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REVIEW

Nitrogen-Containing Heterocyclic Compounds Obtained from Monoterpenes or Their Derivatives: Synthesis and Properties

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Abstract

Directed transformation of available natural compounds with native biological activity is a promising area of research in organic and medicinal chemistry aimed at finding effective drug substances. The number of scientific publications devoted to the transformation of natural compounds and investigations of their pharmacological properties, in particular, monoterpenes and their nearest derivatives, increases every year. At the same time, the chemistry of nitrogen-containing heterocyclic compounds has been actively developed since the 1950s after the news that the benzimidazole core is an integral part of the structure of vitamin B_{12}. At the time of writing this review, the data on chemical modifications of monoterpenes and their nearest derivatives leading to formation of compounds with a nitrogen-containing heterocycle core have not been summarized and systematized in terms of chemical transformations. In this review, we tried to summarize the literature data on the preparation and properties of nitrogen-containing heterocyclic compounds synthesized from monoterpenes/monoterpenoids and their nearest derivatives for the period from 2000 to 2021.

Keywords Monoterpenes · Monoterpenoids · Nitrogen-containing heterocycles · Biological activity · Catalytic activity

Abbreviations

A2780	Ovarian cancer cell line that was established from an ovarian endometroid adenocarcinoma tumor in an untreated patient

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ATCC 14470	*Mycobacterium gordonae Bojalil* Et al. (https://www.atcc.org/products/14470)
ATCC 27294	*Mycobacterium tuberculosis subsp. Tuberculosis* (https://www.atcc.org/products/27294)
ATCC 35743	*Mycobacterium bovis Karlson and Lessel* (https://www.atcc.org/products/35743)
ATCC 35751	*Mycobacterium abscessus (Moore and Frerichs) Kusunoki and Ezaki* (https://www.atcc.org/products/35751)
ATCC 35797	*Mycobacterium smegmatis (Trevisan) Lehmann and Neumann* (https://www.atcc.org/products/35797)
Boc	*tert*-Butoxycarbonyl protecting group
BSA	*N*,*O*-Bis-(trimethylsilyl)acetamide
Cbz	Benzyloxycarbonyl protecting group
CC_{50}	50% Cytotoxic concentration
CDI	1,1′-Carbonyldiimidazole
CGP12177	4-[3-[(1,1-Dimethylethyl)amino]2-hydroxypropoxy]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride
CHEF	Chelation-enhanced fluorescence
CNS	Central nervous system
CSI	Chlorosulfonyl isocyanate
CT-26	Colon tumor 26
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCyEA	Dicyclohexylethylamine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
Dowtherm A	Eutectic mixture of biphenyl with diphenyl oxide
EBOV	Ebola virus
ee	Enantiomeric excess
er	Enantiomer ratio
EPI	Efflux pump inhibitor
fac	Facial (when three identical ligands occupy one face of an octahedron)
GP	Glycoprotein
hCA	Human carbonic anhydrases
HeLa	The cells line is named after and derived from cervical cancer cells taken from Henrietta Lacks
HL	Human leukemia
i	*iso*-
IC_{50}	50% Inhibitory concentration
MARV	Marburg virus
MCPBA	*meta*-Chloroperbenzoic acid
MCF7	A breast cancer cell line which was established in institute in Detroit (Michigan Cancer Foundation-7)
MDA-MB-231	An epithelial, human breast cancer cell line (M.D. Anderson-Metastatic Breast 231)

MDCK	Madin–Darby canine kidney cells
m	*meta-*
MIC	Minimum inhibitory concentration
MTT	((3-(4,5-Dimethyldiazol-2-yl)-2,5-diphenyl tetrazolium bromide))
MW	Microwave irradiation
Naph	Naphthalene
NHC	*N*-Heterocyclic carbene
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
NorA	Most studied pump in *S. aureus*
o	*ortho-*
p	*para-*
PEG	Polyethylene glycol
PPA	Polyphosphoric acid
PPY	2-Phenylpyridine
rVSV-ΔG-EBOV-GP	Recombinant vesicular stomatitis virus in which the glycoprotein G gene was a deleted Ebola virus glycoprotein
rVSIV-ΔG-MarV-GP	Recombinant vesicular stomatitis virus in which the glycoprotein G gene was a deleted Marburg virus glycoprotein
SI	Selectivity Index (ratio of CC50 to IC_{50})
SMMC-7721	Human hepatocarcinoma cell line
TBAF	Tetrabutylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBSOTf	*tert*-Butyldimethylsilyl triflate
TC_{50}	50% Toxic concentration
TFA	Trifluoroacetic acid
tmp	2,2,6,6-Tetramethylpiperidyl
TMSCN	Trimethylsilyl cyanide
WT	Wild-type

1 Introduction

Monoterpenes represent the largest class of secondary plant metabolites, ingredients of essential oils with a wide range of biological activities such as anticancer, antimicrobial, antioxidant, antiviral, analgesic, and anti-inflammatory [1–7]. Monoterpenes, in particular bicyclic monoterpenes with two condensed cycles, and their derivatives are key ingredients in the development and production of novel pharmacologically active compounds [8–11]. However, in addition to a wide range of native biological activity, monoterpenes and their derivatives possess high enantiomeric purity, which makes them a promising starting material for the synthesis of complexes used further in heterogeneous catalysis [12, 13]. Numerous reviews have now been published in the scientific literature detailing advances in research into the pharmacological properties of monoterpenes and their derivatives [14–17].

At the same time, the chemistry of nitrogen-containing (*N*-containing) heterocyclic compounds, both aliphatic and aromatic, is an important and unique area among the applied fields of organic chemistry. Much of the research is directed towards the development of new molecules and investigation of their physicochemical and biological properties. Molecules with *N*-containing cycle nuclei in their structure have attracted increasing attention of chemists in the last few decades. They have gained prominence in the rapidly developing fields of organic and medicinal chemistry, as well as in the pharmaceutical industry, due to their biological activity and ability both to protonate or deprotonate easily and to form various weak interactions, such as H-bonds, dipole–dipole interactions, and π-stacking [16, 18]. The ability of *N*-containing heterocycles to form these interactions allows them to easily form bonds with a variety of enzymes and receptors in biological targets, which increases their importance in the field of medicinal chemistry [19].

One promising direction in the search for organic compounds with targeted pharmacological activity could be combination of two fragments with proven biological activity in one molecule. Such a strategy could lead to compounds with novel pharmacological properties in comparison with the original molecules, as was clearly demonstrated in [15, 20–26]. Thus, substances combining fragments of an *N*-containing heterocycle and a monoterpene in their structure could prove to be valuable materials for both organic chemistry and medicinal chemistry.

Herein, we will summarize recent developments in the synthesis of *N*-containing heterocyclic compounds through modifications of different monoterpenes, monoterpenoids, and their derivatives. Chemical modifications of monoterpenes and monoterpenoids, structured according to the type of *N*-containing heterocyclic compounds obtained (spirocyclic, annulated, etc.), are discussed first, and then the properties of the target compounds (in particular catalytic or biological activity) are discussed. It is worth noting that the starting compounds are commercially available and their synthesis does not require discussion.

This review consists of two parts (Fig. 1). The first part (Sect. 2) includes the consideration of works devoted to the synthesis of compounds combining a heterocyclic nucleus with a monoterpene frame via a linker (Sects. 2.1, 2.2) or directly (Sect. 2.3), which do not include the stages of formation of the heterocyclic nucleus

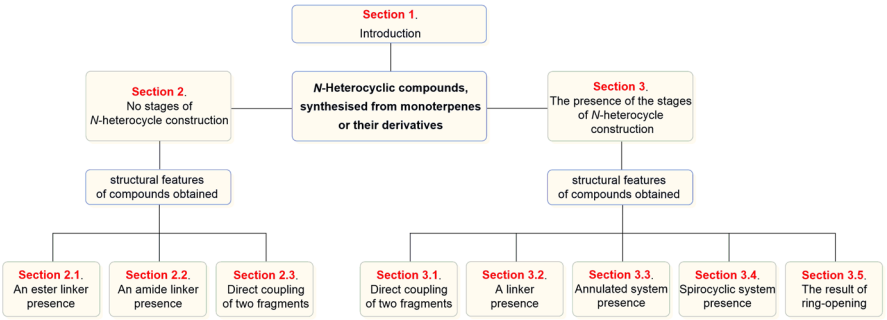


Fig. 1 Structure of review

in the synthesis. In the second part (Sect. 3), studies on the preparation of heterocyclic compounds from monoterpenes and their nearest derivatives, which include the stages of heterocyclic core formation, are reviewed. The second part also includes the works devoted to the synthesis of nitrogen-containing heterocyclic compounds, which contains the stages of breaking the frame of the original natural compound (Sect. 3.5). In both parts, data on the biological/catalytic activity or properties of the compounds obtained are presented.

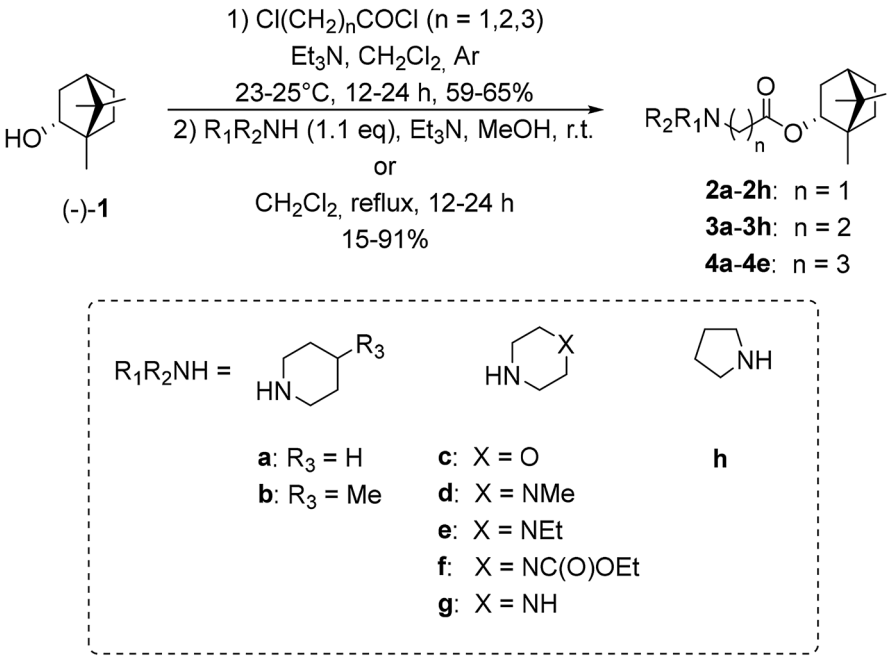
To clarify the concept of the review, below are the necessary terms. Monoterpenes are hydrocarbons (C10) of biological origin having carbon skeletons formally derived from isoprene. Monoterpenoids are natural products and related compounds formally derived from isoprene units (C10) featuring oxygen in various functional groups. Nearest derivatives are chemical compounds structurally derived in one or more steps from others by a process of modification or partial substitution of at least one component wherein at least one structural feature is retained at each process step. Linkers are a group of atoms which connect two mentioned fragments. A monoterpene frame/residue is a fragment of a molecule in which the structure of the original monoterpene, from which this substance was synthesized, can be seen. The number of carbon atoms in this fragment can be 10 or different.

2 Synthesis and Properties of *N*-Containing Heterocyclic Compounds Synthesized from Monoterpenes or Their Derivatives, Not Involving the Formation of a Heterocyclic Nucleus

This section deals with the synthesis of compounds from monoterpenes, monoterpenoids or their derivatives including an *N*-containing heterocycle by combining two molecules via a linker or directly, but not including the step of forming the heterocyclic core. Synthesis of derivatives via a linker implies the addition of a bifunctional linker to the native functional groups of the monoterpenoid, followed by interaction of the resulting compound with the functionalized *N*-containing heterocycle. Another approach is the introduction of new functional groups into the monoterpene molecule and subsequent reaction with the *N*-containing heterocycle (in some cases with additional functional groups). Combining the fragments directly requires an initial modification of a monoterpene and/or heterocycle to create a functional group suitable for further transformation.

2.1 Combination of an *N*-Containing Heterocycle and Monoterpene Frame Via an Ester Linker

A convenient approach to the synthesis of hybrid compounds combining monoterpene and heterocyclic fragments in their structure is modification of native hydroxyl groups of monoterpenoids by esterification using chlorides of halogen-substituted carboxylic acids. The subsequent nucleophilic substitution reaction of the halogen atom with an *N*-containing heterocycle featuring N or S nucleophilic centers gives



Scheme 1 Synthesis of (–)-borneol esters with an *N*-containing heterocycle in structure

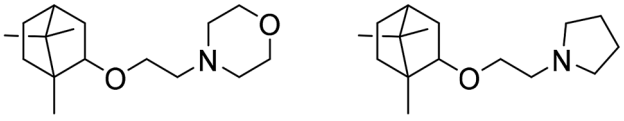
the target hybrid compounds in which the heterocycle nucleus is linked with the monoterpene backbone via an ester linker.

The synthesis of a variety of (–)-borneol esters **2a–2h**, **3a–3h**, and **4a–4e** featuring pyrrolidine, morpholine, piperazine, and piperidine fragments is described by Sokolova et al. (Scheme 1) [21, 26]. Synthesis of target compounds was carried out via acylation of (–)-borneol (–)-**1** with chloroacetic, 3-chloropropionic, and 4-chlorobutyric acids at the first stage followed by the reaction of nucleophilic chlorine atom substitution in obtained esters of (–)-borneol to pyrrolidine, morpholine, piperazine, piperidine, and their derivatives. The compounds obtained were investigated for their inhibitory activity against influenza A/Puerto Rico/8/34 (H1N1) virus replication. Compounds **2c** and **3c** featuring morpholine and monoterpene fragments were the most active (SI(**2c**) = 82; SI(**3c**) = 45; SI (Selectivity Index) is the ratio of 50% cytotoxic concentration of the compound to 50% virus-inhibiting concentration). Compounds **2d** and **3d** with the 1-methylpiperazine cycle in the structure showed moderate antiviral activity (SI(**2d**) = 23; SI(**3d**) = 25) [21]. In another work [26], compound **4c** was shown to have moderate antiviral activity against vaccinia virus (SI(**4c**) = 23), while compounds **2c** and **3c** were more active (SI(**2c**) = 56; SI(**3c**) = 48). The commercially available agent Cidofovir was used as a positive control (SI = 11.8). The authors note that the cytotoxicity increases with increasing linker length connecting the monoterpene and heterocyclic fragments, which results in a decrease in the SI. Kononova et al. [27] showed that compounds **3a**, **3b**, **3e**, **3h**, and **2e** possess antiviral activity (SI varied from 29 to 60) against Marburg virus

(using the rVSIV-ΔG-MarV-GP pseudotype), exceeding that of the reference compound, an ion channel inhibitor verapamil (SI = 21). The authors showed that the starting (–)-borneol has no activity against the studied rVSIV-ΔG-MarV-GP pseudotype and, at the same time, has a low toxicity ($CC_{50} > 3000$ μM, CC_{50} = 50% cytotoxic concentration). It was shown that increasing the length of the linker connecting the (–)-borneol and heterocycle increases the antiviral activity against the rVSIV-ΔG-MarV-GP pseudotype.

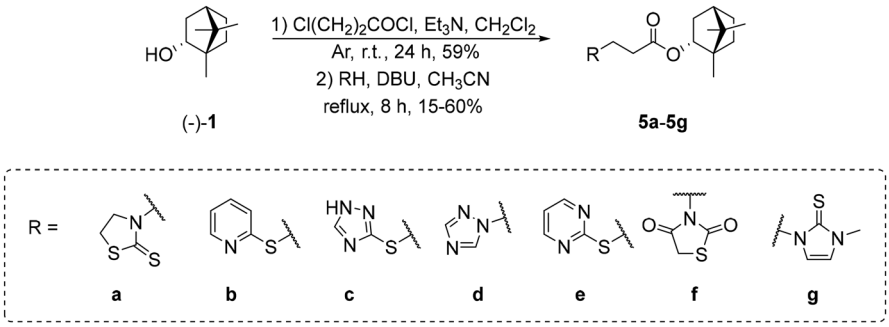
It should be noted that the same group of authors [28] also obtained structural analogues of compounds **2a–2h** and **3a–3h**: (±)-borneol ethers with the same heterocyclic moieties. The compounds desired were synthesized in two steps: alkylation of 2-bromoethanol and 3-bromoethanol with (±)-camphene in the presence of montmorillonite clay K-10 and, as a consequence of the Wagner–Meerwein rearrangement, the formation of bromine-containing ethers as a racemate; the next stage involved the nucleophilic substitution reaction of the halogen atom with secondary amines of cyclic structure under the conditions mentioned earlier. It should be noted that all the target products with a monoterpene frame connected through an ether linker with an *N*-containing heterocycle were racemates, and further evaluation of pharmacological activity was performed for racemates [28]. Thus, their antiviral activity against influenza A/Puerto Rico/8/34 (H1N1) virus was weaker than that of the (–)-borneol ester derivatives shown in Scheme 1. Also, as shown by biological studies, simple esters synthesized have no antiviral activity against vaccinia virus. But compounds **2c′** and **2h′** (Fig. 2) are efficient inhibitors of Ebola pseudotype virus (rVSV-ΔG-EBOV-GP) according to biological studies (IC_{50}(**2c′**) = 0.6 ± 0.2 μM; SI(2c′) = 1433; IC_{50}(**2h′**) = 0.12 ± 0.04 μM; SI(**2h′**) = 4166; IC_{50} = 50% inhibitory concentrations); the reference drug used was sertraline (IC_{50} = 0.7 ± 0.07 μM; SI = 582). It should be also noted that compounds **2c′** and **2h′** were much less active in biological studies of their antiviral properties against Ebola virus (strain Zaire); their selectivity indexes (SI) did not exceed 12.

Then, in the next work [29], the library of (–)-borneol derivatives was extended (Scheme 2), and their antiviral activity against influenza A/Puerto Rico/8/34 (H1N1) virus was investigated. Thus, esters **5a–5g** featuring aliphatic and aromatic heterocyclic nuclei were synthesized by acylation of (–)-borneol with 3-chloropropanoyl chloride and further interaction with heterocyclic N and S nucleophiles. The results of biological studies showed that the esters **5d** and **5g** with triazole and imidazole rings, respectively, possess moderate antiviral activity against influenza A/Puerto Rico/8/34 (H1N1) virus (SI(**5d**) = 24; SI(**5g**) = 15). Compounds **5a**, **5c**, **5e**, and **5f** in turn exhibited lower 50% inhibitory concentrations (IC_{50}) as compared to **5d** and **5g**



2c' **2h'**

Fig. 2 Borneol ethers: efficient inhibitors of Ebola pseudotype virus



Scheme 2 Synthesis of (–)-borneol esters by acylation of (–)-borneol with 3-propanoyl chloride and further interaction with N and S nucleophiles

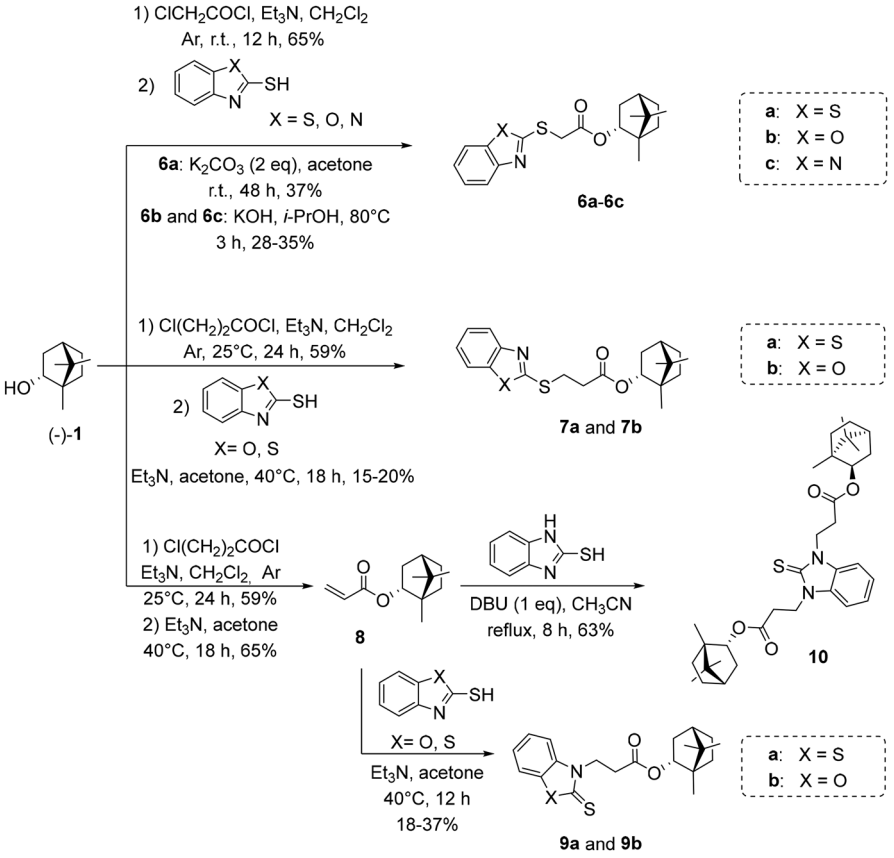
(IC_{50} ranged from 7.1 to 17.5 μM), but were more cytotoxic (CC_{50} ranged from 10.1 to 116.9 μM).

The synthesis of (–)-borneol esters **6a–6c**, **7a**, **7b**, **9a**, **9b**, and **10** featuring a benzoazole moiety (Scheme 3) and investigation of their antiviral activity against influenza virus A/Puerto Rico/8/34 (H1N1) are also described by Sokolova et al. [29]. Synthesis was performed by linker addition to (–)-borneol by acylation with chloroacetic and 3-chloropropionic acids in the presence of Et_3N. Subsequent nucleophilic interaction of obtained (–)-borneol esters with 2-mercaptobenzoazoles in the presence of bases (Et_3N, K_2CO_3 or KOH) led to compounds **6a–6c**, **7a**, and **7b**. Upon acylation of (–)-borneol with 3-chloropropionyl chloride and subsequent elimination reaction in acetone with Et_3N α,β-unsaturated carbonyl, compound **8** was obtained. The Michael addition of 2-mercaptobenzothiazole and 2-mercaptobenzoxazole to compound **8** in the presence of Et_3N resulted in the formation of compounds **9a** and **9b**, respectively. Substitution of the base with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in the formation of compound **10** with two (–)-borneol fragments, whereas the reactions with 2-mercaptobenzothiazole and 2-mercaptobenzoxazole led to the formation of a complicated product mixture. A study of the antiviral activity against influenza virus A/Puerto Rico/8/34 (H1N1) revealed compound **10** as the lead compound (SI(**10**) = 67).

2.2 Combination of an *N*-Containing Heterocycle and Monoterpene Frame Via an Amide Linker

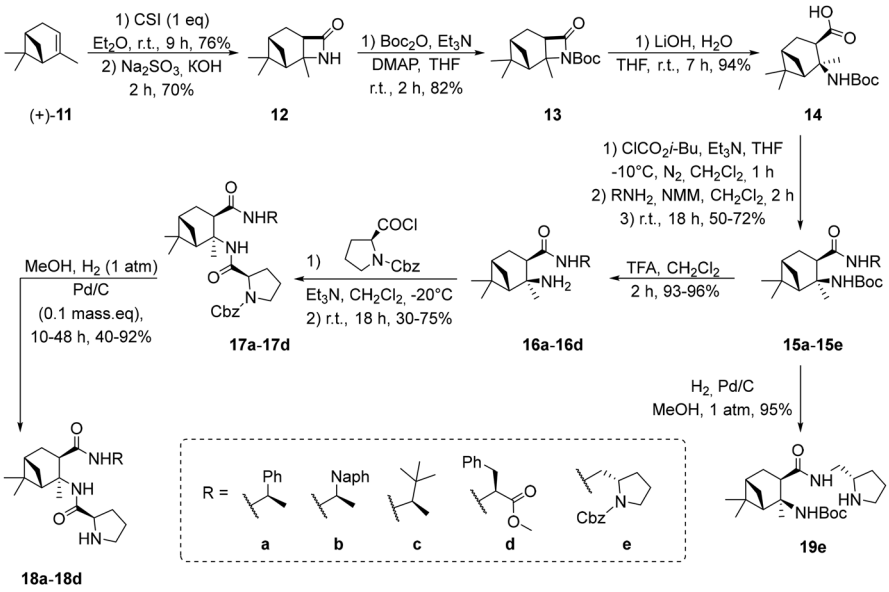
In order to combine an *N*-heterocycle nucleus and a monoterpene fragment in one molecule, the latter must first be modified to introduce a carboxyl or amino group into the molecule. Subsequent interaction with *N*-heterocyclic compounds featuring an amino or carboxyl group leads to the formation of target products containing an amide bond.

Thus, the synthesis of several enantiopure proline amides **18a–18d** from *N*-Boc-protected β-amino acid **14** was described in [30] (Scheme 4). Compound **14** was prepared from (+)-α-pinene (+)-**11** according to the previously developed methodology



Scheme 3 Synthesis of (–)-borneol esters featuring a benzoxazole moiety

[31]. First of all, (+)-α-pinene interacted with chlorosulfonyl isocyanate (CSI), which led to the stereoselective formation of compound **12**. Subsequent reaction of lactam **12** with di-*tert*-butyl dicarbonate gave compound **13** in good yield, alkaline hydrolysis of which resulted in formation of *N*-Boc-protected β-amino acid **14** in excellent yield. Amino amides **15a–15e** were prepared by coupling *N*-Boc-protected β-amino acid **14** with various amines using the mixed anhydride activation method. Removal of the Boc-protecting group using trifluoroacetic acid (TFA) resulted in the formation of chiral amino amides **16a–16d** in excellent yields. Subsequent acylation of compounds **16a–16d** by *N*-Cbz-protected (*S*)-proline and deprotection of **17a–17d** with H_2 and Pd/C afforded the desired proline amides **18a–18d** in moderate to good yields. Compound **19e** was obtained by deprotection of compound **15e** with H_2 and Pd/C. The catalytic activity of compounds **18a–18c** in the asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde was examined. The reaction was carried out under neat conditions using 10 mol% of catalyst. Compound **18a** incorporating a chiral and bulky amide in its structure catalyzed

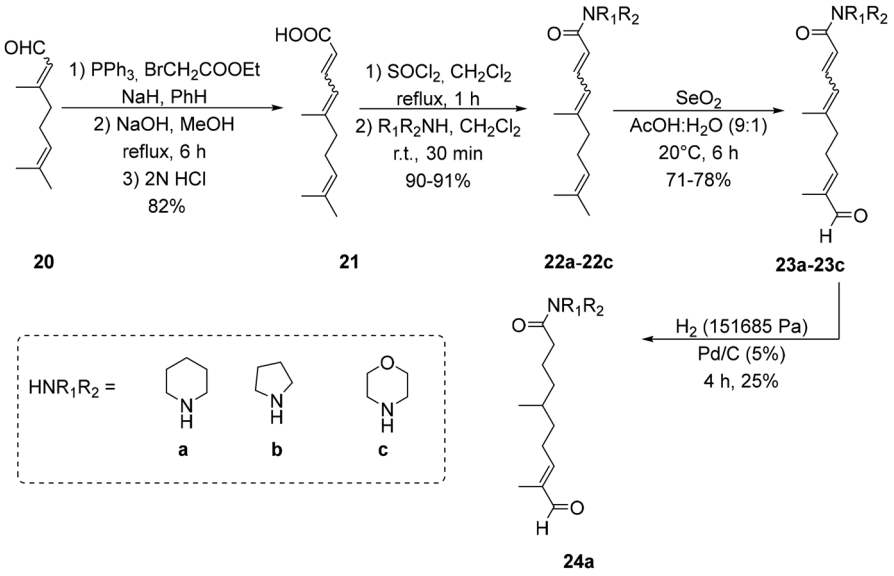


Scheme 4 Synthesis of (*S*)-proline amides from (+)-α-pinene

the asymmetric aldol reaction with significant stereoselectivity in favor of (2*S*,1′*R*)-enantiomer (yield of 87%; *ee* (enantiomeric excess) 78%).

A convenient synthesis of amides **22a–22c**, **23a–23c**, and **24a**, their bioevaluation and identification as efflux pump inhibitors (EPIs) against *S. aureus* are reported in (Scheme 5). The synthesis of the target compounds was carried out from citral **20**. The first step involved building up the carbon chain of citral **20** by the Wittig reaction using PPh_3 and $BrCH_2CO_2Et$ followed by alkaline hydrolysis, leading to the formation of acid **21**. Subsequent interaction of acid **21** with $SOCl_2$ and then with piperidine, pyrrolidine, and morpholine afforded amides **22a–22c**, respectively, in excellent yields. It is worth noting that 14 amines of different structures were used in this work, but only the amines with the *N*-heterocyclic nucleus in their structure are shown in Scheme 5. Further oxidation of amides **22a–22c** with SeO_2 resulted in the formation of compounds **23a–23c** featuring an aldehyde group at the end of the chain in the moderate yields. Reduction of C_2–C_3 and C_4–C_5 bonds with H_2 and Pd/C in compound **23a** resulted in the formation of compound **24a**. Compounds **22a–22c**, **23a–23c**, and **24a** in combination with antibacterial drug ciprofloxacin were subjected to bioevaluation for their possible role as EPI against *S. aureus* 1199 and NorA overexpressing *S. aureus* 1199B. As a result, compound **23a** proved to be one of the most effective inhibitors (along with the other six compounds that do not contain a heterocyclic nucleus in their structure), which at concentration of 25 mg/ml, reduced the minimum inhibitory concentration of ciprofloxacin by a factor of 4.

The transformation of the carbonyl group of the monoterpenoid into an amino group allows further nucleophilic substitution reactions with chloro-substituted esters, after which the addition of a heterocyclic nucleus to the resulting molecule

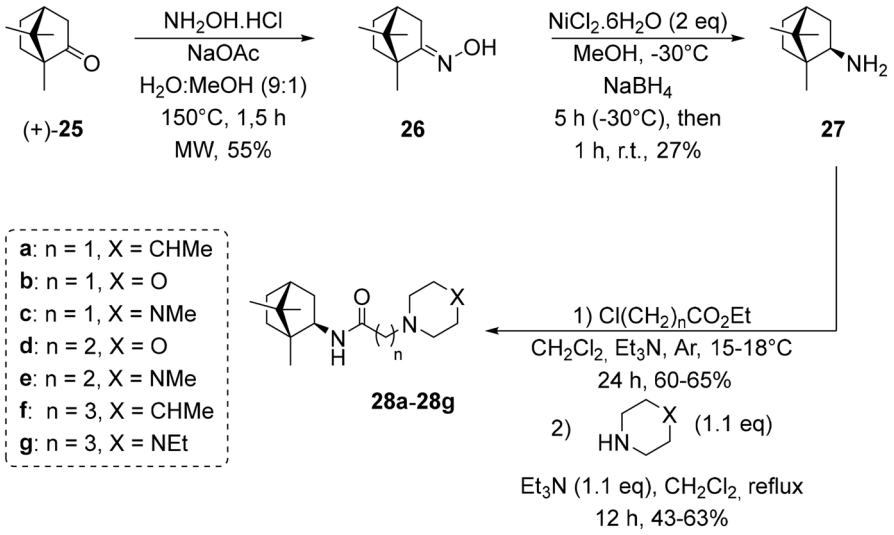


Scheme 5 Synthesis of potential efflux pump inhibitors from citral

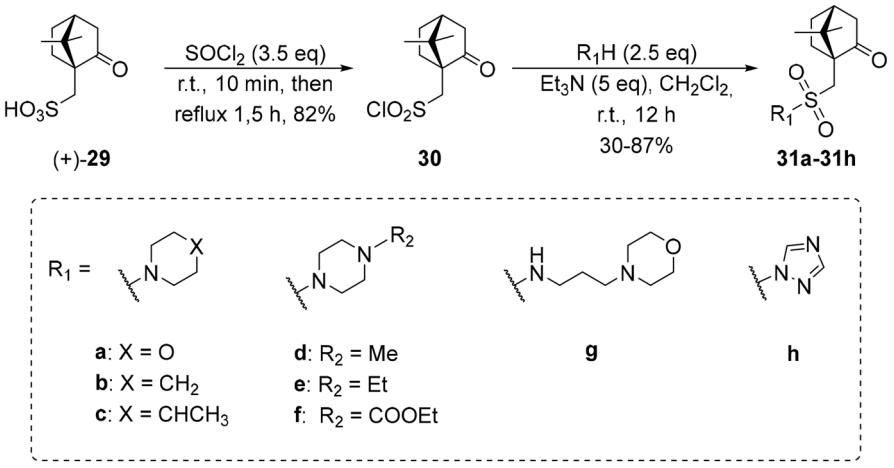
by a nucleophilic substitution reaction with an *N*-heterocycle as the *N*-nucleophile becomes possible.

The synthesis of (+)-camphor derivatives **28a–28g** with a piperidine, morpholine, and piperazine cycle attached to the molecule by amide bond through a linker of acetic, propionic, and butyric acid was described in [26] (Scheme 6). For the synthesis of target compounds, (+)-camphor (+)-**25** was transformed into *exo*-bornylamine **27** by interaction with hydroxylamine and subsequent reduction with $NaBH_4$ in the presence of $NiCl_2$•$6H_2O$ according to previously developed methodology [32]. By further interaction of amine **27** with ethyl esters of chloroacetic, 3-chloropropionic, and 4-chlorobutyric acids and subsequent nucleophilic chlorine atom substitution with *N*-methylpiperidine, morpholine, and *N*-ethylpiperidine compounds **28a–28g** were obtained in moderate yields. The antiviral activity and cytotoxicity of the synthesized derivatives against vaccinia virus were evaluated. The commercially available agent cidofovir (SI = 11.8) was used as a positive control. It is worth noting that the lead compounds in this series were compounds **28a**, **28b**, and **28d**, whose selectivity indices were 54, 40, and 63, respectively. Compound **28a** exhibited the lowest 50% inhibitory concentration (IC_{50}(**28a**) = 2.50 ± 0.17 μM), and at the same time it was the most cytotoxic of the three lead compounds (CC_{50}(**28a**) = 134.99 ± 33.37 μM). Compound **28d** was the least cytotoxic among the lead compounds (CC_{50}(**28d**) = 501.80 ± 16.90 μM), but at the same time, its 50% inhibitory concentration (IC_{50}(**28d**) = 12.55 ± 4.24 μM) was five times higher than that of **28a**.

An alternative approach is to use sulfonic acids as starting compounds. Thus, the synthesis and antiviral activity against Ebola and Marburg viruses of (1*S*)-(+)-camphor-10-sulfonamides **31a–31h** was described in [33] (Scheme 7). Synthesis was

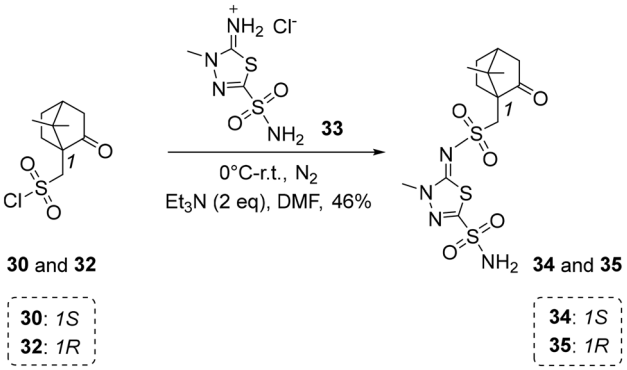


Scheme 6 Synthesis of bornyl amide derivatives with *N*-containing heterocycles as vaccinia virus inhibitors



Scheme 7 Synthesis of sulfonamides of (1*S*)-(+)-camphor-10-sulfonic acid

performed in two stages: from (1*S*)-(+)-camphor-10-sulfonic acid (+)-**29** (which can be obtained by the action of concentrated H_2SO_4 on (+)-camphor in Ac_2O solution), camphorsulfochloride **30** was obtained according to the known procedure [34]; further amidation of compound **30** resulted in obtaining the desired sulfonamides **31a–31h** with moderate yields. The antiviral activity against Ebola and Marburg viruses was estimated using a pseudovirus system based on the vesicular stomatitis virus for all compounds synthesized. According to the acquired experimental data,



Scheme 8 Synthesis of sulfonamides of (1*S*)- and (1*R*)-(+)-camphor-10-sulfonic acid as hCA VA and hCA VB inhibitors

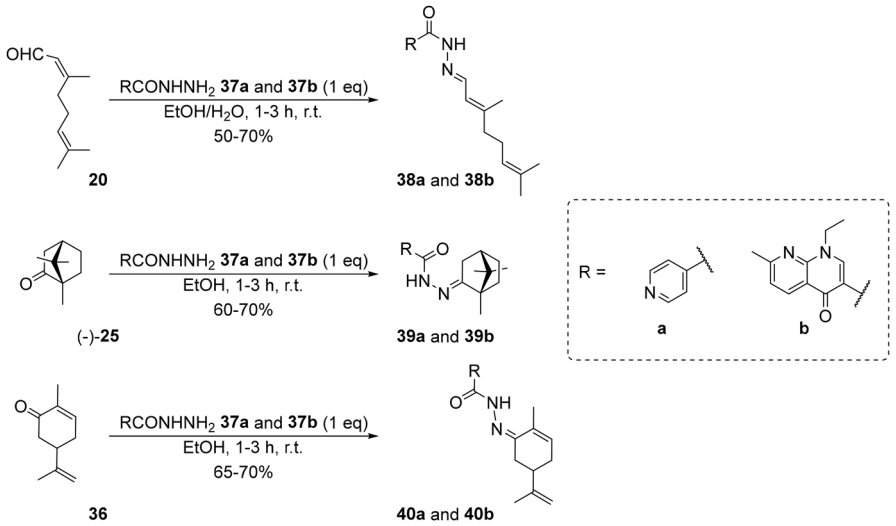
the compounds inhibit the glycoprotein of the Ebola virus (GP EBOV) more efficiently than the glycoprotein of the Marburg virus (GP MARV). Compounds **31a** and **31h** (SI(**31a**) = 921; SI(**31h**) = 1764) proved to be the most effective inhibitors of the Ebola virus glycoprotein with activity exceeding that of the reference drug sertraline (SI = 543).

The authors of [35] obtained a series of sulfonamides (1*S*)- and (1*R*)-(+)-camphor-10-sulfonic acid, among which amides **34** and **35** featuring an *N*-heterocycle are present (Scheme 8). The desired sulfonamides were prepared in a similar way as described above by amidation of enantiomeric camphorsulfochlorides **30** and **32**. It was shown that sulfonamides synthesized selectively inhibited the mitochondrial isozymes hCA VA and VB (h = human isoform; CA = carbonic anhydrases) over the cytosolic, off-target ones hCA I and II, with inhibition constants in the low nanomolar range. The best hCA VA and hCA VB inhibitors were the heterocyclic sulfonamides **34** and **35**. The authors submitted that compound **35** was the most effective hCA VA inhibitor (inhibition constant $K_1 = 5.9$ nM) reported in the literature at the time of publication. Its enantiomer, compound **34**, was 3.5 times less effective an hCA VA inhibitor, but was not inferior to the comparison drug zonisamide ($K_1 = 20.0$ nM). Also compounds **34** and **35** were the most effective hCA VB inhibitors with inhibition constants 7.3 and 7.8 nM, respectively, while the inhibition constants of all reference drugs were over 19.0 nM.

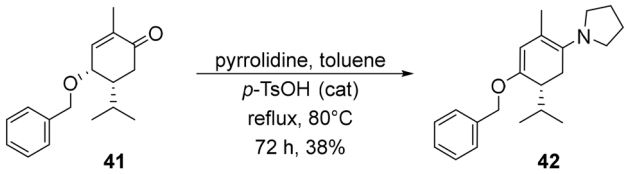
2.3 Combination of an *N*-Containing Heterocycle and Monoterpene Frame by Forming C–N or C=N, C–S, C–O, and C–C Bonds

Condensation of monoterpenoids featuring a carbonyl group with amines or other classes of compounds with an amino group in the structure allows the *N*-containing heterocyclic compounds and the monoterpene backbone to be joined directly by forming a single or double C–N bond.

Thus, the synthesis of hydrazide derivatives of citral **38a** and **38b**, (–)-camphor **39a** and **39b**, and carvone **40a** and **40b**, which contain an additional amide group



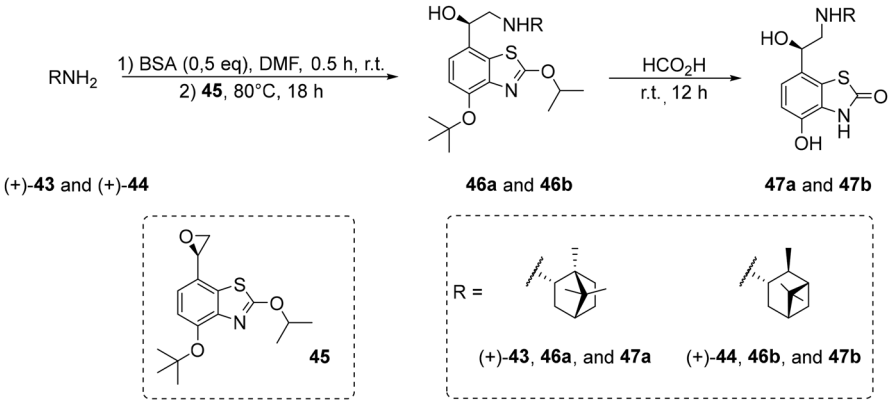
Scheme 9 Synthesis of citral, (–)-camphor and carvone hydrazides using isoniazid and nalidixic acid hydrazide



Scheme 10 Synthesis of pyrrolidine derivative with a piperitone fragment

besides the C=N bond, was described in [36] (Scheme 9). Monoterpenoids were introduced in a nucleophilic carbonyl group addition reaction with isoniazid **37a**, nalidixic acid hydrazide **37b**, and other drug hydrazides. As a result, hydrazides combining a monoterpene fragment and a heteroaromatic fragment were obtained. The anti-mycobacterial activity of the compounds synthesized was investigated against four *Mycobacterium strains*: *Mycobacterium intercellulari* (ATCC 35743), *Mycobacterium xenopi* (ATCC 14470), *Mycobacterium cheleneo* (ATCC 35751), and *Mycobacterium smegmatis* (ATCC 35797). Compound **40a** exhibited significant growth inhibition of all tested mycobacterial strains with a MIC = 12.0 ± 0.03 mg/ml (MIC is minimum inhibitory concentration), comparable to that of the reference drug isoniazid (MIC = 12.5 mg/ml). Compounds **39a** and **39b** showed weak growth inhibition of all strains (MIC = 50 mg/ml).

Pyrrolidine derivative of 3-*O*-benzylcarvotacetone ((4*S*,5*R*)-4-(benzyloxy)-5-isopropyl-2-methylcyclohex-2-en-1-one) **41** was prepared in [37], and its anti-bacterial activity against methicillin-resistant *Staphylococcus aureus* bacteria and antifungal activity against *Cryptococcus neoformans* fungi were studied

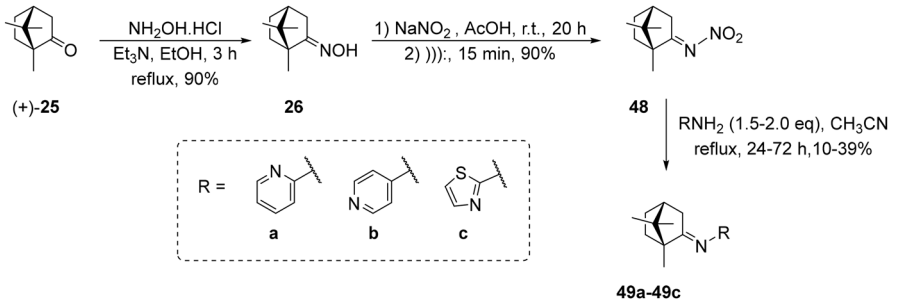


Scheme 11 Synthesis of the 4-hydroxybenzothiazolone β_2-adrenoceptor agonists with a monoterpene fragment

(Scheme 10). Enamine **42** was synthesized by direct interaction of compound **41** with pyrrolidine in the presence of a catalytic amount of *p*-TsOH. Piperitone derivative **42** showed no antifungal and antibacterial activity.

Reaction of epoxides with *N*-nucleophiles is also one of the approaches to forming a C–N bond. The authors of [38] synthesized more than 30 benzothiazole derivatives, including compounds **47a** and **47b** possessing a monoterpene fragment attached through a hydroxyethyl linker at position 7 of the benzothiazole moiety (Scheme 11). The synthesis was carried out by the interaction of protected chiral epoxide **45** with a number of amines (including (*R*)-(+)-bornylamine (+)-**43** and (+)-isopinocampheylamine (+)-**44**). Subsequent removal of the isopropyl and *tert*-butyl protecting groups with HCO_2H resulted in the target compounds **47a** and **47b**. The yields of compounds **46a**, **46b**, **47a**, and **47b** are not reported in the work. The library of all compounds synthesized was screened to determine their affinities for the human β_2-adrenoceptor in a radioligand binding assay versus the β-adrenoceptor antagonist CGP12177. Interestingly, for the compounds bearing monoterpene-derived *N*-substituents, **47a** and **47b**, relatively high binding selectivity for the β_2- over the β_1-adrenoceptor of 37- and 90-fold, respectively, were determined. This work identified monoterpene *N*-substituents to be of particular interest for further evaluation, as exemplified by the structure of **47b**.

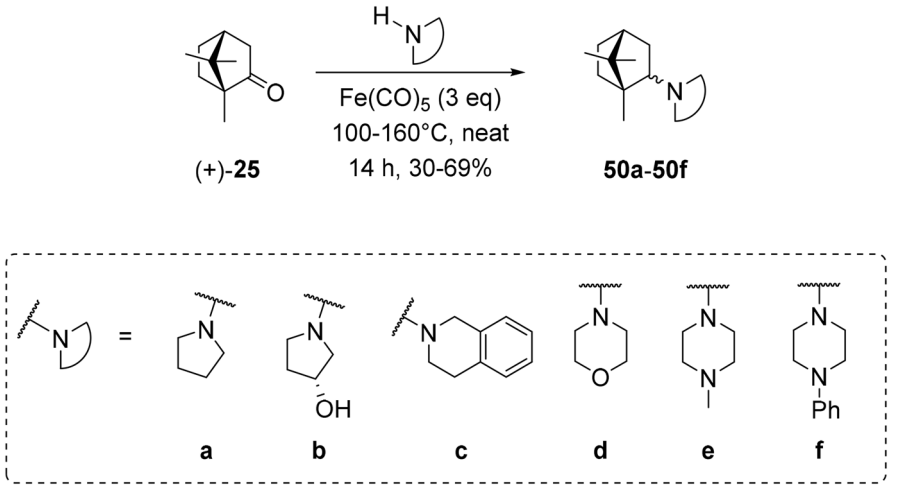
A three-step synthesis of (+)-camphor imines **49a**–**49c** with a pyridine and a thiazole substituent is described in [39] (Scheme 12). Initially, (+)-camphor oxime **26** was obtained from (+)-camphor (+)-**25** in 90% yield. Reaction of the oxime **26** with $NaNO_2$ in AcOH allowed obtaining compound **48**. Interaction of compound **48** with 2-aminopyridine, 4-aminopyridine, and 2-aminothiazole resulted in the formation of imines **49a**–**49c**, respectively. The anti-mycobacterial activity of the compounds synthesized was assessed against *M. tuberculosis* ATCC 27294. The most active compounds were those that did not contain an *N*-heterocyclic nucleus; compounds **49a**–**49c** showed no anti-mycobacterial activity.



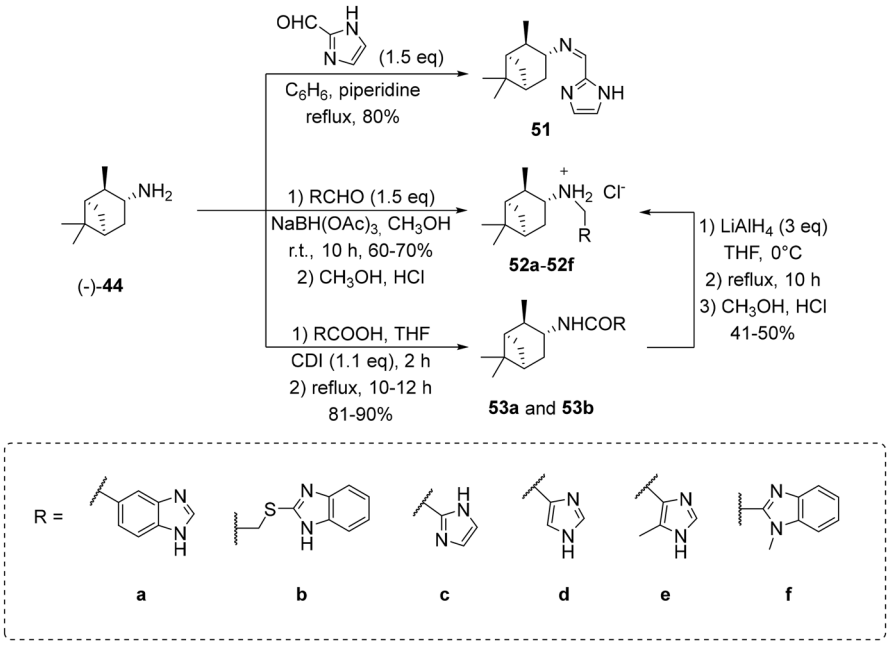
Scheme 12 Synthesis of imines (+)-camphor using nitroimine (+)-camphor

A method for reductive amination of (+)-camphor (+)-**25** was developed, and a library of tertiary amines featuring a bicyclic (+)-camphor fragment as one of substituents was synthesized, including tertiary amines **50a–50f**, which were synthesized using secondary amines of the cyclic structure as initial amines [40] (Scheme 13). It was shown that the most effective reducing agent is $Fe(CO)_5$. The authors showed that all tested primary amines react with the selective formation of only *exo*-products, whereas the use of cyclic secondary amines results in a mixture of *exo*/*endo* products in ratios from 4:1 to 1.8:1. The biological activity or other possible applications of the target tertiary amines **50a–50f** have not been investigated in this work.

The authors of [41] synthesized a number of secondary amine hydrochlorides **52a–52f** with an imidazole core and (–)-isopinocampheylamine (–)-**44** in their structure from aldehydes, and investigated their antiviral activity as inhibitors of the A/M2-WT protein of wild-type influenza A virus ((A/Hong Kong/68 (H3N2)) and the



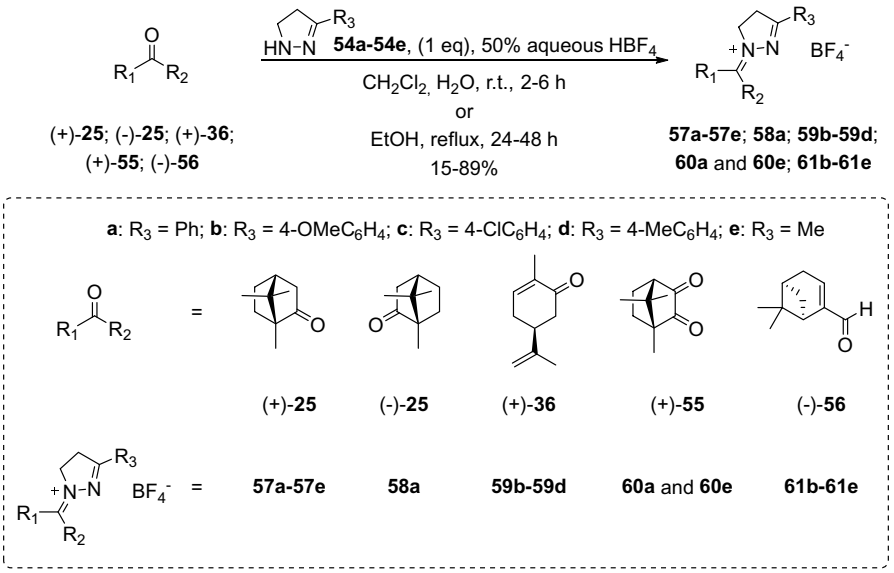
Scheme 13 Direct reductive amination of (+)-camphor using $Fe(CO)_5$ as reducing agent



Scheme 14 Synthesis of (–)-isopinocampheylamine derivatives as anti-influenza A M2 ion channel inhibitors

A/M2-S31N protein of adamantan-resistant influenza A virus (A/WSN/33 (H1N1)) to explore the impact of the imidazole core on the inhibition of the A/M2 channel (Scheme 14). The imidazole-containing imine **51** [42] was the first of compounds synthesized. Subsequently, a reductive amination of different imidazole-containing aldehydes with (–)-**44** using $NaBH(OAc)_3$ as reducing agent in CH_3OH [43], followed by treatment with HCl/CH_3OH, provided the salts of **52c–52f** with good yields. Another two salts, **52a** and **52b**, were obtained via the reduction of corresponding amides **53a** and **53b**, respectively. All of the compounds obtained were examined for cytotoxicity and the inhibitory activity on M2 ion channels (A/M2 WT and A/M2 S31N). This study indicated that linking a secondary amine to an imidazole or guanazole may further increase the inhibition of A/M2 channel activity. Compound **52e**, which was able to inhibit A/M2-WT by more than 95% and had $IC_{50} = 1.86$ μM, was identified as the lead compound in the work. Amantadine was used as a reference drug, which was found to inhibit A/M2-WT by 94% and had $IC_{50} = 0.53$ μM. The inhibitory activity of compound **52e** against mutant M2 ion channels (A/WSN/33 (H1N1)) exceeded that of the reference drug (26.7% inhibition with **52e**; $IC_{50} = 80$ μM; 10% < inhibition with amantadine; $IC_{50} = 102$ μM).

Synthesis of stable pyrazolinium salts based on terpenes and study of their antiviral activity against influenza A/Puerto Rico/8/34 (H1N1) virus were described in [44]. The target compounds **57a–57e**, **58a**, **59b–59d**, **60a**, **60e**, and **61b–61e** were synthesized by interaction of 3-substituted-4,5-dihydro-1*H*-pyrazoles **54a–54e** with (+)-camphor (+)-**25**, (–)-camphor (–)-**25**, (+)-carvone (+)-**36**, (+)-camphorquinone



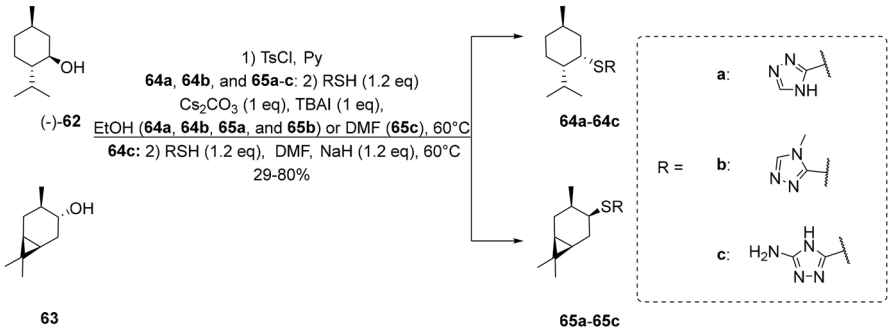
Scheme 15 Synthesis of pyrazolinium salts based on terpenoids and their derivatives

(+)-**55**, and (–)-myrtenal (–)-**56**, respectively, in the presence of HBF_4 as catalyst (Scheme 15). According to the results of biological studies, only compound **57a** showed good activity against influenza virus A/Puerto Rico/8/34 (H1N1) (IC_{50} = 6.2 μM; SI = 107). It is worth noting that its stereoisomer **58a** showed no activity at all.

A convenient approach to the synthesis of compounds combining an *N*-containing heterocycle and a monoterpene framework is the use of the native OH group of monoterpenoids in nucleophilic substitution reactions with the SH group of *N*-heterocyclic compounds.

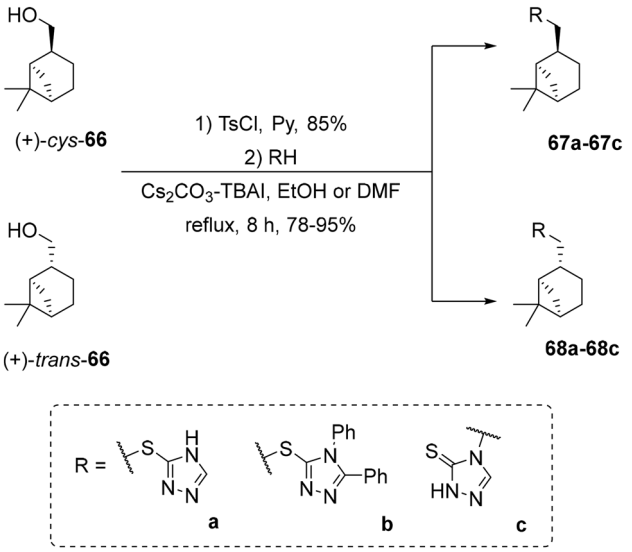
Thioethers **64a–64c** and **65a–65c** were synthesized from (–)-menthol (–)-**62** and 4-isocaranol **63**, respectively, and studied for antioxidant activity in [45] (Scheme 16). The target compounds **64a–64c** and **65a–65c** were prepared by activation of the native hydroxyl group of the starting monoterpenoids (–)-**62** and **63** by interaction with TsCl followed by nucleophilic substitution with various 2-mercaptotriazoles in the presence of a base. The antioxidant activity of compounds **64a–64c** and **65a–65c** was assessed in vitro in cellular (laboratory mouse blood erythrocytes) and acellular (laboratory mouse brain lipids) models. It was shown that isocaranol thioethers **65a–65c** are more active than (–)-menthol thioethers **64a–64c**. The most active compounds were the free amino group compounds **64c** and **65c** at a concentration of 1 μM. However, when the concentration was increased to 10 μM and 100 μM, compounds **64c** and **65c** already showed strong pro-oxidant activity in the H_2O_2-induced hemolysis model.

Synthesis of 1,3,4-triazoles featuring a monoterpene fragment from *cys*- and *trans*-myrtanols was reported in [46]. The synthesis of target compounds was carried out in the same way as described above and resulted in compounds **67a–67c**

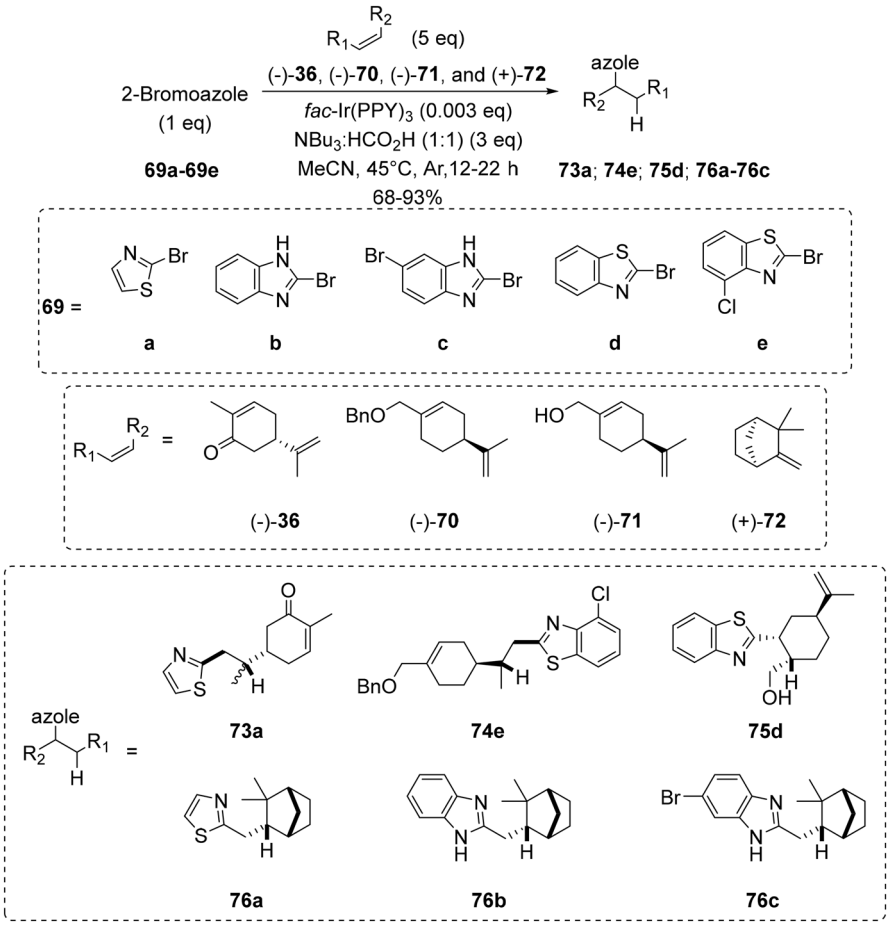


Scheme 16 Synthesis of neomenthyl and caranyl thiotriazoles

and **68a**–**68c** (Scheme 17). It should be noted that during the interaction of alcohols (+)-*cis*-**66** and (+)-*trans*-**66** with 1,2,4-triazol-2-thiol, the nitrogen atom acted as nucleophile in the reaction, which resulted in formation of compounds **67c** and **68c**. Antioxidant activity of synthesized myrtanylthiotriazoles **67a**–**67c** and **68a**–**68c** was studied in vitro in extracellular and cellular model systems. Biological studies in an extracellular model showed that compounds **67a**, **67c**, **68a**, and **68c** without a phenyl substituent have antioxidant activity at a concentration of 1 mM. Compound **68c** exhibited the greatest inhibitory activity if the concentration was reduced to 0.1 mM. All compounds obtained, except **68b** and **68c**, which were highly cytotoxic at a concentration of 0.1 mM, were studied for antioxidant and membrane-protective activities in the cellular model system. The antioxidant activity of compounds **67a**–**67c**



Scheme 17 Synthesis of substituted 1,3,4-triazoles from *cys*- and *trans*-myrtanols

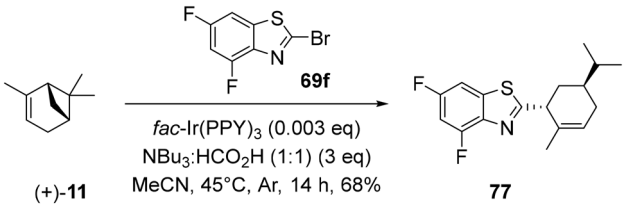


Scheme 18 Photocatalytic reductive coupling of 2-bromoazoles with non-activated alkenes-monoterpenes and their derivatives

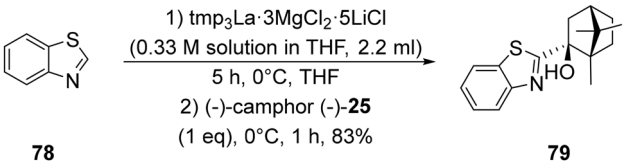
and **68a** in a cellular model was evaluated by their ability to prevent hemoglobin and lipid oxidation. Compounds **67a**, **68a**, and **67c** slowed the oxidation of oxyhemoglobin to methemoglobin by 1.5–1.6 times, whereas **68a** and **67c** reduced the rate of accumulation of secondary products of lipid peroxidation by 1.3–1.4 times.

The coupling of an *N*-containing heterocycle with a monoterpene backbone via C–C bond formation without the use of linkers or heterocycle assembly steps is an unconventional task. It is worth noting that very few works have been devoted to such transformations.

The authors of [47] developed the procedure of photocatalytic reductive coupling of heteroaryl bromides with non-activated alkenes (Scheme 18). The reaction takes place via photoinduced electron transfer from a tertiary amine to an aryl bromide that fragments to provide an aryl radical and subsequently reacts with an alkene to



Scheme 19 Reductive ring opening of (+)-α-pinene in reaction with 2-bromo-4,6-difluorobenzo[d]thiazole



Scheme 20 *Ortho*-metalation of benzothiazole and subsequent interaction with (–)-camphor

form a C–C bond. An amine also serves as the final reductant. The method is unique in that it is easy to operate; it does not affect labile functional groups and is highly selective. Thus, a number of 2-substituted benzimidazoles, benzothiazoles, and thiazoles were synthesized by interaction of various 2-bromoazoles **69a–69e** with various non-activated alkenes, including monoterpenes and their derivatives, such as (–)-carvone (–)-**36**, (–)-perillyl alcohol (–)-**71** and its benzyl ester (–)-**70**, and (+)-camphene (+)-**72**, respectively. The monoterpene residue is directly linked to the azole ring at position 2 by a single C–C bond in the compounds **73a**, **74e**, **75d**, and **76a**–**76c** obtained.

Also, the authors of this work found that this reaction with terpenes featuring a vinyl cyclobutane motif results in reductive ring opening with good yields, high regioselectivity and diastereoselectivity. For example, the interaction of (+)-α-pinene (+)-**11** with 2-bromo-4,6-difluorobenzo[*d*]thiazole **69f** afforded compound **77** (Scheme 19). No studies on the biological or catalytic activity of all compounds obtained were carried out.

The synthesis and use of $tmp_3La•3MgCl_2•5LiCl$ (tmp-2,2,6,6-tetramethylpiperidyl) base in *ortho*-metalation reactions with subsequent interaction with electrophiles are described in [48]. The authors reported that new base $tmp_3La•3MgCl_2•5LiCl$ is highly chemoselective and displays good atom economy, since all three tmp groups can be used for directed metalation. For example, compound **79** was obtained in a good yield by interaction of (–)-camphor (–)-**25** and benzothiazole **78** using $tmp_3La•3MgCl_2•5LiCl$ as a base (Scheme 20). The authors have shown that this base can be used for the synthesis of organolanthanum compounds, which can further give sterically hindered alcohols in reactions with ketones.

Thus, in this section, we considered the ways to synthesize compounds combining in their structure monoterpene fragments and *N*-containing heterocycles linked via an amide or ester linker or directly through C–N, C–S, C–O, and C–C bonds.

The reactions of esterification or nucleophilic substitution of native hydroxyl groups of monoterpenoids, as well as nucleophilic addition reactions at native carbonyl groups of functionalized *N*-containing heterocycles or linkers to which the heterocyclic nucleus was subsequently attached, were used to form such molecules. The introduction of an amino or carboxylic group into the structure of monoterpenes or their derivatives as well as the use of sulfonic acids as starting compounds allowed the formation of amide bonds to a linker or an *N*-containing heterocycle. The most unfrequently used approach to the synthesis of compounds desired was the reductive coupling of halogen-substituted *N*-containing heterocycles with alkenes and the reactions of organometallic compounds with the ketones. Some of the synthesized compounds presented in this section have exhibited antiviral, anti-mycobacterial, antioxidant, antifungal, herbicidal, and other activities, as well as catalytic properties.

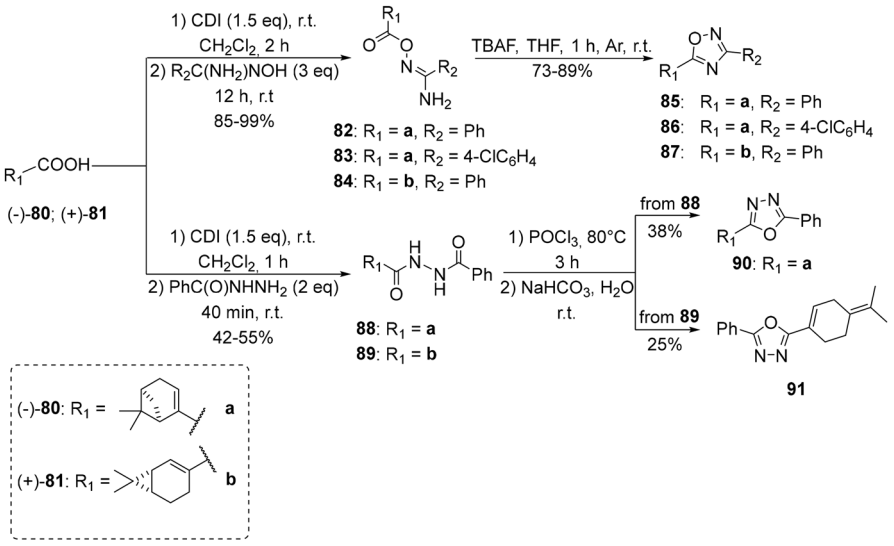
3 Synthesis and Properties of *N*-Containing Heterocyclic Compounds Synthesized from Monoterpenes or Their Derivatives, Including the Formation of a Heterocyclic Nucleus

The synthesis of *N*-containing heterocyclic compounds is an extensive area of synthetic organic chemistry. In this section, approaches to the synthesis of molecules combining in their structure a heterocyclic core and a monoterpene/monoterpenoid or their derivatives will be considered, including the stages of formation of the heterocyclic core. Synthesis of derivatives in which the heterocycle and monoterpene fragment are linked by exocyclic C–C or C–N bonds is performed from monoterpenoids and their derivatives by preparation of carboxylic acid derivatives, reductive amination reactions, or synthesis of semicarbazones followed by cyclization of the intermediate compounds. When a monoterpene fragment and a heterocycle are coupled via a linker, reactions to produce polyfunctional imines based on monoterpenoids and their subsequent cyclization are usually used. To synthesize a heterocyclic nucleus annulated with a monoterpene, the 1,3-dipolar cycloaddition reactions on the monoterpene multiple bond, domino reactions, or functionalization of the original monoterpenoid followed by closure of the *N*-heterocycle are used in most cases. The synthesis of a heterocyclic spirocyclic nucleus coupled with a monoterpene backbone is most often performed from the carbonyl group of the monoterpenoid.

3.1 Formation of an *N*-Containing Heterocycle Nucleus Coupled to the Monoterpene Residue by an Exocyclic C–C or C–N Bond

The heterocycle nucleus is often formed from the carboxylic group by esterification or amidation reactions with subsequent cyclization. In this case, the heterocycle is bound by an exocyclic C–C bond to a carboxylic acid residue.

The authors of [49] synthesized 1,2,4-oxadiazoles **85–87** and 1,3,4-oxadiazoles **90** and **91** from carboxylic acids (–)-**80** and (+)-**81** featuring bicyclic α-(–)-pinene and (+)-carene backbone, respectively, according to the known method [50]

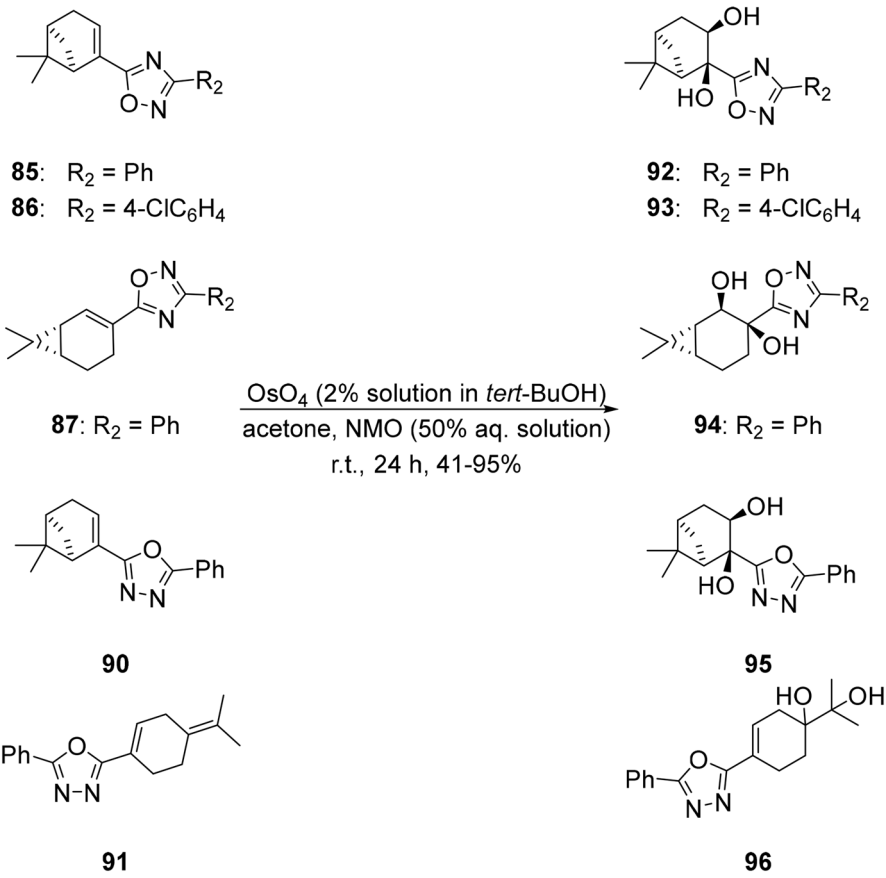


Scheme 21 Synthesis of monoterpene-based 1,2,4- and 1,3,4-oxadiazoles

(Scheme 21). The synthesis of the 1,2,4-oxadiazole heterocyclic nucleus was performed in three stages: in the first step, activation of the carboxyl group of compounds (–)-**80** and (+)-**81** with *N*,*N*-carbonyldiimidazole (CDI) in CH_2Cl_2 was performed, then the reaction with aromatic amidoximes was performed to form O-acylamidoximes **82–84**, and in the final step, an intramolecular cyclization of O-acylamidoximes was carried out in the presence of tetrabutylammonium fluoride (TBAF) as a base, resulting in the formation of 1,2,4-oxadiazoles **85–87** in 73–89% yields. Synthesis of 1,3,4-oxadiazoles **90** and **91** was performed according to a similar method: *N*,*N*-diacylhydrazines **88** and **89** were obtained by sequential activation of the carboxyl group with CDI and interaction with benzhydrazide, and formation of 1,3,4-oxadiazole cycle was performed under the action of $POCl_3$ and subsequent treatment with aqueous $NaHCO_3$ solution. It should be noted that treatment of compound **89** with $POCl_3$ resulted in compound **91** with ring rearrangement of the 2-carene framework accompanied by a loss of chirality.

Subsequent stereoselective *sin*-dihydroxylation of all heterocyclic compounds **85–91** obtained by the Criegee reaction led to the formation of diols **92–96**; compound **96** was obtained as a racemic mixture (Scheme 22). The catalytic activity in enantioselective reaction of Et_2Zn and PhCHO affording the formation of chiral 1-phenyl-1-propanol as a reference product was studied for compounds **92–96**. The best enantioselectivity was observed for compound **92** with *S* selectivity (74% *ee*; 87% yield).

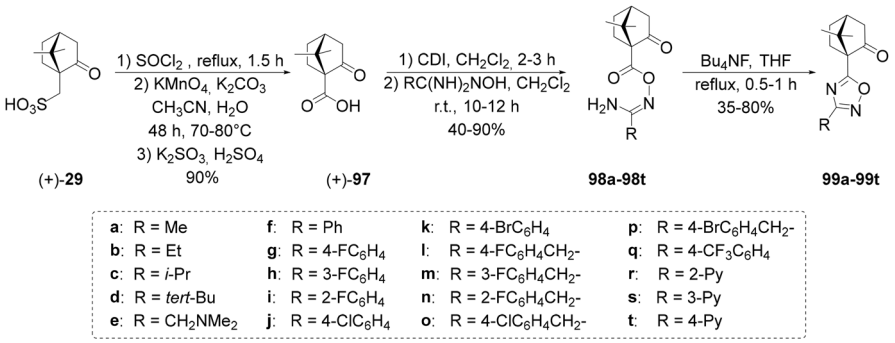
The antiproliferative activities of compounds **82–88**, **90**, **92**, **93**, and **95** against a panel of human malignant cell lines isolated from cervical (HeLa), ovarian (A2780), and breast (MCF7 and MDA-MB-231) cancers was also investigated. O-Acylated amidoximes **82–84** exhibited remarkable growth inhibitory activities against HeLa (IC_{50} values ranged from 11.46 to 13.62 μM) comparable to those of reference agent



Scheme 22 Dihydroxylation of monoterpene-based 1,2,4- and 1,3,4-oxadiazoles

cisplatin (IC_{50} = 12.43 μM). Compounds **82–84** showed inhibitory activity (IC_{50} values ranged from 1.44 to 2.05 μM), lower than that of the comparison drug cisplatin (IC_{50} = 1.30 μM) against A2780 cell lines. Compounds **82–84** showed no inhibitory activity against breast tumor cell lines (MCF7 and MDA-MB-231). All oxadiazoles **85–87**, **90**, **93**, **93**, and **95** showed no activity against all the tumor cell lines studied.

A set of O-acylamidoximes **98a–98t** and 1,2,4-oxadiazoles **99a–99t** from (+)-ketopinic acid (+)-**97** (a derivative of (+)-camphor) were synthesized in a similar way [50] in a recent publication [51] (Scheme 23). (+)-Ketopinic acid was synthesized from (1*S*)-(+)-camphor-10-sulfonic acid (+)-**29**, as was published previously [52]. All compounds synthesized were tested in vitro for cytotoxicity against the MDCK cell line and for antiviral activity against influenza viruses A\Puerto Rico/8/34 (H1N1) and A/Anhui/1/2013 (H7N9). It was shown that of 40 tested compounds, 17 had SI values of 10 and higher, making them good candidates for further studies. Compounds **99g**, **99h**, **99m**, **99p**, and **99s** had SI values higher than 56 against A\Puerto Rico/8/34 (H1N1). It should be noted that some of

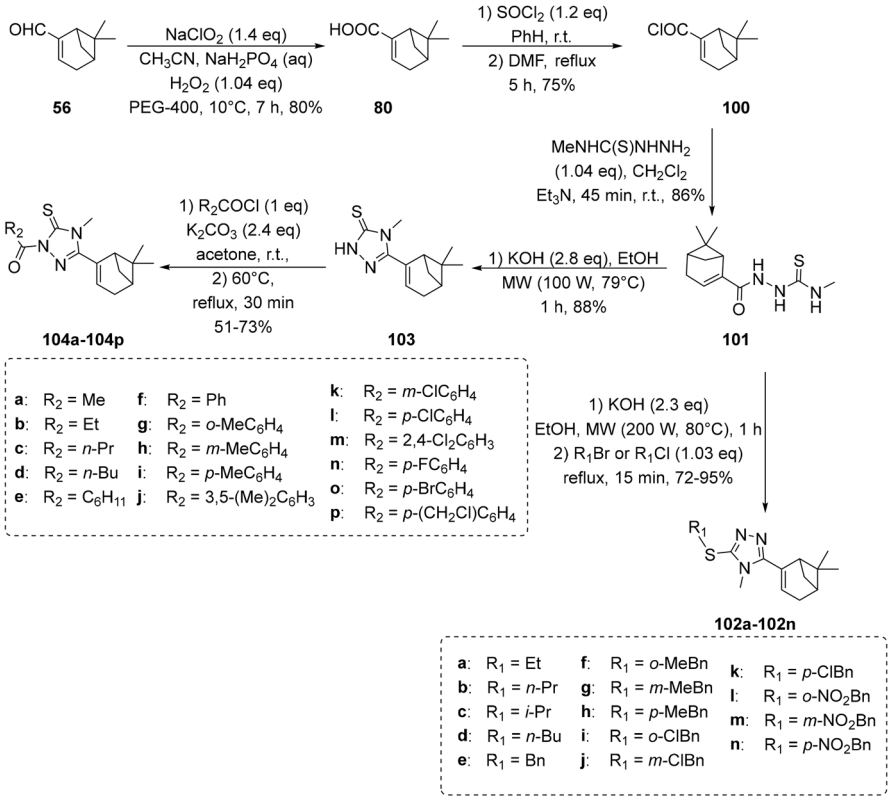


Scheme 23 Synthesis of O-acylamidoximes and 1,2,4-oxadiazoles from (+)-ketopinic acid

the compounds synthesized show good antiviral properties against a genetically distinct influenza virus of the H7N9 subtype (IC_{50}(**98k**) = 3 ± 0.4 μM; SI(**98k**) = 118; IC_{50}(**99o**) = 8 ± 1 μM; SI(**99o**) = 120).

Triazole derivatives with a monoterpene fragment in their structure were synthesized by the authors of [53] from myrtenal **56** (Scheme 24). It is worth noting that in [53, 54], myrtenal **56** was synthesized by oxidation of α-pinene with SeO_2, but configuration of the stereocenters in the aliphatic cycle was not indicated. At the first stage, myrtenal **56** was oxidized with $NaClO_2$-H_2O_2 as oxidant in aqueous solution to give myrtenic acid **80** in 80% yield. Subsequent interaction of acid **80** with $SOCl_2$ and further acylation of methylthiosemicarbazide resulted in product **101**. Further, compounds **102a–102n** featuring a heterocyclic 1,2,4-triazole nucleus were synthesized by one-pot sequential processes involving the cyclization reaction of compound **101** under microwave irradiation and the nucleophilic substitution with different alkyl halides. Antifungal activity of the compounds **102a–102n** was evaluated by the in vitro method against *Fusarium oxysporum cucumerinum*, *Physalospora piricola*, *Alternaria solani*, *Cercospora arachidicola*, and *Gibberella zeae* at 50 μg/ml. Compounds **102a**, **102c**, and **102l** showed 91–98% inhibition of *Physalospora piricola* growth, comparable to the 96% inhibition of the commercial reference drug azoxystrobinoma.

Within the scope of continuing the search for new biologically active myrtenal derivatives, the same authors [54] synthesized and evaluated antifungal and herbicidal activity of a number of *N*-acylated derivatives **104a–104p** synthesized from 4-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-thione **103** (Scheme 24). Compound **103**, in turn, was obtained by cyclization of compound **101** in the presence of KOH under microwave irradiation. The authors assumed that acylation of the triazole fragment would produce more active agents than **102a–102n**. However, the antifungal activity of synthesized compounds **104a–104p** was lower than that of **102a–102n**. Most of the compounds synthesized showed excellent herbicidal activity (more than 80% growth inhibition of *Brassica campestris* at a concentration of 100 mg/l). It was shown that myrtenal exhibited weak herbicidal activity (20% inhibition of *B. campestris*), and the comparison drug flumioxazin showed 63% growth inhibition of *B. campestris* at concentrations of 100 mg/l. Thus, the

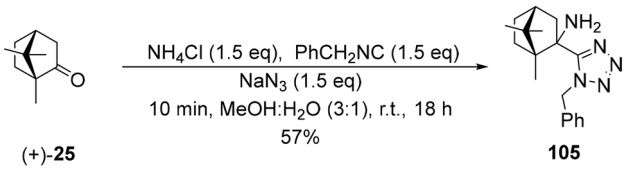


Scheme 24 Synthesis of myrtenal-based triazole derivatives

authors were able to synthesize a library of compounds with myrtenal and triazole fragments in their structure that are promising for further biological research.

Another approach to creating a monoterpenoid-based heterocyclic core is to modify the carbonyl group. For example, the authors of [55] synthesized more than 50 tetrazole derivatives using the Ugi reaction. The authors reported for the first time the use of ammonia in the Ugi tetrazoles variation, leading to unprotected amino tetrazoles, which then can be used to carry out many transformations for the synthesis of biologically active substances. It was found that aliphatic ketones enter the investigated transformations perfectly, and target tetrazoles are obtained in good yields. In addition, sterically hindered (+)-camphor (+)-**25** enters into this transformation with the formation of compound **105** in 57% yield (Scheme 25). Other monoterpenoids were not used by the authors of this work.

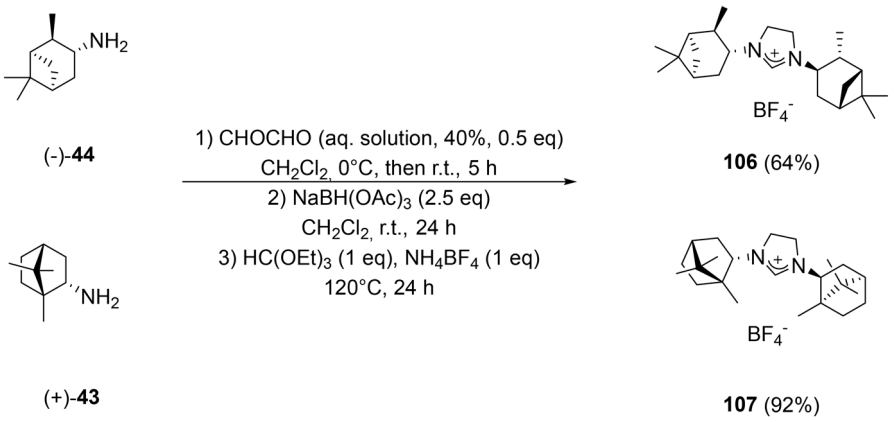
Synthesis of molecules featuring an imidazoline cycle and a monoterpene fragment is performed by dimerization of initial monoterpenoid by the reaction of a carbonyl group with a diamine or amino group of the monoterpenoid derivative with dialdehyde followed by cyclization. In this case, the heterocyclic nucleus is linked directly to the monoterpene residue by an exocyclic C–N bond.



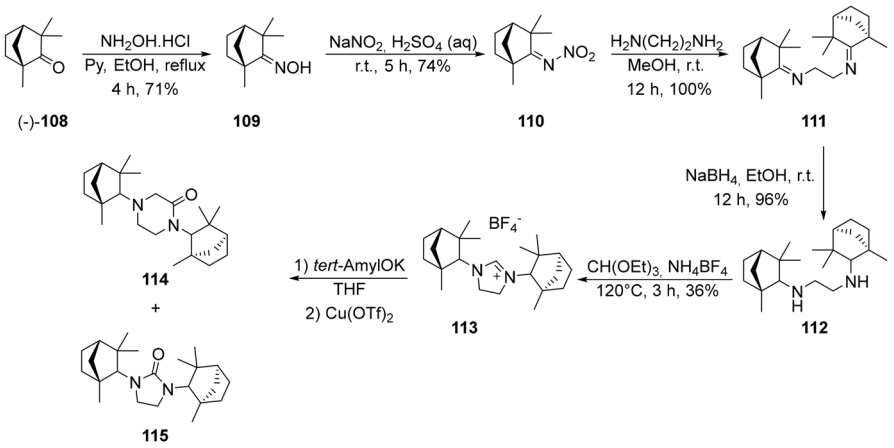
Scheme 25 (+)-Camphor as an oxo-component in the Ugi reaction

The synthesis of imidazolidene ligands **106** and **107** from bicyclic amines –(–)-isopinocampheylamine (–)-**44** and (+)-bornylamine (+)-**43**, respectively, was described in [56] (Scheme 26). The synthesis of salts **106** and **107** was carried out by interaction of amines (–)-**44** and (+)-**43** with glyoxal, followed by reduction of the C=N bond with $NaBH(OAc)_3$ and condensation with triethyl orthoformate ($HC(OEt)_3$) in the presence of ammonium tetrafluoroborate (NH_4BF_4) at the final stage. The yields of salts **106** and **107** at the final stage were 64 and 92%, respectively. These salts were further used as ligands in the asymmetric synthesis of oxindoles with 67 and 71% enantioselectivity, respectively.

The authors of [57] suggested that an increase in the volume of the substituents in the imidazolinium salts could lead to an increase in enantioselectivity of the corresponding imidazoline carbene ligands in asymmetric reactions. Thus, they synthesized imidazolinium salt **113** from (–)-fenchone (–)-**108** (Scheme 27). Interaction of (–)-fenchone with hydroxylamine hydrochloride in the presence of pyridine as a base led to the formation of oxime **109**, whose heating with aqueous $NaNO_2$ solution allowed generation of nitroimine **110**. Reaction of **110** with a half of a molar equivalent of ethylenediamine was accompanied by the formation of diimine **111** in a quantitative yield. Reduction of diimine **111** with $NaBH_4$ in EtOH resulted in the formation of compound **112** in a high yield. Condensation of diamine **112** with $HC(OEt)_3$ in the presence of NH_4BF_4 led to the formation of imidazolium salt **113** in 36% yield. The authors of the work planned to synthesize *N*-heterocyclic carbene



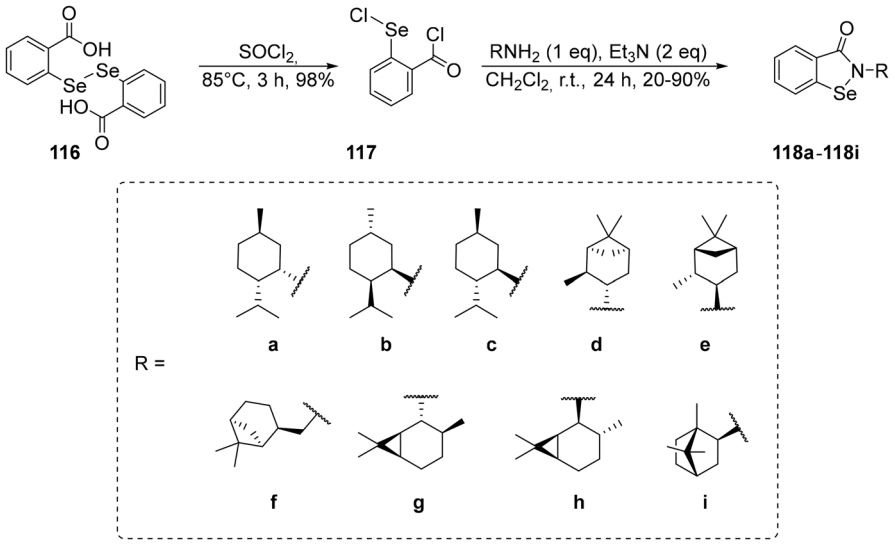
Scheme 26 Synthesis of imidazolidene ligands from (–)-isopinocampheylamine and (+)-bornylamine



Scheme 27 Synthesis of the difenchylimidazolinium tetrafluoroborate carbene ligand precursor from (–)-fenchone

by interaction of the salt **113** with potassium *tert*-amylate (*tert*-AmylOK) and copper(II) triflate ($Cu(OTf)_2$) at the next stage, but this reaction led to an unexpected transformation of the imidazoline core of compound **113** in a mixture of substituted piperazine-2-one **114** and urea derivative **115**. The possible mechanism of this reaction is discussed in detail in the work. The biological or catalytic activity of compounds obtained has not been investigated.

Acylation and subsequent intramolecular cyclization of monoterpene derivatives containing an amino group can also lead to the formation of heterocyclic compounds of interesting structure. For example, in [58], the synthesis of chiral benzisoselenazol-3(2*H*)-ones substituted on the nitrogen atom with monoterpene fragments was described. Compounds synthesized were studied for antioxidant and anticancer activity. Thus, a series of compounds **118a–118h** were synthesized from acid **116**, containing monoterpene moieties *p*-menthane **118a–118c**, pinane **118d–118f**, and carane **118g**, and **118h** in their structure (Scheme 28). Acid **116** was obtained by a multistep procedure from anthranilic acid according to the previously described procedure [59], the subsequent reaction of acid **116** with $SOCl_2$ led to the formation of compound **117**. Interaction of compound **117** with monoterpene amines allowed obtaining compounds **118a–118h** with yields from 20 to 90%. The ability to reduce H_2O_2 was tested by a frequently used procedure, where the Se-catalyst reduces the peroxide and, in the oxidized form, is able to transform the dithiol to a disulfide. The most efficient H_2O_2 reduction was observed for compounds possessing pinane fragment **118d** and **118f**, with the total substrate conversion observed in 30 and 60 min, respectively. The antiproliferative capacity was measured by the MTT ((3-(4,5-dimethyldiazol-2-yl)-2,5-diphenyl tetrazolium bromide)) assay on breast cancer MCF-7 and human promyelocytic leukemia HL-60 cell lines. According to biological investigations, compound **118d** exhibited the highest antiproliferative potential (IC_{50}(**118d**) = 7.1 ± 0.4 μM). It is worth noting that the presence of methylene groups between the fragments of the heterocycle and the monoterpene



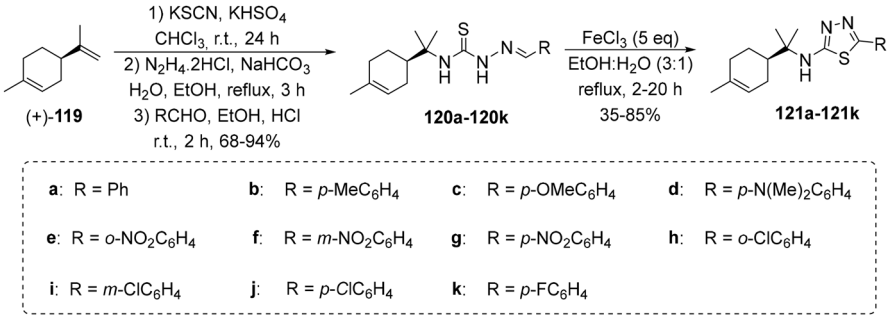
Scheme 28 Synthesis of chiral benzisoselenazol-3(2*H*)-ones containing a monoterpene moiety

(compound **118f**) significantly decreases the activity (IC_{50}(**118f**) = 250.0 ± 24.7 μM). The best anticancer activity against MCF-7 cells was observed for compound **118c** (IC_{50}(**118c**) = 11.9 ± 0.2 μM). In [59], compound **118i** with a bicyclic *exo*-borneol moiety showed high antioxidant activity (total substrate conversion was observed in 15 min) (Scheme 28).

3.2 Formation of an *N*-Containing Heterocycle Nucleus Coupled to the Monoterpene Frame Via a Linker

A common approach to the synthesis of *N*-containing heterocycles that are coupled via a linker to a monoterpene fragment is the modification of the monoterpene/monoterpenoid with a linker, such as thiosemicarbazide, polyfunctional amines, or an aromatic fragment, which are then used to form the heterocyclic core. In this case, there is an acyclic or alicyclic linker between the heterocyclic nucleus and the monoterpene moiety.

The synthesis of 1,3,4-thiadiazoles derivatives **121a–121k** with an aromatic substituent and *R*-(+)-limonene fragment in their structure and possessing trypanocidal activity against epimastigote and trypomastigote forms of *Trypanosoma cruzi* was described in [60] (Scheme 29). The target 1,3,4-thiadiazoles **121a–121k** were synthesized by cyclization of benzaldehyde thiosemicarbazones **120a–120k** under reflux in an aqueous alcoholic solution in the presence of $FeCl_3$ in 35–85% yields. Compounds **120a–120k** were prepared by a multistep procedure from *R*-(+)-limonene-(+)-**119** according to the previously described procedure [61]. The results of biological studies of trypanocidal activity showed that the limonene fragment significantly increases the biological activity of 1,3,4-thiadiazoles, since the **121a–121k** compounds were much more active than similar derivatives but with a free amino

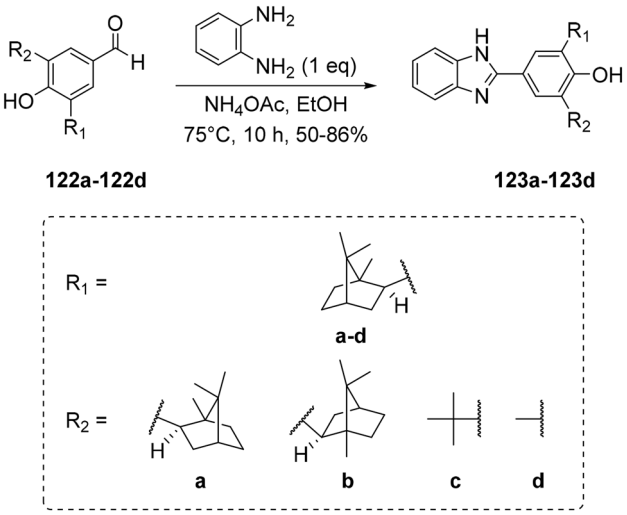


Scheme 29 Synthesis of 1,3,4-thiadiazoles with an *R*-(+)-limonene fragment as substituent

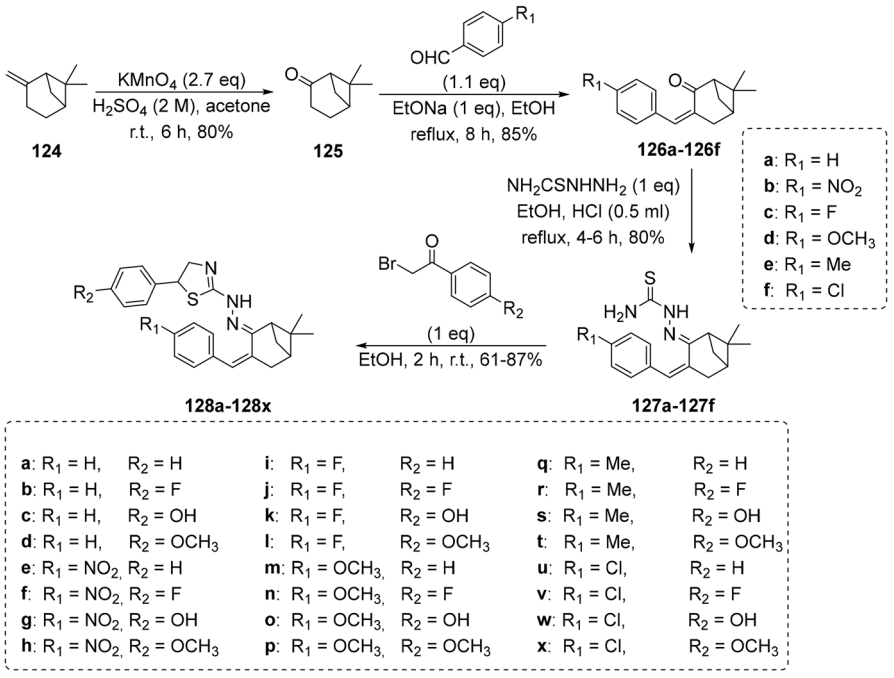
group. Also, all compounds with a *R*-(+)-limonene fragment were less cytotoxic as compared to compounds with a free amino group. The 50% inhibitory concentration against *T. cruzi* compound **121k** with a fluorine atom in the fourth position of the benzene ring was 6.9 ± 1.6 μM. A comparison of the activity of compounds **121e–121g** showed that the compound with a nitro group in the *ortho*-position of the benzene ring has the lowest 50% inhibitory concentration, but the compound **121g** featuring a nitro group in the *para*-position was the least cytotoxic. Among the chloride-containing compounds **121h–121j**, the lowest 50% inhibitory concentration of 1.6 μM was observed for compound **121i** (IC_{50}(**121i**) = 1.6 μM), but it proved to be the most cytotoxic (CC_{50}(**121h**) = 950.0 ± 25.4 μM; CC_{50}(**121i**) = 166.7 ± 17.9 μM; CC_{50}(**121j**) = 793.3 ± 60.4 μM).

The authors of [62] synthesized 2-substituted 1*H*-benzimidazoles containing a phenol fragment with isobornyl and *tert*-butyl groups. Thus, the condensation of substituted benzaldehydes **122a–122d** with *o*-phenylenediamine allowed obtaining a series of 2-substituted benzimidazoles **123a–123d** (Scheme 30). Their antioxidant and membrane-protective properties were evaluated in in vitro models and compared with those of known analogues. The greatest antioxidant activity was observed for compounds **123c** and **123d**, which contain bicyclic and aliphatic substituents in the phenol *ortho*-positions. The less antioxidant activity was observed for compounds with two isobornyl fragments **123a** and **123b**. The highest membrane-protective activity was observed for compounds **123c** and **123d** (the percent of hemolysis after 5 h of the experiment was 5.8 ± 0.3 and 16.1 ± 0.7 for compounds **123c** and **123d**, respectively, while in the control experiment, the percent of hemolysis was 49.8 ± 0.7).

The synthesis of β-pinene-based thiazole derivatives **128a–128x** was described in a recent publication [58] (Scheme 31). It is worth noting that the configuration of the optical centers in the original β-pinene **124** is not specified in the work. At the first stage, β-pinene was oxidized with $KMnO_4$ to form compound **125**. Subsequent aldol condensation of ketone **125** with a series of 4-substituted benzaldehydes allowed compounds **126a–126f** to be obtained, and further nucleophilic addition of thiosemicarbazide to compounds **126a–126f** led to the formation of thiosemicarbazones **127a–127f**. Compounds **127a–127f** were cyclized with *para*-substituted phenacyl

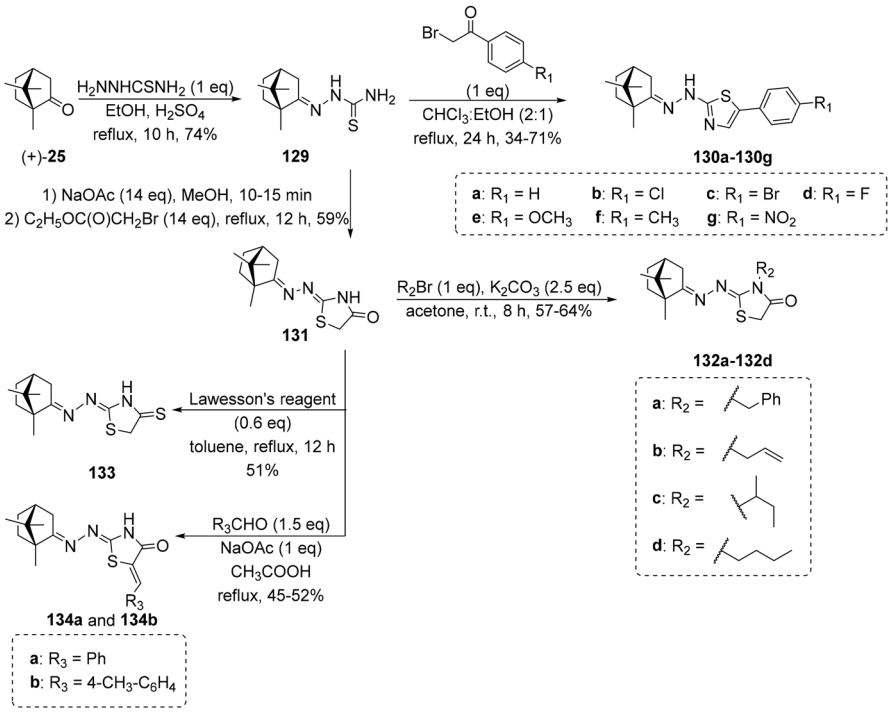


Scheme 30 Synthesis of 2-substituted benzimidazoles containing an isobornyl moiety



Scheme 31 Synthesis of β-pinene-based thiazole derivatives

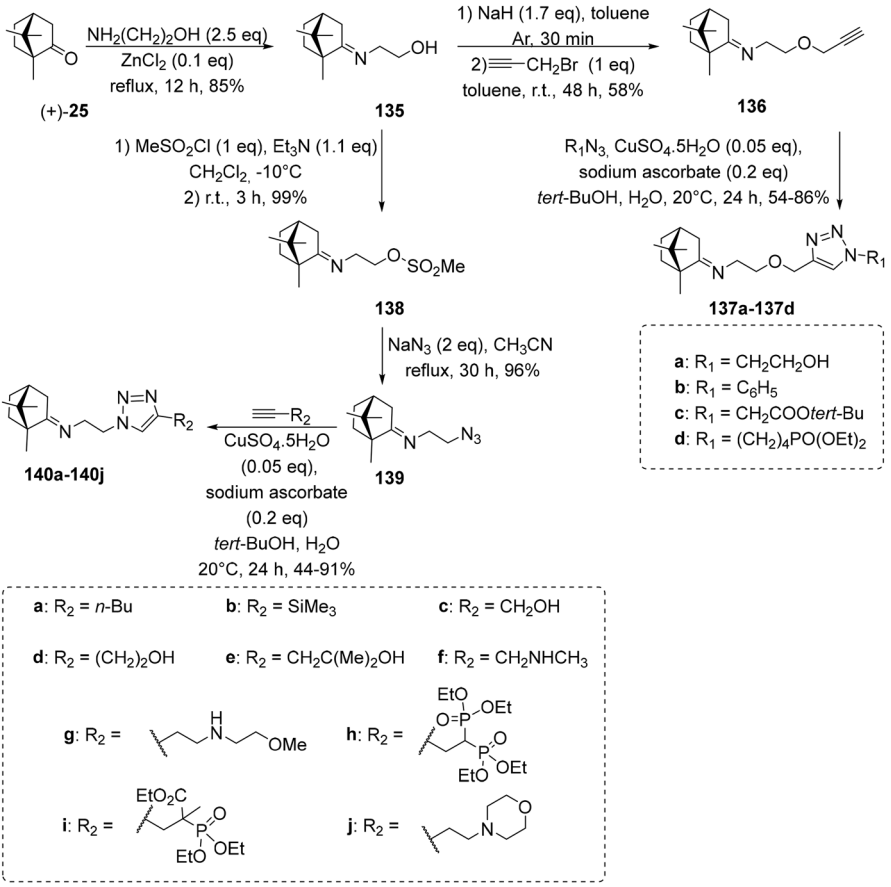
bromides to form the target compounds **128a–128x** with a substituted thiazole heterocycle in their structure. The designed 24 compounds were evaluated for cytotoxicity against three cancer cell lines (colon tumor CT-26 cells, human cervical carcinoma



Scheme 32 Synthesis of (+)-camphor-based thiazole and thiazolidin-4-one derivatives

Hela cells, and human hepatocarcinoma SMMC-7721 cells) using the MTT assay with etoposide (IC_{50}(Hela) = 7.89 ± 1.37 μM; IC_{50}(CT-26) = 2.22 ± 1.26 μM; IC_{50}(SMMC-7721) = 40.44 ± 0.29 μM) as a positive control. Compound **128g** showed the lowest IC_{50} values (IC_{50}(Hela) = 3.48 ± 0.14 μM; IC_{50}(CT-26) = 8.84 ± 0.16 μM; IC_{50}(SMMC-7721) = 6.69 ± 0.15 μM). The results of a study of the mechanism of compound **128g** action were also described in [58].

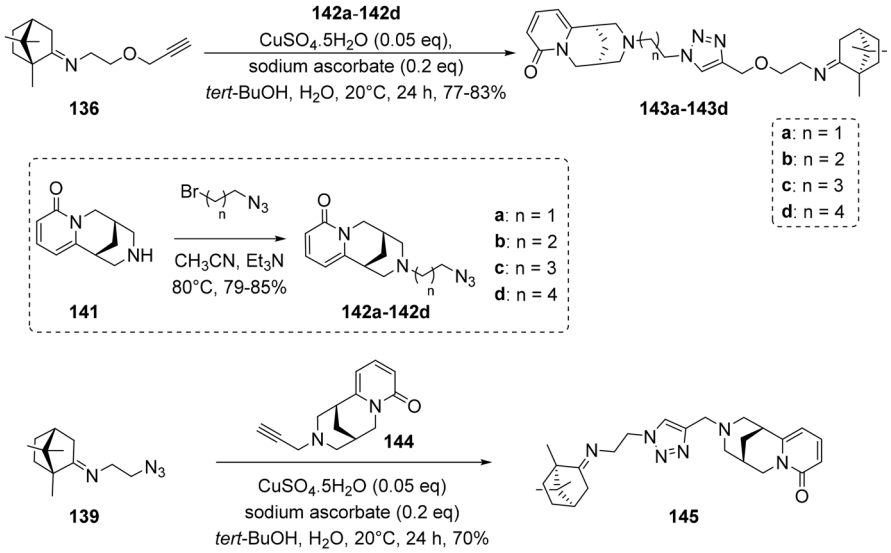
The synthesis of a set of *N*-containing heterocyclic compounds **130a–130g**, **132a–132d**, **133**, **134a**, and **134b** with thiazole and thiazolidin-4-one nuclei from (+)-camphor (+)-**25** was described in [63] (Scheme 32). In the first step, (+)-camphor thiosemicarbazone **129** was synthesized. Further, thiazole derivatives **130a–130g** were obtained by interaction of thiosemicarbazone **129** with different *para*-substituted phenacyl bromides. Interaction of thiosemicarbazone **129** with $BrCH_2CO_2Et$ resulted in the formation of thiazolidin-4-one **131** in 59% yield. Compounds **132a–132d** featuring different substituents at the nitrogen atom of the heterocyclic nucleus, thiazolidinedione **133**, and compounds **134a** and **134b** with an aromatic substituent at the fifth position of the heterocyclic nucleus were obtained by modification of compound **131**. The antiviral activity and cytotoxicity of the synthesized derivatives **130a–130g**, **132a–132d**, **133**, **134a**, and **134b** against vaccinia virus were evaluated; cidofovir (IC_{50} = 40.01 ± 2.8 μM; TC_{50} = 475.3 ± 74.9 μM) was used as a positive control. The IC_{50} values for compounds **130b**, **130c**, and **130e** containing the thiazole and aromatic fragments ranged from 2.4 to 3.7 μM.



Scheme 33 Synthesis of (+)-camphor-based 1,2,3-triazole derivatives

However, the cytotoxicity (TC_{50}) of these compounds was rather high and ranged from 64.1 to 93.6 μM. This work shows that modifications of compound **131** ($TC_{50} = 305.2 \pm 74.3$ μM) lead to increased toxicity in its derivatives **132–134** ($TC_{50} = 17.5–287.8$ μM). Of all thiazolidin-4-one derivatives, compound **134b** exhibits moderate antiviral activity and is the least cytotoxic ($IC_{50} = 9.5 \pm 2.5$ μM; $TC_{50} = 120.5 \pm 4.7$ μM). It is worth noting that all compounds synthesized in this work were more cytotoxic as compared to the reference drug Cidofovir.

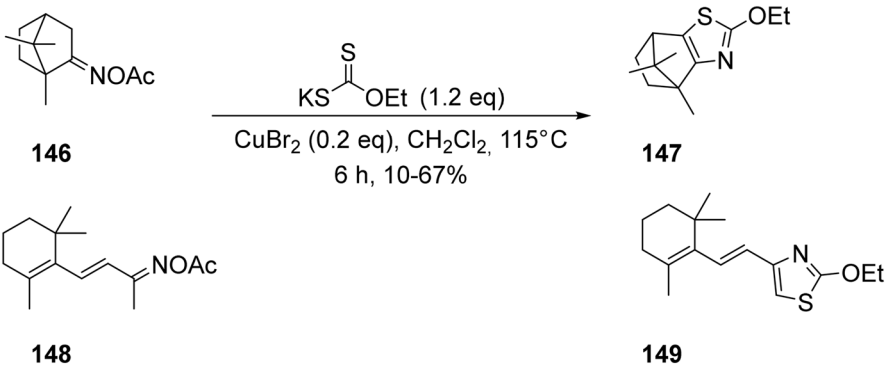
A series of 1,2,3-triazole derivatives **137a–137d** and **140a–140j** featuring the (+)-camphor (+)-**25** frame in their structure was synthesized in [64] by the [2+3] cycloaddition reaction of azides to acetylenes catalyzed by Cu (II) salts (Scheme 33). At the first stage, the interaction of (+)-camphor with 2-aminoethanol resulted in compound **135**. Further transformations were carried out with the OH group, whereby the carbon residue of ethanol acted as a linker between the (+)-camphor residue and the heterocyclic nucleus. Interaction of **135** with NaH and



Scheme 34 Synthesis 1,2,3-triazoles-conjugates (+)-camphor and (–)-cytisine

the subsequent nucleophilic substitution reaction with propargyl bromide resulted in the formation of propargyl ether **136**, which was then used in reactions with different azides to obtain 1,2,3-triazoles **137a–137d** in good yields. Compound **139** was obtained by sequential interaction of alcohol **135** with MsCl followed by nucleophilic substitution with NaN_3. Further reaction of azide **139** with a number of substituted acetylenes resulted in the formation of the target 4-substituted 1,2,3-triazoles **140a–140j** in good yields. Cytotoxicity and antiviral activity against influenza virus A/Puerto Rico/8/34 (H1N1) were evaluated in vitro for all compounds synthesized. Compounds **140d**, **140e**, **140g**, and **140j** as well as compound **137a** had low cytotoxicity ($CC_{50} > 800$ μM), while the 50% inhibitory concentration was below 60 μM, so that all these compounds had a selectivity index greater than 10. It is also worth noting that the mentioned compounds were more active than three reference drugs (amantadine (SI = 4), rimantadine (SI = 5), and deitiforin (SI = 6)) and much less cytotoxic.

The same research group [65] synthesized a series of (+)-camphor and (–)-cytisine conjugates and studied their antiviral activity (Scheme 34). Coupling of two pharmacophore blocks was also performed by the [2 + 3] cycloaddition of azides to acetylenes catalyzed by Cu (II) salts. It should be noted that in this case, the 1,2,3-triazole nucleus served as a linker between the cytisine and camphor moieties. Cytisine **141** underwent a nucleophilic substitution reaction with bromoalkyl azides to form compounds **142a–142d**. Next, the azides **142a–142d** obtained reacted with compound **136**, the synthesis of which from (+)-camphor has been described earlier, to form 1,2,3-triazoles **143a–143d**. Compound **145** was obtained by the interaction of azide **139** and propargyl **144** in 70% yield. Cytotoxicity and antiviral activity against influenza virus A/Puerto Rico/8/34 (H1N1) were evaluated in vitro



Scheme 35 Synthesis of thiazole derivatives from cyclocitral and camphor oxime acetates

for all compounds synthesized. The lead compound **143d** ($IC_{50} = 8.0 \pm 1.0$ μM; $CC_{50} = 168 \pm 11.0$ μM) was more effective than the reference drug rimantadine ($IC_{50} = 67.0 \pm 5.0$ μM; $CC_{50} = 335 \pm 16.0$ μM), and the 50% inhibitory concentration of the remaining compounds ranged from 65 to 519 μM, according to biological studies.

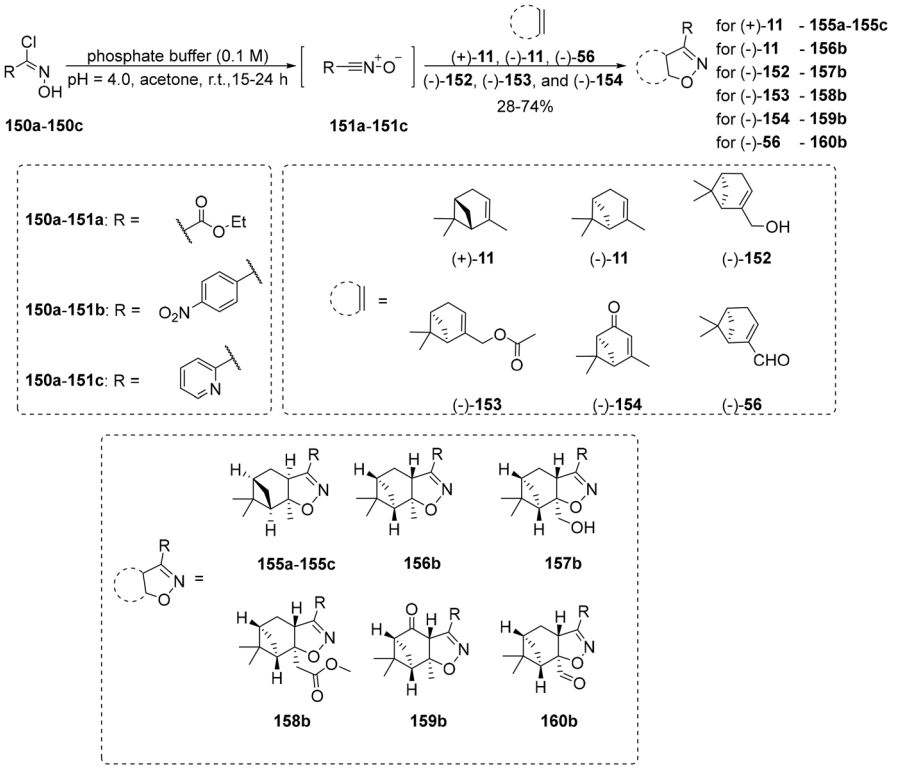
3.3 Synthesis of Annulated *N*-Containing Heterocyclic Compounds from Monoterpene and Their Derivatives

The main approaches to the synthesis of an *N*-containing heterocyclic derivatives featuring a heterocycle condensed with a monoterpene framework are reactions of 1,3-dipolar addition to multiple C–C bonds, as well as modification of native or introduction of new functional groups into the original monoterpene/monoterpenoid and further cyclization reactions.

A novel copper-catalyzed annulation of oxime acetates and xanthates for the synthesis of thiazole derivatives was developed in [66]. The authors show that this transformation is applicable to a wide range of compounds, both aromatic and aliphatic as well as natural. Thus, the [3+2] annulation reaction produced thiazol-2-yl ethers **147** and **149** with cyclocitral and camphor fragments in their structure, respectively (Scheme 35). The work also presents the proposed mechanism of transformations under study, while the biological or catalytic activity of the compounds obtained has not been investigated.

Reactions of 1,3-dipolar addition are often used for the convenient one-step synthesis of five-membered heterocyclic compounds. For example, the cycloaddition of nitrile oxides to multiple bonds is of a great synthetic value, since the reaction produces the isoxazoline core, which occurs in many compounds that have a wide spectrum of biological activity [67, 68].

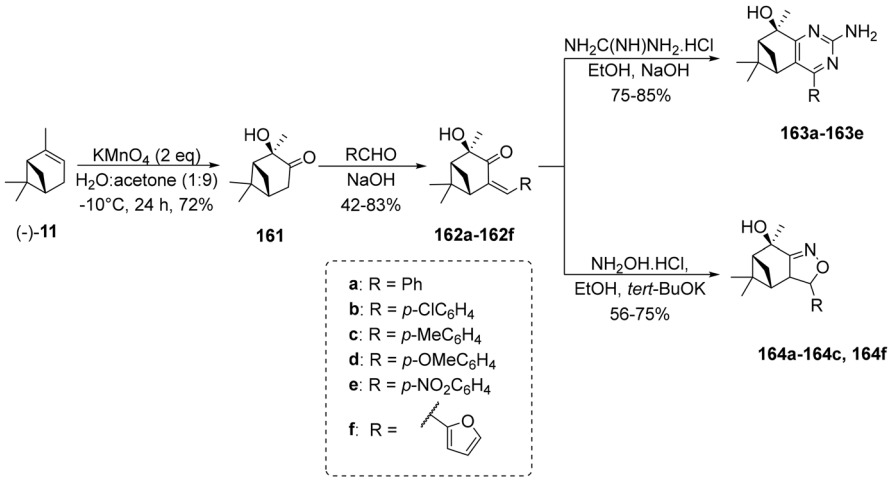
In [69], compounds **155a–155c** and **156b–160b** (Scheme 36) featuring an isoxazoline cycle condensed with a bicyclic monoterpene fragment were synthesized by cycloaddition of nitrile oxides **151a**–**151c** to different alkenes. The parent compounds containing the double C–C bond were used: (1*R*)-(+)-α-pinene



Scheme 36 Synthesis of isoxazoline derivatives from monoterpenes/monoterpenoids containing a double C–C bond

(+)-**11**, (1*S*)-(–)-α-pinene (–)-**11**, (1*R*)-(–)-myrtenol (–)-**152**, (1*R*)-(–)-myrtenol acetate (–)-**153**, (1*S*)-(–)-verbenone (–)-**154**, and (1*R*)-(–)-myrtenal (–)-**56**. The biological or catalytic activity of the synthesized compounds **155a–155c** and **156b–160b** has not been investigated, but the authors of [69] suggest that these compounds could find application as ligands in asymmetric catalysis.

The authors of [70] synthesized a series of 2-aminopyrimidines **163a–163e** and isoxazolines **164a–164c** and **164f** condensed with a bicyclic alcohol derived from α-(–)-pinene (–)-**11** (Scheme 37). In the first step, α-(–)-pinene (–)-**11** was oxidized with $KMnO_4$ to give (+)-2-hydroxy-3-pinanone **161**. Subsequent aldol condensation of **161** with aromatic aldehydes led to the formation of conjugated enones **162a–162f** in yields of 42–83%. Interaction of enones **162a–162f** with guanidine hydrochloride and hydroxylamine hydrochloride led to the formation of the target 2-aminopyrimidines **163a–163e** and isoxazolines **164a–164c** and **164f**, respectively. A study of the antibacterial activity against *C. albicans*, *A. niger*, *G. tropicalis*, *E. coli*, *S. aureus*, *B. subtilis*, and *P. fluorescens* of all compounds obtained showed that compounds **163b** and **164b** exhibited strong antibacterial activity against *E. coli* bacteria (MIC = 3.9 μg/ml), and compounds **163a**, **163d**,



Scheme 37 Synthesis of 2-aminopyrimidines and isoxazolines from α-(–)-pinene

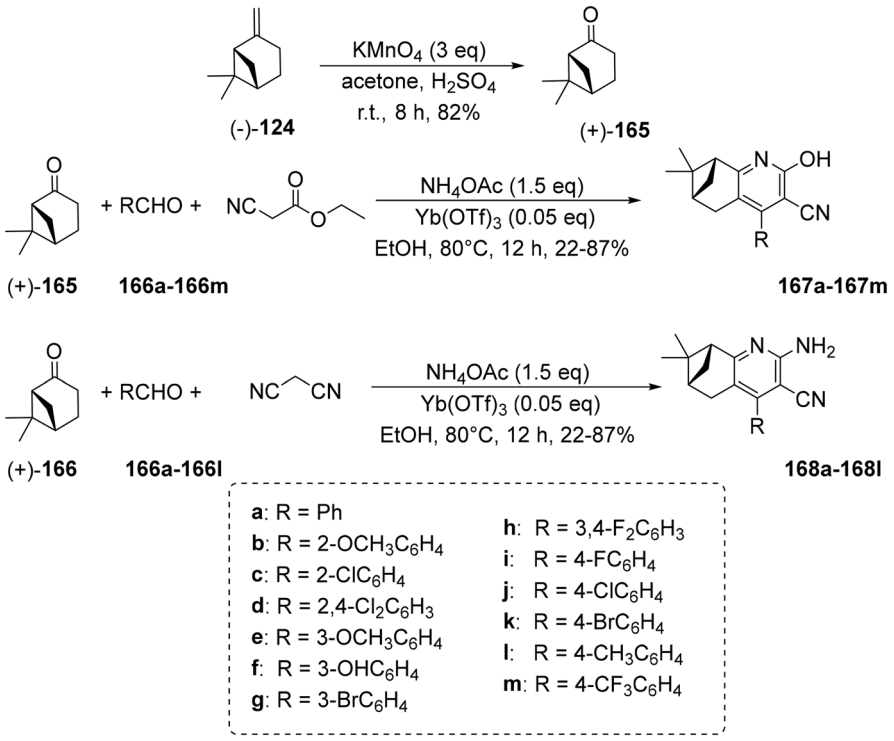
and **163e** exhibited moderate activity against *E. coli* bacteria (MIC = 7.8 µg/ml). Compounds **163b** and **163e** have moderate antibacterial activity against *B. subtilis* bacteria (MIC = 7.8 µg/ml).

A series of novel 3-cyanopyridine derivatives **167a–167m** and **168a–168l** of β-(–)-pinene.

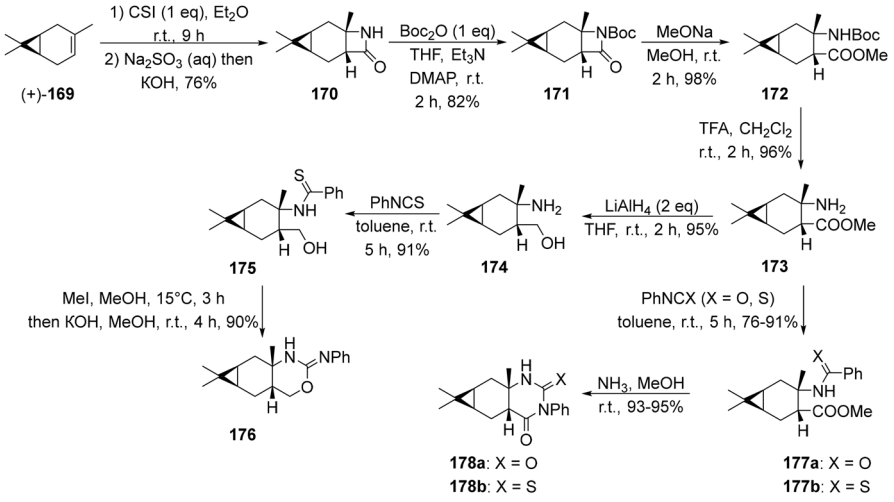
(–)-**124** was synthesized by one-pot four-component domino reactions in [71] (Scheme 38). In the first step, (+)-nopinone (+)-**165** was synthesized by oxidation of commercially available.

β-(–)-pinene (–)-**124** with $KMnO_4$. Further compounds **167a–167m** and **168a–168l** were synthesized by one-pot four-component domino reactions between (+)-nopinone (+)-**165**, different aromatic aldehydes **166a–166m**, ethyl cyanoacetate (or malononitrile), and NH_4OAc using $Yb(OTf)_3$ as catalyst. The authors of [71] suggested that combining two biologically active molecules, cyanopyridine [72] and pinene, would produce compounds with new biological activity. The targeted compounds were evaluated for their antimicrobial activity against four bacteria (*Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*) and a fungus (*Candida albicans*). Among all compounds synthesized, compound **167h** featuring an aromatic ring with two fluorine atoms (MIC = 15.6 mg/l) was the most active against *S. epidermidis* and *E. aerogenes* bacteria, whereas the MIC of the reference drug kanamycin was 3.9 mg/l.

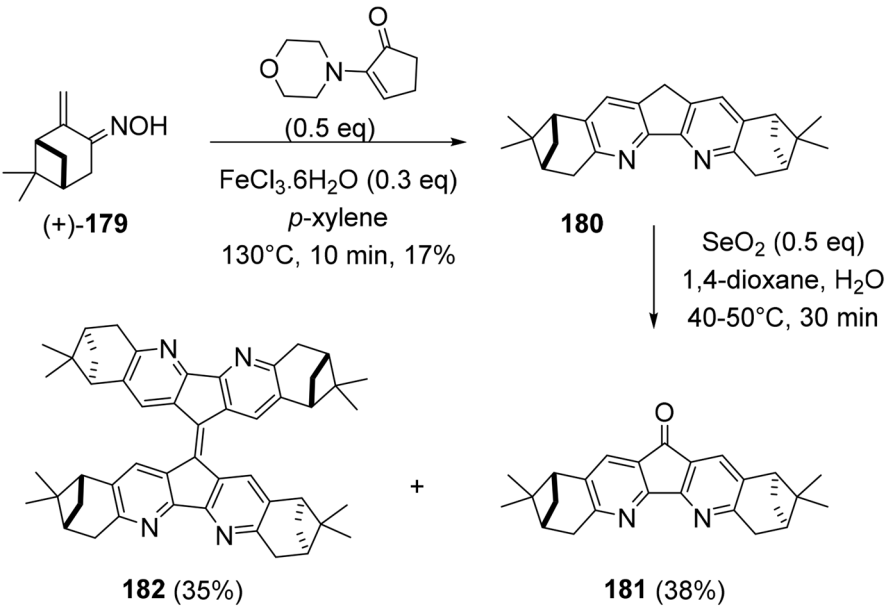
The pyrimidine derivatives **178a** and **178b** and 1,3-oxazine **176** were synthesized by the authors of [31] from (+)-3-carene (+)-**169** (Scheme 39). In the first step, the cycloaddition reaction of (+)-3-carene with chlorosulfonyl isocyanate (CSI) led to the stereoselective formation of compound **170** in 76% yield. Subsequent reaction of lactam **170** with di-*tert*-butyl dicarbonate resulted in compound **171**, alkaline hydrolysis of which led to the formation of *N*-Boc-protected ester **172** in 98% yield. Removal of the Boc-protective group with trifluoroacetic acid (TFA) resulted in ester **173** in 96% yield. Ester **173** was reduced by $LiAlH_4$ to amino alcohol **174**.



Scheme 38 Synthesis of 3-cyanopyridine derivatives of β-(−)-pinene



Scheme 39 Synthesis of pyrimidine derivatives and 1,3-oxazine from (+)-3-carene

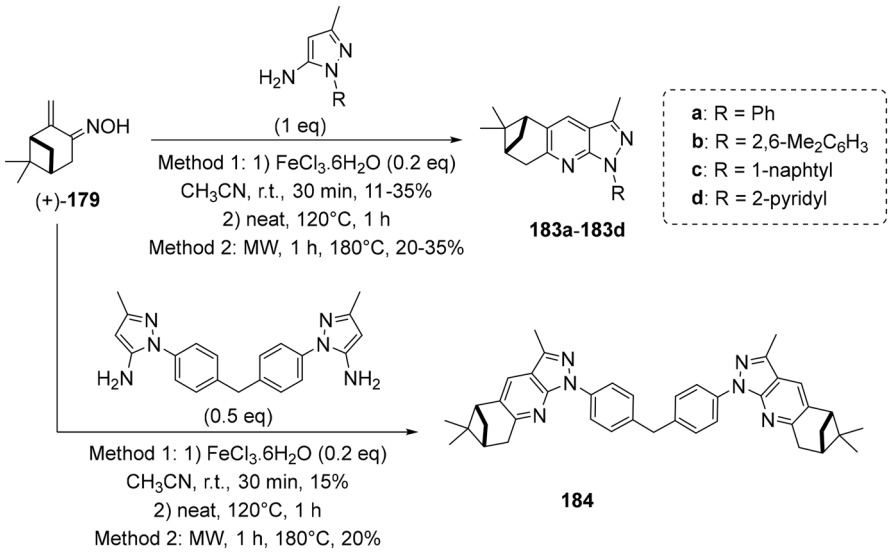


Scheme 40 Synthesis of chiral nopinane-annulated pyridine and obtaining its oxidation products

By reaction of the amino group of compound **174** with PhNCS thiosemicarbazide **175** was obtained, which was further converted to 2-phenylimino-1,3-oxazine **176** condensed with the residue of the initial (+)-3-carene. The reaction of methyl ester **173** with PhNCO and PhNCS allowed obtaining urea **177a** and thiourea **177b** in 76 and 91% yield, respectively. The compounds **177a** and **177b**, in turn, were easily converted to 2-thioxo-4-pyrimidinone **178b** and 2,4-pyrimidinedione **178a** by base-catalyzed cyclizations. The biological activity or other applications of the target compounds were not discussed in this work.

A simple method for the synthesis of chiral nopinane-annulated pyridine **180** and obtaining its oxidation products **181** and **182** is presented in [73] (Scheme 40). Compound **180** was synthesized by treatment of (+)-pinocarvone oxime (+)-**179** with 2-morpholino-cyclopent-2-enone in the presence of $FeCl_3$. Oxidation of compound **180** with SeO_2 led to the formation of a mixture of compounds **181** and **182**, the latter of which was obtained as a product of oxidative dimerization. The structure of compounds **180–182** was confirmed by X-ray crystallography. The authors of [74] have obtained chiral luminescent $ZnLCl_2$ and $[CdLCl_2]_n$ complexes where L is chiral compound **180** and investigated their fluorescent properties. It was shown that the chelation-enhanced fluorescence (CHEF) effect is manifested in the complexes.

The synthesis of chiral 1*H*-pyrazolo[3,4-b]pyridines **183a–183d** and **184** condensed with a nopinene frame from (+)-pinocarvone oxime (+)-**179** is described in [75] (Scheme 41). Interaction of oxime (+)-**178** with 1-aryl-1*H*-pyrazol-5-amines without solvent in the presence of $FeCl_3$ upon heating gave corresponding 3-methyl-1-aryl-1*H*-pyrazolo[3,4-*b*]pyridines **183a–183d** and **184** in 15–35% yield. Compounds **183a–183d** and **184** were also obtained under microwave irradiation, the

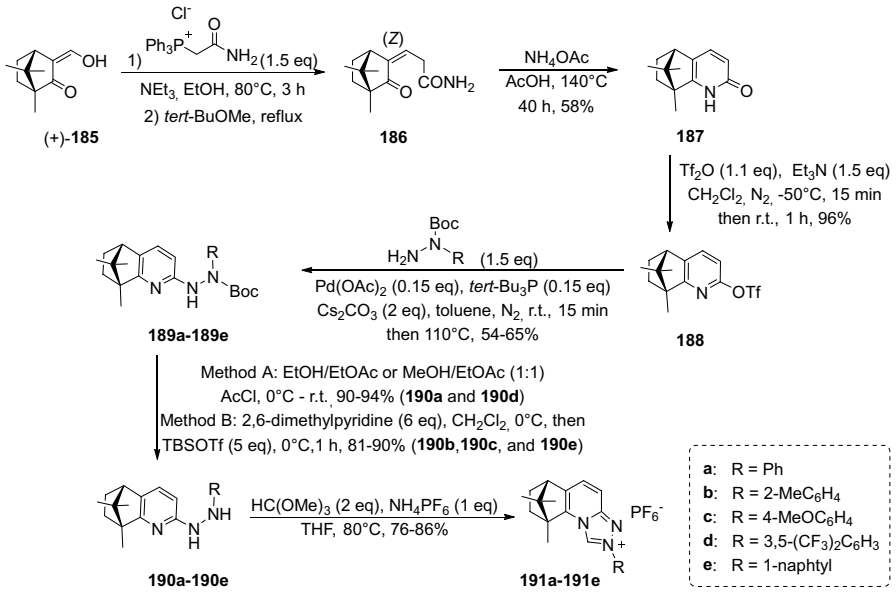


Scheme 41 Synthesis of chiral 1*H*-pyrazolo[3,4-b]pyridines from (+)-pinocarvone

addition of $FeCl_3$•$6H_2O$ did not increase the yield of the target products. Biological activity or other applications are not described in the work, but the authors hope to use the synthesized compounds **183a–183d** and **184** as ligands or fluorescent markers and investigate their biological activity in the future.

The synthesis of triazolium salts **191a–191e** from (+)-hydroxymethylenecamphor (+)-**185** was described in [76] (Scheme 42). The synthesis started with (+)-3-(hydroxymethylene)camphor (+)-**185**, whose interaction with (carbamoylmethyl)triphenylphosphonium chloride resulted in compound **186**. Heating compound **186** in acetate buffer for 40 h led to the closure of 2-pyridinone cycle and formation of compound **187** in 58% yield, in which the bicyclic frame of (+)-camphor condensed with *N*-heterocycle according to previously published work [77]. Treatment of **187** with Tf_2O in the presence of Et_3N gave **188** in 96% yield. The key step in the synthesis of the compounds desired was the Pd-catalyzed coupling of arylhydrazines with pyridyltriflate **188** which resulted in compounds **189a–189e**. Further removal of the Boc-protecting group by AcCl or 2,6-dimethylpyridine with *tert*-butyldimethylsilyl triflate (TBSOTf) (method A and method B, respectively) led to the formation of hydrazines **190a–190e**. In the final step of the synthesis, compounds **190a–190e** underwent condensation with $HC(OMe)_3$ in the presence of NH_4PF_6 to form triazolium salts **191a–191e**.

The triazolium salts are used as precursors for the production of *N*-heterocyclic carbenes (NHC), which have found wide application as ligands in metal-based catalysis [78–81]. In the basic medium, the detachment of hexafluorophosphate ion from the triazolium salts (e.g. **191a–191e**), the migration of the double C=N bond electrons to the nitrogen atom, and the subsequent detachment of the proton from the carbon atom to form a stable *N*-heterocyclic carbenes (e.g. **192a–192e**) occur



Scheme 42 Synthesis of triazolium salts from (+)-hydroxymethylenecamphor

(Fig. 3). The annulation of NHC with aliphatic rings having optical centers can be considered as a promising approach for the synthesis of ligands for asymmetric catalysis with high reactivity and enantio-/diastereoselectivity [82–84].

A series of chiral triazolium salts **196a–196e** has been synthesized from (+)-camphor (+)-**25** in [85], and their catalytic activity in intramolecular crossed aldehyde–ketone benzoin reactions affording α-ketols has been evaluated (Scheme 43). At the first stage, camphorquinone-3-oxime **193** was synthesized in 89% yield from (+)-camphor and *i*-amylnitrite in the presence of *tert*-BuOK according to procedure [86]. The reduction of oxime **193** with $LiAlH_4$ in an inert atmosphere led to the formation of 3-*exo*-aminoisoborneol **194** in 92% yield. Subsequent interaction of *exo*-amino alcohol **194** with $ClCH_2COCl$ resulted in lactam **195**, in which the morpholine-3-one cycle is condensed with a bicyclic (+)-camphor frame. At the next stage, a series of triazolium salts **196a–196e** was synthesized by interaction of compound **195** with arylhydrazides and further condensation with $HC(OEt)_3$ in accordance with previously developed methodology [87].

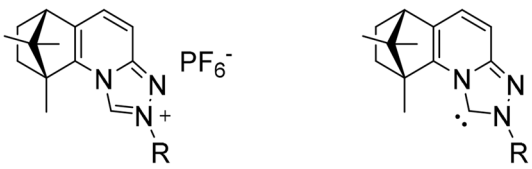
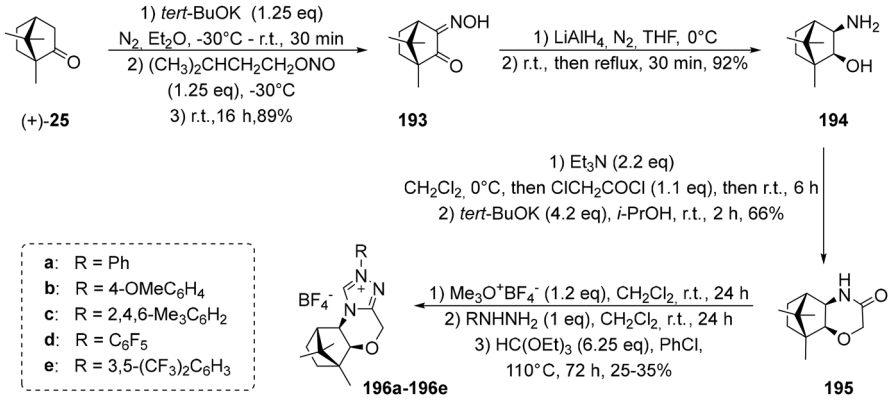


Fig. 3 Structures of triazolium salts and NHC



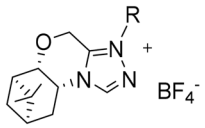
Scheme 43 Synthesis of triazolium salts from (+)-camphor

All the salts **196a–196e** obtained were evaluated for their catalytic activity in intramolecular benzoin condensation of 2-(2-oxo-2-phenylethoxy)benzaldehyde into optically active tertiary alcohol in the presence of 10 mol % Et_3N as a base. The best results (95% yield; *ee* 71%) were observed using salt **196d** (12 mol%) as a pre-catalyst. Only trace amounts of the desired α-ketole were observed when using salts **196a–196c** as precatalysts in the similar conditions. As a result, the use of salt **196e** as a precatalyst turned out to be worse than that of **196d**. The authors have studied the obtained triazolium salt **196d** as a precatalyst in the reactions of intramolecular benzoin condensation of other 2-substituted benzaldehydes: the *ee* of the target products exceeded 76%; the yields were 90% or more (using 6 mol% **196d**). The use of triazolium salt **196d** as a precursor of NHC and the catalytic activity of the latter in intramolecular benzoin condensations of other aldehydes have been described in [88].

It is worth noting that subsequent work by the same scientific group found that the **196a–196e** salts could also be used as catalysts for the asymmetric intramolecular Michael reactions. As it was mentioned in [89], the NHC generated from salt **196c** (5 mol%) and DIPEA proved to be highly efficient for a wide range of substrates in intramolecular Michael reaction (up to 99% yield; 99% *ee*).

It was shown that the NHCs generated from salts **196a–196e** are highly efficient for the asymmetric intramolecular Stetter reaction. With 10 mol% of the catalyst, the target products were obtained in excellent yields with up to 97% *ee* [90, 91]. Although in these works the use of salt **196c** as precatalyst did not show the desired result, when using 10 mol% **196d** salt as NHC precursor in the presence of DIPEA (10 mol%), the target products of the intramolecular Stetter reaction were obtained in good yields with over 90% *ee* [88]. In [91], the best results were also observed when using **196d** salt as a precatalyst (target products were obtained in yields over 50%; *ee* higher than 70%).

Another research group [92] synthesized chiral triazolium salts **197a–197c** from (–)-β-pinene using the above-mentioned methodology (Fig. 4). It was shown that NHC generated from triazolium salt **197b** exhibited excellent catalytic activity



197a: R = C_6H_5
197b: R = C_6F_5
197c: R = 2,4,6-$(CH_3)_3C_6H_2$

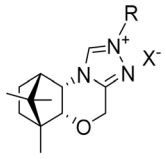
Fig. 4 Chiral triazolium salts synthesized from (–)-β-pinene

(yield of over 90%; er (enantiomer ratio) of up to 99:1) in the intramolecular Stetter reaction. It was also shown by the authors of this work that the use of triazolium salts **197a** and **197c** reduced significantly the yield of the target products in the intramolecular Stetter reaction.

The authors of [93] synthesized triazolium salts **198–201** in a similar way to the above-mentioned method (Fig. 5), but in this case, the salts were synthesized from (–)-3-*endo*-aminoborneol, obtained by the well-known method [94]. The potential of four new catalysts and several readily available chiral NHC precursors in the enantioselective intramolecular crossed-benzoin reaction of 2-(2-oxo-2-phenylethoxy)benzaldehyde and its derivatives was investigated. The target acyloins were obtained in yields above 80% (after column chromatography) and with an *ee* of over 90% when using 15 mol% salt **201** as a precatalyst. It is also worth mentioning that NHC generated from salt **201** proved to be such an effective catalyst that complete conversion of 2-substituted benzaldehydes was already observed after 1 h.

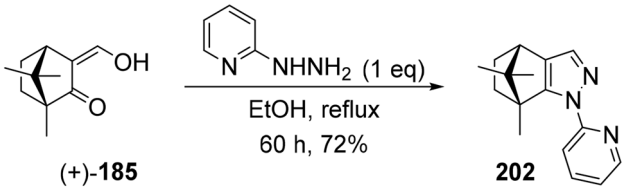
The authors of [95] synthesized a series of compounds containing annulated pyrazole cycle; in particular, compound **202** was synthesized in one step from (+)-3-(hydroxymethylene)camphor (+)-**185** and 2-hydrazinopyridine (Scheme 44). No biological activity or other studies have been carried out, but the authors suggest that the compounds obtained will find application in the chemistry of luminescent metal chelates.

The authors of [96] synthesized a series of compounds **203**, **206**, **209a**, and **209b** possessing an annulated pyrazole cycle from (+)-camphor (+)-**25**, (–)-menthone (–)-**204**, and (+)-pulegone (+)-**207** (Scheme 45). The procedure involves formylation at the less hindered α position of starting ketone followed by cyclocondensation of resulting compounds (+)-**185**, **205**, and **208** with N_2H_4 to obtain pyrazoles **203**, **206**, **209a**, and **209b**. It should be noted that condensation of ketone (–)-**204**



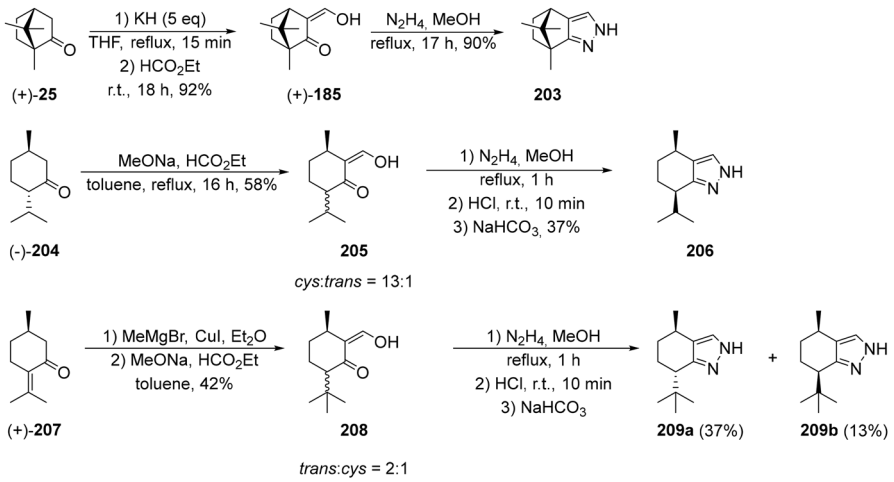
198: R = C_6H_5, X = BF_4
199: R = C_6F_5, X = BF_4
200: R = 2,4,6-$(CH_3)_3C_6H_2$, X = Cl
201: R = 2,4,6-$Cl_3C_6H_2$, X = BPh_4

Fig. 5 Chiral triazolium salts synthesized from (–)-3-*endo*-aminoborneol



(+)-**185** **202**

Scheme 44 Synthesis of annulated pyrazole derivative from (+)-3-(hydroxymethylene)camphor

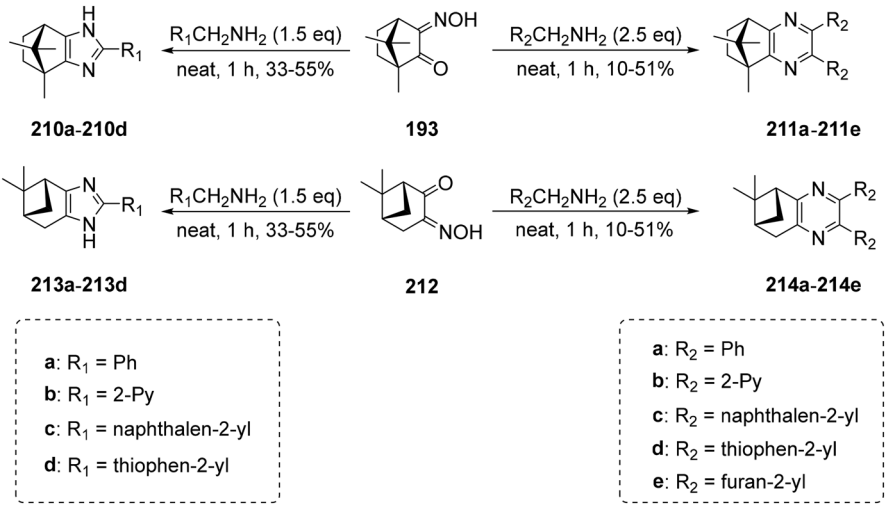


Scheme 45 Synthesis of pyrazole derivatives from (+)-camphor, (–)-menthone, and (+)-pulegone

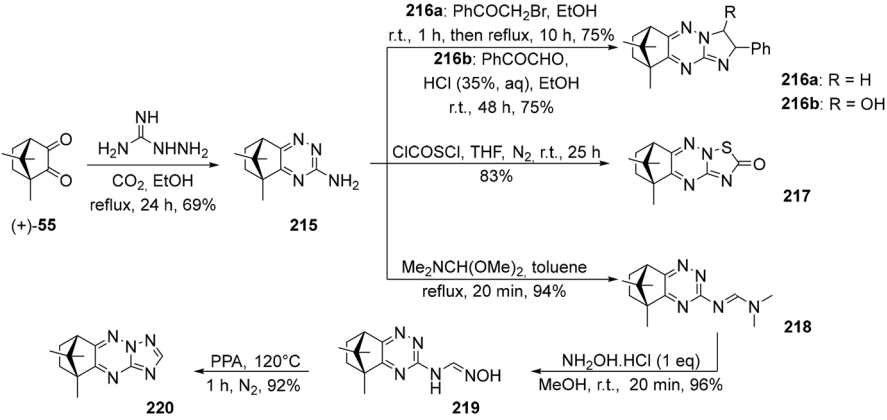
with HCO_2Et resulted in the formation of compound **205** as a mixture of *cis*/*trans* isomers in a 13:1 ratio. Subsequent cyclocondensation of the mixture of isomers **205** with N_2H_4 led to the formation of the target pyrazoles. The separation of isomers was carried out by HCl treatment and further recrystallization of *cis*-**206** from a mixture of chloroform/methyl *tert*-butyl ether followed by treatment with $NaHCO_3$ in 37% yield. Compound **208** as a mixture of *cis*/*trans* isomers in the ratio of 1:2 was obtained by interaction of (+)-pulegone (+)-**207** with the Grignard reagent and subsequent condensation with HCO_2Et. Further cyclocondensation of the mixture of isomers **208** with N_2H_4 resulted in a mixture of pyrazoles **209a** and **209b**, which were separated as hydrochlorides by recrystallization from hexane (*trans*-isomer) and toluene (*cis*-isomer). After treatment with $NaHCO_3$, the target compounds **209a** and **209b** were obtained in 37 and 13% yields, respectively. Biological activity or other applications are not described in the work.

A series of imidazoles **210a–210d** and **213a–213d**, pyrazines **211a–211e** and **214a–214e** annulated with a bicyclic (+)-camphor and a (+)-nopinane frames was synthesized in [97] (Scheme 46). The synthesis of the target compounds was carried out in one step by condensation of a number of primary amines with camphor-3-oxime **193** and nopinone-3-oxime **212**. It is worth noting that when oximes **193** and **212** were condensed with 1.5 equiv. of primary amines, pyrazines **211a–211e** and **214a–214e** were observed as by-products, but when the amount of reacting amines was increased to 2.5 equiv., pyrazines **211a–211e** and **214a–214e** became the main products of condensation. The use of amines with an aliphatic substituent at the α-carbon atom resulted in the formation of imino-oximes only. The biological activity or other applications of the synthesized compounds were not investigated in this work.

The synthesis of camphor-1,2,4-triazines **216a**, **216b**, **217**, and **220** fused with five-membered *N*-heterocycles was described in [98] (Scheme 47). Starting 3-amino-camphor-1,2,4-triazine **215** was obtained in one step by condensation of

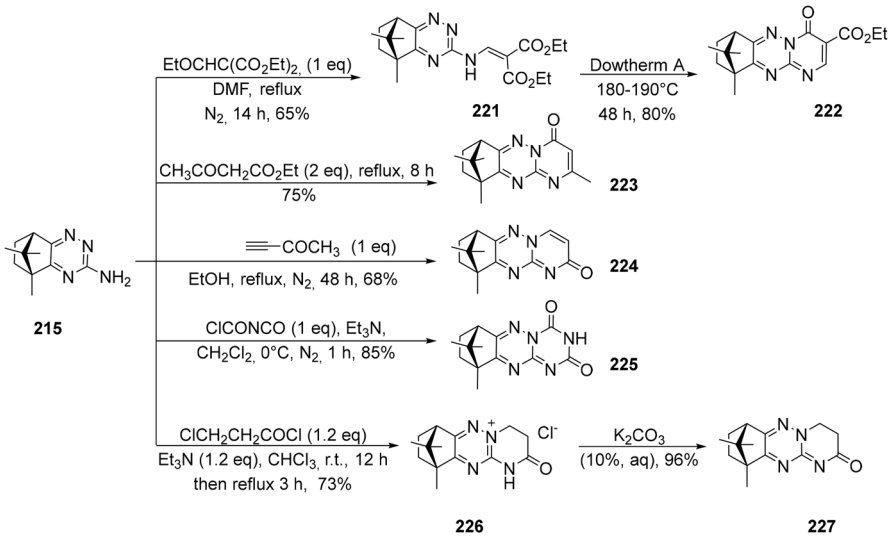


Scheme 46 Solvent-free synthesis of imidazoles and pyrazines annulated with (+)-camphor and (+)-nopinone frames



Scheme 47 Synthesis of camphor-1,2,4-triazines fused with five-membered *N*-heterocycles

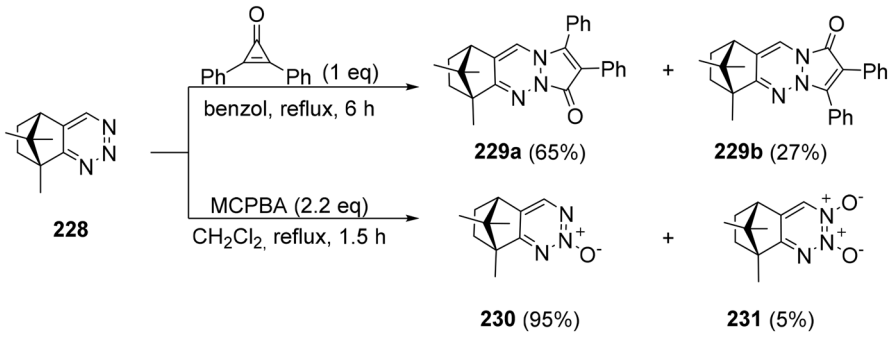
(+)-camphorquinone (+)-**55** with guanidine bicarbonate. Compounds **216a** and **216b** were obtained by condensation of compound **215** with 2-bromoacetophenone and 2-oxo-2-phenylacetaldehyde, respectively. Construction of a thiadiazole ring was carried out by treatment of triazine **215** with chlorocarbonylsulfenyl chloride resulted in the formation of compound **217**. Compound **220** containing the triazole cycle was synthesized from 2-aminotriazine **215** in three steps: first, compound **215** was converted to the corresponding formamidine **218**, which was subsequently treated with NH_2OH•HCl to obtain oxime **219**, which was further cyclized to the target triazotriazine **220**.



Scheme 48 Synthesis of camphor-1,2,4-triazines fused with six-membered *N*-heterocycles

The compounds **222–227** in which a six-membered ring is annulated to camphor-1,2,4-triazine were synthesized as shown in Scheme 48. Condensation of the triazine **215** with diethyl ethoxymethylenemalonate and subsequent cyclization upon heating in a eutectic mixture of biphenyl with diphenyl oxide (Dowtherm A) resulted in the formation of compound **222** in 80% yield. Its structural analogue, compound **223**, was obtained by condensation of compound **215** with ethyl acetoacetate. Heating 2-aminotriazine **215** with methyl propiolate in EtOH resulted in the formation of compound **224**. The bifunctional electrophilic reagent *N*-(chlorocarbonyl)-isocyanate reacted with compound **215** in the presence of Et_3N to form compound **225**. Treatment of 2-aminotriazine **215** with 3-chloropropionyl chloride yielded salt **226**, which further converted to the free base **227** in an alkaline medium. The CNS stimulant activity of all compounds shown in Schemes 47 and 48 was investigated using mice. The target compounds do not have CNS stimulant activity according to biological evaluation.

As a continuation of their work on the search for CNS stimulants, the aforementioned research group [99] reported the cycloaddition reaction of camphor-1,2,3-triazine **228** with diphenylcyclopropenone and oxidation of 1,2,3-triazine **228** with *meta*-chloroperbenzoic acid (MCPBA) (Scheme 49). The synthesis of 1,2,3-triazine **228** was not described in [99]. The interaction of triazine **228** with diphenylcyclopropenone resulted in the formation of two regioisomers **229a** and **229b** in a 2:1 ratio. Oxidation of triazine **228** resulted in the formation of triazine-2-oxide **230** as the main product and triazine-2,3-dioxide **231** as a by-product. A study of the CNS stimulant activity of compounds **229a**, **229b**, and **230** showed that compound **230** had the strongest effect at a dose of 50 mg/kg. Its activity was comparable to that of the reference drug pentylenetetrazole. Compounds **229a** and **229b** had no CNS stimulant activity.



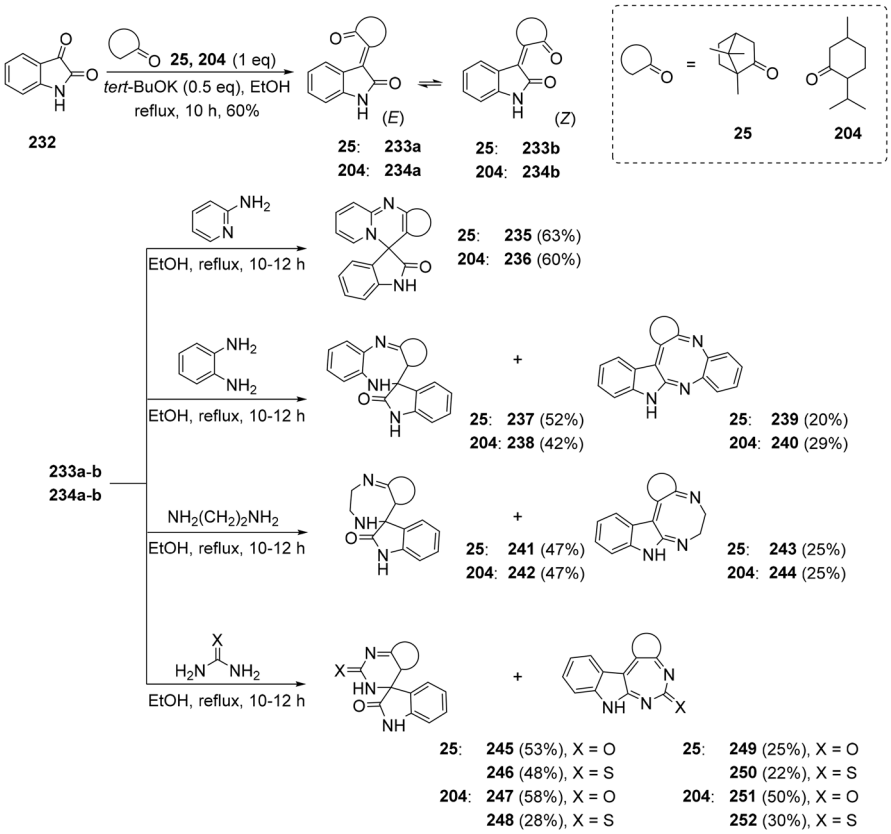
Scheme 49 Synthesis of benzotriazinones and triazine-oxides from camphor-1,2,3-triazine

The authors of [100] synthesized a racemic mixture of indole derivatives of (±)-camphor **233a**, **233b** and (±)-menthone **234a**, **234b** by the aldol reaction of isatin **232** with ketones **25** and **204**, respectively, in the presence of *tert*-BuOK (Scheme 50). The authors failed to separate the isomers **233a**, **233b** and **234a**, **234b** neither by recrystallization nor by column chromatography. Further condensation of mixtures **233a**, **233b** and **234a**, **234b** with *o*-phenylenediamine, ethylenediamine, urea, and thiourea was accompanied by the formation of mixtures of spirocyclic compounds **237**, **241**, **245**, and **246** (from (±)-camphor), **238**, **242**, **247**, and **248** (from (±)-menthone) and polycyclic compounds **239**, **243**, **249**, and **250** (from (±)-camphor), **240**, **244**, **251**, and **252** (from (±)-menthone); each of them was isolated individually. The interaction of 2-aminopyridine with mixtures **233a**, **233b** and **234a**, **233b** resulted in the formation of spirocyclic compounds **235** and **236**, respectively, as the sole reaction products. All compounds synthesized were screened for their antibacterial activity against *E. coli*, *B. sublitis*, and *B. cereus* bacteria and for antifungal activity against *Aspergillus niger*, *Pencillium* species, and *Cladosporium* species. However, none of the compounds synthesized showed either antibacterial or antifungal activity comparable to the reference drugs norfloxacin (antibacterial) and fluconazole (antifungal).

3.4 Synthesis of *N*-Heterocyclic Compounds, Incorporating a Spirocyclic System, from Monoterpenoids and Their Derivatives

The main approach to the synthesis of spirocyclic compounds containing an *N*-heterocyclic core and monoterpene frame is represented by nucleophilic addition reactions on the native carbonyl group of monoterpenoids with simultaneous or subsequent cyclization of the heterocycle.

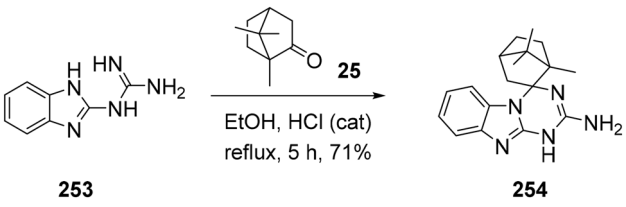
Spirocyclic triazin derivatives were synthesized in [101] by interaction of 2-guanidinobenzimidazole **253** with a number of ketones of various structures, including camphor **25**. It is worth noting that the configuration of stereocenters in the original camphor **25** is not specified in the work. The synthesis of compound **254** was performed by nucleophilic addition of the guanidine imino group to the carbonyl group of camphor **25** followed by cyclization by nucleophilic addition of the nitrogen atom



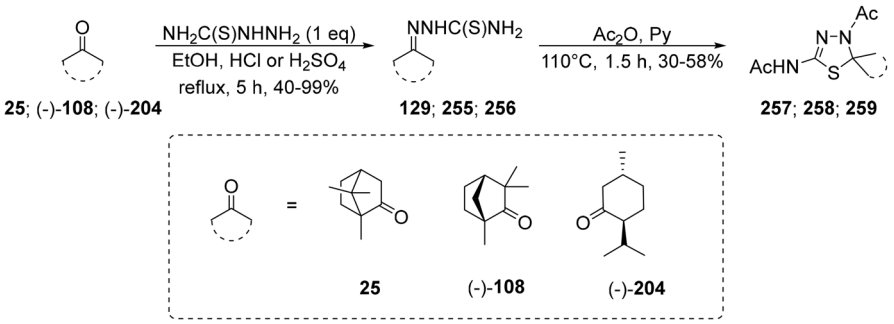
Scheme 50 Synthesis of some indole-based spiro and condensed heterocycles from camphor and menthone

of the benzimidazole nucleus (Scheme 51). The antibacterial activity of all synthesized spirocyclic compounds featuring the 1,3,5-triazine core was also investigated against gram-positive and gram-negative bacteria. Unfortunately, compound **254** had the weakest antibacterial activity against all types of bacteria.

The synthesis of chiral spirocyclic 1,3,4-thiadiazoline derivatives **257–259** with a monoterpene frame in structure was described in [102] (Scheme 52). The



Scheme 51 Synthesis of substituted triazin-2-amine from camphor

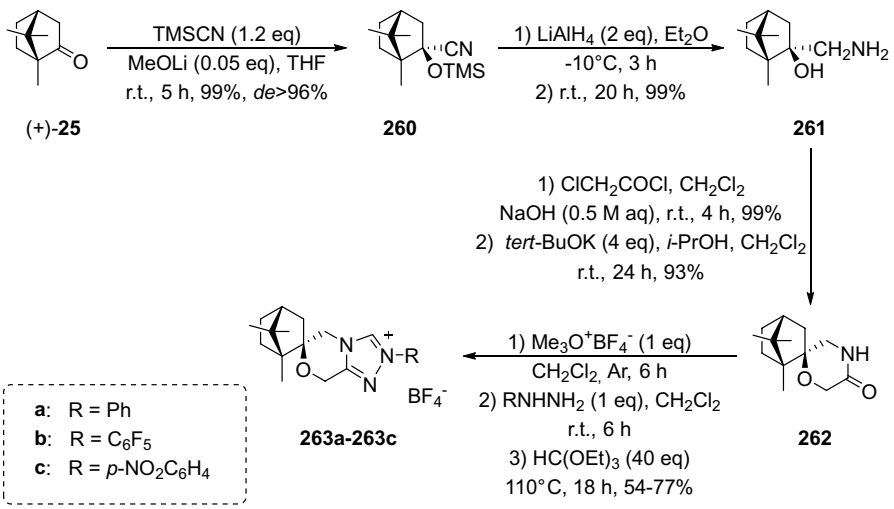


Scheme 52 Synthesis of spirocyclic 1,3,4-thiadiazoline derivatives from camphor, (–)-fenchone, and (–)-menthone

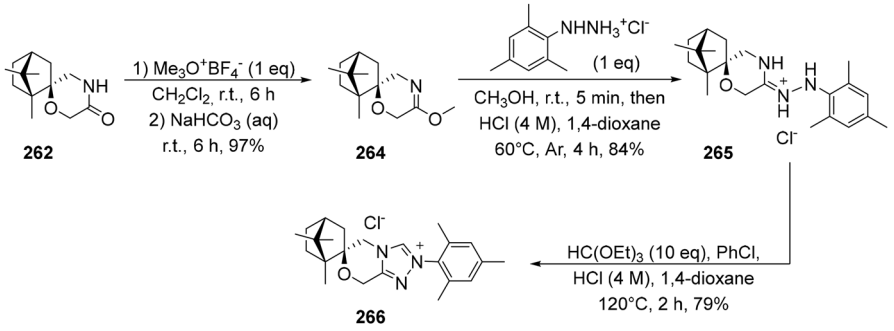
synthesis was carried out by interaction of (±)-camphor **25**, (–)-fenchone (–)-**108**, and (–)-menthone **204** with thiosemicarbazide at the first stage to form thiosemicarbazones **129**, **255**, and **256**, respectively, in yields of 40–99%. In the next step, treatment of the thiosemicarbazones in acetylation conditions with Ac_2O afforded spirocycles **257–259**. The reaction proceeded with the formation of one stereoisomer in each case. The configuration of the spirocyclic stereocenter was established by X-ray analysis and two-dimensional nuclear magnetic resonance (NMR) spectroscopy. Thus, for spirocyclic compounds **257** and **258** (obtained from (±)-camphor and (–)-fenchone, respectively), the spirocyclic stereocenter possessed configuration *R*, and for compound **259** (obtained from (–)-menthone), it had configuration *S*. The biological or catalytic activity of the compounds obtained was not investigated.

In continuation of the works devoted to the synthesis of triazolium salts and the study of their catalytic activity, the (+)-camphor-derived triazolium salts **263a–263c** incorporating a spirocyclic system were synthesized in [103] (Scheme 53). At the first stage, (+)-camphor (+)-**25** reacted diastereoselectively with trimethylsilyl cyanide (TMSCN) to form compound **260**. Further reduction of ether **260** by $LiAlH_4$ resulted in almost quantitative formation of amino alcohol **261**. Spirocyclic lactam **262** was obtained in two stages: at the first stage, amino alcohol **261** was acylated with $ClCH_2COCl$, and then the resulting amide was cyclized under the action of *tert*-BuOK. Further interaction of morpholine-3-one **262** with arylhydrazines and condensation with $HC(OEt)_3$ resulted in spirocyclic triazolium salts **263a–263c**. The precatalysts obtained were investigated as NHC precursors for their catalytic activity in the asymmetric benzoin condensation of PhCHO in (*R*)-2-hydroxy-1,2-diphenylethan-1-one. The catalyst derived from salt **263a** showed low selectivity (71:29 er; yield of 31%). The catalyst derived from salt **263b** gave desired benzoin in an excellent yield with low selectivity (52:48 er; yield of 99%).

The authors of [103] further synthesized the triazolium salt **266** from lactam **262** (Scheme 54). Interaction of lactam **262** with trimethyloxonium tetrafluoroborate resulted in compound **264** in 97% yield. In the next step, salt **265** was obtained by interaction of compound **264** and 2,4,6-trimethylphenylhydrazine hydrochloride. Condensation of salt **265** with $HC(OEt)_3$ resulted in the formation of spirocyclic triazolium salt **266**. The catalyst derived from salt **266** gave the best results [103],



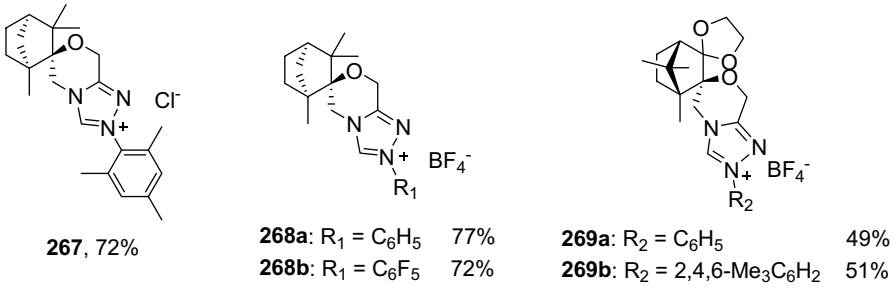
Scheme 53 Synthesis of (+)-camphor-derived triazolium salts, incorporating a spirocyclic system



Scheme 54 Synthesis of (+)-camphor-derived triazolium salt, incorporating a spirocyclic system and mesitylene fragment

affording the benzoin product in 98% yield and 71.5:28.5 enantiomeric ratio. The catalyst derived from salt **266** and DIPEA was successfully employed in the asymmetric benzoin condensation of substituted benzaldehydes. The resulting acyloins were obtained in moderate to excellent yields and acceptable enantioselectivities.

The preparation of triazolium salts **267**, **268a**, **268b**, **269a**, and **269b** containing a spirocyclic system from (+)-fenchone and (+)-camphorquinone was described in [104] (Fig. 6). The NHC precursors synthesized were employed in the catalytic asymmetric benzoin condensation of different benzaldehydes. The synthesis was carried out similarly to the methods described above, except for the synthesis of (+)-camphorquinone-derived triazolium salts **269a** and **269b**, where the carbonyl group at the 3 position was protected in the first step. The yields in Fig. 6 are shown for the last stage of synthesis of the target compounds. The catalyst derived from salt



267, 72%

268a: $R_1 = C_6H_5$ 77%
268b: $R_1 = C_6F_5$ 72%

269a: $R_2 = C_6H_5$ 49%
269b: $R_2 = 2,4,6\text{-}Me_3C_6H_2$ 51%

Fig. 6 (+)-Fenchone- and (+)-camphorquinone-derived triazolium salts containing a spirocyclic system

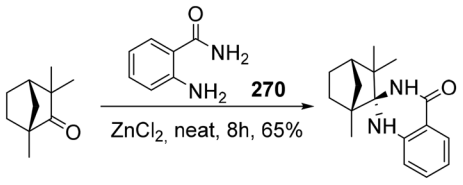
269b (10 mol%) and dicyclohexylethylamine (DCyEA) turned out to be the most active as a chiral NHC catalyst for the benzoin condensation of benzaldehyde and its derivatives (more than 70:30 er; yield of isolated benzoin over 26%).

The authors of [105] performed a one-step diastereoselective synthesis of spirocyclic compound **271** from (–)-fenchone(–)-**108** and anthranilamide **270** (Scheme 55). Solvent-free condensation of (–)-fenchone and anthranilamide in the presence of $ZnCl_2$ resulted in the formation of a diastereomeric mixture of spirocyclic quinazolinones, whose subsequent column chromatography isolated the compound **271** in 65% yield. The authors were able to isolate a crystal of compound **271** and study its crystal structure and porosity. Biological studies of compound **271** were not carried out in [105].

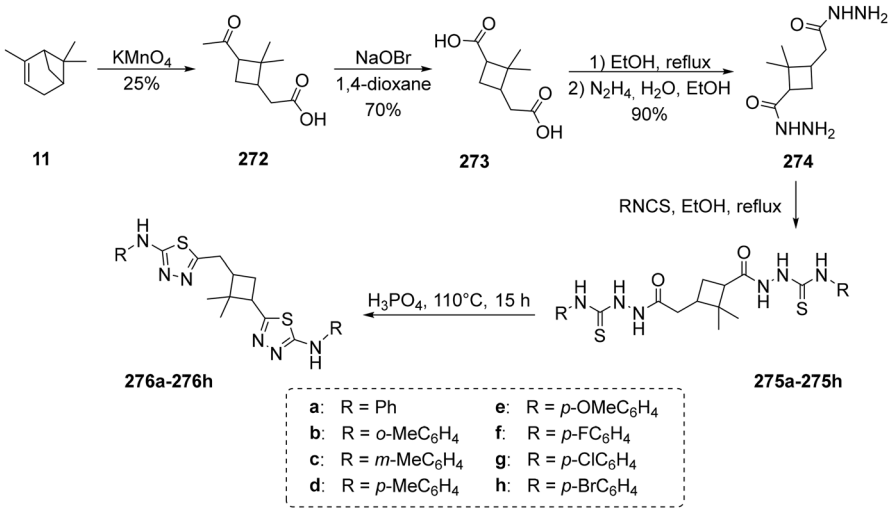
3.5 Synthesis of *N*-Containing Compounds from Monoterpenes, Monoterpenoids, and Their Derivatives Including the Stages of Breaking the Frame of the Starting Compound

Bicyclic monoterpenes and monoterpenoids have a rigid and strained structure. Some monoterpenes contain a cyclopropane or cyclobutane ring in their structure. Therefore, during chemical reactions, the structural integrity of such monoterpenes and monoterpenoids can be disturbed, leading to the frame breaking. However, the synthesis of new heterocyclic compounds, from monoterpenes and monoterpenoids, during which the bicyclic frame of a native molecule is broken, is an urgent research area. Such transformations open the way to obtain optically active compounds, promising objects for the study of their biological or catalytic properties.

Scheme 55 Synthesis of spirocyclic quinazolinone derivative from (–)-fenchone



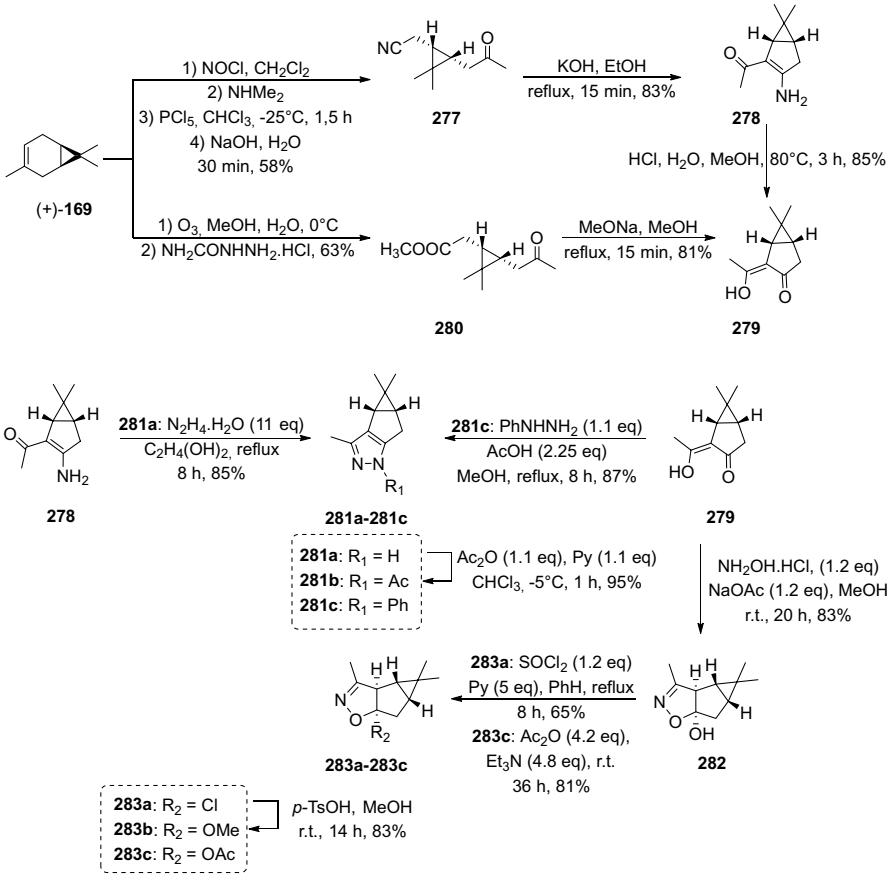
(-)-**108** **271**



Scheme 56 Synthesis of 1,3,4-thiadiazole derivatives from α-pinene

The synthesis and study of the herbicidal activity of 1,3,4-thiadiazole derivatives **276a–276h** synthesized from α-pinene **11** (the configuration of the stereocenters is not specified in the work) was described in [106] (Scheme 56). At the first stage of the synthesis, α-pinene was oxidized with $KMnO_4$ to form acid **272**. Further oxidation of acid **272** by NaOBr resulted in the formation of dicarboxylic acid **273** possessing a cyclobutane ring. Successive esterification and nucleophilic substitution reactions with N_2H_4 led to the formation of dihydrazide **274**. Interaction of the latter with isothiocyanates led to the formation of compounds **275a–275h**, whose intramolecular cyclization in acidic medium gave *N*-substituted 2-aminothiadiazoles **276a–276h** connected through a methylcyclobutane linker. It is worth noting that the study lacks a number of experimental data, including the yields of the target and intermediate products of the synthesis. It was found that most of the target compounds exhibited a certain growth inhibition activity against root of rape *B. Campestris*, in which compounds **276b** and **276c** had inhibition rates of 72.3% and 68.3%, respectively. Biological studies have shown that compounds **275a–275h** do not exhibit herbicidal activity, contrary to compounds **276a–276h**. Thus, the authors claim that cyclization of compounds **275a–275h** enhances herbicidal activity.

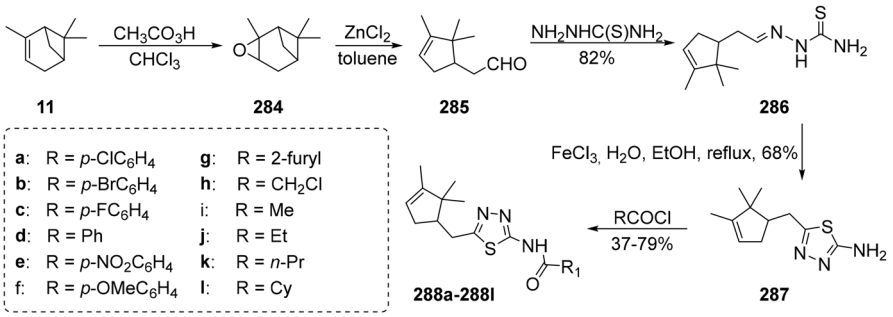
The authors of [107] synthesized pyrazole **281a–281c** and 2-isoxazoline **282** and **283a–283c** derivatives from (+)-3-carene (+)-**168** (Scheme 57). Thus, cyclopropane derivative **277** possessing a cyano and carbonyl group was obtained from (+)-3-carene (+)-**168** in several steps by the known method [108] in 58% yield. Subsequent intramolecular cyclization of compound **277** in an alkaline medium led to the formation of bicyclic enaminone **278** [109]. Its treatment with HCl in an aqueous-alcoholic solution resulted in hydrolysis of the enamine fragment and formation of enol **279** in 85% yield. Compound **279** can be also obtained by another route: oxidative cleavage of the (+)-3-carene double bond by the known method [110] to obtain a substituted cyclopropane **280**, which is further cyclized by the action of



Scheme 57 Synthesis of pyrazole and 2-isoxazoline derivatives from (+)-3-carene

MeONa into enol **279** in yield of 81%. Pyrazoles **281a** and **281c** were obtained by the interaction of compound **278** with N_2H_4 and compound **279** with $PhNHNH_2$, respectively. Compound **281b**, in turn, was obtained by acylation of **281a** in the presence of pyridine. The reaction of enol **279** with NH_2OH resulted in 2-isoxazoline **282**. Compounds **283a–283c** were synthesized by subsequent substitution of the hydroxyl group in compound **282** with a chlorine atom, methoxy group or acetoxy group. The biological activity of the compounds obtained was not investigated in this work, and their applications were not discussed.

The synthesis of substituted 1,3,4-thiadiazoles **288a–288l** from α-pinene **11** (the configuration of the stereocenters is not specified in the work) and their antifungal activity against *Fusarium graminearum* and *Physalospora piricola* were described in [111] (Scheme 58). Compound **286** was synthesized by nucleophilic addition of thiosemicarbazide to campholenic aldehyde **285**, which was obtained by epoxidation of α-pinene **11** and further rearrangement under the action of $ZnCl_2$ in toluene [112]. Its subsequent cyclization in an aqueous-alcoholic

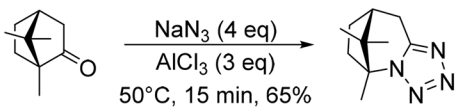


Scheme 58 Synthesis of substituted 1,3,4-thiadiazoles from α-pinene

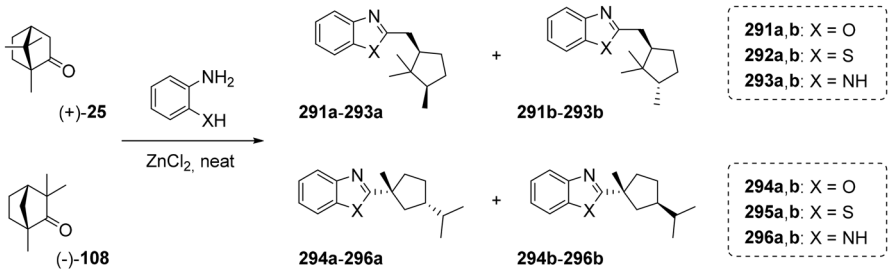
solution of $FeCl_3$ led to the formation of 5-substituted 2-amino-1,3,4-thiadiazole **287**. The target amides **288a–288l** were obtained by acylation of the free amino group with acyl chlorides of various structures. Compounds **288h** and **288j** inhibit the growth of the fungi *Physalospora piricola* and *Fusarium graminearum* by 98 and 94%, respectively, according to biological evaluation.

Tetrazoles and their derivatives are considered important pharmacophores in medicinal chemistry because of their unique structure and a wide range of biological activities [113–115]. Therefore, the synthesis of tetrazole derivatives with a monoterpene fragment in the structure is of great interest for medicinal chemistry. A facile procedure of the synthesis of 1,5-disubstituted tetrazole from cyclic ketones was developed in [116]. Tetrazole **289** was synthesized by grinding a mixture of (+)-camphor (+)-**25** and NaN_3 in the presence of $AlCl_3$ at 50 °C without solvent (Scheme 59). The advantages of this method for the synthesis of 1,5-disubstituted tetrazoles are short reaction time and good yields. The biological or catalytic activity of the compounds obtained was not investigated.

An interesting study of the interaction of bicyclic ketones with *o*-substituted anilines was performed in [117]. The investigation describes a solvent-free one-step interaction of (+)-camphor (+)-**25** and (–)-fenchone (–)-**108** with *o*-substituted anilines in the presence of $ZnCl_2$, which resulted in a series of 2-substituted benzoazoles **291a**–**296a** and **291b–296b** (benzoxazoles, benzothiazoles, and benzimidazoles) (Scheme 60). Condensation of monoterpenoids with *o*-substituted anilines was accompanied by breaking of a bicyclic frame of the starting ketones at the most substituted C–C bond (C_1–C_2 in the case of (+)-camphor; C_2–C_3 in the case of (–)-fenchone) and formation of mixture of two diastereomers in all cases. The configuration of stereocenters in the obtained benzoazoles was established by X-ray analysis of some complex compounds, which were also



Scheme 59 Synthesis of 1,5-fused tetrazole from (+)-camphor

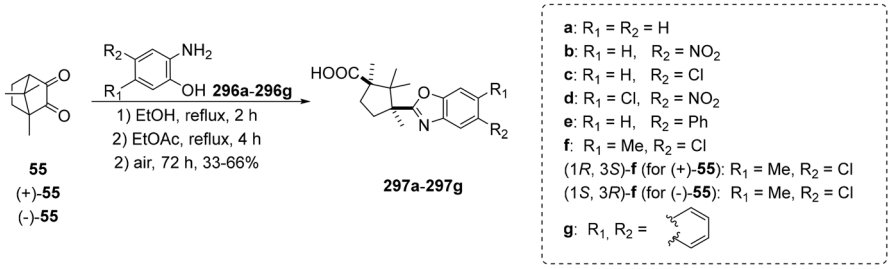


Scheme 60 Solvent-free interaction of (+)-camphor and (–)-fenchone with *o*-substituted anilines

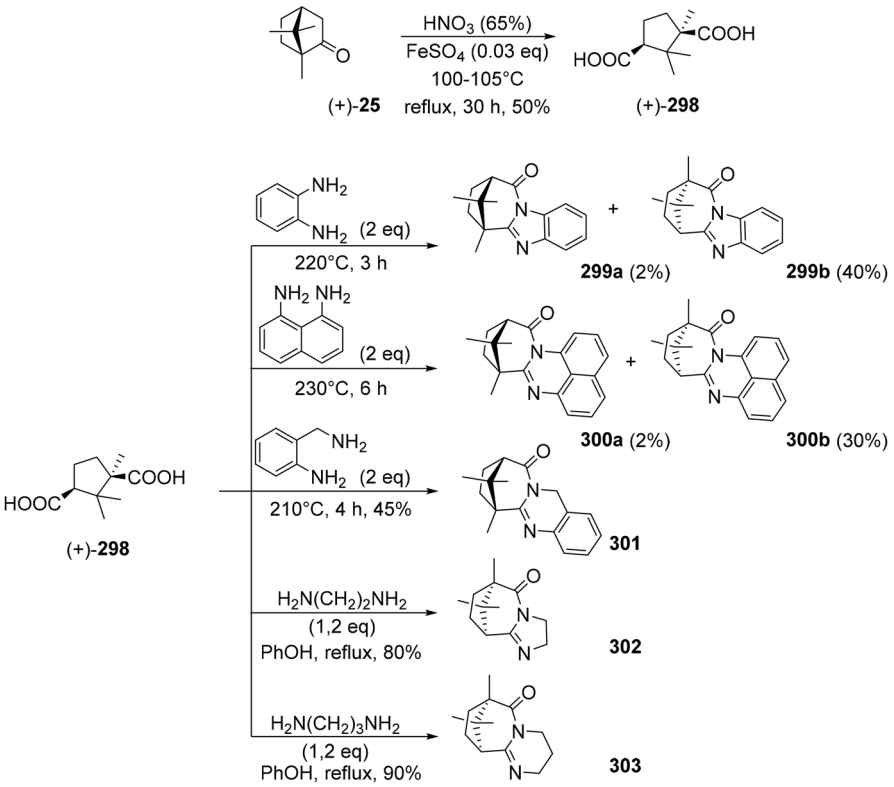
synthesized in this work. The assumed mechanism of the investigated transformations was established; biological studies were not carried out.

A similar breaking of the bicyclic (+)-camphor frame in the condensation of camphorquinone **55** and a series of 4,5-disubstituted *o*-aminophenols **296a–296g** were described in [118] (Scheme 61). A series of *cis*-(benzoxazole-2-yl)cyclopentanecarboxylic acids **297a–297g** was synthesized by interaction of (±)-camphorquinone **55**, (+)-camphorquinone (+)-**55**, and (–)-camphorquinone (–)-**55** with *o*-aminophenols **296a–296g** in EtOH. Using enantiomerically pure camphorquinones ((+)-**55** and (–)-**55**), compounds (1*R*, 3*S*)-**297f** and (1*S*, 3*R*)-**297f** were obtained, respectively. The structure of compound **297f** was confirmed by X-ray diffraction analysis.

The authors of [119] synthesized a number of polycyclic compounds **299–303** from (+)-camphoric acid (+)-**298** and a number of diamines of various structures, and studied their antiviral activity against influenza A virus (strains H1N1, H3N2, and H5N2) (Scheme 62). (+)-Camphoric acid is a dicarboxylic acid that is formed by oxidation of bicyclic monoterpenoid (+)-camphor (+)-**25** by the known method [120], and it is a commercially available reagent. Solvent-free cyclocondensation of (+)-camphoric acid with *o*-phenylenediamine and 1,8-diaminonaphthalene resulted in formation of isomeric compounds **299a**, **299b** and **300a**, **300b**, respectively. Each isomer was isolated in pure form by column chromatography. At the same time, it is worth noting that the interaction of (+)-camphoric acid with *o*-phenylenediamine under other conditions was already studied by another group of researchers [121]. The structural analogue of quinazoline alkaloids **301** was obtained by interaction of acid (+)-**298** with *o*-aminobenzylamine.



Scheme 61 Condensation of camphorquinone with 4,5-disubstituted *o*-aminophenols



Scheme 62 Synthesis of imidazole and pyrimidine derivatives from (+)-camphoric acid

The reaction of (+)-camphoric acid with aliphatic diamines was carried out in phenol as a solvent, resulting in individual compounds **302** and **303**. According to biological studies, compounds **299a**, **302**, and **303** exhibited moderate antiviral activity against A/Puerto Rico/8/34 (H1N1), higher than that of the reference drugs: rimantadine, amantadine, and deitiforin (SI(**299a**) = 21; SI(**302**) = 28; SI(**303**) = 37; SI(rimantadine) = 6; SI(amantadine) = 5; SI(deitiforin) = 7), while compound **301** proved to be the lead compound (SI(**301**) = 62). It is worth noting that compound **301** exhibited antiviral activity against other strains of influenza A virus (SI(**301**(H3N2) = 41; SI(**301**(H5N2) = 53), comparable with that of the reference drugs mentioned above (SI(H3N2) reference drugs varied from 56 to 82, and SI(H5N2) reference drugs varied from 50 to 55).

Thus, in this section, the ways to synthesize *N*-containing heterocycles derivatives by modification of carboxyl, carbonyl, or amino groups of monoterpene derivatives, including the stages of heterocycle core formation, were considered. In such compounds, the heterocycle and the monoterpene frame are connected directly by an exocyclic C–C or C–N bond, or through a linker attached to the monoterpene frame by a C=N or C–C bond. The construction of a heterocycle

core condensed with a monoterpene frame is performed by the reactions of 1,3-dipolar cycloaddition of nitriloxides at the double C=C bonds of monoterpenes or their derivatives; aldol reaction with monoterpenoids featuring a carbonyl group or synthesis of amino alcohols on their basis with subsequent interaction with nucleophilic agents accompanied by closure of the heterocycle; or multicomponent domino reactions with carbonyl-containing monoterpenoids. The synthesis of functionalized *N*-containing heterocycles condensed with the monoterpene frame allows the synthesis of condensed polycyclic systems by forming an additional five- or six-membered heterocycle by modifications of the heterocycle already present in the molecule. A good example is the triazolium salts, which are used as NHC precursors in asymmetric reactions. Monoterpenoids with a carbonyl group are used in the synthesis of heterocycles containing a spirocyclic system. The synthesis of *N*-containing derivatives of heterocycles containing cyclobutane or cyclopentane fragments obtained by modification of monoterpenes and monoterpenoids accompanied by a rupture of the bicyclic frame was also considered.

4 Conclusions and Outlook

The present review aims to provide essential support to chemists in the search for new N-heterocyclic compounds with a monoterpene frame in the structure, which may have wide potential in medicinal chemistry and catalysis. We have reviewed the approaches to the synthesis of *N*-containing heterocyclic compounds with spirocyclic or annulated structures as well as the coupling to the monoterpene frame via C–C, C–N, and other bonds directly or via linkers of different structures. The properties of the heterocyclic compounds obtained, the commercial availability of the initial monoterpenes and their derivatives, and the acceptable yields of the target compounds considered in this review, indicate that the combination of the N-heterocycle nucleus and monoterpene frame in one molecule is a promising direction of investigation in the field of natural product chemistry. Despite numerous exciting advances in the synthesis of N-heterocyclic compounds from monoterpenes and their derivatives, there is still an urgent need both to develop new approaches to synthesis and to expand the libraries of synthesized heterocycles. Work in this direction could lead to the discovery of pharmacologically active and, at the same time, nontoxic substances and to the obtaining of metal complex systems in which the active center and its near surroundings possess a sufficiently rigid framework for the further obtaining of highly stereoselective catalytic systems. On the basis of the review presented, the following can be assumed:

1. Much effort will further be invested in developing robust, flexible and scalable approaches to the synthesis of *N*-containing heterocyclic compounds based on monoterpenes and their derivatives and the subsequent structure–activity relationship for each biological target. An important strategy will be the use of some functional groups or structural fragments that are favorable for affinity to specific

target sites. Such a strategy will produce compounds capable of forming intermediate target/substrate complexes with reduced transition-state energies.

2. The structural modification of natural compounds will be actively used by chemists in the near future. Such an approach may make it possible to obtain surface-active substances with an amphiphilic structure. Currently, researchers pay special attention to surface-active substances with a natural biocompatible fragment. Such amphiphiles can provide additional affinity of surface-active substances to biological systems. Additionally, the modification of monoterpenes and their derivatives leads to the formation of small molecules that can often penetrate through the lipid bilayer of the cell membrane and reach their intracellular targets quite quickly (provided they are sufficiently lipophilic).
3. The study of stereoselective reactions will continue to be one of the most important tasks of modern organic chemistry and will play a fundamental role in the pharmaceutical industry. Considerable efforts will be devoted to the synthesis of highly efficient metal complex systems used in asymmetric catalysis, which still remains one of the most powerful and cost-effective ways to produce enantiomerically enhanced compounds needed for pharmacology. In particular, the synthesis of *N*-heterocyclic carbenes using monoterpenes and their derivatives as starting platforms shows good prospects. The molecular design of new NHCs will focus primarily on steric factors, as it has been found to increase the steric hindrance of the carbene carbon atom which often leads to increased stereoselectivity of NHC–metal complexes.

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Declarations

Competing interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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