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Chalcones-Sulphonamide Hybrids: Synthesis, Characterization and Anticancer Evaluation

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ABSTRACT. A panel of chalcone-sulphonamide hybrids has been designed by tethering appropriate sulphonamide scaffold with substituted chalcones as a multi-target drug for anticancer screening. Chalcones were prepared by Claisen-Schmidt condensation reaction of a substituted aldehyde with para aminoacetophenone. All the synthesized compounds were evaluated against selected five cancer cell lines, MCF-7 (Breast cancer), DU-145 (Human prostate Carcinoma), HCT-15 (Colon cancer), NCIH-522 (stage 2, adenocarcinoma; non-small cell lung cancer) and HT-3 (Human cervical cancer). Most of the synthesized chalcone-sulphonamide hybrids showed amended cytotoxic activity against various cancer cell lines which may be attributed to the linkage of sulphonamide with chalcone skeleton. The synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and HR-LCMS and spectral study assert the structures of synthesized sulphonamide-chalcone hybrids.

Key words: Chalcones-sulphonamide hybrid, Anticancer, Cell Lines, Cytotoxicity

INTRODUCTION

An affliction of cancer is raised world widely, with the changes in the living environment and also one of the most dominant causes of the morbidity and mortality. Worldwide deaths related to cancer are estimated to elongate 12 million in the year 2015.[1] Uncontrollable cell replication and rapid proliferation are the most important mechanism that causes cancer.[2] During proliferation, microtubules or tubulins are most important molecular targets for cancer chemotherapeutic agents since they play a vital role and involve in cellular functions.[3] The new generation of anticancer drugs affects the signals that promote or regulate cell cycle, growth factor, pathway affecting DNA repair and apoptosis.

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 are 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 chalcones are highly favorable to elicit numerous therapeutic activities.[4–13] Previous literature revealed that the anticancer activity of chalcone might be due to molecular alteration such as tubulin inhibition, kinase inhibition, apoptosis, DNA and mitochondrial damage, inhibition of angiogenesis and also drug efflux protein activities.

Sulphonamides were found to possess many types of biologically interesting activities including antitumor activity. Many sulphonamide compounds exhibited their anticancer activity by inhibiting tubulin to form microtubule.[14] The synthesized sulphonamides selectively inhibit proliferation, block the cell cycle and induce apoptosis in human cancer cells but not in normal cells.[15,16] Chalcones containing a sulphonyl or sulphonamide group for cytotoxic effect on cells of many types of cancer. Anticancer activity of sulphonamide chalcone hybrid 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 anticancer activity.[17]

The anticancer activity of chalcone and sulphonamide set off medicinal chemistry researcher to synthesize novel sulphonamide-chalcone hybrids possessing such important properties and evaluate for their cytotoxic effect against various cancer cell lines in vitro.

EXPERIMENTAL

General Information

All the starting materials and solvents were purchased from SD Fine limited and Sigma-Aldrich and used with-

out any further purification. Melting points were determined by the conventional method and then by electrocapillary apparatus and were uncorrected. All the synthesized compounds were monitored by thin layer chromatography (TLC) with precoated Aluminium sheets on silica gel (E-Merck) and the spots were visualized by the 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 **1d–1f** was synthesized as shown in *Scheme* 1. Commercially available sulphonamides were treated with chloroacetyl chloride and synthesized chalcones to provide the target sulphonamide-chalcone hybrids was depicted in *Scheme* 2. 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 (1d–1f): The synthesis of chalcone derivatives was conducted according to the procedure reported in the reference by Claisen-Schmidt condensation reaction.[18–20] Acetophenone derivative (2.5 mmol) and substituted benzaldehydes (2.5 mmol) were dissolved in 30 mL methanol. To the solution, 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 Sulphonamide Chalcone (6a–8f): To a stirred solution of sulphonamide (2 mmol), chloroacetylchloride (2 mL) and try ethylamine (0.1 mL) in dry dimethylformamide at 0–5 ºC, aminochalcone **1d–1f** (2 mmol) was added and stirred at room temperature for 3–4 hours by a magnetic stirrer. The stirred reaction mixture was then refluxed for 8–9 hours. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture on hot was poured to crushed ice afforded precipitates of chalcone-sulphonamide hybrids **3a–6f.** Precipitates then washed with cold aqueous sodium carbonate and the crude product was recrystallized in acetone.

Characterization

The synthesis of chalcone derivatives **1d–1f** was carried out by simple base catalyzed Claisen-Schmidt condensation[21,22] 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 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).

(E)-2-((4-(3-(2,4-Dihydroxyphenyl)acryloyl)phenyl) amino)-*N*-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl) phenyl) acetamide(6a): Red solid, mp 121–124 ºC Yield 84.4%, R_f 0.62. FT-IR (ν, cm^{-1}): 3741 (-OH), 3672 (-OH), 3649, 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): 8.48 (s, 1H, -OH), 8.49 (s, 1H, -OH), 7.95 (s, 1H, CONH-), 7.70 (s, 1H, -SO_2NH-), 7.65 (d, 1H$_\beta$ -CH=CH-), 6.54 (d, 1H$_\alpha$ -CH=CH-), 6.02–7.93 (m, 10H, Ar-H), 6.01 (t, 1H, -NH-), 3.53 (s, 1H, CH=C$_{isoxazole}$), 2.88 (d, 2H, -CH_2-), 2.73 (s, 3H, -CH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 195.17, 167.08, 153.09, 151.03, 144.34, 138.80, 130.54, 127.02, 126.00, 125.54, 122.95, 119.07, 119.07, 112.40, 40.80, 39.67, 39.46, 39.07, 38.83, 30.73, 25.82. HR-MS (ESI) Calculated for $C_{27}H_{24}N_4O_7S$ [M+H$^+$] 548.146, found 548.136. Molecular formula: Calculated $C_{27}H_{24}N_4O_7S$, found $C_{27}H_{24}N_4O_7S$.

(E)-2-((4-(3-(2,4-Dihydroxyphenyl)acryloyl)phenyl) amino)-*N*-(4-sulfamoylphenyl) acetamide (6b): Brick red solid, mp 118–120 ºC, 70.7%, R_f 0.66. FT-IR (ν, cm^{-1}): 3741 (-OH), 3672 (-OH), 3591, 3566, 3365, 3280 (2-NH, -NH_2), 3101 (Ar C-H), 2974 (Aliphatic-CH), 1739 (-CONH-), 1678 (-CO), 1593 (-HC=CH-), 1456 (C-O), 1315, 1153(-SO_2-), 952 (S-N), 833 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.10 (s, 1H, -OH), 7.95 (s, 1H, CONH-), 7.71 (s, 2H, -SO_2NH_2), 7.64 (d, 1H$_\beta$ -CH=CH-), 6.56 (d, 1H$_\alpha$ -CH=CH-), 6.02-7.86 (m, 10H, Ar-H), 6.54 (t, 1H, -NH-), 3.13 (s, 2H, -CH_2-). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 195.34, 169.88, 162.48, 159.63, 153.67, 141.60, 138.61, 137.27, 130.64, 130.44, 127.07, 126.75, 119.09, 118.89, 112.57, 111.37, 60.91, 46.44, 42.85, 40.95, 40.02, 35.89, 30.87. HR-MS (ESI) Calculated for

$C_{23}H_{21}N_3O_6S$ [M+H$^+$] 467.116, found 467.115. Molecular formula: Calculated $C_{23}H_{21}N_3O_6S$, found $C_{23}H_{21}N_3O_6S$.

(E)-2-((4-(3-(2,4-Dihydroxyphenyl)acryloyl)phenyl) amino)-*N*-(4-(*N*-(4,6-dimethylpyrimidin-2-yl)sulfamoyl) phenyl)acetamide (6c): Brickred solid, mp 130–133 °C, Yield 74.5%, R_f 0.57. FT-IR (ν, cm^{-1}): 3736 (-OH), 3597 (-OH), 3360, 3344, 3261 (3-NH-), 2929 (Ar C-H), 2846 (Aliphatic-CH), 1739 (-CONH-), 1651 (-CO), 1645 (-C=N), 1521 (-HC=CH-), 1400 (C-O), 1396, 1153 (-SO_2-), 960 (S-N), 827 (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}C NMR (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) Calculated for $C_{29}H_{27}N_5O_6S$ [M+H$^+$] 573.148, found 573.168. Molecular formula: Calculated $C_{29}H_{27}N_5O_6S$, found $C_{29}H_{27}N_5O_6S$.

(E)-*N*-(4-(*N*-Acetylsulfamoyl)phenyl)-2-((4-(3-(2,4-dihydroxyphenyl)acryloyl)phenyl) amino)acetamide (6d): Black solid, M.p 128–130 °C, Yield 59.90%, R_f 0.56. FT-IR (ν, cm^{-1}): 3741, 3672 (-OH), 3647, 3591, 3360 (3-NH-), 3000–3120 (Ar C-H), 2974 (Aliphatic-CH), 1734 (-CONH-), 1678 (-CO), 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): 8.10 (s, 1H, -OH), 7.95 (s, 1H, CONH-), 7.67 (d,1H$_\beta$ -CH=CH-), 7.64 (s, 1H, -SO_2NH-) , 6.64 (d, 1H$_\alpha$ -CH=CH-), 6.04–7.95 (m, 10H, Ar-H), 6.54 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-), 2.73 (s, 3H, -CH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 195.67, 162.94, 159.56, 154.09, 141.66, 138.80, 131.09, 129.06, 129.06, 125.02, 122.95, 119.08, 119.12, 113.02, 40.46, 39.67, 39.46, 39.07, 38.83, 36.34, 31.33, 26.33. HR-MS (ESI) Calculated for $C_{25}H_{23}N_3O_7S$ [M+H$^+$] 509.122, found 509.125. Molecular formula: Calculated $C_{25}H_{23}N_3O_7S$, found $C_{25}H_{23}N_3O_7S$.

(E)-2-((4-(3-(2,4-Dihydroxyphenyl)acryloyl)phenyl) amino)-*N*-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl) acetamide (6e): Red Brick solid, mp 142–144 °C, Yield 66.4%, R_f 0.60 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): 8.49 (s, 1H, -OH), 8.48 (s, 1H, CONH-), 7.76 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.65 (d, 1H$_\alpha$ -CH=CH-), 6.09–7.95 (m, 10H, Ar-H), 6.01 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.54 (t, 1H, -NH-), 3.35 (d, 2H, -CH_2-). ^{13}C NMR (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) Calculated for $C_{27}H_{23}N_5O_6S$ [M+H$^+$] 545.1363, found 545.1369. Molecular formula: Calculated $C_{27}H_{23}N_5O_6S$, found $C_{27}H_{23}N_5O_6S$.

(E)-*N*-(4-(*N*-(6-Chloropyridazin-3-yl)sulfamoyl)phenyl)-2-((4-(3-(2,4-dihydroxyphenyl)acryloyl)phenyl)amino) acetamide (6f): Red solid, mp 134–137 °C, Yield 65%, 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), 1363, 1172 (-SO_2-), 937 (S-N), 833 (C-S), 597.93 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 8.20 (s, 1H, -OH), 7.95 (s, 1H, CONH-), 7.77 (d, 1H$_\beta$, -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.54 (d, 1H$_\alpha$ -CH=CH-), 6.09–7.84 (m, 10H, Ar-H), 6.53 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.46 (t, 1H, -NH-), 3.40 (d, 2H, -CH_2-). ^{13}C NMR (500 MHz, DMSOd_6, ppm): 195.49, 195.26, 164.45, 162.51, 153.58, 152.59, 151.92, 141.10 140.36, 137.52, 134.23, 130.47, 129.86, 128.31, 126.97, 124.98, 119.02, 118.30, 112.63, 111.33, 108.78, 61.98, 60.25, 45.85, 40.40, 35.91, 30.90. HR-MS (ESI) Calculated for $C_{27}H_{22}ClN_5O_6S$ [M+H$^+$] 579.0912, found 579.0979. Molecular formula: Calculated $C_{27}H_{22}ClN_5O_6S$, found $C_{27}H_{22}ClN_5O_6S$.

(E)-2-((4-(3-(4-Methoxyphenyl)acryloyl)phenyl)amino)-*N*-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)acetamide (7a): Red solid, mp 116–118 °C, Yield 76.2%, R_f 0.42. FT-IR (ν, cm^{-1}): 3391, 3360, 3331(3-NH-), 3000–3100 (Ar C-H), 2974 (Aliphatic-CH), 1699 (-CO), 1629 (-C=N), 1595 (-HC=CH-), 1460 (C-O), 1336, 1166 (-SO_2-), 979 (S-N), 819 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.95 (s, 1H, CONH-), 7.66 (d, 1H$_\beta$ -CH=CH-), 7.61 (s, 1H, -SO_2NH-), 6.60 (d,1H$_\alpha$ -CH=CH-), 6.13–7.92 (m, Ar-H), 6.62 (t, 1H, -NH-), 3.36 (d, 2H, -CH_2-), 2.73 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 185.17, 162.08, 160.79, 153.67, 141.66, 130.94, 130.23, 127.75, 125.48, 125.54, 119.85, 112.40, 55.28, 40.80, 39.88, 39.67, 39.46, 39.04, 38.83, 35.74, 30.73. HR-MS (ESI) Calculated for $C_{28}H_{26}N_4O_6S$ [M+H$^+$] 546.1573, found 546.1354. Molecular formula: Calculated $C_{28}H_{26}N_4O_6S$, found $C_{28}H_{26}N_4O_6S$.

(E)-2-((4-(3-(4-Methoxyphenyl)acryloyl)phenyl)amino)-*N*-(4-sulfamoylphenyl) acetamide (7b): Yellow solid, mp 117–120 °C, Yield 80.5%, R_f 0.67. FT-IR (ν, cm^{-1}): 3510, 3505, 3350, 3240 (2-NH, -NH_2), 3000–3100 (Ar C-H), 1728 (-CONH-), 1685 (-CO), 1593 (-HC=CH-), 1440 (C-O), 1334, 1163 (-SO_2-), 977 (S-N), 817 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.95 (s, 1H, CONH-), 7.72 (d, 1H$_\beta$

-CH=CH-), 7.57 (s, 2H, -SO_2NH_2), 6.61 (d, 1H$_\alpha$ -CH=CH-), 6.13–7.93 (m, Ar-H), 6.63 (t, 1H, -NH-), 3.85 (s, 2H, -CH_2-), 3.45 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 191.30, 185.83, 169.73, 162.27, 160.79, 159.56, 153.67, 141.54, 141.31, 131.79, 130.23, 129.91, 128.46, 127.75, 126.67, 125.49, 121.15, 119.45, 118.74, 114.27, 112.66, 60.79, 54.94, 55.28, 40.81, 39.25, 38.83, 30.73. HR-MS (ESI) Calculated for $C_{24}H_{23}N_3O_5S$ [M+H$^+$] 465.1358, found 465.1153. Molecular formula: Calculated $C_{24}H_{23}N_3O_5S$, found $C_{24}H_{23}N_3O_5S$.

(E)-*N*-(4-(*N*-(4,6-Dimethylpyrimidin-2-yl)sulfamoyl) phenyl)-2-((4-(3-(4-methoxyphenyl)acryloyl)phenyl) amino) acetamide (7c): Light yellow solid, mp 109–111 ºC, Yield 62.0%, R_f 0.43. FT-IR (ν, cm^{-1}): 3601, 3590, 3353 (3-NH-), 3000–3100 (Ar C-H), 2974, 2883 (Aliphatic-CH), 1747 (-CONH-), 1680 (-CO), 1649 (-C=N), 1595 (-HC=CH-), 1456 (C-O), 1396, 1165 (-SO_2-), 977 (S-N), 819 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.93 (s, 1H, CONH-), 7.72 (d, 1H$_\beta$ -CH=CH-), 7.57 (s, 1H, -SO_2NH-), 6.63 (d, 1H$_\alpha$ -CH=CH-), 6.13–7.91 (m, Ar-H), 6.13 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.61 (t, 1H, -NH-), 3.70 (d, 2H, -CH_2-), 2.50 (s, 3H, -CH_3), 3.37 (s, 3H, -OCH_3), 2.31 (s, 3H, -CH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 187.69, 186.82, 167.79, 161.38, 160.92, 153.76, 143.61, 141.51, 131.05, 130.76, 129.92, 128.56, 127.83, 125.67, 119.98, 118.79, 114.49, 114.41, 113.89, 112.86, 55.37, 55.10, 47.83, 40.40, 40.03, 39.90, 39.07, 29.69, 23.18, 22.89. HR-MS (ESI) Calculated for $C_{30}H_{29}N_5O_5S$ [M+H$^+$] 571.1889, found 571.1909. Molecular formula: Calculated $C_{30}H_{29}N_5O_5S$, found $C_{30}H_{29}N_5O_5S$.

(E)-*N*-(4-(*N*-Acetylsulfamoyl)phenyl)-2-((4-(3-(4-methoxyphenyl)acryloyl)phenyl) amino)acetamide (7d): Yellow solid, mp 98–100 ºC, Yield 67.4%, R_f 0.56. FT-IR (ν, cm^{-1}): 3568, 3360, 3246 (3-NH-), 3000-3100 (Ar C-H), 2839 (Aliphatic-CH), 1741 (-CONH-), 1674 (-CO), 1651 (-C-N), 1595 (-HC=CH-), 1456 (C-O), 1338, 1166 (-SO_2-), 1024 (S-N), 821 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.96 (s, 1H, CONH-), 7.86 (d, 1H$_\beta$ -CH=CH-), 7.58 (s, 1H, -SO_2NH-), 6.62 (d, 1H$_\alpha$ -CH=CH-), 6.02–8.02 (m, 10H, Ar-H), 6.88 (t, 1H, -NH-), 3.70 (d, 2H, -CH_2-), 3.39 (s, 3H, -CH_3), 2.51 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 197.17, 185.84, 162.27, 160.79, 153.67, 141.31, 130.94, 130.94, 129.72, 129.85, 127.75, 126.88, 125.00, 119.34, 118.61, 114.40, 113.77, 112.67, 111.32, 55.27, 54.99, 40.08, 39.46, 38.83, 35.74,30.72. HR-MS (ESI) Calculated for $C_{26}H_{25}N_3O_6S$ [M+H$^+$] 507.1464, found 507.1447. Molecular formula: Calculated $C_{26}H_{25}N_3O_6S$, found $C_{26}H_{25}N_3O_6S$.

(E)-2-((4-(3-(4-Methoxyphenyl)acryloyl)phenyl)amino)-*N*-(4-(*N*-(pyrimidin-2-yl) sulfamoyl)phenyl)acetamide (7e): Red solid, mp 124–125 ºC, Yield 69.0%, R_f 0.58. FT-IR (ν, cm^{-1}): 3360, 3340, 3228 (3-NH-), 3000–3100 (Ar C-H), 2918 (Aliphatic-CH), 1738 (-CONH-), 1665 (-CO), 1508 (-C=N), 1593 (-HC=CH-), 1421 (C-O), 1338, 1155 (-SO_2-), 981 (S-N), 819 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.94 (s, 1H, CONH-), 7.79 (d, 1H$_\beta$ -CH=CH-), 7.62 (s, 1H, -SO_2NH-), 6.64 (d, 1H$_\alpha$ -CH=CH-), 6.14–7.94 (m, Ar-H), 6.14 (1H, s, -CH=CH$_{(pyrimidine)}$), 3.39 (d, 2H, -CH_2-), 2.88 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 185.84, 162.27, 160.79, 153.67, 141.32,130.95, 130.23, 128.45, 127.75, 125.50, 119.85, 118.60, 114.27, 113.77, 112.67, 55.27, 54.98, 41.17, 40.08, 39.87, 39.66, 39.04, 38.83, 35.74, 30.72. HR-MS (ESI) Calculated for $C_{28}H_{25}N_5O_5S$ [M+H$^+$] 543.1576, found 543.1527. Molecular formula: Calculated $C_{28}H_{25}N_5O_5S$, found $C_{28}H_{25}N_5O_5S$.

(E)-*N*-(4-(*N*-(6-Chloropyridazin-3-yl)sulfamoyl)phenyl)-2-((4-(3-(4-methoxyphenyl)acryloyl)phenyl)amino) acetamide (7f): Yellow solid, mp 133–135 ºC, Yield 67.1%, R_f 0.72. FT-IR (ν, cm^{-1}): 3385, 3356, 3143 (3-NH-), 3000–3100 (Ar C-H), 1747 (-CONH-), 1700 (-CO), 1647 (-C=N), 1593 (-HC=CH-), 1460 (C-O), 1338, 1165 (-SO_2-), 979 (S-N), 817 (C-S), 563 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.96 (s, 1H, CONH-), 7.75 (d, 1H$_\beta$ -CH=CH-), 7.61 (s, 1H, -SO_2NH-), 6.67 (d, 1H$_\alpha$ -CH=CH-), 6.17–7.96 (m, Ar-H), 6.90 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.17 (t, 1H, -NH-), 3.72 (d, 2H, -CH_2-), 2.52 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 191.25, 185.86, 162.27, 161.29, 160.79, 158.21, 153.69, 143.47, 141.34, 132.02, 131.78, 130.23, 129.90, 128.47, 127.36, 125.52, 121.15, 119.85, 118.62, 114.00, 113.75, 112.49, 111.34, 55.62, 54.96, 52.09, 45.29, 41.92, 40.07, 39.24, 38.82, 35.73, 30.71. HR-MS (ESI) Calculated for $C_{28}H_{24}ClN_5O_5S$ [M+H$^+$] 577.1187, found 577.1089. Molecular formula: Calculated $C_{28}H_{24}ClN_5O_5S$, found $C_{28}H_{24}ClN_5O_5S$.

(E)-2-((4-(3-(3,4-Dimethoxyphenyl)acryloyl)phenyl) amino)-*N*-(4-(*N*-(5-methylisoxazol-3-yl)sulfamoyl) phenyl)acetamide (8a): Red solid, mp 140–141 ºC, Yield 80.5%, R_f 0.55. FT-IR (ν, cm^{-1}): 3450, 3490, 3331 (3-NH-), 3000–3100 (Ar C-H), 1701 (-CO), 1649 (-C=N), 1591 (-HC=CH-), 1456 (C-O), 1336, 1172 (-SO_2-), 979 (S-N), 833 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.96 (s, 1H, CONH-), 7.61 (d, 1H$_\beta$ -CH=CH-), 7.50 (s, 1H, -SO_2NH-), 6.63 (d, 1H$_\alpha$ -CH=CH-), 6.14–7.94 (m, Ar-H), 6.14 (t, 1H, -NH-), 3.81 (d, 2H, -CH_2-), 2.73 (s, 3H, -OCH_3), 2.71 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 206.90, 187.75, 186.26, 171.09, 162.53, 160.35, 159.26, 153.82, 151.35, 150.89, 149.13, 144.21, 131.18, 130.20, 129.57, 128.12, 125.78, 123.93, 120.12, 119.62, 118.85, 112.93, 110.64, 96.62, 62.02, 60.94, 55.81, 48.15, 45.91, 40.03, 39.92,

35.90, 32.16, 30.90. MS (ESI) Calculated for $C_{29}H_{28}N_4O_7S$ [M+H$^+$] 576.62, found 576.10.

(E)-2-((4-(3-(3,4-Dimethoxyphenyl)acryloyl)phenyl) amino)-*N*-(4-sulfamoylphenyl) acetamide (8b): Yellow solid, mp 127–129 ºC, Yield 88.0%, R_f 0.57. FT-IR (ν, cm^{-1}): 3410, 3375, 3305, 3240 (2-NH, -NH_2), 3000–3100 (Ar C-H), 1741 (-CONH-), 1627 (-CO), 1591 (-HC=CH-), 1456 (C-O), 1338, 1136 (-SO_2-), 977 (S-N), 833 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.97 (s, 1H, CONH-), 7.67 (d, 1H$_\beta$ -CH=CH-), 7.53 (s, 2H, -SO_2NH_2), 6.041 (d, 1H$_\alpha$ -CH=CH-), 6.04–7.97 (m, Ar-H), 3.95 (s, 2H, -CH_2-), 3.35 (s, 3H, -OCH_3), 2.89 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 191.30, 185.83, 162.27, 153.68, 151.16, 150.67, 148.94, 141.86, 130.99, 129.88, 127.95, 127.53, 125.50, 123.27, 119.90, 112.64, 111.45, 110.37, 55.66, 55.50, 40.08, 39.87, 39.04, 38.83, 35.74, 30.65, 29.56. MS (ESI) Calculated for $C_{25}H_{25}N_3O_6S$ [M+H$^+$] 495.54, found 494.40.

(E)-2-((4-(3-(3,4-Dimethoxyphenyl)acryloyl)phenyl) amino)-*N*-(4-(*N*-(4,6-dimethylpyrimidin-2-yl)sulfamoyl) phenyl)acetamide (8c): Red solid, M.p 155–156 ºC, Yield 66.0%, R_f 0.63. FT-IR (ν, cm^{-1}): 3401, 3390, 3353 (3-NH-), 3000–3100 (Ar C-H), 2883 (Aliphatic-CH), 1701 (-CONH-), 1681 (-CO), 1649 (-C=N), 1593 (-HC=CH-), 1456 (C-O), 1365, 1136 (-SO_2-), 977 (S-N), 833 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.95 (s, 1H, CONH-), 7.75 (d, 1H$_\beta$ -CH=CH-), 7.56 (s, 1H, -SO_2NH-), 6.62 (d, 1H$_\alpha$ -CH=CH-), 6.14–7.93 (m, Ar-H), 6.98 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.62 (t, 1H, -NH-), 3.82 (d, 2H, -CH_2-), 3.37 (s, 3H, -CH_3), 2.80 (s, 3H, -OCH_3), 2.50 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 185.82, 162.27, 153.67, 150.67, 148.94, 141.30, 130.94, 129.88, 127.53, 127.95, 125.50, 123.37, 119.90, 119.39, 112.65, 111.45, 110.37, 55.66, 40.08, 39.88, 39.67, 39.46, 39.04, 38.83, 35.74, 30.65, 29.64. MS (ESI): Calculated for $C_{31}H_{31}N_5O_6S$ [M+H$^+$] 601.67, found 601.1.

(E)-*N*-(4-(*N*-Acetylsulfamoyl)phenyl)-2-((4-(3-(3,4-dimethoxyphenyl)acryloyl)phenyl) amino)acetamide (8d): Red solid, mp 158–160 ºC, Yield 71.0%, R_f 0.59. FT-IR (ν, cm^{-1}): 3568, 3360, 3246 (3-NH-), 3000–3100 (Ar C-H), 2839 (Aliphatic-CH), 1745 (-CONH-), 1681 (-CO), 1647 (-C-N), 1595 (-HC=CH-), 1456 (C-O), 1338, 1157 (-SO_2-), 1020 (S-N), 835 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.87 (s, 1H, CONH-), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.58 (s, 1H, -SO_2NH-), 6.62 (d, 1H$_\alpha$ -CH=CH-), 6.13–7.82 (m, Ar-H), 6.98 (t, 1H, -NH-), 3.81 (d, 2H, -CH_2-), 3.37 (s, 3H, -CH_3), 2.88 (s, 3H, -OCH_3), 2.73 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 185.84, 162.27, 153.67, 150.67, 148.94, 141.86, 130.99, 129.88, 129.76, 128.90, 127.75, 125.50, 123.27, 119.34, 118.61, 112.67, 111.45, 110.30, 55.50, 40.08, 39.87, 38.83, 35.74, 30.72, 29.56, 23.25. MS (ESI): Calculated for $C_{27}H_{27}N_3O_7S$ [M+H$^+$] 537.58, found 537.2.

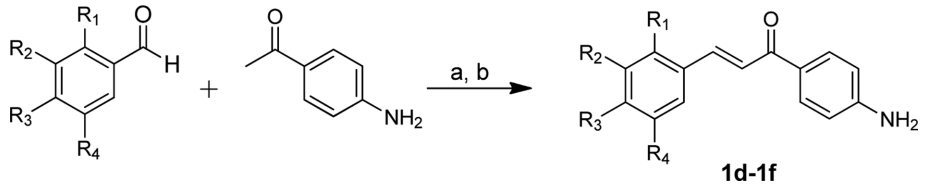
(E)-2-((4-(3-(3,4-Dimethoxyphenyl)acryloyl)phenyl) amino)-*N*-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl) acetamide (8e): Red-orange solid, mp 152–154 ºC, Yield 68.0%, R_f 0.66. FT-IR (ν, cm^{-1}): 3348, 3340, 3244 (3-NH-), 3000–3100 (Ar C-H), 2929 (Aliphatic-CH), 1738 (-CONH-), 1631 (-CO), 1506 (-C=N), 1593 (-HC=CH-), 1438 (C-O), 1338, 1155 (-SO_2-), 977 (S-N), 831 (C-S). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.98 (s, 1H, CONH-), 7.79 (d, 1H$_\beta$ -CH=CH-), 7.63 (s, 1H, -SO_2NH-), 6.64 (d, 1H$_\alpha$ -CH=CH-), 6.15–7.96 (m, Ar-H), 6.15 (1H, s, -CH=CH$_{(pyrimidine)}$), 3.73 (d, 2H, -CH_2-), 2.88 (s, 3H, -OCH_3), 2.73 (s, 3H, -OCH_3). ^{13}CNMR (500MHz, DMSO-d_6, ppm): 185.87, 162.26, 153.68, 151.17, 150.48, 148.74, 144.01, 141.88, 131.0, 130.75, 129.88, 128.45, 127.54, 125.50, 123.84, 119.85, 118.60, 112.66, 111.45, 110.39, 55.27, 54.98, 40.07, 39.66, 39.04, 38.83, 35.72, 30.72, 29.56. MS (ESI): Calculated for $C_{29}H_{27}N_5O_6S$ [M+H$^+$] 573.61, found 573.2.

(E)-*N*-(4-(*N*-(6-Chloropyridazin-3-yl)sulfamoyl)phenyl)-2-((4-(3-(3,4-dimethoxyphenyl)acryloyl)phenyl)amino) acetamide (8f): Light yellow solid, mp 146–148 ºC, Yield 62.6%, R_f 0.70. FT-IR (ν, cm^{-1}): 3739, 3556, 3354 (3-NH-), 3000–3100 (Ar C-H), 2918 (Aliphatic-CH), 1747 (-CONH-), 1700 (-CO), 1647 (-C=N), 1587 (-HC=CH-), 1408 (C-O), 1309, 1138 (-SO_2-), 975 (S-N), 827 (C-S), 599 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6, ppm): 7.95 (s, 1H, CONH-), 7.77 (d, 1H$_\beta$ -CH=CH-), 7.65 (s, 1H, -SO_2NH-), 6.61 (d, 1H$_\alpha$ -CH=CH-), 6.17–7.84 (m, Ar-H), 6.56 (1H, s, -CH=CH$_{(pyrimidine)}$), 6.46 (t, 1H, -NH-), 3.40 (d, 2H, -CH_2-), 2.89 (s, 3H, -OCH_3), 2.73 (s, 3H, -OCH_3). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): 185.87, 164.34, 162.27, 153.68, 151.77, 150.67, 148.93, 141.34, 140.15, 137.36, 134.08, 131.08, 128.15, 127.95, 126.87, 125.53, 123.27, 119.90, 118.12, 112.67, 111.43, 110.35, 55.65, 45.58, 40.05, 39.84, 30.71, 29.56. MS (ESI) Calculated for $C_{29}H_{26}ClN_5O_6S$ [M+H$^+$] 608.06, found 609.0.

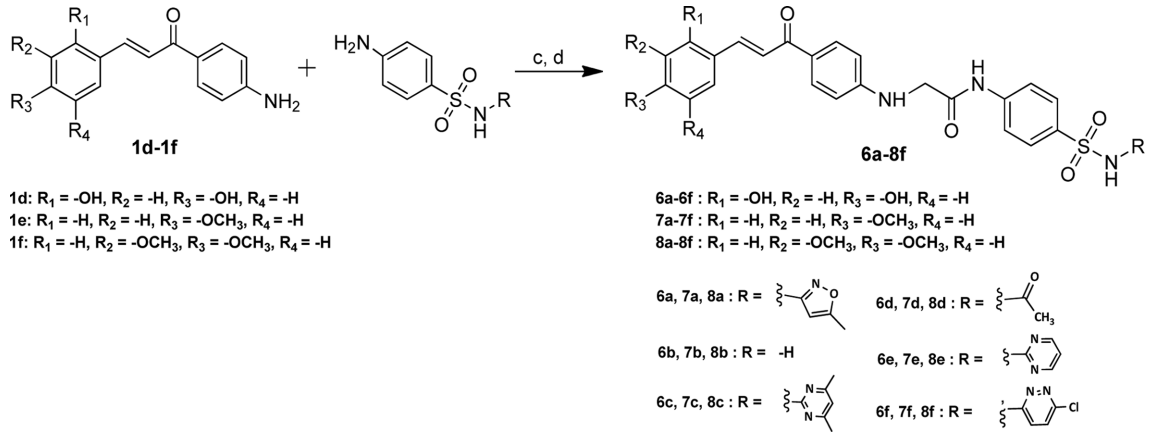
RESULTS AND DISCUSSION

Chemistry

The synthetic outline utilized for the synthesis of the targeted chalcone-sulphonamides hybrids are depicted in *Scheme* 1 and *Scheme* 2. Hydroxy and methoxy introduction on the benzene ring of chalcone scaffold could play a significant role in displaying remarkable cytotoxic effect.[23,24] Base-catalyzed Claisen-Schmidt condensation between commercially available 4-aminoacetophenone and substituted aromatic aldehydes gave chalcones **1d–1f** in good



***Scheme* 1.** Synthesis of chalcone compounds **1d–1f**. Reagent and condition: **a.** 20% NaOH, CH_3OH, 25–30 °C, overnight. **b**. 25% HCl, ethyl acetate.



***Scheme* 2.** Synthesis of targeted Chalcone-sulphonamide hybrids **6a–8f**. Reagent and condition: **c.** DMF, chloroacetylchloride, triethylamine, 0–5 °C. **d.** Reflux, 8–9 h.

yield (*Scheme* 1).

The structural investigation to synthesized compounds was based on their spectroscopic (IR, NMR, MS) data. IR spectrum of compound **1a** revealed characteristic strong intensity bands at 3340, 3219 cm^{-1}, for carbonyl at 1647–1680, -CH=CH- at 1590-1610 and for -OH at 3570–3395 cm^{-1}. The ^1H NMR spectra of compounds **1d–1f** displayed downfield doublets at 8.06 and 7.5 ppm assigned for CH =CO and CH=CH respectively. Broad singlet in upfield at 3.47–3.50 ppm appeared for -NH_2 group and singlet of methoxy proton in **1d** and **1f** appeared about at 3.87 ppm.

The further approach was drawn to design and synthesize novel chalcone-sulphonamide hybrids which are found an imperial class of anticancer agents.[25,26] Thus, the treatment of chalcone **1d–1f** with sulphonamide in DMF yielded the desired hybrids **6a–8f** (*Scheme* 2). The key reaction complied is the formation of a C-N bond between the nitrogen of chalcone and carbon of sulphonamide derivatives. Structures of all the synthesized hybrids **6a–8f** are further supported by IR, NMR, and HRMS. IR spectra of **6a–8f** displayed -NH- absorption band at 3330–3360 cm^{-1} and stretching band of amide carbonyl at 1734–1739 cm^{-1}. The broad singlet in ^1H NMR of **6a–8f** has disappeared which implies the absence of free -NH_2 group of chalcone moiety and further resulted in the formation of a C-N bond between two pharmacophores. In the ^1H NMR spectra, methylene protons present between -NH- and -CO- appear as a doublet at 3.36 ppm. ^{13}C NMR spectrum of **6a** revealed different characteristic signals at 44.54 ppm for methylene, 56.79 ppm for methoxy, 167.97 ppm for amide carbonyl and 190.97 ppm for vinyl carbonyl also reinforce the proposed structure. High-resolution mass spectroscopy reveals that hybrid **6a** showed molecular ion ($M+H^+$) peak at 546.157 corresponding to the molecular formula of $C_{28}H_{26}N_4O_6S$.

Anticancer Activity

Chemically synthesized all chalcone-sulphonamide hybrids **6a–8f** were screened for their anticancer activity against MCF-7(Breast cancer), DU-145(Human prostate Carcinoma), HCT-15 (Colon cancer), NCIH-522 (stage 2, adenocarcinoma; non-small cell lung cancer) and HT-3 (Human cervical cancer) cell lines. *Table* 2 list the IC_{50} values of the hybrids against respective cell lines. IC_{50} values of all synthesized compound against test organism were compared to standard doxorubicin drug.

The result of anticancer activity revealed that most of the synthesized chalcone-sulphonamide hybrids exhibited significant in-vitro cytotoxicity. It was found that compounds

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

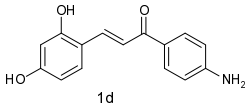
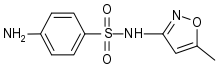
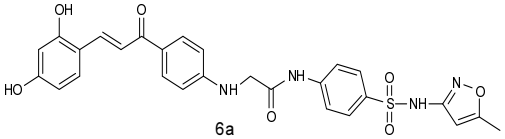
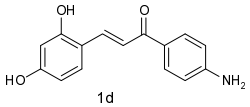
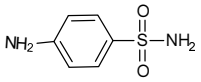
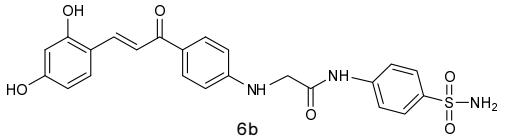
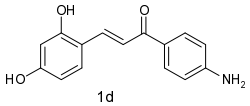
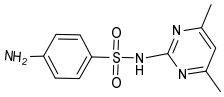
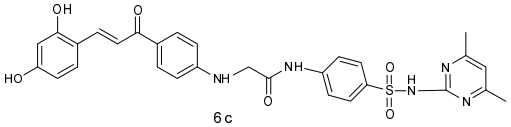
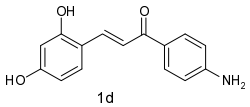
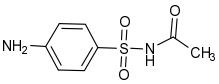
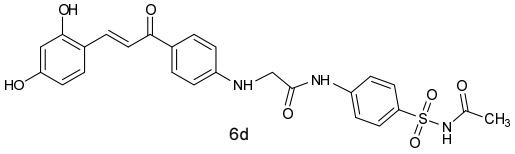
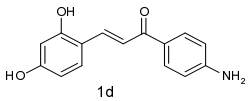
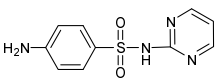
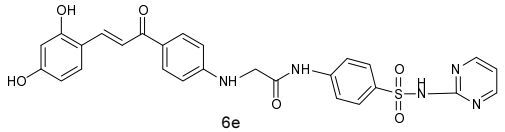
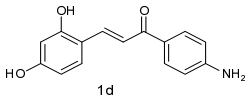
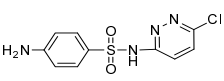
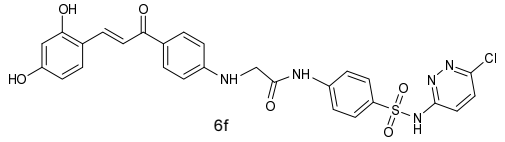
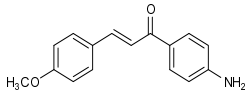
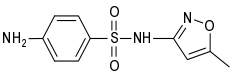
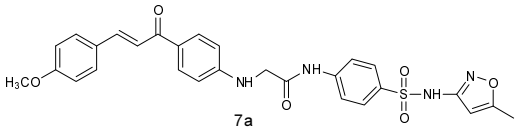
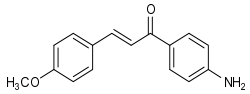
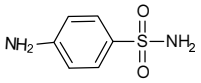
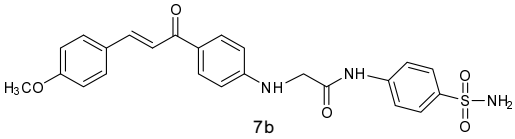
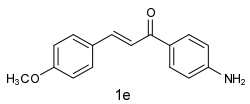
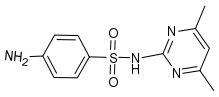
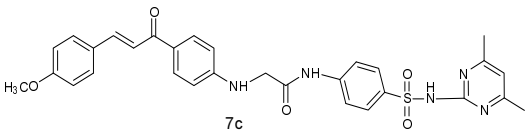
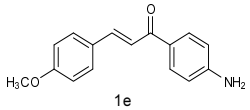
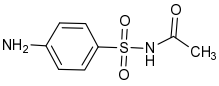
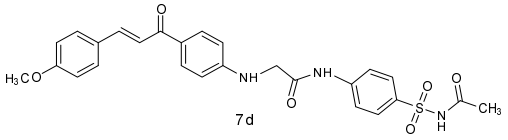
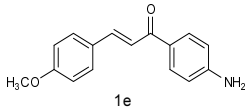
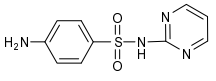
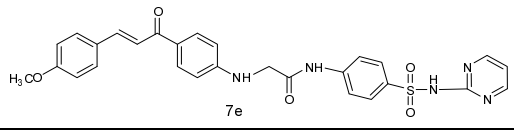
Entry	Aldehyde **(1d–1f)**	Sulphonamide	Chalcone-sulphonamide hybrids **(6a–8f)**	Yield (%)
1	 1d	 2a	 6a	84.4%
2	 1d	 2b	 6b	70.7%
3	 1d	 2c	 6c	74.5%
4	 1d	 2d	 6d	59.0%
5	 1d	 2e	 6e	66.4%
6	 1d	 2f	 6f	65.0%
7	 1e	 2a	 7a	76.0%
8	 1e	 2b	 7b	80.0%
9	 1e	 2c	 7c	61.0%
10	 1e	 2d	 7d	67.0%
11	 1e	 2e	 7e	69.0%

***Table* 1.** (continued)

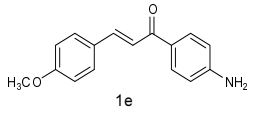
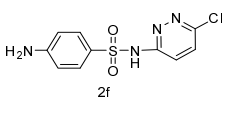
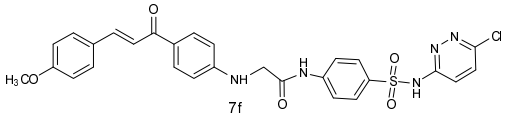
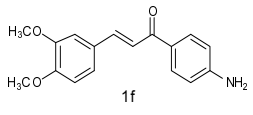
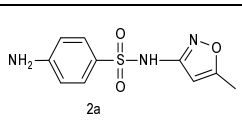
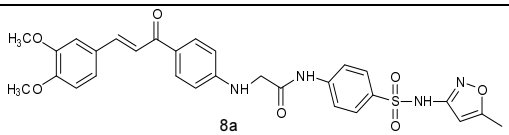
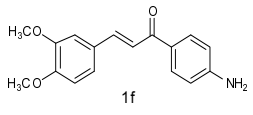
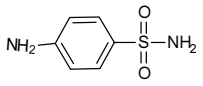
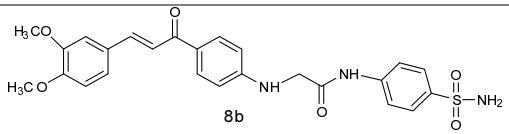
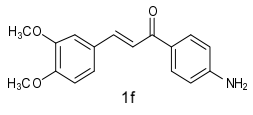
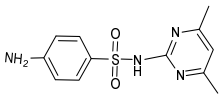
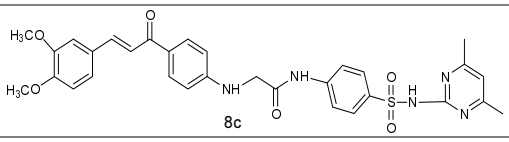
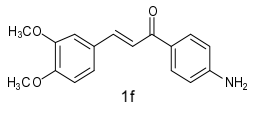
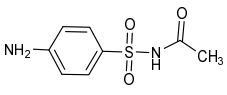
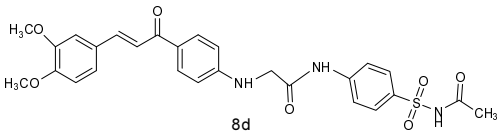
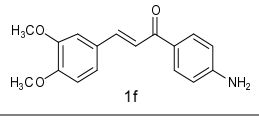
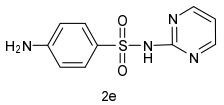
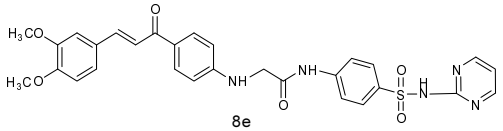
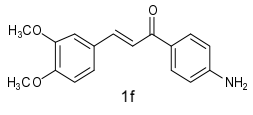
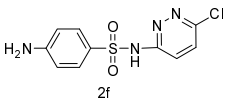
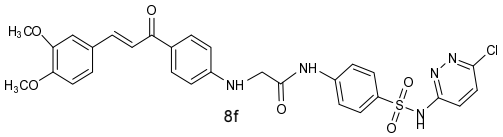
Entry	Aldehyde **(1d–1f)**	Sulphonamide	Chalcone-sulphonamide hybrids **(6a–8f)**	Yield (%)
12	 1e	 2f	 7f	59.0%
13	 1f	 2a	 8a	80.0%
14	 1f	 2b	 8b	88.0%
15	 1f	 2c	 8c	66.0%
16	 1f	 2d	 8d	71.0%
17	 1f	 2e	 8e	68.0%
18	 1f	 2f	 8f	62.0%

***Table* 2.** Percentage cell inhibition by chalcone-sulphonamide hybrids **6a–8f** against various cancer cell lines

Hybrids	IC_{50} (μM/ml)				
	MCF-7	HCT-15	DU-145	NCIH-522	HT-3
6a	>100	55.20	14.40	6.53	54.36
6b	>100	51.92	99.05	11.81	17.90
6c	68.52	53.70	22.50	10.08	14.48
6d	36.53	49.57	24.82	>100	17.89
6e	>100	16.24	19.26	12.49	116.4
6f	3.774	15.09	16.90	18.87	12.10
7a	19.75	19.48	1.952	13.72	8.626
7b	24.61	8.061	83.56	7.951	30.33
7c	>100	77.33	62.70	43.09	8.889
7d	71.33	12.80	8.565	88.03	>100
7e	>100	84.45	5.451	20.26	6.334
7f	25.71	89.34	>100	>100	2.708
8a	3.579	1.599	59.74	>100	7.179
8b	12.43	1.937	94.08	26.84	5.755
8c	6.209	>100	>100	14.39	21.42
8d	1.514	67.32	11.48	32.21	15.04
8e	>100	13.21	4.892	18.82	>100
8f	7.94	43.01	11.00	23.47	6.70
Doxorubicin	**12.19**	**8.772**	**4.152**	**7.784**	**3.740**

6f, **8a**, **8b**, **8c**, **8d** and **8f** showed more potent activity against human breast cancer line MCF-7 compared to Doxorubicin reference drug. **7b**, **8a** and **8b** exhibited promising anticancer activity against HCT-15 cancer cell line. While compound **7a**, **7e** and **8e** showed higher activity than Doxorubicin against human prostate cancer cells DU-145. Compounds **6a** and **7b** exhibited significant activity against human lung cancer cells NCIH-522. Against HT-3 cancer cell lines hybrids **7f** and **8b** are found to be potent. Generally, the anticancer activity shown by **6a**, **7a** and **8a** may attribute to isoxazole heterocycle present. In compounds **6f**, **7e**, **7f**, **8c**, **8e** and **8f** anticancer potency may be due to the presence of pyridine heterocycles while in **7b**, **8b** and **8d** cytotoxicity may attribute to the linkage of chalcone moiety to sulphonamide scaffold.

CONCLUSION

Sulphonamide-chalcone hybrids have been synthesized by conjugating sulphonamide pharmacophore with substituted chalcones as anticancer agents. A panel of chalcone-sulphonamide derivatives was synthesized, characterized and evaluated for their potential in vitro anticancer activity against various human cancer cell lines. Among all the compounds, **6a**, **6f**, **7a**, **7b**, **7e**, **7f**, **8a**, **8b**, **8c**, **8d**, **8e** and **8f** show a significant cytotoxicity against various cancer cell lines than doxorubicin. From the SAR (Structural Activity Relationship) we may conclude that the introduction of oxazole or pyrimidine scaffold is associated with enhanced anticancer activity and gave more potent compounds. This study may provide valuable information for further investigation as anticancer agents.

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