ANTI-INFLAMMATORY ACTIVITY OF ISOBORNYLPHENOL DERIVATIVES

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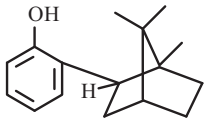
Nonsteroidal anti-inflammatory drugs and non-narcotic analgesics are widely used to treat various inflammatory diseases of infectious and noninfectious nature [1].

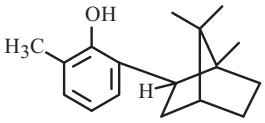
The development of new drugs based on terpenophenols, which have a unique set of pharmacological properties [2], is highly promising. The literature teaches that phenols with a bicyclic isobornyl moiety exhibit anti-infection activity [3]. The series of studies performed by us on the synthesis and investigation of terpenophenols showed that some alkylphenols exhibit hemorheological properties and improve brain blood flow [4, 5]. Thus, the synthesis of terpenophenols is critical for further studies of their physiological properties.

Herein we present results from a study of the anti-inflammatory activity of the synthesized terpenophenols and their aminomethyl derivatives.

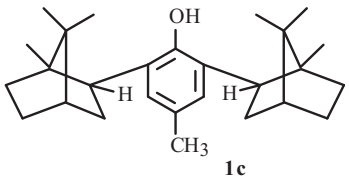
A series of isobornylphenols (**1a**–**e**) with various substituents in the aromatic ring were prepared earlier via alkylation of phenols by the natural monoterpenoid camphene in the presence of the corresponding aluminum phenolates [6–8].



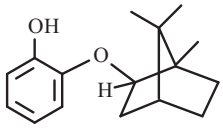
1a



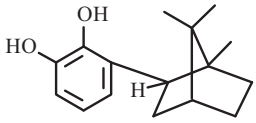
1b



1c

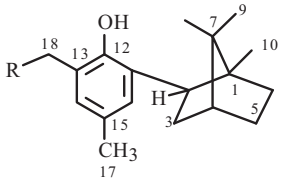


1d

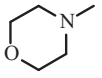


1e

Continued functionalization of the terpenophenols by introducing aminomethyl moieties using the Mannich reaction synthesized the previously prepared compounds **2a**, **2b**, and **2d** [9] and newly synthesized **2c**, the structure of which was confirmed by IR, PMR, and ^{13}C NMR spectral data.

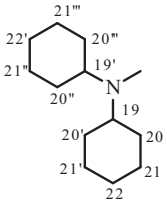


2a - d

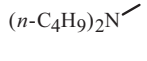


a

b



c



d

The anti-inflammatory activity of terpenophenols **1**–**2** was studied using a formalin-induced acute inflammation model in mice [10] (Table 1). Compounds **1a** and **2a** exhibited reliable anti-inflammatory activity upon parenteral administration. Compound **1a** was less active and showed only 10% more inhibition than this control group.

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TABLE 1. Anti-inflammatory Activity of Isobornylphenols

Compound	Mass increase of inflamed paw, %	Degree of edema inhibition, %	Compound	Mass increase of inflamed paw, %	Degree of edema inhibition, %
1c	61.22±3.83	2	**2b**	74.31±2.24	–8
2a	39.95±5.14*	33	**2c**	71.46±2.95	–4
Sodium diclofenac	46.41±4.83*	22	Control 2	68.99±1.79	–
Control 1	59.81±2.49	–	**1b**	64.73±6.49	–6
1d	65.84±2.09	5	**2d****	61.94±2.87	–2
1e	72.95±2.83	–6	Control 3	60.77±3.16	–
1a	62.09±1.53*	10			

*$p \leq 0.05$ relative to the corresponding control; **using **2d**·HCl.

Edema of an inflamed paw was reduced by 33% compared with the control upon administration of **2a**. The anti-inflammatory activity of **2a** was studied upon i.p. administration because of its high hydrophobicity. However, it did not exhibit anti-inflammatory activity for this model at a dose of 50 mg/kg. This indicated that it was poorly assimilated from the GI tract.

A toxicity study gave LD_{50} values for **1**–**2** that were greater than 500 mg/kg. This meant that these compounds had class 3 toxicity and hazard (GOST 12.1007-76).

Synthesis of the Amine (2c). 2-Isobornyl-4-methylphenol (0.86 g, 3.5 mmol) and paraformaldehyde (0.13 g, 4.2 mmol) were stirred in anhydrous benzene (15 mL) at room temperature for 30 min, treated with dicyclohexylamine (0.83 mL, 4.2 mmol), and refluxed for 6 h. Upon completion of the reaction, the excess of solvent was evaporated at reduced pressure. The mixture was separated over a column of silica gel (Alfa Aesar, 70/230 μ) with elution by petroleum ether:Et_2O with increasing fraction of the latter to afford **2c** (1.45 g, 95%).

2-((Dicyclohexylamino)methyl)-4-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol (2c). Colorless crystals, mp 161–163°C, $C_{30}H_{47}NO$. IR spectrum (KBr, ν, cm^{-1}): 3437 (OH), 2930, 2855, 1468, 1381, 1605. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.76 (3H, s, Me-10), 0.82 (3H, s, Me-9), 0.90 (3H, s, Me-8), 1.04–1.62 and 1.74–1.89 (16H and 10H, both m, H-3, H-4, CH_2-5, CH_2-6, CH_2-20, CH_2-20′, CH_2-20″, CH_2-20‴, CH_2-21, CH_2-21′, CH_2-21″, CH_2-21‴, CH_2-22, CH_2-22′), 2.14-2.21 (1H, m, H-3), 2.23 (3H, s, Me-17), 2.68 (2H, t, J = 11.6, H-19, H-19′), 3.28 (1H, t, J = 9.1, H-2), 3.78 and 3.95 (2H, both d, J = 14.5 and J = 14.5, CH_2-18), 6.58 and 6.97 (2H, both s, H-14, H-16), 11.79 (1H, br.s, OH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 11.85 (C-10), 20.28 (C-9), 20.94, 21.51 (C-8, C-17), 26.09, 26.17 (C-21, C-21′, C-21″, C-21‴), 27.54 (C-5), 29.63 (C-22, C-22′), 31.68 (C-20, C-20′, C-20″, C-20‴), 33.59 (C-3), 39.48 (C-6), 44.39 (C-2), 45.77 (C-4), 47.87 (C-7), 49.46 (C-18), 49.78 (C-1), 57.15 (C-19, C-19′), 121.72, 126.35, 129.90 (C-11, C-13, C-15), 126.12, 127.19 (C-14, C-16), 155.28 (C-12).

Anti-inflammatory Properties of 1–2. We used mongrel white male mice (mass 22-24 g) for the formalin test. The tested compounds were injected i.p. at a dose of 50 mg/kg in physiological solution with added Tween-80. The reference drug was sodium diclofenac at a dose of 8 mg/kg [11]. Compound **2a** had the highest anti-inflammatory activity and was also studied upon oral administration. The control group of animals received physiological solution. Inflammation was induced 1 h after injecting the compounds using formalin solution (3%) that was injected (0.05 mL) into the aponeurosis of the right hind paw.

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