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Original Research Article

In silico studies-assisted design, synthesis, and discovery of biologically active isatin derivatives

Mohd Imran*, Abida Ash Mohd, Naira Nayeem, Saleh Ibrahim Alaqel
Department of Pharmaceutical Chemistry, College of Pharmacy, Northern Border University, Rafha 91911, Saudi Arabia

For correspondence:* ***Email:* *mohammad.Baks@nbu.edu.sa; imran.pchem@gmail.com;* ***Tel:*** *+966-599577945*

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Abstract

Purpose: *To design isatin-based compounds, carry out in silico studies, and identify the biologically active isatin derivatives.*
Methods: *Fourteen isatin-based compounds (A to N) were designed using ChemDraw. In addition, in silico studies (molecular docking, prediction of drug likeliness, gastrointestinal absorption, log P, and toxicity) of the designed compounds were compared to ciprofloxacin. Based on the results of the in silico studies, three compounds (G, H, and L) were selected for synthesis, and the chemical structures of G, H, and L were elucidated via spectral analysis. The antimicrobial activity and DNA gyrase inhibitory activity of G, H, and L were evaluated and compared to those of ciprofloxacin.*
Results: *The docking scores of compounds G, H, and L (-5.90, -5.72, and -5.98 kcal/mol, respectively) were comparatively better than that of ciprofloxacin (-5.41 kcal/mol). In silico studies data also revealed the non-hepatotoxic nature, drug-likeliness properties, and good gastrointestinal absorption for G, H, L, and ciprofloxacin. The in vitro antimicrobial activity ($p < 0.05$) and DNA gyrase inhibitory activity of G (102.33 %, $p < 0.05$), H (104.43 %, $p < 0.05$), and L (106.77 %, $p < 0.05$) were better than those of ciprofloxacin (100.0 %, $p < 0.05$).*
Conclusion: *Compounds G, H, and L are promising DNA gyrase inhibitors. These compounds should be explored further to determine their broad-spectrum antimicrobial potency, safety, and efficacy.*

Keywords: *Isatin, Molecular docking, Synthesis, Antimicrobial activity, DNA gyrase inhibitor*

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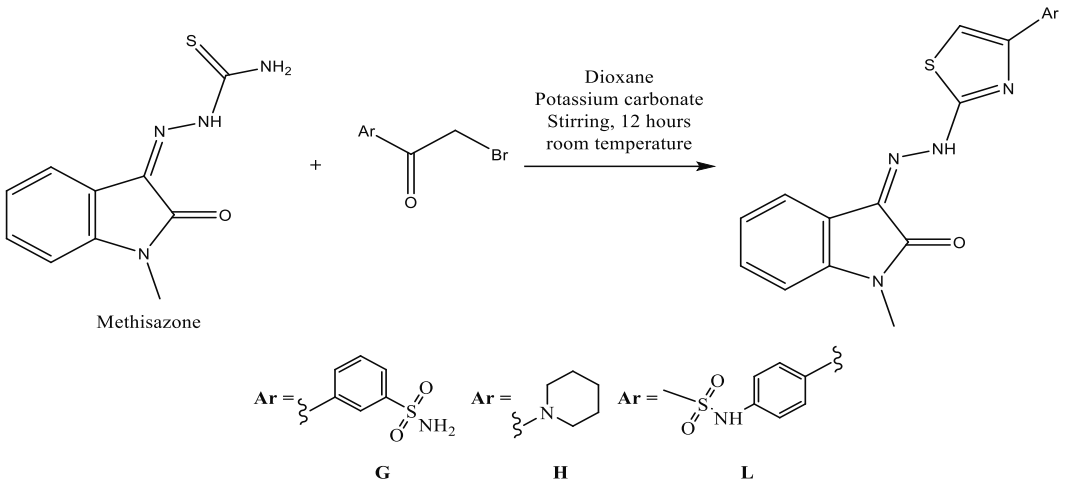
INTRODUCTION

Isatin (2,3-indolindione) is an important and interesting heterocyclic compound to medicinal chemists. It is found endogenously in mammalian tissues and the *Isatis* genus plant and can also be synthesized [1,2]. Many structural modifications are possible at different positions (N-1, C-2, C-3, C-5, and C-6) of isatin. This feature of isatin has led to the identification and development of many isatin-based therapeutic agents, encompassing methisazone, sunitinib, and nintedanib [2]. Isatin derivatives have demonstrated a variety of pharmacological properties, including antimicrobial, antitubercular, anti-HIV, anticancer, anticonvulsant, anti-inflammatory, antioxidant, and antidiabetic activities [2-4].

Methisazone, a C3-substituted isatin derivative



Scheme 1: Preparation of compounds G, H, and L from methisazone

(Scheme 1), is an antiviral drug that demonstrated appreciable efficacy against smallpox and other orthopoxvirus infections [5,6]. However, limited studies on the antimicrobial activity of methisazone derivates are available [1,2]. The thiazole ring is an integral part of many antimicrobial compounds, including cephalosporin antibiotics, sulfathiazole, and abafungin [1,7]. A recent Chinese patent reported methisazone-based thiazole derivatives as potent and broad-spectrum antimicrobial agents (Figure 1) [1]. This study was carried out based on these facts and in pursuit of the development of potent and effective antimicrobial agents from isatin derivatives [9-14].

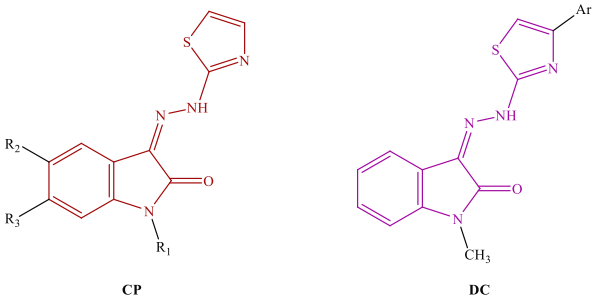


Figure 1: General chemical structures of antimicrobial compounds reported in the Chinese patent number CN109575007B (CP) and designed compounds (DC)

EXPERIMENTAL

General

All the chemicals and solvents used in this study were purchased from Sigma Aldrich (USA). The R_f value of the synthesized compounds was determined in benzene and acetone mixture (8:2). The Gallenkamp apparatus, Shimadzu 440 spectrometer, Varian Gemini 500/125 MHz spectrometer, and GCMS/QP 1000 Ex mass spectrometer (70 eV) were employed to record the melting points (°C), Fourier-Transform Infrared data (FTIR, KBr, ν_{max} in cm^{-1}), Nuclear Magnetic Resonance (^{1}H-NMR in DMSO-d_6, 500 MHz, δ in ppm; ^{13}C-NMR in DMSO-d_6, 125 MHz, δ in ppm), and mass spectra (MS, m/z), respectively.

Design of the compounds

Fourteen isatin-based compounds' chemical structures were designed using ChemDraw (version 21) software (Figure 2). The design of these compounds was based on the reaction between the carbothioamide group of methisazone (an isatin derivative) and alpha-bromoketone group of commercially available compounds [15-17].

Molecular docking

This study was performed utilizing the Molecular Operating Environment software (MOE) (2019.0102 version, Chemical Computing Group Inc., Canada) [17]. The DNA gyrase protein (PDB ID: 6F86) was retrieved from protein data bank (https://www.rcsb.org/structure/6F86), and its chain A was isolated with the software. The selected chain was purified utilizing the Quickprep button of MOE software. The MDB files of the ligands (compounds A-N and ciprofloxacin) were prepared, and docking was done using the default setting of MOE with 10 poses. Docking score (DS in kcal/mol) and root mean square deviation (RMSD) of the docked ligands (compounds A-N and ciprofloxacin) are provided in Table 1.

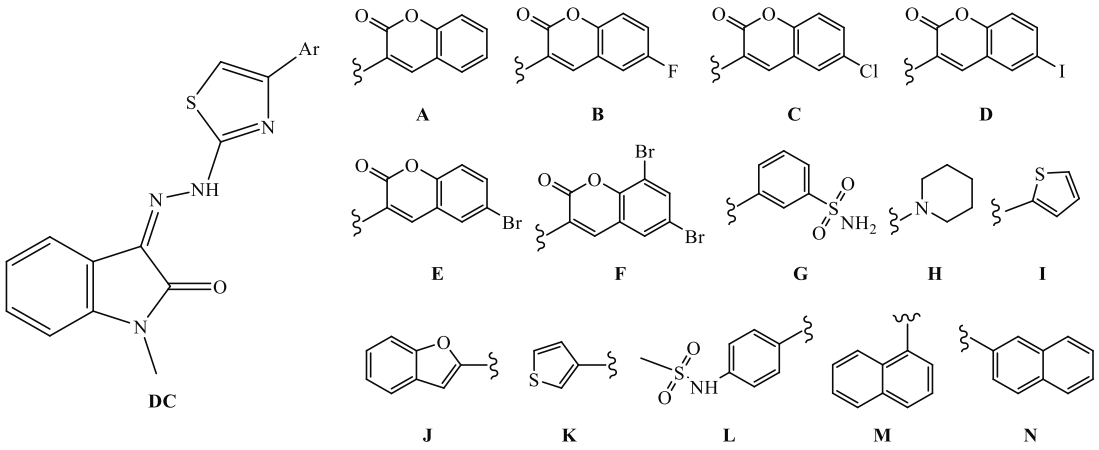


Figure 2: The chemical structures of the designed compounds (DC) and the chemical structure of Ar-groups (A-N)

Table 1: Results of *in silico* studies of compounds A-N and ciprofloxacin

Compound	Docking result		Swiss-ADME data			Toxicity parameter			
	DS	*RMSD*	*Drug likeness (Lipinski's rule violations)*	*GI absorption*	*Log $P_{o/w}$*	*LD_{50} (mg/kg)*	*Toxicity class*	*Hepatotoxicity (%)*	*Carcinogenicity (%)*
A	-5.75	1.44	Yes (Zero)	High	3.43	1600	4	Active (55)	Active (53)
B	-5.51	0.90	Yes (Zero)	High	3.69	1600	4	Active (63)	Inactive (59)
C	-5.55	1.69	Yes (Zero)	High	3.92	2001	5	Active (59)	Inactive (60)
D	-5.95	1.46	Yes (One)	High	3.99	1600	4	Active (58)	Inactive (58)
E	-6.24	1.56	Yes (Zero)	High	3.99	1600	4	Active (59)	Inactive (59)
F	-5.42	1.44	Yes (One)	High	4.55	1600	4	Active (59)	Inactive (59)
G	-5.90	1.96	Yes (Zero)	Low	1.94	1600	4	Inactive (63)	Inactive (55)
H	-5.72	1.28	Yes (Zero)	High	2.73	3009	5	Inactive (59)	Active (53)
I	-6.03	0.67	Yes (Zero)	High	3.24	750	4	Active (53)	Active (58)
J	-6.18	1.12	Yes (Zero)	High	3.53	750	4	Active (56)	Active (57)
K	-.5.78	1.02	Yes (Zero)	High	3.26	2100	5	Active (53)	Active (58)
L	-5.98	1.44	Yes (Zero)	Low	2.36	2100	5	Inactive (59)	Inactive (57)
M	-3.8	0.72	Yes (Zero)	High	4.17	2100	5	Active (54)	Active (56)
N	-5.17	1.03	Yes (Zero)	High	4.17	2100	5	Active (54)	Active (56)
Ciprofloxacin	-5.41	1.18	Yes (Zero)	High	1.10	2000	4	Inactive (65)	Inactive (57)

Prediction of drug-likeliness and gastrointestinal absorption prediction

Swiss-ADME software was employed to predict drug-likeliness and gastrointestinal absorption of compounds A-N and ciprofloxacin [17,18]. The SMILES notations of compounds were inserted into Swiss-ADME software, the run button was pressed, and data generated was noted (Table 1).

Prediction of toxicity

The ProTox-II web server was employed to predict the toxicity of compounds A-N and ciprofloxacin [19,20]. The SMILES notations of compounds were inserted in ProTox-II web server, the start button was pressed, and toxicity data was noted (Table 1).

Synthesis of compounds G, H, and L

A mixture of methisazone (0.01 mole), 3-(2-bromoacetyl) benzenesulfonamide (0.01 mole), dioxane (20 mL), and potassium carbonate (0.02 moles) was stirred for 12 h at 25 ^{o}C. The precipitate was filtered, washed with the acetone-water mixture (1:1), and recrystallized from dioxane to provide the compound G. The compounds H and L were prepared by a similar method by replacing 3-(2-bromoacetyl) benzenesulfonamide with 2-bromo-1-(piperidin-1-yl) ethan-1-one and N-(4-(2-bromoacetyl) phenyl) methanesulfonamide, respectively (Scheme 1).

The structure elucidation data of compounds G, H, and L is provided in Table 2.

Evaluation of antimicrobial activity

The serial dilution method was used to determine the minimum inhibitory concentration (MIC) of compounds G, H, and L against four microorganisms [15,16]. Different dilutions of compounds (200 to 6.25 µg/mL) were prepared in sterile dimethyl sulfoxide (DMSO). Ciprofloxacin was utilized as a standard drug, whereas pure DMSO was used as a control. The antimicrobial activity data of G, H, L, and ciprofloxacin are provided in Table 3.

Determination of DNA gyrase inhibitory activity

E. coli DNA gyrase test kit was procured from TopoGEN, Inc. (Cat no. TG1003, Port Orange, FL). Test was conducted according to the manufacturer's guidelines [21]. Briefly, the dilutions of compounds G, H, L, and ciprofloxacin (0.1 - 50 µM) were prepared in DMSO along with the prescribed amounts of the specified substances (buffer, KCl, DTT, $MgCl_2$, acetylated BSA, spermidine, ATP, glycerol, pBR322 substrate, and album). The 2 U of *E. coli* DNA gyrase was mixed with the solution (3 µL) of each compound and stored for 30 min at 37 ^oC. The 3X gel-loading buffer (10 µL) was added to end the reaction. The obtained mixture (20 µL) was loaded on agarose (1 %)-TAE gel and run for 3 h (60 V). Ethidium bromide (0.5 mg/L in TAE) was used to stain the gel, and the gel was de-stained with water after 30 minutes. Fluorescent data were taken at 300 nm using UV transilluminator imaging equipment. Quantification of fluorescence intensity of the supercoiled plasmid reaction result was performed with the help of ImagQuant software (Molecular Dynamics, Sunnyvale, CA, USA). Each compound was tested three times, and the IC_{50} values were determined using nonlinear regression analysis (Table 3).

Table 2: Structure characterization data of compounds G, H, and L

Compound (Molecular formula; R_f; M.P.; FTIR)	^{1}H-NMR	^{13}C-NMR	Mass
G ($C_{18}H_{15}N_5O_3S_2$; 0.88; 230-232^{o}C; C=O (1734), N-H (3410), and NH_2 (3361))	3.46 (s, 3H, -CH_3), 7.23 (s, 2H, NH_2), 7.27 (s, 1H, Ar-H), 7.34 (dd, 1H, Ar-H), 7.63-7.67 (m, 2H, Ar-H), 7.79 (dd, 1H, Ar-H), 7.91-7.95 (m, 2H, Ar-H), 8.19 (d, 1H, Ar-H), 8.28 (s, 1H, Ar-H), 11.99 (s, 1H, NH)	30.1 (-CH_3), 105.0, 115.8, 117.7, 124.0, 124.4, 127.3, 129.4 (2C), 130.7, 131.2, 133.0 (2C), 140.2, 141.2, 150.2, 163.5 (C=O, isatin), 171.7 (C-2, Thiazole)	413 (M^+, 100 %), 414 (M^++1), 254, 257, 174, 159, 156, 145, 99
H ($C_{17}H_{19}N_5OS$; 0.72; 175-177^{o}C; C=O (1738) and N-H (3414))	1.62 (m, 6H, C3, C4, and C5 of piperidine), 3.38 (t, 4H, C2, and C6 of piperidine), 3.46 (s, 3H, -CH_3), 6.46 (s, 1H, Ar-H), 7.34 (dd, 1H, Ar-H), 7.62-7.68 (m, 2H, Ar-H), 7.91 (d, 1H, Ar-H), 11.99 (s, 1H, NH)	24.5 (1C, C-4 of piperidine), 25.5 (2C, C-3 & C-5 of piperidine), 30.1 (-CH_3), 52.4 (2C, C-2 & C-6 of piperidine), 110.5, 115.8, 117.7, 124.4 (2C), 131.2, 133.0, 141.2, 142.0, 163.5 (C=O, isatin), 170.2 (C-2, Thiazole)	341 (M^+, 100 %), 342 (M^++1), 257, 182, 174, 159, 145, 99, 84
L ($C_{19}H_{17}N_5O_3S_2$; 0.70; 209-211^{o}C; C=O (1737), N-H (3413), and NH_2 (3355))	3.22 (s, 3H, CH_3-SO_2-), 3.46 (s, 3H, -CH_3), 6.99- 6.99 (d, 2H, Ar-H), 7.27-7.34 (m, 2H, Ar-H), 7.60-7.73 (m, 4H, Ar-H), 7.91 (d, 1H, Ar-H), 10.58 (s, 1H, -NH-SO_2-), 11.99 (s, 1H, -NH=N-)	30.1 (-CH_3, isatin), 42.9 (-CH_3, sulfonamide), 105.0, 115.8, 116.8 (2C), 117.7, 123.0, 124.4, 128.3 (2C), 129.4, 131.2, 133.0, 137.7, 141.2, 150.2, 163.5 (C=O, isatin), 171.7 (C-2, Thiazole)	427 (M^+, 100 %), 268, 257, 170, 174, 159, 145, 99

Table 3: Antimicrobial activity data of compounds G, H, and L

Compound	Zone of inhibition in mm (MIC in µg/mL)				DNA GyrB Inhibitory activity (IC_{50} in µM)
	S. aureus **(ATCC 25923)**	***B. subtilis*** **(ATCC 6633)**	***E. coli*** **(ATCC 25922)**	***K. pneumonia*** **(ATCC 700603)**	
G	23.08±0.12* (12.5)	22.34±0.22* (12.5)	23.18±0.18* (12.5)	23.25±0.14* (12.5)	4.38±0.11* (102.33 %)
H	23.67±0.44* (12.5)	22.94±0.20* (12.5)	24.10±0.10* (12.5)	23.75±0.15* (12.5)	4.47±0.05* (104.43 %)
L	23.95±0.22* (12.5)	23.44±0.14* (12.5)	23.20±0.33* (12.5)	23.50±0.28* (12.5)	4.57±0.18* (106.77 %)
Ciprofloxacin	23.56±0.25* (12.5)	22.13±0.41* (12.5)	23.80±0.15* (12.5)	23.20±0.30* (12.5)	4.28±0.22* (100.0 %)

*$p < 0.05$

Statistical analysis

The SPSS software (version 20, Chicago, IL, USA) was utilized for the statistical analysis of the experimental data. The data are presented as mean ± standard deviation (SD) while $p < 0.05$ was considered statistically significant.

RESULTS

Fourteen compounds (A to N) were designed (Figure 1). The *in silico* studies (molecular docking utilizing the DNA gyrase 6F86 protein and the prediction of drug likeliness, gastrointestinal absorption, and toxicity) of the designed fourteen compounds were compared to ciprofloxacin (Table 1).

Eleven compounds (A, B, C, D, E, F, G, H, I, J, and L) displayed better DS than ciprofloxacin (-5.41 kcal/mol). Three compounds (N = -5.17 kcal/mol; M = -3.8 kcal/mol; K = -.5.78 kcal/mol) showed less DS than ciprofloxacin (-5.41 kcal/mol). All the compounds demonstrated drug-likeliness properties, GI absorption, and toxicity class comparable to ciprofloxacin. The hepatotoxicity was associated with all compounds except G, H, L, and ciprofloxacin. Therefore, compounds G, H, and L were selected for synthesis (Scheme 1). The characterization data of compounds G, H, and L is mentioned in Table 2.

The spectral data of compounds, G, H, and L was in accordance with the designated structures provided in Figure 1 and Scheme 1. Compounds G, H, and L were evaluated for their antimicrobial activity and DNA gyrase inhibitory activity compared to ciprofloxacin. The results of the antimicrobial activity are provided in Table 3.

The antimicrobial activity ($p < 0.05$) of G, H, and L was superior to ciprofloxacin against all tested microorganisms. However, the minimum inhibitory concentrations of G, H, L, and ciprofloxacin were similar (12.5 µg/mL). The DNA gyrase inhibitory activity of G (102.33 %, $p < 0.05$), H (104.43 %, $p < 0.05$), and L (106.77 %, $p < 0.05$) was also better than ciprofloxacin (100.0 %, $p < 0.05$) (Figure 3).

DISCUSSION

Fourteen isatin-based compounds were designed and *in silico* studies (molecular docking and prediction of drug-likeliness, GI absorption, log P, LD_{50}, toxicity class, hepatotoxicity, and carcinogenicity) were performed. All the compounds demonstrated drug-likeliness properties and good GI absorption. The LD_{50} and toxicity class of all compounds (A - N) were comparable to ciprofloxacin. A higher value of toxicity class reflects a better safety profile.

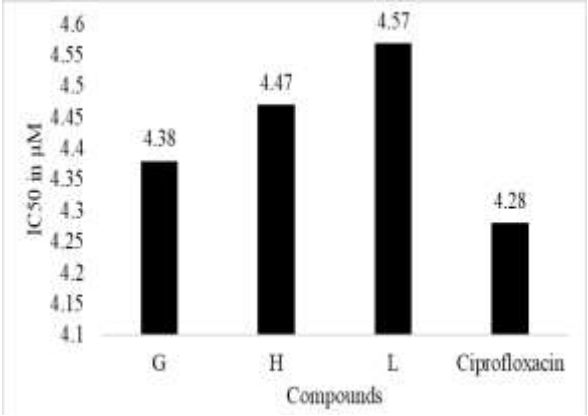


Figure 3: DNA gyrase inhibitory activity (IC50 in µM) of G, H, L, and ciprofloxacin

Docking score (DS) of a compound reflects its potency. The greater the negative value of the DS, the more potent the compound. A lesser value (< 1.5) of RMSD implies tight binding of ligands with the receptor site [22]. Lipophilic coumarin ring-bearing compounds, A (-5.75 kcal/mol), B (-5.51 kcal/mol), C (-5.55 kcal/mol), D (-5.95 kcal/mol), E (-6.24 kcal/mol), and F (-5.42 kcal/mol) exhibited better DS than ciprofloxacin (-5.41 kcal/mol) indicating their potency against DNA gyrase. However, these compounds (A-F) also displayed hepatotoxic character. Similar effects were observed with other lipophilic ring-bearing compounds, I (thiophene) and J (benzofuran). Accordingly, it may be inferred that incorporating a lipophilic ring (coumarin, thiophene, and benzofuran) in the designed compound provides inhibitory potency against DNA gyrase, but it also makes the compound hepatotoxic. At the same time, incorporating a naphthalene ring (compounds M and N) reduces the DNA gyrase inhibitory activity of the designed compounds and makes them hepatotoxic.

Three hydrophilic group-bearing compounds, G (sulfonamide group), H (piperidine ring), and L (sulfonamide group) displayed better DS (-5.90, -5.72, and -5.98 kcal/mol, respectively) than ciprofloxacin (-5.41 kcal/mol). The compounds G, H, and L also displayed non-hepatotoxic character. The non-hepatotoxic nature of the designed compounds seems to be related to lipophilicity of the compounds. This understanding is supported by the predicted log P values of the designed compounds (Table 1) as log P values are proportional to the

lipophilicity of a compound. Compounds G, H, L, and ciprofloxacin had lop P < 3 while other hepatotoxic compounds had lop P > 3.

This observation suggests that incorporating an Ar-group in the designed compounds provides a lop P < 3, resulting in non-hepatotoxic compounds. Literature also states that removing or replacing the N-methyl group of isatin with a higher alkyl group reduces its antimicrobial effect [1]. Accordingly, the presence of methyl group at the N-1 position of the synthesized compounds seems essential. Based on the above facts, compounds G, H, and L were selected for synthesis, and *in vitro* antimicrobial activity evaluation. Compounds G, H, and L displayed better antimicrobial activity and DNA gyrase inhibitory activity than ciprofloxacin. These findings were in agreement with this *in silico* study data.

The C-3 position of isatin is important in developing antimicrobial agents [2]. The Schiff base-bearing thiazole fragment at C-3 position of isatin is expected to provide new high-activity broad-spectrum antibacterial agents, antifungal agents, and DNA intercalators [1]. Triazole and imidazole-containing antifungals are used in clinical practice [9] and it is believed that replacing thiazole ring of G, H, and L with triazole or imidazole could result in the development of potent antifungal drugs. Compounds G, H, and L demonstrated potent DNA gyrase inhibitory activity. DNA gyrase is an important enzyme in different microbes, including *Mycobacterium tuberculosis* (Mtb) [23]. Therefore, assessing the efficacy of compounds G, H, and L against Mtb may be worthwhile. Methisazone is an antiviral drug for orthopoxvirus infections, including smallpox and monkeypox disease [5,6], with compounds G, H, and L being derivatives of methisazone. This signifies that G, H, and L may also possess activity against diseases caused by orthopoxvirus infections.

CONCLUSION

The new template of these designed compounds, including G, H, and L, have the potential to become potent and broad-spectrum antibacterial, antifungal, and antiviral agents. However, further studies are recommended to establish these possibilities regarding these synthesized compounds as well as determine the structural alteration of the isatin-thiazole-based template. This study may help to identify and discover new high-activity broad-spectrum antimicrobial drugs.

DECLARATIONS

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Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities about claims relating to the content of this article will be borne by the authors. Mohd. Imran and Saleh Ibrahin Alaqel conceived and designed the study. Abida performed the *in silico* experiments. Mohd. Imran, Abida, and Naira Nayeem carried out all experiments and analyzed the data. All authors were involved in writing the project/manuscript, and read and approved the project/manuscript for publication.

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