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Synthesis, characterization and pharmacological evaluation of certain sulfonamide containing heterocyclic motifs

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ABSTRACT

Introduction: Heterocycles containing nitrogen, oxygen and sulphur have diverse and exceptional therapeutical and industrial significance. Particularly sulfonamides containing pyrrolidine and thiophene moieties constitute an important class of drugs and display a variety of pharmacological activities.

Aim: To design, synthesize and characterize substituted sulfonamides and evaluate their *in vitro* antimicrobial activity and *in silico* HMG-CoA reductase inhibitory activity.

Material and methods: The synthetic investigations have been well supported by elemental analysis data and standard modern spectroscopic techniques. The compounds were evaluated for their *in vitro* antimicrobial activity against *Staphylococcus aureus* NCCS 2079, *Bacillus cereus* NCCS 2106, *Escherichia coli* NCCS 2065, *Aspergillus niger* NCCS 1196 and *Candida albicans* NCCS 2106. *In silico* studies were done against 3VKK (PDB Id). Pharmacophore mapping studies were reported to analyze the important pharmacophore features and to predict the quantitative structure-activity relationship.

Results and discussion: The antibacterial activity data revealed that compounds of 8 series were more active than the compounds of 7 series followed by compounds of series 6. *In silico* studies revealed that HMG-CoA reductase inhibitory activity of these drugs is of the order 'a > b > c > d > e > f'.

Conclusions: Antibacterial activity studies indicate that nitro and halo substituted sulfonamides of each series were more active than the other members. A detailed analysis from virtual screening data led to the conclusion that all these compounds are potential HMG-CoA

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reductase inhibitors and within each series, nitro substituted sulfonamide has demonstrated least drug score.

1. Introduction

An exhaustive range of heterocycles containing nitrogen, oxygen and sulphur are currently in use due to their diverse therapeutical and industrial significance. Particularly sulfonamides containing these heterocyclic moieties namely pyrrolidine[1–5] and thiophene[6–10] constitute an important class of drugs and display a variety of activities including antibacterial, antifungal, anticancer, antitumor, anti HIV, anti viral, anti inflammatory, enzyme inhibitory, etc.

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase catalyzes the biosynthesis of cholesterol. Cholesterol synthesis has been the subject of recent research as high levels of cholesterol or hypercholesterolemia is an important factor for the development of cardiovascular diseases (coronary heart disease). HMG-CoA reductase inhibitors are effective and safe drugs and are prescribed for the treatment of hypercholesterolemia i.e. to block the pathway for the synthesis of cholesterol in the liver.[11–14] The therapy by HMG-CoA reductase inhibitors has an added advantage of targeting coronary risks.[15,16] Compared to other HMG-CoA reductase inhibitors, it has been reported that sulfonamides possess advantageous pharmacological properties, hydrophilicity and highest bonding interactions with HMG-CoA reductase, resulting in the most potent inhibition of cholesterol synthesis.[17–19]

2. Aim

This article demonstrates the antimicrobial activity and significant HMG-CoA reductase inhibitory activity of sulfonamides containing pyrrolidine and thiophene moieties. To design, synthesize and characterize substituted sulfonamides and evaluate their *in vitro* antimicrobial activity and *in silico* HMG-CoA reductase inhibitory activity.

3. Material and methods

All chemicals and reagents were procured from Merck India Ltd. Melting points were determined using X-6 digital display binocular microscope. Infrared spectra were taken on a nicolet nexus 470 FT-IR spectrometer using smear KBr crystal or KBr plate. NMR spectra were recorded on a Bruker Avance (300 MHz) spectrometer. The standard bacterial and fungal stains were procured from National Centre for Cell Science, Pune, India. The antimicrobial activity was expressed in terms of minimum inhibitory concentration (MIC). MIC was found out by broth dilution method.[20] Docking was carried out using GOLD (Genetic Optimization of Ligand Docking) software. The compounds were docked to the active site of the HMG-CoA reductase. The crystal structure of the protein was taken from the Protein Data Bank (PDB Id: 3VKK). The parameters used for genetic algorithm (GA) were: population size (100), selection pressure (1.1), number of operations (10 000), number of island (1) and niche size (2). Operator parameters for crossover, mutation and migration were set to 100, 100 and 10, respectively.

3.1. *Synthesis of title compounds*

The sequence of reactions corresponding to the synthesis of title compounds is shown in Fig. 1.

3.1.1. *Synthesis of ethyl 2-((3S,4S)-3,4-diazidopyrrolidin-1-yl) acetate (2)*[21]

A mixture of ethyl 2-((3R,4R)-3,4-bis((methylsulphonyl)oxy) pyrrolidin-1-yl)acetate (**1**) (4.3 g, 1.22 mmol) and aqueous sodium azide (3.43 g, 7.35 mmol) in DMF (40 mL) was heated to 120°C for 18 hours. After completion of reaction as indicated by TLC, the reaction mixture was poured onto crushed ice and extracted with ethylacetate. The ethylacetate extract was subjected to flash chromatography to give **2** (yield: 68%; melting point: 176°C–177°C).

3.1.2. *Synthesis of ethyl 2-((3S,4S)-3,4-diaminopyrrolidin-1-yl)acetate (3)*[22]

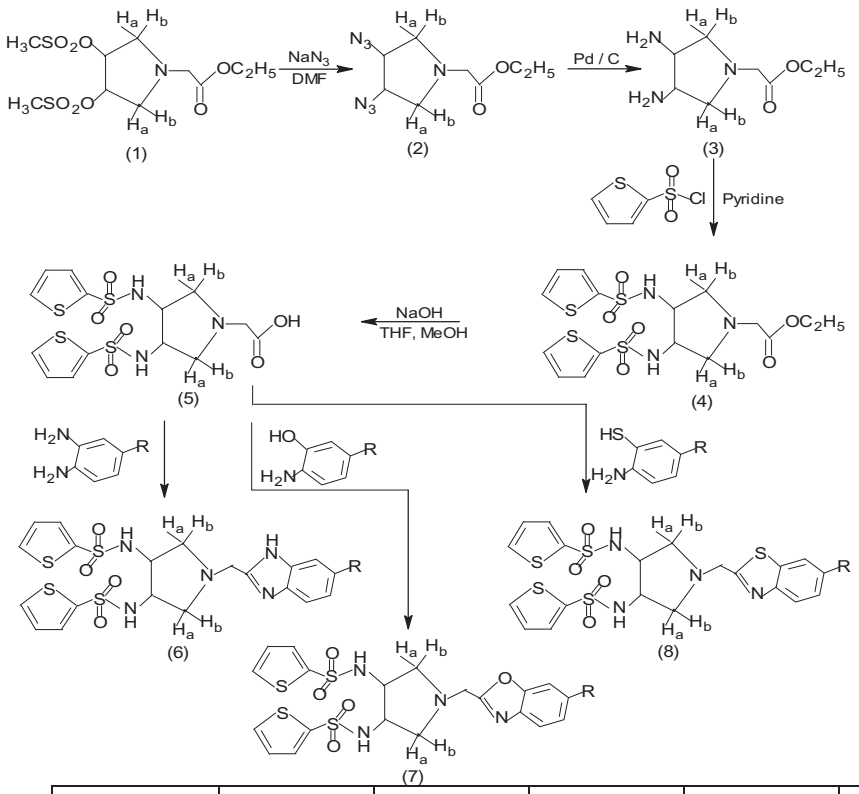
A mixture of ethyl 2-((3R,4R)-3,4-diazidopyrrolidin-1-yl)acetate (**2**) (2.39 g, 10 mM), 10% Pd/C (5 g) and methanol (20 mL) was hydrogenated for 10 hours in a pressure reactor. After completion of reaction, catalyst was filtered through celite and washed with methanol. Filtrate was concentrated under reduced pressure to get colorless solid (yield: 77%; melting point: 154°C–155°C).

3.1.3. *Synthesis of ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulphonamido)pyrrolidin-1-yl)acetate (4)*

A mixture of (**3**) (1.2 g, 25 mM) and thiophen-2-sulphonyl chloride (0.91 g, 5 mM) and 5 mL of pyridine was refluxed for 3 hours. The reaction mixture was poured into cold water (25 mL) and stirred well to crystallize the product. The solid so obtained was filtered and recrystallized from ethanol (yield: 82%; melting point: 184°C–185°C).

3.1.4. *Synthesis of [3-(1-Mercapto-prop-1-ene-1-sulfonylamino)-4-(thiophene-2-sulfonylamino)-pyrrolidin-1-yl]-acetic acid (5)*[23]

A solution of ester (4.79 g, 10 mM) in tetrahydrofuran, MeOH, and H_2O (1:1:1) and LiOH (9.6 g, 4 mM) or aqueous NaOH (2 N) were stirred at room temperature or refluxed for 4–16 hours.



Compound	a	b	c	d	e	f
-R	H	CH_3	OCH_3	Cl	Br	NO_2

Fig. 1 – Synthesis of sulfonamide derivatives.

The excess of solvent was evaporated under vacuum to give crude residue. The residue was washed with EtOAc, acidified with 1 N HCl to pH 2. The suspension obtained was filtered under vacuum. If solid is not obtained, the solution was extracted with two 100 mL portions of the EtOAc. The organic layer was collected, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to get crude product. This was purified by column chromatography (60–120 mesh-silica gel, eluent: 70% EtOAc-petroleum ether) to give acid compound (yield: 76%; melting point: 191°C–192°C).

3.1.5. *Synthesis of N,N′-((3S,4S)-1-((1H-benzo[d]imidazol-2-yl)methyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (**6a–f**)*

A mixture of [3-(1-Mercapto-prop-1-ene-1-sulfonylamino)-4-(thiophene-2-sulfonylamino)-pyrrolidin-1-yl]-acetic acid (**5**) (4.41 g, 10 mM), benzene-1,2-diamine (1.08 g, 10 mM) and 6 N HCl (15 mL) was boiled under reflux with constant stirring at 140°C for 1.5 hours. The mixture was neutralized with excess of $NaHCO_3$. The precipitate so collected was washed with water, dried in vacuum, and purified by flash chromatography (with chloroform). Similar procedure was adopted for the synthesis of other compounds of the series (**6a–f**).

3.1.6. *Synthesis of N,N′-((3S,4S)-1-(benzo[d]oxazol-2-ylmethyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (**7a–f**)*

A mixture of [3-(1-Mercapto-prop-1-ene-1-sulfonylamino)-4-(thiophene-2-sulfonylamino)-pyrrolidin-1-yl]-acetic acid (**5**) (4.41 g, 10 mM), 2-aminophenol (1.09 g, 10 mM) and polyphosphoric acid trimethylsilyl ester (15 mL) was heated under reflux with constant stirring at 100°C for 2.5 hours. The reaction mixture was added to dichloromethane (30 mL) and neutralized with aqueous 1 N NaOH (50 mL). The organic layer was separated and the aqueous solution was extracted with three 25 mL portions of CH_2Cl_2. The combined extracts were boiled and dried on Na_2SO_4, filtered and the solvent was removed with rotary evaporator. The residue was purified by flash chromatography (with chloroform). The procedure was adopted for the synthesis of other compounds of the series (**7a–f**) using appropriate reactants.

3.1.7. *Synthesis of N,N′-((3S,4S)-1-(benzo[d]thiazol-2-ylmethyl)pyrrolidine-3,4-diyl)bis(thiophene-2-sulfonamide) (**8a–f**)*

A mixture of [3-(1-Mercapto-prop-1-ene-1-sulfonylamino)-4-(thiophene-2-sulfonylamino)-pyrrolidin-1-yl]-acetic acid (**5**) (4.41 g, 10 mM) and 2-aminobenzenethiol (1.25 g, 10 mM) was

Table 1 – Antimicrobial activity of title compounds.

Compound	MIC, μg/mL				
	Antibacterial activity			Antifungal activity	
	Staphylococcus aureus NCCS 2079	*Bacillus cereus* NCCS 2106	*Escherichia coli* NCCS2065	*Aspergillus niger* NCCS 1196	*Candida albicans* NCCS 2106
6a	12.36	19.40	19.42	13.24	14.38
6b	13.62	27.90	19.40	16.28	15.26
6c	20.46	37.20	35.16	19.20	19.86
6d	9.26	11.36	16.28	8.06	9.80
6e	9.82	11.86	16.34	8.29	10.54
6f	2.98	6.40	7.96	5.46	4.82
7a	11.32	13.49	16.60	11.22	10.26
7b	11.84	19.36	17.54	13.58	15.38
7c	17.92	29.08	25.14	18.56	19.04
7d	5.86	9.82	14.08	9.26	9.12
7e	6.28	10.94	14.26	9.58	9.28
7f	2.46	5.80	7.90	3.26	4.80
8a	9.86	11.02	14.26	7.56	10.20
8b	11.63	18.22	18.44	13.44	14.58
8c	16.52	25.30	18.46	14.96	15.08
8d	4.86	7.94	9.28	4.28	5.28
8e	4.98	8.67	11.20	4.20	5.32
8f	2.22	3.56	5.29	3.10	4.26
Cefaclor	2	4	3	—	—
Ketoconazole	—	—	—	0.75	0.4

refluxed for 2 hours at 150°C in the presence of polyphosphoric acid trimethylsilyl ester (15 mL). The progress of the reaction was monitored by TLC using acetone and ethylacetate (6:4) as eluent. The reaction mixture was dissolved in dichloromethane and neutralized with aqueous NaOH (1 N). The organic layer was extracted with three 25 mL portions of dichloromethane. The combined extracts were boiled and dried over anhydrous Na_2SO_4, filtered and the solvent was removed with rotary evaporator. The crude solid (**8a**) was purified by column chromatography using chloroform as eluent. Similar procedure was adopted for the synthesis of other compounds of the series (**8b–f**).

4. Results

The critical intermediate compounds were characterized by elemental, IR spectral and ^{1}H NMR spectral data. In addition to elemental, IR spectral and ^{1}H NMR spectral analysis of all the title compounds, the model title compounds were analyzed by ^{13}C NMR spectral data. The elemental analysis data in each case was found to be very close to the theoretically calculated values. The formation compounds in each case were confirmed by the presence of characteristic peaks in the respective spectra. The compounds were *in vitro* screened for antimicrobial activity against certain bacteria and fungi. It can be seen from Table 1 that MIC of **6f**, **7f**, **8d**, **8e**, **8f** are very close to that of standards employed in the studies. The compounds were *in silico* screened for their HMG-CoA reductase inhibitory activity. The respective Gold fitness score indicative of their inhibition ability is given in Table 2.

The detailed pharmacophoric features indicative of hydrophobicity, oral bioavailability, solubility and toxicity are detailed in Table 3. The results indicate that the derivative ''a'' in each series of compounds has highest drug score.

Table 2 – Docking results of model compounds as indicted by GOLD.

Compound	Number of hydrogen bonds	Atoms involved in H bonding		Bond length (Å)	Fitness score
		Protein	Sulfonamide		
6f	5	H of Val 148	O35	2.365	48.074
		O of Val 148	H56	2.039	
		O of Val 148	H52	1.853	
		H of Gly 101	O26	2.163	
		H of Gly 101	O25	2.603	
7f	3	H of Lys 22	O35	2.308	53.698
		H of Arg 109	O7	2.283	
		H of Asp 111	O18	2.690	
8f	1	H of Arg 109	O26	2.365	48.252

Table 3 – Pharmacophoric features of title compounds.

Parameter	6a	6b	6c	6d	6e	6f	7a	7b	7c	7d	7e	7f	8a	8b	8c	8d	8e	8f
#miLogP	2.46	2.88	2.49	3.11	3.42	2.39	2.89	3.31	2.92	3.54	3.68	2.83	3.0	3.45	3.06	3.68	3.81	2.96
#TPSA	124.25	124.26	133.49	124.26	124.26	170.08	121.61	121.61	130.84	121.91	121.61	167.43	108.47	108.47	117.70	108.47	108.47	154.29
#GPCR ligand	0.18	0.15	0.14	0.19	0.11	0.05	0.04	0.00	−0.01	0.05	−0.09	−0.10	0.03	−0.02	−0.03	0.02	−0.06	−0.12
#Ion channel modulator	−0.11	−0.15	−0.17	−0.08	−0.13	−0.16	−0.32	−0.37	−0.39	−0.28	−0.37	−0.37	−0.29	−0.35	−0.35	−0.30	−0.39	−0.35
#Kinase inhibitor	−0.12	−0.14	−0.11	−0.13	−0.14	−0.20	−0.33	−0.38	−0.35	−0.38	−0.41	−0.43	−0.20	−0.24	−0.24	−0.28	−0.29	−0.29
#Nuclear receptor ligand	−0.36	−0.36	−0.33	−0.37	−0.42	−0.39	−0.31	−0.34	−0.29	−0.29	−0.44	−0.35	−0.53	−0.56	−0.48	−0.53	−0.64	−0.63
#Protease inhibitor	0.21	0.16	0.15	0.17	0.11	0.07	0.24	0.17	0.15	0.19	0.08	0.09	0.21	0.13	0.15	0.19	0.10	0.07
#Enzyme inhibitor	0.04	0	0.01	0.02	−0.02	−0.05	0.01	−0.04	−0.02	0.01	−0.66	−0.08	−0.01	−0.05	−0.04	−0.05	−0.07	−0.08
*Solubility	−2.33	−2.68	−2.35	−3.07	−3.16	−2.79	−2.97	−3.31	−2.98	−3.70	−3.80	−3.43	−3.10	−3.44	−3.12	−3.84	−3.93	−3.56
*Drug-likeness	5.3	4.52	5.79	6.01	3.85	−0.89	5.53	1.16	2.48	2.65	0.47	−4.24	5.96	4.44	5.7	5.93	3.76	−0.98
*Drug score	0.67	0.64	0.63	0.6	0.54	0.4	0.52	0.43	0.47	0.43	0.32	0.24	0.62	0.57	0.35	0.53	0.47	0.36
*Mutagenic	No	No	No	No	No	No	No	No	No	No	No	No	No	No	High risk	No	No	No
*Tumerogenic	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
*Irritant	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
*Reproductive effect	No	No	No	No	No	No				Medium risk			No	No	No	No	No	No

From Molinspiration Cheminformatics 2014.
* From openmolecules.org.

5. Discussion

The title compounds containing thiophene, oxazole and imidazole moieties were synthesized and characterized. The yield, melting point and characterization details were reported in each case. The compounds were characterized by elemental analysis, IR and NMR spectral data to confirm the formation of respective compounds.

5.1. *Antimicrobial activity*

The sulfonamide derivatives under study were screened for antibacterial activity and antifungal activity. The antimicrobial activity was expressed in terms of minimum inhibitory concentration (MIC). MIC was found out by broth dilution method.[20] The bacteria screened were *Staphylococcus aureus* NCCS 2079, *Bacillus cereus* NCCS 2106, *Escherichia coli* NCCS 2065 and fungi screened were *Aspergillus niger* NCCS 1196 and *Candida albicans* NCCS 2106. It is evident from Table 1 that the compounds of **8** series containing 6-substituted-1H-benzothiazole moiety have exhibited higher activity than the compounds of **7** series containing 6-substituted benzoxazole moiety followed by the compounds of **6** series containing 6-substituted 1H-benzoimidazole moiety. Further within each series, the order of antimicrobial activity observed was f > d > e > a > b > c. Compounds with electron withdrawing substituents showed greater antimicrobial activity than those with electron donating substituent groups. Similar observations were reported in the literature.[24,25]

In silico studies have potential use in the discovery and evaluation of novel molecules, predicting their affinity to the target, their ability for absorption, distribution, metabolism, excretion, toxicity, etc.[26] The HMG-CoA reductase inhibitory activity of sulfonamides was determined by docking studies. It is well known that hydrogen bonding plays crucial role in the structure and function of biological molecules, especially for inhibition in a complex. The inhibitory activity of the title compounds might be due to the formation of hydrogen bond with the enzyme backbone, thus stabilizing the binding between the title compound and the enzyme. The GOLD score fitness and bonding interactions of model compounds **6f**, **7f** and **8f** are given in the following Table 2 and Figs. 2–4.

Octanol-water partition coefficient is expressed in terms of milogP and is a measure of molecular hydrophobicity of the drug. Hydrophobicity affects drug absorption, bioavailability, hydrophobic drug–receptor interactions, metabolism of molecules, etc. All the values were found to be well within the accepted range.[27]

The drug-likeness score was obtained by utilizing open cheminformatics software and was analyzed to make a detailed pharmacological comparison of title compounds. Drug-likeness determines the extent to which a particular molecule is similar to the known drugs in terms of molecular properties and structural and pharmacophoric features. The results are shown in Table 3. The higher the score in each case, the higher is the probability of the molecule to be active. It can be seen from Table 3 that nitro derivative in each of the series 6 (−0.89), 7 (−4.24) and 8 (−0.98) has low drug score due to the comparatively high polar surface area[28] 170.08, 167.43 and

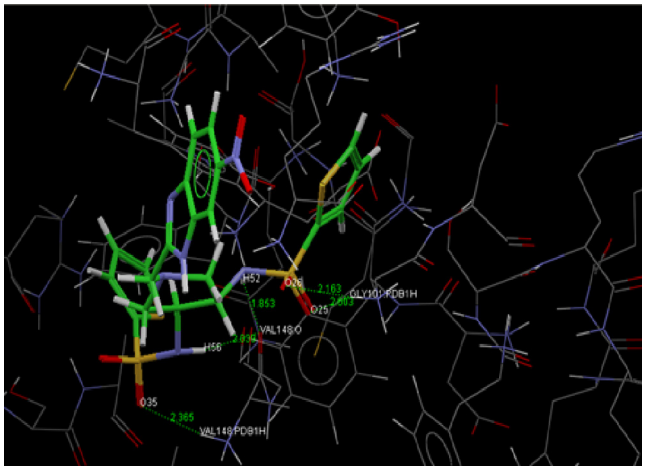


Fig. 2 – Docking result of *6f*.

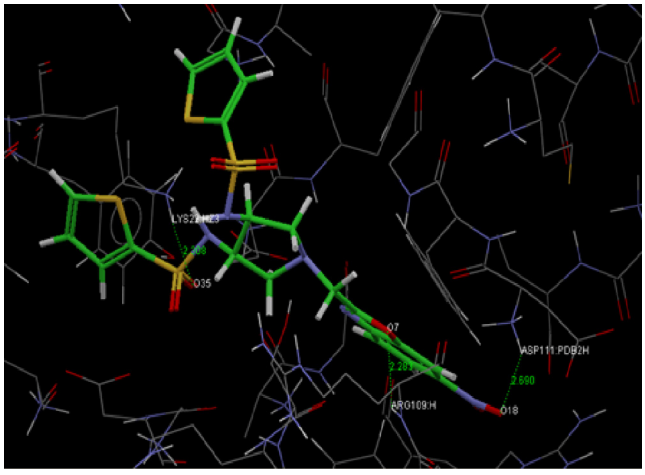


Fig. 3 – Docking result of *7f*.

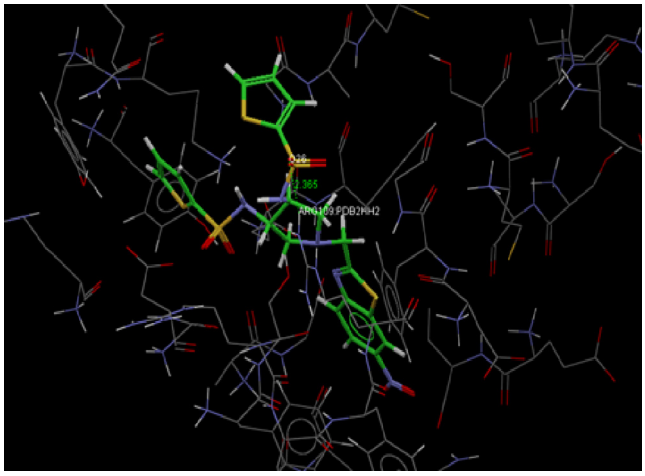


Fig. 4 – Docking result of *8f*.

154.29 respectively for **6f**, **7f** and **8f**. Polar surface area is very useful parameter in the prediction of transport properties of drugs.[29] The parameter provides very useful correlation with the human intestinal absorption,[30] Caco-2 monolayers permeability,[31,32] and blood-brain barrier penetration.[33]

The negative impact of a high polar surface area on intestinal absorption is well recognized and reported in the literature.[30,34] The aqueous solubility of a drug affects its absorption and distribution characteristics. Low solubility corresponds to bad absorption and usually a solubility value greater than −4 is preferred. Table 3 indicates that all the compounds under study have acceptable values of solubility. The least drug score of **8c** among the compounds of series **8** was due to the high mutagenic nature of 6-Methoxy benzothiazole fragment. The medium risk pertaining to reproductive effect was attributed to the presence of 1-(2-phenoxy-ethyl)-pyrrolidine moeity (attached to nitrogen of the thiophene sufonamides) in series 7 compounds. This has negative effect on the overall drug score. With these exceptions, the trend of overall drug activity as revealed by drug score was 'a > b > c > d > e > f'.

6. Conclusion

Series of pyrrolidine sulfonamide derivatives containing imidazole (series **6**), oxazole (series **7**) and thiophene moieties (series **8**) were synthesized and characterized. The compounds were *in vitro* screened against certain selected bacteria and fungi. It was reported that compounds of **8** series were more active than the compounds of 7 series followed by compounds of series **6**. Within each series, the observed order of activity was f > d > e > a > b > c. The results of *in silico* studies revealed that all these compounds are potential HMG-CoA reductase inhibitors and there is a necessity to conduct wet lab clinical trials to confirm the *in silico* predictions. The pharmacophore studies indicated that the general trend of drug activity of these compounds is 'a > b > c > d > e > f'.

Conflict of interest

None declared.

REFERENCES

1. Oh C-H, Cho H-W, Baek D, Cho J-H. Synthesis and antibacterial activity of 1β-methyl-2-(5-substituted thiazolo pyrrolidin-3-ylthio)carbapenem derivatives. *Eur J Med Chem*. 2002;37(9):743–754.
2. Qiu M, Chen Y, Cheng L, Chu Y, Song HY, Wu ZW. Pyrrolidine dithiocarbamate inhibits herpes simplex virus 1 and 2 replication and its activity may be mediated through dysregulation of the ubiquitin–proteasome system. *J Virol*. 2013;87(15):8675–8686.
3. Muhammad S, Amin B, Shah NA, et al. Antitumor antioxidant and antimicrobial studies of substituted pyridylguanidines. *Molecules*. 2013;18:10378–10396.
4. Kleanthous S, Borthwick AD, Brown D, et al. Structure and property based design of factor Xa inhibitors: pyrrolidin-2-ones with monoaryl P4 motifs. *Bioorg Med Chem Lett*. 2010;20(2):618–622.
5. Stefanie K, Matthias U, Wolfgang W, et al. Annelated pyrrolidin sulfonamides with oxadiazolone headgroup, processes for their preparation and their use as pharmaceuticals. US8329725 B2; 2012.

6. de Melo EB, Adriane da Silveira G, Ivone C. α- and β-glucosidase inhibitors: chemical structure and biological activity. *Tetrahedron*. 2006;62(44):10277–10302.
7. Egbertson MS, Cook JJ, Bednar B, et al. Non-peptide GPIIb/IIIa inhibitors. 20. Centrally constrained thienothiophene alpha-sulfonamides are potent, long acting in vivo inhibitors of platelet aggregation. *J Med Chem*. 1999;42:2409–2421.
8. Alsaid MS, El-Gazzar MG, Ghorab MM. Anticancer activity of novel thiophenes containing a biological active diphenylsulfone, diazepin, piperidine, oxazepine, acryladehyde and sulfonamide moieties. *Drug Res (Stuttg)*. 2013;63(5):263–269.
9. Alfred LW, John S, Yeh L-A, Matthew Robert R. Phenoxy thiophene sulfonamides and other compounds for use as inhibitors of bacterial glucuronidase. US20130345196 A1; 2013
10. Raju B, Chengde W, Rosario C, Ilya O, Fiona S, Chan MF. 2-Aryloxycarbonylthiophene-3-sulfonamides: highly potent and etA selective endothelin receptor antagonists. *Bioorg Med Chem Lett*. 1997;7(16):2093–2098.
11. Maggo S, Ashton JC. Effects of HMG-CoA reductase inhibitors on learning and memory in the guinea pig. *Eur J Pharmacol*. 2014;723:294–304.
12. Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences. *Clin Pharmacokinet*. 1997;32 (5):403–425.
13. Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. *Ann Pharmacother*. 1995;29(7–8): 743–759.
14. Harley CR, Gandhi S, Blasetto J, Heien H, Sasane R, Nelson SP. Low-density lipoprotein cholesterol (LDL-C) levels and LDL-C goal attainment among elderly patients treated with rosuvastatin compared with other statins in routine clinical practice. *Am J Geriatr Pharmacother*. 2007;5(3):185–194.
15. Akira E. The discovery and development of HMG-CoA reductase inhibitors. *J Lipid Res*. 1992;33:1569–1582.
16. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013. http://dx.doi.org/10.1002/14651858.CD004816.pub5.
17. Jones PH, Davidson MH, Stein EA, et al. Comparison of efficacy and safety of Rosuvastatin versus atorvastatin, simvastatin and pravastatin across doses. *Am J Cardiol*. 2003;92:152–160.
18. Olsson AG, McTaggart F, Raza A, Rosuvastatin:. A highly effective new HMG-CoA reductase inhibitor. *Cardiovasc Drug Rev*. 2002;20:303–328.
19. McTaggart F, Buckett L, Davidson R, et al. Preclinical and clinical pharmacology of Rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol*. 2001;87(5A):28B–32B.
20. Wiegand I, Hilpert K, Hancock RE. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. *Nat Protoc*. 2008;3:163–175.
21. Dirk K, Jürgen S, Christian R, et al. The coordination chemistry of cis-3,4-diaminopyrrolidine and related polyamines. *Eur J Inorg Chem*. 2001;10:2525–2542.
22. Hossein B, Seyed MS, Mina R, Mousa G. Synthesis of new disulfonamides from different substituted diamino pyridines. *Eclet Quim*. 2009;34:27–31.
23. Yildiz-Oren I, Ismail Y, Aki-Sener E, Nejat U. Synthesis and structure–activity relationships of new antimicrobial active multisubstituted benzazole derivatives. *Eur J Med Chem*. 2004;39:291–298.
24. Narayana Rao DV, Raghavendra Guru Prasad A, Spoorthy YN, Pariplavi M, Ravindranath LK. Synthesis, characterization and biological studies of substituted quinozoline-4-(3H)-one containing diazepine moiety. *Ann Pharm Fr*. 2014;72:51–58.
25. Sri Krishnanjaneyulu I, Saravanan G, Vamsi J, Supriya P, Udaya Bhavana J, Venkata Sunil Kumar M. Synthesis, characterization and antimicrobial activity of some novel benzimidazole derivatives. *J Adv Pharm Technol Res*. 2014;5:21–27.
26. Ekins S, Mestres J, Testa B. In silico pharmacology for drug discovery: applications to targets and beyond. *Br J Pharm*. 2007;152:21–37.
27. Shamsuzzaman. Ashraf M, Anis A, et al. Synthesis, evaluation and docking studies on steroidal pyrazolones as anticancer and antimicrobial agents. *Med Chem Res*. 2014;23:348–362.
28. Veber DF, Johnson SR, Cheng H-Y, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem*. 2002;4s:2615–2623.
29. Peter E, Bernhard R, Paul S. Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *J Med Chem*. 2000;43:3714–3717.
30. Clark DE. Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena, prediction of intestinal absorption. *J Pharm Sci*. 1999;88:807–814.
31. Palm K, Luthman K, Ungell AL, Strandlund G, Artursson P. Correlation of drug absorption with molecular surface properties. *J Pharm Sci*. 1996;85:32–39.
32. van Breemen RB, Li Y. Caco-2 cell permeability assays to measure drug absorption. *Expert Opin Drug Metab Toxicol*. 2005;1:175–185.
33. Shityakov S, Neuhaus W, Dandekar T, Förster C. Analysing molecular polar surface descriptors to predict blood–brain barrier permeation. *Int J Comput Biol Drug Des*. 2013;6:146–156.
34. Palm K, Stenberg P, Luthman K, Artursson P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharm Res*. 1997;14:568–571.