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Original article

Synthesis and serotonin receptor activity of the arylpiperazine alkyl/propoxy derivatives of new azatricycloundecanes

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Abstract

A set of 36 arylpiperazine derivatives with two novel complex terminal imide fragments, 8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate and 1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione, were synthesized and tested for their affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. The Fujita–Ban analysis showed that the influence of structural modifications on the affinity for both receptor subtypes is additive and that the activity of similar compounds could be predicted with high accuracy. Compounds **46**, **48** and **18** out of 14 screened in a functional model of anxiety and depression demonstrated antidepressant activity in the forced swimming tests in mice, and were devoid of neurotoxic effects (chimney test in mice).

Keywords: Arylpiperazine; Azatricycloundecane; 5-HT$_{1A}$ receptor; 5-HT$_{2A}$ receptor; Fujita–Ban analysis; Antidepressant activity

1. Introduction

The serotonergic system has been consistently implicated in the pathophysiology of a number of psychiatric disorders including depression and anxiety [1]. Of the 13 different serotonin receptors belonging to GPCR superfamily [2], the 5-HT$_{1A}$ and 5-HT$_{2A}$ subtypes are most frequently considered to be the targets for anxiolytic and antidepressant drugs [3]. Indeed, 5-HT$_{1A}$ agonists and partial agonists (e.g. buspirone (**1**) and tandospirone) [4], as well as 5-HT$_{2A}$ antagonists (e.g. ritanserin and mirtazapine) [5] demonstrate clinical effectiveness in the treatment of either disorder. However, development of agents of this type is still a topical subject of investigations and lies within the area of our interest. In the group of previously investigated compounds, several *o*-methoxyphenylpiperazines (**2**–**4**) showing a similar 5-HT$_{1A}$/5-HT$_{2A}$ binding profile as buspirone (Fig. 1) exhibit anxiolytic- and/or antidepressant-like activity in some behavioral models in rats [6–8]. On the basis of their structures, we synthesized a series of new arylpiperazine derivatives with two novel complex terminal imide fragments: 8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate and 1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione.

Besides pyrimidynyl and *o*–OCH$_3$–phenyl, 5 other classic aryl groups, as well as such standard linkers as: propyl, butyl and propoxyl were used (Table 1). In addition, benzylpiperazine derivatives were also investigated, since for some close analogs a high 5-HT$_{1A}$ receptor affinity was reported [9,10]. Of the 36 new compounds, 25 were tested for their affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. The influence of structural modifications on serotonin activity was analyzed using a non-parameter Fujita–Ban method [11], and the binding constants of the remaining 11 derivatives were predicted on the basis of derived equations. In addition, the pharmacological properties of several selected compounds were evaluated in one anxiety test and one "behavioral despair" test.

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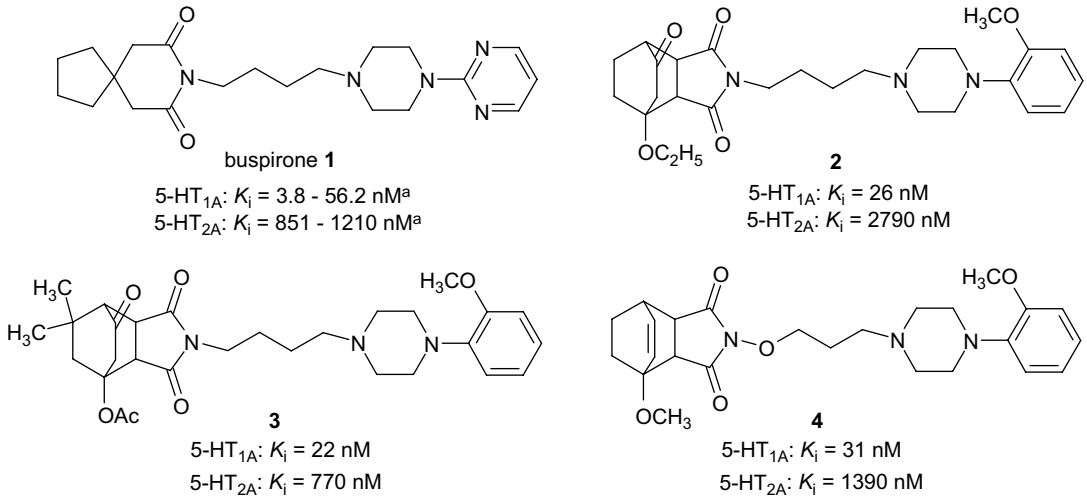


Fig. 1. Structure and affinity data for buspirone (**1**) and compounds **2**–**4**. [a]Range of K_i values taken from PDSB K_i Database (http://pdsp.med.unc.edu/kidb.php).

2. Chemistry

The synthesis of the target compounds **18**–**53** started with the preparation of appropriate imides in the Diels–Alder reaction. Imides **5** and **7** were obtained in a reaction of 3,5-dimethylcyclohex-2-en-1-one with 1*H*-pyrrole-2,5-dione, *p*-toluenosulphonic acid and isopropenyl acetate followed by hydrolysis (Scheme 1). The *N*-hydroxyimides **10** and **11** were initially prepared by an analogous method using 1-hydroxy-substituted 1*H*-pyrrole-2,5-dione (Scheme 2). Unfortunately, targeted imides were obtained in low yield, and, additionally, two by-products (**8** and **9**) were identified. Therefore an alternative substrate, i.e. furan-2,5-dione, was used, and the obtained two anhydrides were subsequently condensed with hydroxylamine, giving *N*-hydroxyimides **10** and **11** with good yield (Scheme 3). The standard alkylation procedure of intermediates **5**, **7**, **10** and **11** with 1,4-dibromobutane or 1,3-dibromopropane led to 4-bromobutyl (**12**, **13**), 3-bromopropyl (**14**, **15**) or 3-bromopropoxy (**16**, **17**) derivatives which were then condensed with appropriate amines to yield the final compounds **18**–**53** (Scheme 4).

3. Pharmacology

The 5-HT_{1A} and 5-HT_{2A} receptor affinities were determined for 25 compounds (**18**–**30**, **33**, **36**, **39**, **42**–**44**, **46**–**48**, **50** and **52**–**53**) in *in vitro* studies on the basis of their ability to displace [^{3}H]-8-OH-DPAT [8-hydroxy-2-(di-*n*-propylamino)tetraline] and [^{3}H]-ketanserin [3-{2-[4-(4-fluorobenzoyl)piperidino]ethyl}quinazoline-2,4(1*H*,3*H*)-dione], respectively. The results are presented in Table 1.

The neurotoxic effects of compounds showing significant affinity for 5-HT_{1A} receptors ($K_i < 130$ nM) were quantified by the Boissier chimney test [12]. Next, potential anxiolytic and antidepressant activities were evaluated by a four-plate test [13] and a forced swimming test [14] in mice, respectively. The effect of active compounds on the spontaneous locomotor activity of mice was also tested.

4. Results and discussion

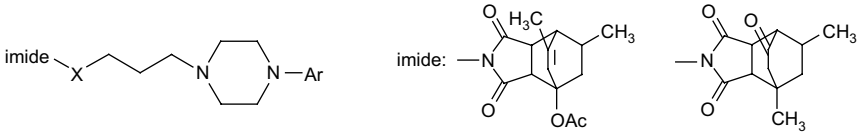
In general, the tested compounds were more active for 5-HT_{1A} receptors ($K_i = 10$–2730 nM) than for 5-HT_{2A} ones ($K_i = 102$–9720 nM). Eleven ligands showed 5-HT_{1A} affinity below 100 nM, but benzyl and pyrimidinyl derivatives were practically inactive. The highest K_i value was found for the *o*-methoxyphenylpiperazine derivative **18**, which was also the most selective 5-HT_{1A}/5-HT_{2A} ligand (K_i ratio 5-HT_{2A}/5-$HT_{1A} = 74$). As regards to 5-HT_{2A} receptors, only four compounds displayed K_i values below 200 nM, and among them derivative **53** could be classified as a dual 5-HT_{1A}/5-HT_{2A} agent of moderate activity.

A qualitative data analysis indicated that the affinities of the investigated compounds strongly and systematically depended on the 13 structural variables applied (eight aryl substituents, three linkers and two imide terminals). To quantitatively determine that relationship, we applied a Fujita–Ban analysis [11] – a simple QSAR technique that directly relates structural features to biological activity [15]. Using that non-parameter method, compound affinity was expressed in a logarithmic scale (pK_i) as a sum of the calculated theoretical activity of the arbitrarily chosen reference derivative **33** (μ) and activity contributions of the respective structural fragments (α_{Ar}, α_{spacer} and α_{imide}).

$$pK_i = \mu + \alpha_{Ar} + \alpha_{spacer} + \alpha_{imide}$$

As shown in Table 2, the results of the Fujita–Ban analysis indicated that the effect of structural modifications on the affinity for both receptor subtypes is additive and the majority of activity contributions α are significant at a 95% confidence level (*t*-test). The most negative values were obtained for α_{Bz} and $\alpha_{pyrimidinyl}$ (from -0.554 to -0.705), which reflected the above-mentioned, and confirmed previously observed [16,17], poor affinity of benzyl and pyrimidinyl derivatives. The contributions of pyridyl substituent were also negative ($\alpha_{pyridyl}$[5-HT_{1A}] $= -0.145$ and $\alpha_{pyridyl}$[5-HT_{2A}] $= -0.346$) when compared to the reference phenyl fragment ($\alpha_{Ph} = 0$).

Table 1
Structure, physical data and 5-HT_{1A} and 5-HT_{2A} binding affinities of compounds **18–53**



Compound	Ar	X	Imide	Yield[a] (%)	M.p.[b] (°C)	Molecular formula[c]	$K_i \pm$ SEM (nM)	
							5-HT_{1A}	5-HT_{2A}
18	*o*-OCH_3–Ph	$-CH_2-$	a	75	182–184	$C_{29}H_{39}O_5N_3$	10 ± 1	737 ± 49
19	Pyrimidyl	$-CH_2-$	a	57	154–155	$C_{26}H_{35}O_4N_5$	800 ± 30	6019 ± 420
20	Pyridyl	$-CH_2-$	a	50	164–165	$C_{27}H_{36}O_4N_4$	97 ± 5	965 ± 32
21	Ph	$-CH_2-$	a	78	173–174	$C_{28}H_{37}O_4N_3$	34 ± 3	286 ± 8
22	*p*-F–Ph	$-CH_2-$	a	80	168–169	$C_{28}H_{36}O_4N_3F$	286 ± 18	170 ± 14
23	Benzyl	$-CH_2-$	a	80	234–235	$C_{29}H_{39}O_4N_3$	1416 ± 75	9720 ± 650
24	*o*-OCH_3–Ph	$-CH_2-$	b	73	209–210	$C_{27}H_{37}O_4N_3 \cdot HCl \cdot 3H_2O$	25 ± 3	522 ± 38
25	Pyrimidyl	$-CH_2-$	b	67	156–157	$C_{24}H_{33}O_3N_5$ 1/2H_2O	1516 ± 120	3380 ± 245
26	Pyridyl	$-CH_2-$	b	75	197–198	$C_{25}H_{34}O_3N_4$	202 ± 24	577 ± 35
27	Ph	$-CH_2-$	b	78	193–194	$C_{26}H_{35}O_3N_3$	50 ± 7	181 ± 12
28	*p*-F–Ph	$-CH_2-$	b	80	192–193	$C_{26}H_{34}O_3N_3F$	521 ± 36	102 ± 8
29	Benzyl	$-CH_2-$	b	89	263–264	$C_{27}H_{37}O_3N_3 \cdot HCl \cdot 2½H_2O$	2730 ± 158	2092 ± 143
30	*o*-OCH_3–Ph	–	a	75	165–166	$C_{28}H_{37}O_5N_3 \cdot 2HCl$	35 ± 4	1024 ± 63
31	Pyrimidyl	–	a	78	149–150	$C_{25}H_{33}O_4N_5 \cdot 1/2H_2O$	–	–
32	Pyridyl	–	a	80	164–165	$C_{26}H_{34}O_4N_4 \cdot 1/2H_2O$	–	–
33	Ph	–	a	78	169–170	$C_{27}H_{35}O_4N_3$	294 ± 18	575 ± 45
34	*p*-F–Ph	–	a	88	176–177	$C_{27}H_{34}O_4N_3F$	–	–
35	Benzyl	–	a	89	231–232	$C_{28}H_{37}O_4N_3$	–	–
36	*o*-OCH_3–Ph	–	b	87	173–175	$C_{26}H_{35}O_4N_3$	44 ± 3	429 ± 56
37	Pyrimidyl	–	b	85	155–157	$C_{23}H_{31}O_3N_5$	–	–
38	Pyridyl	–	b	89	179–180	$C_{24}H_{32}O_3N_4$	–	–
39	Ph	–	b	86	220–221	$C_{25}H_{33}O_3N_3$	344 ± 12	292 ± 24
40	*p*-F–Ph	–	b	80	180–181	$C_{25}H_{32}O_3N_3F \cdot 1½H_2O$	–	–
41	Benzyl	–	b	78	269–270	$C_{26}H_{35}O_3N_3 \cdot HCl \cdot 2½H_2O$	–	–
42	*o*-OCH_3–Ph	–O–	a	85	165–166	$C_{28}H_{37}O_6N_3 \cdot 2HCl \cdot 13/4H_2O$	27 ± 4	681 ± 73
43	Pyridyl	–O–	a	88	165–166	$C_{26}H_{34}O_5N_4 \cdot 2HCl \cdot 2H_2O$	200 ± 15	1836 ± 72
44	Ph	–O–	a	87	199–200	$C_{27}H_{35}O_5N_3 \cdot 2HCl \cdot 1/3H_2O$	115 ± 7	375 ± 19
45	*p*-F–Ph	–O–	a	86	178–179	$C_{27}H_{34}O_5N_3F$	–	–
46	*o*-F–Ph	–O–	a	80	142–143	$C_{27}H_{34}O_5N_3F \cdot 2HCl \cdot 1/2H_2O$	80 ± 9	1073 ± 62
47	*m*-Cl–Ph	–O–	a	82	149–150	$C_{27}H_{34}O_5N_3Cl \cdot 2HCl \cdot 1H_2O$	37 ± 3	376 ± 29
48	*o*-OCH_3–Ph	–O–	b	85	164–165	$C_{26}H_{35}O_5N_3 \cdot 2HCl$	124 ± 14	637 ± 48
49	Pyridyl	–O–	b	60	168–170	$C_{24}H_{32}O_4N_4 \cdot 2HCl$	–	–
50	Ph	–O–	b	78	189–190	$C_{25}H_{33}O_4N_3 \cdot 2HCl$	616 ± 28	300 ± 25
51	*p*-F–Ph	–O–	b	61	175–176	$C_{25}H_{32}O_4N_3F \cdot 2HCl \cdot 1½H_2O$	–	–
52	*o*-F–Ph	–O–	b	85	136–137	$C_{25}H_{32}O_4N_3F \cdot 2HCl \cdot 1/2H_2O$	331 ± 24	910 ± 57
53	*m*-Cl–Ph	–O–	b	83	152–153	$C_{25}H_{32}O_4N_3Cl \cdot 2HCl$	92 ± 12	110 ± 9

[a] Free base.
[b] Salt.
[c] Anal. C, H, N.

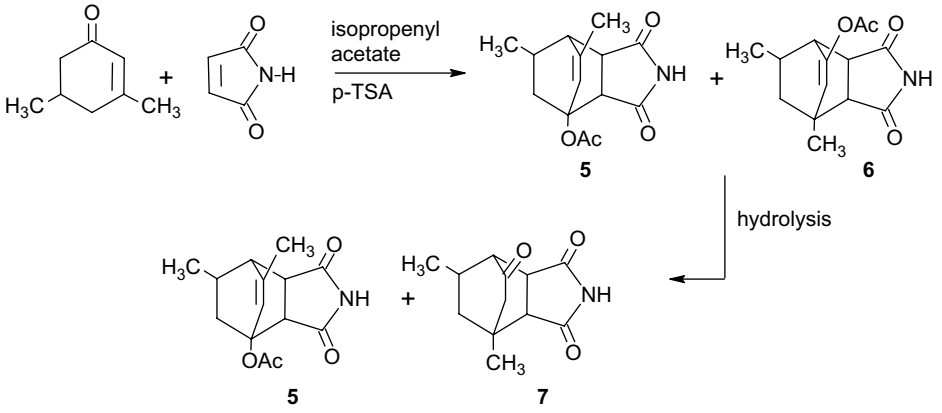
Both *ortho*-substituted aromatic moieties had a positive impact on 5-HT_{1A} affinity ($\alpha_{o\text{-}OCH_3\text{–}Ph} = 0.459$; $\alpha_{o\text{-F–Ph}} = 0.109$), but they produced an opposite effect in the case of 5-HT_{2A} receptors ($\alpha_{o\text{-}OCH_3\text{–}Ph} = -0.276$; $\alpha_{o\text{-F–Ph}} = -0.258$). Reverse influence was found for *p*-F–Ph, which was detrimental on 5-HT_{1A} and beneficial on 5-HT_{2A} binding, whereas the *m*-Cl–Ph substituent positively contributed to the affinity for either of those serotonin receptors.

The highest activity contribution was found for the C4 alkyl chain (in relation to the C3 spacer) for 5-HT_{1A} subtype (α_{C4}[5-HT_{1A}] = 0.483); that fragment also showed positive contribution to 5-HT_{2A} receptors, but its value was lower (α_{C4}[5-HT_{2A}] = 0.168). On the other hand, introduction of an oxygen atom into the spacer structure was not relevant to affinities for both those receptors.

Only two different imide terminals were investigated, and their mutual relationship was established (in relation to imide a) as strong negative contribution of imide b on 5-HT_{1A} receptors and favorable influence on 5-HT_{2A} ones.

The results discussed above are in line with the general view on the serotonin receptor affinity of arylpiperazine derivatives; however, additional information on structural features important for 5-HT_{2A} activity (i.e. presence of imide b) should be helpful in designing more active agents.

Excellent correlations between calculated and experimental affinities were obtained for both receptors ($r^2 = 0.957$ and



Scheme 1. Synthesis of imides **5** and **7**.

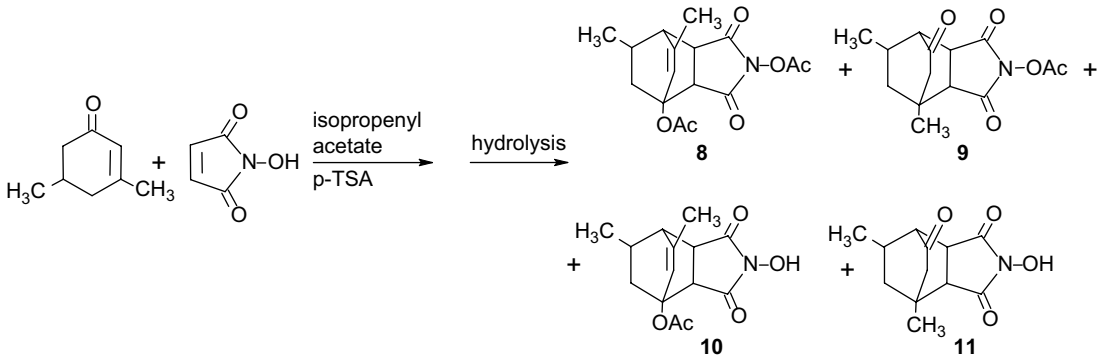
0.960 for 5-HT_{1A} and 5-HT_{2A}, respectively), and next, binding constants of the remaining 11 compounds were predicted. The results presented in Table 3 and Fig. 2 show that these additional compounds should display fairly low 5-HT_{1A} affinity, however, the predicted potencies of **40** and **52** towards 5-HT_{2A} receptors had relatively high values ($pK_{i(pred.)} = 6.85$ and 6.88, respectively). The experimentally measured affinities of these two compounds ($pK_{i(exp.)} = 7.06$ and 6.94, respectively) were close to the predicted ones, which confirmed the quality and usefulness of the developed model.

As an integral part of our investigation, the therapeutic potential of agents active *in vitro* (of $K_i < 130$ nM) was screened in one dose (equivalent to 0.1 of LD_{50}) in a functional test of neurotoxicity and in two models of anxiety and depression in mice. No neurotoxic effects were detected in the chimney test for any of the 14 investigated compounds (**18**, **20**, **21**, **24**, **27**, **28**, **30**, **36**, **42**, **44**, **46**–**48**, **53**), nor did any of them (administered in the screening dose) show anxiolytic properties in the four-plate test in mice. Strong antidepressant-like action was observed for **46** and **48**, while **18** only slightly shortened the total immobility time of mice. These effects seem to be specific, since screened compounds did not affect the locomotor activity with respect to the control group. Furthermore, it was found that the antidepressant effects produced by **46** and **48** were dose-dependent up to 0.0125 of LD_{50}, and when given in doses of 2.5 and 5.0 mg/kg they revealed similar antidepressive profile to imipramine in a dose 15 mg/kg (Table 4). It is rather unlikely that the observed activity was mediated solely by 5-HT_{1A} receptors, since – in contrast to compound **18** ($K_{i5\text{-}HT_{1A}} = 10$ nM) and the other ligands tested – the two most *in vivo* active derivatives showed only moderate affinity ($K_{i5\text{-}HT_{1A}} = 80$ and 124 nM for **46** and **48**, respectively). Indeed, many different receptor systems can be involved in antidepressant-like activity observed in forced swimming test, and piperazine derivatives may produce their effects via e.g. other serotonin [18], sigma 1 [19] and melanocortin-4 [20] receptors. The confirmation of therapeutic potential and explanation of molecular mechanism by which investigated compounds exerted their action require further pharmacological studies.

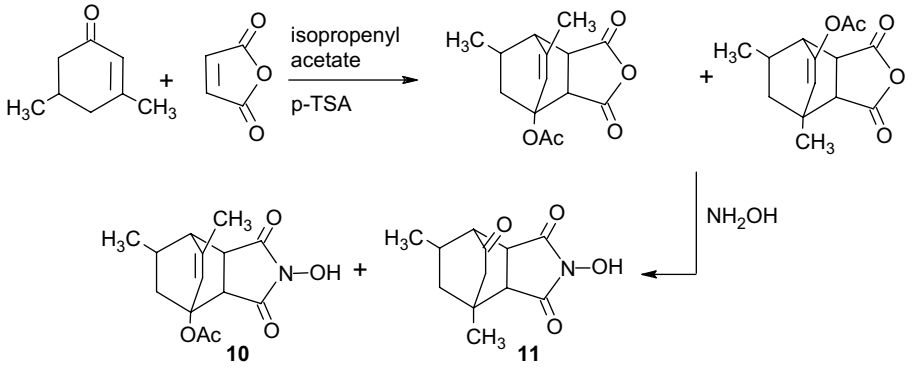
5. Experimental

5.1. Chemistry

Melting points were determined in a capillary in Electrothermal 9100 apparatus and are uncorrected. The nuclear magnetic resonance spectra of protons (^{1}H NMR) were recorded in a Bruker AVANCE DMX400 spectrometer, operating at 200 or 400 MHz for ^{1}H in $CDCl_3$ or DMSO. Chemical shift values are expressed in ppm (parts per million) in relation to



Scheme 2. Synthesis of imides **8**–**11**.



Scheme 3. Modified synthesis of imides **10** and **11**.

tetramethylsilane as an internal standard and coupling constants J are given in hertz.

A chromatographic column was filled with silica gel: Kieselgel 0.05–0.2 mm reinst (70–325 mesh ASTM) Merck. ESI-MS spectra were recorded by a Mariner Perspective – Biosystem.

Reactions were monitored by TLC on silica gel (plates with a fluorescent indicator 254 nm, layer thickness 0.2 mm, Kieselgel G., Merck).

5.1.1. Synthesis of imides **5** and **7**

A mixture of 3,5-dimethylcyclohex-2-en-1-one (0.008 mol), 1*H*-pyrrole-2,5-dione (0.01 mol) and a catalytic amount of *p*TSA (*p*-toluenosulphonic acid) in isopropenyl acetate (15 mL) was refluxed for 14 h. The boiling mixture was filtered and the solvent was evaporated. The residue was crystallized from hexane/ethyl acetate (60:40). A mixture of isomers (**5** and **6**) was hydrolyzed using anhydrous ethanol (10 mL) with 25% NH_3 (2 mL). That mixture was refluxed for 50 min, and when the reaction was finished the solvent was evaporated and the crude product was recrystallized from anhydrous ethanol. Finally, the mixture of products **5** and **7** was separated by column chromatography on silica gel, eluent: chloroform and chloroform/methanol 100:0.5.

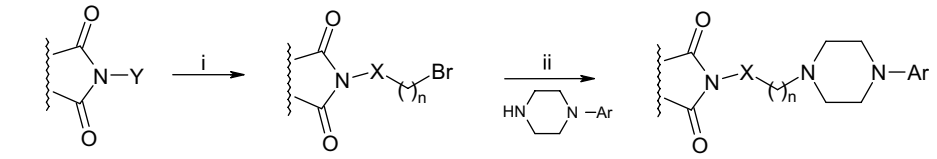
*5.1.1.1. 8,11-Dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**5**).* M.p. 151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (s, 1H, N*H*), 5.83 (s, 1H, H-9), 3.91 (d, $J = 8.2$ Hz, 1H, H-2), 3.02 (m, 1H, H-6), 2.72 (m, 1H, H-7), 2.66 (m, 1H, $H_{(eq)}$-10), 2.13 (s, 3H, $-COCH_3$), 2.01 (m, 1H, H-11), 1.79 (s, 3H, $-CH_3$), 1.07 (dd, $J = 11.6$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{14}H_{17}NO_4$: 63.87% C, 6.51% H, 5.32% N; found: 63.83% C, 6.67% H, 5.39% N.

*5.1.1.2. 1,11-Dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**7**).* M.p. 175–175.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (s, 1H, N*H*), 3.21 (dd, $J = 9.2$, 3.6 Hz, 1H, H-6), 2.75 (d, $J = 9.6$ Hz, 1H, H-2), 2.70 (m, 1H, H-7), 2.17 (m, 2H, H-9, H-11), 2.09 (s, 1H, H-9), 1.96 (m, 1H, $H_{(eq)}$-10), 1.31 (s, 3H, $-CH_3$), 1.10 (dd, $J = 14.0$, 4.8 Hz, 1H, $H_{(ax)}$-10), 1.0 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{12}H_{14}NO_3$: 65.14% C, 6.83% H, 6.33% N; found: 65.14% C, 6.69% H, 6.35% N.

5.1.2. Synthesis of imides **10** and **11**

Method 1. A mixture of 3,5-dimethylcyclohex-2-en-1-one (0.05 mol), 1-hydroxy-1*H*-pyrrole-2,5-dione (0.04 mol) and a catalytic amount of *p*TSA (*p*-toluenosulphonic acid) in isopropenyl acetate (20 mL) was refluxed for 2 h. The boiling mixture was filtered and the solvent was evaporated. The residue was crystallized from hexane/ethyl acetate (60:40). The crude product was hydrolyzed using anhydrous ethanol (40 mL) with 25% NH_3 (7 mL). The obtained mixture was separated by column chromatography on silica gel, eluent: chloroform and chloroform/methanol 100:0.5. Finally, four solid products were isolated.

*5.1.2.1. 4-(Acetoxy)-8,11-dimethyl-3,5-dioxo-4-azatricyclo-[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**8**).* M.p. 146.7–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.86 (s, 1H, H-9),



Scheme 4. Synthesis of compounds **12–53**. (i) Acetonitrile, anhydrous K_2CO_3, 1,4-dibromobutane or 1,3-dibromopropane; (ii) acetone, anhydrous K_2CO_3, KI.

Table 2
Intercept (μ), individual fragment contributions (α) and statistical data obtained by the Fujita–Ban analysis of 25 compounds

		Fragment	5-HT_{1A}	5-HT_{2A}
μ			6.800 ± 0.105	6.306 ± 0.079
α	Ar	*o*-OMe–PhP	0.459 ± 0.068	-0.276 ± 0.066
		1-PP	-0.554 ± 0.067	-0.705 ± 0.065
		Pyridylpiperazine	-0.145 ± 0.067	-0.346 ± 0.065
		PhP	0	0
		p-F–PhP	-0.353 ± 0.067	0.157 ± 0.065
		Bz–PhP	-0.664 ± 0.067	-0.705 ± 0.065
		o-F–PhP	0.109 ± 0.067[a]	-0.258 ± 0.065
		m-Cl–PhP	0.270 ± 0.067	0.127 ± 0.065[a]
	Spacer	C4	0.483 ± 0.095	0.168 ± 0.092[a]
		C3	0	0
		C3–O	-0.001 ± 0.091[a]	0.025 ± 0.088[a]
	Imide	a	0	0
		b	-0.290 ± 0.056	0.275 ± 0.054
Number of compounds			25	25
Correlation coefficient (r^2)			0.957	0.960
Standard error of regression			0.108	0.079
Calculated *F*0.01 ratio			31.09	33.48

[a] α did not pass the *t*-test at a 95% confidence level.

4.02 (d, $J = 8.4$ Hz, 1H, H-2), 3.09 (m, 1H, H-6), 2.77 (s, 1H, H-7), 2.73 (m, 1H, $H_{(eq)}$-10), 2.29 (s, 3H, H-1′), 2.13 (s, 3H, $-OCOCH_3$), 2.06 (m, 1H, H-11), 1.80 (s, 3H, $-CH_3$), 1.12 (dd, $J = 12.0$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.91 (d, $J = 6.8$ Hz, 3H, $-CH_3$). ESI-MS $m/z = 321.3$: 344.1 (100%), 322.2 (39%). Anal. Calcd for $C_{16}H_{19}NO_6$: 59.80% C, 5.96% H, 4.36% N; found: 59.94% C, 5.58% H, 4.30% N.

*5.1.2.2. 4-(Acetoxy)-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**9**).* M.p. 197–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.27 (m, 1H, H-6), 2.83 (m, 1H, H-2), 2.74 (m, 1H, H-7), 2.32 (s, 3H, H-1′), 2.20 (m, 1H, H-9), 2.03–1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.32 (s, 3H, $-CH_3$), 1.16 (m, 1H, $H_{(ax)}$-10), 1.02 (d, $J = 7.2$ Hz, 3H, $-CH_3$), ESI-MS $m/z = 279.29$: 302.1 (100%), 280.1 (24%). Anal. Calcd for $C_{14}H_{17}NO_5$: 60.11% C, 6.13% H, 5.01% N; found: 59.95% C, 5.90% H, 4.93% N.

*5.1.2.3. 4-Hydroxy-8,11-dimethyl-3,5-dioxo-4-azatricyclo-[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**10**).* M.p. 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (s, 1H, H-9), 3.86 (d, $J = 8.0$ Hz, 1H, H-2), 2.99 (dd, $J = 8.0$, 3.2 Hz, 1H, H-6), 2.72 (s, 1H, H-7), 2.65 (m, 1H, $H_{(eq)}$-10), 2.11 (m, 4H, $-OH$, $-OCOCH_3$), 2.03 (m, 1H, H-11), 1.74 (m, 3H, $-CH_3$), 1.07 (m, 1H, $H_{(ax)}$-10), 0.87 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{14}H_{17}NO_5$: 60.20% C, 6.09% H, 5.01% N; found: 60.36% C, 6.15% H, 4.96% N.

*5.1.2.4. 4-Hydroxy-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**11**).* M.p. 189.5–190.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.22 (dd, $J = 3.2$, 8.8 Hz, 1H, H-6), 2.77 (d, $J = 9.2$ Hz, 1H, H-2), 2.71 (m, 1H, H-7), 2.22 (m, 1H, $-OH$), 2.12 (m, 2H, H-9), 2.00 (m, 2H, $H_{(eq)}$-10, H-11), 1.33 (s, 3H, $-CH_3$), 1.13 (dd, $J = 14.0$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.99 (d, $J = 7.2$ Hz, 3H, $-CH_3$), ESI-MS $m/z = 236.25$: 236.1 (100%).

*5.1.3. Synthesis of imides **10** and **11***

Method 2. A mixture of 3,5-dimethylcyclohex-2-en-1-one (0.03 mol), furan-2,5-dione (0.04 mol) and a catalytic amount of *p*TSA (*p*-toluenosulphonic acid) in isopropenyl acetate (15 mL) was refluxed for 8 h. The boiling mixture was filtered and the solvent was evaporated. The residue was separated by column chromatography on silica gel, eluent: chloroform.

The obtained product (5.4 g) was dissolved in methanol, next an aqueous solution of hydroxylamine (6 mL), following Fieser method [21], was added. The reaction mixture was heated in a water bath at 70 °C for 4 h. When the reaction was completed, the mixture was cooled and left in a fridge. The residue was separated by column chromatography on silica gel; developing system: chloroform/methanol from 100:0.2 to 100:5. Finally, 3.6 g of **10** and 1.5 g of **11** were obtained.

*5.1.4. Synthesis of alkyl derivatives **12–17***

An appropriate imide (0.01 mol) was dissolved in acetonitrile (30 mL), next anhydrous K_2CO_3 (0.01 mol) and 1,4-dibromobutane (0.03 mol) or 1,3-dibromopropane (0.05 mol) were added, respectively. The mixture was refluxed for 7–15 h. When the reaction was completed, the mixture was filtered and the solvent was evaporated. The residue was purified by column chromatography, eluent: chloroform.

*5.1.4.1. 4-(4-Bromobutyl)-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**12**).* M.p. 70.3–71 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.78 (s, 1H, H-9), 3.88 (d, $J = 8.2$ Hz, 1H, H-2), 3.52–3.36 (m, 4H, H-1′, H-4′), 2.97 (dd, $J = 8.2$, 3.6 Hz, 1H, H-6), 2.77–2.65 (m, 2H, H-7, $H_{(eq)}$-10), 2.15 (s, 3H, $-OCOCH_3$), 2.10–1.98 (m, 1H, H-11), 1.77 (d, $J = 1.8$ Hz, 3H, $-CH_3$), 1.74–1.60 (m, 4H, H-2′, H–C3′), 1.09 (dd, $J = 12$, 4.6 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{18}H_{24}NBrO_4$: 54.27% C, 6.07% H, 3.52% N; found: 54.26% C, 6.24% H, 3.66% N.

*5.1.4.2. 4-(4-Bromobutyl)-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]-undecane-3,5,8-trione (**13**).* Yield 60%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.43 (m, 2H, H-1′), 3.34 (m, 2H, H-4′), 3.09 (dd, $J = 9.4$, 3.2 Hz, 1H, H-6), 2.63 (m, 2H, H-2, H-7), 2.13 (m, 1H, H-9), 1.91 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.72 (m, 2H, H-2′), 1.61 (m, 2H, H-3′), 1.27 (s, 3H, $-CH_3$), 1.06 (dd, $J = 14.4$, 4.0 Hz, 1H, $H_{(ax)}$-10), 0.93 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{16}H_{22}NO_3Br$: 53.94% C, 6.22% H, 3.93% N; found: 53.79% C, 6.29% H, 3.98% N.

*5.1.4.3. 4-(3-Bromopropyl)-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**14**).* Yield 60%, m.p. 106.9–107.2 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.78 (s, 1H, H-9), 3.90 (d, $J = 8.4$ Hz, 1H, H-2), 3.54 (t, $J = 6.8$ Hz, 2H, H-1′), 3.28 (t, $J = 6.9$ Hz, 2H, H-3′), 2.98 (dd, $J = 3.2$, 8.6 Hz, 1H, H-6), 2.76 (m, 1H, H-7), 2.72–2.60 (m, 1H, $H_{(eq)}$-10), 2.15 (s, 3H, $-OCOCH_3$), 2.11–1.90 (m,

Table 3
The observed and calculated affinity (pK_i) for 5-HT_{1A} and 5-HT_{2A} receptors of compounds from the training set, and predicted pK_i for the remaining compounds

Compound	5-HT_{1A}				5-HT_{2A}			
	pK_i		Residual	Std. Err.	pKi		Residual	Std. Err.
	Observed	Predicted			Observed	Predicted		
18	8.00	8.06	−0.06	0.10	6.13	6.16	−0.02	0.08
19	6.10	6.14	−0.04	0.13	5.22	5.21	0.01	0.10
20	7.01	7.12	−0.11	0.11	6.02	5.95	0.06	0.08
21	7.47	7.40	0.07	0.10	6.54	6.47	0.08	0.08
22	6.54	6.59	−0.05	0.13	6.77	6.75	0.02	0.10
23	5.85	5.89	−0.04	0.13	5.01	5.21	−0.20	0.10
24	7.60	7.70	−0.10	0.10	6.28	6.42	−0.14	0.07
25	5.82	5.78	0.04	0.13	5.47	5.48	−0.01	0.10
26	6.69	6.76	−0.07	0.11	6.24	6.22	0.02	0.09
27	7.30	7.04	0.26	0.10	6.74	6.73	0.01	0.07
28	6.28	6.23	0.05	0.13	6.99	7.01	−0.02	0.10
29	5.56	5.53	0.04	0.13	5.68	5.48	0.20	0.10
30	7.46	7.46	−0.01	0.10	5.99	5.99	0.00	0.08
31		5.54				5.05		
32		6.52				5.79		
33	6.53	6.80	−0.27	0.10	6.24	6.31	−0.07	0.08
34		6.00				6.59		
35		5.29				5.05		
36	7.36	7.10	0.25	0.10	6.37	6.26	0.11	0.08
37		5.18				5.31		
38		6.17				6.06		
39	6.46	6.44	0.02	0.10	6.53	6.57	−0.04	0.08
40		5.64				6.85		
41		4.93				5.32		
42	7.57	7.46	0.11	0.10	6.17	6.02	0.15	0.07
43	6.70	6.52	0.18	0.12	5.74	5.82	−0.08	0.09
44	6.94	6.80	0.14	0.10	6.43	6.33	0.10	0.07
45		5.99				6.61		
46	7.10	7.05	0.05	0.13	5.97	5.87	0.10	0.10
47	7.43	7.41	0.02	0.13	6.42	6.56	−0.13	0.10
48	6.91	7.10	−0.20	0.10	6.20	6.28	−0.09	0.08
49		6.16				5.34		
50	6.21	6.44	−0.23	0.10	6.52	6.60	−0.07	0.08
51		5.64				6.88		
52	6.64	6.69	−0.05	0.13	6.04	6.14	−0.10	0.10
53	7.04	7.05	−0.02	0.13	6.96	6.82	0.13	0.10

3H, H-11, H-2′), 1.78 (d, $J = 1.6$ Hz, 3H, $-CH_3$), 1.08 (dd, $J = 12$, 4.6 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 7.0$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{17}H_{22}NO_4Br$: 53.14% C, 5.77% H, 3.64% N; found: 53.12% C, 5.54% H, 3.65% N.

*5.1.4.4. 4-(3-Bromopropyl)-1,11-dimethyl-4-azatricyclo-[5.2.2.0^{2,6}]undecane-3,5,8-trione (**15**).* Yield 83%, m.p. 125.9–126.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.61 (m, 2H, H-1′), 3.32 (t, $J = 6.4$ Hz, 2H, H-3′), 3.15 (dd, $J = 9.2$, 3.2 Hz, 1H, H-6), 2.70 (m, 2H, H-2, H-7), 2.19 (m, 1H, H-9), 2.15–1.94 (m, 5H, H-9, $H_{(eq)}$-10, H-11, H-2′), 1.34 (s, 3H, $-CH_3$), 1.13 (dd, $J = 14.4$, 4.0 Hz, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{15}H_{20}NO_3Br$: 52.64% C, 5.89% H, 4.09% N; found: 52.41% C, 5.34% H, 4.47% N.

*5.1.4.5. 4-(3-Bromopropoxy)-8,11-dimethyl-3,5-dioxo-4- azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**16**).* Yield 80%, m.p. 94–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (s, 1H, H-9), 4.15–4.11 (m, 2H, H-1′), 3.88 (d, $J = 8.4$ Hz, 1H, H-2), 3.60 (t, $J = 6.4$ Hz, 2H, H-3′), 2.98–2.95 (dd, $J = = 8.4$, 2.8 Hz, 1H, H-6), 2.77 (s, 1H, H-7), 2.71 (t, $J = 10.8$ Hz, 1H, $H_{(eq)}$-10), 2.17 (m, 5H, $-OCOCH_3$, H-2′), 2.05 (m, 1H, H-11), 1.81 (s, 3H, $-CH_3$), 1.13–1.09 (dd, $J = 12.0$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 8.8$ Hz, 3H, $-CH_3$), ESI-MS *m/z* = 400.26: 422.1 (100%), 424.1 (96%). Anal. Calcd for $C_{17}H_{22}NBrO_5$: 51.01% C, 5.54% H, 3.50% N; found: 51.21% C, 5.28% H, 3.45% N.

*5.1.4.6. 4-(3-Bromopropoxy)-1,11-dimethyl-4-azatricyclo-[5.2.2.0^{2,6}]undecane-3,5,8-trione (**17**).* Yield 74%, m.p. 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.16 (t, $J = 5.6$ Hz, 2H, H-1′), 3.65–3.57 (m, 2H, H-3′), 3.15 (dd, $J = 9.2$, 2.8 Hz, 1H, H-6), 2.71 (m, 2H, H-2, H-7), 2.21–2.17 (m, 3H, H-9, H-2′), 2.05–1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.34 (s, 3H, $-CH_3$), 1.16 (dd, $J = 13.6$, 4.4 Hz, 1H, $H_{(ax)}$-10), 1.01 (d, $J = 6.8$ Hz, 3H, $-CH_3$). ESI-MS *m/*

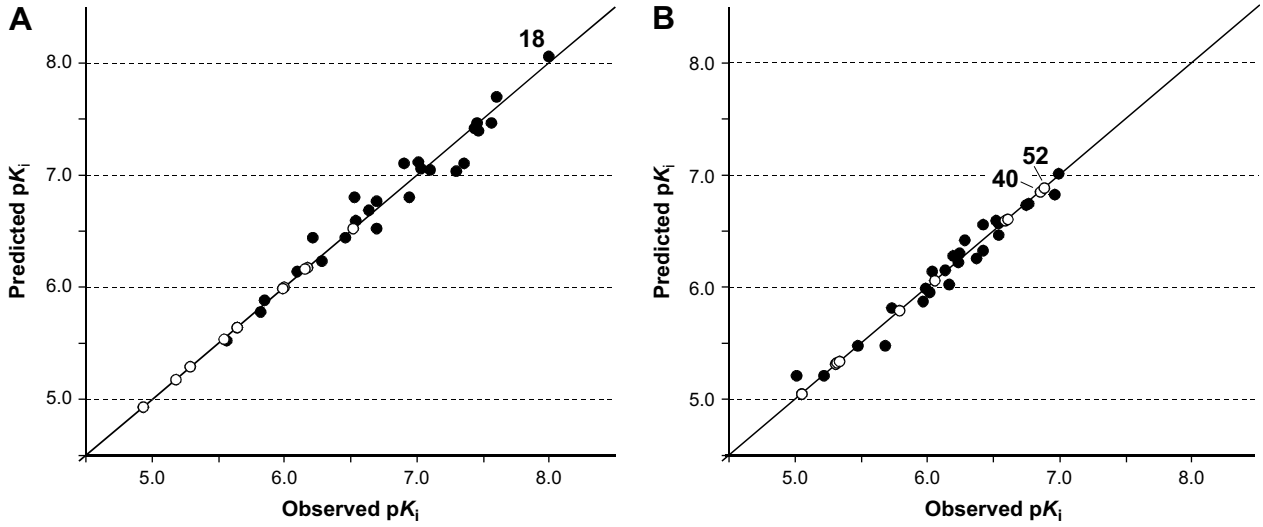


Fig. 2. The correlation between the observed and calculated pK_i (•), and the predicted pK_i (○) of the remaining compounds, for (A) 5-HT_{1A} and (B) 5-HT_{2A} receptors.

$z = 358.24$: 382.1 (100%), 380.1 (97%). Anal. Calcd for $C_{15}H_{20}NO_4Br$: 50.29% C, 5.63% H, 3.91% N; found: 50.46% C, 5.26% H, 3.78% N.

5.1.5. Synthesis of 4-arylpiperazinyl derivatives of N-substituted imides

To a mixture of *N*-bromoalkanyl/-alkanolimide (0.01 mol), a powdered anhydrous K_2CO_3 (0.01 mol), a catalytic amount of KI in acetone (30 mL) and an appropriate amine (0.01 mol) were added. The reaction mixture was stirred at room temperature for 10–20 h. Then, an inorganic residue was filtered off and the solvent was evaporated. The obtained compound was purified by column chromatography, eluent: chloroform, chloroform/methanol 50:0.2.

Table 4
Antidepressive effects of compounds **18**, **46** and **48** in the "forced swimming" test in mice

Treatment[a]	Dose (mg/kg ip)	The total immobility time[b] (s)
Control	–	140.8 ± 9.54
Imipramine	15	69.5 ± 16.1*
18	5	113.8 ± 18.2
	10	71.7 ± 22.7*
46	1.25	114.3 ± 17.4
	2.5	56.8 ± 16.1*
	5	48.3 ± 18.7*
	10	27.5 ± 7.1*#
	20	18.4 ± 7.8*#
48	1.25	123.7 ± 15.0
	2.5	83.5 ± 8.8*
	5	63.5 ± 10.1*
	10	31.2 ± 9.2*#
	20	29.4 ± 7.6*#

*#$p < 0.001$; *comp. with control group; #comp. with imipramine.
[a] Imipramine and investigated compounds were given 30 min before the test.
[b] The data represent mean ± SEM.

*5.1.5.1. 4-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**18**).* Yield 75%, m.p. 111.2–112 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.22 (m, 4H, H-arom.), 5.77 (s, 1H, H-9), 3.82 (m, 4H, $-OCH_3$, H-2), 3.42 (m, 2H, H-1′), 3.08 (m, 4H, H-piper.), 2.94 (dd, $J = 8.4$, 3.2 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.69 (m, 1H, $H_{(eq)}$-10), 2.60 (m, 4H, H-piper.), 2.38 (t, $J = 6.6$ Hz, 2H, H-4′), 2.14 (s, 3H, $-OCOCH_3$), 2.02 (m, 1H, H-11), 1.76 (d, $J = 7.6$ Hz, 3H, $-CH_3$), 1.49 (m, 4H, H-2′, H-3′), 1.07 (dd, $J = 12$, 4.6 Hz, 1H, $H_{(ax)}$-10), 0.88 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{29}H_{39}O_5N_3$: 68.34% C, 7.71% H, 8.24% N; found: 68.32% C, 7.75% H, 8.14% N.

*5.1.5.2. 4-{4-[4-(2-Pyrimidyl)piperazin-1-yl]butyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**19**).* Yield 57%, oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.30 (d, $J = 4.6$ Hz, 2H, H-arom.), 6.47 (t, $J = 4.6$ Hz, 1H, H-arom.), 5.77 (s, 1H, H-9), 3.85 (m, 5H, H-2, H-piper.), 3.42 (t, $J = 6.6$ Hz, 2H, H-1′), 2.96 (dd, $J = 8.2$, 3.2 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.69 (m, 1H, $H_{(eq)}$-10), 2.48 (m, 4H, H-piper.), 2.36 (t, $J = 6.8$ Hz, 2H, H-4′), 2.15 (s, 3H, $-OCOCH_3$), 2.09–1.98 (m, 1H, H-11), 1.76 (d, $J = 1.8$ Hz, 3H, $-CH_3$), 1.49 (m, 4H, H-2′, H-C3′), 1.08 (dd, $J = 12$, 4.6 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{26}H_{35}O_4N_5$: 64.85% C, 7.33% H, 14.54% N; found: 64.92% C, 7.33% H, 14.07% N.

*5.1.5.3. 4-{4-[4-(2-Pyridyl)piperazin-1-yl]butyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**20**).* Yield 50%, oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.19 (m, 1H, H-arom.), 7.47 (m, 1H, H-arom.), 6.62 (m, 2H, H-arom.), 5.77 (s, 1H, H-9), 3.87 (d, $J = 8.4$ Hz, 1H, H-2), 3.53

(m, 4H, H-piper.), 3.42 (t, $J = 6.7$ Hz, 2H, H-1′), 2.96 (dd, $J = 8.4$, 3.2 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.66 (m, 1H, $H_{(eq)}$-10), 2.53 (m, 4H, H-piper.), 2.37 (t, $J = 6.6$ Hz, 2H, H-4′), 2.15 (s, 3H, −OCOCH_3), 2.09–1.98 (m, 1H, H-11), 1.76 (d, $J = 1.4$ Hz, 3H, −CH_3), 1.49 (m, 4H, H-2′, H-3′), 1.08 (dd, $J = 12$, 4.6 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 7.0$ Hz, 3H, −CH_3). Anal. Calcd for $C_{27}H_{36}O_4N_4$: 67.48% C, 7.55% H, 11.66% N; found: 67.16% C, 7.57% H, 11.43% N.

*5.1.5.4. 4-[4-(4-Phenylpiperazin-1-yl)butyl]-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**21**).* Yield 78%, m.p. 111.8–112 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.26 (m, 2H, H-arom.), 6.95 (m, 3H, H-arom.), 5.77 (s, 1H, H-9), 3.86 (d, $J = 8.4$ Hz, 1H, H-2), 3.42 (t, $J = 6.6$ Hz, 2H, H-1′), 3.19 (m, 4H, H-piper.), 2.95 (dd, $J = 8.4$, 3.2 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.69 (m, 1H, $H_{(eq)}$-10), 2.58 (m, 4H, H-piper.), 2.38 (t, $J = 6.7$ Hz, 2H, H-4′), 2.15 (s, 3H, −OCOCH_3), 2.09–1.97 (m, 1H, H-11), 1.76 (d, $J = 1.8$ Hz, 3H, −CH_3), 1.49 (m, 4H, H-2′, H-3′), 1.08 (dd, $J = 12$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 7.0$ Hz, 3H, −CH_3). Anal. Calcd for $C_{28}H_{37}O_4N_3$: 70.12% C, 7.78% H, 8.76% N; found: 69.74% C, 7.53% H, 8.78% N.

*5.1.5.5. 4-{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**22**).* Yield 80%, m.p. 100.8–101 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.90 (m, 4H, H-arom.), 5.77 (s, 1H, H-9), 3.87 (d, $J = 8.4$ Hz, 1H, H-2), 3.42 (t, $J = 6.7$ Hz, 2H, H-1′), 3.11 (m, 4H, H-piper.), 2.96 (dd, $J = 8.2$, 3.0 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.66 (m, 1H, $H_{(eq)}$-10), 2.57 (m, 4H, H-piper.), 2.37 (t, $J = 6.7$ Hz, 2H, H-4′), 2.15 (s, 3H, −OCOCH_3), 2.09–1.98 (m, 1H, H-11), 1.76 (d, $J = 1.4$ Hz, 3H, −CH_3), 1.49 (m, 4H, H-2′, H-3′), 1.08 (dd, $J = 12$, 4.6 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 7.0$ Hz, 3H, −CH_3). Anal. Calcd for $C_{28}H_{36}O_4N_3F$: 67.58% C, 7.29% H, 8.44% N; found: 67.80% C, 7.23% H, 8.33% N.

*5.1.5.6. 4-[4-(4-Benzylpiperazin-1-yl)butyl]-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**23**).* Yield 80%, m.p. 103.5–104.8 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.30 (m, 5H, H-arom.), 5.75 (s, 1H, H-9), 3.85 (d, $J = 8.4$ Hz, 1H, H-2), 3.50 (s, 2H, H-5′), 3.39 (t, $J = 6.8$ Hz, 2H, H-1′), 2.94 (dd, $J = 8.4$, 3.2 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.65 (m, 1H, $H_{(eq)}$-10), 2.46 (m, 8H, H-piper.), 2.31 (t, $J = 7.0$ Hz, 2H, H-4′), 2.14 (s, 3H, −OCOCH_3), 2.09–1.97 (m, 1H, H-11), 1.75 (d, $J = 1.4$ Hz, 3H, −CH_3), 1.44 (m, 4H, H-2′, H-3′), 1.08 (dd, $J = 12$, 4.6 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, −CH_3). Anal. Calcd for $C_{29}H_{39}O_4N_3$: 70.56% C, 7.96% H, 8.51% N; found: 70.79% C, 7.79% H, 8.59% N.

*5.1.5.7. 4-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**24**).* Yield 73%, m.p. 209–210 °C. ^{1}H NMR (400 MHz, DMSO) δ: 10.75 (s, 1H, HCl), 7.04–6.89 (m, 4H, H-arom.), 5.31 (m, 4H, H-piper.), 3.79 (s, 3H, −OCH_3), 3.47 (d, $J = 9.2$ Hz, 2H, H-1′), 3.34 (m, 2H, H-4′), 3.08 (m, 5H, H-6, H-piper.), 2.80 (d, $J = 9.2$ Hz, 1H, H-7), 2.45 (m, 1H, H-2), 2.20 (m, 1H, H-9), 2.11–2.06 (m, 1H, $H_{(eq)}$-10), 1.92 (m, 1H, H-11), 1.80–1.75 (m, 1H, H-9), 1.62 (m, 2H, H-3′), 1.43 (m, 2H, H-2′), 1.20 (s, 3H, −OCOCH_3), 1.05 (dd, $J = 13.2$, 4.8 Hz, 1H, $H_{(ax)}$-10), 0.87 (d, $J = 6.8$ Hz, 3H, −CH_3). Anal. Calcd for $C_{27}H_{37}O_4N_3 \cdot HCl \cdot 3H_2O$: 58.10% C, 7.58% H, 7.53% N; found: 58.76% C, 6.99% H, 7.75% N.

*5.1.5.8. 4-{4-[4-(2-Pyrimidyl)piperazin-1-yl]butyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**25**).* Yield 67%, m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, $J = 4.8$ Hz, 2H, H-arom.), 6.45 (t, $J = 4.6$ Hz, 1H, H-arom.), 3.80 (m, 4H, H-piper.), 3.45 (m, 2H, H-1′), 3.10 (dd, $J = 9.2$, 2.8 Hz, 1H, H-6), 2.69 (m, 1H, H-7), 2.65 (d, $J = 9.2$ Hz, 1H, H-2), 2.46 (t, $J = 4.6$ Hz, 4H, H-piper.), 2.34 (t, $J = 7.0$ Hz, 2H, H-4′), 2.16 (m, 1H, H-9), 1.95 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.48 (m, 4H, H-2′, H-3′), 1.31 (s, 3H, −CH_3), 1.09 (dd, $J = 14$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.97 (d, $J = 6.8$ Hz, 3H, −CH_3). Anal. Calcd for $C_{24}H_{33}O_3N_5 \cdot 1/2H_2O$: 64.26% C, 7.64% H, 15.61% N; found: 64.34% C, 7.38% H, 14.69% N.

*5.1.5.9. 4-{4-[4-(2-Pyridyl)piperazin-1-yl]butyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**26**).* Yield 75%, m.p. 125.8–126.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (m, 1H, H-arom.), 7.47 (m, 1H, H-arom.), 6.61 (m, 2H, H-arom.), 3.50 (m, 6H, H-1′, H-piper.), 3.11 (dd, $J = 9.6$, 2.8 Hz, 1H, H-6), 2.72 (m, 1H, H-7), 2.67 (d, $J = 9.2$ Hz, 1H, H-2), 2.53 (m, 4H, H-piper.), 2.38 (t, $J = 7.0$ Hz, 2H, H-4′), 2.18 (m, 1H, H-9), 1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.51 (m, 4H, H-2′, H-3′), 1.33 (s, 3H, −CH_3), 1.11 (dd, $J = 14.0$, 4.4 Hz, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 7.2$ Hz, 3H, −CH_3). Anal. Calcd for $C_{25}H_{34}O_3N_4$: 68.47% C, 7.81% H, 12.77% N; found: 68.70% C, 7.77% H, 12.66% N.

*5.1.5.10. 4-[4-(4-Phenylpiperazin-1-yl)butyl]-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**27**).* Yield 78%, m.p. 159.8–160.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (m, 2H, H-arom.), 6.92 (d, $J = 8.0$ Hz, 2H, H-arom.), 6.84 (t, $J = 7.2$ Hz, 1H, H-arom.), 3.49 (m, 2H, H-1′), 3.19 (t, $J = 4.6$ Hz, 4H, H-piper.), 3.11 (dd, $J = 9.2$, 3.2 Hz, 1H, H-6), 2.72 (d, $J = 2.8$ Hz, 1H, H-7), 2.66 (d, $J = 9.2$ Hz, 1H, H-2), 2.58 (t, $J = 4.6$ Hz, 4H, H-piper.), 2.38 (t, $J = 7.2$ Hz, 2H, H-4′), 2.18 (m, 1H, H-9), 1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.50 (m, 4H, H-2′, H-3′), 1.33 (s, 3H, −CH_3), 1.11 (dd, $J = 4.8$, 13.6 Hz, 1H, $H_{(ax)}$-10), 0.99 (d, $J = 7.2$ Hz, 3H, −CH_3). Anal. Calcd for $C_{26}H_{35}O_3N_3$: 71.37% C, 8.06% H, 9.60% N; found: 70.89% C, 8.36% H, 9.56% N.

*5.1.5.11. 4-{4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}] undecane-3,5,8-trione (**28**).* Yield 80%, m.p. 110.8–111.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94 (m, 2H, H-arom.), 6.86 (m, 2H, H-arom.), 3.49 (m, 2H, H-1′), 3.11 (m, 5H, H-6, H-piper.), 2.71 (m, 1H, H-7), 2.66 (d, $J = 9.6$ Hz, 1H, H-2), 2.57 (t, $J = 4.8$ Hz, 4H, H-piper.), 2.38 (t, $J = 7.2$ Hz, 2H, H-4′), 2.18 (m, 1H, H-9), 1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.50 (m, 4H, H-2′, H-3′), 1.33 (s, 3H, −CH_3), 1.11 (dd, $J = 14$, 4.4 Hz, 1H,

$H_{(ax)}$-10), 0.99 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{26}H_{34}O_3N_3F$: 68.55% C, 7.52% H, 9.22% N; found: 68.39% C, 7.80% H, 9.30% N.

*5.1.5.12. 4-[4-(4-Benzylpiperazin-1-yl)butyl]-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**29**).* Yield 89%, m.p. 263.5–264.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (m, 2H, H-arom.), 7.47 (m, 3H, H-arom.), 4.19 (m, 2H, H-4′), 3.96 (m, 4H, H-piper.), 3.60–3.40 (m, 6H, H-1′, H-5′, H-piper.), 3.22 (m, 1H, H-6), 3.10 (m, 2H, H-piper.), 2.70 (m, 1H, H-7), 2.19 (m, 1H, H-9), 1.98 (m, 2H, H-9, $H_{(eq)}$-10), 1.77 (m, 1H, H-11), 1.60 (m, 4H, H-2′, H-3′), 1.33 (s, 3H, $-CH_3$), 1.14 (dd, $J = 14$, 4.0 Hz, 1H, $H_{(ax)}$-10), 0.99 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{27}H_{37}O_3N_3 \cdot HCl \cdot 2½H_2O$: 60.83% C, 7.75% H, 7.88% N; found: 60.93% C, 7.69% H, 7.89% N.

*5.1.5.13. 4-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**30**).* Yield 75%, m.p. 165–166 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 13.49 (s, 1H, HCl), 7.99 (m, 1H, H-arom.), 7.40 (t, $J = 7.9$ Hz, 1H, H-arom.), 7.06 (m, 2H, H-arom.), 5.85 (s, 1H, H-9), 4.81 (m, 2H, H-3′), 4.03–3.82 (m, 6H, $-OCH_3$, H-2, H-piper.), 3.78–3.4 (m, 6H, H-1′, H-piper.), 3.09 (m, 3H, H-6, H-piper.), 2.88–2.56 (m, 2H, H-7, $H_{(eq)}$-10), 2.14–1.99 (m, 6H, $-OCOCH_3$, H-11, H-2′), 1.84–1.79 (m, 3H, $-CH_3$), 1.11–1.03 (dd, $J = 11.6$, 5 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{28}H_{37}O_5N_3 \cdot 2HCl$: 59.15% C, 6.91% H, 7.39% N; found: 59.56% C, 6.73% H, 7.44% N.

*5.1.5.14. 4-{3-[4-(2-Pyrimidyl)piperazin-1-yl]propyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**31**).* Yield 78%, oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.30 (d, $J = 4.8$ Hz, 2H, H-arom.), 6.47 (t, $J = 4.7$ Hz, 1H, H-arom.), 5.77 (s, 1H, H-9), 3.91–3.74 (m, 5H, H-2, H-piper.), 3.42 (t, $J = 6.7$ Hz, 2H, H-1′), 2.96 (dd, $J = 8.4$, 3.2 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.72–2.61 (m, 1H, $H_{(eq)}$-10), 2.47 (t, $J = 5.1$ Hz, 4H, H-piper.), 2.35 (t, $J = 6.8$ Hz, 2H, H-3′), 2.15 (s, 3H, $-OCOCH_3$), 2.12–1.94 (m, 1H, H-11), 1.76 (d, $J = 1.4$ Hz, 3H, $-CH_3$), 1.58–1.38 (m, 2H, H-2′), 1.08 (dd, $J = 12$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{25}H_{33}O_4N_5 \cdot 1/2H_2O$: 63.01% C, 7.19% H, 14.69% N; found: 63.28% C, 7.26% H, 13.71% N.

*5.1.5.15. 4-{3-[4-(2-Pyridyl)piperazin-1-yl]propyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**32**).* Yield 80%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, $J = 3.6$ Hz, 1H, H-arom.), 7.47 (m, 1H, H-arom.), 6.61 (m, 2H, H-arom.), 5.77 (s, 1H, H-9), 3.86 (d, $J = 8.0$ Hz, 1H, H-2), 3.53–3.46 (m, 6H, H-1′, H-piper.), 2.97 (dd, $J = 8.4$, 3.2 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.72–2.66 (m, 1H, $H_{(eq)}$-10), 2.50 (t, $J = 4.8$ Hz, 4H, H-piper.), 2.34 (t, $J = 7.2$ Hz, 2H, H-3′), 2.15 (s, 3H, $-OCOCH_3$), 2.03 (m, 1H, H-11), 1.77 (m, 3H, $-CH_3$), 1.70 (m, 2H, H-2′), 1.08 (dd, $J = 12$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.88 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{26}H_{34}O_4N_4 \cdot 1/2H_2O$: 65.66% C, 7.34% H, 11.78% N; found: 65.01% C, 7.40% H, 11.28% N.

*5.1.5.16. 4-[3-(4-Phenylpiperazin-1-yl)propyl]-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**33**).* Yield 78%, m.p. 95–95.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (t, $J = 8.0$ Hz, 2H, H-arom.), 6.92 (d, $J = 8.4$ Hz, 2H, H-arom.), 6.85 (t, $J = 7.2$ Hz, 1H, H-arom.), 5.77 (s, 1H, H-9), 3.86 (d, $J = 8.4$ Hz, 1H, H-2), 3.47 (t, $J = 7.2$ Hz, 2H, H-1′), 3.18 (t, $J = 4.8$ Hz, 4H, H-piper.), 2.96 (dd, $J = 8.4$, 2.8 Hz, 1H, H-6), 2.75 (m, 1H, H-7), 2.69 (m, 1H, $H_{(eq)}$-10), 2.56 (t, $J = 4.6$ Hz, 4H, H-piper.), 2.31 (t, $J = 7.2$ Hz, 2H, H-3′), 2.15 (s, 3H, $-OCOCH_3$), 2.03 (m, 1H, H-11), 1.77 (s, 3H, $-CH_3$), 1.70 (m, 2H, H-2′), 1.08 (dd, $J = 12$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{27}H_{35}O_4N_3$: 69.65% C, 7.58% H, 9.03% N; found: 69.47% C, 7.54% H, 9.12% N.

*5.1.5.17. 4-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**34**).* Yield 88%, m.p. 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.96 (m, 2H, H-arom.), 6.82 (m, 2H, H-arom.), 5.78 (s, 1H, H-9), 3.88 (d, $J = 8.3$ Hz, 1H, H-2), 3.47 (t, $J = 7.1$ Hz, 2H, H-1′), 3.10 (s, 4H, H-piper.), 2.95 (dd, $J = 8.0$, 2.7 Hz, 1H, H-6), 2.75 (s, 1H, H-7), 2.69 (m, 1H, $H_{(eq)}$-10), 2.58 (m, 4H, H-piper.), 2.35 (t, $J = 7.0$ Hz, 2H, H-3′), 2.15 (s, 3H, $-OCOCH_3$), 2.01 (m, 1H, H-11), 1.77 (s, 3H, $-CH_3$), 1.70 (m, 2H, H-2′), 1.08 (dd, $J = 12$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{27}H_{34}O_4N_3F$: 67.06% C, 7.09% H, 8.69% N; found: 67.03% C, 6.87% H, 8.82% N.

*5.1.5.18. 4-[3-(4-Benzylpiperazin-1-yl)propyl]-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**35**).* Yield 89%, m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (m, 4H, H-arom.), 7.26–7.23 (m, 1H, H-arom.), 5.75 (s, 1H, H-9), 3.83 (d, $J = 8.4$ Hz, 1H, H-2), 3.50 (s, 2H, H-4′), 3.40 (t, $J = 7.12$ Hz, 2H, H-1′), 2.93 (dd, $J = 8.4$, 2.8 Hz, 1H, H-6), 2.74 (m, 1H, H-7), 2.68 (m, 1H, $H_{(eq)}$-10), 2.45 (m, 8H, H-piper.), 2.29 (t, $J = 7.2$ Hz, 2H, H-3′), 2.14 (s, 3H, $-OCOCH_3$), 2.02 (m, 1H, H-11), 1.75 (s, 3H, $-CH_3$), 1.64 (m, 2H, H-2′), 1.08 (dd, $J = 12$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.88 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{28}H_{37}O_4N_3$: 70.12% C, 7.78% H, 8.76% N; found: 70.30% C, 7.82% H, 8.88% N.

*5.1.5.19. 4-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**36**).* Yield 87%, m.p. 106–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 (m, 4H, H-arom.), 3.83 (s, 3H, $-OCH_3$), 3.52 (t, $J = 7.2$ Hz, 2H, H-1′), 3.06 (m, 5H, H-6, H-piper.), 2.68 (m, 1H, H-7), 2.63 (m, 5H, H-2, H-piper.), 2.36 (t, $J = 7.0$ Hz, 2H, H-3′), 2.15 (m, 1H, H-9), 1.94 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.70 (m, 2H, H-2′), 1.30 (s, 3H, $-CH_3$), 1.08 (dd, $J = 4.8$, 13.6 Hz, 1H, $H_{(ax)}$-10), 0.96 (m, 3H, $-CH_3$). Anal. Calcd for $C_{26}H_{35}O_4N_3$: 68.85% C, 7.78% H, 9.26% N; found: 69.05% C, 8.04% H, 9.20% N.

*5.1.5.20. 4-{3-[4-(2-Pyrimidyl)piperazin-1-yl]propyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**37**).* Yield 85%, m.p. 165.8–166.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, $J = 4.8$ Hz, 2H, H-arom.), 6.44 (t, $J = 4.7$ Hz, 1H, H-arom.), 3.77 (t, $J = 4.6$ Hz, 4H, H-piper.), 3.52 (t, $J = 7.0$ Hz, 2H, H-1′), 3.10 (dd, $J = 3.2$, 9.6 Hz, 1H, H-6), 2.69 (m, 1H, H-7), 2.65 (d, $J = 9.6$ Hz, 1H, H-2), 2.43 (t, $J = 5.0$ Hz, 4H, H-piper.), 2.32 (t, $J = 6.8$ Hz, 2H, H-3′), 2.16 (m, 1H, H-9), 1.95 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.70 (m, 2H, H-2′), 1.31 (s, 3H, $-CH_3$), 1.10 (dd, $J = 13.6$, 4.8 Hz, 1H, $H_{(ax)}$-10), 0.97 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{23}H_{31}O_3N_5$: 64.92% C, 7.34% H, 16.46% N; found: 64.42% C, 7.24% H, 15.96% N.

*5.1.5.21. 4-{3-[4-(2-Pyridyl)piperazin-1-yl]propyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**38**).* Yield 89%, m.p. 93.3–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (m, 1H, H-arom.), 7.46 (m, 1H, H-arom.), 6.61 (m, 2H, H-arom.), 3.54 (m, 6H, H-1′, H-piper.), 3.12 (dd, $J = 9.2$, 3.2 Hz, 1H, H-6), 2.72 (m, 1H, H-7), 2.67 (d, $J = 9.6$ Hz, 1H, H-2), 2.52 (t, $J = 4.6$ Hz, 4H, H-piper.), 2.36 (t, $J = 7.0$ Hz, 2H, H-3′), 2.18 (m, 1H, H-9), 1.98 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.74 (m, 2H, H-2′), 1.33 (s, 3H, $-CH_3$), 1.11 (dd, $J = 13.6$, 4.8 Hz, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{24}H_{32}O_3N_4$: 67.90% C, 7.60% H, 13.20% N; found: 66.83% C, 7.72% H, 13.03% N.

*5.1.5.22. 4-[3-(4-Phenylpiperazin-1-yl)propyl]-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**39**).* Yield 86%, m.p. 132–132.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (t, $J = 7.9$ Hz, 2H, H-arom.), 6.91 (d, $J = 8.4$ Hz, 2H, H-arom.), 6.84 (t, $J = 7.2$ Hz, 1H, H-arom.), 3.54 (t, $J = 7.2$ Hz, 2H, H-1′), 3.18 (t, $J = 4.8$ Hz, 4H, H-piper.), 3.11 (dd, $J = 3.2$, 9.2 Hz, 1H, H-6), 2.71 (m, 1H, H-7), 2.65 (d, $J = 9.2$ Hz, 1H, C2–H), 2.57 (t, $J = 4.8$ Hz, 4H, H-piper.), 2.36 (t, $J = 7.0$ Hz, 2H, H-3′), 2.17 (m, 1H, H-9), 1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.73 (m, 2H, H-2′), 1.33 (s, 3H, $-CH_3$), 1.10 (dd, $J = 13.2$, 5.2 Hz, 1H, $H_{(ax)}$-10), 0.99 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{25}H_{33}O_3N_3$: 70.89% C, 7.85% H, 9.92% N; found: 70.503% C, 7.78% H, 10.03% N.

*5.1.5.23. 4-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**40**).* Yield 80%, oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.95 (m, 2H, H-arom.), 6.87 (m, 2H, H-arom.), 3.55 (t, $J = 7.2$ Hz, 2H, H-1′), 3.12 (m, 5H, H-6, H-piper.), 2.72 (m, 1H, H-7), 2.67 (d, $J = 9.2$ Hz, 1H, C2–H), 2.59 (m, 4H, H-piper.), 2.37 (t, $J = 7.0$ Hz, 2H, H-3′), 2.19 (m, 1H, H-9), 1.96 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.74 (m, 2H, H-2′), 1.34 (s, 3H, $-CH_3$), 1.12 (dd, $J = 13.2$, 4.8 Hz, 1H, $H_{(ax)}$-10), 0.99 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{25}H_{32}O_3N_3F \cdot 1½H_2O$: 64.08% C, 7.53% H, 8.97% N; found: 64.27% C, 6.91% H, 8.93% N.

*5.1.5.24. 4-[3-(4-Benzylpiperazin-1-yl)propyl]-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**41**).* Yield 78%, m.p. 278–279 °C. ^{1}H NMR (400 MHz, DMSO) δ: 11.75 (s, 1H, HCl), 7.60 (s, 2H, H-arom.), 7.45 (s, 3H, H-arom.), 4.32 (m, 2H, H-3′), 3.54 (m, 8H, H-1′, H-4′, H-piper.), 3.36 (m, 3H, H-6, H-piper.), 2.95 (m, 2H, H-piper.), 2.79 (m, 1H, H-2), 2.44 (m, 1H, H-7), 2.19 (m, 1H, H-9), 2.06 (d, $J = 18.8$ Hz, 1H, H-9), 1.88 (m, 4H, $H_{(eq)}$-10, H-11, H-2′), 2.00 (s, 3H, $-CH_3$), 1.03 (m, 1H, $H_{(ax)}$-10), 0.87 (d, $J = 4.4$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{26}H_{35}O_3N_3 \cdot HCl \cdot 2½H_2O$: 60.16% C, 7.96% H, 8.09% N; found: 60.51% C, 7.29% H, 8.09% N.

*5.1.5.25. 4-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**42**).* Yield 85%, m.p. 165.8–166.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.47 (s, 1H, HCl), 8.20 (d, $J = 7.6$ Hz, 1H, H-arom.), 7.46 (t, $J = 8.0$ Hz, 1H, H-arom.), 7.06 (m, 2H, H-arom.), 5.86 (s, 1H, H-9), 5.03 (m, 2H, H-piper.), 4.40 (m, 2H, H-piper.), 4.16 (m, 2H, H-1′), 4.07 (s, 3H, $-OCH_3$), 3.91 (d, $J = 8.0$ Hz, 1H, H-2), 3.68–3.41 (m, 6H, H-3′, H-piper.), 3.04 (dd, $J = 8.0$, 3.2 Hz, 1H, H-6), 2.76 (m, 1H, H-7), 2.69 (t, $J = 11.6$ Hz, 1H, $H_{(eq)}$-10), 2.32 (m, 2H, H-2′), 2.15 (s, 3H, $-OCOCH_3$), 2.05 (m, 1H, H-11), 1.81 (s, 3H, $-CH_3$), 1.11 (dd, $J = 12$, 4.4 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{28}H_{37}O_6N_3 \cdot 2HCl \cdot 13/4H_2O$: 54.59% C, 7.06% H, 6.82% N; found: 54.63% C, 7.30% H, 6.85% N.

*5.1.5.26. 4-{3-[4-(2-Pyridyl)piperazin-1-yl]propoxy}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**43**).* Yield 88%, m.p. 165–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.25 (s, 1H, HCl), 8.22 (d, $J = 5.2$ Hz, 1H, H-arom.), 8.01 (t, $J = 7.0$ Hz, 1H, H-arom.), 7.10–7.03 (m, 2H, H-arom.), 5.85 (s, 1H, H-9), 4.59 (m, 2H, H-piper.), 4.26 (m, 2H, H-piper.), 4.15 (m, 2H, H-1′), 3.91 (d, $J = 8.4$ Hz, 1H, H-2), 3.76 (m, 2H, H-piper.), 3.50–3.40 (m, 2H, H-3′), 3.27 (m, 2H, H-piper.), 3.04 (m, 1H, H-6), 2.76 (s, 1H, H-7), 2.69 (t, $J = 10.6$ Hz, 1H, $H_{(eq)}$-10), 2.32 (m, 2H, H-2′), 2.15 (s, 3H, $-OCOCH_3$), 2.05 (m, 1H, H-11), 1.81 (s, 3H, $-CH_3$), 1.11 (dd, $J = 12$, 4.8 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{26}H_{34}O_5N_4 \cdot 2HCl \cdot 2H_2O$: 52.79% C, 6.82% H, 9.47% N; found: 52.50% C, 6.79% H, 9.57% N.

*5.1.5.27. 4-[3-(4-Phenylpiperazin-1-yl)propoxy]-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**44**).* Yield 87%, m.p. 199–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.40 (s, 1H, HCl), 7.90 (d, $J = 7.2$ Hz, 2H, H-arom.), 7.53 (m, 3H, H-arom.), 5.86 (s, 1H, H-9), 4.80 (m, 2H, H-piper.), 4.35–4.22 (m, 4H, H-1′, H-piper.), 3.91 (d, $J = 8.0$ Hz, 1H, H-2), 3.75 (m, 2H, H-piper.), 3.67 (m, 2H, H-3′), 3.50–3.45 (m, 2H, H-piper.), 3.06 (m, 1H, H-6), 2.76 (s, 1H, H-7), 2.69 (t, $J = 10.6$ Hz, 1H, $H_{(eq)}$-10), 2.29 (m, 2H, H-2′), 2.14 (s, 3H, $-OCOCH_3$), 2.06 (m, 1H, H-11), 1.81 (s, 3H, $-CH_3$), 1.11 (dd, $J = 12$, 4.8 Hz, 1H, $H_{(ax)}$-10), 0.89 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{27}H_{35}O_5N_3 \cdot 2HCl \cdot 1/3H_2O$: 57.86% C, 6.77% H, 7.50% N; found: 57.40% C, 6.80% H, 7.38% N.

*5.1.5.28. 4-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propoxy}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**45**).* Yield 86%, m.p. 103–104 °C. ^{1}H NMR

(400 MHz, $CDCl_3$) δ: 6.96 (m, 2H, H-arom.), 6.86 (m, 2H, H-arom.), 5.83 (s, 1H, H-9), 4.06 (m, 2H, H-1′), 3.87 (d, $J = 8.4$ Hz, 1H, H-2), 3.10 (t, $J = 4.8$ Hz, 4H, H-piper.), 2.95 (dd, $J = 8.4$, 3.2 Hz, 1H, H-6), 2.77 (m, 1H, H-7), 2.71 (m, 1H, $H_{(eq)}$-10), 2.60 (m, 6H, H-3′, H-piper.), 2.15 (s, 3H, $-OCOCH_3$), 2.04 (m, 1H, H-11), 1.88 (m, 2H, H-2′), 1.80 (s, 3H, $-CH_3$), 1.09 (dd, $J = 12$, 4.8 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 7.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{27}H_{34}O_5N_3F$: 64.91% C, 6.86% H, 8.41% N; found: 64.93% C, 6.93% H, 8.46% N.

*5.1.5.29. 4-{3-[4-(2-Fluorophenyl)piperazin-1-yl]propoxy}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**46**).* Yield 80%, m.p. 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.13 (s, 1H, HCl), 7.53 (m, 1H, H-arom.), 7.27–7.14 (m, 3H, H-arom.), 5.85 (s, 1H, H-9), 4.17 (m, 4H, H-1′, H-piper.), 3.92 (d, $J = 7.2$ Hz, 1H, H-2), 3.69 (m, 6H, H-piper.), 2.35 (m, 2H, H-3′), 3.04 (m, 1H, H-6), 2.76 (s, 1H, H-7), 2.71 (m, 1H, $H_{(eq)}$-10), 2.34 (m, 2H, H-2′), 2.14 (s, 3H, $-OCOCH_3$), 2.05 (m, 1H, H-11), 1.81 (s, 3H, $-CH_3$), 1.10 (m, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 6.4$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{27}H_{34}O_5N_3F \cdot 2HCl \cdot 1/2H_2O$: 55.71% C, 6.41% H, 7.23% N; found: 55.67% C, 6.00% H, 7.13% N.

*5.1.5.30. 4-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propoxy}-8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**47**).* Yield 82%, m.p. 149–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.26 (s, 1H, HCl), 7.66 (s, 1H, H-arom.), 7.54 (d, $J = 7.6$ Hz, 1H, H-arom.), 7.42 (t, $J = 7.6$ Hz, 1H, H-arom.), 7.33 (d, $J = 7.6$ Hz, 1H, H-arom.), 5.86 (s, 1H, H-9), 4.49 (m, 2H, H-piper.), 4.20 (m, 2H, H-piper.), 3.93 (m, 2H, H-1′), 3.80–3.40 (m, 7H, H-2, H-3′, H-piper.), 3.05 (m, 1H, H-6), 2.76 (s, 1H, H-7), 2.70 (m, 1H, $H_{(eq)}$-10), 2.32 (m, 2H, H-2′), 2.14 (s, 3H, $-OCOCH_3$), 2.06 (m, 1H, H-11), 1.81 (s, 3H, $-CH_3$), 1.11 (dd, $J = 12$, 4.0 Hz, 1H, $H_{(ax)}$-10), 0.90 (d, $J = 6.4$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{27}H_{34}O_5N_3Cl \cdot 2HCl \cdot 1H_2O$: 53.43% C, 6.31% H, 7.00% N; found: 53.53% C, 6.56% H, 7.27% N.

*5.1.5.31. 4-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**48**).* Yield 85%, m.p. 164–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.20 (s, 1H, HCl), 8.20 (d, $J = 7.6$ Hz, 1H, H-arom.), 7.46 (t, $J = 7.8$ Hz, 1H, H-arom.), 7.06 (m, 2H, H-arom.), 5.05 (m, 2H, H-1′), 3.35 (m, 4H, H-piper.), 4.07 (s, 3H, $-OCH_3$), 3.70–3.60 (m, 6H, H-3′, H-piper.), 3.31 (m, 1H, H-6), 2.80 (d, $J = 8.4$ Hz, 1H, H-2), 2.72 (s, 1H, H-7), 2.23 (m, 1H, H-9), 2.21 (m, 2H, H-2′), 2.05–1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.33 (s, 3H, $-CH_3$), 1.14 (dd, $J = 14$, 4.4 Hz, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{26}H_{35}O_5N_3 \cdot 2HCl$: 57.56% C, 6.87% H, 7.46% N; found: 57.38% C, 6.75% H, 7.68% N.

*5.1.5.32. 4-{3-[4-(2-Pyridyl)piperazin-1-yl]propoxy}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**49**).* Yield 60%, m.p. 168–170 °C. ^{1}H NMR (400 MHz, DMSO) δ: 10.61 (s, 1H, HCl), 8.14 (m, 1H, H-arom.), 7.84 (m, 1H, H-arom.), 7.19 (m, 1H, H-arom.), 6.90 (m, 1H, H-arom.), 4.43 (m, 2H, H-1′), 4.01 (m, 4H, H-piper.), 3.59 (m, 2H, H-3′), 3.47 (m, 2H, H-piper.), 3.30 (m, 2H, H-piper.), 3.11 (m, 2H, H-6, H-7), 2.70 (m, 1H, H-2), 2.01 (m, 5H, H-9, H-11, H-2′), 1.83 (m, 1H, $H_{(eq)}$-10), 1.17 (s, 3H, $-CH_3$), 0.86 (m, 4H, $H_{(ax)}$-10, $-CH_3$). Anal. Calcd for $C_{24}H_{32}O_4N_4 \cdot 2HCl$: 56.14% C, 6.67% H, 10.91% N; found: 56.23% C, 6.73% H, 10.63% N.

*5.1.5.33. 4-[3-(4-Phenylpiperazin-1-yl)propoxy]-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**50**).* Yield 78%, m.p. 189–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.99 (s, 1H, HCl), 7.95 (m, 2H, H-arom.), 7.54 (m, 3H, H-arom.), 4.85 (m, 2H, H-1′), 4.04 (m, 4H, H-piper.), 3.80 (m, 2H, H-3′), 3.67 (m, 4H, H-piper.), 3.32 (m, 1H, H-6), 2.81 (m, 1H, H-2), 2.72 (m, 1H, H-7), 2.21 (m, 3H, H-9, H-2′), 2.06 (m, 2H, H-9, H-11), 2.00 (m, 1H, $H_{(eq)}$-10), 1.33 (s, 3H, $-CH_3$), 1.15 (dd, $J = 13.6$, 4.0 Hz, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{25}H_{33}O_4N_3 \cdot 2HCl$: 58.59% C, 6.88% H, 8.20% N; found: 58.60% C, 6.88% H, 8.02% N.

*5.1.5.34. 4-{3-[4-(4-Fluorophenyl)piperazin-1-yl]propoxy}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**51**).* Yield 61%, m.p. 175–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.96 (s, 1H, HCl), 8.00 (m, 2H, H-arom.), 7.22 (m, 2H, H-arom.), 4.87 (m, 2H, H-1′), 4.41–4.28 (m, 4H, H-piper.), 3.83–3.67 (m, 6H, H-3′, H-piper.), 3.33 (m, 1H, H-6), 2.57 (m, 1H, H-2), 2.62 (m, 1H, H-7), 2.21 (m, 2H, H-9, H-2′), 2.00 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.33 (s, 3H, $-CH_3$), 1.14 (m, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 5.2$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{25}H_{32}O_4N_3F \cdot 2HCl \cdot 1½H_2O$: 54.00% C, 6.66% H, 7.56% N; found: 53.83% C, 6.20% H, 7.31% N.

*5.1.5.35. 4-{3-[4-(2-Fluorophenyl)piperazin-1-yl]propoxy}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**52**).* Yield 85%, m.p. 136–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.79 (s, 1H, HCl), 7.34 (m, 1H, H-arom.), 7.14 (m, 3H, H-arom.), 4.30 (m, 2H, H-1′), 4.05–3.95 (m, 2H, H-piper.), 3.68 (m, 2H, H-3′), 3.60–3.46 (m, 6H, H-piper.), 3.28 (m, 1H, H-6), 2.79 (m, 1H, H-2), 2.72 (s, 1H, H-7), 2.36 (m, 1H, H-9), 2.21 (m, 2H, H-2′), 2.05–1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.33 (s, 3H, $-CH_3$), 1.18–1.13 (m, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for $C_{25}H_{32}O_4N_3F \cdot 2HCl \cdot 1/2H_2O$: 55.66% C, 6.45% H, 7.79% N; found: 55.70% C, 6.13% H, 8.05% N.

*5.1.5.36. 4-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propoxy}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**53**).* Yield 83%, m.p. 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.90 (s, 1H, HCl), 7.54 (s, 1H, H-arom.), 7.37 (m, 3H, H-arom.), 4.35 (m, 4H, H-1′, H-piper.), 3.19–3.52 (m, 8H, H-3′, H-piper.), 3.30 (m, 1H, H-6), 2.79 (d, $J = 8.8$ Hz, 1H, H-2), 2.71 (s, 1H, H-7), 2.32 (m, 1H, H-9), 2.18 (m, 2H, H-2′), 2.06–1.97 (m, 3H, H-9, $H_{(eq)}$-10, H-11), 1.33 (s, 3H, $-CH_3$), 1.15 (dd, $J = 14.4$, 3.6 Hz, 1H, $H_{(ax)}$-10), 1.00 (d, $J = 6.8$ Hz, 3H, $-CH_3$). Anal. Calcd for

$C_{25}H_{32}O_4N_3Cl \cdot 2HCl$: 54.90% C, 6.27% H, 7.68% N; found: 54.95% C, 6.07% H, 7.71% N.

5.2. Serotonin 5-HT_{1A} and 5-HT_{2A} binding assays

Radioligand studies with native 5-HT_{1A} and 5-HT_{2A} receptors were conducted according to the methods described previously [22]. Briefly, the following were used: for 5-HT_{1A} assays – rat hippocampal membranes, [^{3}H]-8-OH-DPAT (170 Ci/mmol, NEN Chemicals) and 5-HT (10 μM) for non-specific binding; for 5-HT_{2A} assays – [^{3}H]-ketanserin (88.0 Ci/mmol, NEN Chemicals) and methysergide (1 μM) for non-specific binding.

5.3. Pharmacology

The experiments were carried out on male Albino Swiss mice (20–24 g) kept at a room temperature of 18–20 °C on a natural day–night cycle, with free access to food and water. Permission to carry out animal tests and experiments was issued by the Ethical Board at the Medical University of Lublin. The investigated compounds were administered intraperitoneally (ip) as suspensions in 1% Tween 80 at a constant volume of 0.1 mL/10 g body weight of mice. Control animals received the some volume of a solvent. The compounds were administered in doses equivalent to 0.1 or 0.05 of their LD_{50}. Each experimental group consisted of eight animals.

Motor coordination in a ''chimney test'' was measured according to the method of Boissier et al. [12], at 30 min after administration of the investigated compounds in a dose equivalent to 0.1 of their LD_{50}. The mice had to climb up backwards in a plastic tube (inner diameter: 3 cm, length: 25 cm). The mice that were unable to perform the three tasks within 60 s were considered to display motor impairment. The motor impairment was quantified as percentage of animals which failed to complete the test.

Spontaneous locomotor activity. Locomotor activity of mice was measured by automatic photoresistor actometers (DIGISCAN Optical Animal Activity Monitoring System, Omnitech Electronics, Inc.). Thirty minutes after the administration of the investigated compounds in a dose equivalent to 0.1 of their LD_{50}, the animals were placed in the actometers for 60 min and the total distance, horizontal activity and vertical activity were recorded automatically.

Anxiolytic activity was assessed by a ''four-plate'' test in mice according to Aron et al. [13], at 30 min after injection of the investigated compounds in a dose of 0.1 of their LD_{50}. The number of punished crossings was counted for 1 min.

Antidepressant properties were assessed by a ''forced swimming'' test according to Porsolt et al. [14], at 30 min after administration of investigated compounds in doses of 0.1–0.00635 of their LD_{50} or imipramine in a dose of 15 mg/kg ip. The mice were individually placed and forced to swim in a glass cylinder (27 × 16 cm) containing 15 cm of water (25 °C). The mice were left in the cylinder for 6 min. After the first 2 min, the total duration of immobility was measured during a 4-min test. A mouse was judged to be immobile when it remained floating passively, making slow movements to keep its head above the water.

References

[1] J.A. Den Boer, F.J. Bosker, B.R. Slaap, Hum. Psychopharmacol. 15 (2000) 315–336.
[2] D. Hoyer, J.P. Hannon, G.R. Martin, Pharmacol. Biochem. Behav. 71 (2002) 533–554.
[3] P. Celada, M. Puig, M. Amargos-Bosch, A. Adell, F. Artigas, J. Psychiatry Neurosci. 29 (2004) 252–265.
[4] B. Fulton, R.N. Brogden, CNS Drugs 7 (1997) 68–88.
[5] G.J. Marek, L.L. Carpenter, C.J. McDougle, L.H. Price, Neuropsychopharmacology 28 (2003) 402–412.
[6] J. Kossakowski, M. Jarocka, Farmaco 56 (2001) 785–789.
[7] J. Kossakowski, M. Krawiecka, Acta Pol. Pharm. 60 (2003) 177–182.
[8] J. Kossakowski, E. Hejchman, Acta Pol. Pharm. 60 (2003) 61–66.
[9] F. Berardi, N.A. Colabufo, G. Giudice, R. Perrone, V. Tortorella, S. Govoni, L. Lucchi, J. Med. Chem. 39 (1996) 176–182.
[10] L. Costantino, F. Gandolfi, C. Sorbi, S. Franchini, O. Prezzavento, F. Vittorio, G. Ronsisvalle, A. Leonardi, E. Poggesi, L. Brasili, J. Med. Chem. 48 (2005) 266–273.
[11] T. Fujita, T. Ban, J. Med. Chem. 14 (1971) 148–152.
[12] J.R. Boissier, J. Tardy, J.C. Diverres, Med. Exp. 3 (1960) 81–84.
[13] C. Aron, P. Simon, C. Larousse, J.R. Boissier, Neuropharmacology 10 (1971) 459–469.
[14] R.D. Porsolt, A. Bertin, M. Jalfre, Arch. Int. Pharmacodyn. Ther. 229 (1977) 327–336.
[15] H. Kubinyi, Quant. Struct.–Act. Relat. 7 (1988) 121–133.
[16] J.L. Mokrosz, M.J. Mokrosz, S. Charakchieva-Minol, M.H. Paluchowska, A.J. Bojarski, B. Duszyńska, Arch. Pharm. (Weinheim) 328 (1995) 143–148.
[17] J. Obniska, M. Kolaczkowski, S. Charakchieva-Minol, K. Nedza, M. Dybala, A.J. Bojarski, Pharmacol. Rep. 57 (2005) 336–344.
[18] A.D.E. Zomkowski, A.O. Rosa, J. Lin, A.R. Santos, J.B. Calixto, A.L.S. Rodrigues, Brain Res. 1023 (2004) 253–263.
[19] K. Matsuno, T. Kobayashi, M.K. Tanaka, S. Mita, Eur. J. Pharmacol. 312 (1996) 267–271.
[20] S. Chaki, S. Hirota, T. Funakoshi, Y. Suzuki, S. Suetake, T. Okubo, T. Ishii, A. Nakazato, S. Okuyama, J. Pharmacol. Exp. Ther. 304 (2003) 818–826.
[21] M. Fieser, L.F. Fieser, J.G. Smith, Reagents for Organic Synthesis (1990) p. 290.
[22] A.J. Bojarski, M.T. Cegła, S. Charakchieva-Minol, M.J. Mokrosz, M. Maćkowiak, J.L. Mokrosz, Pharmazie 48 (1993) 289–294.