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SYNTHESIS AND EVALUATION OF SOME NEW SUBSTITUTED PIPERAZINYL-ARYL AMIDE, ACETAMIDE, AND SULFONAMIDE DERIVATIVES OF ROSUVASTATIN INTERMEDIATE AND THEIR ANTI-MICROBIAL ACTIVITY

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ABSTRACT
In pursuit of a biodynamically potent molecule, we have attempted to synthesize derivatives of piperazine by incorporating them into the Rosuvastatin intermediate. The reason behind this is that heterocyclic compounds with nitrogen atoms in their ring structure, such as pyrimidine, have great potential as drug design scaffolds. By doping piperazine into the Rosuvastatin intermediate, a series of new derivatives made up of aryl-amides, acetamides, and sulfonamides were produced. These derivatives were then assessed for their antimicrobial activity, with a few showing promising results.
Keywords: Rosuvastatin Intermediate, Piperazine, Amide, Anti-microbial activity.
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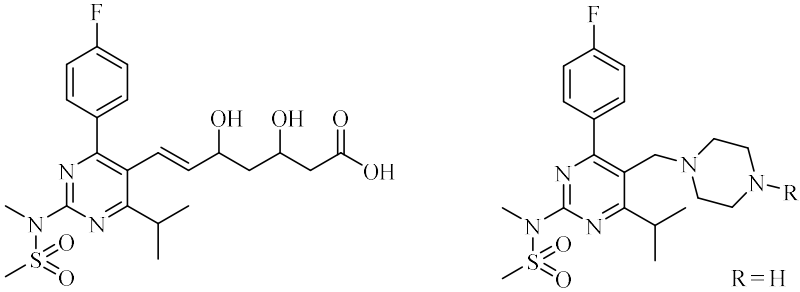
INTRODUCTION

Heterocycles containing pyrimidine moieties are found to possess antimicrobial[1,2,3,4,5], antileishmanial[6], antiinflammatory[7], analgesic[8], antihypertensive[9], antipyretic[10], antiviral[11], antidiabetic[12], antiallergic[13], anticonvulsant[14], antioxidant[15,16], antihistaminic[17], and anticancer activities.[18,19] Besides, pyrimidine along with piperazine containing heterocyclic compounds possesses more potent biological assays and acts as an effective antimicrobial agent. Piperazine derivatives are important pharmacophores in chemotherapy as well as important building blocks of biologically active molecule construction. In the piperazine ring, nitrogen atoms enhance favorable interaction with biomacromolecules hence explored for several biological activities.[20,21] Sulfonamide drugs are an important group of organic compounds that hold several types of biological activities.[22,23] Rosuvastatin[24] is a statin-class drug, used to treat high cholesterol, and cardiovascular disease, and is stated to be antimicrobial in nature.[25] For the enhancement of antimicrobial activity, piperazine derivatives are incorporated into the structure of Rosuvastatin and its modified intermediate shown in Fig.-1.



Rosuvastatin Rosuvastatin Piperazine Intermediate

Fig.-1: Rosuvastatin and incorporated Piperazine-Rosuvastatin analogs

In light of the above-aforementioned outlines, we have been attentive to the design and synthesis of novel pyrimidine-containing Rosuvastatin derivatives. Furtherly, piperazine moiety was incorporated to

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enhance its biological activity. So, herein we reported the synthesis and screened for antimicrobial activity of piperazine Rosuvastatin pyrimidine derivatives.

EXPERIMENTAL

Chemical Materials and Apparatus

Aromatic acids, phenylacetic acids, benzene sulfonyl chlorides, and all chemicals, and solvents were utilized after being obtained from merk, TCI, and AVRA. Melting points of respective final derivatives determined in exposed capillaries on GUNA, and were uncorrected, ^{1}HNMR and ^{13}CNMR bands executed on Bruker 400 MHz, the FT-IR spectrum was performed on JASCO IR 5300 using KBR pallets, and the LC-Mass spectra were noted on API 3000 mass spectrometer.

Biological Materials and Apparatus

All chemicals, buffer solutions, and agarose gel were purchased from Thermo Fischer Scientific and Sigma Aldrich. Electrophoresis was performed in agarose gels with 4% Tris-Borate-EDTA (TBE). Fluorescence emissions were screened and quantified by double fluorescence FMYG100 microscope. Cytofluorometric analysis was noted on Beckman Coulter's Gallio's 10/3 Cytofluorometer.

Chemistry

The designed new series of aryl amide, acetamide, and sulfonamide derivatives of piperazine-rosuvastatin hybrid final Compounds 3(a-d), 4(a-d), and 5(a-h) have been illustrated as outlined in Fig.-2. Initially, the piperazine intermediate (2), was obtained from the starting compound (1) with piperazine, the presence of K_2CO_3 in 1,4-dioxane at 80 °C. Furtherly, piperazine intermediate (2), was treated with several substituted benzoic acids, and phenylacetic acids, using triethylamine, EDC, and HOBT, to afford titled compounds 3 (a-d) and 4 (a-d) in good yields. Besides, piperazine intermediate (2) was treated with several aromatic sulphonyl chlorides with TEA in DCM to get compounds 5 (a-h) with high yields. All the derivatives were characterized through ^{1}HNMR, ^{13}CNMR, IR, and Mass spectral analysis in the experimental section.

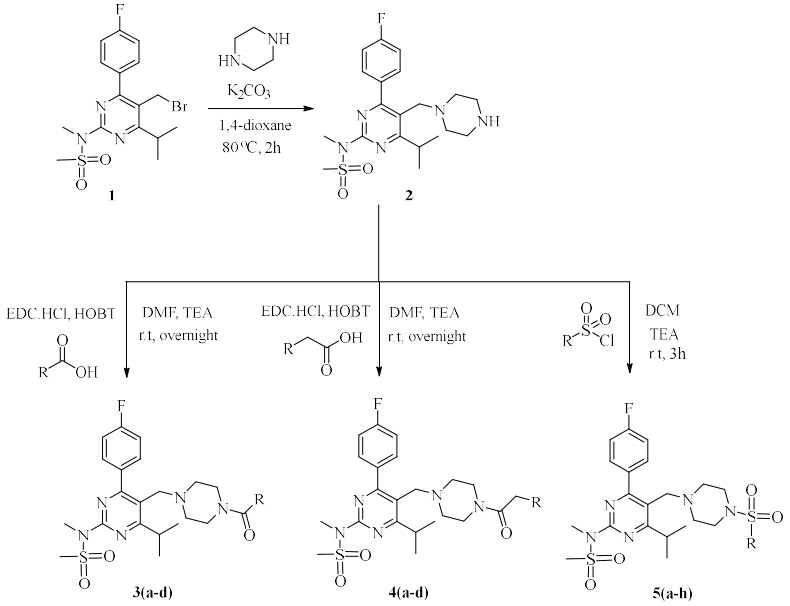
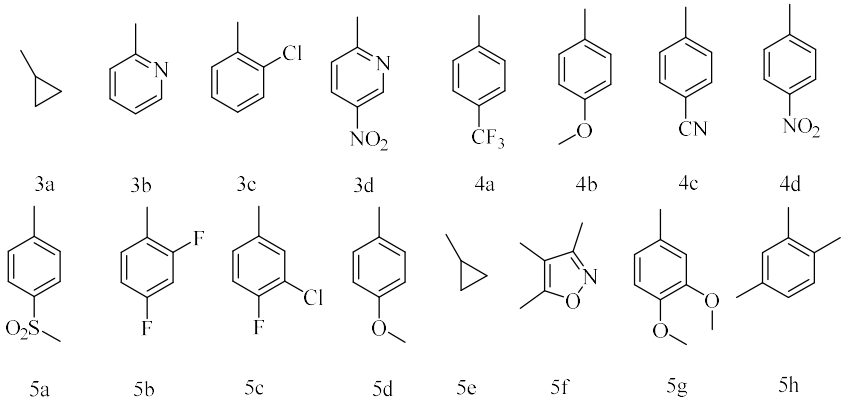


Fig.-2

Synthesis of the compound (2)

Piperazine (1.2 eq), potassium carbonate (2.5 eq), and compound-1 (1 eq) were all gently dissolved in 1,4-dioxane. The above reaction refluxed for 2-3 hours at 80-90 °C. After chilling, added cold water, extracted by 10% methanol in DCM, collective-organic layers were dehydrated with Na_2SO_4, sieved, and concentrated under vacuum pressure, the reaction product was purified through column-chromatography at 5-10% methanol in dichloromethane as eluent, and the compound (2) was obtained. Yield: 3.2 g (79%), M.P- 121-123 °C, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.608-7.512 (m, 2H), δH 7.136-7.071 (m, 2H), δH

3.952 (s, 2H), δH 3.511-3.392 (m, 7H), δH 2.954-2.772 (m, 4H), δH2.431-2.192 (m, 4H), δH 1.264 (d, 6H), (+)ESI-MS m/z: calculated for [$C_{20}H_{28}FN_5O_2S + H^+$] 421.54, observed 422.6.



Scheme-1: Synthesis of Aryl Amide, Acetamide, and Sulfonamide derivatives of Piperazinyl Rosuvastatin Intermediate 3(a-d), 4(a-d), and 5(a-h)

General Procedure of the Compounds 3(a-d) and 4(a-d)

Compound-2 (1 eq) in DMF (10 mL), then added triethylamine (3 eq), EDC (2.5 eq), and HOBT (2.5 eq). successively, followed by the addition of substituted phenyl acids and phenylacetic acids (1.5 eq), the above reaction was agitated at ambient temperature for 12-13 hours under nitrogen, the reaction was quenched through saturated $NaHCO_3$ solution, added water, EtOAc was used to extract the product, splashed with brine solution, separated organic layer dehydrated with Na_2SO_4, sieved, and concentrated, acquired crude was refined by column-chromatography at 40-60% EtOAc-Hexane as eluent to get compounds 3(a-d), and 4(a-d) with admirable yields.

Analytical Data for 3 (a-d) and 4 (a-d)

3a: *N*-(5-(4-(cyclopropanecarbonyl-piperazin-1-ylmethyl)-4-(4-Fluoro-Phenyl)-6-Iso-Propyl-pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Pale-yellow solid, M.P- 131-133 °C, Yield (74%). FT-IR(KBr, cm^{-1}): 2933, 1735, 1620, 1543, 1338, 1243, 1140, 961, 773, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.572-7.537 (m, 2H,), δH 7.133 (t, 2H), δH 3.556-3.514 (m, 13H), δH 2.263 (bs, 4H), δH 1.313 (d, 6H), δH 1.297-1.184 (m, 1H), δH ,0.953-0.915 (m, 2H), δH 0.740-0.694 (m, 2H); ^{13}C-NMR ($CDCl_3$): δC 177.9, δC 167.0, δC 164.5, δC 162.1, δC 134.8, δC 131.4, δC 119.1, δC 115.4, δC 115.2, δC 53.7, δC 42.6, δC 33.2, δC 31.9, δC 22.3, δC 10.9, δC 7.55, (+)ESI-MS m/z: calculated for [$C_{12}H_{32}FN_6O_3S + H^+$] 489.61, observed 490.1

3b: *N*-(-4-(4-Fluoro-Phenyl)-6-Iso-Propyl-5-(-4-picolinoylpiperazin-1-ylmethyl)-pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P-185-187 ºC, Yield (70%). FT-IR (KBr, cm^{-1}): 2931, 1730, 1629, 1546, 1337, 1224, 1151, 960, 771, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 8.652-8.596 (m, 2H), δH 7.715-7.686 (m, 1H), δH 7.544-7.509 (m, 2H), δH 7.359-7.327 (,m, 1H), δH 7.164-7.121 (,m, 2H), δH 3.682-3.327 (,m, 13H), δH 2.421-2.196 (m, 4H), δH 1.308 (d, 6H); ^{13}CNMR (100.6 MHz, $CDCl_3$, δC): δC 177.9, δC 167.7, δC 167.1, δC 164.5, δC 157.8, δC 151.0, δC 148.0, δC 135.3, δC 134.5, δC 124.2, δC 123.5, δC 118.9, δC 115.5, δC 115.3, δC 53.7, δC 42.7, δC 33.2, δC 31.9, δC 22.3, (+)ESI-MS m/z: calculated for [$C_{26}H_{31}FN_6O_3S + H^+$] 526.63, observed 527.1

3c: *N*-(5-(4-2-chlorobenzoyl-piperazin-1-ylmethyl)-4-(-4-Fluoro-phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P- 105-107 °C, Yield (77%). FT-IR (KBr cm^{-1}): 2929, 1735, 1637, 1544, 1342, 1224, 1151, 960, 769, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 9.404-9.323 (m, 1H), δH 8.579 (d, 2H), δ H7.843 (d, 1H), δH 7.558-7.536 (m, 3H). δH 7.164 (d, 2H), δH 3.785 (s, 2H), δH 3.566-3.516 (m, 11H), δH 2.400-2.286 (m, 4H), δH 1.324 (d, 6H), ^{13}C-NMR ($CDCl_3$):- δC 177.9, δC 167.0, δC 165.2, δC 162.2, δC 158.7, δC 157.7, δC 144.1, δC 143.8, δC 132.3, δC 131.3, δC 124.6, δC 118.7, δC 115.4, δC 115.2, δC 53.6, δC 52.5, δC 51.8, δC 47.2, δC 42.6, δC 33.1, δC 31.9, δC 22.2; (+)-ESI-MS m/z: calculated for [$C_{27}H_{31}ClFN_5O_3S + H^+$] 560.08, observed 561.0.

3d: *N*-(-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-5-(-4-5-nitropicolinoyl-Piperazin-1-ylMethyl)-Pyrimidin-2-yl)-*N*-Methyl-methanesulfonamide. Off-White solid, M.P- 221-223 °C, Yield (75%). FT-IR (KBr, cm^{-1}): 2930, 1734, 1632, 1545, 1340, 1232, 1149, 960, 772; ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.560-7.530 (m, 2H), δH 7.525-7.388 (,m, 1H), δH 7.383-7.305 (m, 1H), δH 7.231-7.208 (m, 1H), δH 7.136 (t, 2H), δH 3.696 (s, 2H), δH 3.544-3.092 (m, 11H), δH 2.385-2.269 (m, 4H), δH 1.309 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.9, δC 167.1, δC 166.8, δC 164.6, δC 162.1, δC 157.8, δC 135.9, δC 134.6, δC 131.4, δC 130.4, δC 127.9, δC 119.0, δC 115.4, δC 115.2, δC 53.7, δC 52.6, δC 51.9, δC 46.8, δC 42.6, δC 41.8, δC 33.2, δC 31.9, δC 22.3, (+)ESI-MS m/z: calculated for [$C_{26}H_{30}FN_7O_5S + H^+$] 571.62, observed 572.2.

4a: *N*-(-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-5-(4-(-2-4,trifluoromethyl-phenyl-acetyl)-Piperazin-1-yl-Methyl)pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. White solid, M.P- 138-140 °C, Yield (80%). FT-IR (KBr, cm^{-1}): 2970, 1735, 1643, 1546, 1313, 1226, 1153, 962, 769, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.645 (d, 1H), δH 7.549-7.460 (m, 3H), δH 7.372-7.292 (m, 2H), δH 7.136 (t, 2H), δH 3.810 (s, 2H), δH 3.542-3.291 (m, 11H), δH 3.311 (t, 2H), δH 2.274-2.156 (m, 4H), δH 1.303 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.9, δC 167.0, δC 165.2, δC 162.2, δC 158.7, δC 157.7, δC 144.1, δC 143.8, δC 132.3, δC 131.3, δC 124.8, δC 118.9, δC 115.4, δC 115.2, δC 53.6, δC 52.5, δC 51.8, δC 47.2, δC 42.6, δC 33.1, δC 31.9, δC 22.3, (+)ESI-MS m/z: calculated for [$C_{29}H_{33}F_4N_5O_3S + H^+$] 607.66, observed 608.2.

4b: *N*-(-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-5-(,4-(-2-4-methoxyphenyl-acetyl)-piperazin-1-ylMethyl)Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P- 118-120 °C, Yield (76%). FT-IR (KBr, cm^{-1}):- 2953, 1734, 1637, 1543, 1336, 1230, 1151, 964, 771, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.533-7.498 (m, 2H), δH 7.145-7.088 (m, 4H), δH 6.834 (d, 2H), δH 3.782 (s, 3H), δH 3.603 (s, 2H), δH 3.552-3.446 (m, 11H), δH 3.316 (t, 2H), δH 2.238-2.049 (m, 4H), δH 1.283 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.9, δC 169.7, δC 167.1, δC 164.5, δC 162.2, δC 158.5, δC 131.4, δC 131.3, δC 129.7, δC 127.0, δC 119.0, δC 115.4, δC 115.2, δC 114.2, δC 55.3, δC 53.6, δC 52.2, δC 52.1, δC 46.4, δC 42.5, δC 41.9, δC 40.1, δC 33.2, δC 31.8, δC 22.6; (+)ESI-MS m/z: calculated for [$C_{29}H_{33}F_4N_5O_3S + H^+$] 569.69, observed 571.2.

4c: *N*-(-5-(-4-(2-4-cyanophenyl-acetyl)piperazin-1-ylMethyl)-4-(4-Fluoro-phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P-141-143 °C, Yield (73%). FT-IR (KBr, cm^{-1}): 2931, 1755, 1606, 1546, 1332, 1224, 1149, 962, 773; ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.602 (d, 2H), δH 7.539-7.504 (m, 2H), δH 7.314 (d, 2H), δH 7.138 (t, 2H), δH 3.702 (s, 2H), δH 3.545-3.412 (m, 11H), δH 3.318 (s, 2H), δH 2.466-2.132 (m, 4H), δH 1.296 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 168.7, δC 167.1, δC 162.0, δC 157.8, δC 140.5, δC 134.8, δC 132.4, δC 131.4, δC 131.3, δC 129.9, δC 118.8, δC 115.4, δC 115.2, δC 111.0, δC 53.6, δC 52.3, δC 52.0, δC 46.1, δC 42.6, δC 42.0, δC 40.5, δC 33.2, δC 31.9, δC 22.5, (+)ESI-MS m/z: calculated for [$C_{29}H_{33}F_4N_5O_3S + H^+$] 564.67, observed 565.6.

4d: *N*-(-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-5-(-4-(-2-4-nitrophenyl-acetyl)-piperazin-1-ylMethyl)-pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off-white solid, M.P- 162-164 °C, Yield (72%). FT-IR (KBr, cm^{-1}): 2956, 1735, 1647, 1541, 1338, 1228, 1151, 947, 771, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 8.168 (d, 2H), δH 7.534-7.499 (m, 2H), δH 7.372 (d, 2H), δH 7.129 (t, 2H), δH 3.747 (s, 2H), δH 3.545-3.412 (m, 11H), δH 3.335-3.325 (m, 2H), δH 2.263-2.147 (m, 4H), δH 1.294 (d, 6H); ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 167.9, δC 167.2, δC 162.1, δC 157.8, δC 147.1, δC 142.6, δC 131.4, δC 131.3, δC 130.0, δC 123.9, δC 118.9, δC 115.4, δC 115.2, δC 53.6, δC 52.3, δC 52.0, δC 46.2, δC 42.6, δC 42.1, δC 40.2, δC 33.3, δC 31.9, δC 22.4, (+)ESI-MS m/z: calculated for [$C_{28}H_{33}FN_6O_5S + H^+$] 584.66, observed 585.1.

General Procedure of the Compounds 5(a-h)

At 0 °C, Compound-2 (1 eq) in DCM, treated with substituted benzene sulfonyl chlorides (1.5 eq) was used in combination with triethylamine (3.0 eq). In a nitrogen environment, the reaction mixture was agitated for three hours at ambient temperature. Following the completion of the reaction, water was added and the residue was extracted with DCM. The collective organic layer, washed with water and brine solution, dehydrated over anhydrous Na_2SO_4, sieved, and concentrated. The acquired crude was purified by column chromatography at 40-60% ethylacetate-hexane as an eluent to get compounds 5(a-h) in good yields.

Analytical Data for 5(a-h)

5a:*N*-(4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-5-(-4(-4-Methyl-sulfonyl-benzenesulfonyl)-Piperazin-1-ylMethyl)-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off-White solid, M.P-116-118 °C, Yield (84%). FT-IR (KBr, cm^{-1}): 2964, 1604, 1546, 1315, 1226, 1151, 956, 746, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 8.113 (d, 2H), δH 7.904 (d, 2H), δH 7.498-7.463 (m, 2H), δH 7.131-7.088 (m, 2H), δH 3.526-3.486 (m, 8H), δH 3.417-3.298 (m, 1H), δH 3.108 (s, 3H), δH 2.947 (bs, 4H), δH 2.346 (bs, 4H), δH 1.227 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 167.0, δC 159.1, δC 144.61, δ, C 131.4, δC 131.2, δC 128.6, δC 128.4, δC 115.6, δC 115.3, δC 53.3, δC 51.5, δC 46.0, δC 44.4, δC 42.7, δC 33.2, δC 31.8, δC 31.7, δC 22.3, (+)ESI-MS m/z: calculated for [$C_{27}H_{34}FN_5O_6S_3 + H^+$] 639.78, observed 640.2.

5b: *N*-(-5-(-4-2,4-difluoro-benzenesulfonyl-piperazin-1-ylmethyl-)-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. White-solid, M.P- 144-146 °C, Yield (85%). FT-IR (KBr, cm^{-1}): 2852, 1598, 1541, 1361, 1217, 1145, 948, 769, ^{1}H-NMR (400 MHz, CDCl3): δH 7.843-7.7802 (m, 1H), δH 7.524-7.489 (m, 2H), δH 7.119 (t, 2H), δH 7.017-6.929 (m, 2H), δH 3.534-3.495 (m, 8H), δH 3.416-3.309 (m, 1H), δH 3.074 (bs, 4H), δH 2.340 (bs, 4H), δH 1.258 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 167.1, δC 165.1, δC 162.6, δC 157.2, δC 133.0, δC 131.4, δ, C 131.5, δC 122.2, δC 115.3, δC 115.2, δC 112.2, δC 112.0, δC 105.9, δC 53.4, δC 51.8, δC 42.6, δC 33.2, δC 31.8, δC 31.7, δC 22.3, (+)ESI-MS m/z: calculated for [$C_{26}H_{30}F_3N_5O_4S_2 + H^+$] 597.67, observed 598.5.

5c: *N*-(5-(-4-(3-chloro-4-fluoro-benzenesulfonyl)-piperazin-1-ylmethyl)-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P-148-150 °C, Yield (79%). FT-IR (KBr, cm^{-1}): 2974, 1604, 1543, 1350, 1226, 1153, 943, 734, ^{1}H-NMR(400 MHz, $CDCl_3$): δ,H 7.779 (d, 1H), δH 7.596-7.474 (m, 3H), δH 7.313 (d, 1H), δH 7.141 (d, 2H), δH 3.712-3.486 (m, 8H), δH 3.489-3.312 (m, 1H), δH 2.985 (bs, 4H), δH 2.397 (bs, 4H), δH 1.252 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.1, δC 167.3, δC 165.4, δC 162.5, δC 133.1, δC 131.3, δC 131.4, δC 130.9, δC 128.7, δC 128.2, δC 128.0, δC 117.8, δC 117.5, δC 115.8, δC 54.1, δC 51.4, δC 42.6, δC 33.2, δC 22.31, (+)ESI-MS m/z: calculated for [$C_{26}H_{30}ClF_2N_5O_4S_2 + H^+$] 614.13, observed 615.2.

5d: *N*-(-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-5-(-4-4-methoxy-benzeneSulfonyl-piperazin-1-yl-Methyl)-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. White solid, M.P- 160-162 °C, Yield (82%). FT-IR (KBr, cm^{-1}): 2958, 1593, 1543, 1330, 1226, 1149, 960, 736, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.646 (d, 2H), δH 7.505-7.471 (m, 2H), δH 7.086 (t, 2H), δH 6.994 (d, 2H), δH 3.875 (s, 3H), δH 3.589-3.421 (m, 8H), δH 3.381-3.316 (m, 1H), δH 2.862 (bs, 4H), δH 2.330 (bs, 4H), δH 1.223 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 167.2, δC 163.2, δC 162.0, δC 157.7, δC 134.8, δC 131.3, δC 131.2, δC 129.9, δC 127.41, δC 118.9, δC 115.4, δC 115.1, δC 114.3, δC 55.7, δC 53.2, δC 51.5, 46.1, δC 42.6, δC 33.2, δC 31.7, δC 22.2; (+)ESI-MS m/z: calculated for [$C_{27}H_{34}FN_5O_5S_2 + H^+$] 591.72, observed 592.2.

5e: *N*-(-5-(-4-cyclopropylsulfonyl-Piperazin-1-yl-Methyl)-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P- 174-176 °C, Yield (75%). FT-IR(KBr, cm^{-1}): 2850, 1604, 1552, 1327, 1296, 1153, 958, 744, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.561-7.526 (m, 2H), δH 7.162-7.119 (m, 2H), δH 3.625-3.504 (m, 8H), δH 3.475-3.409 (m, 1H), δH 3.178 (bs, 4H), δH 2.362 (bs, 4H), δH 2.239-2.215 (m, 1H), δH 1.308 (d, 6H), δH 1.145-1.105 (m, 2H), δH 0.985-0.936 (m, 2H), ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 167.1, δC 162.1, δC 157.8, δC 134.7, δ, C 131.4, δC 131.3, δC 118.9, δC 115.7, δC 115.2, δC 53.6, δC 51.9, δC 46.3, δC 42.7, δC 33.2, δC 31.9, δC 25.7, δC 22.3, (+)ESI-MS m/z: calculated for [$C_{23}H_{32}FN_5O_4S_2 + H^+$] 525.66, observed 526.2.

5f: *N*-(5-(-4-3,5-Dimethylisoxazol-4-yl-sulfonyl-piperazin-1-yl-Methyl)-4-(4-Fluoro-Phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P-207-209 °C, Yield (76%). FT-IR (KBr, cm^{-1}): 2976, 1587, 1543, 1330, 1222, 1151, 943, 734, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.694-7.352 (m, 2H), δH 7.260-6.984 (m, 2H), δH 3.795-3.224 (m, 9H), δH 2.992 (bs, 4H), δH 2.598 (bs, 4H), δH 2.357 (s, 6H), δH 1.271 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 173.9, δC 167.1, δC 164.6, δC 162.1, δC 158.1, δC 134.7, δ, C 131.1, δC 131.2, δC 118.6, δC 115.5, δC 115.3, δC 113.3, δC 53.3, δC 51.5, δC 45.8, δC 42.7, δC 33.2, δC 31.8, δC 22.3, δC 13.0, δC 11.4, (+)ESI-MS m/z: calculated for [$C_{25}H_{33}FN_6O_5S_2 + H^+$] 580.70, observed 581.2.

5g: *N*-(-5-(-4-3,4-Dimethoxy-benzenesulfonyl-Piperazin-1-yl-methyl)-4-(-4-Fluoro-Phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. Off white solid, M.P-198-200 °C, Yield (81%). FT-IR (KBr, cm^{-1}): 2980, 1589, 1543, 1338, 1267, 1153, 948, 732, ^{1}H-NMR (400 MHz, $CDCl_3$):- δH 7.501-7.468 (m, 2H), δ, H 7.321 (d, 1H), δH 7.145-7.070 (m, 3H), δ, H 6.956 (d, 1H), δH 3.945 (d, 6H), δH 3.584-3.423 (m, 8H), δH 3.380-3.316 (m, 1H), δH 2.879 (bs, 4H), δH 2.329 (bs, 4H), δH 1.225 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.7, δC 167.0, δC 164.5, δC 162.0, δC 152.8, δC 149.1, δC 134.7, δC 131.3, δC 131.2, δC 127.5, δC 121.7, δC 118.9, δC 115.4, δC 115.2, δC 110.7, δC 56.3, δC 53.3, δC 51.5, δC 46.1, δC 42.6, δC 33.1, δC 31.7, δC 22.22; (+)ESI-MS m/z: calculated for [$C_{28}H_{36}FN_5O_6S_2$ + H^+] 621.74, observed 622.2.

5h: *N*-(5-(-4-2,5-Dimethyl-benzenesulfonylpiperazin-1-ylMethyl)-4-(-4-Fluoro-phenyl)-6-Iso-Propyl-Pyrimidin-2-yl)-*N*-Methyl-Methanesulfonamide. (5h): Off white solid, M.P-168-170 °C; Yield (80%). FT-IR (KBr, cm^{-1}): 2937, 1602, 1544, 1338, 1226, 1151, 941, 732, ^{1}H-NMR (400 MHz, $CDCl_3$): δH 7.669 (s, 1H), δH 7.516 (t, 2H),δH 7.260 (d, 1H), δH 7.185 (d, 1H), δH 7.133-7.092 (m, 2H), δH 3.582-3.515 (m, 8H), δH 3.429-3.380 (m, 1H), δH 3.051 (bs, 4H),δH 2.519 (s, 3H), δH 2.355 (s, 3H), δH 2.306 (bs, 4H), δH 1.268 (d, 6H), ^{13}C-NMR ($CDCl_3$): δC 177.8, δC 167.1, δC 162.4, δC 157.7, δC 136.1, δC 135.2, δC 134.9, δC 133.8, δC 132.8, δC 131.4, δC 131.3, δC 130.8, δC 118.9, δC 115.4, δC 115.2, δC 53.5, δC 51.8, δC 45.3, δC 42.6, δC 33.2, δC 31.8, δC 22.3, δC 20.9, δC 20.33, (+)ESI-MS m/z: calculated for [$C_{28}H_{36}FN_5O_4S_2$ + H^+] 589.74, observed 590.2

Biological Activity

The antibacterial activity of synthesized compounds 3(a-d), 4(a-d), and 5(a-h) was assessed against one strain of Gram-negative (*Escherichia coli*) and two strains of Gram-positive (*Staphylococcus aureus* and *Lactobacillus acidophilus*) bacteria strains using the agar well diffusion method.[26,27] The antibacterial activity results were measured as the diameter of the inhibition zone, and streptomycin as a standard drug. Titled Compounds 3(a-d), 4(a-d), and 5(a-h) were screened against four fungal strains, namely the *Clostridium tetani*, *Aspergillus niger*, *Aspergillus fumigatus*, and *Trichoderma harzianum* using the agar disc diffusion method[28]. The antifungal activity results are expressed in the diameter of the inhibition zone, and Nystatin is a standard drug.

RESULTS AND DISCUSSION

Chemistry

A series of new Rosuvastatin-piperazine derivatives of aryl amide, acetamide, and sulfonamide were synthesized by compound (1) with piperazine in presence of K_2CO_3 in 1,4-dioxane to afford compound (2). Subsequently, the substituted phenyl acids and phenylacetic acids are allowed to react with compound 2 in DMF by using amide coupling agents, to afford titled compounds 3 (a-d) and 4 (a-d) in good yields (70-80%). Further, compound 2 was treated with aromatic sulfonyl chlorides in DCM to get compound 5 (a-h) in high yields. Titled derivatives were characterized by FT-IR, ^{1}H and ^{13}C NMR and mass spectra.

Biological Activity

The results revealed that Compounds 5a, 5b, and 5e showed high activity, compounds 3a, 3b, 3c, and 5f have shown moderate activity, rest of the compounds are low antibacterial activity against the *Staphylococcus aureus*. Compounds 3b, 5a, and 5b showed high activity, compounds 3a, 3c, 5c, and 5e have shown moderate activity, remaining compounds exhibited low activity against *lactobacillus acidophilus*. Compounds 3b, 5a, 5b, 5e, 5f, and 3c, 5c have shown high activity and moderate activity respectively, the remaining compounds showed low activity against *Escherichia coli*. Apart from the individual study, 5a, and 5b bearing 4-SO_2-CH_3, and 2,4-difluoro groups on the phenyl sulfonamide ring showed good activity. Compound 3b bearing 2-pyridyl amide ring showed good activity in *Staphylococcus aureus* and *Escherichia coli*. In addition, compounds 5e and 5f exhibited good activity, against *Escherichia coli*-negative bacteria in presence of cyclopropyl and 2,3-dimethyl isoxazole sulfonamide functionality. The majority of the compounds having electron-withdrawing groups showed antibacterial activity against the bacteria. The obtained antibacterial activity result is presented in Table-1.

Table-1: Antibacterial Activity of Compounds 3(a-d), 4(a-d) and 5(a-h)

Diameter of the inhibition zone (in mm) at conc. 200 μg/mL				
Compound	*Staphylococcus aureus*	*Lactobacillus acidophilus*	*Escherichia coli*	Standard drug (Streptomycin)
3a	0. 6	0. 5	0. 3	1. 5
3b	0. 8	0. 9	1. 2	1. 5
3c	0. 6	0. 5	0. 8	1. 5
3d	0. 3	--	--	1. 5
4a	0. 2	--	--	1. 5
4b	0. 3	--	--	1. 5
4c	0. 2	--	0. 3	1. 5
4d	--	--	--	1. 5
5a	1. 2	1. 0	1. 6	1. 5
5b	1. 0	0. 8	1. 4	1. 5
5c	0. 4	0. 6	0. 8	1. 5
5d	--	--	--	1. 5
5e	0. 9	0. 6	1. 2	1. 5
5f	0. 6	0. 4	1. 0	1. 5
5g	0. 2	--	0. 4	1. 5
5h	--	0. 4	--	1. 5

The antifungal results revealed that compounds 3a, 5b, 5c, 5e, and 5f have shown good antifungal activity against the tested bacterial strains. And, compound 3b bearing the 2-pyridyl amide group has shown effective antifungal activity against tested microbes, while the rest of the compounds have shown moderate antifungal activity against the *Clostridium tetani* strain. The results of the antifungal activity testing are shown in Table-2.

Table-2: Antifungal Activity of Compounds 3(a-d), 4(a-d) and 5(a-h)

Zone of Inhibition (in mm) at conc. 200 μg/mL				
Compound	*Clostridium tetani*	*Aspergillus Niger*	*Aspergillus fumigates*	*Trichoderma*
3a	1.0	1.2	0.9	0.6
3b	1.2	1.6	1.8	1.4
3c	1.2	0.2	--	--
3d	1.2	--	0.4	0.6
4a	1.2	--	--	--
4b	1.2	--	--	--
4c	1.2	--	--	--
4d	1.2	--	0.8	1.3
5a	--	--	--	--
5b	1.0	0.6	0.6	1.1
5c	1.3	1.0	0.8	0.4
5d	--	--	--	1.3
5e	1.4	0.9	0.8	1.2
5f	1.2	0.4	0.7	1.0
5g	--	--	--	1.0
5h	--	--	0.9	--
Nystatin	2.5	2.5	2.5	2.5

CONCLUSION

Title compounds 3(a-d), 4(a-d), and 5(a-h) were synthesized and characterized by different spectroscopic techniques. Titled compounds 3a, 3b, 5a, 5b, 5e, 5f and 5c have shown good to moderate antimicrobial activity. The above results revealed that the significance of amide and sulfonamide analogues may be

efficient drug candidates designed for the action of diverse bacteriological contagions instigated through multi-drug unaffected pathogens.

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CONFLICT OF INTERESTS

All the authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this work, took part in its reviewing, editing, and characterizing, and gave their final approval for publication. The author's ORCID IDs which is listed below can be used to confirm their research profile.

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