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Synthesis and evaluation of azaindole-α-alkyloxyphenylpropionic acid analogues as PPARα/γ agonists

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Abstract—A series of azaindole-α-alkyloxyphenylpropionic acid analogues was synthesized and evaluated for PPAR agonist activities. Structure–activity relationship was developed for PPARα/γ dual agonism. One of the synthesized compound **7a** was identified as a potent, selective PPARα/γ dual agonist.

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily, which includes the receptors for steroid hormones, retinoids, thyroid hormone, and vitamin D.[1] Like other nuclear receptors, PPARs are ligand-dependent transcription factors. Upon binding an agonist, the conformation of a PPAR is altered and stabilized such that a binding cleft is created and recruitment of transcriptional coactivators occurs.[2] After heterodimerization with another nuclear receptor, retinoid X receptor (RXR), the PPARs regulate target gene expression by binding to specific consensus DNA sequences, termed PPRE (peroxisome proliferator responsive element),[3] which are located in the regulatory regions of the target gene,[4] and result in an increase in gene transcription.

The PPARs play a critical physiological role as regulators of lipid and glucose metabolism. Three subtypes of PPARs, termed PPARδ, PPARα, and PPARγ, have been identified so far in various species, including humans.[5] PPARδ exhibits a wide tissue distribution and is poorly understood to date. However, PPARδ binds fatty acids and eicosanoids, which suggests an involvement in lipid metabolism.[6] PPARα regulates lipid homeostasis via its role in fatty acid catabolism including fatty acid binding, uptake, and oxidation as well as lipoprotein assembly and transport.[7] Fibrates (PPARα agonists, e.g., fenofibrate and clofibrate) primarily decrease serum triglyceride levels and increase HDL cholesterol (HDLc) levels, but they also improve glucose tolerance in type 2 diabetic patients.[8,9] Furthermore, fibrates have been reported to reduce weight gain in rodents without effects on food intake.[10] PPARγ is an important component in the adipogenic signaling cascade, and in lipid storage and utilization. A lot of synthetic compounds, such as the thiazolidinediones (TZDs), have been reported to function as high affinity PPARγ agonists.[11,12] These selective PPARγ agonists are potent agents with the ability to improve insulin sensitivity and glucose tolerance, and normalize elevated plasma glucose and insulin levels in type 2 diabetic patients. But the improvement in insulin sensitivity is accompanied with a body weight gain.[13,14] Therefore, recently, there has been considerable interest in combining the beneficial activities of PPARα activation and PPARγ activation, because the dual agonist approach should be well suited for the treatment of patients with type 2 diabetes.[15–17]

We have designed several series of compounds by in silico screening of the virtual library of potential PPAR agonists.[18] The present paper reports the synthesis and biological studies of the series of azaindole-α-alkyloxyphenylpropionic acid analogues.

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2. Chemistry

A general strategy to synthesize **6** and **7** is shown in Scheme 1. The key intermediate **3** undergoes condensation with ethyl α-alkyloxyl acetate in the presence of *t*-BuOK to give **5** in 30–60% yield.

The aldehydes **3** were synthesized as described in Scheme 2. Dibromoethane or dibromopropane was treated with 4-hydroxybenzaldehyde in acetone in the presence of K_2CO_3 as base to give compound **2** in 60–70% yield. The aldehyde **2** was then treated with 7-azaindole to give compound **3**.

The compounds obtained are summarized in Table 1.

3. Characterization of the olefinic configuration of 6

The configuration of olefinic intermediate **6** was identified by 1H NMR and X-ray crystallography. When R is an alkyl group in compounds **6**, the chemical shift of the olefin proton ranged between 6.83 and 6.87 ppm. According to the theoretical calculation,[19] the chemical shift of the olefinic proton in the *cis*-isomer with an alkyl R group is 6.83 ppm, which coincides with our observed values, while in the corresponding *trans*-isomer, the calculated chemical shift of the proton is 6.27 ppm. With an unsaturated R group, the calculated olefinic proton signal in the *cis*-isomers moved to 7.04 ppm. It can be derived that with an aryl R group, the olefinic proton signal in the *cis*-isomer is expected to further shift to downfield.[20] For the synthesized compounds with an aryloxy group, the observed olefin proton signal shifted to 7.28–7.35 ppm, which was indeed more downfield than the calculated value of 7.04 ppm for that in the *cis*-isomer with an unsaturated R group. Therefore, we assume the compounds exist in the *cis*-configuration. Such an assumption was supported by the X-ray crystallography of compound **61** (Fig. 1).

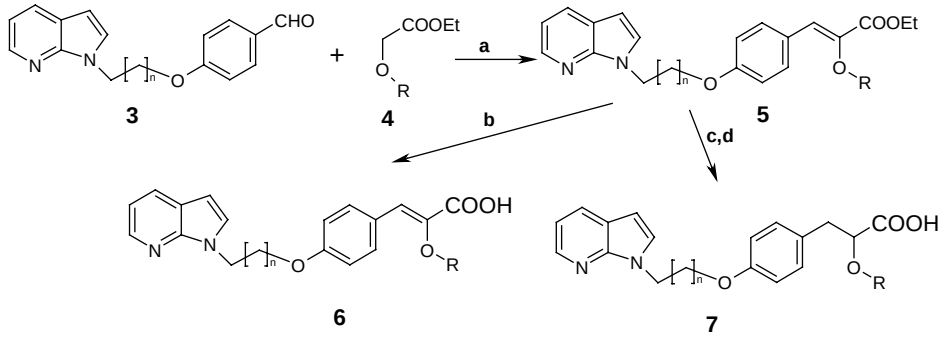
4. Results and discussion

4.1. In vitro

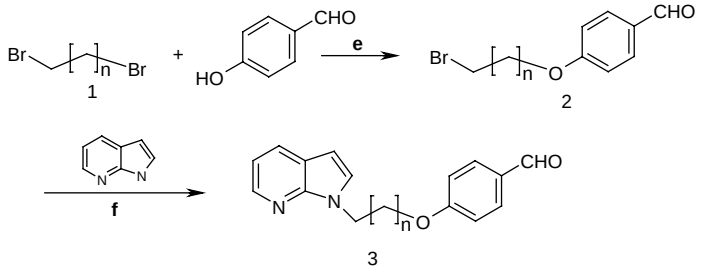
Compounds were screened in cell-based transcription assays using GAL4-PPAR chimeric receptors. Rosiglitazone and WY14643 were used as reference agonists in the PPARγ and PPARα transactivation assays, respectively. Maximal activation obtained with the reference agonist was defined as 100%.

The structures and transactivation activity of the series of compounds are summarized in Table 1.

As indicated in Table 1, the size of the substituent at the α-position of the carboxyl group significantly affected PPARγ and PPARα transactivation activity. Bulky groups generally led to decreased activity with a relative activity rank of *p*-methoxylphenyl < *p*/*m*-methylphenyl < phenyl < cyclohexyl < cyclopentyl. However, the methyl, ethyl, and *iso*-propyl substituents appear to be favorable for transactivation activity. In addition, the unsaturation of the compounds conducts an interesting result. Vinyl derivatives with small substituents, such as $-CH_3$, $-C_2H_5$, and $-CH(CH_3)_2$, at the α-position of the carboxyl group, were less potent than their saturated congeners. In contrast, vinyl derivatives with bulky substituents,

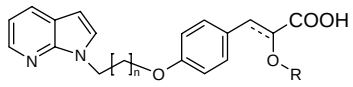


Scheme 1. Reagents and conditions: (a) *t*-BuOK, DMF, 2 h; (b) 1 N NaOH, EtOH; (c) 10% Pd/C, H_2, EtOH; (d) 1 N NaOH, EtOH.



Scheme 2. Reagents and conditions: (e) K_2CO_3, acetone; (f) KOH, DMSO, rt, 2 h.

Table 1. Structures and transactivation activity of the compounds



Compound	*n*	R	Single/double	PPARγ		PPARα	
				EC_{50} (μM)	% max	EC_{50} (μM)	% max
6a	2	Et	Double	0.6	129	3.63	65
7a	2	Et	Single	0.11	109	0.75	65
6b	2	Me	Double	1.413	104	4.57	15
7b	2	Me	Single	0.091	89	0.46	21
6c	2	*i*-Pr	Double	0.603	93	3.09	18
7c	2	*i*-Pr	Single	0.024	108	0.50	24
6d	2	Cyclopentyl	Double	0.871	85	3.24	16
7d	2	Cyclopentyl	Single	0.977	93	3.89	23
6e	2	Cyclohexyl	Double	0.776	85	3.80	19
7e	2	Cyclohexyl	Single	2.951	79	6.03	12
6f	2	Ph	Double	1.413	60	5.13	6
7f	2	Ph	Single	4.365	70	5.50	6
6g	2	*m*-Me-Ph	Double	1.122	85	ia	ia
7g	2	*m*-Me-Ph	Single	3.715	78	ia	ia
6h	2	*p*-Me-Ph	Double	0.81	66	3.46	37
7h	2	*p*-Me-Ph	Single	5.37	47	2.57	37
6i	2	*p*-MeO-Ph	Double	1.230	88	4.27	14
7i	2	*p*-MeO-Ph	Single	5.623	49	5.50	14
6j	3	Et	Double	5.370	68	5.37	17
7j	3	Et	Single	1.318	102	0.79	25
6k	3	Cyclopentyl	Double	4.467	21	5.50	7
7k	3	Cyclopentyl	Single	3.236	50	5.37	12
6l	3	Ph	Double	6.026	7	ia	ia
7l	3	Ph	Single	6.457	6	ia	ia
Rosiglitazone				0.068	100		
WY14643						39.0	100

ia, inactive.

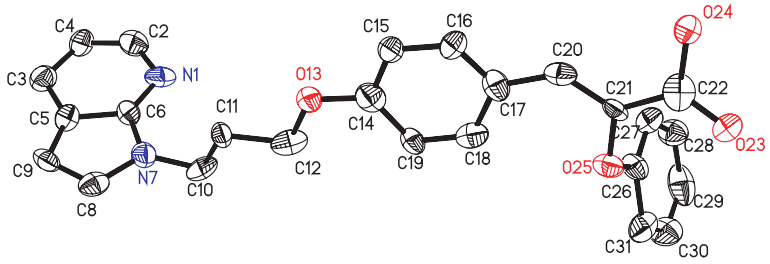


Figure 1. Structure of compound **61** as determined by X-ray diffraction.

such as cyclopentyl, cyclohexyl, phenyl, methylphenyl, and metheoxylphenyl, were slightly more potent than their saturated congeners. The relative activity rank is probably because of the conformational preference. Due to a restriction in rotation caused by the double bonds, the unsaturated compounds are rigid, therefore, the activity of these compounds would not significantly change. As for the saturated congeners, the flexibility of the molecules resulted in a fluctuation in activity. Compounds with small α-substituents can assume an energetically favorable conformation to fit the receptor, which leads to a better activity. However, compounds with bulky α-substituents may be excluded by the receptor and cause unfavorable activity profiles. This interesting phenomenon showed a strict steric restriction of the right pocket of the PPARγ and PPARα.

The distance between the azaindole group and middle benzene ring also conveys an important impact on the PPAR transactivation potency. The change of the spacer from two to three carbon atoms, as in **6j**, **7j**, **6k**, **7k**, **61**, and **71**, led to a decrease in potency.

The series of compounds were more potent on PPARγ than on PPARα. However, compound **7a** was a full

PPARγ agonist and an almost full PPARα agonist. It was selected for animal experiments.

4.2. In vivo

In vivo studies were carried out in KK^{AY} mice, which were used as a type 2 diabetic animal model. Mice (six to eight per group) were orally administered with vehicle, compound **7a** or positive drug AZ242 at a dose of 7 μmol/kg body weight daily. The blood was collected at days 0, 15, and 25 for measurement of the plasma glucose and triglyceride. The insulin tolerance test (ITT) and the oral glucose tolerance test (OGTT) were performed on the 15th and 25th day of treatment, respectively. Plasma glucose level was significantly reduced by **7a** (Table 2). Moreover, **7a** improved the impaired insulin and glucose tolerance of KK^{AY} mice (Fig. 2, Fig. 3), suggesting that **7a** is an effective anti-diabetic agent. Although **7a** did not produce a significant reduction in plasma triglyceride level after 15 days of treatment in the KK^{AY} mice that may be insensitive to triglyceride metabolizing, there was a decrease by 30.4% compared with the control group (Table 3). The efficacy of **7a** on hypetriglyceride is to be evaluated in a diet-induced obese model or a genetic obese model (ob/ob).

5. Experimental

5.1. Biology

5.1.1. In vitro transactivation. cDNAs for Human RXR, PPAR were obtained by RTPCR from the human liver or adipose tissues. Amplified cDNAs were cloned into pcDNA3.1 expression vector and the inserts were confirmed by sequencing. U2OS cells were cultured in McCoy's 5A with 10% heat-inactivated fetal bovine serum in a humidified 5% CO_2 atmosphere at 37 °C. Cells were seeded in 96-well plates the day before transfection to give a confluence of 50–80% at transfection. A total of 60 ng DNA containing 10 ng hRXR, 10 ng of pCMV Gal, 10 ng of nuclear receptor expression vectors, and 30 ng of the corresponding reporters were cotransfected per well using FuGene6 transfection reagent according to the manufacturer's instructions. Following 24 h after transfection, cells were incubated with 10% charcoal-stripped FBS DMEM and were treated with the individual compound dissolved in DMSO. The final concentration of DMSO in culture medium was 0.1%. Cells were treated with compound for 24 h and then collected with Cell Culture Lysis buffer. Luciferase activity was monitored using the luciferase assay kit according to the manufacturer's instructions. Light emission was read in a Labsystems Ascent Fluoroskan reader. To measure the galactosidase activity to normalize the luciferase data, 50 μL of supernatant from each transfection lysate was transferred to a new microplate. Galactosidase assays were performed in the microwell plates using a kit from Promega and read in a microplate reader.

5.1.2. In vivo animal study. Spontaneous diabetic KK^{AY} mice were procured from Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences (Beijing, China), and were used experimentally when they reach an age of 10–12 weeks. KK^{AY} mice were bred at specific pathogen free (SPF) animal house.

Table 2. Effect of compound **7a** on plasma glucose in KK^{AY} mice

Group	Plasma glucose (mg/dl)		
	0 day	15 day	25 day
Con	149.1 ± 31.8	228.4 ± 49.0	159.3 ± 31.3
AZ242	163.7 ± 52.5	95.6 ± 5.5*	85.6 ± 2.8*
7a	139.0 ± 26.5	101.0 ± 4.4*	85.9 ± 1.1*

Values are means ± SE. $n = 6–8$.
* $p < 0.05$ versus Con group in each group during the same day.

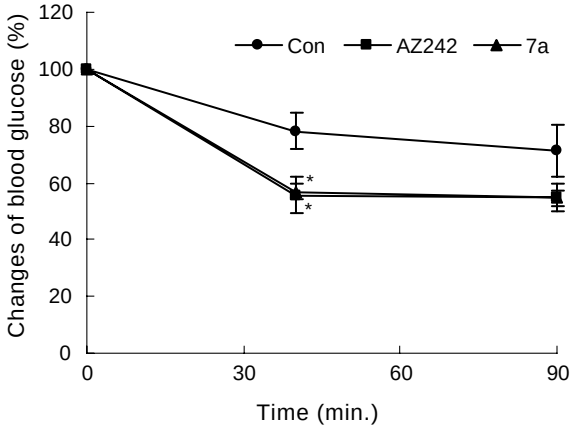


Figure 2. Insulin tolerance test in KK^{AY} mice. Insulin tolerance test was conducted at 15 days of treatment. *$p < 0.05$ versus Con group in each group during the same time; $n = 6–8$.

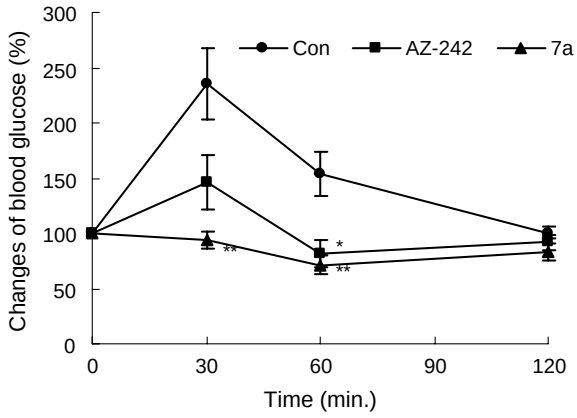


Figure 3. Glucose tolerance test in KK^{AY} mice. Glucose tolerance test was conducted at 25 days of treatment. *$p < 0.05$, **$p < 0.01$ vs. Con group in each group during the same time; $n = 6–8$.

Table 3. Effect of compound **7a** on plasma triglycerides in KK^{AY} mice

Group	Plasma triglycerides (mg/dl)	
	0 day	15 day
Con	263.2 ± 37.3	394.9 ± 53.3
AZ242	252.8 ± 37.6	201.2 ± 8.2**
7a	249.0 ± 45.7	274.8 ± 27.9

Values are means ± SE. $n = 6–8$.
** $p < 0.01$ vs. Con group in each group during the same day.

All animals were maintained at controlled temperature (22 ± 1 °C), under 12 h light/dark cycles, and given high fat diet and water ad libitum. For insulin and glucose tolerance tests, animals were fasted for 4 h and a basal blood sample was taken, followed by sc insulin (0.5 IU/kg) or i.g. injection of glucose (2 g/kg). Blood samples were drawn at 0, 40, and 90 min or at 0, 30, 60, and 120 min after the administration.

6. Chemistry

6.1. General methods

All melting points were determined with a Yanaco micromelting point apparatus without correction.^{1}H NMR spectra were measured using a Varian Unity INOVA 300 MHz instrument. Chemical shifts were reported in ppm (δ) values, based on tetramethylsilane as an internal standard. Ms spectra were recorded using an AutoSpec Ultima-TOF mass spectrometer. Column chromatography was performed on silica gel (QingDao HaiYang Chemical Co., Ltd., 200–300 mesh).

6.2. 2-Ethoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6a)

4-(2-Pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde (1.622 g, 6 mmol) and ethyl-ethoxyl acetate (0.872 g, 6.6 mmol) were added to 20 ml anhydrous DMF solvent. Then IN *t*-BuOK(7 ml) was added dropwise to the solution under ice bath cooling and the mixture was stirred for 4 h at room temperature. After adding 1 N HCl to pH 7, the solution was diluted with H_2O and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was separated by silica gel column chromatography (hexanes/AcOEt, 6:1 as an eluent) to give 2-ethoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester 853 mg (36.8%). The ester (503 mg, 1.32 mmol) was dissolved in ethanol (20 ml) and 1 N sodium hydroxide (5 ml) was added. The mixture was stirred for 3 h at room temperature. The ethanol was evaporated in vacuo, water and 1 N HCl were added to pH 2. The acid solution was extracted three times with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was crystallized to give title compound (**6a**) 147 mg (31.6%). Mp 135–139 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.246 (d, 1H, J = 4.8 Hz, ArH), 7.962 (d, 1H, J = 7.8 Hz, ArH), 7.705 (d, 2H, J = 8.7 Hz, ArH), 7.608 (d, 1H, J = 3.6 Hz, ArH), 7.088 (dd, 1H, J = 7.8 Hz, J = 4.8 Hz, ArH), 6.926 (d, 2H, J = 8.7 Hz, ArH), 6.857 (s, 1H, =CH–), 6.472 (d, 1H, J = 3.6 Hz, ArH), 4.642 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.379 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.905 (q, 2H, J = 6.9 Hz, –OCH_2–), 1.233 (t, 3H, –CH_3).

HRFAB-MS calcd for $C_{20}H_{21}N_2O_4$ $[M+H]^+$: 353.150132. Found: 353.152184.

6.3. 2-Ethoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7a)

A solution of the appropriate 2-ethoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester (300 mg, 0.78 mmol) in ethanol was added to 10% Pd-C and hydrogenated at 3 atm for 6 h. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was hydrolyzed according to the procedure described for **6a** and recrystallized to give white crystals in 66.9% yield. Mp 124–126 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.246 (dd, 1H, J = 5.1 Hz, J = 1.5 Hz, ArH), 7.959 (dd, 1H, J = 7.5 Hz, J = 1.5 Hz, ArH), 7.606 (d, 1H, J = 3.3 Hz, ArH), 7.090 (d, 2H, J = 8.7 Hz, ArH), 7.076 (d, 1H, J = 7.5 Hz, ArH), 6.805 (d, 2H, J = 8.7 Hz, ArH), 6.470 (d, 1H, J = 3.3 Hz, ArH), 4.620 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.300 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.927–3.883 (m, 1H, –OCH–), 3.502–3.209 (m, 2H, –OCH_2–), 2.878–2.721 (m, 2H, –$ArCH_2$–), 1.008 (t, 3H, –CH_3).

HRFAB-MS calcd for $C_{20}H_{23}N_2O_4$ $[M+H]^+$: 355.165782. Found: 355.165161.

6.4. 2-Methoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6b)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and ethyl α-methoxyl acetate according to the procedure described for **6a**. Mp 157–159 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.253 (d, 1H, J = 4.2 Hz, ArH), 7.966 (d, 1H, J = 7.8 Hz, ArH), 7.673 (d, 2H, J = 8.7 Hz, ArH), 7.618 (d, 1H, J = 3.5 Hz, ArH), 7.093 (dd, 1H, J = 7.8 Hz, J = 4.2 Hz, ArH), 6.939 (d, 2H, J = 8.7 Hz, ArH), 6.855 (s, 1H, =CH–), 6.478 (d, 1H, J = 3.5 Hz, ArH), 4.649 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.389 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.656 (s, 3H, –CH_3).

HRFAB-MS calcd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$: 339.134482. Found: 339.131874.

6.5. 2-Methoxy-3-[4-(2-pyrrolo [2,3-*b*] pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7b)

The compound was prepared from 2-methoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 118–119 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.25l (dd, 1H, J = 4.8 Hz, J = 1.2 Hz, ArH), 7.963 (dd, 1H, J = 7.5 Hz, J = 1.2 Hz, ArH), 7.611 (d, 1H, J = 3.6 Hz, ArH), 7.109–7.070 (m, 3H, ArH), 6.811 (d, 2H, J = 8.7 Hz, ArH), 6.480 (d, 1H, J = 3.6 Hz, ArH), 4.625 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.308 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.862–3.820 (m, 1H, –OCH–), 3.183 (s, 3H, –OCH_3), 2.898–2.726 (m, 2H, $ArCH_2$–).

HRFAB-MS calcd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$: 341.150132. Found: 341.149010.

6.6. 2-Isopropoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6c)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and ethyl α-isopropoxyl acetate according to the procedure described for **6a**. Mp 112–113 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.249 (d, 1H, J = 4.8 Hz, ArH), 7.959 (d, 1H, J = 7.6 Hz, ArH), 7.750 (d, 2H, J = 8.8 Hz, ArH), 7.615 (d, 1H, J = 3.6 Hz, ArH), 7.088 (dd, 1H, J = 7.6 Hz, J = 4.8 Hz, ArH), 6.912 (d, 2H, J = 8.8 Hz, ArH), 6.858 (s, 1H, =CH–), 6.472 (d, 1H, J = 3.6 Hz, ArH), 4.643 (t, 2H, J = 5.2 Hz, –OCH_2–), 4.431–4.416 (m, 1H, –OCH–), 4.376 (t, 2H, J = 5.2 Hz, –NCH_2–), 1.174 (s, 3H, –CH_3), 1.158 (s, 3H, -CH_3).

HRFAB-MS calcd for $C_{21}H_{23}N_2O_4$ $[M+H]^+$: 367.165782. Found: 367.163269.

6.7. 2-Isopropoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7c)

The compound was prepared from 2-isopropoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 85–87 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.236 (d, 1H, J = 3.3 Hz, ArH), 7.949 (d, 1H, J = 7.6 Hz, ArH), 7.595 (d, 1H, J = 3.6 Hz, ArH), 7.096–7.060 (m, 3H, ArH), 6.794 (d, 2H, J = 8.4 Hz, ArH), 6.459 (d, 1H, J = 3.6 Hz, ArH), 4.609 (t, 2H, J = 5.6 Hz, –OCH_2–), 4.289 (t, 2H, J = 5.6 Hz, –NCH_2–), 3.958–3.926 (m, 1H, –OCH–), 3.456–3.426 (m, 1H, –OCH–), 2.836–2.658 (m, 2H, –$ArCH_2$–), 1.008 (d, 2H, J = 6.0 Hz, –CH_3), 0.845 (d, 2H, J = 6.0 Hz, –CH_3).

HRFAB-MS calcd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$: 369.181433. Found: 369.182716.

6.8. 2-Cyclopentyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6d)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and ethyl α-cyclopentyloxyl acetate according to the procedure described for **6a**. Mp 123–125 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.248 (d, 1H, J = 4.4 Hz, ArH), 7.960 (d, 1H, J = 7.6 Hz, ArH), 7.678 (d, 2H, J = 8.4 Hz, ArH), 7.616 (d, 1H, J = 3.6 Hz, ArH), 7.088 (dd, 1H, J = 7.6 Hz, J = 4.4 Hz, ArH), 6.909 (d, 2H, J = 8.4 Hz, ArH), 6.835 (s, 1H, =CH–), 6.472 (d, 1H, J = 3.6 Hz, ArH), 4.83l (s, 1H, –OCH–), 4.640 (t, 2H, J = 5.2 Hz, –OCH_2–), 4.372 (t, 2H, J = 5.2 Hz, –NCH_2–), 1.633–1.487 (m, 8H, –CH_2–).

HRFAB-MS calcd for $C_{23}H_{27}N_2O_4$ $[M+H]^+$: 393.181433. Found: 393.181343.

6.9. 2-Cyclopentyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7d)

The compound was prepared from 2-cyclopentyloxyl-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 94–96 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.246 (d, 1H, J = 4.8 Hz, ArH), 7.959 (d, 1H, J = 7.6 Hz, ArH), 7.600 (d, 1H, J = 3.6 Hz, ArH), 7.101–7.071 (m, 3H, ArH), 6.805 (d, 2H, J = 8.0 Hz, ArH), 6.470 (d, 1H, J = 3.6 Hz, ArH), 4.618 (t, 2H, J = 5.6 Hz, –OCH_2–), 4.300 (t, 2H, J = 5.6 Hz, –NCH_2–), 3.881–3.848 (m, 1H, –OCH–), 3.828–3.821 (m, 1H, –OCH–), 2.842–2.649 (m, 2H, –$ArCH_2$–), 1.567–1.276 (m, 8H, –CH_2–).

HRFAB-MS calcd for $C_{23}H_{27}N_2O_4$ $[M+H]^+$: 395.197083. Found: 395.195595.

6.10. 2-Cyclohexyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6e)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and ethyl α-cyclohexyloxyl acetate according to the procedure described for **6a**. Mp 87–89 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.248 (d, 1H, J = 4.4 Hz, ArH), 7.958 (d, 1H, J = 8.0 Hz, ArH), 7.733 (d, 2H, J = 8.8 Hz, ArH), 7.612 (d, 1H, J = 3.2 Hz, ArH), 7.087 (dd, 1H, J = 8.0 Hz, J = 4.4 Hz, ArH), 6.910 (d, 2H, J = 8.8 Hz, ArH), 6.826 (s, 1H, =CH–), 6.472 (d, 1H, J = 3.2 Hz, ArH), 4.643 (t, 2H, J = 5.2 Hz, –OCH_2–), 4.377 (t, 2H, J = 5.2 Hz, –NCH_2–), 4.154–4.107 (m, 1H, –OCH–), 1.897–1.093 (m, 10H, –CH_2–).

HRFAB-MS calcd for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407.197083. Found: 407.193535.

6.11. 2-Cyclohexyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7e)

The compound was prepared from 2-cyclohexyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 83–85 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.246 (dd, 1H, J = 4.8 Hz, J = 1.6 Hz, ArH), 7.957 (dd, 1H, J = 7.6 Hz, J = 1.6 Hz, ArH), 7.596 (d, 1H, J = 3.6 Hz, ArH), 7.113–7.069 (m, 3H, ArH), 6.805 (d, 2H, J = 8.8 Hz, ArH), 6.469 (d, 1H, J = 3.6 Hz, ArH), 4.618 (t, 2H, J = 5.6 Hz, –OCH_2–), 4.303 (t, 2H, J = 5.6 Hz, –NCH_2–), 4.007–3.974 (m, 1H, –OCH–), 3.196–3.153 (m, 1H, –OCH–), 2.857–2.679 (m, 2H, –$ArCH_2$–), 1.708–0.974 (m, 10H, –CH_2–).

HRFAB-MS calcd for $C_{24}H_{29}N_2O_4$ $[M+H]^+$: 409.212733. Found: 409.213448.

6.12. 2-Phenoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6f)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and ethyl α-phenoxyl acetate according to the procedure described for **6a**. Mp 192–193 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.226 (d, 1H, J = 4.8 Hz, ArH), 7.942 (d, 1H, J = 7.6 Hz, ArH), 7.617 (d, 2H, J = 8.8 Hz, ArH), 7.579 (d, 1H, J = 3.6 Hz, ArH), 7.339 (s, 1H, =CH–), 7.315–7.274 (m, 2H, ArH), 7.072 (dd, 1H, J = 7.6 Hz, J = 4.8 Hz, ArH), 7.026–6.989 (m, 1H, ArH), 6.937–6.900 (m, 4H, ArH), 6.449 (d, 1H, J = 3.6 Hz, ArH), 4.612 (t, 2H, J = 5.2 Hz, –OCH_2–), 4.354 (t, 2H, J = 5.2 Hz, –NCH_2–).

HRFAB-MS calcd for $C_{24}H_{21}N_2O_4$ $[M+H]^+$: 401.150132. Found: 401.149345.

6.13. 2-Phenoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7f)

The compound was prepared from 2-phenoxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 120–123 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.243 (d, 1H, J = 4.5 Hz, ArH), 7.947 (d, 1H, J = 7.8 Hz, ArH), 7.599 (d, 1H, J = 3.6 Hz, ArH), 7.250–7.057 (m, 5H, ArH), 6.918–6.784 (m, 5H, ArH), 6.458 (d, 1H, J = 3.6 Hz, ArH), 4.841–4.799 (m, 1H, –OCH–), 4.612 (t, 2H, J = 5.4 Hz, –OC_2–), 4.301 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.129–2.994 (m, 2H, –$ArCH_2$–).

HRFAB-MS calcd for $C_{24}H_{23}N_2O_4$ $[M+H]^+$: 403.165782. Found: 403.167694.

6.14. 2-*m*-Tolyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6g)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and ethyl α-*m*-tolyloxyl acetate according to the procedure described for **6a**. Mp 165–167 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.230 (d, 1H, J = 4.8 Hz, ArH), 7.946 (d, 1H, J = 7.5 Hz, ArH), 7.618 (d, 2H, J = 8.7 Hz, ArH), 7.582 (d, 1H, J = 3.3 Hz, ArH), 7.319 (s, 1H, =CH–), 7.197–7.145 (m, 1H, ArH), 7.076 (dd, 1H, J = 7.5 Hz, J = 4.8 Hz, ArH), 6.917 (d, 2H, J = 8.7 Hz, ArH), 6.838–6.694 (m, 3H, ArH), 6.453 (d, 1H, J = 3.3 Hz, ArH), 4.617 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.359 (t, 2H, J = 5.4 Hz, –NCH_2–), 2.254 (s, 3H, –CH_3).

HRFAB-MS calcd for $C_{25}H_{23}N_2O_4$ $[M+H]^+$: 415.165782. Found: 415.166252.

6.15. 2-*m*-Tolyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7g)

The compound was prepared from 2-*m*-tolyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 160–162 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.238 (dd, 1H, J = 5.1 Hz, J = 1.2 Hz, ArH), 7.950 (dd, 1H, J = 8.1 Hz, J = 1.2 Hz, ArH), 7.595 (d, 1H, J = 3.9 Hz, ArH), 7.182 (d, 2H, J = 9.0 Hz, ArH), 7.114–7.058 (m, 2H, ArH), 6.826 (d, 2H, J = 9.0 Hz, ArH), 6.707 (d, 1H, J = 7.5 Hz, ArH), 6.620–6.571 (m, 2H, ArH), 6.459 (d, 1H, J = 3.9 Hz, ArH), 4.809-4.767 (m, 1H, –OCH–), 4.612 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.301 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.066–3.022 (m, 2H, –$ArCH_2$–), 2.206 (s, 3H, –CH_3).

HRFAB-MS calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$: 417.181433. Found: 417.180496.

6.16. 2-*p*-Tolyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6h)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and ethyl α-*p*-tolyloxyl acetate according to the procedure described for **6a**. Mp 187–190 °C.

^{2}H NMR(DMSO-d_6, 300 MHz) 5 ppm: 8.225 (d, 1H, J = 4.2 Hz, ArH), 7.942 (d, 1H, J = 6.6 Hz, ArH), 7.609 (d, 2H, J = 8.7 Hz, ArH), 7.577 (d, 1H, J = 3.3 Hz, ArH), 7.304 (s, 1H, =CH–), 7.102–7.052 (m, 3H, ArH), 6.905 (d, 2H, J = 8.7 Hz, ArH), 6.806(d, 2H, J = 8.1 Hz, ArH), 6.449 (d, 1H, J = 3.3 Hz, ArH), 4.613 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.354 (t, 2H, J = 5.4 Hz, –NCH^{2-}), 2.216 (s, 3H, –CH_3).

HRFAB-MS calcd for $C_{25}H_{23}N_2O_4$ $[M+H]^+$: 415.165782. Found: 415.165710.

6.17. 2-*p*-Tolyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-propionic acid (7h)

The compound was prepared from 2-*p*-tolyloxy-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 109–115 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.240 (d, 1H, J = 4.5 Hz, ArH), 7.953 (d, 1H, J = 8.1 Hz, ArH), 7.593 (d, 1H, J = 3.3 Hz, ArH), 7.177 (d, 2H, J = 8.1 Hz, ArH), 7.087 (m, 1H, ArH), 7.071 (m, 1H, ArH), 7.014 (m, 1H, ArH), 6.837–6.794 (m, 2H, ArH), 6.689 (d, 2H, J = 8.1 Hz, ArH), 6.459 (d, 1H, J = 3.3 Hz, ArH), 4.780–4.738 (m, 1H, –OCH–), 4.612 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.300 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.058–3.021 (m, 2H, $ArCH_2$–), 2.176 (s, 3H, –CH_3).

HRFAB-MS calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$: 417.181433. Found: 417.180962.

6.18. 2-(4-Methoxy-phenoxy)-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid (6i)

The compound was prepared from 4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-benzaldehyde and (4-methoxy-phenoxy)-acetic acid ethyl ester according to the procedure described for **6a**. Mp 170–173 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.233 (d, 1H, J = 4.5 Hz, ArH), 7.948 (d, 1H, J = 7.5 Hz, ArH), 7.628 (d, 2H, J = 8.7 Hz, ArH), 7.585 (d, 1H, J = 3.6 Hz, ArH), 7.283 (s, 1H, =CH–), 7.078 (dd, 1H, J = 7.5 Hz, J = 4.5 Hz, ArH), 6.915 (d, 2H, J = 8.7 Hz, ArH), 6.880–6.823 (m, 4H, ArH), 6.456 (d, 1H, J = 3.6 Hz, ArH), 4.621 (t, 2H, J = 5.4 Hz, –OCH_2–), 4.361 (t, 2H, J = 5.4 Hz, –NCH_2–), 3.677 (s, 3H, –OCH_3).

HRFAB-MS calcd for $C_{25}H_{23}N_2O_5$ $[M+H]^+$: 431.160697. Found: 431.162766.

6.19. 2-(4-Methoxy-phenoxy)-3-[4-(2-pyrrolo[2,3-*b*]py ridine-1-yl-ethoxy)-phenyl]-propionic acid (7i)

The compound was prepared from 2-(4-methoxy-phenoxy)-3-[4-(2-pyrrolo[2,3-*b*]pyridine-1-yl-ethoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 152–153 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.243 (d, 1H, J = 3.3 Hz, ArH), 7.956 (d, 1H, J = 7.8 Hz, ArH), 7.600 (d, 1H, J = 2.7 Hz, ArH), 7.181 (d, 2H, J = 8.4 Hz, ArH), 7.088 (m, 1H, J = 3.3 Hz, J = 7.8 Hz, ArH), 6.844–6.717 (m, 6H, ArH), 6.463(d, 1H, J = 2.7 Hz, ArH), 4.725–4.683 (m, 1H, –OCH–), 4.616 (t, 2H, J = 5.1 Hz, –OCH_2–), 4.305 (t, 2H, J = 5.1 Hz, –NCH_2–), 3.650 (s, 3H, –OCH_3, 3.035–3.010 (m, 2H, ArCH_2).

HRFAB-MS calcd for $C_{25}H_{25}N_2O_5$ $[M+H]^+$: 433.176347. Found: 433.175362.

6.20. 2-Ethoxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-arylic acid (6j)

The compound was prepared from 4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-benzaldehyde and ethyl α-ethoxyl acetate according to the procedure described for **6a**. Mp 166–167 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.233 (d, 1H, J = 4.8 Hz, ArH), 7.950 (d, 1H, J = 7.8 Hz, ArH), 7.723 (d, 2H, J = 8.7 Hz, ArH), 7.543 (d, 1H, J = 3.3 Hz, ArH), 7.065 (dd, 1H, J = 7.8 Hz, J = 4.8 Hz, ArH), 6.910 (d, 2H, J = 8.7 Hz, ArH), 6.873 (s, 1H, =CH–), 6.456 (d, 1H, J = 3.3 Hz, ArH), 4.428 (t, 2H, J = 6.9 Hz, –OCH_2–), 3.991–3.894 (m, 4H, –CH_2–), 2.302–2.216 (m, 2H, –CH_2–), 1.255 (t, 3H, –CH_3).

HRFAB-MS calcd for $C_{21}H_{23}N_2O_4$ $[M+H]^+$: 367.165782. Found: 367.164642.

6.21. 2-Ethoxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-propionic acid (7j)

The compound was prepared from 2-ethoxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 90–92 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.229 (dd, 1H, J = 4.4 Hz, J = 1.6 Hz, ArH), 7.948 (dd, 1H, J = 7.6 Hz, J = 1.6 Hz, ArH), 7.532 (d, 1H, J = 3.6 Hz, ArH), 7.105 (d, 2H, J = 8.4 Hz, ArH), 7.066 (d, 1H, J = 7.6 Hz, J = 4.4 Hz, ArH), 6.795 (d, 2H, J = 8.4 Hz, ArH), 6.452 (d, 1H, J = 3.6 Hz, ArH), 4.419 (t, 2H, J = 6.8 Hz, –OCH_2–), 3.938–3.884 (m, 3H, –NCH_2–, –OCH–), 3.535–3.248 (m, 2H, –OCH_2–), 2.886–2.752 (m, 2H, –ArCH_2–), 2.267–2.201 (m, 2H, –CH_2–), 1.028 (t, 3H, –CH_3).

HRFAB-MS calcd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$: 369.181433. Found: 369.182671.

6.22. 2-Cyclopentyloxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-arylic acid (6k)

The compound was prepared from 4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-benzaldehyde and ethyl α-cyclopentyloxyl acetate according to the procedure described for **6a**. Mp 169–171 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.214 (d, 1H, J = 4.8 Hz, ArH), 7.947 (d, 1H, J = 7.6 Hz, ArH), 7.689 (d, 2H, J = 8.8 Hz, ArH), 7.542 (d, 1H, J = 3.6 Hz, ArH), 7.06l (dd, 1H, J = 7.6 Hz, J = 4.8 Hz, ArH), 6.883 (d, 2H, J = 8.8 Hz, ArH), 6.836 (s, 1H, =CH–), 6.454 (d, 1H, J = 3.6 Hz, ArH), 4.842 (s, 1H, –OCH–), 4.425 (t, 2H, J = 6.8 Hz, –OCH_2–), 3.967 (t, 2H, J = 6.8 Hz, –NCH_2–), 2.285–2.220 (m, 2H, –CH_2–), 1.653–1.466 (m, 8H, –CH_2–).

HRFAB-MS calcd for $C_{24}H_{27}N_2O_4$ $[M+H]^+$: 407.197083. Found: 407.199821.

6.23. 2-Cyclopentyloxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-propionic acid (7k)

The compound was prepared from 2-cyclopentyloxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 118–121 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.225 (d, 1H, J = 4.4 Hz, ArH), 7.945 (d, 1H, J = 7.6 Hz, ArH), 7.517 (d, 1H, J = 3.2 Hz, ArH), 7.104–7.046 (m, 3H, ArH), 6.787 (d, 2H, J = 7.6 Hz, ArH), 6.443 (d, 1H, J = 3.6 Hz, ArH), 4.416 (t, 2H, J = 6.8 Hz, –OCH–), 3.907–3.838 (m, 3H, –NCH_2–, –OCH–), 2.858–2.663 (m, 2H, –ArCH_2–), 2.260–2.195 (m, 2H, –CH_2–), 1.598–1.292 (m, 2H, -CH_2–).

HRFAB-MS calcd for $C_{24}H_{29}N_2O_4$ $[M+H]^+$: 409.212733. Found: 409.214523.

6.24. 2-Phenoxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-arylic acid (6l)

The compound was prepared from 4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-benzaldehyde and ethyl α-phenoxyl acetate according to the procedure described for **6a**. Mp 190–191 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.193 (d, 1H, J = 4.4 Hz, ArH), 7.929 (d, 1H, J = 7.6 Hz, ArH), 7.628 (d, 2H, J = 8.7 Hz, ArH), 7.510 (d, 1H, J = 3.6 Hz, ArH), 7.347 (s, 1H, =CH–), 7.330-7.290 (m, 2H, ArH), 7.059–6.868 (m, 5H, ArH),6.432 (d, 1H, J = 3.6 Hz, ArH), 4.393 (t, 2H, J = 6.8 Hz, –OCH_2–), 3.939 (t, 2H, J = 6.8 Hz, –NCH_2–), 2.258–2.210 (m, 2H, –CH_2–).

HRFAB-MS calcd for $C_{25}H_{23}N_2O_4$ $[M+H]^+$: 415.165782. Found: 415.169762.

6.25. 2-Phenoxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-propionic acid (7l)

The compound was prepared from 2-phenoxy-3-[4-(3-pyrrolo[2,3-*b*]pyridine-1-yl-propoxy)-phenyl]-arylic acid ethyl ester according to the procedure described for **7a**. Mp 106–108 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 8.216 (dd, 1H, J = 4.8 Hz, J = 1.6 Hz, ArH), 7.940 (dd, 1H, J = 8.0 Hz, J = 1.6 Hz, ArH), 7.522 (d, 1H, J = 3.6 Hz, ArH), 7.254–7.191 (m, 4H, ArH), 7.055 (d, 1H, J = 8.0 Hz, J = 4.8 Hz, ArH), 6.903 (t, 1H, J = 7.2 Hz, ArH), 6.827–6.799 (m, 4H, ArH), 6.443 (d, 1H, J = 3.6 Hz, ArH), 4.848–4.816 (m, 1H, –OCH–),4.409 (t, 2H, J = 6.8 Hz, –OCH_2–), 3.895 (t, 3H, J = 6.0 Hz, –NCH_2–), 3.133–3.020 (m, 2H, –$ArCH_2$–), 2.257–2.192 (m, 2H, –CH_2–).

HRFAB-MS calcd for $C_{25}H_{25}N_2O_4$ $[M+H]^+$: 417.181433. Found: 417.184296.

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