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RESEARCH ARTICLE

Synthesis, Computational Studies, and Biological Evaluation of Sulphamethoxazole-Based Schiff Bases as Antimicrobial Agents

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Abstract: ***Background*:** Sulphamethoxazole-based Schiff-base compounds display potential antibacterial and antifungal activity. Sulphamethoxazole is considered to be a versatile pharmacophore that can be utilized for designing and developing numerous bioactive lead compounds. In this work, some new sulphamethoxazole-based Schiff base compounds were synthesized, which are expected to possess antimicrobial activity, making them potentially useful for treating microbial infections.

***Objective*:** Concerning issues of drug resistance in presently available drugs, this study aimed to synthesize new sulphamethoxazole-based Schiff bases and evaluate their antimicrobial activity.

***Methods*:** New sulphamethoxazole-based Schiff bases were synthesized by condensing sulphamethoxazole with various acetophenones in methanol in the presence of glacial acetic acid. The synthesized compounds were characterized using various techniques, such as TLC, melting point, IR, NMR, and mass analysis. The computational properties of the compounds were also assessed using online software programs, and the similarity of the target compounds was also calculated as compared to sulphamethoxazole and clotrimazole. The antimicrobial activity of the target compounds was tested against *Bacillus subtilis* (Gram-positive), *Escherichia coli* (Gram-negative), and *Candida albicans.*

***Results*:** The target compounds (3a-f) were successfully synthesized and characterized by spectroscopic and analytical methods. The results of computational properties, similarity, and antimicrobial activity against *B. subtilis*, *E. coli*, and *C. albicans* of new sulphamethoxazole-based Schiff bases showed significant antimicrobial potential.

***Conclusion*:** The synthesized new Schiff bases, particularly compound 3c, exhibited promising antimicrobial activity and good physicochemical properties as compared to standard drugs, indicating their potential for further development as antimicrobial agents.

Keywords: Schiff base, sulphamethoxazole, acetophenones, computational studies, biological evaluation, antimicrobial activity.

1. INTRODUCTION

A Schiff base is a type of imine with the general structure $R_2C=NR'$, which can be either a secondary aldehyde or a secondary ketamine, depending on its structure. It is formed through the reaction between a primary amine and a carbonyl compound and was initially reported by Hugo Schiff [1, 2]. Various strategies have been utilized in the synthesis of Schiff base derivatives. The conventional method involves condensing carbonyl derivatives and primary amines in methanol and glacial acetic acid medium [3, 4]. Due to their versatile chemical nature [5, 6], Schiff bases have gained attention in the development of bioactive lead compounds with various ranges of biological activities, including anti-inflammatory, analgesic, antioxidant, anti-microbial, anticonvulsant, antituberculosis, anticancer, and antidepressant activities [7-37]. In this study, we present the synthesis of computational studies of new sulphamethoxazole-based Schiff bases with the aim of evaluating their antimicrobial potential as therapeutic agents.

2. MATERIALS AND METHODS

2.1. Chemistry

Sulphamethoxazole was purchased from Sigma, and other chemicals, including acetophenone, 4-methoxyacetophenone, 4-chlroracetophenone, 4-bromoacetophenone, 3-nitroacetophenone, and 4-hydroxyacetophenone, were purchased from CDH. All chemicals were of analytical grade and purified prior to their use in the experiment. The melting points of the prepared derivatives were determined using the open capillary

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method and were uncorrected. IR spectra of the prepared derivatives were recorded on KBr discs using a Perkin Elmer RX1 spectrometer. The 1H-NMR spectra were recorded on a Bruker Advance Neo spectrophotometer at 500 MHz in DMSO (dimethyl sulfoxide) as the solvent, with TMS (tetramethyl silane) serving as the internal standard. The chemical shift values are reported in ppm (δ). The progress of the reactions was monitored using thin-layer chromatography (TLC) on silica gel G, and the spots were visualized using an iodine chamber. The target compounds underwent recrystallization, followed by drying, and were subsequently stored under a vacuum desiccator. The successful synthesis and structural characterization of the compounds were confirmed through melting point, TLC, IR, 1H-NMR, and mass spectrometry methods.

2.1.1. General procedure for the synthesis of Schiff bases (3a-f)

Equimolar amounts of sulphamethoxazole (**1)** (0.01mol) and appropriate acetophenone (**2)** (0.01 mol) were dissolved in 50 ml of methanol, and a few drops of glacial acetic acid were added in a 250 ml round bottom flask. The mixture was then refluxed for approximately 6 hrs. The resulting mixture was filtered, and the solvent was evaporated under reduced pressure. The resulting solid was washed with cold water, and the crude product was purified by recrystallization [38] from ethanol to yield the target compounds **(3a-f) (Scheme 1)**.

2.1.1.1. Synthesis of N-(5-methylisoxazol-3-yl)-4-((1-phenylethylidene) amino) benzene sulfonamide (3a)

IR (KBr)cm^{-1}: 3410 (N-H Str), 3060 (C-H Str Ar), 2927 (C-H Str Ali), 1632 (C=C Str Ar), 1308 (C=N Str), 1143 (C-N Str).^{1}H-NMR (500MHz, DMSO) δ: 10.97 (s, 1H, NH), 7.93 (d, 2H, J= 8.85 Hz), 7.56 (d, 2H, J= 8.8 Hz), 7.01 (d, 2H, J= 8.85 Hz), 6.66 (t, 1H, J= 8.75 Hz), 6.64 (t, 1H, J= 8.75 Hz), 6.14 (t, 1H, J= 8.75 Hz),6.04 (s, 1H, CH isoxazole), 2.50 (s, 3H. CH_3), 2.27 (s, 3H, CH_3isoxazole). MS (TOF MS ES^+): *m/z*: 355.29. Yield: 65.63% M.P: 145-148ºC, R_f: 0.64 (n-Hexane: Ethyl acetate; 2:1).

2.1.1.2. Synthesis of 4-((1-(4-methoxyphenyl) ethylidene) amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (3b)

IR (KBr) cm^{-1}: 3430 (N-H Str), 3055 (C-H Str Ar), 2930 (C-H Str Ali), 1634 (C=C Str Ar), 1308 (C=N Str), 1143 (C-N Str). ^{1}H-NMR (500MHz, DMSO) δ: 10.93 (1H, NH), 7.51 (d, 2H, J= 8.85 Hz), 7.50 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 8.85 Hz), 6.62 (t, 1H, J= 8.75 Hz), 6.61 (t, 1H, J= 8.75 Hz),6.06 (1H, CH isoxazole), 2.51 (s, 3H, OCH_3), 2.50 (3H, CH_3), 2.28 (3H, CH_3isoxazole). MS (TOF MS ES^+): *m/z*: 385.32. Yield: 50.38% M.P: 144-146ºC, R_f: 0.87 (n-Hexane: Ethyl acetate; 2:1).

2.1.1.3. Synthesis of 4-((1-(4-chlorophenyl) ethylidene) amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (3c)

IR (KBr)cm^{-1}: 3431 (N-H Str), 3060 (C-H Str Ar), 2900 (C-H Str Ali), 1635 (C=C Str Ar), 1308 (C=N Str), 1145 (C-N Str). ^{1}H-NMR (500MHz, DMSO) δ: 10.96 (1H, NH), 7.54 (d, 2H, J= 8.85 Hz), 7.52 (d, 2H, J= 8.8 Hz), 6.65 (d, 2H, J= 8.85 Hz), 6.63 (t, 1H, J= 8.75 Hz), 6.13 (t, 1H, J= 8.75 Hz),6.05 (1H, CH isoxazole), 2.50 (3H, CH_3), 2.27 (3H, CH_3isoxazole). MS (TOF MS ES^+): *m/z*: 389.74.Yield: 65.55% M.P: 135-138ºC, R_f: 0.72 (n-Hexane: Ethyl acetate; 2:1).

2.1.1.4. Synthesis of 4-((1-(4-bromophenyl) ethylidene) amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (3d)

IR (KBr)cm^{-1}: 3410 (N-H Str), 3060 (C-H Str Ar), 2925 (C-H Str Ali), 1631 (C=C Str Ar), 1308 (C=N Str), 1143 (C-N Str). ^{1}H-NMR (500MHz, DMSO) δ: 10.74 (1H, NH),7.83 (d, 2H, J= 8.85 Hz), 7.66 (d, 2H, J= 8.8 Hz), 7.57 (d, 2H, J= 8.85 Hz), 6.67 (t, 1H, J= 8.75 Hz), 6.13 (t, 1H, J= 8.75 Hz),6.05 (1H, CH isoxazole), 2.50 (3H, CH_3), 2.26 (3H, CH_3isoxazole). MS (TOF MS ES^+): *m/z*: 434.19. Yield: 90.16% M.P: 125-128ºC, R_f: 0.82 (n-Hexane: Ethyl acetate; 2:1).

2.1.1.5. Synthesis of 4-((1-(3-nitrophenyl) ethylidene) amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (3e)

IR (KBr)cm^{-1}: 3462 (N-H Str), 3064 (C-H Str Ar), 2928 (C-H Str Ali), 1633 (C=C Str Ar), 1437 (N-O Str), 1308 (C=N Str), 1143 (C-N Str). ^{1}H-NMR (500MHz, DMSO) δ: 10.93 (1H, NH), 8.57 (d, 2H, J= 8.85 Hz), 8.39 (d, 2H, J= 8.8 Hz), 8.37 (d, 2H, J= 8.85 Hz), 6.63 (t, 1H, J= 8.75 Hz), 6.11 (t, 1H, J= 8.75 Hz),6.03 (1H, CH isoxazole), 2.50 (3H, CH_3), 2.27 (3H, CH_3isoxazole). MS (TOF MS ES^+): *m/z*: 400.29. Yield: 80.0% M.P: 90-93ºC, R_f: 0.80 (n-Hexane: Ethyl acetate; 2:1).

2.1.1.6. Synthesis of 4-((1-(4-hydroxyphenyl) ethylidene) amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (3f)

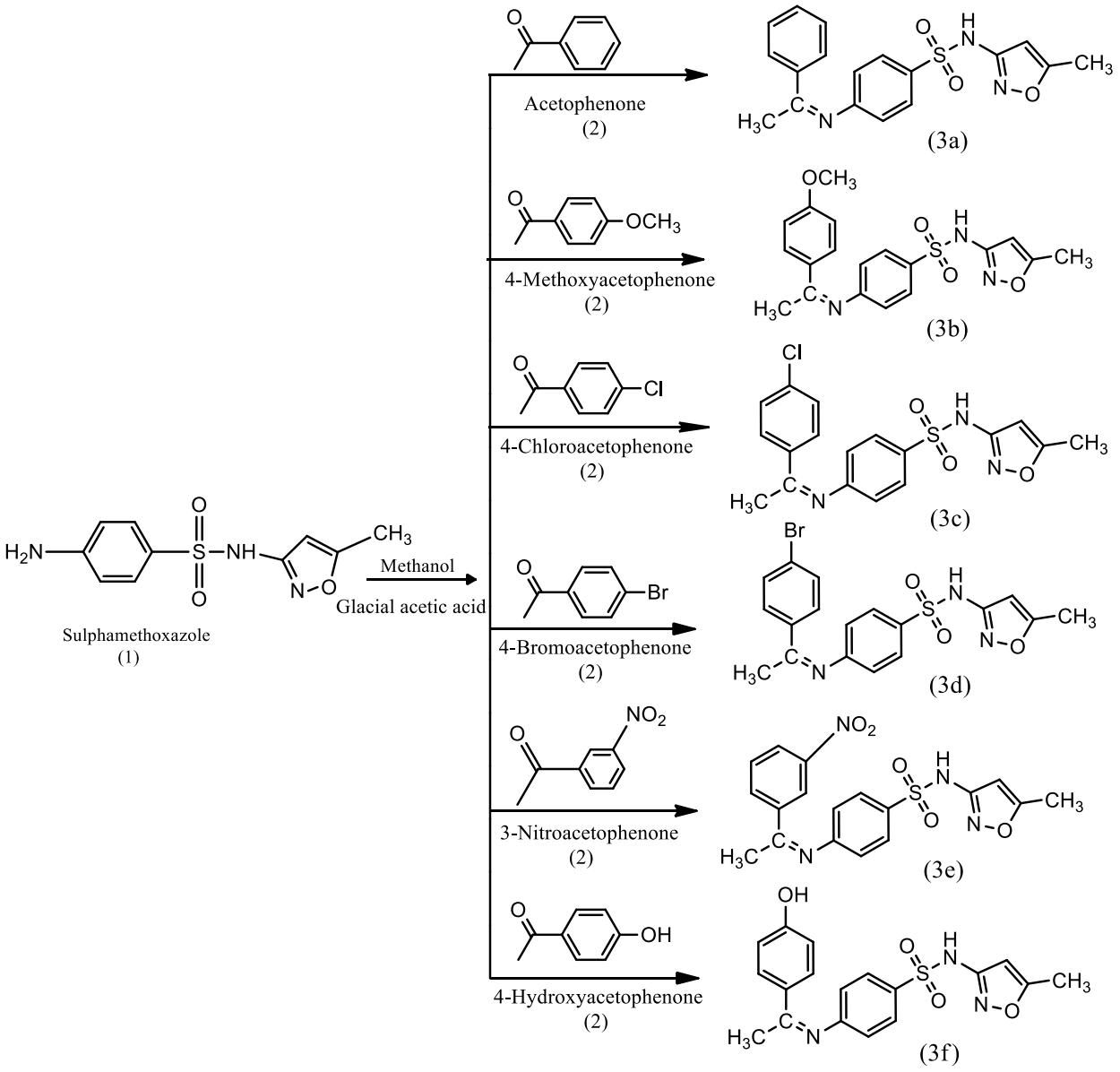
IR (KBr) cm^{-1}: 3461 (N-H Str), 3060 (C-H Str Ar), 2915 (C-H Str Ali), 1634 (C=C Str Ar), 1308 (C=N Str), 1159 (C-N Str). ^{1}H-NMR (500MHz, DMSO) δ: 10.93 (1H, NH), 7.84 (d, 2H, J= 8.85 Hz), 7.58 (d, 2H, J= 8.8 Hz), 6.89 (d, 2H, J= 8.85 Hz), 6.68 (t, 1H, J= 8.75 Hz), 6.66 (t, 1H, J= 8.75 Hz), 6.14 (s, 1H, OH), 6.02 (1H, CH isoxazole), 2.50 (3H, CH_3), 2.25 (3H, CH_3isoxazole). MS (TOF MS ES^+): *m/z*: 371.39. Yield: 92.0% M.P: 92-95ºC, R_f: 0.75 (n-Hexane: Ethyl acetate; 2:1).

2.2. Computational Studies

The physicochemical properties (MW, MR, CAA, CMA, CSEV, Ovality, LogP, number of rotatable bonds, H-bonds, GI absorption, synthetic accessibility, Abbott bioavailability score, Lipinski filter) of the target compounds (3a-f) and standard drugs (Sulphamethoxazole and Clotrimazole) were calculated using Chem 3D Ultra version 12.0 and SwissADME free software programs. The comparison of physicochemical characteristics was made, and the similarity of target compounds was measured with respect to standard drugs [39-51].

2.3. Antimicrobial Activity of Schiff Bases

The *in vitro* antimicrobial activity of the target compounds was tested against the bacterial and fungal species, *Bacillus subtilis*, *Escherichia coli*, and *Candida albicans* by agar disc diffusion method. Sulphamethoxazole and clotrimazole were used as standards for antibacterial and antifungal agents. The standard samples for antimicrobial activity were used at 100 µg/ml concentration in DMSO. The test organisms were grown on nutrient agar medium in petri plates. The discs were placed on the previously seeded plates and incubated at 37ºC. The diameter of the inhibition zone around each disc was measured after 24 h for bacterial and 72 h for fungal species. Antimicrobial activity was determined by measuring the diameter of the zone showing complete inhibition (mm) [52-61].



Scheme 1. Synthesis of target compounds (3a-f).

2.3.1. Statistical Analysis

The obtained values of antimicrobial activity were expressed as mean ± standard deviation. Statistical analysis was carried out by one-way ANOVA; a value of $P < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Synthesis of Schiff bases (3a-f)

The synthesis of Schiff bases with specific acetophenones in methanol as a solvent and catalyst (glacial acetic acid) resulted in six new sulphamethoxazole-based target compounds (3a-f) (Scheme 1). Target compounds were characterized by spectroscopic methods. The FTIR spectra of target compounds showed that the band of C=N at 1308 and the band of NH appeared in the prepared target compounds with different shifting from 3410 to 3462 cm^{-1}. The ^{1}H-NMR spectrum of the target compounds showed the following characteristic chemical shifts: the singlet signal in between δ = 2.25-2.28 ppm suggested the attribution of the protons of the CH_3 group, the singlet signal at δ = 6.02-6.06 ppm suggested the attribution of the proton of CH of the isoxazole ring, the signal at δ = 8.57 to 6.11 ppm suggested the attribution of the protons of two aromatic benzene rings, and the singlet signal at δ = 10.97 to 10.74 ppm suggested the attribution of the proton of the NH group. The mass spectra of target compounds showed the molecular ion peaks corresponding to the respective molecular masses.

3.2 Computational studies

3.2.1. Calculation of physicochemical properties

The physicochemical properties of target compounds were calculated and are given in Tables **1** and **2**.

Table 1. Physicochemical properties of target compounds (3a-f).

Cpd. Code	MW[a]	MR[b]	CAA[c]	CMA[d]	CSEV[e]	Ov[f]	Log P[g]
3a	355.41	97.63	594.54	308.65	262.60	1.5563	3.10
3b	385.44	104.88	641.30	334.96	285.74	1.5966	2.97
3c	389.86	102.24	631.59	397.99	281.21	1.5801	3.66
3d	434.31	105.32	627.73	328.85	282.71	1.5786	3.93
3e	400.41	105.91	638.63	335.62	291.86	1.5773	2.37
3f	371.41	99.45	562.88	299.19	261.13	1.5143	2.71
Clotrimazole	344.84	102.07	540.04	284.91	270.20	1.4096	5.19
Sulphamethox-azole	253.28	64.83	446.49	219.81	181.31	1.4189	0.86

Abbreviations: MW[a] = Molecular Weight, MR[b] = Molar Refractivity, CAA[c] = Connolly Accessible Area, CMA[d] = Connolly Molecular Area, CSEV[e] = Connolly Solvent Excluded Volume, Ov[f] = Ovality, Log P[g] = Log of the partition coefficient.

Table 2. Physicochemical properties of target compounds (3a-f).

Cpd. Code	Number of Rotatable Bonds	Number of H-bond Acceptors	Number of H-bond Donors	GI Absorption	Synthetic Accessibility	Abbott Bioavailability Score	Lipinski Filter
3a	5	5	1	High	3.31	0.55	Yes; 0 violation
3b	6	6	1	High	3.33	0.55	Yes; 0 violation
3c	5	5	1	High	3.29	0.55	Yes; 0 violation
3d	5	5	1	High	3.33	0.55	Yes; 0 violation
3e	6	7	1	Low	3.46	0.55	Yes; 0 violation
3f	5	6	2	High	3.26	0.55	Yes; 0 violation
Cl*	4	1	0	High	2.25	0.55	Yes; 1 violation: MLOGP>4.15
Sul*	3	4	2	High	2.73	0.55	Yes; 0 violation

Abbreviations: Cl*; Clotrimazole: Sul*; Sulphamethoxazole.

Target compounds (3a-f) demonstrated lipophilicity in between ranges of standard drugs, indicating their ability to penetrate the lipophilic cell membrane. Molecular size is a significant factor in determining both the physicochemical and biological properties of compounds, as they are often size-dependent. Various methods can be employed to measure molecular size, such as calculating molecular weight from the molecular formula or counting the number of atoms in the molecule. The permeability of compounds is usually influenced by their molecular size. Most drugs commercially available have molecular weights ranging from 200 to 600 Daltons. The molecular weight of the target compounds falls within the range of the standard drugs. Molar refractivity (MR) is a size descriptor that is related to the molecular weight and polarizability of molecules. Molar refractivity is calculated as the ratio of the liquid density and is also influenced by the refractive index of the liquid. In this study, we used molar refractivity as a physicochemical property to evaluate the target compounds and standard drugs, which can provide valuable information for drug design and optimization [62]. Ovality, which measures the ratio of the surface area of a molecule to the surface area of a sphere with the same volume, was calculated as a size descriptor. The results showed that the ovality values of the target compounds were within the range observed for the standard drugs. The physicochemical properties of the test compounds, including CAA, CMA, CSEV, number of rotatable bonds, number of hydrogen bond acceptors, number of hydrogen bond donors, GI absorption, Synthetic Accessibility (SA) score, Abbott bioavailability, and Lipinski rule of five criteria, were evaluated and compared to those of standard drugs [63-75]. The values obtained for these descriptors were found to be within the range observed for the standard drugs.

3.2.2. Similarity Calculation

A comparison of physicochemical characteristics was made, and the similarity of target compounds (3a-f) with respect to standard drugs was calculated using six physicochemical properties. Firstly, the distance (d_i) of a particular target compound (j) to the drug molecule, *e.g.*, sulphamethoxazole and clotrimazole, was calculated by the following formula:

$$di^2 = \sum_{j=1}^{n} \frac{\left(\frac{1 - X_{i,j}}{X_{i,std}}\right)^2}{n}$$

Where Xi.j represents the value of molecular parameter 'i' for compound 'j', and Xi,std is the value of the same molecular parameter for the standard drugs, *e.g*., sulphamethoxazole and clotrimazole. Then, the similarity between compound 'j' and the standard drug was calculated using the following equation:

Similarity (%) = (1 - R) × 100, where R = $\sqrt{d^2}$, representing the quadratic mean (root mean square) and indicating a measure of central tendency. Among the compounds analyzed, (3a) and (3f) showed the highest structural similarity to both sulphamethoxazole and clotrimazole, as detailed in Table **3**.

Table 3. Similarity of the target compounds (3a-f) with respect to the standard drugs.

Cpd.Code	Similarity[a,b](in%) to Sulphamethoxazole	Similarity[a,b](in%) to Clotrimazole
3a	61.70	92.84
3b	51.07	87.56
3c	46.09	81.27
3d	48.31	85.58
3e	49.00	85.00
3f	60.86	94.81

Note: a (1 - R) · 100, where R= quadratic mean (root mean square mean). [b]Calcd. from physicochemical properties: molecular weight; molar refractivity, Connolly solvent accessible surface area; Connolly molecular surface area; Connolly solvent excluded volume; ovality.

3.3. Antimicrobial Activity for Target Compounds (3a-f)

The antimicrobial activity of the target compounds (3a-f) against *Bacillus subtilis*, *Escherichia coli*, and *Candida albicans* was compared to standard drugs sulphamethoxazole and clotrimazole. The results of antimicrobial activity are given in Table **4**.

Table 4. The Antimicrobial Activity of target compounds (3a-f).

Cpd.Code	Zone of Inhibition (mm) Against *B. Subtilis*	Zone of Inhibition (mm) Against *E. Coli*	Zone of Inhibition (mm) Against *C. Albicans*
3a	20 ±0.00	21±0.03	20±0.01
3b	21 ±0.04	22±0.05	20±0.02
3c	23±0.04	25±0.02	22±0.64
3d	22±0.08	24±0.01	21±0.04
3e	21±0.05	22±0.08	19±0.04
3f	19±0.03	20±0.04	18±0.08
Sulphamethoxazole	26±0.00	29±0.00	-
Clotrimazole	-	-	24±0.02

The compound with a 4-chloro (3c) exhibited the highest activity against all tested microorganisms, with inhibition zones measuring 23 mm for *B. subtilis* and 25 mm for *E. coli*, as compared to 26 and 29 mm of sulphamethoxazole, respectively. A 22 mm zone of inhibition was observed for *C. albicans* compared to 24 mm of clotrimazole. However, other compounds, such as 3a, 3b, 3d, 3e, and 3f, demonstrated moderate antimicrobial activity as compared with standard drugs. The antimicrobial results revealed that the synthesized target compounds exerted a stronger inhibitory effect on these microorganisms compared to standard drugs, which may be due to the presence of imine or azomethine group of Schiff base containing the basic skeleton of sulphamethoxazole in their structure. Additionally, the extent of inhibition varied depending on the specific substitution within the Schiff bases.

CONCLUSION

In the present work, we synthesized six new sulphamethoxazole-based Schiff bases together with their predictions of computational properties and antimicrobial activity. The structures of the target compounds (3a-f) were determined using spectroscopic techniques (FTIR, ^{1}H NMR, and Mass spectra). The physicochemical properties of the target compounds were found to be as good as standard drugs and significantly obeyed Lipinski's rule of 5. The target compounds showed good similarity (46.09 - 94.81%) with respect to standard drugs. The target compounds were evaluated for antimicrobial activity against *B. subtilis*, *E. coli*, and *Candida albicans.* The results of the study revealed that Schiff bases with a 4-chloro group (**3c**) demonstrated the highest antibacterial potency against *B. subtilis*, *E. coli*, and *C. albicans* due to the presence of an electron-withdrawing group, indicating their potential for further development as antimicrobial agents.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

This research did not involve any human or animal subjects.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article are available within the article.

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CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

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Declared none.

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