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Original article

Synthesis, antimicrobial, antiquorum-sensing and cytotoxic activities of new series of benzothiazole derivatives

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ABSTRACT

New series of benzothiazole derivatives were designed and synthesized. The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus cereus*. Compounds **6j** and **6o** showed the highest activity against *E. coli* and *S. aureus*. The antifungal activity of these compounds was also tested against *Candida albicans* and *Aspergillus fumigatus* 293. Compounds **4c**, **4g** and **6j** exhibited the highest activity against *C. albicans*. In addition, compounds **4a** and **6j** displayed promising activity against *A. fumigatus* 293. The same compounds were examined for their antiquorum-sensing activity against *Chromobacterium violaceum* ATCC 12472, whereas compounds **4a**, **6j** and **6p** showed moderate activity. The *in vitro* cytotoxicity testing of the synthesized compounds was performed against cervical cancer (Hela) and kidney fibroblast cancer (COS-7) cell lines. Results indicated that all tested compounds have IC_{50} values >50 μM against both cell lines. Molecular properties, toxicities, drug-likeness, and drug score profiles of compounds **4a**–**c**, **5a**, **6g**,**h**, **6j**, **6l**, **6o** and **7c**,**d** were also assessed.

1. Introduction

The traditional antibacterial agents either kill bacteria (bactericidal) or inhibit their growth (bacteriostatic). Typically, the targets for the conventional antibiotics are the essential cellular processes such as bacterial cell wall biosynthesis, bacterial protein synthesis, and bacterial DNA replication and repair [1]. The eventual growth arrest and cell death can be followed by rapid expansion of resistant subpopulations, making subsequent treatment difficult or impossible [2]. Therefore, new antibacterial strategies are required. An alternative to killing or inhibiting growth of pathogenic bacteria is the specific attenuation of bacterial virulence, which could be attained by targeting key regulatory systems that mediate the expression of virulence factors. One of the target regulatory systems is quorum sensing (QS) [1]. QS is a phenomenon used by bacteria for coordination of population-wide phenotypes, such as expression of virulence genes, antibiotic resistance and biofilm formation. QS disruption is one of the emerging anti-virulence strategies that promises a lower risk of resistance development [3]. Many quorum quenching methods have been developed against various clinically significant bacterial pathogens [4].

The benzothiazole nucleus is a unique scaffold for further molecular exploration to synthesize novel compounds. Literature survey revealed that benzothiazole analogs are assosciated with diverse pharmacological effects, including antimicrobial activity [5–9]. In addition, benzothiazoles incorporating pyrazole moiety demonstrated remarkable antimicrobial activity [10,11]. On the same line, benzothiazoles incorporating isatin moiety have received considerable attention owing to their diverse chemotherapeutic potentials, including antimicrobial activity [12,13]. In addition, various Schiff bases of 2-hydrazinobenzothiazole derivatives (Fig. 1) were previously synthesized and screened for their antimicrobial activity [14–16]. Some of these derivatives displayed promising activity.

Therefore, we found it interesting to design new compounds within the scope of synthetic procedures using the benzothiazole

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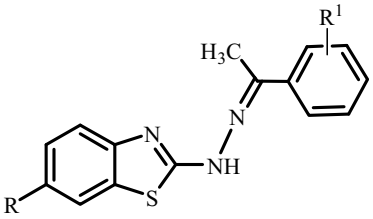

R = CH_3; F
R^1 = 2-F; 3-F; 2-Cl; 4-OH; 2,5-$(OH)_2$; 3,4-$(OCH_3)_2$

Fig. 1. Schiff bases of 2-hydrazinobenzothiazole derivatives with reported antimicrobial activity.

scaffold followed by suitable modifications to generate new series of compounds with expected antimicrobial activity. The manipulation strategy embraces the incorporation of pyrazole, isatin and arylidene moieties into the benzothiazole ring in order to verify the importance of these moieties for the antimicrobial activity (Fig. 2).

2. Experimental

A general approach for the synthesis of the designed compounds is outlined in Scheme 1. The starting compound, 2-amino-6-fluorobenzothiazole **(1)** was reacted with hydrazine hydrate in refluxing ethylene glycol in the presence of hydrochloric acid to produce the hydrazine derivative **2** [17]. Refluxing compound **2** with ethyl 3-oxo-2-((2-substituted phenyl)hydrazono)butanoates **3a–e** [18] in glacial acetic acid yielded the corresponding pyrazole analogs **4a–e**. In addition, the reaction of the key intermediate **2** with the appropriate isatin in ethanol in the presence of glacial acetic acid gave compounds **5a–c**. Reaction of **2** with the appropriate aromatic aldehyde in ethanol under microwave irradiation gave the corresponding Schiff bases **6a–r** in 64–82% yields. Moreover, refluxing the hydrazine analog **2** with the appopriate acetophenone in ethanol in the presence of glacial acetic acid furnished compounds **7a–d** in 61–73% yields. The synthesized compounds, **4a–e**, **5a–c**, **6a–r** and **7a–d** were screened for their *in vitro* antibacterial activity against two species of Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and one Gram-negative bacterium (*Escherichia coli*) [19,20]. Antifungal screening against *Candida albicans* and *Aspergillus fumigatus* 293 was also performed [20,21]. The same compounds were examined for their antiquorum-sensing activity against *Chromobacterium violaceum* ATCC 12472 [22]. Additionally, the *in vitro* cytotoxicity testing of compounds **4a–e**, **5a–c**, **6a–r** and **7a–d** was performed against cervical cancer (Hela) and kidney fibroblast cancer (COS-7) cell lines adopting MTT assay [23–25].

The synthetic details and related spectra of the compounds as well as their biological testing are deposited in Supporting information.

3. Results and discussion

3.1. Chemistry

The structures of all the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. ^{1}H NMR spectra of compounds **4a–e** showed a characteristic singlet signal at δ 2.05–2.50 ppm for the methyl protons at the 3-position of the pyrazole ring. In the ^{1}H NMR spectra of compounds **6a–r**, a singlet signal at δ 7.95–8.83 ppm was due to CH=N proton. Regarding ^{1}H NMR spectra of compounds **7a–d**, methyl protons were observed as a singlet signal at δ 1.90–2.35 ppm.

3.2. Biological screening

The antimicrobial screening results (Table 1) were determined by measuring the average diameter of the inhibition zones, expressed in millimeters (mm) [19,21]. The minimum inhibitory concentration (MIC, μg/mL) of the most active compounds against *E. coli*, *S. aureus*, *C. albicans* and *A. fumigatus* 293 was carried out by broth microdilution method using 96-multiwell microtiter plates [20]. As shown in the results (Table 2), compound **6j** showed the highest activity against *E. coli* with MIC value of 312 μg/mL. Furthermore, compound **6j** exhibited good antibacterial activity against *S. aureus* with MIC value of 156.25 μg/mL. The results are compared to ampicillin as a reference antibacterial agent. Regarding the antifungal activity, compounds **4c**, **6g** and **6j** displayed the highest activity against *C. albicans* with MIC value of 312.5 μg/mL. In addition, compounds **4a** and **6j** demonstrated strong antifungal activity against *A. fumigatus* 293 with MIC value of 156.25 μg/mL (Table 2). The results are compared to fluconazole as a reference antifungal agent. *A. fumigatus* 293 was resistant to fluconazole [26]. These observations may promote further development of benzothiazole derivatives and may lead to compounds with potent antibacterial and antifungal activities.

While antibiotics kill or slow down the growth of bacteria, quorum sensing inhibitors (QSIs) or quorum quenchers (QQs) attenuate bacterial virulence and appear to be a promising strategy to control bacterial resistance to antibiotics [27]. Thus, the same compounds were examined for antiquorum-sensing activity

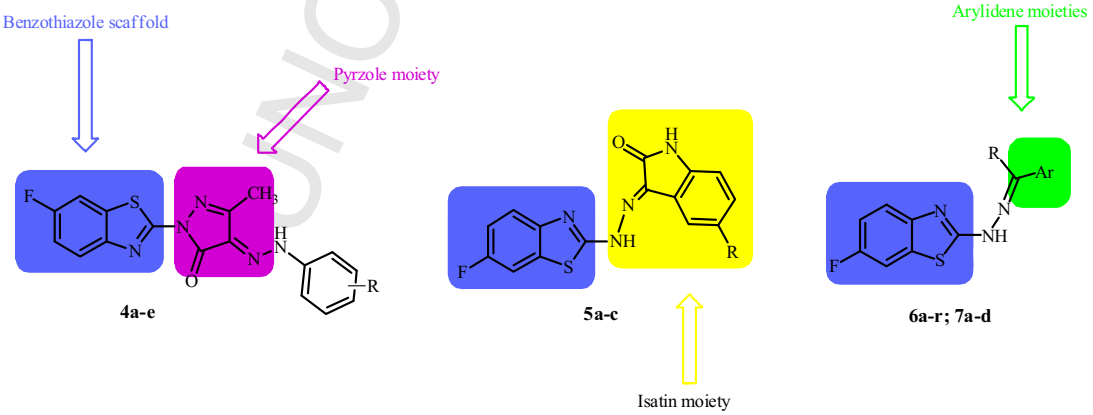

Fig. 2. Designed strategy of the titled compounds.

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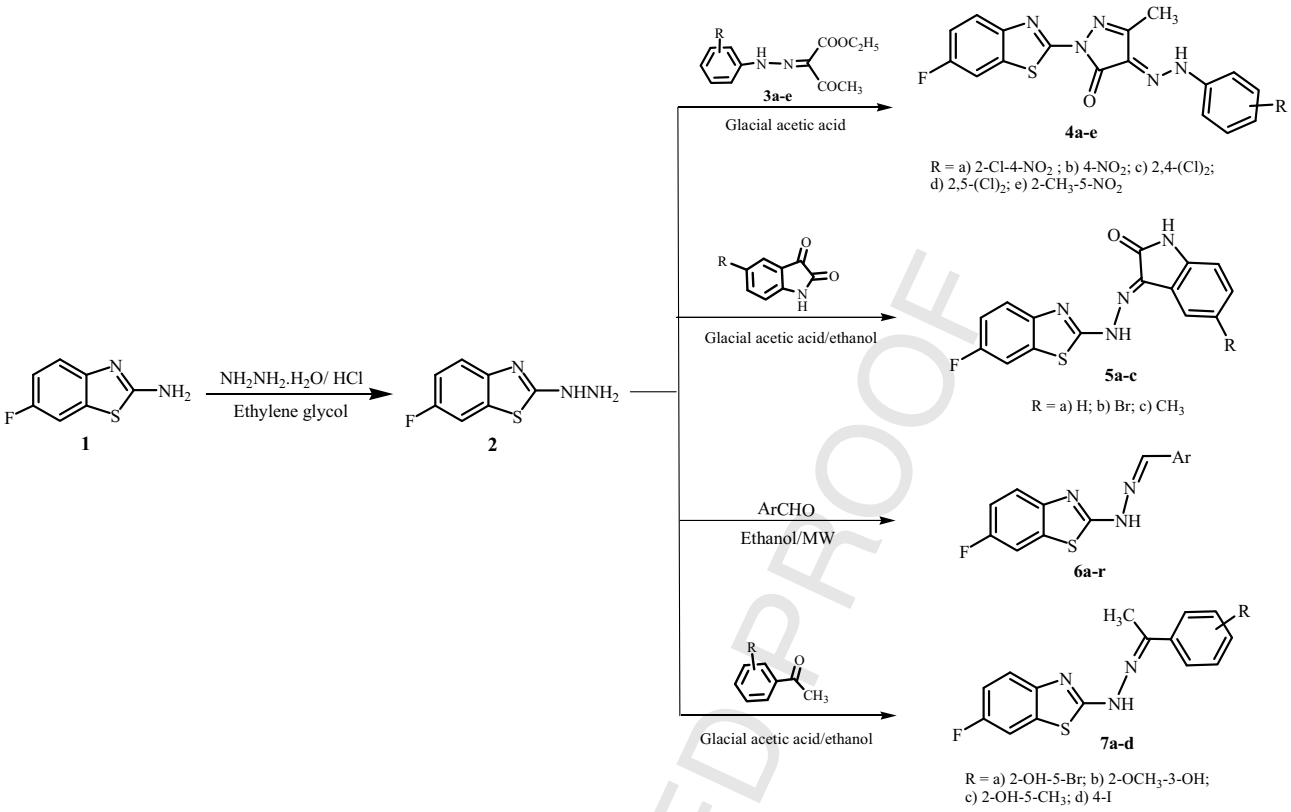
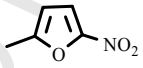
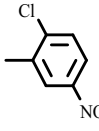
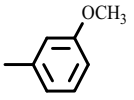
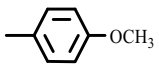
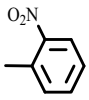
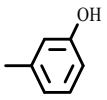
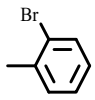
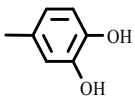
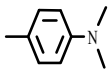
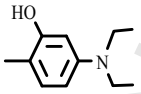
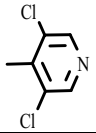
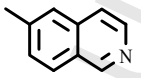
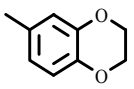
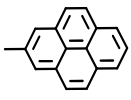


Comp. No.	Ar	Comp. No.	Ar	Comp. No.	Ar
6a		**6b**		**6c**	
6d		**6e**		**6f**	
6g		**6h**		**6i**	
6j		**6k**		**6l**	
6m		**6n**		**6o**	
6p		**6q**		**6r**	

Scheme 1. Synthesis of compounds **4a–e**, **5a–c**, **6a–r** and **7a–d**.

against *Ch. violaceum* ATCC 12472 [22]. The QS system of *Ch. violaceum* was used for this assay. QS in this wild type strain of bacteria produces violacein (a purple pigment) in response to autoinducer molecules known as acyl HSLs [28,29]. Thus, drugs that inhibit acyl HSL-mediated QS activity in *Ch. violaceum* would prevent the production of this purple pigment. Screening results for their ability to inhibit QS regulated violacein production against *Ch. violaceum* (based on measuring the radius of pigment inhibition

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Table 1
Antimicrobial and antiquorum-sensing activities of compounds **4a–e**, **5a–c**, **6a–r** and **7a–d**.

Comp. No.	Inhibition zone diameter (mm)[a,b]					QS inhibition (mm)[c]
	E. coli	*B. cereus*	*S. aureus*	*C. albicans*	*A. fumigatus*	*Ch. violaceum*
4a	6	8	–	–	**28**	11
4b	3	6	4	**17**	–	6
4c	4	8	4	**28**	–	–
4d	4	4	–	–	5	4
4e	4	4	–	–	5	4
5a	–	–	–	2	**26**	–
5b	2	2	2	2	14	4
5c	–	–	–	–	–	4
6a	2	3	–	–	–	–
6b	5	7	–	–	–	–
6c	–	–	–	–	–	–
6d	5	3	14	–	–	–
6e	–	14	–	7	–	–
6f	–	2	3	10	–	6
6g	14	10	11	**19**	–	–
6h	–	8	–	8	**17**	–
6i	5	4	3	10	–	–
6j	**18**	14	**26**	**28**	**32**	14
6k	–	–	3	4	–	–
6l	2	4	4	6	**20**	–
6m	4	8	10	6	–	–
6n	–	4	–	8	–	5
6o	**16**	12	**19**	12	–	–
6p	–	5	5	7	–	14
6q	–	3	–	–	–	–
6r	5	4	15	–	–	–
7a	–	–	–	–	11	–
7b	4	2	–	–	–	–
7c	–	–	–	–	**26**	–
7d	–	2	–	2	**30**	–
Ampicillin	26	12	30	nt	nt	nt
Fluconazole	nt	nt	nt	22	–	nt
Catechin	nt	nt	nt	nt	nt	4

Bold values point out the best results. nt, not tested.
[a] Results are calculated after substraction of DMSO activity.
[b] Not active (–, inhibition zone <2 mm); weak activity (2–9 mm); moderate activity (10–15) mm; strong activity (16–25 mm); very strong activity (26–35 mm).
[c] QS inhibition (radius of pigment inhibition in mm) = radius of growth and pigment inhibition (r_2) – radius of bacterial growth inhibition (r_1).

Table 2
MIC values of the most active compounds.

Comp. No.	MIC (μg/mL)[a]			
	E. coli	*S. aureus*	*C. albicans*	*A. fumigatus*
4a	nt	nt	nt	156.25
4b	nt	nt	625	nt
4c	nt	nt	312.5	nt
5a	nt	nt	nt	312.5
6g	nt	nt	312.5	nt
6h	nt	nt	nt	625
6j	312.5	156.25	312.5	156.25
6l	nt	nt	nt	625
6o	625	625	nt	nt
7c	nt	nt	nt	312.5
7d	nt	nt	nt	312.5
Ampicillin	19.531	312.5	nt	nt
Fluconazole	nt	nt	1250	–

[a] –, MIC > 2500 μg/mL. nt, not tested.

in mm) are presented in Table 1 and revealed that compounds **4a**, **6j** and **6p** have moderate antiquorum-sensing activity. The rest of the tested compounds were found to be less active or completely inactive. The results are compared to catechin as a positive control. The results of *in vitro* cytotoxicity testing against cervical cancer (Hela) and kidney fibroblast cancer (COS-7) cell lines indicated that all tested compounds have IC_{50} values >50 μM against both cell lines.

3.3. Structure–activity relationship (SAR) studies

Compounds **4a–e**: Removal of the 2-chloro substituent from the phenyl ring of compound **4a** increased the activity against *C. albicans* but abolished the activity against *A. fumigatus* 293 (compound **4b**). Moreover, replacement of the 4-nitro substituent in the same compound with 4-chloro substituent resulted in excellent activity against *C. albicans* (compound **4c**) but abolished activity against *A. fumigatus* 293. Compounds bearing 2,4-disubstituted phenyl and 4-substituted phenyl moieties exhibited stronger activity against *C. albicans* compared to compounds bearing 2,5-disubstituted phenyl moiety (compounds **4b**,**c** vs. **4d**,**e**).

Compounds **5a–c**: Replacement of 2-oxoindolin-3-ylidene moiety (compound **5a**) with 5-bromo-2-oxoindolin-3-ylidene (compound **5b**) resulted in decreased antifungal activity against *A. fumigatus* 293, while its replacement with 5-methyl-2-oxoindolin-3-ylidene abolished the antifungal activity against both of the tested fungi (compound **5c**).

Compounds **6a–r**: Compounds **6a**,**b** bearing (furan-2-yl)methylene moiety were inactive as antifungal agents and revealed weak activity against *E. coli* and *B. cereus*. Replacement of (furan-2-yl)methylene moiety with (1*H*-pyrrol-2-yl)methylene moiety completely abolished the antibacterial activity against *E. coli* and *B. cereus* (compound **6c** vs. **6a**,**b**). The presence of 2-nitrobenzylidene moiety resulted in acceptable antibacterial activity against the three tested microorganisms as well as antifungal activity against *C. albicans* (compound **6g**), while its replacement with 2-bromobenzylidene or 2-cyanobenzylidene

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resulted in decreased antibacterial and antifungal activities (compounds **6i** and **6k**). Furthermore, the presence of 3-hydroxybenzylidene moiety revealed strong antifungal activity against *A. fumigatus* 293 (compound **6h**). Incorporation of 3,4-dihydroxybenzylidene moiety into the benzothiazole nucleus resulted in promising activity against *E. coli, S. aureus*, *C. albicans* and *A. fumigatus* 293 as well as moderate antiquorum-sensing activity (compound **6j**). Replacement of 4-*N*,*N*-dimethylaminobenzylidene moiety with 4-*N*,*N*-diethylamino-2-hydroxybenzylidene increased the antibacterial activity against the three tested microorganisms but abolished the antifungal activity against *A. fumigatus* 293 (compound **6m** vs. **6l**). Replacement of (pyridin-2-yl)methylene moiety with (3,5-dichloropyridin-4-yl)methylene increased the antibacterial activity against the three tested microorganisms as well as antifungal activity against *C. albicans* (compound **6o** vs. **6n**). Incorporation of (isoquinolin-5-yl)methylene moiety into the benzothiazole nucleus improved the antiquorum-sensing activity (compound **6p**), while incorporation of (pyren-2-yl)methylene moiety enhanced the antibacterial activity against *S. aureus* (compound **6r**).

Compounds **7a–d**: The presence of 2-hydroxy-5-methylphenyl and 4-iodophenyl moieties resulted in promising anifungal activity against *A. fumigatus* 293 (compounds **7c**,**d**), while incorporation of 5-bromo-2-hydroxyphenyl moiety into the benzothiazole nucleus resulted in moderate antifungal activity against the same microrganism (compound **7a**). On the other hand, incorporation of 3-hydroxy-2-methoxyphenyl moiety abolished the antifungal activity against the same microrganism (compound **7b**).

3.4. Molecular properties and drug-likeness

A molecular property is a complex balance of various structural features which determine whether a particular molecule is similar to the known drugs. It generally means "molecules which contain functional groups and/or have physical properties consistent with most of the known drugs". Hydrophobicity, molecular size, flexibility and presence of various pharmacophoric features are the main physical properties that influence the behavior of molecules in a living organism. Computational chemists have a wide array of tools and approaches available for the assessment of molecular diversity. Diversity analysis has been shown to be an important ingredient in designing drugs. So, computational sensitivity and structural analyses have been used to study the drug-likeness of the candidate drug. As good bioavailability can be achieved with an appropriate balance between solubility and partitioning properties. Thus, in order to achieve good oral drugs, compounds **4a–c**, **5a**, **6g**,**h**, **6j**, **6l**, **6o** and **7c**,**d** which exhibited the highest antibacterial and/or antifungal activity, were analyzed for the prediction of solubility and Lipinski's rule of five [30] as well as other properties (Tables 3 and 4) for filtering compounds for subsequent synthesis and antimicrobial screening.

Table 3
Topological polar surface area, number of rotatable bonds and calculated Lipinski's rule of five for compounds **4a–c**, **5a**, **6g**,**h**, **6j**, **6l**, **6o** and **7c**,**d**.

Comp. No.	Molecular properties						
	TPSA[a]	Nrotb[b]	miLogP[c]	OH–NH interact	O–N interact	MW	No. of violations
4a	118.04	4	4.406	1	9	432.8	0
4b	118.00	4	3.800	1	9	398.39	0
4c	72.18	3	5.125	1	6	422.7	1
5a	70.145	2	3.695	2	5	312.2	0
6g	83.107	4	3.838	1	6	316.3	0
6h	57.511	3	3.424	2	4	287.3	0
6j	77.739	3	2.958	3	5	303.3	0
6l	40.521	4	4.029	1	4	314.4	0
6o	50.175	3	4.286	1	4	341.1	0
7c	57.511	3	4.738	2	4	315.3	0
7d	37.283	3	5.456	1	3	411.2	1
Ampicillin	112.73	4	−0.87	4	7	349.4	0
Fluconazole	81.664	5	−0.118	1	7	306.2	0

[a] TPSA, topological polar surface area.
[b] Nrotb, number of rotatable bonds.
[c] miLogP, the parameter of lipophilicity.

3.4.1. Molinspiration calculations

As a part of our study; the compliance of compounds to the Lipinski's rule of five was evaluated [30], this simple rule is based on the observation that most biologically active drugs have molecular weight of 500 or less, logP values not higher than 5, hydrogen bond donor sites not higher than 5 and hydrogen bond acceptor sites not higher than 10. In addition, topological polar surface area (TPSA) and number of rotatable bonds have been linked to drug bioavailability [31]. Molecular properties (TPSA, nrotb, miLogP, OH–NH interaction, O–N interaction, molecular weight and number of violations from Lipinski's rule) of the newly synthesized compounds were calculated using molinspiration software and compared to the values of the standard drugs, ampicillin and fluconazole (Table 3).

Topological polar surface area (TPSA) and number of rotatable bonds are two important properties for the prediction of oral bioavailability of drug molecules [32–35]. TPSA is calculated based

Table 4
Toxicity risks, drug-likeness and drug score of compounds **4a–c**, **5a**, **6g**,**h**, **6j**, **6l**, **6o** and **7c**,**d**.

Comp. No.	Toxicity risks				Drug-likeness	Drug score
	Mutagenicity	Tumorogenicity	Irritancy	Reproductive effects		
4a	high	high	low	high	1.13	0.08
4b	low	low	low	high	−6.99	0.18
4c	low	low	low	high	4.83	0.20
5a	low	low	low	low	3.92	**0.62**
6g	high	high	low	low	0.94	0.15
6h	low	low	low	low	1.49	**0.52**
6j	low	low	low	low	2.35	**0.60**
6l	low	high	low	low	0.45	0.25
6o	low	low	low	low	1.45	0.40
7c	low	low	low	low	−0.27	0.35
7d	low	low	low	low	0.93	0.31
Ampicillin	low	low	low	low	10.72	0.91
Fluconazole	low	low	low	low	1.99	0.87

Bold values point out the best drug score values.
low risk; high risk.

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on the methodology published by Ertl et al. [35] as the surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them. Thus, it is closely related to the hydrogen bonding potential of a compound [32–35]. TPSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability and blood–brain barrier penetration. Molecules with TPSA values around 140 $Å^2$ or more are expected to exhibit poor intestinal absorption [31]. Results shown in Table 3 indicated that all of the analyzed compounds have TPSA values <140 $Å^2$; thus, they are expected to have good intestinal absorption. Molecules with more than 10 rotatable bonds may have problems with bioavailability [31]. All the tested compounds have 2 to 4 rotatable bonds and they might not have problems with bioavailability (Table 3). MiLogP is calculated adopting the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (http://www.molinspiration.com). It has been shown that for the compound to have a reasonable probability of being well absorbed, miLogP value must be in the range of −0.4 to +5 [31]. On this basis, all compounds under investigation (except **4c** and **7d**) were found to have miLogP values under the acceptable criteria and they are expected to have reasonable oral absorption (Table 3). It is worth mentioning that all of the analyzed compounds have one or zero violation of Lipinski's rule; therefore, they are expected not to have problems with bioavailability (Table 3). Molecules violating more than one may have problems with bioavailability [36].

3.4.2. Osiris calculations

Toxicity risks (mutagenicity, tumorogenicity, irritancy and reproductive effects) and physicochemical properties (drug-likeness and drug score) of the synthesized compounds were calculated by the methodology developed by Osiris [32]. The toxicity risk predictor locates fragments within a molecule which indicate a potential toxicity risk. Toxicity risk alerts indicate that the drawn structure may be harmful concerning the risk category specified. From the data presented in Table 4, it is obvious that the analyzed compounds are supposed to be non-mutagenic (except **4a** and **6g**), non-tumorigenic (except **4a**, **6g** and **6l**), non-irritating, and with no reproductive effects (except **4a–c**).

Drug-likeness is defined as a complex balance of various molecular properties and structural features which indicates whether a particular molecule is similar to the known drugs or not [37]. Osiris program was used for calculating the fragment-based drug-likeness of compounds **4a–c**, **5a**, **6g**,**h**, **6j**, **6l**, **6o** and **7c**,**d**, a positive value indicates that the designed molecule contains fragments which are frequently present in commercial drugs. Results shown in Table 4 indicated that compounds **4c**, **5a** and **6j** have higher drug-likeness values than the standard drug, fluconazole. The drug score combines drug-likeness, miLogP, solubility, molecular weight and toxicity risks in one handy value that may be used to judge the compound's overall potential to qualify for a drug [32]. A value of 0.5 or more makes the compound a promising lead for future development of safe and efficient drugs. The overall drug score values for compounds **4a–c**, **5a**, **6g**,**h**, **6j**, **6l**, **6o** and **7c**,**d** were calculated and compared to that of the standard drugs, ampicllin and fluconazole. Compounds **5a**, **6h** and **6j** possess good drug score values (Table 4).

4. Conclusion

In a summary, compounds **6j** and **6o** are good antibacterial agents. Compounds **4c** and **6j** showed the highest antifungal activity against *C. albicans*. In addition, compounds **4a** and **6j** displayed the best antifungal activity against *A. fumigatus* 293. Furthermore, compounds **4a**, **6j** and **6p** showed moderate antiquorum-sensing activity. These active compounds were proved to be good scaffolds for the development of new potent antibacterial and antifungal agents.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2015.09.004.

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