Stereoselective synthesis and application of isopulegol-based bi- and trifunctional chiral compounds†

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A new family of isopulegol-based bi- and trifunctional chiral ligands was developed from commercially available (−)-isopulegol. Nucleophilic addition of primary amines towards (+)-α-methylene-γ-butyrolactone was accomplished, followed by reduction of the obtained β-aminolactones to provide aminodiols in highly stereoselective reactions. Epoxidation of (−)-isopulegol and subsequent oxirane ring opening with primary amines resulted in N-substituted aminodiols. The regioselective ring closure of these aminodiols with formaldehyde was also investigated. Benzylolation of isopulegol furnished O-benzyl-protected isopulegol, which was transformed into aminoaacohols via epoxidation and ring opening of the corresponding epoxides. First benzyl-protected isopulegol was subjected to hydroxylation and epoxidation, then aminolysis of the served oxiranes delivered aminodiols. On the other hand, (−)-isopulegol was oxidised to diol, which was again converted into both dibenzyl- and monobenzyl-protected diol derivatives. The products were transformed into aminoaacohols and aminodiols, respectively, by aminolysis of their epoxides. The ring opening of epoxides, derived from diols with primary amines was also performed producing aminotriols. Dihydroxylation of (−)-isopulegol or derivatives with OsO4/NMO gave isopulegol-based di-, tri- and tetaols. The antimicrobial activity and antioxidant property, measuring DPPH" radical scavenging activity of aminodiol and aminotriol derivatives as well as di-, tri- and tetaols were also explored. In addition, structure–activity relationships were examined from the aspects of substituent effects and stereochemistry on the aminodiol and aminotriol systems.

Introduction

Monoterpenes constitute an interesting group of plant secondary metabolites.1,2 They are readily available, relatively nontoxic and inexpensive constituents. Moreover, monoterpenes possess many important pharmacological activities.3 For example, limonene and perillyl alcohol have chemopreventive activity against cancer,4,6 whereas linalool and eucalyptol exert synergistic antiproliferative and anticholinesterase effects.7,8 In addition, some of these compounds, such as 1,8-cineole, geraniol, linalool,9 thymol10 along with limonene, α-pinene, β-pinene, γ-terpinene and linalyl acetate,8 as well as santolina alcohol, borneol, sabinol, trans-sabinyl acetate and α-thujone,11 have been found to be relatively potent DPPH" radical scavengers. This property is directly related to their structures.11 It is worth pointing out that essential oils also display excellent antimicrobial activity.12-14 For instance, linalool and α-terpinene exhibited strong activity against periodontopathic and cariogenic bacteria,15 while citral, linalool and β-pinene had an effect on Saccharomyces cerevisiae.16 Furthermore, linalyl acetate, (+)-menthol and thymol were found to be efficient against Staphylococcus aureus and Escherichia coli,17 while thymol, carvacrol, p-cymene and γ-terpinene showed inhibitory activity towards S. aureus and E. coli.18 Apart from proven properties, many monoterpenes exert antibiotic,19,20 nematicidal,21 anti-inflammatory22,23 and analgesic24 influences. Some monoterpenes are used as important flavour agents in foods, drinks, perfumes, cosmetics and tobacco,25 while others such as 1,8-cineole and pinene26 have been considered as important biopesticides. Monoterpenes, therefore, are widely used in medicine, industry and agriculture.26-28
We have planned to combine aminodiol moieties of cardiovascular, cytostatic and antiviral effectiveness with monoterpenic skeletons.\textsuperscript{31–33} Aristomycin analogues, for example, are widely used as effective agents against a range of viruses, including the human immunodeficiency, hepatitis B, herpes simplex, varicella-zoster, influenza and hepatitis C viruses.\textsuperscript{34–36} The Abbott aminodiol, found to be a useful building block for the preparation of potent renin inhibitors Zankiren\textsuperscript{®} and Enalkiren\textsuperscript{®}, was introduced into the therapy of hypertension.\textsuperscript{37,38} Aminodiols can also exert antidepressive activity. For instance, (S,S)-reboxetine is a selective norepinephrine reuptake inhibitor for the treatment of unipolar depression,\textsuperscript{39} while others such as (2R,3R,7Z)-2-amino-10,12-tridecadiene-13-diol are potent antimicrobial metabolites.\textsuperscript{40} Besides their varied, well-known influences, aminodiols may serve as starting materials for the synthesis of biologically active natural compounds, e.g. cytoxazone, a selective modulator of the secretion of T_{h}2 cytokine.\textsuperscript{41,42} Apart from their biological interest, monoterpenic-based aminodiols have been demonstrated to be excellent chiral auxiliaries in a wide range of stereoselective transformations including intramolecular radical cyclisation,\textsuperscript{43} intramolecular \([2 + 2]\) photocycloaddition\textsuperscript{44} and Grignard addition.\textsuperscript{45,46}

In order to combine the properties of monoterpenes and aminodiols as well as to develop new, efficient and commercially available chiral ligands, naturally occurring chiral monoterpenes such as (+) and (−)-\(\alpha\)-pinene,\textsuperscript{47–49} (+)-carene,\textsuperscript{50,51} (+)-camphor,\textsuperscript{52,53} (−)-fenchone,\textsuperscript{54} (−)-menthone,\textsuperscript{55} (−)-myrtenol,\textsuperscript{56,57} (+)-neoisopulegol,\textsuperscript{58,59} (S)-perillyl alcohol,\textsuperscript{60} (−)-pulegone,\textsuperscript{61} or (−)-sabinol\textsuperscript{62} have been widely used as key intermediates for the synthesis of aminodiols.

Monoterpene-based diols also possess marked biological properties, e.g. antiparkinsonian activity\textsuperscript{63} and skin microcirculatory improvement,\textsuperscript{64,65} whereas monoterpenic-based triols have been utilised as cytotoxic\textsuperscript{66,67} and anti-inflammatory agents.\textsuperscript{68}

Therefore, our primary objective of the present research was to prepare a new library of isopulegol-based bi-, tri- or even tetrafunctionalised chiral synthons, such as aminodiols and aminotriols as well as di-, tri- and tetraols, starting from commercially available natural (−)-isopulegol and to evaluate the influence of these new isopulegol derivatives on antimicrobial attributes on multiple bacterial and yeast strains and their DPPH\textsuperscript{1} free-radical scavenging activity.

Results and discussion

The key intermediate (+)-\(\alpha\)-methylene-\(\gamma\)-butyrolactone 4 was prepared from commercially available (−)-isopulegol 1. Acetylation of alcohol 1 to its acetate 2, followed by regioselective oxidation of 2 gave diol 3, which was transformed to lactone 4 by two-step oxidation and ring closure of obtained \(\gamma\)-hydroxy-substituted \(\alpha,\beta\)-unsaturated carboxylic acid applying literature methods (Fig. 1).\textsuperscript{69–74}

Nucleophilic addition of primary amines to \(\alpha\)-methylene-\(\gamma\)-butyrolactone 4 has proved to be an efficient method for the preparation of a highly diversified library of \(\beta\)-aminolactones 5–8.\textsuperscript{58,75} Treatment of \(\beta\)-aminolactones with Li\(\text{AlH}_4\) resulted in secondary aminolactons 9–12. Debenzylation via hydrogenolysis of aminolactons 9–11 over Pd/C in MeOH gave primary aminolacton 13 in moderate yields. In order to study the regioselectivity of ring closure of the aminolacton function, we attempted to incorporate one of the hydroxy groups of aminolactons into 1,3-oxazinane or 1,3-oxazepinane rings.\textsuperscript{51,61,76} When aminolacton 9–12 were reacted with HCHO under mild conditions, 1,3-oxazinanes were obtained in highly regioselective ring closure. Since either the hydrogenolysis of \(N\)-benzyl analogues 9–11 or the formation of the oxazine ring system (14–17) had no effect on the absolute configuration, the relative configuration of the chiral centres of 13–17 is known to be the same as that of 9–12 (Scheme 1).\textsuperscript{31,76}

Dihydroxylation of 4 with the Os\(\text{O}_2\)/NMO system furnished 18 in low yield.\textsuperscript{51,61} The ring opening of \(\alpha,\beta\)-dihydroxylactone 18 was performed by using 4 equivalents of primary amines under reflux conditions in anhydrous THF to form \(\alpha,\beta\)-dihydroxyamides 19–21. It is important to mention that the ring opening of lactones with (R)- and (S)-\(\alpha\)-methylbenzylamine required longer reactions than utilizing benzylamine. This is probably due to steric hindrance exerted by the \(\alpha\)-methyl group (Scheme 1). Note that the acylation of diols bearing an adjacent amide function forms an important structural moiety with potential biological applications.\textsuperscript{77} For example, asterobactin and vio-prolide A have been identified as a new antibiotic and a new antifungal peptolide, respectively.\textsuperscript{78–79}

The relative configuration of compound 18 was determined by means of NOESY experiments: clear NOE signals were
observed between the OH-8 and H-3 as well as OH-9 and H-4 protons (Fig. 2).

Homoallylic epoxidation of (−)-isopulegol 1 with m-CPBA provided a 1 : 1 mixture of epoxides 23a and 23b in good yield. The two epoxides were separated by column chromatography to give more polar isomer 23a and less polar isomer 23b. The ring opening of epoxy 23a with different primary amines in the presence of LiClO4 as catalyst delivered aminodiols 24a–27a. 

Debenzylation of 24a–26a by hydrogenolysis over Pd/C in MeOH resulted in aminodiol 28a in excellent yields. When aminodiols 24a–27a were treated with HCHO at room temperature, oxazolidines 29a–32a were obtained via highly regioselective ring closures, similar to the regioisomeric 1,3-oxazinane analogues. The other epoxide 23b underwent similar reactions to afford 24b–32b in excellent yields. Dihydroxylation of (−)-isopulegol 1 was performed with OsO4 in the presence of a stoichiometric amount of co-oxidant NMO to afford a diastereoisomeric mixture of 22a and 22b in a ratio of 1 : 1. The epimeric mixture was purified by column chromatography followed by recrystallisation to provide 22b in crystalline form and 22a as a colourless oil (Scheme 2).

Gram-scale separation of 23a and 23b turned out to be difficult. In order to enhance the resolution by column chromatography, benzyl-protected isopulegol 33 was prepared.

Epoxidation of 33 with mCPBA furnished a 1 : 1 mixture of epoxides 34a and 34b. After separation by column chromatography, they were subjected to aminolysis with primary amines. Interestingly, epoxy 34b upon aminolysis was transformed preferentially, while 34a did not react. This is probably due to steric hindrance exerted by either the benzyl or the methyl group at the α position in epoxy 34a. Consequently, the mixture of 34a and 34b was used for the ring-opening reaction. The resulting aminoolcohols (35b–38b) could be easily separated from 34a on a gram scale by simple column chromatography with good yields. The synthesis of primary aminodiol 28b was accomplished by hydrolysis of 35b–37b over Pd/C in high yields, while debenzylation of 34a provided 23a in a moderate yield of 53% (Scheme 3).

Syn-Selective dihydroxylation of compound 33 with OsO4 in the presence of a stoichiometric amount of co-oxidant NMO produced a 1 : 1.7 epimeric mixture of 39a and 39b in a favourable yield. Our effort to separate the mixture failed. Fortunately, their carbonates, obtained from the diols with triphosgene, could be easily isolated. It is well known that this carbonation reaction maintains the stereochemical configuration of the original diol. Accordingly, the reactions of 39a and 39b with triphosgene successfully afforded 40a and 40b, respectively. After purification, carbonates 40a and 40b were reduced by LiAlH4 (LAH). The reaction proceeded smoothly giving the corresponding diols 39a and 39b in good yields. It has been reported that reduction with LAH gives the corresponding diol with the same stereochemical configuration of the carbon atoms as of the original moiety. 

Debenzylation

Scheme 2

Synthesis of (−)-isopulegol-based aminodiols. Reaction conditions: (i) 2% OsO4/10% BuOH, 50% NMO/H2O, acetone, 25 °C, 24 h, 33% (22a), 33% (22b); (ii) mCPBA (2 equiv.), Na2HPO4·12H2O (3 equiv.), CH2Cl2, 25 °C, 2 h, 29% (23a), 43% (23b); (iii) RNH2 (2 equiv.), LiClO4 (1 equiv.), MeCN, 70–80 °C, 8 h, 75–95% (25a), 50–90% (25b); (iv) 5% Pd/C, H2 (1 atm), MeOH, 25 °C, 24 h, 87–95% (28a), 85–90% (28b); (v) 35% HCHO, Et2O, 25 °C, 1 h, 89–97% (29a–32a), 85–90% (29b–32b).

Scheme 3

Synthesis of (−)-isopulegol-based aminodial derivatives. Reaction conditions: (i) NaH (1.5 equiv.), BnBr (1.5 equiv.), KI (1.5 equiv.), dry THF, 60 °C, 12 h, 70%; (ii) mCPBA (2 equiv.), Na2HPO4·12H2O (3 equiv.), CH2Cl2, 25 °C, 2 h, 43% (34a), 25% (34b); (iii) RNH2 (2 equiv.), LiClO4 (1 equiv.), MeCN, 70–80 °C, 20 h, 31–45%; (iv) 5% Pd/C, H2 (1 atm), MeOH, 25 °C, 24 h, 65–70%; (v) 5% Pd/C, H2 (1 atm), n-hexane : ETOAc = 9 : 1, 25 °C, 24 h, 53%.

Fig. 2 Determination of the structure of diol 18 by NOESY.
of 39a and 39b by hydrogenolysis over Pd/C resulted in triols 22a and 22b, respectively, with excellent yields (Scheme 4).

To extend the investigation of the substituent effects in the ring opening of epoxide, 33 was oxidised to 41. The epoxidation of 41 with mCPBA delivered a 4 : 1 mixture of epoxides 42a and 42b. The separation of 42a and 42b was not satisfactory on a gram scale; therefore, the mixture was treated with different primary amines in the presence of LiClO₄ resulting in a library of aminodiols. In our delight, aminodiols were well-separated when chiral amines (R)- and (S)-methylbenzylamines were applied, while in the case of benzylamine and isopropylamine, only the major products were isolated. The debenzylation of 43a–45a by hydrogenolysis over Pd/C gave aminodiol 47a with satisfactory yields. Tetraol 49 was prepared by dihydroxylation of 48 over Pd/C (Scheme 5).

During our attempt to improve the resolution of aminodiols 43b–46b, we realised that O-benzylation of 41 could serve this purpose; however, the synthesis of 50b starting from 41 failed. Fortunately, it was achieved by reacting 3 with benzyl bromide under reflux condition in dry THF. Besides expected product 50b, 50a also formed as a side product. Epoxidation of 50b with mCPBA produced a 1 : 1 mixture of epoxides 51a and 51b. The ring opening of the oxirane mixture was accomplished with different primary amines resulting in a library of aminaoxiranes 52a–55a and 52b–55b, respectively. The debenzylation of 52a–54a and 52b–54b by hydrogenolysis over Pd/C gave, respectively, aminotriols 47a and 47b with exceptional yields. Compound 50b was treated with the OsO₄/NMO system providing a 3 : 1 mixture of diols 56a and 56b. Removal of the protecting group of 56a gave tetraol 49 with good yield (Scheme 6).

The epoxidation of 50a with mCPBA gave a 2 : 1 mixture of epoxides 57a and 57b. The ring opening of this epoxide mixture was carried out with different primary amines to form a library of aminodiols 58a–61a and 58b–61b, respectively. Primary aminotriols 47a and 47b were prepared via the usual way by hydrogenolysis of aminodiols 58a–60a and 58b–60b over Pd/C. Dihydroxylation of 50b with the OsO₄/NMO system provided triols 62a and 62b in a 2 : 1 ratio with an excellent yield of 90%.

Debenzylation of 62a–b by hydrogenolysis over Pd/C resulted in tetraol 49 with excellent yields (Scheme 7).

On the other hand, epoxidation of allylic diol 3 with mCPBA was successfully applied to form the mixture of epoxy diols 63a and 63b in a 3.5 : 1 ratio. After separation by chromatography, the oxirane ring of 63a was opened with primary amines and LiClO₄ as catalyst to deliver aminotriol library 64a–67a. Primary aminotriol 47a was obtained by debenzylation of the corresponding aminotriols 64a–66a under standard conditions by hydrogenation in the presence of a Pd/C catalyst. Diastereoisomeric aminotriols 65b–66b were prepared by ring opening of 63b with chiral amines (R)- and (S)-methylbenzylamine. The synthesis of tetraol 49 was effectively performed by selective dihydroxylation of 3 with the OsO₄/NMO system (Scheme 8).

The relative configuration of primary aminotriol 47a was determined through epoxide 63a. To this aim, epoxide 63a was reduced with LiAlH₄ (LAH) to the corresponding triol 22a (see
configurations in Scheme 9). It has been reported that reduction with LAH gives the corresponding triol with the same stereochemical conformation as of the original moiety. The stereochemical structures of triol 22a could also be determined.

The absolute configuration of 42a, 51a and 57a was confirmed by debenzylation via hydrogenolysis over Pd/C to provide triol 22a with stereochemical retention. To prove that the stereochemical configuration of the epoxide was maintained during reaction, 57a was reduced with LiAlH4 then debenzylated applying the 5% Pd/C/H2 system to give 22a in good yield. The stereostructure of 56b and 62b were assigned by treatment of 51a and 57a with NaOH taking place with retention of stereochemistry (Scheme 9).

Since several aminodiols as well as aminotriols exerted antimicrobial activities on various microorganisms, antimicrobial activities of the prepared aminodiol and aminotriol analogues were also explored against two yeasts as well as two Gram-positive and two Gram-negative bacteria (Table 1, only the best results are shown).

Our tests revealed that di-O-benzyl aminotriol derivatives (52a-b) possess potential antimicrobial properties over 80% against both the two Gram-positive and the yeast species. In the case of B. subtilis, this compounds proved to be the most effective agents even at a low concentration of 10 μg mL⁻¹, while other derivatives (45a-b and 58a-b) showed lower activities. Removal of one of the two benzyl protecting groups in aminotriol derivatives (45a-b and 58a-b) led to improved selective inhibition on B. subtilis. The almost complete loss of antibacterial activity resulting from the replacement of all O-benzylxoy groups with hydroxyl group as demonstrated with aminotriol derivatives 66a-b suggests that the benzyl moiety is a key element to have satisfactory antimicrobial activity in the case of aminotriols.

Among aminodiol derivatives, only O-benzyl aminodiol 35b presented activity against B. subtilis, whereas debenzylated derivative 9 had no effect. This result indicates that the O-benzylxoy group attached to the cyclohexyl ring is responsible for activity of the studied antibacterial agents.

The available data demonstrated that the O-benzylxoy group on the cyclohexyl ring (41 and 50b) is much more effective to induce antimicrobial activity than the 1-BnO-propen-2-yl group (50a).

In comparison, α-methylene-γ-butyrolactone 4, the most effective compound against C. albicans and C. krusei, was found to possess highly selective effectiveness on the yeast species. The synthetic aminodiol and aminotriol derivatives were also evaluated for their antioxidant activity using DPPH assays (Table 2, only the detected activities are shown).

In the DPPH study, aminodiol 9 displayed a potential antioxidant effect, while the aminotriol derivatives (58a-b) had only moderate effects. The results of this survey, namely improvement of antioxidant activity alongside with the
replacement of the O-benzyl group with a hydroxyl group, 
show that efficiency depends on the hydroxyl function of 
the cyclohexyl ring more significantly than on the 1-
hydroxypropen-2-yl group.

The hydroxyl group of molecules play remarkable role in 
their antioxidant property. Recently, there are two proposed 
mechanisms by which antioxidants containing hydroxyl group 
can act protectively. In the first mechanism, the free radical (e.g. 
DPPH) removes a hydrogen atom from the hydroxyl group that 
results in a free radical more reactive than the original hydroxyl group. This free radical (or the hydroxyl group itself) becomes a radical, in this way the functional group 
donates a proton to the free radicals and neutralise it (e.g. 
DPPH-H). In the second mechanism, called as one-electron transfer, the hydroxyl group can give an electron to the free radical becoming itself a radical cation.91

Although aminotriol 58a was less active than aminodiols, its 
antioxidant property is still considered to be notable compared 
with aminotriol 45a. This result again demonstrates that the 
hydroxyl group on the cyclohexyl ring is necessary for antioxidant property.

### Conclusion

A new library of isopulegol-based chiral aminodiols and ami-
notriols was developed from commercially available (−)-iso-
pulegol. The isopulegol-based chiral di-, tri- and tetraols are 
promising substrates for the preparation of chiral crown ethers. 
\(\alpha,\beta\)-Dihydroxyamides, accessed through the ring opening of \(\alpha,\beta\)-

### Table 1 Antimicrobial activity of derivatives expressed in % values

| Anal | Conc. (µg mL\(^{-1}\)) | Gram positive  | Gram negative | Yeast |
|------|----------------|----------------|---------------|-------|
|      |                | B. subtilis | S. aureus | E. coli | P. aeruginosa | C. albicans | C. krusei |
| 4    | 100            | 31.51 ± 4.38 | — | — | 94.30 ± 5.46 | 88.22 ± 5.36 |
|      | 10             | —            | — | — | — | — |
| 30a  | 100            | 46.53 ± 2.55 | — | — | — | — |
|      | 10             | 34.92 ± 6.84 | — | — | — | — |
| 30b  | 100            | 52.97 ± 8.35 | — | — | 23.00 ± 9.26 | — |
|      | 10             | 41.69 ± 10.35 | — | — | — | — |
| 35b  | 100            | 92.04 ± 3.18 | — | — | — | — |
|      | 10             | 57.37 ± 6.13 | — | — | — | — |
| 41   | 100            | 76.58 ± 11.68 | — | — | — | — |
|      | 10             | 25.17 ± 6.00 | — | — | — | — |
| 43a  | 100            | 91.72 ± 3.98 | — | — | 30.58 ± 1.51 | 22.64 ± 6.99 |
|      | 10             | —            | — | — | — | — |
| 45a  | 100            | 91.29 ± 1.86 | — | — | 23.37 ± 2.81 | — |
|      | 10             | —            | — | — | — | — |
| 45b  | 100            | 77.98 ± 6.27 | — | — | — | — |
|      | 10             | 1.53 ± 2.93 | — | — | — | — |
| 50a  | 100            | 76.30 ± 16.90 | — | — | — | — |
|      | 10             | 45.25 ± 11.25 | — | — | — | — |
| 52a  | 100            | 77.67 ± 3.81 | 73.44 ± 1.78 | — | — | 86.64 ± 2.54 | 84.92 ± 4.20 |
|      | 10             | 93.88 ± 1.77 | — | — | — | — |
| 52b  | 100            | 87.23 ± 4.17 | 68.03 ± 4.74 | — | — | 81.47 ± 5.04 | 81.00 ± 4.03 |
|      | 10             | 94.63 ± 1.01 | — | — | — | 41.25 ± 9.35 |
| 56a  | 100            | 78.20 ± 7.98 | — | — | — | — |
|      | 10             | —            | — | — | — | — |
| 58a  | 100            | 60.52 ± 2.49 | — | — | 26.09 ± 4.61 | — |
|      | 10             | —            | — | — | — | — |
| 58b  | 100            | 68.93 ± 6.85 | — | — | — | — |
|      | 10             | 34.63 ± 7.99 | — | — | — | — |
| 66a  | 100            | 31.48 ± 11.69 | — | — | — | 39.76 ± 3.24 |
|      | 10             | —            | — | — | — | — |

a Inhibitory effect values less than 20% are considered negligible and not presented numerically. Compounds 1, 3, 9, 13, 14, 18, 19, 22a-b, 24a-b, 28a-b, 30a, 33, 39a-b, 47a-b, 48, 49, 50a, 56b, 62a-b, 64a and 66b were also examined but did not elicit 20% inhibitory effect even at 100 µg mL\(^{-1}\).

### Table 2 Antioxidant effects of active synthetic derivatives expressed in IC\(_{50}\) values

| Compound | DPPH antioxidant activity (µmol mL\(^{-1}\)) ± SD |
|----------|---------------------------------------------|
| 9        | 8.47 ± 0.56                                |
| 24b      | 75.63 ± 0.01                               |
| 28a      | 204.77 ± 9.1                               |
| 30a      | 72.76 ± 0.03                               |
| 45a      | 87.61 ± 0.14                               |
| 58a      | 33.74 ± 3.74                               |
| 58b      | 56.63 ± 0.01                               |
| Gallic acid | 0.16 ± 0.01                          |
dihydroxylactones, are widely applicable in the synthesis of natural products and in saccharide chemistry.

Our result proved again that steric hindrance exerted by both benzyl and methyl groups at the $\alpha$ position in epoxide $34a$ makes its conformationally constrained structure to restrict the approach of nucleophiles in aminolysis.

$O$-Benzyl aminotriol and aminodiol derivatives exert markedly selective antibacterial action on $B. subtilis$, while di-$O$-benzyl aminotriols have also shown significant effectiveness not only against Gram-positive bacteria strains but also against yeast species. Moreover, our result also indicated the potential antifungal activity of $\alpha$-methylene-$\gamma$-butyrolactones.

In addition, aminodiol and aminotriol derivatives were applied as antioxidant agents in DPPH assay. $N$-Benzyl aminodiols are still considered to exert notable antioxidant property.

Finally, in vitro studies have clearly shown that the $O$-benzyl substituent on the cyclohexyl ring in aminodiol and aminotriol derivatives is essential to have antimicrobial effect, whereas the hydroxyl group on this ring is crucial on the antioxidant property. The stereochemistry of the aminotriol and aminodiol derivatives has no influence on either effect.

Conflicts of interest
The authors declare no conflict of interest.

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