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Molecular modeling, synthesis, antibacterial and cytotoxicity evaluation of sulfonamide derivatives of benzimidazole, indazole, benzothiazole and thiazole

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ABSTRACT

A new series of heterocyclic molecules bearing sulfonamide linkage has been synthesized and screened for antibacterial activity. During antibacterial screening using broath dilution method, molecules were found to be highly active (MIC value 50–3.1 μg/mL) against different human pathogens, namely *B. cerus, S. aureus, E. coli* and *P. aeruginosa*, and most effective against *E. coli*. A great synergistic effect was observed during determination of FIC where molecules were used in combination with reference drugs chloramphenicol and sulfamethoxazole. The MIC value of the combination – varying concentration of test compounds and ½ MIC of reference drugs or varying concentration of reference drugs and ½ MIC of test compounds, was reduced up to $^{1}/_{4}$ or $^{1}/_{32}$ of the original value, indicating thereby the combination was 4–32 times more potent than the test molecule. The molecules also showed low degree of cytotoxicity against PBM, CEM and VERO cell lines. The results positively indicated towards the development of lead antibacterials using the combination approach.

1. Introduction

The incidence of bacterial infection has been one of the most multifaceted global health issues in past and is escalating at an alarming rate and thereby presenting an extraordinary challenge to health care professionals.[1,2] Furthermore, many drug-resistant pathogenic microbes have emerged in recent years because of increasing use or abuse of antibacterial agents as well as inaccurate diagnosis.[3] Antibiotic resistance, a concomitant problem, has become the limiting factor to the effectiveness of current drugs; therefore, there is an imperious need for the development of new treatment approaches with minimal adverse effects.[4,5] To combat drug-resistant microorganism, best scientific strategies include discovery and development of new, cost-effective and more potent pioneering antibacterial agents with minimum adverse effects.[6,7] Sulfonamide derivatives have been the focus of attention for the chemists and biologists for a long time due to their wide array of biological activities.[8–21] Some derivatives of this class are efficient for healing of urinary infections, arthritis and Alzheimer's disease.[22] In search of some new antibiotics, we have focused on sulfonamide nucleus, which has significance in the area of medicinal chemistry and drug development and used as a core substituent of antibacterial agents. In order to overcome the resistance and to reduce the adverse effects, continuous efforts are made to synthesize novel antibacterial compounds. In this regard, combinations of certain sulfonamides and other drug molecules are being used to develop novel formulations. The current work is an effort to develop certain drug regimens as effective antibacterial agents against drug resistant/mutant bacterial strains. The, sulfonamides still represent the drugs of first choice for the treatment of some conditions and diseases.

Sulfonamides suppress the bacterial growth by targeting the folate pathway enzyme dihydropteroate synthase (DHPS), which catalyzes the condensation of p-aminobenzoic acid (PABA) and 6-hydroxymethyl-7, 8-dihydropterin-pyrophosphate (DHPPP) into dihydropteroate (DHPt). Antimicrobial sulfonamide exert their effect by acting as competitive inhibitors of PABA and thus inhibit biosynthesis of dihydrofolic acid, which prevents the growth and reproduction of microorganisms.[23] Sulfamethoxazole is an available sulfa drug acting as PABA competitive inhibitor. Keeping in view the wide range of pharmaceutical activities of sulfa drugs and to explore the development of new generation sulfa drugs with improved therapeutic effect and longevity, we report herein the design consideration of compounds introducing certain modifications in the A and B unit of sulfur antibiotic sulfamethoxazole. 'A' unit is replaced by methyl (**a**); chloro (**b**) and nitro (**c**) group whereas 'B' unit is replaced by different heterocyclic rings as shown in Fig. 1. Thus, a

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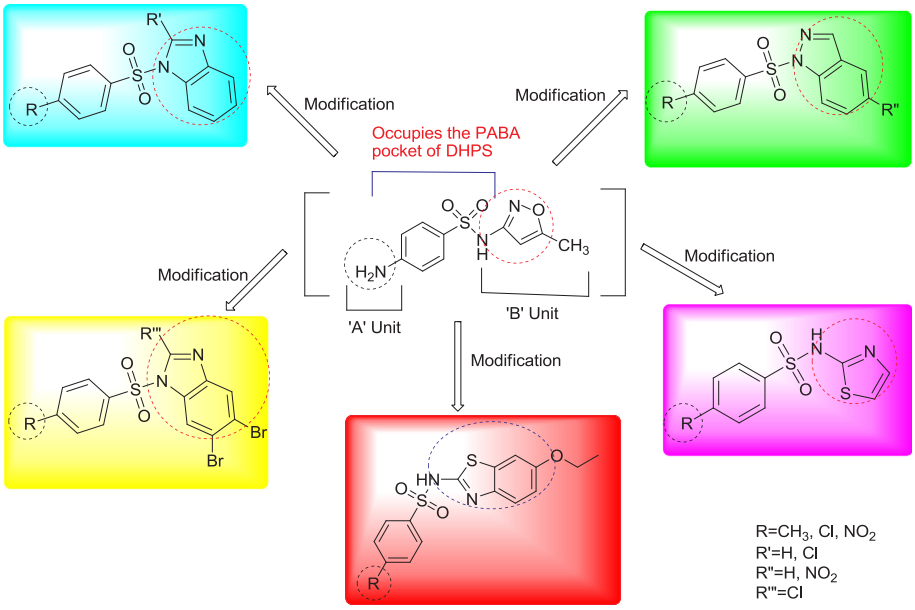

Fig. 1. Design of sulfonamide derivatives bearing sulfamethoxazole moiety as DHPS inhibitors.

series of *N*-heterocyclic sulfonamides **1–7** and derivatives bearing different heterocyclic rings of versatile biological importance was designed, synthesized and evaluated for antibacterial activity. The combined virtual screening, molecular docking and ADMET analysis on modified derivatives of sulfamethoxazole (**1-7a/b/c**) were used to elucidate the mechanism of mode of action.

2. Results and discussion

2.1. Physicochemical descriptors of sulfonamide derivatives

A good number of *N*-heterocyclic sulfonamide derivatives have been designed as probable antibacterial agents using *in silico* structure based approach. The physicochemical data of all compounds and standard antibacterial agents were calculated using online Molinspiration and ChemDraw software using Discovery Studio 2.5 software. To find out the drug-like characteristics, molecules were assessed using Lipinski's rule of five, which specifies that a probable drug molecule should have log P ≤ 5, molecular weight ≤500, hydrogen bond acceptors ≤10 and donor ≤5 and polar surface area ≤ 140 Å^2.[24] As rule of five compliance ensures the bioavailability, the molecules in the designed library were assumed to have better intestinal permeability. The presence of C-N, *N*-C, S═O and S—N dipoles allowed these molecules to function as H-bond acceptors as well as H-bond donors. The results summarized in Table 1 revealed that compounds possessed the drug-like characteristics, as standard antibiotics. The lipophilicity of compounds was reported in the form of log P and indicated that compounds should have no problem to passage through cell membrane. The intermediate TPSA values of all compounds predicted their good cell internalization, similar to standard drugs. Therefore, results revealed that none of the designed ligands violated the rule of five and may be developed as potent drug-like antibacterial agents.

Table 1
In silico Predicted Physicochemical Properties of all compounds (**1–7** and derivatives).

Compound	MW	H-A	H-D	Log P	TPSA	Rotatable bonds	ROF
	< 500	≤10	≤5	≤5	≤140	≤10	≤1
1a	272.33	4	0	2.58	51.97	2	0
1b	292.75	4	0	2.92	51.97	2	0
2a	306.77	4	0	3.23	51.97	2	0
2b	327.19	4	0	3.58	51.97	2	0
2c	337.74	7	0	2.83	97.79	3	0
3a	272.33	4	0	2.58	51.97	2	0
3b	292.75	4	0	2.92	51.97	2	0
3c	303.30	7	0	2.18	97.79	3	0
4a	317.33	7	0	2.48	97.79	3	0
4b	337.74	7	0	2.83	97.79	3	0
4c	348.30	10	0	2.08	143.62	4	0
5a	348.45	5	1	3.88	68.30	5	0
5b	368.87	5	1	4.14	68.30	5	0
5c	379.42	8	1	3.40	114.12	6	0
6a	254.34	4	1	2.21	59.06	3	0
6b	274.75	4	1	2.44	59.06	3	0
7a	464.57	4	0	4.76	51.97	2	1
7c	495.45	7	0	4.35	97.79	3	0
Sulfamethoxazole	253.28	6	3	1.36	98.22	3	0
Chloramphenicol	323.12	7	3	0.73	115.38	7	0
Cycloheximide	281.35	5	2	0.76	83.47	3	0

MW: Molecular weight; H-A: number of H bond acceptors; H-D: number of H bond donors; Log P: predicted octanol-water partition coefficient; TPSA: total polar surface area; ROF: Rule of five.

2.2. Chemistry

The synthetic strategy adopted for the preparation of compounds **1–7** and derivatives (**a/b/c**) is outlined in Scheme 1 and that of compound **7** in Scheme 2. Commercially available different *N*-heterocyclic compounds – **1** (1-*H*-benzimidazole), **2** (2-Cl-1-*H*- benzimidazole), **3** (1-*H*-indazole), **4** (5-NO_2-indazole), **5** (2-amino-6-ethoxy-benzothiazole), **6** (2-amino-thiazole), indigenously synthesized **7** (5,6-dibromo-2-Cl-benzimidazole) and aromatic sulfonyl chlorides, like p-toluene sulfonyl chloride **(a)**, 4-chloro-benzene-sulfonyl chloride **(b)**, 4-nitro-benzene-sulfonyl chloride **(c)** have been used as starting materials. The reaction condition was optimized using various bases and the best result – short reaction time and good yield, was obtained using DMAP as base in place of pyridine or TEA (Scheme 1).

Bromination of compound **2** in MeOH was performed using a solution of Br_2/MeOH as a brominating agent followed by addition of H_2O at room temperature to synthesize compound **7** (5,6-dibromo-2-chloro-1*H*-benzimidazole) (Scheme 2).[25] The compounds **1–7** and derivatives were synthesized by reacting the respective heterocyclic molecule and sulfonyl chloride. The products were purified by column chromatography and crystallization and characterized by ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis techniques.