DOI 10.1007/s11094-020-02185-z
Pharmaceutical Chemistry Journal, Vol. 54, No. 3, June, 2020 (Russian Original Vol. 54, No. 3, March, 2020)

SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 3-PHENOXYBENZOIC ACID DERIVATIVES

A. A. Spasov,[1,*] V. S. Lobasenko,[1] V. A. Kosolapov,[1] D. A. Babkov,[1] V. A. Kuznetsova,[1] O. Yu. Maika,[1] Yu. V. Popov,[1] and T. K. Korchagina[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 54, No. 3, pp. 20 – 26, March, 2020.

Original article submitted November 30, 2016.

3-Phenoxybenzoic acid derivatives were synthesized. Their pharmacological activity was studied. Several compounds, in particular 2-cyanoprop-2-yl 3-phenoxybenzoate, were found to exhibit peroxisome proliferator-activated receptor γ agonist activity and to be capable of activating glucokinase and inhibiting protein glycation. The studied compounds did not influence dipeptidyl peptidase-4 activity.

Keywords: synthesis, 3-phenoxybenzoic acid derivatives, peroxisome proliferator-activated receptor γ, glucokinase, dipeptidyl peptidase-4, protein glycation.

The broad spectrum of indications for compounds containing a diphenyloxide fragment is a result of their structural features and properties [1].

Compounds in this series possess high biological activity and include highly efficacious antioxidant, marginally toxic nonsteroidal anti-inflammatory, anti-allergic, immunomodulating, cardiologic, and antimicrobial drugs.

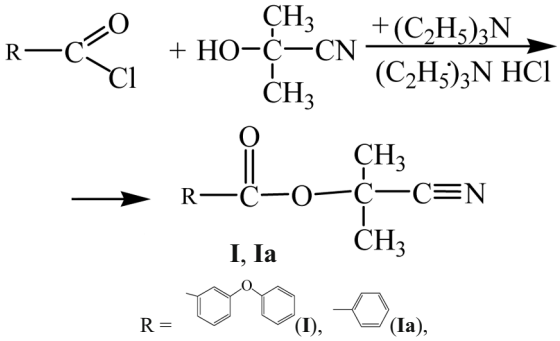
Substituted hydrazones exhibited spasmolytic and hypotensive activity and were active against leukemia, sarcoma, and other malignant neoplasms [2]. They were also used to treat schizophrenia, leprosy, and other diseases [3].

It seemed worthwhile to synthesize and study the activity of 3-phenoxybenzoic acid derivatives for diabetes development targets such as peroxisome proliferator-activated receptor ((PPAR-() and AMP-activated kinase (AMPK) and their antiglycating properties.

2-Cyanoprop-2-yl 3-phenoxybenzoate (**I**) and 2-cyanoprop-2-yl benzoate (**Ia**) were synthesized via reaction of 3-phenoxybenzoylchloride and benzoylchloride with acetone cyanohydrin in anhydrous Et_2O in the presence of Et_3N as an HCl acceptor (Scheme 1).

The synthesis was carried out at room temperature (20 – 25°C) with vigorous stirring for 1 h. A quantitative yield of $Et_3N{\cdot}HCl$ was already obtained 1 h after mixing the starting reagents. The yields of the nitriles were 90 – 95%.

Scheme 1

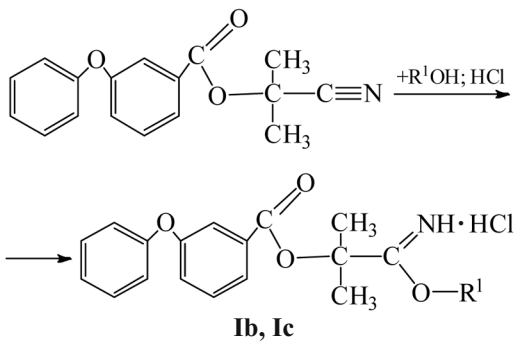


I, **Ia**

R = (**I**), (**Ia**),

The aromatic nitriles reacted with alcohols and HCl under Pinner conditions to form imidate hydrochlorides.

Scheme 2



Ib, Ic

$R^1 = C_2H_5$ (**Ib**); $CH(CH_3)_2$ (**Ic**).

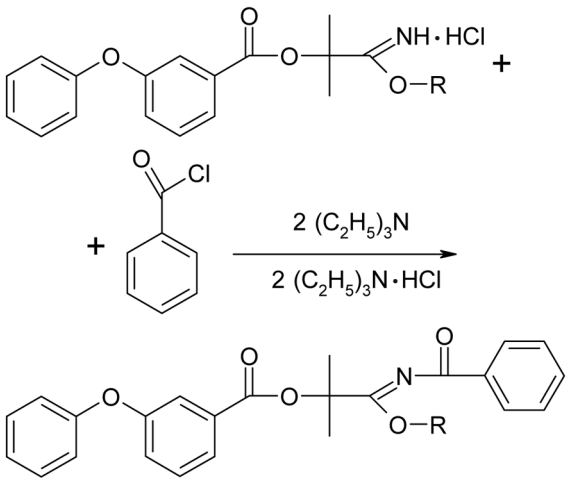
[1] Volgogard State Medical University, Volgograd, 400131 Russia.
[2] Volgograd State Technical University, Volgograd, 400005 Russia.
* e-mail: vad-ak@mail.ru

The reaction of 2-cyanoprop-2-yl 3-phenoxybenzoate with aliphatic alcohols and HCl (Scheme 2) produced ethyl- and isopropylimidates of 2-methyl-2-(3-phenoxybenzoate)-propionic acid (**Ib** and **Ic**).

The reaction was carried out with an equimolar ratio of reagents and stirring at 0 – 5°C for 1 – 2 h. The reaction was considered to have ended when the mixture gained weight and crystallized. The yields were 94 – 95%.

Ethyl and butyl *N*-(benzoyl)-2-methyl-2-(3-phenoxybenzoate)propiocarboximidates (**Id** and **Ie**) were synthesized via acylation of 2-(3-phenoxybenzoate)propionic acid imidate hydrochlorides by benzoylchloride (Scheme 3).

Scheme 3



Id, Ie

Esters of *N*-substituted 3-phenoxyphenylcarboximidic acid (**If** and **IIa-IIf**) were prepared via sequential hydrochlorination of 3-phenoxybenzonitrile under Pinner conditions and acylation of the resulting imidate hydrochlorides by carboxylic acid chlorides (Scheme 4).

The HCl acceptor was Et_3N. The reactions were carried out with a molar ratio of the reagents and a two-fold excess of Et_3N in anhydrous 1,4-dioxane at 60 – 65°C for 2 h.

EXPERIMENTAL CHEMICAL PART

IR spectra (ν, cm^{-1}) of liquid compounds were taken from thin layers (films); of solids, from mineral-oil mulls on Specord M82 (Germany) and PerkinElmer instruments (USA).

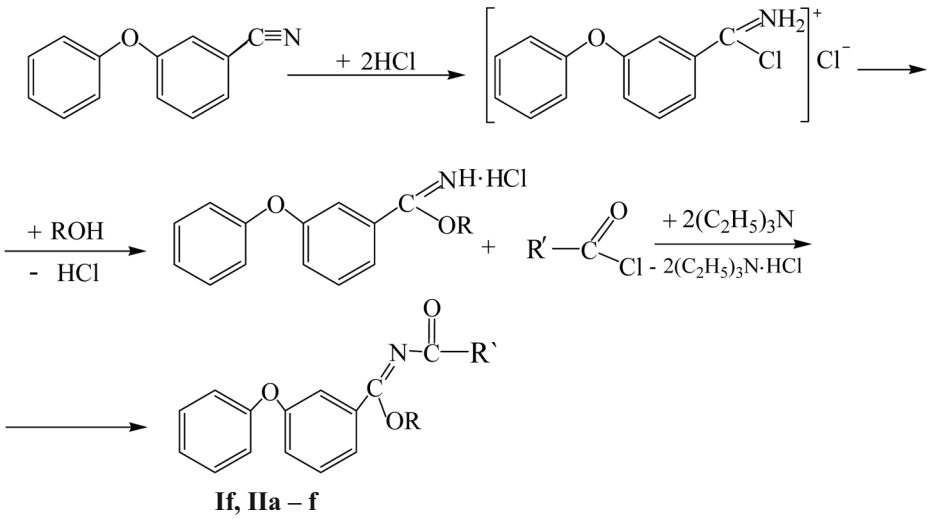
PMR spectra (δ, ppm) were recorded in DMSO-d_6 with hexamethyldisiloxane internal standard on a Varian Mercury 300BB instrument (USA, operating frequency 300 MHz).

GC-MS were obtained on a Varian MAT-11 instrument (USA) at ionizing potential 70 eV and cathode emission current 240 μA. Samples were directly introduced into the ion source.

The structures of the obtained compounds were elucidated using elemental analyses and IR and PMR spectroscopy. Table 1 presents the results.

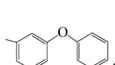
2-Cyanoprop-2-yl 3-phenoxybenzoate (I). A three-necked reactor equipped with a mechanical stirrer and reflux condenser was charged with 3-phenoxybenzoylchloride (10.00 g, 46.2 mmol) and anhydrous Et_2O. Et_3N (5.60 g, 55.4 mmol) in anhydrous Et_2O was added dropwise. The

Scheme 4



If, IIa – f

R′ =  (**IIa, IIc**);  (**If**);

R= -C_2H_5 (**If, IId**);  (**IIa, IIb**);  (**IIc**).

mixture was treated dropwise with acetone cyanohydrin (4.71 g, 55.4 mmol) in anhydrous Et_2O. The reaction was carried out at 20 – 25°C for 1 h. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. The product was purified by vacuum distillation. Yield 11.10 g (95%). bp 190 – 192°C (2 mm Hg). Mass spectrum, *m*/*z*: 281 [M^+]: 50 (12%), 77 (15%), 115.2 (17%), 169 (35%), 197 (53%), 214 (25%), 281 (100%). $C_{17}H_{15}O_3N$.

2-Cyanoprop-2-yl benzoate (Ia). A three-necked reactor equipped with a mechanical stirrer and reflux condenser was charged with benzoylchloride (10.00 g, 70.7 mmol) in anhydrous Et_2O. Et_3N (7.15 g, 70.7 mmol) in anhydrous Et_2O was added dropwise. The mixture was treated dropwise with acetone cyanohydrin (6.00 g, 70.7 mmol) in anhydrous Et_2O. The synthesis was carried out at 20 – 25°C for 1 h. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. The product was purified by vacuum distillation. Yield 11.10 g (90%). bp = 180 – 185°C (2 mm Hg) Mass spectrum, *m*/*z*: 189 [M^+]: 30 (10%), 71 (13%), 98.3 (20%), 123 (31%), 165 (55%), 174 (22%), 189 (100%). $C_{11}H_{11}O_2N$.

2-methyl-2-(3-phenoxybenzoate)propionic acid ethylimidate hydrochloride (Ib). A tared reactor was loaded with 2-methyl-2-(3-phenoxybenzoate)propionitrile (6.00 g, 20.9 mmol) and anhydrous EtOH (0.96 g, 20.9 mmol). The mixture was cooled to 0 – 5°C in an ice bath and saturated with dry HCl with stirring for 1 – 1.5 h. The end of the reaction was inferred from the weight gain of the mixture and its crystallization. The mixture was left overnight at 5°C. Yield 8.10 g (94%), $C_{19}H_{22}O_4NCl$.

2-Methyl-2-(3-phenoxybenzoate)propionic acid isopropylimidate hydrochloride (Ic). A tared reactor was loaded with 2-methyl-2-(3-phenoxybenzoate)propionitrile (6.00 g, 20.9 mmol) and anhydrous *i*-PrOH (1.25 g, 20.9 mmol). The mixture was cooled to 0 – 5°C in an ice bath and saturated with dry HCl with stirring for 1 – 1.5 h. The end of the reaction was inferred from the weight gain of the mixture and its crystallization. The mixture was left overnight at 5°C. Yield 8.40 g (94%), $C_{20}H_{24}O_4NCl$.

Ethyl *N*-(benzoyl)$_2$-(3-phenoxybenzoate)propiocarboximidate (Id). A four-necked reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with ethyl 2-(3-phenoxybenzoate)propiocarboximidic acid hydrochloride (5.00 g, 14.2 mmol) in anhydrous dioxane. The mixture was stirred, cooled to 5 – 10°C in an ice bath, treated dropwise with Et_3N (2.87 g, 28.4 mmol) in anhydrous dioxane and benzoylchloride (1.99 g 14.2 mmol) in anhydrous dioxane, and stirred for 30 min at room temperature and 2 h at 60 – 65°C. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. Crystals formed as the solvent was removed. The product was purified by recrystallization from anhydrous Et_2O. Yield 4.80 g (85%), $C_{26}H_{26}O_5N$.

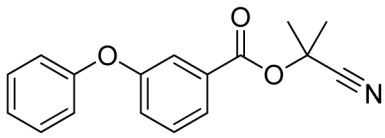
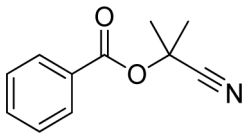
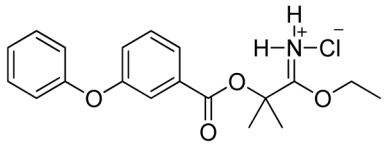
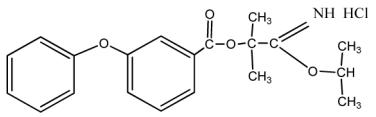
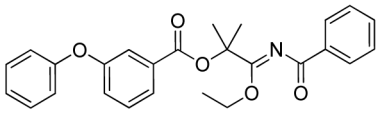
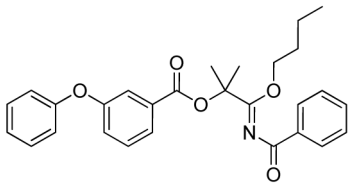
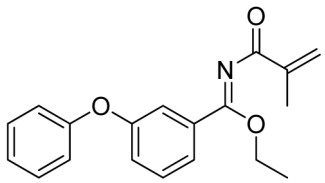
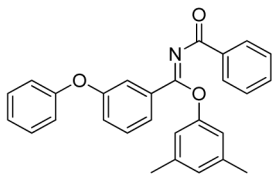
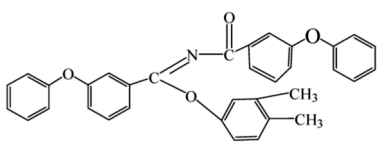
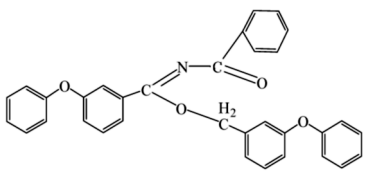
Butyl *N*-(benzoyl)-2-(3-phenoxybenzoate)propiocarboxyimidate (Ie). A four-necked reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with 2-cyanoprop-2-yl 3-phenoxybenzoate hydrochloride (5.00 g, 13.2 mmol) in anhydrous dioxane. The mixture was stirred, cooled to 5 – 10°C in an ice bath, treated dropwise with Et_3N (2.67 g, 26.4 mmol) in anhydrous dioxane and benzoylchloride (1.85 g, 13.2 mmol) in anhydrous dioxane, and stirred for 30 min at room temperature and 2 h at 60 – 65°C. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. Crystals formed as the solvent was removed. The product was purified by recrystallization from anhydrous Et_2O. Yield 82%, $C_{28}H_{29}O_5N$.

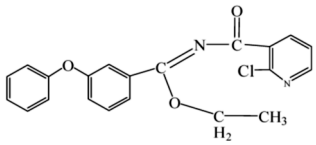
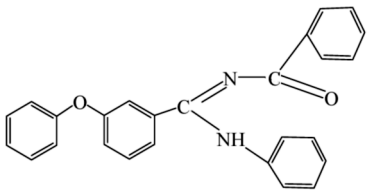
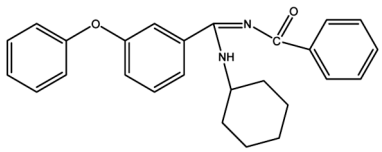
Ethyl *N*-(methacryloyl)-3-phenoxyphenylcarboximidate (If). A four-necked reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with 3-phenoxybenzoic acid ethylimidate hydrochloride (5.00 g, 24.3 mmol) in anhydrous dioxane. The mixture was stirred, cooled to 5 – 10°C in an ice bath, treated dropwise with Et_3N (4.92 g, 48.6 mmol) in anhydrous dioxane and methacryloyl chloride (2.54 g, 24.3 mmol) in anhydrous dioxane, and stirred for 30 min at room temperature and 2 h at 60 – 65°C. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. Crystals formed as the solvent was removed. The product was purified by recrystallization from anhydrous CCl_4. Yield 4.60 g (82%), $C_{19}H_{19}O_3N$.

3,5-Dimethylphenyl *N*-(benzoyl)-3-phenoxyphenylcarboximidate (IIa). A four-necked reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with 3-phenoxybenzoic acid 3,5-dimethylphenylimidate hydrochloride (5.00 g, 14.3 mmol) in anhydrous dioxane. The mixture was stirred, cooled to 5 – 10°C in an ice bath, treated dropwise with Et_3N (2.89 g, 28.6 mmol) in anhydrous dioxane and benzoylchloride (2.00 g, 14.3 mmol) in anhydrous dioxane, and stirred for 30 min at room temperature and 2 h at 60 – 65°C. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. Crystals formed as the solvent was removed. The product was purified by recrystallization from anhydrous CCl_4. Yield 83%, $C_{28}H_{23}O_3N$.

3,4-Dimethylphenyl *N*-(3-phenoxyphenyl)-3-phenoxyphenylcarboximidate (IIb). A four-necked reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with 3-phenoxybenzoic acid 3,4-dimethylphenylimidate hydrochloride (5.00 g, 14.3 mmol) in anhydrous dioxane. The mixture was stirred, cooled to 5 – 10°C in an ice bath, treated dropwise with Et_3N (2.89 g, 28.6 mmol) in anhydrous dioxane and 3-phenoxyphenylchloride (3.32 g, 14.3 mmol) in anhydrous dioxane, and stirred for 30 min at room temperature and 2 h at 60 – 65°C. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. Crystals formed as the solvent was removed. The prod-

TABLE 1. Structures and IR and PMR Spectra of Synthesized Compounds

No.	Compound	PMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}
I		1.85 (6H, s, CH_3), 6.56 – 7.69 (9H, m, $C_6H_5ÎC_6H_4$)	1600 – 700 (Ar), 2224 (C≡N), 2938 (CH), 1287 (CH_3), 1732 (C=O)
Ia		1.72 (6H, s, CH_3), 6.4 – 6.8 (5H, m, C_6H_5)	1600 – 700 (Ar), 2224 (C≡N), 2938 (CH), 1287 (CH_3), 1732 (C=O)
Ib		11.1 (s, 1H, HCl), 6.94 – 7.21 (m, 9H, m, $C_6H_5OC_6H_4$), 1.2 s (6H, CH_3), 1.4 – 1.5 (m, 3H, CH_3), 4.1 – 4.3 (m, 2H, CH_2)	1630 (C=N), 1294 – 970 (C-O-C), 3400, 1830 – 1690 (N-H)
Ic		10.8 (s, 1H, HCl), 6.94 – 7.21 (m, 9H, m, $C_6H_5OC_6H_4$), 6.90 – 7.08 (m, 1H, NH), 1.27 – 1.36 (m, 3H, CH_3), 4.26 (m, 2H, CH_2)	1650 (C=N), 1300 – 980 (C-O-C), 3450, 3490, 1810 – 1690 (N-H)
Id		1.05 – 1.37 (9H, m, CH_3), 4.25 – 4.27 (2H, d, CH_2), 6.89 – 7.56 (14H, m, $C_6H_5OC_6H_4$, C_6H_5)	1702 (C=O), 1648 (C=N), 1246 – 1072 (Ñ-O-C)
Ie		1.09 – 1.14 (9H, m, CH_3), 2.38 – 2.51 (m, 2H, CH_2), 3.01 – 3.05 (m, 2H, CH_2), 3.23 – 3.37 (t, 2H, CH_2), 6.67 – 7.98 (14H, m, $C_6H_5OC_6H_4$, C_6H_5)	1750 (C=O), 1678 (C=N), 1266 – 1350 (C-O-C)
If		0.83 – 1.20 (6H, m, $2CH_3$), 2.22 – 3.15 (2H, m, CH_2), 5.13 (2H, s, $=CH_2$), 6.78 – 7.76 (9H, m, $C_6H_5OC_6H_4$)	1732 (C=O), 1650 (C=N), 1620 (C=C), 1072 – 1246 (C-O-C)
IIa		1.89 (6H, s, $2CH_3$), 6.68 – 7.32 (17H, m, $C_6H_5OC_6H_4$, C_6H_3, C_6H_5)	1689 (C=O), 1654 (C=N), 1246 – 1272 (C-O-C)
IIb		1.83 (6H, s, $2CH_3$), 6.95 – 7.78 (21H, m, $C_6H_5OC_6H_4$, $C_6H_5OC_6H_4$, C_6H_3)	1716 (C=O), 1653 (C=N), 1041 – 1072 (C-O-C)
IIc		2.92 (2H, s, CH_2), 6.9 – 7.8 (23H, m, $C_6H_5OC_6H_4$, $C_6H_5OC_6H_4$, C_6H_5)	1748 – 1760 (C=O), 1660 (C=N), 1235 – 1326 (C-O-C)

No.	Compound	PMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}
IId		0.98 – 1.13 (3H, t, $2CH_3$), 2.22 – 3.13 (2H, m, CH_2), 6.91 – 7.87 (9H, m, $C_6H_5OC_6H_4$), (3H, m, C_5H_3NCl)	1780 – 1793 (C=O), 1660 – 1640 (C=C), 1648 (C=N), 1246 – 1072 (C-O-C), 1800 – 1770 (C-Cl)
IIe		6.82 – 7.76 (m, 19H, Ar), 3.61 (s, 1H, NH)	1290 – 1072 (C-O-C), 1648 (C=N), 1702 (C=O), 3430 – 3394.1204 (N-H, C-N)
IIf		6.89 – 7.82 (m, 14H, Ar), 4.17 (s, 1H, NH), 2.62 – 2.73 (m, 1H, CH), 1.42 – 1.72 (m, 6H, CH_2), 1.1 – 1.2 (m, 4H, CH_2)	1290 – 1100 (C-O-C), 1634 (C=N), 1780 – 1670 (C=O), 1360 – 1000 (C-N), 3430 – 3394 (N-H)

uct was purified by recrystallization from anhydrous CCl_4. Yield 88%, $C_{34}H_{27}O_4N$.

3-Phenoxybenzyl *N*-(benzoyl)-3-phenoxyphenylcarboximidate (IIc). A four-necked reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with 3-phenoxybenzoic acid 3-phenoxyphenylimidate hydrochloride (5.00 g, 11.6 mmol) in anhydrous dioxane. The mixture was stirred, cooled to 5 – 10°C in an ice bath, treated dropwise with Et_3N (2.89 g, 28.6 mmol) in anhydrous dioxane and benzoylchloride (2.00 g, 14.3 mmol) in anhydrous dioxane, and stirred for 30 min at room temperature and 2 h at 60 – 65°C. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. Crystals formed as the solvent was removed. The product was purified by recrystallization from anhydrous CCl_4. Yield 84%, $C_{33}H_{25}O_4N$.

Ethyl *N*-(chloronicotinoyl)-3-phenoxyphenylcarboximidate (IId). A four-necked reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with 3-phenoxybenzoic acid ethylimidate hydrochloride (5.00 g, 24.3 mmol) in anhydrous dioxane. The mixture was stirred, cooled to 5 – 10°C in an ice bath, treated dropwise with Et_3N (4.92 g, 48.6 mmol) in anhydrous dioxane and 2-chloronicotinoylchloride (4.28 g, 24.3 mmol) in anhydrous dioxane, and stirred for 30 min at room temperature and 2 h at 60 – 65°C. The precipitate of $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated first at atmospheric pressure and then under vacuum. Crystals formed as the solvent was removed. The product was purified by recrystallization from anhydrous CCl_4. Yield 87%, $C_{21}H_{17}O_3N_2Cl$.

***N*-Benzoyl-*N*′-phenyl-3-phenoxybenzamidine (IIe).** A reactor was charged with *N*-benzoyl-substituted 3-phenoxybenzoic acid ethylimidate (4.80 g, 14 mmol) in anhydrous benzene. The mixture was stirred, cooled to 15 – 20°C in a water bath, treated dropwise with aniline (5.44 g, 17 mmol), and held for 2 h at 75 – 80°C. The solvent was evaporated. The solid crystallized. The product was purified by recrystallization from anhydrous CCl_4. Yield 80%, mp 127 – 128°C, $C_{26}H_{23}O_2N_2$.

***N*-Benzoyl-*N*′-cyclohexyl-3-phenoxybenzamidine (IIf).** A reactor was charged with ethyl *N*-(benzoyl)-3-phenoxyphenylcarboximidate (5.00 g, 13 mmol) in anhydrous benzene. The mixture was stirred, cooled to 15 – 20°C in a water bath, treated dropwise with cyclohexylamine (5.60 g, 17 mmol), and held for 2 h at 75 – 80°C. Th solvent was evaporated. The solid crystallized. The product was purified by recrystallization from anhydrous CCl_4. Yield 85%, mp 115 – 120°C, $C_{26}H_{25}O_2N_2$.

EXPERIMENTAL PHARMACOLOGICAL PART

The compounds and reference drug pioglitazone were studied at a concentration of 10^{-5} M in the *in vitro* test of PPARγ (Eurofins Cerep, France) activation using the literature method [4]. Agonist activity of the compounds was calculated from the ratio to the control agonist activity.

Activity *in vitro* of glucokinase (GK). The activity of recombinant human liver GK expressed in *E. coli* (Sigma #SRP6045, USA) was determined using the coupled formation of glucoso-6-phosphate with NADN generation and glucoso-6-phosphate dehydrogenase (G6PDH, *L. mesenteroides*, 550 – 1100 U/mg, Sigma #G2921, USA). The analysis was performed at 37°C in flat-bottomed transparent polystyrene 96-well plates (Costar 9018, USA) with a final incubated volume of 210 μL. The incubation mixture contained HEPES (25 mM, pH 7.2), KCl (25 mM), D-glucose (5 mM),

ATP (1 mM), NAD (1.8 mM), $MgCl_2$ (2 mM), DTT (1 mM), test compound or DMSO (5%), G6PDH (1.8 U/mg), and GK (2 μg/mL). The compounds being tested were dissolved (5%) in DMSO and incubated beforehand with GK in a PST-60HL thermostatted shaker (Biosan, Latvia) for10 min to equilibrate the temperature. Then, the reaction was initiated by adding D-glucose solution (10 μL) [5]. GK activity was measured using the increase of optical density at 340 nm during incubation for 20 min after the reaction started. The measurements were made using an Infinite M200 PRO microplate reader (Tecan, Austria). The positive control was MBX-2982 experimental GK activator [6].

Activity *in vitro* of dipeptidyl peptidase-4 (DPP-4). The inhibitory activity of the compounds for DPP-4 was assessed by placing healthy volunteer blood plasma (40 μL) into Tris-HCl buffer solution (50 μL, 0.1 M, pH 8.0), treating the mixture with a solution (10 μL) of the tested compound at the given concentration in Tris buffer, incubating beforehand at 37°C for 5 min, treating the reaction mixture with DPP-4 substrate solution (Gly-Pro-*p*-nitroanilide, 100 μL, 1 mM; Sigma, USA), incubating at 37°C for 15 min, and recording the formation of *p*-nitroaniline from the increase of optical density at 405 nm [7] using an Infinite M200 PRO microplate reader (Tecan, Austria). The positive control was vildagliptin (Sigma, USA) [8].

The *in vitro* antiglycating activity of the compounds was determined by the literature method [9]. Glycation of proteins was modeled in a reaction mixture containing glucose (500 mM) and bovine serum albumin (BSA, 1 mg/mL) dissolved in phosphate buffer solution (pH 7.4). Compounds were dissolved in DMSO (Fisher Scientific, USA). Experimental samples were treated with solutions of the tested compounds at a final concentration of 1 mM; control samples, with an equivalent volume of DMSO. The reference drug was aminoguanidine. Samples were incubated at 60°C for 1 d. The specific fluorescence of glycated BSA after incubation was determined on an MPF-400 fluorescence spectrometer (Hitachi, Japan) at excitation wavelength 370 nm and emission wavelength 440 nm. The antiglycating activity of the compounds was calculated from the ratio to the fluorescence of control samples.

Data were statistically processed using the Student *t*-criterion (*T*).

RESULTS AND DISCUSSION

Table 2 presents results from the experimental studies.

TABLE 2. PPARγ-Agonist, Glucokinase, DPP-4-Inhibitory, and Antiglycation Activity of **Ia-f** and **IIa-f**

Compound	$PPAR_\gamma$ activation, 10^{-5} M, %	Glucokinase activation, 10^{-4} M, % ($M \pm m$)	DPP-4 inhibition, 10^{-4} M, % ($M \pm m$)	Antiglycation activity, 10^{-3} M, % ($M \pm m$)
I	44.6 ± 4.32*	21.77 ± 0.52*	– 6.1 ± 1.33**	29.10 ± 2.98*
Ia	0.5 ± 0.02**	3.42 ± 0.39**	0.65 ± 2.63**	– 20.32 ± 5.08
Ib	0.3 ± 0.01**	6.13 ± 0.89**	– 4.49 ± 2.74**	– 24.88 ± 6.82
Ic	0.6 ± 0.02**	2.24 ± 1.69**	– 3.69 ± 1.96**	– 35.84 ± 12.58
Id	– 0.1 ± 0.02**	3.06 ± 1.31**	5.42 ± 1.14**	2.34 ± 8.20
Ie	0.1 ± 0.01**	– 0.72 ± 1.55**	– 5.11 ± 1.06**	…
If	– 0.1 ± 0.02**	6.4 ± 2.00**	– 1.67 ± 2.08**	– 2.63 ± 0.02
IIa	…	0.53 ± 0.91	– 8.09 ± 2.29**	– 1.55 ± 2.78
IIb	…	24.27 ± 2.04*	– 36.7 ± 5.82**	13.37 ± 2.14
IIc	…	– 0.75 ± 1.41	0.46 ± 3.37**	– 18.22 ± 7.58
IId	…	0.99 ± 1.41	4.38 ± 3.37**	8.89 ± 6.00
IIe	…	1.74 ± 0.73	– 2.41 ± 2.8**	– 11.71 ± 6.93
IIf	…	1.63 ± 1.82	– 13.84 ± 2.63**	– 10.61 ± 0.34
Pioglitazone	68.9 ± 8.58*	…	…	…
MBX-2982	…	67.76 ± 0.87*	…	…
Vildagliptin	…	…	98.69 ± 0.42*	…
Aminoguanidine	…	…	…	57.83 ± 0.58*

* Data statistically significant (*T*) vs. control ($p < 0.05$);
** data statistically significant (*T*) vs.
…, compound not studied.

Compound **I** had the highest PPAR(agonist activity of the 3-phenoxybenzoic acid derivatives and activated this type of nuclear receptor by 44.6% ($p < 0.05$). The activity of reference drug pioglitazone was slightly greater although the difference was not statistically significant. The other compounds did not demonstrate activity for PPAR(.

Compounds **I** and **IIb** showed the ability to activate GK, increased its activity by 21.8 and 24.3%, respectively ($p < 0.05$), and were inferior to the standard compound MBX-2982 (67.7%, $p < 0.05$). The other 3-phenoxybenzoic acid derivatives were inactive for GK.

None of the studied compounds were capable of inhibiting DPP-4 activity.

Compound **I** possessed moderate antiglycating activity and inhibited statistically significantly fluorescence of glycated BSA by 29.1%, which was inferior to the reference drug aminoguanidine. Compound **IIb** of the other compounds showed a tendency to decrease glycation. The others did not exhibit this capability.

In summary, it was concluded that the most promising of the synthesized 3-phenoxybenzoic acid derivatives for further research was **I**.

ACKNOWLEDGMENTS

The research was sponsored by a Russian Science Foundation Grant (Project No. 14-25-00139).

REFERENCES

1. Yu. V. Popov, T. K. Korchagina, and V. S. Lobasenko, *Synthesis, Reactions, and Applications* [in Russian], VolgGTU, Volgograd (2015).
2. N. O. Saldabol, *Ways to Synthesize and Develop Antitumor Drugs* [in Russian], Collect. Sci. Works, Medgiz, Moscow (1962), p. 186.
3. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 1 – 2, Novaya Volna, Moscow (2001).
4. W. Yang, C. Rachez, L. P. Freedman, et al., *Mol. Cell. Biol.*, **20**(21), 8008 – 8017 (2000).
5. D. Salt, *Sigma Quality Control Test Procedure Enzymatic Assay of Glucokinase (EC 2.7.1.2) Principle*, pp. 7 – 10.
6. T. Ohishi and S. Yoshida, *Expert Opin. Invest. Drugs*, **21**(3), 321 – 328 (2012).
7. V. Matheeussen, A.-M. Lambeir, W. Jungraithmayr, et al., *Clin. Chim. Acta*, **413**(3 – 4), 456 – 462 (2012).
8. F. X. Pi-Sunyer, A. Schweizer, D. Mills, et al., *Diabetes Res. Clin. Pract.*, **76**(1), 132 – 138 (2007).
9. A. Jedsadayanmata, *Naresuan Univ. J.*, **13**(2), 35 – 41 (2005).