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DESIGN, SYNTHESIS, MOLECULAR DOCKING AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF 4- AMINO-*N*- [(4-OXO-2-(PHENYLAMINO)-4*H*-CHROMEN-3-YL) METHY-LENE]BENZENESULFONAMIDE AND THEIR DERIVATIVES

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Keywords:

Chromone, Sulfonamides, Vilsmeier haack, Antibacterial, Antifungal

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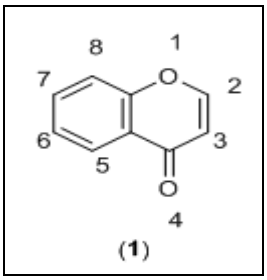
ABSTRACT: 2-Anilino-3-formylchromones are obtained in high yield by rearrangement of differently substituted C-(4-oxo-4*H*[1]-benzopyran-3-yl)-*N*-phenylnitrones. These compounds undergo various facile nucleophilic substitution reactions leading to the synthesis of various pharmacologically active chromone based novel heterocyclic systems like sulphonamides. The C-2 and C-3 are the main positions in the chromone moiety for the attack of nucleophiles and electrophiles, respectively. The chromone system behaves as Micheal acceptor. Generally, the nucleophilic attack at C-2 is accompanied by ring transformation. Protonation and alkylation occur on the oxygen of chromone moiety. In the present study, the substituted 3-Formylchromones were synthesized by Vilsmeyer haack Reaction. These substituted 3-Formylchromones were then reacted with phenyl hydroxyl amine in dry benzene to obtain substituted 2-Anilino-3-formylchromones which were further reacted with various substituted sulphonamides in dry alcohol to furnish final derivatives, *i.e.* chromone based sulphonamide derivatives (8a-h). Chemical structures of these synthesized derivatives were characterized by I.R Spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy analysis. Further, these obtained chromone based sulfonamide derivatives (8a-h) were evaluated *in-vitro* for their antibacterial and antifungal activities. *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aerogenosa,* and *E. coli* bacterial strains were used for the purpose and similarly, the fungal strains used were *Aspergillus niger* and *Candida albicans.* All the tested compounds (8a-h) exhibited potent antimicrobial activities.

INTRODUCTION: Chromones (1) is a group of naturally occurring oxygen-containing heterocyclic compounds. They constitute the largest and most varied family of organic compounds [1].



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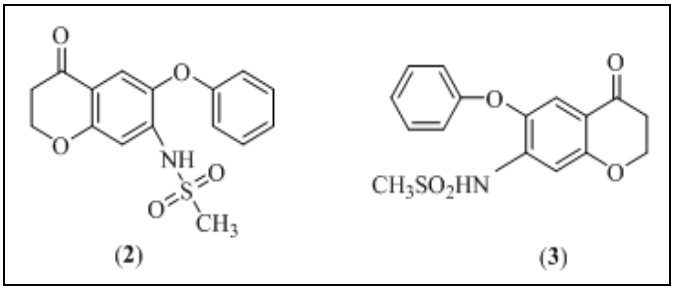
Among their derivatives, 3-Formylchromones bear a unique name for constituting part of the molecular structure of naturally occurring

heterocyclic compounds. Synthetically, these can be prepared through Vilsmeyer haack reaction of various acetophenones. 3-Formylchromone derivatives are known to display several biological activities *viz*. protein tyrosine and kinase inhibition [2, 3], telomerase inhibitors, antifungal, antiviral [4], antihypertensive [5] and anticancer activities [6-10], *etc*.

Similarly, Sulfonamides [–SO_2NH-] represent another very important group of drugs. These are used widely as antiviral [11], antimicrobial, high ceiling diuretics [2], antithyroid and anti-inflammatory agents [13]. The mechanism through which sulfonamides perform their function is to inhibit the conversion of *p*-aminobenzoic acid, thus creating hurdle in the utilization of *p*-amino benzoic acid for bacteria in a folic acid synthesis which leads to the formation of purine and DNA [14]. Many infectious diseases caused by Gram-negative and Gram-positive bacteria are also cured by sulphonamides. Further, these compounds play an essential role as an antitumor, anticancer, and anti-viral agent because they have been reported to inhibit cancer cell growth and ceasing tumor invasion [15].

The synthetic utility of 3-Formylchromones can be explored by exploiting three electron deficient centers: the keto carbonyl carbon, the C-2 carbon and the aldehyde group at C-3. In the present work, the electron deficient C-2 position has been made electron rich by attaching anilino group [16, 17] there. It acts as the main site for the attack of sulphonamide moiety leading to the synthesis of chromone based novel sulphonamide derivatives [16, 18].



Though, modern research involves synthesis of chromone based more complex (2) and hybridized sulphonamide analogs [19] (3) with a focus to get improved antibacterial and antifungal activities, as far as simple derivatives are concerned, a lot is yet to be explored. Keeping this in view, it was decided to explore reactions of some differently substituted 2-Anilino-3-formylchromones with variedly substituted sulphonamides to design and synthesize some novel chromone based sulphonamide derivatives and to evaluate their *in-vitro* antimicrobial activities.

MATERIALS AND METHODS:

Materials: Solvents, starting materials, and reagents were purchased from commercial suppliers and used after purification. All the solvents were purified by the standard procedure before use.

The melting points of all the synthesized compounds were measured on a liquid paraffin bath in open glass capillary tubes using Digital Melting point apparatus by Nutronics Popular Ltd. The reaction progress and product purity were checked by thin layer chromatography using silica gel-G coated glass plates (TLC plates) which were visualized by exposure to iodine vapor as a visualizing agent. IR spectrum was recorded on Perkin Elmer 882 model spectrometer by KBr pellets. Frequencies were recorded in wave number.

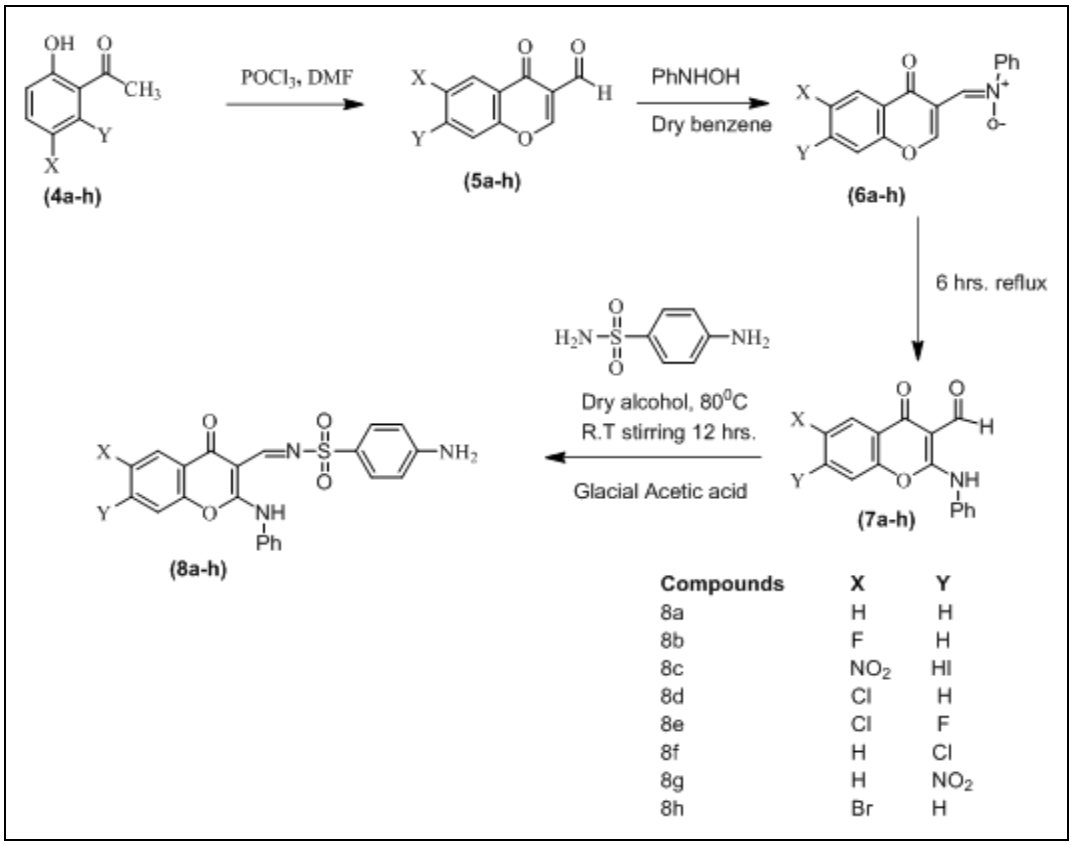
Proton NMR spectroscopy was performed using Bruker Advance II (300 MHz) NMR spectrometer for the solution in $CDCl_3$/DMSO-d6 using tetramethylsilane (TMS) as an internal reference. All chemical shift were reported in parts per million (ppm). Chemical shifts were reported in ppm (δ) and coupling constant (J) values in Hertz.

The mass spectra were recorded on the Q-TOF Micromass (LC-MS) instrument. The m/e values were obtained. The bacterial and fungal strains for antimicrobial activity used were obtained from freeze-dried ampoules that were collected from Microbial Type Collection and Gene Bank, Institute of Microbial Technology, Chandigarh.

Methods:

General Procedure for the Synthesis of chromone based sulphonamide derivatives i.e substituted 4-Amino-*N*-[(4-oxo-2-(phenylamino) -4*H*- chromen- 3- yl) methylene] benzenesulfonamide (8a-h) from substituted 4-Oxo -2 -(phenyl-amino) -4*H*- chromene-3-carbaldehyde (7a-h): Initially, synthesis of substituted 4-Oxo-2-(phenylamino)-4*H*-chromen-3-

carbaldehyde (7a-h) was carried from substituted acetophenones (4a-h) using earlier reported method [20-22]. Substituted 4-Oxo-2-(phenylamino)-4*H*-chromen-3-carbaldehyde (7a-h) was then refluxed with sulfanilamide in dry ethanol at 80 ºC with continuous stirring. After 10 minutes, 1 mL glacial acetic acid was added, and stirring was continued for 1 hr under reflux conditions. After that, continuous stirring was carried out at room temperature for 12 h leading to the formation of a solid product. The solid formed was filtered and re-crystallized with alcohol [23] furnishing the final compounds (**8a-h, Scheme 1**). The completion of the reaction was monitored by TLC in hexane: ethyl acetate (9:1). The reaction conditions are summarised in **Table 1,** given below:



SCHEME 1

TABLE 1: % AGE YIELD AND REACTION CONDITIONS OF COMPOUNDS (8a-h) ARE SUMMARIZED BELOW

S. no.	Compound no.	X	Y	Solvent (Dry)	Reaction Condition	Product (%Yield)
1	8a	H	H	Ethanol	Reflux, 80 ºC, 1 h, Stir, R.T., (12h)	70
2	8b	F	H			75
3	8c	NO_2	H			66
4	8d	Cl	H			74
5	8e	Cl	F			80
6	8f	H	Cl			76
7	8g	H	NO_2			74
8	8h	Br	H			69

Note: The reaction was tried in several solvents like dry acetone, pyridine, benzene, and acetonitrile but the reaction became feasible only in dry ethanol.

Molecular Docking: The X-ray crystal structure of structure *S. aureus* TyrRS (PDB: 1JIK) with the resolution of 2.8 Å was downloaded from the protein data bank, complexed with chromone based heterocyclic (ligand) to understand the structural basis of this protein target specificity [24, 25]. Water molecules were removed, and hydrogen was added to the crystal structure of the protein, and finally refined by completing the incomplete residues and missing residues. The optimized receptor was then saved as a mol2 file and used for docking simulation. The 2D structures of test compounds were built and converted into the 3D using Chem Draw Ultra 8.0 software. The 3D structures were

subjected to energy minimization using Merck Molecular Force Field (MMFF). Docking simulation was done by GRIP batch docking method, a novel way for fast and accurate capturing of ligand-receptor interactions in the active site of proteins.

All optimized ligands were docked into the active site of 1JIK; before interpretation and analysis of interactions, correct ligand pose assessment generally remains an important criterion for the optimal binding affinity prediction using scoring functions. All the docked ligands were scored using the lower Dock Score function, and the pose that matched the assumed binding mode was considered valid and put to the separate set (Valid Poses). The best pose was identified for subsequent analysis.

Pharmacological Activity: The obtained compounds, that is, substituted 4-Amino-*N*-[(4-oxo-2-(phenylamino)-4*H*-chromen-3-yl)methylene] benzenesulfonamide derivatives (8a-h) were evaluated for their *in-vitro* antimicrobial activities against different strains of bacteria (*S. aureus, Bacillus subtilis*, *Pseudomonas aeruginosa,* and *Escherichia coli*) and fungi (*Aspergillus niger* and *Candida albicans*) as per the reported methods [24].

The upper top of the ampoule was disinfected with alcohol, marking of the ampoule was done near the middle of the cotton wool with a sharp knife, disinfected the surface around the mark with alcohol, and ampoule was broken at the marked area. The cotton plug was removed from the ampoule, the freeze-dried powder was suspended in water for injection and suspension was taken from ampoule [23] and swabbing was done on sterile nutrient broth medium and incubated at 37 ºC for 48 h.

RESULTS AND DISCUSSION: The synthesized compounds were analyzed by ^{1}H-NMR, ^{13}C-NMR, Mass spectroscopy, and the results of experimental work are given below:

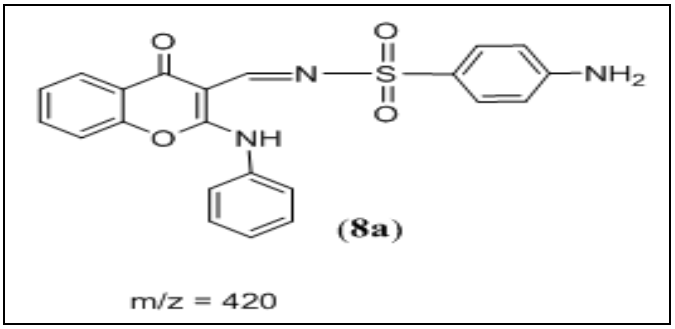
4- Amino- *N*- [(4- Oxo- 2- (phenylamino)- 4*H*-chromen- 3- yl) methylene]benzenesulfon-amide (8a): Reaction of 4-Oxo-2-(phenylamino)-4*H*-chromen-3-carbaldehyde (7a, 1.0g) with sulfanilamide (0.5g) was carried out, and compound (8a) was obtained as pale yellow crystals (70% yield), melting point 260-268 ºC, $C_{22}H_{18}N_3O_4S$, molecular weight 420 g, solubility in DMSO.

IR (KBr): υ_{max} cm^{-1}: 3024 (-C-H, Ar, s), 1710.18 (-C=O), 1257.6 (-C-O-C, s), 1184 (-C-N, m), 1629.8 (-C=N), 1316 (-S=O), 1455 (-C=C, Ar stretch), 3465 (N-H, stretch).

^{1}H NMR: δ_{ppm} (DMSO; 400MHz): 3.97 (s, 3H, NH-phenyl), 7.18-6.47 (m, 5H, Ar, N-phenyl), 7.49-7.22 (m, 4H, SO_2 ring), 8.52-7.65 (m, 3H, chromone), 7.60 (dd, 1H, *J*=8.6, C_5 chromone), 7.52 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 175.1 (C-2), 78.4 (C-3), 159.1 (C-3a), 176.5 (C-4), 124.7 (C-4a), 134.1 (C-5), 124.5 (C-6), 136 (C-7), 118.4 (C-8), 155.7 (C-8a), 146.1 (C-1'), 119.4 (C-2', 6'd), 129.2 (C-3', 5'd), 120.9 (C-4'), 134.3 (C-1''), 130.2 (C-2'', 6''d), 116.7 (C-3'', 5''d), 151.8 (C-4'').

Mass: M^+ m/z: 420 (C_{22} $H_{18}N_3O_4S$)



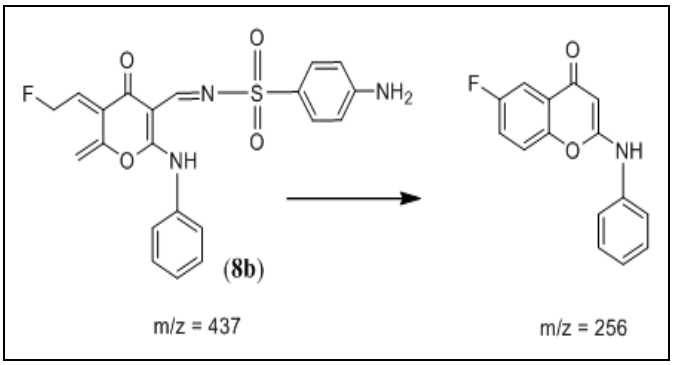
4- Amino- *N*- [(6-Fluoro-4-oxo-2-(phenylamino)-4*H*- chromen- 3- yl) methylene] benzenesulfon-amide(8b): Reaction of 6-Fluoro-4-Oxo-2-(phenyl-amino)-4*H*-chromen-3-carbaldehyde (7b,1.0g) with sulfanilamide (0.5g) was carried out and compound (8b) was obtained as light brown crystals (75% yield), melting point 230-238 ºC, $C_{22}H_{16}FN_3O_4S$, molecular weight 437g, solubility in DMSO.

IR (KBr): υ_{max} cm^{-1}: 1373.15 (C-F, s), 1629.8 (-C=O, s), 1230.1 (-C-O-C, m), 1096 (-C-N, m), 1596 (-C=N), 1313.7 (-S=O), 1455 (C=C, Ar, stretch), 3478 (N-H, stretch)**.**

^{1}H NMR: δ_{ppm} (DMSO; 400MHz): 3.95 (s, 3H, NH-phenyl), 6.98-6.35 (m, 5H, Ar, N-phenyl), 7.48-7.05 (m, 4H, SO_2 ring), 7.92-7.65 (m, 3H, chromone), 7.58 (d, 1H, *J*=8.30, C_5chromone), 7.52 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 172.02 (C-2), 78.7 (C-3), 164.4 (C-3a), 176.5 (C-4), 126.6 (C-4a), 115.3 (C-5), 156.4 (C-6), 120.2 (C-7), 118.9 (C-8), 152.1 (C-8a), 145.2 (C-1'), 115.8 (C-2',6' d), 129.9 (C-3', 5'd), 118.9 (C-4'), 137.2 (C-1''), 129.3 (C-2'', 6''d), 118.4 (C-3'', 5'' d), 151.8 (C-4'').

Mass: M^+: 437 ($C_{22}H_{16}FN_3O_4S$), 256 ($C_{15}H_{10}FO_2N$)



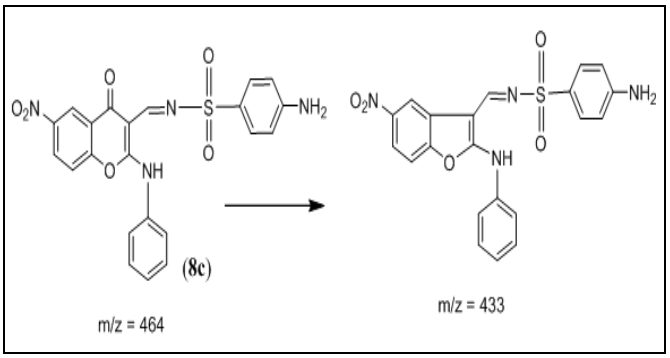
4- Amino- *N*- [(6- Nitro- 4- oxo-2-(phenylamino)- 4*H*- chromen- 3- yl) methylene]benzene sulfonamide (8c): Reaction of 6-Nitro-4-oxo-2-(phenylamino)- 4*H*- chromen- 3- carbaldehyde (7c, 1.0g) with sulfanilamide (0.5 g) was carried out and compound (8c) was obtained as brown crystals (66% yield), melting point 200-220 ºC, $C_{22}H_{16}N_4O_6S$, molecular weight 464 g, solubility in DMSO.

IR: υ_{max} (KBr) cm^{-1}: 1530.1 (NO_2, Ar, s), 1690.1 (-C=O, s), 1179 (-C-O-C, s), 1097.1 (-C-N, m), 1630.5 (-C=N, m), 1313.3 (-S=O), 1597.5 (-C=C, Ar, stretch), 3463 (N-H, stretch).

^{1}H NMR: δ_{ppm}(DMSO; 400MHz): 3.93(s, 3H, NH-phenyl), 6.81-6.54 (m, 5H, Ar, N-phenyl), 7.22-6.98 (m, 4H, SO_2 ring), 7.83-7.68 (m, 3H, chromone), 7.43 (d, 1H, *J*=8.43,C_5 chromone), 7.53 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 174.1 (C-2), 78.3 (C-3), 160.2 (C-3a), 175.5 (C-4), 123.9 (C-4a), 125.4 (C-5), 140.5 (C-6), 127.3 (C-7), 118.3 (C-8), 162.8 (C-8a), 134.1 (C-1'), 112.4 (C-2',6' d), 130.2 (C-3',5'd), 119.9 (C-4'), 134.1 (C-1''), 127.6 (C-2'', 6''d), 116.3 (C-3'', 5'' d), 151.6 (C-4'').

Mass: (M^+): 464 ($C_{22}H_{16}N_4O_6S$), 433 ($C_{21}H_{16}N_4O_5S$)



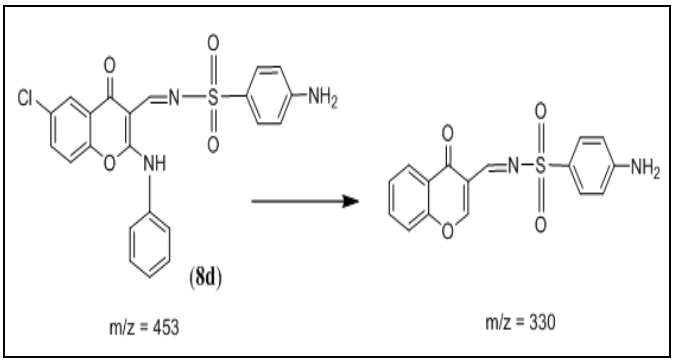
4- Amino-*N*- [(6-Chloro- 4-oxo-2-(phenylamino)- 4*H*- chromen- 3- yl) methylene] benzenesulfonamide (8d): Reaction of 6-Chloro-4-oxo-2-(phenylamino)- 4*H*- chromen- 3- carbaldehyde (7d, 1.0g) with sulfanilamide (0.5g) was carried out and compound (8d) was obtained as pale yellow crystals (74% yield), melting point 258-262 ºC, $C_{22}H_{16}ClN_3O_4S$, molecular weight 453 g, solubility in DMSO.

IR: υ_{max} (KBr) cm^{-1}: 751.1 (C-Cl, m), 1629.29 (-C=O,s), 1186.2 (-C-O-C, m), 1094 (-C-N, m), 1611 (-C=N), 1312.1 (-S=O), 1596 (-C=C, Ar, stretch), 3377 (N-H, stretch).

^{1}H NMR: δ_{ppm} (DMSO; 400MHz): 3.95 (s, 3H, NH-phenyl), 6.78-6.43 (m, 5H, Ar, N-phenyl), 7.28-6.92 (m, 4H, SO_2 ring), 7.93-7.58 (m, 3H, chromone), 7.50 (d, 1H, *J*=8.41, C_5 chromone), 7.42 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 172.3 (C-2), 78.5 (C-3), 162.1 (C-3a), 174.1 (C-4), 127.3 (C-4a), 131.8 (C-5), 128.5 (C-6), 134.5 (C-7), 119.6 (C-8), 152.4 (C-8a), 142.4 (C-1'), 112.4 (C-2',6' d), 129.9 (C-3', 5'd), 117.1 (C-4'), 138.8 (C-1''), 129.9 (C-2'', 6''d), 118.4 (C-3'', 5'' d), 151.8 (C-4'').

Mass: 453 ($C_{22}H_{16}ClN_3O_4S$), 330 ($C_{16}H_{10}N_2O_4S$)



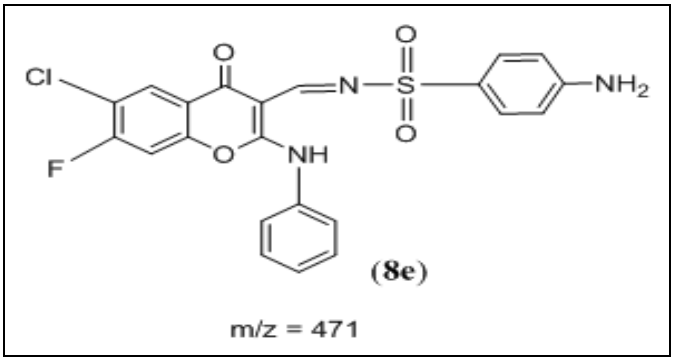
-Amino-*N*-[(6-Chloro-7-fluoro-4-oxo-2-(phenylo-amino)- 4*H*- chromen- 3- yl) methylene]benzene sulfonamide(8e): Reaction of 6-Chloro-7-fluoro-4-oxo- 2- (phenyloamino)- 4*H*- chromen- 3-carbaldehyde (7e, 1.0g) with sulfanilamide (0.5g) was carried out and compound (8e) was obtained as pale yellow crystals, (80% yield), melting point 245-252 ºC, $C_{22}H_{15}ClFN_3O_4S$, molecular weight 471 g, solubility in DMSO.

IR: υ_{max} (KBr) cm^{-1}: 779.5 (C-Cl, s), 1385.3 (C-F, s), 1656 (-C=O,s), 1256 (-C-O-C, s), 1025 (-C-N, m), 1565.1 (-C=N, s), 1271.3 (-S=O), 1497 (-C=C, Ar, stretch), 3368 (N-H, stretch).

^{1}H NMR: δ_{ppm} (DMSO; 400MHz): 3.94 (s, 3H, NH-phenyl), 7.28-6.58 (m, 5H, Ar, N-phenyl), 7.58-7.42 (m, 4H, SO_2 ring), 7.61 (d,1H, J=8.23, C_8), 7.68 (t, 1H, *J*=8.72, C_5 chromone), 7.39 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 173.9 (C-2), 79.5 (C-3), 160.6 (C-3a), 179.5 (C-4), 124.9 (C-4a), 133.4 (C-5), 115.5 (C-6), 170.4 (C-7), 112.8 (C-8), 156.6 (C-8a), 145.0 (C-1'), 117.3 (C-2',6' d), 127.1 (C-3', 5'd), 119.6 (C-4'), 135.4 (C-1''), 129.1 (C-2'', 6''d), 120.6 (C-3'', 5''d), 154.6 (C-4'').

Mass: M^+ = 471



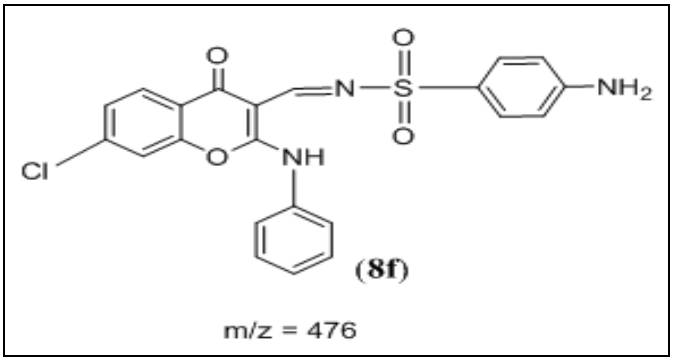
4-Amino-*N*-[(7-Chloro-4-oxo-2-(phenyloamino)-4*H*- chromen- 3- yl) methylene] benzenesulfon-amide (8f): Reaction of 7- Chloro- 4- oxo- 2-(phenylamino)- 4*H*-chromen-3-carbaldehyde (7f, 1.0) with sulfanilamide (0.5g) was carried out and compound (8f) was obtained as pale yellow crystals (76% yield), melting point 240-248 ºC, $C_{22}H_{16}ClN_3O_4S$, molecular weight 476 g, solubility in DMSO.

IR: υ_{max} (KBr) cm^{-1}: 771.4 (-C-Cl, m), 1656.2 (-C=O, s), 1286.2 (-C-O-C, s), 1344.3 (-C-N, m), 1619 (-C=N), 1203.4 (-S=O), 1483.6 (-C=C, Ar, stretch), 3364 (N-H, stretch).

^{1}H NMR: δ_{ppm} (DMSO; 400MHz): 3.92(s, 3H, NH-phenyl), 7.25-6.93 (m, 5H, Ar, N-phenyl), 7.51-7.34 (m, 4H, SO_2 ring), 7.81-7.68 (m, 3H, chromone), 7.60 (d, 1H, *J*=8.42, C_5 chromone), 7.52 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 174.7 (C-2), 77.4 (C-3), 168.4 (C-3a), 175.5 (C-4), 122.5 (C-4a), 129.5 (C-5), 123.3 (C-6), 138.7 (C-7), 117.1 (C-8), 156.3 (C-8a), 144.7 (C-1'), 115.6 (C-2',6' d), 127.9 (C-3',5'd), 119.6 (C-4'), 138.7 (C-1''), 129.04 (C-2'', 6''d), 117.0 (C-3'', 5'' d), 153.9 (C-4'').

Mass: = 476 (M^++Na)



4- Amino- *N*- [(7-Nitro-4-oxo-2-(phenylamino)-4*H*- chromen-3-yl) methylene] benzene sulfon-amide (8g): Reaction of 7-Nitro-4-oxo-2-(phenyl-amino)- 4*H*- chromene- 3- carbaldehyde (7g, 1.0) with sulfanilamide (0.5g) was carried out and compound (8g) was obtained as buff crystals (74% yield), melting point 252-259 ºC, $C_{22}H_{16}N_4O_6S$, molecular weight 464 g, solubility in DMSO.

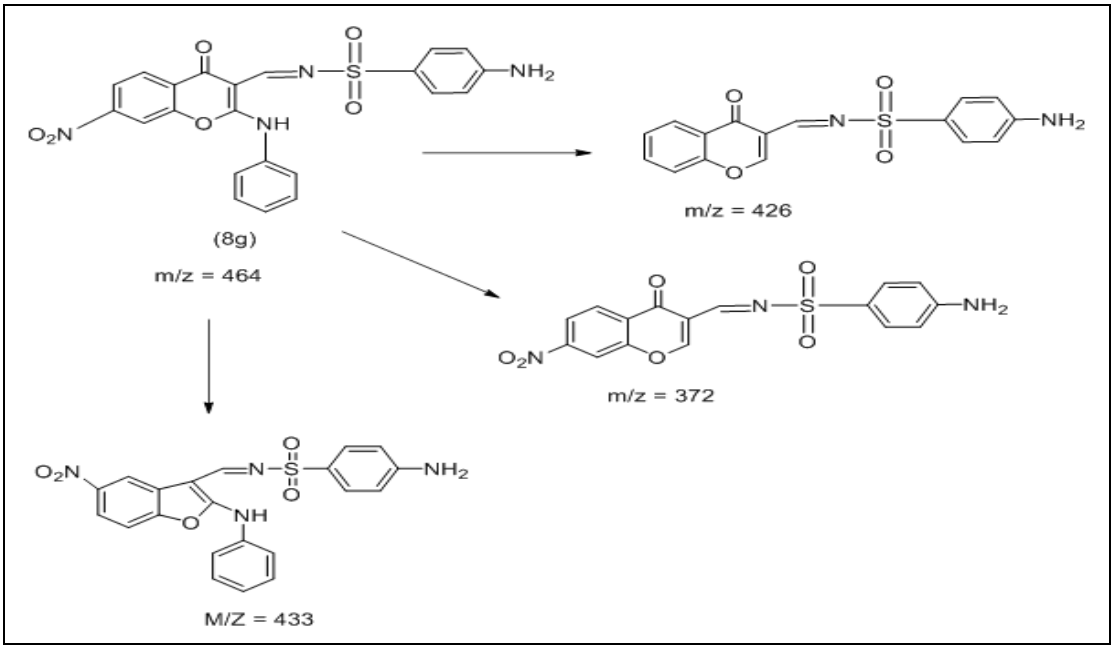
IR: υ_{max} (KBr) cm^{-1}: 1560.1 (NO_2, Ar, s), 1610.1 (-C=O, s), 1147.6 (-C-O-C, s), 1350.7 (-C-N, m), 1611.1 (-C=N), 1147.6 (-S=O), 1491.1 (-C=C, Ar, stretch), 3408 .1 (-N-H, stre).

^{1}H NMR: δ_{ppm} (DMSO; 400MHz): 3.90 (s, 3H, NH-phenyl), 6.59-6.27 (m, 5H, Ar, N-phenyl), 7.12-6.63 (m, 4H, SO_2 ring), 7.88-7.63 (m, 3H, chromone), 7.57 (d, 1H, *J*=8.51, C_5 chromone), 7.49 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 172.1 (C-2), 78.4 (C-3), 163.1 (C-3a), 177.5 (C-4), 130.2 (C-4a), 130.8 (C-5), 114.6 (C-6), 153.4 (C-7), 113.2

(C-8), 159.4 (C-8a), 145.2 (C-1'), 112.3 (C-2',6' d), 129.6 (C-3', 5'd), 115.6 (C-4'), 137.8 (C-1''), 127.3 (C-2'',6''d), 117.2 (C-3'', 5'' d), 154.0 (C-4'').

Mass: 464 ($C_{22}H_{16}N_4O_6S$), 426 ($C_{16}H_{11}N_2O_4S$), 372 ($C_{16}H_{11}N_3O_6S$), 433 ($C_{21}H_{16}N_4O_5S$).

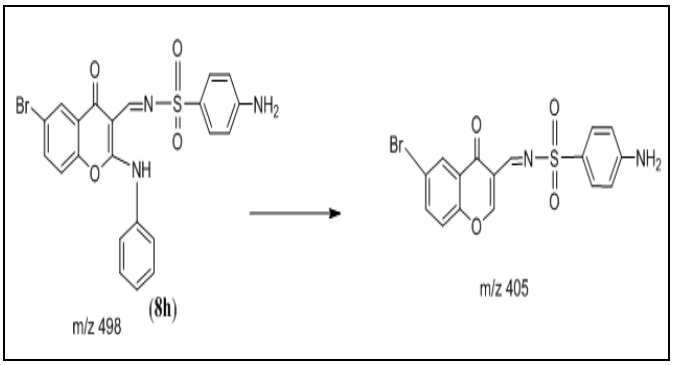


4- Amino- *N*- [(6-Bromo-4-oxo-2-(phenylamino)-4*H*- chromen- 3- yl) methylene] benzenesulfonamide (8h): Reaction of 6-Bromo-4-oxo-2-(phenylamino)- 4*H*- chromen- 3- carbaldehyde (7h, 1.0g) with sulfanilamide (0.5g) was carried out and compound (8h) was obtained as brown crystals (69% yield), melting point 225-232 ºC, $C_{22}H_{16}BrN_3O_4S$, molecular weight 498g, solubility in DMSO.

IR: υ_{max} (KBr) cm^{-1}: 690.1 (C-Br, s), 1632.10 (-C=O, s), 1244.15 (-C-O-C, s), 1314.10 (-C-N, m), 1595.8 (-C=N), 1154.9 (-S=O), 1570.11 (-C=C, Ar, stretch), 3478 (-N-H, stretch).

^{1}H NMR: δ_{ppm}(DMSO; 400MHz: 4.07 (s, 3H, NH-phenyl), 6.83-6.56 (m, 5H, Ar, N-phenyl), 7.43-6.91 (m, 4H, SO_2 ring), 7.92-7.72 (m, 3H, chromone), 7.61 (d, 1H, *J*=8.42, C_5 chromone), 7.53 (s, 1H, C-3a methylene).

^{13}CNMR: δ_{ppm} (DMSO, 400MHz): 170.2 (C-2), 78.7 (C-3), 166.1 (C-3a), 175.9 (C-4), 125.0 (C-4a), 131.6 (C-5), 120.1 (C-6), 137.8 (C-7), 118.0 (C-8), 158.1 (C-8a), 142.1 (C-1'), 112.5 (C-2',6' d), 129.05 (C-3',5'd), 119.0 (C-4'), 139.8 (C-1''), 129.1 (C-2'', 6''d), 117.4(C-3'', 5''d), 151.6 (C-4''). **Mass:** m/z: 498 ($C_{22}H_{16}BrN_3O_4S$), 405 ($C_{16}H_{11}BrO_4N_2S$)



Molecular Docking: The docking study was performed using the VLife MDS 4.6. All the substituted 4-Amino-*N*-[(4-oxo-2-(phenylamino)-4*H*-chromen-3-yl) methylene] benzenesulfonamide (8a-h) derivatives were docked into the active site of the enzymes *S. aureus TyrRS* (PDB: 1JIK). The results of the docking simulation studies represented as D-Score are shown in **Table 2**.

TABLE 2: SHOWING D-SCORE OF SYNTHESIZED COMPOUNDS (8a-h)

S. no.	Compound no.	X	Y	D-score
1	8a	H	H	-69.721018
2	8b	F	H	-68.831358
3	8c	NO_2	H	-69.666214
4	8d	Cl	H	-68.201575
5	8e	Cl	F	-69.666214
6	8f	H	Cl	-71.059263
7	8g	H	NO_2	-70.571883
8	8h	Br	H	-66.395113

The obtained binding interactions revealed that all the newly synthesized compounds bind well within the binding site of the enzyme. Further, it determined that the number of these substituents and their respective positions on the aryl moiety effect the orientation and interaction pattern of the compounds in the binding pocket of the receptor. Based on D-Score observations, further detailed interaction studies were performed on selected compound (8a, 8f, and 8g).

Most stable conformers of (8a, 8f and 8g) *i.e.* LP-4, LP-8 & LP-1 afforded -69.721, -71.059 and -70.059 D Score respectively, as compared to the ciprofloxacin, D-score -43.93 against TyrRS (PDB: 1JIK). **Table 3** is indicating the potential interactions like hydrogen bonding, aromatic, Vander Waal (VDW) and hydrophobic interaction between the protein and the synthesized compounds 8a, 8f, and 8g as well as Ciprofloxacin, respectively.

TABLE 3: DETAILS OF THE OBSERVED POTENTIAL INTERACTIONS

S. no.	Compound no.	X	Y	Ligand Pose	D-Score	Residues	Hydrogen	Hydrophobic	Aromatic
1	8a	H	H	LP4	-69.721	GLY193Å, GLY38Å GLN190Å HIS 47Å HIS 50Å,	++++	-	++
2	8f	H	Cl	LP8	-71.057	GLY 38Å, HIS 50Å,	+	-	+
3	8g	H	NO_2	LP1	- 70.571	HIS 50Å	-	-	+
4	Ciprofloxacin	-	-	LP1	- 43.934	ALA39Å, ASP 40Å, HIS 50Å,	-	+++	_

It has been noticed that in compound 4-Amino-*N*-[(4- Oxo- 2- (phenylamino)- 4*H*- chromen- 3- yl) methylene] benzenesulfonamide (8a, an unsubstituted derivative), chromen-4-one group interacts through hydrogen bonding and aromatic interactions with GLY193Å, GLY38Å, GLN190Å, HIS 47Å and HIS 50A exhibiting the bond distance of 1.83Å, 2.55Å, 1.61Å, 2.52Å, 5.36Å, and 5.00Å respectively (shown in **Fig. 1a-c**) whereas, 4-Amino-*N*-[(7-Chloro-4-oxo-2-(phenylo-amino)- 4*H*- chromen- 3- yl) methylene] benzene sulfonamide (8f, having O=S=O, sulphonyl group) was found to display hydrogen bonding between N and GLY 38A with a force-distance of 2.07Å (as shown in **Fig. 2a-c**). Aromatic interactions were also observed in binding of 8f and 8g with residue HIS 50A (a bond distance of 3.86Å and3.51Å, respectively) as shown in **Fig. 3a-c**. The D-score of the 8b is in agreement with its *in-vitro* antibacterial and antifungal activity expressions.

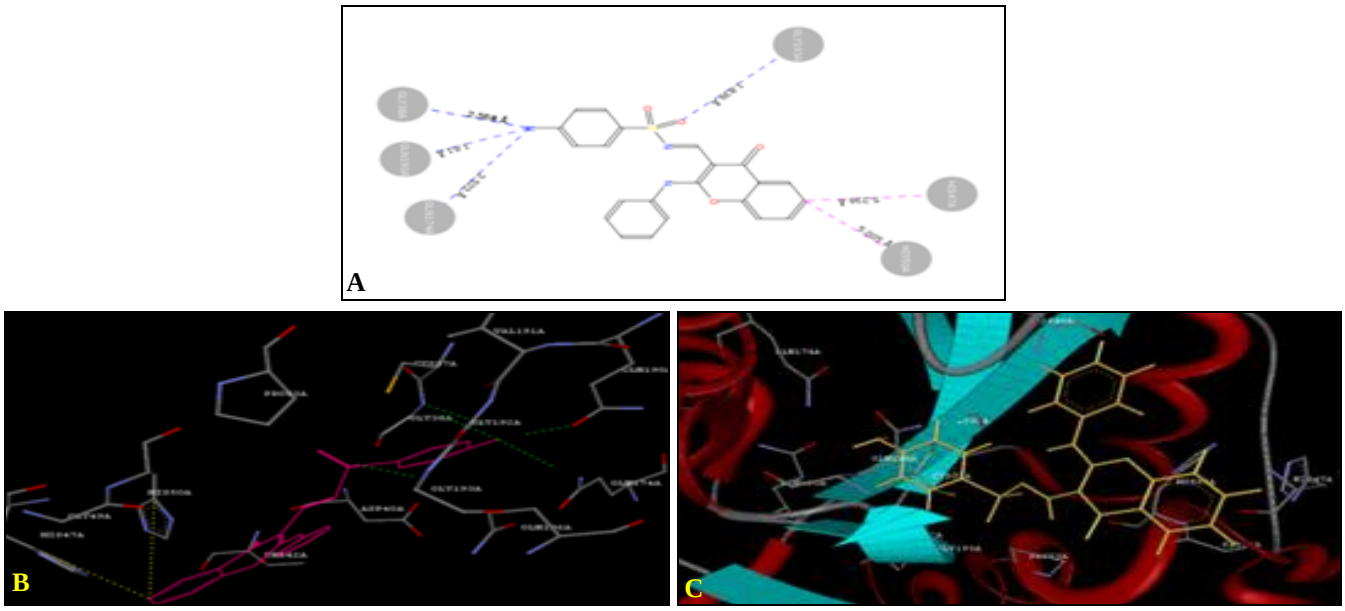


FIG. (1A-C): 2D AND 3D REPRESENTATION OF THE COMPOUND (8a) DOCKED IN THE POCKET SITE OF DNA GYRASE; INDICATING DIFFERENT INTERACTIONS INVOLVED WITH AMINO RESIDUE

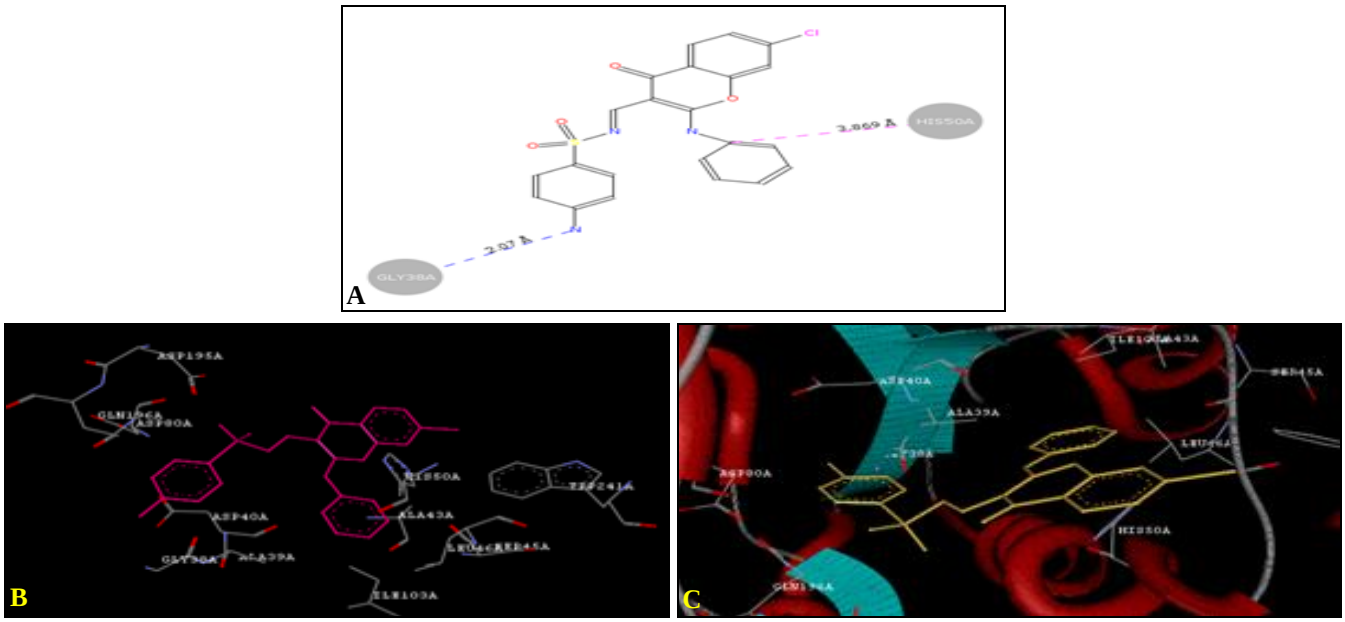


FIG. (2A-C): 2D AND 3D REPRESENTATION OF THE COMPOUND (8f) DOCKED IN POCKET SITE OF DNA GYRASE; INDICATING DIFFERENT INTERACTIONS INVOLVED WITH AMINO RESIDUE

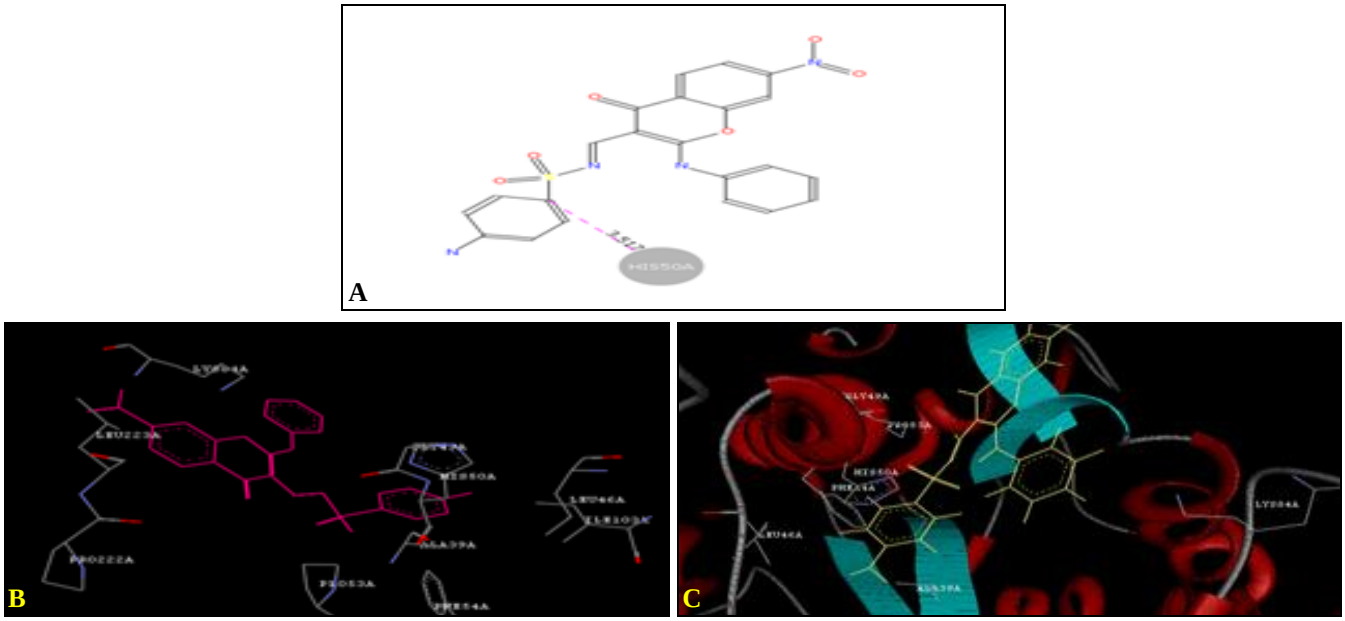


FIG. (3A-C): 2D AND 3D REPRESENTATION OF THE COMPOUND (8g) DOCKED IN POCKET SITE OF DNA GYRASE; INDICATING DIFFERENT INTERACTIONS INVOLVED WITH AMINO RESIDUE

Evaluation of Antimicrobial Activity: The title compounds were evaluated for their *in-vitro* antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aerogenosa* as well as for their *in-vitro* antifungal activity against *Aspergillus niger* and *Candida albicans* fungal strains by the Zone of inhibition method (Agar well diffusion assay or Kirby-Bauer disc diffusion method) [20] and their MICs were calculated. The comparative study of these chromone based novel sulfonamide derivatives was performed using the standard drugs ciprofloxacin (30 µg/mL) for bacterial and fluconazole (30µg/mL) for fungal strains, respectively. The test compounds were dissolved in DMSO at different concentrations of (100, 50, 30 µg/mL).

The results of antibacterial and antifungal activities are shown in **Table 4**, **5,** and **6,** respectively. The compounds exhibited dose-dependent moderate to potent antibacterial and antifungal activities against all the microbes used during testing.

TABLE 4: ANTIBACTERIAL ACTIVITY OF COMPOUNDS (8a-h) AGAINST *S. AUREUS, B. SUBTILIS, P. AEROGENOSA,* AND *E. COLI* BY USING KIRBY-BAUER DISC DIFFUSION METHOD

Compounds	Zone of Inhibition (mm)											
	Staphylococcus aureus			*Bacillus subtilis*			*Pseudomonas aerogenosa*			*Erschenia coli*		
	30	**50**	**100**	**30**	**50**	**100**	**30**	**50**	**100**	**30**	**50**	**100**
8a	7	8	9	1	2	3	-	2	3	-	-	20
8b	22	23	24	-	3	4	4	5	6	6	7	8
8c	-	18	19	-	19	20	7	8	9	25	26	27
8d	-	20	21	15	16	17	-	-	11	-	28	29
8e	9	10	11	-	6	7	9	10	11	13	15	17
8f	29	30	32	28	30	31	20	21	23	30	30	31
8g	28	29	30	26	27	28	-	22	23	29	30	31
8h	-	9	10	-	6	7	-	18	19	8	9	10
DMSO (Ctrl)	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin (Std.)	33			29			29			32		

TABLE 5: ANTIFUNGAL ACTIVITY OF COMPOUNDS (8a-h) AGAINST *A. NIGER* AND *C. ALBICANS* BY USING KIRBY-BAUER DISC DIFFUSION METHOD

Compounds	Zone of inhibitions (mm)					
	Aspergillus niger (Concentration in µg/mL)			*Candida albicans* (Concentration in µg/mL)		
	30	**50**	**100**	**30**	**50**	**100**
8a	12	13	14	5	6	7
8b	1	1	13	11	12	13
8c	-	19	22	-	11	12
8d	-	2	3	-	2	3
8e	-	15	17	-	15	17
8f	20	22	23	17	21	22
8g	18	19	2	18	19	20
8h	17	19	2	14	14	15
DMSO (Ctrl)	-	-	-	-	-	-
Fluconazole (Std.)	22			21		

TABLE 6: THE ACTIVE CONCENTRATIONS OF COMPOUNDS (8a-h) FOR THEIR ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES IN COMPARISON WITH THE STANDARD DRUGS (CIPROFLOXACIN FOR ANTIBACTERIAL ACTIVITY AND FLUCONAZOLE FOR ANTIFUNGAL ACTIVITY) IN µg/ml ARE GIVEN BELOW

Compounds	Antibacterial activity (µg/mL) w.r.t				Antifungal activity (µg/mL)	
	S. aureus	*B. subtilis*	*P. aerogenosa*	*E. coli*	*A. niger*	*C. albicans*
8a	30	30	50	100	30	30
8b	30	50	30	30	30	30
8c	50	50	30	30	50	50
8d	50	30	100	50	50	50
8e	30	50	30	30	50	50
8f	30	100	50	50	100	100
8g	30	30	50	30	30	30
8h	50	50	50	30	30	30

The results have revealed (Table-6) that compounds (8a and 8g) (at 30 µg/mL conc.) are most potent against *S. aureus* and *B. subtilis* (Gram Positive bacteria) and compounds (8b, 8c, and 8e) (at 30 µg/mL conc.) are most potent against *P. aerogenosa* and *E. coli* (Gram negative bacteria) when compared with standard drug Ciprofloxacin at the same 30 µg/mL conc.

Similarly, it was found that the compounds (8a, 8b, 8g, and 8h) at 30µg/mL conc. have proven most potent against *Aspergillus niger* and *Candida albicans* when compared with standard drug Fluconazole at the same conc. The above results concluded that at 30 µg/mL conc. the Compounds (8a-h) possesses potent antibacterial and antifungal activities as compared to the standard drugs Ciprofloxacin and Fluconazole, respectively.

CONCLUSION: Some novel chromone based sulphonamide derivatives were designed, synthesized and evaluated for their antibacterial

and antifungal activities against gram positive and gram negative bacterial strains (*Escherichia coli, Staphylococcus aureus, Bacillis subtilis, Pseudomonas aerogenosa)* and fungal strains (*Aspergillus niger* and *Candida albicans*) respectively. All the synthesized compounds were found to be active against bacterial and fungal strains when compared with standard drugs (Ciprofloxacin for bacterial strains and Fluconazole for fungal strains).

Different compounds have shown their most potent antimicrobial activities at 30 µg/mL conc. *viz.* compounds 8a and 8g have proven most potent against *S. aureus* and *B. subtilis* (Gram positive bacterial strains) and compounds 8b, 8c and 8e have exhibited most significant antibacterial activity against *P. aerogenosa* and *E. coli* (Gram Negative bacteria) while the compounds 8a, 8b, 8g, and 8h have been found most active against *Aspergillus niger* and *Candida albicans* when compared with standard drugs Ciprofloxacin and Fluconazole, respectively. The rest of the compounds expressed significant activity against *A. niger* and *C. albicans* at MIC 50 µg/ml in comparison to the standard drugs used. Hence, these molecules can potentially serve as the useful 'lead' compounds for further development.

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