Synthesis of new hexahydro- and octahydropyrido[1,2-c]pyrimidine derivatives with an arylpiperazine moiety as ligands for 5-HT(1A) and 5-HT(2A) receptors, Part 2

ARTICLE *in* IL FARMACO · JANUARY 2003

DOI: 10.1016/S0014-827X(02)01274-0 · Source: PubMed

4 AUTHORS, INCLUDING:

Franciszek Herold
Medical University of Warsaw
65 PUBLICATIONS **349** CITATIONS
SEE PROFILE

Gabriel Nowak
Polish Academy of Sciences
281 PUBLICATIONS **5,734** CITATIONS
SEE PROFILE

Acta Poloniae Pharmaceutica – Drug Research, Vol. 61 No. 2 pp. 139–150, 2004

ISSN 0001-6837
Polish Pharmaceutical Society

SYNTHESIS OF NEW HEXAHYDRO– AND OCTAHYDROPYRIDO[1,2–*c*]PYRIMIDINE DERIVATIVES WITH AN ARYLPIPERAZINE MOIETY AS LIGANDS FOR 5–HT_{1A} AND 5–HT_{2A} RECEPTORS. PART III

FRACISZEK HEROLD, MAREK KRÓL and JERZY KLEPS

Department of Drug Technology, Faculty of Pharmacy, The Medical University of Warsaw, 1 Banacha Str., 02–970 Warsaw, Poland

Abstract: The preparation of new 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine derivatives **III–XXVI** with an arylpiperazinylbutyl moiety in N–2 position has been described. Multi–stage synthesis techniques were used to obtain 4–arylhexahydro–1H,3H–pyrido[1,2–*c*]pyrimidine–1,3–dione **Ia–f** derivatives, being the starting compounds for further modification. N–alkylation of the imide group in compounds **Ia–f** followed, using 1,4–dibromobutane to yield bromobutyl derivatives **IIa–f**. The final products **III–XXVI** were obtained by condensation of aryl– or heteroaryl– piperazine with the bromobutyl derivatives **IIa–f**. Compounds **XII, XIV, XIX, XX, XXIV–XXVI** will be submitted to a pharmacological investigation for their affinity towards 5–HT_{1A}, 5–HT_{2A} and α_1 adrenergic receptor, using radioligand binding assay.

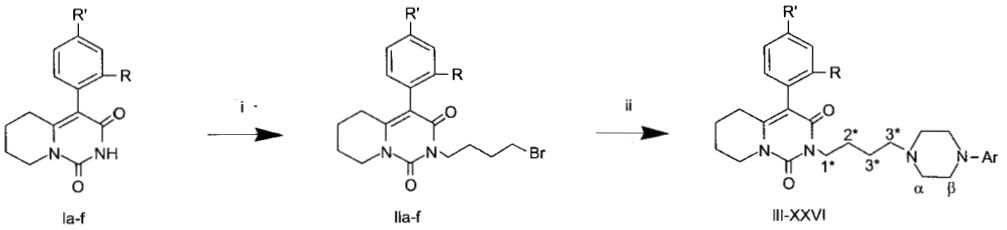
Keywords: Hexahydropyrido[1,2–*c*]pyrimidine derivatives; arylpiperazine moiety; ligands for 5–HT_{1A} and 5–HT_{2A} receptors

The neurotransmitter serotonin (5–HT, 5–hydroxytryptamin) is involved in various physiological and pathophysiological processes (1–4). Particular attention, over the last decade, has been focused on 5–HT_{1A} because this receptor plays an important role in the central nervous system modulating a number of behaviours such as impulsivity, sexual behaviour and food intake (1, 3). Moreover, several agonists for this receptor have been shown to exhibit anxiolytic and antidepressant properties in human (3–7). The development of non–benzodiazepine anxiolytics, such as buspirone, a partial agonist at 5–HT_{1A} receptors, has substantiated the correlation between serotonin and anxiety. Buspirone, an arylpiperazine derivative with high affinity for the 5–HT_{1A} receptor, was the first agent to be approved for clinical use (3, 4, 7, 9). The arylpiperazines are a relatively new class of psychotherapeutic drugs which possess high affinity for the 5–HT_{1A} receptor site, however with low selectivity (Figure 1) (3, 4, 8–19). Most of the ligands with affinity for the 5–HT_{1A} receptor exhibit a high level of undesired affinity for the α_1–adrenergic receptor, because these receptors have a high degree of similarity (~45%) in their amino acid sequence (20). The aim of the present study was to synthesize the new analogues of buspirone with hypothetically higher affinity and selectivity to 5–HT_{1A} receptors. In this study buspirone was the key structure to which certain modifications were made in the non–pharmacophoric part, namely by introducing the 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine–1,3–dione residue (see Scheme 1 and Figure 2). Other modifications were made by introducing different substituents at the piperazine ring nitrogen N–4 (pharmacophoric part) (see Scheme 1).

Thus, we designed and synthesized a number of new arylpiperazinylalkyl derivatives **III–XXVI**. These derivatives contain a fragment of 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine–1,3–dione ring system in which the imide group is incorporated (Figure 2).

EXPERIMENTAL

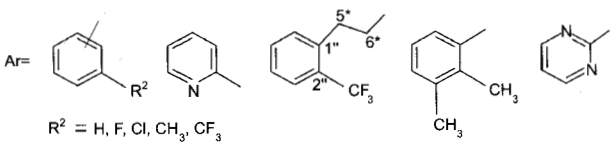
The IR spectra (KBr pellets) were recorded on a Perkin–Elmer FT–IR spectrometer Spectrum 1000, PE Auto IMAGE System. The NMR spectra were recorded on a Unity Plus Varian 500 MHz and Avance DMX 400 WB Bruker 400 MHz (500 MHz for ^1H, 125 MHz for ^{13}C, and 400 MHz for ^1H and 1000 MHz for ^{13}C, respectively). Two–dimensional NMR ^1H–^1H COSY and ^1H–^{13}C HETCOR experiments were performed on a Bruker DMX 400 MHz and Varian Unity plus 500 MHz spectrometers. For the two dimensional experiments the pulse sequences, acquisition and processing parameters were taken from standard Bruker and Varian software library.



Ia-f IIa-f III-XXVI

R,R'=H,H-**a**; Cl,H-**b**; F,H-**c**; MeO,H-**d**; CH_3,H-**e**; H,CH_3-**f**

R,R^1,Ar=**III**-H, H, phenyl; **IV**-H, H, 2-fluorophenyl; **V**-H, H, 2-chlorophenyl; **VI**-H, H, 4-fluorophenyl; **VII**-H, H, 4-tolyl; **VIII**-H, H, 2-(2-trifluoromethylphenyl) ethyl; **IX**-Cl, H, 2-chlorophenyl; **X**-Cl, H, 2-(2-trifluoromethylphenyl)ethyl; **XI**-F, H, 2-tolyl; **XII**-F, H, 2,3-xylyl; **XIII**-F, H, 2-chlorophenyl; **XIV**-F, H, 2-pyridyl; **XV**-MeO, H, 2-chlorophenyl; **XVI**-MeO, H, 2-fluorophenyl; **XVII**-MeO, H, 2-(2-trifluoromethylphenyl)ethyl; **XVIII**-MeO, H, 2-tolyl; **XIX**-MeO, H, 2,3-xylyl; **XX**-MeO, H, 3-trifluoromethylphenyl; **XXI**-H, CH_3, 2-fluorophenyl; **XXII**-H, CH_3, 2-chlorophenyl; **XXIII**-H, CH_3, 2-(2-trifluoromethylphenyl)ethyl; **XXIV**-H, CH_3, 2-pyridyl; **XXV**-CH_3, H, 2-pyrimidynyl; **XXVI**-CH_3, H, 3-trifluoromethylphenyl;



Reagents: (i) 1,4-dibromobutane, K_2CO_3, acetone, Δ; (II) 1-aryl or heteroarylpiperazine K_2CO_3, acetonitrile, Δ.

Scheme 1.

The flash column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). TLC was performed on the plates Kieselgel 60 F_{254} Multiformat of Merck, using a mobile phase toluene, dioxan, ethanol, 25% NH_4OH (6:3.2:0.5:0.2 v/v) and visualized using a UV lamp or dyed with benzene solution of *p*–chloranil.

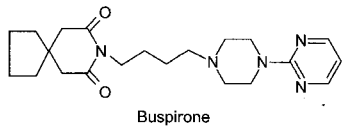
Melting points were determined on Mel–Temp® 3.0 (Barnstead/Thermolyne; USA) instrument without corrections.

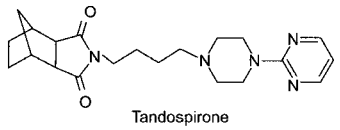
Microanalytical data were obtained on a Perkin Elmer Analyser CHN 2400 in the Department of Chemistry, Technical University of Warsaw and are within ±0.4 of the theoretical values.

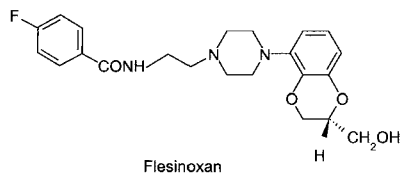
The starting materials 4–aryl–hexahydro–1H,3H–pyrido[1,2–*c*]pyrimidin–1,3–diones **Ia–f** and 2–(4–bromobutyl)–4–aryl–hexahydro–1H,3H–pyrido[1,2–*c*]pyrimidine–1,3–diones **IIa–d** and **f** were prepared according to the reported procedure (21, 22).

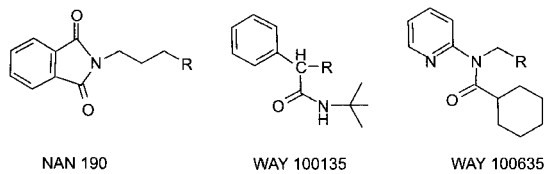
2–(4–BROMOBUTYL)–4–(2–TOLYL)–HEXAHYDRO–1H,3 H–PYRIDO[1,2–*C*]PYRIMIDINE –1,3–DIONE **IIe**

To the mixture of 0.04 mole of imide **Ie**, and 70 ml of acetone was added, while stirring 0.06 mole of K_2CO_3 and 0.12 mole of 1,4–dibromobutane. The obtained mixture was stirred under reflux. The time of the reaction was monitored by TLC (~20 h). After cooling the mixture was filtered and the filtrate was evaporated to dryness. The obtained residue was purified by flash chromatography (with CH_2Cl_2–MeOH, 97:2 v/v) to provide compound **IIe** as a colorless solid. Yield: 79.7%, m.p. 78.5–79°C (from heptane) IR (KBr, cm^{-1}) 1691.2, 1643.8 C=O; ^{1}H NMR 2.19 (m, 1H, C–5H_2), 2.37 (m, 1H, C–5H_2), 1.61 (m, 2H, C–6H_2), 1.85 (m, 2H, C–7H_2), 3.86 (m, 2H, C–8H_2), 7.18 (m, 1H, C–3'H), 7.18 (m, 1H, C–4'H), 7.14 (m, 1H, C–5'H), 7.96 (d, 1H, C–6'H), ^{3}J=7.2, 3.97 (t, 2H, C–1^xH_2), ^{3}J=6.8, 1.85 (m, 2H, C–2^xH_2), 1.78 (m, 2H, C–3^xH_2), 3.37 (t, 2H, C–4^xH_2), ^{3}J=6.4, 2.06 (s, 3H, CH_3); ^{13}C NMR 152.1 C–1, 161.7 C–3, 112.0 C–4, 149.9 C–4a, 26.8 C–5, 18.9 C–6, 22.2 C–7, 43.2 C–8, 137.9 C–1', 133.1 C–2', 130.6 C–3', 128.5 C–4', 126.5 C–5', 131.0 C–6', 40.8 C–1^x, 26.7 C–2^x, 30.4 C–3^x, 33.5 C–4^x, 20.0 CH_3.









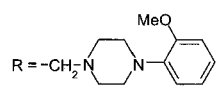


Figure 1.

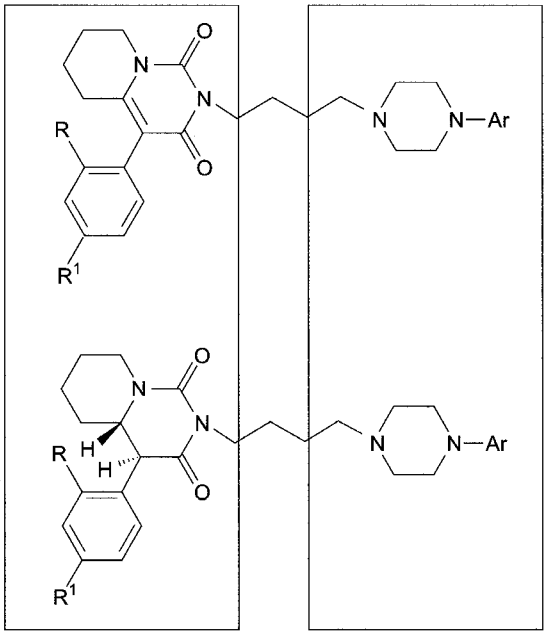


Figure 2.

potassium iodate. The mixture was refluxed under stirring for about 30 h. The time of the reaction was controlled by TLC. The cooled reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography (with CH_2Cl_2–MeOH, 97–3 v/v) to afford the product as a white solid. The purified compounds were crystallized from: **III–VII** from ethanol, **IX, XI–XIV, XX–XXII, XXV, XXVI** from heptane, **XVI** from hexane. The other products were obtained as oil. The oil was dissolved in methanol and then an excess of the solution of methanol saturated with hydrogen chloride was added. A white solid was obtained. The obtained hydrochlorides were crystallized: **VII–X** from methanol, **XV, XVII–XIX, XXIII, XXIV** from abs. ethanol. The reaction yields, melting points, results of elemental analysis and IR data are given in Table 1. The results obtained by NMR are collected in Table 2 (^{1}H NMR) and Table 3 (^{13}C NMR).

Anal. Calcd. For **IIe**: C, 58.31; H, 5.94; N, 7.16. Found: C, 58.32; H, 5.67; N, 7.21.

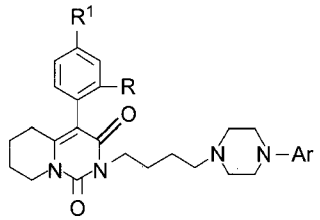
GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-[4-[4-ARYL OR HETEROARYL-1-PIPERAZINYL]BUTYL]-4-ARYL-HEXAHYDRO-1H,3H-PYRIDO[1,2-C]PYRIMIDINE-1,3-DIONES **III–XXVI**

The 5 mmole of the appropriate bromobutyl derivatives **IIa–f** was added under stirring to a mixturecomposed of 80 ml acetonitrile and 5 mmole of

RESULTS AND DISCUSSION

The new compounds described in this paper **III–XXVI** were obtained as shown in Scheme 1. The starting substances for the synthesis were 4-aryl-hexahydropyrido[1,2-*c*]pyrimidine-1,3-dione derivatives **Ia–f**, obtained as the final products of the several-stage synthesis (21). Next the imide group in compounds **Ia–f** was N-alkylated by the

Table 1. Physical, analytical and IR spectroscopic data of compounds **III–XXVI**



No.	R	R^1	Ar	Yield (%)	Base/Hydrochloride m.p. (°C)	Formula	Analysis Calcd./Found C	H	N	IR (C=O) (KBr, cm^{-1})
III	H	H	phenyl	72.2	139–141	$C_{28}H_{34}N_4O_2$	73.33	7.47	12.21	1695
					–		73.27	7.65	12.10	1635
IV	H	H	2–fluorophenyl	73.1	101.5–102	$C_{28}H_{33}FN_4O_2$	70.57	6.98	11.75	1670
					–		70.51	6.96	11.75	1610
V	H	H	2–chlorophenyl	78.6	120.5–121	$C_{28}H_{33}ClN_4O_2$	68.21	6.75	11.36	1670
					–		68.15	6.73	11.09	1630
VI	H	H	4–fluorophenyl	89.3	105.5–106.5	$C_{28}H_{33}FN_4O_2$	70.57	6.98	11.75	1670
					–		70.61	7.03	11.76	1630
VII	H	H	4–tolyl	83.3	125.5–126	$C_{29}H_{36}N_4O_2$	73.70	7.68	11.85	1670
					–		73.64	7.68	11.67	1610
VIII	H	H	2–(2–trifluoromethyl-phenyl)ethyl	71.4	oil	$C_{31}H_{37}F_3N_4O_2$	56.72	6.48	8.53	1696
					277–278	$\cdot 2HCl \cdot 1.6H_2O$	56.74	6.22	8.48	1646
IX	Cl	H	2–chlorophenyl	70.3	160.1–161.6	$C_{28}H_{32}Cl_2N_4O_2$	56.91	6.14	9.48	1692
					198.5–200.2	$\cdot HCl \cdot 1.5H_2O$	56.98	6.05	9.41	1635
X	Cl	H	2–(2–trifluoromethyl-phenyl)ethyl	63.9	oil	$C_{31}H_{36}F_3ClN_4O_2$	54.75	5.93	8.24	1694
					231–232	$\cdot 2HCl \cdot H_2O$	55.14	5.70	8.16	1642
XI	F	H	2–tolyl	89.7	114–115.5	$C_{29}H_{35}FN_4O_2$	71.00	7.19	11.42	1693
					–		71.09	7.12	11.22	1643
XII	F	H	2.3–xylyl	85.0	128.5–130.5	$C_{30}H_{37}FN_4O_2$	71.40	7.39	11.10	1697
					–		71.35	7.43	11.10	1645
XIII	F	H	2–chlorophenyl	90.0	117–118.5	$C_{28}H_{32}FClN_4O_2$	65.81	6.31	10.96	1693
					–		65.85	6.30	10.86	1643

Table 1. (cont.)

No.	R	R^1	Ar	Yield (%)	Base/Hydrochloride m.p. (°C)	Formula	Analysis Calcd./Found C	H	N	IR (C=O) (KBr, cm^{-1})
XIV	F	H	2–pyridyl	92.1	138–139.5	$C_{27}H_{32}FN_5O_2$	67.91	6.75	14.66	1693
					–		67.85	6.72	14.43	1640
XV	OCH_3	H	2–chlorophenyl	40.7	oil	$C_{29}H_{35}ClN_4O_3$	62.25	6.48	10.01	1694
					222–224	·2HCl	62.20	6.47	9.91	1649
XVI	OCH_3	H	2–fluorophenyl	50.6	115–118	$C_{29}H_{35}FN_4O_3$	68.75	6.96	11.05	1695
					–		68.89	6.99	10.98	1633
XVII	OCH_3	H	2–(2–trifluoromethyl-phenyl)ethyl	59.2	oil	$C_{32}H_{39}F_3N_4O_3$	58.05	6.32	8.45	1692
					238.2–238.5	·2HCl·0.25H_2O	57.95	6.24	8.42	1649
XVIII	OCH_3	H	2–tolyl	33.8	oil	$C_{30}H_{38}N_4O_3$	59.80	7.19	9.29	1690
					116.4–117	·2HCl·1.5H_2O	59.75	7.19	8.87	1638
XIX	OCH_3	H	2.3–xylyl	31.7	oil	$C_{31}H_{40}N_4O_3$	57.85	7.52	8.70	1692
					112.7–113	·2HCl·3H_2O	57.80	7.41	8.49	1641
XX	OCH_3	H	3–trifluoromethyl-phenyl	52.0	113.7–114	$C_{30}H_{35}F_3N_4O_3$	64.73	6.34	10.07	1690
					–		64.43	6.22	9.96	1640
XXI	H	CH_3	2–fluorophenyl	82.0	119–120	$C_{29}H_{35}FN_4O_2$	61.81	6.62	9.94	1694
					168–169	.2HCl	61.42	6.63	9.94	1637
XXII	H	CH_3	2–chlorophenyl	55.0	156–157	$C_{29}H_{35}ClN_4O_2$	68.69	6.96	11.04	1692
					–		68.61	6.91	10.82	1639
XXIII	H	CH_3	2–(2–trifluoromethyl-phenyl)ethyl	84.0	oil	$C_{32}H_{39}F_3N_4O_2$	53.18	6.97	7.75	1688
					248–249	·2HCl·4.5H_2O	52.84	6.47	7.74	1641
XXIV	H	CH_3	2–pyridyl	61.0	oil	$C_{28}H_{35}N_5O_2$	60.54	6.89	12.60	1684
					287–288	·2HCl·0.5H_2O	60.58	6.85	12.41	1636
XXV	CH_3	H	2–pyrimidynyl	79.7	105–109	$C_{27}H_{34}N_6O_2$	68.31	7.23	17.71	1695
					–		68.60	6.98	17.73	1630
XXVI	CH_3	H	3–trifluoromethyl-phenyl	96.5	88–91	$C_{30}H_{35}F_3N_4O_2$	66.64	6.54	10.36	1679
					–		66.59	6.61	10.32	1643

Table 2. ^{1}H NMR chemical shifts ([σ, ppm, deuteriochloroform) and coupling constans (Hz) of hexahydropyrido[1,2–*c*]pyrimidine derivatives **III–XXVI**[a]

No.	C–5H_2	C–6H_2	C–7H_2	C–8H_2	C–1^xH_2	C–2^xH_2	C–3^xH_2	C–4^xH_2	Cα H_2	Cβ H2	Aromatic rings
III	2.52 (t, 2H) ^{3}J=6.5	1.69 (q, 2H)	1.92 (q, 2H) ^{3}J=7.0	3.93 (t, 2H) ^{3}J=6.5	4.04 (t, 2H) ^{3}J=7.0	1.73 (m, 2H)	1.60 (m, 2H)	2.43 (t, 2H) ^{3}J=7.5	2.59 (pt, 4H) ^{3}J=5.5	3.19 (pt, 4H)	7.39 (m, 2H, C–2'H, C–6'H), 7.32 (m, 1H, C–4'H), 7.25 (m, 2H, C–3'H, C–5'H), 7.19 (m, 2H, C–3''H, C–5''H), 6.92 (m, 2H, C–2''H, C–6''H), 6.84 (m, 1H, C–4''H).
IV	2.53 (t, 2H) ^{3}J=7.0	1.69 (q, 2H)	1.92 (q, 2H) ^{3}J=6.5	3.94 (t, 2H) ^{3}J=6.5	4.04 (t, 2H) ^{3}J=7.5	1.73 (q, 2H)	1.60 (m, 2H)	2.44 (pt, 2H)	2.62 (m, 4H)	3.10 (pt, 4H)	7.39 (m, 2H, C–2'H, C–6'H), 7.32 (m, 1H, C–4'H), 7.19 (m, 2H, C–3'H, C–5'H), 7.03 (m, 2H, C–3''H, C–5''H), 6.92 (m, 2H, C–4''H, C–6''H).
V	2.53 (t, 2H) ^{3}J=6.5	1.50–1.82 (m, 6H) C–2^xH_2, C–3^xH_2	1.94 (m, 2H) ^{3}J=6.5	3.94 (t, 2H) ^{3}J=6.5	4.04 (t, 2H) ^{3}J=7.0	–	–	2.45 (m, 2H)	2.63 (bs, 4H)	3.07 (pt, 4H)	7.30–7.45 (m, 5H, C–2'H, C–6'H, C–4'H, C–3''H, C–5''H), 7.15–7.23 (m, 2H, C–3'H, C–5'H), 6.90–7.07 (m, 2H, C–4''H, C–6''H).
VI	2.52 (t, 2H) ^{3}J=6.5	1.68 (q, 2H) ^{3}J=6.5	1.91 (q, 2H) ^{3}J=6.5	3.93 (t, 2H) ^{3}J=6.5	4.04 (t, 2H) ^{3}J=7.5	1.73 (m, 2H)	1.60 (m, 2H)	2.43 (pt, 2H)	2.59 (pt, 4H)	3.11 (pt, 4H)	7.39 (m, 2H, C–2'H, C–6'H), 7.32 (m, 1H, C–4'H), 7.19 (m, 2H, C–3'H, C–5'H), 6.94 (m, 2H, C–3''H, C–5''H), 6.86 (m, 2H, C–2''H, C–6''H).
VII	2.51 (t, 2H) ^{3}J=6.5	1.68 (q, 2H) ^{3}J=6.5	1.90 (q, 2H)	3.92 (t, 2H) ^{3}J=6.5	4.04 (t, 2H) ^{3}J=7.5	1.73 (m, 2H)	1.60 (m, 2H)	2.42 (pt, 2H)	2.59 (pt, 4H)	3.13 (pt, 4H)	7.39 (m, 2H, C–2'H, C–6'H), 7.32 (m, 1H, C–4'H), 7.19 (m, 2H, C–3'H, C–5'H), 7.06 (pd, 2H, C–3''H, C–5''H), 6.84 (pd, 2H, C–2''H, C–6''H), 2.26 (s, 3H, CH_3).
VIII	2.52 (t, 2H) ^{3}J=7.0	1.68 (q, 2H) ^{3}J=7.0	1.90 (q, 2H) ^{3}J=7.0	3.93 (t, 2H) ^{3}J=6.5	4.03 (t, 2H) ^{3}J=7.5	1.70 (q, 2H) ^{3}J=7.5	1.58 (q, 2H) ^{3}J=7.5	2.40 (t, 2H) ^{3}J=7.5	2.43–2.76 (m, 8H) +Cβ–H_2	–	7.59 (d, 1H, C–3''H), ^3J_o=7.5, 7.45 (t, 1H, C–5''H), ^3J_o=7.0, 7.39 (t, 1H, C–4''H), ^3J_o=8.0, 7.26–7.36 (m, 4H, C–6''H, C–3'H, C–5'H, C–4'H), 7.20 (d, 2H, C–2'H, C–6'H), ^3J_o=8.0, 2.99 (t, 2H, C–5^xH_2), ^{3}J=7.5, 2.60 (m, 2H, C–6^xH_2), ^{3}J=8.0.
IX	2.39 (m, 2H)	1.70 (q, 2H) ^{3}J=6.0	1.92 (q, d, 2H) ^{3}J=6.0	3.93 (m, 2H) ^{2}J=14.0 ^{3}J=7.0	4.05 (t, 2H) ^{2}J=7.0	1.73 (q, 2H) ^{3}J=6.5	1.61 (q, 2H) ^{3}J=8.0	2.48 (t, 2H) ^{3}J=7.5	2.65 (bs, 4H)	3.08 (bs, 4H)	7.46 (m, 1H, C–3'H), 7.33 (dd, 1H, C–3''H), ^3J_o=8.0, ^4J_m=1.5, 7.30 (m, 2H, C–4'H, C–5'H), 7.20 (m, 2H, C–6'H, C–5''H), 7.04 (dd, 1H, C–6''H), ^3J_o=8.0, ^4J_m=1.5, 6.95 (td, 1H, C–4''H), ^3J_o=7.5, ^4J_m=1.0.
X	2.41 (m, 4H) +C–4^xH_2	1.72 (m, 4H) +C–2^xH_2,	1.92 (m, 2H) ^{3}J=6.0	3.93 (m, 2H) ^{2}J=14.0 ^{3}J=7.5	4.03 (t, 2H) ^{3}J=7.5	–	1.58 (q, 2H) ^{3}J=7.0	–	2.34–2.74 (m, 8H) +Cβ–H_2	–	7.60 (d, 1H, C–3''H), ^3J_o=7.5, 7.46 (m, 2H, C–4''H, C–5''H), 7.35 (d, 1H, C–6''H), ^3J_o=7.5, 7.30 (m, 3H, C–3'H, C–4'H, C–5'H), 7.20 (m, 1H, C–6'H), 2.98 (t, 2H, C–5^xH_2), J=7.5, 2.61 (m, 2H, C–6^xH_2), ^{3}J=8.5.

Table 2. (cont)

No.	C–5H_2	C–6H_2	C–7H_2	C–8H_2	C–1^xH_2	C–2^xH_2	C–3^xH_2	C–4^xH_2	Cα H_2	Cβ H2	Aromatic rings
XI	2.51 (m, 4H) +C–4^xH_2	1.74 (m, 4H) +C–2^xH_2,	1.94 (m, 2H)	3.93 (m, 2H)	4.04 (t, 2H) ^3J=7.2	–	1.62 (m, 2H)	–	2.62 (bs, 4H)	2.95 (bs, 4H)	7.34 (m, 1H, C–4'H), 7.22 (m, 1H, C–5'H), 7.20 (m, 1H, C–6'H), 7.17 (m, 1H, C–3''H), 7.15 (m, 1H, C–5''H), 7.11 (m, 1H, C–3''H), 7.02 (d, 1H, C–6''H), ^3J_o=7.6, 6.97 (t, 1H, C–4''H), ^3J_o=7.6, 2.29 (s, 3H, CH_3).
XII	2.50 (m, 4H) +C–4^xH_2	1.73 (m, 4H) +C–2^xH_2,	1.93 (q, 2H) ^3J=6.4	3.93 (m, 2H)	4.04 (t, 2H) ^3J=7.2	–	1.64 (m, 2H)	–	2.64 (bs, 4H)	2.92 (bs, 4H)	7.32 (m, 1H, C–4'H), 7.19 (m, 2H, C–5'H, C–6''H), 7.08 (m, 2H, C–3''H, C–4''H), 6.90 (m, 2H, C–6'H, C–5''H), 2.25 (s, 3H, CH_3*orto*), 2.20 (s, 3H, CH_3*meta*).
XIII	2.49 (m, 2H)	1.70 (m, 2H)	1.94 (q, 2H) ^3J=6.4	3.93 (m, 2H)	4.04 (t, 2H) ^3J=7.2	1.77 (m, 2H)	1.65 (m, 2H)	2.46 (m, 2H)	2.72 (bs, 4H)	3.13 (s, 4H)	7.33 (m, 1H, C–4'H), 7.22 (m, 2H, C–3''H, C–5''H), 7.19 (m, 2H, C–5'H, C–6'H), 7.11 (m, 1H, C–3'H), 7.04 (m, 1H, C–6''H), 6.96 (m, 1H, C–4''H).
XIV	2.48 (m, 4H) +C–4^xH_2	1.72 (m, 4H) +C–2^xH_2,	1.92 (q, 2H) ^3J=6.8	3.94 (m, 2H)	4.03 (t, 2H) ^3J=6.8	–	1.64 (m, 2H)	–	2.59 (bs, 4H)	3.57 (bs, 4H)	8.17 (d, 1H, C–6''H) ^3J=3.2, 7.45 (t, 1H, C–4''H), ^3J_o=8.4, 7.33 (m, 1H, C–4'H), 7.19 (m, 2H, C–5'H, C–6'H), 7.10 (t, 1H, C–3'H) J_o=8.8, 6.61 (m, 2H, C–3''H, C–5''H).
XV	2.44 (m, 2H) ^2J=17.0 ^3J=7.0	1.69 (m, 2H)	1.92 (m, 2H) ^3J=6.5	3.92 (m, 2H) ^2J=13.5 ^3J=6.8 ^3J=6.5	4.04 (m, 2H)	1.76 (m,4H) +C–3^xH_2	–	3.22 (m, 6H) +CαH_2	–	3.03 (m, 4H)	7.34–7.42 (m, 2H, C–3''H, C–5''H), 7.29 (m, 2H, C–4'H, C–6'H), 7.04–7.12 (m, 3H, C–5'H, C–4''H, C–6''H), 7.00 (m, 1H, C–3'H), 3.77 (s, 3H, OCH_3).
XVI	2.43 (m, 4H) +C–4^xH_2	1.55–1.78 (m, 6H) +C–2^xH_2 C–3^xH_2	1.91 (m, 2H) ^3J=6.51	3.92 (m, 2H) ^2J=13.5 ^3J+6.8 ^3J=6.0	4.03 (t, 2H) ^3J=7.5	–	–	–	2.62 (m, 4H)	3.11 (t, 4H) ^3J=4.5	7.33 (dd, 1H, C–4'H), ^3J=7.3, ^4J=2.0, 7.11 (m, 1–H, C–6'H), 6.88–7.07 (m, 6H, C–3'H, C–5'H, C–3''H, C–4''H, C–5''H, C–6''H), 3.70 (s, 3H, OCH_3).
XVII	2.39 (t, 2H) ^3J=6.5	1.66 (m, 2H)	1.89 (m, 2H) ^3J=6.5	3.88 (m, 2H) ^2J=13.5 ^3J=7.0	3.97 (t, 2H) ^3J=6.0	1.74 (m, 2H)	1.86 (m, 2H)	3.13 (m, 2H)	3.51 (m, 8H) +Cβ–H_2	–	7.57 (d, 1H, C–3''H), ^3J_o=7.5, 7.49 (m, 2H, C–5''H, C–6''H), 7.31 (m, 2H, C–4'H, C–4''H), 7.09 (dd, 1H, C 6'H), ^3J_o=7.5, ^4J_m=1.5, 6.97 (m, 2H, C–3'H, C–5'H), 3.19 (m, 4H, C–5^xH_2, C–6 ^{x}H_2), 3.76 (s, 3H, OCH_3).
XVIII	2,42 (m, 2H) ^2J=17 ^3J=6.5	1.67 (m, 2H)	1.89 (m, 2H)	3.91 (m, 2H)	3.98 (t, 2H) ^3J=7.0	1.71 (q, 2H) ^2J=7.5	1.97 (m, 2H)	3.20–3.35 (m, 6H) +CβH_2	3.47–3.62 (m, 4H)	–	7.37 (m, 1H, C–6'H), 7.21 (m, 2H, C–3''H, C–5''H), 7.10 (m, 2H, C–3'H, C–5'H), 7.18 (m, 1H, C–4'H), 6.98–7.07 (m, 2H, C–4''H, C–6''H), 3.79 (s, 3H, CH_3O), 2.31 (s, 3H, CH_3).

Table 2. (cont.)

No.	C–5H_2	C–6H_2	C–7H_2	C–8H_2	C–1^xH_2	C–2^xH_2	C–3^xH_2	C–4^xH_2	Cα H_2	Cβ H2	Aromatic rings
XIX	2.44 (m, 2H) ^2J=17.0 ^3J=7.0	1.69 (q, 2H) ^3J=7.5	1.91 (q, 2H) ^3J=7.5	3.92 (m, 2H) ^2J=13.5 ^3J=6.5	4.05 (t, 2H) ^3J=6.5	1.76–1.88 (m, 4H) +C3^xH_2	–	3.30 (m, 2H)	3.30–3.63 (m, 4H)	3.17–3.73 (m, 4H)	7.37 (m, 1H, C–6'H), 7.10 (m, 1H, C–4'H), 7.07 (m, 2H, C–3''H, C–5''H), 6.95–7.03 (m, 4H, C–3'H, C–5'H, C–4''H, C–6''H), 3.77 (s, 3H, CH_3O), 2.27 (s, 3H, CH_{3orto}), 2.25 (s, 3H, CH_{3meta}).
XX	2.43 (m,4H) +C–4^xH_2	1.55–1.80 (m, 6H) +C–2^xH_2 +C–3^xH_2	1.91 (m, 2H) ^3J=6.5	3.92 (m, 2H) ^2J=13.5 ^3J=7.0	4.04 (t, 2H) ^3J=7.0	–	–	–	2.59 (t, 4H) ^3J=5.0	3.23 (t, 4H)	7.33(m, 2H,C–4'H, C–5''H), 7.10(dd, 2H, C–6'H, C–4''H), 7.05(m, 2H, C–2''H, C–6''H), 6.99(td, 1H, C–5'H), 6.94(d, 1H, C–3'H), ^3J_o=8.0, ^4J_m=1.5
XXI	2.53 (t,2H) ^3J=6.7	1.68 (q, 2H) ^3J=6.7	1.91 (q, 2H) ^3J=6.4	3.92 (t, 2H) ^3J=6.4	4.03 (t, 2H) ^3J=7.3	1.73 (q, 2H) ^3J=7.6	1.60 (q, 2H) ^3J=7.3	2.45 (t, 2H) ^3J=7.3	2.63 (bs, 4H)	3.11 (bs, 4H)	7.20(d, 2H, C–3'H, C–5'H), ^3J_m=7.6 7.08(d, 2H, C–2'H, C–6'H), 6.97 – 7.07(m, 2H, C–3''H, C–6''H), 6.88 – 6.97(m, 2H, C–5''H,C–4''H), 2.36(s, 3H, CH_3
XXII	2.54 (t, 2H) ^3J=6.7	1.69 (q, 2H) ^3J=7.0	1.92 (q, 2H) ^3J=6.7	3.93 (t, 2H) ^3J=6.4	4.04 (t, 2H) ^3J=7.0	1.74 (q, 2H) ^3J=7.9	1.64 (m, 2H)	2.52 (bs, 2H)	2.69 (bs, 2H)	3.11 (bs, 4H)	7.34(dd, 2H, C–3''H), ^3J_o=7.9, ^4J_m=1.5, 7.21(m, 3H, C–5''H, C–3'H, C–5'H), 7.08(d, 2H, C–2'H, C–6'H), $^3J_0$=7.9, 7.04(dd, 1H, C–6''H), ^3J_o=8.0, ^4J_m=1.5, 6.96(td, 1H, C–4''H), ^3J_o=7.8, ^4J=1.5, 2.36(s, 3H, CH_3)
XXIII	2.44 (t,2H) ^3J=6.6	1.58 (m, 4H) +C–3^xH_2	1.80 (q, 2H) ^3J=6.6	3.82 (t, 2H) ^3J=6.3	3.86 (t, 2H) ^3J=6.8	1.75 (q, 2H)	–	3.25 (bm, 2H)		3.59 (bs, 8H) + Cα H_2	11.88(bs, 1H, Nβ$^+$H), 9.94(s, 1H, Nα$^+$H), 7.71(d, 1H, C–3''H), ^3J_o=7.8, 7.67(t, 1H, C–5''H), 7.62(d, 1H, C–6''H), 7.49(t, 1H, C–4''H), 7.18)(d, 2H, C–3'H, C–5'H), ^3J_o=8.1, 7.07(d, 2H, C–2'H, C–6'H), 3.36(bm, 2H, C–5^xH_2), 3.20(bs, 2H, C–6^xH_2), 2.30(s, 3H, CH_3)
XXIV	2.46 (t, 2H) ^3J=6.0	1.59 (m, 4H) +C– +$C_α$–H_{2a}	1.81 (q, 2H) ^3J=6.5	3.82 (t, 2H) ^3J=6.5	3.87 (t, 2H) ^3J=7.0	1.75 (m, 2H)	–	3.11 (bs, 4H) + $C_β$–H_{2a}	4.41 (bd, 2H) $C_α$–H_{2e}	3.48 (bs, 4H) $C_β$–H_{2e} 3×H_2	11.03(s, 1H, NH^+), 8.12(dd, 1H, C–6''H), ^3J_o=5.7, ^4J_m=1.0, 7.86(t, 1H, C–4''H),^{3}J=7.0,7.18 (2H,C–3'H,C–5'H)^3J_o=7.5, 7.06(d, 2H, C–2'H, C–6'H)6.90(m, 2H, C–4''H, C–5''H), ^3J_o=6.5
XXV	2.27 (m, 1H)	1.69 (m, 2H)	1.93 (m, 2H)	3.93 (m, 2H)	4.05 (t, 2H) ^3J=7.2	1.74 (m, 2H)	1.62 (m, 2H)	2.42 (m, 2H)	2.49 (pt, 4H)	3.82 (pt, 4H)	7.27(m, 1H, C–3'H), 7.27(m, 1H,C–4'H), 7.21(m, 1H, C–5'H), 7.04(d, 1H, C6'H), ^{3}J=7.2, 8.30(d, 2H, C–3''H, C–5''H), ^{3}J=4.8, 6.47(t, 1H, C–4''H), ^{3}J=4.8, 2.14(s, 3H, CH_3)
XXVI	2.29 (m, 1H)	1.72 (m, 2H)	1.95 (m, 2H)	3.96 (m, 2H)	4.08 (t, 2H) ^3J=7.2	1.75 (m, 2H)	1.65 (m, 2H)	2.47 (m, 3H) + C–5H	2.63 (pt, 4H)	3.26 (pt, 4H)	7.29(m, 1H, C–3'H), 7.29(m, 1H, C–4'H), 7.24(m, 1H, C–5'H), 7.08(m, 1H, C–6'H), 7.13(ps, 1H, C–2''H), 7.08(m, 2H, C–4''H, C–6''H), 7.36(t, 1H, C–5''H), ^{3}J=8.0, 2.17(s, 3H, CH_3)

[a] *d*, doublet; *pd*, pseudodoublet; *bs*, broad singlet; *m*, multiplet; *t*, triplet; *pt*, pseudotriplet; *q*, quartet; *a*, axial; *e*, equatorial

Compounds **III–XVI, XX–XXIII, XXV–XXVI** were perfomedas bases ($CDCl^3$); compands **XVII–XIX, XXIII, XXIV** were performed as hydrochloride (D_2O).

Table 3. ^{13}C NMR spectral data of compounds **III–XXVI**

	III	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**	**XII**	**XIII**	**XIV**	**XV**
C–1	151.7	151.7	151.7	151.6	151.6	151.5	151.8	151.7	151.7	151.7	151.7	151.7	153.5
C–3	162.0	162.0	161.9	161.8	161.8	161.7	161.2	161.1	161.7	161.4	161.4	161.4	164.0
C–4	**112.5**	**112.5**	**112.5**	**112.3**	**112.3**	**112.1**	**110.1**	**110.1**	**115.9**	**106.1**	**106.1**	**106.1**	**109.8**
C–4a	**151.4**	**149.6**	**149.6**	**149.6**	**149.6**	**149.5**	**150.4**	**150.4**	**150.9**	**150.9**	**151.0**	**150.9**	**153.3**
C–5	26.7	26.7	26.7	26.6	26.6	26.5	26.4	26.4	26.5	26.5	26.5	26.5	27.5
C–6	18.6	18.6	18.6	18.5	18.5	18.3	18.4	18.4	18.4	18.4	18.4	18.4	19.4
C–7	21.8	21.8	21.8	21.7	21.7	21.5	21.8	21.8	21.8	21.8	21.8	21.7	22.7
C–8	42.6	42.6	42.6	42.5	42.5	42.4	51.1	42.9	42.9	42.8	42.9	42.9	44.3
C–1'	**133.4**	**133.4**	**133.4**	**133.3**	**133.3**	**133.2**	**132.5**	**131.7**	**119.0**	**120.8**	**120.5**	**120.8**	**123.2**
C–2'	128.5	128.5	128.5	128.4	128.4	128.2	**135.1**	**135.1**	**159.2**	**159.2**	**159.0**	**159.2**	**159.0**
C–3'	130.8	130.8	130.7	130.7	130.7	130.5	132.6	129.5	115.9	115.8	115.9	115.7	112.4
C–4'	127.7	127.7	127.7	127.6	127.6	127.4	129.7	129.7	130.0	130.0	130.0	130.0	131.7
C–5'	130.8	130.8	130.7	130.7	130.7	130.5	127.1	127.1	124.2	124.2	124.2	124.2	121.9
C–6'	128.5	128.5	128.5	128.4	128.4	128.2	129.5	131.6	133.0	133.0	133.0	133.0	133.4
C–1^x	41.6	41.6	41.6	41.5	41.5	41.3	41.4	41.4	41.6	41.5	41.4	41.4	41.8
C–2^x	25.7	25.7	25.7	25.6	25.6	25.4	25.6	25.6	25.7	25.6	25.6	25.6	26.1
C–3^x	24.4	24.4	24.4	24.3	24.3	24.1	24.1	24.2	24.2	24.1	23.8	23.9	23.1
C–4^x	58.4	58.4	58.3	58.2	58.3	58.1	58.2	58.2	58.4	58.3	58.1	58.2	58.2
C–α	53.3	53.3	53.4	53.1	53.2	52.9	53.3	53.1	53.7	53.7	53.2	53.0	53.9
C–β	49.1	50.6[b]	51.2	50.0	49.6	52.7	42.9	52.8	51.6	51.9	50.8	44.9	50.4
C–1''	**149.6**	**140.2[b]**	**149.4**	**147.9[b]**	**149.2**	**138.7[b]**	**149.3**	**138.9[b]**	**149.2**	**150.9**	**149.1**	–	**149.3**
C–2''	116.0	**155.7[b]**	**128.7**	117.6[b]	116.2	**128.4[b]**	**128.7**	**128.6[a]**	**132.6**	**132.9**	**128.8**	**159.4**	**130.0**
C–3''	129.1	116.1[b]	127.5	115.3[b]	129.5	125.6[a]	127.5	125.9	126.5	**132,8**	127.6	107.0	131.0
C–4''	119.6	122.3[b]	123.5	**157.0[b]**	**128.9**	125.9	123.6	126.1	123.1	137.9	123.8	137.4	126.0
C–5''	129.1	118.9[b]	130.6	115.3[b]	129.5	131.5	130.6	132.6	131.0	131.3	130.6	113.3	129.1
C–6''	116.0	124.4[b]	120.3	117.6[b]	116.2	131.4	120.4	132.5	119.0	120.8	120.4	148.0	121.9
R, R^1													56.1
													CH_3O
R^2–					20.3	124.3[b]		124.5[a]	17.9	13.9;			
					CH_3	CF_3		CF_3	CH_3	18.4			
										CH_3			
C–5^x						60.0		60.2					
C–6^x						29.7		30.0					

Table 3 (cont.)

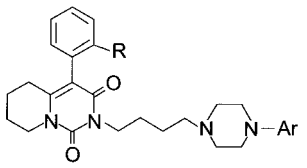
	XVI	XVII	XVIII	XIX	XX	XXI	XXII	XXIII	XXIV	XXV	XXVI
C–1	152.7	151.8	151.5	153.2	152.0	151.7	151.7	151.0	151.0	151.9	151.8
C–3	161.7	162.0	161.8	164.0	161.7	162.0	162.1	161.2	161.1	161.7	162.1
C–4	**108.6**	**108.3**	**108.4**	**109.6**	**108.6**	**112.4**	**112.4**	**110.7**	**110.4**	**111.8**	**112.4**
C–4a	**150.0**	**150.9**	**152.1**	**153.5**	**150.1**	**149.4**	**149.5**	**149.3**	**150.6**	**149.4**	**149.8**
C–5	26.3	26.4	26.7	27.5	26.3	26.7	26.7	26.2	26.2	26.5	26.9
C–6	18.6	18.4	18.8	20.7	18.5	18.6	18.6	17.9	17.8	18.7	19.0
C–7	22.0	21.7	22.1	22.7	21.9	21.8	21.8	20.5	21.0	21.9	22.2
C–8	42.8	43.1	43.1	44.3	42.8	42.5	42.5	42.2	42.5	42.9	43.2
C–1'	**122.2**	**121.9**	**123.5**	**123.2**	**122.1**	**130.3**	**130.3**	**130.7**	**130.8**	**137.6**	**138.0**
C–2'	**157.4**	**157.3**	**158.4**	**159.0**	**157.4**	130.5	130.6	130.8	130.7	**133.0**	**133.3**
C–3'	111.1	111.1	111.9	112.3	111.1	129.2	129.2	128.7	128.7	130.3	130.6
C–4'	129.5	129.7	129.9	130.9	129.5	**137.3**	**137.4**	**136.4**	**136.4**	128.1	128.6
C–5'	120.8	120.8	121.0	121.9	120.8	129.2	129.2	128.7	128.7	126.2	127.0
C–6'	132.4	132.1	133.1	133.4	132.4	130.5	130.6	130.8	130.7	130.7	131.1
C–1^{x}	41.5	40.4	40.7	41.4	41.5	41.5	41.4	40.4	42.2	41.4	41.7
C–2^{x}	25.7	24.6	25.4	25.8	25.7	25.7	25.6	24.3	24.4	25.7	26.0
C–3^{x}	24.3	21.0	21.2	22.3	24.4	24.3	24.0	21.0	20.6	24.3	25.0
C–4^{x}	58.4	56.3	56.2	57.6	58.3	58.3	58.2	55.8	55.1	58.4	59.0
C–α	53.3	49.5	52.3	53.6	53.0	53.2	53.2	47.7	50.0	53.1	53.3
C–β	50.6	48.9	49.0	50.7	48.6	50.5	50.9	40.0	40.1	43.7	49.0
C–1''	**140.3**[b]	**135.4**	**150.7**	**150.4**	**151.5**	**140.2**	**149.3**	**150.7**	–	–	**153.5**
C–2''	**155.8**[b]	**128.5**[a]	**133.1**	**127.6**	112.0[c]	**155.7**	**128.8**	**127.5**[a]	**154.8**	**166.0**	109.9
C–3''	116.1[b]	126.0[c]	127.4	**139.5**	**131.2**[a]	115.8	130.6	126.0[a]	110.7	–	**129.8**
C–4''	122.9[b]	127.2	124.6	127.3	156.6[b]	122.3	123.7	134.9	141.2	157.7	116.0
C–5''	118.9[b]	132.4	131.8	132.5	118.6	118.9	127.6	132.9	114.0	110.0	118.9
C–6''	124.7[b]	132.3	110.8	118.0	129.5	124.4	120.5	131.9	142.4	157.7	129.8
R, R^{1}	55.6	55.6[b]	55.9	56.0	55.5[b]	21.2	21.2	20.8	20.8	19.7	20.0
	CH_3O	CH_3O	CH_3O	CH_3O	CH_3O	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
R^{2}–	–	124.4[a]	17.7	19.4;	124.4[a]	–	–	124.3[a]	–	–	127.3
		CF_3	CH_3	14.0 CH_3	CF_3			CF_3			CF_3
C–5^{x}	–	57.8	–	–	–	–	–	58.7	–	–	–
C–6^{x}	–	28.0	–	–	–	–	–	26.1	–	–	–

a – appear as quartet, b – appear as doublet, c – appear as triplet

Coupling constant ^{n}J (^{13}C–^{19}F) **IV**: $^{1}J_{2''-F}$=245.8, $^{2}J_{3''-F}$=20.6, $^{2}J_{1''-F}$=8.7, $^{3}J_{6''-F}$=3.6, $^{3}J_{4''-F}$=8.3, $^{4}J_{5''-F}$=3.1; **VI**: $^{1}J_{4''-F}$=238.5, $^{2}J_{3'',5''-F}$=22.0, $^{3}J_{2'',6''-F}$=7.8, $^{4}J_{1''-F}$=2.3; **VIII**: $^{1}J_{CF3}$=237.9, $^{2}J_{2''}$=29.7, $^{3}J_{3''}$=5.9, $^{3}J_{1''}$=1.9; **X**: $^{1}J_{CF3}$=273.9, $^{2}J_{2''}$=29.8, $^{3}J_{3''}$=6.0, $^{3}J_{1''}$=1.9; **XX**: $^{1}J_{CF3}$=272.5, $^{2}J_{3''}$=31.6, $^{3}J_{2''}$=4.1, $^{3}J_{4''}$=4.1, (^{17}O–^{12}C) 1J=1.9; **XVI**: $^{1}J_{2''}$=245.8, $^{2}J_{1''}$=8.7, $^{3}J_{6''}$=3.7, $^{3}J_{4''}$=7.8, $^{4}J_{5''}$=3.2, $^{2}J_{3''}$=21.2; **XVII**: $^{1}J_{CF3}$=273.4, $^{2}J_{2''}$=29.7, $^{3}J_{3''}$=5.5, (^{17}O–^{12}C) ^{1}J=1.4; **XXI**: $^{1}J_{2''}$=246.1, $^{2}J_{3''}$=21.5, $^{3}J_{4''}$=7.9, $^{3}J_{6''}$=2.9, $^{4}J_{5''}$=3.0; **XXIII**: $^{1}J_{CF3}$=274.4, $^{2}J_{2''}$=29.3, $^{3}J_{3''}$=5.9.

^{13}C chemical shifts of the ipso carbon atoms of the pyridopyrimidine and phenyl rings are given in bold numbers ({d, ppm); compounds **III–XVI, XX–XXIII, XXV–XXVI** were performed as bases ($CDCl_3$); compounds **XVII–XIX, XXIII, XXIV** were performed as hydrochloride (D_2O), TMS as internal standard.

Table 4. Binding affinities data for 5–HT_{1A}, 5–HT_{2A} and [a] receptors in compounds **1–5**[a]



R/Ar=H, 2–pyrimidynyl, **1**;
2–F, 2–pyrimidynyl **2**;
2–Cl, 2–pyrimidynyl **3**;
2–OCH_3, 2–pyrimidynyl **4**;
2–F, 3–trifluoromethyl phenyl **5**;

No	Ki (nM)			Selectivity versus 5–HT_{1A} receptor Ki ratio	
	5–HT_{1A} [^{3}H] 8–OH–DPTA	5–HT_{2A} [^{3}H] Ketanserin	α_1 [^{3}H] Prazosin	5–HT_{2A}	α_1
1	45.6	336	1202	7.4	26.4
2	69.2	374	742	5.4	10.7
3	78.7	607	642	7.7	8.2
4	56.4	871	1597	15.4	28.3
5	72.2	216.9	2300	3.0	31.8

[a] see ref. (22), data for compounds signed **1–4** and (23) for compound **5**.

1,4–dibromobutane, yielding the monobromobutyl derivatives **IIa–f** (22).

The final products in the series of 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine **III–XXIV** derivatives were obtained by the condensation of the appropriate 1–aryl– or 1–heteroarylpiperazine with the above described monobromobutyl derivatives **IIa–f**.

All new compounds **III–XXIV** were identified and proven by the IR and elemental analysis C, H, N (Table 1), ^{1}H (Table 2) and ^{13}C NMR (Table 3).

The ^{1}H–NMR spectra of the compounds non-substituted in *ortho* position of the aromatic ring in 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine are typical; the shape of proton signals of piperidine ring points to fast dynamic processes of the type: chair ↔ chair. Similar results were obtained for the piperazine ring. Substitution in the *ortho* position (the aromatic ring in 4–aryl–hexahydropyrido [1,2–*c*]pyrimidine) hinders inversion of the ring and, as a result, distinct signals of equatorial and axial protons can be observed. For the protons of piperidine ring some multiplets with geminal and vicinal coupling constants were noted. The ^{13}C–NMR spectra are typical. After substitution of the aromatic ring by fluorine, the C–F couplings were observed.

In our further study on the synthesis of new ligands with potentially higher affinity and selectivity to 5–HT_{1A} receptors, the investigations have been restrained to the derivatives of 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine. Formerly, 21 compounds representing a series of 4–aryl–hexahydro– and 4–aryl–octahydropyrido[1,2–*c*]pyrimidine derivatives were examined and it was shown that the 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine derivatives were definitely more selective to 5–HT_{1A} receptors regarding to receptors 5–HT_{2A} and α_1 as compared with the derivatives of 4–aryl–octahydropyrido[1,2–*c*]pyrimidine (22, 23). Within tested group of compounds, 5 display high selectivity to 5–HT_{1A} receptors regarding to receptors 5–HT_{2A} and α_1 (see Table 4).

Moreover, we have noted that the increase of affinity for the receptor 5–HT_{1A} and also higher selectivity of the studied ligands are closely related to the presence of substituents F, OCH_3, Cl and H located in the *ortho*–position in the rest of 4–aryl–hexahydropyrido[1,2–*c*]pyrimidine (22, 23). It was also observed that the presence of 2–pyrimidynyl(compounds signed **1–4**) and 3–trifluoromethylphenyl(compound **5**) radicals bonded to piperazine in the pharmacophoric part has in influence on affinity and selectivity of investigated compounds.

From among the derivatives **III–XXVI** obtained, seven new compounds (**XII, XIV, XIX, XX, XXIV–XXVI**) were selected for the study of their affinity to 5–HT_{1A}, 5–HT_{2A} and α_1 adrenergic receptors, using radioligand binding assay. The investigations will be carried out in the Institute of Pharmacology of the Polish Academy of Sciences in Cracow and the results will be published elsewhere.

REFERENCES

1. Zifa E., Fillion G.: Pharmacol. Rev. 44, 401 (1992).
2. Raymond J.R., Mukhin Y.V., Gettys T.W., Garnovskaya M.N.: Br. J. Pharmacol 127, 1751 (1999).

3. Hamon M.: In Serotoninergic Neurons and 5–HT Receptors in the CNS, Handbook of Experimental Pharmacology, Baumgarten H.G., Göthert M., Eds.; pp 239–268, Springer, Berlin Ch. 9, (1997).
4. Glennon R.A., Dukat M.: Serotonin ID Res. Alert 2, 351 (1997).
5. Barness N.M., Sharp T.: Neuropharmacology 38, 1083 (1999).
6. Barros M., Mello E.L., Huston J.P., Tomaz C.: Pharmacol. Biochem Behav. 68, 255 (2001).
7. Dekeyne A., Brocco M., Adhumeau A., Gobert A., Millan M.J.: Psychopharmacology 152, 55 (2000).
8. Orjales A., Alonso–Cires L., Labeaga L., Corcostegui R.: J. Med. Chem. 38, 1273 (1995).
9. Kuipers W., Kruse C.G., van Wijngaarden J., Standarr P.J., Tulp M.Th.M., Veldman N., Spek A.L., Ijzerman A.P.: J. Med. Chem. 40, 300 (1997).
10. Lopéz–Rodriguez M.L., Morcillo M.J., Rovat T.K., Fernández E., Vicente B., Sanz A.M., Hernandez M., Orensanz L.: J. Med. Chem. 42, 36 (1999).
11. Perrone R., Berardi F., Colabufo N.A., Leopoldo M., Tortorella V.: Bioorg. Med. Chem. 8, 873 (2000).
12. Abou–Gharbia M.A., Childres W.E. Jr., Fletcher H., McGaughey G., Patel U., Webb M.B., Yardley J., Andree T., Boast C., Kucharik R.J. Jr., Marquis K., Morris H., Scerni R., Moyer I.A.: J. Med. Chem. 42, 5077 (1999).
13. Bronowska A., Leś A., Chilmończyk Z., Filipek S., Edvardsen Ø., Østensen R., Sylte I.: Bioorg. Med. Chem. 9, 881 (2001).
14. Caliendo G., Fiorino F., Grieco P., Perissutti E., Santagada V., Severino B., Bruni G., Romeo M.R.: Bioorg. Med. Chem. 8, 533 (2000).
15. Lopéz–Rodriguez M.L., Morcillo M.J., Fernández E., Porras E., Orensanz L., Beneytez M.E., Manzanares J., Fuentes J.A.: J. Med. Chem. 44, 186 (2001).
16. Paluchowska M.H., Bojarski A.J., Charakchieva–Minol S., Wesołowska A.: Eur. J. Med. Chem. 37, 273 (2002).
17. Sabb A.L., Vogel R.L., Kelly M.G., Palmer Y., Smith D.L., Andree T.H., Schechter L.E.: Bioorg. Med. Chem. Lett. 11, 1069 (2001).
18. Bojarski A.J., Mokrosz M.J., Charakchieva–Minol S., Kozioł A., Wesołowska A., Tatarczyńska E., Kłodziński A., Chojnacka–Wójcik E.: Bioorg. Med. Chem. 10, 87 (2002).
19. Peglion J.L., Goument B., Despaux N., Charlot V., Giraud H., Nisole Ch., Newman–Tancredi A., Dekeyne A., Bertrand M., Genissel P., Millan M.J.: J. Med. Chem. 45, 165 (2002).
20. Trumpp–Kallmeyer S., Haflack J., Bruinvels A., Hibert M.: J. Med. Chem. 35, 3448 (1992).
21. Herold F., Wolska I., Helbin E., Król M., Kleps J.: J. Heterocycl. Chem. 36, 389 (1999).
22. Herold F., Kleps J., Wolska I., Nowak G.: Farmaco 57, 959 (2002).
23. Herold F., Kleps J., Maj M., Nowak G.: Pharmazie 59,99 (2004).

Received: 18.04.2003