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THE INTERACTION OF (2-FLUOROPHENYL)- AND (4-FLUOROPHENYL)-(2-NITOMETHYLCYCLOPENTYL)METHANONE WITH PHENYLACETYLENE

The synthesis of corresponding isoxazoles and unsaturated oximes has been realized via the 1,3-dipolar cycloaddition reaction of phenylacetylene with nitrile oxides generated from (2-fluorophenyl)- or (4-fluorophenyl)-(2-nitomethylcyclopentyl)methanone by the action of phenyl isocyanate. The synthesized compounds are new fluorinated prostanoids and appear to be of great interest as potential biologically active substances.

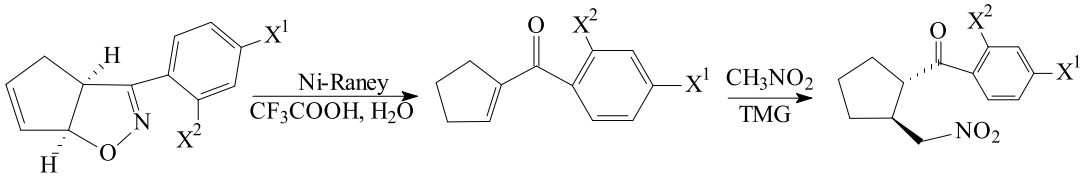
Key words: fluorinated prostanoids, 1,3-dipolar cycloaddition, nitrile oxides, nitrocompounds, isoxazoles, oximes.

Introduction. It is known that more than 150 drugs among many pharmaceuticals sold all over the world are fluorinated compounds [1−3]. This is due to the fact that the introduction of fluorine atom which is small in size and possesses high electronegativity [4] can play a remarkable role in medicinal chemistry [1], particularly, may cause an increase in compounds' activity and stability as well [2]. These factors are of especially great significance for prostanoids, which along with acetogenines, thromboxanes, etc. belong to the most important fatty acid oxidation products formed in vivo [5]. Prostanoids' importance is due to the fact that these compounds participate in regulation of a wide variety of physiological processes, acting in the extremly low concentrations. However, the use of prostanoids as drugs is constrained by a wide spectrum of biological activities as well as by high chemical and metabolic instability of these compounds. In this regard, the synthesis of fluorinated prostaglandins (PG) analogues seems to be of particular interest and is aimed to obtain the compounds having more targeted and prolonged action. For example, one of the most instable metabolites of arachidonic acid is prostacyclin PGI_2, which inhibits platelet adhesion and has vasodilating activity [1], but for prostacyclin $t_{1/2}$ = 5–10 min under physiological conditions that hinders its clinical employment. On the other hand, the fluorine-containing prostacyclin analogue − 18,19-didehydro-7,7-difluoro-16-methyl PGI_2 (AFP-07) − possesses good metabolic stability while keeping a strong activity as inhibitor of platelet aghesion [1]. In this work, the prostanoids ω-chain formation was realized using the nitrile oxide method [6] by the interacting of phenylacetylene and nitrile oxides generated from (2-fluorophenyl)- and (4-fluorophenyl)-(2-nitrometiltcyclopentil)methan-ones [7].

Main part. The initial primary nitrocompounds **3** were previously obtained [7] by 1,4-conjugated Michael addition of nitromethane to the corresponding enones **2** available via the reductive cleavage of cyclopent-5-ene[d]isoxazolines **1a** and **1b** containing phenyl-fluorinated substituent (Scheme 1) [8].

The synthesized nitrocompounds **3a** and **3b** were transformed by phenylisocyanate to the corresponding nitrile oxides **4a** and **4b**, which then were trapped with phenylacetylene (Scheme 2). The reaction was carried out under mild conditions with stirring at room temperature. The purification of the products was performed by preparative thin layer chromatography (TLC).

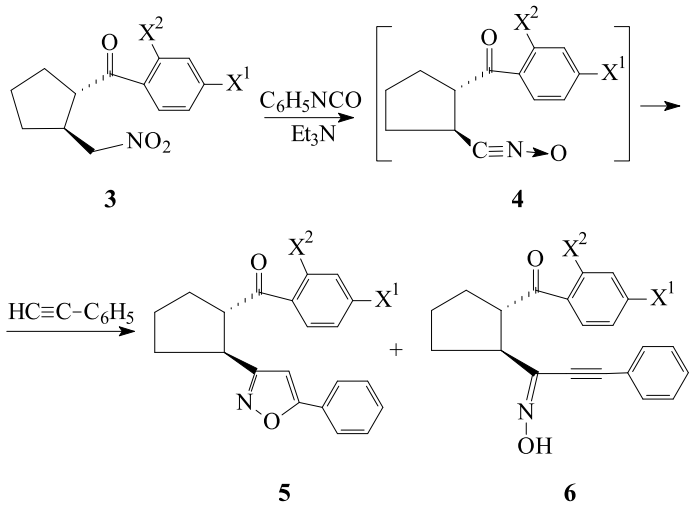
Thus, the interaction of nitroderivative **3a** with phenylacetylene provided isoxazole **5a** in 47% yield. It should be noted that along with isoxazole **5a** a second product formation was observed at a ratio of about 1 : 1. For this second reaction product the structure of unsaturated oxime **6a** (42% yield) has been established on the basis of spectral and literature data.



1 **2** **3**

(**a**) X^1 = F, X^2 = H; (**b**) X^1 = H, X^2 = F

Scheme 1



3 **4**

5 **6**

(**a**) $X^1 = F$, $X^2 = H$; (**b**) $X^1 = H$, $X^2 = F$

Scheme 2

According to the literature such unsaturated oximes were known to form via the preparation of nitrile oxides from the corresponding hydroxymoylchlorides [9], while in our case the oxime **6** was prepared using the nitrocompound as a precursor of corresponding nitrile oxide.

Similarly, the reaction of nitrocompound **3b** with phenylacetylene led to the formation of isoxazole **5b**, along with the oxime **6b** in 50 and 30% yields respectively.

Structure of the obtained compounds was proved by means of modern spectral methods of organic compounds analysis: ^{1}H NMR and ^{13}C NMR spectroscopy (Table 1, 2). The PG numeration of atoms is used for spectral data discussion.

Table 1

Comparison of characteristic signals in ^{1}H NMR spectra of the 1,3-dipolar cycloaddition reaction products

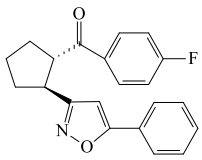
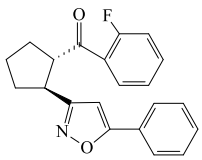
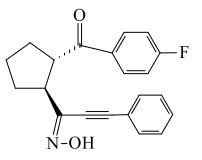
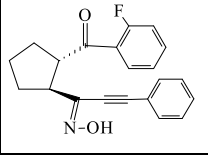
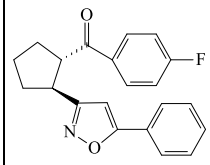
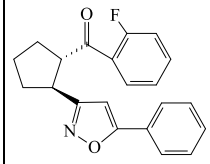
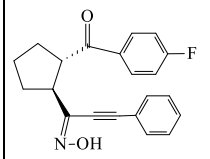
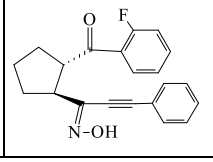
The compound number	Structural formula	H-8	H-12	H-10; H-11	ω-chain
5a		4.10 m (1H; $J_1 = 7.7$; $J_2 = 1.0$)	3.82 q (1H; $J_1 = 7.7$)	2.28 m (2H; H^A-11 + + H^A-9); 1.96 m (1H, $H^Б$-11); 1.87 m (3H, H^B-9 + CH_2-10)	7.72 dd (2H; J_1 = 7.9; J_2 = 1.8; H_{ar}-18 + H_{ar}-20); 7.39 m (3H; H_{ar}-17 + + H_{ar}-19 + H_{ar}-21); 6.34 s (1H; H_{is}-14)
5b		4.01 m (1H; $J_1 = 8.2$; $J_2 = 7.9$; $J_3 = 1.0$)	3.86 m (1H; $J_1 = 8.2$; $J_2 = 7.7$; $J_3 = 2.0$)	2.30 m (2H; H^A-11 + + H^A-9); 1.99 m (1H, H^B-11); 1.85 m (3H, H^B-9 + CH_2-10)	7.72 dd (2H; J_1 = 8.2; J_2 = 1.8; H_{ar}-18 + H_{ar}-20); 7.41 m (3H; H_{ar}-17 + + H_{ar}-19 + H_{ar}-20; J_1 = = 8.2; J_2 = 1.8); 6.39 s (1H; H_{is}-14)
6a		4.07 m (1H; $J_1 = 7.4$; $J_2 = 6.9$)	3.72 q (1H; H-8; $J_1 = 8.4$; $J_2 = 8.2$)	2.26 m (2H; H^A-9 + + H^A-11); 2.03 m (1H, H^B-11); 1.88 m (3H, H^B-9 + CH_2-10)	8.92 + 7.85 br. s. (1H; C=N-OH); 7.50 d (2H; J = 7.4; H_{ar}-18 + H_{ar}-20); 7.30 m (3H; H_{ar}-17 + + H_{ar}-19 + H_{ar}-21)
6b		4.12 dd (1H; $J_1 = 8.4$; $J_2 = 7.7$)	3.72 dd (1H; $J_1 = 8.2$; $J_2 = 7.9$)	2.28 m (2H; H^A-9 + + H^A-11); 2.02 m (1H, H^B-11); 1.92 m (2H, H^B-9 + H^A-10); 1.84 m (1H, H^B-10)	8.86 + 8.03 br s (1H; C=N-OH); 7.54 d (2H; J_1 = 6.9; H_{ar}-18 + H_{ar}-20); 7.33–7.44 m (3H; H_{ar}-17 + + H_{ar}-19 + H_{ar}-21)

Table 2

Comparison of characteristic signals in ^{13}C NMR spectra of the 1,3-dipolar cycloaddition reaction products

The compound number	Structure formula	C-7 (C=O)	C-8	C-12	C-9	C-10	C-11	C=N
5a		199.81	51.36	39.44	31.49	25.31	32.49	166.59
5b		199.89	56.17	39.00	30.46	24.94	32.21	166.73
6a		199.81	49.92	46.71	31.36	25.33	31.77	151.47
6b		199.39	54.43	46.31	30.74	25.12	31.58	151.68

Thus, the comparision of ^{1}H NMR spectrum of isoxazole **5a** (Fig. 2) and this of the initial nitrocompound **3a** (Fig. 1) reveales the disappearance of nitromethyl group protons signals at δ 4.5 ppm while the signals for aromatic protons of the second benzene ring appear alog with the characteristic singlet signal (6.34 ppm) for isoxazole heterocycle proton. The product spectrum also contains signals corresponding to all other proposed structure fragments. The structure of product **3b** was confirmed similarly by its ^{1}H NMR spectrum (Fig. 3) analysis.

In ^{1}H NMR spectrum of oxime **6a** in comparison with this of initial nitrocompound **3a** signals for nitromethyl group protons disappear while signals for the second benzene ring protons and for the hydroxygroup appear, also signals for protons of the cyclopentane fragment are observed as well.

In ^{13}C NMR spectra of isoxazoles **5** and oximes **6** along with the signals for C-atoms of two aromatic substituents and C=N bond the most typical signals are those for carbon atoms of carbonyl group and C-8, which are observed at δ 200 ppm (C=O) and 50–56 ppm (C-8), respectively. It should be mentioned that C-8 is less shielded for a compound with *o*-fluorophenyl substituent as compared with the product with *p*-fluorophenyl fragment.

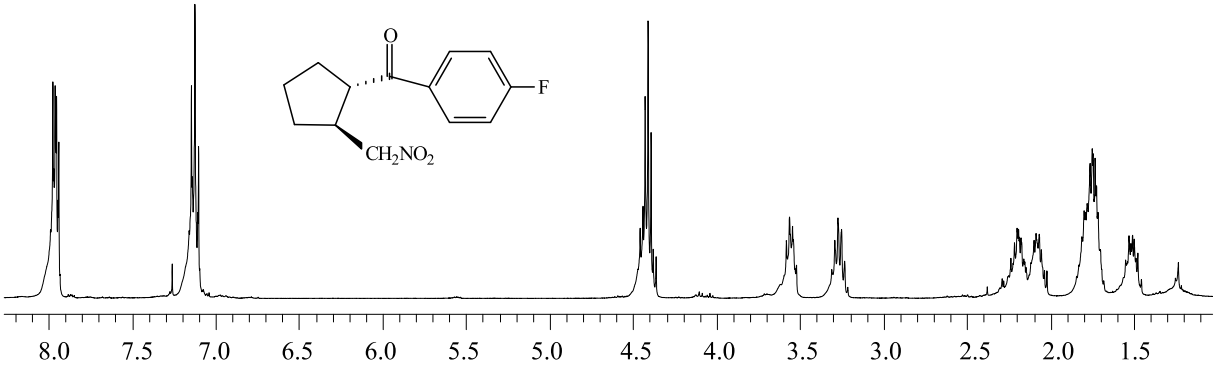


Fig. 1. ^{1}H NMR spectrum of (4-fluorophenyl)-(2 nitromethylcyclopentyl)methanone

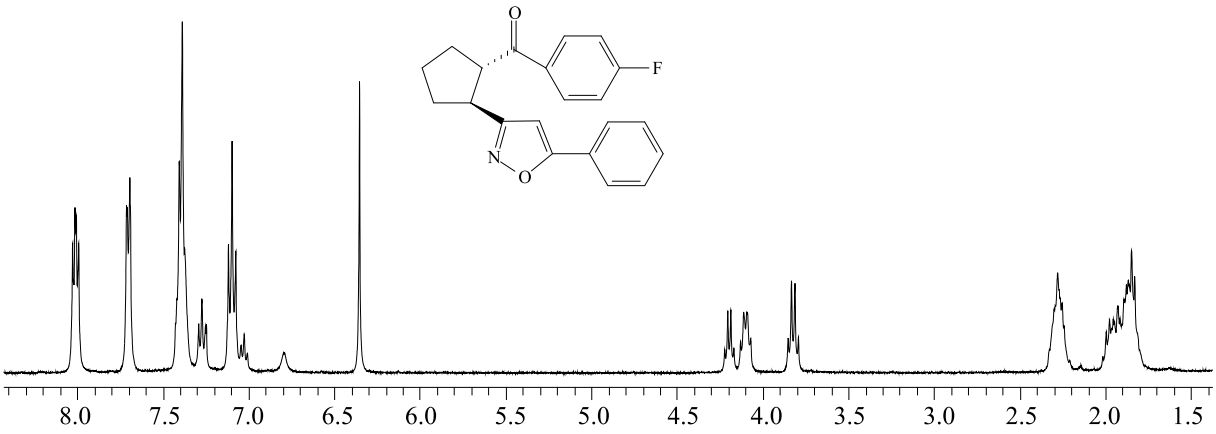


Fig. 2. ^{1}H NMR spectrum of (4-fluorophenyl)-[2-(5-phenylisoxazole-3-yl)-cyclopentyl]methanon

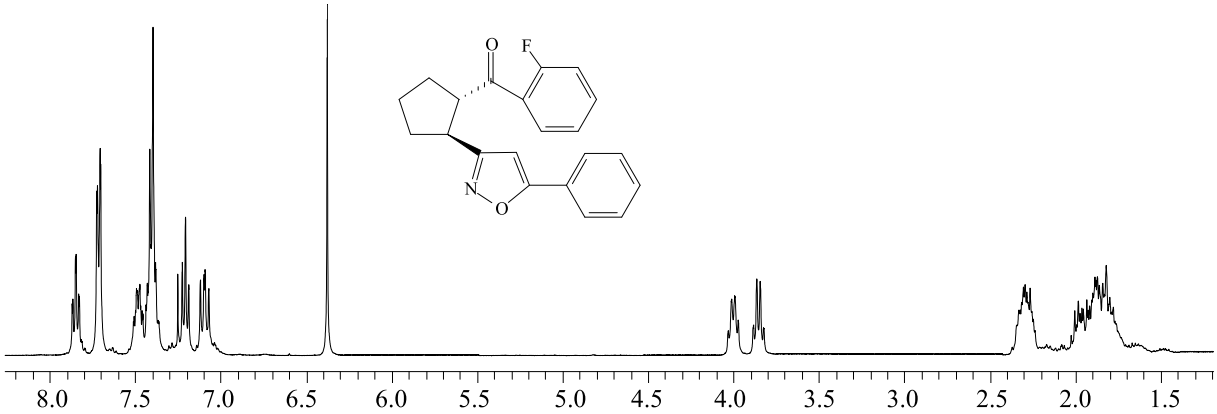


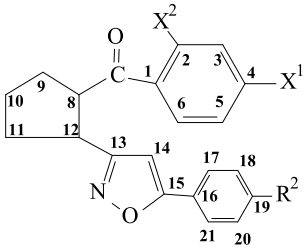
Fig. 3. ^{1}H NMR spectrum of (2-fluorophenyl)-[2-(5-phenylisoxazole-3-yl)-cyclopentyl]methanon

The corresponding coupling constants for C-atoms of fluorinated benzene ring are observed due to the spin-spin coupling with fluorine nuclei. The signals for C-atoms of cyclopentane ring appear at corresponding chemical shifts in the spectrum. There are also signals which are characteristic for C≡C bond at δ 78.5 and 103.7 ppm, respectively in the ^{13}C NMR spectra of oximes **6**.

The synthesized isoxazoles and oximes proved to be fluorinated prostanoids and are of considerable interest as potential biologically active compounds.

Experimental part. ^{1}H and ^{13}C NMR spectra of substances' solutions in $CDCl_3$ were recorded with Bruker AVANCE-400 spectrometer (400 MHz). Chemical shifts are reported in δ units relative to hexamethyldisiloxane (HMDS) as internal standard. Coupling constants *(J)* are given in Hz. Analytical TLC was carried out on silica gel plates Kieselgel 60 F_{254} (Merck), the eluent being ether – petroleum ether, visualization was effected with short-wave-length UV light (254 nm) or with iodine. All solvents were purified according to standard procedures [10].

The following atoms numeration is used for spectral data discussion:



Interaction of phenylacetylene with (4-fluorophenyl)-(2-nitromethylcyclopentyl)-methanone. 0.111 g (0.10 ml, 0.94 mmol) of phenylisocyanate was added to a stirred mixture of 0.100 g (0.42 mmol) of (4-fluorophenyl)-(2-nitrometylcyclopentyl)methanone and 0.069 g (0.075 ml, 0.68 mmol) of phenylacetylene in 50 ml of absolute ether at room temperature following by the addition of triethylamine (3 drops). The reaction mixture was stirred at room temperature until the disappearance of initial nitrocompound, the reaction course being monitored by analytical TLC. Afterwards the reaction was quenched by adding water (2 drops) with stirring. The reaction mixture was filtered through a layer of aluminum oxide to remove diphenylurea residue, the adsorbent was eluted additionally by

ether. Then the solvent was removed by evaporation at reduced pressure to give a residue (0.195 g) that was purified by preparative thin layer chromatography. As a result (4-fluorophenyl)-[2-(5-phenylisoxazole-3-yl)cyclopentyl]methanone in 47% yield and [2-(1-(hydroxyimino)-3-phenylprop-2-ynyl)-cyclopentyl]-(4-fluorophenyl)methanon in 42% yield were obtained. Similarly, the interaction of (2-fluorophenyl)-(2-nitromethylcyclopentyl)methanone with phenylacetylene gave (2-fluorophenyl)-[2-(5-phenylisoxazole-3-yl)cyclopentyl]methanone in 50% yield and [2-(1-(hydroxyimino)-3-phenylprop-2-ynyl)cyclopentyl]-(2-fluorophenyl)-methanon in 30% yield.

(4-Fluorophenyl)-[2-(5-phenylisoxazole-3-yl)-cyclopentyl]methanone was obtained as oil in 47% yield.

^{1}H NMR, δ, ppm (*J*, Hz): 8.05 dd (1H; J_1 = 7.6; J_2 = 1.8; H_{ar} + H_{ar}-6); 7.72 dd (2H; J_1 = 7.9; J_2 = 1.8; H_{ar}-18 + H_{ar}-20); 7.39 m (3H; H_{ar}-17 + H_{ar}-19 + H_{ar}-21); 7.10 dd (2H; J_1 = 8.7; H_{ar}-3 + H_{ar}-5); 6.34 c (1H; H_{is}-14); 4.10 m (1H; J_1 = 7.7; J_2 = 1.0; H-8); 3.82 q (1H; J_1 = 7.7; H-12); 2.28 m (2H; H^A-11 + H^A-9); 1.96 m (1H, H^B-11); 1.87 m (3H, H^B-9 + CH_2-10).

^{13}C NMR, δ, ppm (*J*, Hz): 199.81 (C=O); 169.72 (C_{is}-15); 166.59 (C=N); 166.31 (*J* = 253; C–F); 132.87 (C_{ar}-16); 131.20 (*J* = 9; C_{ar}-1); 129.45 (*J* = 17; C_{ar}-2 + C_{ar}-6); 128.83 (C_{ar}-17 + + C_{ar}-21); 127.42 (C_{ar}-19); 115.61 (*J* = 22; C_{ar}-3 + + C_{ar}-5); 98.95 (C-14); 51.36 (C-8); 39.44 (C-12); 32.49 (C-11); 31.49 (C-9); 25.31 (C-10).

[2-(1-(Hydroxyimino)-3-phenylprop-2-ynyl)-cyclopentyl]-(4-fluorophenyl)methanon was obtained as oil in 42% yield.

^{1}H NMR, δ, ppm (*J*, Hz): 8.92 + 7.85 br s (1H; C=N-OH); 8.04 dd (2H; J_1 = 8.2; J_2 = 5.4; H_{ar}-2 + H_{ar}-6); 7.50 d (2H; *J* = 7.4; H_{ar}-18 + H_{ar}-20); 7.30 m (3H; H_{ar}-17 + H_{ar}-19 + H_{ar}-21); 7.10 m (2H; *J* = 8.4; H_{ar}-3 + H_{ar}-5); 4.07 dd (1H; J_1= 7.4; J_2 = 6.9; H-8); 3.72 q (1H; H-12; J_1 = 8.4; J_2 = 8.2); 2.26 m (2H; H^A-9 + H^A-11); 2.03 m (1H, H^B-11); 1.88 m (3H, H^B-9 + CH_2-10).

^{13}C NMR, δ, ppm (*J*, Hz): 199.121 (C=O); 165.87 (*J* = 255; C–F); 151.47 (C=N); 132.82 (*J* = 3; C_{ar}-1); 131.17 (*J* = 10; C_{ar}-2 + C_{ar}-6); 129.75 (C_{ar}-19); 128.96 (C_{ar}-17 + C_{ar}-21); 128.51 (C_{ar}-18 + C_{ap}-20); 124.21(C_{ar}-16); 115.86 (*J* = 22; C_{ar}-3 + C_{ar}-5); 103.72 (C^{14}≡C); 78.55(C≡C^{15}); 49.92 (C-8); 46.71 (C-12); 31.77 (C-11); 31.36 (C-9); 25.33 (C-10).

(2-Fluorophenyl)-[2-(5-phenylisoxazole-3-yl)-cyclopentyl]methanone was obtained as oil in 50% yield.

^{1}H NMR, δ, ppm (*J*, Hz): 7.85 dt (1H; J_1 = 7.6; J_2 = 1.8; H_{ar}-6); 7.72 dd (2H; J_1 = 8.2; J_2 = 1.8; H_{ar}-18 + H_{ar}-20); 7.49 m (1H; H_{ar}-4; J_1 = 7.2; J_2 = 1.8); 7.41 m (3H; H_{ar}-17 + H_{ar}-19 + + H_{ar}-20; J_1 = 8.2; J_2 = 1.8); 7.21 dd (1H; J_1 = 7.7;J_2 = 6.6; H_{ar}-5); 7.11 dd(1H; J_1 = 8.2; H_{ar}-3); 6.39 s (1H; H_{is}-14); 4.01 m (1H; J_1 = 8.2; J_2 = 7.9; J_3 = 1.0; H-8); 3.86 m (1H; J_1 = 8.2; J_2 = 7.7 J_3 = 2.0; H-12); 2.30 m (2H; H^A-11 + H^A-9); 1.99 m (1H, H^B-11); 1.85 m (3H, H^B-9 + CH_2-10).

^{13}C NMR, δ, ppm (*J*, Hz): 199.89 (*J* = 4; C=O); 169.58 (C-15); 66.73 (C=N); 161.36 (*J* = 255; C–F);); 134.36 (*J* = 9; C_{ar}-4); 130.87 (*J* = 3; C_{ar}-6); 129.90 (C_{ar}-19); 128.81 (C_{ar}-18 + C_{ar}-20); 127.54 (C_{ar}-16); 125.67 (C_{ar}-17 + C_{ar}-21); 125.65 (*J* = 12; C_{ar}-1); 124.37 (*J* = 4; C_{ar}-5); 116.64 (*J* = 23; C_{ar}-3); 98.86 (C_{is}-14); 56.17 (*J* = 6; C-8); 39.00 (C-12); 32.21 (C-11); 30.46 (C-9); 24.94 (C-10).

[2-(1-(Hydroxyimino)-3-phenylprop-2-ynyl)-cyclopentyl]-(2-fluorophenyl)methanon was obtained as oil in 30% yield.

^{1}H NMR, δ, ppm (*J*, Hz): 8.86 + 8.03 br s (1H; C=N-OH); 7.85 dt (1H; J_1 = 7.7; J_2 = 1.8; H_{ar}-6); 7.54 d (2H; J_1 = 6.9; H_{ar}-18 + H_{ar}-20); 7.46 m (1H; H_{ar}-4); 7.33–7.44 m (3H; H_{ar}-17 + + H_{ar}-19 + H_{ar}-21); 7.23 td (1H; J_1 = 7.7; J_2 = 3.1; H_{ar}-5); 7.12 dd (1H; J_1 = 7.4; J_2 = 7.2; H_{ar}-3); 4.12 dd (1H; J_1 = 8.4; J_2 = 7.7; H-8); 3.72 dd (1H; J_1 = 8.2; J_2 = 7.9; H-12); 2.28 m (2H; H^A-9 + H^A-11); 2.02 m (1H, H^B-11); 1.92 m (2H, H^B-9 + H^A-10); 1.84 m (1H, H^B-10).

^{13}C NMR, δ, ppm (*J*, Hz): 199.39 (*J* = 4; C=O); 161.47 (*J* = 253; C–F); 151.68 (C=N); 134.62 (*J* = 10; C_{ar}-4); 132.46 (C_{ar}-17 + C_{ar}-21); 130.90 (*J* = 2; C_{ar}-6); 129.01 (C_{ar}-19); 128.49 (C_{ar}-18 + C_{ar}-20); 125.61 (*J* = 13; C_{ar}-1); 124.62 (*J* = 3; C_{ar}-5); 124.26 (C_{ar}-16); 116.73 (*J* = 24; C_{ar}-3); 103.75 (C^{14}≡C); 78.32 (C≡C^{15}); 54.43 (*J* = 6; C-8); 46.31 (C-12); 31.58 (C-11); 30.74 (C-9); 25.12 (C-10).

Conclusion. These investigations led to the following results:

– synthesis of isoxazoles and oximes containing phenyl-fluorinated substituent was accomplished via 1,3-dipolar cycloaddition reaction of corresponding nitrile oxides and phenylacetylene;

– the key stage in scheme of PG second side chain formation was realized using the nitrile oxide method;

– the synthesized compounds belong to fluorinated prostanoids and are of interest as potential biologically active substances;

– new possibilities of nitrile oxide method employment in synthesis of complex natural compound analogues have been demonstrated.

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