Stereoselective syntheses and application of (–)-isopulegol and (+)-neoisopulegol-based bi-, tri- and tetrafunctionalised monoterpenes

Ph.D. Thesis

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LIST OF ABBREVIATIONS

BHA: *Bis*-hydroxamic acid

Boc: *tert*-Butyloxycarbonyl

Cbz: Carbobenzyloxyl

CSI: Chlorosulfonyl isocyante

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DMAP: 4-Dimethylaminopyridine

DMDO: Dimethyldioxirane

DMF: Dimethylformamide

GC: Gas chromatography

HNE: Hydroxynonenal

HPLC: High Performance Liquid Chromatography

m-CPBA: *m*-Chloroperbenzoic acid

NMO: *N*-Methylmorpholine *N*-oxide

NOESY: Nuclear Overhauser Effect Spectroscopy

PCC: Pyridinium chlorochromate

RNAs: Ribonucleic acids

SFC: Supercritical Fluid Chromatography

S_NAr: Nucleophilic Aromatic Substitution

TBHP: *tert*-Butyl hydroperoxide

TBSCl: *tert*-Butyldimethylsilyl chloride

TEA: Triethylamine

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

$VO(acac)_2$: Vanadyl acetylacetonate

1. Introduction and aims

In the past decade, chiral synthons have received much attention in organic synthesis due to their application as starting materials in asymmetric transformations as well as auxiliaries or chiral catalysts in enantioselective syntheses.[1-3] Among them, 1,2-aminoalcohols, aminodiols and aminotriols are of increasing importance, which are not only known to be used as building blocks, but also possess significant biological activities. A large majority of these compounds are derived from commercially available monoterpenes, such as (–)-isopulegol, α- or β-pinene, etc.

Several different substances with the 1,2-aminoalcohol structure provide physiologically and pharmaceutically interesting characteristics.[4] For instance, substances with a backbone bearing hydroxyethylamine may block aspartic protease enzymes and they are frequently employed as anti-HIV,[5,6] anti-malarial[7] and anti-leishmanial agents.[8] Furthermore, a wide variety of β-adrenergic blockers,[9] used to treat high blood pressure, angina pectoris, cardiac arrhythmias and other problems of the sympathetic nervous system, have the 1,2-aminoalcohol moiety.[10] Besides pharmacological interest, 1,2-aminoalcohols have also been demonstrated to be excellent chiral auxiliaries and chiral catalysts in asymmetric synthesis.[11]

Chiral aminodiols and aminotriols derived from available natural monoterpenes are also well-known as excellent chiral catalysts in asymmetric addition reactions, including Grignard addition,[12] intramolecular [2 + 2] photocycloaddition[13] and intramolecular radical cyclisation.[14] In addition, they are useful as building blocks for the preparation of heterocyclic ring systems, mainly 1,3-oxazines and 1,3-thiazines,[15,16] that have a wide range of biological properties, such as antiproliferative,[17] analgesic,[18] anticonvulsant,[19] anti-inflammatory,[20,21] antibiotic,[22] antimicrobial,[23,24] antimalarial,[25] antihypertensive[26] and anticancer properties.[27] For example, Aristeromycin analogues are widely used as antiviral agents against hepatitis B and C, human immunodeficiency, influenza, herpes simplex and other viruses.[28-30] Moreover, (2*R*,3*R*,7*Z*)-2-aminotetradec-7-ene-1,3-diol are known as potent antimicrobial metabolites.[31] In addition, sphingolipid analogues have diverse biological roles, including the treatment of inflammation,[32] cancer[33] and Alzheimer's disease.[34]

O-Benzyl azole derivatives have been widely employed as pharmacophores and synthons in organic chemistry and drug discovery and they have played key roles in the history of heterocyclic chemistry.[35] As a result of their high therapeutic index, superior absorption and acceptable safety profile,[36] azoles such as imidazole[37] and triazole[38] have become the most researched class of

antifungal drugs. Note, that the *O*-benzyl substituent is crucial to the enhanced antibacterial action of these compounds.[39]

On the other hand, pyrimidines are determined to be a prominent group in heterocyclic chemistry due to their considerable biological activity. According to their significant chemopreventive and chemotherapeutic properties, 2,4-diaminopyrimidines have gained substantial attention among the enormous number of structurally varied pyrimidine derivatives now available.[40-48] In the domain of drug research and development, 2,4-diaminopyrimidine derivatives with antiviral,[49] antiparasitic,[50] antibacterial[51] and anti-inflammatory properties[52] have attracted substantial attention in recent years.

The aim of this PhD work was to synthesise (–)-isopulegol- and (+)-neoisopulegol-based bi-, tri- and tetrafunctionalised building blocks such as 1,2-aminoalcohols, aminodiols and aminotriols, whereas the amino function can be primary, secondary, or tertiary, a part of azole or pyrimidine ring system, starting from commercially available (–)-isopulegol.

Furthermore, we planned to study the ring-closure properties of the prepared 1,2-aminoalcohols, as well as the synthesis of 1,3-oxazines, 1,3-oxazoles, 1,3-thiazines and 1,3-thiazoles. In addition, to expand our work, we prepared a new series of 2,4-diaminopyrimidine derivatives.
The resulting 1,2-aminoalcohols and their ring-closed derivatives were planned to apply as chiral catalysts in the enantioselective addition of Et_2Zn to aldehydes.

On the other hand, according to the literature background, we planned to study the antimicrobial activities of the prepared 1,2-aminoalcohol, aminodiol and aminotriol chiral synthons against two yeast species as well as against two Gram-positive and two Gram-negative bacteria. The antiproliferative activities, in turn, were determined in the case of 1,3-oxazine, 1,3-oxazole, 1,3-thiazine and 2,4-diaminopyrimidine derivatives using *in vitro* assay against different human cancer cell lines.

2. Literature survey

2.1. Importance and synthesis of aminodiols

2.1.1. Pharmacological importance of chiral aminodiols

Aminodiols represent an important class in organic chemistry due to their remarkable chemical as well as medicinal relevance. Numerous compounds containing aminodiol motifs in the backbone exhibit significant biological activity. For example, chloramphenicol, one of the earliest used antibiotics[53] and cytoxazone, which was originally isolated from cultures of a *Streptomyces species*, express cytokine modulator activity by inhibiting the signalling pathway of Th2 cells.[54,55]

In addition, other compounds containing aminodiol as a building block have shown potency over HIV protease inhibition.[56] For instance, the Abbott aminodiol was found to be a useful synthon for the preparation of potent renin inhibitors (Zankiren® and Enalkiren®).[57] (*S*)-(–)-Metoprolol, in turn, was used for the treatment of high blood pressure.[58] Furthermore, aminodiols may also exhibit antidepressant properties. (*S*,*S*)-Reboxetine, for example, an inhibitor of norepinephrine reuptake, was used to treat unipolar depression (Figure 1).[59,60]

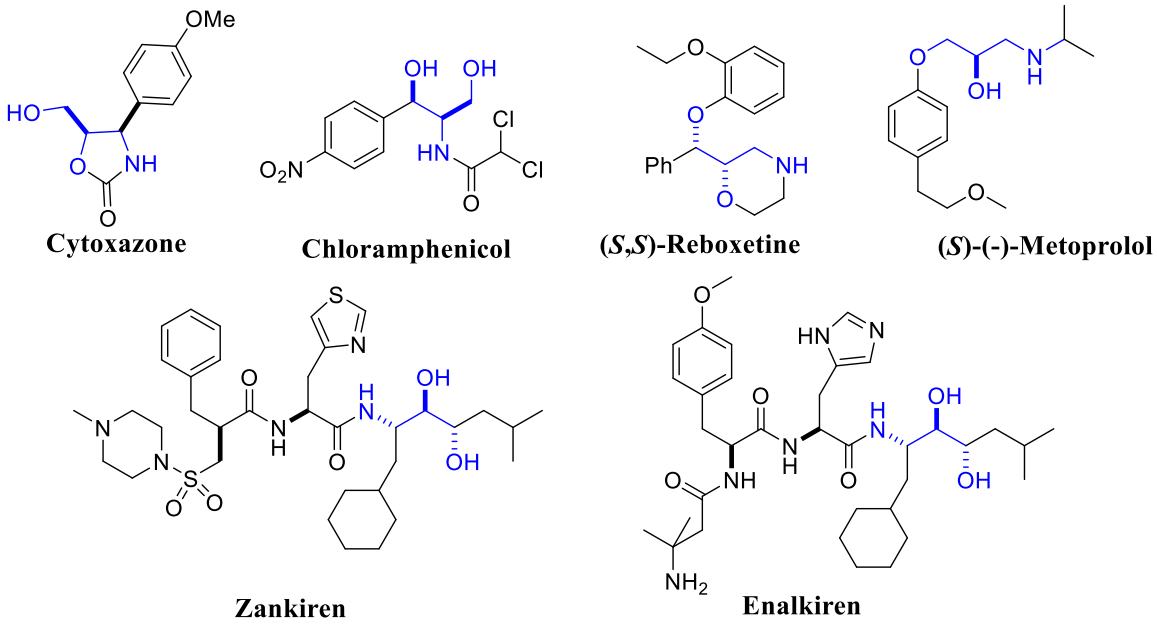
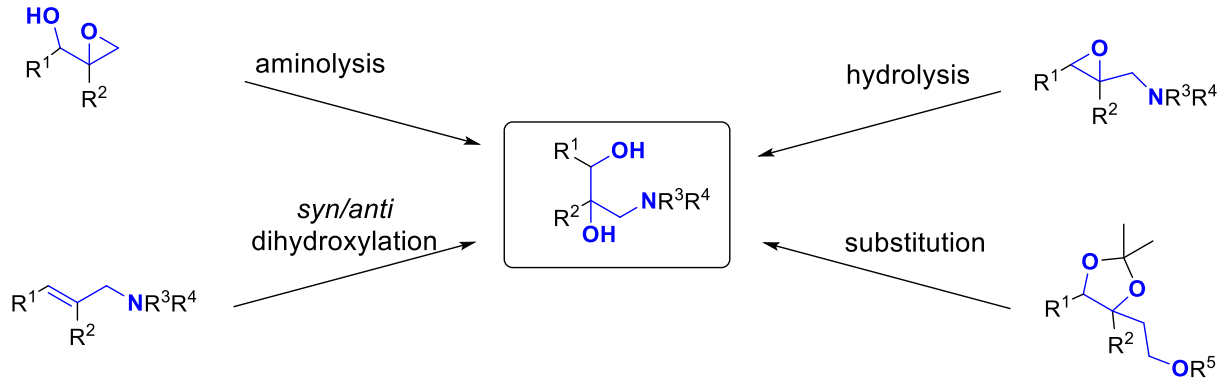


Figure 1. Aminodiols with pharmalogical importance

2.1.2. Synthesis of chiral aminodiols

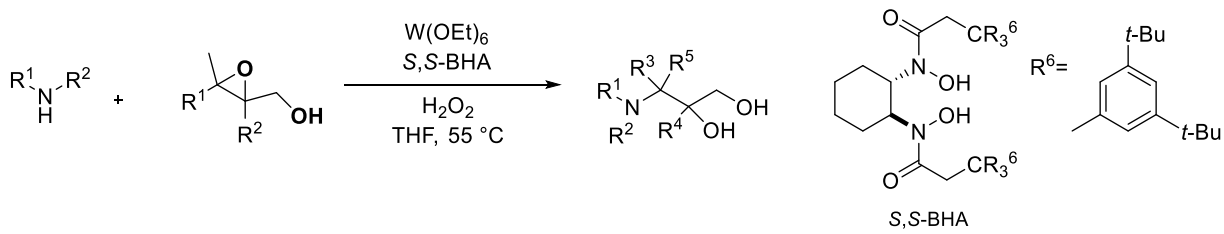
Several procedures were employed to prepare aminodiols including aminolysis of epoxyalcohols,[61,62] dihydroxylation of amino alkenes[63,64] and hydrolyses of protected epoxy amines.[65] In an additional method, mesylation or tosylation[66] of the hydroxy functional group of allylic alcohol followed by dihydroxylation and Mitsunobu reaction and subsequent conversion of the resulting azido group to 3-amino-1,2-diol moiety was performed.

In asymmetric synthesis, the most frequent technique for the preparation of aminodiols is Sharpless epoxidation of allylic alcohols,[67-71] then ring opening with different nucleophiles, such as amines, azides and ammonia (Scheme 1).[72-75]



Scheme 1. Methods for preparation of aminodiols

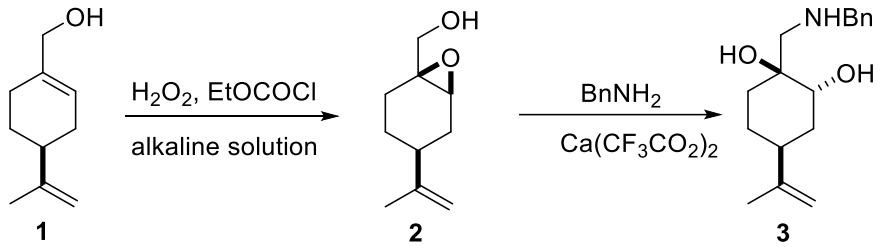
Wang and Yamamoto[61] reported the enantioselective synthesis of various *anti*-3-amino-1,2-diols by enantioselective aminolysis of racemic *trans*-2,3-epoxy alcohols utilising different amines as nucleophiles in the presence of the tungsten W-BHA [$(W(OEt)_6)$/(*S*,S-BHA: *bis*-hydroxamic acid)] catalytic system. This method showed a high regiocontrol as well as excellent enantioselectivity with 95% *ee* (Scheme 2).



Scheme 2. Tungsten-catalysed synthesis of 3-amino-1,2-diols

Various chiral catalysts obtained from commercially available optically active monoterpenes including (+)- and (–)-α-pinene,[76] (–)-β-pinene,[77,78] (+)-carene,[62-64] (+)-sabinol,[79] (+)-pulegone,[80] steviol[81] and limonene[82,83] were applied in enantioselective transformations.

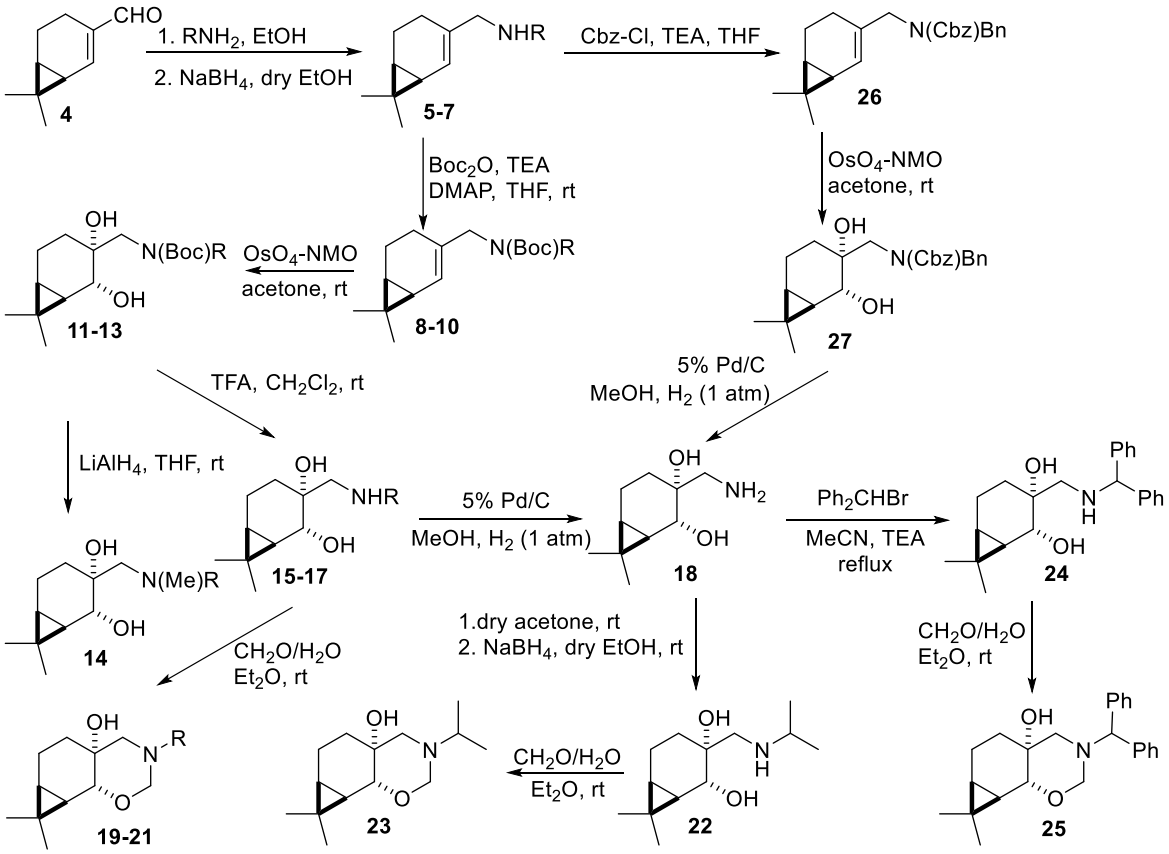
The synthesis of chiral aminodiol **3** was reported by Outouch *et al*.[84] utilising (*S*)-perillyl alcohol **1** as starting material. Its epoxidation followed by epoxide ring opening using benzylamine in the presence of $Ca(CF_3COO)_2$ as catalyst under solvent-free conditions resulted in aminodiol **3** (Scheme 3).



Scheme 3. Synthesis of chiral aminodiol **3** based on (*S*)-perillyl alcohol

Furthermore, natural monoterpene-based aminodiols, obtained from (+)-carene, were synthesised by Szakonyi *et al*.[63] via amination of allylic aldehyde **4** using varied amines and then protection of the amine functional group with Boc_2O yielding *N*-Boc allylic amines **8–10**. Compounds **11–13** were obtained by dihydroxylation with the OsO_4/NMO (4-methylmorpholine *N*-oxide) system, followed by a $LiAlH_4$-mediated reduction of **11** to obtain compound **14**. Removal of the Boc protecting group of **11–13** in acidic conditions furnished *N*-benzyl aminodiols **15**–**17** which, upon hydrogenation over Pd/C, led to primary aminodiol **18**. On the other hand, aminodiols **15–17** in the presence of CH_2O solution yielded 1,3-oxazines **19–21**. 1,3-Oxazines **23** and **25** were also prepared according to the method described above.

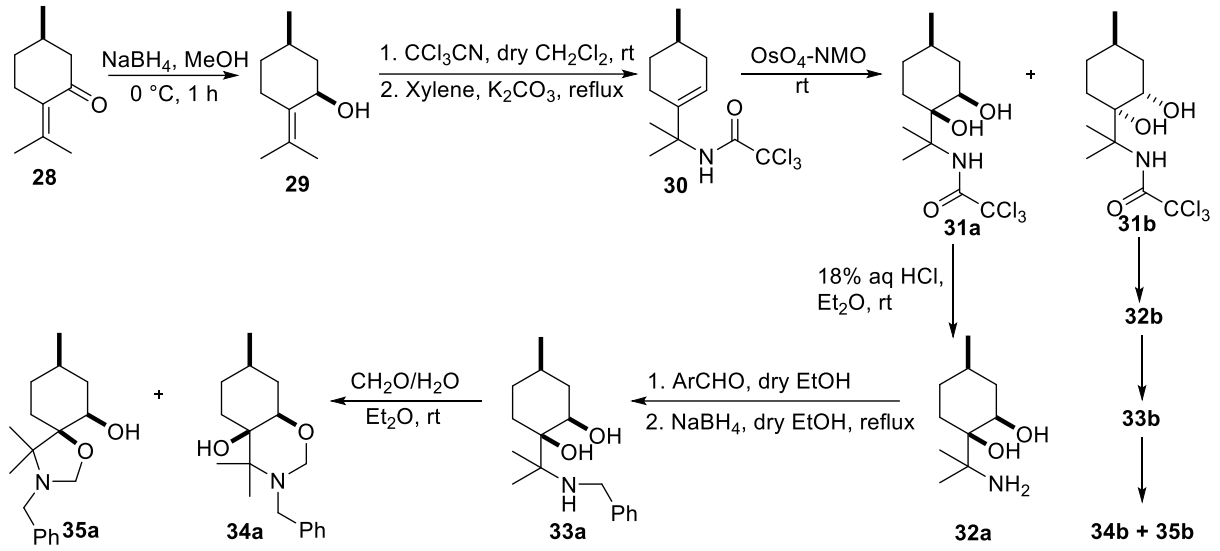
In addition, in order to investigate the effect of the *N*-protection during the dihydroxylation process, secondary amines **5–7** were protected with Cbz-Cl in the presence of TFA to form **26** that was dihydroxylated with the OsO_4/NMO system to obtain compound **27** in a stereoselective manner. Finally, debenzylation of aminodiol **27** furnished primary aminodiol **18** (Scheme 4).



5, 8, 11, 15, 19: R= Bn; **6, 9, 12, 16, 20**: R = CH(Me)Ph(*R*); **7, 10, 13, 17, 21**: R = CH(Me)Ph(*S*)

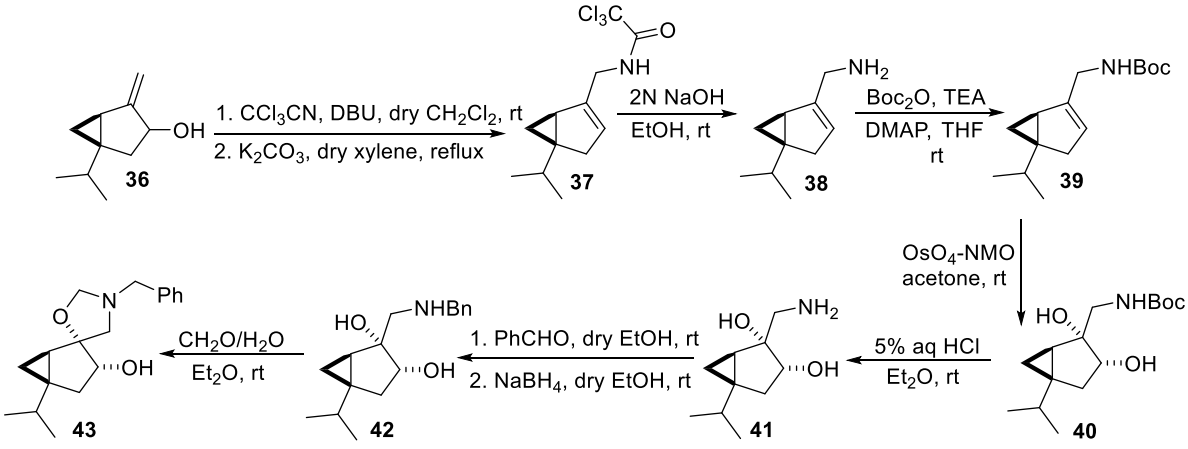
Scheme 4. Synthesis of carene-based aminodiols

A series of (+)-pulegone-based aminodiols were prepared by Gonda *et al*.[80] by stereoselective reduction of (+)-pulegone **28** with $NaBH_4$ resulting in the formation of alcohol **29,** followed by a two-step reaction to form trichloroacetamide **30**. Compounds **31a** and **31b** were obtained by dihydroxylation of **30** with the OsO_4/NMO system. Primary aminodiol **32a** was produced by elimination of the trichloroacetyl group of **31a** under acidic conditions. Reductive alkylation of **32a** with benzaldehyde yielded secondary aminodiol **33a**, which then was treated with CH_2O resulting in a 1:2 mixture of 1,3-oxazine **34a** and oxazolidine **35a**. In the same manner, the mixture of **34b** and **35b** was obtained from **31b** using this latter process (Scheme 5).



Scheme 5. Preparation of (+)-pulegone-based chiral aminodiols

A library of monoterpene-based chiral aminodiols was prepared by Tashenov *et al*.[79] from (+)-sabinol, a natural product, the essential oil of *Juniperus sabina* (*ee* = 98%). Conversion of sabinol **36** to allylamine **38** under Overmann rearrangement, followed by *N*-Boc protection and subsequent stereoselective dihydroxylation provided *N*-Boc-protected aminodiol **40**, which was treated with 5% aqueous HCl to give primary aminodiol **41**. This compound was then converted into *N*-benzyl aminodiol **42** followed by ring-closure with CH_2O forming *N*-benzyl spiro-oxazolidine **43** regioselectively (Scheme **6**).

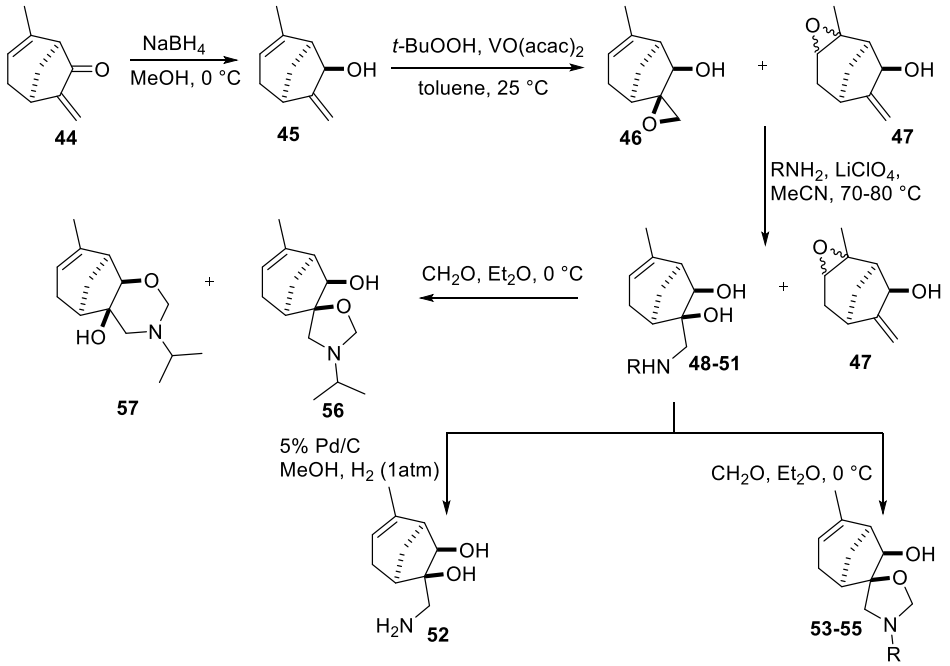


Scheme 6. Preparation of (+)-sabinol-based chiral aminodiols

Le *et al*. also reported the synthesis of bicyclic limonene-based chiral aminodiols.[82] Stereoselective reduction of bicyclic methylene ketone **44**, synthesised from commercially

available (–)-limonene, gave allylic alcohol **45**. Epoxidation with *t*-BuOOH in the presence of vanadyl acetylacetonate [$VO(acac)_2$] as catalyst resulted in a 4:1 mixture of **46** and **47**. It was impossible to properly separate epoxides **46** and **47** without degradation of the compounds. Aminolysis of the mixture of epoxides **46** and **47** with different primary amines using $LiClO_4$ as a catalyst furnished aminodiols **48**–**51** while **47** remained unreacted.

According to the steric hindrance exerted by the methyl group of **47** in the alpha position, epoxide **46** was converted selectively. Therefore, the mixture of secondary amines **48**–**51** and epoxide **47** was easily separated by column chromatography. The catalytic hydrogenation of **48** was achieved in the presence of Pd/C to form primary aminodiol **52**. Ring closure of the resulting aminodiols **48**–**51** furnished spiro-oxazolidines **53**–**55** in a regioselective manner, whereas treatment of aminodiol **48** with CH_2O afforded a mixture of spiro-oxazolidine **56** and 1,3-oxazine **57** (Scheme 7).

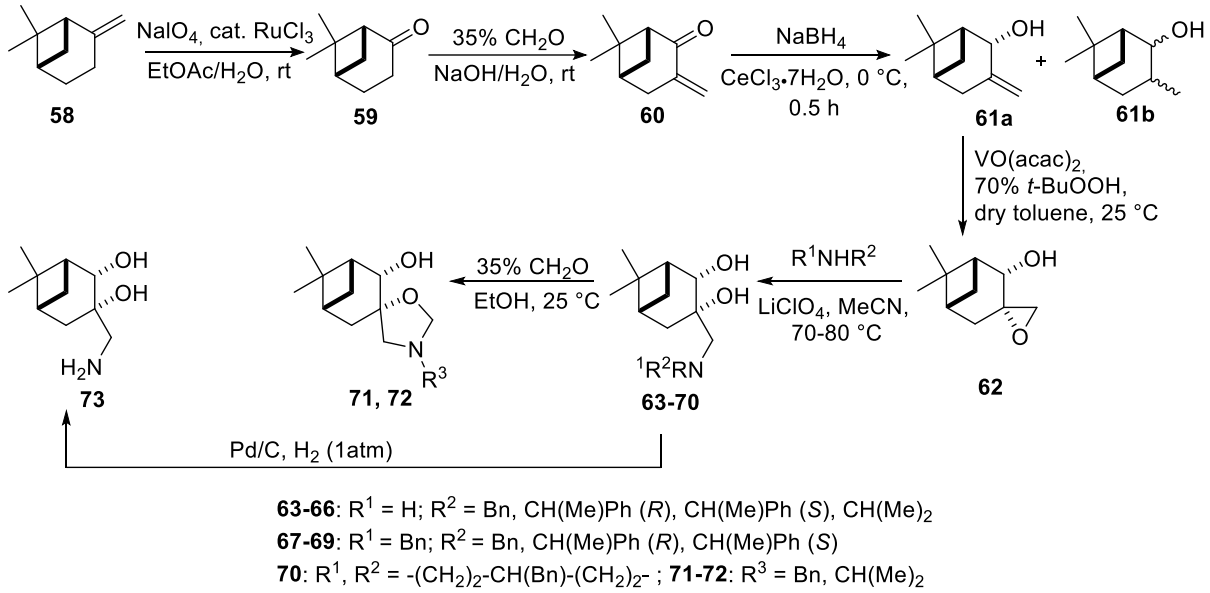


Scheme 7. Preparation of bicyclic limonene-based chiral aminodiols

In addition, Raji *et al*.[77] reported the preparation of a library of (–)-*β*-pinene-based aminodiols. The natural compound (–)-*β*-pinene **58** was oxidised with $NaIO_4$ in the presence of $RuCl_3$ as a catalyst to provide (–)-nopinone **59** which, upon treatment with CH_2O under alkaline conditions,

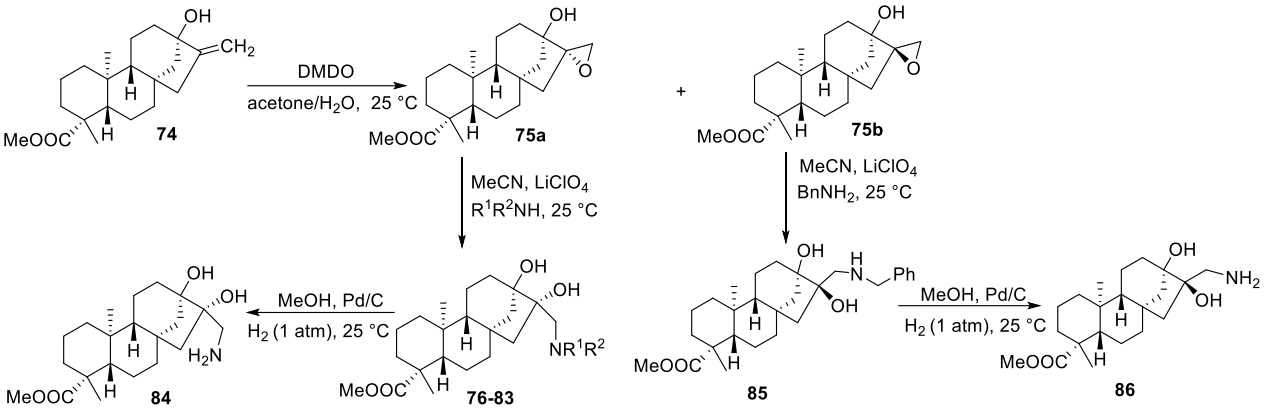
yielded 3-methylenenopinone **60**. A diastereomeric 4:1 mixture of **61a** and **61b** was obtained with high stereoselectivity by reduction of **60** using $NaBH_4$.

Through a stereoselective epoxidation of **61a**, epoxide **62** was obtained as a single product using *t*-BuOOH with $VO(acac)_2$ as catalyst. Aminodiol library **63**–**70** was then synthesised by aminolysis of **62** with different amines in the presence of $LiClO_4$ as catalyst. Subsequently, primary aminodiol **73** was synthesised by hydrogenation of aminodiol **63** over Pd/C in a moderate yield. Moreover, ring closure of aminodiols **63** and **66** under mild conditions utilising formaldehyde formed spiro-oxazolidine **71** and **72** with high regioselectivity (Scheme 8).



Scheme 8. Preparation of (-)-*β*-pinene-based aminodiols

Beside monoterpene-derived aminodiols, the synthesis of diterpene-based aminodiols is a new approach to design biologically active aminodiols. Hence, Ozsvár *et al*. disclosed the preparation of a library of steviol-based aminodiols.[81] Steviol methyl ester **74**, prepared from commercially available natural stevioside in the presence of *in situ*-prepared dimethyldioxirane (DMDO) as a mild epoxidation reagent, gave diastereomers **75a** and **75b** with a 2:1 ratio, which were separated by preparative column chromatography. The ring opening of epoxide **75a** with various amines was successfully achieved, forming a series of steviol-based aminodiol derivatives **76**–**83**. Subsequent catalytic debenzylation yielded primary aminodiol **84**. On the other hand, debenzylation of diastereoisomeric secondary aminodiol **85** over Pd/C, obtained by ring opening of *trans*-epoxyalcohol **75b** with benzylamine, yielded primary aminodiol **86** (Scheme 9).



76, **78**, **79**, **80**, **82**, **83**: R^1 = H; R^2 = Bn, CH(Me)Ph (*R*), CH(Me)Ph (*S*), *i*-pr, propargyl, 3,5-*bis*(trifluoromethyl)benzyl
77: R^1 = Me, R^2 = Bn; **81**: R^1 = Et, R^2 = Et

Scheme 9. Preparation of steviol-based aminodiols

2.2. Importance and synthesis of aminotriols

2.2.1. Pharmacological importance of aminotriols

Compounds, containing an aminotriol moiety, are known for their biological activities. For example, pactamycin, the structurally most intricate aminocyclopentitol antibiotic, displays potent antiproliferative properties[85] and myriocin is an immunosuppressant antibiotic.[72,86] Furthermore, penaresdin A and B were identified as potent actomyosin ATP-ase activators.[87] Besides, penaresidin B demonstrates cytotoxicity on murine lymphoma L1210 cells.[88] Moreover, risteromycin, a natural carbocyclic nucleoside,[89] shows antibiotic and antitumour effects, while 1,2-deoxyazasugars from the fagomine family[90] represent a significant type of glycosidase inhibitors (Figure 2).

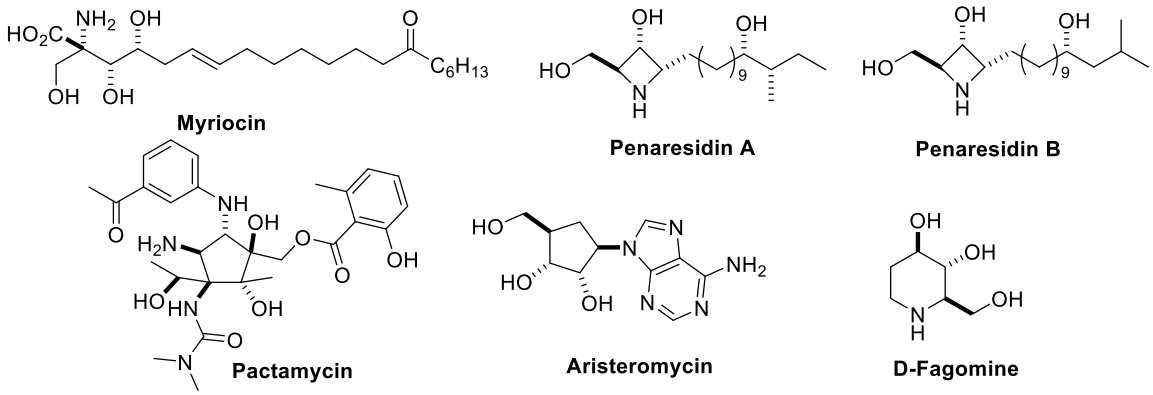
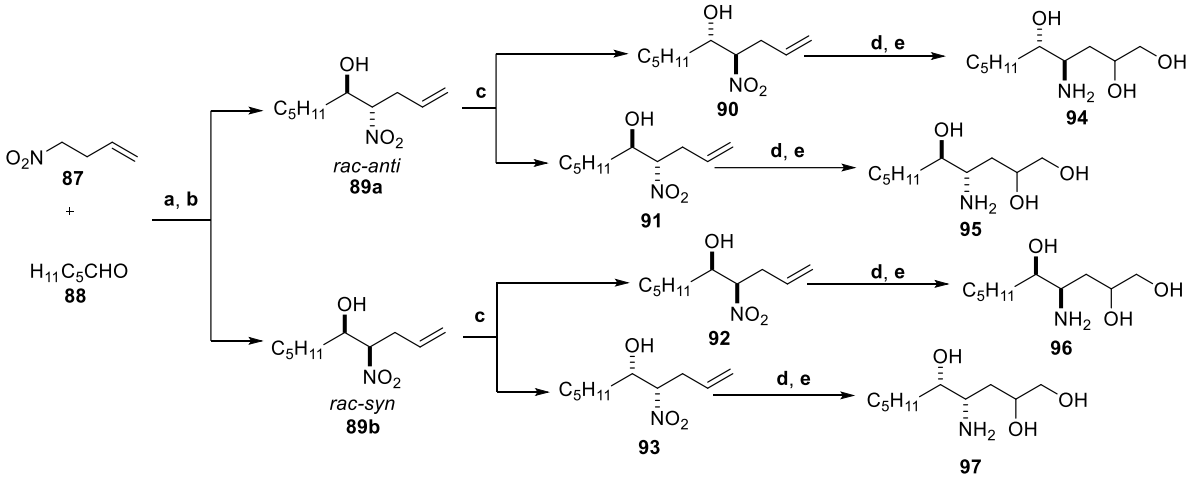


Figure 2. Aminotriols of pharmacological importance

2.2.2. Synthesis of aminotriols

Plamen *et al*. described the most significant pathway for the preparation of stereoisomeric aminotriols[91] by a nitroaldol (Henry) reaction of 4-nitro-1-butene **87** and hexanal **88** to obtain vicinal aminoalcohols. The vicinal diol group is the main structural group of the 4-hydroxynonenal (HNE) synthon. Using 25 mM NaOH and *n*-$Bu_4N^+Cl^-$ as catalyst, the Henry reaction was successfully conducted to produce a 1:1 mixture of diastereomers **89a** and **89b** in good yields. After diastereomeric separation with medium-pressure chromatography, followed by enantiomeric separation with supercritical fluid chromatography (SFC), compounds **90–93** were obtained as single enantiomers.

Dihydroxylation of **90–93** with the retention of stereochemistry using OsO_4 and *t*-BuOOH and subsequent hydrogenation of the resulting products over Pd/C was achieved to obtain aminotriols **94**–**97** (Scheme 10).



a: NaOH, H_2O, THF, *n*-$Bu_4N^+Cl^-$; **b**: medium pressure chromatography (silica gel, 80%); **c**: supercritical fluid chromatography; **d**: OsO_4, *t*-BuOOH, *n*-Bu_4NOAc, acetone/water; **e**: H_2, Pd/C, MeOH.

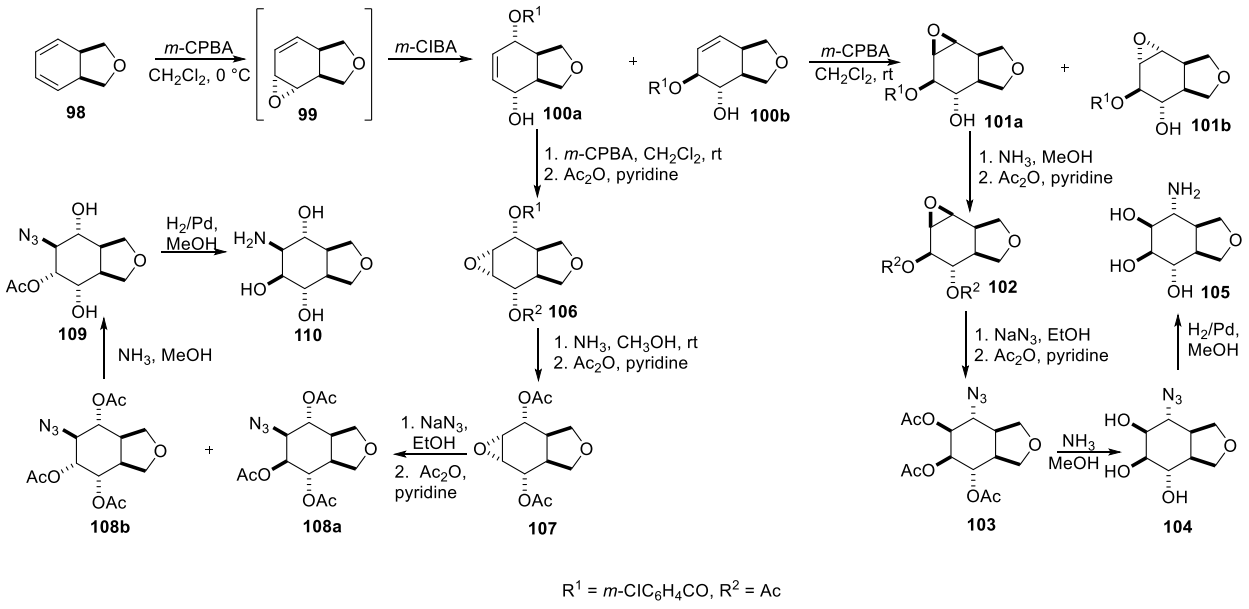
Scheme 10. Synthesis of the aminotriols **94**–**97**

Due to the remarkable biological activities of aminocyclitols, Aydin *et al*. prepared aminotriols[92] **105** and **110** starting from diene **98** and used them for the synthesis of various aminocyclitol analogues. Treatment of diene **98** with *m*-CPBA (*meta*-chloroperoxybenzoic acid) yielded 41% and 22% of two regioisomers **100a** and **100b**, respectively. Compound **100b** was further reacted with *m*-CPBA to afford epoxides **101a** and **101b** in 77% and 5% yields, respectively. The major

compound **101a** was then converted into diacetate **102**, which was applied in the opening of the epoxide ring with NaN_3 and subsequent acetylation resulting in compound **103**.

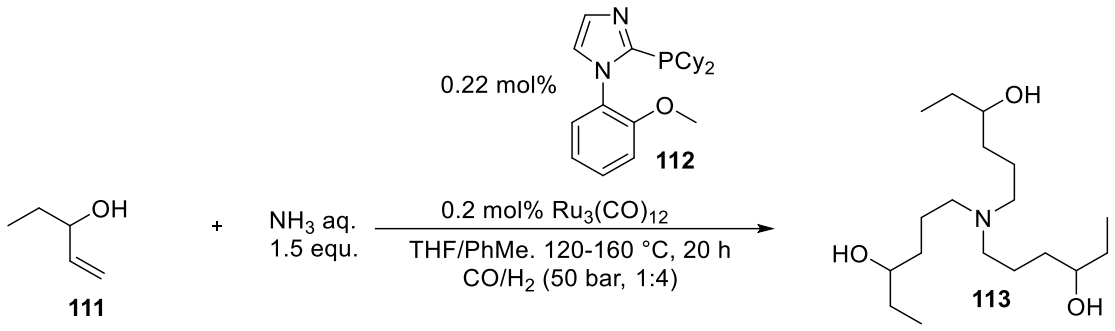
The position and stereochemistry of azide functionality were determined by 2D NMR spectroscopy. Aminotriol **105** was obtained by deacetylation of **103**, followed by catalytic hydrogenation over Pd/C. The epoxide ring opening reaction of epoxydiacetate **107** using NaN_3 and then acetylation of the azidoalcohol yielded azidotriacetate **108b** (69%) as major product together with the minor isomer **108a** in 2% yield.

Position of the azide group of azidotriacetate **108b** was established by NMR analysis (COSY spectrum). **108b** was subjected to aminolysis with NH_3 in MeOH followed by catalytic hydrogenation over Pd/C to give aminotriol **110** (Scheme 11).



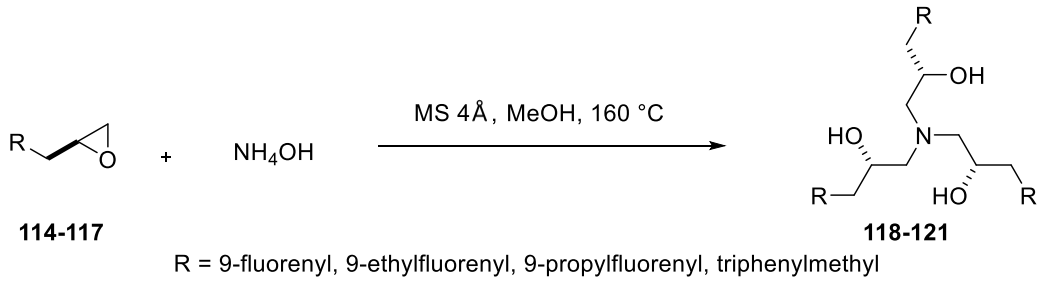
Scheme 11. Synthesis of aminotriols **105**–**110**

In 2014, Wu *et al*. developed a hydroaminomethylation approach with varied alkenes, including allylic alcohol **111** in aqueous NH_3 solution.[93] High regioselectivity of the reaction was observed by using $Ru_3(CO)_{12}$ and 2-phosphino-substituted imidazole **112** as catalyst, resulting in 76% of aminotriol **113** (Scheme 12).



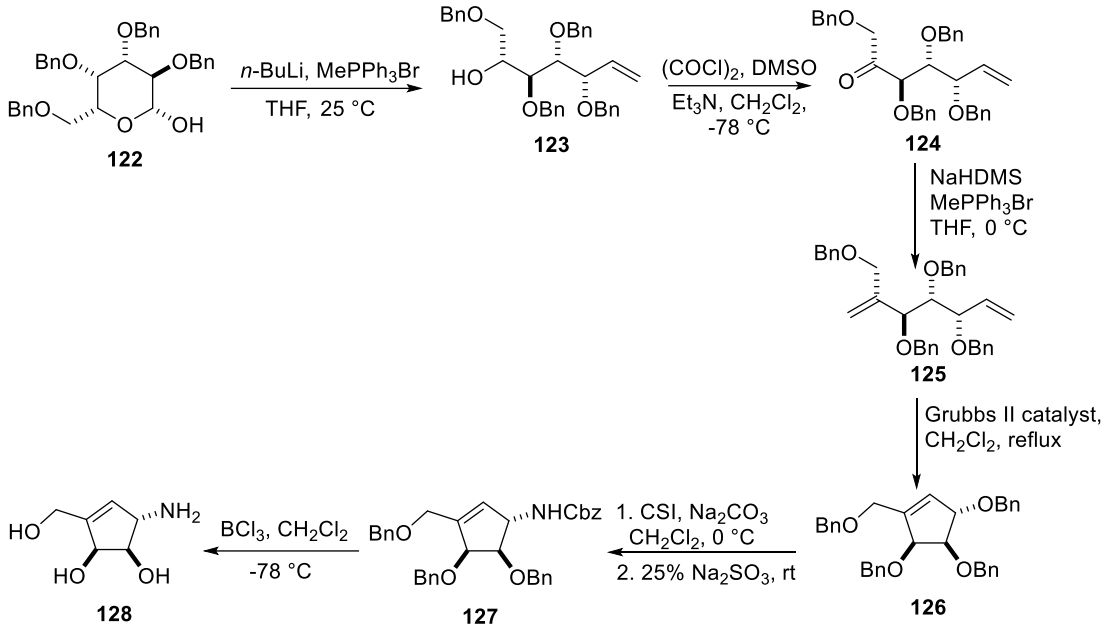
Scheme 12. Synthesis of aminotriol **113**

In 2015 Yang *et al*. reported the ring opening of oxiranes **114**–**117** with NH_3 in MeOH in the presence of molecular sieves to increase the rate of the reaction, producing chiral aminotriols **118**–**121** with bulky substituents in excellent yields (Scheme 13).[94]



Scheme 13. Synthesis of chiral aminotriols **118**–**121**

Furthermore, aminotriol **128** was prepared by Jung *et al.*[95] from benzyl-protected lactol **122,** derived from D-galactose. Starting from **122** under Wittig reaction conditions, the resulting alcohol **123** was subjected to Swern oxidation providing ketone **124**. The following oxidation reaction utilising NaHDMS and $MePPh_3Br$ resulted in the formation of diene **125**. Subsequently, the latter product, treated in the presence of Grubbs II catalyst under reflux, yielded 90% of carbocyclic polybenzyl ether **126**. The *N*-protected carbocyclic product **127** formed in an excellent yield and with significant diastereoselectivity (*anti*/*syn* = >50:1) under CSI was deprotected with BCl_3 affording primary aminotriol **128** (Scheme 14).



Scheme 14. Synthesis of aminotriol **128**

2.3. Application of aminodiols and aminotriols

2.3.1. Application of aminodiols

Chiral aminodiols are commonly used as building blocks[80,96-98] for the preparation of bioactive compounds, and they also have been employed as chiral auxiliaries and chiral catalysts in enantioselective syntheses.[99-101]

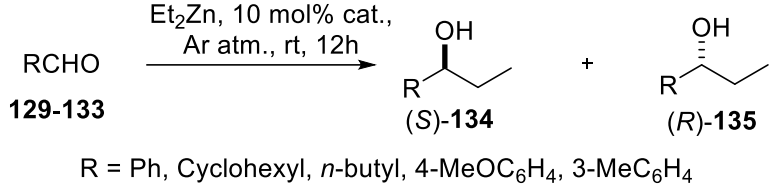
2.3.1.1. Application of aminodiols as chiral catalysts

Due to the high demand for enantiopure compounds, considerable progress has been achieved in asymmetric synthesis, which represents three essential methods including chiral auxiliary method, chiral pool synthesis and asymmetric catalysis. Of these three approaches, asymmetric catalysis has become the most researched subject in the field of organic synthesis in the past decade.

In asymmetric catalysis, the enantioselective addition of organozinc reagents to prochiral aldehydes, specifically the nucleophilic addition of diethylzinc to benzaldehyde as a model reaction, is considered to be the most studied reaction involving aminodiols as chiral catalysts.[63,64,79-83] It is due to the significance of the resulting optically active secondary alcohols that are often utilised as chiral building blocks for the synthesis of novel bioactive products.

Furthermore, to examine the catalytic efficiency of novel chiral ligands, the enantioselective alkylation of aldehydes has also become a classic model reaction.

The carane-based aminodiols[63] prepared by Szakonyi *et al*. (see Scheme 4) were evaluated on the catalytic addition of diethylzinc to benzaldehyde to form chiral 1-phenyl-1-propanol (*S*)-**134** and (*R*)-**135** as chiral ligands (Scheme 15). The results showed that the prepared 1,3-oxazines and aminodiols have significant catalytic activity and opposite selectivity on both aromatic and aliphatic aldehydes (Scheme 15).



Scheme 15. Model reaction for enantioselective catalysis

The preparation of 3-amino-1,2-diols with the camphane moiety was disclosed by Stoyanova *et al*.[102] using commercially available 10-camphorsulfonyl chloride **136**. First, a mixture of diastereomeric oxiranes was synthesised and their configuration was then determined. The aminolysis of the obtained epoxides proceeded regioselectively to form compounds **138**, whose carbonyl group was reduced with $LiAlH_4$ resulting in compounds **139**. The chiral aminodiols thus prepared were investigated as chiral catalysts in the model reaction showing a moderate catalytic activity (16–74% *ee*) with (*R*)-selectivity (Figure 3).[102]

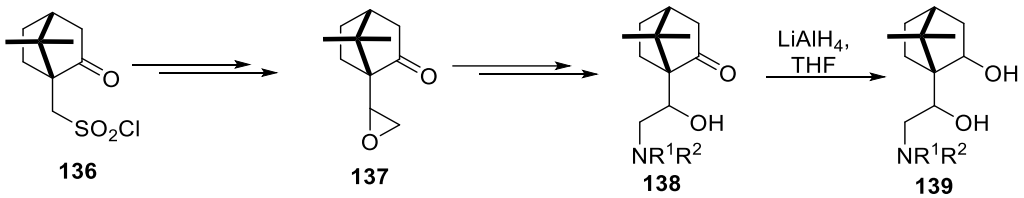
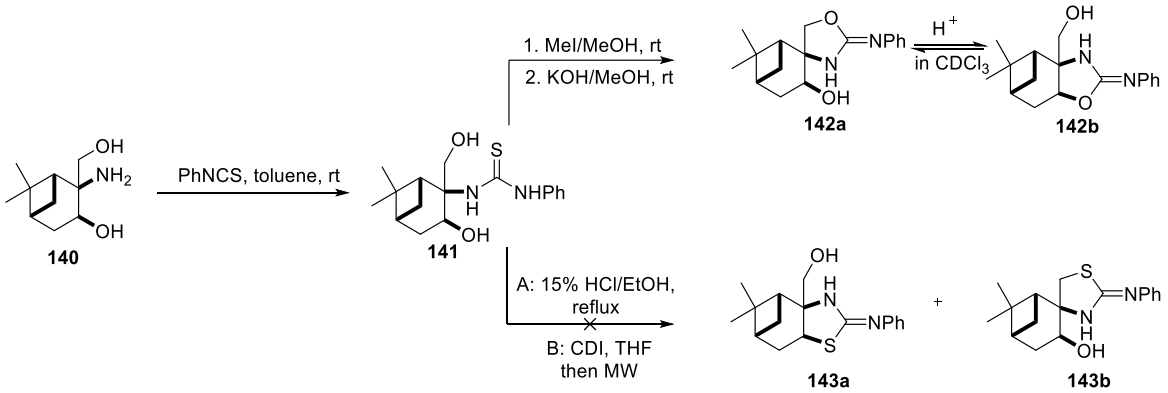


Figure 3. Preparation of camphane-based aminodiols

2.3.1.2. Application of aminodiols as building blocks

Aminodiols have been applied as starting materials in the stereoselective synthesis of various compounds of pharmacological interest, including 1,3-oxazolidines, 1,3-thiazolidines and 2,4-diaminopyrimidines.[96,98]

In 2021 Bajtel *et al*. carried out the synthesis of 1,3-oxazolidines from pinane-based 2-amino-1,3-diol.[96] We followed their approach and starting with aminodiol **140** in the presence of phenylisothiocyanate in toluene, thiourea **141** was formed, which underwent a regioselective ring closure to afford oxazolidine **142a**. The structure of **142a** was determined by modern spectroscopic techniques, and a tautomerisation was noticed during the NMR analysis with the formation of a 1:1 mixture of isomers **142a** and **142b**. Subsequently, the mixture was successfully separated using column chromatography to obtain **142b** as a single diastereomer. However, tautomerisation took place again after dissolving the compound in $CDCl_3$. Unfortunately, any attempt for the synthesis of thiazolidine analogues **143a** and **143b** was unsuccessful either in acidic conditions or under microwave irradiations (Scheme 16).

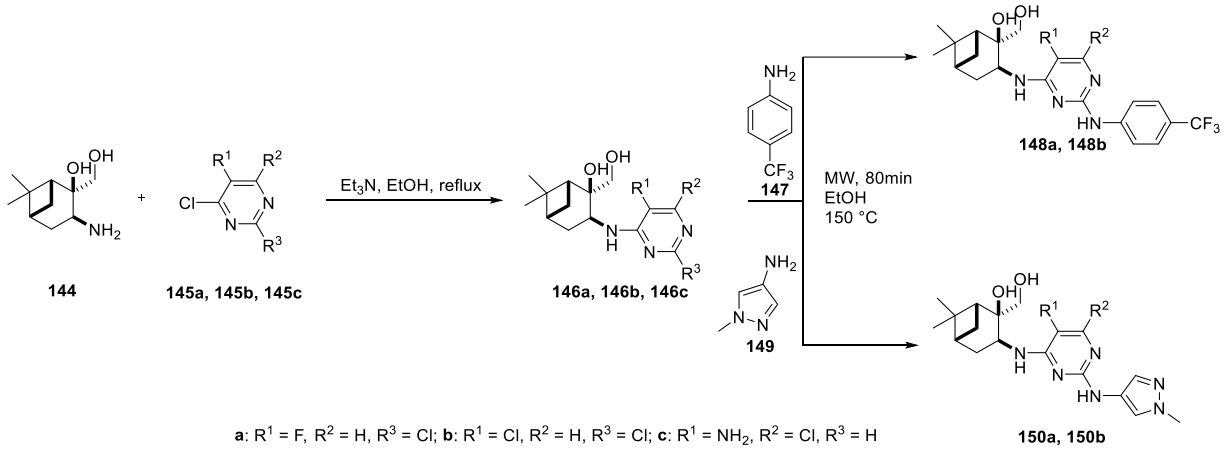


Scheme 16. Synthesis of 2-phenyliminothiazolidines

Due to the well-known biological activities of aminopyrimidines, Raji *et al*. reported the synthesis of a series of novel diaminopyrimidines[98] coupled with aminoalcohols and aminodiols containing pinane moieties.

3-Amino-1,2-diols were prepared from (1*R*)-myrtenol[64] according to literature methods. Key intermediates **146a**–**c** were obtained by addition of 3-amino-1,2-diol **144** to 2,4-dichloro-5-fluoropyrimidine **145a**, 2,4,5-trichloropyrimidine **145b** and 5-amino-4,6-dichloropyrimidine **145c** in the presence of Et_3N in EtOH. Products were purified by column chromatography to produce excellent to moderate yields. Under microwave irradiation, the prepared key intermediates **146a**–**c** were coupled with 4-aminobenzotrifluoride **147** to form N^2-aryl-substituted pyrimidines **148a,b**, whereas the S_NAr coupling reaction with 4-amino-1-methylpyrazole **149** yielded pyrazole pyrimidines **150a**,**b** (Scheme 17). Unfortunately, however, the coupling reactions at position 6 of compound **146c** was not successful either under standard heating or microwave irradiations.

The antiproliferative activity determined on a panel of human cancer cell lines of the resulting pyrimidine derivatives shows that *p*-CF_3-phenyl 2,4-diaminopyrimidines **148a**,**b** display better effects compared to those of 4-pyrazolyl 2,4-diaminopyrimidines **150a**,**b**.

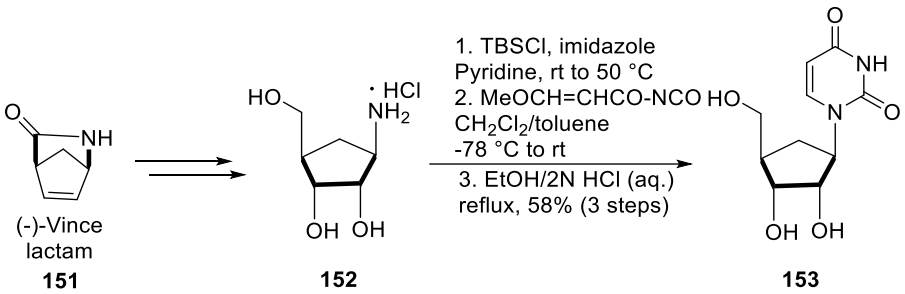


Scheme 17. Synthesis of 5-fluoro-2,4-diaminopyrimidine, 5-chloro-2,4-diaminopyrimidine and 6-chloro-4,5-diaminopyrimidine derivatives

2.3.2. Application of aminotriols

Aminotriols can be used as starting materials for the synthesis of several active compounds, such as (–)-jaspine B,[103] carbocyclic ribonucleotides[104,105] and oxazolines.[86]

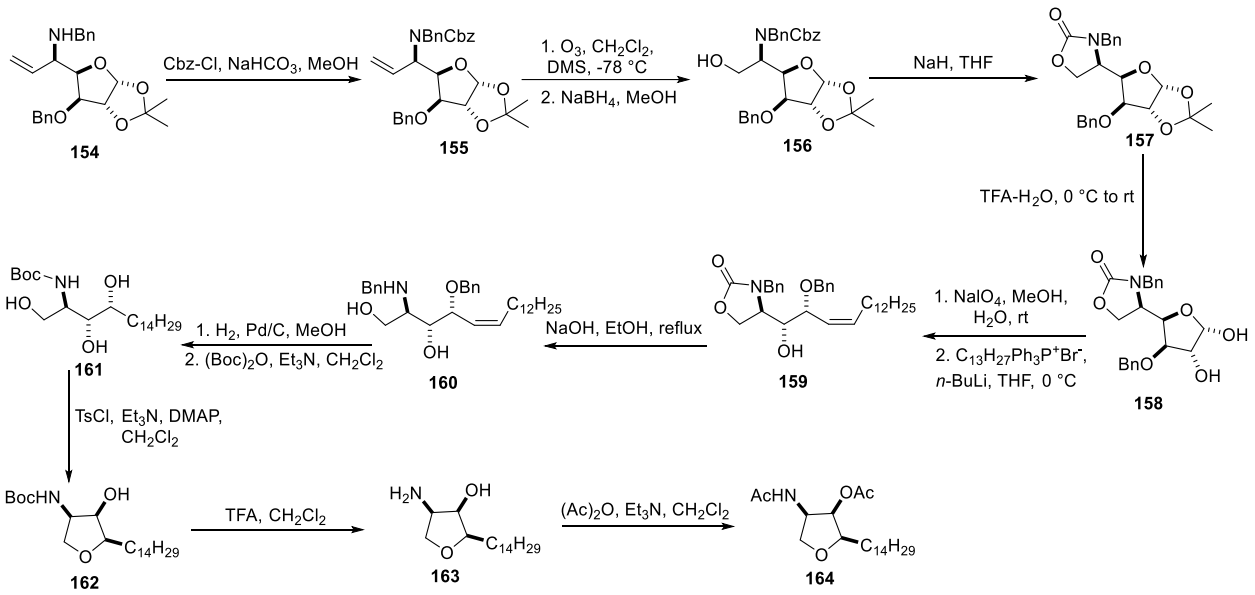
Akabane-Nakata *et al*. reported the synthesis of RNAs containing carbocyclic ribonucleotides.[104] Aminotriol **152**, derived from (–)-Vince lactam **151**, was protected at the hydroxy groups by using TBSCl. The resulting silyl-protected compound was then coupled with 3-methoxyacryloyl isocyanate followed by cyclisation under acidic conditions to yield uridine nucleoside **153** (Scheme 18).



Scheme 18. Synthesis of uridine nucleoside **153**

In addition, the synthesis of diacetyl (–)-jaspine B was performed by Rao *et al.*[103] starting from compound **154**, synthesised from commercially available D-glucose. Protection of the amino functional group in **154** afforded compound **155**. Ozonolysis of the latter with O_3 followed by reduction of the resulting aldehyde with $NaBH_4$ gave alcohol **156**, which underwent cyclisation utilising NaH yielding cyclic carbamate **157** (Scheme 19).

Hemiacetal **158** was formed by removing the 2,3-*O*-isopropylidene protecting group of compound **157** in acidic conditions. Product **158** thus formed was subjected to oxidative cleavage with $NaIO_4$, followed by a Witting reaction using $C_{12}H_{25}P^{+}Ph_3Br^{-}$ resulting in **159**. Deprotection of the carbamate in **159** was achieved with 4M NaOH to produce **160.** The latter, after debenzylation over Pd/C and then *N*-Boc protection, formed *N*-protected aminotriol **161**. Primary alcohol **161** was subjected to regioselective tosylation together with cyclisation to form tetrahydrofuran derivative **162**. Removal of the Boc protecting group in **162** under acidic conditions produced (–)-jaspine B **163**, followed by *N*- and *O*-acetylation to obtain (–)-jaspine B **164** (Scheme 19).



Scheme 19. Synthesis of (–)-jaspine B from aminotriol **161**

A copper-catalysed enantioselective transformation of aminotriols derived from *tris*(hydroxymethyl)aminomethane was developed by Yamamoto *et al*. to provide optically active 4,4-disubstituted oxazolines.[86] This transformation was proposed to take place in a three-step sequence including Cu-catalysed mono-sulfonylation of aminotriols, intramolecular cyclisation and Cu-catalysed asymmetric desymmetrisation of the obtained prochiral oxazolines (Figure 4).

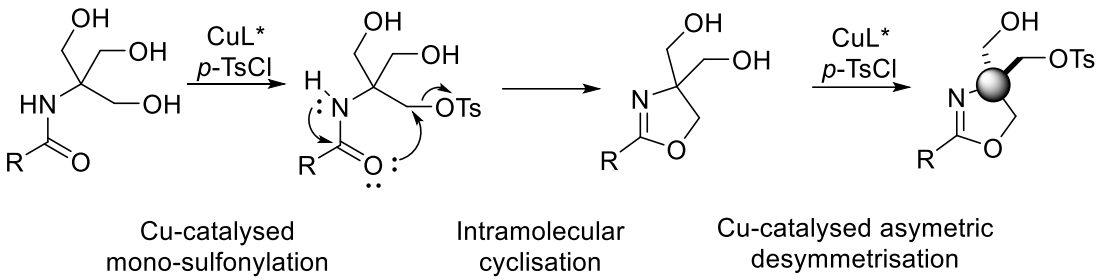
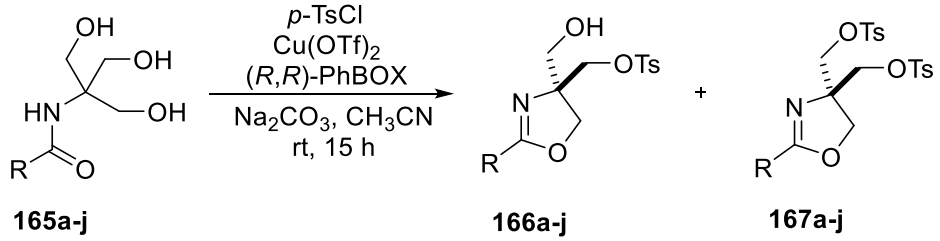


Figure 4. Enantioselective transformation of TRIS-derived aminotriols

A variety of *N*-acyl aminotriols[86] were used in this reaction in the presence of Na_2CO_3 as base affording **166a**–**j** in high yields with good to excellent enantioselectivities (Scheme 20).



a: R = C_6H_5, b: R = 4-MeC_6H_4, c: R = 3-MeC_6H_4, d: R = 2-MeC_6H_4, e: R =4-$MeOC_6H_4$, f: R = 4-ClC_6H_4, g: R = 3-ClC_6H_4, h: R = 2-ClC_6H_4, i: R = 2-furyl, j: R = 2-thienyl

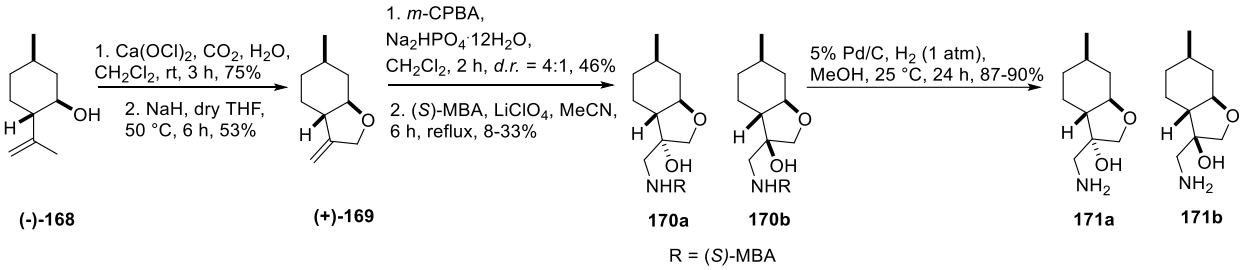
Scheme 20. Enantioselective transformation of *N*-acyl aminotriols

3. Results and discussion

3.1. Synthesis of aminoalcohols

3.1.1. Synthesis of (–)-isopulegol-based 1,2-aminoalcohols [III]

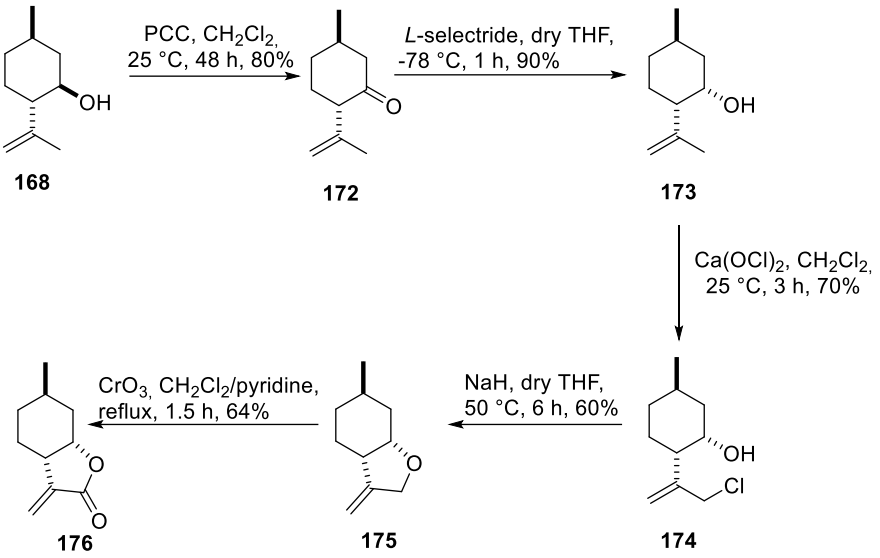
Primary aminoalcohols **171a**–**b** were derived from (–)-isopulegol **(–)-168**. Allylic chlorination of **(–)-168** followed by cyclisation provided *exo*-methylene tetrahydrofuran **169**.[106] The epoxidation of **169** using *m*-CPBA produced a mixture of epoxides with a 4:1 ratio. The ring opening reaction of the epoxide mixture using (*S*)-methylbenzylamine gave secondary aminoalcohols **170a**,**b** after chromatographic separation. Individual aminoalcohols **170a,b** were subjected to catalytic hydrogenation over Pd/C to furnish primary aminoalcohols **171a** and **171b**, respectively (Scheme 21).[107]



Scheme 21. Synthesis of (–)-isopulegol-based 1,2-aminoalcohols **171a**,**b**

3.1.2. Synthesis of (+)-neoisopulegol-based 1,2-aminoalcohols [I]

(+)-Neoisopulegol **173**, the starting material, was obtained by oxidation of the commercially available (–)-isopulegol **168** and subsequent stereoselective reduction of the resulting carbonyl function using L-selectride.[108-111] In the next step, allylic chlorination of **173** followed by cyclisation using NaH produced (–)-methylenetetrahydrofuran **175**.[106,112-114] This latter compound was subjected to allylic oxidation to obtain (–)-α-methylene-γ-butyrolactone **176** according to a literature method[106,115] (Scheme 22).



Scheme 22. Synthesis of (–)-isopulegol-based methylenetetrahydrofuran **175**

Our earlier research has demonstrated that epoxidation applying *t*-BuOOH with vanadyl acetylacetonate [VO(acac)$_2$] as catalyst may effectively be used to generate a novel series of neoisopulegol-based chiral aminodiols.[116] However, when this condition was used to treat **175**, (–)-α-methylene-γ-butyrolactone **176** was formed as the major product. This was probably due to the allylic oxidation mechanism explained in Figure 5.[117,118] Fortunately, epoxide **177** in a stereoselective manner was successfully achieved by reacting **175** with *m*-CPBA (Scheme 23).[119-122]

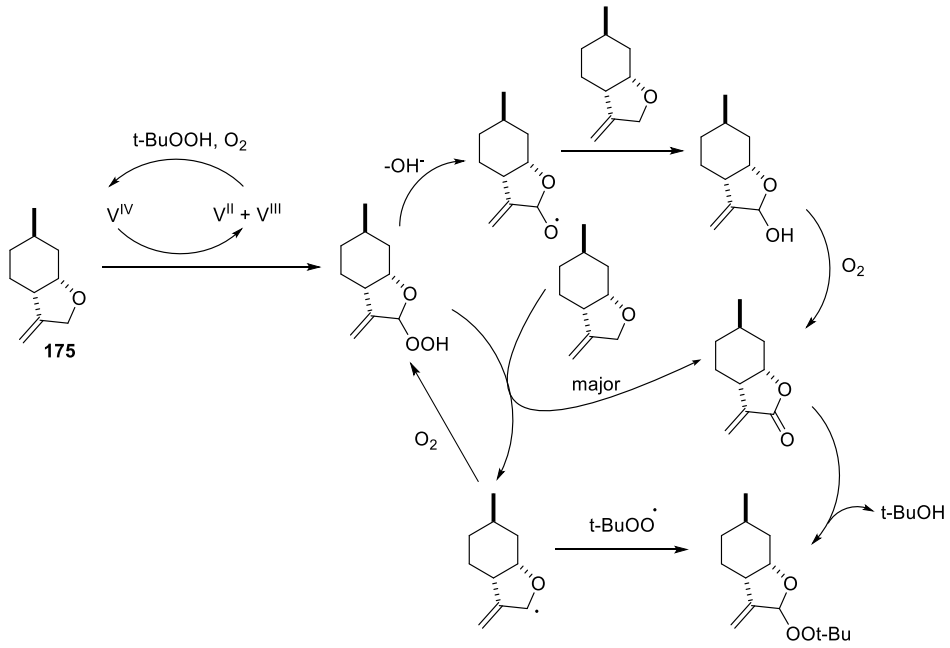
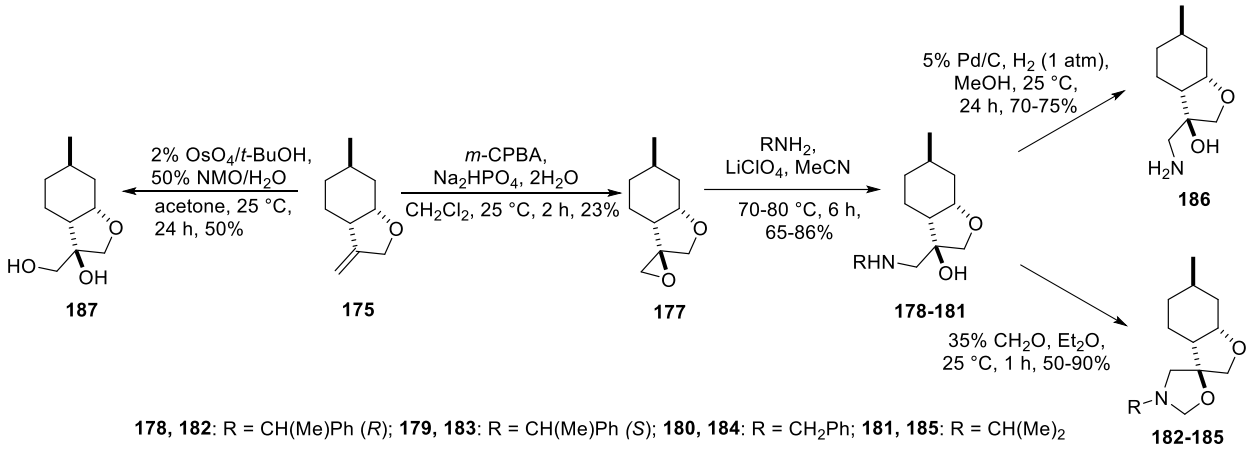


Figure 5. Proposed reaction pathway of allylic oxidation of **175**

Knowing that the *N*-substitution of aminoalcohols has an effect on the efficiency of their catalytic activity,[62,63] a library of aminoalcohols **178**–**181** was prepared by aminolysis of epoxide **177** with primary amines in the presence of $LiClO_4$ as catalyst.[123,124] It was shown in earlier investigations, that the ring closure of monoterpene-based aminoalcohols with rigid structures increases their catalytic activity.[63,80] Therefore, the resulting aminoalcohols **178**–**181** were treated with formaldehyde to form spiro-oxazolidines **182**–**185**. Debenzylation of aminoalcohols **178**–**181** by hydrogenolysis over Pd/C resulted in the formation of primary aminoalcohol **186** in 70–75% yields (Scheme 22). It is known that neither debenzylation of secondary aminoalcohols **178**–**181** nor the synthesis of spiro-oxazolidines using CH_2O had any influence on the configuration of chiral centre C-3. Therefore, the relative stereochemistry of the stereogenic centres in **182**–**185** is identical to that of **178**–**181**.[62,63,80] The *syn*-selective dihydroxylation of key intermediate **175** in the OsO_4/NMO system generated product **187** as a single diastereomer with a reasonable yield[80,125] (Scheme 23).



Scheme 23. Synthesis of (+)-neoisopulegol-based aminoalcohols

Using NMR spectroscopy, the relative configuration of aminoalcohols **178**–**181** and diol **187** was identified. The coupling constant data demonstrated that the highest coupling constant value $J_{4,9}$ in compounds **178**–**181** and **187** refers to the axial orientation of H-9, while the lower coupling constant values $J_{4,3}$ and $J_{3,4}$ in compounds **178**–**181** and **187** confirm that both H-4 and H-3 should be oriented equatorially. Moreover, the NOESY (Nuclear Overhauser Effect SpectroscopY) spectrum analysis in DMSO-d_6 also showed the correlation between protons H-3 and OH-7 as well as H-4 and OH-7, which confirms that both are equatorially oriented. Consequently, the structures of **178**–**181** and **187** were concluded as shown in Figure 6. In a similar manner, 1D and 2D NMR experiments confirmed the configuration of compounds **186** and **182**–**185**.

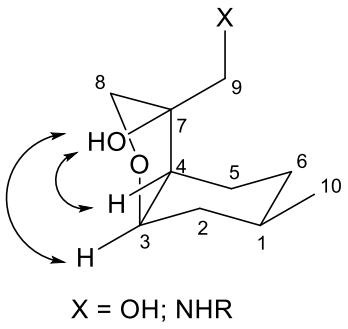
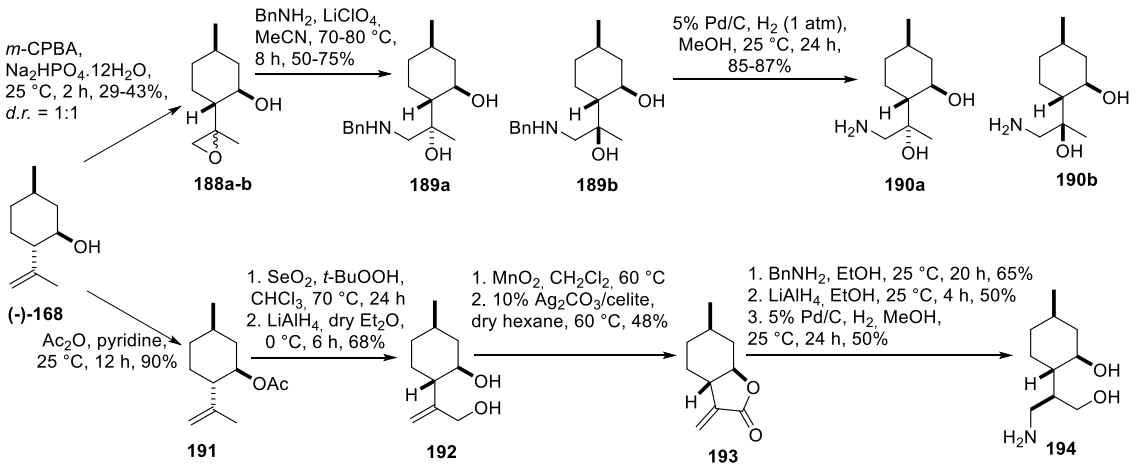


Figure 6. Determination of relative configuration of aminoalcohols **178**–**181** and diol **187**

3.2. Synthesis of (–)-isopulegol- and (+)-neoisopulegol-based chiral aminodiols

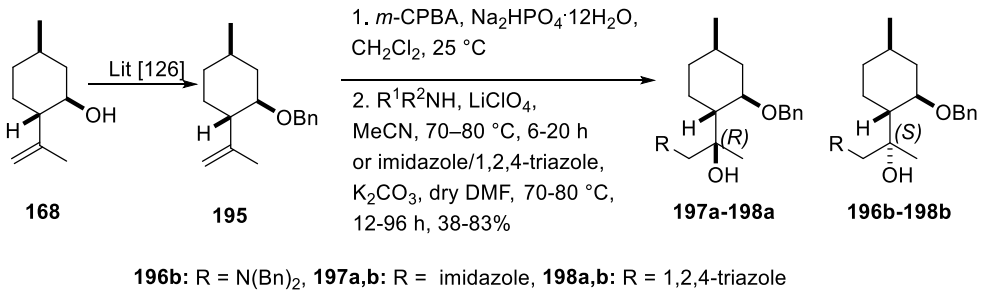
3.2.1. Synthesis of (–)-isopulegol-based aminodiols [II, III]

Primary aminodiols **190a**,**b** were obtained from (–)-isopulegol **168** by a three-step sequence including epoxidation with *m*-CPBA, followed by ring opening of the individual oxiranes with benzylamine after chromatographic separation and subsequent hydrogenolysis on 5% Pd/C.[126] On the other hand, (–)-isopulegol was converted to (+)-α-methylene-γ-butyrolactone **193** by acetylation followed by regioselective oxidation, which gave diol **192**. Subsequent transformation to lactone **193** was carried out in a two-step oxidation and *in situ* ring closure of the obtained γ-hydroxy-substituted α,β-unsaturated carboxylic acid.[108] Reduction of β-aminolactone, produced by nucleophilic addition of benzylamine to **193**, with $LiAlH_4$ then debenzylation of the resulting secondary aminodiol over 5% Pd/C gave primary aminodiol **194** (Scheme 24).[126]



Scheme 24. Preparation of (–)-isopulegol-based aminodiols **190a**,**b** and **194**

Furthermore, our previous works demonstrated the efficacy of the *O*-benzyloxy group on the cyclohexyl ring including antimicrobial activity.[126] Therefore, the (–)-isopulegol-based *O*-benzyl aminodiols **196b**, **197a**,**b** and **198a**,**b** were prepared using a literature method[126] under optimised conditions. *O*-Protection of the hydroxy group of **168** with benzyl bromide, followed by epoxidation of **195** with *m*-CPBA then aminolysis of the resulting epoxides with different nucleophiles such as dibenzylamine, imidazole and 1,2,4-triazole yielded **196–198**. Compound **196a** was not obtained probably due to the steric effect between the methyl or the benzyl group at the alpha position of the oxirane ring (Scheme 25).

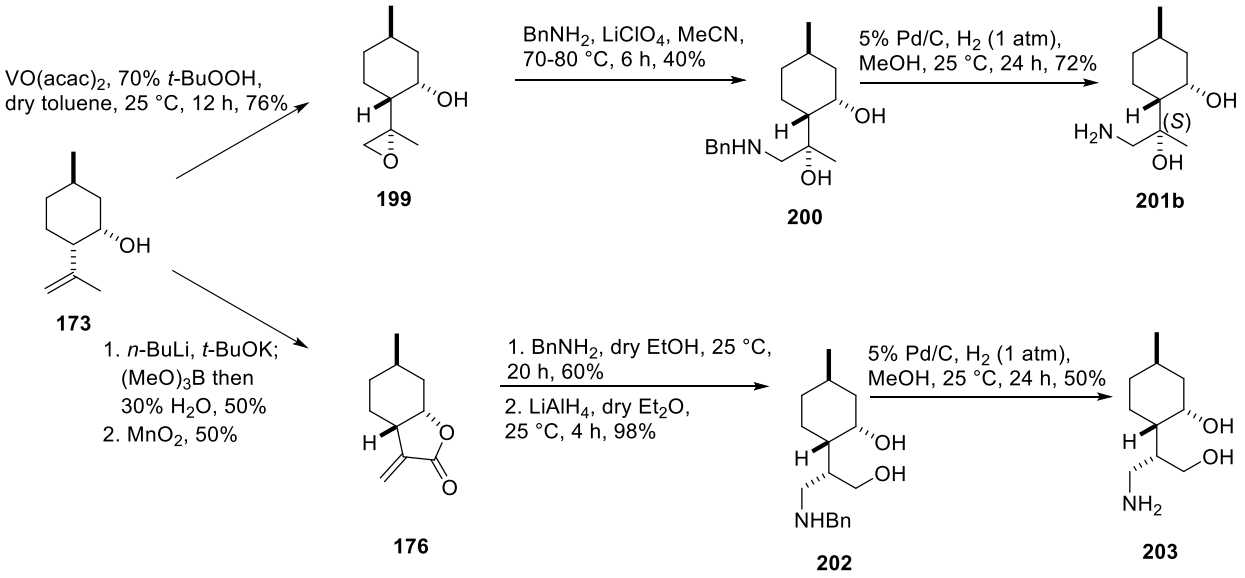


Scheme 25. Synthesis of (–)-isopulegol-based *O*-benzyl derivatives **196**–**198**

3.2.2. Synthesis of (+)-neoisopulegol-based chiral aminodiols [II]

The synthesis of regioisomeric aminodiols[116] **201b** was performed from (+)-neoisopulegol **173** by stereoselective epoxidation with *t*-BuOOH applying $VO(acac)_2$ as catalyst, followed by ring opening of epoxide **199** with benzylamine and then catalytic debenzylation (Scheme 26).

Regioisomeric aminodiol **203** was synthesised from (–)-*α*-methylene-*γ*-butyrolactone **176,** derived from (+)-neoisopulegol **173** according to a literature method.[116] Nucleophilic addition of benzylamine towards **176** followed by treatment with $LiAlH_4$ produced secondary aminodiol **202**, which was easily transformed to **203** by hydrogenolysis on Pd/C (Scheme 26).



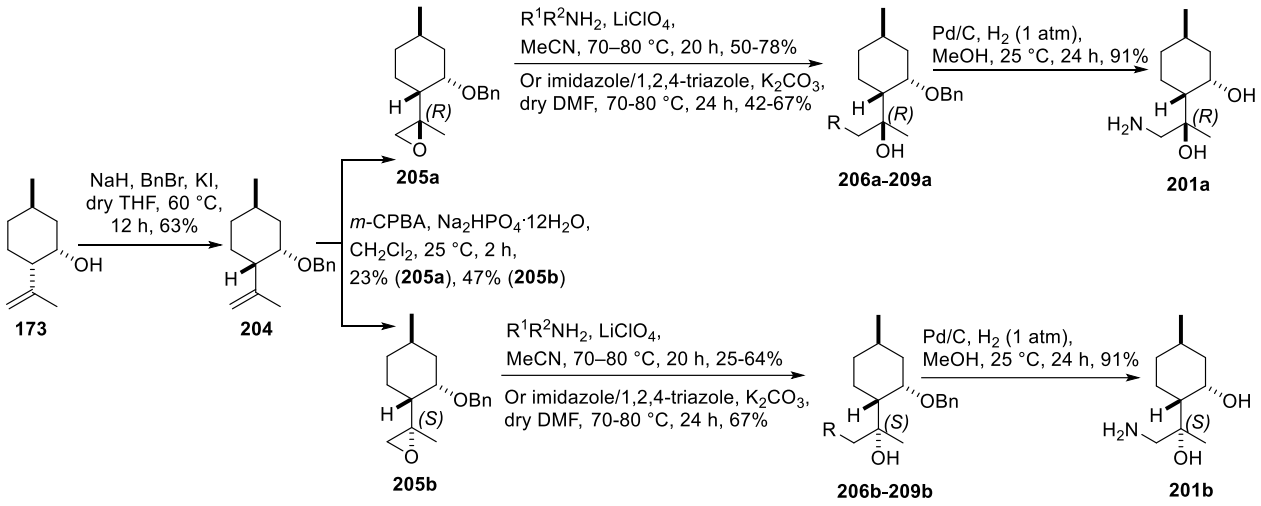
Scheme 26. Preparation of (+)-neoisopulegol-based aminodiols **201b** and **203**

In order to obtain (+)-neoisopulegol-based *O*-benzyl derivatives, (+)-neoisopulegol was subjected to the *O*-benzylation with BnBr in the presence of KI as catalyst.[127,128] The presence of was essential to accelerate the rate of the reaction through the formation of the reactive BnI from BnBr.[129]

Epoxidation of the resulting **204** with *m*-CPBA in the presence of Na_2HPO_4 as buffer produced the mixture of epoxides **205a** and **205b** with a 1:2 ratio in good yields.[130] The epoxide mixture was easily separated using column chromatography to obtain individual isomers **205a** and **205b**. Ring opening of epoxide **205a** with benzylamine and dibenzylamine using a catalytic amount of $LiClO_4$ resulted in the formation of *O*-benzyl derivatives **206a** and **207a**.[123,131] The use of $LiClO_4$ as catalyst was responsible for increasing product yields by enhancing the reactivity of the ring-opening process through the coordination of Li^+ with the oxygen the epoxide ring thereby making the nucleophilic attack by amines to proceed smoothly.[132,133]

Due to the different reactivities of amines and azoles, when ring-opening condition as described above was applied to oxirane **205a** with azoles using $LiClO_4$, no transformation was observed. Fortunately, the reaction was successful by using K_2CO_3.[134] (+)-Neoisopulegol-based *O*-benzyl derivatives **208a** and **209a** were obtained from the ring opening of epoxide **205a** with imidazole and 1,2,4-triazole in the presence of K_2CO_3.[135] In the next step, hydrogenolysis of compound **206a** over Pd/C produced primary aminodiol **201a** in a high yield.

Based on the configuration of epoxide **205a**, the relative stereochemistry of the stereogenic centres of **206a**–**209a** and **201a** remains the same, since there is no influence in the ring opening of epoxide **205a** in alkaline conditions or the debenzylation of compound **206a**.[63,80] In similar methods as mentioned above, compounds **206b**–**209b** and **201b** were obtained from epoxide **205b** in good yields (Scheme 27).

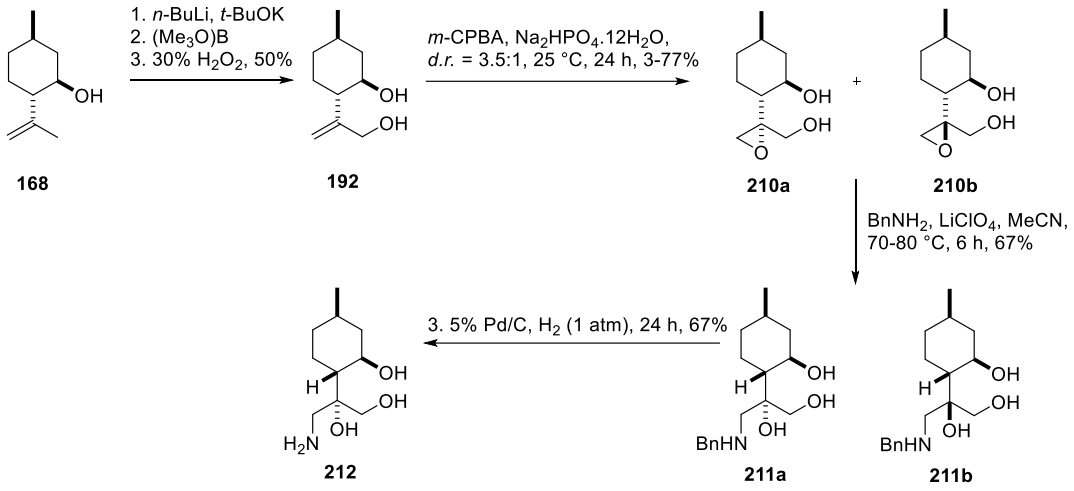


Scheme 27. Synthesis of (+)-neoisopulegol-based *O*-benzyl aminodiols

3.3. Synthesis of (–)-isopulegol-based and (+)-neoisopulegol chiral aminotriols

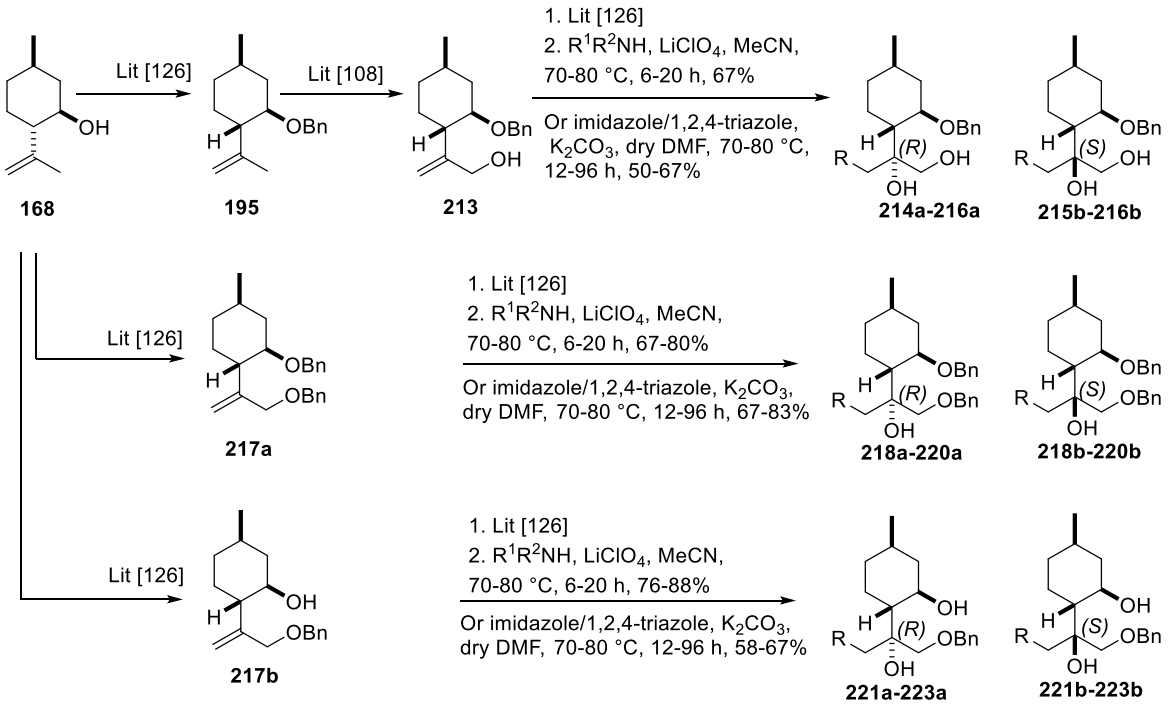
3.3.1. Synthesis of (–)-isopulegol-based chiral aminotriols [II]

Aminotriol **212** was successfully synthesised by regioselective oxidation of (–)-isopulegol, which gave diol **192**,[115] followed by epoxidation and separation by column chromatography to yield oxiranes **210a**,**b**. Ring opening of the individual epoxides using benzylamine furnished secondary aminotriols **211a,b**. Debenzylation of major compound **211a** according to a literature method produced primary aminotriol **212** (Scheme 28).[126]



Scheme 28. Synthesis of isopulegol-based aminotriol **212**

Furthermore, (–)-isopulegol-based *O*-benzyl aminotriol derivatives were also synthesised under optimised condition applying a literature method[126] (Scheme 29).

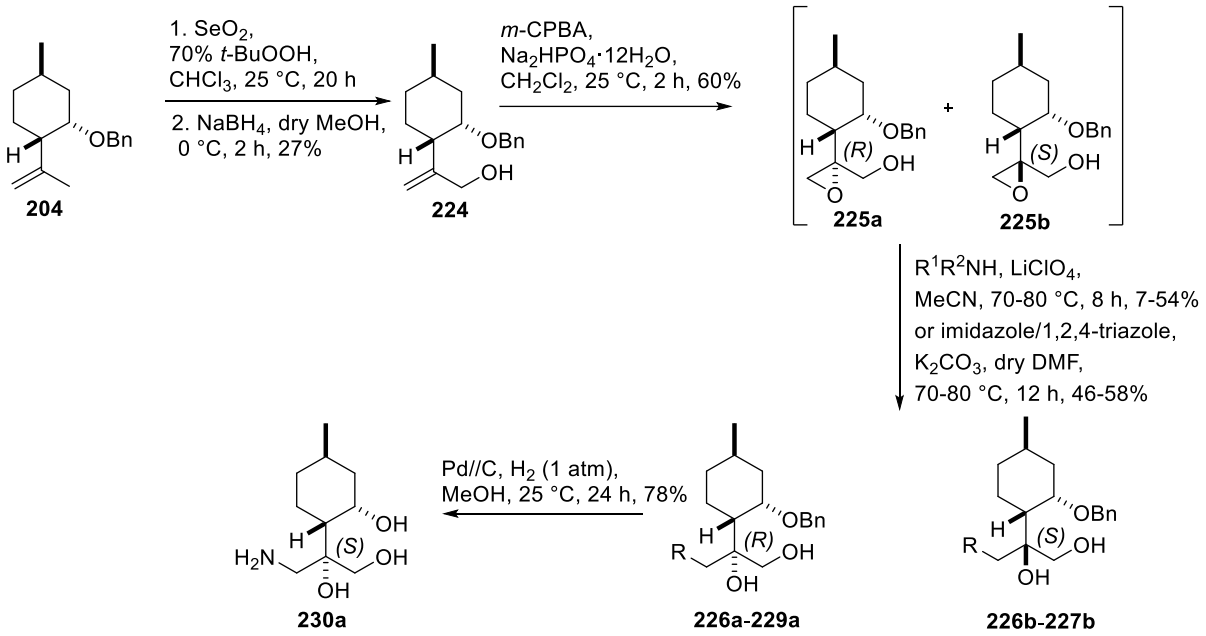


Scheme 29. Synthesis of (–)-isopulegol-based *O*-benzyl aminotriol derivatives

3.3.2. Synthesis of (+)-neoisopulegol-based chiral aminotriols [II]

To access the library of *O*-benzyl aminotriols, allylic oxidation of **204** was performed using the SeO_2/*t*-BuOOH (TBHP) system to form **224**.[136] Epoxidation of **224** was accomplished with *m*-

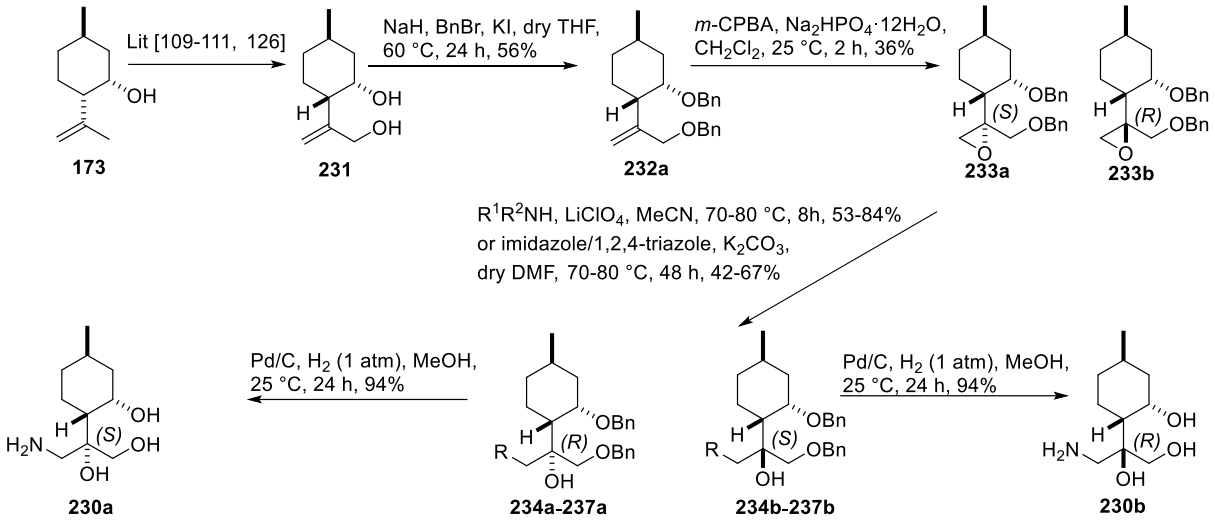
CPBA resulting in a 4:1 mixture of epoxides **225a** and **225b.** The epoxide mixture without separation was directly subjected to ring opening by different nucleophiles novel *O*-benzyl derivatives **226**–**229** after column chromatography. However, in the case of azole derivatives, only the major compounds were isolated. Hydrogenation of **226a** over 5% Pd/C furnished primary aminotriol **230a** in 78% yield (Scheme 30).



226a,**b**: R = NHBn, **227a**,**b**: R = $N(Bn)_2$, **228a**: R = imidazole, **229a**: R = 1,2,4-triazole

Scheme 30. Synthesis of (+)-neoisopulegol-based *O*-benzyl aminotriols

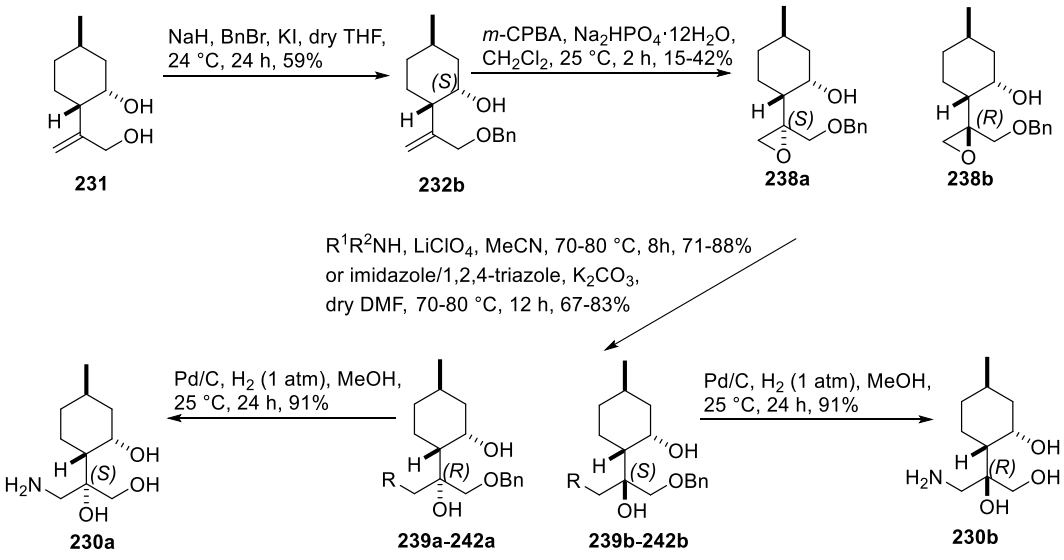
During our efforts we discovered that *O*-benzylation of **224** might be beneficial to enhance the separation of epoxides **225a**,**b**. However, the preparation of di-*O*-benzyl **232a** from **224** using NaH and BnBr in the presence of KI resulted in a low-yield transformation (20%). Therefore, in order to achieve a good result, diol **231**, obtained from oxidation of (+)-neoisopulegol **173**,[108-111] was subjected to di-*O*-benzylation applying instead the NaH/BnBr/KI system under reflux conditions resulting in **232a**. In contrast, only **232b** was obtained at room temperature. Epoxides **233a** and **233b**, formed by epoxidation of **232a** with the *m*-CPBA system (*d.r.* = 1:1), after chromatographic purification were subjected to ring opening with multiple nucleophiles giving a family of di-*O*-benzyl derivatives **234a**–**237a** and **234b**–**237b**, respectively. Hydrogenation of **234a** and **234b** over Pd/C resulted in primary aminotriols **230a** and **230b** in excellent yields (Scheme 31).



234a,**b**: R = NHBn, **235a**,**b**: R = $N(Bn)_2$, **236a**,**b**: R = imidazole, **237a**,**b**: 1,2,4-triazole

Scheme 31. Synthesis of (+)-neoisopulegol-based di-*O*-benzyl aminotriols

On the other hand, epoxidation of **232b** with *m*-CPBA produced a mixture of epoxides **238a** and **238b** with a 3:1 ratio. After separation by column chromatography, aminolysis of the individual compounds with different nucleophiles led to the formation of novel *O*-benzyl derivatives **239a**–**242a** and **239b**–**242b**, respectively. Catalytic hydrogenation of **239a** and **239b** on Pd/C subsequently yielded primary aminotriols **230a** and **230b** (Scheme 32).



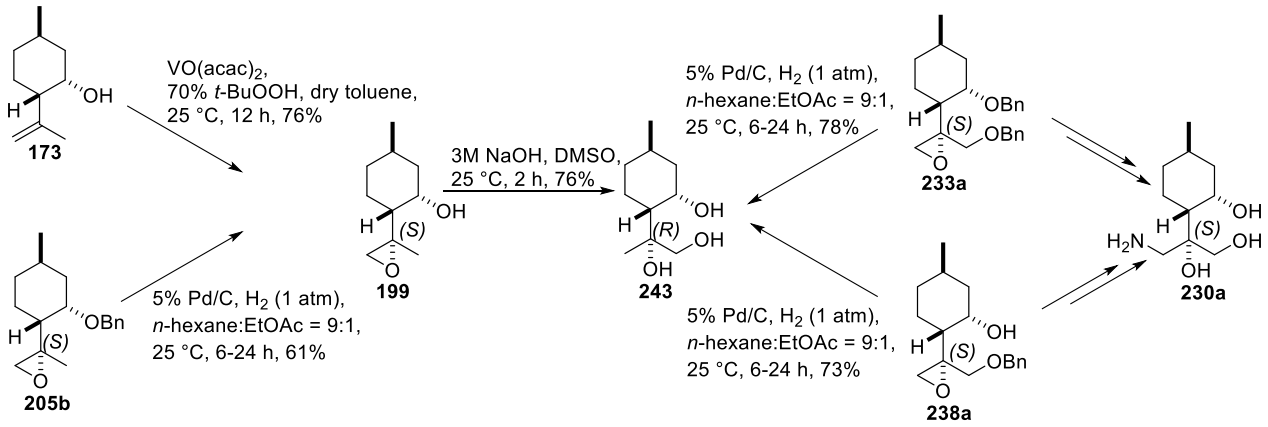
239a,**b**: R = NHBn, **240a**,**b**: R = $N(Bn)_2$, **241a**,**b**: imidazole, **242a**,**b**: 1,2,4-triazole

Scheme 32. Synthesis of (+)-neoisopulegol-based *O*-benzyl aminotriols

To determine the absolute configuration of aminodiols, hydrogenation of **205b** over Pd/C was performed to provide **199** in a moderate yield. The stereochemical structure is similar to that of epoxide **199**, prepared by epoxidation of **173** with *t*-BuOOH in the presence of $VO(acac)_2$ according to a literature method.[108]

On the other hand, the stereochemistry of *O*-benzyl derivatives **233a** and **238a** was identified by catalytic hydrogenation over 5% Pd/C[137,138] to produce triol **243** with stereochemical retention,[126] whereas treatment of **199** with NaOH also furnished **243** with the retention of stereochemistry.[139]

The absolute configuration of epoxide **199** is well-known in the literature;[108] therefore, the absolute configuration of epoxides **205b**, **233a** and **238a** could be determined. The aminolysis of the epoxides and the hydrogenolysis of *N*-benzyl derivatives are known to have no influence on the stereochemistry. Consequently, the absolute configuration of primary aminodiol **201b** and aminotriol **230a** is the same as that of epoxides **205b, 233a** and **238a** (Scheme 33).



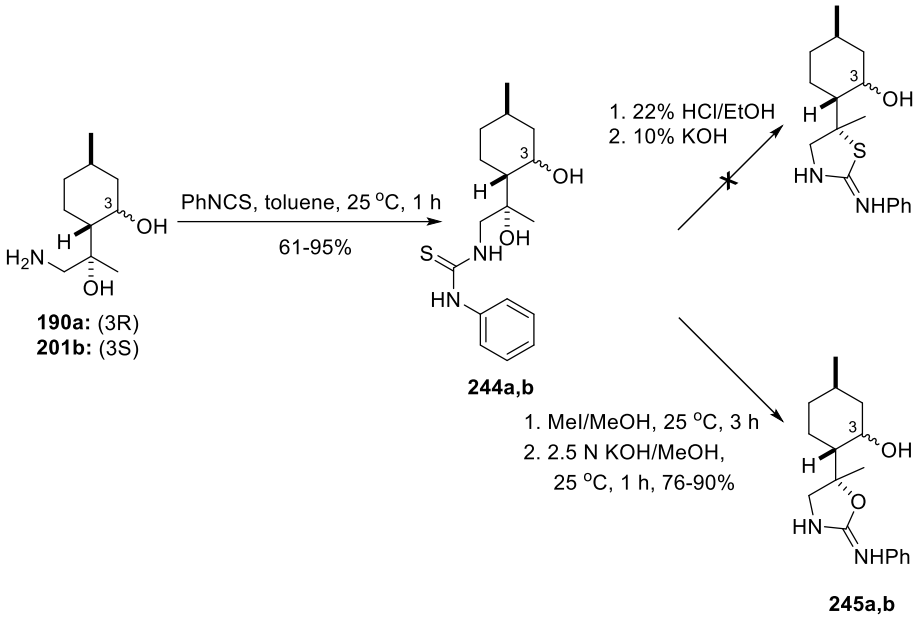
Scheme 33. Determination of the structure of (+)-neoisopulegol-based-*O*-benzyl derivatives

3.4. Application of aminoalcohols, aminodiols and aminotriols as building blocks

3.4.1. Synthesis of 1,3-oxazines, oxazolidines, 1,3-thiazines and thiazolidines [III]

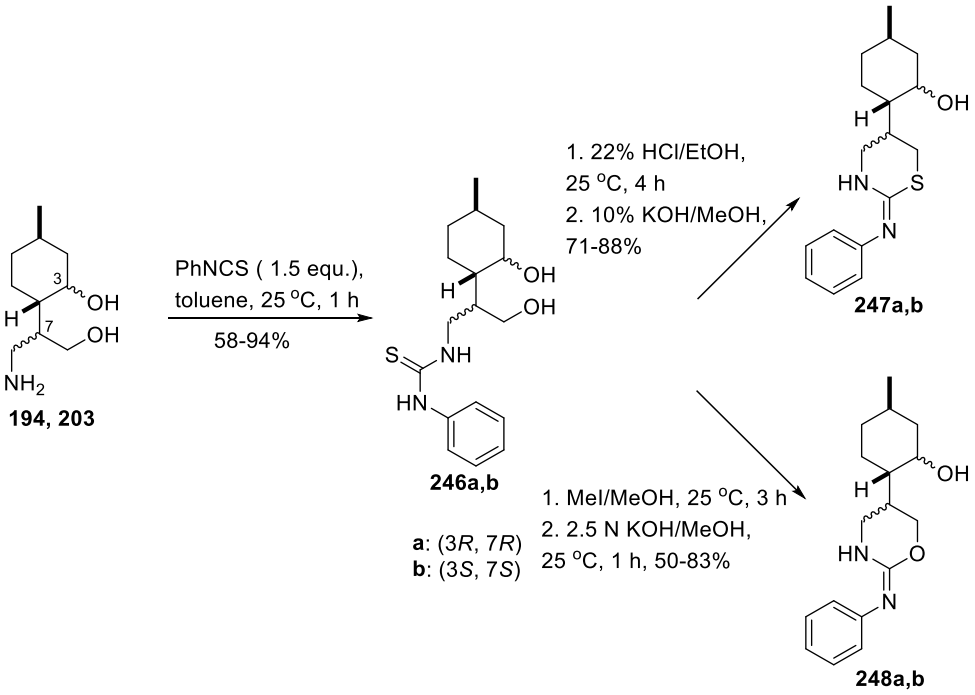
Starting from aminodiols **190a** and **201b**, the synthesis of 1,3-oxazines[140] and 1,3-thiazines[141] was achieved by different transformations.[142] Aminodiols **190a** and **201b** in the presence of phenyl isothiocyanate at room temperature provided thioureas **244a**,**b** in moderate to good yields. However, the transformation of **190b** was an exception, since no product was formed under the applied conditions. This is proposed to be due to the steric hindrance between the hydroxy group of the aminodiol system and the methyl substituent at the α position of aminodiol **190b**.[126] In the next step, the ring closure of the resulting thioureas **244a**,**b** with 22% HCl was unsuccessful

probably due to the steric effect of the methyl group at the α position, whereas the treatment of **244a**,**b** with MeI gave thioethers, which were easily transformed in alkaline medium to 2-phenylimino-oxazolidines **245a**,**b** (Scheme 34).



Scheme 34: Synthesis of oxazolidines **245a**,**b**

Using the same methods as described above, aminodiols **194** and **203** was transformed to the corresponding thiourea adducts **246a**,**b** with moderate to good yields. Subsequent acid-catalysed cyclisation with 22% HCl provided 2-phenylimino-1,3-thiazines **247a**,**b**. It was in our previous works that the cyclisation process could be carried out easily in this case due to the less hindered structures of thioureas.[141] On the other hand, 2-phenylimino-1,3-oxazines **248a**,**b** were prepared by treatment of thioureas **246a**,**b** with the MeI/KOH system (Scheme 35).

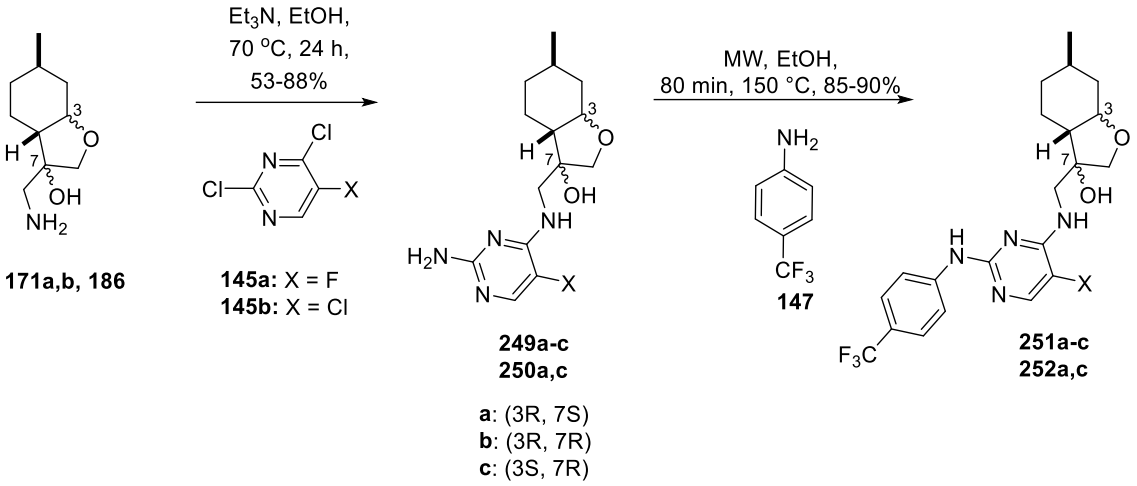


Scheme 35. Synthesis of 1,3-thiazines **247a**,**b** and 1,3-oxazines **248a**,**b**

3.4.2. Synthesis of 2,4-diaminopyrimidine derivatives [III]

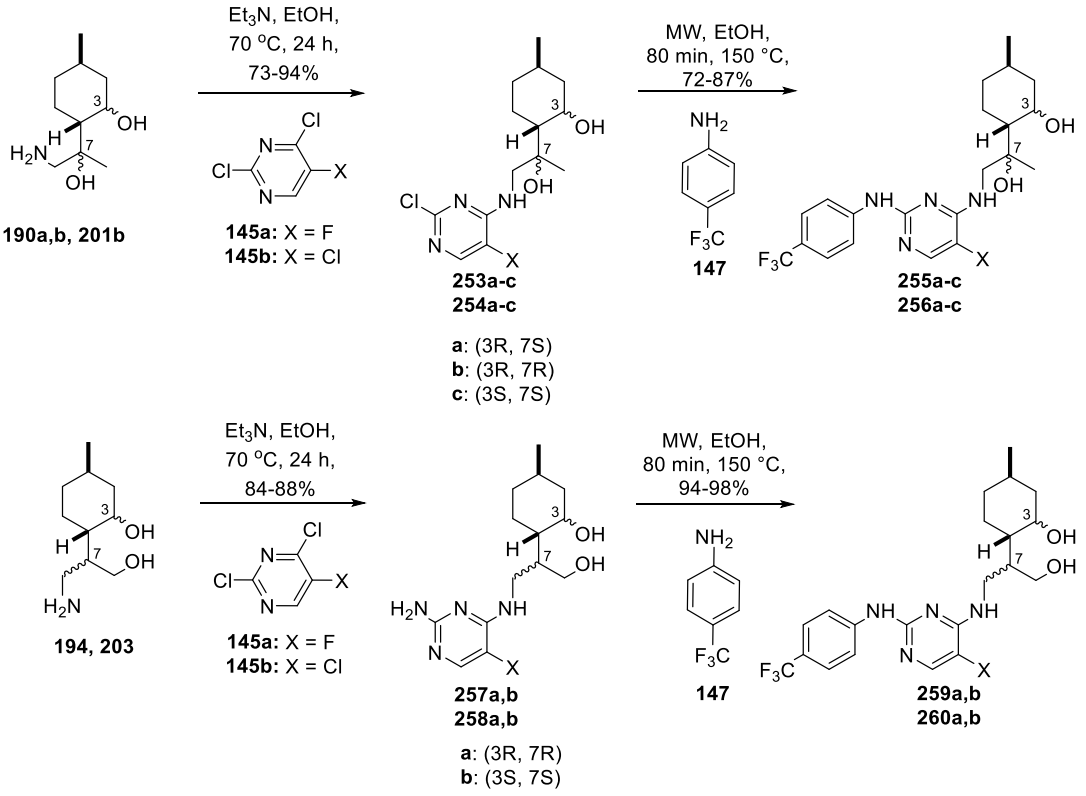
In addition to the significance of monoterpene-fused 2-phenylimino-1,3-oxazines and 1,3-thiazines as antiproliferative agents, a recent publication emphasised the anticancer potential of the pyrimidine-based structures.[143] Therefore, we planned to prepare pyrimidine derivatives starting from primary aminoalcohols **171a**,**b**, **186**, together with aminodiols **190a**,**b**, **194**, **201b**, **203** as well as aminotriol **212**.

The addition of 2,4-dichloro-5-fluoropyrimidine **145a** and 2,4,5-trichloropyrimidine **145b** to 1,2-aminoalcohols **171a**,**b** and **186** in the presence of Et_3N led to the formation of key intermediates **249a**–**c** and **250a,c**.[144] Then the products were applied in microwave-assisted S_NAr coupling reaction with 4-aminobenzotrifluoride **147** to produce **251a**–**c** and **252a,c** as solid precipitates in good yields (Scheme 36).[145]



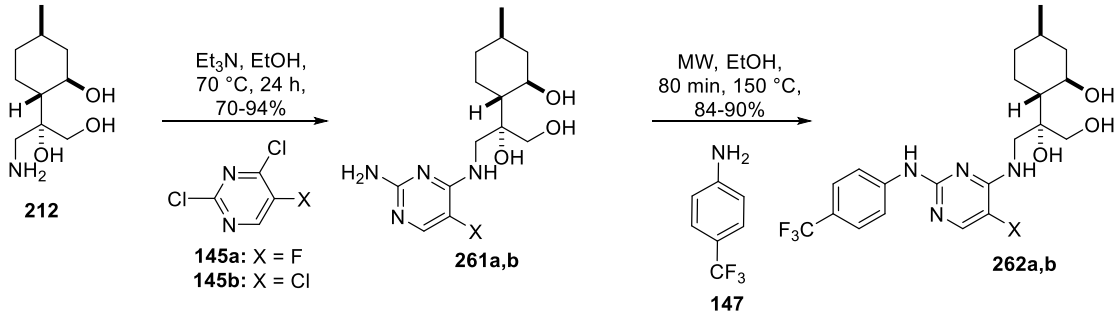
Scheme 36. Synthesis of 2,4-diaminopyrimidines **251a**–**c** and **252a,c**

In a similar manner, the reaction between aminodiols **190a**,**b**, **201b**, **194** and **203** with 2,4-dichloro-5-fluoropyrimidine **145a** and 2,4,5-trichloropyrimidine **145b** in the presence of Et_3N successfully delivered **253a**–**c**, **254a**–**c**, **257a**,**b** and **258a**,**b**. Subsequent S_NAr coupling reaction with 4-aminobenzotrifluoride **147** yielded **255a**–**c**, **256a**–**c**, **259a**,**b** and **260a**,**b** (Scheme 37).



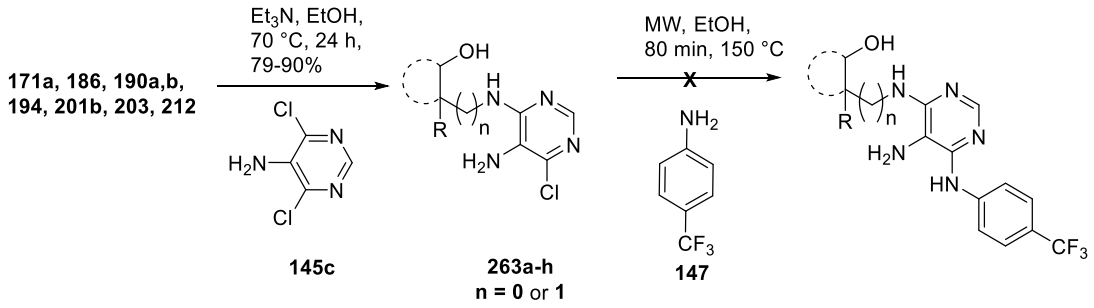
Scheme 37. Synthesis of 2,4-diaminopyrimidines **255a**–**c**, **256a**–**c**, **259a**,**b** and **260a**,**b**

Likewise, aminotriol **212** was also used as starting material to prepare the analogues 2,4-diaminopyrimidines **261a**,**b**. Their further coupling with 4-aminobenzotrifluoride afforded **262a**,**b** (Scheme 38).



Scheme 38. Synthesis of 2,4-diaminopyrimidines **262a**,**b**

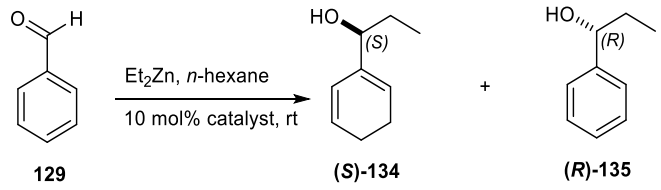
Due to the anticancer potential of pyrimidines substituted at various positions as well as pyrimidine fused with other heterocyclic rings,[146] we managed to perform another coupling reaction by using 5-amino-4,6-dichloropyrimidine **145c** as the reagent. The desired (–)-isopulegol-based pyrimidines **263a**–**h** were formed in good yields. In the next step, however, couplings at the remaining chlorine at position 6 in adducts **263a**–**h** were unsuccessful either under standard heating or microwave-assisted treatment. This is probably due to the steric effect of the amino group at the *ortho* position, preventing **263a**–**h** to establish the desired interactions (Scheme 39).[147,148]



Scheme 39. Synthesis of 2,4-diaminopyrimidines **263a**–**h**

3.5. Application of aminoalcohol derivatives as chiral ligands for catalytic addition of diethylzinc to benzaldehyde [I]

To explore the catalytic efficacy of the prepared ligands, aminoalcohol derivatives **178**–**186** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde **129** to form (*S*)- and (*R*)-1-phenyl-1-propanol **134**–**135** (Scheme 40).



Scheme 40. Model reaction for enantioselective catalysis

The enantiomeric purity of 1-phenyl-1-propanols (*S*)-**134** and (*R*)-**135** was determined by GC analysis on a Chirasil-DEX CB column using literature methods.[149,150] Based on the results, secondary aminoalcohols produced low to moderate enantiomeric excess (*ee*%) values with (*S*) selectivity, except in the case of ligand **178**, which provided the (*R*) enantiomer, whereas (*R*) enantioselectivity was observed for all spiro-oxazolidines (Table 1). The highest catalytic performance was found in the case of ligand **179** with a 40% *ee* value with (*S*) selectivity (entry 2), while poor catalytic activity was observed in the case of spiro-oxazolidines. This might be explained by the flexibility of the spiro system. In fact, these results are similar to those mentioned in previous studies of pinane- or sabinane-based spiro-oxazolidines.[79,151]

Table 1. Addition of diethylzinc to benzaldehyde catalysed by aminoalcohol derivatives

Entry	Ligand	Yield [a] (%)	*ee* [b] (%)	Configuration of the Major Product [c]
1	**178**	86	8	*(R)*
2	**179**	90	40	*(S)*
3	**180**	89	11	*(S)*
4	**181**	93	4	*(S)*
5	**182**	88	11	*(R)*

6	**183**	90	3	*(R)*
7	**184**	82	6	*(R)*
8	**185**	80	7	*(R)*
9	**186**	95	7	*(S)*

[a] After chromatography on a silica column. [b] Determined using the crude product by GC analysis (Chirasil-DEX CBcolumn). [c] Determined by comparing the t_R of GC analysis and optical rotations with literature data.

3.6. Antimicrobial effects and antiproliferative activity [I, II, III]

It has been shown that different aminoalcohols and *O*-benzyl derivatives have antimicrobial effects on different bacterial and fungal strains.[126,152,153] Consequently, the antimicrobial effects of the prepared aminoalcohols and *O*-benzyl analogues were tested on two yeasts, two gram-positive bacteria and two gram-negative bacteria.

The results strongly indicated that *N*-substituted aminoalcohols have a moderate antibacterial effect on multiple bacterial strains, whereas diol **187** showed considerable antifungal activity. Moreover, according to the *in vitro* pharmacological results, the *O*-benzyl substituent on the cyclohexyl ring of aminodiol and aminotriol derivatives is also responsible for the antibacterial activity (Table 2). Additionally, the antiproliferative activity of synthetic 2,4-diaminopyrimidines was tested on various human cancer cell lines. The results showed that N^2-(*p*-trifluorophenyl) amino- and N^4-(–)-isopulegol-based aminodiol derivatives coupled pyrimidines were more effective against cancer than the clinically used anticancer drug, cisplatin (Table 3).

Although the literature[148] reported the interactions between 2,4-diaminopyrimidine scaffolds bearing the N^2-(*p*-trifluoromethyl) phenyl group and the availability of crystallisation-grade protein Aurora A, the simulation of molecular docking could enlarge our understanding of the binding pattern between ligand and protein Aurora A intuitively. These various interactions play a significant role in the high *in vitro* potency of **255b** (Figure 7).

Table 2. Most relevant antimicrobial activitiy

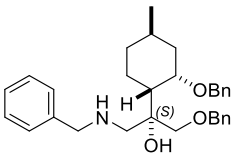
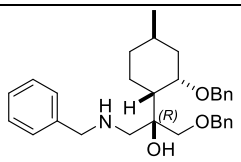
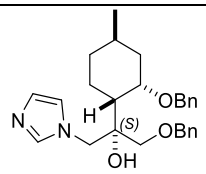
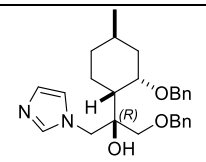
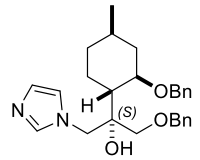
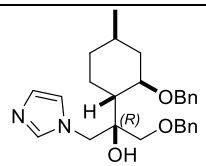
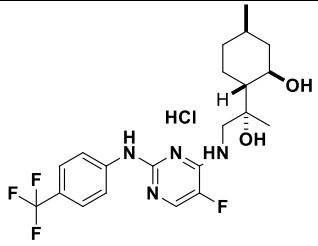
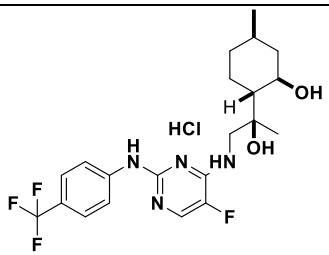
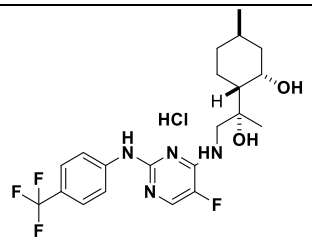
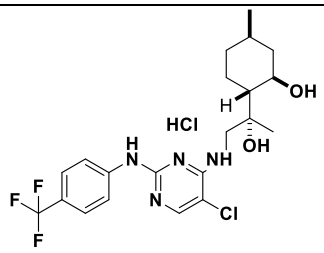
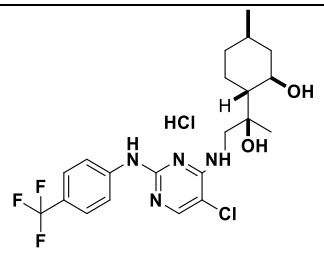
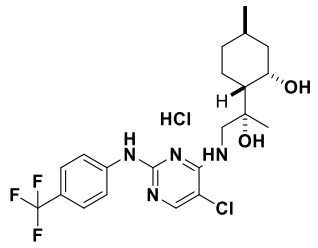
Inhibitory effect (%) ± RSD (%)							
		Gram positive		Gram negative		Yeast	
Analogue	**Conc. (µg/mL)**	***B. subtilis* SZMC0209**	***S. aureus* SZMC14611**	***E. coli* SZMC6271**	***P. aeruginosa* SZMC23290**	***C. albicans* SZMC1533**	***C. krusei* SZMC1352**
Nystatin	100	–	–	–	–	93.38 ± 2.13 (100 µg/mL)	92.01 ± 3.64 (100 µg/mL)
	10	–	–	–	–	92.88 ± 10.18	58.00 ± 9.21
Ampicillin	100	95.22 ± 8.40 (<0.78 µg/mL)	81.88 ± 8.99 (<0.78 µg/mL)	94.07 ± 3.61 (100 µg/mL)	29.03 ± 2.06	–	–
	10	93.00 ± 3.20	70.37 ± 6.15	89.37 ± 0.39	–	–	–
 **234a**	100	84.57 ± 3.18 (6.25 µg/mL)	70.13 ± 0.90	–	–	91.35 ± 1.07 (>100 µg/mL)	–
	10	89.70 ± 1.32	65.81 ± 0.51	–	–	–	–
 **234b**	100	78.34 ± 2.51	69.49 ± 0.57	–	–	90.74 ± 2.90 (>100 µg/mL)	79.88 ± 3.39
	10	78.43 ± 5.39	61.84 ± 0.27	–	–	80.54 ± 17.23	–
 **236a**	100	83.44 ± 20.97	76.39 ± 1.13	–	–	–	–
	10	81.63 ± 1.22 (25 µg/mL)	70.02 ± 1.01	–	–	–	–
 **236b**	100	78.43 ± 10.14 (<0.78 µg/mL)	60.32 ± 1.11	–	–	81.97 ± 4.00 (>100 µg/mL)	–
	10	81.01 ± 1.08	62.77 ± 0.27	–	–	61.02 ± 6.51	–
 **197b**	100	79.38 ± 4.19 (3.13 µg/mL)	63.47 ± 4.90	–	–	88.22 ± 3.96 (>100 µg/mL)	–
	10	82.73 ± 0.52	69.84 ± 0.00	–	–	–	–
 **197a**	100	87.80 ± 7.04 (1.56 µg/mL)	79.66 ± 2.59 (3.13 µg/mL)	–	48.09 ± 1.38	90.89 ± 13.31 (>100 µg/mL)	91.08 ± 4.90 (100 µg/mL)
	10	92.94 ± 1.46	83.69 ± 38.18	–	33.59 ± 6.43	85.10 ± 9.56	–

Table 3. Antiproliferative properties of the heterocyclic derivatives

Analogue	*Conc. (μM)*	Growth Inhibition (%) ± SEM			
		HeLa	***SiHa***	***A2780***	***MDA-MB-231***
 **255a**	10	75.38 ± 0.53	54.14 ± 1.05	75.64 ± 2.25	32.06 ± 1.94
	30	86.75 ± 0.41	89.19 ± 0.81	92.14 ± 0.49	67.79 ± 1.09
 **255b**	10	94.62 ± 0.35	84.94 ± 1.11	91.50 ± 0.36	55.65 ± 1.26
	30	96.90 ± 0.46 (IC_{50}: 7.20 μM)	95.89 ± 0.74 (IC_{50}: 2.62 μM)	96.58 ± 0.76 (IC_{50}: 4.98 μM)	99.82 ± 1.61 (IC_{50}: 9.91 μM)**
 **255c**	10	37.11 ± 3.39	32.92 ± 0.91	31.49 ±2 .40	-
	30	70.69 ± 1.19	58.90 ± 0.48	98.36 ± 0.29	56.98 ± 2.27
 **256a**	10	27.66 ± 0.60	35.35 ± 1.00	78.25 ± 0.75	29.03 ± 2.20
	30	93.40 ± 0.26	89.59 ± 0.54	92.12 ± 0.32	88.09 ± 0.54
 **256b**	10	96.00 ± 0.39	76.02 ± 2.05	96.26 ± 0.58	40.32 ± 2.18
	30	96.55 ± 0.43 (IC_{50}: 9.03 μM)**	95.32 ± 0.43 (IC_{50}: 5.69 μM)	96.69 ± 0.23 (IC_{50}: 4.13 μM)	96.16 ± 1.09 (IC_{50}: 11.47 μM)

 **256c**	10	87.71 ± 1.54	64.44 ± 3.50	97.23 ± 0.31	75.56 ± 2.58
	30	96.06 ± 0.27	88.34 ± 0.46	98.33 ± 0.25	93.30 ± 1.16
Cisplatin	10	42.61 ± 2.33	60.98 ± 0.92	83.57 ± 2.21	42.72 ± 2.68
	30	99.93 ± 0.26	88.95 ± 0.53	95.02 ± 0.28	86.44 ± 0.42
		(IC_{50}: 12.43 μM)**	(IC_{50}: 4.29 μM)	(IC_{50}: 1.30 μM)	(IC_{50}: 10.17 μM)

* Cancer cell growth inhibition values less than 10% were considered insignificant and are not given numerically

** In the case of the most effective test compounds (**255b** and **256b**) and reference agent cisplatin, the viability assays were repeated with a set of dilutions (0.1–30 μM), and the IC_{50} values were determined using the GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, CA, USA).

Discovery Studio 2.5's docking analysis was used to investigate the potential interactions between ligand **255b** and Aurora A kinase PDB (Code: 4DEE).

The 2D diagram of key binding interactions of the hit (compound **255b**) with Aurora A (Figure 7) demonstrated that the methylcyclohexyl moiety forms a hydrophobic alkyl interaction with a hydrophobic pocket formed by Phe144, Leu164 and Lys162, whereas the aromatic ring has a variety of *pi*-alkyl interactions between another hydrophobic pocket formed by Leu139, Val147 and Leu263. Alongside Lys141 and the amine of aminodiol forms a strong hydrogen bond.

The molecular properties of ligand **255b** was established, and the results indicated that it conforms to Lipinski's rule of five. Moreover, the *in-silico* ADMET analysis indicated that this ligand is well absorbed by the human intestine. Additionally, it is assumed to possess a limited capacity to traverse the blood-brain barrier (BBB) (Figure 7).

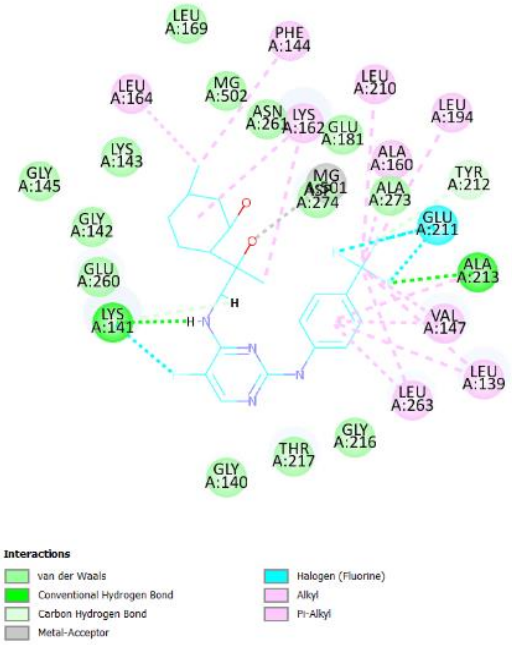


Figure 7. 2D diagram of key binding interactions of hit (compound **255b**) with Aurora A

4. Summary

During my PhD research work, starting from commercially available (**–**)-isopulegol, we were able to successfully synthesise oxirane **177** whose aminolysis with different amines afforded a new series of neoisopulegol-based chiral 1,2-aminoalcohols **178**–**181**. Subsequent debenzylation over Pd/C resulted in primary aminoalcohol **186**. In addition, stereoselective dihydroxylation was performed to prepare diol **187**. Ring closure of 1,2-aminoalcohols **178**–**181** led to the formation of spiro-oxazolidines **182**–**185**.

The relative stereochemistry of 1,2-aminoalcohols **178**–**181** together with diol **187** was established by coupling constant data and NOESY spectral analysis.

The prepared aminoalcohol derivatives were evaluated as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde to form (*S*)- and (*R*)-phenyl propanol. Aminoalcohol **179** showed the most significant catalytic activity affording (*S*)-selectivity up to *ee* = 40%.

On the other hand, a library of (+)-neoisopulegol-based *O*-benzyl derivatives of aminodiols **206–209** as well as aminotriols **226–229, 234–237, 239–242** was reported by ring opening of the corresponding epoxides with different nucleophiles such as amines (benzylamine, dibenzylamine) as well as azoles (imidazole and 1,2,4-triazole). Besides, to determine the effect of the configuration on the *O*-benzyl group, (**–**)-isopulegol-based *O*-benzyl derivatives were also synthesised.

In addition, primary aminodiols and aminoltriols based on (+)-neoisopulegol and (**–**)-isopulegol were generated through hydrogenation over Pd/C.

Starting from primary aminodiols **190a**, **201b**, **194** and **203**, key intermediates thioureas **244a**,**b** and **246a**,**b** were prepared followed by cyclisation to afford 1,3-oxazoles **245a**,**b**, 1,3-thiazines **247a**,**b** and 1,3-oxazines **248a**,**b**. Unfortunately, the synthesis of 1,3-thiazoles was unsuccessful due the steric hindrance.

Furthermore, 2,4-diaminopyrimidine derivatives **251a**–**c**, **252a,c**, **255a**–**c**, **256a**–**c**, **259a**,**b**, **260a**,**b** and **262a**,**b** were also prepared from primary aminodiols **171a**,**b**, **186**, **190a**,**b**, **201b**, **194** and **203** and aminotriol **212**, respectively, by coupling reaction using pyrimidine reagents **145a**–**c**, followed by an S_NAr coupling reaction with 4-aminobenzotrifluoride **147** under microwave irradiation. It is noted that further coupling reaction at the remaining chlorine at position 6 of intermediates **263a**–**h** was unsuccessful.

In vitro antimicrobial activity of 1,2-aminoalcohol derivatives **178**–**186** and diol **187** was evaluated against two yeasts as well as two Gram-positive and two Gram-negative bacteria. Results clearly showed that *N*-substituted aminoalcohols have moderate antibacterial effect on multiple bacterial strains, while a significant antifungal action was found in the case of diol **187**.

In addition, *in vitro* antimicrobial effects were also examined for the *O*-benzyl derivatives. The studies have clearly demonstrated that the *O*-benzyl substituent on the cyclohexyl ring in aminodiol and aminotriol derivatives is essential to have an antimicrobial effect, whereas the stereochemistry of the *O*-benzyl substituent attached to the cyclohexane ring in the aminodiol and aminotriol function has no influence on the antimicrobial effect. Furthermore, the antifungal activity was found to be affected by the stereochemistry of the derivatives. Namely, the *S*-isomers were more potent than the corresponding *R*-isomers against fungi, while the antibacterial effect did not distinguish between the different stereoisomers.

In vitro antiproliferative properties of the prepared 2,4-diaminopyrimidine derivatives indicated that the introduction of the N^2-aryl function into the 2,4-diaminopyrimidine skeleton has an important impact on high potency. The stereochemistry of the hydroxy group on the alkyl chain of the aminodiol has an influence on the antiproliferative activity with the *R*-isomers having a stringer effect than the *S*-isomers.

Docking studies were employed to examine the interactions between ligand **255b** and Aurora A kinase PDB (Code: 4DEE). The results revealed that compound **255b** has several interactions with Aurora A, which lead to a high *in vitro* potency. Moreover, the molecular properties and the *in silico* ADMET study confirmed that **255b** meets the Lipinski's rule of five and has good absorption throughout the human intestine.

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Annex

I.

molecules

MDPI

Article

Synthesis and Application of 1,2-Aminoalcohols with Neoisopulegol-Based Octahydrobenzofuran Core

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Abstract: A library of 1,2-aminoalcohol derivatives with a neoisopulegol-based octahydrobenzofuran core was developed and applied as chiral catalysts in the addition of diethylzinc to benzaldehyde. The allylic chlorination of (+)-neoisopulegol, derived from natural (–)-isopulegol followed by cyclization, gave the key methyleneoctahydrobenzofuran intermediate. The stereoselective epoxidation of the key intermediate and subsequent oxirane ring opening with primary amines afforded the required 1,2-aminoalcohols. The ring closure of the secondary amine analogues with formaldehyde provided spiro-oxazolidine ring systems. The dihydroxylation of the methylenetetrahydrofuran moiety with OsO_4/NMO (4-methylmorpholine *N*-oxide) resulted in the formation of a neoisopulegol-based diol in a highly stereoselective reaction. The antimicrobial activity of both the aminoalcohol derivatives and the diol was also explored.

Keywords: neoisopulegol; octahydrobenzofuran; 1,2-aminoalcohol; chiral catalyst; antimicrobial activity

1. Introduction

The benzofuran moiety is prevalent in a great number of biologically active compounds and natural products [1,2]. Moreover, compounds bearing this ring system are also promising key intermediates in the preparation of natural products and clinical medicines [3–5]. Due to the availability of these building blocks, numerous methods have been developed for the preparation of benzofuran systems [6–11]. However, only a few examples of the synthesis of octahydrobenzofuran derivatives have been reported including free-radical reactions [12,13], hydrogenation [14,15], tandem conjugate addition [16], base- [17] or acid-catalyzed cyclization [18], and photochemical rearrangement [19]. Furthermore, octabenzohydrofuran derivatives are well-known versatile precursors for the construction of a variety of therapeutic drugs [20]. For example, (±)-adunctin B and its modified derivatives that bear a hexahydrobenzofurane moiety have shown antibacterial effects toward *Micrococcus luteus* [21]. (–)-Siccanin exhibits potent antifungal activity against several pathogenic fungi, and its clinical effectiveness against surface mycosis is also known [22].

The 1,2-aminoalcohol moiety is present in a wide range of compounds that exhibit pharmaceutically and biologically interesting properties [23]. For example, compounds bearing the hydroxyethylamine core have the capacity to inhibit aspartic protease enzymes and are widely used as anti-HIV [24,25],

antimalarial [26–28], and antileishmanial [29] agents. The 1,2-aminoalcohol function is found in a broad range of β-adrenergic blockers that are used extensively in the management of cardiovascular disorders [30], including hypertension, angina pectoris and cardiac arrhythmias, and other disorders that are related to the sympathetic nervous system [31,32].

1,2-aminoalcohols have also been demonstrated to be excellent chiral auxiliaries and chiral catalysts in asymmetric synthesis [33]. To achieve new, efficient, and commercially available chiral catalysts, natural chiral terpenes, such as α-pinene [34–38], β-pinene [34,39], (–)-3-carene [39,40], (–)-verbenone [41,42], (–)-fenchone [43,44], (+)-camphor [43,45,46], and (–)-menthone [47] have proven to be excellent sources for the synthesis of bifunctional chiral compounds and heterocycles.

In the present work, we set out to create a compound library with a (+)-neoisopulegol-based octahydrobenzofuran core and 1,2-aminoalcohol moieties. The synthesis started from commercially available (–)-isopulegol and then utilizing the resulting 1,2-aminoalcohol derivatives as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde. Furthermore, the antimicrobial activities of the synthesized compounds were also tested on multiple bacterial and fungal strains.

2. Results

2.1. Synthesis of Key Intermediate 3

Key intermediate (–)-3-methylenetetrahydrofuran **3** was prepared from commercially available (–)-isopulegol **1** by oxidizing its hydroxyl function, followed by the stereoselective reduction of the resulting carbonyl group, thus providing (+)-neoisopulegol **2** [48–51]. The allylic chlorination of (+)-neoisopulegol **2** was followed by the cyclization-produced (–)-methylenetetrahydrofuran **3** [52–55], which was transformed into (−)-methylenetetrahydrofuran **4** by allylic oxidation after applying the literature method [55,56] (Figure 1).

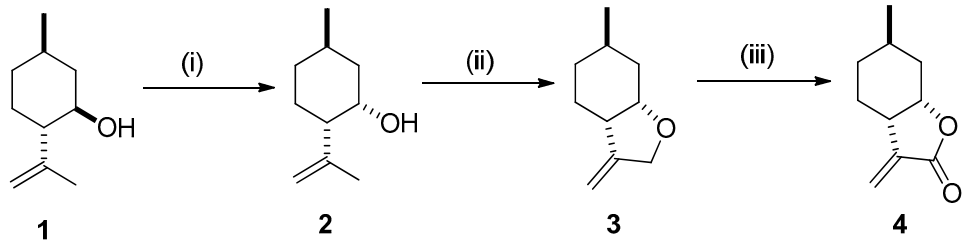


Figure 1. Synthesis of (–)-isopulegol-based methylenetetrahydrofuran **3**: (**i**) PCC (2 equivalents), DCM (Dichloromethane), 25 °C, 48 h, 80% than L-selectride (1.5 equivalents) dry THF, −78 °C, 1 h, 90% [48–51]; (**ii**) $Ca(OCl)_2$, DCM, rt 25 °C, 3 h, 70% than NaH (2 equivalents), dry THF, 50 °C, 6 h [52–55]; (**iii**) CrO_3 (3 equivalents), DCM/pyridine, reflux, 1.5 h, 84% [55,56].

2.2. Synthesis of Ispulegol-Based 1,2-Aminoalcohols

Our previous work has shown that epoxidation with *t*-BuOOH in the presence of vanadyl acetylacetonate ($VO(acac)_2$) as a catalyst can be successfully applied to prepare a new family of neoisopulegol-based chiral aminodiol libraries [57]. However, upon applying this condition with **3**, (–)-α-methylene-γ-butyrolactone **4** was observed as the major product. The formation of **4** was explained by the allylic oxidation process shown in Figure 2 [58,59]. Finally, the synthesis of epoxide **5** was achieved by reacting **3** with mCPBA (*meta*-Chloroperoxybenzoic acid) in a stereoselective reaction (Scheme 1) [60–63].

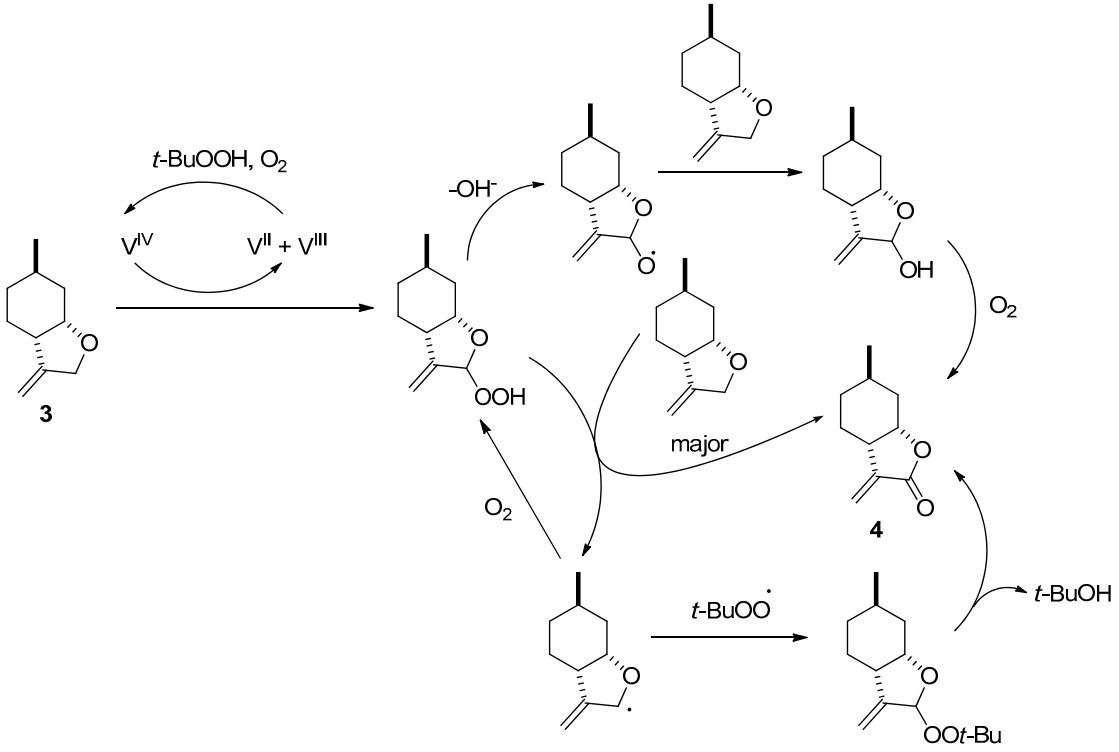
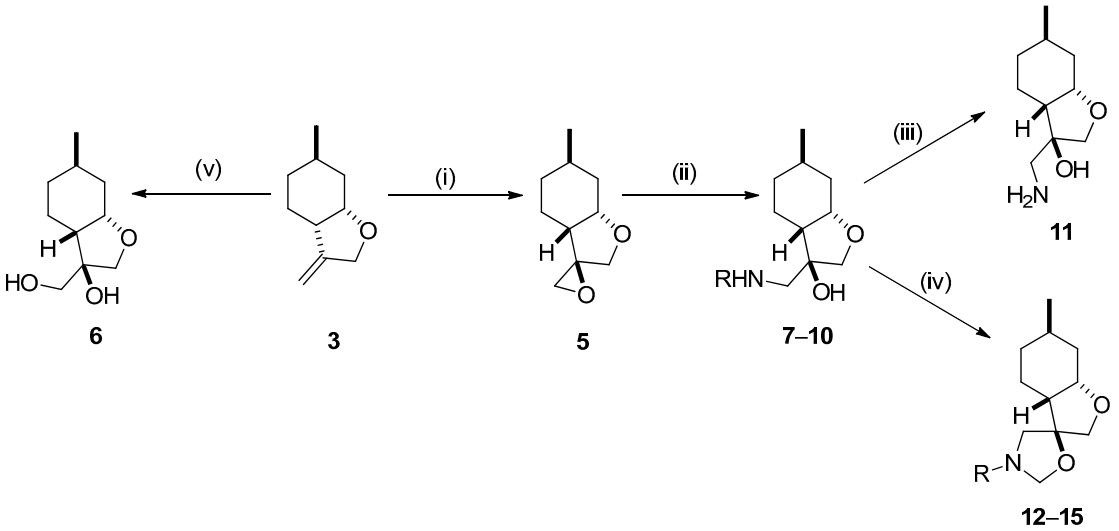


Figure 2. Proposed reaction pathway of allylic oxidation of **3**.



7, 12: R = CH(Me)Ph (*R*); **8, 13**: R = CH(Me)Ph (*S*); **9, 14**: R = CH_2Ph; **10, 15**: R = $CH(Me)_2$

Scheme 1. (**i**) mCPBA (2 equivalents), $Na_2HPO_4 \cdot 2H_2O$ (3 equivalents), 25 °C, 2 h, 23%; (**ii**) RNH_2 (2 equivalents), $LiClO_4$ (1 equivalent), MeCN, 70–80 °C, 6 h, 65–85%; (**iii**) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 70–75%; (**iv**) 35% HCHO, Et_2O, 25 °C, 1 h, 50–90%; (**v**) 2% OsO_4/*t*-BuOH, 50% NMO/H_2O, acetone, 25 °C, 24 h, 50%.

Given that we clearly demonstrated in previous works [64,65] that the substitution of the nitrogen atom of aminoalcohols definitely influences the efficiency of their catalytic activity, aminoalcohol library **7**–**10** was prepared through the aminolysis of epoxide **5** with primary amines and lithium perchlorate as a catalyst [66,67]. Since the ring closure of monoterpene-based aminoalcohols with rigid structures has been shown to enhance their catalytic potential in our earlier experiments [64,65,68], the treatment of aminoalcohols **7**–**10** with formaldehyde at room temperature resulted in the formation

of spiro-oxazolidines **12**–**15**. The debenzylation by hydrogenolysis of compounds **7**–**9** over Pd/C in MeOH provided primary aminoalcohol **11** in moderate yields (Scheme 1). Since neither the hydrogenolysis of *N*-benzyl analogues **7**–**10** nor the formation of an oxazolidine ring system by ring closure with formaldehyde had an effect on the absolute configuration of C-3, the relative configuration of the chiral centers of **11**–**15** is known to be the same as that of **7**–**10** [64,65,68].

The syn-selective dihydroxylation of compound **3** with OsO_4 in the presence of a stoichiometric amount of the co-oxidant, NMO (4-methylmorpholine *N*-oxide) produced product **6** as a single diastereomer in a moderate yield [68,69] (Scheme 1).

The relative stereochemistry of aminoalcohols **7**–**10** and diol **6** was established by coupling constant data and the NOESY (Nuclear Overhauser Effect SpecroscopY) spectral analysis. The large coupling constant of H-9 ($J_{4,9}$ = 11.2 Hz with **6** and $J_{4,9}$ = 12.2 Hz with **7**–**10**) indicated that it should be axially oriented, while the coupling constant values between H-3 and H-4 ($J_{4,3} = J_{3,4}$ = 2.3 Hz with **6** and $J_{4,3} = J_{3,4}$ = 2.2–3.0 Hz with **7**–**10**) supported their equatorial orientation. Furthermore, NOESY correlations between OH-7 and H-3 as well as OH-7 and H-4 protons in DMSO-*d*6 (Dimethylsulfoxide-*d*6) indicated that these groups were oriented in the same direction (see Supporting Information), Therefore, the structures of **6**–**10** were concluded, as shown on Figure 3. The stereochemistry of **11** and **12**–**15** was proven in a similar manner by 1D and 2D NMR measurements.

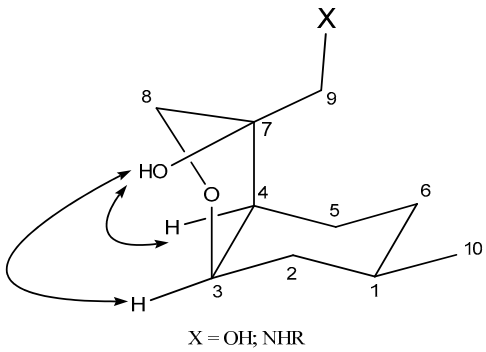
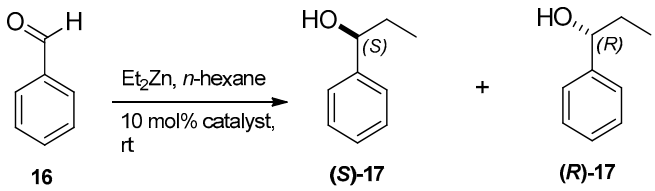


Figure 3. Determination of relative configuration of aminoalcohols **7**–**10** and diol **6**.

2.3. Application of Aminoalcohol Derivatives as Chiral Ligands for Catalytic Addition of Diethylzinc to Benzaldehyde

Aminoalcohol derivatives **7**–**15** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde **16** to form (*S*)- and (*R*)-1-phenyl-1-propanol **17** (Scheme 2).



Scheme 2. Model reaction for enantioselective catalysis.

The enantiomeric purity of 1-phenyl-1-propanols (*S*)-**17** and (*R*)-**17** was determined by GC analysis on a Chirasil-DEX CB column using literature methods [70,71]. A low-to-moderate enantioselectivity was observed. Aminoalcohols afforded the (S)-enantiomer (except **7**, where a weak (*R*) selectivity was observed), while the formation of the (*R*)-enantiomer was predominant when spiro-oxazolidines were applied as catalysts (Table 1). Aminoalcohol **8** showed the best catalytic activity (*ee* = 40%) with an (*S*)-selectivity (entry 2). The obtained results clearly indicate that the spiro-oxazolidine ring had a poorer catalytic performance, probably due to the flexible spiro system. These results are in good correlation with those observed with pinane- or sabinane-based spiro-oxazolidines in our earlier studies [72,73].

Table 1. Addition of diethylzinc to benzaldehyde catalyzed by aminoalcohol derivatives.

Entry	Ligand	Yield [a] (%)	*ee* [b] (%)	Configuration of the Major Product [c]
1	**7**	86	8	*(R)*
2	**8**	90	40	*(S)*
3	**9**	89	11	*(S)*
4	**10**	93	4	*(S)*
5	**11**	95	7	*(S)*
6	**12**	88	11	*(R)*
7	**13**	90	3	*(R)*
8	**14**	82	6	*(R)*
9	**15**	80	7	*(R)*

[a] After silica column chromatography. [b] Determined using the crude product by GC analysis (Chirasil-DEX CB column). [c] Determined by comparing the t_R of GC analysis and optical rotations with literature data.

2.4. Antimicrobial Effects

Since several aminoalcohols have been shown to exert antimicrobial activities on various bacterial and fungal strains [74,75], the antimicrobial activities of the prepared aminoalcohol analogues and diol **6** were tested against two yeasts, as well as two Gram-positive and two Gram-negative bacteria (Table 2). Compounds **8** and **12** inhibited the studied Gram-positive bacteria with efficiencies over 20%, while other derivatives showed weak activities. In the case of *Bacillus subtilis*, **8** showed more potential antimicrobial activity, while for *Staphylococcus aureus*, **12** proved to be the most effective agent. Furthermore, only **9** showed an inhibition activity over 30% for *Pseudomonas aeruginosa*, while it had only a moderate effect against *Escherichia coli*. All compounds presented low-to-moderate inhibitions against *E. coli* in the range of 5–30%.

Table 2. Antimicrobial activities of the synthesized compounds.

		Inhibitory effect (%) ± RSD (%)					
		Yeast		*Gram-Negative*		*Gram-Positive*	
Analogue	**Conc. (μg/mL)**	***C. albicans***	***C. krusei***	***E. coli***	***P. aeruginosa***	***B. subtilis***	***S. aureus***
6	10	–	36.5 ± 8.43	–	–	–	–
	100	–	58.4 ± 14.41	–	–	21.7 ± 6.05	–
7	10	–	–	8.7 ± 3.15	7.5 ± 1.54	–	–
	100	–	–	20.0 ± 2.81	8.7 ± 0.49	–	7.1 ± 4.3
8	10	–	–	–	–	19.0 ± 2.61	–
	100	–	–	17.1 ± 4.94	5.3 ± 4.31	31.9 ± 2.74	–
9	10	–	–	16.7 ± 6.68	9.9 ± 1.8	–	–
	100	–	–	21.0 ± 5.05	31.6 ± 1.73	9.8 ± 11.2	13.8 ± 1.73
10	10	–	–	3.7 ± 1.68	–	–	–
	100	–	–	4.3 ± 10.71	2.3 ± 5.93	10.5 ± 10.12	–
11	10	–	3.7 ± 0.04	–	–	–	–
	100	–	16.0 ± 14.5	–	–	–	–
12	10	–	–	15.3 ± 4.35	–	–	9.2 ± 7.75
	100	–	–	26.2 ± 4.06	1.8 ± 6.28	–	20.2 ± 8.92
13	10	–	–	17.1 ± 8.19	–	–	–
	100	–	–	27.7 ± 8.54	7.0 ± 4.62	–	3.9 ± 3.39
14	10	–	–	14.6 ± 4.38	4.1 ± 7.10	–	12.6 ± 0.57
	100	–	–	25.3 ± 2.99	16.8 ± 5.69	–	14.0 ± 3.68
15	10	–	–	5.1 ± 7.92	–	–	–
	100	–	–	14.8 ± 4.87	–	1.5 ± 11.4	–

According to our results, *N*-substituted 1,2-aminoalcohols **7–10** had a moderate activity against both Gram-negative and Gram-positive bacteria. Most of the ring-closing oxazolidine products (**12–14**)

showed a similar moderate antibacterial activity. The removal of the nitrogen substituent of the aminoalcohols led to the loss of antibacterial activity (see amino diol **6**). None of the aminoalcohol derivatives exhibited any remarkable antifungal effect, while diol **6** showed significant antifungal activity against *Candida krusei* (Table 2).

3. Materials and Methods

3.1. Materials and General Methods

Commercially available compounds were used as-obtained from suppliers (Molar Chemicals Ltd., Halásztelek, Hungary; Merck Ltd., Budapest, Hungary and VWR International Ltd., Debrecen, Hungary), while solvents were dried according to standard procedures. Optical rotations were measured in MeOH at 20 °C with a PerkinElmer 341 polarimeter (PerkinElmer Inc., Shelton, CT, USA). Chromatographic separations and monitoring of reactions were carried out on a Merck Kieselgel 60 (Merck Ltd., Budapest, Hungary). Elemental analyses of all compounds were performed on a PerkinElmer 2400 Elemental Analyzer (PerkinElmer Inc., Waltham, MA, USA). GC measurements for the direct separation of commercially available enantiomers of isopulegol to determine the enantiomeric purity of starting material **1** and the separation of *O*-acetyl derivatives of enantiomers were performed on a Chirasil-DEX CB column (2500 × 0.25 mm I.D.) on a PerkinElmer Autosystem XL GC consisting of a flame ionization detector (PerkinElmer Corporation, Norwalk, CT, USA) and a Turbochrom Workstation data system (PerkinElmer Corp., Norwalk, CT, USA). Melting points were determined on a Kofler apparatus (Nagema, Dresden, Germany) and were uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Brucker Avance DRX 500 spectrometer [500 MHz (^{1}H) and 125 MHz (^{13}C), δ = 0 (TMS, Tetramethylsilane)]. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given by Hz.

(–)-Isopulegol **1** is commercially available from Merck Co with *ee* = 95%. (+)-Neoisopulegol **2** and (–)-6-methyl-3-methylenetetrahydrofuran **3** were prepared according to literature procedures. All spectroscopic data of the synthesized compounds were similar to those described therein [55]. ^{1}H, ^{13}C, HSQC, HMBC and NOESY NMR spectra of new compounds are available in Supplementary Materials.

*3.2. (2′R,3aR,6R,7aS)-6-Methylhexahydro-2H-spiro[benzofuran-3,2′-oxirane] (**5**)*

m-chloroperbenzoic acid (70% purity, 5.87 g, 23.8 mmol) was added at 0 °C to a solution of 3 (11.9 mmol) in CH_2Cl_2 (50 mL) and $Na_2HPO_4{\cdot}12H_2O$ (6.35 g, 35.7 mmol) in water (130 mL), and the mixture was stirred at room temperature. When the reaction was complete, as indicated by TLC (Thin layer chromatography) (2 h), the mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with a 5% KOH solution (3 × 50 mL), then dried (Na_2SO_4) and evaporated to provide 5 as the single product.

Yield: 23%, colorless oil. $[\alpha]_D^{20}$ = −26.0 (c 0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.93 (1H, m), 0.90 (3H, d, *J* = 6.5 Hz), 1.18–1.26 (1H, m), 1.32–1.42 (1H, m), 1.55–1.75 (4H, m), 2.03–2.10 (1H, m), 2.83 (1H, d, *J* = 4.2 Hz), 2.96 (1H, d, *J* = 4.2 Hz), 3.63 (1H, d, *J* = 10.6 Hz), 4.21 (1H, d, *J* = 10.6 Hz), 4.25 (1H, d, *J* = 2.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 24.7, 26.4, 33.0, 36.5, 42.7, 47.4, 68.0, 70.1, 77.9. Anal. Calculated for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.52.

3.3. General Procedure for Ring-Opening of Epoxide with Primary Amines

A solution of the appropriate amine (5.88 mmol) in MeCN (10 mL) and $LiClO_4$ (0.31 g, 2.94 mmol) was added to a solution of epoxide **5** (0.50 g, 2.94 mmol) in MeCN (30 mL). The mixture was kept at reflux temperature for 6 h. When the reaction was completed (indicated by TLC), the mixture was evaporated to dryness, and the residue was dissolved in water (15 mL) then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel with an appropriate solvent mixture

($CHCl_3$:MeOH = 19:1). Further purification by recrystallization from a mixture of *n*-hexane:Et_2O resulted in compounds **7**–**10**.

3.3.1. (3*R*,3a*R*,6*R*,7a*S*)-6-Methyl-3-((((*R*)-1-phenylethyl)amino)methyl)octahydrobenzofuran-3-ol (**7**)

Yield: 65%, white crystals, m.p.: 77–81 °C. $[\alpha]_D^{20}$ = +27.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.78–0.87 (1H, m), 0.86 (3H, d, *J* = 6.5 Hz), 0.98–1.06 (1H, m), 1.12–1.18 (1H, m), 1.38 (3H, d, *J* = 6.6 Hz), 1.45–1.50 (1H, m), 1.51–1.63 (3H, m), 1.66–1.72 (1H, m), 2.00–2.05 (1H, m), 2.42 (1H, d, *J* = 12.1 Hz), 2.77 (1H, d, *J* = 12.1 Hz), 3.64 (1H, d, *J* = 9.5 Hz), 3.70 (1H, d, *J* = 9.6 Hz), 3.79 (1H, q, *J* = 6.5 Hz), 4.37 (1H, q, *J* = 3.0 Hz), 7.25–7.35 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 24.4, 24.5, 26.5, 33.2, 37.0, 47.1, 49.5, 58.6, 76.3, 77.6, 82.4, 126.7, 127.4, 128.8. Anal. Calculated for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.73; H, 9.45; N, 4.80.

3.3.2. (3*R*,3a*R*,6*R*,7a*S*)-6-Methyl-3-((((*S*)-1-phenylethyl)amino)methyl)octahydrobenzofuran-3-ol (**8**)

Yield: 75%, colorless oil. $[\alpha]_D^{20}$ = −23.0 (c 0.255, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75–0.85 (1H, m), 0.85 (3H, d, *J* = 6.3 Hz), 0.90–1.00 (1H, m), 1.10–1.16 (1H, m), 1.35–1.40 (1H, m), 1.39 (3H, d, *J* = 6.6 Hz), 1.50–1.60 (2H, m), 1.63–1.67 (1H, m), 2.01 (1H, d, *J* = 14.5 Hz), 2.46 (1H, d, *J* = 12.2 Hz), 2.65 (1H, d, *J* = 12.2 Hz), 3.73 (3H, dd, *J* = 9.5, 20.2 Hz), 4.37 (1H, s), 7.25–7.40 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 24.2, 24.3, 26.5, 33.1, 37.0, 46.9, 49.6, 58.9, 76.2, 77.6, 82.3, 126.4, 127.4, 128.8, 144.9. Anal. Calculated for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.68; H, 9.43; N, 4.85.

3.3.3. (3*R*,3a*R*,6*R*,7a*S*)-3-((Benzylamino)methyl)-6-methyloctahydrobenzofuran-3-ol (**9**)

Yield: 78%, white crystals, m.p.: 55–56 °C. $[\alpha]_D^{20}$ = −7.0 (c 0.255, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80–0.87 (1H, m), 0.87 (3H, d, *J* = 6.5 Hz), 1.03–1.06 (1H, m), 1.11–1.17 (1H, m), 1.45–1.49 (1H, m), 1.55–1.62 (2H, m), 2.01–2.05 (1H, m), 2.58 (1H, d, *J* = 12.1 Hz), 2.70 (1H, brs), 2.86 (1H, d, *J* = 12.2 Hz), 3.70 (1H, d, *J* = 9.5 Hz), 3.79 (1H, d, *J* = 9.6 Hz), 3.80 (1H, s), 4.39 (1H, dd, *J* = 3.0, 6.0 Hz), 7.25-7.35 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 24.3, 26.4, 33.1, 36.9, 47.1, 51.1, 54.3, 76.3, 77.6, 82.4, 127.4, 128.1, 128.6, 139.7. Anal. Calculated for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.20; H, 9.10; N, 4.05.

3.3.4. (3*R*,3a*R*,6*R*,7a*S*)-3-((Isopropylamino)methyl)-6-methyloctahydrobenzofuran-3-ol (**10**)

Yield: 83%, white crystals, m.p.: 171–173 °C. $[\alpha]_D^{20}$ = −7.0 (c 0.28, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.75–1.00 (2H, m), 0.84 (3H, d, *J* = 3.5 Hz), 1.10–1.30 (2H, m), 1.22 (6H, s), 1.48 (1H, brs), 1.57 (2H, d, *J* = 8.7 Hz), 1.75–1.95 (2H, m), 2.91 (1H, d, *J* = 12.2 Hz), 3.06 (1H, d, *J* = 12.3 Hz), 3.28 (1H, brs), 3.60 (1H, d, *J* = 8.8 Hz), 3.81 (1H, d, *J* = 8.9 Hz), 4.30 (1H, brs). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.3, 18.6, 22.1, 23.2, 26.0, 32.4, 36.3, 46.1, 46.6, 50.5, 75.1., 76.4, 80.1. Anal. Calculated for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.70; H, 11.03; N, 6.18.

3.4. General Procedure for Ring Closure of Aminoalcohols ***7–10*** *with Formaldehyde*

Thirty-five percent aqueous formaldehyde (20 mL) was added to a solution of aminoalcohols **7**–**10** (1.8 mmol) in Et_2O (5 mL), and the mixture was stirred at room temperature. After 1 h, it was made alkaline with 10% aqueous KOH (20 mL) and extracted with Et_2O (3 × 50 mL). After drying (Na_2SO_4) and solvent evaporation, crude products **12**–**15** were purified by column chromatography ($CHCl_3$:MeOH = 19:1).

3.4.1. (3*R*,3a*R*,6*R*,7a*S*)-6-Methyl-3′-((*R*)-1-phenylethyl)hexahydro-2H-spiro[benzofuran-3,5′-oxazolidine] (**12**)

Yield: 50%, colorless oil. $[\alpha]_D^{20}$ = +27.0 (c, 0.275 MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84–0.95 (2H, m), 0.87 (3H, d, *J* = 6.3 Hz), 1.10–1.17(1H, m), 1.34 (3H, d, *J* = 6.4 Hz), 1.50–1.65 (3H, m), 1.78–1.83 (1H, m), 2.02 (1H, d, *J* = 14.4 Hz), 2.57 (1H, d, *J* = 10.5 Hz), 2.94 (1H, d, *J* = 10.6 Hz), 3.35–3.40 (1H,

m), 3.88 (2H, dd, *J* = 9.7, 19.1 Hz), 4.24–4.30 (3H, m), 7.22–7.33 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 23.4, 24.6, 26.3, 33.2, 36.9, 45.7, 53.3, 62.5, 76.4, 78.3, 84.6, 91.5, 127.2, 127.4, 128.6, 144.8. Anal. Calculated for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.73; H, 9.00; N, 4.68.

3.4.2. (3*R*,3a*R*,6*R*,7a*S*)-6-Methyl-3′-((*S*)-1-phenylethyl)hexahydro-2H-spiro[benzofuran-3,5′-oxazolidine] (**13**)

Yield: 95%, colorless oil. $[\alpha]_D^{20}$ = −27.0 (c, 0.25 MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82–0.96 (3H, m), 0.87 (3H, d, *J* = 6.3 Hz), 1.12–1.20 (1H, m), 1.25 (1H, s), 1.36 (3H, d, *J* = 6.2 Hz), 1.54–1.65 (3H, m), 1.80–1.85 (2H, m), 2.02 (1H, d, *J* = 14.4 Hz), 2.53 (1H, d, *J* = 10.6 Hz), 2.94 (1H, d, *J* = 10.7 Hz), 3.35–3.45 (1H, m), 3.87 (2H, t, *J* = 10.7 Hz), 4.26 (2H, s), 4.36 (1H, s), 7.20–7.40 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 23.5, 24.5, 26.3, 33.2, 36.8, 45.7, 53.4, 62.5, 76.2, 78.2, 84.8, 127.2, 127.4, 128.7. Anal. Calculated for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.70; H, 9.07; N, 4.63.

3.4.3. (3*R*,3a*R*,6*R*,7a*S*)-3′-Benzyl-6-methylhexahydro-2H-spiro[benzofuran-3,5′-oxazolidine] (**14**)

Yield: 90%, white crystals, m.p.: 76–77 °C. $[\alpha]_D^{20}$ = -9.0 (c, 0.25 MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84–1.00 (2H, m), 0.88 (3H, d, *J* = 6.5 Hz), 1.14–1.21 (1H, m), 1.55–1.65 (3H, m), 1.80–1.84 (1H, m), 2.04 (1H, d, *J* = 13.8 Hz), 2.70 (1H, d, *J* = 11.8 Hz), 3.09 (1H, d, *J* = 11.8 Hz), 3.68 (2H, dd, *J* = 13.0, 18.4 Hz), 3.91 (2H, dd, *J* = 9.8, 11.2 Hz), 4.31 (1H, d, *J* = 2.7 Hz), 4.35 (2H, s), 7.25–7.35 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 24.6, 26.3, 33.2, 36.8, 46.1, 54.5, 58.7, 76.7, 78.6, 86.0, 90.5, 127.5, 128.6, 128.8, 138.6. Anal. Calculated for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.25; H, 9.73; N, 4.90.

3.4.4. (3*R*,3a*R*,6*R*,7a*S*)-3′-Isopropyl-6-methylhexahydro-2H-spiro[benzofuran-3,5′-oxazolidine] (**15**)

Yield: 95%, colorless oil. $[\alpha]_D^{20}$ = −13.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.79–0.86 (1H, m), 0.83 (3H, d, *J* = 6.6 Hz), 0.89–1.01 (2H, m), 0.99 (6H, d, *J* = 6.2 Hz), 1.07–1.13 (1H, m), 1.45–1.55 (1H, m), 1.55–1.60 (2H, m), 1.68–1.73 (1H, m), 1.86 (1H, d, *J* = 14.2 Hz), 2.35–2.40 (1H, m), 2.60 (1H, d, *J* = 10.1 Hz), 2.87 (1H, d, *J* = 10.2 Hz), 3.64 (1H, d, *J* = 9.6 Hz), 3.84 (1H, d, *J* = 9.6 Hz), 4.09 (1H, d, *J* = 2.6 Hz), 4.18 (1H, d, *J* = 3.2 Hz), 4.20 (1H, d, *J* = 3.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.7, 21.8, 22.2, 23.7, 25.8, 32.5, 36.4, 44.9, 51.8, 51.9, 75.4, 77.1, 83.6, 91.1. Anal. Calculated for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.28; H, 10.50; N, 5.83.

*3.5. (3R,3aR,6R,7aS)-3-(Aminomethyl)-6-methyloctahydrobenzofuran-3-ol (**11**)*

Aminoalcohols **7**–**9** (14.0 mmol) in MeOH (100 mL) were added to a suspension of palladium-on-carbon (5% Pd, 0.22 g) in MeOH (50 mL), and the mixture was stirred under an H_2 atmosphere (1 atm) at room temperature. After the completion of the reaction (as monitored by TLC, 24 h), the mixture was filtered through a Celite pad, and the solution was evaporated to dryness. The crude product was recrystallized in Et_2O, resulting in primary aminoalcohol **11**.

Yield: 73% (with **7**); 75% (with **8**); 70% (with **9**), white crystals, m.p.: 217–221 °C. $[\alpha]_D^{20}$ = +7.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.74–0.89 (2H, m), 0.83 (3H, d, *J* = 5.7 Hz), 1.46 (1H, brs), 1.53–1.65 (2H, m), 1.75–1.83 (1H, m), 1.87 (1H, d, *J* = 13.8 Hz), 2.83 (1H, d, *J* = 12.9 Hz), 2.95 (1H, d, *J* = 12.9 Hz), 3.56 (1H, d, *J* = 9.2 Hz), 3.80 (1H, d, *J* = 9.2 Hz), 4.28 (1H, s), 5.45 (1H, s), 8.04 (3H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.2, 23.2, 25.9, 32.4, 36.4, 41.8, 45.7, 74.9, 76.5, 80.3. Anal. Calculated for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.85; H, 10.32; N, 7.60.

*3.6. (3R,3aR,6R,7aS)-3-(Hydroxymethyl)-6-methyloctahydrobenzofuran-3-ol (**6**)*

An aqueous solution of NMO (12 mL, 50% aqueous solution) and a solution of OsO_4 in *t*-BuOH (6 mL, 2% *t*-BuOH solution) were added in one portion to a solution of compound **3** (2.13 g, 14 mmol) in acetone (60 mL). The reaction mixture was stirred at room temperature for 24 h, then quenched by the addition of a saturated aqueous solution of Na_2SO_3 (100 mL), and extracted with EtOAc (Ethyl acetate, 3 × 80 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified

by chromatography on silica gel by using *n*-hexane:EtOAc = 1:4. The product after purification was recrystallized in Et_2O resulting in compound **6** as white crystals.

Yield: 50%, white crystals, m.p.: 67–68 °C. $[\alpha]_D^{20}$ = +3.0 (c 0.27, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.75–0.80 (1H, m), 0.82 (3H, d, *J* = 6.5 Hz), 0.94–1.03 (1H, m), 1.04–1.11 (1H, m), 1.40–1.50 (1H, m), 1.50–1.57 (2H, m), 1.62–1.67 (1H, m), 1.85 (1H, d, *J* = 14.3 Hz), 3.34–3.38 (1H, m), 3.42 (1H, d, *J* = 9.2 Hz), 3.47 (1H, dd, *J* = 5.5, 11.1Hz), 3.68 (1H, d, *J* = 9.2 Hz), 4.23 (1H, d, *J* = 2.2 Hz), 4.49 (1H, s), 4.52 (1H, t, *J* = 5.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.3, 23.4, 26.2, 32.8, 36.7, 46.2, 63.2, 74.8, 76.5, 83.5. Anal. Calculated for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.55; H, 9.69.

3.7. General Procedure for the Reaction of Benzaldehyde with Diethylzinc in the Presence of Chiral Catalysts

To the respective catalyst (0.1 mmol), 1 M Et_2Zn in an *n*-hexane solution (3 mL, 3 mmol) was added under argon atmosphere at room temperature. The solution was stirred for 25 min at room temperature, and then benzaldehyde (1 mmol) was added. After stirring at room temperature for a further 20 h, the reaction was quenched with a saturated NH_4Cl solution (15 mL), and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with H_2O (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The obtained crude secondary alcohols were purified by flash column chromatography (*n*-hexane:EtOAc = 4:1). The *ee* and absolute configuration of the resulting material were determined by chiral GC on a Chirasil-DEX CB column after *O*-acetylation in Ac_2O/DMPA/pyridine.

3.8. Antimicrobial Analyses

For the antimicrobial analyses, the pure synthesized compounds were dissolved in MeOH and diluted with H_2O to reach concentration levels up to 400 and 40 μg/mL with a final MeOH content of 10%. Then, these test solutions were investigated in a microdilution assay with two Gram-positive bacteria (*Bacillus subtilis* SZMC 0209 and *Staphylococcus aureus* SZMC 14611), two Gram-negative bacteria (*Escherichia coli* SZMC 6271 and *Pseudomonas aeruginosa* SZMC 23290), and two yeast strains (*Candida albicans* SZMC 1533 and *C. krusei* SZMC 1352) according to the M07-A10 CLSI guideline [76] and our previous work [57,77]. For the assay, the suspensions of the microbes were prepared from overnight cultures that were cultivated in a ferment broth (bacteria: 10 g/L peptone, 5 g/L NaCl, 5 g/L yeast extract; yeast: 20 g/L peptone, 10 g/L yeast extract, and 20 g/L glucose) at 37 °C, and their concentrations were set to 2 × 10^5 cells/mL with sterile media. Then, 96-well plates were prepared by dispensing 100 μL of suspension containing the bacterial or yeast cells, 50 μL of sterile broth, and 50 μL of the test solutions into each well, which were then incubated for 24 h at 37 °C. The mixture of 150 μL of broth and 50 μL of 10% MeOH was used as the blank sample for background correction, while 100 μL of the microbial suspension supplemented with 50 μL of the sterile broth and 50 μL of 10% MeOH was applied as the negative control. The positive control contained ampicillin (Sigma) or nystatin (Sigma) for bacteria or fungi, respectively, at two concentration levels (100 μg/mL and 10 μg/mL). The inhibitory effects of each derivative were spectrophotometrically determined at 620 nm after incubation, and the inhibition rate was calculated as the percentage of the positive control after blank correction.

4. Conclusions

A new library of neoisopulegol-based chiral 1,2-aminoalcohols and a diol were developed from (+)-neoisopulegol, as derived from commercially available (–)-isopulegol. The obtained aminoalcohols and diol may serve as useful building blocks for the synthesis of new heterocyclic ring systems and biologically active compounds.

The in vitro antimicrobial studies have clearly shown that the resulting *N*-substituted aminoalcohols possess moderate antibacterial action on different bacterial strains, while the diol has a remarkable antifungal effect.

Aminoalcohol derivatives were also applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde with moderate but opposite enantioselectivity.

Supplementary Materials: The following are available online, Figures S3–S31: 1H, 13C, HSQC, HMBC and NOESY NMR spectra of new compounds.

Author Contributions: The listed authors contributed to this work as described in the following. Z.S., T.M.L. and A.S. designed, planned the research and interpreted the results. F.Z.B. and B.V. carried out the synthetic work. F.Z.B. and T.M.L. discussed the results and contributed to the writing of the paper. All authors discussed the results, and they also prepared and commented on the manuscript. All authors have read and agreed to the published version of the manuscript.

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II.

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Novel (+)-Neoisopulegol-Based *O*-Benzyl Derivatives as Antimicrobial Agents

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Abstract: Discovery of novel antibacterial agents with new structures, which combat pathogens is an urgent task. In this study, a new library of (+)-neoisopulegol-based *O*-benzyl derivatives of aminodiols and aminotriols was designed and synthesized, and their antimicrobial activity against different bacterial and fungal strains were evaluated. The results showed that this new series of synthetic *O*-benzyl compounds exhibit potent antimicrobial activity. Di-*O*-benzyl derivatives showed high activity against Gram-positive bacteria and fungi, but moderate activity against Gram-negative bacteria. Therefore, these compounds may serve a good basis for antibacterial and antifungal drug discovery. Structure–activity relationships were also studied from the aspects of stereochemistry of the *O*-benzyl group on cyclohexane ring and the substituent effects on the ring system.

Keywords: (+)-neoisopulegol; *O*-Benzyl derivatives; imidazole; 1,2,4-triazole; aminodiol; aminotriol

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1. Introduction

Heterocyclic compounds, occurring both naturally and produced synthetically, exhibit various pharmacological and biological properties and, therefore, they are interesting synthetic targets in the search of therapeutic agents [1,2]. *O*-Benzyl azole derivatives have played crucial roles in the history of heterocyclic chemistry and have been used extensively as important pharmacophores and synthons in the field of organic chemistry and drug design [1]. Azoles such as imidazole [3] and triazole [4] are the most extensively studied classes of antifungal agents due to their high therapeutic index, good bioavailability, and favorable safety profile [5] while the *O*-benzyl substituent plays an important role in the increased antimicrobial activity of these molecules [6] (Figure 1).

O-Benzyl-1,2,4-triazole derivatives were reported to exhibit various pharmacological activities such as antimicrobial [7,8], analgesic [9], anti-inflammatory [10], anticancer [8], antitubercular [11], anti-HIV [12], and antioxidant [13] properties. In addition, drugs with chemotherapeutic effect such as Anastrozole [14] and Letrozole [15] (chemotherapeutic anticancer drug), Ribavirin [16–19] (antiviral agent), Rizatriptan [20] (antimigraine agent), Alprazolam [21] (anxiolytic agent), Fluconazole [22], and Itraconazole [23] (antifungal agent) as well as Prothioconazole [21] (plant-pathogenic effect) are examples of potent molecules possessing a triazole nucleus [24,25].

O-Benzyl imidazole derivatives have evoked considerable attention in recent years because these are endowed with a wide range of pharmaceutical activities. These include antifungal [26], antiparasitic [27], antigiardiasis [28], antitubercular [29], antihistaminic [30], antineuropathic [31], antiobesity [32], antihypertensive [33], antioxidant [34], cardiotonic [35], antithrombotic [36], anti-convulsant [37,38], antiviral [39], and anti-hepatitis B and C virus activity [40] and they may also act as HIV-IPR [41] and IL-1 [42] inhibitors. In particular, a large number of imidazole-based compounds have been widely used drugs such as anticancer [43,44] (dacarbazine, zoledronicacid, azathioprine, and tipifarnib), antifungal [45,46] (clotrimazole, miconazole, ketoconazole, and oxiconazole), antibacterial [47,48] (metronidazole, ornidazole, and secnidazole), antiprotozoal [49–54] (megazol, benznidazole, and metronidazole), antihistaminic [55–57] (cimetidine, imetit, immepip, and thioperamide), antineuropathic [31,58–64] (nafimidone, fipamezole, and dexmedetomidine), and antihypertensive [65,66] (losartan, eprosartan, and olmesartan) agents to treat various types of diseases with high therapeutic potency, which shows their huge development value [40].

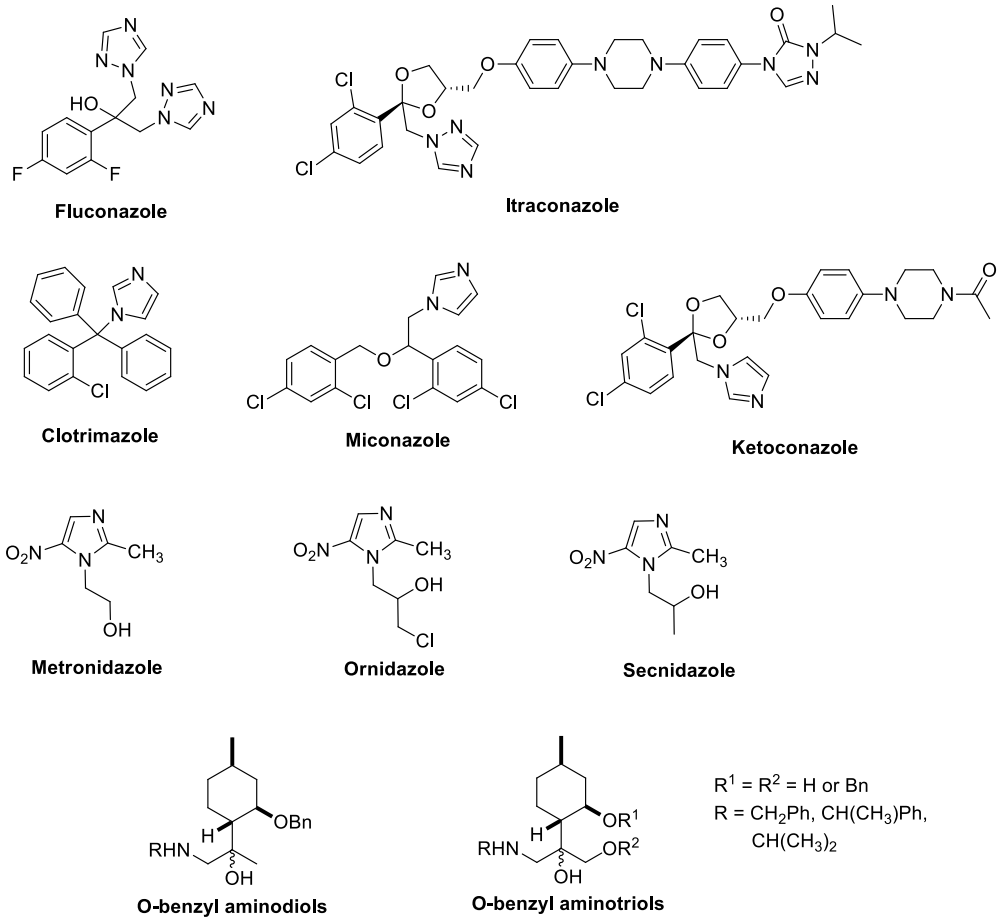


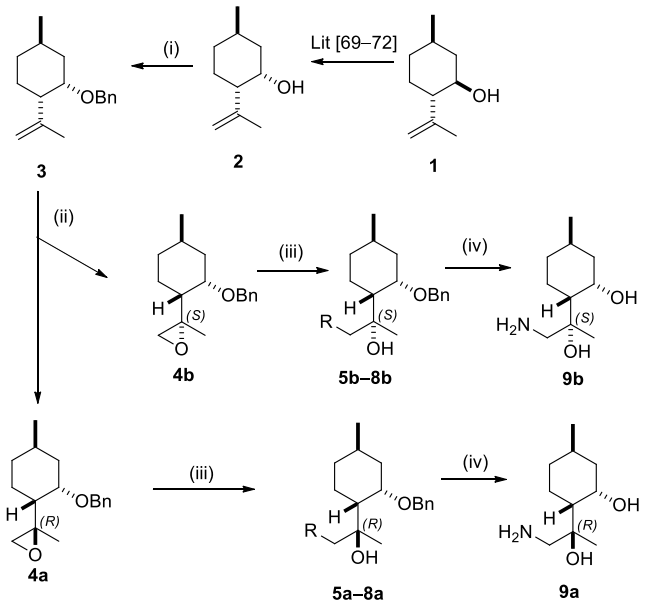
Figure 1. Azoles as potent antimicrobial agents.

The increasing number of multidrug-resistant pathogen infections has led to the discovery of new antimicrobial drugs with activity against resistant clinical isolates [67]. In our long-term program toward the synthesis of new antimicrobial agents, we demonstrated that (−)-isopulegol-based *O*-benzyl aminotriol and aminodiol derivatives exert marked antimicrobial effectiveness [68]. Therefore, the present study reports the synthesis of a series of novel (+)-neoisopulegol-based *O*-benzyl derivatives of aminodiols and aminotriols with nitrogen atoms usually incorporated in an imidazole or triazole ring system possessing activity against various bacteria and yeast strains. According to their antimicrobial activities, structure–activity relationships have also been discussed.

2. Results

2.1. Synthesis of (+)-Neoisopulegol-Based O-Benzyl Derivatives

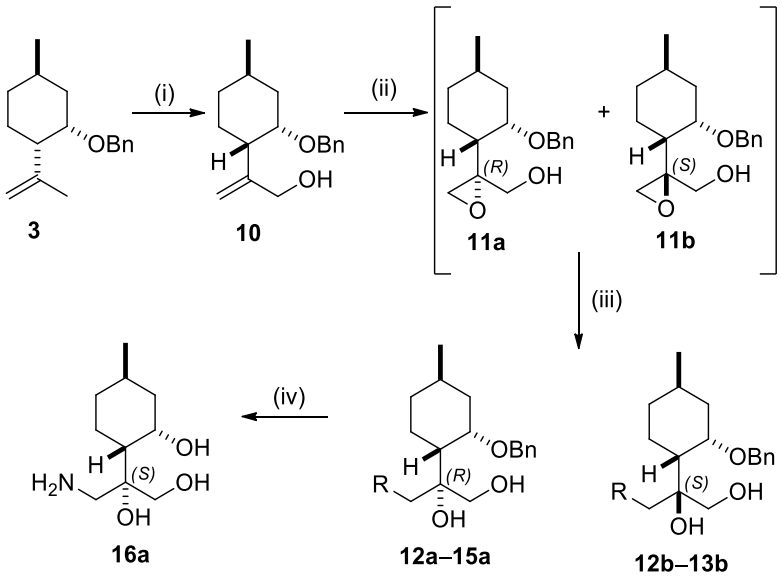
(+)-Neoisopulegol **2** was prepared from commercially available (−)-isopulegol **1** by oxidizing its hydroxyl function followed by the stereoselective reduction of the resulting carbonyl group applying literature methods [69–72]. In order to produce *O*-benzyl derivatives, benzyl-protected neoisopulegol **3** was prepared by reacting of **2** with BnBr in the presence of a catalytic amount of KI [73,74]. Without the addition of KI, the reaction proceeded very slowly whereas with the addition of 1 equiv. of KI, the reaction proceeded rapidly due to the formation of more reactive BnI from BnBr [75]. Epoxidation of **3** with *m*-CPBA buffered with Na_2HPO_4 provided a 1:2 mixture of epoxides **4a** and **4b** in good yield good yields [76]. The two epoxides were separated by column chromatography to give less polar isomer **4a** and more polar isomer **4b**. Aminolysis of epoxide **4a** with different amines in the presence of $LiClO_4$ delivered *O*-benzyl derivatives **5a**–**6a** [77,78]. The role of $LiClO_4$ shows enhanced reactivity for the ring opening of epoxides through the coordination of Li^+ with epoxide oxygen, rendering the epoxide more susceptible to nucleophilic attack by amines, therefore reducing the reaction times dramatically and improved the yields [79,80]. Likewise, no products were observed during ring-opening of the oxirane **3a** with azoles and $LiClO_4$. This is probably the difference in reactivity between amines and azoles. Fortunately, it was achieved by reacting **4a** with azoles promoted by K_2CO_3 [81]. A possible reaction pathway through potassium carbonate-mediated ring-opening reaction of epoxide **4a** and subsequent nucleophilic addition afforded *O*-benzyl derivatives **7a**–**8a** [82]. Debenzylation of **5a** by hydrogenolysis over Pd/C in MeOH resulted in primary aminodiol **9a** in excellent yield. Since neither aminolysis of the served oxirane **4a** in alkaline condition nor the hydrogenolysis of *N*-benzyl analogue **5a** had an effect on the absolute configuration, the relative configuration of the chiral centers of **5a**–**9a** is known to be the same as that of epoxide **4a** [83,84]. The other epoxide (**4b**) underwent similar reactions to afford **5b**–**9b** in valuable yields (Scheme 1).



5a–b: R = $NHCH_2Ph$; **6a–b**: R = $N(CH_2Ph)_2$; **7a–b**: R = imidazole; **8a–b**: 1,2,4-triazole

Scheme 1. Synthesis of (+)-neoisopulegol-based *O*-benzyl aminodiols. Reaction conditions: (i) NaH (1 equ.), BnBr (1.5 equ.), KI (1 equ.), dry THF, 60 °C, 12 h, 63%; (ii) *m*-CPBA (2 equ.), Na_2HPO_4. $12H_2O$ (3 equ.), CH_2Cl_2, 25 °C, 2 h, 23% (**4a**), 47% (**4b**); (iii) R^1R^2NH (2 equ.), $LiClO_4$ (1 equ.), MeCN, 70–80 °C, 20 h, 25–78% (for **5a**–**b** and **6a**–**b**) or imidazole/1,2,4-triazol (3 equ.), K_2CO_3 (5 equ.), dry DMF, 70–80 °C, 24 h, 42–67% (for **7a**–**b** and **8a**–**b**); (iv) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 91% (from **5a** or **5b**).

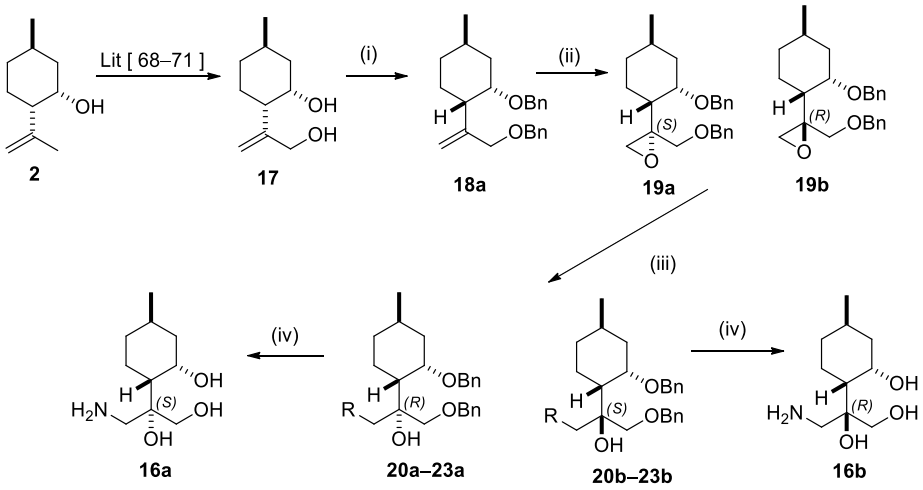
To prepare a highly diverse library of *O*-benzyl aminotriols, **3** was oxidized to **10** using SeO_2/*t*-BuOOH (TBHP) as oxidant [85]. The epoxidation of **10** with *m*-CPBA delivered a 4:1 mixture of epoxides **11a** and **11b**. The separation of **11a** and **11b** was not satisfactory on a gram scale; therefore, the mixture was treated with different nucleophiles resulting in a library of *O*-benzyl derivatives **12**–**15**. In our delight, amine-substituted *O*-benzyl derivatives could easily be separated while in the case of azoles, only the major products were isolated. The debenzylation of **12a** by hydrogenolysis over Pd/C gave primary aminotriol **16a** with good yield (Scheme 2).



12a–b: R = $NHCH_2Ph$; **13a–b**: R = $N(CH_2Ph)_2$; **14a**: R = imidazole; **15a**: 1,2,4-triazole

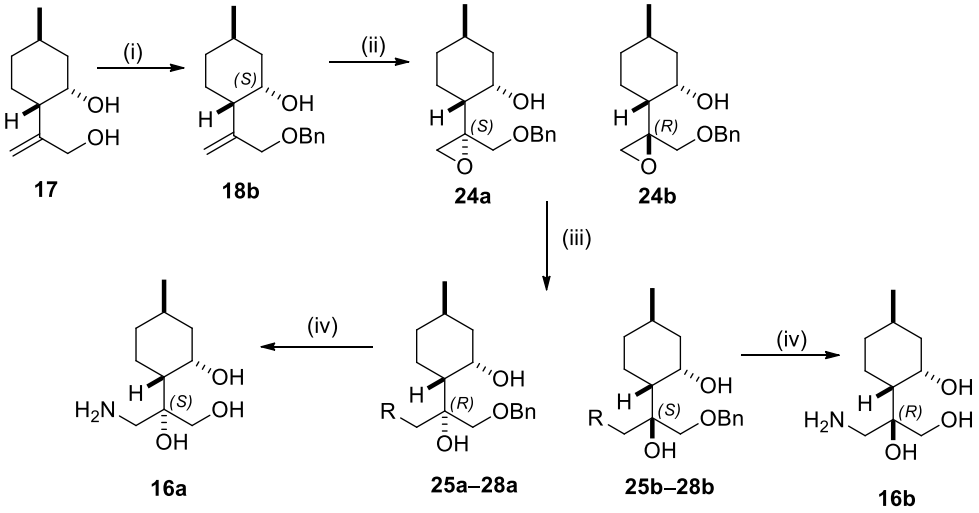
Scheme 2. Synthesis of (+)-neoisopulegol-based *O*-benzyl aminotriols. Reaction conditions: (i) SeO_2 (0.24 equ.), 70% *t*-BuOOH (4 equ.), $CHCl_3$, 25 °C, 20 h, then $NaBH_4$ (3 equ.), dry MeOH, 0 °C, 2 h, 27%; (ii) *m*-CPBA (2 equ.), Na_2HPO_4. $12H_2O$ (3 equ.), CH_2Cl_2, 25 °C, 2 h, 60% (**11a** + **11b**); (iii) R^1R^2NH (2 equ.), $LiClO_4$ (1 equ.), MeCN, 70–80 °C, 8 h, 7–54% (for **12a**–**b** and **13a**–**b**) or imidazole/1,2,4-triazol (3 equ.), K_2CO_3 (5 equ.), dry DMF, 70–80 °C, 12 h, **14a**: 58%, **15a**: 46%; (iv) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 78% (from **12a**).

During our attempt to improve the separation of epoxides **11a**–**b**, we realized that *O*-benzylation of **10** could serve this purpose. The synthesis of **18a** starting from **10** with NaH/BnBr/KI system, however, provided low-yield transformation (20%). Fortunately, it was achieved starting from **17**, made by the oxidation of **2** [69–72]. Diol **17** was reacted with benzyl bromide under reflux condition in dry THF to give **18a**, whereas **18b** was prepared at room temperature. Epoxidation of **18a** with *m*-CPBA produced a 1:1 mixture of epoxides **19a** and **19b**. After purification, ring opening of oxiranes **19a**–**b** was accomplished with different nucleophiles resulting in a library of di-*O*-benzyl derivatives **20a**–**24a** and **20b**–**24b**, respectively. The debenzylation of **20a** and **20b** by hydrogenolysis over Pd/C gave, respectively, primary aminotriols **16a** and **16b** in exceptionally high yields (Scheme 3).



Scheme 3. Synthesis of (+)-neoisopulegol-based di-*O*-benzyl aminotriols. Reaction conditions: (i) NaH (1 equ.), BnBr (1.5 equ.), KI (1 equ.), dry THF, 60 °C, 24 h, 56%; (ii) *m*-CPBA (2 equ.), Na_2HPO_4. $12H_2O$ (3 equ.), CH_2Cl_2, 25 °C, 2 h, 36% (**19a**), 36% (**19b**); (iii) R^1R^2NH (2 equ.), $LiClO_4$ (1 equ.), MeCN, 70–80 °C, 6 h, 53–84% (for **20a**–**b** and **21a**–**b**) or imidazole/1,2,4-triazol (3 equ.), K_2CO_3 (5 equ.), dry DMF, 70–80 °C, 48 h, 42–67% (for **22a**–**b** and **23a**–**b**); (iv) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 94% (from **20a** or **20b**).

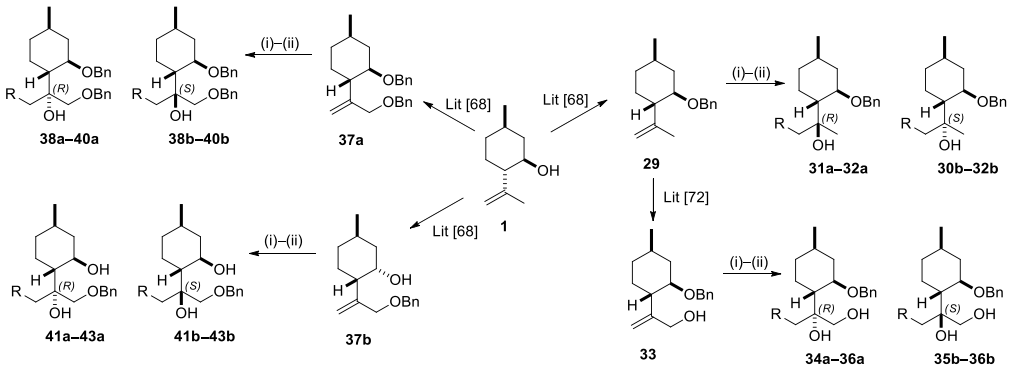
The epoxidation of **18b** with *m*-CPBA gave a 3:1 mixture of epoxides **24a** and **24b**. After separation by column chromatography, they were subjected to aminolysis with different nucleophiles to form a library of *O*-benzyl derivatives **25a**–**28a** and **25b**–**28b**, respectively. Primary aminotriols **16a** and **16b** were prepared via the usual way by hydrogenolysis of aminodiols **25a** and **25b** over Pd/C (Scheme 4).



Scheme 4. Synthesis of (+)-neoisopulegol-based *O*-benzyl aminotriols. Reaction conditions: (i) NaH (1 equ.), BnBr (1.5 equ.), KI (1 equ.), dry THF, 24 °C, 24 h, 59%; (ii) *m*-CPBA (2 equ.), Na_2HPO_4. $12H_2O$ (3 equ.), CH_2Cl_2, 25 °C, 2 h, 42% (**25a**), 15% (**25b**); (iii) R^1R^2NH (2 equ.), $LiClO_4$ (1 equ.), MeCN, 70–80 °C, 8 h, 71–88% (for **25a**–**b** and **26a**–**b**) or imidazole/1,2,4-triazol (3 equ.), K_2CO_3 (5 equ.), dry DMF, 70–80 °C, 12 h, 67–83% (for **27a**–**b** and **28a**–**b**); (iv) 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 91% (from **25a** or **25b**).

2.2. Synthesis of (−)-Isopulegol-Based O-Benzyl Derivatives

Our previous work demonstrated that the *O*-benzyloxy group on the cyclohexyl ring is much more effective to induce antimicrobial activity. Therefore, to explore the role of the configuration of the *O*-benzyloxy group, some (−)-isopulegol-based *O*-benzyl derivatives were also prepared under optimized condition and using literature information [68] (Scheme 5).

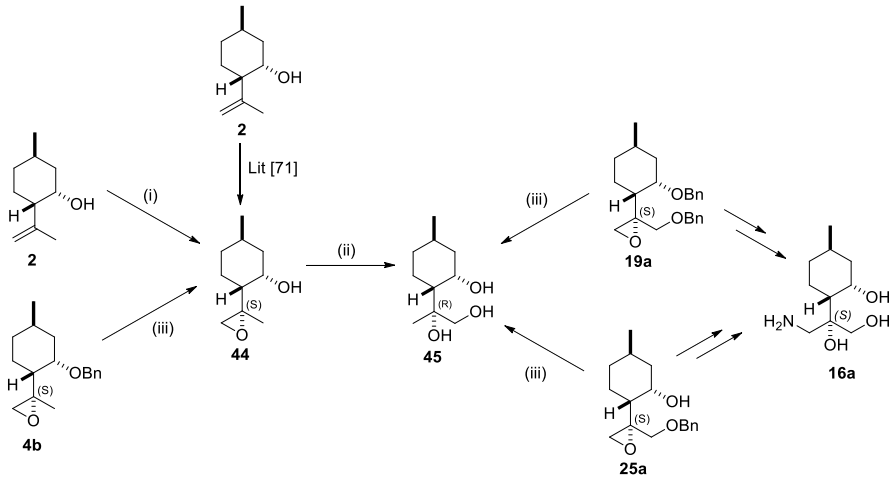


30b, 34a, 38, 41: R = $N(CH_2Ph)_2$; **31, 35, 39, 42**: R = imidazole; **33, 35, 40, 43**: 1,2,4-triazole

Scheme 5. Synthesis of (−)-isopulegol-based *O*-benzyl derivatives. Reaction conditions: (i) epoxidation according to our previous work [68], (ii) R^1R^2NH (2 equ.), $LiClO_4$ (1 equ.), MeCN, 70–80 °C, 6–20 h, 47% (**30b**), 76% (**34a**), 67–80% (**38a**–**b**), 76–88% (**41a**–**b**) or imidazole/1,2,4-triazol (3 equ.), K_2CO_3 (5 equ.), dry DMF, 70–80 °C, 12–96 h, 38–83% (for **31a**–**b** and **32a**–**b**), 50–67% (for **35a**–**b** and **36a**–**b**), 67–83% (for **39a**–**b** and **40a**–**b**), 58–67% (for **41a**–**b** and **42a**–**b**).

2.3. Determine Relative Configuration of (+)-Neoisopulegol-Based O-Benzyl Derivatives

Epoxidation of **2** with *t*-BuOOH in the presence of vanadyl acetylacetonate ($VO(acac)_2$) as catalyst furnished epoxide **44** in a stereoselective reaction [72]. Debenzylation of **4b** provided **44** in a moderate yield whereas exposure of **44** to NaOH furnished **45** with the retention of stereochemistry [86]. The absolute configuration of *O*-benzyl derivatives **19a** and **25a** was determined by debenzylation together with reduction via hydrogenolysis over Pd/C [87,88] to provide triol **45** with stereochemical retention [68]. The stereochemical structure of epoxide **44** is well-known in the literature [72]; therefore, the absolute configuration of *O*-benzyl derivatives could also be determined (Scheme 6).



Scheme 6. Determination of the structure of (+)-neoisopulegol-based- *O*-benzyl derivatives. Reaction conditions: (i) $VO(acac)_2$, 70% *t*-BuOOH (2 equ.), dry toluene, 25 °C, 12 h, 76%; (ii) 3M NaOH, DMSO, 25 °C, 2 h, 76%; (iii) 5% Pd/C, H_2 (1 atm), *n*-hexane:EtOAc = 9:1, 25 °C, 6–24 h, 61% (**4b**), 78% (**19a**), 73% (**25a**).

2.4. Antimicrobial Effects

Since several *O*-benzyl derivatives exerted antimicrobial activities on various microorganisms [68], antimicrobial activities of the prepared *O*-benzyl 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). Furthermore, the minimal inhibitory concentrations (MIC) of the compounds showed significantly high level (>80%) antimicrobial activity and their MIC values were determined against the test microorganism, where the high inhibition activity was detected (Table 1, in brackets).

Table 1. Most relevant antimicrobial activity of *O*-benzyl derivatives expressed as inhibitory effect (%) and MIC values (in brackets).

		Inhibitory Effect (%) ± RSD (%)					
		Gram Positive		**Gram Negative**		**Yeast**	
Analogue	**Conc. (μg/mL)**	***B. subtilis* SZMC0209**	***S. aureus* SZMC14611**	***E. coli* SZMC6271**	***P. aeruginosa* SZMC23290**	***C. albicans* SZMC1533**	***C. krusei* SZMC1352**
Nystatin	100	-	-	-	-	93.38 ± 2.13 (100 μg/mL)	92.01 ± 3.64 (100 μg/mL)
	10	-	-	-	-	92.88 ± 10.18	58.00 ± 9.21
Ampicillin	100	95.22 ± 8.40 (<0.78 μg/mL)	81.88 ± 8.99 (<0.78 μg/mL)	94.07 ± 3.61 (100 μg/mL)	29.03 ± 2.06	-	-
	10	93.00 ± 3.20	70.37 ± 6.15	89.37 ± 0.39	-	-	-
3	100	97.60 ± 6.42 (100 μg/mL)	57.57 ± 9.93	-	49.10 ± 7.52	-	-
	10	59.58 ± 8.06	-	-	-	-	-
5a	100	92.82 ± 4.69 (25 μg/mL)	80.07 ± 2.21 (50 μg/mL)	-	54.06 ± 9.08	91.56 ± 1.27 (>100 μg/mL)	94.88 ± 2.18 (100 μg/mL)
	10	48.25 ± 6.16	-	-	-	-	-
5b	100	86.35 ± 1.88 (50 μg/mL)	71.48 ± 1.28	-	46.66 ± 1.37	92.88 ± 2.63 (>100 μg/mL)	93.62 ± 0.80
	10	23.23 ± 3.15	-	-	-	-	-
7a	100	81.51 ± 4.73 (50 μg/mL)	70.66 ± 0.91	-	-	87.90 ± 10.46 (>100 μg/mL)	-
	10	-	-	-	-	-	-
7b	100	95.34 ± 4.81 (50 μg/mL)	92.34 ± 1.32 (100 μg/mL)	-	41.59 ± 3.53	-	-
	10	50.00 ± 7.21	-	-	-	-	-
10	100	95.16 ± 2.81 (100 μg/mL)	90.71 ± 3.27 (100 μg/mL)	-	50.87 ± 9.72	95.91 ± 16.31 (>100 μg/mL)	-
	10	55.43 ± 15.48	-	-	44.05 ± 7.57	-	-
12a	100	95.16 ± 6.46 (100 μg/mL)	-	-	70.85 ± 6.49	95.83 ± 11.18 (>100 μg/mL)	-
	10	73.41 ± 5.45	-	-	47.81 ± 7.92	-	-
12b	100	91.84 ± 6.01 (100 μg/mL)	83.11 ± 2.61 (100 μg/mL)	50.07 ± 10.97	75.84 ± 7.14	94.50 ± 0.97 (>100 μg/mL)	67.59 ± 16.45
	10	32.17 ± 11.19	-	-	58.24 ± 4.20	-	-
14a	100	92.67 ± 3.90 (100 μg/mL)	82.35 ± 3.19 (100 μg/mL)	-	52.97 ± 7.47	-	-
	10	-	-	-	44.00 ± 1.32	-	-
20a	100	84.57 ± 3.18 (6.25 μg/mL)	70.13 ± 0.90	-	-	91.35 ± 1.07 (>100 μg/mL)	-
	10	89.70 ± 1.32	65.81 ± 0.51	-	-	-	-
20b	100	78.34 ± 2.51	69.49 ± 0.57	-	-	90.74 ± 2.90 (>100 μg/mL)	79.88 ± 3.39
	10	78.43 ± 5.39	61.84 ± 0.27	-	-	80.54 ± 17.23	-

Table 1. *Cont.*

Inhibitory Effect (%) ± RSD (%)							
		Gram Positive		Gram Negative		Yeast	
Analogue	**Conc. (μg/mL)**	***B. subtilis* SZMC0209**	***S. aureus* SZMC14611**	***E. coli* SZMC6271**	***P. aeruginosa* SZMC23290**	***C. albicans* SZMC1533**	***C. krusei* SZMC1352**
22a	100	83.44 ± 20.97	76.39 ± 1.13	-	-	-	-
	10	81.63 ± 1.22 (25 μg/mL)	70.02 ± 1.01	-	-	-	-
22b	100	78.43 ± 10.14 (<0.78 μg/mL)	60.32 ± 1.11	-	-	81.97 ± 4.00 (>100 μg/mL)	-
	10	81.01 ± 1.08	62.77 ± 0.27	-	-	61.02 ± 6.51	-
23a	100	73.83 ± 4.14 (<0.78 μg/mL)	73.99 ± 5.15	-	47.92 ± 1.67	-	-
	10	83.29 ± 5.94	-	-	47.78 ± 3.40	-	-
23b	100	75.64 ± 0.21	71.95 ± 4.38	-	46.03 ± 2.10	-	-
	10	77.54 ± 5.94	-	-	42.22 ± 1.49	-	-
25a	100	78.96 ± 0.88	-	-	-	-	-
	10	-	-	-	-	-	-
27a	100	71.13 ± 4.78	-	-	43.48 ± 3.42	-	-
	10	-	-	-	38.95 ± 9.32	-	-
27b	100	-	-	-	34.19 ± 6.00	80.58 ± 12.34 (>100 μg/mL)	-
	10	-	-	-	33.16 ± 8.01	-	-
31a	100	95.13 ± 9.21 (100 μg/mL)	82.58 ± 10.08 (>100 μg/mL)	-	48.38 ± 1.94	-	-
	10	12.76 ± 9.95	-	-	32.10 ± 3.98	-	-
31b	100	93.89 ± 5.51 (21 μg/mL)	86.85 ± 4.00 (50 μg/mL)	-	53.31 ± 4.84	95.21 ± 3.59 (100 μg/mL)	-
	10	47.83 ± 9.92	-	-	47.81 ± 6.60	-	-
39a	100	79.38 ± 4.19 (3.13 μg/mL)	63.47 ± 4.90	-	-	88.22 ± 3.96 (>100 μg/mL)	-
	10	82.73 ± 0.52	69.84 ± 0.00	-	-	-	-
39b	100	87.80 ± 7.04 (1.56 μg/mL)	79.66 ± 2.59 (3.13 μg/mL)	-	48.09 ± 1.38	90.89 ± 13.31 (>100 μg/mL)	91.08 ± 4.90 (>100 μg/mL)
	10	92.94 ± 1.46	83.69 ± 38.18	-	33.59 ± 6.43	85.10 ± 9.56	-
40a	100	72.88 ± 1.68	68.26 ± 1.66	-	37.66 ± 2.39	-	-
	10	55.43 ± 5.07	-	-	38.89 ± 1.13	-	-
40b	100	71.39 ± 3.84	69.37 ± 1.44	-	42.13 ± 2.25	-	-
	10	65.82 ± 4.56	-	-	39.58 ± 0.73	-	-
42a	100	69.05 ± 10.02	-	-	-	-	-
	10	51.75 ± 11.13	-	-	-	-	-
42b	100	86.62 ± 8.48 (>100 μg/mL)	66.22 ± 4.03	-	-	-	-
	10	43.95 ± 5.65	-	-	-	-	-
43b	100	-	-	-	-	80.90 ± 4.76 (>100 μg/mL)	-
	10	-	-	-	-	-	-

3. Discussion

3.1. Antimicrobial Activity

The MIC values of significant O-benzyl derivatives (I% > 80%) obtained against the tested microorganisms are presented in Table 1. The strongest antifungal activity was shown by compound **22b**, **23a** (di *O*-benzyl aminotriols) at a concentration of 0.78 μg/mL, they were as same as the reference drug ampicillin (0.78 μg/mL). Another di O-benzyl aminotriols **20a** and **39a**–**b** were effective against *B. subtilis* below than 10 μg/mL of MIC values. Moreover, *O*-benzyl aminotriols **5a**–**b**, **7a**–**b**, **31b** together with imidazole-substituted di *O*-benzyl aminotriol **22a** showed lower activity against *B. subtilis* with MIC values in the range between 20 and 50 μg/mL. The weak effect on *B. subtilis* was observed for compounds **3**, **10**, **12a**–**b**, **14a**, **31a**, **42a** (MIC $\geq$ 100 μg/mL).

Growth inhibition of *S. aureus* was observed at the concentration of 50 μg/mL of *O*-benzyl aminodiols **5a** and **31a**. Imidazole-substituted di *O*-benzyl aminotriol **39b** exhibited relatively high antibacterial potency against *S. aureus* at the MIC values of 3.13 μg/mL, whereas derivatives **7b**, **10**, **12b,** and **14a** was less active against *S. aureus* and inhibited bacterial growth at the concentration of 100 μg/mL. The MICs of standard drug ampicillin for the *S. aureus* were 0.78 μg/mL.

On the other hand, regarding MIC for pathogenic fungi, *O*-benzyl derivatives showed poor activity against all the tested fungal strains, which obtained by the MIC values against *C. albicans* and *C. krusei* (>100 μg/mL).

As shown in Table 1, *N*-benzyl and imidazole-substituted *O*-benzyl derivatives showed significant inhibitory activity against Gram-positive bacteria *B. subtilis* and *S. aureus*. Di-*O*-benzyl-substituted derivatives (**20**, **22**–**23**, **39**–**40**) exerted bactericidal activities against the bacterial species of *B. subtilis* and *S. aureus* at low concentrations (10 μM). Only **12a**–**b** showed significant effect against Gram-negative bacterium *P. aeruginosa* as well as a moderate effect against *E. coli* (**12b**). Other derivatives possessed moderate antibacterial activity against *P. aeruginosa*. Three di-*O*-benzyl derivatives (**20b**, **22b**, **39b**) were highly effective against both *C. albicans* and *C. krusei*. Furthermore, *O*-benzyl derivatives **27b** and **43b** were found to exhibit marked growth inhibition against *C. albicans*. *N*-Dibenzyl-substituted *O*-benzyl derivatives were found to be weakly active or inactive against all tested strains.

The obtained results showed that all synthetic derivatives proved to be more active against Gram-positive than against Gram-negative bacteria. *O*-benzyl derivatives that contain *N*-benzyl and imidazole substitution were the most active compounds against Gram-positive bacteria and had moderate antimicrobial effect against the *P. aeruginosa* (Gram-negative) strain. The mechanism of bactericidal action of heterocycles containing the imidazole ring is thought to be due to disruption of intermolecular interactions in the cell membrane. This can cause dissociation of cellular membrane lipid bilayers, which compromises cellular permeability controls and induces leakage of cellular contents [89].

Regarding the yeasts, *N*-benzyl- and imidazole-substituted *O*-benzyl derivatives were also found to be the most active compounds against *C. albicans*. The imidazole derivatives can inhibit the transformation of blastospores of *C. albicans* into the invasive mycelial form [90]. In addition, the preliminary in vitro antifungal screening indicated that *S*-isomers showed better potency compared to *R*-isomers against *C. albicans*. Since the widely accepted primary effect of imidazoles is the inhibition of cytochrome P450-mediated 14a-sterol demethylase of the ergosterol precursor lanosterol from *C. albians* [91]. This enzyme with strict substrate requirements interacted differentially with the stereoisomers of *O*-benzyl derivatives, therefore the affinity of *O*-benzyl derivatives for cytochrome P-450 enzymes involved in steroid synthesis is highly dependent on the stereochemistry of the entire molecule.

The results obtained showed that the tested *O*-benzyl derivatives that contain *N*-dibenzyl substituents have no antibacterial or antifungal activity against any of the tested pathogenic species of bacteria and fungi. The steric hindrance of the substituents, which prevents the destruction of normal permeability, might be the reason for the low antimi-

crobial and antifungal activity of the *N*-dibenzyl-substituted derivatives. Therefore, the inactivity of *N*-dibenzyl derivatives observed in the present study can be due to the mode of substitution.

3.2. Structure-Activity Relationship

(i) *N*,*O*-dibenzyl aminodiols (**5a**–**b**) exhibited significant inhibitory activity against both Gram-positive bacteria (*B. subtilis* and *S. aureus*) and Gram-positive bacteria (*P. aeruginosa*) as well as yeast (*C. albicans* and *C. krusei*). Replacing *N*-benzyl substitution by imidazole (**7a**–**b**) led to the loss of activity against *C. krusei.*

(ii) When the -CH_3 group of isopropyl part was changed to -CH_2OH, disappearance on inhibitory activity against *S. aureus* and *C. krusei* was observed on *N*,*O*-dibenzyl aminodiol containing *R*-isomer (**12a**) whereas the other stereoisomer (**12b**) exhibited an additive effect on *E. coli*. In the case of imidazole *O*-benzyl aminotriols, this route reduced activity on *C. albicans* with *R*-isomer (**14a**) and totally lost on antifungal effectiveness on the other isomer (**14b**).

(iii) Benzylation of -CH_2OH provided di *O*-benzyl aminotriols. Our tests revealed that the lack of antifungal activity and high potency against positive-Gram bacteria in both *N*-benzyl (**20a**–**b**) and imidazole (**24a**–**b**) aminotriols were produced at a low concentration (10 μM). This modification probably improves the lipophilic properties that enhanced interactions in the cell membrane. In addition, the synthesized triazole analogues (**23a**–**b**) also exhibit marked growth inhibition against Gram-positive bacteria (*B. subtilis* and *S. aureus*) and Gram-positive bacteria (*P. aeruginosa*).

(iv) The almost complete loss of antimicrobial activity resulting from the debenzylation on the cyclohexane ring demonstrated with aminotriol derivatives (**25a**–**b**) suggests that the benzyl moiety on cyclohexyl ring is a key element to have satisfactory antimicrobial activity in the case of *N*,*O*-dibenzyl aminotriol whereas they exert markedly selective antibacterial action on *P. aeruginosa* in the case of imidazole *O*-benzyl aminotriol.

(v) In the stereochemistry study of the OH group on the cyclohexyl ring, aminodiol with *S*-configuration (**27a**–**b**) displayed a potential negative-Gram bacterial effect (*P. aeruginosa)* while derivatives with *R*-configuration (**42a**–**b**) had significant positive-Gram bacterial effect (*B. subtilis*) whereas the stereochemistry of the *O*-benzyl substituent on the cyclohexane ring in the aminodiol and aminotriol function has no influence on the antimicrobial effect.

(vi) The available data demonstrated that most of the *N*-benzyl and imidazole-substituted *O*-benzyl derivatives exhibited more antimicrobial potency than triazole or *N*,*N*-dibenzyl *O*-benzyl ones.

(vii) Further, this result indicates that *S*-isomer showed better potency compared to *R*-isomer against fungi.

4. Materials and Methods

4.1. General Methods

Commercially available compounds were used as obtained from suppliers (Molar Chemicals Ltd., Halásztelek, Hungary; Merck Ltd., Budapest, Hungary and VWR International Ltd., Debrecen, Hungary), while solvents were dried according to standard procedures. Optical rotations were measured in MeOH at 20 °C, with a Perkin-Elmer 341 polarimeter (PerkinElmer Inc., Shelton, CT, USA). Chromatographic separations and monitoring of reactions were carried out on Merck Kieselgel 60 (Merck Ltd., Budapest, Hungary). Elemental analyses for all prepared compounds were performed on a Perkin-Elmer 2400 Elemental Analyzer (PerkinElmer Inc., Waltham, MA, USA). GC measurements for direct separation of commercially available enantiomers of isopulegol to determine the enantiomeric purity of starting material **1** were performed on a Chirasil-DEX CB column (2500 × 0.25 mm I.D.) on a Perkin-Elmer Autosystem XL GC equipped with a Flame Ionization Detector (Perkin-Elmer Corporation, Norwalk, CT, USA) and a Turbochrom Workstation data system (Perkin-Elmer Corp., Norwalk, CT, USA). Melting points were

determined on a Kofler apparatus (Nagema, Dresden, Germany) and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on Brucker Avance DRX 500 spectrometer (Bruker Biospin, Karlsruhe, Baden Württemberg, Germany) [500 MHz (^{1}H) and 125 MHz (^{13}C), δ = 0 (TMS)]. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given by Hz.

(−)-Isopulegol (**1**) is commercially available from Merck Co with *ee* = 95%, ($[\alpha]_D^{20}$ = −22.0, neat) and its enatimomer (+)-**1** (*ee* = 90%, [$[\alpha]_D^{20}$ = +22.0, neat). (+)-Neoisopulegol (**2**) ($[\alpha]_D^{20}$ = +28.7, c = 17.2, $CHCl_3$) and its enatimomer (−)-**2** ($[\alpha]_D^{20}$ = −22.2, c = 2.0, $CHCl_3$) were synthesized from (−)-**1** and its isomer (+)-**1** following a reported procedure, respectively [71]. Diol **17**, epoxide **44** [72] as well as compounds **29**, **33,** and **37a–b** [68] were prepared according to literature procedures. All spectroscopic data were similar to those described therein. Since any of the applied transformations do not reach all the four chiral centers at the same time, giving rise to racemization, rather only the formation of the prescribed and isolated diastereoisomers, we believe that the enantiomer purity of the prepared compounds can be defined as *ee* ≥ 95% (commercial (−)-isopulegol). ^{1}H, ^{13}C, HSQC, HMBC and NOESY NMR spectra of new compounds and GC chromatograms of isopulegol enantiomers are available in Supplementary Materials.

4.2. Experimental Section and Compound Characterisations

4.2.1. (*S*)-2-((1*R*,2*R*,4*R*)-2-Hydroxy-4-methylcyclohexyl)propane-1,2-diol (**45**)

Compound **44** (0.60 mmol) was treated with DMSO (3.0 mL) and 3 M NaOH (3.0 mL). The resulting homogenous solution was stirred at 80 °C for 2 h. After being cooled to room temperature, EtOAc (20 mL) was added, and the aqueous layer was washed with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:4) to provide compound **45**.

Yield: 76%, colorless oil. $[\alpha]_D^{20}$ = +14.0 (c 0.22, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (3H, d, *J* = 6.2 Hz), 0.91–0.97 (1H, m), 1.10–1.16 (1H, m), 1.25 (3H, s), 1.35–1.39 (1H, m), 1.49–1.53 (1H, m), 1.62–1.70 (1H, m), 1.76–1.85 (3H, m), 3.23 (2H, brs), 3.29 (1H, d, *J* = 11.1 Hz), 3.63 (1H, d, *J* = 11.1 Hz), 4.38 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 22.3, 25.0, 25.9, 35.2, 42.8, 48.9, 67.0, 67.3, 74.4. Found: C, 63.83; H, 10.69. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71.

4.2.2. 2-((1*S*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)prop-2-en-1-ol (**10**)

To a solution of *t*-BuOOH (70% purity in H_2O, 32.80 mmol) in CH_2Cl_2 (50 mL), dried briefly (Na_2SO_4), was added finely powdered SeO_2 (1.96 mmol) followed by 30 minutes by the addition of **3** (8.20 mmol). After stirring for 20 h at 25 °C, saturated $NaHCO_3$ solution (50 mL) was added, then CH_2Cl_2 phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford colorless oil, which was added at 0 °C to a suspension of $NaBH_4$ (24.60 mmol) in dry MeOH (50 mL). The reaction mixture was stirred for 2 h at 0 °C while the reaction progress was monitored by TLC. When the reaction was complete, the mixture was poured into brine (100 mL) and the product was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo. The crude product was purified by column chromatography on silica gel using *n*-hexane:EtOAc = 4:1.

Yield: 27%, colorless oil. $[\alpha]_D^{20}$ = +29.0 (c 0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3H, d, *J* = 6.4 Hz), 0.94–1.07 (2H, m), 1.50–1.55 (1H, m), 1.76–1.80 (2H, m), 1.87–1.95 (1H, m), 2.07–2.11 (1H, m), 2.24 (1H, d, *J* = 13.0 Hz), 2.67 (1H, t, *J* = 5.4 Hz), 3.71 (1H, d, *J* = 2.4 Hz), 3.94 (1H, dd, *J* = 12.7, 5.8 Hz), 4.06 (1H, dd, *J* = 12.7, 4.1 Hz), 4.34 (1H, d, *J* = 11.6 Hz), 4.60 (1H, d, *J* = 11.7 Hz), 4.96 (1H, s), 5.07 (1H, d, *J* = 1.0 Hz), 7.25–7.32 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 25.0, 26.0, 35.0, 37.5, 46.6, 65.2, 70.6, 77.3, 113.2, 127.7, 127.9, 128.4, 138.4, 151.0. Found: C, 78.40; H, 9.33. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29.

4.2.3. General Procedure for Benzylation

A suspension of NaH (60% purity, 6.6 mmol) in dry THF (10 mL) was added to a solution of alcohol (6.6 mmol) in dry THF (20 mL). The reaction mixture was stirred at 25 °C for 30 min before benzyl bromide (9.9–19.8 mmol) and KI (6.6 mmol) were added to the mixture. Stirring was continued for 12–24 h at 25–60 °C. When the reaction was complete, the mixture was poured into saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by column chromatography on silica gel to provide **3** or **18a**–**b**, respectively.

((((1*S*,2*S*,5*R*)-5-Methyl-2-(prop-1-en-2-yl)cyclohexyl)oxy)methyl)benzene (**3**)

Prepared with **2** and benzyl bromide (9.9 mmol) at reflux for 12 h and eluted by *n*-hexane:EtOAc = 19:1. Yield: 63%, colorless oil. $[\alpha]_D^{20}$ = +24.0 (c 0.28, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.4 Hz), 0.86–0.89 (2H, m), 0.92–1.00 (2H, m), 1.25–1.31 (2H, m), 1.51–1.54 (1H, m), 1.73 (3H, s), 1.74–1.80 (2H, m), 1.85–1.95 (2H, m), 2.01–2.06 (1H, m), 3.75 (1H, d, *J* = 1.6 Hz), 4.38 (1H, d, *J* = 12.1 Hz), 4.56 (1H, d, *J* = 12.1 Hz), 4.77 (1H, d, *J* = 0.5 Hz), 4.80 (1H, s), 7.21–7.32 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 22.5, 22.8, 25.2, 26.3, 35.2, 38.6, 48.6, 70.8, 76.1, 110.5, 127.2, 127.5, 128.2, 139.8, 148.0. Found: C, 83.50; H, 9.93. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90.

(((2-((1*S*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)allyl)oxy)methyl)benzene (**18a**)

Prepared with **17** and benzyl bromide (19.8 mmol) at reflux for 24 h and eluted by *n*-hexane:EtOAc = 19:1. Yield: 56%, colorless oil. $[\alpha]_D^{20}$ = +20.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (3H, d, *J* = 6.4 Hz), 0.94–1.01 (2H, m), 1.20–1.30 (3H, m), 1.52–1.57 (5H, m), 1.75–1.78 (2H, m), 1.83–1.91 (1H, m), 2.02–2.05 (1H, m), 2.13–2.17 (1H, m), 3.71 (1H, s), 3.89 (1H, d, *J* = 12.5 Hz), 3.99 (1H, d, *J* = 12.5 Hz), 4.31 (1H, d, *J* = 12.0 Hz), 4.38 (1H, d, *J* = 11.9 Hz), 4.46 (1H, d, *J* = 12.0 Hz), 4.54 (1H, d, *J* = 12.0 Hz), 5.06 (1H, s), 5.14 (1H, s), 7.23–7.36 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 25.2, 26.3, 35.2, 38.2, 44.5, 70.6, 72.0, 73.2, 112.9, 127.3, 127.5, 127.6, 127.8, 128.3, 128.5, 147.8. Found: C, 82.27; H, 8.67. Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63.

(1*S*,2*S*,5*R*)-2-(3-(Benzyloxy)prop-1-en-2-yl)-5-methylcyclohexanol (**18b**)

Prepared with **17** and benzyl bromide (9.9 mmol) at 25 °C for 12 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 59%, colorless oil. $[\alpha]_D^{20}$ = +33.0 (c 0.28, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (3H, d, *J* = 6.5 Hz), 0.91–1.01 (1H, m), 1.13 (1H, t, *J* = 12.9 Hz), 1.41–1.47 (1H, m), 1.62 (1H, s), 1.74–1.83 (3H, m), 1.90–1.95 (1H, m), 2.21 (1H, d, *J* = 12.7 Hz), 2.26 (1H, s), 3.91 (1H, d, *J* = 11.8 Hz), 3.96 (1H, s), 4.07 (1H, d, *J* = 11.7 Hz), 4.48 (1H, d, *J* = 11.9 Hz), 4.54 (1H, d, *J* = 11.8 Hz), 5.06 (1H, s), 5.21 (1H, s), 7.25–7.36 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 24.1, 25.8, 35.0, 41.3, 45.9, 67.7, 72.5, 72.7, 115.2, 127.9, 128.6, 138.0, 143.4, 147.8. Found: C, 78.45; H, 9.27. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29.

4.2.4. General Procedure of Epoxidation

To the solution of allylic alcohol derivatives (11.9 mmol) in CH_2Cl_2 (50 mL), $Na_2HPO_4 \cdot 12H_2O$ (35.7 mmol) in water (130 mL) and *m*-CPBA (70% purity, 23.8 mmol) were added at 0 °C, then the mixture was stirred at room temperature. When the reaction was complete (2 h), the mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with 5% KOH solution (3 × 50 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel with an appropriate solvent mixture to afford epoxides.

(*R*)-2-((1*R*,2*S*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)-2-methyloxirane (**4a**)

Prepared with **3** eluted by *n*-hexane:EtOAc = 9:1. Yield: 23%, colorless oil. $[\alpha]_D^{20}$ = +32.0 (c 0.285, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.5 Hz), 0.85–0.95 (2H, m), 1.28 (3H, s), 1.44–1.56 (3H, m), 1.71–1.76 (2H, m), 2.06–2.11 (1H, m), 2.51 (1H, d, *J* = 4.9 Hz),

2.73 (1H, d, *J* = 4.9 Hz), 3.87 (1H, d, *J* = 2.1 Hz), 4.39 (1H, d, *J* = 11.8 Hz), 4.62 (1H, d, *J* = 11.8 Hz), 7.25–7.33 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 22.1, 22.4, 26.4, 34.6, 37.7, 47.2, 53.6, 58.5, 70.3, 74.9, 127.4, 127.5, 128.4, 139.4. Found: C, 78.47; H 9.33. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-2-methyloxirane (**4b**)

Prepared with **3** eluted by *n*-hexane:EtOAc = 9:1. Yield: 47%, colorless oil. $[\alpha]_D^{20}$ = +88.7 (c 0.385, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.4 Hz), 0.84–0.95 (2H, m), 1.19–1.24 (1H, m), 1.33 (3H, s), 1.62–1.66 (1H, m), 1.77–1.82 (3H, m), 2.02–2.07 (1H, m), 2.49 (1H, d, *J* = 4.9 Hz), 2.68 (1H, d, *J* = 4.9 Hz), 2.72 (1H, d, *J* = 2.2 Hz), 4.35 (1H, d, *J* = 11.7 Hz), 4.60 (1H, d, *J* = 11.7 Hz), 7.25–7.34 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 22.4, 23.2, 26.3, 34.8, 37.6, 53.4, 59.4, 70.1, 75.6, 76.9, 77.1, 127.4, 127.6, 128.4, 139.2. Found: C, 78.40; H 9.25. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-2-((benzyloxy)methyl)oxirane (**19a**)

Prepared with **18a** eluted by *n*-hexane:EtOAc = 9:1. Yield: 36%, colorless oil. $[\alpha]_D^{20}$ = +47.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.4 Hz), 0.86–0.97 (2H, m), 1.40–1.50 (2H, m), 1.69–1.75 (2H, m), 1.89–1.93 (1H, m), 2.04–2.09 (1H, m), 2.64 (1H, d, *J* = 4.7 Hz), 2.80 (1H, d, *J* = 4.8 Hz), 2.87 (1H, d, *J* = 11.6 Hz), 3.73 (1H, d, *J* = 11.6 Hz), 3.83 (1H, d, *J* = 5.4 Hz), 4.25 (1H, d, *J* = 11.8 Hz), 4.40 (1H, d, *J* = 12.1 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.57 (1H, d, *J* = 11.9 Hz), 7.24–7.34 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 22.4, 26.4, 34.5, 37.3, 42.4, 48.3, 60.1, 70.1, 71.6, 73.2, 74.3, 127.4, 127.5, 127.7, 127.8, 128.4, 128.5. Found: C, 78.67; H 8.23. Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25.

(*R*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-2-((benzyloxy)methyl)oxirane (**19b**)

Prepared with **18a** eluted by *n*-hexane:EtOAc = 9:1. Yield: 36%, colorless oil. $[\alpha]_D^{20}$ = +54.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3H, d, *J* = 6.5 Hz), 0.85–0.95 (4H, m), 1.26–1.29 (2H, m), 1.50 (2H, m), 1.62–1.76 (5H, m), 2.01–2.04 (1H, m), 2.69 (1H, d, *J* = 5.3 Hz), 2.84 (1H, d, *J* = 5.4 Hz), 3.58 (1H, d, *J* = 10.9 Hz), 3.70 (1H, d, *J* = 11.4 Hz), 3.76 (1H, s) 4.32 (1H, d, *J* = 11.6 Hz), 4.48 (2H, s), 4.54 (1H, d, *J* = 11.6 Hz), 7.23–7.32 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 23.1, 26.3, 34.9, 37.7, 43.9, 48.9, 60.8, 70.2, 71.3, 73.5, 74.8, 127.4, 127.7, 127.8, 128.4, 128.4, 128.5, 138.6, 139.3. Found: C, 78.62; H 8.23. Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25.

(1*R*,2*R*,5*R*)-2-((*S*)-2-((Benzyloxy)methyl)oxiran-2-yl)-5-methylcyclohexanol (**24a**)

Prepared with **18b** eluted by *n*-hexane:EtOAc = 4:1. Yield: 42%, colorless oil. $[\alpha]_D^{20}$ = +37.0 (c 0.275, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3H, d, *J* = 6.4 Hz), 0.88–0.96 (1H, m), 1.00–1.06 (1H, m), 1.45–1.49 (1H, m), 1.55–1.59 (2H, m), 1.66–1.1.78 (2H, m), 1.82–1.87 (2H, m), 2.67 (1H, d, *J* = 4.6 Hz), 2.80 (1H, d, *J* = 4.6 Hz), 3.22 (1H, d, *J* = 10.3 Hz), 3.37 (1H, s), 3.82 (1H, d, *J* = 10.3 Hz), 4.18 (1H, s), 4.53 (1H, d, *J* = 11.6 Hz), 4.57 (1H, d, *J* = 11.8 Hz), 7.25–7.37 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 22.3, 25.6, 34.7, 41.7, 44.0, 50.2, 60.6, 67.8, 72.1, 73.7, 127.9, 128.0, 128.5, 137.1. Found: C, 78.90; H 8.77. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75.

(1*R*,2*R*,5*R*)-2-((*R*)-2-((Benzyloxy)methyl)oxiran-2-yl)-5-methylcyclohexanol (**24b**)

Prepared with **18b** eluted by *n*-hexane:EtOAc = 4:1. Yield: 15%, colorless oil. $[\alpha]_D^{20}$ = +24.0 (c 0.295, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3H, d, *J* = 6.4 Hz), 0.88–0.95 (1H, m), 1.02–1.07 (1H, m), 1.47–1.50 (1H, m), 1.57 (1H, s), 1.59–1.66 (2H, m), 1.74–1.77 (1H, m), 1.82–1.88 (2H, m), 2.69 (1H, d, *J* = 4.6 Hz), 2.85 (1H, d, *J* = 4.6 Hz), 3.24 (1H, s), 3.43 (1H, d, *J* = 10.8 Hz), 3.69 (1H, d, *J* = 10.9 Hz), 4.14 (1H, s), 4.53 (1H, d, *J* = 11.8 Hz), 4.61 (1H, d, *J* = 11.9 Hz), 7.25–7.35 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 22.3, 25.9, 34.9, 41.8, 44.3, 50.7, 66.7, 72.2, 73.8, 128.0, 128.1, 128.7, 137.4. Found: C, 78.85; H 8.74. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75.

4.2.5. General Procedure for Ring-Opening of Epoxides with Different Amines

A solution of epoxides (2.9 mmol) in MeCN (30 mL) was added to the appropriate amines (5.8 mmol) in MeCN (10 mL) and $LiClO_4$ (2.9 mmol). The mixture was kept at reflux temperature for 6–20 h. When the reaction was completed (indicated by TLC), the mixture was evaporated to dryness, the residue was again dissolved in water (15 mL), and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel with an appropriate solvent mixture, resulting in *O*-benzyl derivatives, respectively.

(*R*)-1-(Benzylamino)-2-((1*R*,2*S*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)propan-2-ol (**5a**)

Prepared with **4a** with benzylamine at reflux for 20 h and eluted by *n*-hexane:EtOAc = 1:1. Yield: 78%, colorless oil. $[\alpha]_D^{20}$ = +41.0 (c 0.275, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.6 Hz), 0.83–0.97 (2H, m), 1.17 (3H, s), 1.42–1.46 (1H, m), 1.62–1.80 (4H, m), 2.05–2.09 (1H, m), 2.54 (1H, d, *J* = 11.6 Hz), 2.63 (1H, d, *J* = 11.6 Hz), 3.71 (1H, d, *J* = 13.3 Hz), 3.80 (1H, d, *J* = 13.3 Hz), 3.92 (1H, d, *J* = 1.5 Hz), 4.13 (1H, d, *J* = 11.3 Hz), 4.50 (1H, d, *J* = 11.2 Hz), 7.23–7.33 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 22.4, 24.3, 26.1, 35.1, 37.1, 46.6, 54.5, 58.2, 69.7, 73.8, 75.5, 127.1, 127.8, 127.9, 128.5, 128.6, 138.4, 140.4. Found: C, 78.45; H, 9.07; N, 3.79. Anal. Calcd for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81.

(*S*)-1-(Benzylamino)-2-((1*R*,2*S*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)propan-2-ol (**5b**)

Prepared with **4** with benzylamine at reflux for 20 h and eluted by *n*-hexane:EtOAc = 1:1. Yield: 64%, colorless oil. $[\alpha]_D^{20}$ = +7.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (3H, d, *J* = 6.4 Hz), 0.85–0.93 (2H, m), 0.93–1.00 (1H, m), 1.02–1.07 (1H, m), 1.20–1.29 (4H, m), 1.26 (3H, s), 1.53–1.57 (1H, m), 1.63–1.71 (2H, m), 2.16–2.22 (1H, m), 2.58 (1H, d, *J* = 12.4 Hz), 2.78 (1H, d, *J* = 12.4 Hz), 3.53 (1H, d, *J* = 13.4 Hz), 3.63 (1H, d, *J* = 13.4 Hz), 4.20 (1H, s), 4.37 (1H, d, *J* = 10.3 Hz), 4.63 (1H, d, *J* = 10.4 Hz), 7.02–7.04 (2H, m), 7.28–7.45 (8H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 26.2, 28.1, 29.8, 35.0, 36.9, 49.9, 52.0, 52.7, 70.8, 72.3, 75.0, 128.8, 129.0, 129.1, 129.3, 129.5, 137.2. Found: C, 78.40; H, 9.03; N, 3.84. Anal. Calcd for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81.

(*R*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(dibenzylamino)propan-2-ol (**6a**)

Prepared with **4** with dibenzylamine at reflux for 20 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 50%, white crystal, m.p = 138–140 °C. $[\alpha]_D^{20}$ = +30.0 (c 0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83–0.92 (2H, m), 0.84 (3H, d, *J* = 6.5 Hz), 1.13 (3H, s), 1.53–1.56 (4H, m), 1.63–1.75 (3H, m), 2.01 (1H, dd, *J* = 14.1, 1.9 Hz), 2.86 (1H, d, *J* = 13.8 Hz), 3.3. (1H, dd, *J* = 13.6, 4.9 Hz), 3.67 (2H, d, *J* = 12.4 Hz), 4.06 (1H, d, *J* = 11.9 Hz), 4.43 (2H, t, *J* = 13.1 Hz), 4.53–4.62 (3H, m), 7.13–7.57 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 22.2, 25.6, 26.4, 34.9, 37.3, 52.3, 57.0, 59.5, 61.1, 69.5, 72.8, 74.3, 126.8, 127.5, 128.4, 129.2, 129.4, 130.1, 130.3, 132.2, 132.7, 139.1. Found: C, 81.33; H, 8.63; N, 3.04. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(dibenzylamino)propan-2-ol (**6b**)

Prepared with **4** with dibenzylamine at reflux for 20 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 25%, white crystal, m.p = 164–166 °C. $[\alpha]_D^{20}$ = −4.0 (c 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82-0.89 (1H, m), 0.86 (3H, d, *J* = 6.4 Hz), 1.29–1.33 (2H, m), 1.32 (3H, s), 1.56–1.61 (3H, m), 1.73 (1H, dd, *J* = 12.2, 2.1 Hz), 2.10 (1H, dd, *J* = 14.4, 2.4 Hz), 2.63 (1H, d, *J* = 13.2 Hz), 3.48–3.53 (1H, m), 3.60–3.64 (1H, m), 4.04 (1H, s), 4.26 (1H, d, *J* = 11.3 Hz), 4.47–4.66 (5H, m), 7.25–7.65 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 22.2, 26.1, 26.2, 34.8, 37.0, 50.2, 57.1, 58.9, 60.7, 69.9, 73.0, 74.5, 127.8, 127.9, 128.7, 129.2, 129.4, 130.0, 130.1, 132.0, 132.8, 138.4. Found: C, 81.40; H, 8.55; N, 3.07. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06.

(*S*)-3-(Benzylamino)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)propane-1,2-diol (**12a**)

Prepared with **11a** with benzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 1:2. Yield: 45%, colorless oil. $[\alpha]_D^{20}$ = +28.0 (c 0.40, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82–

0.89 (1H, m), 0.86 (3H, d, *J* = 6.4 Hz), 1.29–1.33 (2H, m), 1.32 (3H, s), 1.56–1.61 (3H, m), 1.73 (1H, dd, *J* = 12.2, 2.1 Hz), 2.10 (1H, dd, *J* = 14.4, 2.4 Hz), 2.63 (1H, d, *J* = 13.2 Hz), 3.48–3.53 (1H, m), 3.60–3.64 (1H, m), 4.04 (1H, s), 4.26 (1H, d, *J* = 11.3 Hz), 4.47–4.66 (5H, m), 7.25–7.65 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 22.2, 26.1, 26.2, 34.8, 37.0, 50.2, 57.1, 58.9, 60.7, 69.9, 73.0, 74.5, 127.8, 127.9, 128.7, 129.2, 129.4, 130.0, 130.1, 132.0, 132.8, 138.4. Found: C, 81.40; H, 8.55; N, 3.07. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06.

(*R*)-3-(Benzylamino)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)propane-1,2-diol (**12b**)

Prepared with **11a** with benzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 1:2. Yield: 11%, colorless oil. $[\alpha]_D^{20}$ = +19.0 (c 0.30, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86-0.97 (6H, m), 0.88 (3H, d, *J* = 6.4 Hz), 1.25–1.42 (14H, m), 1.57–1.61 (3H, m), 1.70–1.77 (3H, m), 2.12–2.17 (1H, m), 2.76 (2H, s), 3.48 (1H, s), 3.62 (1H, q, *J* = 11.2 Hz), 3.70 (1H, q, *J* = 13.3 Hz), 3.90 (1H, s), 4.23 (1H, d, *J* = 11.0 Hz), 4.57 (1H, d, *J* = 11.0 Hz), 7.22–7.38 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 22.3, 26.1, 34.9, 37.1, 45.1, 54.0, 54.9, 67.3, 70.0, 74.4, 74.8, 127.7, 128.2, 128.3, 128.6, 128.7, 128, 8, 137.8. Found: C, 81.33; H, 8.62; N, 3.11. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(dibenzylamino)propane-1,2-diol (**13a**)

Prepared with **11a** with dibenzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 4:1. Yield: 54%, colorless oil. $[\alpha]_D^{20}$ = −2.0 (c 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.2 Hz), 0.80–1.00 (4H, m), 1.10–1.25 (1H, m), 1.25–1.35 (2H, m), 1.45–1.80 (7H, m), 2.11 (1H, d, *J* = 14.0 Hz), 3.10 (1H, d, *J* = 13.0 Hz), 3.32 (1H, d, *J* = 8.6 Hz), 3.51 (1H, d, *J* = 12.5 Hz), 3.60 (1H, brs), 3.90–4.10 (1H, m), 4.04 (1H, d, *J* = 12.6 Hz), 4.24 (1H, s), 4.30 (1H, d, *J* = 11.1 H), 4.38 (1H, d, *J* = 11.7 Hz), 4.95 (1H, d, *J* = 11.9 Hz), 5.21 (1H, s), 5.91 (1H, s), 7.25–7.62 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 22.2, 26.1, 34.6, 36.9, 46.4, 57.3, 58.3, 59.5, 66.0, 70.2, 74.8, 74.9, 128.1, 128.2, 128.7, 129.4, 129.6, 130.2, 130.4, 131.5, 138.3. Found: C, 78.63; H, 8.27; N, 3.00. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

(*R*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(dibenzylamino)propane-1,2-diol (**13b**)

Prepared with **11b** with dibenzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 4:1. Yield: 7%, colorless oil. $[\alpha]_D^{20}$ = +5.0 (c 0.20, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (3H, d, *J* = 6.5 Hz), 0.84–0.90 (3H, m), 1.26 (3H, s), 1.25–1.29 (1H, m), 1.48–1.55 (1H, m), 1.57–1.62 (1H, m), 1.70–1.80 (3H, m), 2.05–2.13 (1H, m), 2.69 (2H, m), 3.37 (1H, d, *J* = 11.3 Hz), 3.41 (2H, d, *J* = 13.3 Hz), 3.51 (1H, d, *J* = 11.3 Hz), 3.85 (2H, d, *J* = 13.3 Hz), 4.00 (1H, s), 4.25 (11.1 Hz), 4.55 (1H, d, *J* = 11.2 Hz), 7.23–7.49 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 22.3, 26.2, 34.9, 37.0, 59.2, 60.6, 67.2, 69.9, 75.4, 75.6, 127.5, 127.9, 128.6, 128.7, 129.5, 139.0. Found: C, 78.57; H, 8.33; N, 2.94. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

(*S*)-1-(Benzylamino)-3-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)propan-2-ol (**20a**)

Prepared with **19a** and benzylamine at reflux for 6 h and eluted by *n*-hexane:EtOAc = 2:1. Yield: 77%, colorless oil. $[\alpha]_D^{20}$ = +51.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.4 Hz), 0.86-0.95 (2H, m), 1.48-1.51 (1H, m), 1.64–1.76 (4H, m), 2.05–2.08 (1H, m), 2.72 (1H, dd, *J* = 16.4, 11.7 Hz), 3.44 (1H, d, *J* = 9.2 Hz), 3.50 (1H, d, *J* = 9.2 Hz), 3.67 (1H, d, *J* = 13.3 Hz), 3.78 (1H, d, *J* = 13.4 Hz), 3.99 (1H, s), 4.13 (1H, d, *J* = 11.2 Hz), 4.42 (1H, d, *J* = 12.0 Hz), 4.49 (1H, d, *J* = 11.2 Hz), 4.50 (1H, d, *J* = 12.0 Hz), 7.22–7.32 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 22.4, 26.2, 35.0, 37.0, 43.8, 54.3, 55.2, 69.8, 73.6, 73.8, 74.9, 75.6, 127.0, 127.7, 127.8, 128.0, 128.4, 128.5, 128.6, 138.4, 138.5. Found: C, 78.59; H, 8.33; N, 2.98. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

(*R*)-1-(Benzylamino)-3-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)propan-2-ol (**20b**)

Prepared with **19b** and benzylamine at reflux for 6 h and eluted by *n*-hexane:EtOAc = 1:2. Yield: 84%, colorless oil. $[\alpha]_D^{20}$ = +42.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85–0.97 (3H, m), 0.88 (1H, d, *J* = 6.4 Hz), 1.25–1.29 (1H, m), 1.41–1.46 (1H, m), 1.57–1.65 (2H, m), 1.71–1.77 (2H, m), 2.13–2.17 (1H, m), 2.74 (1H, d, *J* = 12.2 Hz), 2.91 (1H, d, *J* = 12.2 Hz), 3.58 (1H, d, *J* = 11.3 Hz), 3.62 (1H, d, *J* = 11.3 Hz), 3.74 (2H, s), 4.10 (1H, s), 4.33 (1H, d, *J* = 10.9 Hz), 4.60 (1H, d, *J* = 10.9 Hz), 7.20–7.35 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 22.3, 26.1, 34.9, 37.0, 53.5, 53.8, 68.9, 70.2, 74.1, 75.2, 127.9, 128.2, 128.3, 128.8, 137.9. Found: C, 75.12; H, 8.70; N, 2.63. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65.

(*S*)-1-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(dibenzylamino)propan-2-ol (**21a**)

Prepared with **19a** and dibenzylamine at reflux for 6 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 67%, white crystal, m.p. = 54–55 °C. $[\alpha]_D^{20}$ = +39.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (3H, d, *J* = 6.5 Hz), 0.79–0.90 (2H, m), 1.39–1.41 (1H, m), 1.57–1.69 (4H, m), 1.97–2.00 (1H, m), 2.70 (1H, d, *J* = 13.9 Hz), 2.77 (1H, d, *J* = 13.9 Hz), 3.33 (1H, d, *J* = 9.1 Hz), 3.49 (1H, d, *J* = 13.7 Hz), 3.60 (1H, d, *J* = 9.1 Hz), 3.77 (1H, d, *J* = 13.7 Hz), 3.80 (1H, d, *J* = 9.7 Hz), 3.87 (1H, s), 4.12 (1H, d, *J* = 11.5 Hz), 4.35 (1H, d, *J* = 16.6 Hz), 4.66 (1H, d, *J* = 16.7 Hz), 4.44 (1H, d, *J* = 11.4 Hz), 7.16–7.31 (20H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 22.4, 26.3, 35.2, 37.4, 45.4, 58.2, 60.0, 69.8, 73.1, 73.4, 75.3, 76.0, 126.9, 127.5, 127.6, 127.8, 127.9, 128.2, 128.3, 128.5, 129.3, 138.7, 138.9, 140.0. Found: C, 80.95; H, 8.03; N, 2.50. Anal. Calcd for $C_{38}H_{45}NO_3$: C, 80.96; H, 8.05; N, 2.48.

(*R*)-1-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(dibenzylamino)propan-2-ol (**21b**)

Prepared with **19b** and dibenzylamine at reflux for 6 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 53%, colorless oil. $[\alpha]_D^{20}$ = +26.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (3H, d, *J* = 6.5 Hz), 0.79–0.83 (3H, m), 1.51–1.58 (4H, m), 1.67–1.76 (3H, m), 1.97–2.01 (1H, m), 2.60 (1H, d, *J* = 13.7 Hz), 2.71 (1H, d, *J* = 13.6 Hz), 3.23 (1H, d, *J* = 8.7 Hz), 3.40 (2H, d, *J* = 13.9 Hz), 3.65 (1H, s), 3.73 (1H, d, *J* = 8.7 Hz), 3.80 (1H, s), 3.88 (2H, d, *J* = 13.9 Hz), 3.96 (1H, d, *J* = 12.7 Hz), 4.17 (1H, d, *J* = 11.9 Hz), 4.34 (1H, d, *J* = 12.0 Hz), 4.40 (1H, d, *J* = 11.3 Hz), 7.17–7.32 (20H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 22.4, 26.2, 35.0, 36.9, 44.3, 57.5, 59.8, 69.5, 72.5, 73.2, 75.9, 76.5, 126.7, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.5, 129.2, 138.5, 138.6, 140.2. Found: C, 81.00; H, 8.10; N, 2.45. Anal. Calcd for $C_{38}H_{45}NO_3$: C, 80.96; H, 8.05; N, 2.48.

(1*S*,2*R*,5*R*)-2-((*S*)-1-(Benzylamino)-3-(Benzyloxy)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**25a**)

Prepared with **25a** and benzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 1:2. Yield: 71%, colorless oil. $[\alpha]_D^{20}$ = +18.0 (c 0.29, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3H, d, *J* = 6.4 Hz), 0.84–0.92 (2H, m), 1.00–1.06 (1H, m), 1.20–1.29 (2H, m), 1.53–1.62 (2H, m), 1.70–1.73 (1H, m), 1.86–1.94 (2H, m), 2.64 (1H, d, *J* = 11.9 Hz), 2.75 (1H, d, *J* = 12.0 Hz), 3.33 (1H, d, *J* = 9.2 Hz), 3.38 (1H, d, *J* = 9.2 Hz), 3.80 (2H, s), 4.23 (1H, s), 4.51 (1H, d, *J* = 16.8 Hz), 4.52 (1H, d, *J* = 16.8 Hz), 7.25–7.35 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 22.4, 26.0, 35.5, 42.4, 48.2, 50.6, 53.8, 64.6, 73.8, 74.7, 75.1, 127.7, 127.9, 128.1, 128.6, 128.7, 128.8, 137.7, 138.1. Found: C, 75.13; H, 8.65; N, 3.70. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65.

(1*S*,2*R*,5*R*)-2-((*R*)-1-(Benzylamino)-3-(Benzyloxy)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**25b**)

Prepared with **25b** and benzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 1:2. Yield: 85%, colorless oil. $[\alpha]_D^{20}$ = +4.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3H, d, *J* = 6.4 Hz), 0.84–0.90 (3H, m), 0.98–1.03 (1H, m), 1.25–1.42 (7H, m), 1.48–1.56 (2H, m), 1.63–1.77 (2H, m), 1.82–1.90 (2H, m), 2.80 (2H, s), 3.37 (1H, d, *J* = 9.3 Hz), 3.53 (1H, d, *J* = 9.3 Hz), 3.77 (2H, s), 4.07 (1H, s), 4.47 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 11.9 Hz), 7.24–7.34 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4, 22.4, 26.0, 29.8, 35.3, 42.3, 46.8, 52.1, 54.2, 66.2, 73.4, 73.6, 75.0, 127.6, 127.9, 128.1, 128.5, 128.7, 128.8, 137.8, 138.6. Found: C, 75.20; H, 8.70; N, 3.63. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65.

(1*S*,2*R*,5*R*)-2-((*S*)-1-(Benzyloxy)-3-(dibenzylamino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**26a**)

Prepared with **25a** and dibenzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 88%, colorless oil. $[\alpha]_D^{20}$ = +23.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (3H, d, *J* = 6.4 Hz), 0.76–0.89 (2H, m), 0.92–0.98 (1H, m), 1.19–1.45 (3H, m), 1.60–1.64 (1H, m), 1.77–1.83 (2H, m), 2.67 (1H, d, *J* = 14.0 Hz), 2.79 (1H, d, *J* = 14.0 Hz), 3.25 (1H, d, *J* = 9.0 Hz), 3.42 (1H, d, *J* = 9.0 Hz), 3.53 (2H, d, *J* = 13.5 Hz), 3.80 (2H, d, *J* = 13.5 Hz), 4.16 (1H, s), 4.33 (1H, d, *J* = 11.7 Hz), 4.39 (1H, d, *J* = 11.7 Hz), 7.21–7.33 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2, 22.4, 25.9, 35.3, 42.1, 46.1, 56.1, 60.3, 66.2, 72.5, 73.5, 74.8, 127.5, 128.0, 128.5, 128.6, 129.5, 137.6, 138.6. Found: C, 78.63; H, 8.33; N, 2.98. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

(1*S*,2*R*,5*R*)-2-((*R*)-1-(Benzyloxy)-3-(dibenzylamino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**26b**)

Prepared with **25b** and dibenzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 88%, colorless oil. $[\alpha]_D^{20}$ = +8.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (3H, d, *J* = 6.3 Hz), 0.77–0.85 (1H, m), 0.88–0.94 (1H, m), 1.29–1.33 (1H, m), 1.39–1.42 (1H, m), 1.49–1.55 (3H, m), 1.64–1.67 (1H, m), 1.77–1.80 (2H, m), 2.82 (1H, d, *J* = 17.0 Hz), 2.83 (1H, d, *J* = 16.9 Hz), 3.16 (1H, brs), 3.18 (1H, d, *J* = 9.1 Hz), 3.34 (1H, d, *J* = 9.1 Hz), 3.61 (2H, d, *J* = 13.5 Hz), 3.72 (2H, d, *J* = 13.5 Hz), 3.76 (1H, brs), 4.06 (1H, s), 4.36 (2H, s), 7.22–7.33 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 22.4, 25.8, 35.4, 42.2, 44.6, 57.0, 60.6, 66.7, 71.7, 73.5, 75.4, 127.5, 128.0, 128.5, 128.7, 129.4, 137.8, 139.1. Found: C, 78.57; H, 8.35; N, 2.93. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

(*S*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(dibenzylamino)propan-2-ol (**30b**)

Prepared with **29** and dibenzylamine at reflux for 20 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 47%, colorless oil. $[\alpha]_D^{20}$ = −40.0 (c 0.255, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.45–0.53 (1H, m), 0.84–0.90 (1H, m), 0.93 (3H, s), 0.96 (3H, d, *J* = 5.5 Hz), 1.04 (1H, q, *J* = 12.0 Hz), 1.23–1.43 (3H, m), 1.55 (3H, s), 2.03–2.08 (1H, m), 2.22–2.26 (1H, m), 2.31 (1H, d, *J* = 13.6 Hz), 2.45 (1H, d, *J* = 13.7 Hz), 3.23 (2H, d, *J* = 13.7 hz), 3.54 (1H, td, *J* = 10.6, 3.9 Hz), 4.18 (2H, d, *J* = 13.6 Hz), 4.39 (1H, d, *J* = 11.0 Hz), 4.66 (1H, d, *J* = 11.0 Hz), 5.25 (1H, s), 7.18–7.35 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 23.6, 26.6, 31.8, 35.8, 40.0, 47.9, 59.8, 61.4, 70.2, 76.8, 81.2, 126.7, 128.1, 128.3, 128.7, 129.5, 137.6, 140.4. Found: C, 81.37; H, 8.35; N, 2.93. Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.33; N, 2.94.

(*S*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(dibenzylamino)propane-1,2-diol (**34a**)

Prepared with **33** and dibenzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 76%, colorless oil. $[\alpha]_D^{20}$ = −126.0 (c 0.30, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.55–0.64 (1H, m), 0.77–0.86 (1H, m), 0.87–0.94 (1H, m), 0.90 (3H, d, *J* = 6.5 Hz), 1.22–1.32 (1H, m), 1.51–1.61 (5H, m), 2.22 (1H, d, *J* = 12.1 Hz), 2.43 (1H, d, *J* = 13.6 Hz), 3.13 (2H, d, *J* = 13.3 Hz),

3.38 (1H, d, *J* = 11.5 Hz), 3.46 (1H td, *J* = 10.5, 3.95 Hz), 3.60 (1H, d, *J* = 11.4 Hz), 4.14 (2H, d, *J* = 13.3 Hz), 4.39 (1H, d, *J* = 11.1 Hz), 4.68 (1H, d, *J* = 11.1 Hz), 7.21–7.38 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 26.0, 31.2, 34.4, 40.0, 49.8, 57.2, 60.6, 67.8, 70.1, 76.7, 80.0, 127.2, 128.2, 128.3, 128.5, 128.8, 129.3, 137.7, 139.2. Found: C, 78.58; H, 8.33; N, 2.94. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

(*S*)-1-(Benzyloxy)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(dibenzylamino)propan-2-ol (**38a**)

Prepared with **37a** and dibenzylamine at reflux for 6 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 80%, colorless oil. $[\alpha]_D^{20}$ = −68.0 (c 0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.52–0.60 (1H, m), 0.79–0.87 (1H, m), 0.89 (3H, d, *J* = 6.5 Hz), 0.89–0.96 (1H, m), 1.20–1.35 (H, m), 1.45–1.55 (3H, m), 1.86 (1H, td, *J* = 12.2, 3.2 Hz), 2.16 (1H, d, *J* = 12.2 Hz), 2.43 (1H, d, *J* = 13.6 Hz), 2.61 (1H, d, *J* = 13.6 Hz), 3.13 (1H, d, *J* = 10.6 Hz), 3.19 (2H, d, *J* = 13.6 Hz), 3.45 (1H, td, *J* = 10.6, 3.9 Hz), 3.71 (1H, d, *J* = 10.6 Hz), 4.04 (2H, d, *J* = 13.6 Hz), 4.34 (1H, d, *J* = 11.2 Hz), 4.42 (1H, d, *J* = 12.1 Hz), 4.63 (1H, d, *J* = 12.2 Hz), 4.64 (1H, d, *J* = 11.2 Hz), 4.77 (1H, brs), 7.16–7.34 (20H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 26.5, 31.5, 34.6, 40.2, 48.6, 57.7, 60.2, 70.0, 73.8, 74.3, 77.7, 80.1, 126.8, 127.4, 127.9, 128.1, 128.2, 128.3, 128.6, 129.2, 138.1, 139.0, 140.0. Found: C, 80.93; H, 8.07; N, 2.50. Anal. Calcd for $C_{38}H_{45}NO_3$: C, 80.96; H, 8.05; N, 2.48.

(*R*)-1-(Benzyloxy)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(dibenzylamino)propan-2-ol (**38b**)

Prepared with **37a** and dibenzylamine at reflux for 6 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 67%, colorless oil. $[\alpha]_D^{20}$ = −37.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82–0.99 (3H, m), 0.93 (3H, d, *J* = 6.5 Hz), 1.29–1.35 (1H, m), 1.44–1.50 (1H, m), 1.55 (1H, brs), 2.00–2.04 (1H, m), 2.17 (1H, dd, *J* = 12.1, 1.4 Hz), 2.39 (1H, d, *J* = 13.7 Hz), 2.62 (1H, d, *J* = 13.7 Hz), 3.29 (2H, s), 3.33 (2H, d, *J* = 13.7 Hz), 3.68 (1H, td, *J* = 10.7, 3.9 Hz), 4.08 (2H, d, *J* = 13.7 Hz), 4.19 (1H, d, *J* = 10.9 Hz), 4.41 (2H, q, *J* = 12.1 Hz), 4.51 (1H, d, *J* = 10.9 Hz), 5.35 (1H, brs), 7.18–7.33 (20H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 26.3, 31.7, 35.1, 40.5, 47.7, 58.0, 59.9, 70.1, 73.7, 74.8, 77.9, 81.6, 126.7, 127.6, 127.9, 128.1, 128.4, 128.6, 129.5, 138.0, 138.7, 140.2. Found: C, 80.95; H, 8.07; N, 2.52. Anal. Calcd for $C_{38}H_{45}NO_3$: C, 80.96; H, 8.05; N, 2.48.

(1*R*,2*R*,5*R*)-2-((*S*)-1-(Benzyloxy)-3-(dibenzylamino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**41a**)

Prepared with **37b** and dibenzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 88%, colorless oil. $[\alpha]_D^{20}$ = −5.0 (c 0.285, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.60–0.69 (1H, m), 0.74–0.83 (1H, m), 0.85–0.95 (1H, m), 0.86 (3H, d, *J* = 6.5 Hz), 1.22–1.32 (1H, m), 1.45–1.55 (2H, m), 1.55 (1H, s), 1.64–1.69 (1H, m), 1.86–1.89 (1H, m), 2.62 (1H, d, *J* = 14.1 Hz), 2.83 (1H, d, *J* = 14.1 Hz), 3.16 (1H, d, *J* = 9.9 Hz), 3.41–3.47 (2H, m), 3.58 (2H, d, *J* = 13.4 Hz), 3.75 (2H, d, *J* = 13.4 Hz), 3.88 (1H, brs), 4.41 (1H, d, *J* = 12.0 Hz), 4.52 (1H, d, *J* = 12.0 Hz), 4.77 (1H, brs), 7.24–7.32 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 25.6, 31.2, 34.7, 44.4, 49.3, 54.9, 60.4, 71.0, 73.6, 74.8, 77.5, 127.4, 127.8, 128.0, 128.5, 128.6, 129.4, 138.2, 139.1. Found: C, 78.58; H, 8.27; N, 2.95. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

(1*R*,2*R*,5*R*)-2-((*R*)-1-(Benzyloxy)-3-(dibenzylamino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**41b**)

Prepared with **37b** and dibenzylamine at reflux for 8 h and eluted by *n*-hexane:EtOAc = 9:1. Yield: 76%, colorless oil. $[\alpha]_D^{20}$ = −22.0 (c 0.28, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.64–0.72 (1H, m), 0.87 (3H, d, *J* = 6.4 Hz), 0.86–0.95 (2H, m), 1.26–1.49 (5H, m), 1.59 (1H, brs), 1.92 (1H, d, *J* = 12.4 Hz), 2.62 (1H, d, *J* = 13.9 Hz), 2.87 (1H, d, *J* = 13.9 Hz), 3.39 (2H, s), 3.51 (1H, d, *J* = 13.4 Hz), 3.70 (1H, td, *J* = 10.3, 4.3 Hz), 3.87 (1H, d, *J* = 13.4 Hz), 4.43 (2H, t, *J* = 12.3 Hz),

7.24–7.32 (15H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 24.5, 31.3, 34.9, 44.7, 50.5, 58.1, 60.1, 71.8, 73.2, 73.7, 76.3, 127.4, 127.8, 128.5, 128.6, 129.4, 138.1, 139.0. Found: C, 78.64; H, 8.33; N, 2.99. Anal. Calcd for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96.

4.2.6. General Procedure for Ring-Opening of Epoxide with Azoles

A solution of epoxides (2.9 mmol) in dry DMF (30 mL) was added to the triazole or imidazole (8.7 mmol) in dry DMF (10 mL) and K_2CO_3 (14.5 mmol). The mixture was kept at reflux temperature for 12–96 h. When the reaction completed (indicated by TLC), the mixture was dissolved in water (15 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was again extracted with saturated NaCl solution (3 × 50 mL) then dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel with $CHCl_3$:MeOH = 19:1, resulting in *O*-benzyl derivatives, respectively.

(*R*)-2-((1R,2S,4R)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-imidazol-1-yl)propan-2-ol (**7a**)

Prepared with **4a** and imidazole at reflux for 24 h. Yield: 42%, colorless oil. $[\alpha]_D^{20}$ = +27.0 (c 0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–0.97 (3H, m), 0.91 (3H, d, *J* = 6.5 Hz), 0.94 (3H, s), 1.23–1.42 (7H, m), 1.68–1.85 (4H, m), 2.22 (1H, dd, *J* = 14.4, 2.2 Hz), 3.82 (2H, d, *J* = 2.8 Hz), 4.07 (1H, s), 4.33 (1H, d, *J* = 11.4 Hz), 4.70 (1H, d, *J* = 11.4 Hz), 6.85 (1H, s), 7.00 (1H, s), 7.25–7.39 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 22.2, 23.3, 26.0, 29.8, 34.8, 36.9, 47.3, 56.2, 69.8, 74.0, 74.6, 120.7, 128.4, 128.5, 128.8, 128.9, 137.6, 138.5. Found: C, 73.10; H, 8.57; N, 8.55. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-imidazol-1-yl)propan-2-ol (**7b**)

Prepared with **4b** and imidazole at reflux for 24 h. Yield: 67%, colorless oil. $[\alpha]_D^{20}$ = +30.0 (c 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–0.94 (1H, m), 0.91 (3H, d, *J* = 6.6 Hz), 0.96–1.02 (1H, m), 1.07 (3H, s), 1.25–1.31 (2H, m), 1.69–1.98 (6H, m), 2.16–2.22 (1H, m), 3.82 (1H, d, *J* = 14.1 Hz), 3.96 (1H, d, *J* = 14.1 Hz), 4.06 (1H, d, *J* = 1.7 Hz), 4.33 (1H, d, *J* = 11.1 Hz), 4.65 (1H, d, *J* = 11.1 Hz), 6.90 (1H, s), 7.02 (1H, s), 7.25–7.26 (5H, m), 7.43 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 22.2, 24.7, 26.0, 34.6, 37.0, 46.4, 55.1, 70.0, 73.8, 75.7, 120.7, 128.1, 128.2, 128.8, 129.0, 137.8, 138.5. Found: C, 73.17; H, 8.62; N, 8.50. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53.

(*R*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**8a**)

Prepared with **4a** and 1,2,4-triazole at reflux for 24 h. Yield: 67%, colorless oil. $[\alpha]_D^{20}$ = +42.0 (c 0.275, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (3H, d, *J* = 6.5 Hz), 0.94 (3H, s), 0.90–0.98 (2H, m), 1.39–1.43 (1H, m), 1.61 (1H, brs), 1.71–1.84 (4H, m), 2.19–2.23 (1H, m), 4.00 (1H, d, *J* = 13.9 Hz), 4.21 (3H, t, *J* = 14.0 Hz), 4.34 (1H, d, *J* = 11.3 Hz), 4.71 (1H, d, *J* = 11.3 Hz), 7.26 (1H, s), 7.31–7.40 (5H, m), 7.89 (1H, d, *J* = 2.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 22.3, 23.6, 26.0, 34.8, 36.9, 47.0, 57.9, 69.9, 74.0, 75.0, 128.4, 128.9, 137.9, 144.4, 151.6. Found: C, 69.30; H, 8.24; N, 12.80. Anal. Calcd for $C_{20}H_{28}N_2O_2$: $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**8b**)

Prepared with **4b** and 1,2,4-triazole at reflux for 24 h. Yield: 67%, colorless oil. $[\alpha]_D^{20}$ = +73.0 (c 0.28, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–1.03 (2H, m), 0.91 (3H, d, *J* = 6.5 Hz), 1.06 (3H, s), 1.37–1.41 (1H, m), 1.56 (1H, s), 1.71–1.90 (4H, m), 2.16–2.21 (1H, m), 3.86 (1H, s), 4.10 (1H, d, *J* = 1.8 Hz), 4.11 (1H, d, *J* = 13.9 Hz), 4.21 (1H, d, *J* = 14.0 Hz), 4.34 (1H, d, *J* = 11.2 Hz), 4.64 (1H, d, *J* = 11.2 Hz), 7.25–7.35 (5H, m), 7.89 (1H, s), 8.06 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 22.3, 24.7, 26.0, 47.0, 57.2, 70.0, 73.7, 75.4, 128.1, 128.7, 137.9, 144.6, 151.5. Found: C, 69.24; H, 8.30; N, 12.73. Anal. Calcd for $C_{20}H_{28}N_2O_2$: $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-imidazol-1-yl)propane-1,2-diol (**14a**)

Prepared with **11a** and 1,2,4-triazole at reflux for 12 h. Yield: 58%, colorless oil. $[\alpha]_D^{20}$ = +44.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (3H, d, *J* = 6.6 Hz), 0.94–1.03 (2H, m), 1.65–1.71 (2H, m), 1.77–1.80 (1H, m), 1.85–1.95 (2H, m), 2.10–2.20 (1H, m), 3.05 (1H, d, *J* = 10.9 Hz), 3.32 (1H, d, *J* = 10.9 Hz), 3.45 (1H, s), 4.00 (1H, d, *J* = 14.0 Hz), 4.06 (1H, d, *J* = 14.0 Hz), 4.33 (1H, d, *J* = 11.1 Hz), 4.63 (1H, d, *J* = 11.1 Hz), 6.92 (1H, s), 6.96 (1H, s), 7.25–7.33 (5H, m), 7.46 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 22.3, 26.0, 34.7, 36.8, 42.7, 50.7, 62.4, 69.9, 75.6, 75.8, 120.9, 128.1, 128.7, 137.7, 138.7. Found: C, 69.77; H, 8.16; N, 8.10. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.

(*S*)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-1,2,4-triazol-1-yl)propane-1,2-diol (**15a**)

Prepared with **11a** and 1,2,4-triazole at reflux for 12 h. Yield: 46%, colorless oil. $[\alpha]_D^{20}$ = +50.0 (c 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–0.93 (1H, m), 0.91 (3H, d, *J* = 6.6 Hz), 0.95–1.05 (2H, m), 1.25–1.29 (1H, m), 1.55 (2H, s), 1.65–1.70 (1H, m), 1.73–1.85 (1H, m), 1.84–1.93 (2H, m), 2.15–2.23 (1H, m), 2.99 (1H, t, *J* = 7.6 Hz), 3.07 (1H, dd, *J* = 12.0, 4.4 Hz), 3.36 (1H, dd, *J* = 11.9, 7.9 Hz), 4.12 (2H, s), 4.28 (1H, d, *J* = 6.9 Hz), 4.32 (1H, d, *J* = 11.2 Hz), 4.64 (1H, d, *J* = 11.1 Hz), 7.25–7.34 (5H, m), 7.92 (1H, s), 8.05 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 22.2, 26.0, 34.6, 36.7, 42.5, 53.7, 64.3, 69.9, 75.2, 75.9, 128.2, 128.8, 137.5, 151.9. Found: C, 66.10; H, 7.83; N, 12.11. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16.

(*S*)-1-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-imidazol-1-yl)propan-2-ol (**22a**)

Prepared with **19a** and imidazole at reflux for 48 h. Yield: 50%, colorless oil. $[\alpha]_D^{20}$ = +47.0 (c 0.20, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (3H, d, *J* = 6.4 Hz), 0.91–0.97 (2H, m), 1.52–1.81 (8H, m), 2.21 (1H, dd, *J* = 14.3, 2.4 Hz), 2.65 (1H, d, *J* = 9.3 Hz), 3.17 (1H, d, *J* = 9.3 Hz), 3.81 (1H, d, *J* = 13.8 Hz), 4.02 (1H, d, *J* = 13.8 Hz), 4.02 (1H, brs), 4.11 (1H, brs), 4.27 (1H, d, *J* = 11.7 Hz), 4.31 (1H, d, *J* = 11.4 Hz), 4.40 (1H, d, *J* = 11.7 Hz), 4.69 (1H, d, *J* = 11.3 Hz), 6.84 (1H, s), 6.98 (1H, s), 7.25–7.40 (11H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7, 22.3, 25.9, 34.6, 36.8, 42.7, 52.5, 69.1, 69.8, 73.2, 75.0, 75.4, 120.8, 127.9, 128.5, 128.6, 128.9, 137.4, 137.9, 138.6. Found: C, 74.63; H, 7.93; N, 6.47. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45.

(*R*)-1-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-imidazol-1-yl)propan-2-ol (**22b**)

Prepared with **19b** and imidazole at reflux for 48 h. Yield: 42%, colorless oil. $[\alpha]_D^{20}$ = +71.0 (c 0.20, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87–0.92 (1H, m), 0.95–1.03 (1H, m), 1.57–1.68 (6H, m), 1.73–1.76 (1H, m), 1.82–1.87 (1H, m), 1.90–1.94 (1H, m), 2.09–1.13 (1H, m), 2.74 (1H, d, *J* = 9.4 Hz), 3.06 (1H, d, *J* = 9.4 Hz), 3.82 (1H, s), 3.93 (1H, d, *J* = 14.0 Hz), 3.95 (1H, d, *J* = 14.1 Hz), 4.04 (1H, d, *J* = 11.1 Hz), 4.08 (1H, d, *J* = 13.9 Hz), 4.19 (1H, d, *J* = 11.7 Hz), 4.53 (1H, d, *J* = 11.7 Hz), 4.50 (1H, d, *J* = 11.1 Hz), 6.90 (1H, s), 6.99 (1H, s), 7.19–7.42 (11H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 22.3, 25.9, 34.5, 36.6, 42.4, 51.6, 69.7, 69.9, 73.2, 75.0, 75.5, 120.9, 128.2, 128.3, 128.6, 128.7, 137.5. Found: C, 74.59; H, 7.87; N, 6.43. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45.

(*S*)-1-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (**23a**)

Prepared with **19a** and 1,2,4-triazole at reflux for 48 h. Yield: 67%, colorless oil. $[\alpha]_D^{20}$ = +52.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89–0.98 (2H, m), 0.90 (3H,

d, *J* = 6.4 Hz), 1.54–1.65 (3H, m), 1.71–7.79 (3H, m), 2.18 (1H, dd, *J* = 14.4, 2.2 Hz), 3.05 (1H, d, *J* = 9.7 Hz), 3.15 (1H, d, *J* = 9.7 Hz), 4.22 (2H, d, *J* = 14.1 Hz), 4.31–4.39 (4H, m), 4.46 (1H, d, *J* = 11.7 Hz), 4.65 (1H, d, *J* = 11.2 Hz), 7.25–7.36 (10H, m), 7.88 (1H, s), 7.94 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 22.3, 26.0, 34.7, 36.8, 43.4, 53.7, 69.9, 71.3, 73.6, 75.1, 75.6, 128.0, 128.1, 128.2, 128.3, 128.5, 128.8, 137.8, 137.9, 144.8, 151.4. Found: C, 71.67; H, 7.69; N, 9.63. Anal. Calcd for $C_{26}H_{33}N_3O_3$: C, 71.70; H, 7.64; N, 9.65.

(*R*)-1-(Benzyloxy)-2-((1*R*,2*S*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (**23b**)

Prepared with **19b** and 1,2,4-triazole at reflux for 48 h. Yield: 67%, colorless oil. $[\alpha]_D^{20}$ = +60.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88–0.94 (2H, m), 0.90 (3H, d, *J* = 6.6 Hz), 0.98–1.02 (1H, m), 1.56 (3H, s), 1.63–1.89 (5H, m), 2.09–2.13 (1H, m), 2.94 (1H, d, *J* = 9.6 Hz), 3.11 (1H, d, *J* = 9.6 Hz), 3.90 (1H, s), 4.00 (1H, s), 4.09 (1H, d, *J* = 11.1 Hz), 4.27 (1H, d, *J* = 11.7 Hz), 4.28 (1H, d, *J* = 15.9 Hz), 4.35 (1H, d, *J* = 14.0 Hz), 4.49 (1H, d, *J* = 11.8 Hz), 4.52 (1H, d, *J* = 11.1 Hz), 7.21–7.37 (10H, m), 7.89 (1H, s), 8.04 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7, 22.3, 26.0, 34.6, 36.7, 42.6, 53.4, 69.8, 70.8, 73.4, 74.9, 75.3, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 137.7, 144.9, 151.3. Found: C, 71.73; H, 7.60; N, 9.68. Anal. Calcd for $C_{26}H_{33}N_3O_3$: C, 71.70; H, 7.64; N, 9.65.

(1*S*,2*R*,5*R*)-2-((*S*)-1-(Benzyloxy)-2-hydroxy-3-(1H-imidazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**27a**)

Prepared with **25a** and imidazole at reflux for 12 h. Yield: 67%, white crystal, m.p. = 118–119 °C. $[\alpha]_D^{20}$ = +11.0 (c 0.30, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3H, d, *J* = 6.2 Hz), 0.92–1.02 (1H, m), 1.12 (1H, t, *J* = 12.2 Hz), 1.56–1.64 (2H, m), 1.74–1.90 (4H, m), 2.95 (1H, d, *J* = 9.4 Hz), 3.40 (1H, d, *J* = 9.4 Hz), 4.00 (1H, d, *J* = 13.9 Hz), 4.11 (1H, d, *J* = 13.9 Hz), 4.21 (1H, s), 4.37 (1H, d, *J* = 11.7 Hz), 4.48 (1H, d, *J* = 11.7 Hz), 6.90 (1H, s), 6.96 (1H, s), 7.25–7.37 (1H, s), 7.43 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0, 22.2, 25.8, 34.7, 42.5, 42.9, 51.4, 68.1, 70.3, 73.5, 75.5, 120.8, 128.1, 128.2, 128.6, 128.7, 137.7, 138.7. Found: C, 69.77; H, 8.15; N, 8.12. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.

(1*S*,2*R*,5*R*)-2-((*R*)-1-(Benzyloxy)-2-hydroxy-3-(1H-imidazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**27b**)

Prepared with **25b** and imidazole at reflux for 12 h. Yield: 83%, white crystal, m.p. = 149–150 °C. $[\alpha]_D^{20}$ = +20.0 (c 0.275, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3H, d, *J* = 6.2 Hz), 0.90–0.95 (1H, m), 1.15 (1H, td, *J* = 12.7, 2.0 Hz), 1.46–1.50 (1H, m), 1.62–1.65 (1H, m), 1.69–1.85 (4H, m), 2.81 (1H, d, *J* = 9.3 Hz), 3.24 (1H, d, *J* = 9.2 Hz), 4.17 (2H, q, *J* = 14.0 Hz), 4.35 (1H, d, *J* = 11.7 Hz), 4.37 (1H, d, *J* = 1.5 Hz), 4.46 (1H, d, *J* = 11.7 Hz), 6.94 (1H, s), 6.97 (1H, s), 7.29–7.37 (5H, m), 747 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3, 22.2, 25.8, 34.7, 42.6, 42.9, 52.4, 67.9, 69.3, 73.4, 75.8, 120.9, 128.0, 128.1, 128.5, 128.6, 137.7, 138.6. Found: C, 69.79; H, 8.22; N, 8.17. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.

(1*S*,2*R*,5*R*)-2-((*S*)-1-(Benzyloxy)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**28a**)

Prepared with **25a** and 1,2,4-triazole at reflux for 12 h. Yield: 83%, colorless oil. $[\alpha]_D^{20}$ = +12.0 (c 0.30, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (3H, d, *J* = 6.4 Hz), 0.92–0.99 (1H, m), 1.07 (1H, td, *J* = 12.0, 1.7 Hz), 1.61–1.66 (2H, m), 1.78–1.91 (4H, m), 0.86 (1H, d, *J* = 9.5 Hz), 2.87 (1H, s), 2.94 (1H, s), 3.46 (1H, d, *J* = 9.6 Hz), 4.22 (1H, s), 4.35–4.46 (4H, m), 7.25–7.37 (5H, m), 7.92 (1H, s), 8.02 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0, 22.2, 25.8, 34.9, 42.5, 43.4, 53.2, 67.5, 70.5, 73.7, 75.9, 128.1, 128.2, 1287, 137.5, 151.9. Found: C, 66.03; H, 7.90; N, 12.20. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16.

(1*S*,2*R*,5*R*)-2-((*R*)-1-(Benzyloxy)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**28b**)

Prepared with **25b** and 1,2,4-triazole at reflux for 12 h. Yield: 83%, colorless oil. $[\alpha]_D^{20}$ = +15.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (3H, d, *J* = 6.3 Hz), 0.87–0.95 (1H, m), 1.10 (1H, td, *J* = 12.6, 1.6 Hz), 1.22–1.29 (1H, m), 1.49–1.52 (1H, m), 1.60–1.64 (1H, m), 1.70–1.81 (2H, m), 1.81–1.87 (2H, m), 2.81 (1H, d, *J* = 9.6 Hz), 3.28 (1H, d, *J* = 9.6 Hz), 4.35–4.52 (5H, m), 7.25–7.36 (5H, m), 7.93 (1H, s), 8.05 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3, 22.2, 25.8, 34.9, 42.6, 43.6, 53.7, 67.6, 70.4, 73.7, 76.3, 128.1, 128.3, 128.7, 137.5. Found: C, 66.10; H, 7.85; N, 12.14. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16.

(*R*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-imidazol-1-yl)propan-2-ol (**31a**)

Prepared with **29** and imidazole at reflux for 96 h. Yield: 38%, colorless oil. $[\alpha]_D^{20}$ = −34.0 (c 0.20, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80–1.01 (2H, m), 0.96 (3H, d, *J* = 6.1 Hz), 1.01 (3H, s), 1.10–1.20 (1H, m), 1.40–1.55 (1H, m), 1.72 (1H, d, *J* = 12.7 Hz), 1.97 (1H, d, *J* = 10.7 Hz), 2.30 (1H, d, *J* = 11.9 Hz), 3.46 (1H, t, *J* = 7.8 Hz), 4.18 (1H, s), 4.35 (1H, d, *J* = 10.9 Hz), 4.50 (1H, s), 4.76 (1H, d, *J* = 10.8 Hz), 7.02 (1H, s), 7.16 (1H, s), 7.31–7.39 (5H, m), 9.26 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 26.0, 31.6, 34.5, 40.1, 49.7, 57.6, 70.6, 73.4, 80.3, 118.2, 122.9, 128.6, 128.7, 129.0, 137.7. Found: C, 73.17; H, 8.60; N, 8.55. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53.

(*S*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-imidazol-1-yl)propan-2-ol (**31b**)

Prepared with **29** and imidazole at reflux for 96 h. Yield: 58%, white crystal, m.p = 170–172 °C. $[\alpha]_D^{20}$ = −48.0 (c 0.21, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87–1.00 (2H, m), 0.95 (3H, d, *J* = 5.4 Hz), 1.05–1.16 (4H, m), 1.32 (1H, s), 1.43 (1H, s), 1.70–1.90 (2H, m), 2.29 (1H, d, *J* = 11.2 Hz), 3.62 (1H, s), 4.19 (1H, brs), 4.39 (1H, d, *J* = 10.9 Hz), 4.70 (1H, d, *J* = 10.9 Hz), 5.65 (1H, s), 7.28–7.38 (7H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 27.5, 31.3, 34.2, 39.5, 48.2, 70.4, 74.4, 80.2, 128.5, 128.6, 128.9. Found: C, 73.10; H, 8.55; N, 8.57. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53.

(*R*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**32a**)

Prepared with **29** and 1,2,4-triazole at reflux for 24 h. Yield: 67%, colorless oil. $[\alpha]_D^{20}$ = −40.0 (c 0.265, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85–0.94 (1H, m), 0.96 (3H, d, *J* = 6.6 Hz), 0.97 (3H, s), 1.05–1.13 (1H, m), 1.40–1.45 (1H, m), 1.50 (1H, td, *J* = 9.7, 3.1 Hz), 1.63 (1H, brs), 1.72 (1H, d, *J* = 13.0 Hz), 1.93 (1H, dd, *J* = 13.2, 3.2 Hz), 2.28 (1H, d, *J* = 12.1 Hz), 3.39 (1H, td, *J* = 10.5, 3.8 Hz), 4.12 (2H, q, *J* = 13.8 Hz), 4.26 (1H, d, *J* = 11.0 Hz), 4.72 (1H, d, *J* = 10.9 Hz), 4.98 (1H, s), 7.26–7.40 (5H, m), 7.88 (1H, s), 7.91 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 23.4, 26.5, 31.5, 34.6, 39.9, 50.8, 57.1, 70.3, 74.4, 80.3, 128.5, 128.6, 129.0, 137.5, 144.8, 151.1. Found: C, 69.32; H, 8.24; N, 12.80. Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76.

(*S*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-1-(1H-1,2,4-triazol-1-yl)propan-2-ol (**32b**)

Prepared with **29** and 1,2,4-triazole at reflux for 24 h. Yield: 83%, colorless oil. $[\alpha]_D^{20}$ = −41.0 (c 0.285, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.78–0.87 (1H, m), 0.89–0.96 (1H, m), 0.93 (3H, d, *J* = 6.5 Hz), 0.97–1.04 (1H, m), 1.13 (3H, s), 1.15–1.21 (1H, m), 1.35–1.45 (1H, m), 1.62 (1H, s), 1.66 (1H, d, *J* = 13.1 Hz), 2.09 (1H, dd, *J* = 12.8, 3.1 Hz), 2.23 (1H, d, *J* = 12.1 Hz), 3.59 (1H, td, *J* = 10.4, 3.8 Hz), 3.99 (1H, d, *J* = 14.2 Hz), 4.26 (1H, d, *J* = 14.1 Hz), 4.39 (1H, d, *J* = 11.0 Hz), 4.67 (1H, d, *J* = 11.0 Hz), 5.46 (1H, s), 7.29–7.35 (5H, m), 7.87 (1H, s), 8.31 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 22.1, 27.0, 31.4, 34.0, 39.5, 47.4, 58.0,

70.2, 74.8, 80.4, 128.3, 128.4, 128.8, 137.2, 145.2, 150.7. Found: C, 69.25; H, 8.28; N, 12.73. Anal. Calcd for $C_{19}H_{27}N_3O_2$: C, 69.27; H, 8.26; N, 12.76.

(*S*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-imidazol-1-yl)propane-1,2-diol (**35a**)

Prepared with **33** and imidazole at reflux for 12 h. Yield: 67%, white crystal, m.p. = 135–136 °C. $[\alpha]_D^{20} = -42.0$ (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92–1.02 (2H, m), 0.96 (3H, d, *J* = 6.5 Hz), 1.03–1.09 (1H, m), 1.35–1.43 (1H, m), 1.69–1.72 (1H, m), 1.83–1.92 (3H, m), 2.27 (1H, d, *J* = 10.9 Hz), 3.21 (1H, d, *J* = 11.3 Hz), 3.32 (1H, td, *J* = 10.6, 4.0 Hz), 3.39 (1H, d, *J* = 11.2 Hz), 3.90 (2H, s), 4.21 (1H, d, *J* = 11.0 Hz), 4.64 (1H, d, *J* = 11.0 Hz), 6.93 (1H, s), 7.02 (1H, s), 7.30–7.39 (5H, m), 7.44 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 26.5, 31.3, 34.4, 40.1, 46.7, 50.5, 65.8, 70.0, 76.3, 79.7, 121.0, 128.5, 128.6, 128.9, 129.0, 137.2, 138.5. Found: C, 69.77; H, 8.17; N, 8.10. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.

(*R*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-imidazol-1-yl)propane-1,2-diol (**35b**)

Prepared with **33** and imidazole at reflux for 12 h. Yield: 50%, colorless oil. $[\alpha]_D^{20} = -45.0$ (c 0.185, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.78–0.87 (1H, m), 0.88–0.96 (1H, m), 0.92 (3H, d, *J* = 6.5 Hz), 1.13–1.19 (1H, m), 1.35–1.41 (2H, m), 1.67 (1H, d, *J* = 13.2 Hz), 1.75 (1H, dd, *J* = 13.1, 2.9 Hz), 1.85–2.10 (2H, m), 2.22 (1H, d, *J* = 12.3 Hz), 3.40 (1H, d, *J* = 11.2 Hz), 3.50 (1H, t, *J* = 11.1 Hz), 3.70 (1H, td, *J* = 10.5, 3.8 Hz), 3.90 (1H, d, *J* = 14.4 Hz), 4.06 (1H, d, *J* = 14.5 Hz), 4.37 (1H, d, *J* = 11.1 Hz), 4.66 (1H, d, *J* = 11.1 Hz), 7.01 (2H, s), 7.25–7.37 (5H, m), 7.54 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 26.7, 31.4, 34.2, 39.9, 45.6, 51.6, 64.7, 70.2, 76.5, 80.0, 121.0, 128.4, 128.5, 128.6, 128.9, 137.1, 138.7. Found: C, 69.73; H, 8.22; N, 8.17. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.

(*S*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-1,2,4-triazol-1-yl)propane-1,2-diol (**36a**)

Prepared with **33** and 1,2,4-triazole at reflux for 12 h. Yield: 58%, colorless oil. $[\alpha]_D^{20} = -32.0$ (c 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88–1.01 (2H, m), 0.97 (3H, d, *J* = 6.5 Hz), 1.07–1.15 (1H, m), 1.39–1.46 (1H, m), 1.70–1.80 (2H, m), 1.95–2.00 (1H, m), 2.30 (1H, dd, *J* = 12.3, 1.5 Hz), 3.28 (2H, dd, *J* = 13.5, 12.2 Hz), 3.46 (1H, td, *J* = 10.5, 4.0 Hz), 4.03 (1H, d, *J* = 14.1 Hz), 4.27 (1H, d, *J* = 11.1 Hz), 4.28 (1H, d, *J* = 14.1 Hz), 4.70 (1H, d, *J* = 11.1 Hz), 7.33–7.42 (5H, m), 7.91 (1H, s), 7.92 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 26.1, 31.2, 34.5, 40.0, 48.2, 52.9, 66.1, 70.0, 76.1, 79.5, 128.7, 129.0, 137.2, 151.2. Found: C, 66.10; H, 7.89; N, 12.12. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16.

(*R*)-2-((1*R*,2*R*,4*R*)-2-(Benzyloxy)-4-methylcyclohexyl)-3-(1H-1,2,4-triazol-1-yl)propane-1,2-diol (**36b**)

Prepared with **33** and 1,2,4-triazole at reflux for 12 h. Yield: 50%, colorless oil. $[\alpha]_D^{20} = -32.0$ (c 0.24, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79–0.97 (3H, m), 0.93 (3H, d, *J* = 6.5 Hz), 1.07–1.17 (1H, m), 1.26 (2H, s), 1.28–1.43 (4H, m), 1.69 (1H, d, *J* = 13.2 Hz), 2.06–2.09 (1H, m), 2.23 (1H, d, *J* = 12.2 Hz), 3.43–3.49 (2H, m), 3.68 (1H, td, *J* = 10.5, 3.9 Hz), 4.23 (1H, d, *J* = 14.4 Hz), 4.35 (1H, d, *J* = 14.3 Hz), 4.36 (1H, d, *J* = 11.0 Hz), 4.66 (1H, d, *J* = 11.1 Hz), 5.50 (1H, brs), 7.25–7.37 (5H, m), 7.91 (1H, s), 8.23 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 26.4, 29.8, 31.3, 34.3, 39.9, 46.2, 54.3, 64.4, 70.2, 76.4, 80.0, 128.4, 128.5, 128.9, 137.1, 150.6. Found: C, 66.03; H, 7.92; N, 12.18. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16.

(*S*)-1-(Benzyloxy)-2-((1*R*,2*R*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)-3-(1H-imidazol-1-yl)propan-2-ol (**39a**)

Prepared with **35a** and imidazole at reflux for 48 h. Yield: 67%, colorless oil. $[\alpha]_D^{20} = -72.0$ (c 0.28, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86–1.10 (3H, m), 0.96 (3H, d, *J* = 6.5 Hz), 1.37–1.42 (1H, m), 1.69 (1H, d, *J* = 12.6 Hz), 1.79 (1H, td, *J* = 12.6, 3.2 Hz), 2.00–2.04 (2H, m), 2.28 (1H, d, *J* = 12.1 Hz), 3.13 (2H, d, *J* = 8.9 Hz), 3.39 (1H, td, *J* = 10.6, 3.9 Hz), 3.83 (1H, d, *J* = 13.9 Hz), 4.07 (1H, d, *J* = 14.0 Hz), 4.24 (1H, d, *J* = 11.0 Hz), 4.33 (1H, d, *J* = 11.8 Hz), 4.43 (1H, d, *J* = 11.8 Hz), 4.70 (1H, d, *J* = 11.1 Hz), 4.82 (1H, brs), 6.90 (1H, s), 7.00 (1H, s), 7.25–7.37 (10H, m), 7.47 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 26.4, 31.4, 34.6, 40.0, 49.0, 51.4, 70.2, 73.6, 75.6, 79.8, 121.4, 127.9, 128.6, 128.9, 137.3, 137.9. Found: C, 74.65; H, 7.93; N, 6.48. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45.

(*R*)-1-(Benzyloxy)-2-((1*R*,2*R*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)-3-(1H-imidazol-1-yl)propan-2-ol (**39b**)

Prepared with **35a** and imidazole at reflux for 48 h. Yield: 83%, colorless oil. $[\alpha]_D^{20} = -48.0$ (c 0.285, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76–0.95 (3H, m), 0.93 (1H, d, *J* = 6.5 Hz), 1.38–1.50 (3H, m), 1.65 (1H, d, *J* = 13.2 Hz), 1.73 (1H, d, *J* = 10.2 Hz), 1.96 (2H, brs), 2.20 (1H, d, *J* = 12.3 Hz), 3.11 (1H, d, *J* = 9.7 Hz), 3.32 (1H, d, *J* = 9.7 Hz), 3.54 (1H, td, *J* = 10.2, 3.8 Hz), 3.96 (1H, d, *J* = 14.0 Hz), 4.12 (1H, d, *J* = 14.1 Hz), 4.16 (1H, d, *J* = 11.0 Hz), 4.34 (1H, d, *J* = 11.9 Hz), 4.49 (1H, d, *J* = 11.9 Hz), 4.56 (1H, d, *J* = 11.0 Hz), 5.17 (1H, s), 7.00 (1H, s), 7.01 (1H, s), 7.21–7.38 (10H, m), 7.55 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 26.7, 31.4, 34.6, 39.8, 48.1, 52.2, 70.1, 72.1, 73.7, 75.3, 80.5, 121.3, 128.2, 128.6, 128.8, 137.2, 137.9, 138.7. Found: C, 74.60; H, 7.87; N, 6.50. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45.

(*S*)-1-(Benzyloxy)-2-((1*R*,2*R*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (**40a**)

Prepared with **35a** and 1,2,4-triazole at reflux for 48 h. Yield: 83%, colorless oil. $[\alpha]_D^{20} = -58.0$ (c 0.265, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84–0.97 (2H, m), 0.94 (3H, d, *J* = 6.5 Hz), 1.04–1.13 (1H, m), 1.38–1.45 (1H, m), 1.67 (1H, d, *J* = 12.8 Hz), 1.78 (1H, td, *J* = 12.5, 3.2 Hz), 1.90–1.94 (1H, m), 2.25 (1H, d, *J* =12.3 Hz), 2.59 (2H, s), 3.18 (1H, d, *J* = 10.0 Hz), 3.32 (1H, d, *J* = 10.0 Hz), 3.43 (1H, td, *J* = 10.6, 3.9 Hz), 4.18 (1H, d, *J* = 14.1 Hz), 4.20 (1H, d, *J* = 10.9 Hz), 4.33 (1H, d, *J* = 14.0 Hz), 4.40 (1H, d, *J* = 11.9 Hz), 4.50 (1H, d, *J* = 11.9 Hz), 4.64 (1H, d, *J* = 10.9 Hz), 5.02 (1H, brs), 7.25–7.36 (10H, m), 7.88 (1H, s), 7.97 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 26.1, 31.4, 34.5, 40.1, 47.7, 54.3, 70.1, 73.1, 73.8, 75.9, 79.5, 127.9, 128.0, 128.4, 128.5, 128.6, 128.9, 137.5, 138.0, 150.5. Found: C, 71.69; H, 7.67; N, 9.66. Anal. Calcd for $C_{26}H_{33}N_3O_3$: C, 71.70; H, 7.64; N, 9.65.

(*R*)-1-(Benzyloxy)-2-((1*R*,2*R*,4*R*)-2-(benzyloxy)-4-methylcyclohexyl)-3-(1H-1,2,4-triazol-1-yl)propan-2-ol (**40b**)

Prepared with **35a** and 1,2,4-triazole at reflux for 48 h. Yield: 83%, colorless oil. $[\alpha]_D^{20} = -57.0$ (c 0.265, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74–0.95 (3H, m), 0.91 (3H, d, *J* = 6.5 Hz), 1.17–1.42 (6H, m), 1.64 (1H, d, *J* = 13.7 Hz), 2.06 (1H, d, *J* = 10.1 Hz), 2.18 (1H, d, *J* = 12.2 Hz), 3.28 (1H, d, *J* = 9.8 Hz), 3.41 (1H, d, *J* = 9.7 Hz), 3.59 (1H, td, *J* = 10.2, 3.8 Hz), 4.19 (1H, d, *J* = 10.9 Hz), 4.27 (1H, d, *J* = 14.3 Hz), 4.40 (1H, d, *J* = 14.3 Hz), 4.41 (1H, d, *J* = 12.0 Hz), 4.55 (1H, d, *J* = 11.9 Hz), 456 (1H, d, *J* = 10.9 Hz), 5.35 (1H, s), 7.21–7.37 (10H, m), 7.89 (1H, s), 8.28 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 26.6, 31.4, 34.5, 39.9, 47.4, 54.8, 70.1, 72.6, 73.8, 75.8, 80.4, 128.0, 128.1, 128.2, 128.4, 128.7, 137.3, 138.0, 150.7. Found: C, 71.73; H, 7.60; N, 9.62. Anal. Calcd for $C_{26}H_{33}N_3O_3$: C, 71.70; H, 7.64; N, 9.65.

(1*R*,2*R*,5*R*)-2-((*S*)-1-(Benzyloxy)-2-hydroxy-3-(1H-imidazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**42a**)

Prepared with **35b** and imidazole at reflux for 12 h. Yield: 58%, white crystal, m.p. = 133–134 °C. $[\alpha]_D^{20}$ = −22.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84–0.92 (1H, m), 0.92 (3H, d, *J* = 6.5 Hz), 0.97–1.07 (2H, m), 1.39–1.47 (1H, m), 1.65–1.77 (2H, m), 1.84–1.88 (1H, m), 1.94–1.97 (H, m), 3.16 (1H, d, *J* = 9.5 Hz), 3.28 (1H, d, *J* = 9.5 Hz), 3.64 (1H, td, *J* = 10.5, 4.2 Hz), 4.11 (1H, d, *J* = 14.3 Hz), 4.20 (1H, d, *J* = 14.2 Hz), 4.38 (1H, d, *J* = 11.8 Hz), 4.48 (1H, d, *J* = 11.8 Hz), 7.00 (2H, s), 7.25–7.35 (5H, m), 7.53 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 26.2, 31.4, 34.6, 45.5, 49.7, 50.6, 72.0, 73.3, 73.7, 76.5, 121.2, 127.9, 128.1, 128.6, 128.7, 137.7, 138.8. Found: C, 69.71; H, 8.16; N, 8.15. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.

(1*R*,2*R*,5*R*)-2-((*R*)-1-(Benzyloxy)-2-hydroxy-3-(1H-imidazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**42b**)

Prepared with **35b** and imidazole at reflux for 12 h. Yield: 58%, colorless oil. $[\alpha]_D^{20}$ = −8.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (1H, q, *J* = 11.6 Hz), 0.89 (3H, d, *J* = 6.4 Hz), 0.99 (1H, d, *J* = 11.6 Hz), 1.26–1.42 (3H, m), 1.64 (1H, d, *J* = 13.3 Hz), 1.69 (1H, d, *J* = 8.5 Hz), 1.91 (1H, d, *J* = 12.1 Hz), 3.38 (1H, d, *J* = 9.7 Hz), 3.57 (1H, d, *J* = 9.6 Hz), 3.80 (1H, t, *J* = 7.4 Hz), 4.02 (1H, d, *J* = 14.2 Hz), 4.16 (1H, d, *J* = 14.2 Hz), 4.49 (1H, d, *J* = 11.9 Hz), 4.55 (1H, d, *J* = 11.8 Hz), 6.98 (1H, s), 6.99 (1H, s), 7.25–7.38 (5H, m), 7.52 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 26.4, 31.5, 34.5, 45.3, 48.3, 52.4, 72.2, 72.5, 73.9, 76.3, 121.1, 127.9, 128.1, 128.3, 128.7, 137.8, 138.7. Found: C, 69.77; H, 8.17; N, 8.10. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.

(1*R*,2*R*,5*R*)-2-((*S*)-1-(Benzyloxy)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**43a**)

Prepared with **35b** and 1,2,4-triazole at reflux for 12 h. Yield: 67%, white crystal, m.p. = 53–54 °C. $[\alpha]_D^{20}$ = −16.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80–0.89 (1H, m), 0.91 (1H, d, *J* = 6.5 Hz), 0.96–1.07 (2H, m), 1.21–1.46 (3H, m), 1.62–1.68 (2H, m), 181–1.85 (1H, m), 1.95–1.99 (1H, m), 3.27 (1H, d, *J* = 9.7 Hz), 3.34 (1H, d, *J* = 9.7 Hz), 3.58 (1H, td, *J* = 10.6, 4.1 Hz), 4.37–4.53 (4H, m), 7.25–7.36 (5H, m), 7.91 (1H, s), 8.17 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 25.8, 31.4, 34.5, 45.4, 48.9, 53.6, 71.7, 72.8, 73.8, 76.5, 127.9, 128.1, 128.6, 137.5, 151.3. Found: C, 66.10; H, 7.85; N, 12.12. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16.

(1*R*,2*R*,5*R*)-2-((*R*)-1-(Benzyloxy)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propan-2-yl)-5-methylcyclohexanol (**43b**)

Prepared with **35b** and 1,2,4-triazole at reflux for 12 h. Yield: 58%, colorless oil. $[\alpha]_D^{20}$ = −6.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.71–0.79 (1H, m), 0.88 (1H, d, *J* = 6.5 Hz), 0.93 (1H, q, *J* = 12.0 Hz), 1.26–1.29 (2H, m), 1.36–1.43 (1H, m), 1.63 (1H, d, *J* = 13.2 Hz), 1.88–1.94 (2H, m), 3.45 (1H, d, *J* = 9.8 Hz), 3.61 (1H, d, *J* = 9.8 Hz), 3.79 (1H, td, *J* = 10.4, 4.1 Hz), 4.37 (1H, d, *J* = 14.3 Hz), 4.41 (1H, d, *J* = 14.3 Hz), 4.50 (1H, d, *J* = 11.9 Hz), 4.56 (1H, d, *J* = 11.9 Hz), 7.26–7.37 (5H, m), 7.89 (1H, s), 8.21 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 26.2, 31.4, 34.5, 45.2, 48.2, 54.7, 72.2, 74.0, 127.9, 128.1, 128.6, 137.7, 145.0, 151.1. Found: C, 66.03; H, 7.90; N, 12.19. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16.

4.2.7. General Procedure for Debenzylation

A suspension of palladium-on-carbon (5% Pd/C, 0.22 g) in MeOH (50 mL) was added to (+)-neoisopulegol-based *O*-benzyl derivatives (14.0 mmol) in MeOH (100 mL) and the mixture was stirred under a H_2 atmosphere (1 atm) at room temperature. After completion

of the reaction (as monitored by TLC, 24 h), the mixture was filtered through a Celite pad and the solution was evaporated to dryness. The crude products were recrystallized in diethyl ether, resulting in primary aminodiols (**9a**–**b**) and aminotriols (**16a**–**b**).

(1*S*,2*R*,5*R*)-2-((*R*)-1-Amino-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**9a**)

Prepared with **5a**. Yield: 91%, white crystal, m.p. = 100–110 °C $[\alpha]_D^{20}$ = +14.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.75–0.85 (2H, m), 0.80 (3H, d, *J* = 5.3 Hz), 0.99 (1H, d, *J* = 12.1 Hz), 1.17 (3H, s), 1.31 (1H, d, *J* = 11.7 Hz), 1.45 (1H, q, *J* = 10.9 Hz), 1.58 (1H, d, *J* = 10.4 Hz), 1.65–1.80 (3H, m), 2.70 (1H, d, *J* = 12.7 Hz), 2.89 (1H, d, *J* = 12.7 Hz), 4.04 (1H, s), 4.95 (1H, brs). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.1, 22.2, 23.3, 25.4, 34.7, 42.8, 45.9, 49.0, 65.1, 71.3. Found: C, 64.09; H, 11.35; N, 7.50. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48.

(1*S*,2*R*,5*R*)-2-((*S*)-1-Amino-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**9b**)

Prepared with **5b**. Yield: 91%, white crystal, m.p. = 138–140 °C. $[\alpha]_D^{20}$ = +10.0 (c 0.25, MeOH). ^{1}H NMR (500 MHz, DMSO–d_6): δ = 0.82 (3H, d, *J* = 5.7 Hz), 0.81–0.88 (1H, m), 1.02 (1H, t, *J* = 12.5 Hz), 1.17 (3H, s), 1.32 (1H, d, *J* = 10.2 Hz), 1.45–1.55 (2H, m), 1.65–1.80 (3H, m), 2.62 (1H, d, *J* = 12.7 Hz), 2.91 (1H, d, *J* = 12.8 Hz), 4.12 (1H, s), 4.86 (1H, brs), 6.85 (3H, brs). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.7, 22.0, 25.1, 25.2, 34.7, 42.4, 45.2, 49.5, 64.3, 70.9. Found: C, 64.15; H, 11.27; N, 7.45. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48.

(*S*)-3-Amino-2-((1*R*,2*S*,4*R*)-2-hydroxy-4-methylcyclohexyl)propane-1,2-diol (**16a**)

Prepared with **12a**, **20a** or **25a**. Yield: 78% (**12a**), 94% (**20a**), 91% (**25a**), white crystal, m.p. = 107–106 °C. $[\alpha]_D^{20}$ = +18.0 (c 0.30, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.80 (3H, d, *J* = 6.6 Hz), 0.79–0.90 (1H, m), 0.93–1.00 (1H, m), 1.38–1.41 (1H, m), 1.45–1.54 (2H, m), 1.60–1.70 (2H, m), 1.73–1.85 (1H, m), 2.60 (1H, d, *J* = 12.6 Hz), 3.30 (2H, q, *J* = 10.9 Hz), 4.07 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.3, 22.4, 25.4, 35.1, 42.3, 44.1, 45.2, 64.4, 65.2, 74.9. Found: C, 59.10; H, 10.38; N, 6.93. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89.

(*R*)-3-Amino-2-((1*R*,2*S*,4*R*)-2-hydroxy-4-methylcyclohexyl)propane-1,2-diol (**16b)**

Prepared with **20b** or **25b**. Yield: 94% (**20b**), 91% (**25b**), white crystal, m.p. = 80–82 °C. $[\alpha]_D^{20}$ = +13.0 (c 0.30, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.80 (3H, d, *J* = 6.6 Hz), 0.82–0.88 (1H, m), 0.94–0.99 (1H, m), 1.44–1.57 (3H, m), 1.64–1.69 (2H, m), 1.73–1.77 (1H, m), 2.57 (2H, q, *J* = 12.7 Hz), 3.32 (1H, d, *J* = 11.0 Hz), 3.39 (1H, d, *J* = 11.0 Hz), 4.00 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.8, 22.4, 25.4, 35.1, 42.4, 44.7, 45.3, 64.2, 64.8, 75.3. Found: C, 59.05; H, 10.43; N, 6.87. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89.

4.3. General Procedure for Antimicrobial Assays

For the antimicrobial analyses the pure compounds were first dissolved in MeOH and diluted with H_2O to two concentration levels (400 μg mL^{-1} and 40 μg mL^{-1}) keeping the final MeOH content at 10%. Then these solutions were investigated in microdilution assay with two Gram-positive bacteria including *Bacillus subtilis* SZMC 0209 and *Staphylococcus aureus* SZMC 14611, two Gram-negative bacteria *Escherichia coli* SZMC 6271 and *Pseudomonas aeruginosa* SZMC 23290, as well as two yeast strains *Candida albicans* SZMC 1533 and *C. krusei* SZMC 1352 according to the M07-A10 CLSI guideline [92] and our previous work [93]. Suspensions of the test microbes were prepared from overnight cultures cultivated in ferment broth (bacteria: 10 g L^{-1} peptone, 5 g L^{-1} NaCl, 5 g L^{-1} yeast extract; yeast: 20 g L^{-1} peptone, 10 g L^{-1} yeast extract, 20 g L^{-1} glucose) at 37 °C. Then the concentrations of the suspensions were set to 2 × 10^5 cells mL^{-1} with sterile media. For the assay, 96-well plates were prepared by dispensing into each well 100 μL of suspension containing the bacterial or yeast cells and 50 μL of sterile broth as well as 50 μL of the test solutions and incubated for 24 h at 37 °C. The mixture of 150 μL broth

and 50 µL of 10% methanol was used as the blank sample for the background correction, while 100 µL of microbial suspension supplemented with 50 µL sterile broth and 50 µL of 10% methanol was applied as negative control. The positive control contained ampicillin (Sigma) or nystatin (Sigma) for bacteria or fungi, respectively, at two final concentration levels (100 µg mL^{-1} and 10 µg mL^{-1}). The inhibitory effects of the derivatives were observed spectrophotometrically at 620 nm after the incubation, and inhibition was calculated as the percentage of the positive control after blank correction.

The MIC was also determined for certain compounds, which were based on the broth microdilution method described above and in the M07-A10 CLSI guideline [92]. The compounds were prepared in two-fold dilutions in 10% MeOH covering the final concentration range of 0.78–100.00 µg/mL. The MIC was observed as the lowest concentration level of the compound that completely inhibits the growth of the organism in microdilution wells as detected by the unaided eye. All experiments were repeated three times.

5. Conclusions

The results of the present study establishing antimicrobial and antifungal behavior of some synthetic derivatives are promising with respect to possible clinical application. It is strongly believed that it will serve a suitable basis for future research on developing alternative antibiotics focusing on the development of better antibiotics against infectious organisms. The obtained results indicate that the di-*O*-benzyl derivatives may have considerable potential for therapeutic application as novel drug candidates against bacterial and fungal infections. Based on the results obtained, some of the studied compounds have proved to be promising candidates for additional efficacy evaluation.

Furthermore, in vitro studies have clearly shown that the *O*-benzyl substituent on the cyclohexyl ring in aminodiol and aminotriol derivatives is essential to have an antimicrobial effect whereas the stereochemistry of the *O*-benzyl substituent on the cyclohexane ring in the aminodiol and aminotriol function has no influence on the antimicrobial effect.

In addition, the antifungal activity was found to be affected by the stereochemistry of the derivatives, namely the *S*-isomers were more potent than the corresponding *R*-isomers against fungi while the antibacterial effect did not distinguish between the different stereoisomers.

In the next stage of our project, we plan to obtain *N*-benzyl and imidazole *O*-benzyl analogs, preferably different substitutions on *N*-benzyl and imidazole systems, to increase their antimicrobial activities on various microorganisms. For the optimized compounds, additionally, docking studies and molecular dynamics study will also be performed to get an insight into the dynamics of ligand interaction.

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Author Contributions: Z.S. and A.S. conceived and designed the experiments; T.M.L., T.H. and F.Z.B. performed the experiments, analyzed the data, and wrote the experimental part; Z.S., F.F. and A.S. discussed the results and contributed to manuscript writing. All authors have read and agreed to the published version of the manuscript.

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III.

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Antiproliferative Activity of (−)-Isopulegol-based 1,3-Oxazine, 1,3-Thiazine and 2,4-Diaminopyrimidine Derivatives

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A series of novel heterocyclic structures, namely 1,3-oxazines, 1,3-thiazines and 2,4-diaminopyrimidines, were designed and synthesised. The bioassay tests demonstrated that, among these analogues, 2,4-diaminopyridine derivatives showed significant antiproliferative activity against different human cancer cell lines (A2780, SiHa, HeLa, MCF-7 and MDA-MB-231). Pyrimidines substituted with N^2-(*p*-trifluoromethyl)aniline, in particular, displayed a potent inhibitory effect on the growth of cancer cells. Structure–activity relationships were also studied from the aspects of stereochemistry on the aminodiol moiety as well as exploring the effects of substituents on the pyrimidine scaffold.

Introduction

2-Amino-1,3-diol derivatives, important functional motifs, are found in a diverse range of bioactive natural products. Sphingoid bases,[1] sphinganines and clavaminol derivatives,[2,3] among others, play unique and crucial roles in many physiological processes. In particular, sphingolipids have been reported to be involved in cell recognition and signal transduction and exhibit prominent antitumor, immune-modulatory and immunosuppressive activities.[4] In addition, many synthetic compounds have 3-amino-1,2-diol moieties in their backbones, including the antitumor agent aminocyclopentitol pactamycin, the proteasome inhibitor TMC-95 A, the immunosuppressant antibiotic myriocin, riboflavin (vitamin B2) and the hydrogenase coenzyme F420.[5] Besides being of pharmacological interest, 3-amino-1,2-diols have proven to be excellent building blocks for the synthesis of various heterocyclic compounds such as 1,3-oxazine,[6,7] 1,3-thiazine[8] and pyrimidines.[9]

Pyrimidines belong to an important class of heterocyclic structures found in many synthetic and naturally occurring products with a remarkable spectrum of biological activities.[10–15] Several valuable reviews illustrate the medicinal and therapeutic properties of pyrimidine derivatives.[16–18] Among the existing large numbers of structurally diverse pyrimidine derivatives, 2,4-diaminopyrimidines have attracted considerable attention due to their important chemopreventive and chemotherapeutic effects.[19–37] This structural motif is involved in numerous biological activities – mainly concerning cancer – with action mechanisms related to folate metabolism inhibition,[38] kinase inhibitor activity[26,39–44] and apoptosis induction.[22,45,46] For example, Ceritinib (Zykadia™),[47] Alectinib (Alecensa™),[48] Brigatinib (Alunbrig™),[49] Lorlatinib, (Lorbrena™),[50] small-molecule antineoplastic anaplastic lymphoma kinase (ALK) inhibitors, and others are used for the treatment of patients with non-small cell lung cancer. More interestingly, a number of pyrimidine derivatives have recently been identified to have the capacity to inhibit growth of the Aurora kinase-associated tumors, including VX-680 (tozasertib)[51] and AZD-1152 (barasertib).[52,53]

Furthermore, 2,4-diaminopyrimidine-derived drugs with extensive biological activities, such as anti-obesity,[54] antiviral,[55] antiparasitics,[56–59] antibacterial,[60,61] analgesic,[62] and anti-inflammatory[63–65] effects have also received consideration in the field of drug design and development in recent years.

On the other hand, 1,3-thiazine derivatives, an important class of heterocyclic compounds, have a wide range of biological properties[66,67] including antiproliferative,[68–72] analgesic,[73] anticonvulsant,[74,75] anti-inflammatory,[76] antibiotic,[77] antimicrobial,[75,78–80] antimalarial,[81] and antihypertensive[82] properties. A literature survey revealed that also 1,3-oxazine moieties exhibit a broad range of pharmacological activities,[83,84] such as anticancer,[85–89] antimicrobial[90,91] and anti-inflammatory[92,93] effects, which showed their potential value in developing new therapeutic agents.

Based on the above consideration and in a continuation of our interest in the synthesis of heterocyclic compounds with anticancer activity,[68,94,95] starting from isopulegol-derived aminodiols, a new series of 1,3-oxazines, oxazoles, 1,3-thiazines, thiazoles and 2,4-diaminopyrimidine derivatives was designed,

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synthesised and trsted for their antiproliferative activities using in vitro assay against different cancer cell lines.

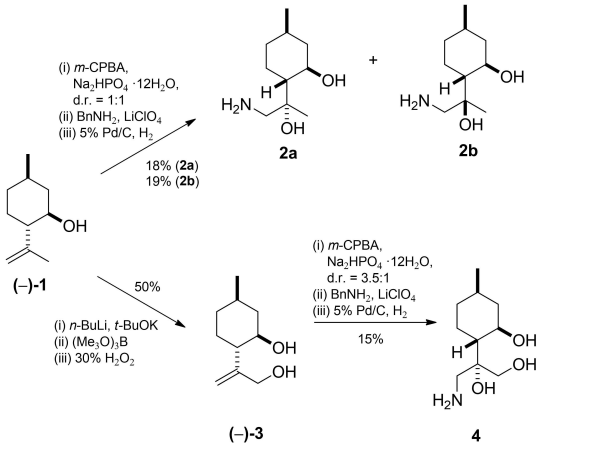
Results and Discussion

The synthetic routes started with the preparation of building blocks such as aminodiols, aminotriols and amino alcohols as key intermediates. In the first step, aminodiols **2a**, **b** were obtained from commercially available (−)-isopulegol **1** by a three-step sequence including epoxidation with *m*-CPBA followed by ring-opening of the corresponding oxiranes with benzylamine and subsequent hydrogenolysis on 5% Pd/C.[96] Moreover, regioselective oxidation of **1** gave diol **3**,[97] which was transformed to primary aminotriol **4** according to a literature method (Scheme 1).[96]

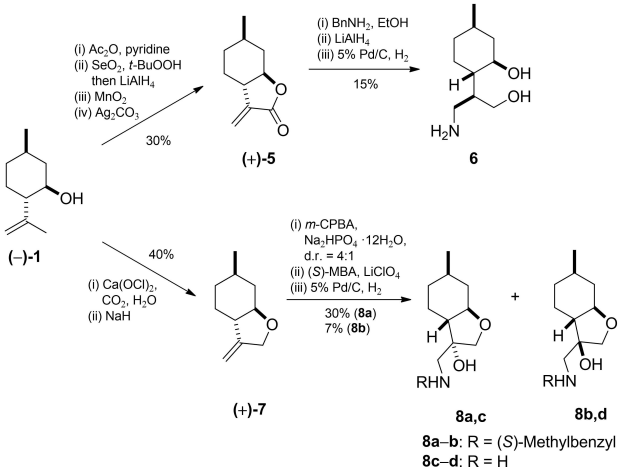
Furthermore, diol **3** was subsequently converted into (+)-α-methylene-γ-butyrolactone **5** through a two-step oxidation and ring closure of the γ-hydroxy-substituted α,β-unsaturated carboxylic acid thus obtained.[98] Reduction of the β-amino lactone, produced by nucleophilic addition of benzylamine to **5**, with $LiAlH_4$ followed by debenzylation of the resulting secondary aminodiol over 5% Pd/C gave primary aminodiol **6**.[96] On the other hand, allylic chlorination of (−)-**1** and subsequent cyclisation produced *exo*-methylene tetrahydrofuran **7**.[99] The epoxidation of **7** with *m*-CPBA delivered a 4:1 mixture of epoxides, which was then treated with (*S*)-methylbenzylamine [(*S*)-MBA] to provide primary aminoalcohols **8c**–**d** after debenzylation via hydrogenolysis of corresponding secondary aminoalcohols **8a**, **b** over 5% Pd/C (Scheme 2).[100]

In the same manner, (+)-neoisopulegol-based aminodiols[101] and an aminoalcohol[100] were also prepared from (+)-neoisopulegol **9**, obtained from (−)-**1** in two steps by Jones oxidation of the hydroxy group followed by stereospecific reduction of (*S*)-isopulegone over a stoichiometric amount of L-selectride at −78 °C in THF into the desired *cis* diastereoisomer (Scheme 3).[98]

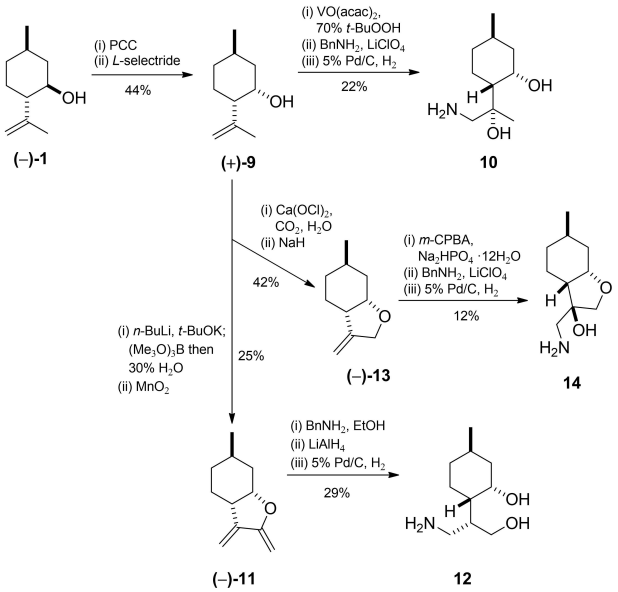
With key intermediates in hand, the synthesis of 1,3-oxazine[94] and 1,3-thiazine[68] derivatives was carried out by different transformations.[102] Rapid conversion of aminodiols **2a**, **6**, **10** and **12** with phenyl isothiocyanate in toluene at room temperature provided the corresponding thiourea adducts **15a**–**d** in moderate yields. The transformation of **2b**, however, was an exception since no product formation was observed under the applied conditions. This is probably due to steric hindrance exerted by both the methyl substituent at the α position and the neighboring hydroxy group of the aminodiol moiety in **2b**.[96] In the next step, the acid-catalysed cyclisation of thiourea derivatives **15a**–**d** could be carried out in one step to yield 1,3-thiazines. Interestingly, during the ring-closure process with 22% HCl in EtOH under the applied conditions, thiourea adducts **15b**, **d** were preferentially transformed into 2-phenylimino-1,3-thiazines **16a**, **b**. In contrast, **15a**, **c** did not react as a result of steric hindrance of the methyl group at the



Scheme 1. Preparation of (−)-isopulegol-based aminodiols **2a**, **b** and aminotriol **4**.



Scheme 2. Preparation of (−)-isopulegol-based aminodiol **6** and aminoalcohols **8a**, **b**.



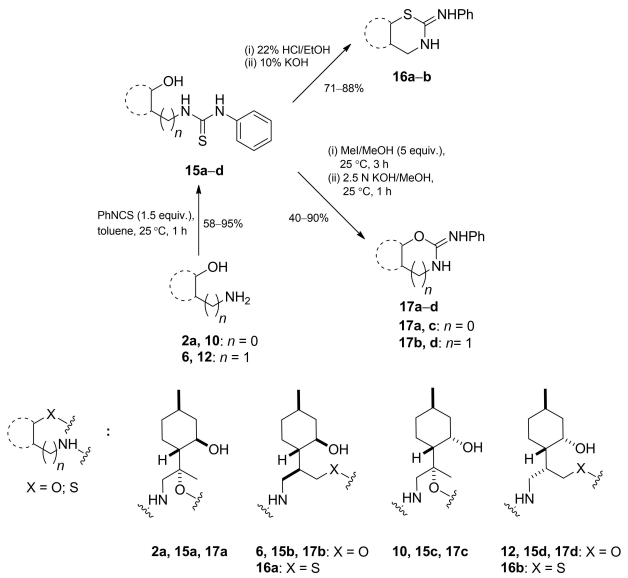
Scheme 3. Preparation of (+)-neoisopulegol-based aminodiols **10**–**12** and aminoalcohol **14**.

α position. We also noticed in our previous work that the cyclisation could be conveniently carried out in the case of thioureas with sterically less hindered structures.[68] On the other hand, treatment of **15a–d** with MeI gave thioethers, which were easily transformed in alkaline medium to 2-phenylimino-oxazoles (**17a,c**) or 2-phenylimino-1,3-oxazines (**17b**, **d**) (Scheme 4).

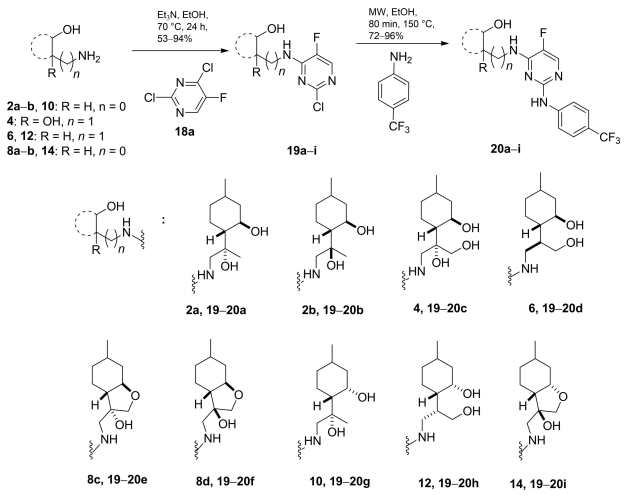
In addition to the importance of monoterpene-fused 2-phenylimino-1,3-oxazines and 1,3-thiazines as antiproliferative agents, a recent report also highlight the anticancer potential of the pyrimidine-based structures.[17] Consequently, we decided to convert primary aminodiols **2a**, **b**, **6**, **10**, **12** and aminotriol **4** as well as aminoalcohols **8a**, **b** and **14** into their pyrimidine scaffolds. Addition of 2,4-dichloro-5-fluoropyrimidine **18a** to these building blocks in the presence of Et_3N in EtOH provided 5-fluoro analogues **19a–i**.[103] These were then applied in microwave-assisted S_NAr coupling reactions with 4-aminobenzotrifluoride in EtOH at 150 °C to produce **20a–i** as solid precipitates in good yields (Scheme 5).[104]

Due to the anticancer potential of pyrimidines substituted at various positions as well as fused with other heterocyclic rings,[105] coupling reactions were performed by utilising 2,4,5-trichloropyrimidine **18b** and 5-amino-4,6-dichloropyrimidine **18c** as reagents. The desired (−)-isopulegol-based pyrimidines **21a–h** and **23a–h** were formed in good yields. In the next step, conversion of **21a–g** with 4-aminobenzotrifluoride smoothly provided analogues **22a–h** in excellent yields. The next couplings at the remaining chlorine at position 6 in adducts **23a–h**, in turn, were unsuccessful either under standard heating or microwave-assisted conditions. This is probably due to the steric effect of the amino group at the *ortho* position, making **23a–h** unable to establish the desired interactions (Scheme 6).[35,106]

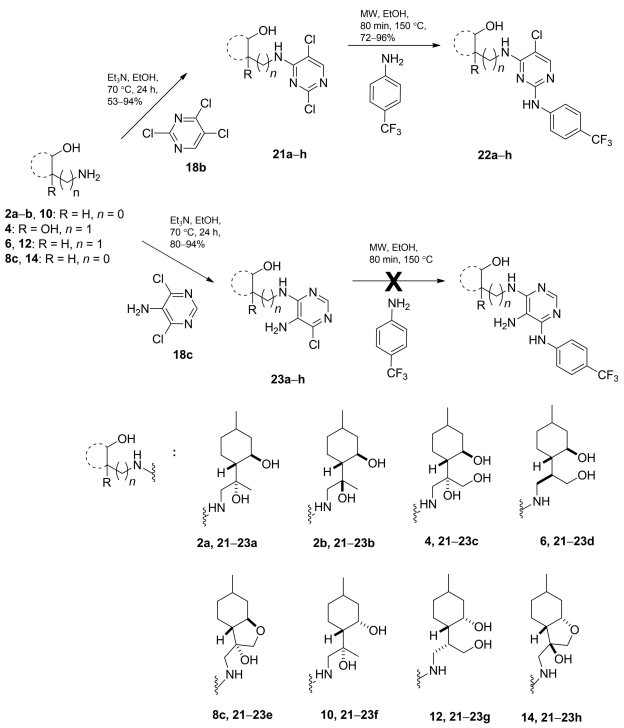
The novel heterocyclic compounds, namely 1,3-thiazines **16a,–b**, 1,3-oxazines **17a–d** and diaminopyrimidine analogues **19–23** were investigated for their in vitro antiproliferative properties on a panel of different human cancer cell lines (HeLa, SiHa, A2780, and MDA-MB-231). The results of MTT assays are presented in Table S1 in the Supporting Information, while selected results (over 70% inhibition) of the best compounds are given in Figure 1. HeLa and A2780 cells were generally more sensitive to the tested substances than the other two cell lines. (−)-Isopulegol-based 2,4-diaminopyrimidines **19–22** were found to show substantial effects of the tested compounds, exhibiting cell growth-inhibiting capacities comparable to that of the reference agent cisplatin. Among them, 2,4-diaminopyrimidines **20a–i** and **22a–h** containing the N^2-(trifluoromethyl)phenyl



Scheme 4. Preparation of (< M-)-isopulegol-based thiazines **16a**, **b** and oxazines **17a–d**.



Scheme 5. Preparation of (−)-isopulegol-based pyrimidine derivatives **19–20**.



Scheme 6. Preparation of (−)-isopulegol-based pyrimidine derivatives **21–23**.

group favoured the action, while the absence of this substituent on **19a–i** and **21a–h** led to a generally lesser potency. These results indicate that the introduction of a N^2-aryl function into the 2,4-diaminopyrimidine skeleton has a significant impact on their efficacy. Since no substantial difference was observed between the effects of **20b** and **22b**, the type of halogen substituent at the 5 position on the pyrimidine scaffold also seems irrelevant. On the other hand, pyrimidine analogues **22a**, **b**, **22d**, **22f**, **22g** were highly effective, indicating that the aminodiol system is an essential part of the molecule. Among the series of pyrimidine derivatives derived from aminodiols, antiproliferative activities were influenced by the aminodiol structure. Overall, aminodiols with the presence of a methyl group (**22a**, **b**, **22f**) resulted in higher effects against all tested cell lines than the corresponding compounds without a methyl group in the aminodiol moiety (**22d**, **22g**). This illustrates that the methyl group may be helpful to increase the cytotoxicity of this compound class. Replacement of the aminodiol system of **22a** by an aminotriol moiety (**22c**) was detrimental for antiproliferative inhibitory activity owing to the introduction of water-solubilising groups to reduce cell permeability,[104] while replacing both aminodiol moieties in **22a** with an amino-alcohol, such as **22e**, produced a similar effect, demonstrating the crucial role of a building block for the design and synthesis of novel antiproliferative agents. Furthermore, the comparison of the antiproliferative activities of **22a** and **22f** as well as those of **22a** and **22b** confirmed that both the stereochemistry of the aminodiol and the presence of the hydroxy moiety on the cyclohexane ring have influence on antiproliferative activity. Considering the effect of the stereochemistry of the OH group on the alkyl chain to the antiproliferative activity, aminodiol **22b** with *R* configuration was found to be more effective compared to its corresponding isomer (**22a**), whereas the stereochemistry of the hydroxy substituent on the cyclohexane ring in the aminodiol function did not contribute to activity improvement.

The effects of the most promising analogues (**20b** and **22b**) are comparable to that of the reference agent cisplatin, as reflected in their calculated IC_{50} values (Figure 1 and Table S1 in the Supporting Information).

Although the interactions between 2,4-diaminopyrimidine scaffolds containing the N^2-(*p*-trifluoromethyl)phenyl group and Aurora A have already been studied on the molecular level using X-ray crystallography,[104] molecular docking simulations could also enable us to comprehend the binding pattern between ligand and protein intuitively. These key interactions contribute to the high in vitro potency of compound **20b**. A docking study using Discovery Studio 2.5 was thus conducted investigate the possible interactions between compound **20b** and Aurora A kinase PDB (Code: 4DEE).

The 2D diagram of key binding interactions of hit (compound 20b) with Aurora A (Figure 2) shows that the methylcyclohexyl moiety forms hydrophobic alkyl interaction with a hydrophobic pocket formed by Phe144, Leu164 and Lys162, while the aromatic ring has a variety of pi-alkyl interaction with another hydrophobic pocket Leu139, Val147 and Leu263. The amine group of aminodiol also creates a significant hydrogen

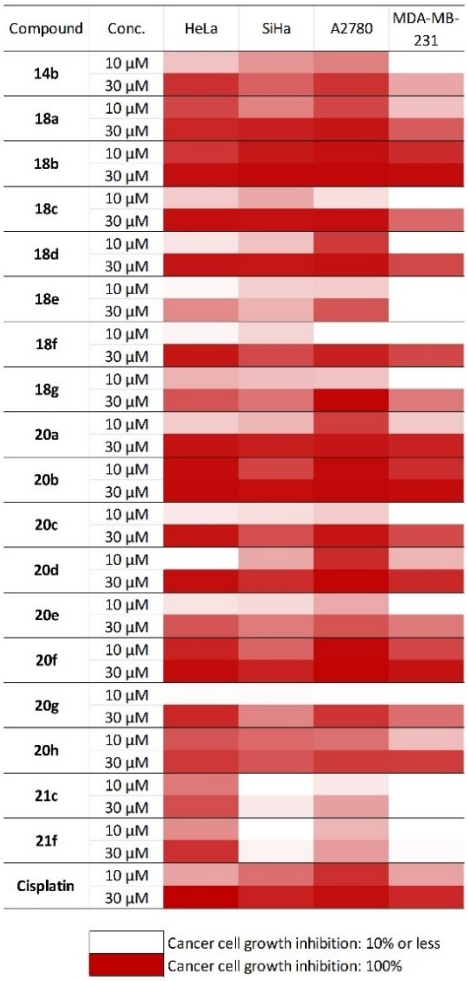


Figure 1. Antiproliferative properties of the selected isopulegol-based pyrimidine derivatives.

bond with Lys141. These key interactions contribute to the high in vitro potency of compound 20b.

The molecular properties of **20b** were determined and the results show that compound **20b** meets Lipinski's rules of five. Furthermore, an in-silico ADMET study confirmed that this compound has good absorption through human intestinal. Additionally, it is proposed to exhibit low ability to penetrate the blood–brain barrier (BBB), as shown in the Supporting Information.

Conclusion

A library of heterocylic compounds such as 1,3-oxazines, oxazoles, 1,3-thiazines, thiazoles and 2,4-diaminopyrimidines, was prepared from commercially available (−)-isopulegol.

The in vitro pharmacological studies showed that 2,4-diaminopyrimidines exerted antiproliferative action on different human cancer cell lines. Among them, aminodiols based on N^2-(*p*-trifluorophenyl)amino and N^4-(−)-isopulegol, simultaneously

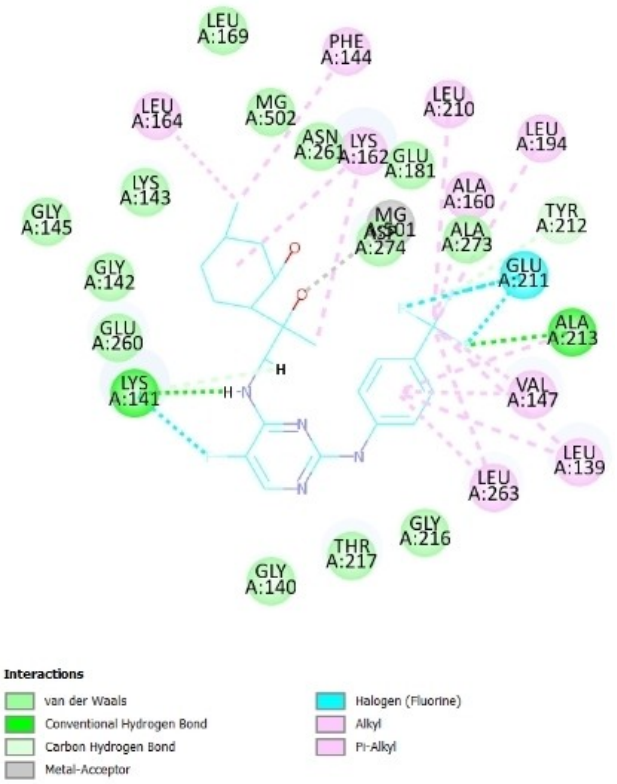


Figure 2. 2D diagram of key binding interactions of hit (compound **20 b**) with Aurora A.

incorporating diaminopyrimidines, proved to be more potent than the clinically used anticancer agent cisplatin.

Furthermore, the in vitro experiments also clearly demonstrated that the stereochemistry of the hydroxy substituent on the cyclohexane ring in the aminodiol moiety has no influence on the antiproliferative effect, whereas the inhibitory activity was found to be affected by the stereochemistry of the alkyl chain. *R*-isomers were more potent than the corresponding *S*-isomers against different cancer cell lines

Preliminary exploration indicated that compounds **20 b** and **22 b** have great promise against different cancer cell lines. To our delight, molecular docking results exemplified that **20 b** could foster potent affinity by forming significant hydrogen and hydrophobic interactions with Aurora A kinase (PDB Code: 4DEE), a target for anticancer drugs in preclinical models.[104] In summary, compounds **20 b** and **22 b** can be regarded as new potential inhibitors. Further studies will be performed and reported in the future. Therefore, in the next stage of our project, we plan to obtain N^2-substituted aryl analogues, preferably with different substitutions on *N*-phenyl systems, to improve their antiproliferative activities on a panel of different cancer cell lines. Additionally, docking studies and molecular dynamics studies with the optimised derivatives will also be performed to get an insight into the dynamics of ligand interaction.

Experimental Section

General methods: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer (500 and 125 MHz, respectively, $\delta = 0$ ppm (TMS)). Chemical shifts (δ) are expressed in [ppm] relative to TMS as internal reference. *J* values are given in [Hz]. HRMS flow injection analysis was performed with a Thermo Scientific Q Exactive Plus hybrid quadrupole-Orbitrap (Thermo Fisher Scientific, Waltham, MA, USA) mass spectrometer coupled to a Waters Acquity I–Class UPLC™ (Waters, Manchester, UK). Optical rotations were determined with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and they are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness). Commercially available reagents were used as obtained from suppliers (Molar Chemicals Ltd., Halásztelek, Hungary; Merck Ltd., Budapest, Hungary and VWR International Ltd., Debrecen, Hungary), while solvents were dried according to standard procedures.

Starting materials: (−)-Isopulegol (**1**) is commercially available from Merck Co with *ee* = 95 %, ([α]20 D = −22.0, neat) and its enatiomer (+)-**1** (*ee* = 90 %, [α]20 D = + 22.0, neat). (+)-Neoisopulegol (**2**) ([α]20 D = + 28.7, c = 17.2, $CHCl_3$) and its enatimomer (−)-**2** ([α]20 D = −22.2, c = 2.0, $CHCl_3$) were synthesized from (−)-**1** and its isomer (+)-**1** following a reported procedure, respectively.[107] (−)-Isopulegol- based aminodiols **2 a**, **b** and **6**,[96] (+)-neoisopulegol-based aminodiols **10** and **12**[101] together with aminotriol **4**[96] as well as aminoalcohols **14**[100] were prepared according to literature procedures. All spectroscopic data were similar to those described therein.

Docking Study: Aurora A kinase crystal structure was obtained from PDB (protein data bank). ChemBioDraw Ultra 11.0 was used to design the compound for the docking study. The docking study and in silico ADMET predictions were performed by Accelrys discovery studio 2.5 software.

Choosing the template crystal structure: Aiming to choose the most valid crystal structure to be used in our study, we first downloaded the available Aurora A crystal structure from PDB.

Preparation of the crystal structure of Aurora A: It is well known that the extracted crystal structure from PDB does not have hydrogen atoms, so firstly, hydrogen atoms must be added by applying several force fields (CHARMm). Adding hydrogen atoms leads to steric hindrance and subsequently to high energy and unstable molecule, which should be minimised. Minimisation of the crystal structure was performed by using adopted basis minimisation aiming at finding the most stable and least energy structure and reducing H–H interactions without affecting the basic protein skeleton atoms. Then, the active site was determined and the sphere surrounded.[108]

Docking study (CDocker): By using CDocker method, we can generate all the possible conformations of the compound in the protein active site. Then the results can be assessed by both the CDocker energy and the number of interactions between the ligand and active site. This method requires preparing the crystal structure (as mentioned before) and preparing the designed compound by using Accelrys Discovery Studio protocol and applying force field.[109]

Before starting this study, it is important to make sure that the used method is valid by comparing the conformation of the reference compound with its conformations generated by the docking method, where RMSD (Root Mean Square Deviation) should not exceed 2 Å.

(3S,3aR,6R,7aR)-6-Methyl-3-((((S)-1-phenylethyl)amino)methyl)octahydrobenzofuran-3-ol (**8a**) *and (3R,3aR,6R,7aR)-6-Methyl-3-((((S)-1-phenylethyl)amino)methyl)octahydrobenzofuran-3-ol* (**8b**)

m-CPBA (70% purity, 5.87 g, 23.8 mmol) was added at 0 °C to a solution of **7** (11.9 mmol) in CH_2Cl_2 (50 mL) and $Na_2HPO_4 \cdot 12H_2O$ (6.35 g, 35.7 mmol) in water (130 mL), and the mixture was stirred at room temperature. When the reaction was complete, as indicated by TLC (2 h), the mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with a 5% KOH solution (3×50 mL), then dried (Na_2SO_4) and evaporated to provide a 4:1 mixture of epoxides as a pale-yellow oil, which was added to the solution of (*S*)-methylbenzylamine (0.80 mL, 6.20 mmol) in MeCN (30 mL) and $LiClO_4$ (0.31 g, 2.94 mmol). The mixture was kept at reflux temperature for 6 h. When the reaction was completed (indicated by TLC), the mixture was evaporated to dryness, and the residue was dissolved in water (15 mL) and then extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on silica gel with an appropriate solvent mixture ($CHCl_3$:MeOH = 19:1) to provide **8a** and **8b**.

8a: Yellow crystals (33%); m.p. 54–55 °C; $[\alpha]20$ D = −51.0 (c 0.1275, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

8b: White crystals (8%); m.p. 68–69 °C; $[\alpha]20$ D = −46.0 (c 0.21, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3S,3aR,6R,7aR)-3-(Aminomethyl)-6-methyloctahydrobenzofuran-3-ol (**8c**) *and (3R,3aR,6R,7aR)-3-(Aminomethyl)-6-methyloctahydrobenzofuran-3-ol* (**8d**)

Aminoalcohols **8a–b** (14.0 mmol) in MeOH (100 mL) were added to a suspension of palladium-on-carbon (5% Pd, 0.22 g) in MeOH (50 mL), and the mixture was stirred under an H_2 atmosphere (1 atm) at room temperature. After completion of the reaction (as monitored by TLC, 24 h), the mixture was filtered through a Celite pad, and the solution was evaporated to dryness. The crude product was recrystallised in Et_2O, resulting in primary aminoalcohols **8c–d** as white crystals.

8c: White crystals (90%); m.p. 190–192 °C; $[\alpha]20$ D = −3.0 (c 0.26, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

8d: White crystals (87%); m.p. 193–196 °C; $[\alpha]20$ D = −12.0 (c 0.14, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

General procedure for the preparation of thioureas (15a–d): Aminodiols **2a, 6, 10** and **12** (0.53 mmol) and the appropriate phenylisothiocyanate (0.79 mmol) were dissolved in toluene (40 mL), and the mixture was stirred at room temperature for 1 h, except that in the case of **6** when a treatment at reflux temperature for 3 h was carried out. The resulting mixtures were then evaporated then the residue was purified by column chromatography on silica gel (eluted with $CHCl_3$:MeOH = 19:1).

1-((S)-2-Hydroxy-2-((1R,2R,4R)-2-hydroxy-4-methylcyclohexyl)propyl)-3-phenylthiourea (**15a**): Prepared from **2a**. White crystals (95%); m.p. 162–163 °C; $[\alpha]20$ D = −33.0 (c 0.28, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

1-((R)-3-Hydroxy-2-((1S,2R,4R)-2-hydroxy-4-methylcyclohexyl)propyl)-3-phenylthiourea (**15b**): Prepared from **6**. White crystals (58%); m.p. 97–98 °C; $[\alpha]20$ D = −22.0 (c 0.28, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

1-((S)-2-Hydroxy-2-((1R,2S,4R)-2-hydroxy-4-methylcyclohexyl)propyl)-3-phenylthiourea (**15c**): Prepared from **10**. Yellow oil (61%); $[\alpha]20$ D = −5.0 (c 0.295, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

1-((S)-3-Hydroxy-2-((1S,2S,4R)-2-hydroxy-4-methylcyclohexyl)propyl)-3-phenylthiourea (**15d**): Prepared from **12**. White crystals (94%); m.p. 50–52 °C; $[\alpha]20$ D = +25.0 (c 0.265, MeOH). All spectroscopic data (^{1}H- and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

General procedure for the preparation of 1,3–thiazines (16a, b): A solution of thioureas **15b** or **15d** (0.31 mmol) in dry EtOH (1 mL) was added 22% HCl in EtOH (5 mL) and the mixture was stirred at room temperature for 4 h and then concentrated under vacuum. The residue was treated with 10% KOH in MeOH (20 mL) followed by evaporation, and the crude product was again dissolved in water (10 mL) and extracted with $CHCl_3$ (3×20 mL). The combined organic layer was washed with saturated NaCl aqueous solution (15 mL), dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel with $CHCl_3$:MeOH = 19:1.

(1R,2S,5R)-5-Methyl-2-((R)-2-(phenylimino)-1,3-thiazinan-5-yl)cyclohexanol (**16a**): Prepared from **15b**. White crystals (71%); m.p. 73–75 °C; $[\alpha]20$ D = −46.0 (c 0.9, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2S,5R)-5-Methyl-2-((S)-2-(phenylimino)-1,3-thiazinan-5-yl)cyclohexanol (**16b**): Prepared from **15d**. White crystals (88%); m.p. 224–225 °C; $[\alpha]20$ D = +9.0 (c 0.29, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

General procedure for the synthesis of 1.3-oxazines (17a–d): To a solution of **15a–d** (0.31 mmol) in MeOH (4 mL), MeI (1.50 mmol) was added. After 3 h stirring at room temperature, the mixture was evaporated, followed by adding 2.5 M KOH in MeOH (20 mL) and subsequently stirred for 1 h before evaporation. The residue was dissolved in water (20 mL) and extracted with $CHCl_3$ (3×20 mL). The organic phase was then dried with Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography on silica gel ($CHCl_3$:MeOH = 19:1).

(1R,2R,5R)-5-Methyl-2-((S)-5-methyl-2-(phenylimino)oxazolidin-5-yl)cyclohexanol (**17a**): Prepared from **15a**. White crystals (76%); m.p. 94–96 °C; $[\alpha]20$ D = −5.0 (c 0.28, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2S,5R)-5-Methyl-2-((R)-2-(phenylimino)-1,3-oxazinan-5-yl)cyclohexanol (**17b**): Prepared from **15b**. White crystals (50%); m.p. 166–168 °C; $[\alpha]20$ D = −37.0 (c 0.25, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2R,5R)-5-Methyl-2-((S)-5-methyl-2-(phenylimino)oxazolidin-5-yl)cyclohexanol (**17c**): Prepared from **15c**. White crystals (90%); m.p. 94–95 °C; $[\alpha]20$ D = −16.0 (c 0.25, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2S,5R)-5-Methyl-2-((S)-2-(phenylimino)-1,3-oxazinan-5-yl)cyclohexanol (**17d**): Prepared from **15d**. White crystals (83%); m.p. 171–172 °C; $[\alpha]20$ D = +49.0 (c 0.27, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

General procedure for the preparation of pyrimidine analogues (**19a–h**), (**21a–g**) and (**23a–g**): To a solution of aminodiols **2a**, **b**, **6**, **10**, and **12** together with aminotriol **4** as well as aminoalcohols **8a**, **b**, **14** (0.6 mmol) in EtOH (2 mL), 2,4-dichloro-5-fluoropyrimidine **18a**, 2,4,5-trichloropyrimidine **18b** or 4,6-dichloropyrimidine-5-amine **18c** (0.6 mmol) and Et_3N (1.8 mmol, 182 mg) were added. After a treatment at reflux temperature for 24 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was dissolved in EtOAc (15 mL) and washed with H_2O (3×15 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with $CHCl_3$:MeOH = 19:1.

(1R,2R,5R)-2-((S)-1-((2-Chloro-5-fluoropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**19a**): Prepared from **2a** and **18a**. Brown crystals (94%); m.p. 66–69 °C; [α]20 D = +63.0 (c 0.13, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2R,5R)-2-((R)-1-((2-Chloro-5-fluoropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**19b**): Prepared from **2b** and **18a**. White crystals (88%); m.p. 100–104 °C; [α]20 D = +4.0 (c 0.13, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(*S*)-3-((2-Chloro-5-fluoropyrimidin-4-yl)amino)-2-((1*R*,2*R*,4*R*)-2-hydroxy-4-methylcyclohexyl)propane-1,2-diol (**19c**): Prepared from **4** and **18a**. Yellow oil (94%); [α]20 D = +8.0 (c 0.1375, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2S,5R)-2-((R)-1-((2-Chloro-5-fluoropyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexanol (**19d**): Prepared from **6** and **18a**. White crystals (84%); m.p. 172–174 °C; [α]20 D = −55.0 (c 0.13, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3S,3aR,6R,7aR)-3-(((2-Chloro-5-fluoropyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol (**19e**): Prepared from **8a** and **18a**. White crystals (53%); m.p. 175–177 °C; [α]20 D = −3.0 (c 0.1150, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3R,3aR,6R,7aR)-3-(((2-Chloro-5-fluoropyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol (**19f**): Prepared from **8b** and **18a**. Colorless oil (70%); [α]20 D = −3.0 (c 0.1425, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2R,5R)-2-((S)-1-((2-Chloro-5-fluoropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**19g**): Prepared from **10** and **18a**. White crystals (75%); m.p. 158–160 °C; [α]20 D = +36.0 (c 0.1450, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2S,5R)-2-((S)-1-((2-Chloro-5-fluoropyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexanol (**19h**): Prepared from **12** and **18a**. White crystals (88%); m.p. 142–144 °C; [α]20 D = +26.0 (c 0.1250, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3R,3aR,6R,7aS)-3-(((2-Chloro-5-fluoropyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol (**19i**): Prepared from **14** and **18a**. White crystals (72%); m.p. 156–158 °C; [α]20 D = −7.0 (c 0.1375, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2R,5R)-2-((S)-1-((2,5-Dichloropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**21a**): Prepared from **2a** and **18b**. White crystals (73%); m.p. 110–113 °C; [α]20 D = +66.0 (c 0.15, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2R,5R)-2-((R)-1-((2,5-Dichloropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**21b**): Prepared from **2b** and **18b**. White crystals (75%); m.p. 94–96 °C; [α]20 D = +3.0 (c 0.1350, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(S)-3-((2,5-Dichloropyrimidin-4-yl)amino)-2-((1R,2R,4R)-2-hydroxy-4-methylcyclohexyl)propane-1,2-diol (**21c**): Prepared from **4** and **18b**. White crystals (70%); m.p. 118–120 °C; [α]20 D = +1.0 (c 0.1150, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2S,5R)-2-((R)-1-((2,5-Dichloropyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexanol (**21d**): Prepared from **6** and **18b**. White crystals (84%); m.p. 138–140 °C; [α]20 D = −45.0 (c 0.1150, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3S,3aR,6R,7aR)-3-(((2,5-Dichloropyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol (**21e**): Prepared from **8a** and **18b**. Yellow crystals (88%); m.p. 90–91 °C; [α]20 D = −6.0 (c 0.13, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2R,5R)-2-((S)-1-((2,5-Dichloropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**21f**): Prepared from **10** and **18b**. Yellow oil (84%); [α]20 D = +17.0 (c 0.1375, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2S,5R)-2-((S)-1-((2,5-Dichloropyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexanol (**21g**): Prepared from **12** and **18b**. White crystals (85%); m.p. 184–186 °C; [α]20 D = +6.0 (c 0.1425, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3R,3aR,6R,7aS)-3-(((2,5-Dichloropyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol (**21h**): Prepared from **14** and **18b**. White crystals (80%); m.p. 185–186 °C; [α]20 D = +3.0 (c 0.13, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2R,5R)-2-((S)-1-((5-Amino-6-chloropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**23a**): Prepared from **2a** and **18c**. Yellow oil (82%); [α]20 D = −10.0 (c 0.13, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2R,5R)-2-((R)-1-((5-Amino-6-chloropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**23b**): Prepared from **2b** and **18c**. White crystals (80%); m.p. 213–214 °C; [α]20 D = −20.0 (c 0.12, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(S)-3-((5-Amino-6-chloropyrimidin-4-yl)amino)-2-((1R,2R,4R)-2-hydroxy-4-methylcyclohexyl)propane-1,2-diol (**23c**): Prepared from **4** and **18c**. Yellow crystals (79%); m.p. 160–162 °C; [α]20 D = −6.0 (c 0.1325, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2S,5R)-2-((R)-1-((5-Amino-6-chloropyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexanol (**23d**): Prepared from **6** and **18c**. Yellow crystals (88%); m.p. 187–189 °C; [α]20 D = −32.0 (c 0.1375, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3S,3aR,6R,7aR)-3-(((5-Amino-6-chloropyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol (**23e**): Prepared from **8a** and **18c**.

White crystals (88%); m.p. 171–172 °C; [α]20 D = −30.0 (c 0.1425, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2R,5R)-2-((S)-1-((5-Amino-6-chloropyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexanol (**23f**): Prepared from **10** and **18c**. Brown oil (83%); [α]20 D = −7.0 (c 0.1825, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2S,5R)-2-((S)-1-((5-Amino-6-chloropyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexanol (**23g**): Prepared from **12** and **18c**. Yellow crystals (90%); m.p. 182–183 °C; [α]20 D = +19.0 (c 0.1150, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3R,3aR,6R,7aS)-3-(((5-Amino-6-chloropyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol (**23h**): Prepared from **14** and **18c**. Brown oil (86%); [α]20 D = −6.0 (c 0.1250, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

General procedure for the preparation of N^2-(*p*–trifluoromethyl)aniline substituted pyrimidines (**20a–i**) and (**22a–h**): A mixture of pyrimidines **19a–i** or **21a–h** (0.16 mmol) and 4-trifluoromethylaniline (0.24 mmol) in EtOH (200 μL) was heated in microwave reactor at 150 °C, 200 W, 19 bar for 80 min. The formed precipitate was filtered off and washed with CH_2Cl_2 to afford the desired product in pure form without further purification.

(1R,2R,5R)-2-((S)-1-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**20a**): Prepared from **19a**. White crystals (72%); m.p. 154–156 °C; [α]20 D = +43.0 (c 0.1150, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2R,5R)-2-((R)-1-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**20b**): Prepared from **19b**. Yellow crystals (87%); m.p. 154–156 °C; [α]20 D = +16.0 (c 0.14, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(S)-3-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-((1R,2R,4R)-2-hydroxy-4-methylcyclohexyl)propane-1,2-diol hydrochloride (**20c**): Prepared from **19c**. White crystals (84%); m.p. 158–160 °C; [α]20 D = +18.0 (c 0.1075, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2S,5R)-2-((R)-1-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**20d**): Prepared from **19d**. Yellow crystals (94%); m.p. 179–181 °C; [α]20 D = −23.0 (c 0.1375, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3S,3aR,6R,7aR)-3-(((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol hydrochloride (**20e**): Prepared from **19e**. White crystals (87%); m.p. 150–152 °C; [α]20 D = −33.0 (c 0.1350, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3R,3aR,6R,7aR)-3-(((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol hydrochloride (**20f**): Prepared from **19f**. Yellow crystals (90%); m.p. 156–158 °C; [α]20 D = −40.0 (c 0.1450, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2R,5R)-2-((S)-1-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**20g**): Prepared from **19g**. White crystals (80%); m.p. 166–168 °C; [α]20 D = +18.0 (c 0.1350, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2S,5R)-2-((S)-1-((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**20h**): Prepared from **20h**. Yellow crystals (96%); m.p. 145–147 °C; [α]20 D = +15.0 (c 0.13, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3R,3aR,6R,7aS)-3-(((5-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol hydrochloride (**20i**): Prepared from **19i**. Yellow crystals (87%); m.p. 238–240 °C; [α]20 D = −61.0 (c 0.1250, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2R,5R)-2-((S)-1-((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**22a**): Prepared from **21a**. White crystals (80%); m.p. 167–169 °C; [α]20 D = +54.0 (c 0.1225, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

((1R,2R,5R)-2-((R)-1-((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**22b**): Prepared from **21b**. White crystals (82%); m.p. 82–84 °C; [α]20 D = +12.0 (c 0.1325, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(S)-3-((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-((1R,2R,4R)-2-hydroxy-4-methylcyclohexyl)propane-1,2-diol hydrochloride (**22c**): Prepared from **21c**. Yellow crystals (90%); m.p. 163–165 °C; [α]20 D = −4.0 (c 0.1300, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1R,2S,5R)-2-((R)-1-((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**22d**): Prepared from **21d**. Yellow crystals (98%); m.p. 173–175 °C; [α]20 D = 29.0 (c 0.1250, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3S,3aR,6R,7aR)-3-(((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol hydrochloride (**22e**): Prepared from **21e**. White crystals (85%); m.p. 188–190 °C; [α]20 D = −23.0 (c 0.1350, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2R,5R)-2-((S)-1-((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**22f**): Prepared from **21f**. White crystals (87%); m.p. 137–140 °C; [α]20 D = +29.0 (c 0.1325, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(1S,2S,5R)-2-((S)-1-((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)-3-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol hydrochloride (**22g**): Prepared from **21g**. White crystals (95%); m.p. 162–164 °C; [α]20 D = +2.0 (c 0.1150, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

(3R,3aR,6R,7aS)-3-(((5-Chloro-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)amino)methyl)-6-methyloctahydrobenzofuran-3-ol hydrochloride (**22 h**): Prepared from **21 h**. Yellow crystals (85 %); m.p. 223–225 °C; [[α]20 D = −30.0 (c 0.1350, MeOH). All spectroscopic data (^{1}H and ^{13}C NMR together with HRMS) can be found in the Supporting Information.

Determination of antiproliferative effect: The growth-inhibitory effects of the presented heterocyclic compounds were determined by a standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay on a panel of human adherent cancer cell lines of gynecological origin containing HeLa and SiHa (cervical cancers), A2780 (ovarian cancer) and MDA-MB-231 (breast cancer) cells.[110] All cell lines were purchased from the European Collection of Cell Cultures (Salisbury, UK) except the SiHa, obtained from the American Tissue Culture Collection (Manassas, VA, USA). The cells were cultivated in minimal essential medium (MEM) supplemented with fetal bovine serum (10 %), non-essential amino acids, and penicillin-streptomycin (1 % each) at 37 °C in a humidified atmosphere containing 5% CO_2. All media and supplements were obtained from Lonza Group Ltd. (Basel, Switzerland). Cancer cells were plated into 96-well plates at the density of 5000 cells/well. After overnight incubation, the test compound was added in two concentrations (10 μM and 30 μM) and incubated for 72 h under cell-culturing conditions. Then, MTT solution (5 mg mL^{-1}, 20 μL) was added to each well and incubated for 4 h. Finally, the medium was removed, and the precipitated formazan was dissolved in DMSO during 60 min of shaking at 37 °C. The absorbance was measured at 545 nm using a microplate reader (SpectoStarNano, BMG Labtech, Ortenberg, Germany). Two independent experiments were carried out with five wells for each condition. Cisplatin (Ebewe GmbH, Unterach, Austria) was used as a positive control. Calculations were performed utilising the GraphPad Prism 5.01 software (GraphPad Software Inc., San Diego, CA, USA).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: (−)-isopulegol · (+)-neoisopulegol · 1,3-oxazines · 1,3-thiazines · 2,4-diaminopyrimidines

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