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Synthesis and SAR Studies of Some Novel Series of Pyrimidine Analogues

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A series of novel ethyl-4-methyl-6-phenyl-2-(substituted thio)pyrimidine-5-carboxylate (**4a-m**), ethyl-4-methyl-phenyl-2-(substituted sulfinyl)pyrimidine-5-carboxylate (**5a-m**) and ethyl-4-methyl-phenyl-2-(substituted sulfonyl)pyrimidine-5-carboxylate (**6a-m**) were synthesized by multi-step organic synthesis. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, LCMS and elemental analysis. Most of the compounds showed significant antibacterial and anticancer activity comparable to or higher than the standard employed.

Keywords: Pyrimidine analogues, Sulfinyl pyrimidine, Sulfonyl derivatives, Antibacterial activity, Anticancer activity.

INTRODUCTION

The nucleophilic substitution of 2-halo pyrimidine derivatives with alkyl or aryl thiols followed by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) to produce corresponding sulfoxides and sulfones, has garnered significant interest in the synthesis of novel pyrimidine compounds with enhanced pharmacological activity [1,2]. Compounds bearing sulfanyl, sulfinyl and sulfonyl moieties are crucial both medicinally and industrially. They serve as antivirals [3], antineoplastic agents [4] and agrochemicals. For instance, 4-alkylthiopyrimidine derivatives demonstrate broad-spectrum herbicidal activity in transplanted paddy rice [5] and have applications as fungicides [6,7]. Additionally, 6-*n*-propyl-2-thiouracil functions as an antithyroid drug [8], while its S-alkylated and N-alkylated derivatives exhibit novel antibacterial, antimalarial and cytotoxic properties [9].

Thiouracils and their nucleoside analogues are naturally occurring, with 2-thiouracil commonly found in the t-RNA of *Escherichia coli* [10]. A series of sulfanyl pyrimidine analogues, such as S-DABO, have been reported to possess anti-HIV activities [11,12]. These findings underscore the importance of pyrimidine derivatives in medicinal chemistry and their potential in drug development.

In light of these observations and as part of our ongoing research to identify biologically active pyrimidine derivatives [13-17], we have synthesized a novel series of ethyl-4-methyl-6-phenyl-2-(substituted thio)pyrimidine-5-carboxylates (**4a-m**), ethyl-4-methyl-6-phenyl-2-(substituted sulfinyl)pyrimidine-5-carboxylates (**5a-m**) and ethyl-4-methyl-6-phenyl-2-(substituted sulfonyl)pyrimidine-5-carboxylates (**6a-m**). These compounds were specifically designed and synthesized focusing on 2-position of the pyrimidine ring, as substitution at this site is known to significantly impact the biological activity of the molecules.

So, present work distinguishes itself by the systematic exploration of the structure-activity relationships (SAR) of these novel pyrimidine analogues, with a particular emphasis on their antibacterial and anticancer activities. This work attempts to clarify the differences in the thio, sulfinyl and sulfonyl substituents influence the pharmacological profiles of these molecules, therefore influencing the development of more potent medicinal drugs.

EXPERIMENTAL

Unless otherwise specified, all chemicals and solvents were obtained from commercial suppliers and used with proper purification whenever required. Reaction time and purity of the products were monitored by TLC on Merck KGaA silica gel $60F_{254}$ aluminium sheets 20 cm × 20 cm with fluorescent indicator at 254 nm. Column chromatography was run on silica gel (230-400 mesh). All the melting points were recorded on

Buchi M-565 instrument and are uncorrected. The mass spectra (MS) were taken in ESI mode on Agilent Tech 1290 LC-MS. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker ARX-400, 400 MHz spectrometer with TMS as an internal standard.

General procedure

Ethyl-4-methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1): A mixture of benzaldehyde (25 g, 9.41 mmol) ethyl acetoacetate (33.7 g, 10.35 mmol), urea (15.56 g, 10.35 mmol) and a catalytic amount of conc. HCl in ethyl alcohol (100 mL) was stirred under reflux for 6 h. The reaction mass was cooled to room temperature and poured into ice-water (500 mL). The resulting precipitate was filtered, washed with water (200 mL), dried under reduced pressure to afford product **1** as an off-white solid (50 g, 82%), m.p.: 122.5-117.9 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.09 (t, 3H, *J* = 7.2 Hz), 2.25 (s, 3H), 3.98 (q, 2H, *J* = 7.2 Hz), 7.25-7.32 (m, 5H, Ar-H), 7.73(br s, 1H), 9.19(br s 1H), ^{13}C NMR (DMSO-d_6) δ ppm: 14.5,18.2, 54.4, 59.6, 99.7, 126.7, 127.7, 128.8, 145.33, 148.7, 152.5), 165.7; Mass: *m/z*, 261.2 (M+1).

Ethyl-4-methyl-2-oxo-6-phenyl-1,2-dihydropyrimidine-5-carboxylate (2): To a cooled solution of compound **1** (20 g, 3.84 mmol) in acetone (400 mL) and ceric ammonium nitrate (126.38 g, 11.52 mmol) in water (400 mL) and $NaHCO_3$ (32.27 g, 19.21 mmol) was added and stirred at room temperature for 12 h. The reaction mass was concentrated under reduced pressure to remove acetone. The aqueous phase was extracted with ether, dried over Na_2SO_4 filtered and concentrated to afford compound **2** as a colourless liquid (yield: 15 g, 75%). ^{1}H NMR (DMSO-d_6) δ ppm: 0.82 (t, 3H, *J* = 7.2 Hz), 2.39 (s, 3H), 3.94 (q, 2H, *J* = 7.2 Hz), 7.45 (m, 5H), 12.39 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ: 13.6, 61.2, 126.6, 127.9, 128.6, 128.8, 130.5, 155.8, 166.3; Mass: *m/z*, 259.2 (M+1).

Ethyl-2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate (3): A solution of compound **2** (10 g, 3.87 mmol) and $POCl_3$ (36.19 mL, d = 1.64 g/cm^3, 38.71 mmol) was heated at 120 °C for 2 h. The reaction mass was concentrated under reduced pressure, the residue was dissolved in chloroform and was washed with water and a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford compound **3**. The crude compound **3** was purified by silica gel column chromatography (eluent, 25% EtOAc in petroleum ether) to afford compound **3** as brown liquid (yield: 6 g, 56%). ^{1}H NMR (DMSO-d_6) δ ppm:1.03 (t, 3H, *J* = 7.2 Hz), 2.56 (s, 3H), 4.21 (q, 2H, *J* = 7.2 Hz), 7.58 (m, 5H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.6, 62.6, 79.6, 124.7, 128.6, 129.3, 131.4, 136.1, 159.9, 166.0, 166.7, 169.2; Mass: *m/z*, 277.2 (M+1).

Ethyl-4-methyl-6-phenyl-2-(alkyl/aryl thio)pyrimidine-5-carboxylates (4a-m): To a solution of NaH (1.8 mmol) in dry THF (2 mL) was added alkyl/aryl thiols (1.08 mmol) in THF (2 mL) dropwise at 0 ºC and stirred at room temperature for 30 min. A solution of ethyl-2-chlorol-4-methyl-6-phenyl-pyrimidine-5-carboxylate (**3**, 0.905 mmol) in dry THF (2 mL) was added dropwise at 0 ºC, slowly the reaction mass was warmed to room temperature and stirred for 2h. The reaction mass was poured into ice water (10 mL), extracted with EtOAc (25 mL × 2), washed with brine (25mL) and dried over Na_2SO_4. The resulting solution was concentrated. The crude was purified by silica gel column chromatography (eluent, 20% EtOAc in petroleum ether) to afford compounds **4a-m**.

Ethyl-4-methyl-6-phenyl-2-(ethylthiopyrimidine-5-carboxylate (4a): Off white solid; yield: 78%, m.p.: 100-102 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 0.90 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.1 Hz), 2.68 (s, 3H, CH_3), 4.18 (q, 2H, *J* = 7.2 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 7.39-7.51 (m, 5H); Mass: *m/z*, 302 (M^++1); Anal. calcd. (found) % for $C_{16}H_{18}N_2O_2S$: C, 63.55 (66.32); H, 6.00 (5.28); N, 9.26 (5.38).

Ethyl-4-methyl-6-phenyl-2-(phenyl)thiopyrimidine-5-carboxylate (4b): Off white solid; yield: 81%, m.p.: 95-98 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 0.90 (t, 3H, *J* = 7.2 Hz, CH_3), 2.69 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 7.2 Hz, CH_2), 7.45-7.52 (m, 6H, Ar-H), 7.64 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.94 (d, 2H, *J* = 4 Hz, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.8, 62.9, 125.5, 129.3 (t, *J* = 256 Hz), 131.8 (d, 232 Hz), 136.3,143.5 (C-S, benzene-S), 164.1 (C=O), 166.6, 167.7, 170.3 (C-S of pyrimidine-S); Mass: *m/z*, 352 (M^++1); Anal. calcd. (found) % for $C_{20}H_{18}N_2O_2S$: C, 68.55 (68.51); H, 5.18 (5.20); N, 7.99 (7.97).

Ethyl-4-methyl-6-phenyl-2-(*p*-anisyl)thiopyrimidine-5-carboxylate (4c): Off white solid; yield: 96%, m.p.: 85-87 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 0.88 (t, 3H, *J* = 7.2 Hz, CH_3), 2.58 (s, 3H, CH_3), 4.09 (q, *J* = 7.2 Hz, 2H, CH_2), 7.12 (d, 2H, *J* = 7.8 Hz, *ortho* protons of *p*-anisyl), 7.38 (d, 2H, *J* = 7.8 Hz *meta* protons of *p*-anisyl), 7.49-7.56 (m, 5H, Ar-H); Mass: *m/z*, 381 (M^++1); Anal. calcd. (found) % for $C_{21}H_{20}N_2O_3S$: C, 66.29 (66.32); H, 5.30 (5.28); N, 7.36 (7.38).

Ethyl-4-methyl-6-phenyl-2-(*m*-anisyl)thiopyrimidine-5-carboxylate (4d): White solid; yield: 67%, m.p.: 100-102 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.01 (t, 3H, *J* = 7.2 Hz, CH_3), 2.45 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.16 (q, 2H, *J* = 7.2 Hz), 7.0-7.4 (m, 4H, Ar-H), 7.46-7.53 (m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.8, 55.8. 62.1, 115.9, 120.1, 121.3, 127.1, 128.4, 129.0, 130.1, 130.4, 130.9,137.1 (C-S, benzene-S), 159.9, 163.3 (C=O), 166.2, 167.4, 171.2 (C-S of pyrimidine-S); Mass: *m/z*, 397 (M^++1); Anal. calcd. (found) % for $C_{21}H_{20}N_2O_3S$: C, 66.29 (66.32); H, 5.30 (5.28); N, 7.36 (7.38).

Ethyl-4-methyl-6-phenyl-2-(propyl)thiopyrimidine-5-carboxylate (4e): Off white solid; yield: 80%, m.p.: 130-132 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 0.83 (t, 3H, *J* = 7.1 Hz, CH_3 of propyl), 0.92 (t, *J* = 7.2 Hz, CH_3 of ethyl),1.2 (m, 2H, CH_2 of propyl) 4.18 (t, *J* = 7.1 Hz, CH_2), 2.51 (s, 3H, CH_3), 4.48 (q, 2H, *J* = 7.4 Hz, S-CH_2) 7.38-7.49 (m, 5H, Ar-H); Mass: *m/z*, 317 (M^++1); Anal. calcd. (found) % for $C_{17}H_{20}N_2O_2S$: C, 64.53 (64.55); H, 6.37 (6.39); N, 8.85 (8.86).

Ethyl-4-methyl-6-phenyl-2-(*p*-aminophenyl)thiopyrimidine-5-carboxylate (4f): White solid; yield: 88%, m.p.: 125-128 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.0 (t, 3H, *J* = 7.2 Hz, CH_3), 2.42 (s, 3H, Ar-CH_3), 4.14 (q, 2H, *J* = 7.2 Hz, CH_2), 5.54 (s, 2H, Ar-NH_2), 6.62 (d, 2H, *J* = 8.8 Hz, Ar-H of *p*-amino phenyl), 7.24 (d, 2H, 8.8 Hz, Ar-H of *p*-amino phenyl), 7.43-7.50 (m, 5 H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.7, 62.0, 112.3, 114.7, 121.3, 128.7 (d, *J* = 224 Hz), 130.8, 137.0, 137.3, 150.6, 163.2 (C=O) 165.8, 167.6, 173.3 (C-S of pyrimi-

dine-S); Mass: *m/z*, 366 (M^++1). Anal. calcd. (found) % for $C_{20}H_{19}N_3O_2S$: C, 65.73 (65.77); H, 5.24 (5.23); N, 11.50 (11.53).

Ethyl-4-methyl-6-phenyl-2-(*o*-chlorophenyl)thiopyrimidine-5-carboxylate (4g): Off white solid; yield: 75%, m.p.: 134-136 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.1 (t, 3H, *J* = 7.2 Hz, CH_3), 2.38 (s, 3H, Ar-CH_3), 4.08 (q, 2H, *J* = 7.2 Hz, CH_2), 7.38-7.86 (m, 9H, Ar-H); Mass: *m/z*, 386 (M^++1) 388 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_2$: C, 62.41 (62.42); H, 4.45 (4.46); N, 7.28 (7.29).

Ethyl-4-methyl-6-phenyl-2-(*p*-chlorophenyl)thiopyrimidine-5-carboxylate (4h): Off white solid; yield: 79%, m.p.: 146-148 ºC; ^{1}H NMR (DMSO- d_6) δ ppm: 1.00 (t, 3H, *J* = 7.2 Hz, CH_3), 2.45 (s, 3H, CH_3), 4.16 (q, 2H, *J* = 7.2 Hz, CH_2) 7.41 (d, 2H, *J* = 8.8 Hz, Ar-H of *p*-chlorophenyl),7.55 (d, 2H, 8.8 Hz, Ar-H of *p*-chlorophenyl), 7.45-7.53 (m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.7, 62.2, 122.0, 128.0, 128.4, 129.3 (d, *J* = 232 Hz),130.9, 134.8, 137.0, 163.4 (C=O) 166.3, 167.3, 170.8 (C-S of pyrimidine-S); Mass: *m/z*, 386 (M^++1), 388 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_2SCl$: C, 62.41 (62.43); H, 4.45 (4.42); N, 7.28 (7.27).

Ethyl-4-methyl-6-phenyl-2-(*o*-bromophenyl)thiopyrimidine-5-carboxylate (4i): White solid; yield: 81%, m.p.: 120-122 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: δ 0.91 (t, 3H, *J* = 7.2 Hz, CH_3), 2.39 (s, 3H, Ar-CH_3),4.21 (q, 2H, *J* = 7.2 Hz, CH_2), 7.32-7.51 (m, 9H, Ar-H); Mass: *m/z*, 429 (M^++1), 437 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_2SBr$: C, 55.95 (55.93); H, 3.99 (3.97); N, 6.52 (6.50).

Ethyl-4-methyl-6-phenyl-2-(*m*-bromophenyl)thiopyrimidine-5-carboxylate (4j): Off white solid; yield: 82%, m.p.: 110-112 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 0.98 (t, 3H, *J* = 7.2 Hz, CH_3), 2.41 (s, 3H, Ar-CH_3), 4.18 (q, 2H, *J* = 7.2 Hz, CH_2), 7.18-7.63 (m, 9H, Ar-H); Mass: *m/z*, 429 (M^++1), 437 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_2SBr$: C, 55.95 (55.90); H, 3.99 (3.98); N, 6.52 (6.51).

Ethyl-4-methyl-6-phenyl-2-(*p*-bromophenyl)thiopyrimidine-5-carboxylate (4k): White solid; yield: 86%, m.p.: 104-106 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.01 (t, 3H, *J* = 7.2 Hz, CH_3), 2.45 (s, 3H, CH_3), 4.16 (q, 2H, *J* = 7.2 Hz, CH_2), 7.41 (d, 2H, *J* = 8.8 Hz, Ar-H of *p*-chlorophenyl), 7.63 (d, 2H, 8.8 Hz, *ortho* protons of *p*-chlorophenyl), 7.47-7.51 (m, 5H, Ar-H), 7.69 (d, 2H, 8.8 Hz, *meta* protons of *p*-chlorophenyl); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.7, 62.2, 122.0, 123.5, 128.4, 128.6, 129.1, 131.0, 132.6, 137.0, 137.2, 164.4 (C=O), 167.3, 170.7 (C-S of pyrimidine-S), Mass: *m/z*, 429 (M^++1), 437 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_2SBr$: C, 55.95 (55.90); H, 3.99 (3.97); N, 6.52 (6.53).

Ethyl-4-methyl-6-phenyl-2-(*o*-fluorophenyl)thiopyrimidine-5-carboxylate (4l): Brown solid; yield: 82%, m.p.: 78-80 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.03 (t, 3H, *J* = 7.2 Hz, CH_3), 2.36 (s, 3H, CH_3), 4.21 (q, 2H, *J* = 7.2 Hz, CH_2), 7.18-7.53 (m, 9H, Ar-H); Mass: *m/z*, 369 (M^++1); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_2SF$: C, 65.20 (65.21); H, 4.65 (4.66); N, 7.60 (7.61).

Ethyl-4-methyl-6-phenyl-2-(*p*-fluorophenyl)thiopyrimidine-5-carboxylate (4m): Off white solid; yield: 69%, m.p.: 127-129 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.07 (t, 3H, *J* = 7.2 Hz, CH_3), 2.53 (s, 3H, CH_3), 4.18 (q, 2H, *J* = 7.2 Hz, CH_2), 7.14-7.44 (m, 5H, Ar-H), 7.52 (d, 2H, *J* = 6.8 Hz, Ar-H), 7.65-7.62(m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.7, 62.2, 66.89, 121.9, 124.7, 128.4, 129.1, 130.9, 137.0, 137.9, 138.0, 163.3, 164.2 (C=O), 164.5, 166.2, 167.4, 171.3 (C-S of pyrimidine-S); Mass: *m/z*, 369 (M^++1); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_2SF$: C, 65.20 (65.21); H, 4.65 (4.66); N, 7.60 (7.61).

Ethyl-4-methyl-6-phenyl-2-(substituted sulfinyl)-pyrimidine-5-carboxylate (5a-m): A solution of ethyl-4-methyl-6-phenyl-2-(alkyl/aryl thio)pyrimidine-5-carboxylates (**4a-m**) (0.66mmol) in MDC (20 mL) at 0 ºC was added *m*-chloroperbenzoic acid (*m*-CPBA) (0.66 mmol) portionwise and stirred at room temperature for 1h. Completion of reaction was monitored by TLC (EtOAC:petroleum ether::1:1). Reaction mass was quenched in ice cold water (20 mL), extracted with EtOAC (25 mL × 2), washed with saturated $NaHCO_3$ (20 mL), washed with brine (25 mL) and dried over Na_2SO_4. The resulting solution was purified by column chromatography (60-120 mesh silica gel, 30% EtOAC in petroleum ether) to afford compounds **5a-m**.

Ethyl-4-methyl-6-phenyl-2-(ethylsulfinyl)pyrimidine-5-carboxylate (5a): Brown solid; yield: 45%, m.p.: 107-111 ºC; IR (KBr, ν_{max}, cm^{-1}): 2921 (C-H *str.*),1688 (C=O of ester), 1250 (S=O, sulfoxide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.12 (t, 3H, *J* = 7.2 Hz, CH_3), 1.28 (t, 3H, *J* = 7.2 Hz, CH_3), 2.58 (s, 3H, pyrimidine CH_3), 4.22 (q, *J* = 7.2 Hz, -OCH_2-CH_3), 4.51 (q, 2H, *J* = 7.2 Hz, O=S-CH_2-CH_3), 7.41-7.52(m, 5H, Ar-H); Mass *m/z*; 313 (M^++1); Anal. calcd. (found) % for $C_{16}H_{18}N_2SO_3$: C, 60.36 (60.32); H, 5.70 (5.71); N, 8.80 (8.82).

Ethyl-4-methyl-6-phenyl-2-(phenylsulfinyl)pyrimidine-5-carboxylate (5b): Off white solid; yield: 60%, m.p.: 112-115 ºC; IR (KBr, ν_{max}, cm^{-1}): 2938 (C-H *str.*), 1676 (C=O of ester), 1221 (S=O); ^{1}H NMR (DMSO-d_6) δ ppm: 0.90 (t, 3H, *J* = 7.2 Hz, CH_3), 2.69 (s, 3H, pyrimidine CH_3), 4.22 (q, *J* = 7.2 Hz, 2H, CH_2), 7.45-7.52(m, 6H, Ar-H), 7.64 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.94 (d, 2H, *J* = 7. Hz, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.8, 62.6, 125.5, 129.3 (t, *J* = 256 Hz), 131.8 (d, *J* = 232 Hz), 136.3, 143.5 (C-S, benzene-S), 164.1 (C=O), 166.6, 167.7, 173.0 (C-S of pyrimidine-S); Mass *m/z*; 367.0 (M^++1); Anal. calcd. (found) % for $C_{20}H_{18}N_2O_3S$: C, 65.55 (65.56); H, 4.95 (4.97); N, 7.64 (7.65).

Ethyl-4-methyl-6-phenyl-2-(*p*-anisylsulfinyl)-pyrimidine-5-carboxylate (5c): Brown solid; yield: 57%, m.p.: 83-89 ºC; IR (KBr, ν_{max}, cm^{-1}): 2908 (C-H *str.*), 1681 (C=O of ester), 1228 (S=O); ^{1}H NMR ($CDCl_3$) δ ppm: 1.10 (t, 3H, *J* = 7.1 Hz, CH_3), 2.70 (s, 3H, pyrimidine CH_3), 3.84 (s, 3H, OCH_3 of anisyl), 4.23 (q, 2H, *J* = 7.1 Hz, CH_2), 7.00 (d, 2H, *J* = 6.8 Hz, *p*-anisyl protons), 7.45-7.65(m, 5H, Ar-H), 7.85 (d, 2H, *J* = 6.8 Hz, *p*-anisyl protons); ^{13}C NMR ($CDCl_3$) δ ppm: 13.6, 22.7, 55.5, 62.3, 62.0, 114.7, 127.3, 128.7 (d, *J* = 40 Hz), 130.8, 136.4, 162.3, 164.4 (C=O), 167.1, 167.5, 173.0 (C-S of pyrimidine); Mass *m/z*; 397.0 (M^++2); Anal. calcd. (found) % for $C_{21}H_{20}N_2O_4S$: C, 63.62 (63.65); H, 5.08 (5.10); N, 7.07 (7.08).

Ethyl-4-methyl-6-phenyl-2-(*m*-anisylsulfinyl)-pyrimidine-5-carboxylate (5d): Brown solid; yield: 72%, m.p.: 112-116 ºC; IR (KBr, ν_{max}, cm^{-1}): 2931 (C-H *str.*),1688 (C=O of ester), 1231 (S=O); ^{1}H NMR ($CDCl_3$) δ ppm: 1.08 (t,

3H, *J* = 7.2 Hz, CH_3), 2.6 (s, 3H, pyrimidine CH_3), 3.71 (s, 3H, OCH_3 of an -anisyl), 4.18 (q, 2H, *J* = 7.1 Hz, CH_2), 7.1-7.65 (m, 9H, Ar-H); Mass *m/z*; 396 (M^++1); Anal. calcd. (found) % for $C_{21}H_{20}N_2O_4S$: C, 63.62 (63.65); H, 5.08 (5.10); N, 7.07 (7.09).

Ethyl-4-methyl-6-phenyl-(propylsulfinyl)pyrimidine-5-carboxylate (5e): Off white solid; yield: 45%, m.p.: 118-121 ºC; IR (KBr, ν_{max}, cm^{-1}): 2948, 3023 (C-H *str.*), 1672 (C=O of ester), 1229 (S=O); ^{1}H NMR ($CDCl_3$) δ ppm: 0.91 (t, 3H, *J* = 7.0 Hz, CH_3), 1.08 (t, 3H, *J* = 7.2 Hz, CH_3), 1.56 (m, 2H), 1.83 (t, 2H, *J* = 7.0 Hz, CH_2), 2.63 (s, 3H, pyrimidine CH_3), 4.12 (q, 2H, *J* = 7.1 Hz, CH_2), 7.41-7.56 (m, 5H, Ar-H); Mass *m/z*; 307 (M^++1); Anal. calcd. (found) % for $C_{17}H_{20}N_2O_3S$: C, 61.42 (61.44); H, 6.06 (6.08); N, 8.43 (8.45).

Ethyl-4-methyl-6-phenyl-(*p*-aminophenylsulfinyl)-pyrimidine-5-carboxylate (5f): Brown solid; yield: 68%, m.p.: 131-134 ºC; IR (KBr, ν_{max}, cm^{-1}): 3240 (N-H *str.*), 3046 (C-H *str.*), 1684 (C=O of ester), 1231 (S=O); ^{1}H NMR ($CDCl_3$) δ ppm: 1.08 (t, 3H, *J* = 7.1 Hz, CH_3), 2.58 (t, 3H, pyrimidine CH_3), 4.03 (q, 2H, *J* = 7.1 Hz, CH_2), 5.61(br, 2H, Ar-NH_2), 6.7 (d, 2H, *J* = 8.2 Hz, *ortho* protons of *p*-aminophenyl), 6.93 (d, 2H, *J* = 8.2 Hz *meta* protons of *p*-aminophenyl), 7.31-7.61 (m, 5H, Ar-H); Mass *m/z*; 383 (M^++1); Anal. calcd. (found) % for $C_{20}H_{19}N_3SO_3$: C, 62.97 (62.99); H, 4.27 (4.29); N, 11.02 (11.05).

Ethyl-4-methyl-6-phenyl-2-(*o*-chlorophenylsulfinyl)-pyrimidine-5-carboxylate (5g): Off white solid; yield: 45%, m.p.: 137-140 ºC; IR (KBr, ν_{max}, cm^{-1}): 3041 (C-H *str.*), 1678 (C=O of ester), 1209 (S=O); ^{1}H NMR ($CDCl_3$) δ ppm: 1.16 (t, 3H, *J* = 7.1 Hz, CH_3), 2.49 (t, 3H, pyrimidine CH_3), 4.11 (q, 2H, *J* = 7.1 Hz, CH_2), 7.01-7.9 (m, 9H, Ar-H); Mass *m/z*: 402 (M^++1), 404 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_3SCl$: C, 59.92 (62.42); H, 4.45 (4.46); N, 6.99 (7.29).

Ethyl-4-methyl-6-phenyl-2-(*p*-chlorophenylsulfinyl)-pyrimidine-5-carboxylate (5h): Off white solid; yield: 45%, m.p.: 125-128 ºC; IR (KBr, ν_{max}, cm^{-1}): 2995 (C-H *str.*), 1681 (C=O of ester), 1219 (S=O); ^{1}H NMR ($CDCl_3$) δ ppm: 1.03 (t, 3H, *J* = 7.2 Hz, CH_3), 2.41 (t, 3H, pyrimidine CH_3), 3.98 (q, 2H, *J* = 7.2 Hz, CH_2), 6.86 (d, 2H, *J* = 8.4 Hz, *ortho* protons of *p*-chloro phenyl) 7.36-7.51 (m, 5H, Ar-H), 7.68 (d, *J* = 8.0 Hz, *meta* protons of *p*-chloro phenyl); Mass *m/z*; 402 (M^++1), 404 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_3SCl$: C, 59.92 (59.95); H, 4.45 (4.46); N, 6.99 (6.98).

Ethyl-4-methyl-6-phenyl-2-(2-bromophenylsulfinyl)-pyrimidine-5-carboxylate (5i): Brown solid; yield: 68%, m.p.: 125-127 °C; IR (KBr, ν_{max}, cm^{-1}): 2968 (C-H *str.*), 1685 (C=O of ester), 1257 (S=O), 781 (C-Br *str.*); ^{1}H NMR (DMSO-d_6) δ ppm: 1.04 (t, 3H, *J* = 7.2 Hz), 2.58 (s, 3H, pyrimidine CH_3), 4.22 (q, 2H, *J* = 7.2 Hz), 7.51-7.60 (m, 6H, Ar-H), 7.67 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.77 (d, 1H, *J* = 7.9 Hz, Ar-H), 7.88 (d,1H, *J* = 7.84 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 13.6, 22.7, 62.2, 121.2, 126.2, 128.4, 128.6, 130.9, 132.8, 136.1, 143.2, 164.3 (C=O), 167.0, 167.8, 171.9 (C-S, pyrimidine-S); Mass *m/z*; 447.3 (M^++2), 449 (M^++4); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_3SBr$: C, 53.94 (53.97); H, 3.85 (3.87); N, 6.29 (6.32).

Ethyl-4-methyl-6-phenyl-2-(*m*-bromophenylsulfinyl)-pyrimidine-5-carboxylate (5j): Brown solid; yield: 67%, m.p.: 115-117 ºC; IR (KBr, ν_{max}, cm^{-1}): 2976 (C-H *str.*), 1681 (C=O of ester), 1256 (S=O); ^{1}H NMR (DMSO-d_6) δ ppm: 1.03 (t, 3H, *J* = 7.1 Hz, CH_3), 2.60 (s, 3H, pyrimidine CH_3), 4.21 (q, 2H, *J* = 7.0 Hz, CH_2), 7.52-7.62 (m, 6H, Ar-H), 7.77 (d, *J* = 7.9 Hz, Ar-H), 7.78 (d, 1H, *J* = 6.9 Hz, Ar-H), 7.98 (t, 1H, *J* = 2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 13.9, 22.6, 63.5, 124.2, 125.1, 127.6, 128.8, 129.8, 132.8, 136.0, 137.5, 145.9, 164.3 (C=O), 166.2, 167.8, 169.5, 172.9 (C-S, pyrimidine-S); Mass *m/z*; 447.3 (M^++2), 449 (M^++4); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_3SBr$: C, 53.94 (53.93); H, 3.85 (3.87); N, 6.29 (6.31).

Ethyl-4-methyl-6-phenyl-2-(*p*-bromophenylsulfinyl)-pyrimidine-5-carboxylate (5k): Brown solid; yield: 49%, m.p.: 118-121 ºC; IR (KBr, ν_{max}, cm^{-1}): 3006 (C-H *str.*), 1679 (C=O of ester), 1251 (S=O, sulfoxide); ^{1}H NMR (DMSO-d_6) δ ppm: 0.93 (t, 3H, *J* = 7.1 Hz, CH_3), 2.48 (s, 3H, pyrimidine CH_3), 4.18 (q, 2H, *J* = 7.1 Hz, CH_3), 6.96 (d, 2H, *J* = 8. Hz, *ortho* protons of *p*-bromophenyl), 7.1-7.62(m, 5H, Ar-H), 7.63 (d, 2H, *J* = 8.4 Hz, *meta* protons of *p*-bromophenyl); Mass *m/z*; 447 (M^++2), 449 (M^++1); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_3SBr$: C, 53.94 (53.93); H, 3.85 (3.87); N, 6.29 (6.32).

Ethyl-4-methyl-6-phenyl-2-(2-fluorophenylsulfinyl)-pyrimidine-5-carboxylate (5l): Brown solid; yield: 82%, m.p.: 89-93 ºC; IR (KBr, ν_{max}, cm^{-1}): 2951 (C-H str.), 1671 (C=O of ester), 1231 (S=O, sulfinyl); ^{1}H NMR (DMSO-d_6) δ ppm: 1.04 (t, 3H, *J* = 7.1 Hz, CH_3), 2.59 (s, 3H, pyrimidine CH_3), 4.22 (q, 2H, *J* = 7.0 Hz, CH_2), 7.41-7.48 (m, 2H, Ar-H), 7.56-7.67(m, 6H, Ar-H), 7.85 (t, 1H, *J* = 6.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 13.8, 22.8, 62.7, 116.8(*J* = 108 Hz), 126.2, 127.5, 128.1 (d, *J* = 2.75 Hz), 131.5, 134.8, 136.2, 160.8, 164.1 (C=O), 166.5, 167.8, 178.1 (C-S, pyrimidine-S); Mass *m/z*: 385.0 (M^++1); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_3SF$: C, 62.49 (62.52); H, 4.46 (4.50); N, 7.29 (7.31).

Ethyl-4-methyl-6-phenyl-2-(*p*-fluorophenylsulfinyl)-pyrimidine-5-carboxylate (5m): Off white solid; yield: 64%, m.p.: 109-112 ºC; IR (KBr, ν_{max}, cm^{-1}): 2967 (C-H *str.*), 1678 (C=O of ester), 1241 (S=O, sulfoxide); ^{1}H NMR (DMSO-d_6) δ ppm: 1.01 (t, 3H, *J* = 7.2 Hz, CH_3), 2.53 (s, 3H, pyrimidine CH_3), 4.18 (q, 2H, *J* = 7.2 Hz, CH_2), 7.38-7.85 (m, 9H, Ar-H); Mass *m/z*: 385 (M^++1); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_3SF$: C, 62.49 (62.51); H, 4.46 (4.48); N, 7.29 (7.32).

Ethyl-4-methyl-6-phenyl-2-(substituted sulfonyl)-pyrimidine-5-carboxylate (6a-m): Ethyl-4-methyl-6-phenyl-2-(alkyl/aryl thio)pyrimidine-5-carboxylates (**4a-m**) (0.66 mmol) in MDC (20 mL) was taken and cooled to 0 ºC to this solution *m*-CPBA (1.32 mmol) was added portionwise and stirred at room temperature for 1h. Completion of reaction was monitored by TLC (EtOAC:petroleum ether :: 1:1). Reaction mass was quenched in ice cold water (20 mL), extracted with EtOAC (25 mL × 2), washed with saturated $NaHCO_3$ (20 mL), washed with brine (25 mL) and dried over Na_2SO_4. The resul-ting solution was purified by column chromatography (60-120 mesh silica gel, 20% EtOAC in petroleum ether) to afford compounds **6a-m**.

Ethyl-2-(ethylsulfonyl)-4-methyl-6-phenylpyrimidine-5- carboxylate (6a): Brown solid; yield: 45%, m.p.: 111-114 ºC; IR (KBr, ν_{max}, cm^{-1}): 2940 (C-H *str.*), 1768 (C=O of ester), 1402 & 1163 (sulfone asymmetric & symmetric); ^{1}H NMR

(DMSO-d_6) δ ppm: 1.14 (t, J = 7.1 Hz, 3H, CH_3), 4.28 (q, J = 7.1 Hz, 2H, CH_2) due to ester CH_3CH_2 1.49 (t, J = 7.4 Hz, 3H, CH_3 of ethyl), 3.64 (q, J = 7.4 Hz, 2H, CH_2 of sulfonyl ester), 2.76 (s, 3H, pyrimidine CH_3), 7.48-7.74 (m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 7.1, 13.8, 22.8, 45.7, 62.8, 129.1 (d, J = 256 Hz), 131.6, 136.0, 164.3 (C=O), 166.3, 168.2 (C-S of pyrimidine-S); Mass: *m/z*, 335 (M^++1); Anal. calcd. (found) % for $C_{16}H_{18}N_2O_4S$: C, 57.47 (57.49); H, 5.43 (5.42); N, 8.38 (8.41).

Ethyl-2-(phenylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6b): Brown solid; yield: 45%, m.p.: 114-117 ºC; IR (KBr, ν_{max}, cm^{-1}): 3040 (C-H *str.*), 1691 (C=O of ester), 1393 & 1152 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.12 (t, 3H, J = 7.2 Hz, CH_3), 2.70 (s, 3H, pyrimidine CH_3), 4.26 (q, J = 7.2 Hz, 2H, CH_2), 7.44-7.63 (m, 7H, Ar-H), 7.65-7.71 (m, 1H, Ar-H), 8.17 (d, 2H, J = 2.0 Hz, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.9, 55.5, 62.0, 62.8, 127.2, 128.7, 129.6, 131.7, 135.1, 135.4, 137.8, 164.2 (C=O) 165.3, 166.2, 168.3 (C-S of pyrimidine-S); Mass: *m/z*, 383 (M^++1); Anal. calcd. (found) % for $C_{20}H_{18}N_2O_5S$: C, 62.81 (62.85); H, 4.74 (4.78); N, 7.33 (7.37).

Ethyl-2-(*p*-anisylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6c): Off white solid; yield: 57%, m.p.: 96-99 ºC; IR (KBr, ν_{max}, cm^{-1}): 2920 (C-H *str.*), 1758 (C=O of ester), 1398 & 1171 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.11 (t, 3H, J = 7.2 Hz, CH_3), 2.70 (s, 3H, pyrimidine CH_3), 3.96 (s, 3H, OCH_3), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 7.05 (d, 2H, J = 8.8 Hz, Ar-H), 7.46 (t, 2H, J = 7.6 Hz, Ar-H), 7.52 (d, 1H, J = 7.2 Hz, Ar-H), 7.65 (d, 2H, J = 7.2 Hz, Ar-H), 8.12 (d, 2H, J = 8.8 Hz, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.9, 55.9, 62.6, 115.5, 125.7, 128.7, 134.7, 136.3, 162.3, 164.1 (C=O), 166.7, 167.6, 173.3 (C-S of pyrimidine-S); Mass: *m/z*, 413 (M^++1); Anal. calcd. (found) % for $C_{21}H_{20}N_2O_5S$: C, 61.15 (61.17); H, 4.89 (4.93); N, 6.79 (6.76).

Ethyl-2-(*m*-anisylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6d): Brown solid; yield: 72%, m.p.: 116-119 ºC; IR (KBr, ν_{max}, cm^{-1}): 2943 (C-H *str.*), 1761 (C=O of ester), 1382 & 1174 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.09 (t, 3H, J = 7.2 Hz, CH_3), 2.58 (s, 3H, pyrimidine CH_3), 3.92 (s, 3H, OCH_3), 4.21 (q, 2H, J = 7.2 Hz, CH_2), 7.11 (s, 1H, Ar-H), 7.46 -7.71 (m, 5H, Ar-H), 7.82-8.1 (m, 3H, Ar-H); Mass: *m/z*, 413 (M^++1); Anal. calcd. (found) % for $C_{21}H_{20}N_2O_5S$: C, 61.15 (61.12); H, 4.89 (4.86); N, 6.79 (6.81).

Ethyl-2-(propylsulfonyl)-4-methyl-6-phenylpyrimidine-5- carboxylate (6e): Off white solid; yield: 45%, m.p.: 145-148 ºC; IR (KBr, ν_{max}, cm^{-1}): 2970, 3041 (C-H *str.*), 1752 (C=O of ester), 1392 & 1203 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 0.88 (t, 3H, J = 7.0 Hz, CH_3 of propyl), 1.12 (t, 3H, J = 7.2 Hz, CH_3 of ester), 1.41 (m, 2H, propyl CH_2), 2.16 (t, 2H, J = 7.0 Hz, CH_2 of propyl), 2.61 (s, 3H, pyrimidine CH_3), 4.08 (q, 2H, J = 7.2 Hz CH_2 of ester), 7.41-7.69 (m, 5H, Ar-H); Mass: *m/z*, 349 (M^++1); Anal. calcd. (found) % for $C_{17}H_{21}N_2O_4S$: C, 58.60 (58.63); H, 5.79 (5.82); N, 8.04 (8.07).

Ethyl-2-(*p*-aminophenylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6f): Brown solid; yield: 68%, m.p.: 133-137 ºC; IR (KBr, ν_{max}, cm^{-1}): 3300 (N-H *str.*), 3040 (C-H *str.*), 1712 (C=O of ester), 1388 & 1191 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.02 (t, 3H, J = 7.2 Hz, CH_3), 2.61 (s, 3H, pyrimidine CH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2), 5.16 (br, 2H, NH_2), 6.8 (d, 2H, J = 8.4 Hz, *ortho* protons of *p*-amino phenyl) 7.1 (d, 2H, J = 5.84 Hz, *meta* protons of *p*-amino phenyl), 7.40-7.64 (m, 5H, Ar-H); Mass: *m/z*, 398 (M^++1); Anal. calcd. (found) % for $C_{20}H_{19}N_3O_4S$: C, 60.44 (60.42); H, 4.82 (4.86); N, 10.57 (10.55).

Ethyl-2-(*o*-chlorophenylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6g): Off white solid; yield: 73%, m.p.: 114-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 2980 (C-H *str.*), 1683 (C=O of ester), 1372 & 1208 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.10 (t, 3H, J = 7.2 Hz, CH_3), 2.63 (s, 3H, pyrimidine CH_3), 4.26 (q, J = 7.1 Hz, 2H, CH_2), 7.49-7.60 (m, 5H, Ar-H), 7.72 -7.77 (m, 2H, Ar-H), 7.83 (t, 1H, Ar-H), 8.30 (d, 1H, J = 1.6 & 8.0 Hz, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.9, 62.9, 127.6, 128.6, 129.4, 131.8, 132.1, 132.7, 135.5 136.6, 164.3 (C=O), 164.7, 166.1, 168.6 (C-S of pyrimidine-S); Mass: *m/z*, 417 (M^++1) 419 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_4SCl$: C, 57.62 (57.65); H, 4.11 (4.13); N, 6.72 (6.74).

Ethyl-2-(*p*-chlorophenylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6h): Brown solid; yield: 63%, m.p.: 146-150 ºC; IR (KBr, ν_{max}, cm^{-1}): 2976 (C-H *str.*), 1673 (C=O of ester) 1381 & 1196 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.06 (t, 3H, J = 7.2 Hz, CH_3), 2.58 (s, 3H, pyrimidine CH_3), 4.08 (q, 2H, J = 7.2 Hz, CH_2) 6.96 (d, 2H, J = 8.4 Hz, *ortho* protons of *p*-chlorophenyl), 7.41-7.58 (m, 5H, Ar-H), 7.71 (d, 2H, 8.4 Hz, *meta* protons of *p*-chloro phenyl); Mass: *m/z*, 417 (M^++1), 419 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}ClN_2O_4S$: C, 57.62 (57.66); H, 4.11 (4.12); N, 6.72 (6.78).

Ethyl-2-(*o*-bromophenylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6i): Brown solid; yield: 68%, m.p.: 126-129 °C; IR (KBr, ν_{max}, cm^{-1}): 3016 (C-H *str.*), 1682 (C=O of ester), 1392 & 1196 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 0.98 (t, 3H, J = 7.2 Hz, CH_3), 2.49 (s, 3H, pyrimidine CH_3), 4.11 (q, J = 7.2 Hz, 2H, CH_2), 7.81-7.58 (m, 9H, Ar-H); Mass: *m/z*, 461 (M^++1), 463 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_4SBr$: C, 52.07 (52.09); H, 3.71 (3.74); N, 6.07 (6.09).

Ethyl-2-(*m*-bromophenylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6j): Brown solid; yield: 67%, m.p.: 119-123 ºC; IR (KBr, ν_{max}, cm^{-1}): 2998 (C-H *str.*), 1693 (C=O of ester), 1401 & 1208 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.03 (t, 3H, J = 7.1 Hz, CH_3), 2.53 (s, 3H, pyrimidine CH_3), 4.08 (q, J = 7.1 Hz, 2H, CH_2), 7.48-7.62 (m, 5H, Ar-H), 7.81 (s,1H, Ar-H), 7.88 (d, 1H, J = 8.8 Hz, Ar-H), 7.90-8.01 (m,1H, Ar-H), 8.03 (d, 1H, J = 8.8 Hz, Ar-H); Mass: *m/z*, 461 (M^++1) 463 (M^++3); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_4SBr$: C, 52.07 (52.08); H, 3.71 (3.69); N, 6.07 (6.09).

Ethyl-2-(*p*-bromophenylsulfonyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (6k): Brown solid; yield: 49%, m.p.: 114-118 ºC; IR (KBr, ν_{max}, cm^{-1}): 3011 (C-H *str.*), 1710 (C=O of ester), 1401 & 1168 (sulfone asymmetric & symmetric);

^{1}H NMR (DMSO-d_6) δ ppm: 1.05 (t, 3H, J = 7.1 Hz, CH_3), 2.61 (s, 3H, pyrimidine CH_3), 4.24 (q, J = 7.1 Hz, 2H, CH_2), 7.55-7.61 (m, 5H, Ar-H), 7.92 (d, 2H, J = 8.6 Hz, Ar-H), 7.98 (d, 2H, J = 8.6 Hz, Ar-H); ^{13}C NMR (DMSO-d_6) δ ppm: 13.8, 22.9, 62.9, 127.3, 128.8, 129.4, 131.8, 133.1, 135.8, 136.6, 164.3 (C=O), 164.9, 166.2, 168.4 (C-S of pyrimidine-S); Mass: *m/z*, 463 (M^++2); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_4SBr$: C, 52.07 (52.08); H, 3.71 (3.68); N, 6.07 (6.09).

Ethyl-2-(*o*-fluorophenylsulfonyl)-4-methyl-6-phenyl-pyrimidine-5-carboxylate (6l): Brown solid; yield: 82%, m.p.: 97-101 ºC; IR (KBr, ν_{max}, cm^{-1}): 3005 (C-H *str.*), 1695 (C=O of ester), 1404 & 1181 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 0.99 (t, 3H, J = 7.2 Hz, CH_3), 2.68 (s, 3H, pyrimidine CH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2), 7.38-8.08 (m, 9H, Ar-H); Mass: *m/z*, 402 (M^++1); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_4SF$: C, 59.99 (59.97); H, 4.28 (4.31); N, 7.00 (7.03).

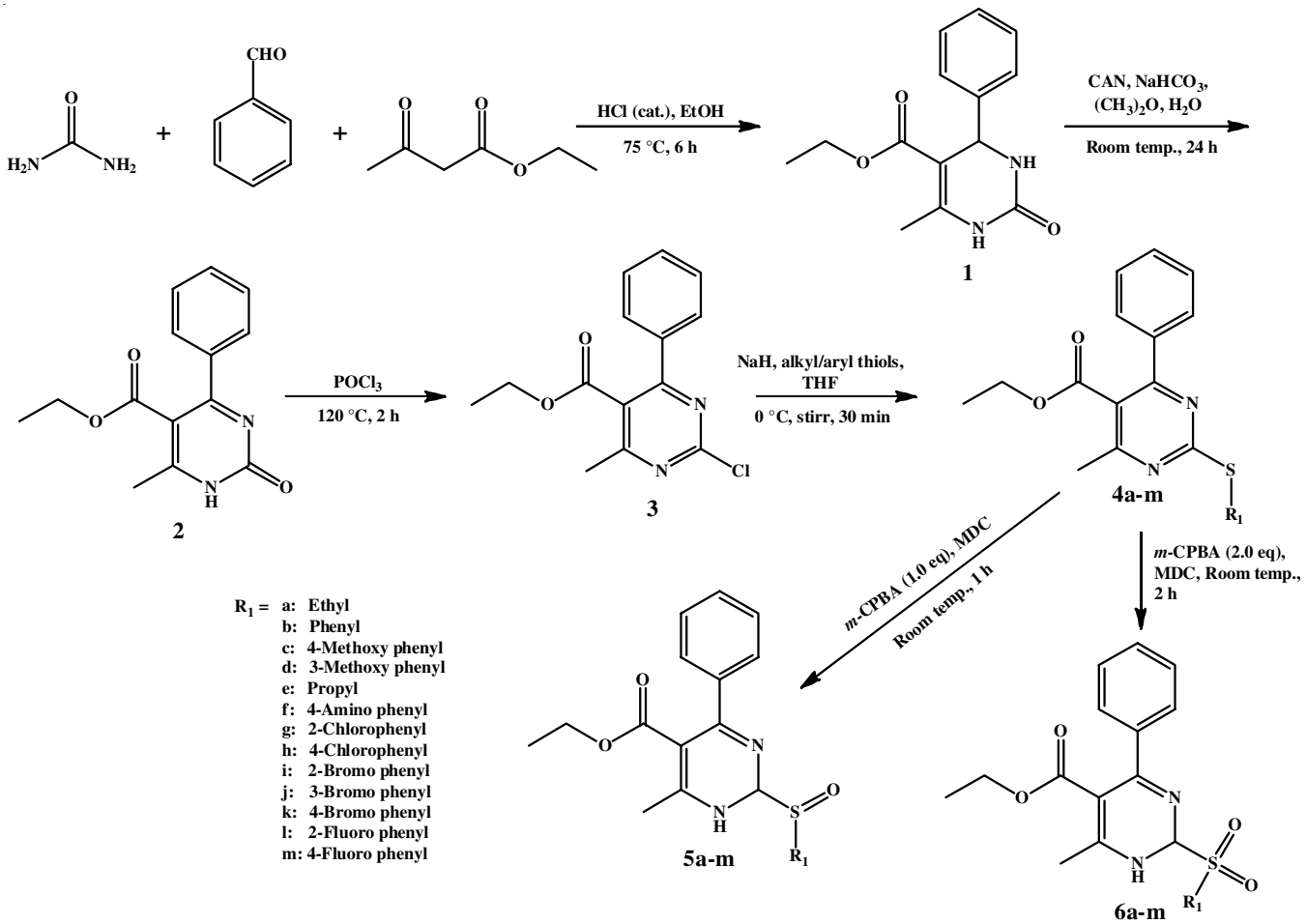
Ethyl-2-(*p*-fluorophenylsulfonyl)-4-methyl-6-phenyl-pyrimidine-5-carboxylate (6m): Off white solid; yield: 64%, m.p.: 129-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 2908 (C-H *str.*), 1691 (C=O of ester), 1395 & 1201 (sulfone asymmetric & symmetric); ^{1}H NMR (DMSO-d_6) δ ppm: 1.03 (t, 3H, J = 7.2 Hz, CH_3), 2.64 (s, 3H, pyrimidine CH_3), 4.09 (q, J = 7.2 Hz, 2H, CH_2) 7.28-8.10 (m, 9H, Ar-H). Mass: *m/z*, 402 (M^++1); Anal. calcd. (found) % for $C_{20}H_{17}N_2O_4SF$: C, 59.99 (59.95); H, 4.28 (4.31); N, 7.00 (6.98).

RESULTS AND DISCUSSION

The synthesis of hitherto unreported title compounds was carried out as outlined in **Scheme-I**. The Biginelli reaction between benzaldehyde, ethyl acetoacetate and urea in ethyl alcohol medium employing catalytic amount of conc. HCl afforded dihydropyrimidinone (**1**) as a white solid in 82% yield, compound **1** on oxidation with ceric ammonium nitrate and sodium bicarbonate in acetone and water yielded **2** as a colourless liquid in 75% yield. This on treatment with $POCl_3$ at 120 ºC provided **3** as a brown liquid in 56% yield. The ethyl-2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate (**3**), when treated with alkyl/aryl/thiols in presence of NaH in THF medium gave ethyl-4-methyl-6-phenyl-2-(alkyl/aryl thio)pyrimidine-5-carboxylates (**4a-m**) in good yields. The ethyl-4-methyl-phenyl-2-(alkyl/aryl sulfinyl)pyrimidine-5-carboxylates (**5a-m**) and ethyl-4-methyl-phenyl-2-(substituted sulfonyl)pyrimidine-5-carboxylate (**6a-m**) were obtained in good yield by treating ethyl-4-methyl-6-phenyl-2-(alkyl/aryl thio)pyrimidine-5-carboxylates (**4a-m**) with 1.0 equiv. and 2.0 equiv. of *m*-CPBA, respectively in dichloromethane medium.

Biological evaluation

***In vitro* antibacterial activity:** The antibacterial activity of the newly synthesized compounds was carried out against four bacterial strains, namely *Staphylococcus aureus*,



Scheme-I

Enterococcus faecalis, *Klebsiella pneumonia* and *Escherichia coli*. The experiment was assessed by Minimum Inhibitory Concentration (MIC) procedure [13]. The results are summarized in Table-1. All the newly synthesized compounds showed moderate to significant antibacterial activity with MIC values ranging from 100 to 0.2 μg/mL. Compounds **4c**, **4d**, **4e**, **4j**, **4k**, **5a**, **6a** and **6c** displayed excellent activity against *S. aureus* and *E. fecalis* with overall MIC values of 0.2 μg/mL, which were superior to standard ciprofloxacin (MIC value 2 μg/mL). However against *E. coli*, compounds **4b**, **4h**, **5a**, **5h**, **6a**, **6d** and **6h** showed moderate activity with overall MIC values of 0.8 μg/mL, which are also superior to standard ciprofloxacin (MIC value 2.0 μg/mL). Surprisingly against *Klebsiella* only compounds **5l** and **5m** with MIC values of 0.8 μg/mL and 0.4 μg/mL, respectively showed moderate activity and none of the other compounds showed any activity comparable with the standard Ciprofloxacin (MIC value 1.0 μg/mL).

TABLE-1
ANTIBACTERIAL ACTIVITY DATA OF THE COMPOUNDS **4a-m**, **5a-m** AND **6a-m** MIC VALUES (μg/mL)

Compd.	*E. coli*	*Klebsiella*	*S. aureus*	*E. fecalis*
4a	1.6	50	0.2	0.8
4b	0.8	50	0.8	0.8
4c	–	25	0.2	0.2
4d	3.12	–	0.2	0.2
4e	3.12	100	0.2	0.4
4f	6.25	–	0.8	0.8
4g	3.12	–	0.8	0.8
4h	0.8	–	0.8	0.4
4i	6.25	–	0.4	0.2
4j	3.12	–	0.2	0.2
4k	6.25	50	0.2	0.2
4l	6.25	–	0.8	0.4
4m	6.25	–	0.2	0.8
Ciprofloxacin (Std)	2.0	1.0	2.0	2.0
5a	0.8	50	0.2	0.2
5b	3.12	100	0.8	0.8
5c	1.6	50	0.2	–
5d	1.6	50	0.2	0.4
5e	1.6	–	0.2	0.4
5f	3.12	–	0.4	0.4
5g	1.6	50	0.4	0.2
5h	0.8	–	0.4	0.2
5i	3.12	–	0.4	0.4
5j	3.12	50	0.2	0.4
5k	1.6	100	0.4	0.8
5l	6.25	0.8	1.6	0.2
5m	12.5	0.4	0.8	0.4
Ciprofloxacin (Std)	2.0	1.0	2.0	2.0
6a	0.8	50	0.2	0.2
6b	12.5	50	0.8	0.4
6c	6.25	100	0.2	0.2
6d	0.8	–	0.2	0.8
6e	50	–	0.4	0.2
6f	1.6	25	0.8	0.4
6g	6.25	–	0.4	0.2
6h	0.8	50	0.8	0.4
6i	25	100	0.4	0.4
6j	6.25	–	0.2	0.4
6k	1.6	100	0.4	0.2
6l	6.25	100	0.4	0.4
6m	12.5	–	0.4	0.2
Ciprofloxacin (Std)	2.0	1.0	2.0	2.0

The introduction of different alkyl/aryl thio groups on C-2 pyrimidine showed major impact on the antibacterial activity against on all four bacterial strains. Particularly, compounds with 4-methoxyphenylthio, 3-methoxyphenylthio and 4-bromophenylthio at C-2 position of pyrimidine (**4c**, **4d** and **4k**) showed marked potency MIC values of 0.2 μg/mL) against *S.aureus* and *E. fecalis*, while introduction of other substituents on the C-2 position of pyrimidine **4a-4b**, **4c-4j** and **4l-m** resulted in a less potency against *S. aureus* and *E. fecalis.*

Similar impact also observed on the oxidation of thio groups into corresponding sulfinyl and sulfonyl groups. In particular, a compound with ethylsulfinyl group at the C-2 position of pyrimidine (**5a**) with MIC value of 0.2 μg/mL showed good activity against *S. aureus* and *E. fecalis*. Also, a compound with ethylsulfonyl and 4-methoxyphenyl sulfonyl groups at the C-2 position of pyrimidine (**6a** and **6c**) showed remarkable activity against *S. aureus* and *E. fecalis*.

***In vitro* anticancer activity:** The *in vitro* anticancer activities of all the newly synthesized compounds were screened against three human cancer cell lines A549, K562 and MCF-7 *in vitro*. The *in vitro* cytotoxicity data of test compounds in cells was determined by MIT assay. The results are summarized in Table-2. All target compounds showed moderate to significant anticancer activity against all three cell lines. The most promising compounds **4g** and **5k** displayed significant activity against A549 with IC_{50} values of 28 μM. Compounds **4c**, **4f**, **4h**, **4l**, **4m**, **5c**, **5f**, **5i**, **5j**, **6c**, **6f**, **6k**, **6l** and **6m** displayed moderate activity against A549 cell lines. Whereas compounds **4f**, **4 g**, **4h**, **5f**, **5l**, **5m**, **6c**, **6j** and **6k** displayed moderate activity against K562 cell lines and compounds **4g**, **4h**, **4l**, **5k** and **6l** also showed moderate activity against MCF-7 cell lines. The introduction of different alkyl/aryl thio groups on the C-2 position of pyrimidine showed major impact on the anticancer activity against all three cell lines. Comparable impacts were also observed in the oxidation of thio groups to their respective sulfinyl and sulfonyl derivatives.

TABLE-2
In vitro CYTOTOXICITY DATA (IC_{50} μM) OF COMPOUNDS **4a-m**, **5a-m** and **6a-m**, AGAINST CANCER CELL LINES BY MTT ASSAY

Compd.	A549 ± SD	K562 ± SD	MCF-7 ± SD
4a	98 ± 1.2	82 ± 1.1	97 ± 1.1
4b	98 ± 1.2	97 ± 1.6	81 ± 1.4
4c	95 ± 1.9	73 ± 1.1	68 ± 1.1
4d	52 ± 1.5	92 ± 1.6	84 ± 1.9
4e	94 ± 1.1	83 ± 1.5	96 ± 1.3
4f	47 ± 1.6	42 ± 1.8	98 ± 1.6
4g	28 ± 1.1	47 ± 1.1	49 ± 1.9
4h	48 ± 1.7	45 ± 1.3	47 ± 1.1
4i	95 ± 1.2	96 ± 1.1	97 ± 1.2
4j	98 ± 1.4	84 ± 1.2	96 ± 1.1
4k	84 ± 1.1	68 ± 1.3	94 ± 1.8
4l	42 ± 1.9	83 ± 1.1	49 ± 1.1
4m	47 ± 1.3	98 ± 1.9	78 ± 1.4
5-Fu	95 ± 1.5	41 ± 1.8	11.5 ± 1.7

5a	96 ± 1.1	93 ± 1.1	94 ± 1.1
5b	81 ± 1.5	97 ± 1.3	99 ± 1.9
5c	43 ± 1.1	95 ± 1.9	96 ± 1.3
5d	99 ± 1.9	83 ± 1.1	82 ± 1.1
5e	96 ± 1.3	69 ± 1.3	67 ± 1.0
5f	48 ± 1.8	49 ± 1.7	97 ± 1.1
5g	84 ± 1.5	98 ± 1.8	95 ± 1.5
5h	94 ± 1.3	93 ± 1.1	96 ± 1.4
5i	43 ± 1.0	84 ± 1.1	99 ± 1.9
5j	47 ± 1.3	93 ± 1.2	73 ± 1.1
5k	28 ± 1.2	94 ± 1.1	43 ± 1.8
5l	99 ± 1.1	43 ± 1.1	96 ± 1.3
5m	97 ± 1.7	48 ± 1.8	97 ± 1.1
5-Fu	95 ± 1.5	41 ± 1.8	11.5 ± 1.7
6a	94 ± 1.1	99 ± 1.1	84 ± 1.9
6b	81 ± 1.2	92 ± 1.1	97 ± 1.2
6c	45 ± 1.9	47 ± 1.6	98 ± 1.4
6d	8.1 ± 1.0	93 ± 1.7	84 ± 1.0
6e	99 ± 1.8	82 ± 1.1	92 ± 1.3
6f	44 ± 1.7	96 ± 1.9	94 ± 1.2
6g	97 ± 1.7	84 ± 1.4	97 ± 1.9
6h	83 ± 1.9	81 ± 1.8	69 ± 1.1
6i	99 ± 1.3	97 ± 1.1	98 ± 1.8
6j	97 ± 1.1	48 ± 1.2	97 ± 1.1
6k	44 ± 1.6	43 ± 1.0	96 ± 1.8
6l	47 ± 1.5	97 ± 1.8	45 ± 1.9
6m	43 ± 1.4	98 ± 1.8	67 ± 1.5
5-Fu	95 ± 1.5	41 ± 1.8	11.5 ± 1.7

Conclusion

In summary, a series of novel pyrimidine derivatives were designed, synthesized and evaluated their antibacterial and anticancer activities. The preliminary investigations showed that several compounds **4c**, **4d**, **4k**, **5a**, **6a** and **6c** possess excellent antibacterial activity against *S. aureus* and *E. fecalis in vitro*. Meanwhile, all the synthesized compounds were also tested for their activity against three cancer cell lines A549, K562 and MCF-7. The most promising compounds **4g** and **5k** showed significant activity with promising IC_{50} values.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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