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Synthesis of novel menthol derivatives containing 1,2,3-triazole group and their *in vitro* antibacterial activities

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Abstract: New *N*-substituted *α*-aminonitrile derivatives from menthol were synthesized by consecutive succinic ester formation, propargylation, 1,3-dipolar Huisgen cycloaddition and Strecker reaction. The structures of the synthesized compounds were confirmed by diverse spectroscopic techniques including ^{1}H-NMR, ^{13}C-NMR, ESI-MS and IR. The novel synthesized compounds were evaluated for their *in vitro* antibacterial activities against *Staphylococcus aureus* as Gram-positive and *Escherichia coli* as Gram-negative bacteria. These compounds demonstrated a strong inhibitory effect against *S. aureus* with the minimum inhibitory concentration (*MIC*) values ranged from 32–128 μg mL^{-1}. Derivatives **6a**$_2$, **6b**$_1$, **6b**$_4$ and **6b**$_5$ with a *MIC* value of 32 μg mL^{-1} exhibited the best inhibitory effects.

Keywords: click reaction; strecker synthesis; *α*-aminonitrile; Huisgen reaction.

INTRODUCTION

Menthol is a naturally occurring terpenoid with three chiral carbon atoms. Among the optical isomers, (–)-menthol is the one that has been found most widely in nature.[1] Various studies have revealed that menthol has significant biological properties such as antimicrobial, anticancer, anti-inflammatory and antifungal.[2,3] What has drawn the researchers' attention more among these biological properties during the past several years is the antibacterial activity and its use in pharmaceutical products designed to care of the oral health, including toothpastes and mouthwashes to diminish bacterial growth and oral offensive odor.[4] Moreover, some menthol derivatives were reported with outstanding spectrum of antibacterial activities against several bacterial strains.[5–7]

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1,2,3-Triazole is a famous scaffold, which can be prepared by 1,3-dipolar Huisgen cycloaddition reaction,[8] and broadly exists in the wide range of compounds with interesting biological properties such as antibacterial, antimalarial, anticancer, antitubercular, anti-inflammatory.[3,9–11] The structural attribute of 1,2,3-triazole allows it to mimic various functional groups such as esters and amides, leading to its widespread applications in the design of drugs and synthesis of chemical compounds to boost the efficacy of the lead molecule.[12] Most commonly, 1,4-disubstituted 1,2,3-triazoles are served as bioisosteres of the amide bond in different therapeutic contexts, such as anticancer, antitubercular and anti-microbial agents.[13–15]

α-Aminonitriles constitute an important class of naturally existing compounds and a salient intermediate to synthesize various *N*-containing heterocycles.[16,17] The *α*-aminonitrile motif is found in different medicines such as, vildagliptin and anagliptin, Fig. 1, as anti-diabetic drugs.[18] In addition, saframycin as a natural product and its synthetic derivative phthalascidin exhibited promising antitumor activities.[19,20] Several studies revealed that *α*-aminonitrile derivatives exhibit good biological properties, for instance: anticancer, antibacterial, antifungal, and antiviral as well as pesticidal agent.[21–23]

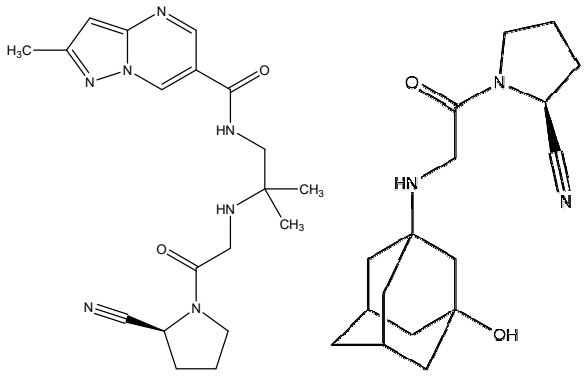


Fig. 1. Structures of biologically active derivatives of *α*-aminonitriles.

The Strecker reaction is a three-component condensation between an aldehyde, an amine and cyanide ion.[24] This valuable reaction leads to the synthesis of *α*-aminonitrile moiety which is of high importance as intermediate in organic synthesis as well as in the pharmaceutical industry.[23,25]

Based on the attributes mentioned above, and in continuation of our interest in evaluating the overall impact of the combination between 1,2,3-triazole ring and natural products,[26,27] here we report the synthesis of new menthol analog containing 1,2,3-triazole and investigation of their antimicrobial activity.

EXPERIMENTAL

General chemistry

Menthol and other starting materials and solvents were purchased from Sigma–Aldrich and Merck chemical companies and used without any further purification. Azides **4a**–**c** were synthesized according to the reported literature procedures.[28–30] ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively, in chloroform ($CDCl_3$) using tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) are given in ppm, and coupling constants (J) are given in Hz. FT-IR spectra were obtained on a Bruker Tensor 27 spectrometer. ESIMS spectra were prepared on a Thermo Fisher Scientific (Waltham, MA, USA) Finnigan TM LCQTM DECA in positive mode. Silica gel F_{254} was employed in column chromatography and thin-layer chromatography (TLC). All analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper.

*Preparation of menthyl succinate (**2**)*

Menthyl succinate was synthesized as reported by a known method in the literature with some modifications.[31,32] To a solution of menthol (5.0 g, 32 mmol) in chloroform, 4-dimethylaminopyridine (0.78 g, 6.4 mmol) and succinic anhydride (3.86 g, 38 mmol) were added. This mixture was stirred overnight under reflux. After solvent evaporation, the crude product was purified using flash column chromatography on silica gel with hexane as eluent to give white crystals (8.0 g, 85 %).

*Preparation of propargyl menthyl succinate (**3**)*

Menthyl succinate (8.0 g, 30 mmol) was dissolved in acetonitrile (50 mL). Propargyl bromide (3.7 mL, 34.8 mmol) and $NaHCO_3$ (8.5 g, 60 mmol) were added. The suspension was stirred for 4 h under reflux condition. Then, acetonitrile was evaporated under vacuum and the reaction mixture was stirred with ethyl acetate. The light brown suspension was filtered and the solid was washed with ethyl acetate (2×30 mL) and dried under vacuum overnight.

*General procedure for the preparation of menthyl di-substituted derivatives possessing 1,2,3--triazole ring (**5a**–**c**)*

In a round-bottom flask, propargylic menthyl succinate **3** (441 mg, 1.5 mmol) and 1.5 mmol of azido-benzaldehyde derivatives **4a**–**c** were dissolved in methanol and dichloromethane mixture (1:1) in the presence of sodium ascorbate (118.8 mg, 0.4 mmol) and $CuSO_4{\cdot}5H_2O$ (149.5 mg, 0.2 mmol), the mixture was stirred at room temperature for 30 min to give exclusively disubstituted 1,2,3-triazoles **5a**–**c**. After completion of the reaction, confirmed by TLC, aqueous ammonia (25 mL, 6N) was added and the whole was extracted with dichloromethane (50 mL) and ethyl acetate (3×50 mL), consequently. In the following, H_2O (20 mL) was added and extracted with EtOAc (3×50 mL). The organic layers were combined and washed with H_2O (3×50 mL), dried over Na_2SO_4 and solvent was removed under reduced pressure. Final purification of analogs **5a**–**c** by flash chromatography on silica gel afforded pure products in 90, 80 and 75 % yields, respectively.

General procedure for the preparation of α*-aminonitrile derivatives* via *Strecker reaction (**6a**$_1$, **a**$_2$, **6b**$_1$–**b**$_7$, **6c**$_1$–**c**$_5$)*

A mixture of azido-benzaldehyde derivatives **4a**–**c** (0.5 mmol, 200 mg) and the corresponding aromatic amine (1.1 mmol) was stirred in acetic acid (10 mL) for 30 min. Then, 6 mmol of potassium cyanide was added to the mixture. Progress of the reaction mixture was monitored by TLC. The mixture was neutralized with (2×25 mL) potassium carbonate solut-

ion, 2 M, and extracted with ethyl acetate (3×50) mL. The organic layers were combined and washed with H_2O (3×50 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure. Final purification by crystallization afforded pure products in 60–80 % yields.

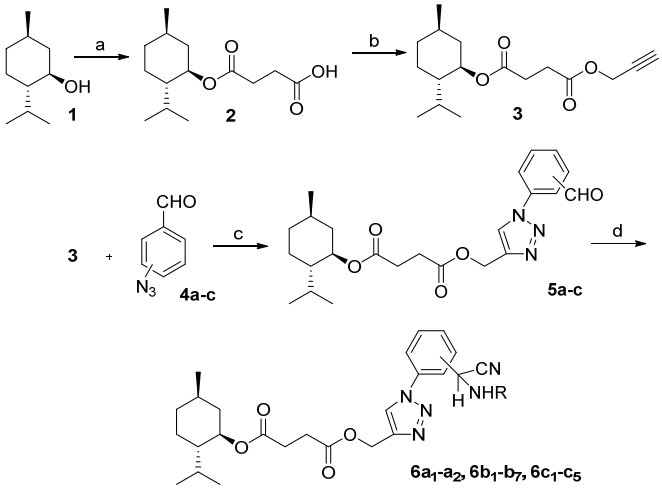
Biological tests

Antibacterial activity of the compounds (mixture of two diastereomers) was evaluated by determination of *MIC*, as the lowest concentration that could inhibit the visible growth of assessed bacterial strains. Broth micro-dilution technique was performed as recommended by Clinical Laboratory Standard Institute (J. Jorgensen). Concisely, a two-fold serial dilution of each compound was prepared using sterile Mueller Hinton broth (MHB) medium in 96 well plates in the concentration range from 0.128–0.256 μg mL^{-1}. Consequently, a freshly cultured *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 were used to prepare a bacterial suspension with turbidity of 0.5 McFarland standard. Prior to adding bacterial suspensions to trays by sterile MHB, it was further diluted (1:100) to achieve 0.5–1×10^6 colony forming unit mL^{-1}. *MIC* was documented after 20 h incubation at 37 °C. Each experiment was performed in triplicate and cefixime was assessed as a standard antibiotic.

RESULTS AND DISCUSSION

Chemistry

Our strategy for the synthesis of novel *α*-aminonitrile derivatives containing 1,2,3-triazole ring is illustrated in Scheme 1. Since succinate has been widely used as a linker in the synthesis of several chemical compounds and drugs with biological activities,[33] it was chosen in order to link to (–)-menthol (**1**), and as a result, the menthyl succinate (**2**) was obtained.[31]



Scheme 1. Preparation of novel triazole derivatives from menthol.

Propargylation of the terminal oxygen in the presence of propargyl bromide and potassium carbonate resulted in the formation of the corresponding propergylated ester (**3**).[34] Then, derivatives **5a**–**c** were synthesized with three *ortho*,

meta and *para* substituted azido-benzaldehydes **4a**–**c** *via* 1,3-dipolar cycloaddition in high yields and purity, using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as catalysts at room temperature.[35] In the following, a series of *α*-aminonitriles were produced by adopting three-component Strecker reaction in the presence of various amines, potassium cyanide and compounds **5a**–**c** as the aldehyde source.[36]

Reagents and conditions: a) succinic anhydride, DMAP, $CHCl_3$, reflux overnight; b) propargyl bromide, K_2CO_3, ACN, 4 h, room temperature (r.t.); c) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, MeOH:H_2O, r.t., 45 min; d) RNH_2, KCN, CH_3COOH, 2 h, r.t.

To synthesize a diverse range of products, three different azido benzaldehydes, *i.e.*, **4a**–**b** were employed. Also, several aromatic amines bearing halogens (F, Cl, Br) and other electron-withdrawing (NO_2, CN) and electron-releasing (CH_3, CH_2CH_3) functional groups were used to reach a library with a collection of pharmacophores (Table I).

TABLE I. Yields and structure of the synthesized α-aminonitriles

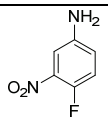
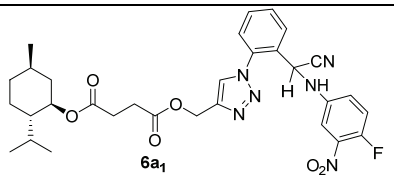
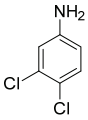
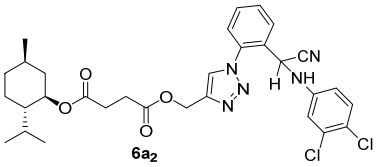
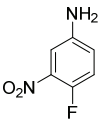
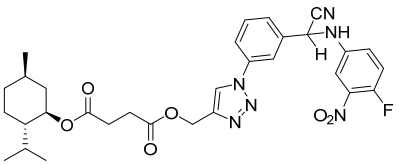
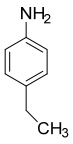
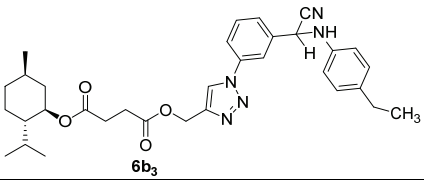
Aldehyde	Amine	Product	Yield, %
5a		 **6a$_1$**	70
5a		 **6a$_2$**	65
5b		 **6b$_1$**	80
5b		 **6b$_3$**	70

TABLE I. Continued

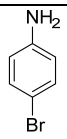
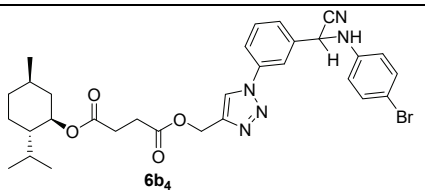
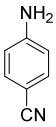
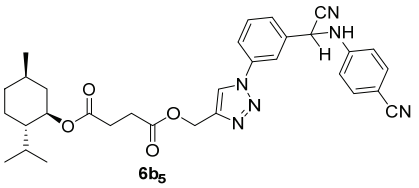
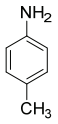
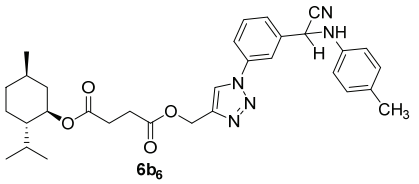
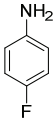
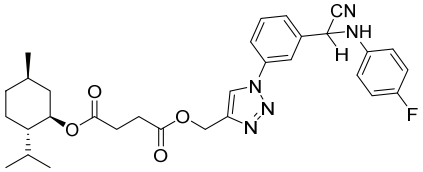
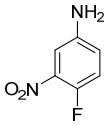
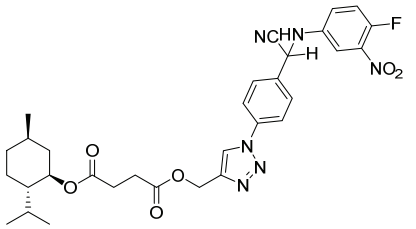
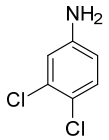
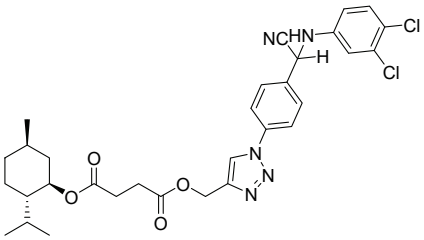
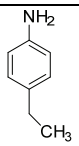
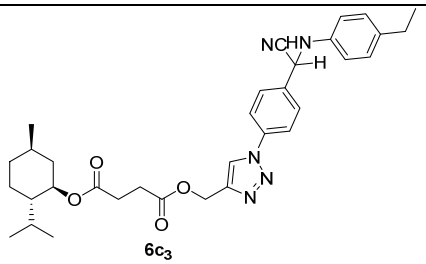
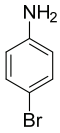
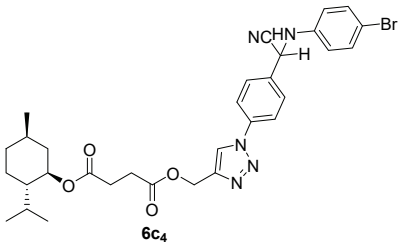
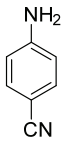
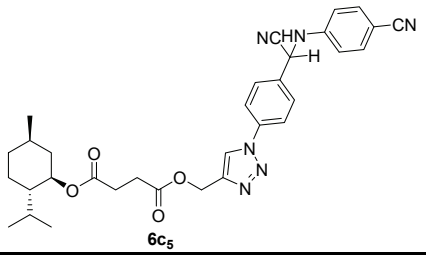
Aldehyde	Amine	Product	Yield, %
5b		 **6b$_4$**	70
5b		 **6b$_5$**	65
5b		 **6b$_6$**	70
5b		 **6b$_7$**	70
5c		 **6c$_1$**	65
5c		 **6c$_2$**	75

TABLE I. Continued

Aldehyde	Amine	Product	Yield, %
5c		 **6c$_3$**	70
5c		 **6c$_4$**	0
5c		 **6c$_5$**	70

Due to the similarity of structures and polarities of the produced diastereomers, we could not separate them by the conventional chromatographic techniques. Surprisingly, almost all of the twin diastereomers exhibited the same NMR spectra. The difference in NMR spectra was only observed for compound **6a1**. The large distance between the newly formed chiral center with other stereogenic centers could be an explanation for this observation.

Biological evaluation

Strong ability of menthol to inhibit different bacterial strains' growth, inspired us to choose it as a lead compound and link it to different scaffolds to discover and develop new antibacterial analogs. *In vitro* antibacterial activities of the newly synthesized compounds **6a**$_1$**,** **a**$_2$, **6b**$_1$–**b**$_7$, **6c**$_1$–**c**$_5$ against Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* were evaluated by determining the minimum inhibitory concentrations (*MIC*), defined as the lowest concentration of the compound that inhibits the visible bacteria growth and compared them with menthol and cefixime (standard antibiotic). As shown in Table II, it is obvious that all novel synthesized compounds exhi-

bited better inhibition activity compared with menthol, however, neither of them was as potent as cefixime. It was revealed that compounds **6a**$_2$, **6b**$_1$, **6b**$_4$ and **6b**$_5$ showed promising antibacterial activity against *S. aureus* with *MIC* of 32 μg mL^{-1}. Apparently, the *meta*-substituted products bearing halogen and/or other electron--withdrawing moieties like NO_2 and CN groups exhibited the best antibacterial activities.

TABLE II. *In vitro* (*MIC* / μg mL^{-1}) antibacterial activity of the α-aminonitrile derivatives

Compound	Bacterium	
	S. aureus ATCC (25923)	*E. coli* ATCC (25922)
6a$_1$	64	>128
6a$_2$	32	>128
6b$_1$	32	>128
6b$_3$	64	>128
6b$_4$	32	>128
6b$_5$	32	>128
6b$_6$	>128	>128
6b$_7$	>128	>128
6c$_1$	64	>128
6c$_2$	64	>128
6c$_3$	> 128	>128
6c$_4$	64	>128
6c$_5$	64	>128
Cefixime	2	7.5
Menthol	> 128	>256

Also, all of them displayed weak activity but stronger than menthol, against *E. coli MIC* > 128 μg mL^{-1}. Due to the obtained results, the significant role of the 1,2,3-triazole ring in boosting the antibacterial activity of menthol derivatives was obvious. Several studies displayed a similar trend (synergistic effect) for improving the antibacterial activity of various lead compounds when linked with a triazole ring.[27,37]

CONCLUSION

One of the most underlying problems facing human beings is bacterial resistance**.** Menthol is the widely used natural compound in different areas of industries. Several reports have indicated the synergistic and boosting effects of triazoles in terms of biological activities. In this study we aimed to synthesize an α-aminonitrile library of novel 1,2,3-triazole tethered menthol derivatives by a combination of Huisgen 1,3-dipolar cycloaddition and Strecker reactions. Assessment of the antibacterial activity of the products against *Staphylococcus aureus* and *Escherichia coli* revealed that most of them had a stronger activity than menthol itself, while neither were as efficient as cefixime.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12030, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА НОВИХ ДЕРИВАТА МЕНТОЛА КОЈИ САДРЖЕ 1,2,3-ТРИАЗОЛСКУ ГРУПУ И ИСПИТИВАЊЕ ЊИХОВЕ *IN VITRO* АНТИБАКТЕРИЈСКЕ АКТИВНОСТИ

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Синтетисани су нови *N*-супституисани α-аминонитрилни деривати ментола, узастопном секвенцом реакција коју чине добијање естра ћилибарне киселине, пропаргиловање, 1,3-диполарне Хизгенове (Huisgen) циклоадиције и Стрекерове (Strecker) синтезе. Структуре синтетисаних производа одређене су на основу анализе спектара, што укључује ^{1}H-NMR, ^{13}C-NMR, ESI-MS и IC. Испитана је *in vitro* антибактеријска активност нових једињења према Грам-позитивној бактерији *Staphylococcus aureus* и Грам-негативној бактерији *Escherichia coli*. Једињења су показала јаку инхибицију према *S. aureus* и минималне инхибиторне концентрације (*MIC*) у опсегу 32–128 μg mL^{-1}. Деривати **6a**$_2$, **6b**$_1$, **6b**$_4$ и **6b**$_5$ показују највећи инхибиторни ефекат и имају *MIC* вредност од 32 μg mL^{-1}.

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