

Full Paper

Synthesis of Conformationally Constrained Aryl- or Heteroaryl-piperazinyl Derivatives of Selected Imides as 5-HT_{1A} Receptor Ligands

Jerzy Kossakowski *, Mariola Krawiecka and Bożena Kuran

Department of Medical Chemistry, Medical University, 3 Oczki St., 02-007 Warsaw, Poland

* Author to whom correspondence should be addressed: email: jerzykos@amwaw.edu.pl; Tel.: (+48) 22 628 06 79

Received: 14 June 2006; in revised form: 3 August 2006 / Accepted: 11 August 2006 / Published: 22 August 2006

Abstract: The preparation of a number of cyclic imide 5-HT_{1A} receptor ligand derivatives has been described. Their structures were conformationally constrained by introducing rigid linkers containing unsaturated bonds or aromatic benzene rings. These compounds are expected to possess anxiolytic and antidepressant activity.

Keywords: Conformational constraints, *cis*- and *trans*-2-butene derivatives, 1,2-bismethylbenzene derivatives, imides, 5-HT_{1A} receptor ligands.

Introduction

Many compounds containing the arylpiperazine moiety possess high affinity and selectivity for 5-HT_{1A} receptors (e.g. buspirone, gepirone, tandospirone, NAN-190, BMY7378) and have been applied as anxiolytic and antidepressant drugs [1-4]. Recent studies show that constraining the chain in the ligands can have a significant influence on their affinities towards serotonin receptors [5, 6].

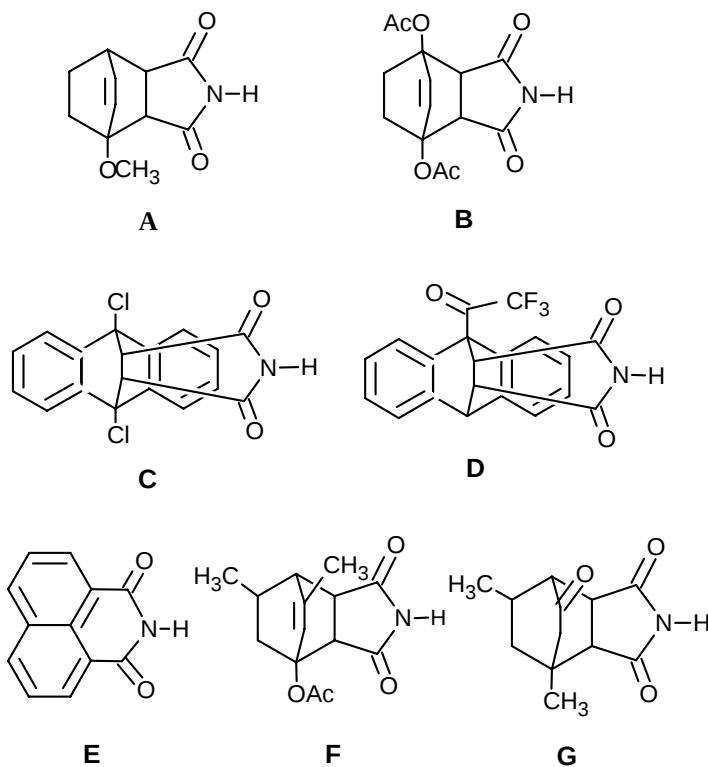
We have previously described the synthesis of select aryl- or heteroarylpiperazinylimide derivatives with constrained alkyl chains. This work is a continuation of our previous studies in search for compounds with anxiolytic and antidepressant activity among a group of long-chain arylpiperazine ligands [7-15].

Results and Discussion

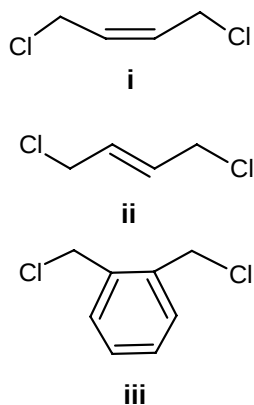
The synthesis of the target compounds is presented in Scheme 1. The starting materials for the synthesis of the new compounds were a selection of imides **A-E**, the linkers *cis*- and *trans*-1,4-dichloro-2-butene and 1,2-bis(chloromethyl)benzene and the amines 1-(2-methoxyphenyl)piperazine and 1-(2-pyrimidyl)piperazine (Figure 1). Imides **A-D**, **F-G** were obtained from the Diels-Alder reactions of maleimide and an appropriate diene and imide **E** was a commercially available reagent. They were reacted in acetonitrile or acetone in the presence of anhydrous K_2CO_3 and KI with the linkers *cis*-, or *trans*-1,4-dichloro-2-butene and 1,2-bis-(chloromethyl)benzene. Finally, the resulting N-substituted imides were used to alkylate 1-(2-methoxyphenyl)piperazine or 1-(2-pyrimidinyl)-piperazine in acetone, again in the presence of anhydrous K_2CO_3 and KI, to give new derivatives **I-XXXIV** (Table 1).

Figure 1. The components used in the reactions.

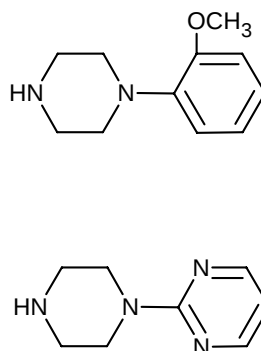
imides

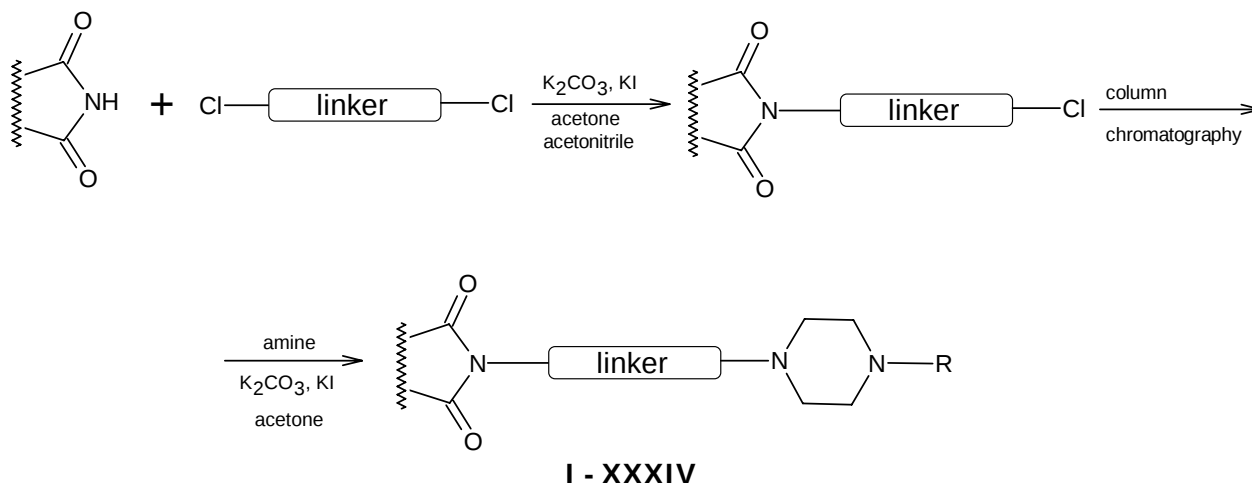


linkers



amines



Scheme 1. The syntheses of the target compounds **I-XXXIV**

The structures of the all compounds obtained were confirmed by ^1H -NMR spectra, elemental analysis and/or ESI MS.

Conclusions

In continuation of our research on cyclic imides with potential anxiolytic and antidepressive activity we have obtained thirty four new compounds belonging to the long-chain arylpiperazine ligand class. From the chemical and pharmacological point of view, these compounds are the basis for further research in the field of the potential drugs derived from cyclic imides.

Experimental

General

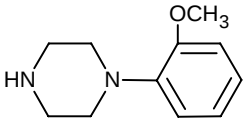
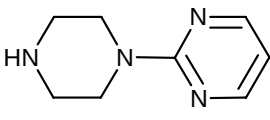
Melting points were determined in a capillary on an Electrothermal 9100 apparatus and are given uncorrected. ^1H -NMR spectra were recorded in DMSO-d_6 on a Bruker AVANCE DMX400 spectrometer operating at 400 MHz. The chemical shift values are expressed in ppm (parts per million) relatively to tetramethylsilane used as an internal standard and coupling constants J are given in Hz. The ESI MS were recorded on a Mariner Perspective–Biosystem instrument. Column chromatography was done using 0.05–0.2 mm Kieselgel (70–325 mesh ASTM, Merck). Reactions were monitored by TLC on 0.2 mm thick Kieselgel G plates with 254 nm fluorescent indicator (Merck), eluted with 9.8:0.2 or 9.5:0.5 chloroform-methanol. The imides **A**, **C**, **D**, **F**, **G** were obtained according to the methods described previously [13–15]. The imide **E** was commercially available (Aldrich).

Synthesis of 1,7-diacetoxy-4-azatricyclo[5.2.2.0^{2,6}]undecan-3,5-dione (**B**)

A mixture of 2-cyclohexene-1,4-dione (0.01 mol), maleimide (0.01 mol) and a catalytic amount of *p*-toluenesulphonic acid (PTSA) was refluxed for 2h in isopropenyl acetate (30 mL). The boiling mixture was filtered and the solvent was evaporated. The residue was crystallized from ethyl acetate;

m.p. 246°C; $^1\text{H-NMR}$ δ (ppm): 11.26 (s, 1H, NH), 6.17 (s, 2H, C8-H, C9-H), 3.86 (s, 2H, C2-H, C6-H), 2.35 (m, 2H, C10-H), 2.06 (s, 6H, C1-OAc, C7-OAc), 1.6 (d, C11-H, $^3J=4.8$); Anal. Calc. for $\text{C}_{14}\text{H}_{15}\text{NO}_6$: 57.34 % C, 6.16 % H, 4.78% N; found: 57.43 % C, 5.21 % H, 4.80 % N.

Table 1. Numbering of derivatives obtained in the described reactions.

imide	linker		
A	i	I	II
	ii	III	IV
	iii	V	VI
B	i	VII	VIII
	ii	IX	X
	iii	XI	XII
C	i	XIII	XIV
	ii	XV	XVI
	iii	XVII	XVIII
D	i	XIX	XX
	ii	XXI	XXII
	iii	XXIII	XXIV
E	iii	XXV	XXVI
F	i	XXVII	XXVIII
	ii	XXIX	
	iii	XXX	XXXI
G	i	XXXII	
	iii	XXXIII	XXXIV

General method for the preparation of the target compounds I-XXXIV: Synthesis of N- chloroalkenyl derivatives of the imides

The appropriate imide (0.01 mol) was dissolved in acetonitrile (30 mL, for **C-E**) or acetone (30 mL, for **A-B, F-G**), then anhydrous K_2CO_3 (0.01 mol), a catalytic amount of KI and the appropriate linker - *cis*-, or *trans*-1,4-dichloro-2-butene or 1,2-bis(chloromethyl)benzene (0.01 mol) - were added. The mixture was stirred at room temperature for 12-24 h. When the reaction was complete, as indicated by TLC, the mixture was filtered and the solvent was evaporated. The residue was purified by flash chromatography (eluent: chloroform-methanol 100:0.2).

Synthesis of aryl- and heteroaryl piperazinyl N-substituted imide derivatives

1-(2-Methoxyphenyl)piperazine or 1-(2-pyrimidinyl)piperazine (0.01 mol) were added to a mixture of N-chloroalkenylimide (0.01 mol), powdered anhydrous K_2CO_3 (0.01 mol), and a catalytic amount of KI in acetone (30 mL). The reaction mixture was stirred at a room temperature for 24 h. After the reaction completion the inorganic residue was filtered off and the solvent was evaporated. The crude compound obtained was purified by flash chromatography (eluents: chloroform or chloroform-methanol 100:0.2). All new derivatives were converted into their corresponding hydrochlorides with ethereal HCl and recrystallized from methanol.

4- $\{(2E)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl\}$ -1-methoxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**I**): m.p. 166 °C; 1H -NMR δ (ppm): 10.63 (s, 1H, NH^+), 7.04–6.09 (m, 4H, $H_{arom.}$), 6.07–6.01 (m, 2H, C8-H, C9-H), 5.76–5.74 (m, 1H, C2'-H), 5.60–5.54 (m, 1H, C3'-H), 4.05 (d, 2H, C4'-H, $^3J=8.0$), 3.95 (m, 2H, C1'-H), 3.79 (s, 3H, OCH_3), 3.52–3.45 (m, 4H, C5'-H, C7'-H), 3.36 (s, 3H, C1- OCH_3), 3.27–3.29 (m, 1H, C2-H), 3.21–3.16 (m, 2H, C6'-H), 3.08–3.06 (m, 1H, C6-H), 3.02–2.92 (m, 3H, C7-H, C8'-H), 1.94–1.87 (m, 1H, C10-H), 1.74–1.71 (m, 1H, C10-H), 1.41–1.34 (m, 1H, C11-H), 1.23–1.20 (m, 1H, C11-H); Anal. Calc. for $C_{26}H_{33}N_3O_4 \cdot HCl \cdot 2H_2O$: 59.59 % C, 7.31 % H, 8.01% N; found: 59.01 % C, 6.86 % H, 7.97 % N.

4- $\{(2Z)-[4-pyrimidylpiperazin-1-yl]but-2-en-1-yl\}$ -1-methoxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**II**): m.p. 230 °C; 1H -NMR δ (ppm): 11.53 (s, 1H, NH^+), 8.45 (d, 2H, $^3J=4.0$, C9'-H, C11'-H), 6.77 (t, 1H, $^3J=4.4$, 4.8, C10'-H), 6.08–6.00 (m, 2H, C8-H, C9-H), 5.80–5.75 (m, 1H, C2'-H), 5.59–5.55 (m, 1H, C3'-H), 4.72 (d, 2H, $^3J=14$, C4'-H), 4.01 (d, 2H, $^3J=6.8$, C1'-H), 3.89 (m, 2H, C5'-H, C7'-H), 3.47–3.38 (m, 4H, C5'-H, C6'-H, C7'-H), 3.35 (s, 3H, C1- OCH_3), 3.28–3.26 (m, 1H, C2-H), 3.07–3.01 (m, 1H, C6-H, C8'-H), 2.91 (m, 1H, C7-H), 1.91–1.87 (m, 1H, C10-H), 1.73–1.68 (m, 1H, C10-H), 1.40–1.33 (m, 1H, C11-H), 1.22–1.16 (m, 1H, C11-H); Anal. Calc. for $C_{23}H_{29}N_5O_3 \cdot HCl \cdot 2H_2O$: 60.06 % C, 6.57 % H, 15.23% N; found: 59.98 % C, 6.63 % H, 15.07 % N.

4- $\{(2Z)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl\}$ -1-methoxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**III**): m.p. 153 °C; 1H -NMR δ (ppm): 11.21 (s, 1H, NH^+), 7.03–6.88 (m, 4H, $H_{arom.}$), 6.18–6.12 (m, 2H, C8-H, C9-H), 5.86–5.79 (m, 1H, C2'-H), 5.65–5.57 (m, 1H, C3'-H), 3.94–3.93 (d, 2H, $^3J=4.4$, C4'-H), 3.78 (s, 3H, OCH_3), 3.73 (m, 2H, C5'-H, C7'-H), 3.48 (m, 2H, C1'-H), 3.36 (s, 3H, C1- OCH_3), 3.33–3.28 (m, 4H, C5'-H, C6'-H, C7'-H), 3.09–3.07 (m, 4H, C2-H, C6-H, C8'-H), 3.00 (m, 1H, C7-H), 1.92–1.97 (m, 1H, C10-H), 1.74–1.69 (m, 1H, C10-H), 1.41–1.35 (m, 1H, C11-H), 1.24–1.18 (m, 1H, C11-H); ESI MS: m/z = 451.56:452.2 (100%).

4- $\{(2E)-[4-pyrimidylpiperazin-1-yl]but-2-en-1-yl\}$ -1-methoxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**IV**): m.p. 147–152 °C; 1H -NMR δ (ppm): 11.29 (s, 1H, NH^+), 8.45–8.44 (d, 2H, $^3J=4.4$, C9'-H, C11'-H), 6.76 (t, 1H, $^3J=4.8$, C10'-H), 6.15–6.09 (m, 2H, C8-H, C9-H), 5.82–5.76 (m, 1H, C2'-H), 5.64–5.56 (m, 1H, C3'-H), 4.68 (d, 2H, $^3J=14$, C4'-H), 3.93–3.92 (m, 2H, C1'-H), 3.70 (m, 2H, C5'-H, C7'-H), 3.40–3.27 (m, 7H, C1- OCH_3 , C5'-H, C6'-H, C7'-H), 3.29–3.27 (m, 1H, C2-H), 3.08–3.06 (m, 1H, C6-H), 2.92–2.88 (m, 2H, C7-H, C8'-H), 1.93–1.87 (m, 1H, C10-H), 1.74–1.69 (m, 1H, C10-H),

1.41-1.35 (m, 1H, C11-H), 1.24-1.17 (m, 1H, C11-H); ESI MS: m/z = 423.51:424.4 (100%), 446.6 (5%).

4-{2-[4-(2-methoxyphenyl)-piperazin-1-yl]methylbenzyl}-1-methoxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**V**): m.p. 189 °C (for HCl); ¹H-NMR (free base) δ (ppm): 7.17 (m, 4H, C7'-H, C8'-H, C9'-H, C10'-H), 7.01-6.96 (m, 1H, C11'-H), 6.91-6.90 (m, 2H, C12'-H, C13'-H), 6.84 (m, 1H, C14'-H), 6.18-6.08 (m, 1H, C8-H), 6.05-6.02 (m, 1H, C9-H), 4.88-4.79 (m, 4H, C1'-H, C2'-H), 3.85 (s, 3H, OCH₃), 3.69 (m, 2H, C3'-H, C5'-H), 3.50 (s, 3H, C1-OCH₃), 3.14-2.88 (m, 5H, C2-H, C6-H, C7-H, C3'-H, C5'-H), 2.61 (m, 4H, C4'-H, C6'-H), 1.85-1.68 (m, 2H, C10-H), 1.55-1.47 (m, 2H, C11-H); Anal. Calc. for C₃₀H₃₅N₃O₄·6H₂O (free base): 59.12 % C, 5.78 % H, 6.89% N; found: 59.35 % C, 5.44 % H, 6.45 % N; ESI MS: m/z = 501.2:502.2 (100%).

4-[2-(4-pyrimidyl)piperazin-1-yl]methylbenzyl]-1-methoxy-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-3,5-dione (**VI**): m.p. 163 °C; ¹H-NMR δ (ppm): 10.32 (s, 1H, NH⁺), 8.01 (d, 2H, ³J=4.4, C7'-H, C10'-H), 7.26-7.25 (d, 1H, ³J=7.2, C11'-H), 7.00-6.92 (m, 2H, C8'-H, C9'-H), 6.70-6.68 (d, 1H, ³J=7.2, C13'-H), 6.32 (t, 1H, ³J=4.8, C12'-H), 5.61-5.53 (m, 2H, C8-H, C9-H), 4.30-4.24 (m, 4H, C1'-H, C2'-H), 4.08 (m, 2H, C3'-H, C5'-H), 3.17 (m, 3H, C1-OCH₃, C3'-H, C5'-H), 2.99-2.91 (m, 4H, C4'-H, C6'-H), 2.77-2.69 (m, 3H, C2-H, C6-H, C7-H), 1.49-1.45 (m, 1H, C10-H), 1.31-1.25 (m, 1H, C10-H), 0.97-0.91 (m, 1H, C11-H), 0.79-0.74 (m, 1H, C11-H); Anal. Calc. for C₂₇H₃₁N₅O₃·HCl·½H₂O: 63.58 % C, 6.32 % H, 13.73% N; found: 62.27 % C, 6.43 % H, 13.41 % N; ESI MS: m/z = 473.5:474.2 (100%).

4-[(2E)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-1,7-diyl diacetate (**VII**): m.p. 206 °C; ¹H-NMR δ (ppm): 10.88 (s, 1H, NH⁺), 7.00-6.90 (m, 4H, H_{arom.}), 6.14 (s, 2H, C8-H, C9-H), 5.78 (m, 1H, C2'-H), 5.60 (m, 1H, C3'-H), 4.08 (d, 2H, ²J=8.0, C4'-H), 3.96 (m, 4H, C2-H, C6-H, C5'-H, C6'-H), 3.79 (s, 3H, OCH₃), 3.49 (m, 4H, C1'-H, C5'-H, C7'-H), 3.18 (m, 2H, C6'-H), 3.02 (m, 2H, C8'-H), 2.41 (d, 1H, ²J=5.6, C10-H), 2.07 (m, 6H, C1-OAc, C7-OAc), 1.72 (d, 1H, ²J=6.8, C11-H); ESI MS: m/z = 537.6:532.5 (100%).

4-[(2Z)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-1,7-diyl diacetate (**VIII**): m.p. 215 °C; ¹H-NMR δ (ppm): 11.83 (s, 1H, NH⁺), 8.46-8.45 (m, 2H, C9'-H, C11'-H), 6.79-6.77 (m, 1H, C10'-H), 6.13 (s, 2H, C8-H, C9-H), 5.89-5.79 (m, 1H, C2'-H), 5.64-5.5 (m, 1H, C3'-H), 4.72-4.69 (m, 2H, C5'-H, C7'-H), 4.03-4.02 (m, 2H, C4'-H), 3.96 (m, 2H, C2-H, C6-H), 3.89 (m, 2H, C1'-H), 3.46-4.34 (m, 4H, C6'-H, C8'-H), 3.04-3.01 (m, 2H, C5'-H, C7'-H), 2.4-2.39 (m, 2H, C10-H), 2.07 (m, 6H, C1-OAc, C7-OAc), 1.73-1.71 (m, 2H, C11-H); ESI MS: m/z = 509.5:510.2 (100%).

4-[(2Z)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-1,7-diyl diacetate (**IX**): m.p. 168 °C; ¹H-NMR δ (ppm): 11.48 (s, 1H, NH⁺), 7.04-6.88 (m, 4H, H_{arom.}), 6.26 (s, 2H, C8-H, C9-H), 5.86-5.80 (m, 1H, C2'-H), 5.66-5.59 (m, 1H, C3'-H), 3.97 (s, 2H, C2-H, C6-H), 3.94 (m, 2H, C4'-H), 3.78 (s, 3H, OCH₃), 3.72 (m, 2H, C1'-H), 3.49-3.47 (m, 2H, C5'-H, C7'-H), 3.38-3.33 (m, 2H, C5'-H, C7'-H), 3.15-3.05 (m, 4H, C6'-H, C8'-H), 2.40 (d, 2H,

$^3J=6.4$, C10-H), 2.07 (s, 6H, C1-OAc, C7-OAc), 2.72 (d, 2H, $^3J=6.8$, C11-H); ESI MS: m/z = 537.3:538.2 (100%).

4-[(2E)-[4-pirimidylpiperazin-1-yl]but-2-en-1-yl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-1,7-diyl diacetate (**X**): m.p. 198 °C; $^1\text{H-NMR}$ δ (ppm): 11.80 (s, 1H, NH^+), 8.45-8.44 (d, 2H, $^3J=4.4$, C9'-H, C11'-H), 6.77 (t, 1H, $^3J=4.8$, C10'-H), 6.24 (s, 2H, C8-H, C9-H), 5.83-5.76 (m, 1H, C2'-H), 5.65-5.58 (m, 1H, C3'-H), 3.97 (s, 2H, C2-H, C6-H), 4.67 (d, 2H, $^3J=14$, C4'-H), 3.96 (s, 2H, C2-H, C6-H), 3.98-3.82 (m, 2H, C1'-H), 3.70 (m, 2H, C5'-H, C7'-H), 3.45-3.34 (m, 4H, C6'-H, C8'-H), 2.94-2.87 (m, 2H, C5'-H, C7'-H), 2.39 (d, 2H, $^3J=6.8$, C10-H), 2.07 (s, 6H, C1-OAc, C7-OAc), 2.72 (d, 2H, $^3J=6.8$, C11-H); ESI MS: m/z = 509.5:510.2 (100%), 532.2 (15%).

4-{2-[4-(2-methoxyphenyl)-piperazin-1-yl]methylbenzyl}-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-1,7-diyl diacetate (**XI**): m.p. 215 °C; $^1\text{H-NMR}$ δ (ppm): 7.58-7.56 (m, 1H, C7'-H), 7.46-7.38 (m, 1H, C10'-H), 7.22-7.19 (m, 1H, C8'-H), 7.13-7.11 (m, 1H, C9'-H), 7.03-6.95 (m, 2H, C11'-H, C14'-H), 6.92-6.87 (m, 2H, C12', C13'-H), 6.15-6.12 (m, 2H, C8-H, C9-H), 4.70-4.68 (m, 1H, C2'-H), 4.55-4.48 (m, 2H, C1'-H), 4.07 (s, 1H, C2-H), 4.01 (s, 1H, C6-H), 3.77 (s, 3H, OCH_3), 3.55-3.33 (m, 6H, C3'-H, C4'-H, C5'-H, C6'-H), 2.96-2.90 (m, 1H, C2'-H), 2.49-2.39 (m, 2H, C10-H), 2.05 (s, 6H, C1-OAc, C7-OAc), 1.73-1.71 (m, 2H, C11-H); ESI MS: m/z = 587.6:588.3 (100%).

4-[2-(4-pirimidylpiperazin-1-yl)methylbenzyl]-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-ene-1,7-diyl diacetate (**XII**): m.p. 197 °C; $^1\text{H-NMR}$ δ (ppm): 11.22 (s, 1H, NH^+), 8.45 (m, 2H, C11'-H, C13'-H), 7.76-7.74 (m, 1H, C10'-H), 7.44-7.35 (m, 2H, C8'-H, C9'-H), 7.14-7.12 (m, 1H, C7'-H), 6.76 (t, 1H, $^3J=4.8$, C12'), 6.12 (s, 2H, C8-H, C9-H), 4.70-4.68 (m, 4H, C3'-H, C5'-H), 4.49-4.48 (m, 2H, C2'-H), 4.06-4.04 (m, 2H, C2-H, C6-H), 3.51-3.35 (m, 4H, C4'-H, C6'-H), 3.20-3.16 (m, 2H, C1'-H), 2.42-2.41 (m, 2H, C10-H), 2.06 (s, 6H, C1-OAc, C7-OAc), 1.73-1.71 (m, 2H, C11-H); ESI MS: m/z = 559.6:560.4 (100%).

2-[(2Z)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl]-4,7-dichloro-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (**XIII**): m.p. 175 °C (for HCl); $^1\text{H-NMR}$ (free base) δ (ppm): 7.77 (m, 2H, C8-H, C11-H), 7.57 (m, 2H, C12-H, C15-H), 7.43 (m, 2H, C9-H, C10-H), 7.37 (m, 2H, C13-H, C14-H), 6.90-6.85 (m, 4H, C9'-H-C12'-H), 5.25-5.23 (m, 1H, C2'-H), 4.34-4.32 (m, 1H, C3'-H), 3.75 (s, 3H, OCH_3), 3.68 (d, 2H, $^3J=6.4$, C1'-H), 3.60 (s, 2H, C2-H, C6-H), 2.89 (m, 6H, C4'-H, C6'-H, C8'-H), 2.40 (m, 4H, C5'-H, C7'-H); Anal. Calc. for $\text{C}_{33}\text{H}_{31}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 1\frac{1}{2}\text{H}_2\text{O}$ (free base): 64.40 % C, 5.55 % H, 6.83% N; found: 68.62 % C, 5.35 % H, 6.75 % N; ESI MS: m/z = 588.5:589.2 (100%).

2-[(2Z)-[4-pirimidylpiperazin-1-yl]but-2-en-1-yl]-4,7-dichloro-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (**XIV**): m.p. 188 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ (ppm): 11.73 (s, 1H, NH^+), 8.46 (d, 2H, $^3J=4.4$, C9'-H, C11'-H), 7.82-7.80 (m, 2H, C8-H, C11-H), 7.61-7.59 (m, 2H, C12-H, C15-H), 7.47-7.46 (m, 2H, C9-H, C10-H), 7.42-7.40 (m, 2H, C13-H, C14-H), 6.78 (t, 1H, $^3J=4.4$, 4.8, C10'-H), 5.59-5.53 (m, 1H, C2'-H), 4.72-4.69 (m, 2H, C4'-H), 4.63-4.57 (m, 1H, C3'-H), 3.77-3.76 (m, 4H, C5'-H, C7'-H), 3.68-3.64 (s, 2H, C2-H, C6-H), 3.46-3.36 (m, 4H, C6'-H, C8'-H), 2.98-2.95 (m, 2H, C1'-H); ESI MS: m/z = 559.5:560.1 (100%), 562.1 (65%).

2-[(2E)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl]-4,7-dichloro-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (XV): m.p. 240 °C; $^1\text{H-NMR}$ δ (ppm): 10.40 (s, 1H, NH^+), 7.83-7.81 (m, 2H, C11-H, C12-H), 7.65-7.63 (m, 2H, C8-H, C15-H), 7.48-7.45 (m, 4H, C9-H, C10-H, C13-H, C14-H), 7.05-6.90 (m, 4H, C9'-H-C12'-H), 5.28 (m, 1H, C3'-H), 5.02-4.95 (m, 2H, C4'-H), 4.61-4.57 (m, 1H, C2'-H), 3.80 (s, 3H, OCH_3), 3.71 (d, 2H, $^3J = 5.6$, C1'-H), 3.66 (s, 2H, C2-H, C6-H), 3.55-3.52 (m, 2H, C5'-H, C7'-H), 3.35-3.33 (m, 2H, C5'-H, C7'-H), 3.09-2.96 (m, 4H, C6'-H, C8'-H); ESI MS: $m/z = 588.5:589.2$ (100%).

2-[(2E)-[4-pyrimidylpiperazin-1-yl]but-2-en-1-yl]-4,7-dichloro-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (XVI): m.p. 210 °C; $^1\text{H-NMR}$ δ (ppm): 11.48 (s, 1H, NH^+), 8.47 (d, 2H, $^3J = 4.4$, C9'-H, C11'-H), 7.81-7.80 (m, 2H, C8-H, C15-H), 7.62-7.61 (m, 2H, C9-H, C10-H), 7.47-7.44 (m, 4H, C13-H, C14-H, C11-H, C12-H), 6.78 (t, 1H, $^3J = 4.4$, C10'-H), 5.35-5.27 (m, 1H, C3'-H), 4.97-4.92 (m, 2H, C2'-H), 4.74-4.71 (m, 1H, C4'-H), 3.70-3.65 (s, 4H, C1'-H, C2-H, C6-H), 3.49 (m, 2H, C5'-H, C7'-H), 3.43-3.32 (m, 4H, C6'-H, C8'-H), 2.91-2.88 (m, 2H, C5'-H, C7'-H); ESI MS: $m/z = 559.5:560.2$ (100%).

2-[2-[4-(2-methoxyphenyl)-piperazin-1-yl]methylbenzyl]-4,7-dichloro-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (XVII): m.p. 225 °C; $^1\text{H-NMR}$ δ (ppm): 7.83-7.80 (m, 2H, C11-H, C12-H), 7.67-7.65 (m, 2H, C8-H, C15-H), 7.52-7.50 (m, 2H, C10-H, C9-H), 7.48-7.46 (m, 2H, C13-H, C14-H), 7.13-7.10 (m, 2H, C8'-H, C9'-H), 6.91-6.84 (m, 5H, C7'-H, C10'-H, C11'-H, C12'-H, C14'-H), 4.99-4.97 (m, 1H, C13'-H), 4.60 (s, 2H, C2'-H), 3.75 (s, 3H, OCH_3), 3.72 (m, 2H, C1'-H), 3.46 (m, 2H, C2-H, C6-H), 2.87 (m, 4H, C3'-H, C5'-H), 2.33 (m, 4H, C4'-H, C6'-H); Anal. Calc. for $\text{C}_{37}\text{H}_{33}\text{Cl}_2\text{N}_3\text{O}_3 \cdot 2\text{HCl} \cdot 5\text{H}_2\text{O}$: 58.35 % C, 5.65 % H, 5.52% N; found: 58.61 % C, 5.68 % H, 5.10 % N; ESI MS: $m/z = 637.5:638.1$ (100%), 640.2 (60%).

2-[2-(4-pyrimidylpiperazin-1-yl)methylbenzyl]-4,7-dichloro-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (XVIII): m.p. 273 °C; $^1\text{H-NMR}$ (for HCl) δ (ppm): 8.33-8.30 (m, C11'-H, C13'-H), 7.81-7.79 (m, 2H, C11-H, C8-H), 7.65-7.63 (m, 2H, C12-H, C15-H), 7.49-7.44 (m, 4H, C10-H, C9-H, C13-H, C14-H), 7.13-7.07 (m, 2H, C8'-H, C9'-H), 6.86-6.83 (m, 1H, C10'-H), 6.61-6.58 (m, 1H, C7'-H), 5.03-5.01 (d, 1H, C12'-H), 4.60 (m, 2H, C2'-H), 3.71 (m, 2H, C1'-H), 3.63 (m, 4H, C3'-H, C6'-H), 3.44 (m, 2H, C2-H, C6-H), 2.33 (m, 4H, C4'-H, C5'-H); Anal. Calc. for $\text{C}_{34}\text{H}_{29}\text{Cl}_2\text{N}_5\text{O}_2 \cdot 2\frac{1}{2}\text{H}_2\text{O}$ (free base): 62.29 % C, 4.45 % H, 10.68% N; found: 62.72 % C, 4.79 % H, 10.76 % N; ESI MS: $m/z = 609.5:610.1$ (100%), 612.1 (60%).

2-[(2Z)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl]-4-trifluoroacetyl-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (XIX): m.p. 168 °C; $^1\text{H-NMR}$ δ (ppm): 11.39 (s, 1H, NH^+), 7.66-7.58 (m, 2H, C8-H, C11-H), 7.34-7.26 (m, 5H, C10-H, C12-H, C13-H, C14-H, C15-H), 7.05-6.89 (m, 5H, C9-H, C9'-H, C10'-H, C11'-H, C12'-H), 5.56-5.50 (m, 1H, C2'-H), 4.92 (m, 1H, C7-H), 4.50-4.45 (m, 1H, C6-H), 4.16-4.14 (m, 1H, C3'-H), 3.80 (s, 3H, OCH_3), 3.76 (m, 3H, C2-H, C5'-H, C7'-H), 3.49-3.48 (m, 2H, C4'-H), 3.40-3.32 (m, 2H, C5'-H, C7'-H), 3.16-3.03 (m, 4H, C1'-H, C6'-H), 2.08 (m, 2H, C8'-H); ESI MS: $m/z = 615.6:616.3$ (100%).

2-[(2Z)-[4-pyrimidylpiperazin-1-yl]but-2-en-1-yl]-4-trifluoroacetyl-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (**XX**): m.p. 163 °C; $^1\text{H-NMR}$ δ (ppm): 8.33-8.31 (m, 2H, C9'-H, C11'-H), 7.64 (m, 1H, C11-H), 7.47-7.45 (m, 1H, C12-H), 7.31-7.21 (m, 5H, C8-H, C9-H, C10-H, C13-H, C14-H), 7.05-7.03 (m, 1H, C15-H), 6.51 (m, 1H, C10'-H), 5.44 (m, 1H, C2'-H), 4.78 (m, 1H, C7-H), 4.51 (m, 1H, C3'-H), 3.98 (d, 1H, $^3J=8.4$, C2-H), 3.83 (m, 4H, C5'-H, C7'-H), 3.72-3.65 (m, 2H, C4'-H), 3.30-3.28 (m, 1H, C6-H), 3.04 (m, 2H, C1'-H), 2.48 (m, 4H, C6'-H, C8'-H); ESI MS: m/z = 587.5:588.2 (100%), 610.2 (2%).

2-[(2E)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl]-4-trifluoroacetyl-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (**XXI**): m.p. 180 °C; $^1\text{H-NMR}$ δ (ppm): 11.47 (s, 1H, NH^+), 7.59 (m, 2H, C11-H, C12-H), 7.34-7.26 (m, 5H, C8-H, C10-H, C13-H, C14-H, C15-H), 7.05-6.91 (m, 5H, C9-H, C9'-H, C10'-H, C11'-H, C12'-H), 5.56-5.48 (m, 1H, C3'-H), 4.93 (s, 1H, C7-H), 4.82-4.75 (m, 1H, C2'-H), 4.15 (d, 1H, $^3J=8.4$, C2-H), 3.80 (s, 3H, $-\text{OCH}_3$), 3.63 (m, 2H, C4'-H), 3.52-3.49 (m, 5H, C6-H, C5'-H, C7'-H), 3.38-3.33 (m, 2H, C1'-H), 3.07 (m, 4H, C6'-H, C8'-H); ESI MS: m/z = 615.6:616.3 (100%).

2-[(2E)-[4-pyrimidylpiperazin-1-yl]but-2-en-1-yl]-4-trifluoroacetyl-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (**XXII**): m.p. 204 °C; $^1\text{H-NMR}$ δ (ppm): 11.67 (s, 1H, NH^+), 8.45 (d, 2H, $^3J=4.4$, C9'-H, C11'-H), 7.66-7.57 (m, 2H, C11-H, C12-H), 7.36-7.28 (m, 5H, C8-H, C9-H, C10-H, C13-H, C14-H), 6.97-6.95 (m, 1H, C15-H), 5.52-5.48 (m, 1H, C3'-H), 4.92 (s, 1H, C7-H), 4.79-4.69 (m, 1H, C2'-H), 4.14 (d, 1H, $^3J=8$, C2-H), 3.62-3.61 (m, 2H, C4'-H), 3.49-3.35 (m, 9H, C6-H, C5'-H, C7'-H), 2.92-2.89 (m, 2H, C1'-H); ESI MS: m/z = 587.5:588.2 (100%), 610.2 (2%).

2-[2-[4-(2-methoxyphenyl)-piperazin-1-yl]methylbenzyl]-4-trifluoroacetyl-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (**XXIII**): m.p. 190 °C; $^1\text{H-NMR}$ δ (ppm): 10.67 (s, 1H, NH^+), 7.65-7.59 (m, 3H, C8-H, C11-H, C12-H), 7.36-7.25 (m, 5H, C9-H, C10-H, C13-H, C14-H, C15-H), 7.20-7.14 (m, 3H, C7'-H, C10'-H, C14-H), 7.02-6.95 (m, 3H, C8'-H, C9'-H, C11'-H), 6.91 (m, 2H, C12'-H, C14'-H), 5.93-5.91 (m, 1H, C13'-H), 4.94-4.93 (m, 1H, C7-H), 4.49 (m, 2H, C2'-H), 4.38-4.37 (m, 2H, C1'-H), 4.28-4.26 (m, 1H, C2-H), 4.12 (m, 4H, C3'-H, C5'-H), 3.79 (s, 3H, OCH_3), 3.58-3.56 (m, 1H, C6-H), 3.47-3.44 (m, 2H, C4'-H), 3.08 (m, 2H, C6'-H); ESI MS: m/z = 665.7:666.2 (100%).

2-[2-[4-(2-methoxyphenyl)piperazin-1-yl]methylbenzyl]-4-trifluoroacetyl-4,7-ethano-3a,4,9,9a-tetrahydro-1H-dibenzo[fi]isoindole-1,3-(2H)-dione (**XXIV**): m.p. 196 °C; $^1\text{H-NMR}$ δ (ppm): 11.16 (s, 1H, NH^+), 8.45-8.43 (m, 2H, C11'-H, C13'-H), 7.65-7.63 (m, 2H, C11-H, C12-H), 7.58-7.56 (m, 1H, C15-H), 7.35-7.25 (m, 4H, C9-H, C10-H, C13-H, C14-H), 7.20-7.13 (m, 3H, C7'-H, C9'-H, C10'-H), 6.96-6.94 (m, 1H, C8-H), 6.77 (m, 1H, C12'-H), 5.91-5.89 (d, 1H, $^3J=7.6$, C8'-H), 4.93 (m, 1H, C7-H), 4.70-4.66 (m, 4H, C3'-H, C5'-H), 4.53-4.49 (m, 2H, C2'-H), 4.33-4.32 (m, 2H, C1'-H), 4.26-4.24 (m, 1H, C2-H), 3.56-3.54 (m, 1H, C6-H), 3.35-3.31 (m, 2H, C4'-H), 3.16-3.11 (m, 2H, C6'-H); Anal. Calc. for $\text{C}_{36}\text{H}_{30}\text{F}_3\text{N}_5\text{O}_3\cdot\text{HCl}\cdot 4\text{H}_2\text{O}$: 57.95 % C, 5.27 % H, 9.39% N; found: 58.47 % C, 5.12 % H, 9.34 % N.

2-[2-[4-(2-methoxyphenyl)-piperazin-1-yl]methylbenzyl]-3a,6-dihydro-1H-benzo[de]isoquinoline-1,3-(2H)-dione (**XXV**): m.p. 239 °C; $^1\text{H-NMR}$ δ (ppm): 10.32 (s, 1H, NH^+), 8.54 (t, 4H, $^3J=9.6$, 8.0,

C6-H, C8-H, C10-H, C12-H), 7.91 (t, 2H, $^3J=7.6$, C7-H, C11-H), 7.74 (d, 1H, $^3J=6.4$, C10'-H), 7.38-7.32 (m, 2H, C8'-H, C9'-H), 7.26 (m, 1H, C7'-H), 7.05-6.98 (m, 4H, C12'-H, C13'-H, C14'-H, C15'-H), 5.49 (m, 2H, C2'-H), 4.76 (m, 2H, C1'-H), 3.81 (s, 3H, OCH₃), 3.56-3.46 (m, 6H, C3'-H, C4'-H, C5'-H), 3.15-3.09 (m, 2H, C6'-H); Anal. Calc. for C₃₁H₂₉N₃O₃·HCl·4H₂O: 61.84 % C, 6.64 % H, 6.98% N; found: 61.43 % C, 5.81 % H, 6.74 % N.

2-[2-(4-pirimidylpiperazin-1-yl)methylbenzyl]-3a,6-dihydro-1H-benzo[de]isoquinoline-1,3(2H)-dione (XXVI): m.p. 258 °C; $^1\text{H-NMR}$ δ (ppm): 10.48 (s, 1H, NH⁺), 8.54 (t, 4H, $^3J=8.0$, C6-H, C8-H, C10-H, C12-H), 8.46 (d, 2H, $^3J=4.8$, C7-H, C11-H), 7.91 (t, 1H, $^3J=7.6$, C8'-H, C9'-H), 7.72 (m, 1H, C7'-H), 7.35 (m, 2H, C11'-H, C13'-H), 7.25 (m, 1H, C10'-H), 6.78 (t, 1H, $^3J=4.8$, C12'-H), 5.45 (s, 2H, C2'-H), 4.80 (m, 2H, C1'-H), 4.70 (m, 2H, C3'-H, C5'-H), 3.56-3.53 (m, 2H, C3'-H, C5'-H), 3.47-3.31 (m, 4H, C4'-H, C6'-H); Anal. Calc. for C₂₈H₂₅N₅O₂·HCl·H₂O: 64.61 % C, 5.38 % H, 13.47% N; found: 64.34 % C, 5.32 % H, 13.50 % N.

4-{(2E)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl}-7,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (XXVII): m.p. 144 °C; $^1\text{H-NMR}$ δ (ppm): 7.04-6.91 (m, 2H, C9'-H, C12'-H), 5.99-5.94 (m, 2H, C10'-H, C11'-H), 5.72 (s, 1H, C9-H), 5.63-5.60 (m, 1H, C3'-H), 4.15-4.13 (m, 2H, C4'-H), 4.06-3.94 (m, 3H, C1'-H, C2'-H), 3.81-3.79 (m, 8H, C2-H, C5'-H, C7'-H, OCH₃), 3.40-3.35 (m, 4H, C6'-H, C8'-H), 3.20-3.18 (m, 1H, C6-H), 2.61-2.54 (m, 2H, C7-H, C10-H), 2.04 (m, 4H, C1-OAc, C11-H), 1.53 (s, 3H, C8-CH₃), 0.98-0.94 (m, 1H, C10-H), 0.79 (d, 3H, $^3J=16.8$, C11-CH₃); ESI MS: m/z = 507.6:508.3 (100%).

4-{(2Z)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl}-7,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (XXVIII): m.p. 190 °C; $^1\text{H-NMR}$ δ (ppm): 11.79 (s, 1H, NH⁺), 8.45 (d, 2H, $^3J=4.8$, C9'-H, C11'-H), 6.77 (t, 1H, $^3J=4.8$, C10'-H), 5.70 (s, 1H, C9-H), 5.55-5.49 (m, 1H, C2'-H), 4.72-4.68 (m, 2H, C4'-H), 4.02-4.01 (m, 2H, C5'-H, C7'-H), 3.90-3.88 (m, 2H, C4'-H), 3.78-3.76 (m, 1H, C3'-H), 3.47-3.41 (m, 4H, C6'-H, C8'-H), 3.17-3.14 (m, 1H, C6-H), 3.03 (m, 2H, C5'-H, C6'-H), 2.59-2.52 (m, 2H, C7-H, C10-H), 2.08-2.03 (m, 5H, C1-OAc, C2-H, C11-H), 1.65 (s, 3H, C8-CH₃), 0.97-0.93 (m, 1H, C10-H), 0.79 (d, 3H, $^3J=6.4$, C11-CH₃); ESI MS: m/z = 479.5:480.3 (100%).

4-{(2Z)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl}-7,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (XXIX): m.p. 149 °C; $^1\text{H-NMR}$ δ (ppm): 11.50 (s, 1H, NH⁺), 7.02-6.90 (m, 4H, H_{arom.}), 5.89-5.60 (m, 3H, C9-H, C2'-H, C3'-H), 3.94 (m, 2H, C4'-H), 3.78 (s, 3H, OCH₃), 3.73 (m, 2H, C5'-H), 3.48 (m, 2H, C7'-H), 3.40-3.35 (m, 3H, C2-H, C1'-H), 3.17 (m, 1H, C6-H), 3.07 (m, 4H, C6'-H, C8'-H), 2.60-2.55 (m, 2H, C7-H, C10-H), 2.04 (s, 4H, C1-OAc, C11-H), 1.71 (s, 3H, C8-CH₃), 0.98-0.95 (m, 1H, C10-H), 0.81 (d, 3H, $^3J=6.4$, C11-CH₃); ESI MS: m/z = 507.6:508.4 (100%).

4-{2-[4-(2-methoxyphenyl)-piperazin-1-yl]methylbenzyl}-7,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (XXX): m.p. 153 °C; $^1\text{H-NMR}$ δ (ppm): 10.95 (s, 1H, NH⁺), 7.77-7.76 (m, 1H, C10'-H), 7.44-7.35 (m, 2H, C8'-H, C9'-H), 7.09-7.07 (m, 1H, C7'-H), 7.03-6.91 (m, 4H, C11'-H, C12'-H, C13'-H, C14'-H), 5.67 (s, 1H, C9-H), 4.78-4.68 (m, 2H, C2'-H), 4.59-4.50 (m, 2H, C1'-H), 3.88-3.86 (m, 1H, C2-H), 3.78 (s, 3H, OCH₃), 3.49-3.35 (m, 6H, C3'-H, C4'-H, C5'-H), 3.25-

3.23 (m, 1H, C6-H), 3.18-3.13 (m, 2H, C6'-H), 2.59-2.54 (m, 2H, C7-H, C10-H), 2.04 (m, 4H, C1-OAc, C11-H), 1.53 (s, 3H, C8-CH₃), 0.98-0.94 (m, 1H, C10-H), 0.79 (d, 3H, ³J=6.4, C11-CH₃); ESI MS: m/z = 557.6:558.3 (100%).

4-[2-(4-pirimidylpiperazin-1-yl)methylbenzyl]-7,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate (**XXXI**): m.p. 173°C; ¹H-NMR δ (ppm): 8.43 (d, 2H, ³J=4.0, C11'-H, C13'-H), 7.67 (d, 1H, ³J=5.6, C10'-H), 7.46-7.34 (m, 2H, C8'-H, C9'-H), 7.05 (d, 1H, ³J=8.0, C7'-H), 6.76 (t, 1H, ³J=4.0, C12'-H), 5.67 (s, 1H, C9-H), 4.72-4.62 (m, 4H, C3'-H, C5'-H), 4.56-4.42 (m, 2H, C2'-H), 3.84 (d, 1H, ³J=8.0, C2-H), 3.40-3.33 (m, 6H, C1'-H, C4'-H, C6'-H), 3.23-3.20 (m, 2H, C6-H, C7-H), 2.55 (m, 1H, C10-H), 2.01 (m, 4H, C1-OAc, C11-H), 1.50 (s, 3H, C8-CH₃), 0.95-0.92 (m, 1H, C10-H), 0.77 (d, 3H, ³J=8.2, C11-CH₃); Anal. Calc. for C₃₀H₃₅N₅O₄·HCl·3¹/₂H₂O: 57.23 % C, 6.83 % H, 11.13% N; found: 57.44 % C, 6.41 % H, 11.08 % N.

4-{(2E)-[4-(2-methoxyphenyl)piperazin-1-yl]but-2-en-1-yl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**XXXII**): m.p. 175 °C; ¹H-NMR δ (ppm): 10.94 (s, 1H, NH⁺), 7.03-6.90 (m, 4H, H_{arom.}), 5.84-5.78 (m, 1H, C2'-H), 5.64-5.58 (m, 1H, C3'-H), 4.16-4.07 (m, 2H, C5'-H, C7'-H), 3.96 (m, 2H, C4'-H), 3.79 (s, 3H, OCH₃), 3.49-3.43 (m, 4H, C6'-H, C8'-H), 3.37-3.34 (m, 1H, C6-H), 3.21-3.16 (m, 2H, C5'-H, C7'-H), 3.05-2.99 (m, 2H, C1'-H), 2.84-2.82 (m, 1H, C2-H), 2.44 (m, 1H, C7-H), 2.19 (m, 1H, C11-H), 2.09-2.05 (m, 1H, C9-H), 1.94-1.88 (m, 1H, C10-H), 1.77-1.71 (m, 1H, C9-H), 1.99 (s, 3H, C1-CH₃), 1.09-1.01 (m, 1H, C10-H), 0.85 (d, 3H, ³J=7.2, C11-CH₃); ESI MS: m/z = 465.5:466.2 (100%).

4-{2-[4-(2-methoxyphenyl)-piperazin-1-yl]methylbenzyl}-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**XXXIII**): m.p. 186 °C; ¹H-NMR δ (ppm): 7.70 (m, 1H, C7'-H), 7.46-7.43 (m, 2H, C8'-H, C9'-H), 7.10 (m, 1H, C10'-H), 7.03-6.82 (m, 4H, C11'-H, C12'-H, C13'-H, C14'-H), 4.82-4.64 (m, 2H, C5'-H, C3'-H), 4.61 (s, 2H, C2'-H), 3.86 (s, 3H, OCH₃), 3.50-3.33 (m, 7H, C6-H, C3'-H, C4'-H, C5'-H, C6'-H), 3.11-3.05 (m, 2H, C1'-H), 2.87 (d, 1H, ³J=9.2, C2-H), 2.49-2.45 (m, 1H, C7-H), 2.17 (m, 1H, C11-H), 2.00 (d, 1H, ³J=20, C9-H), 1.89 (t, 1H, ³J=12, C10-H), 1.60 (d, 1H, ³J=20, C9-H), 1.14 (s, 3H, C1-CH₃), 1.05-0.97 (m, 1H, C10-H), 0.84 (d, 3H, ³J=8, C11-CH₃); Anal. Calc. for C₃₁H₃₇N₃O₄·HCl·3¹/₂H₂O: 60.49 % C, 7.32 % H, 6.83% N; found: 60.98 % C, 7.08 % H, 6.31 % N.

4-[2-(4-pirimidylpiperazin-1-yl)methylbenzyl]-1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione (**XXXIV**): m.p. 176 °C; ¹H-NMR δ (ppm): 8.43 (d, 2H, ³J=4.6, C11'-H, C13'-H), 8.29-8.12 (m, 1H, C10'-H), 7.35 (m, 2H, C8'-H, C9'-H), 7.09 (m, 1H, C7'-H), 6.75 (t, 1H, ³J=4.8, C12'-H), 4.78-4.57 (m, 4H, C3'-H, C5'-H), 4.53 (s, 2H, C2'-H), 3.44-3.33 (m, 4H, C4'-H, C6'-H), 3.23-3.14 (m, 3H, C6-H, C1'-H), 2.87 (d, 1H, ³J=8, C2-H), 2.43 (m, 1H, C7-H), 2.18 (m, 1H, C11-H), 2.10-1.95 (m, 1H, C9-H), 1.93-1.81 (m, 1H, C10-H), 1.60-1.57 (m, 1H, C9-H), 1.13 (s, 3H, C1-CH₃), 1.05-0.97 (m, 1H, C10-H), 0.84 (d, 3H, ³J=8, C11-CH₃); Anal. Calc. for C₂₈H₃₃N₅O₃·HCl·3¹/₂H₂O: 57.24 % C, 6.98 % H, 11.93% N; found: 57.23 % C, 6.39 % H, 11.89 % N.

References

1. Nelson, D.L. *Pharmacol. Biochem. Behav.* **1991**, *40*, 1041-1051.
2. Glennon, R.A. *Drug. Dev. Res.*, **1992**, *26*, 251-274.
3. Heiser, F.; Wilcox, Ch. S. *Drugs* **1998**, *10*, 343-353.
4. Saurbie P. *5HT_{1A} Receptors: a Bridge between Anxiety and Depression, Behavioral Pharmacology of 5HT_{1A}*; Lawrence Erlbaum Ass. Publ.: Hillsdale, NJ, **1999**; pp. 337-359.
5. Bojarski, A. J.; Duszyńska, B.; Kołaczkowski, M.; Kowalski, P.; Kowalska, T. *J. Bioorg. Med. Chem. Lett.* **2004**, *14*, 5863-5866.
6. Bojarski, A. J.; Paluchowska, M. H.; Duszyńska, B.; Bugno, R.; Kłodzińska, A.; Tatarczyńska, E.; Chojnacka-Wójcik, E. *J. Bioorg. Med. Chem.* **2006**, *14*, 1391-1402.
7. Kossakowski, J.; Sroka, T. K. *Acta Polon. Pharm.-Drug Res.* **1999**, *56* (Suppl.), 89-91.
8. Kossakowski, J.; Kuśmierczyk, J. *Pharmazie*. **2000**, *55*, 5-8.
9. Kossakowski, J.; Hejchman, E. *Acta Polon. Pharm.-Drug Res.* **2000**, *57* (Suppl.), 57-60.
10. Kossakowski, J.; Jarocka, M. *Acta Polon. Pharm.-Drug Res.* **2000**, *57* (Suppl.), 60-62.
11. Kossakowski, J.; Maleszewska, E. *Acta Polon. Pharm.-Drug Res.* **2000**, *57* (Suppl.), 47-50.
12. Kossakowski, J.; Krawiecka, M. *Acta Polon. Pharm.-Drug Res.* **2000**, *57* (Suppl.), 53-56.
13. Kossakowski, J.; Perliński, M. *Acta Polon. Pharm.-Drug Res.* **2001**, *58*, 257-262.
14. Kossakowski, J.; Perliński, M. *Acta Polon. Pharm.-Drug Res.* **2003**, *60*, 183-189.
15. Kossakowski, J.; Kuran, B. *Ann. Pol. Chem. Soc.* **2003**, 284-288.

Sample availability: Samples of the compounds are available from authors.