Indian Journal of Chemistry
Vol. 61, June 2022, pp. 671-677

Synthesis, characterization and molecular docking study of novel *N*-substituted sulfadiazine derivatives as potential anti-mycobacterial agents

Ayad Kareem Khan*, Basma M Abd Razik & Dina Saleem M Ameen

Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq

*E-mail: ayad@uomustansiriyah.edu.iq

Received 30 June 2021; accepted (revised) 21 December 2021

A new series *N*-substituted sulfadiazine derivatives attached with different heterocyclic rings such as 4-oxo-1, 4-dihydroquinazolin[7-12], 4-oxo-2*H*-benzo[1,3]thiazin[13-18] have been synthesized by condensation reactions. The structures of synthesized derivatives are characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR spectroscopic techniques, and some physicochemical properties. A molecular docking study is performed and the binding values show very good matching with experimentally result. The present work deals with newly synthesized sulfadiazine derivatives that are screened for their *(In-vitro)* antitubercular activity of compounds [7-18] is carried out against Mycobacterium tuberculosis H_{37}Rv. compounds [8,11,13,14,15,17] are found most active (MIC=4-16 µg/mL) and compounds [7, 9,10,12,16,18] are found good to moderately active (MIC = 62.5-125 µg/mL) by using isoniazid as standard drug.

Keywords: Synthesis, Characterization, Molecular Docking, Sulfadiazines, Anti-mycobacterial

Sulfadiazine (SDZ) is considered to be one of the most important *N*-substituted derivatives of the original compound, sulfanilamide, used as ideal sulfonamides antibacterial drug for the treatment of the moderate and mild infections of susceptible microorganisms[1,2]. Comparable to different sulfonamides, sulfadiazine is applied for the isosyncratic liver injury treatment[3]. In addition, sulfadiazine has displayed activity against Mycobacterium tuberculosis[4]. Heterocyclic compounds, especially those heterocycles that contain nitrogen and sulfur atoms, are very essential due to their broad utilization in industrial drug designs[5,6], biological fields[7], and medicinal chemistry[8]. Quinazoline ring analogs began to take a lot of space in pharmaceutical applications due to their broad range of chemotherapeutic activities containing antibacterial[9], antifungal[10], antiviral[11], antihypertensive[12], analgesic[13], anticancer[14], antimalarial[15], anti-inflammatory[16], cyclooxygenase (I-II) inhibitors[17], anticonvulsant[18], diuretic agents[19], and antitubercular activity[20]. On the other hand, Benzothiazines are regarded as suitable heterocyclic compounds for various pharmacological activities like antimicrobial[21], antifungal[22], antiproliferative agents[23], anticancer[24], and antioxidant effects[25] besides many other medicinal applications[26].

In this paper, to treat drug-resistant tuberculosis a novel method is reported. Design and synthesis of several sulfadiazine derivatives with structure modifications involving incorporation to six-membered heterocyclic rings such as 2,3-dihydro quinazoline-4(1*H*)-one and 2,3-dihydro-4*H*-benzo [1,3]thiazin-4-one moieties and evaluate these new products as potential anti-mycobacterial (anti-tuberculosis) activity comparison with isoniazid references drug is presented in this paper. A molecular docking study is performed and the binding values were matched with the experimentally result.

Experimental Details

Materials and methods

The starting raw material sulfadiazine{4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide}was received from the wadi al-rafidain for pharmaceutical products factory (Iraq). Other chemical materials and reagents applied in this research are purchased from commercial suppliers with no extra purification. Melting points were determined in open capillaries on a *STUART* (SMP30) digitally melting point-device and have not been corrected. The reactions progress was monitored by thin-layer chromatography (TLC) using Fertigfollen precoated sheets type Polygram Silg, the detection was followed by colouring with iodine vapour and the chromatograms were eluted by acetone/chloroform (7:3) solvent system. The synthesized compounds were identified by the following spectroscopic techniques.

Fourier-transform infrared spectrophotometer (FTIR) was recorded on Shimadzu (8400, Kyoto, Japan) and in the range of 4000 - 400 cm^{-1} using KBr discs. Proton nuclear magnetic resonance (^{1}H-NMR) spectra and carbon nuclear magnetic resonance (^{13}C-NMR) were recorded using BRUKER (400 MHz) NMR spectrometer using deuterated dimethyl sulfoxide (DMSO-d6) as solvent. Chemical shifts (δ) were recorded in parts per million (ppm) and tetramethylsilane was used as an internal standard. The logarithm of partition coefficient (C logP) values were calculated on ChemDraw professional v:19.0 (Cambridge software).The docking score for ligands towards each protein was calculated to estimate the binding free energy, with the best docking score (lowest energy value) indicating the highest predicted ligand/protein affinity. The anti-mycobacterial activity was performed in the National Center for Chest and Respiratory Diseases, Baghdad-Iraq.

Synthesis of 4-((4-substituted benzylidene)amino)-*N*-(pyrimidin-2-yl)benzenesulfonamide [1-6]

An equimolar quantity of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (sulfadiazine) (0.01 mol) and appropriate aryl aldehydes (0.01 mol) were dissolved in a (20 mL) of methanol then a few drops of glacial acetic acid was added as catalyst. The reaction mixture was heated under reflux at (100 °C) with stirring overnight. The end of the reaction was monitored by a TLC plate then the mixture was poured onto crushed ice. The formed solid was filtered off and washed with (2%) solution of $NaHCO_3$ and distilled water then recrystallized from absolute ethanol.

Synthesis of 4-(2-(4-substituted phenyl)-4-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)-*N*-(pyrimidin-2-yl) benzenesulfonamide [7-12]

A mixture of appropriate 4-((4-substituted benzylidene)amino)-*N*-(pyrimidin-2-yl) benzenesulfonamide [1-6] (0.01 mol), 2-aminobenzoic acid (0.01 mol, 1.37 g) in (30 mL) absolute ethanol was mixed and refluxed about 14-16 h. The progress of the reaction was checked by TLC. The excess solvent was evaporated under reduced pressure after the reaction is complete. The reaction mixture then cooled and solid precipitate was filtered, washed with distilled water, and recrystallized from ethanol.

Synthesis of 4-(2-(4-subtituted phenyl)-4-oxo-2*H*-benzo[e][1,3]thiazin-3(4*H*)-yl)-*N*-(pyrimidin-2-yl)benzene-sulfonamide [13-18]

2-mercaptobenzoic acid (0.01 mol, 1.54 g) dissolved in (30 mL) of dry benzene was added gradually to appropriate Schiff bases 4-((4-substituted benzylidene)amino)-*N*-(pyrimidin-2-yl) benzene-sulfonamide [**1-6**] (0.01 mol) duration of 5 min. with constant stirring for 2 h. The reaction mixture was then refluxed on a water bath for about (20-24 h.). The excess solvent was evaporated and the remaining mixture has been treated with 2% sodium bicarbonate, filtered then recrystallized from ethanol.

Docking Study

A total of 12 sulfadiazine derivatives were drawn as separate files by using ChemDraw 18.0 software (ChemDraw, 2018). Molecular docking study and binding evaluation were performed by using the Glide tool included in the Schrodinger program (Schrodinger, 2017). All computational process were running on Windows 10 operating system Dell T-1872 laptop (Intel(R) Core(TM) i7 CPU 968 @ 4.54GHz, 16 GB RAM, 2 GB VGA card, 2 TB HD). The MM+ force field is selected for geometry optimization and kept as mol format by Hyperchem version 8.0. with addition semi-empirical optimization by semi-empirical. The crystal structures of Mycobacterium tuberculosis protein as tyrosine phosphatase were downloaded from Protein Data Bank (PDB: 2OZ5) with a crystallographic resolution of 2.00 Å. In the maestro site, the ProPrep tool is used for the receptor (Mycobacterium tuberculosis protein) preparation, optimization, cleaning, filling missing loops, and energy minimization of downloaded PDB crystal files. For ligands (sulfadiazine derivatives) preparation, the LigPrep tool is used to identify the ionization level and adding of missing hydrogen atoms using OPLS 2005 force field molecular mechanics. To apply the docking study, the grid docking box was adjusted to 10 Å by 0.25 atomic charge. The flexible method using Glide-extra precision (XP) was selected for simulations prosses for the active binding site of the receptor. During all docking processes, the protein (receptor) was kept rigid while sulfadiazine derivatives (ligands) were set as flexible. The highest best orientation poses with low RMSD were saved and recorded for comparison.

Anti-mycobacterial activity

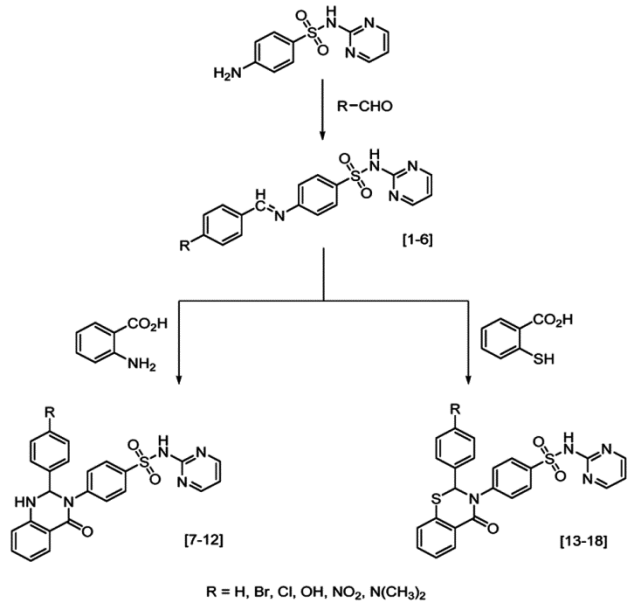
The *N*-substituted sulfadiazine derivatives attached with various heterocyclic such as 4-oxo-1,4-dihydro quinazoline (**7-12**) and 4-oxo-2*H*-benzo[1,3]thiazin (13-18) were evaluated to confirm their *(in vitro)* antimycobacterial activity against Mycobacterium tuberculosis 331/88 (H37Rv; This strain has been

diluted to 10^{-3}) which is susceptible to all newly synthesized compounds. All derivatives inspected were dissolved in dimethylsulfoxide and their dilutions were ready in 0.2 mL tubes utilized by Middlebrook Broth 7H9 using the method mentioned in the literature.[27] Concentrations with 1000, 500, 250, 125, 62.5, 32, 16, 8, 4,2 and 1 µM was used to determine the minimum inhibitory concentration (MIC) by a micro broth dilution procedure at which the complete inhibition of mycobacterial growth was observed. Slight colonies from freshly grown M. tuberculosis H37Rv were hanging in Middlebrook Broth to obtain 1.0 McFarland turbidity and diluted ten times using the same medium 50 µL of this suspension was collected to tubes containing 50 µL of medium with a different concentration of the tested compounds and to a positive control tube containing Broth only. A tube of negative control was also inserted in the test to screen that the incubation was completed without any contamination. The MICs were tested after incubation at 37 °C for 14 days until mycobacterial growth was visibly observed in the positive control tube as white sediment at the tube bottom. Isoniazid was chosen as the standard drug. The inhibitions are determined according to the procedure listed in the reference.[28]

Results and Discussion

Chemistry

Newly synthesized *N*-substituted sulfadiazines derivatives are outlined in Scheme 1. Sulfadiazine Schiff bases 4-((4-substituted benzylidene)amino)-*N*-(pyrimidin-2-yl)benzenesulfonamide derivatives [**1-6**] were synthesized by the condensation reactions of various aryl aldehydes such as benzeldehyde, *p*-bromobenzeldehyde, *p*-chlorobenzeldehyde, *p*-hydroxybenzeldehyde, *p*-nitrobenzeldehyde and *p*-(*N*,*N*-dimethylamino)benzeldehyde with sulfadiazine row material in the existence of glacial acetic acid as catalyst in absolute ethanol.



Scheme 1 — Newly synthesized *N*-substituted sulfadiazines derivatives

The physicochemical properties of prepared sulfadiazine Schiff bases derivatives [**1-6**] and all other synthesized compounds [**7-18**] are described in Table 1. To show the extent of hydrophilicity for absorption and permeation of all synthesized compounds [**1-18**], the logarithm of partition coefficient (C logP) values was measured to estimate this property and ranging between 1.8 to 5.0. According to Lipinski, due to ClogP being less than 5, such compound's absorbability or permeability should be good. Imine derivatives [**1-6**] are characterized by FTIR spectrum which showed bands at (1603-1610) cm^{-1} of stretching vibration of imine group (C=N) as shown in Table 2. Other spectroscopic methods such as ^{1}H-NMR, ^{13}C-NMR were used for structure elucidation for these series of Schiff bases derivatives as appeared in Table 3 and 4, respictevely.^{1}H-NMR (δ ppm) spectrum for these series derivatives [1-6] evidenced signals back to (CH=N) benzylidenimin protons besides to other identifying signals of aromatic and (NH) sulfonamide protons respectively. ^{13}C-NMR (δppm) spectrum analysis results denoted signals for (CH=N) benzylidenimin carbons as well other diagnostic signals of aromatic and sulfadiazine carbon rings.

4-oxo-1,4-dihydro quinazoline ring derivatives of sulfadiazine [7-12], were synthesized by refluxing equimolar amounts from the appropriate imines [**1-6**] with 2-aminobenzoic acid in absolute ethyl alcohol. Cyclization happens where the functional group in 2-aminobenzoic acid attacks as a nucleophile the carbon of imine (C=N) bond. FTIR of these compounds [**7-12**] showed the presence of carbonyl (C=O) vibration of 4-oxo-1,4-dihydro quinazoline rings in the extended spectral range (1674-1688 cm^{-1}) as shown in Table 2.

^{1}H-NMR (δ ppm) spectrum for these series derivatives [**7-12**] displayed sharp signals belonging to (CH_2), (NH) protons of 4-oxo-1,4-dihydro quinazoline rings besides to other characteristic signals of aromatic and (NH) sulfonamide protons

Table 1 — Physicochemical parameters for sulfadiazine derivatives [1-18]

Comp. No.	Molecular Formula	Color	M.p. (°C)	Yield (%)	C logP*	Ref
1	$C_{17}H_{14}N_4O_2S$	Yellow solid	245-247	88	1.898	0.64
2	$C_{17}H_{13}BrN_4O_2S$	Yellow-orange	221-223	92	2.761	0.82
3	$C_{17}H_{13}ClN_4O_2S$	Dark Orange	212-214	89	2.611	0.87
4	$C_{17}H_{14}N_4O_3S$	Orange	238-240	86	2.132	0.55
5	$C_{17}H_{13}N_5O_4S$	Yellow-green	267-269	90	1.641	0.64
6	$C_{19}H_{19}N_5O_2S$	Light Orange	248-249	87	2.581	0.41
7	$C_{24}H_{19}N_5O_3S$	Off white	174-176	91	3.553	0.60
8	$C_{24}H_{18}BrN_5O_3S$	Brown	208-210	82	4.416	0.69
9	$C_{24}H_{18}ClN_5O_3S$	Light brown	191-193	90	4.266	0.67
10	$C_{24}H_{19}N_5O_4S$	Dark brown	178-180	87	2.886	0.76
11	$C_{24}H_{18}N_6O_5S$	Off white	187-189	74	3.296	0.73
12	$C_{26}H_{24}N_6O_3S$	White	199-201	69	3.718	0.58
13	$C_{24}H_{18}N_4O_3S_2$	Light yellow	231-233	71	4.196	0.62
14	$C_{24}H_{17}BrN_4O_3S_2$	Brown	237-239	61	5.059	0.83
15	$C_{24}H_{17}ClN_4O_3S_2$	Light brown	169-171	65	4.909	0.57
16	$C_{24}H_{18}N_4O_4S_2$	White	210-212	78	3.529	0.61
17	$C_{24}H_{17}N_5O_5S_2$	Brown	158-160	73	3.939	0.68
18	$C_{26}H_{23}N_5O_3S_2$	Dark yellow	195-197	81	4.361	0.74

*Calculated on ChemDraw Professional v:19.0 (Cambridge software**).**

Table 2 — FTIR υ (cm^{-1}) spectral data for sulfadiazine derivatives [1-18]

Comp. No.	υ(N-H)	υ(C-H) Ar.	υ(C=N)	υ(C=C) Ar.	υ(SO_2) Asym.	Others
1	3215	3046	1604	1572	1341	-
2	3266	3051	1608	1584	1358	υ (C-Br) 879
3	3280	3033	1609	1566	1377	υ (C-Cl) 774
4	3224	3048	1612	1531	1334	υ (OH) 3195
5	3289	3075	1603	1543	1346	υ (NO_2) 1451, 1318
6	3272	3070	1610	1555	1371	υ (C-H) 2955
7	3290	3020	1601	1562	1347	υ (C=O) 1688
8	3285	3081	1603	1559	1362	υ (C=O) 1681,υ (C-Br) 861
9	3290	3026	1602	1571	1355	υ (C=O)1687,υ (C-Cl) 778
10	3233	3073	1609	1577	1359	υ (OH) 3127,υ (C=O) 1674
11	3247	3053	1608	1548	1369	υ (C=O) 1678,υ (NO_2) 1477, 1326
12	3266	3047	1603	1522	1338	υ (C-H) 2961,υ (C=O)1680
13	3283	3025	1607	1563	1342	υ (C=O) 1689
14	3252	3034	1606	1572	1361	υ (C=O) 1685,υ (C-Br) 863
15	3273	3029	1605	1529	1348	υ (C=O) 1677,υ (C-Cl) 772
16	3244	3031	1608	1545	1365	υ (OH) 3154,υ (C=O) 1679
17	3256	3018	1611	1533	1331	υ(C=O) 1676,υ (NO_2) 1451, 1318
18	3267	3027	1613	1581	1370	υ(C=O) 1690,υ (C-H) 2944

respectively just as shown in Table 3. ^{13}C-NMR (δ ppm) spectrum for the same derivatives [7-**12**] indicated signals due to (CH_2), (C=O) carbons of 4-oxo-1,4-dihydro quinazoline rings in addition to other diagnostic signals of aromatic and sulfadiazine carbon rings as it appears in Table 4.

Six membered heterocyclic compounds are known as 4-oxo-2*H*-benzo[1,3]thiazin [**13-18**] were synthesized from the reaction of suitable azomethine derivatives [**1-6**] with 2-mercaptobenzoic acid in the dry benzene as solvent. FTIR spectra of the synthesized compounds [**13-18**] appeared vibration of the (C=O) group of thiazine at the spectral range (1676-1690 cm^{-1}). ^{1}H-NMR (δ ppm) spectral data for these group derivatives [**13-18**] exhibited clear signals back to methylene (CH_2) protons of 4-oxo-2*H*-benzo [1,3]thiazin rings besides to other diagnostic signals of aromatic and (NH) sulfonamide protons

Table 3 — ^{1}H-NMR spectral data for sulfadiazine derivatives [1-18]

Comp No.	^{1}H-NMR parameters (δppm)
1	6.86-7.95 (m, 12H, Ar-H), 8.51 (s, 1H, CH=N, benzylidenimin), 10.22 (s, 1H, NH, N-sulfonamide).
2	6.55-7.49 (m, 11H, Ar-H), 8.37 (s, 1H, CH=N, benzylidenimin), 10.12 (s, 1H, NH, N-sulfonamide).
3	6.59-7.72 (m, 11H, Ar-H),8.59 (s, 1H, CH=N, benzylidenimin), 10.38 (s, 1H, NH, N-sulfonamide).
4	6.69-7.81 (m, 11H, Ar-H), 8.63 (s, 1H, CH=N, benzylidenimin), 9.44 (s, 1H, OH), 10.33 (s, 1H, NH, N-sulfonamide).
5	6.58-7.88 (m, 11H, Ar-H), 8.71 (s, 1H, CH=N, benzylidenimin), 10.41 (s, 1H, NH, N-sulfonamide).
6	3.55 (s, 6H, CH_3, methyl), 6.73-7.84 (m, 11H, Ar-H), 8.74 (s, 1H, CH=N, benzylidenimin), 10.31 (s, 1H, NH, N-sulfonamide)
7	5.82 (s, 2H, CH_2), 6.08 (s,1H, NH), 6.81-7.91(m, 16H, Ar-H), 10.24 (s, 1H, NH, N-sulfonamide).
8	5.79 (s, 2H, CH_2), 6.10 (s,1H, NH), 6.85-7.79 (m, 15H, Ar-H), 10.29 (s, 1H, NH, N-sulfonamide).
9	5.73 (s, 2H, CH_2), 6.03 (s,1H, NH), 6.83-7.89 (m, 15H, Ar-H), 10.40 (s, 1H, NH, N-sulfonamide).
10	5.66 (s, 2H, CH_2), 6.13 (s,1H, NH), 6.74-7.90 (m, 15H, Ar-H), 9.35 (s, 1H, OH), 10.42 (s, 1H, NH, N-sulfonamide).
11	5.49 (s, 2H, CH_2), 6.07 (s,1H, NH), 6.79-7.98 (m, 15H, Ar-H), 10.34 (s, 1H, NH, N-sulfonamide).
12	3.61 (s, 6H, CH_3, methyl), 5.54 (s, 2H, CH_2), 6.22 (s,1H, NH), 6.80-7.95 (m, 15H, Ar-H), 10.23 (s, 1H, NH, N-sulfonamide).
13	5.22 (s, 2H, CH_2), 6.69-7.86 (m, 16H, Ar-H), 10.29 (s, 1H, NH, N-sulfonamide).
14	5.78 (s, 2H, CH_2), 6.92-7.97 (m, 15H, Ar-H), 10.49 (s, 1H, NH, N-sulfonamide).
15	5.63 (s, 2H, CH_2), 6.88-7.91 (m, 15H, Ar-H), 10.36 (s, 1H, NH, N-sulfonamide).
16	5.67 (s, 2H, CH_2), 6.79-7.87 (m, 15H, Ar-H), 9.47 (s, 1H, OH), 10.38 (s, 1H, NH, N-sulfonamide).
17	5.77 (s, 2H, CH_2), 6.83-7.95 (m, 15H, Ar-H), 10.55 (s, 1H, NH, N-sulfonamide).
18	3.69 (s, 6H, CH_3, methyl), 5.53 (s, 2H, CH_2), 6.72-7.94 (m, 15H, Ar-H), 10.52 (s, 1H, NH, N-sulfonamide).

Table 4 — ^{13}C-NMR spectral data for sulfadiazine derivatives [1-18].

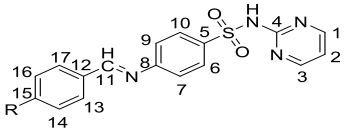
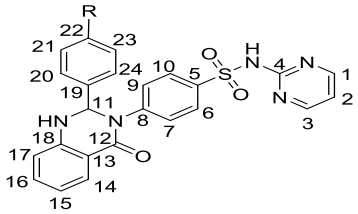
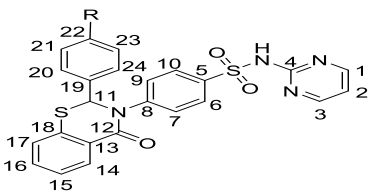
Comp. No.	^{13}C-NMR parameters (δ ppm)	General structure of compound with numbering of C-atoms
1	121.35-139.66 [(C_2), (C_5-C_7), (C_9-C_{10}), (C_{12}-C_{17})], 159.23 (C_1,C_3,C_8), 162.75 (C_{11}), 168.47 (C_4).	
2	122.52-137.99 [(C_2), (C_5-C_7), (C_9-C_{10}), (C_{12}-C_{17})], 158.12 (C_1,C_3,C_8), 163.39 (C_{11}),169.85 (C_4).	
3	123.41-140.21[(C_2), (C_5-C_7), (C_9-C_{10}), (C_{12}-C_{17})], 160.11 (C_1,C_3,C_8), 163.43 (C_{11}), 170.14 (C_4).	
4	124.52-139-77 [(C_2), (C_5-C_7), (C_9-C_{10}), (C_{12}-C_{17})], 159.48 (C_1,C_3,C_8), 161.29 (C_{11}), 169.37 (C_4).	
5	122.55-141.16 [(C_2), (C_5-C_7), (C_9-C_{10}), (C_{12}-C_{17})], 158.79 (C_1,C_3,C_8), 163.11 (C_{11}), 170.24 (C_4).	
6	46.27 (CH_3-N-ph),123.72-140.31 [(C_2), (C_5-C_7), (C_9-C_{10}), (C_{12}-C_{17})], 159.37 (C_1,C_3,C_8), 161.78 (C_{11}), 169.59 (C_4).	
7	96.37 (C_{11}),119.83-139.71 [(C_2), (C_5-C_{10}), (C_{13}- C_{18}), (C_{19}-C_{24})],158.27 (C_1,C_3), 162.41 (C_{12}),168.81 (C_4).	
8	97.22 (C_{11}),118.61-138.98 [(C_2), (C_5-C_{10}), (C_{13}- C_{18}), (C_{19}-C_{24})],157.54 (C_1,C_3), 161.77 (C_{12}),169.49 (C_4).	
9	96.18 (C_{11}),121.52-141.61 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})],159.12 (C_1,C_3), 163.20 (C_{12}),169.74 (C_4).	
10	94.73 (C_{11}),118.59-140.63 [(C_2), (C_5-C_{10}), (C_{13}- C_{18}), (C_{19}-C_{24})],156.39 (C_1,C_3), 161.58 (C_{12}),170.23 (C_4).	
11	96.58 (C_{11}),120.77-141.62 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})],157.28 (C_1,C_3), 161.75 (C_{12}),169.38 (C_4).	
12	44.91 (CH_3-N-ph), 95.67 (C_{11}), 120.19-138.52 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})], 156.25 (C_1,C_3), 160.72 (C_{12}),169.49 (C_4).	R = H, Br, Cl, OH, NO_2, $N(CH_3)_2$
13	94.88 (C_{11}),118.91-140.22 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})],160.33 (C_1,C_3), 163.51 (C_{12}),169.72(C_4).	
14	96.12 (C_{11}),119.52-140.44 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})],156.51 (C_1,C_3), 161.27 (C_{12}),170.38 (C_4).	
15	96.39 (C_{11}),119.25-137.47 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})],155.67 (C_1,C_3), 160.45 (C_{12}),169.33 (C_4).	
16	93.98 (C_{11}),118.58-141.21 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})],156.21 (C_1,C_3), 161.57 (C_{12}),168.91 (C_4).	
17	95.11 (C_{11}),121.52-138.61 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})],156.37 (C_1,C_3), 160.48 (C_{12}),170.13 (C_4).	
18	47.91 (CH_3-N-ph), 95.32 (C_{11}),120.73-138.54 [(C_2), (C_5-C_{10}), (C_{13}-C_{18}), (C_{19}-C_{24})], 157.23 (C_1,C_3), 163.61 (C_{12}),170.31 (C_4).	R = H, Br, Cl, OH, NO_2, $N(CH_3)_2$

Table 5 — Antimycobacterial activity resultsand docking scores of the synthesized sulfadiazine derivatives [7-18]

Compound No.	R-Substituents	Minimal inhibition concentrations MIC in (µg/mL) (M. tuberculosis $H_{37}Rv$ strains)	Docking score
7	H	125	-5.433
8	Br	4	-7.556
9	Cl	125	-5.315
10	OH	62.5	-5.766
11	NO_2	4	-7.6
12	$N(CH_3)_2$	62.5	-5.021
13	H	16	-6.769
14	Br	4	-7.243
15	Cl	8	-7.023
16	OH	62.5	-5.494
17	NO_2	16	-6.45
18	$N(CH_3)_2$	125	-3.529
INH (Std.)		1	-3.539

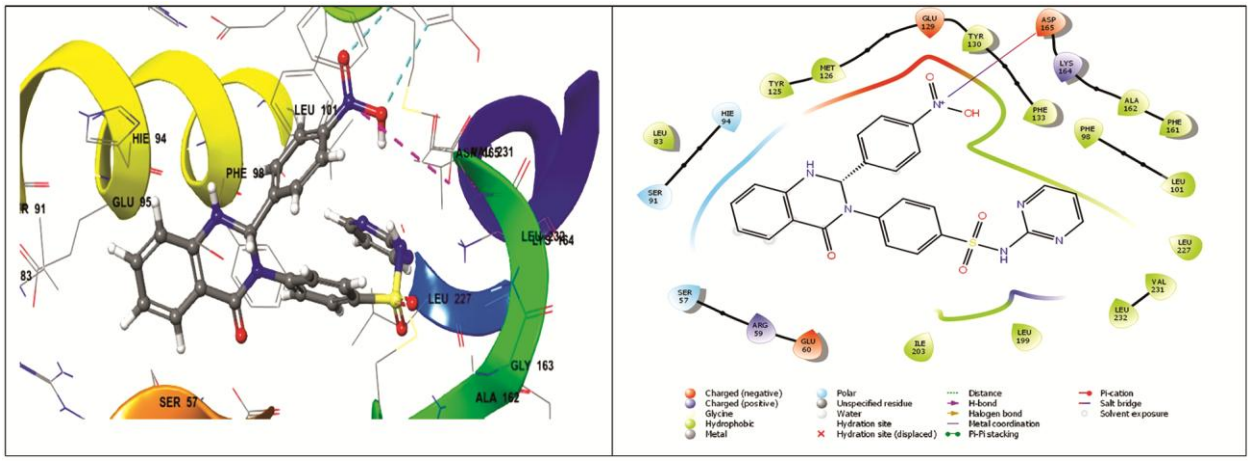


Fig. 1 — Compound 11 in 2D & 3D form inside active site surrounded by amino acids

respectively as shown in Table 3. Furthermore, ^{13}C-NMR (δ ppm) spectral values for the related derivatives [**13-18**] demonstration signals belongs to methylene (CH_2), (C=O) carbons of 4-oxo-2*H*-benzo[1,3]thiazin rings in addition to other distinctive signals of aromatic and sulfadiazine carbon rings as noted in Table 4.

Antituberculosis activity

All the tested compounds showed antituberculosis activity and minimum inhibition concentrations are between 125 to 4 µg/mL. Here, compounds showed the remarkable docking score -7.556 to -3.529 which can be compared with the standard drug isoniazid with -3.539 as docking scores. The docking scores of synthesized compounds with Inh A and MIC values in (µg/mL) against M. tuberculosis $H_{37}Rv$ strains are shown in Table 5.

In the series of synthesized compounds, bromophenyl substituted compound [**8,14**] demonstrated enhanced activities in each 4-oxo-1,4-dihydro quinazoline and 4-oxo-2H-benzo[1,3]thiazin derivatives besides nitrophenyl substituted compound [**11**] in 4-oxo-1,4-dihydro quinazoline rings only. Other compounds such as [**13**, **15** and **17**] also exhibited good efficiency toward tuberculosis bacterial isolates. The remaining compounds as [**10**, **12** and **16**] proofed moderate efficacy, while compounds [**7**, **18**] were the least effective.

Molecular Docking

Fig. 1 shows compound [**11**] inside Mycobacterium tuberculosis protein active site with a very high docking score at 7.60 kcal/mol surrounded by a list of amino acids related to the high ability of this compound to bind inside the protein. The list of these amino acids is SER57, ARG 59, GLU60, PRO81, LEU83, SER91, HIE94, PHE98, LEU101, TYR125, MET126, GLU129, TYR130, PHE133, PHE161,

ALA162, LYS164, ASP165, ARG166, LEU199, LEU227, VAL231, LEU232.

Inside the active site, the compound [**11**] interact by a salt bridge between the nitro group and ASP165. Moreover, this compound bind by obvious polar interaction aromatic rings with MET126, GLU129, TYR130, and PHE133 with negatively charged interaction between ketone group and GLU60 & LEU199, and with hydrophobic interaction around pyrimidine aromatic ring. Compared with all substitutions docking results approve the ability to withdraw group substitution to increase binding ability inside the active site. This finding can be used for future work to evaluate the effect of other withdrawing chemical groups on activity and use compound [**11**] as a hit for more molecular design studies. Interestingly, docking binding values matted with experimentally minimal inhibition concentrations values.

Conclusion

A successful attempt has been made for the synthesis of sulfadiazine derivatives with 4-oxo-1,4-dihydro quinazoline and 4-oxo-2H-benzo[1,3]thiazin functionality. The most of synthesized compounds showed excellent antituberculosis activity. The MIC values were up to 16 µg/mL, which is also corroborated using molecular docking study. Some of the derivatives also offered noteworthy Anti-TB effectiveness with MIC values of 125 µg/mL. The 4-oxo-1,4-dihydro quinazoline and 4-oxo-2H-benzo[1,3]thiazin heterocycles were mainly responsible for the observed activities and different groups on phenyl rings of influence the efficiency.

Acknowledgement

The authors would like to thank Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad-Iraq for its support in the present work.

References

1 Blanchard C, Brooks L, Ebsworth-Mojica K, Didione L, Wucher B, Dewhurst S, Krysan D, Dunman P M & R A F Wozniak, *mSphere*, 1 (2016) e00194.
2 Liu X, Gan H, Hu C, Sun W, Zhu X, Meng Z, Gu R, Wu Z & Dou G, *Int J Nanomed,* 14, (2019) 289.
3 Galati G, Tafazoli S, Sabzevari O, Chan T S & P J O'Brien, *Chemico-Biol Interact,* 142(1–2) (2002) 25.
4 M Krátký, M Dzurková, J Janoušek, K Konecná, F Trejtnar, J Stolaríková & J Vinšová, *Molecules,* 22 (2017) 1573.
5 Taylor A P, Robinson R P, Fobian Y M, Blakemore D C, Jones L H & Fadeyi O, *Org Biomole Chem,* 14 (2016) 6611.
6 Gupta A & Halve A K, *Int J Pharm Sci Res,* 6 (2015) 978.
7 Al-Mulla A, *Der Pharma Chemica,* 9 (2017) 141.
8 Arya N, Jagdale A Y, Patil T A, Yeramwar S S, Holikatti S S, Dwivedi J, Shishoo C J & Jain K S, *Euro J Med Chem,* 74 (2014) 619.
9 Zayed M F & Hassan M H, *Saudi Pharm J,* 22 (2014) 157.
10 Hassanzadeh F, Jafari E, Hakimelahi G H, Khajouei M R, Jalali M & Khodarahmi G A, *Res Pharm Sci,* 7 (2012) 87.
11 Krishnan S N, Ganguly S, Veerasamy R & Jan B, *Eur Rev Med Pharmacol Sci*, 15 (2011) 673.
12 Rahman M U, Rathore A, Siddiqui A A, Parveen G & Yar M S, *J Enzyme Inhib Med Chem*, 29 (2014) 733.
13 Alafeefya A M, Kadia A A, Al-Deeba O A, El-Tahirb K E H & Al-Jaber N A, *Euro J Med Chem,* 45 (2010) 4947.
14 Abuelizz H A, Marzouk M, Ghabbour H & Al-Salahi Rashad, *Saudi Pharm J*, 25 (2017) 1047.
15 Fröhlich T, Reiter C, Ibrahim M M, Beutel J, Hutterer C, Zeitträger I, Bahsi H, Leidenberger M, Friedrich O, Kappes B, Efferth T, Marschall M & Tsogoeva S B, *ACS Omega*, 2 (2017) 2422.
16 Poojari S, Naik P P, Krishnamurthy G, Kumara K S J, Kumar N S & Naik S, *J Taibah Uni Sci*, 11 (2017) 497.
17 Abdel-Aziz Al A M, Abou-Zeid L A, ElTahir K E H, Ayyad R R, El-Sayed M A A & El-Azab A S, *Eur J Med Chem*, 121 (2016) 410.
18 Abuelizz H A, Dib R E, Marzouk M, Anouar E H, Maklad Y A, Attia H N & Al-Salahi R, *Molecules,* 22 (2017) 1094.
19 Maarouf A R, El-Bendary E R & Goda F E, *Arch Pharm (Weinheim),* 337 (2004) 527.
20 Jiri K, Jaroslav B, Milan P, Karel W, Milan S & Jiri J, *IL Farmaco,* 55 (2000) 725.
21 Patel C, Bassin J P, Scott M, Flye J, Hunter A P, Martin L & Goyal M, *Molecules,* 21 (2016) 861.
22 Matysiak J, Skrzypek A, Głaszcz U, Matwijczuk A, Senczyna B, Wietrzyk J, Krajewska-Kułak E & Niewiadomy A, *Res Chem Intermed*, 44 (2018) 6169.
23 Zięba A, Latocha M & Sochanik A, *Med Chem Res*, 22 (2013) 4158.
24 Aslam S, Wang F, Ahmad M, Zahoor A F, Mansha A, Rasul A & Fu L, *Pak J Pharm Sci,* 32 (2019) 2795.
25 Sankar P S, Rekha T, Padmaja A, Padmavathi V, Krishna N S & Kondaiah P, *Res Chem Intermed*, 45 (2019) 3053.
26 Badshah S L & Naeem A, *Molecules,* 21 (2016) 1054.
27 Jarrad A M, Ang C W, Debnath A, Hahn H J, Woods K, Tan Ll, Sykes M L, Jones A J, Pelingon R, Butler M S, Avery V M, West N P, Karoli T, Blaskovich M A T & Cooper M A, *J Med Chem,* 61 (2018) 11349.
28 Akgüna H, Karamelekoğlua İ, Berka B, Kurnazb I, Sarıbıyıkb G, Öktemc S & Kocagöz T, *Bioorg Med Chem,* 20 (2012) 4149.