine (2b). Yield = 1.1g (81%). M.P = 216-218^{o}C. IR (KBr): 3037, 3016, 2937, 1580, 1471, 1379, 1313 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.29 (s, 3H), 4.11 (s, *6*H); ^{13}C-NMR ($CDCl_3$) δ 39.2, 56.5, 93.2, 162.1, 167.8; ESI-MS: *m/z* 297 $[M+H]^{+\cdot}$ Analysis Calculated: C, 28.30; H, 3.05; Br, 26.89; N, 9.43; O, 21.54; S, 10.79; Found C, 28.28; H, 3.02; Br, 26.91; N, 9.44; O, 21.53; S, 10.76.

General procedure for the preparation of 5-Halo-4,6-dimethoxy-2-(alkoxy or aryloxy) pyrimidines 4 (a-r).

To a mixture of acetone (10 mL), potassium carbonate (30 mmole) and 5-Halo-4, 6-dimethoxy-2-methylsulphonyl pyrimidine **(2a or 2b)** (10.0 mmole) was added respective alcohol (10.0 mmole) and heated to reflux for 6-8 hours. After completion of the reaction, cooled to room

temperature, filtered and washed with acetone. The filtrate was evaporated under reduced pressure to get the crude compounds. The crude compounds were recrystallised in methanol to get pure products **(4a-r)**.

2-Butoxy-5-chloro-4,6-dimethoxypyrimidine (4a). White solid; M.P = 59-60 ^{o}C. IR (KBr): 3039, 3018, 2937, 1577, 1473, 1382, 1315cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.97 (t, 3H), 1.45-1.48 m, 2H), 1.75-1.82 (m, 2H), 4.02 (s, 6H), 4.33 (t, 2H); ^{13}C-NMR ($CDCl_3$) δ 13.9, 19.3, 30.9, 55.1, 68.0, 92.3, 161.5, 166.8; ESI-MS: *m/z* 247 $[M+H]^+$. Analysis Calculated for $C_{10}H_{15}ClN_2O_3$: C, 48.69; H, 6.13; Cl, 14.37; N, 11.36; O, 19.46; Found C, 48.26; H, 6.09; Cl, 14.22; N, 11.41; O, 19.41.

5-Bromo-2-butoxy-4,6-dimethoxypyrimidine (4b). White solid; M.P = 42-43 ^{o}C. IR (KBr): 3037, 3016, 2937, 1580, 1471, 1379, 1313cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.97 (t, 3H), 1.45-1.50 (m, 2H), 1.77 - 1.80 (m, 2H), 4.02 (s, 6H), 4.33 (t, 2H); ^{13}C-NMR ($CDCl_3$) δ 14.0, 19.3, 31.0, 55.3, 68.1, 80.0, 162.9, 167.8; ESI-MS: *m/z* 291 $[M+H]^+$. Analysis Calculated for $C_{10}H_{15}BrN_2O_3$: C, 41.25; H, 5.19; Br, 27.45; N, 9.62; O, 16.49; Found C, 41.09; H, 5.10; Br, 27.52; N, 9.52; O, 16.42.

5-Chloro-4,6-dimethoxy-2-(prop-2-yn-1-yloxy)pyrimidine (4c). White solid; M.P = 45-46 ^{o}C. IR (KBr): 3039, 3018, 2937, 2150, 1542, 1424, 1316, 1197, 821, 731 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.47 (t, *J* = 2.4 Hz, 1H), 4.04 (s, 6H), 4.96 (d, *J* = 2.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 55.3, 55.4, 75.0, 78.2, 93.2, 160.2, 166.9; ESI-MS: *m/z* 229$[M+H]^+$. Analysis Calculated for $C_9H_9ClN_2O_3$: C, 47.28; H, 3.97; Cl, 15.51; N, 12.25; O, 20.99; Found C, 47.15; H, 3.85; Cl, 15.42; N, 12.15; O, 20.88.

5-Bromo-4,6-dimethoxy-2-(prop-2-yn-1-yloxy)pyrimidine (4d). White solid; M.P = 39-40 ^{o}C. IR (KBr): 3037, 3016, 2937, 2155, 1540, 1426, 1317, 1192, 827, 732cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.46 (t, *J* = 2.4 Hz, 1H), 4.04 (s, 6H), 4.96 (d, *J* = 2.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 54.24, 54.25, 73.8, 77.06, 79.8, 160.4, 166.8; ESI-MS: *m/z* 273$[M+H]^+$. Analysis Calculated for $C_9H_9BrN_2O_3$: C, 39.58; H, 3.32; Br, 29.26; N, 10.26; O, 17.58; Found C, 39.41; H, 3.25; Br, 29.31; N, 10.21; O, 17.47.

Ethyl 2-[(5-chloro-4, 6-dimethoxypyrimidin-2-yl) oxy]propanoate (4e). Light brown solid; M.P = 68-69 ^{o}C. IR (KBr): 3039, 3018, 2937, 1735, 1577, 1473, 1382, 1315, 1020cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, *J*=7.2 Hz, 3H), 1.64 (d, *J* = 7.2 Hz, 3H), 3.99(s, 6H), 4.22 (q, *J* = 7.2 Hz, 2H), 5.16(q, *J* = 7.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.3, 17.5, 55.3, 61.2, 72.3, 93.2, 160.4, 166.8, 171.7; ESI-MS: *m/z* 291$[M+H]^+$. Analysis Calculated for $C_{11}H_{15}ClN_2O_5$: C, 45.45; H, 5.20; Cl, 12.2; N, 9.64; O, 27.52; Found C, 45.40; H, 5.15; Cl, 12.17; N, 9.52; O, 27.55.

Ethyl 2-[(5-bromo-4, 6-dimethoxypyrimidin-2-yl) oxy]propanoate (4f). Brown solid; M.P =101-103 ^{o}C. IR (KBr): 3037, 3016, 2937, 1740, 1580, 1471, 1379, 1313, 1030cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.21 (t, *J* = 7.2Hz, 3H),1.64 (d, *J* = 7.2 Hz, 3H), 3.99 (s, 6H), 4.20 (q, *J* = 7.2 Hz, 2H), 5.16(q, *J* = 7.2 Hz,1H); ^{13}C-NMR ($CDCl_3$) δ 14.3, 17.5, 55.4, 61.3, 72.3, 80.9,161.7, 167.9, 171.7; ESI-MS: *m/z* 335$[M+H]^+$. Analysis Calculated for $C_{11}H_{15}BrN_2O_5$: C, 39.42; H, 4.51; Br, 23.84; N, 8.36; O, 23.87; Found C, 39.40; H, 4.55; Br, 23.71; N, 8.30; O, 23.72.

5-Chloro-2-[(6-chloropyridin-3-yl)methoxy]-4,6-dimethoxypyrimidine (4g). White solid; M.P = 135-137 ^{o}C. IR (KBr): 3039, 3018, 2937, 1577, 1473, 1382, 1315, 1262, 819, 712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.02 (s, 6H), 5.37 (s, 2H), 7.34 (d, *J* = 8.0Hz, 1H), 7.78(d, *J* = 8.0Hz, 1H), 8.49 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 55.3, 66.2, 93.2, 124.4, 131.1, 138.9, 149.6, 151.4, 160.6, 166.8; ESI-MS: *m/z* 316[M+H]$^{+}$. Analysis Calculated for $C_{12}H_{11}Cl_2N_3O_3$: C, 45.59; H, 3.51; Cl, 22.43; N, 13.29; O, 15.18; Found C, 45.45; H, 3.55; Cl, 22.41; N, 13.32; O, 15.15.

5-Bromo-2-[(6-chloropyridin-3-yl) methoxy]-4,6-dimethoxypyrimidine (4h). White solid; M.P = 146-148 ^{o}C. (KBr): 3037, 3016, 2937, 1580, 1471, 1379, 1313, 1262, 819, 712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.01 (s, 6H), 5.38 (s, 2H), 7.33 - 7.35(d, *J* = 8.0Hz,1H), 7.77 - 7.79(dd, *J* = 5.2Hz, 1H), 8.49 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 54.2, 65.0, 79.8, 123.2, 129.9, 137.7, 148.4, 150.2, 160.7, 166.8; ESI-MS: *m/z* 360[M+H]$^{+}$. Analysis Calculated for $C_{12}H_{11}BrClN_3O_3$: C, 39.97; H, 3.07; Br, 22.16; Cl, 9.83; N, 11.65; O, 13.31; Found C, 39.82; H, 3.15; Br, 22.15; Cl, 9.72; N, 11.61; O, 13.23.

2-[(5-Chloro-4,6-dimethoxypyrimidin-2-yl)oxy]benzonitrile (4i). White solid; M.P = 196-198 ^{o}C. IR (KBr): 3039, 3018, 2937, 2245, 1577, 1473, 1382, 1315, 1120, 815, 785cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.91 (s, 6H), 7.31 - 7.38 (m, 2H), 7.63 - 7.68 (m, 1H), 7.70 - 7.73 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 54.2, 93.6, 106.5, 114.3, 122.1, 124.9, 132.2, 133.1, 153.2, 158.9, 165.9; ESI-MS: *m/z* 292[M+H]$^{+}$. Analysis Calculated for $C_{13}H_{10}ClN_3O_3$: C, 53.53; H, 3.46; Cl, 12.15; N, 14.41; O, 16.46; Found C, 53.12; H, 3.39; Cl, 12.16; N, 14.35; O, 16.32.

2-[(5-Bromo-4,6-dimethoxypyrimidin-2-yl)oxy]benzonitrile (4j). White solid; M.P = 212-214 ^{o}C. IR (KBr): 3037, 3016, 2937, 2248, 1580, 1471, 1379, 1313, 1120, 815, 785cm^{-1};^{1}H-NMR ($CDCl_3$) δ 3.92(s, 6H), 7.33 - 7.39 (m, 2H), 7.65 - 7.70 (m, 1H), 7.72 - 7.74 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 55.6, 82.7, 107.7, 115.5, 123.3, 126.1, 133.5, 134.3, 154.4, 161.5, 168.3; ESI-MS: *m/z* 336[M+H]$^{+}$. Analysis Calculated for $C_{13}H_{10}BrN_3O_3$: C, 46.45; H, 3.00; Br, 23.77; N, 12.50; O, 14.28; Found C, 46.12; H, 3.15; Br, 23.15; N, 12.61; O, 14.12.

Methyl {2-[(5-chloro-4,6-dimethoxypyrimidin-2-yl)oxy]phenyl}acetate (4k). Light brown solid; M.P = 103-105 ^{o}C. IR (KBr): 3039, 3015, 2937, 1739, 1575, 1473, 1382, 1315, 1040, 814, 785cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.57 (s, 3H), 3.61 (s, 2H), 3.87 (s, 6H), 7.13 - 7.15 (d, *J* = 8.0Hz,1H), 7.21-7.27(t, *J* = 8.0Hz, 1H), 7.29 - 7.33(t, *J* = 8.0Hz, 1H), 7.37 - 7.38 (d, *J* = 8.0Hz,1H); ^{13}C-NMR ($CDCl_3$) δ 35.6, 52.0, 55.3, 93.7, 122.6, 125.9, 127.1, 128.4, 131.4, 151.2, 161.0, 167.0, 171.3; ESI-MS: *m/z* 339[M+H]$^{+}$. Analysis Calculated for $C_{15}H_{15}ClN_2O_5$: C, 53.19; H, 4.46; Cl, 10.47; N, 8.27; O, 23.62; Found C, 53.12; H, 4.39; Cl, 10.39; N, 8.35; O, 23.52.

Methyl {2-[(5-bromo-4,6-dimethoxypyrimidin-2-yl) oxy] phenyl} acetate (4l). Light brown solid; M.P = 106-107 ^{o}C. IR (KBr): 3037, 3016, 2937, 1743, 1580, 1471, 1379, 1313, 1045, 815, 784 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.56 (s, 3H), 3.61 (s, 2H), 3.86 (s, 6H), 7.12 - 7.14 (d, *J* = 8.0Hz,1H), 7.29 - 7.33 (t, *J* = 8.0Hz, 1H), 7.36 - 7.38 (t, *J* = 8.0Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 35.6, 52.0, 55.4, 81.5, 122.6, 125.9, 127.0, 128.4, 131.3, 151.2, 162.4, 168.1, 171.3; ESI-MS: *m/z* 383[M+H]$^{+}$. Analysis Calculated for $C_{15}H_{15}BrN_2O_5$: C, 47.02; H, 3.95; Br, 20.85; N, 7.31; O, 20.88; Found C, 46.92; H, 3.92; Br, 20.92; N, 7.29; O, 20.67.

5-Chloro-4,6-dimethoxy-2-(2-methylphenoxy) pyrimidine (4m). White solid; M.P = 165-166 ^{o}C. IR (KBr); 3039, 3018, 2937, 1577, 1473, 1382, 1315, 1129, 817, 710cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.19 (s, 3H), 3.88 (s, 6H), 7.06 - 7.08 (d, *J* = 8.0Hz,1H), 7.12 - 7.16 (t, *J* = 8.0Hz, 1H), 7.19 - 7.21 (t, *J* = 8.0Hz, 1H), 7.23 - 7.25 (d, *J* = 8.0Hz,1H); ^{13}C-NMR ($CDCl_3$) δ 16.52, 55.3, 93.5, 122.1, 125.7, 126.9, 130.7, 131.1, 151.5, 161.0, 167.1; ESI-MS: *m/z* 281[M+H]$^{+}$. Analysis Calculated for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98; O, 17.10; Found C, 55.55; H, 4.69; Cl, 12.52; N, 9.87; O, 17.01.

5-Bromo-4,6-dimethoxy-2-(2-methylphenoxy) pyrimidine (4n). White solid; M.P = 156-158 ^{o}C. IR (KBr): 3035, 3016, 2937, 1581, 1471, 1379, 1313, 1129, 817, 713cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.19 (s, 3H), 3.87 (s, 6H), 7.06 - 7.08 (d, *J* = 8.0Hz,1H), 7.12 - 7.16 (t, *J* = 8.0Hz, 1H), 7.19 - 7.21 (t, *J* = 8.0Hz, 1H), 7.22 - 7.25(d, *J* = 8.0Hz,1H); ^{13}C-NMR ($CDCl_3$)δ 16.52, 55.4, 81.2, 122.1, 125.7, 126.9, 130.7, 131.1, 151.5, 162.4, 168.1; ESI-MS: *m/z* 325[M+H]$^{+}$. Analysis Calculated for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; Br, 24.57; N, 8.62; O, 14.76; Found C, 47.92; H, 4.02; Br, 24.49; N, 8.73; O, 14.72.

5-Chloro-4,6-dimethoxy-2-(4-methylphenoxy) pyrimidine (4o). White solid; M.P = 133-135 ^{o}C. IR (KBr): 3039, 3017, 2937, 1577, 1472, 1382, 1315, 1129, 815, 710cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.91 (s, 6H), 7.06 - 7.08 (d, *J* = 8.0Hz, 2H), 7.16 - 7.18 (d, *J* = 8.0Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 16.33, 50.6, 88.8, 116.7, 125.1, 130.1, 145.9, 156.4, 162.2; ESI-MS: *m/z* 281[M+H]$^{+}$. Analysis Calculated for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98; O, 17.10; Found C, 55.56; H, 4.72; Cl, 12.54; N, 9.82; O, 17.12.

5-Bromo-4,6-dimethoxy-2-(4-methylphenoxy) pyrimidine (4p). White solid; M.P = 131-132 ^{o}C. IR (KBr): 3037, 3016, 2935, 1580, 1471, 1377, 1312, 1129, 817, 710cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.90 (s, 6H), 7.06 - 7.08 (d, *J* = 8.0Hz, 2H), 7.16-7.18 (d, *J* = 8.0Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 21.1, 55.4, 81.3, 121.5, 129.8, 134.9, 150.7, 162.5, 168.1; ESI-MS: *m/z* 325[M+H]$^{+}$. Analysis Calculated for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; Br, 24.57; N, 8.62; O, 14.76; Found C, 47.91; H, 4.01; Br, 24.59; N, 8.71; O, 14.75.

2-(2,4-bis(2-phenylpropan-2-yl)phenoxy)-5-chloro-4,6-dimethoxypyrimidine (4q). White solid; M.P = 139-140 ^{o}C. IR (KBr): 3039, 3018, 2937, 1577, 1473, 1382, 1315, 1129, 817, 709cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.69 (s, 6H), 1.75 (s, 6H), 3.74 (s, 6H), 6.84 - 6.91 (m, 4H), 7.04 - 7.09 (m, 3H), 7.18 - 7.27 (m, 5H), 7.49 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 25.1, 25.2, 26.3, 26.4, 37.3, 38.4, 50.1, 51.6, 87.8, 119.8, 120.3, 120.6, 121.0 121.1, 121.9, 122.1, 122.6, 123.4, 135.9, 142.8, 144.1, 144.3, 146.4, 155.7, 161.3; ESI-MS: *m/z* 503[M+H]$^{+}$. Analysis Calculated for $C_{30}H_{31}ClN_2O_3$: C, 71.63; H,6.21; Cl, 7.05; N,5.57; O, 9.54; Found C, 71.52; H, 6.22; Cl, 7.04; N, 5.32; O, 9.52.

2-(2,4-bis(2-phenylpropan-2-yl)phenoxy)-5-Bromo-4,6-dimethoxypyrimidine (4r). White solid; M.P = 137-138 ^{o}C. IR (KBr): 3037, 3016, 2937, 1580, 1471, 1379, 1313, 1129, 820, 715cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.69 (s, 6H), 1.75 (s, 6H), 3.73 (s, 6H), 6.84 - 6.91 (m, 4H), 7.04 - 7.09 (m, 3H), 7.19 - 7.30 (m, 5H), 7.50 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 29.9, 31.1, 42.0, 43.2, 55.0, 80.3, 124.5, 125.0, 125.3, 125.8, 125.9, 126.7, 126.9, 127.3, 128.2, 140.7, 147.6, 148.8, 149.0, 151.1, 161.8, 167.1; ESI-MS: *m/z* 547[M+H]$^{+}$. Analysis Calculated for $C_{30}H_{31}BrN_2O_3$: C, 65.81; H, 5.71; Br, 14.59; N, 5.12; O, 8.77; Found C, 65.72; H, 5.75; Br, 14.46; N, 5.32; O, 8.52.

Biological Activity

The antimicrobial activity of newly synthesized compounds **4(a-r)** was determined by well plate method in nutrient agar (antibacterial activity) and Sabouraud dextrose agar (antifungal activity). In this work, *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (recultured) *were* used to investigate the antibacterial activities and *Aspergilus flavus* (NCIM No.524), *Aspergilus fumigates* (NCIM No. 902), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) were used to investigate the antifungal activities. Minimum inhibitory concentration (MIC) of all compounds was determined, which is defined as the lowest concentration of inhibitor at which bacterial growth was not visually apparent.

Investigation on antibacterial screening data (Table 1) showed some of the compounds were active against four human pathogenic bacteria. Among the compounds **4b, 4c, 4e, 4k,** and **4r** were active against the bacterial strains. Among the compound 4e found to be more active compared to other analogues. The four compounds **4e, 4m, 4n** and **4o** were more active against fungi strains. Among the compound 4e was the most active compared to the other substituted analogues.

Table 1. Antibacterial activity data for the compounds 4(a-r) (MIC in µg/ml)

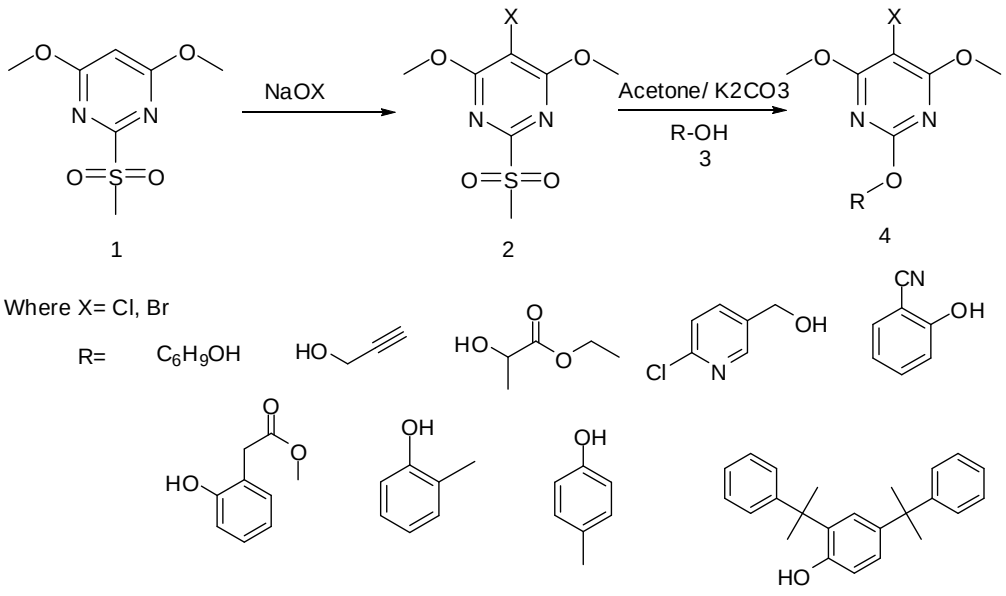
Compound NO	Staphylococcus aureus	Escherichia coli	Pseudomonas aeruginosa	Klebsiella pneumoniae
4a	>100	>100	>100	>100
4b	12.5	12.5	12.5	12.5
4c	12.5	12.5	12.5	12.5
4d	>100	>100	>100	>100
4e	6.25	6.25	6.25	6.25
4f	>100	>100	>100	>100
4g	>100	>100	>100	>100
4h	>100	>100	>100	>100
4i	>100	>100	>100	>100
4j	>100	>100	>100	>100
4k	12.5	12.5	12.5	12.5
4l	>100	>100	>100	>100
4m	>100	>100	>100	>100
4n	>100	>100	>100	>100
4o	>100	>100	>100	>100
4p	>100	>100	>100	>100
4q	>100	>100	>100	>100
4r	6.25	6.25	6.25	6.25
Standard Ampicillin	6.25	6.25	6.25	6.25

Table 2. Antifungal activity data for the compounds 4(a-r) (MIC in µg/ml)

Compound NO	Penicillium marneffei	trichophyton mentagrophytes	aspergillus flavus	aspergillus fumigatus
4a	>100	>100	>100	>100
4b	>100	>100	>100	>100
4c	>100	>100	>100	>100
4d	>100	>100	>100	>100
4e	6.25	6.25	6.25	6.25
4f	>100	>100	>100	>100
4g	>100	>100	>100	>100
4h	>100	>100	>100	>100
4i	>100	>100	>100	>100
4j	>100	>100	>100	>100
4k	>100	>100	>100	>100
4l	>100	>100	>100	>100
4m	12.5	12.5	12.5	12.5
4n	12.5	12.5	12.5	12.5
4o	12.5	12.5	12.5	12.5
4p	>100	>100	>100	>100
4q	>100	>100	>100	>100
4r	>100	>100	>100	>100
Standard Itraconazole	6.25	6.25	6.25	6.25

RESULTS AND DISCUSSION

4,6-dimethoxy-2-methylsulphonyl pyrimidine undergoes chlorination and bromination when treated with sodium hypochlorite and sodium hypobromite to give corresponding 5-chloro-4,6-dimethoxy-2-methyl sulphonyl pyrimidine (**2a)** and 5-bromo-4,6-dimethoxy-2-methylsulphonyl pyrimidine (**2b)** (Scheme 1).

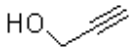
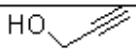
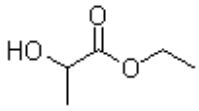
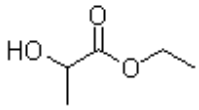
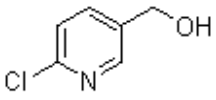
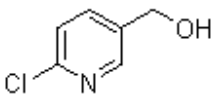


Scheme 1. Pathway for the synthesis of 5-halo-4, 6-dimethoxy-2-methylsulfonylpyrimidine

The structures of synthesized compounds were characterized by their Mass, ^{1}H NMR, ^{13}C and elemental analysis. In ^{1}H NMR the signal due to proton at 5th position of pyrimidine ring was absent shows the halogenation at that position. The mass fragment ion peaks corresponding to their molecular formula in the mass spectrum confirm halogenations. Further 5-halo-4,6-dimethoxy-2-methylsulphonyl pyrimidine (**2a-b)** reacts with aliphatic and aromatic alcohols in presence of acetone and potassium carbonate gave 5-halo-4,6-dimethoxy 2-(alkoxy or aryloxy) pyrimidines as shown in the Scheme 2.

There are two leaving groups in the pyrimidine ring of compound **2**: the chlorine or bromine atom in the 5th position and the methyl sulphonyl group in the 2nd position. However it is well known that 5-chloropyrimidines are not very susceptible to nucleophilic substitution, the methylsulphonyl group in the 2nd position being more active takes part in the nucleophilic substitution reaction. [23]

Table 3. Synthesis of 5-halo-4, 6-dimethoxy-2-(alkoxy or aryloxy) pyrimidines

Entry	Starting materials (x)	R-OH (3)	Product	Yield
1	Cl (**2a**)	C4H9OH	**4a**	85%
2	Br (**2b**)	C4H9OH	**4b**	80%
3	Cl (**2a**)		**4c**	81%
4	Br (**2b**)		**4d**	84%
5	Cl (**2a**)		**4e**	85%
6	Br (**2b**)		**4f**	81%
7	Cl (**2a**)		**4g**	86%
8	Br (**2b**)		**4h**	84%

Antimicrobial activity

All the synthesized 2-alkoxy or aryloxy pyrimidine compounds **4(a-r)** were evaluated for their *in vitro* antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (recultured). Similarly *Aspergilus flavus* (NCIM No.524), *Aspergilus fumigates* (NCIM No. 902), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) were used to investigate the antifungal activity. Ampicillin and Itraconazole were used as standard drugs for bacteria and fungi respectively. Preliminary screening for the test compound and standard drugs were performed at fixed concentrations of 200 µg / mL. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria and 72 h for fungi. Each experiment was repeated twice. Based on the results of zone of inhibition, the minimum inhibitory concentration (MIC) of potent compounds **4(a-r)** against all bacterial and fungal strains was determined by two fold dilution method [29]. Stock solutions of tested compounds with 200, 100, 50, 25, 12.5 and 6.25 µg/mL concentrations were prepared with DMSO as solvent. Inoculums of the bacterial and fungal culture were also prepared. To a series of tubes containing 1 mL each of test compound solution with different concentrations and 0.2 mL of the inoculums was added. Further 3.8 mL of the sterile water was added to each of the test tubes. These test tubes were incubated for 24 h at 37 °C and observed for the presence of turbidity. This method was repeated by changing test compounds with standard drugs Ampicillin and Itraconazole for comparison. The minimum inhibitory concentration at which no growth was observed was taken as the MIC values. The comparison of the MICs (in µg/mL) of potent compounds and standard drug ampicilin against tested strains are presented in Table 1. Similarly the MIC for antifungal activity was determined using 72 h old broth culture. The results were compared with itraconazole and summarized in Table 2.

CONCLUSION

In conclusion, a series of novel 2-alkoxy (aryloxy)-5-halo substituted 4,6-dimethoxy pyrimidines (**4a-r**) were synthesized and their antimicrobial was evaluated. The anti microbial screening suggests that few of the newly synthesized compounds showed moderate to good activity against the tested organisms. Among the synthesized compounds, **4e** was the most promising for both antibacterial and antifungal activity. Hence the fact that the compounds prepared in this study were chemically unrelated to the current medication, suggests that further work with similar analogues is clearly warranted.

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