1-(Substituted-phenylsulfonyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione: Drug likeness, physicochemical, Synthesis, Characterization, antibacterial and cytotoxicity assessment

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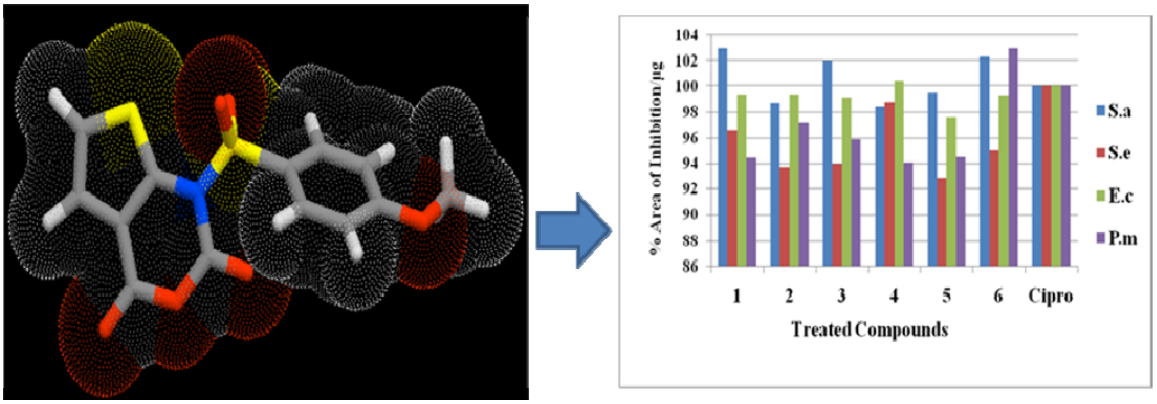
Abstract: A series of 1-(Substituted-phenylsulfonyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione was designed and lead to the bioactivity score and physicochemical property calculations by the online available software. After computational screening the compounds were selected on the basis of their activity level. Only the compounds (1-6) were synthesized as they belong to the zones for active and very near to be active compounds.



FT-IR, NMR, Mass spectroscopy was used for structural confirmation. The antibacterial assessment was performed on pathogens like S. aureus, S. epidermidis, E. Coli and P. mirabilis. MTT assay was done against HepG2 cell line. The findings states that the compounds were found to possess significant antibacterial activity mostly against all the pathogens with less toxic effects

1. Introduction:

Antimicrobial resistance is one of the serious medical issues, as the pathogen developed resistance against the current antimicrobial drugs [1]. The resistance produced by the bacteria through the process of natural selection such as multidrug-resistant gram-positive pathogens, methicillin-resistant *Staphylococci aureus* (MRSA), penicillin resistant *Streptococcus pneumoniae* (PRSP) and vanco- mycin-resistant *Enterrococci* (VRE) [2-4] created difficulties in the therapeutics. Due to this problem the preparation of new antimicrobial therapeutic agents with potential therapeutic effects and different mode of action is necessary which can be effective against the resistance developing pathogens. Heterocyclic compounds, the cyclic compounds with one or more than one heteroatom in its structure, have been investigated a lot and found to possess a significant value in medicinal chemistry [5-17]. The oxazines, are the compounds possessing cyclic structure with one oxygen and one nitrogen atom. The oxazine nucleus and its derivatives were found to exhibit the versatile pharmacological potential such as anti-tubercular, anti-fungal, anti-bacterial, anti-coagulant, cytotoxic [18-23]. Many researchers carried out the large scale investigation has been carried out regarding the synthesis of oxazine-2, 4-dione [24,25]. Besides this the compounds with SO_2N functional group in their structure also attracted the researcher because of their potential therapeutic effects like anti-microbial [26-29], anti-convulsant [30-33], carbonic anhydrase inhibitors [34-35], aromatase inhibitors [36], anti-cancer [37], anti-diabetic [38-39], anti-plasmodial activity [40], anti-cancer and radiosensitizing [41], anti-malaria [42], oxytocin Receptor Agonist [43], anti-proliferative activity [44], COX-2 inhibitors [45].

2. Materials and methods:

2.1. Computational Screening:

To calculate the bioactivity score and the physicochemical properties computationally the online available software was used which can be reached at (www.molinspiration.com). The properties calculated included the LogP, Molar mass, molar refractivity, number of heavy atoms, number of hydrogen atom donar and acceptor, number of violations, GPCR Ligand, ion channel modulator, Kinase inhibitor, nuclear receptor Ligand [46-49].

2.2. Chemistry

2.3. General procedure for the synthesis of 1-(Substituted-phenylsulfonyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione) (1-6): A mixture of compound 2 and substituted sulphonyl chloride in equimolar were dissolved in NaOH soln. (10%, 40 ml) and refluxed to complete the reaction. To get the product in its purest form the final mixture was added to the cold water followed by the addition of some drops of Dil. HCl to produce precipitate, leading to filtering then drying [7].

1. 1-(Phenylsulfonyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione

Yield 85 %; m.p. 110-112 ^{0}C; Creamy crystals; Anal. Calc. For $C_{12}H_7NO_5S_2$: C, 46.60, H, 2.28, N, 4.53; Found: C, 46.64, H, 2.24, N, 4.50; FT-IR (cm^{-1}): 2910 (C–H), 1700 (C=O), 1688 (C=O), 1562 (SO2 Asym.) and 1045 (SO2 Sym.); ^{1}H NMR (DMSO-d6) (ppm): 8.952 (s, 1H, CH), 8.628 (s, 1H, CH), 7.991-7.966 (d, 1H, CH), 7.834-7.801 (d, 1H, CH), 7.037-6.988 (m, 1H, CH), 7.120-7.092 (m, 1H, CH), 7.487-7.436 (m, 1H, CH);

ESI-MS (m/z): [M$^+$ + 1]: 309.98.

2. 1-[(4-Methylphenyl)sulfonyl]-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione

Yield 80 %; m.p. 114-116 ^{0}C; Yellow crystals; Anal. Calc. For $C_{13}H_9NO_5S_2$: C, 48.29, H, 2.81, N, 4.33; Found: C, 48.22, H, 2.92, N, 4.35; FT-IR (cm^{-1}): 2980 (C–H), 1760 (C=O), 1697 (C=O), 1577 (SO2 Asym.) and 1030 (SO2 Sym.); ^{1}H NMR (DMSO-d6) (ppm): 8.873 (s, 1H, CH), 8.734 (s, 1H, CH), 7.973-7.940 (d, 1H, CH), 7.857-7.814 (d, 1H, CH), 7.456-7.410 (m, 1H, CH), 7.118-6.972 (m, 1H, CH), 6.959-6.910 (m, 1H, CH), 2.532 (s, 3H, CH_3); ESI-MS (m/z): [M$^+$ + 1]: 324.00

3. 1-[(4-Chlorophenyl)sulfonyl]-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione

Yield 82 %; m.p. 112-114 ^{0}C; White crystals; Anal. Calc. For $C_{12}H_6ClNO_5S_2$: C, 41.93, H, 1.76, N, 4.07; Found: C, 41.95, H, 1.80, N, 4.12; FT-IR (cm^{-1}): 2950 (C–H), 1729 (C=O), 1685 (C=O), 1570 (SO2 Asym.) and 1039 (SO2 Sym.); ^{1}H NMR (DMSO-d6) (ppm): 8.784 (s, 1H, CH), 8.718 (s, 1H, CH), 7.958-7.922 (d, 1H, CH), 7.849-7.806 (d, 1H, CH), 7.520-7.491 (m, 1H, CH), 7.204-7.182 (m, 1H, CH), 6.973-6.935 (m, 1H, CH), ESI-MS (m/z): [M$^+$ + 1]: 343.94.

4. 1-[(4-Bromophenyl)sulfonyl]-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione

Yield 78 %; m.p. 116-118 ^{0}C; Yellow crystals; Anal. Calc. For $C_{12}H_6BrNO_5S_2$: C, 37.13, H, 1.56, N, 3.61; Found: C, 37.23, H, 1.50, N, 3.72; FT-IR (cm^{-1}): 2958 (C–H), 1710 (C=O), 1680 (C=O), 1582 (SO2 Asym.) and 1040 (SO2 Sym.); ^{1}H NMR (DMSO-d6) (ppm): 8.882 (s, 1H, CH), 8.826 (s, 1H, CH), 8.126-8.080 (d, 1H, CH), 7.900-7.871 (d, 1H, CH), 7.652-7.620 (m, 1H, CH), 7.436-7.392 (m, 1H, CH), 7.148-7.113 (m, 1H, CH); ESI-MS (m/z): [M$^+$ + 1]: 389.89.

5. 1-[(3-Bromophenyl)sulfonyl]-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione

Yield 80 %; m.p. 113-115 ^{0}C; Yellow crystals; Anal. Calc. For $C_{12}H_6BrNO_5S_2$: C, 37.13, H, 1.56, N, 3.61; Found: C, 37.23, H, 1.50, N, 3.72; FT-IR (cm^{-1}): 2964 (C–H), 1743 (C=O), 1697 (C=O), 1568 (SO2 Asym.) and 1046 (SO2 Sym.); ^{1}H NMR (DMSO-d6) (ppm): 8.872 (s, 1H, CH), 8.845 (s, 1H, CH), 8.216-8.188 (d, 1H, CH), 7.883-7.860 (d, 1H, CH), 7.669-7.654 (m, 1H, CH), 7.414-7.381 (m, 1H, CH), 7.211-7.173 (m, 1H, CH); ESI-MS (m/z): [M$^+$ + 1]: 389.89.

6. 1-[(4-Methoxyphenyl)sulfonyl]-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione

Yield 83 %; m.p. 115-117 ^{0}C; Creamy crystals; Anal. Calc. For $C_{13}H_9NO_6S_2$: C, 46.01, H, 2.67, N, 4.13; Found: C, 46.11, H, 2.70, N, 4.25; FT-IR (cm^{-1}): 2935 (C–H), 1734 (C=O), 1705 (C=O), 1566 (SO2 Asym.) and 1052 (SO2 Sym.); ^{1}H NMR (DMSO-d6) (ppm): 8.610 (s, 1H, CH), 8.531 (s, 1H, CH), 7.844-7.808 (d, 1H, CH), 7.718-7.677 (d, 1H, CH), 7.553-7.514 (m, 1H, CH), 7.188-7.147 (m, 1H, CH), 7.080-7.055 (m, 1H, CH); ESI-MS (m/z): [M$^+$ + 1]: 340.98.

2.4. Antibacterial Screening

Antibacterial therapeutic potential of 1-(Substituted-phenylsulfonyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione) (1-6), was estimated using four pathogens such as S. aureus, S. epidermidis, E. Coli and P. mirabilis employing the disc diffusion method with a little bit improvements. The pathogens used for the study included S. Aureus, S. epidermidis, P. Mirabilis and E. coli. The nutrient agar medium was utilized for subculturing of the pathogens and the bacterial cells were suspended according to the McFarland Protocol. The Ciprofloxacin was used as standard and the Zone of inhibition and MIC was estimated [50-56].

2.5. MTT assay:

To estimate the percent viability of the cells MTT assay was performed against the HepG2 (Human hepatocellular carcinoma) cell lines that were cultured in (DMEM + 10% FBS+ 100 U/Ml Penicillin + 100 mg/mL Streptomycin + 2.5 mg/mL Amphotericin B) at 37 ^{O}C in a saturated humidity atmosphere containing 95% air/5% CO2. The results were recorded in triplicate manner to avoid the errors and percent viability of the cells were calculated [57-58].

3. Results and discussion:

In search for new antibacterial therapeutic agents, the recent approach dealt with the designing, synthesis, characterization, antibacterial screening and cyttoxicity evaluation. The structure of the compounds were designed on ChemDrawUltra 8.0 and ChemSketch to generate the smiles that were used to calculate the physicochemical properties and the bioactivity score by the software available online at (www.molinspiration.com). The physicochemical parameters were found in accordance with the Lipinski Rule of Five and the bioactivity score was in the active zone or very near to the active zone **Table-1.** The synthetic route that is represented in **Figure-1,** was followed for the formation of 1-(Substituted-phenylsulfonyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione) (1-6).

Table-1: Representing the drug likeness and the physicochemical properties for the designed compounds (1-6).

Physicochemical property score	**Components**						
	1	**2**	**3**	**4**	**5**	**6**	**STANDARD**
miLogP	1.47	1.92	2.15	2.28	2.25	1.52	-0.071
TPSA	86.36	86.36	86.36	86.36	86.36	95.59	74.569
Natoms	20	21	21	21	21	22	24.0
MW	309.32	323.35	343.77	388.22	388.22	339.35	331.347
nON	6	6	6	6	6	7	6
nOHNH	0	0	0	0	0	0	2
Nviolations	0	0	0	0	0	0	0
Nrotb	2	2	2	2	2	3	3
Volume	226.49	243.05	240.03	244.37	244.37	252.03	285.460
Bioactivity score	**Components**						
	1	**2**	**3**	**4**	**5**	**6**	**STANDARD**
GPCR ligand	-0.22	-0.23	-0.18	-0.30	-0.31	-0.20	0.12
Ion channel modulator	-0.20	-0.28	-0.20	-0.28	-0.32	-0.27	-0.04
Kinase inhibitor	-0.29	-0.31	-0.27	-0.30	-0.34	-0.26	-0.07
Nuclear receptor ligand	-0.61	-0.57	-0.57	-0.67	-0.71	-0.50	-0.19
Protease inhibitor	-0.31	-0.33	-0.31	-0.40	-0.39	-0.28	-0.21
Enzyme inhibitor	**0.06**	**-0.01**	**0.02**	**-0.02**	**-0.03**	**0.00**	**0.28**

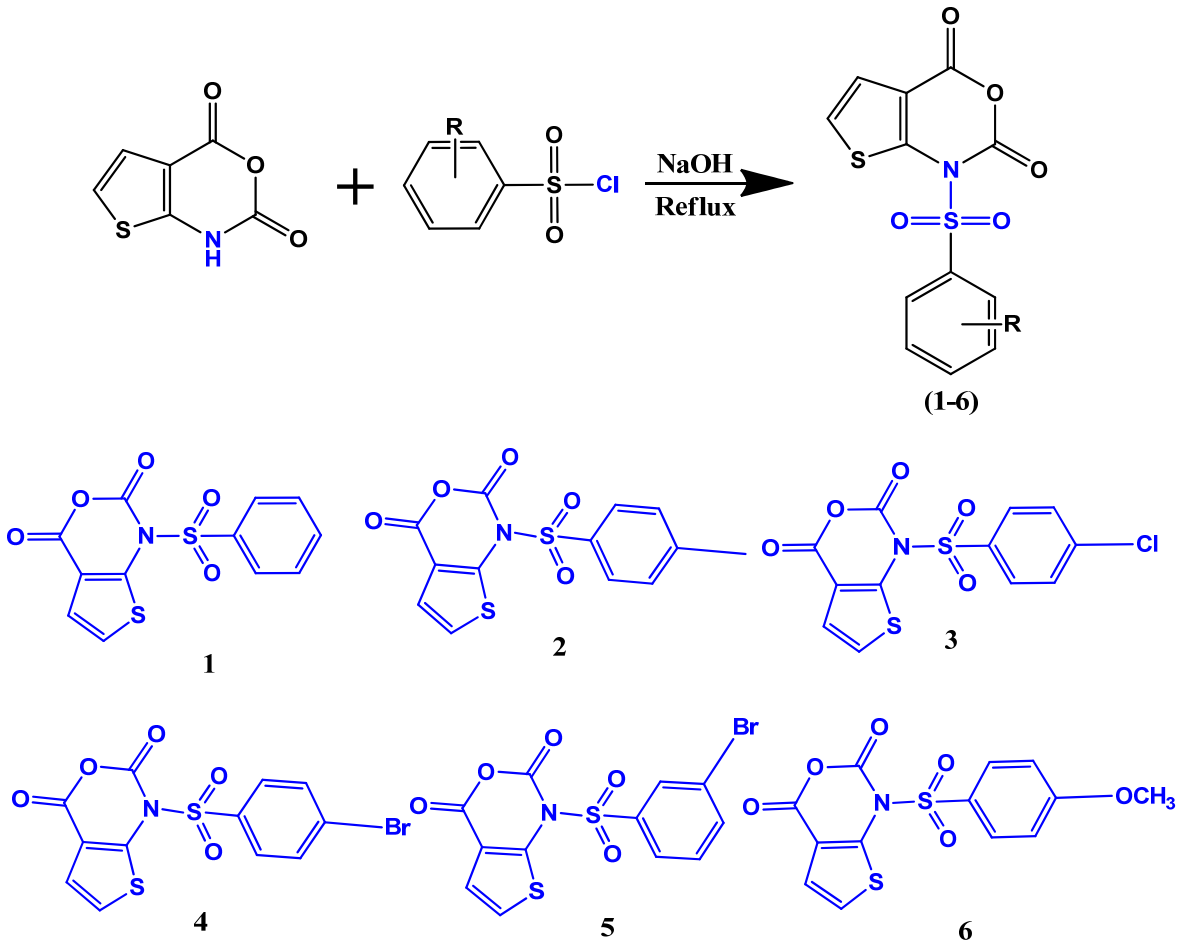


Figure-1: The schematic route followed for the synthesis of compounds 1-6, with their possible structures.

All the prepared components (1-6) were the assessed for structural analyses by the help of spectroscopic studies like FT-IR, NMR, MASS Spectroscopy and Elemental analysis the detailed results are available in experimental part. The Disappearance of the bands in FTIR spectra at or around 3000 cm^{-1} due to the NH functional group in the precursor molecule and the simultaneous observation for the new characteristic bands in the range 1562-1582 and 1030-1052 cm^{-1} due to SO_2 (Asymm.) and SO_2 (Symm.) functional groups strongly confirmed the formation of the compounds (1-6). Some other FT-IR bands were also observed in the range 1700-1760 and 1680-1705 cm^{-1} due to the presence of C=O groups in the structure that also supports the formation. For further justification regarding the synthesis of compounds (1-6) the ^{1}H-NMR spectroscopy were applied. The disappearance of the singlet at or around 11.000 ppm in ^{1}H-NMR spectra due to the presence of NH proton in the precursor molecule and the appearance of additional doublets and multiplets due to the protons of substituted phenyl nucleus. All the compounds were treated for antibacterial evaluation against S. Aureus, S. epidermidis, P. Mirabilis and E. coli. The zone of inhibition, the Minimum Inhibitory Concentration and the area oh Inhibition/µg of all the components (1-6) and the standard drug Ciprofloxacin are presented in **Table-2 and Figure-2.** Results portrayed that the experimental results strongly supported the computational screening and also states that all the components were possessing significant antibacterial activity. Followed by the antibacterial screening all components (1-6) and the standard drug Ciprofloxacin were then treated for MTT assay to test the percent viability of the cells using HepG2 Cells and the results revealed that the compounds are less cytotoxic and have the percent viability of cells >75 % up to the 100mmol/L, **Figure-3**.

Table-2: Representing the zone of inhibition and the minimum inhibitory concentration of the tested compounds and the standard drug Ciprofloxacin.

S. No.	Effect of compounds on microorganism			
	Gram positive		Gram negative	
	S. aureus	*S. epidermidis*	*E. coli*	*P. mirabilis*
1	22.18±0.22	22.11±0.16	23.56±0.26	21.32±0.10
2	21.12±0.24	21.44±0.14	23.48±0.20	21.70±0.26
3	21.96±0.20	22.58±0.18	23.80±0.18	21.44±0.50
4	21.06±0.32	21.22±0.24	23.14±0.14	21.22±0.44
5	21.30±0.26	21.74±0.30	23.52±0.36	21.12±0.36
6	21.89±0.36	23.10±0.34	23.92±0.42	23.08±0.40
Ciprofloxacin	21.39±0.21	22.87±0.37	23.69±0.81	22.34±0.21
S. No.	Minimum Inhibitory Concentration (µg/ml)			
	Gram positive		Gram negative	
	S. aureus	*S. epidermidis*	*E. coli*	*P. mirabilis*
1	6.25	3.125	6.25	12.5
2	6.25	3.125	6.25	12.5
3	6.25	3.125	6.25	12.5
4	6.25	3.125	6.25	12.5
5	6.25	3.125	6.25	12.5
6	6.25	3.125	6.25	12.5
Ciprofloxacin	6.25	3.125	6.25	12.5

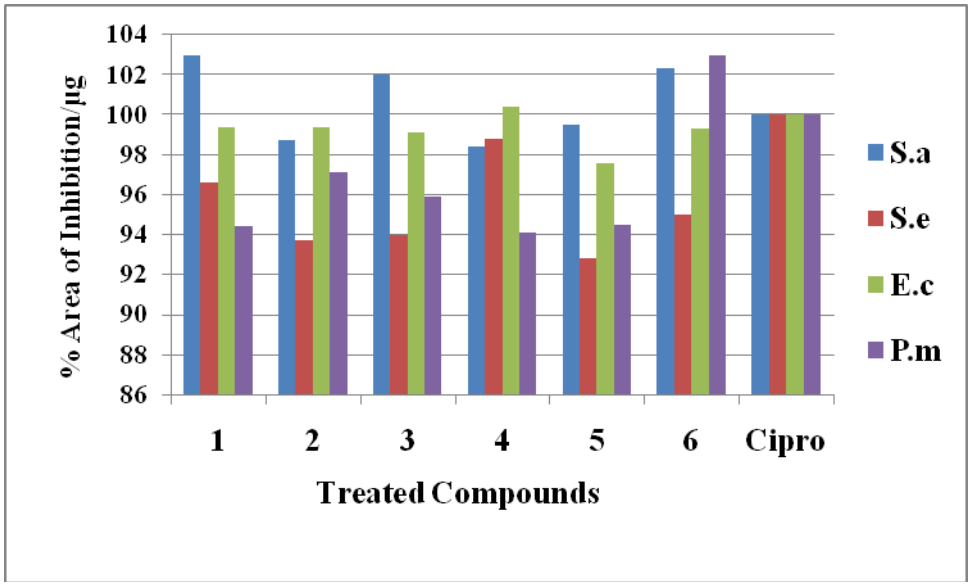


Figure-2: Representing the percent area of inhibition per microgram of the compounds

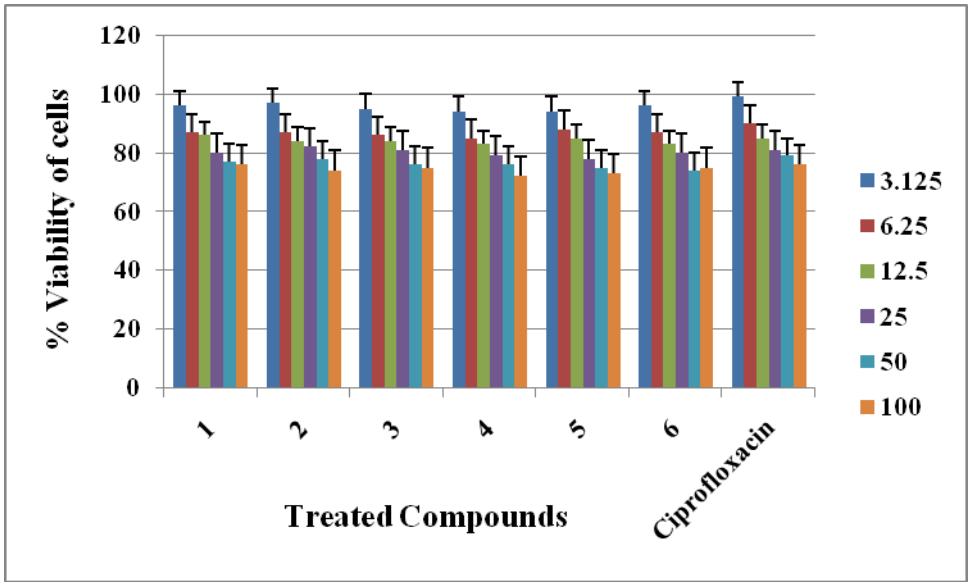


Figure-3: Representing the percent viability of cells for all the tested compounds 1-6, against HepG2 Cell lines.

4. Conclusion:

A new library of 1-(Substituted-phenylsulfonyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione), was designed and subjected for the calculation of physicochemical properties and the drug likeness by the online available software. Only the compounds (1-6) with the bioactivity score in the zone for active or very near to the active were followed for the synthesis, characterization, antibacterial therapeutic effect and the percent viability of the cells. The findings were in recommendation of the computational results and it was concluded that all the prepared compounds were found to possess the significant activity with reduced toxicity.

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