DOI 10.1007/s11094-021-02491-0
Pharmaceutical Chemistry Journal, Vol. 55, No. 8, November, 2021 (Russian Original Vol. 55, No. 8, August, 2021)

SEARCH FOR NEW DRUGS

SYNTHESIS AND ANTIAGGREGANT AND ANTICOAGULANT ACTIVITY OF NEW 1-(4-ALKYLOXYBENZYL)-1*H*-AZOLES AND 1-(ADAMANTYL-1)-2-[4-(1*H*-AZOL-1-YLMETHYL)-PHENOXY]ETHANONES

K. G. Gurevich,[1] A. L. Urakov,[2,*] A. V. Basantsev,[3] T. A. Abzalilov,[4] I. I. Bashirov,[2] A. A. Danilin,[3] P. P. Purygin,[2] A. A. Golovanov,[5] K. A. Khayrzamanova,[4] and A. V. Samorodov[4]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 55, No. 8, pp. 15 – 20, August, 2021.

Original article submitted June 23, 2021.

The development and optimization of synthetic methods for alkyl esters of 4-[(1*H*-azol-1-yl)methyl]phenols enabled the expansion of organic synthesis methodology, which is extremely important for designing new structures with various types of biological activity, e.g., antiaggregant and anticoagulant. The present work studied *O*-alkylation of 4-[(1*H*-azol-1-yl)methyl]phenols with various alkylating agents, e.g., *n*-octyl bromide, *n*-hexadecyl bromide, and (adamantyl-1)bromomethylketone. The newly synthesized compounds were identified using elemental analysis and IR and PMR spectroscopy. Laboratory studies of blood isolated from healthy volunteers revealed compounds with antiaggregant and anticoagulant properties.

Keywords: 4-[(1*H*-azol-1-yl)methyl]phenols, *n*-octyl bromide, *n*-hexadecyl bromide, (adamantyl-1)bromomethylketone, antiaggregant activity, anticoagulant activity.

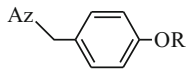
N-Benzylazoles and synthetic substituted phenols based on them exhibit various types of biological activity including antihypertensive [1], antiviral [2], anticoagulant, and antiaggregant [3, 4]. The presence of a carboxylic acid and an *N*-benzylimidazolyl moiety in the hemostatic Ozagrel reduced the formation rate of thromboxane A_2 synthase and cyclooxygenase, which led to decreased blood coagulability [5]. *O*-Alkylation of the free hydroxyl of phenol and its derivatives has been widely used to synthesize ethers containing additional functional groups [6]. This reaction is one of the key steps for producing several drugs, e.g., Phenacetin and Tilorone.

Introduction of highly lipophilic fragments into compounds with a given biological activity increases their membrane affinity and enables the incorporation of various functional groups and substituents into the compounds. Adamantyl-containing aggregants are known to have a relatively high affinity for 5-HT_2 serotonin receptors [7]. The inhibitory activity of the antioxidant hydroxytyrosol for platelet aggregation was improved by adding long-chain hydrocarbon radicals, e.g., *n*-octyl or *n*-dodecyl, which induced the synthesis of arachidonic acid and collagen [8].

Considering the urgency of this work, the goal of the present study was to synthesize and study the antiaggregant and anticoagulant activity of 1-(4-alkyloxybenzyl)-1*H*-azoles and 1-(adamantyl-1)-2-[4-(1*H*-azol-1-ylmethyl)phenoxy]-ethanones (Table 1) of the general formula:

[1] A. I. Evdokimov Moscow State University of Medicine and Dentistry, 20/1 Delegatskaya St., Moscow, 127473 Russia.
[2] Izhevsk State Medical Academy, 281 Kommunarov St., Izhevsk, Udmurtia, 426034 Russia.
[3] Samara National Research University, 34 Moskovskoe Shosse, Samara, 443086 Russia.
[4] Bashkir State Medical University, 3 Lenina St., Ufa, Bashkortostan, 450008 Russia.
[5] Togliatti State University, 14 Belorusskaya St., Togliatti, 445020 Russia.
[*] e-mail: urakoval@live.ru

0091-150X/21/5508-0769 © 2021 Springer Science+Business Media, LLC



Ia,b,d, IIa-c, IIIa-d

EXPERIMENTAL CHEMICAL PART

PMR spectra were recorded (TMS internal standard) on a Bruker AM 400 instrument at operating frequency 400 MHz. IR spectra were recorded using an FT-801 IR-Fourier spectrometer with an ATR accessory. Elemental analyses were performed on a system for rapid gravimetric determination of elements [9]. Elemental analyses agreed with those calculated. TLC used Sorbfil plates (Russia). Detection was made in I_2 vapor and using UV light from a chromatographic UFS 254/365. Melting points of crystalline compounds were determined on a POTP-2 apparatus (Russia) in sealed capillaries.

4-[(1*H*-Azol-1-yl)methyl]phenols (Va-d) were prepared according to the published methods [10, 11].

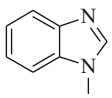
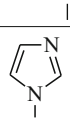
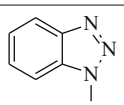
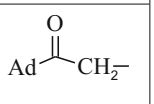
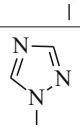
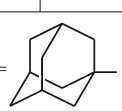
1-(4-Alkyloxybenzyl)-1*H*-azoles (Ia,b,d and IIa-c)

Method A (**Ia**,**b** and **IIa**,**b**). A round-bottomed flask was charged with a solution of **Va**,**b** (1.14 mmol) in DMF (5 mL) that was treated dropwise with the appropriate **VIa**,**b** (1.14 mmol) with vigorous stirring followed by addition of Cs_2CO_3 (2.28 mmol) under a stream of Ar. The reaction mixture was held at 80 – 85ºC for 5 – 7 h and poured into ice water. The resulting precipitate was filtered off, rinsed with H_2O, dried in a refrigerator, and recrystallized from hexane.

1-[4-(*n*-Octyloxy)benzyl]-1*H*-benzimidazole (Ia)

Yield 0.29 g (75%). mp 43 – 45°C (hexane). R_f 0.28 (Me_2CO – CCl_4, 2:1). IR spectrum (ν_{max}, cm^{-1}): 1244 (C-O-C),1457, 1467, 1514, 1612 (C=C, C=N), 2879 (C_8H_{17}). PMR spectrum ($CDCl_3$, δ, ppm): 0.89 – 0.91(t, 3H, CH_3), 1.30 – 1.80 (m, 12H, $6CH_2$), 3.90 – 3.92 (t, 2H, CH_2), 5.33 (s, 2H, CH_2), 6.73 – 6.75 (d, arom 2H, 2CH=), 7.14 – 7.16 (d, arom 2H, 2CH=), 7.21 – 7.30 (m, arom 2H, 2CH=), 7.53 – 7.62 (m, arom 2H, 2CH=), 8.17 (s, arom H, CH=). Calc., %: C 78.28; H 8.37. $C_{22}H_{28}N_2O$. Calc., %: C 78.53; H 8.39.

TABLE 1. 1-(4-Alkyloxybenzyl)-1*H*-azoles (**Ia, b, d**, **IIa-c**) and 1-(Adamantyl-1)-2-[4-(1*H*-azol-1-ylmethyl)phenoxy]ethanones (**IIIa-d**)

Compound	Az	Compound	R
Ia, IIa, IIIa		**Ia, Ib, Id**	*n*-C_8H_{17}-
Ib, IIb, IIIb		**IIa**, **IIb**, **IIc**	*n*-$C_{16}H_{33}$-
IIc, **IIIc**		**IIIa-d**	
Id, **IIId**		Ad = 	

1-[4-(*n*-Octyloxy)benzyl]-1*H*-imidazole (Ib)

Yield 0.13 g (40%). mp 36 – 38°C (hexane). R_f 0.69 (EtOH – CH_2Cl_2, 1:5). IR spectrum (ν_{max}, cm^{-1}): 1250 (C-O-C), 1444, 1472, 1513, 1614 (C=C, C=N), 2872 (C_8H_{17}). PMR spectrum ($CDCl_3$, δ, ppm): 0.88 – 0.91 (t, 3H, CH_3), 1.30 – 1.80 (m, 12H, $6CH_2$), 3.93 – 3.96 (t, 2H, CH_2), 5.05(s, 2H, CH_2), 6.86 – 6.88 (d, arom 2H, 2CH=), 7.08 (d, arom H, CH=), 7.09 – 7.11 (d, arom 2H, 2CH=), 7.28 (d, arom H, CH=), 7.58 (s, arom H, CH=). Calc., %: C 75.29; H 9.18. $C_{18}H_{26}N_2O$. Calc., %: C 75.48; H 9.15.

1-[4-(*n*-Hexadecyloxy)benzyl]-1*H*-benzimidazole (IIa)

Yield 0.33 g (65%). mp 68 – 69°C (hexane). R_f 0.52 (EtOH – CCl_4, 1:6). IR spectrum (ν_{max}, cm– 1): 1249 (C-O-C), 1457, 1467, 1514, 1612 (C=C, C=N), 2849, 2917 ($C_{16}H_{33}$). PMR spectrum ($CDCl_3$, δ, ppm): 0.89 – 0.92 (t, 3H, CH_3), 1.28 – 1.81 (m, 28H, $14CH_2$), 3.92 – 3.96 (t, 2H, CH_2), 5.32 (s, 2H, CH_2), 6.87 – 6.89 (d, arom 2H, CH=), 7.15 – 7.16 (d, arom 2H, CH=), 7.28 – 7.32 (m, arom 2H, 2CH=), 7.33 – 7.37 (m, arom 2H, 2CH=), 8.07 (s, arom H, CH=). Calc., %: C 80.01; H 10.02. $C_{30}H_{44}N_2O$. Calc., %: C 80.31; H 9.88.

1-[4-(*n*-Hexadecyloxy)benzyl]-1*H*-imidazole (IIb)

Yield 0.26 g (57%). mp 63 – 64°C (hexane). R_f 0.36 (EtOH – CCl_4, 1:7). IR spectrum (ν_{max}, cm^{-1}): 1246 (C-O-C), 1444, 1472, 1513, 1614 (C=C, C=N), 2849, 2916 ($C_{16}H_{33}$). PMR spectrum ($CDCl_3$, δ, ppm): 0.89 – 0.92 (t, 3H, CH_3), 1.28 – 1.82 (m, 28H, $14CH_2$), 3.94 – 3.97 (t, 2H, CH_2), 5.08 (s, 2H, CH_2), 6.88 – 6.90 (d, arom 2H, 2CH=), 6.93 (d, arom H, CH=), 7.12 – 7.14 (d, arom 2H, 2CH=), 7.28 (d, arom H, CH=), 7.70 (s, arom H, CH=). Calc., %: C 75.30; H 10.57. $C_{25}H_{41}N_3O$. Calc., %: C 75.14; H 10.34.

Method B (**Id** and **IIc**). A round-bottomed flask was charged with a solution of **Va, b** (1.14 mmol) in anhydrous methylethylketone (8 mL) that was treated dropwise with the appropriate **VIa, b** (1.14 mmol) with vigorous stirring followed by addition of Cs_2CO_3 (2.28 mmol) under a stream of Ar. The reaction mixture was refluxed for 5 – 6 h. The precipitate was filtered off. The solvent was evaporated in a rotary evaporator. The resulting product was rinsed with H_2O, dried in a refrigerator, and recrystallized from hexane.

1-[4-(*n*-Octyloxy)benzyl]-1*H*-1,2,4-triazole (Id)

Yield 0.12 ã (35%). mp 37 – 39°C (hexane). R_f 0.48 (EtOH – CCl_4, 1:3). IR spectrum (ν_{max}, cm^{-1}):1243 (C-O-C), 1453, 1470, 1514, 1610 (C=C, C=N), 2875 (C_8H_{17}). PMR spectrum ($CDCl_3$, δ, ppm): 0.89 – 0.91 (t, 3H, CH_3), 1.30 – 1.80 (m, 12H, $6CH_2$), 3.92 – 3.95 (t, 2H, CH_2), 5.27 (s, 2H, CH_2), 6.75 – 6.76 (d, arom 2H, 2CH=), 7.14 – 7.16 (d, arom 2H, 2CH=), 7.95 (s, arom H, CH=), 8.16 (s, arom H, CH=). Calc., %: C 70.74; H 8.38. $C_{17}H_{25}N_3O$. Calc., %: C 71.04; H 8.77.

1-[4-(*n*-Hexadecyloxy)benzyl]-1*H*-benzotriazole (IIc)

Yield 0.27 g (52%). mp 91 – 92°C (hexane). R_f 0.67 (EtOH – CCl_4, 1:6). IR spectrum (ν_{max}, cm^{-1}): 1246 (C-O-C), 1454, 1471, 1513, 1615 (C=C, C=N), 2850, 2915 ($C_{16}H_{33}$). PMR spectrum ($CDCl_3$, δ, ppm): 0.89 – 0.91 (t, 3H, CH_3), 1.27 – 1.80 (m, 28H, $14CH_2$), 3.91 – 3.94 (t, 2H, CH_2), 5.80 (s, 2H, CH_2), 6.86 – 6.88 (d, arom 2H, 2CH=), 7.24 – 7.25 (d, arom 2H, 2CH=), 7.34 – 7.44 (m, arom 2H, 2CH=), 8.06 – 8.10 (m, arom 2H, 2CH=). Calc., %: C 77.44; H 9.58. $C_{29}H_{43}N_3O$. Calc., %: C 77.46; H 9.64.

1-(Adamantyl-1)-2-[4-(1*H*-azol-1-ylmethyl)phenoxy]ethanones (IIIa-d)

Method A (**IIIa, b**). A round-bottomed flask was charged with a solution of **Va, b** (0.97 mmol) in DMF (5 mL) that was treated with **VII** (0.97 mmol) with vigorous stirring until the solid was completely dissolved followed by the addition of K_2CO_3 (1.94 mmol). The reaction mixture was held at 80 – 85ºC for 6 h and poured into ice water. The resulting white precipitate was filtered off, rinsed with hot hexane, and dried in air.

1-(Adamantyl-1)-2-[4-(1*H*-benzimidazol-1-ylmethyl) phenoxy]ethanone (IIIa)

Yield 0.30 g (79%). mp 103 – 105°C. IR spectrum (ν_{max}, cm^{-1}): 1244 (C-O-C),1453, 1516, 1613 (C=C, C=N), 1707 (C=O), 2905 (Ad). PMR spectrum (DMSO-d_6, δ, ppm): 1.71 – 2.07 (m, 15H, H-Ad), 4.77 (c, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.73 – 6.75 (d, arom 2H, 2CH=), 7.16 – 7.18 (d, arom 2H, 2CH=), 7.20 – 7.23 (m, arom 2H, 2CH=), 7.53 – 7.63 (m, arom 2H, 2CH=), 8.37 (s, arom H, CH=). Calc., %: C 78.01; H 7.02. $C_{26}H_{28}N_2O_2$. Calc., %: C 77.97; H 7.05.

1-(Adamantyl-1)-2-[4-(1*H*-imidazol-1-ylmethyl)phenoxy]ethanone (IIIb)

Yield 0.25 g (74%). mp 138 – 140°C. IR spectrum (ν_{max}, cm^{-1}): 1242 (C-O-C), 1467, 1514, 1610 (C=C, C=N), 1707 (C=O), 2906 (Ad). PMR spectrum (DMSO-d_6, δ, ppm): 1.71 – 2.07 (m, 15H, H-Ad), 4.77 (c, 2H, CH_2), 5.02 (s, 2H, CH_2), 6.86 – 6.88 (d, arom 2H, 2CH=), 6.93 (d, arom H, CH=), 7.12 – 7.14 (d, arom 2H, 2CH=), 7.28 (d, arom H, CH=), 7.68 (s, arom H, CH=). Calc., %: C 75.14; H 7.28. $C_{22}H_{26}N_2O_2$. Calc., %: C 75.40; H 7.48.

Method B (**IIIc, d**). A round-bottomed flask was charged with a solution of **Vc, d** (0.97 mmol) in anhydrous Me_2CO (10 mL) that was treated with **VII** (0.97 mmol) with vigorous stirring until the solid was completely dissolved followed by the addition of K_2CO_3 (1.94 mmol). The reaction mixture was refluxed for 6 h. The precipitate was filtered off. The solvent was evaporated in a rotary evaporator. The resulting white crystals were rinsed with hot hexane and dried in air. Compound **IIIe** was also recrystallized from EtOH.

1-(Adamantyl-1)-2-[4-(1*H*-benzotriazol-1-ylmethyl)phenoxy]ethanone (IIIc)

Yield 0.17 g (44%). mp 144 – 146°C (EtOH). IR spectrum (ν_{max}, cm^{-1}): 1245 (C-O-C), 1450, 1514, 1610 (C=C, C=N), 1714 (C=O), 2902 (Ad). PMR spectrum (DMSO-d_6, δ, ppm): 1.71 – 2.07 (m, 15H, H-Ad), 4.77 (c, 2H, CH_2), 5.82 (s, 2H, CH_2), 6.86 – 6.88 (d, arom 2H, 2CH=), 7.24 – 7.25 (d, arom 2H, 2CH=), 7.34 – 7.44 (m, arom 2H, 2CH=), 8.06 – 8.10 (m, arom 2H, 2CH=). Calc., %: C 74.49; H 6.83. $C_{25}H_{27}N_3O_2$. Calc., %: C 74.79; H 6.78.

1-(Adamantyl-1)-2-[4-(1*H*-1,2,4-triazol-1-ylmethyl)phenoxy]ethanone (IIId)

Yield 0.24 g (70%). mp 91 – 93°C. IR spectrum (ν_{max}, cm^{-1}): 1240 (C-O-C), 1444, 1520, 1611 (C=C, C=N), 1710 (C=O), 2908 (Ad). PMR spectrum (DMSO-d_6, δ, ppm): 1.71 – 2.07 (m, 15H, H-Ad), 4.78 (c, 2H, CH_2), 5.29 (s, 2H, CH_2), 6.75 – 6.76 (d, arom 2H, 2CH=), 7.14 – 7.16 (d, arom 2H, 2CH=), 7.95 (s, arom H, CH=), 8.20 (s, arom H, CH=). Calc., %: C 71.97; H 7.59. $C_{21}H_{25}N_3O_2$. Calc., %: C 71.77; H 7.17.

Experimental methods were used *in vitro* to assess the antiaggregant and anticoagulant activities of the synthesized compounds.

EXPERIMENTAL BIOLOGICAL PART

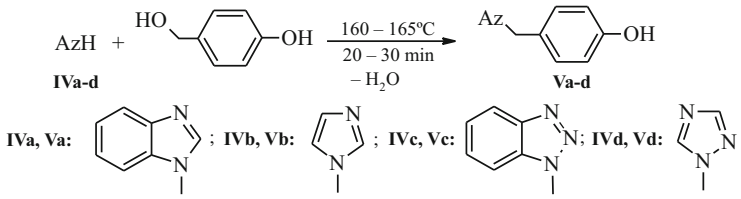
The experiments were performed in compliance with the requirements of Good Laboratory Practice Rules of the Eurasian Economic Union in the field of medicine circulation.

Antiaggregant and anticoagulant activities were assessed under *in vitro* conditions in isolated blood fractions from 42 healthy male volunteers 18 – 24 years old. The research was approved by the Ethics Committee of BSMU, Ministry of Health of Russia (No. 1 dated Feb. 20, 2019). Informed consent was obtained from all participants before collecting blood.

The influence of the compounds on platelet aggregation was studied using the Born method [12] on an AT-02 aggregometer (SPC Medtekh, Russia). The antiaggregant activities of the tested compounds and the reference drug were assessed at a final concentration of 1×10^{-3} M with incubation for 5 min. Adenosine diphosphate (ADP) at a concentration of 20 μg/mL and collagen at a concentration of 5 mg/mL (Tekhnologiya-Standart, Russia) were used as aggregation inductors. The influence of the compounds on the maximum amplitude (MA), aggregation rate, and time to reach MA during ADP-induced platelet aggregation was studied. The latent period of aggregation was estimated in the collagen-induced aggregation test and corresponded to the release of platelets. The reference drug was acetylsalicylic acid (powder substance; Shandong Xinhua Pharmaceutical Co. Ltd., China) [13].

Anticoagulant activity was determined by clotting tests [14] in a Solar CGL2110 turbidimetric hemocoagulometer (ZAO SOLAR, Belarus). The final concentration of the tested compounds and the reference drug was 5×10^{-4} g/mL. The activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen concentration according to Clauss were studied. The reference drug was heparin

Scheme 1



sodium (5000 IU/mL solution for injection, 1-mL ampuls, OAO Sintez, Russia).

Statistical analysis used the Statistica 10.0 software (StatSoft Inc., USA). A check for normal distributions used the Shapiro – Wilk criterion. Variational series were described by calculating the median, 25 and 75 percentiles, and minimum and maximum values. One-factor dispersion analysis (if a dataset obeyed normal distribution laws and the dispersions of all sets were equal; F-criterion) or the Kruskal – Wallis test (if a dataset did not obey normal distribution laws; A-criterion) was performed. The critical significance level *P* for statistical criteria was set to 0.05.

RESULTS AND DISCUSSION

1-(4-Alkyloxybenzyl)-1*H*-azoles **Ia, b, d** and **IIa-c** and 1-(adamantyl-1)-2-[4-(1*H*-azol-1-ylmethyl)phenoxy]ethanon es **IIIa-d** were synthesized in two steps. First, 4-[(1*H*-azol-1-yl)methyl]phenols **Va-d** were synthesized by fusing 4-hydroxybenzyl alcohol with azoles **IVa-d** at 160 – 165°C without a solvent for 20 – 30 min (Scheme 1). The reaction was complete when H_2O was no longer evolved from the reaction mixture. Table 2 presents the characteristics of synthesized phenols **Va-d**.

This reaction was previously shown to pass through reactive *p*-methylenequinone intermediates [15]. The presence of singlets for methylene protons in the range 5.02 – 5.82 ppm in PMR spectra confirmed the structures of 4-[(1*H*-azol-1-yl)methyl]phenols **Va-d**.

The next step involved *O*-alkylation of **Va-d** by various alkylating agents in the presence of an appropriate base and solvent. The reaction of the 4-[(1*H*-azol-1-yl)methyl)phenols with *n*-octyl and *n*-hexyl bromides **VIa, b** in DMF or anhydrous methylethylketone in the presence of Cs_2CO_3 produced 1-(4-*n*-octyloxybenzy)-1*H*-azoles **Ia, b, d** and 1-(4-*n*-hexadecyloxybenzyl)-1*H*-azoles **IIa-d**, respectively (Scheme 2).

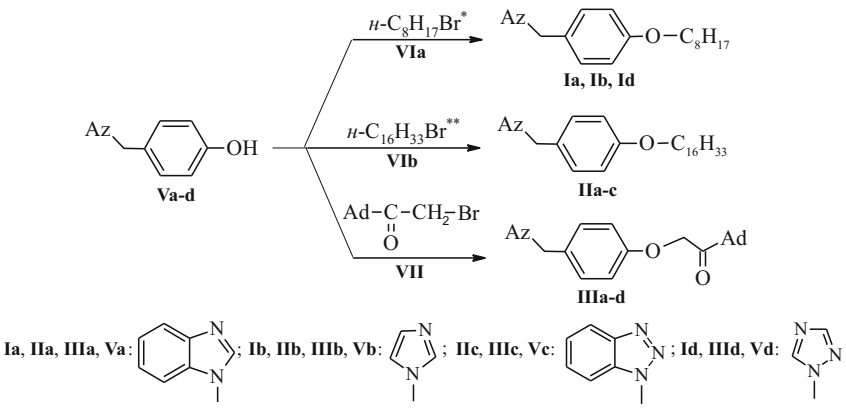
Characteristic absorption bands in IR spectra at 1243 – 1250 and 2849 – 2917 cm^{-1} corresponding to ether and *n*-octyl and *n*-hexyldecyl CH stretching vibrations and the lack of OH vibrations (2470 – 3125 cm^{-1}) indicated that *O*-alkylation of **Va-d** was complete. PMR spectra of **Ia, b, d** and **IIa-c** showed triplets and multiplets for *n*-octyl and *n*-hexadecyl protons in the ranges 0.89 – 0.91, 1.27 – 1.81, and 3.90 – 3.97 ppm, respectively. The lack of an OH singlet in the range 9.47 – 9.50 ppm also confirmed that an ether bond formed in the 1-(4-alkylxoybenzyl)-1*H*-azoles.

O-Alkylation of 4-[(1*H*-azol-1-yl)methyl]phenols **Va-d** by (adamantyl-1)bromomethylketone (**VII**) in the presence of K_2CO_3 in DMF or anhydrous Me_2CO produced 1-(adamantyl-1)-2-[4-(1*H*-azol-1-ylmethyl)phenoxy]ethanones **IIIa-d** in 44 – 79% yields (Scheme 2). Absorption bands at 1240 – 1245, 1707 – 1714, and 2902 – 2908 cm^{-1} in IR spectra of **IIIa-d** corresponded to ether, carbonyl, and

TABLE 2. Physicochemical Characteristics of 4-[(1*H*-Azol-1-yl)methyl]phenols (**Va-d**)

Compound	mp, °C	Yield, %	IR spectrum, ($_{max}$, cm^{-1}	PMR spectrum, δ, ppm
Va	235 – 237	75	3095 – 2470 (OH), 1615, 1595, 1517 (C=C, C=N)	5.35 (s, 2H, CH_2), 6.70 – 6.72 (d, arom 2H, 2CH=), 7.16 – 7.18 (d, arom 2H, 2CH=), 7.20 – 7.30 (m, arom 2H, 2CH=), 7.53 – 7.63 (m, arom 2H, 2CH=), 8.37 (s, arom H, CH=), 9.48 (s, 1H, OH)
Vb	205 – 207	78	3111 – 2490 (OH), 1613, 1594, 1510 (C=C, C=N)	5.02 (s, 2H, CH_2), 6.71 – 6.73 (d, arom 2H, 2CH=), 6.87 (d, arom H, CH=), 7.10 – 7.12 (d, arom 2H, 2CH=), 7.12 (d, arom H, CH=), 7.68 (s, arom H, CH=), 9.47 (s, 1H, OH)
Vc	168 – 170	51	3125 – 2500 (OH), 1620, 1602, 1515 (C=C, C=N)	5.82 (s, 2H, CH_2), 6.70 – 6.72 (d, arom 2H, 2CH=), 7.18 – 7.20 (d, arom 2H, 2CH=), 7.37 – 7.52 (m, arom 2H, 2CH=), 7.82 – 8.03 (m, arom 2H, 2CH=), 9.49 (s, 1H, OH)
Vd	140 – 142	91	3106 – 2482 (OH), 1613, 1596, 1517 (C=C, C=N)	5.27 (s, 2H, CH_2), 6.73 – 6.75 (d, arom 2H, 2CH=), 7.14 – 7.16 (d, arom 2H, 2CH=), 7.95 (s, arom H, CH=), 8.56 (s, arom H, CH=), 9.50 (s, 1H, OH)

Scheme 2



Note: * except **Vc**; ** except **Vd**.

adamantane C–H stretching vibrations. PMR spectra of these compounds exhibited resonances for adamantoylmethyl methylene protons in the range 4.77 – 4.78 ppm and adamantyl protons at 1.71 – 2.07 ppm and lacked a singlet for the phenol OH in the range 9.47 – 9.50 ppm.

Compounds **IIa-c**, **IIIb**, and **IIId** according to the test results exhibited antiaggregant activity on the level of acetylsalicylic acid according to the MA parameter (Table 3). These compounds except for **IIc** gave statistically significant increases of the latent period (release of platelets), in contrast to acetylsalicylic acid. Compounds **Ia** and **IIIc** showed analogous influences that were slightly inferior to the reference drug according to the MA level. All tested compounds except for **IIIa** reduced the platelet aggregation rate more effectively than acetylsalicylic acid.

It is noteworthy that all compounds caused hypocoagulation by increasing the APTT by 1.6 – 10.4% as compared to the control and did not affect the fibrinogen concentration and prothrombin time. The effects of the tested compounds were significantly inferior to that of heparin, which increased the APTT by 20.3%.

Thus, 1-(adamantyl-1)-2-[4-(1*H*-imidazol-1-ylmethyl)-phenoxy]ethanone and 1-[4-(*n*-hexadecyloxy)benzyl]-1*H*-benzimidazole gave the maximum antiaggregant activity combined with the maximum lengthening of the latent period among the newly synthesized compounds.

TABLE 3. Influence of Synthesized Compounds and Reference Drugs on Platelet Aggregation and Hemostasis Coagulation Stage, Me (0.25 – 0.75)

Compound	Latent period, % of control	Maximum amplitude, % of control	Aggregation rate, % of control	Time to reach MA, % of control	APTT, % of control
Ia	+ 20.1 (18.7 – 24.4)$^{\#}$	– 7.9 (7.5 – 8.7)$^{*,\#}$	– 13.4 (11.7 – 14.3)$^{*,\#}$	– 12.4 (10.4 – 15.4)$^{*,\#\#}$	+ 3.8 (3.4 – 5.2)†
Ib	– 3.2 (2.5 – 4.1)	– 1.2 (0.8 – 1.5)$^{\#\#}$	– 32.4 (30.6 – 35.3)$^{**,\#\#}$	+ 13.5 (11.7 – 15.6)*	+ 5.3 (4.9 – 7.2)*,†
Id	– 4.5 (3.7 – 5.9)$^{\#}$	– 7.4 (6.5 – 9.3)$^{*,\#}$	– 38.5 (35.9 – 40.5)$^{**,\#\#}$	+ 13.4 (11.5 – 14.2)*	+ 8.2 (7.5 – 10.2)*,†
IIa	+ 10.4 (8.3 – 12.3)$^{*,\#}$	– 16.7 (14.6 – 20.3)*	– 11.2 (10.5 – 14.5)$^{*,\#\#}$	– 16.5 (14.5 – 20.5)$^{**,\#\#}$	+ 8.3 (6.7 – 10.4)*,†
IIb	+ 7.5 (4.9 – 9.3)$^{*,\#}$	– 11.6 (8.7 – 12.8)*	– 27.1 (24.5 – 31.4)$^{**,\#\#}$	– 22.5 (20.3 – 24.5)$^{**,\#\#}$	+ 10.4 (7.5 – 11.5)*,†
IIc	– 4.2 (3.5 – 6.3)$^{\#}$	– 13.5 (12.7 – 15.4)*	– 12.7 (11.4 – 14.7)$^{*,\#}$	– 23.4 (21.2 – 25.5)$^{**,\#\#}$	+ 9.3 (8.4 – 11.3)*,†
IIIa	– 10.4 (8.6 – 11.1)$^{*,\#}$	– 4.5 (3.2 – 6.5)$^{*,\#}$	+ 2.5 (2.1 – 3.9)$^{\#\#}$	– 9.6 (8.2 – 11.5)$^{\#\#}$	+ 3.6 (3.1 – 4.5)†
IIIb	+ 10.5 (8.5 – 14.5)$^{*,\#}$	– 15.6 (14.3 – 20.5)*	– 19.7 (17.4 – 22.3)$^{*,\#\#}$	– 10.5 (10.1 – 12.6)$^{*,\#\#}$	+ 2.8 (1.9 – 3.4)†
IIIc	+ 13.4 (11.5 – 14.3)$^{*,\#}$	– 8.5 (7.4 – 11.2)$^{*,\#}$	– 20.5 (18.3 – 23.4)$^{*,\#}$	– 8.5 (7.4 – 10.1)$^{\#\#}$	+ 1.6 (1.4 – 3.2)†
IIId	+ 7.4 (5.6 – 8.5)$^{*,\#}$	– 10.5 (9.6 – 11.1)*	– 14.8 (13.7 – 17.8)$^{*,\#}$	– 5.7 (4.5 – 6.8)$^{\#\#}$	+ 2.7 (1.8 – 4.1)†
Acetylsalicylic acid	– 2.1 (1.1 – 2.6)	– 13.7 (10.8 – 16.4)*	– 10.5 (7.6 – 12.3)*	+ 10.5 (8.7 – 13.4)*	+ 1.1 (0.5 – 1.9)†
Heparin sodium	–	–	–	–	+ 20.3 (19.7 – 21.4)**

Note: Latent period is given for aggregation of platelets induced by collagen; other parameters, for ADP-induced platelet aggregation. $^{*}p \le 0.05$; $^{**}p \le 0.001$ vs. the control; $^{\dagger}p \le 0.05$, vs. heparin sodium; $^{\#}p \le 0.05$; $^{\#\#}p \le 0.001$ vs. acetylsalicylic acid; "–", no data; $n = 6$.

Thus, 1-(4-alkyloxybenzyl)-1*H*-azoles and 1-(adamantyl-1)-2-[4-(1*H*-azol-1-ylmethyl)phenoxy]ethanones were synthesized and characterized. An assessment of their biological activities as compared to that of acetylsalicylic acid showed that several of the new compounds lengthened the latent period in a collagen-induced platelet aggregation model (platelet release) and reduced the *in vitro* platelet aggregation rate. The results confirmed the importance of further studies of the mechanisms of action of the new 1-(4-alkyloxybenzyl)-1*H*-azoles and 1-(adamantyl-1)-2-[4-(1*H*-azol-1-ylmethyl)phenoxy]ethanones and the design of antiplatelet drugs based on them.

REFERENCES

1. V. A. Osyanin, P. P. Purygin, and Z. P. Belousova, *Khim. Khim. Tekhnol.*, **46**(6), 23 – 24 (2003).
2. S. Einav, J. S. Glenn, et al., US Pat. 9,101,628, Aug. 11, 2015.
3. P. Cozzi, U. Branzoli, G. Carganico, et al., *Eur. J. Med. Chem.*, **26**(4), 423 – 433 (1991).
4. S.-W. Huang, H.-L. Kuo, M.-T. Hsu, et al., *Thromb. Haemostasis*, **116**(8), 285 – 299 (2016).
5. M. Nakazawa, K. Iizuka, A. Ujiie, et al., *J. Pharm. Soc. Jpn.*, **114**(12), 911 – 933 (1994).
6. S. A. Timofeeva, S. S. Zlotskii, and I. B. Grudnikov, *Bashkir. Khim. Zh.*, **17**(3), 25 – 29 (2010).
7. A. J. Bojarski, M. J. Mocrozs, et al., *J. Bioorg. Med. Chem.*, **10**(5), 87 – 95 (2002).
8. J. J. Reyes., J. P. De la Cruz., J. Munoz-Marin, et al., *Eur. J. Nutr.*, **52**(2), 591 – 599 (2013).
9. V. A. Klimova, *Principles of Microanalytical methods of Organic Compounds* [in Russian], Khimiya, Moscow (1975), pp. 51 – 56.
10. V. A. Osyanin, E. S. Selezneva, Z. P. Belousova, et al., *Khim.-farm. Zh.*, **37**(9), 30 – 31 (2003); *Pharm. Chem. J.*, **37**(9), 482 – 484 (2003).
11. V. A. Osyanin, N. E. Sidorina, and Y. N. Klimochkin, *Synth. Commun.*, **42**, 2639 – 2647 (2012).
12. G. V. R. Born, *J. Physiol.*, **162**, 67 – 68 (1962).
13. D. A. Abaimov, L. R. Spavronskaya, A. A. Shabalina, et al., *Khim.-farm. Zh.*, **53**(1), 52 – 57 (2019); *Pharm. Chem. J.*, **53**(1), 65 – 70 (2019); https: // doi.org/10.1007/s11094-019-01957-6.
14. A. N. Mironov (ed.), *Handbook for Preclinical Drug Trials* [in Russian], Grif i K, Moscow (2013), Vol. 1.
15. M. Wakselman, et al., *Bull. Soc. Chim. Fr.*, **3**, 1179 – 1183 (1973).