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Design, Synthesis and Biological Evaluation of Some Novel Chalcones-sulphonamide Hybrids

Mahammadali Khanusiya* and Zakirhusen Gadhawala
Department of Chemistry, The HNSB Ltd Science College, Himatnagar, Gujarat-India.
**E-mail: khanusiya.mali@gmail.com*
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ABSTRACT. A new class of Chalcone-Sulphonamide hybrids has been designed by condensing appropriate sulphonamide scaffold with substituted chalcones tethered by chloroacetyl chloride as a multi-target drug for therapeutic treatment. Chalcones were prepared by Claisen-Schmidt condensation of a substituted aldehyde with para aminoacetophenone. These Chalcone-Sulphonamide hybrids were screened by means of their antibacterial activity by NCCLS method. Among all these compounds, **5e** and **5c** displayed more potent growth inhibitory activity against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* bacteria respectively. Further, these hybrids were evaluated for their antifungal activity, among all hybrid **5a** exhibited potent antifungal activity. The synthesized compounds were characterized by FT-IR, ^{1}HNMR, ^{13}CNMR and HR-LCMS and spectral study supports the structures of synthesized Chalcone-Sulphonamide hybrids.

Key words: Chalcones, Sulphonamide scaffold, Antibacterial, Antifungal

INTRODUCTION

Chalcone, an exceptional chemical template of two aromatic or heteroaryl rings joined by a three-carbon α, β-unsaturated carbonyl system, demonstrating a class of flavonoids. Flavonoids occur naturally in fruits and vegetables. The plant containing chalcone derivatives are traditionally deputed for therapeutic concern. Chalcones were availed for their multifarious biological activities and there is a number of reviews that had dealt with the pharmacological and chemical basis of the biological activities exhibited by chalcones. Literature reveals that natural and synthetic chalcone is highly favorable to elicit numerous therapeutic activities.[1–10]

The literature on chalcone elucidates the employment of three pointed strategies such as structural modification of both aryl rings, replacement of aryl rings with heteroaryl scaffold and molecular hybridization via conjugation with another potent pharmacophore for the betterment of biological properties. Diverse substitutions on both aryl rings of chalcone, depending upon their position, induce to enhance their biological activities. Replacing aromatic by heteroaryl in chalcone also influence pharmacological activity. Chemically chalcone hybrids are designed by linking chalcone derivative to another biologically potent scaffold such as sulphonamides, benzothiazoles; triazole, benzodiazepines, isoxazolines; imidazolones, indols, quinolines, coumarins etc have displayed promising biological activities.[11]

Sulphonamides are referred to compounds that have sulphonamide moiety ($-SO_2NH_2$) in its structure and were found to possess many types of biologically interesting activities including antitumor activity. Sulpha drugs are known to subscribe good antibacterial and antifungal activities. Sulphadiazine, sulfamerazine, and sulphadimidine are dominant sulpha drugs used in some acute bacterial infections, cerebrospinal meningitis and allergic infections.[12] They consist of additive pharmaceutical drug involving several biological activities including antitumor,[13] antibacterial,[14] antifungal,[15] anti-carbonic anhydrase,[16] diuretic,[17] hypoglycemic,[18] antithyroid[19] and anti HIV.[20] Anticancer activity of sulphonamide chalcone hybrid (*Fig.* 1) has been reported in many types of cancers including pancreatic, hepatic and colon. Structural activity relationship analysis showed that chalcone containing sulphonamide group influences the biological activity.[21]

The biological activities of both pharmacophores motivate us to synthesize novel sulphonamide-chalcone hybrids possessing such important microbial properties. Various aldehydes were chosen to synthesize substituted chalcones

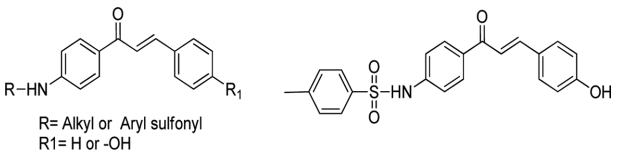


***Figure* 1.** Chalcone-Sulphonamide hybrid.

and these chalcones were condensed with biologically potent sulpha drugs resulting into chalcone-sulphonamide hybrids.

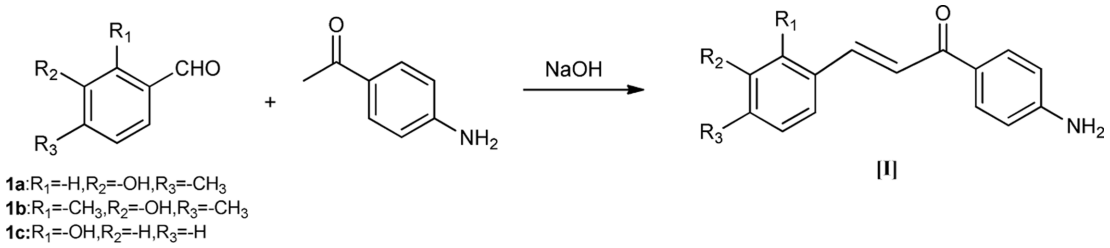
EXPERIMENTAL

General Information

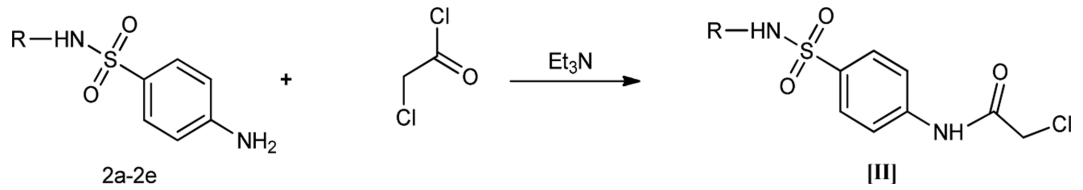
The starting materials and solvents were purchased from Sigma-Aldrich and SD Fine and used without further purification. Melting points were determined by the conventional method and then by electrocapillary apparatus and were uncorrected. All the synthesized compounds were inspected by thin layer chromatography (TLC) with precoated Aluminium sheets on silica gel (E-Merck) and the spots were visualized by UV lamp. The IR spectra of the compounds were recorded on Shimadzu FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker in DMSO at 500 MHz. IR, ^{1}H NMR, and ^{13}C NMR spectra were performed at Centre of Excellence Saurashtra University and High-Resolution Liquid Chromatography-Mass Spectra were performed at the SAIF Indian Institution of Technology. Aminochalcone compounds **1a-1c** was synthesized as shown in *Scheme* 1. Commercially available sulphonamides **2a-2e** were treated with chloroacetyl chloride to provide chlorosulfonyl acetamide depicted in *Scheme* 2. The general route for the synthesis of the target sulphonamide-chalcone hybrids was depicted in *Scheme* 3. The structures of targeted compounds were characterized using spectral methods, and all spectral data corroborated the assumed structures.

Synthesis

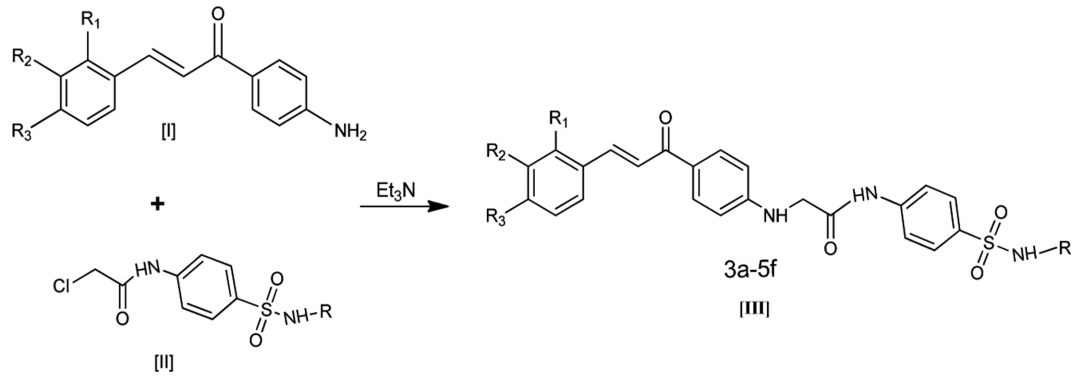
General procedure of synthesis of aminochalcone (1a-1c): The synthesis of chalcone derivatives [I] was conducted according to the procedure reported in the reference by Claisen-Schmidt condensation reaction.[10–12] Acetophenone derivative (2.5 mmol) and substituted benzaldehydes (2.5 mmol) were dissolved in 30 ml methanol. To the solution,



***Scheme* 1.** Synthesis of aminochalcone.



***Scheme* 2.** Synthesis of chlorosulfonyl acetamide.



***Scheme* 3.** Synthesis of chalcone-sulphonamide hybrids.

10 ml NaOH (20%) solution was added dropwise and the reaction mixture was stirred for 1-2 hour at room temperature by a magnetic stirrer and kept for overnight. Subsequently, it was poured into ice water and neutralized. The solid precipitates were filtered off and recrystallized from methanol or ethyl acetate.

General procedure of synthesis of Intermediate (2a-2f): To a stirred solution of sulphonamide (2 mmol) in dimethylformamide at 0-5 °C, chloro acetyl chloride (6 ml) was added dropwise and stirred at room temperature for 3-4 hours by a magnetic stirrer. The reaction mixture was neutralized with triethylamine then the precipitate was filtered, washed with cold water recrystallized from methanol.

General procedure of synthesis of sulphonamide chalcone (3a-5f): To a solution of aminochalcone **1a-1c** (2 mmol) in Dimethylformamide, a solution of an intermediate **2a-2f** (2 mmol) prepared in DMF was added. The stirred reaction mixture was then refluxed for 8-9 h. Upon completion, the reaction mixture was poured onto crushed ice. The precipitate was then washed with cold water and the crude product was recrystallized in acetone.

Characterization

The synthesis of chalcone derivatives **(1a-1c)** was carried out by simple base catalyzed Claisen-Schmidt condensation[22,23] using 10% NaOH solution prepared in methanol between commercially available p-aminoacetophenone and substituted aromatic aldehydes. All the synthesized chalcone derivatives were evaluated by their spectral data (IR, ^{1}HNMR, ^{13}CNMR). IR spectra of chalcone derivatives showed the characteristic bands for carbonyl at 1650, CH=CH at 1590-1610 and for -OH at 3570-3395 cm^{-1}. The ^{1}HNMR spectra indicated broad singlet at 3.47-3.50 ppm appeared for -NH_2 group, singlet of methoxy proton appeared about at 3.87 ppm and multiplets at 7.20-7.90 ppm for phenyl protons. For CO-CH=CH one doublet appears at 7.51-7.68 ppm and another doublet at 6.02-6.57 ppm respectively. The chlorosulphonamide derivatives **2a-2f** were synthesized by treatment of chloroacetyl chloride with various sulpha drugs containing amino group in their structure in presence of triethylamine (Et_3N).

3a: (E)-2-((4-(3-(4-Hydroxy-3-methylphenyl)acryloyl) phenyl)amino)-*N*-(4-(*N*-(5-methylisoxazol-3-yl) sulfamoyl) phenyl)acetamide

Yellow solid, R_f 0.52. FT-IR (ν, cm^{-1}): 3741 (-OH), 3591, 3360,3331 (3-NH-), 3064-3100 (Ar C-H), 2974 (Aliphatic -CH), 1739 (-CONH-), 1678 (-CO), 1608 (-C=N), 1591 (-HC=CH-), 1454 (C-O), 1398, 1157 (-SO_2-) 952 (S-N), 833 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 1H, -SO_2NH-), 6.45 (d,1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 4.63 (s, 1H, CH=C$_{isoxazole}$), 3.36 (d, 2H, -CH_2-), 2.67 (s, 3H, -CH_3), 2.27 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 167.08, 159.56, 154.09, 151.03, 141.66, 144.34, 138.80, 130.80, 127.02, 126.00, 125.54, 122.95, 119.07, 119.07, 112.40, 40.80, 39.67, 39.46, 39.07, 38.83, 27.03, 25.92, 12.11. HR-MS (ESI) Calcd for $C_{28}H_{26}N_4O_6S$ [M+H$^+$] 546.16, found 546.157.

3b: (E)-2-((4-(3-(4-Hydroxy-3-methylphenyl)acryloyl) phenyl)amino)-*N*-(4-sulfamoyl phenyl) acetamide

Brown solid, R_f 0.56. FT-IR (ν, cm^{-1}): 3741 (-OH), 3591, 3566, 3365, 3280 (2-NH, -NH_2), 3005 (Ar C-H), 2976 (Aliphatic -CH), 1734 (-CONH-), 1683 (-CO), 1639 (-C=N), 1595 (-HC=CH-), 1452 (C-O), 1311, 1149 (-SO_2-), 962 (S-N), 829 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s,1H, CONH-), 8.10 (s, 1H, -OH), 7.65 (d,1H$_\beta$ -CH=CH-), 7.56 (s, 2H, -SO_2NH_2), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 3.13 (s, 2H, -CH_2-), 2.67 (s, 3H, -OCH_3), 2.40 (s, 3H, -CH_3).^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 169.08, 159.56, 154.08, 141.66, 138.80, 130.54, 129.62, 127.02, 126.70, 125.54, 122.95, 117.17, 46.32, 40.09, 39.83, 39.09, 38.83, 27.03, 25.92. HR-MS (ESI) Calcd for $C_{24}H_{23}N_3O_5S$ [M+H$^+$] 465.135, found 465.136.

3c: (E)-*N*-(4-(*N*-(4,6-Dimethylpyrimidin-2-yl)sulfamoyl) phenyl)-2-((4-(3-(4-hydroxy-3-methylphenyl)acryloyl) phenyl)amino)acetamide

Brown solid, R_f 0.52. FT-IR (ν, cm^{-1}): 3741 (-OH), 3591, 3360, 3253 (3-NH-), 3000-3100 (Ar C-H), 2974, 2883 (Aliphatic -CH), 1739 (-CONH-), 1678 (-CO), 1647 (-C=N), 1593 (-HC=CH-), 1456 (C-O), 1396, 1157 (-SO_2-) 952 (S-N), 835 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.31 (s, 1H, CONH-), 8.30 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 1H, -SO_2NH-), 6.55 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.02 (m, 10H, Ar-H), 6.45 (1H, s, -CH=CH$_{(pyrimidine)}$) 6.41 (t, 1H, -NH-), 3.36 (d, 2H, -CH_2-), 2.56 (s, 3H, -CH_3), 2.54 (s, 3H, -OCH_3), 2.31 (s, 3H, -CH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 167.08, 159.56, 154.09, 154.09 141.66, 138.80, 130.80, 129.24, 127.02,127.02, 126.00, 125.54, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.07, 38.83, 27.03, 12.11. HR-MS (ESI) Calcd for $C_{30}H_{29}N_5O_5S$ [M+H$^+$] 571.18, found 571.211.

3d: (E)-*N*-(4-(*N*-Acetylsulfamoyl)phenyl)-2-((4-(3-(4-hydroxy-3-methylphenyl)acryloyl) phenyl)amino)acetamide

Red solid, R_f 0.70. FT-IR (ν, cm^{-1}): 3741 (-OH), 3568, 3360, 3246 (3-NH-), 3000 (Ar C-H), 2976, 2889 (Aliphatic -CH), 1734 (-CONH-), 1678 (-CO), 1647 (-C=N), 1597 (-HC=CH-), 1456 (C-O), 1363, 1155 (-SO_2-), 958 (S-N), 839 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.84 (d, 1H$_\beta$ -CH=CH-), 7.76 (s, 1H, -SO_2NH-), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.67 (s, 3H, -CH_3), 2.40 (s, 3H, -OCH_3).^{13}CNMR (500 MHz, DMSO-d_6, ppm): 190.17, 170.20, 167.08, 159.56, 154.09, 141.66, 138.80, 130.80, 129.06, 129.06, 127.02, 122.95, 119.08, 119.12, 114.40, 44.80, 39.67, 39.46, 39.07, 38.83, 21.03, 16.11. HR-MS (ESI) Calcd for $C_{26}H_{25}N_3O_6S$ [M+H^+] 507.14, found 507.23.

3e: (E)-2-((4-(3-(4-Hydroxy-3-methylphenyl) acryloyl) phenyl)amino)-*N*-(4-(*N*-(pyrimidin-2-yl) sulfamoyl) phenyl)acetamide

Red Brick solid, R_f 0.41 FT-IR (ν, cm^{-1}): 3743 (-OH), 3589, 3360, 3153 (3-NH-), 3000-3100 (Ar C-H), 2972, 2918 (Aliphatic -CH), 1738 (-CONH-), 1674 (-CO), 1649 (-C=N), 1590 (-HC=CH-), 1463(C-O), 1399, 1155 (-SO_2-), 954 (S-N), 835 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.50 (s, 1H, CONH-), 8.20 (s, 1H, -OH), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.54 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.05 (m, 10H, Ar-H), 6.65 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.41 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.38 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 194.87, 167.08, 159.56, 154.09, 153.58, 138.80, 130.80, 129.24, 127.02, 124.78, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.25, 39.07, 38.83, 27.03, 25.11. HR-MS (ESI) Calcd for $C_{28}H_{25}N_5O_5S$ [M+H^+] 543.157, found 543.159.

3f: (E)-*N*-(4-(*N*-(6-Chloropyridazin-3-yl)sulfamoyl) phenyl)-2-((4-(3-(4-hydroxy-3-methoxyphenyl) acryloyl) phenyl)amino) acetamide

Black solid, R_f 0.61 FT-IR (ν, cm^{-1}): 3750 (-OH), 3585, 3356, 3143 (3-NH-), 3000-3100 (Ar C-H), 2972, 2918 (Aliphatic -CH), 1738 (-CONH-), 1674 (-CO), 1649 (-C=N), 1590 (-HC=CH-), 1463 (C-O), 1399, 1155 (-SO_2-), 954 (S-N), 835(C-S), 595(C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.50 (s, 1H, CONH-), 8.20 (s, 1H, -OH), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.54 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.05 (m, 10H, Ar-H), 6.65 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.41 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.38 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 194.87, 167.08, 159.56, 154.09, 153.58, 146.52, 138.80, 130.80, 129.24, 127.02, 124.78, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.25, 39.07, 38.83, 27.03, 25.11. HR-MS (ESI) Calcd for $C_{28}H_{24}ClN_5O_6S$ [M+H^+] 593.118, found 593.113.

4a: (E)-2-((4-(3-(4-Hydroxy-3,5-dimethylphenyl)acryloyl)phenyl)amino)-*N*-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl) phenyl)acetamide

Red solid, R_f 0.51. FT-IR (ν, cm^{-1}): 3741 (-OH), 3566, 3360, 3331 (3-NH-), 3064-3100 (Ar C-H), 2974, 2883 (Aliphatic -CH), 1772 (-CONH-), 1678 (-CO), 1653 (-C=N), 1591 (-HC=CH-), 1456 (C-O), 1398, 1159 (-SO_2-) 952 (S-N), 831 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 1H, -SO_2NH-), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 4.63 (s, 1H, CH=C $_{isoxazole}$), 3.36 (d, 2H, -CH_2-), 2.67 (s, 3H, -CH_3), 2.50 (s, 3H, -OCH_3), 2.27 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 167.08, 159.56, 154.09, 151.03, 141.66, 144.34, 138.80, 130.80, 127.02, 126.00, 125.54, 122.95, 119.07, 119.07, 112.40, 40.80, 39.67, 39.46, 39.07, 38.83, 27.03, 25.92, 12.11, 12.03. HR-MS (ESI) Calcd for $C_{29}H_{28}N_4O_6S$ [M+H^+] 560.173, found 560.175.

4b: (E)-2-((4-(3-(4-Hydroxy-3,5-dimethylphenyl)acryloyl) phenyl)amino)-*N*-(4-sulfamoyl phenyl)acetamide

Pale yellow solid, R_f 0.69. FT-IR (ν, cm^{-1}): 3741 (-OH), 3591, 3566, 3365, 3280 (2-NH, -NH_2), 3005 (Ar C-H), 2976 (Aliphatic -CH), 1734 (-CONH-), 1683 (-CO), 1639 (-C=N), 1595 (-HC=CH-), 1452 (C-O), 1311, 1149 (-SO_2-), 962 (S-N), 829 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 2H, -SO_2NH_2), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 3.13 (s, 2H, -CH_2-), 2.67 (s, 3H, -CH_3), 2.50 (s, 3H, -OCH_3), 2.40 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 169.08, 159.56, 154.08, 141.66, 138.80, 130.54, 129.62, 127.02, 126.70, 125.54, 122.95, 117.17, 46.32, 40.09, 39.83, 39.09, 38.83, 27.03, 25.92, 12.54. HR-MS (ESI) Calcd for $C_{25}H_{25}N_3O_7S$ [M+H^+] 479.52, found 479.53.

4c: (E)-*N*-(4-(*N*-(4,6-Dimethylpyrimidin-2-yl) sulfamoyl)phenyl)-2-((4-(3-(4-hydroxy-3,5-dimethyl phenyl) acryloyl)phenyl)amino)acetamide

Black solid, R_f 0.57. FT-IR (ν, cm^{-1}): 3741 (-OH), 3591, 3560, 3329 (3-NH-), 3000 (Ar C-H), 2974, 2883 (Aliphatic -CH), 1739 (-CONH-), 1678 (-CO), 1645 (-C=N), 1593 (-HC=CH-), 1456 (C-O), 1396, 1157 (-SO_2-) 952 (S-N),

835 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.31 (s, 1H, CONH-), 8.30 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 1H, -SO_2NH-), 6.55 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.02 (m, 10H, Ar-H), 6.45 (1H, s, -CH=CH$_{(pyrimidine)}$) 6.41 (t, 1H, -NH-), 3.36 (d, 2H, -CH_2-), 2.56 (s, 3H, -CH_3), 2.54 (s, 3H, -OCH_3), 2.31 (s, 3H, -OCH_3).^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 167.08, 159.56, 154.09, 154.09 141.66, 138.80, 130.80, 129.24, 127.02, 127.02, 126.00, 125.54, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.07, 38.83, 27.03, 12.78, 12.10 HR-MS (ESI) Calcd for $C_{31}H_{31}N_5O_7S$ [M+H$^+$] 585.20, found 585.201.

4d: (E)-*N*-(4-(*N*-Acetylsulfamoyl)phenyl)-2-((4-(3-(4-hydroxy-3,5-dimethylphenyl)acryloyl)phenyl)amino) acetamide

Brown solid, R_f 0.80. FT-IR (ν, cm^{-1}): 3741 (-OH), 3591, 3360, 3255 (3-NH-), 3000-3100 (Ar C-H), 2974, 2883 (Aliphatic -CH), 1734 (-CONH-), 1678 (-CO), 1653 (-C=N), 1591 (-HC=CH-), 1456(C-O), 1363, 1153 (-SO_2-), 952 (S-N), 829 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.84 (d, 1H$_\beta$ -CH=CH-), 7.76 (s, 1H, -SO_2NH-), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.67 (s, 3H, -CH_3), 2.50 (s, 3H, -OCH_3), 2.40 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 190.17, 170.20, 167.08, 159.56, 154.09, 141.66, 138.80, 130.80, 129.06, 129.06, 127.02, 122.95, 119.08, 119.12, 114.40, 44.80, 39.67, 39.46, 39.07, 38.83, 21.03, 16.11, 12.23. HR-MS (ESI) Calcd for $C_{27}H_{27}N_3O_6S$ [M+H$^+$] 521.16, found 521.25.

4e: (E)-2-((4-(3-(4-Hydroxy-3,5-dimethylphenyl)acryloyl) phenyl)amino)-*N*-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl) acetamide

Red solid, R_f 0.61 FT-IR (ν, cm^{-1}): 3743 (-OH), 3649, 3564, 3358 (3-NH-), 3000-3100 (Ar C-H), 2974, (Aliphatic -CH), 1738 (-CONH-), 1674 (-CO), 1687 (-C=N), 1587 (-HC=CH-), 1463 (C-O), 1363, 1153 (-SO_2-), 950 (S-N), 829 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.50 (s, 1H, CONH-), 8.20 (s, 1H, -OH), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.54 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.05 (m, 10H, Ar-H), 6.65 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.41 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.50 (s, 3H, -CH_3), 2.38 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 194.87, 167.08, 159.56, 154.09, 153.58, 138.80, 130.80, 129.24, 127.02, 124.78, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.25, 39.07, 38.83, 27.03, 25.81, 16.12. HR-MS (ESI) Calcd for $C_{29}H_{27}N_5O_5S$ [M+H$^+$] 557.173, found 557.173.

4f: (E)-*N*-(4-(*N*-(6-Chloropyridazin-3-yl)sulfamoyl)phenyl) -2-((4-(3-(4-hydroxy-3,5-dimethoxyphenyl)acryloyl) phenyl) amino)acetamide

Brown solid, R_f 0.65 FT-IR (ν, cm^{-1}): 3745 (-OH), 3638, 3560, 3355 (3-NH-), 3000-3100 (Ar C-H), 2974, (Aliphatic -CH), 1738 (-CONH-), 1674 (-CO), 1687 (-C=N), 1587 (-HC=CH-), 1463 (C-O), 1363, 1153 (-SO_2-), 950 (S-N), 829 (C-S), 590.22 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.50 (s, 1H, CONH-), 8.20 (s, 1H, -OH), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.54 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.05 (m, 10H, Ar-H), 6.65 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.41 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.50 (s, 3H, -CH_3), 2.38 (s, 3H, -OCH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 194.87, 167.08, 159.56, 154.09, 153.58, 144.56, 138.80, 130.80, 129.24, 127.02, 124.78, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.25, 39.07, 38.83, 27.03, 25.81,16.12. HR-MS (ESI) Calcd for $C_{29}H_{26}ClN_5O_7S$ [M+H$^+$] 623.140, found 623.124.

5a: (E)-2-((4-(3-(2-Hydroxyphenyl)acryloyl)phenyl) amino)-*N*-(4-(*N*-(5-methylisoxazol-3-yl) sulfamoyl)phenyl) acetamide

Red solid, R_f 0.68. FT-IR (ν, cm^{-1}): 3741 (-OH), 3672, 3568, 3360 (3-NH-), 3064-3100 (Ar C-H), 2974, 2883 (Aliphatic -CH), 1734 (-CONH-), 1678 (-CO), 1608 (-C=N), 1593 (-HC=CH-), 1454 (C-O), 1396, 1153 (-SO_2-) 954 (S-N), 831 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 1H, -SO_2NH-), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 4.63 (s, 1H, CH=C $_{isoxazole}$), 3.36 (d, 2H, -CH_2-), 2.67 (s, 3H, -CH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 167.08, 159.56, 154.09, 151.03, 141.66, 144.34, 138.80, 130.80, 127.02, 126.00, 125.54, 122.95, 119.07, 119.07, 112.40, 40.80, 39.67, 39.46, 39.07, 38.83, 27.03, 25.92. HR-MS (ESI) Calcd for $C_{27}H_{24}N_4O_6S$ [M+H$^+$] 532.14, found 532.14.

5b: (E)-2-((4-(3-(2-Hydroxyphenyl)acryloyl)phenyl)amino)-*N*-(4-sulfamoylphenyl) acetamide

Red solid, R_f 0.56. FT-IR (ν, cm^{-1}): 3741 (-OH), 3591, 3566, 3365, 3280 (2-NH, -NH_2), 3005 (Ar C-H), 2976 (Aliphatic -CH), 1734 (-CONH-), 1683 (-CO), 1639 (-C=N), 1595 (-HC=CH-), 1452 (C-O), 1311, 1149 (-SO_2-), 962 (S-N), 829 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 2H, -SO_2NH_2), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02

(m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 3.13 (s, 2H, -CH_2-). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 169.08, 159.56, 154.08, 141.66, 138.80, 130.54, 129.62, 127.02, 126.70, 125.54, 122.95, 117.17, 46.32, 40.09, 39.83, 39.09, 38.83, 29.03. HR-MS (ESI) Calcd for $C_{23}H_{21}N_3O_5S$ [M+H^+] 451.120, found 451.117.

5c: (E)-*N*-(4-(*N*-(4,6-Dimethylpyrimidin-2-yl)sulfamoyl)phenyl)-2-((4-(3-(2-hydroxy phenyl)acryloyl) phenyl) amino)acetamide

Red solid, R_f 0.77. FT-IR (ν, cm^{-1}): 3741 (-OH), 3672, 3591, 3360 (3-NH-), 3000-3100 (Ar C-H), 2974, 2883 (Aliphatic -CH), 1739 (-CONH-), 1678 (-CO), 1645 (-C=N), 1593 (-HC=CH-), 1454 (C-O), 1396, 1155 (-SO_2-), 954 (S-N), 835 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.31 (s, 1H, CONH-), 8.30 (s, 1H, -OH), 7.65 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 1H, -SO_2NH-), 6.55 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.02 (m, 10H, Ar-H), 6.45 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.41 (t, 1H, -NH-), 3.36 (d, 2H, -CH_2-), 2.56 (s, 3H, -CH_3), 2.31 (s, 3H, -CH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 195.17, 167.08, 159.56, 154.09, 154.09 141.66, 138.80, 130.80, 129.24, 127.02, 127.02, 126.00, 125.54, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.07, 38.83, 27.03. HR-MS (ESI) Calcd for $C_{29}H_{27}N_5O_5S$ [M+H^+] 557.62, found 557.62.

5d: (E)-*N*-(4-(*N*-Acetylsulfamoyl)phenyl)-2-((4-(3-(2-hydroxyphenyl)acryloyl)phenyl) amino)acetamide

Red solid, R_f 0.70. FT-IR (ν, cm^{-1}): 3741 (-OH), 3672, 3568, 3360 (3-NH-), 3000-3100 (Ar C-H), 2972 (Aliphatic -CH), 1739 (-CONH-), 1678 (-CO), 1647 (-C=N), 1593 (-HC=CH-), 1456 (C-O), 1396, 1155 (-SO_2-), 952 (S-N), 835 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, CONH-), 8.10 (s, 1H, -OH), 7.84 (d, 1H$_\beta$ -CH=CH-), 7.76 (s, 1H, -SO_2NH-), 6.45 (d, 1H$_\alpha$ -CH=CH-), 6.02-8.02 (m, 10H, Ar-H), 6.51 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.40 (s, 3H, -CH_3). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 190.17, 170.20, 167.08, 159.56, 154.09, 141.66, 138.80, 130.80, 129.06, 129.06, 127.02, 122.95, 119.08, 119.12, 114.40, 44.80, 39.67, 39.46, 39.07, 38.83, 29.03. HR-MS (ESI) Calcd for $C_{25}H_{23}N_3O_6S$ [M+H^+] 493.13, found 493.18.

5e: (E)-2-((4-(3-(2-Hydroxyphenyl)acryloyl)phenyl)amino)-*N*-(4-(*N*-(pyrimidin-2-yl) sulfamoyl)phenyl)acetamide

Red Brick solid, R_f 0.53 FT-IR (ν, cm^{-1}): 3743 (-OH), 3672, 3589, 3358 (3-NH-), 3000-3100 (Ar C-H), 2972 (Aliphatic -CH), 1739 (-CONH-), 1678 (-CO), 1649 (-C=N), 1593 (-HC=CH-), 1456 (C-O), 1369, 1157 (-SO_2-), 952 (S-N), 833 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.50 (s, 1H, CONH-), 8.20 (s, 1H, -OH), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.54 (d, 1H$_\alpha$ -CH=CH-), 6.09-8.05 (m, 10H, Ar-H), 6.65 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.41 (t, 1H, -NH-), 3.41 (d, 2H, -CH_2-). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 194.87, 167.08, 159.56, 154.09, 153.58, 138.80, 130.80, 129.24, 127.02, 124.78, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.25, 39.07, 38.83, 29.03. HR-MS (ESI) Calcd for $C_{27}H_{23}N_5O_5S$ [M+H^+] 529.14, found 529.21.

5f: (E)-*N*-(4-(*N*-(6-Chloropyridazin-3-yl)sulfamoyl)phenyl)-2-((4-(3-(2-hydroxyphenyl) acryloyl)phenyl)amino) acetamide

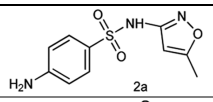
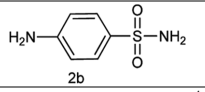
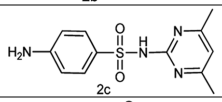
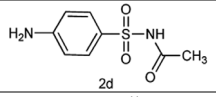
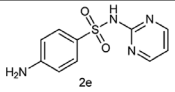
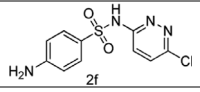
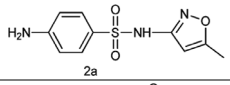
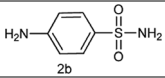
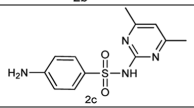
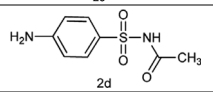
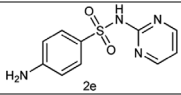
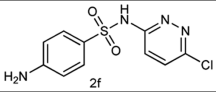
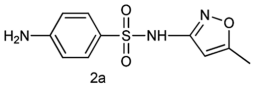
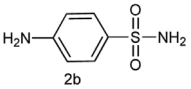
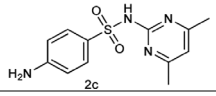
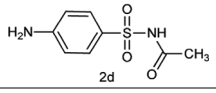
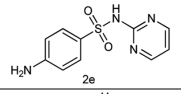
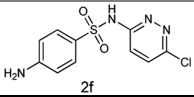
Red Brick solid, R_f 0.60 FT-IR (ν, cm^{-1}): 3745 (-OH), 3670, 3578, 3358 (3-NH-), 3000-3100 (Ar C-H), 2972 (Aliphatic -CH), 1739 (-CONH-), 1678 (-CO), 1649 (-C=N), 1593 (-HC=CH-), 1456 (C-O), 1369, 1157 (-SO_2-), 952 (S-N), 833 (C-S), 597.93 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.50 (s, 1H, CONH-), 8.20 (s, 1H, -OH), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.54 (d,1H$_\alpha$ -CH=CH-), 6.09-8.05 (m, 10H, Ar-H), 6.65 (1H, s, -CH= CH$_{(pyrimidine)}$), 6.41 (t, 1H, -NH-), 3.41 (d, 2H, -CH_2-). ^{13}CNMR (500 MHz, DMSO-d_6, ppm): 194.87, 167.08, 159.56, 154.09, 153.58, 146.36, 138.80, 130.80, 129.24, 127.02, 124.78, 122.95, 112.40, 119.02, 119.12, 114.40, 114.40, 40.80, 39.67, 39.46, 39.25, 39.07, 38.83, 29.03. HR-MS (ESI) Calcd for $C_{27}H_{22}ClN_5O_5S$ [M+H^+] 563.098, found 563.103.

RESULTS AND DISCUSSION

Chemistry

Chalcone **1a-1c** then condensed with chlorosulphonamide derivatives **2a-2f** in dimethylformamide with a few drops of Et_3N afforded Chalcone-Sulphonamide hybrids **3a-5f** (*Scheme* 3). The key reaction involved the formation of a C-N bond between the nitrogen of chalcone and carbon of sulphonamide derivatives. Structures of all obtained hybrids **3a-5f** were further supported by IR, NMR, and HRMS. IR spectra of **3a-5f** displayed -NH- absorption band at 3330-3360 cm^{-1} and stretching band of amide carbonyl at 1734-1739 cm^{-1}. The disappearance of broad singlet in ^{1}HNMR of **3a-5f** implied the absence of free -NH_2 group of chalcone moiety and led to the formation of a C-N bond between two pharmacophores. In the ^{1}HNMR spectra, methylene protons present between -NH- and -CO- appeared as a doublet at 3.36 ppm. ^{13}CNMR spectrum of **3a** revealed different characteristic signals at 44.54 ppm for methy-

***Table* 1.** Structures and % yield of chalcone-sulphonamide hybrids

Entry	Aldehyde (1a-1c)	Sulphonamide (2a-2e)	Yield (%)
3a	**1a**	 2a	60.0%
3b	**1a**	 2b	50.5%
3c	**1a**	 2c	62.0%
3d	**1a**	 2d	58.0%
3e	**1a**	 2e	63.6%
3f	**1a**	 2f	60.0%
4a	**1b**	 2a	60.0%
4b	**1b**	 2b	40.0%
4c	**1b**	 2c	52.0%
4d	**1b**	 2d	58.0%
4e	**1b**	 2e	63.6%
4f	**1b**	 2f	72.0%
5a	**1c**	 2a	82.0%
5b	**1c**	 2b	70.0%
5c	**1c**	 2c	68.0%
5d	**1c**	 2d	78.0%
5e	**1c**	 2e	72.0%
5f	**1c**	 2f	80.0%

lene, 56.79 for methoxy, 167.97 for amide carbonyl and 190.97 for vinyl carbonyl also supported to the proposed structure. The hybrid **3a** showed molecular ion ($M+H^+$) peak at 546.157 corresponding to the molecular formula of $C_{28}H_{26}N_4O_6S$.

Antimicrobial activity

Chemically synthesized all chalcone-sulphonamide hybrids **3a-5f** were screened for their antibacterial activity against *P.aeruginosa* (Gram-negative), *S.epidermidis* (Gram-positive) strains and also for their antifungal activity against *Candida albicans. Table* 2 lists the IC_{50} values of the hybrids against respective test microorganisms and also shows Selectivity ratios. Selectivity ratios of compounds were calculated using following formula.

$$\text{Selectivity ratio} = \frac{IC_{50} \text{ value of reference drug}}{IC_{50} \text{ value of synthesized compound}}$$

The selectivity ratios of chalcone-sulphonamide are shown in *Table* 2. Arbitrarily IC_{50} value of a synthesized compound against test organism was less than the IC_{50} values of reference drug and selectivity ratio ≥1 were used to identify promising compounds. Results of gram-positive organism inhibition study indicate followings compounds were found to be lid among others when it was compared IC_{50} value obtained by *Streptomycin* (8.625 μM/ml) with standard drug inhibitory value. **4f** > **5e** > **4d**. Similarly, results for gram-negative microorganism, most effective compounds were arranged in the following an order when it was compared IC_{50} value obtained by Streptomycin (6.230 μM/ml) with standard drug inhibitory value **4c** > **3e** > **5c**. Fluconazole and test compounds were tested against *Candida albicans* in dose-dependent manner. The table showed that comparative lower IC_{50} value was found with compounds **5a** against *Candida albicans*.

CONCLUSION

Chalcone-Sulphonamide hybrids have been synthesized by conjugating sulphadrugs with substituted chalcones with the objectives of the multi-target drug for therapeutic treatment. Antibacterial and antifungal activities of these hybrids revealed that **4d**, **4f**, and **5e** displayed a significant activity against *Staphylococcus epidermidis* and compounds, **3e**, **4c** and **5c** showed more potent growth inhibitory activity against *Pseudomonas aeruginosa* bacteria strains. While only **5a** is more potent antifungal agent towards *Candida albicans* fungi. Further studies on the application of this method for the synthesis of highly potent biologically

***Table* 2.** Percentage cell inhibition by compounds against *S.epidermidis* (gram-positive bacteria), *P.aeruginosa* (gram-negative bacteria) *and Candida albicans fungi strain*

Entry	*Staphylococcus epidermidis*		*Pseudomonas aeruginosa*		*Candida albicans*	
	IC_{50} μM/ml	Selectivity Ratio	IC_{50} μM/ml	Selectivity Ratio	IC_{50} μM/ml	Selectivity Ratio
3a	>100.0	< 0.100	41.73	0.149	21.30	0.484
3b	20.24	0.426	20.24	0.308	>100	< 0.100
3c	32.40	0.266	22.95	0.272	100.0	0.1000
3d	20.71	0.416	14.52	0.432	16.34	0.630
3e	42.22	0.204	5.940	1.050	>100	< 0.100
3f	>100.0	< 0.100	11.50	0.542	16.69	0.617
4a	41.94	0.206	15.94	0.392	>100.0	< 0.100
4b	22.89	0.377	89.32	< 0.100	13.07	0.788
4c	14.01	0.616	2.523	2.470	>100.0	< 0.100
4d	7.580	1.150	>100.0	< 0.100	25.73	0.400
4e	16.19	0.533	>100.0	< 0.100	>100.0	< 0.100
4f	2.568	3.369	40.30	0.155	25.93	0.397
5a	21.88	0.394	75.19	< 0.100	9.320	1.110
5b	>100	< 0.100	18.71	0.333	75.36	0.139
5c	69.72	0.124	6.050	1.040	27.11	0.380
5d	67.08	0.128	>100.0	< 0.100	76.88	0.134
5e	7.440	1.160	>100.0	< 0.100	>100.0	< 0.100
5f	26.62	0.324	11.18	0.558	38.09	0.270

*STD = Streptomycin for bacterial strains and fluconazole for fungal strain

active chalcones are underway. We may conclude that the sulphonamide pharmacophore possessing pyrimidine scaffold is associated with enhanced antibacterial activity and gave more potent compounds. This study may provide valuable information for further investigation as therapeutic agents.

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