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One-pot multi-component synthesis and cytotoxic activity of terpenoid dimers containing azapolycyclic spacers

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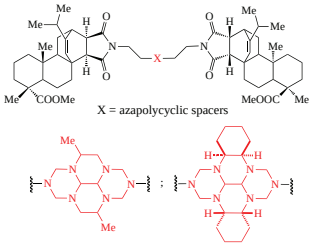
Novel terpenoid dimers linked through the E–E rings were synthesized by catalytic multicomponent condensation of amino derivatives of methyl maleopimarate with formaldehyde and dimethyl-tetraazadecalin or tetraazaperhydrotetracene. Primary screening of the synthesized terpenoid dimers for cytotoxic activity was performed.



Keywords: heterocyclization, maleopimaric acid, terpenoids, zeolite, polycycles, cytotoxic activity.

The diene adduct of levopimaric acid and maleic anhydride, *i.e.* maleopimaric acid, and its methyl ester are of interest as targets for synthesizing compounds with a wide range of biological activity, namely, antitumor,[1–3] antiviral,[4] antimicrobial acivity,[5,6] including the anti-ulcer and anti-inflammatory action[7] (Figure 1). The presence of an anhydride group in maleopimaric acid and its methyl ester makes it possible to obtain *N*-maleopimarimides by reactions with various compounds containing a primary amino group.[8–11] Further modification of *N*-maleopimarimides finds use in the synthesis of various heterocyclic derivatives containing dithiazepane,[12] triazole,[13] tetrazole and oxadiazole rings.[14]

Syntheses of terpenoid[15] and steroid[16] dimers with aliphatic and aromatic moieties as the spacers were described. Recently, dimeric terpenoids bound with a polyazapolycyclic spacer were synthesized on the basis of *N*-maleopimarimides.[17] Our experiments aimed at expanding the library of potentially useful terpenoids included the selective synthesis of new dimeric derivatives of methyl maleopimarate (MEMP). We focused on the one-reactor catalytic condensation of amino derivatives of MEMP with formaldehyde and a regioisomeric mixture (1 : 1) of 2,6(7)-dimethyl-1,4,5,8-tetraazadecalines.[18–20] In this study, the required imido amine **1** and hydrazide **1′** (Scheme 1) were obtained by the reaction of MEMP with ethylenediamine and hydrazine monohydrate, respectively, as reported.[3,21] In fact, MEMP-derived imido amine **1** reacted with formaldehyde and a double excess of regioisomeric tetraazadecalin mixture under

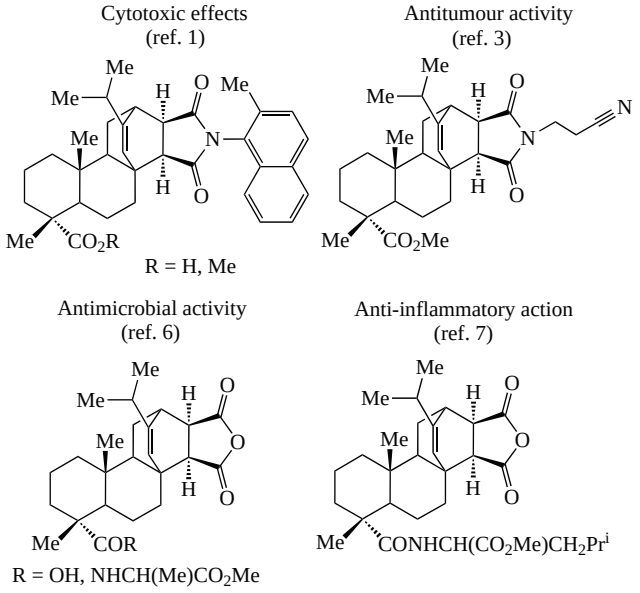
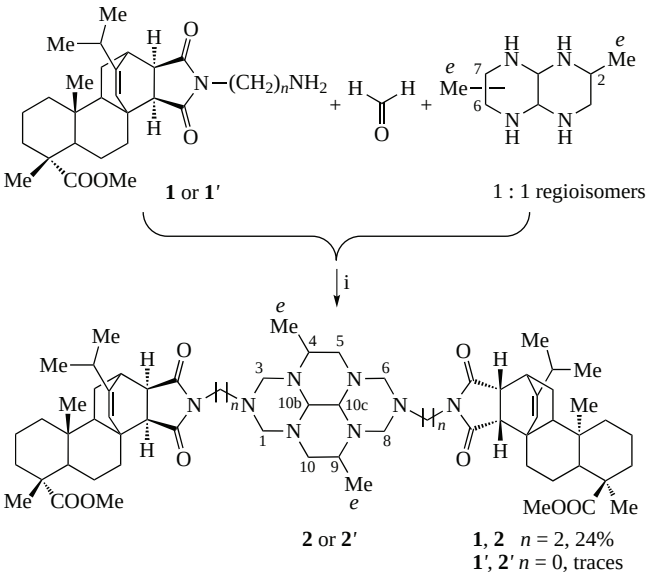


Figure 1 Biological activity of derivatized adducts of levopimaric acid and maleic anhydride.



Scheme 1 *Reagents and conditions*: i, **1** or **1′**, CH_2O (aq., 4 equiv.), 2,6(7)-dimethyl-1,4,5,8-tetraazadecalins (1 : 1 isomer mixture, 2 equiv.), 10 wt% zeolite H–Ymmm (cat.), MeOH–H_2O, room temperature, 3 h.

the conditions we developed (10 wt% zeolite H-Ymmm, 20 °C, 3 h, MeOH–H_2O solvent mixture) to selectively give dimeric terpenoid **2** in 24% yield (see Scheme 1). A double excess of isomeric tetraazadecalin mixture is necessary to maintain the stoichiometry since 2,7-dimethyl-1,4,5,8-tetraazadecalin is not involved in the condensation.

We succeeded in implementing the reaction mentioned above exclusively on 'strong' acid centers of granulated hierarchical zeolite Y with high degree of crystallinity and phase purity in H-form and with a micro-meso-macroporous structure.[22] The catalysts based on salts of rare-earth elements that we used in similar condensation reactions[20,23–25] showed no activity. The high efficiency of the H–Ymmm zeolite catalyst is due to the presence of a hierarchical structure (micro, meso, and macro pores) that provides an improved diffusion of the reactants to the active centers inside the zeolite pores and release of the reaction products from the pores into the reaction medium, thus creating conditions for the formation of bulky molecules.

It should be noted that under the above conditions, we exclusively identified the 4,9-isomer derived from 2,6-dimethyl-1,4,5,8-tetraazadecalin as the main reaction product. The 4,10-isomer was not detected even in minor amounts. Dimeric product **2** precipitates from the reaction mixture and therefore no additional chromatographic purification is required. The mother liquor may contain primary amines in imine form and bis(hydroxymethyl)derivatives of dimethyl-1,4,5,8-tetraazadecalines formed in the reaction of two secondary amino groups of bicyclic compounds with formaldehyde. Previously,[20] molecular ions of the corresponding compounds were detected in the reaction solution by MALDI TOF/TOF mass spectrometry. Unfortunately, an attempt to obtain bis-adduct based on MEMP hydrazide **1′** in a reasonable yield failed, and dimeric terpenoid **2′** was formed only in trace amounts. The MALDI TOF/TOF mass spectrum showed the presence of cationic forms of the molecular ion with mass *m/z* 1097 $[M+Na]^+$ and *m/z* 1113 $[M+K]^+$ corresponding to this bis-adduct.

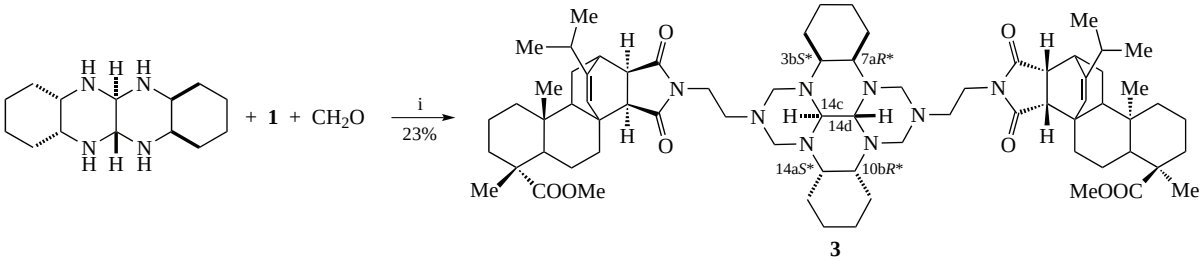
The ^{13}C NMR spectrum of dimeric compound **2** contains all the carbon signals belonging to the dimethyl-substituted hexaazatetracyclic spacer. Two signals in the regions of δ 51.0 and 55.9 belong to the C^4/C^9 and C^5/C^{10} atoms. The other two signals in the regions of δ 70.1 and 73.5 belong to the C^3/C^8 and C^1/C^6 atoms located between the nitrogen atoms. The selective formation of the 4,9-isomer is characterized by the presence of only one signal in the δ 82.6 region corresponding to the C^{10b} and C^{10c} atoms. If the 4,10-isomer is formed, these carbon atoms should resonate differently due to the loss of molecular symmetry.[19] The structure of dimer **2** is also confirmed by the presence of a molecular peak in the MALDI TOF/TOF positive ion mass spectrum.

Our subsequent experiments included the condensation of MEMP amino derivatives **1** and **1′** with formaldehyde and *cis*-1,6,7,12-tetraazaperhydrotetracene[26] obtained *in situ* from (±)-*cis*-1,2-diaminocyclohexane and glyoxal. Under optimal conditions (10 wt% H–Ymmm zeolite, 20 °C, 3 h, MeOH), the reaction of imido amine **1** selectively gives bis-adduct **3** in 23% yield (Scheme 2). The attempted use of MEMP hydrazide **1′** in this multicomponent condensation was unsuccessful.

A distinctive feature of the synthesis based on (±)-*cis*-1,2-diaminocyclohexane is that perhydrotetracenes[26] with *S**,*R**,*R**,*S** relative configuration of chiral centers at carbon atoms C^{3b}, C^{7a}, C^{10b}, and C^{14a} are formed. It should be noted that similar condensation of *trans*-1,6,7,12-tetraazaperhydrotetracene results in (3b*R**,7a*R**,10b*R**,14a*R**)-perhydrotetracenes[17,23] with *cis*-junction of piperazine rings at the C^{14c}–C^{14d} bond.

The assignment of signals in the spectra of terpenoid dimer **3** was based on two-dimensional homo- (COSY) and heteronuclear (HSQC, HMBC) NMR experiments. The structure of compound **3** was confirmed by recording a molecular peak in the positive-ion mass spectrum formed upon ionization by laser desorption from the matrix with measurement of their times-of-flight in reflectance mode (MALDI TOF/TOF, resolution 0.001 a.m.u.).

The new terpenoid dimers **2** and **3** were tested in terms of their effect on the viability of conditionally normal cells [human embryonic kidney cell line (HEC293)] and tumor cells [human hepatocellular carcinoma cell line (HepG2), colon adenocarcinoma (HTC-116), human monocytic leukemia (THP-1), breast carcinoma (MCF-7), lung adenocarcinoma (A549), T-cell leukemia (Jurkat) and human neuroblastoma SH-SY5Y)]. As follows from the results obtained (Table 1), compounds **2** and **3** exhibit moderate cytotoxic effects against HEK293, HTC-116, MCF-7, THP-1, A549, SH-SY5Y and Jurkat cell lines but no effects against the hepatocellular carcinoma line HepG2. It should also be noted that dimeric compound **2** shows a more pronounced effect against all the cell lines studied than bis-adduct **3**.



Scheme 2 *Reagents and conditions*: i, **1** (2 equiv.), CH_2O (aq., 4 equiv.), *cis*-1,6,7,12-tetraazaperhydrotetracene (1 equiv.), 10 wt% zeolite H–Ymmm (cat.), MeOH, room temperature, 3 h.

Table 1 *In vitro* cytotoxic activity of terpenoid dimers **2** and **3** against cell lines HEK293, HepG2, HTC-116, SH-SY5Y, MCF-7, A549, Jurkat and THP-1.[a]

Compound	IC_{50}/μM							
	HEK293	HepG2	HTC-116	SH-SY5Y	MCF-7	A549	Jurkat	THP-1
2	53.5 ± 0.4	~100	68.4 ± 0.5	55.8 ± 0.5	39.5 ± 0.2	73.3 ± 0.8	37.1 ± 0.2	46.8 ± 0.5
3	68.8 ± 1.6	~100	82.3 ± 0.1	77.9 ± 0.2	58.6 ± 1.4	~100	45.9 ± 0.3	60.0 ± 2.9
5-Fluorouracil	6.32 ± 0.71	3.86 ± 0.7	2.38 ± 0.9	1.16 ± 0.3	1.0 ± 0.04	0.28 ± 0.02	0.67 ± 0.10	4.3 ± 0.8

[a] The cells were incubated for 48 h in the presence of the compounds. The data are presented as the arithmetic mean ± standard error of the mean (N = 3, n = 6).

In summary, the H–Ymmm zeolite-catalyzed one-reactor multicomponent condensation of MEMP amino derivatives with formaldehyde and dimethyltetraazadecalin/*cis*-tetraaza-perhydrotetracene is the first example of a synthesis of new terpenoid dimers with azapolycyclic spacers. The suggested synthesis of dimeric terpenoids opens a way to new potentially biologically active hybrid molecules.[27]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.020.

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