Regular Article

Synthesis and *in Vitro* Antibacterial Evaluation of Novel 4-Substituted 1-Menthyl-1,2,3-triazoles

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Menthyl 1,4-disubstituted 1,2,3-triazole derivatives of hydroxybenzaldehydes, phenols and bile acids were synthesized *via* click chemistry. The novel synthesized compounds were evaluated for their *in vitro* antibacterial activity against *Enterococcus faecium*, and *Staphylococcus aureus* as Gram-positive bacteria. Some derivatives illustrated strong inhibitory effect against *E. faecium* with the minimum inhibitory concentration (MIC) values ranged from 1–3 μM, where cefixime as a positive control revealed MIC value of 35 μM. The structures of the synthesized compounds were confirmed by different spectroscopic techniques including ^{1}H-NMR, ^{13}C-NMR, high resolution (HR)-MS, IR and X-ray crystallographic analysis.

Key words menthol; 1,2,3-triazole; click chemistry; antibacterial activity

Menthol is a natural compound with three asymmetric carbon atoms which among the optical isomers, (−)-menthol with the 1*R*, 2*S*, 5*R* configuration found widely in nature.[1)] *In vitro* and *in vivo* researches demonstrated that menthol as a simple monoterpene exhibits significant biological properties such as anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antipruritic, analgesic and antitussive.[2,3)] It is also used in lots of pharmaceutical remedies such as chest rubs, analgesic balm, nose drop and spray, cough drops and lotion.[3)] It has been reported that menthol acts as an enhancer for transdermal delivery of variety of drugs and it is one of the major agonists of transient receptor potential melastatin 8 (TRPM8).[3,4)] There are reports based on synthesis of menthol derivatives and evaluation of their effects such as antitumor, antimicrobial and antifungal activity as well as on penetration of drugs, percutaneous absorption, inhibition of plasminogen activator inhibitor-1 (PAI-1), cooling effect and insecticidal activity.[5–12)] Previous *in vitro* antibacterial investigations of menthol have proved strong antibacterial activity of this compound against a range of bacterial strains.[13–15)]

Bacterial infections progressively avoid standard treatment as resistance to multiple antibiotics is extending throughout the world, as a result there is an urgent medical need for a sustainable supply of novel, effective, and nontoxic antibacterial drugs without cross-resistance to currently used antibiotics.[16)] Among all the medicines currently approved as antibacterial new chemical entities, a significant percentage of them are either natural products or were derived from a natural product base.[17)] As a result, it is not surprising that natural products are hopeful lead structures particularly for antibacterial drugs.[16)] Structural and chemical diversity of natural products is more than synthetic compounds, so they have been the major sources of bioactive factors and the main target for discovering and designing new drugs.[18)]

Nitrogen-containing heterocycles demonstrate outstanding biological potency.[19)] 1,2,3-Triazole is not produced in nature although this moiety and its derivatives are a significant category of nitrogen-containing aromatic heterocyclic compounds, and have been considered because of their various biological properties such as antibacterial, antifungal, anti-human immunodeficiency virus (HIV), antitubercular, anticancer, anti-inflammatory and analgesic, anticonvulsant, antiparasitic, antidiabetic, antihistaminic and antihypertensive activities.[20–22)] Triazole derivatives have increasingly been used as clinical remedies or candidates for the treatment of various types of diseases with powerful pharmacological activities, less side effects, fewer multidrug resistances, high bioavailability, good pharmacokinetic properties and drug targeting, diversity of drug administration and better curative effects. These evidences can be realized broad potential of triazole-based compounds as medicinal agents. A large number of discoveries illustrated that triazole compounds showed enormous potential as antibacterial drugs. Some triazole derivatives exhibited potent activity against the clinical drug resistant bacteria. Therefore researches on triazole antibacterial aspects have been considered and have become one of the directions in the exploitation of antibacterial agents.[21)] Because of importance of disubstituted 1,2,3-triazole in drug discovery, there is an interest to develop new methods for synthesis of this function.[23)]

Nowadays, click chemistry, especially the Huisgen 1,3-dipolar cycloaddition of azides and alkynes has become a powerful methodology to produce 1,2,3-triazole moiety with high reliability and selectivity.[24)] Click chemistry is an attractive trend in various research fields especially in biomedical investigations and drug discovery because of its high yield, high selectivity, simple purification methods, safe and green reaction conditions and the tolerance of various kinds of functional groups. As a result, click chemistry have been used by researchers as a synthetic tool for the creation of pharmacologically valuable drugs.[25,26)]

In the present study, several menthyl tethered 1,4-disubstituted 1,2,3-triazole derivatives of hydroxybenzaldehydes,

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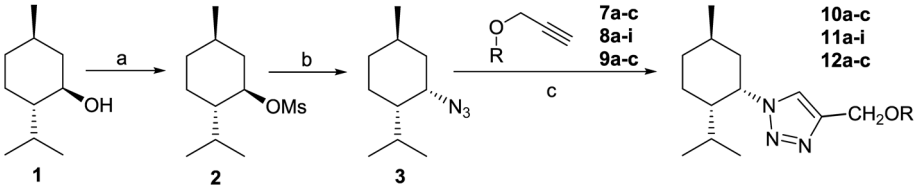
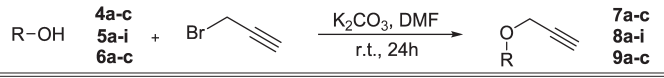
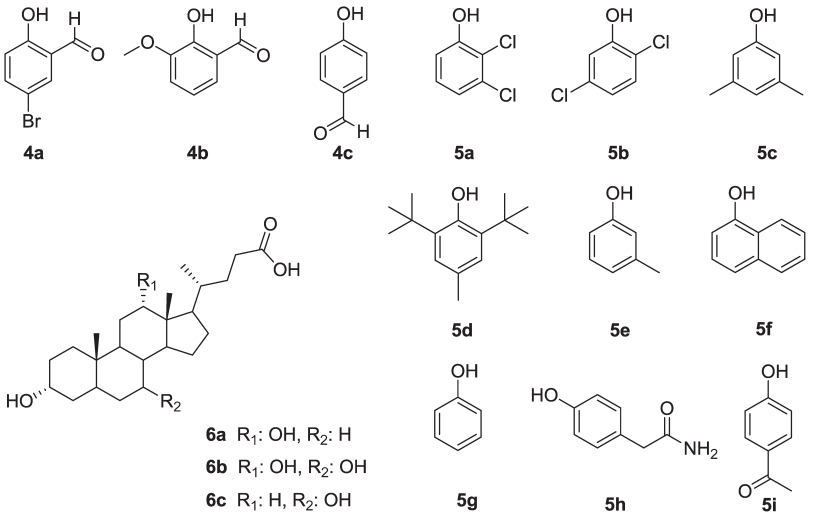


Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, r.t., 2 h, **2**: 90%; b) NaN_3, DMF, 40°C, 48 h, **3**: 70%; c) $CuSO_4 \cdot 5H_2O$ (0.2 eq), sodium ascorbate (0.4 eq), MeOH, r.t., 30 min, **10a–c**, **11a–i** and **12a–c**: 90–98%.

Chart 1. Methods for Preparation of Azide (**3**) and Menthyl 1,4-Disubstituted 1,2,3-Triazole Derivatives (**10a–c**, **11a–i**, **12a–c**)

Table 1. Structures of Hydroxybenzaldehydes (**4a–c**), Phenols (**5a–i**) and Bile Acids (**6a–c**) and the Synthesis Pathway of Propargyl Ethers (**7a–c**, **8a–i**, **9a–c**)





phenols and bile acids have been synthesized and their antibacterial activities were evaluated and compared with parent compounds.

Results and Discussion

Chemistry In this study, our main strategy was the preparation of menthyl azide (**3**) from menthol and synthesis of 1,4-disubstituted 1,2,3-triazoles by the regioselective copper(I) (Cu(I))-catalyzed Huisgen 1,3-dipolar cycloaddition reaction with terminal alkynes. Therefore, in the first step (−)-menthol (**1**) was mesylated in the presence of mesyl chloride followed by reaction with sodium azide which afforded the proper key azide **3** as the building block of all of the target molecules[27,28] (Chart 1). The next step was preparation of the desired alkyne library, therefore three drug-like structures including *ortho*-salicylaldehyde and *para*-hydroxybenzaldehyde derivatives (**4a–c**), phenols (**5a–i**) and bile acids like deoxycholic acid, cholic acid and ursodeoxycholic acid (**6a–c**) were selected to increase the diversity of the propargyl building blocks. *O*-Alkylation of these compounds with propargyl bromide provided the alkyne components **7a–c**, **8a–i** and **9a–c** (Table 1).

Library generation of the menthyl 1,4-disubstituted 1,2,3-triazoles was a paramount part of the research. As a result, functionalizations of the azide and alkyne components were extremely important in increasing the diversity of the desired library. Thus compound **3** as a key azide[29,30] and alkyne building blocks **7a–c**, **8a–i** and **9a–c** with different substituents were subjected to synthesis of novel derivatives **10a–c**, **11a–i** and **12a–c** *via* 1,3-dipolar cycloaddition in high yields and purity in the presence of Cu(I) sulfate and sodium ascorbate as catalysts in methanol at room temperature (Chart 1, Fig. 1).

The use of *ortho*-salicylaldehyde and *para*-hydroxybenzaldehyde derivatives, ended up with the formation of the corresponding 1,2,3-triazoles (**10a–c**) in 90–98% yields. Other phenolic compounds with different functional groups such as halide, alkyl and acyl (**11a–i**) were synthesized and sensitive groups survived under the mild reaction condition. Deoxycholic acid, cholic acid and ursodeoxycholic acid were linked to the 4 position of 1-menthyl-1,2,3-triazol moiety with a methylene spacer in excellent yields (**12a–c**).

The structures of synthesized compounds were confirmed by different spectroscopic techniques including ^{1}H-NMR, ^{13}C-NMR, distortionless enhancement by polarization transfer (DEPT)-135 and HR-MS analyses. In evaluation of ^{1}H-NMR and ^{13}C-NMR spectra of derivatives **10a–c**, **11a–i** and **12a–c** characteristic peaks were clearly evident which indicating certain positions of the molecules. One of these peaks was related to H-1″ as a proton in menthyl ring which carbon is attached to the nitrogen of the triazole moiety and it was found that in all derivatives this peak was appeared in the range of δ=4.93–5.07 ppm. Also, evaluation of ^{1}H-NMR

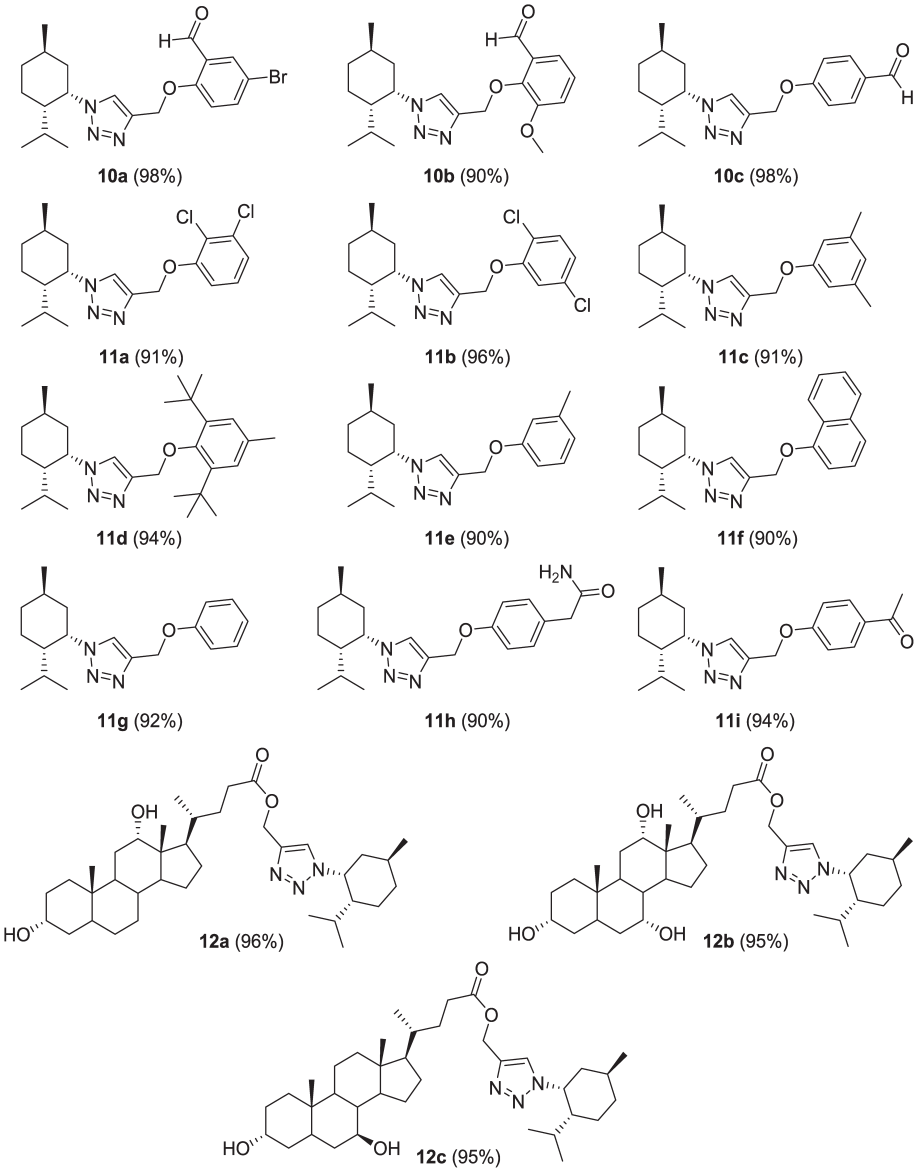


Fig. 1. Structures of 1,2,3-Triazole Derivatives of Menthol (**10a–c**, **11a–i**, **12a–c**)

spectra of products demonstrated chemical shift in the range of δ=7.14–8.34 ppm for H-5′ as a proton of the triazole ring, one of the main scaffolds of all derivatives. Additionally, investigation of spectra revealed chemical shifts in the range of δ=5.09–5.44 and δ=59.3–66.7 ppm for $H_{a,b}$-6′ and C-6′ as protons and carbon of the methylene group attached to the oxygen, respectively. And finally, C-1 as a quaternary aromatic carbon connected to the oxygen in the molecules with the aromatic scaffold, illustrated chemical shift in the range of δ=150.1–163.3 ppm. In assessments, differences in chemical shifts of some of these certain areas in compound **11d** (Fig. 2) compared with others attracted our attention. Differences were related to chemical shifts of protons and carbon in position 6′ with δ=3.04, 3.08 and 37.5 ppm, respectively, and C-1 with δ=186.3 ppm. The reason for these differences is justified by the type of substituents of this compound. In this analogue, aryl moiety is functionalized by two bulky *tert*-butyl groups in the *ortho* positions. These results were probably caused by the influence of bulky substituents on benzene ring which led to a nonplanar mode.[31)]

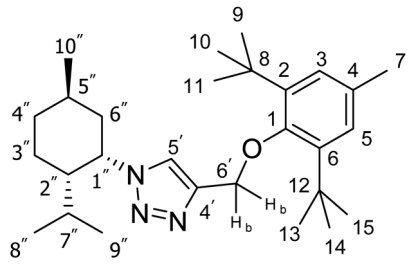


Fig. 2. Atom Numbering of Compound **11d**

Conclusive evidence for the structure of compound **11g** was obtained from single-crystal X-ray diffraction. Single crystal of compound **11g** was obtained by dissolving it in hot *n*-hexane followed by slow evaporation of the solvent. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center, the deposition number is CCDC 1447884. Its ORTEP view is shown in Fig. 3.

Antibacterial Activity Inhibitory effect of menthol on the

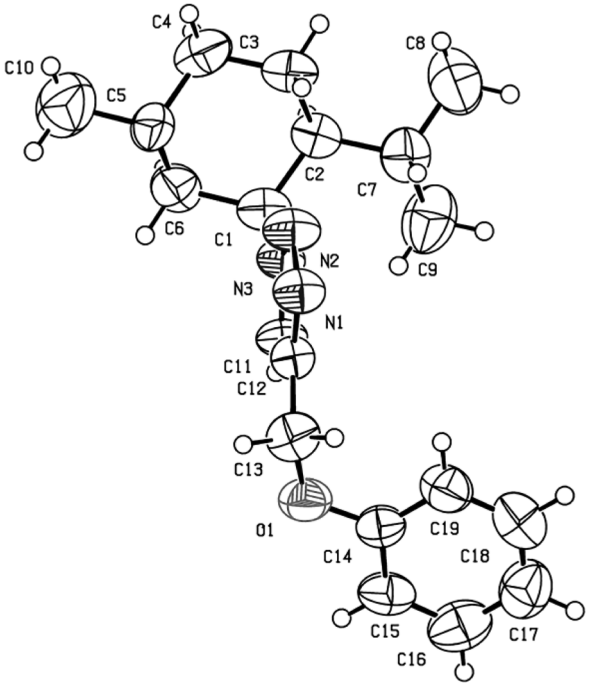


Fig. 3. ORTEP Drawing of Compound **11g**

Table 2. *In Vitro* Antibacterial Activity of Compounds **10a–c**, **11a–i** and **12a–c**

Compounds	Strains MIC[a] (μM)	
	Enterococcus faecium	*Staphylococcus aureus*
10a	2	10
10b	22	345
10c	94	375
11a	21	670
11b	42	670
11c	23	750
11d	1	582
11e	24	782
11f	22	704
11g	26	817
11h	22	86
11i	11	90
12a	3	209
12b	1	204
12c	7	209
13	109	868
(−)-Menthol	410	>1638
Deoxycholic acid	20	>652
Cholic acid	157	>626
Ursodeoxycholic acid	10	>652
Cefixime[b]	35	2

a) Minimum inhibitory concentration. *b*) Positive control.

growth of various strains of bacteria encouraged us to choose this compound as a starting point to optimize biological profile as well as discovering and improving new antibacterial analogues by linking various scaffolds to this lead compound. The synthesized novel triazole derivatives of menthol (**10a–c**, **11a–i**, **12a–c**) were evaluated for their *in vitro* antibacterial activity using standard techniques by determining the minimum inhibitory concentrations (MICs, μM), defined as the lowest concentration of the compound required to give complete inhibition of visible bacterial growth.[32] Evaluations were carried out against *Enterococcus faecium* (ATCC 35667) and *Staphylococcus aureus* (ATCC 25923) as Gram-positive bacteria *via* comparing the results with cefixime as a standard antibiotic and those of parent compounds. MIC values of **10a–c**, **11a–i** and **12a–c** against strains along with cefixime, menthol and bile acids are listed in Table 2. Obtained data demonstrated strong antibacterial activity of derivatives in comparison with menthol against *E. faecium* strain, however all of the synthesized compounds except **10c** and **11b** showed even much stronger effect than cefixime as a standard antibiotic. In the meantime, compounds **12b**, **11d**, **10a** and **12a** with the lowest MIC values of 1, 1, 2 and 3 μM, respectively, were more potent than the positive control cefixime with MIC of 35 μM. Compounds **12a–c** which were derived from triterpenic building blocks (**9a–c**) demonstrated stronger effect than their parent compounds deoxycholic acid, cholic acid and ursodeoxycholic acid with MIC values of 20, 157 and 10 μM, respectively, in which **12b** showed a remarkable change. A similar trend for considerable differences in the antibacterial and antifungal activities of some derivatives of cholic acid and deoxycholic acid has already been reported in the literature.[22] Also, the physiochemical and biological properties of bile acids have been related to the balance between hydroxyls at positions 3, 7 and/or 12 and the carboxylic side chain as hydrophilic groups and hydrophobic methyl groups in their structures. This balance and consequently properties can be modified by the distribution of the number, position and stereochemistry of hydroxyl groups and linking proper substituents that increase either the hydrophilicity or the hydrophobicity of these building blocks depending on the nature of the organic group.[33]

As indicated from the data, for *S. aureus*, while compounds **10a** with MIC of 10 μM along with **11h** and **i** with MIC values of 86 and 90 μM, respectively, exhibited promising activity compared to menthol, others did not show comparable activity than cefixime with MIC of 2 μM. Also, derivatives activity was investigated against two other strain namely *Bacillus subtilis* and *Escherichia coli*, but was not observed significant effect. It was especially noteworthy that menthol as the precursor of the target compounds showed moderate inhibitory activity against all tested strains, while the incorporation of 1,2,3-triazole ring, dramatically enhanced the antibacterial activity of all the derivatives against *E. faecium* and some derivatives against *S. aureus*.

A survey in the literature revealed the same trend for increasing the antibacterial activity of some lead compounds by linking a triazole ring.[20,34–36] This could be due to enhancement of hydrogen bonding and dipole–dipole interaction of the molecules with the biological targets or improvement of their solubility.[21,37,38] 1,2,3-Triazoles are attractive linker units and have become useful and important in creating bioactive and functional molecules *via* linking two pharmacophores to give an innovative bifunctional drug.[20]

To investigate the role of menthyl group on antibacterial activities of the products, we have synthesized compound **13** which is the methyl analogue of compound **10a** (Fig. 4).

While **10a** was one of the strongest antibacterial compounds, the MIC values of 109 and 868 μM were observed for **13** against *E. faecium* and *S. aureus*, respectively. These findings clearly show the importance of menthyl moiety on the

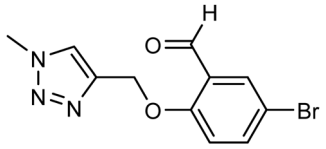


Fig. 4. Structure of Compound **13**

Table 3. Drug Likeness of the Synthesized Derivatives **10a–c**, **11a–i** and **12a–c**

Compound	cLog$P^{a)}$	H-Acceptor	H-Donor	tPSA$^{b)}$	MW$^{c)}$
10a	5.77	5	0	54.26	420.35
10b	4.54	6	0	63.49	371.48
10c	4.87	5	0	54.26	341.46
11a	5.90	4	0	37.19	382.33
11b	6.54	4	0	37.19	382.33
11c	6.15	4	0	37.19	341.50
11d	9.30	4	0	37.19	439.69
11e	5.65	4	0	37.19	327.47
11f	6.33	4	0	37.19	363.50
11g	5.15	4	0	37.19	313.44
11h	3.47	5	1	80.28	370.50
11i	4.89	5	0	54.26	355.48
12a	8.64	6	2	94.72	611.91
12b	6.55	7	3	114.95	627.91
12c	8.64	6	2	94.72	611.91
Menthol	3.23	1	1	20.23	156.27
Deoxycholic acid	4.51	3	3	77.76	392.58
Cholic acid	2.43	4	4	97.99	408.58
Ursodeoxycholic acid	4.51	3	3	77.76	392.58
Cefixime	0.25	8	4	183.98	453.44

a) Logarithm of compound partition coefficient between *n*-octanol and water. *b*) Molecular Polar Surface Area. *c*) Molecular weight.

antibacterial activity of the synthesized compounds.

The drug-likeness properties of synthesized compounds evaluated by physicochemical properties calculation based on Lipinski's rule of five using ChemBio3D package version 14.0.0.117 (Perkin Elmer, Inc. (United States)). The calculation results showed that all compounds except **12a–c** meet the Lipinski rules of the five, suggesting that these compounds theoretically would not have problems with oral bioavailability[39] (Table 3).

Experimental

General Melting points were measured on an Electrothermal 9200 apparatus and were not corrected. HR-electrospray ionization (ESI)-MS spectra in positive mode were recorded on a Bruker micro time-of-flight (TOF) ESI-MS system with a scan range of *m*/*z* 150–1500. Fourier transform (FT)-IR spectra were recorded on a Bruker Tensor 27 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 300 spectrometer operating at 300.13 and 75.47 MHz, respectively, or on a Bruker Avance III 400 spectrometer operating at 400.1 and 100.6 MHz, respectively. The spectra were obtained in chloroform ($CDCl_3$) and dimethyl sulfoxide (DMSO)-d_6 using tetramethylsilane (TMS) as internal standard. X-Ray data were collected on a STOE IPDS-II diffractometer with graphite monochromated Mo$K\alpha$ radiation. GC analysis was carried out on a Thermoquest Finnigan instrument equipped with a flame ionization detector (FID) and Rtx®-5 fused silica column.

Preparation of Mesylate 2 and Azide 3 Menthyl methanesulfonate (**2**) and menthyl azide (**3**) were synthesized according to the known methods reported in the literature.[27,28]

Preparation of Propargylic Compounds 7a–c, 8a–i and 9a–c Compounds **7a–c**, **8a–i** and **9a–c**[22,31,40–47] were synthesized by propargylation of compounds **4a–c**, **5a–i** and **6a–c**, respectively, according to a known procedure.[48]

General Procedure for Preparation of Menthyl 1,4-Disubstituted 1,2,3-Triazole Derivatives (10a–c, 11a–i, 12a–c) Synthesis of the target compounds **10a–c**, **11a–i** and **12a–c** was carried out *via* alkyne-azide Huisgen cycloaddition reaction. Accordingly, propargyl ethers **7a–c**, **8a–i** and **9a–c** (1 eq) were treated with compound **3** (200 mg, 1.1 mmol) in the presence of sodium ascorbate (0.087 mg, 0.44 mmol) and copper sulfate (0.055 mg, 0.22 mmol) in MeOH (5 mL) at room temperature for 30 min to give exclusively 1,4-disubstituted 1,2,3-triazoles (**10a–c**, **11a–i**, **12a–c**). After completion of the reaction confirmed by TLC, aqueous ammonia (10 mL) was added to remove the excess of copper. In the following H_2O (50 mL) was added to the suspension and extracted with EtOAc (3×50 mL). The organic layers were washed with H_2O (3×150 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure. Final purification by flash chromatography on silica gel (25% EtOAc–*n*-hexane) afforded pure products in 90–98% yields.

Preparation of Compound 13 One-pot synthesis of compound **13** was performed using a known method with some modifications by the reaction of methyl iodide (MeI) (1.5 eq), NaN_3 (1.5 eq) and **7a** (1.0 eq) in MeOH–H_2O (1 : 1) as solvent in the presence of $CuSO_4 \cdot 5H_2O$ (0.2 eq) and sodium ascorbate (0.4 eq).[49]

5-Bromo-2-((1-(2-isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4yl)methoxy)benzaldehyde (**10a**)

White solid. mp 72–74°C. Yield 98%. IR (KBr) cm^{-1}: 3119, 3077, 2936, 2861, 1702, 1590, 1450, 1385, 1286, 685. ^{1}H-NMR ($CDCl_3$) δ: 10.36 (s, 1H, $H_{aldehyde}$), 7.91 (d, 1H, H_{Ar}, J=2.1 Hz), 7.77 (s, 1H, $H_{triazole}$), 7.63 (dd, 1H, J=8.7, 2.1 Hz), 7.15 (d, 1H, H_{Ar}, J=8.7 Hz), 5.32 (s, 2H, CH_2–O), 5.05 (brs, 1H, CH–N), 1.81–2.00 (m, 4H), 1.64–1.81 (m, 1H), 1.33–1.56 (m, 2H), 1.00–1.14 (m, 2H), 0.88 (d, 3H, CH_3, J=5.8 Hz), 0.82 (d, 3H, CH_3, J=6.4 Hz), 0.76 (d, 3H, CH_3, J=6.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 188.3, 159.5, 138.4, 138.2, 131.5, 131.1, 126.4, 115.4, 114.1, 63.0, 59.6, 46.6, 40.6, 34.6, 29.1, 26.4, 24.9, 22.2, 21.0, 20.4. NMR purity: >95%. HR-MS (ESI) *m*/*z*: Calcd for $C_{20}H_{27}BrN_3O_2$: 420.1287; Found: 420.1335 $[M+H]^+$. $[\alpha]_D^{20}$ +0.18 (c=0.5, MeOH).

2-((1-(2-Isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3-methoxybenzaldehyde (**10b**)

White solid. mp 129–131°C. Yield 90%. IR (KBr) cm^{-1}: 3118, 3070, 2940, 2861, 1692, 1589, 1474, 1260. ^{1}H-NMR ($CDCl_3$) δ: 10.21 (s, 1H, $H_{aldehyde}$), 7.58 (s, 1H, $H_{triazole}$), 7.35 (dd, 1H, H_{Ar}, J=7.2, 1.9 Hz), 7.10–7.19 (m, 2H, H_{Ar}), 5.37 (s, 2H, CH_2–O), 5.01 (brs, 1H, CH–N), 3.95 (s, 3H, OCH_3), 1.79–1.95 (m, 4H), 1.55–1.72 (m, 1H), 1.28–1.50 (m, 2H), 0.93–1.08 (m, 2H), 0.86 (d, 3H, CH_3, J=6.2 Hz), 0.79 (d, 3H, CH_3, J=6.9 Hz), 0.76 (d, 3H, CH_3, J=6.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 190.2, 153.0, 150.1, 142.1, 139.8, 130.4, 125.1, 124.3, 124.1, 66.7, 59.2, 56.2, 46.5, 40.7, 34.6, 29.0, 26.4, 24.9, 22.3, 21.0, 20.6. NMR purity: >95%. HR-MS (ESI) *m*/*z*: Calcd for

$C_{21}H_{30}N_3O_3$: 372.2287; Found: 372.2271 $[M+H]^+$. $[\alpha]_D^{20}$ +0.10 (c=0.2, MeOH).

4-((1-(2-Isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde (**10c**)

White solid. mp 139–141°C. Yield 98%. IR (KBr) cm^{-1}: 3124, 3070, 2932, 2864, 1699, 1602, 1454, 1251. ^{1}H-NMR ($CDCl_3$) δ: 9.91 (s, 1H, $H_{aldehyde}$), 7.86 (d, 2H, H_{Ar}, J=8.5 Hz), 7.75 (s, 1H, $H_{triazole}$), 7.15 (d, 2H, H_{Ar}, J=8.5 Hz), 5.31 (s, 2H, CH_2–O), 5.07 (brs, 1H, CH–N), 1.84–2.03 (m, 4H), 1.66–1.83 (m, 1H), 1.35–1.56 (m, 2H), 1.01–1.15 (m, 2H), 0.89 (d, 3H, CH_3, J=6.0 Hz), 0.85 (d, 3H, CH_3, J=6.5 Hz), 0.78 (d, 3H, CH_3, J=6.5). ^{13}C-NMR ($CDCl_3$) δ: 190.8, 163.3, 142.0, 132.0, 130.2, 123.9, 115.2, 62.3, 59.4, 46.6, 40.7, 34.6, 29.1, 26.3, 24.9, 22.2, 21.1, 20.5. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{20}H_{28}N_3O_2$: 342.2182; Found: 342.2151 $[M+H]^+$. $[\alpha]_D^{20}$ +0.14 (c=0.5, MeOH).

4-((2,3-Dichlorophenoxy)methyl)-1-(2-isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazole (**11a**)

White solid. mp 123–125°C. Yield 91%. IR (KBr) cm^{-1}: 3119, 3072, 2950, 1638, 1453, 1281, 763. ^{1}H-NMR ($CDCl_3$) δ: 7.75 (s, 1H, $H_{triazole}$), 7.04–7.19 (m, 3H, H_{Ar}), 5.33 (s, 2H, CH_2–O), 5.04 (brs, 1H, CH–N), 1.66–2.00 (m, 5H), 1.33–1.53 (m, 2H), 1.00–1.12 (m, 2H), 0.88 (d, 3H, CH_3, J=5.8 Hz), 0.83 (d, 3H, CH_3, J=6.5 Hz), 0.76 (d, 3H, CH_3, J=6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 155.1, 142.2, 133.8, 127.4, 123.9, 122.9, 122.2, 112.6, 63.9, 59.3, 46.6, 40.8, 34.6, 29.1, 26.3, 24.9, 22.2, 21.0, 20.5. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{19}H_{26}Cl_2N_3O$: 382.1453; Found: 382.1454 $[M+H]^+$. $[\alpha]_D^{20}$ +0.08 (c=0.5, MeOH).

4-((2,5-Dichlorophenoxy)methyl)-1-(2-isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazole (**11b**)

White solid. mp 112–114°C. Yield 96%. IR (KBr) cm^{-1}: 3080, 2951, 1582, 1480, 1262, 799. ^{1}H-NMR ($CDCl_3$) δ: 7.74 (s, 1H, $H_{triazole}$), 7.30 (d, 1H, H_{Ar}, J=8.4 Hz), 7.13 (d, 1H, H_{Ar}, J=2.2 Hz), 6.93 (dd, 1H, H_{Ar}, J=8.4, 2.2 Hz), 5.30 (s, 2H, CH_2–O), 5.05 (brs, 1H, CH–N), 1.67–2.03 (m, 5H), 1.36–1.54 (m, 2H), 1.03–1.13 (m, 2H), 0.89 (d, 3H, CH_3, J=5.9 Hz), 0.84 (d, 3H, CH_3, J=6.5 Hz), 0.78 (d, 3H, CH_3, J=6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 154.3, 142.1, 133.1, 130.8, 130.6, 122.0, 121.7, 115.2, 63.8, 59.3, 46.6, 40.8, 34.7, 29.1, 26.2, 25.0, 22.2, 21.1, 20.5. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{19}H_{26}Cl_2N_3O$: 382.1453; Found: 382.1441 $[M+H]^+$. $[\alpha]_D^{20}$ +0.10 (c=0.5, MeOH).

4-((3,5-Dimethylphenoxy)methyl)-1-(2-isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazole (**11c**)

White solid. mp 110–112°C. Yield 91%. IR (KBr) cm^{-1}: 3100, 2947, 2861, 1603, 1459, 1225. ^{1}H-NMR ($CDCl_3$) δ: 7.69 (s, 1H, $H_{triazole}$), 6.65 (s, 3H, H_{Ar}), 5.20 (s, 2H, CH_2–O), 5.05 (brs, 1H, CH–N), 2.30 (s, 6H, $2CH_3$), 1.72–2.03 (m, 5H), 1.33–1.54 (m, 2H), 1.01–1.18 (m, 2H), 0.89 (d, 3H, CH_3, J=6.1 Hz), 0.86 (d, 3H, CH_3, J=6.6 Hz), 0.79 (d, 3H, CH_3, J=6.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 158.4, 143.3, 139.2, 123.7, 123.0, 112.7, 62.3, 59.2, 46.6, 40.8, 34.7, 29.1, 26.2, 25.0, 22.2, 21.06, 21.3, 20.6. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{21}H_{32}N_3O$: 342.2467; Found: 342.2516 $[M+H]^+$. $[\alpha]_D^{20}$ +0.16 (c=0.5, MeOH).

4-((2,6-Di-*tert*-butyl-4-methylphenoxy)methyl)-1-(2-isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazole (**11d**)

Yellow solid. mp 79–81°C. Yield 94%. IR (KBr) cm^{-1}: 3136, 2954, 2871, 1644, 1457, 1247. ^{1}H-NMR ($CDCl_3$) δ: 7.16 (s, 1H, $H_{triazole}$), 6.56 (d, 1H, H_{Ar}, J=2.9 Hz), 6.53 (d, 1H, H_{Ar}, J=2.9 Hz), 4.92–4.97 (m, 1H, CH–N), 3.08 (d, 1H, CH_2–O, J=14.4 Hz), 3.04 (d, 1H, CH_2–O, J=14.4 Hz), 1.77–1.92 (m, 3H), 1.68–1.77 (m, 1H), 1.58–1.67 (m, 1H), 1.38–1.44 (m, 1H), 1.27–1.35 (m, 4H, CH & CH_3), 1.19 (s, 9H, $3CH_3$), 1.18 (s, 9H, $3CH_3$), 0.96–1.04 (m, 2H), 0.83 (d, 3H, CH_3, J=6.4 Hz), 0.80 (d, 3H, CH_3, J=6.4 Hz), 0.77 (d, 3H, CH_3, J=6.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 186.3, 146.8, 146.7, 145.9, 145.8, 142.3, 122.0, 59.0, 46.5, 40.8, 40.3, 37.5, 34.6, 34.5, 29.4, 29.3, 29.0, 27.0, 26.3, 25.2, 22.1, 21.1, 20.6. HPLC purity: 95%. HR-MS (ESI) m/z: Calcd for $C_{28}H_{46}N_3O$: 440.3641; Found: 440.3627 $[M+H]^+$. $[\alpha]_D^{20}$ +0.10 (c=0.3, MeOH).

1-(2-Isopropyl-5-methylcyclohexyl)-4-((*m*-tolyloxy)-methyl)-1*H*-1,2,3-triazole (**11e**)

Pale yellow needle crystal. mp 80–82°C. Yield 90%. IR (KBr) cm^{-1}: 3191, 3070, 2945, 2849, 1603, 1454, 1252. ^{1}H-NMR ($CDCl_3$) δ: 7.70 (s, 1H, $H_{triazole}$), 7.19 (t, 1H, H_{Ar}, J=7.6 Hz), 6.78–6.87 (m, 3H, H_{Ar}), 5.21 (s, 2H, CH_2–O), 5.05 (brs, 1H, CH–N), 2.34 (s, 3H, CH_3), 1.67–2.02 (m, 5H), 1.33–1.53 (m, 2H), 1.01–1.71 (m, 2H), 0.89 (d, 3H, CH_3, J=6.1 Hz), 0.85 (d, 3H, CH_3, J=6.6 Hz), 0.79 (d, 3H, CH_3, J=6.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 158.3, 143.2, 139.6, 129.3, 123.7, 122.1, 115.8, 111.8, 62.2, 59.5, 46.7, 40.7, 34.6, 29.1, 26.3, 25.0, 22.2, 21.5, 21.1, 20.6. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{20}H_{30}N_3O$: 328.2389; Found: 328.2361 $[M+H]^+$. $[\alpha]_D^{20}$ +0.16 (c=0.5, MeOH).

1-(2-Isopropyl-5-methylcyclohexyl)-4-((naphthalen-1-yloxy)-methyl)-1*H*-1,2,3-triazole (**11f**)

White solid. mp 143–145°C. Yield 90%. IR (KBr) cm^{-1}: 3194, 3128, 2942, 2862, 1584, 1455, 1270. ^{1}H-NMR ($CDCl_3$) δ: 8.29 (d,1H, H_{Ar}, J=7.1 Hz), 7.83 (d, 1H, H_{Ar}, J=6.5 Hz), 7.75 (s, 1H, $H_{triazole}$), 7.35–7.56 (m, 4H, H_{Ar}), 7.02 (d, 1H, H_{Ar}, J=6.9 Hz), 5.44 (s, 2H, CH_2–O), 5.05 (brs, 1H, CH–N), 1.75–2.04 (m, 5H), 1.37–1.55 (m, 2H), 1.01–1.17 (m, 2H), 0.90 (d, 3H, CH_3, J=5.5 Hz), 0.86 (d, 3H, CH_3, J=6.2 Hz), 0.79 (d, 3H, CH_3, J=6.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 154.1, 143.1, 134.5, 127.4, 126.4, 125.9, 125.8, 125.2, 124.1, 121.9, 120.9, 105.7, 62.8, 59.3, 46.7, 40.9, 34.7, 29.1, 26.2, 24.9, 22.3, 21.1, 20.5. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{23}H_{30}N_3O$: 364.2389; Found: 364.2386 $[M+H]^+$. $[\alpha]_D^{20}$ +0.10 (c=0.5, MeOH).

1-(2-Isopropyl-5-methylcyclohexyl)-4-(phenoxymethyl)-1*H*-1,2,3-triazole (**11g**)

Beige crystal. mp 97–99°C. Yield 92%. IR (KBr) cm^{-1}: 3081, 2950, 2860, 1594, 1490, 1238. ^{1}H-NMR ($CDCl_3$) δ: 7.71 (s, 1H, $H_{triazole}$), 7.29–7.36 (m, 2H, H_{Ar}), 6.96–7.06 (m, 3H, H_{Ar}), 5.23 (s, 2H, CH_2–O), 5.06 (brs, 1H, CH–N), 1.84–2.02 (m, 4H), 1.67–1.81 (m, 1H), 1.33–1.54 (m, 2H), 1.01–1.15 (m, 2H), 0.89 (d, 3H, CH_3, J=6.1 Hz), 0.86 (d, 3H, CH_3, J=6.5 Hz), 0.79 (d, 3H, CH_3, J=6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 158.3, 143.1, 129.5, 123.7, 121.2, 114.9, 62.2, 59.3, 46.6, 40.7, 34.6, 29.0, 26.3, 25.0, 22.3, 21.1, 20.6. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{19}H_{28}N_3O$: 314.2232; Found: 314.2205 $[M+H]^+$. $[\alpha]_D^{20}$ +0.16 (c=0.5, MeOH).

2-(4-((1-(2-Isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)acetamide (**11h**)

White solid. mp 182–184°C. Yield 90%. IR (KBr) cm^{-1}: 3424, 3132, 3076, 2950, 2862, 1636, 1513, 1447, 1246. ^{1}H-NMR (DMSO-d_6) δ: 8.35 (s, 1H, $H_{triazole}$), 7.43 (s, 1H, NH), 7.19 (d, 2H, H_{Ar}, J=8.4 Hz), 6.97 (d, 2H, H_{Ar}, J=8.4 Hz), 6.86 (s, 1H, NH), 5.09 (s, 2H, CH_2–O), 5.06 (brs, 1H, CH–N), 3.40 (s, 2H, CH_2), 1.72–1.92 (m, 5H), 1.35–1.54 (m, 2H), 0.90–1.06

(m, 2H), 0.83 (d, 3H, CH_3, J=6.2 Hz), 0.78 (d, 3H, CH_3, J=6.4 Hz), 0.70 (d, 3H, CH_3, J=6.4 Hz). ^{13}C-NMR (DMSO-d_6) δ: 173.0, 157.0, 141.9, 130.6, 129.3, 126.3, 114.9, 61.5, 58.5, 46.0, 41.9, 34.7, 29.2, 26.1, 24.8, 22.6, 21.3, 20.7. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{21}H_{31}N_4O_2$: 371.2447; Found: 371.2441 $[M+H]^+$. $[\alpha]_D^{20}$ +0.14 (c=0.5, MeOH).

1-(4-((1-(2-Isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)ethan-1-one (**11i**)

Pale yellow needle crystal. mp 154–156°C. Yield 94%. IR (KBr) cm^{-1}: 3124, 3077, 2940, 2861, 1677, 1602, 1453, 1253. ^{1}H-NMR ($CDCl_3$) δ: 7.94 (d, 2H, H_{Ar}, J=8.7 Hz), 7.74 (s, 1H, $H_{triazole}$), 7.05 (d, 2H, J=8.7 Hz), 5.27 (s, 2H, CH_2–O), 5.05 (brs, 1H, CH–N), 2.56 (s, 3H, $COCH_3$), 1.83–2.00 (m, 4H), 1.65–1.81 (m, 1H), 1.33–1.53 (m, 2H), 1.00–1.13 (m, 2H), 0.87 (d, 3H, CH_3, J=6.0 Hz), 0.83 (d, 3H, CH_3, J=6.5 Hz), 0.77 (d, 3H, CH_3, J=6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 196.8, 162.2, 142.2, 130.7, 130.6, 123.9, 114.5, 62.2, 59.4, 46.6, 40.7, 34.5, 29.0, 26.4, 26.3, 24.9, 22.2, 21.1, 20.5. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{21}H_{30}N_3O_2$: 356.2338; Found: 356.2322 $[M+H]^+$. $[\alpha]_D^{20}$ +0.14 (c=0.5, MeOH).

(1-(2-Isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4-yl)-methyl 4-(3,12-Dihydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (**12a**)

White solid. mp 97–99°C. Yield 96%. IR (KBr) cm^{-1}: 3465, 2933, 2868, 1731, 1455, 1251. ^{1}H-NMR ($CDCl_3$) δ: 7.67 (s, 1H, $H_{triazole}$), 5.19 (s, 2H, CH_2–O), 5.02 (brs, 1H, CH–N), 3.94 (brs, 1H, C<u>H</u>–OH), 3.50–3.65 (m, 1H, C<u>H</u>–OH), 2.18–2.44 (m, 4H), 0.98–1.99 (m, 33H, 2OH, CH, CH_2), 0.92 (d, 3H, CH_3, J=5.8 Hz), 0.89 (s, 3H, CH_3), 0.86 (d, 3H, CH_3, J=6.2 Hz), 0.82 (d, 3H, CH_3, J=6.6 Hz), 0.76 (d, 3H, CH_3, J=6.6 Hz), 0.64 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 174.2, 141.8, 124.8, 73.1, 71.7, 59.4, 57.5, 48.2, 47.2, 46.7, 46.5, 42.1, 40.7, 36.4, 36.0, 35.2, 35.1, 34.6, 34.1, 33.6, 31.1, 30.8, 30.5, 29.1, 28.7, 27.5, 27.1, 26.3, 26.1, 24.9, 23.7, 23.2, 22.2, 21.1, 20.5, 17.3, 12.7. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{37}H_{62}N_3O_4$: 612.4740; Found: 612.4573 $[M+H]^+$. $[\alpha]_D^{20}$ +0.44 (c=0.5, MeOH).

(1-(2-Isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4-yl)-methyl 4-(3,7,12-Trihydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (**12b**)

White solid. mp 85–87°C. Yield 95%. IR (KBr) cm^{-1}: 3395, 2940, 2870, 1734, 1457, 1241. ^{1}H-NMR ($CDCl_3$) δ: 7.68 (s, 1H, $H_{triazole}$), 5.19 (s, 2H, CH_2–O), 5.02 (brs, 1H, CH–N), 3.92 (brs, 1H, C<u>H</u>–OH), 3.82 (brs, 1H, C<u>H</u>–OH), 3.35–3.55 (m, 4H, C<u>H</u>–OH, 3OH), 2.17–2.45 (m, 4H), 1.17–2.00 (m, 25 H), 0.98–1.14 (m, 4H), 0.93 (d, 3H, CH_3, J=5.2 Hz) 0.86 (s, 3H, CH_3), 0.85 (d, 3H, CH_3, J=5.2 Hz), 0.82 (d, 3H, CH_3, J=6.6 Hz), 0.76 (d, 3H, CH_3, J=6.6 Hz), 0.63 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 174.3, 141.8, 124.8, 73.1, 71.9, 68.5, 59.3, 57.6, 46.9, 46.7, 46.4, 41.6, 41.5, 40.7, 39.5, 35.3, 34.8, 34.7, 34.6, 31.2, 30.8, 30.3, 29.1, 28.2, 27.5, 26.9, 26.3, 25.3, 24.9, 23.2, 22.5, 22.3, 21.1, 20.6, 17.3, 12.5. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{37}H_{62}N_3O_5$: 628.4689; Found: 628.5099 $[M+H]^+$. $[\alpha]_D^{20}$ +0.28 (c=0.5, MeOH).

(1-(2-Isopropyl-5-methylcyclohexyl)-1*H*-1,2,3-triazol-4-yl)-methyl 4-(3,7-Dihydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (**12c**)

White solid. mp 78–80°C. Yield 95%. IR (KBr) cm^{-1}: 3401, 2937, 2866, 1736, 1456, 1238. ^{1}H-NMR ($CDCl_3$) δ: 7.67 (s, 1H, $H_{triazole}$), 5.19 (s, 2H, CH_2–O), 5.01 (brs, 1H, CH–N), 3.50–3.63 (m, 2H, 2C<u>H</u>–OH), 2.14–2.45 (m, 4H), 0.97–2.01 (m, 33H, 2OH, CH, CH_2), 0.92 (s, 3H, CH_3) 0.88 (d, 3H, CH_3, J=6.1 Hz), 0.85 (d, 3H, CH_3, J=6.7 Hz), 0.82 (d, 3H, CH_3, J=6.6 Hz), 0.75 (d, 3H, CH_3, J=6.6 Hz), 0.64 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 174.2, 141.8, 124.8, 71.4, 71.3, 59.4, 57.5, 55.7, 54.9, 46.6, 43.7, 42.5, 40.7, 40.1, 39.2, 37.3, 36.9, 35.3, 35.0, 34.6, 34.1, 31.2, 30.9, 30.3, 29.1, 28.6, 26.9, 26.3, 24.9, 23.4, 22.2, 21.1, 21.2, 20.5, 18.8, 12.1. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{37}H_{62}N_3O_4$: 612.4740; Found: 612.4573 $[M+H]^+$. $[\alpha]_D^{20}$ +0.46 (c=0.5, MeOH).

5-Bromo-2-((1-methyl-1*H*-1,2,3-triazol-4-yl)methoxy)-benzaldehyde (**13**)

Pale yellow solid. mp 130–132°C. Yield 85%. IR (KBr) cm^{-1}: 3152, 2927, 2861, 1676, 1590, 1479, 1400, 1276, 623. ^{1}H-NMR ($CDCl_3$) δ: 10.36 (s, 1H, $H_{aldehyde}$), 7.92 (d, 1H, H_{Ar}, J=2.5 Hz), 7.67 (s, 1H, $H_{triazole}$), 7.64 (dd, 1H, J=8.9, 2.5 Hz), 7.13 (d, 1H, H_{Ar}, J=8.9 Hz), 5.33 (s, 2H, CH_2–O), 4.14 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 188.2, 159.3, 143.1, 138.3, 131.1, 126.3, 124.0, 115.2, 114.1, 62.6, 38.5. NMR purity: >95%. HR-MS (ESI) m/z: Calcd for $C_{11}H_{11}BrN_3O_2$: 296.0035; Found: 296.0065 $[M+H]^+$.

Determination of MICs Broth micro-dilution method was carried out according to the standard protocols recommended by Clinical Laboratory Standard Institute (CLSI) to determine the minimum concentration of each antimicrobial agent required for inhibition (MIC) of visible growth of tested bacterium. In brief, two-fold serial dilutions of each compound were made in a concentration range from 0.125–256 μg/mL in sterile plastic micro-dilution trays containing Mueller–Hinton broth (MHB). Thereafter, bacterial suspension of each bacterial strain was prepared from freshly cultured bacteria in sterile normal saline that were adjusted to 0.5 McFarland standard turbidity. The suspension was further diluted (1 : 100) by sterile MHB just before adding to the trays containing a serial dilution of each compound. MICs were recorded after 22 h incubation at 37°C. Cefixime was used as standard antibiotic and all experiments were done in triplicate.

Conclusion

A facile and efficient method for the synthesis of hydroxybenzaldehydes, phenols and bile acids based 1,4-disubstituted 1,2,3-triazole library have been developed as part of the ongoing efforts to identify their synergistic potential with menthol. The preliminary activity of menthol and the 1,2,3-triazole analogues provide a platform that elevate the plausibility of finding derivatives with enhanced antibacterial activity. Fifteen derivatives were synthesized *via* 1,3-dipolar cycloaddition reactions and were evaluated for their antibacterial activity against *Enterococcus faecium* and *Staphylococcus aureus* bacteria. All derivatives exhibited stronger inhibitory activity than lead compounds towards *E. faecium* and even almost all were more powerful than cefixime as a positive control. The results showed that 1,2,3-triazole ring could be a good linkage for enhancing the antibacterial activity of lead compounds through different mechanisms. Also evaluation of physicochemical properties of the target compounds based on Lipinski's rule of five demonstrated that almost all compounds had desirable profile to be new lead candidates.

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Conflict of Interest The authors declare no conflict of interest.

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References

1) Galeotti N., Mannelli L. D. C., Mazzanti G., Bartolini A., Ghelardini C., *Neurosci. Lett.*, **322**, 145–148 (2002).
2) Kamatou G. P., Vermaak I., Viljoen A. M., Lawrence B. M., *Phytochemistry*, **96**, 15–25 (2013).
3) Kijpornyongpan T., Sereemaspun A., Chanchao C., *Asian Pac. J. Cancer Prev.*, **15**, 1551–1556 (2014).
4) Aqil M., Ahad A., Sultana Y., Ali A., *Drug Discov. Today*, **12**, 1061–1067 (2007).
5) Zhao L., Fang L., Xu Y., Zhao Y., He Z., *Int. J. Pharm.*, **352**, 92–103 (2008).
6) Obata Y., Sato H., Li C. J., Takayama K., Higashiyama K., Nagai T., Isowa K., *Int. J. Pharm.*, **198**, 191–200 (2000).
7) Dewang P. M., Nikumbh V. P., Tare V. S., Mahulikar P. P., *J. Sci. Ind. Res.*, **62**, 990–995 (2003).
8) Samarasekera R., Weerasinghe I. S., Hemalal K., *Pest Manag. Sci.*, **64**, 290–295 (2008).
9) Ye B., Bauer S., Buckman B. O., Ghannam A., Griedel B. D., Khim S.-K., Lee W., Sacchi K. L., Shaw K. J., Liang A., Wu Q., Zhao Z., *Bioorg. Med. Chem. Lett.*, **13**, 3361–3365 (2003).
10) Turcheniuk V., Raks V., Issa R., Cooper I. R., Cragg P. J., Jijie R., Dumitrascu N., Mikhalovska L. I., Barras A., Zaitsev V., Boukherroub R., Szunerits S., *Diamond Related Materials*, **57**, 2–8 (2015).
11) Klein A. H., Carstens M. I., McCluskey T. S., Blancher G., Simons C. T., Slack J. P., Furrer S., Carstens E., *Chem. Senses*, **36**, 649–658 (2011).
12) Zefirova O. N., Nurieva E. V., Nuriev V. N., Kuznetsov S. A., Weiss D. G., Tlegenov R. T., Zyk N. V., Zefirov N. S., *Moscow Univ. Chem. Bull.*, **62**, 261–263 (2007).
13) Soković M., Glamočlija J., Marin P. D., Brkić D., van Griensven L. J. L. D., *Molecules*, **15**, 7532–7546 (2010).
14) Kazemi M., Rostami H., Shafiei S., *J. Plant Sci.*, **7**, 55–66 (2012).
15) Kotan R., Kordali S., Cakir A., *Z. Naturforsch. C*, **62**, 507–513 (2007).
16) von Nussbaum F., Brands M., Hinzen B., Weigand S., Häbich D., *Angew. Chem. Int. Ed.*, **45**, 5072–5129 (2006).
17) Brown D. G., Lister T., May-Dracka T. L., *Bioorg. Med. Chem. Lett.*, **24**, 413–418 (2014).
18) Lahlou M., *Pharmacol. Pharm.*, **4**, 17–31 (2013).
19) Al-Omair M. A., Sayed A. R., Youssef M. M., *Molecules*, **20**, 2591–2610 (2015).
20) Wang X.-L., Wan K., Zhou C.-H., *Eur. J. Med. Chem.*, **45**, 4631–4639 (2010).
21) Zhou C.-H., Wang Y., *Curr. Med. Chem.*, **19**, 239–280 (2012).
22) Vatmurge N. S., Hazra B. G., Pore V. S., Shirazi F., Chavan P. S., Deshpande M. V., *Bioorg. Med. Chem. Lett.*, **18**, 2043–2047 (2008).
23) Totobenazara J., Burke A. J., *Tetrahedron Lett.*, **56**, 2853–2859 (2015).
24) Alonso Valdés F., Moglie Y., Radivoy G., Yus Astiz M., *Heterocycles*, **84**, 1033–1044 (2012).
25) Schulze B., Schubert U. S., *Chem. Soc. Rev.*, **43**, 2522–2571 (2014).
26) Ma N., Wang Y., Zhao B.-X., Ye W.-C., Jiang S. Drug., *Drug. Des. Devel. Ther.*, **9**, 1585–1599 (2015).
27) Shi X.-X., Shen C.-L., Yao J.-Z., Nie L.-D., Quan N., *Tetrahedron Asymmetry*, **21**, 277–284 (2010).
28) Welschoff N., Waldvogel S. R., *Synthesis*, **2010**, 3596–3601 (2010).
29) Mohan A., Ramkumar V., Sankararaman S., *J. Organomet. Chem.*, **799**, 115–121 (2015).
30) Nagender P., Malla Reddy G., Naresh Kumar R., Chandrashekar Reddy A., Reddy Velatooru L., Pamanji R., Venkateswara Rao J., Narsaiah B., *Lett. Drug Des. Discov.*, **10**, 865–871 (2013).
31) Zhang J., Wu J., Shen L., Jin G., Cao S., *Adv. Synth. Catal.*, **353**, 580–584 (2011).
32) Jorgensen J. H., Turnidge J. D., "Manual of clinical microbiology," Vol. 1, Chap. 73, ed. by Murray P. R., Baron E. J., Jorgensen J. H., Pfaller M. A., Louise Landry M., American Society for Microbiology, Washington DC, 2007, pp. 1152–1172.
33) Monte M. J., Marin J., Antelo A., Vazquez-Tato J., *World J. Gastroenterol.*, **15**, 804–816 (2009).
34) Mohebbi M., Salehi P., Bararjanian M., Aliahmadi A., Safavi-Sohi R., Ghasemi J. B., *Med. Chem. Res.*, **23**, 4531–4541 (2014).
35) Aly M. R. E. S., Saad H. A., Mohamed M. A. M., *Bioorg. Med. Chem. Lett.*, **25**, 2824–2830 (2015).
36) Petrova K. T., Potewar T. M., Correia-da-Silva P., Barros M. T., Calhelha R. C., Ćiric A., Soković M., Ferreira I. C., *Carbohydr. Res.*, **417**, 66–71 (2015).
37) Collin M. P., Hobbie S. N., Böttger E. C., Vasella A., *Helv. Chim. Acta*, **91**, 1838–1848 (2008).
38) Wei J. J., Jin L., Wan K., Zhou C. H., *Bull. Korean Chem. Soc.*, **32**, 229–238 (2011).
39) Lipinski C. A., Lombardo F., Dominy B. W., Feeney P. J., *Adv. Drug Deliv. Rev.*, **64**, 4–17 (2012).
40) Khoshkholgh M. J., Balalaie S., Bijanzadeh H. R., Grossc J. H., *Arkivoc*, **9**, 114–121 (2009).
41) Vedachalam S., Wong Q. L., Maji B., Zeng J., Ma J., Liu X. W., *Adv. Synth. Catal.*, **353**, 219–225 (2011).
42) Pal M., Parasuraman K., Yeleswarapu K. R., *Org. Lett.*, **5**, 349–352 (2003).
43) Lingam V. S. P. R., Vinodkumar R., Mukkanti K., Thomas A., Gopalan B., *Tetrahedron Lett.*, **49**, 4260–4264 (2008).
44) Wang Y., Ji K., Lan S., Zhang L., *Angew. Chem. Int. Ed.*, **51**, 1915–1918 (2012).
45) Miyamoto Y., Kalisiak J., Korthals K., Lauwaet T., Cheung D. Y., Lozano R., Cobo E. R., Upcroft P., Upcroft J. A., Berg D. E., Gillin F. D., Fokin V. V., Sharpless K. B., Eckmann L., *Proc. Natl. Acad. Sci. U.S.A.*, **110**, 17564–17569 (2013).
46) Zhao L., Mao L., Hong G., Yang X., Liu T., *Bioorg. Med. Chem. Lett.*, **25**, 2540–2544 (2015).
47) Ikonen S., Macíčková-Cahová H., Pohl R., Šanda M., Hocek M., *Org. Biomol. Chem.*, **8**, 1194–1201 (2010).
48) Kumar S., *Nucleos. Nucleot. Nucl.*, **34**, 371–378 (2015).
49) Schirrmacher R., Lakhrissi Y., Jolly D., Goodstein J., Lucas P., Schirrmacher E., *Tetrahedron Lett.*, **49**, 4824–4827 (2008).