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In vitro antimicrobial and α-glucosidase inhibitory potential of enantiopure cycloalkylglycine derivatives: Insights into their in silico pharmacokinetic, druglikeness, and medicinal chemistry properties

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ABSTRACT

The present investigation deals with the evaluation for the first time of the *in vitro* antimicrobial and α-glucosidase inhibitory potential of a series of 15 enantiopure cycloalkylglycines using agar well diffusion and spectrophotometric methods, respectively. The obtained results were compared to the positive controls. The antimicrobial results revealed that all compounds exerted strongly inhibitory activity, especially against Gram-positive bacterial strains with the most potent activity was ascribed to α-γ-hydroxy-α-amino acids **11–14** [minimum inhibitory concentration (MIC) = 1.58–12.50 mg/ml, minimum bactericidal concentration (MBC) = 3.17–100 mg/ml, and minimum fungicidal concentration (MFC) = 6.25–50 mg/ml], followed by both isoxazolidine **5–9** (MIC = 1.58–12.50 mg/ml, MBC = 6.25–100 mg/ml, and MFC = 25–100 mg/ml) and isoxazine **10** (MIC = 3.17–12.50 mg/ml, MBC = 3.17–50 mg/ml, and MFC = 25–50 mg/ml) compounds, and slightly inhibitory effect with α-amino-γ-lactones series **1–4** (MIC = 3.17–25 mg/ml, MBC = 6.25–100 mg/ml, and MFC = 25–100 mg/ml). All the derivatives exhibited a potent α-glucosidase inhibitory activity with compound **10** (IC_{50} = 30.1 ± 0.6 µM) was found to be the most active. The druglikeness and pharmacokinetic profiles have been also predicted. The *in silico* results indicate that all derivatives showed a resemblance with several parameters of the antimicrobial standards, especially in terms of molecular property, bioavailability, lipophilicity, medicinal chemistry, and enzymatic inhibitory effects as well as they agree with the different drug discovery rules such as Lipinski (Pfizer), Ghose (Amgen), Veber (GlaxoSmithKline), Egan (Pharmacia), and Muegge (Bayer) displaying a higher druglikeness behavior.

INTRODUCTION

Currently, the gradual increase of infections caused by the higher resistance of bacteria and fungi and the widespread use of antibiotics are still the major concerns of human illness or even death due to the dramatically reduced effectiveness of drugs. To overcome the microbial resistance and their emergence, developing a new alternative of the potent antibacterial and antifungal agents with novel scaffolds is essential (Ghannay et al., 2017, 2020a). The α-glucosidase plays a vital role in carbohydrate metabolism and glycoprotein biosynthesis. Its inhibition by acarbose, miglitol, or voglibose is one of the important therapeutic approaches for the management of degenerative diseases, such as type 2 diabetes mellitus and also used to treat anti-HIV (Rawlings *et al*., 2009; Vichayanrat *et al*., 2020), anticancer (Pili *et al*., 1995), and anti-hepatitis diseases (Zitzmann *et al*., 1999). These inhibitors were associated with side effects, such as diarrhea and abdominal discomfort and possess the weaker IC_{50} values (Chougale *et al*., 2009). Therefore, there is an urgency to discover the safe and effective inhibitors of this key enzyme for the control of diabetic disorders.

In this context, we find that many families are eligible for these activities such as isoxazolidines (Chiacchio *et al*., 2016; Ghabi *et al*., 2020), α-amino-lactones (Abda *et al*., 2014), and

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amino acids and their derivatives (Zhou *et al*., 2019). The research work of our team revolves around the synthesis of new series of enantiopure polyfunctional isoxazolidines (Abda *et al*., 2016; Aouadi *et al*., 2006, 2013; Brahmi *et al*., 2016b), which are in turn transformed into aminoalcohol and/or amino acid derivatives (Aouadi *et al.*, 2007, 2008, 2012b), such as trifluoromethylated isoxazolidines (Ghannay *et al*., 2020a), 4-hydroxyisoleucine (Aouadi *et al.*, 2007, 2012b), and its analogs (Aouadi *et al.*, 2008, 2009). We can also give as an example for the synthesis of 4-hydroxy-L-ornithine (Aouadi *et al*., 2012a), 4-hydroxyproline derivatives (Brahmi *et al*., 2016a), 4-hydroxypyrrolidine derivatives (Cecioni *et al*., 2015), and pyrrolidine-2,5-dione derivatives (Ghannay *et al*., 2019).

In continuation of the drug discovery research toward the synthesis of bioactive heterocyclic compounds on potential antimicrobial and antidiabetic agents (Ghannay et al., 2017, 2020a, 2020b), we herein report the biological evaluation of antimicrobial and α-glucosidase inhibitory properties of some enantiopure cycloalkylglycines derivatives. Furthermore, the structure–activity relationship was thoroughly discussed. In addition, in order to get insights into their pharmacodynamic and pharmacokinetic profiles, the compounds were subjected to *in silico* molecular property and absorption, distribution, metabolism, and excretion (ADME) predictions using Molinspiration and SwissADME online software, respectively.

MATERIALS AND METHODS

Chemistry

The various compounds **1–15** were synthesized based on the cycloaddition reaction of a chiral nitrone with various cycloalkenes as was reported in the previous work (Abda *et al*., 2014) (Scheme 1). Basic processing of α-amino-γ-lactones **1–4** has provided the desired α-amino acids **11–15** (Abda *et al*., 2014). The structures of compounds **1–15** have been unambiguously reported (Abda *et al*., 2014).

Computational study

The molecular profile and druglikeness of the tested compounds have been assessed using Molinspiration software (https://www.molinspiration.com/cgi-bin/properties) (Ghannay *et al*., 2017) by calculating the different parameters as shown in Table 3.

The pharmacokinetic and druglikeness properties of the synthesized drugs, such as passive human gastrointestinal absorption (GI), blood–brain barrier (BBB) permeation, skin penetration coefficient, substrate or non-substrate of the permeability glycoprotein (P-gp), and interaction of molecules with five major isoforms of the human cytochromes P450 interfering in the metabolism of numerous endogenous and exogenous compounds, have been predicted using SwissADME online server (http://www.swissadme.ch/) (Daina *et al*., 2017). Furthermore, the medicinal chemistry characteristics such as PAINS for pan-assay interference compounds or promiscuous compounds, Brenk alert which inform about allegedly toxic, metabolically unstable, chemically reactive fragments present in the structure, and leadlikeness and synthetic accessibility have been investigated. In addition, the bioavailability radar was performed by visualizing the pink area that represents the optimal range of each property as plotted: lipophilicity (LIPO): −0.7 < XLOGP 3 < +5.0; SIZE: 150 g/mol < MW < 500 g/mol; POLAR (polarity): 20Å^2 < topological surface area (TPSA) < 130Å^2; INSOLU (insolubility): 0 < log S (ESOL) < 6; INSATU (insaturation): 0.25 < fraction of Csp3 < 1; and FLEX (flexibility): 0 < number of rotatable bonds < 9. Such molecule may be achieved as druglikeness if the pink colored zone of the radar plot of the molecule has to fall entirely in the red zone.

Antimicrobial activities

All the examined compounds were assayed for their antimicrobial activities against three Gram-positive [*Bacillus subtilis* JN 934392, *Bacillus cereus* JN 934390, and *Staphylococcus aureus* American Type Culture Collection (ATCC) 6538] and two Gram-negative (*Salmonella entericsero type Enteritidis* ATCC43972 and *Escherichia coli* ATCC 25922) bacterial strains and two fungal strains (*Fusarium oxysporum* and *Fusarium phyllophilum* AB 587006). The inhibition zone diameter (IZD), minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and minimum fungicidal concentration (MFC) were assessed based on the same protocol as described by Ghannay *et al.* (2020a). About 40 ml of the used agar was poured into Petri dishes. After solidification, 150 ml of the bacterial suspension was speared on the surface. After 5 minutes of contact, the wells with a diameter of 6 mm were excavated in the agar, and each well was filled with 80 µl of each extract (75 mg/ml). Finally, the Petri dishes were incubated in an oven at 37°C for 48 hours.

α-Glucosidase inhibition assay

All targets were tested for their α-glucosidase inhibitory activity using the same protocol as done by Ghabi *et al.* (2020). The % inhibition was determined as follows: % inhibition = $[(Abs_{control} - Abs_{sample})/Abs_{control}] \times 100$, and the IC_{50} values were obtained from the nonlinear regression curve.

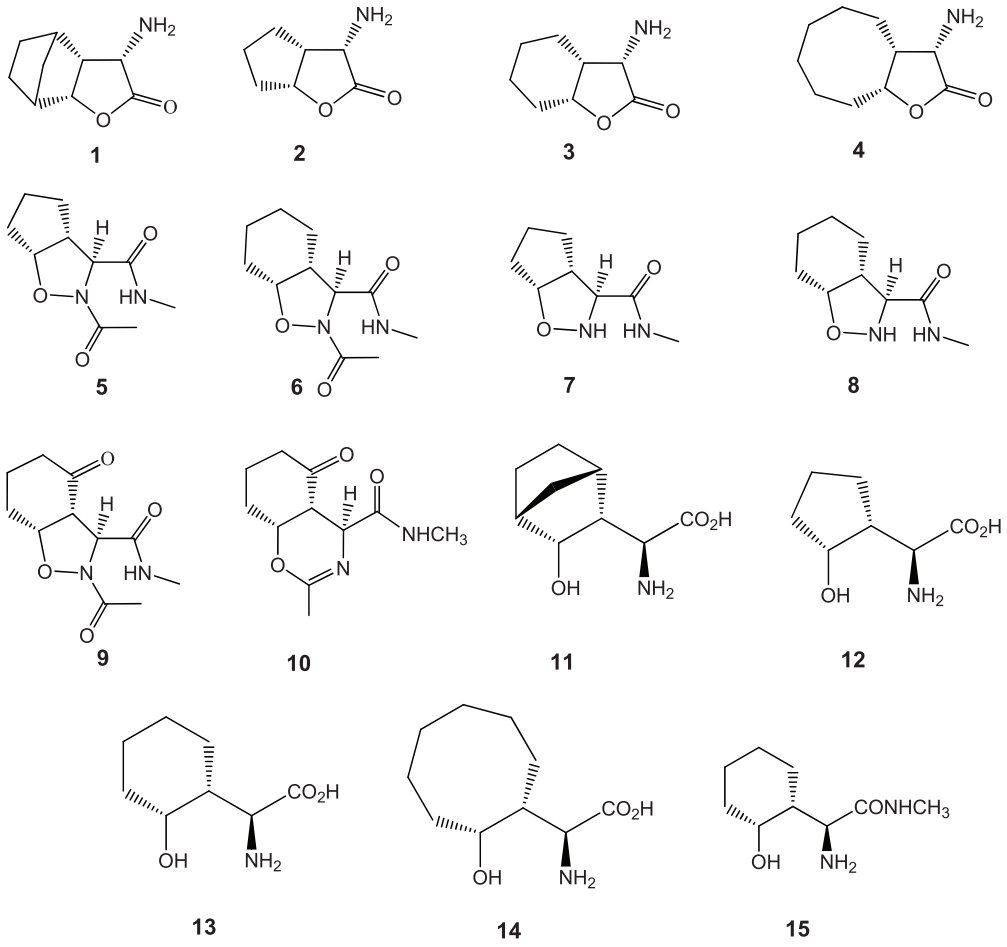
Statistical analysis

All assays were carried out in triplicates, and the results were reported as mean ± standard error calculated by Microsoft Excel 2013.

RESULTS AND DISCUSSION

Antimicrobial properties

As can be seen from the summarized outcomes (Table 1), the α-amino-γ-lactones **1–4** derivatives showed a good-to-moderate antibacterial potencies with the most potent activity observed for compound **2** against *S. aureus* (IZD = 19.00 ± 0.00 mm, MIC = 3.17 mg/ml, and MBC = 6.25 mg/ml) and *B. subtilis* (IZD = 23.00 ± 0.88 mm, MIC = 6.25 mg/ml, and MBC = 12.50 mg/ml) compared to standard drug chloramphenicol. The inhibitory effect of isoxazolidine derivatives **5–9** was similar or even better than standard drugs for compounds **9**, **5**, and **6** against *S. aureus*, for **9** and **5** against *B. subtilis*, and for **9** against



Scheme 1. Structure of compounds **1**–**15**.

B. cereus. Toward Gram-negative strains, these compounds displayed moderate activities. The oxazine derivative **10** has shown a higher potency antimicrobial effect against *S. aureus* and *B. cereus,* very close activity toward *B. subtilis*, *E. coli*, and *S. enteritidis* strains. Regarding the γ-hydroxy-α-amino acid compounds **11–14**, they exhibited better antibacterial properties than the standard drug chloramphenicol with compound **12** which was identified as the most potent, especially against *S. aureus* followed by those **13**, **11**, and **14** which are, respectively, 1.58, 1.47, 1.17, and 0.94 folds higher than chloramphenicol. In addition, compounds **12** and **13** were proved to be more susceptible than **11** and **14** against *E. coli* and *S. enteritidis.* Compound **15** exhibited a moderate-to-mild activity against the tested strains. According to the obtained IZD, MIC, and MFC values (Tables 1 and 2), it was found that all the tested compounds exerted varying degrees of inhibition against *F. oxysporum* and *F. phyllophilum* (except compound **4** for *F. phyllophilum*), in which some of them are good and some are moderately active when compared with the positive control, cycloheximide, with the best inhibitory activity was ascribed for compounds **12** and **13**. The detail results are shown in Table 1.

The results of this study showed that the majority of the compounds displayed a higher bactericidal effect, especially with Gram-positive bacteria in comparison to those Gram negative. Some of them exerted a fungicidal effect against *F. oxysporum* (compounds **2**, **5–7**, and **9–14**) and *F. phyllophilum* (compounds **2**, **5–6**, and **9–13**). The rest are bacteriostatic or fungistatic.

In vitro α-glucosidase inhibitory activity

The results presented in Table 1 showed that the IC_{50} values of all compounds are in the range of 30.1 ± 0.6–256.2 ± 0.5 µM when compared with the positive control acarbose (IC_{50} = 780.4 ± 0.3 µM). Among them, compounds **10**, **9**, **5**, and **6** exhibited the strongest inhibitory activities which are, respectively, about 26, 22, 17, and 14 times higher than the reference, acarbose.

Structure–activity relationships (SARs) of the synthesized compounds

The structure–activity relationship study of the tested compounds has shown that the antimicrobial potency of the title compounds undergoes the following order: α-γ-hydroxy-α-amino acids **11–14** followed by isoxazine **10**, isoxazolidines **5–9,** and in less degree α-amino-γ-lactones **1–4**. It is worth mentioning that the variation in the susceptibility of the

Table 1. Antimicrobial (IZD) and α-glucosidase (IC_{50}) inhibitory activity of the synthesized compounds.

Entry	[a]IZD (mm)							IC_{50} (µM)
	Gram-positive strains			Gram-negative strains		Fungal strains		
	S. aureus	*B. subtilis*	*B. cereus*	*E. coli*	*S. enteritidis*	*F. oxysporum*	*F. phyllophilum*	
1	12.00 ± 0.22	14.00 ± 0.00	18.00 ± 0.22	19.00 ± 0.00	10.00 ± 0.22	12.00 ± 0.22	11.00 ± 0.00	240.6 ± 0.8
2	19.00 ± 0.00	23.00 ± 0.88	21.00 ± 0.00	21.00 ± 0.22	13.00 ± 0.33	18.00 ± 0.00	15.00 ± 0.33	207.2 ± 0.3
3	13.00 ± 0.33	20.00 ± 0.22	14.00 ± 0.00	20.00 ± 0.88	11.00 ± 0.00	15.00 ± 0.33	13.00 ± 0.33	229.5 ± 0.2
4	10.00 ± 0.00	15.00 ± 0.00	–	14.00 ± 0.33	–	08.00 ± 0.88	–	256.2 ± 0.5
5	20.00 ± 0.88	24.00 ± 0.88	22.00 ± 0.33	20.00 ± 0.00	14.00 ± 0.33	19.00 ± 0.22	15.00 ± 0.22	46.3 ± 0.5
6	18.00 ± 0.33	21.00 ± 0.33	18.00 ± 0.88	18.00 ± 0.33	12.00 ± 0.22	16.00 ± 0.00	12.00 ± 0.33	54.5 ± 0.8
7	16.00 ± 0.88	20.00 ± 0.22	21.00 ± 0.00	15.00 ± 0.00	12.00 ± 0.33	14.00 ± 0.33	10.00 ± 0.22	72.8 ± 0.4
8	14.00 ± 0.33	16.00 ± 0.33	18.00 ± 0.00	11.00 ± 0.22	08.00 ± 0.88	11.00 ± 0.22	08.00 ± 0.00	79.4 ± 0.7
9	22.00 ± 0.22	26.00 ± 0.00	27.00 ± 0.22	22.00 ± 0.00	16.00 ± 0.33	18.00 ± 0.33	16.00 ± 0.33	36.2 ± 0.2
10	24.00 ± 0.88	24.00 ± 0.33	29.00 ± 0.00	22.00 ± 0.33	17.00 ± 0.22	15.00 ± 0.22	14.00 ± 0.00	30.1 ± 0.6
11	20.00 ± 0.00	23.00 ± 0.88	22.00 ± 0.22	16.00 ± 0.33	13.00 ± 0.88	16.00 ± 0.00	14.00 ± 0.88	134.6 ± 0.3
12	27.00 ± 0.33	30.00 ± 0.00	29.00 ± 0.00	23.00 ± 0.88	18.00 ± 0.88	18.00 ± 0.00	20.00 ± 0.22	116.7 ± 0.3
13	25.00 ± 0.22	28.00 ± 0.00	27.00 ± 0.22	20.00 ± 0.00	17.00 ± 0.33	17.00 ± 0.33	18.00 ± 0.88	124.4 ± 0.5
14	16.00 ± 0.33	22.00 ± 0.33	19.00 ± 0.00	14.00 ± 0.33	11.00 ± 0.22	16.00 ± 0.00	10.00 ± 0.33	146.2 ± 0.4
15	12.00 ± 0.88	16.00 ± 0.22	18.00 ± 0.33	12.00 ± 0.00	9.00 ± 0.33	10.00 ± 0.22	08.00 ± 0.00	105.4 ± 0.9
Chloramphenicol	17.00 ± 1.00	24.00 ± 0.00	26.00 ± 1.00	23.50 ± 0.00	16.00 ± 0.00	–	–	–
Cycloheximide	–	–	–	–	–	20.00 ± 2.00	18.00 ± 1.50	–
Acarbose	–	–	–	–	–	–	–	780.4 ± 0.3

The data are expressed as mean ± S.D. (n = 3).

[a]Diameter of inhibition zones of extract including diameter of well 6 mm.

Table 2. Determination of MIC, MBC, MBC/MIC, and MFC/MIC of the synthesized compounds.

Strains	MIC, MBC, MBC/MIC, and MFC/MIC																				
	Gram-positive strains									Gram-negative strains						Fungal strains					
	S. aureus			*B. subtilis*			*B. cereus*			*E. coli*			*S. enteritidis*			*F. oxysporum*			*F. phyllophilum*		
Entry	MIC	MBC	*	MIC	MBC	*	MIC	MBC	*	MIC	MBC	*	MIC	MBC	*	MIC	MFC	**	MIC	MFC	**
1	12.50	50	4	12.50	25	2	6.25	12.50	2	6.25	25	4	12.50	50	4	12.50	100	8	12.50	100	8
2	3.17	6.25	2	6.25	12.50	2	3.17	6.25	2	3.17	6.25	2	12.50	50	4	6.25	25	4	12.50	50	4
3	12.50	100	8	6.25	50	8	12.50	100	8	12.50	100	8	6.25	50	8	12.50	100	8	–	–	–
4	25	50	2	12.50	25	2	–	–	–	12.50	100	8	–	–	–	12.50	100	8	6.25	50	8
5	3.17	6.25	2	3.17	6.25	2	3.17	6.25	2	6.25	12.50	2	6.25	12.50	2	6.25	12.50	2	6.25	25	4
6	6.25	12.50	2	3.17	6.25	2	6.25	25	4	6.25	25	4	12.50	50	4	6.25	25	4	12.50	50	4
7	12.50	25	2	6.25	12.50	2	3.17	12.50	4	12.50	100	8	12.50	100	8	12.50	50	4	12.50	100	8
8	12.50	25	2	12.50	50	4	6.25	25	4	12.50	100	8	12.50	100	8	12.50	100	8	12.50	100	8
9	3.17	6.25	2	3.17	12.5	4	1.58	3.17	2	3.17	6.25	2	12.50	25	2	6.25	12.50	2	12.50	25	2
10	3.17	6.25	2	1.58	3.17	2	1.58	6.25	4	6.25	25	4	12.50	50	4	12.50	25	2	12.50	50	4
11	6.25	12.50	2	3.17	6.25	2	3.17	6.25	2	12.50	50	4	12.50	50	4	6.25	25	4	12.50	50	4
12	1.58	3.17	2	1.58	3.17	2	1.58	3.17	2	3.17	6.25	2	6.25	12.50	2	6.25	12.50	2	3.17	6.25	2
13	1.58	3.17	2	1.58	3.17	2	1.58	3.17	2	6.25	12.50	2	6.25	12.50	2	6.25	25	4	6.25	12.50	2
14	12.50	25	2	3.17	6.25	2	6.25	12.50	4	12.50	50	4	12.50	100	8	12.50	50	4	12.50	12.50	8
15	12.50	25	2	12.50	25	2	6.25	12.50	4	12.50	100	8	12.50	100	8	12.50	100	8	12.50	100	8

*MBC/MIC;**MFC/MIC.

examined compounds against the different tested strains depends either on the cell wall of microorganisms or the structure of used derivatives which explain the effectiveness degree of each one. In fact, the cellular wall of Gram strains is formed by a thick lipoprotein–lipopolysaccharide layer which covered a thin layer of peptidoglycan and is very susceptible to the examined cycloalkylglycine derivatives. For α-amino-γ-lactone derivatives **1–4**, the antimicrobial activity enhanced as the size of saturated

carbocyclic ring attached to the lactone moiety decreased with the lowest one, which was observed with (1S,4S)-bicyclo[2.2.1] heptyl and cycloheptyl group, suggesting that a longer carbon chain does not promote activity. On the other hand, regarding the isoxazolidines series **5–9**, the powerful antimicrobial activity was found for all compounds in comparison with that of α-amino-γ-lactone series, owing to the existence of heterocyclic nucleus. Comparing compounds **5** and **6** with those **7** and **8**, respectively, it was found that the presence of acetyl substituent attached to the nitrogen (**5** and **6**) seems to intensify the antimicrobial profile which is in well agreement with the finding of Chawla *et al*. (2010). Furthermore, when we compare compound **9** with oxo-group attached to the saturated carbocyclic ring, to compound **8**, we show an increase in the inhibition effect due to its withdrawing exerted effect. In addition, the presence of toxophoric –N=C–O– linkage group (compound **10**) enhanced the antimicrobial activity in comparison with compound **9**, especially against bacterial strains, due to their facility to react with the nucleophilic centers of the microbial cells (Zheng *et al*., 2018). Comparing γ-hydroxy-α-amino acid derivatives to those of α-amino-γ-lactones, we can conclude that the ones with carboxylic acid group as well as the hydroxycarbocyclic ring exhibited a better inhibitory activity against the examined strains. The highest antimicrobial potency of compound **12** may be explained by the lowest size of saturated carbocyclic ring attached to the α-amino acid moiety as compared to those **13**, **14**, and **11**.

To optimize the α-glucosidase inhibitory potential of the designed scaffold, we are interested to study their SARs. Indeed, the best inhibitory effect was observed with isoxazine (IC_{50} = 30.1 µM), followed by isoxazolidines (36.2 µM < IC_{50} < 79.4 µM), α-γ-hydroxy-α-amino acids (105.4 µM < IC_{50} < 146.2 µM), and α-amino-γ-lactones (207.2 µM < IC_{50} < 256.2 µM). The higher inhibitory activity of compound **10** can be attributed to the presence of oxazine group. In isoxazolidines series, compound **9** with both acetyl and oxo-as electron withdrawing groups attached, respectively, to the nitrogen and saturated carbocyclic ring have displayed the strongest inhibitory activity against α-glucosidase enzyme, followed by **5**, in which the saturated carbocyclic ring did not have attached oxo-group. As the size of the carbocyclic ring increased, the activity was reduced (**5** *vs*. **6** and **7** *vs*. **8**). The removal of acetyl group (compounds **7** and **8**) in comparison with those **5** and **6** also decreased the inhibitory activity, respectively. The inhibitory activity of α-amino-γ-lactones derivatives is due essentially to the presence of aminolactone moiety with the most potent inhibitory effect ascribed to compound **2** which increased generally with decreasing the size of the present carbocyclic ring.

Physicochemical, bioactivity score, and pharmacokinetic profiles

The synthesized compounds were subjected to the prediction of their ADME properties such as oral bioavailability, pharmacokinetic parameters, and the toxicity risks using an *in silico* Molinspiration and SwissADME tools. We explore the concept of druglikeness to reduce the failure in clinical trials.

Physicochemical properties

As can be seen from the results shown in Table 3, there are no violations of Lipinski's rule of five, and therefore, all the tested molecules are expected to be viable drug candidates.

Table 3. ADME properties of compounds **1–15** according to pre-ADMET software.

Entry	m_ilogP^a	TPSA[b]	%ABS[c]	N^d_{atoms}	MW[e]	$N_{ON}{}^f$	$N_{OHNH}{}^g$	$N_{viol}{}^h$	$N_{roth.}{}^i$	Vol[j]	GPCRL[k]	ICM[l]	KI[m]	NCR[n]	PI[o]	EI[p]
1	−0.87	52.33	90.95	12	167.21	3	2	0	0	153.91	−0.42	−0.45	−1.07	−0.84	−0.55	0.04
2	−1.24	52.33	90.95	10	141.17	3	2	0	0	131.10	−0.72	−0.42	−1.40	−1.13	−0.52	−0.07
3	−0.73	52.33	90.95	11	155.20	3	2	0	0	147.90	−0.59	−0.30	−1.20	−0.79	−0.60	0.05
4	0.28	52.33	90.95	13	183.25	3	2	0	0	181.50	−0.38	−0.16	−0.88	−0.53	−0.40	0.15
5	−0.12	58.64	88.77	15	212.25	5	1	0	1	197.10	0.04	0.02	−0.60	−0.44	0.15	0.21
6	0.39	58.64	88.77	16	226.28	5	1	0	1	213.90	0.09	0.06	−0.49	−0.39	0.22	0.19
7	0.28	50.36	91.63	12	170.21	4	2	0	1	161.17	−0.36	−0.10	−0.86	−0.91	−0.17	−0.12
8	0.78	50.36	91.63	13	184.24	4	2	0	1	177.98	−0.28	−0.03	−0.72	−0.83	−0.08	−0.11
9	−0.95	75.71	82.88	17	240.26	6	1	0	1	216.08	0.01	−0.01	−0.72	−0.27	0.17	0.21
10	−0.01	67.77	85.62	16	224.26	5	1	0	1	207.58	−0.34	−0.21	−1.17	−0.45	−0.14	0.08
11	−2.03	83.55	80.17	13	185.22	4	4	0	2	171.80	−0.22	0.03	−0.99	−0.58	−0.23	0.34
12	−2.40	83.55	80.17	11	159.19	4	4	0	2	148.99	−0.20	0.14	−1.03	−0.45	−0.23	0.40
13	−1.90	83.55	80.17	12	173.21	4	4	0	2	165.79	−0.25	0.32	−0.94	−0.45	−0.03	0.39
14	−0.89	83.55	80.17	14	201.27	4	4	0	2	199.40	−0.09	0.36	−0.67	−0.23	0.10	0.43
15	−1.08	75.35	83.00	12	172.23	4	4	0	2	169.94	0.00	−0.10	−0.57	−0.68	0.29	0.34
Chloramphenicol	0.73	115.38	70.40	20	323.13	7	3	0	6	249.16	−0.22	−0.28	−0.38	−0.41	−0.21	−0.00
Cycloheximide	0.76	83.47	80.98	20	281.35	5	2	0	3	269.59	−0.04	−0.21	−0.64	−0.03	0.40	0.26

For bioactivity score (> 0: active, −5.00–0.00: moderately active, < −5.00: inactive).

[a]Octanol-water partition coefficient, calculated by the methodology developed by Molinspiration (<5). [b]Topological polar surface area. [c]%ABS = 109 – (0.3345 × TPSA). [d]Number of nonhydrogen atoms. [e]Molecular weight (< 500). [f]Number of hydrogen-bond acceptors (O and N atoms, <10). [g]Number of hydrogen-bond donors (OH and NH groups, <5). [h]Number of "five" violations. [i]Number of rotatable bonds(<10). [j]Molecular volume. [k]GPCR ligand. [l]Ion channel modulator. [m]Kinase inhibitor. [n]Protease inhibitor. [o]Nuclear receptor ligand. [p]Enzyme inhibitor.

The low molecular weights revealed that all molecules are likely to be readily diffused, absorbed, or transported across cell membrane compared to bulky drug molecules. LIPO (miLogP) values of the title molecules range between −2.40 and 0.78, outlining various possible biological sites with higher hydrophilicity. The TPSA values of the selected compounds were ≤83.55 Å, suggesting a good intestinal absorption and BBB penetration, which also make compounds **6** and **7** (with the lowest TPSA level 50.36 Å) as a promising drug candidate for further research and development. The %ABS of the title compounds demonstrate high %ABS (≥80%), which is an indicator for good oral absorption. Usually, the compounds having more than 80% absorption should possess a good passive oral absorption and can be considered as a good drug. The number of rotatable bonds of the synthesized compounds is in the range $0 \leq N_{rotb} \leq 2$, pointing out their very low conformational flexibility which makes them potentially bioavailable by an oral route. A number of hydrogen bond donors N_{OHNH} ($1 \leq N_{OHNH} \leq 4$) and hydrogen bond acceptors N_{ON} ($3 \leq N_{ON} \leq 6$) are in good accordance with the Lipinski's rule of five and, therefore, reinforce their oral druglikeness properties.

Bioactivity score

The results are analyzed as shown in Table 3, and it was observed that all the evaluated compounds exhibited poor interaction with Kinase inhibitor (KI), poor-to-moderate interaction with nuclear receptor ligand, poor-to-higher interaction with G protein-coupled receptors (GPCRL) and Protease inhibitor (PI), and moderate-to-higher interaction with ICM and Enzyme inhibitor (EI). Interestingly, we note that the most promising compounds as per the bioactivity scores were identified to be **6** > **5** > **9** which are predicted to act by more than three mechanisms. The identified compounds were in applicable domain of bioactivity score as chloramphenicol and cyclohexamide for all drug targets.

Pharmacokinetic druglikeness and medicinal chemistry properties

The pharmacokinetic characteristics (Table 4) state that all the targets are predicted to possess good GI absorption, are not P-gp substrates, and therefore, do not cause any problem in the excretion of drug and also not able to inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, suggesting that they have no toxic ADME properties without accumulation of drug/metabolites. Their negative log *K*p values are in the range from −8.93 (**12**) to −5.78 (**4**) indicating their lowest ability to penetrate through the skin. Druglikeness parameters of the title compounds can be easily assessed from bioavailability radars as expressed in pink area by the optimal range for each property (LIPO, size, polarity, solubility, saturation, and flexibility). The results shown in Table 4 indicated that all analogs displayed

Table 4. Pharmacokinetics, medicinal chemistry and druglikeness of compounds **1–15** according to SwissADME software.

Entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pharmacokinetics															
GI absorption	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High
BBB permeant	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
P-gp substrate	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Log Kp (skin permeation cm/s)	–6.85	–7.03	–6.73	–5.78	–7.53	–7.23	–7.22	–6.92	–8.34	–7.94	–8.75	–8.93	–8.63	–8.02	–7.27
Druglikeness															
Lipinski	1.57	1.32	1.47	2.29	2.33	1.91	1.67	1.90	1.63	1.63	1.21	1.02	1.38	1.17	1.19
Ghose	0.66	0.18	0.73	2.29	0.09	0.63	0.17	0.71	–0.81	–0.38	–1.86	–2.33	–1.79	–0.70	0.24
Veber	0.29	0.04	0.43	2.20	–0.32	0.07	–0.58	–0.19	–0.75	–0.09	–0.19	–0.44	–0.05	0.73	–0.39
Egan	1.00	0.35	0.69	1.67	0.33	0.62	0.24	0.56	–0.29	0.12	–2.06	–2.71	–2.38	–1.76	–0.25
Muegge	0.55	0.49	0.72	1.84	–0.11	0.14	0.11	0.36	–0.16	1.41	–0.41	–0.54	–0.27	0.26	–0.09
Bioavailability score	0.81	0.48	0.81	2.06	0.46	0.68	0.32	0.67	–0.08	0.54	–0.66	–1.00	–0.62	–0.06	0.14
Medicinal chemistry															
PAINS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Brenk	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Leadlikeness	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Synthetic accessibility	3.20	3.78	3.87	3.67	3.77	3.87	3.73	3.83	3.90	4.04	3.79	2.63	2.72	2.86	2.66

an excellent oral bioavailability with a bioavailability score of 0.55. Testing five druglikeness methods, all the designed drug molecules follow completely the Lipinski's (for Pfizer), Egan's (for Pharmacia), and Veber's (for GlaxoSmithKline) rules; however, only compounds 1, 4–6, 8, 10–11, and 13–15 as well as 6, 9–10, and 14 do not violate Ghose's (for Amgen) and Muegge's (for Bayer) rules, respectively. The medicinal chemistry properties of these compounds have been predicted, and the results (Table 4) revealed that the synthetic accessibility scored approximately from 2.5 to 4.0, indicating that all the compounds possess good feasibility to be synthesized. All compounds return any pan-assay interference compounds (PAINS) and Brenk alerts. The polygon of physicochemical space (Fig. 1) showed that all parameters fall in the optimal range, and therefore, all the compounds possess a good oral bioavailability better than the tested standards.

Continued

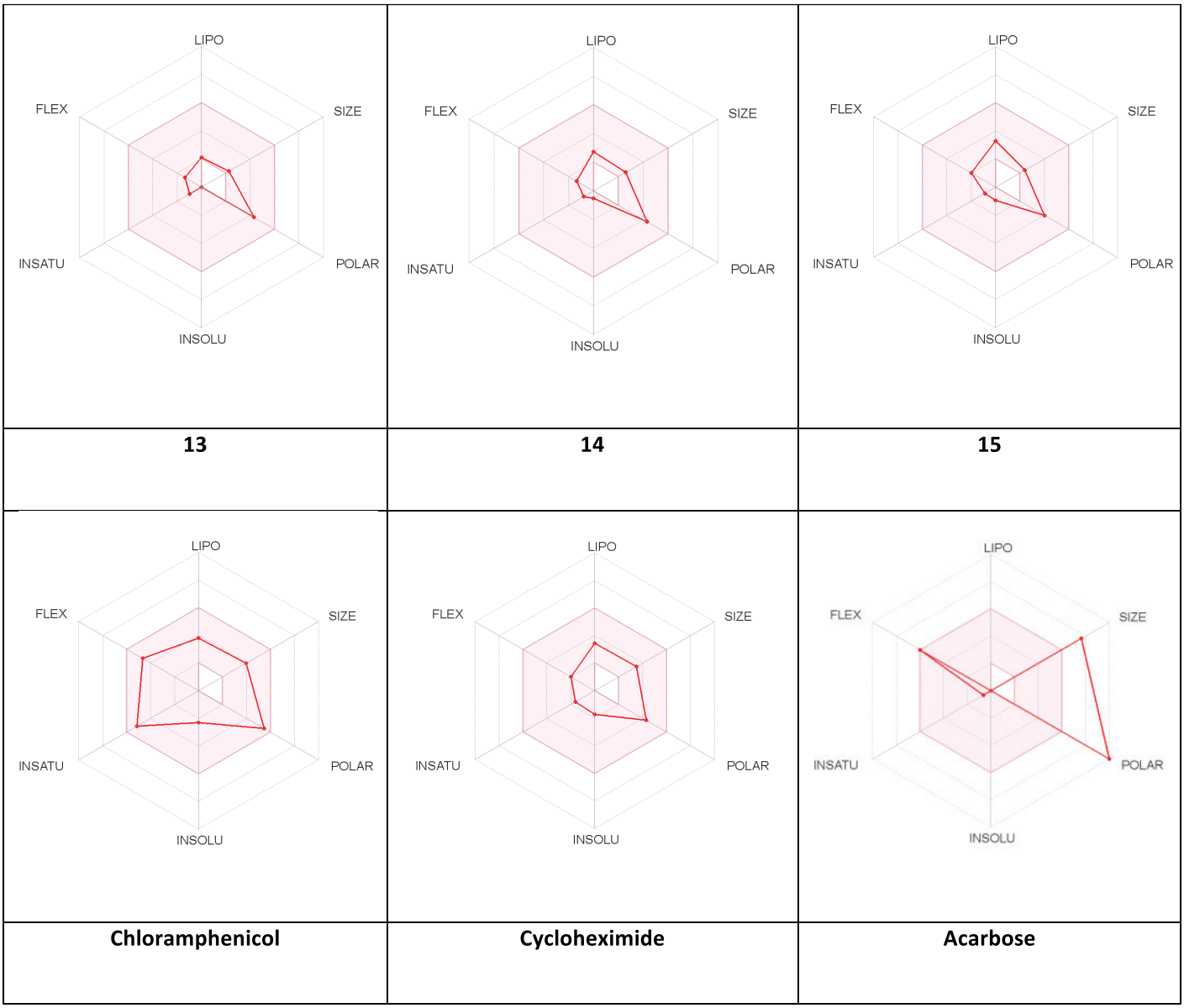


Figure 1. Bioavailability radar of compounds (1–15) using Swiss ADME predictor. The pink area represents the optimal range for each property (LIPO, size, polarity, solubility, saturation and flexibility).

CONCLUSION

In summary, a series of enantiopure cycloalkylglycines derivatives have been evaluated for their antimicrobial and α-glucosidase inhibitory activity. All targets showed a promising antimicrobial activity against different pathogenic strains with the most potent activity was observed, essentially toward Gram-positive strains. Among the different series, γ-hydroxy-α-amino acids exhibited the strongest inhibitory effect followed by oxazine and isoxazolidines compounds and in less degree α-amino-γ-lactones, respectively. Regarding the α-glucosidase inhibitory activity, the results show that the synthesized compounds displayed a significant activity with most potent activity, which was allowed to isoxazine followed by isoxazolidines, γ-hydroxy-α-amino acids, and α-amino-γ-lactones. The physicochemical and ADME parameters show that the reported analogs have a good oral bioavailability and, therefore, could be favorable hit candidates after a systematic *in vivo* analysis for the further drug discovery of new antimicrobial and antidiabetic agents.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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