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Original article

Synthesis, immunomodulating activity and ^{1}H NMR studies of 7-oxo-9,11-ethano-13-azaprostanoids

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Abstract

Novel 9,11-ethano analogues of prostaglandin endoperoxides with a nitrogen in position 13 were synthesized. ^{1}H NMR spectra of the obtained compounds were studied. All prostanoids administered perorally at doses of 2.5–10.0 μg kg^{-1} had specific dose-dependent effects on the B-cellular immunity estimated under in vivo conditions on the model of the B-cellular immune response. In terms of the direction of their activities, eight of the studied compounds were found to be immunostimulators, whereas other three compounds displayed immunosuppressing effect. Two of the compounds increased the amount of antibody-forming cells (AFC) per 10^6 spleen cells by 1.9 times in comparison with the respective parameter of control group.

Keywords: Nucleophilic addition; Bicyclo[2.2.1]heptane derivatives; Prostanoids; Prostaglandin endoperoxide analogues; ^{1}H NMR; B-cellular immune response; Immunomodulating activity

1. Introduction

Synthetic prostaglandin (PG) analogues, like their natural precursors, display a wide range of pharmacological activities. Based on PG structure, a number of remedies for stimulating the childbirth and for curing the stomach and duodenum ulcer have been developed [1,2]. Taking into account the fact that PG plays a substantial role in the immunity regulation [3], we obtained novel low molecular weight immunostimulating agents by a total synthesis. When used at extremely low doses (0.5–10 μg kg^{-1}), the agents had effect on the immunity system. The effect is likely to be specific, i.e. it resulted in a preferential proliferation enhancement of antigen-primed B-immunocytes rather than that of antigen-induced non-specific limphoproliferation [4,5]. To continue the investigation of the novel prototypes of endogenic low molecular weight immunoregulators, we synthesized 15 carbon cyclic PGH analogues and studied their immunopharmacological activities.

2. Chemistry

Nucleophilic 1,4-addition of amines to double bond of conjugated enone fragment in bicycloheptene synthons **1–3** was investigated (see Table 1). Acyclic, cyclic, heterocyclic and aromatic amines were used as nucleophiles. The influence of the various factors on the rate of the reaction was investigated and the optimal conditions for realization of this process were selected. The synthetic routes for the preparation of the 13-azaprostanoids[1] are illustrated in Scheme 1. The acyl bicycloheptenones **1–3** were synthesized using a previously described method [6,7].

It was found that amines with alkyl radical were added in the best way. The addition of alkyl amines **4–7** to bicycloheptenones **1–3** proceeded without the catalyst at room tempera-

Abbreviations: br d, broadened doublet; br s, broadened singlet; d, doublet; DBU, 1,8-diazabicyclo[5.4.0]undec-7-en; d d, double doublet; d m, double multiplet; d t, double triplet; m, multiplet; M/S, mass spectrum; q, quartet; s, singlet; t, triplet; t d, triple doublet; TMG, 1,1,3,3-tetramethylguanidine.

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[1] PG numbering was used.

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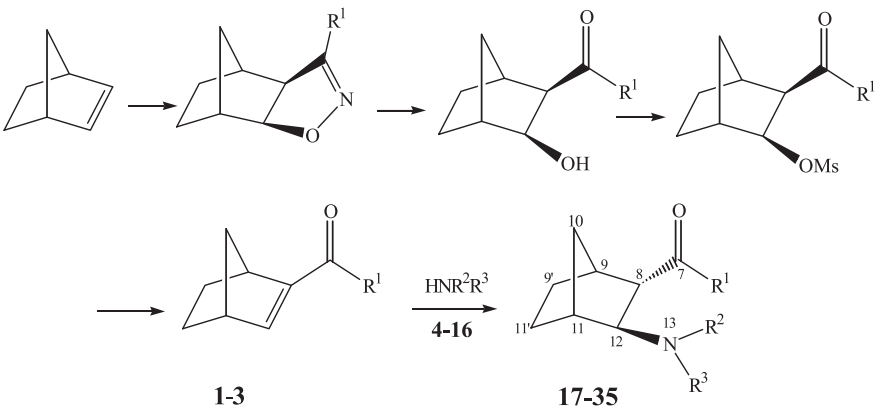
Table 1
Synthesis of 7-oxo-9,11-ethano-13-azaprostanoids

Compound	R^1	R^2	R^3	Precursor	Reagent
17	$(CH_2)_5CO_2Me$	C_7H_{15}	H	**3**	**4**
18	C_2H_5	C_8H_{17}	H	**1**	**5**
19	$(CH_2)_5CO_2Me$	C_8H_{17}	H	**3**	**5**
20	C_2H_5	R_2=R_3=–$(CH_2)_4$–		**1**	**6**
21	$(CH_2)_4CO_2Me$	R_2=R_3=–$(CH_2)_5$–		**2**	**7**
22	$(CH_2)_4CO_2Me$	R_2=R_3=–$(CH_2)_2O(CH_2)_2$–		**2**	**8**
23	$(CH_2)_4CO_2Me$	$(CH_2)_2$–C_6H_3–Ome-*p,m*	H	**2**	**9**
24	$(CH_2)_4CO_2Me$	CH(Me)Ph	H	**2**	**10**
25	$(CH_2)_4CO_2Me$	Ph	H	**2**	**11**
26	$(CH_2)_5CO_2Me$	Ph	H	**3**	**11**
28	$(CH_2)_4CO_2Me$	C_6H_4–Cl-*p*	H	**2**	**13**
29	C_2H_5	C_6H_4–Ome-*p*	H	**1**	**14**
30	$(CH_2)_4CO_2Me$	C_6H_4–OH-*o*	H	**2**	**15**
31	$(CH_2)_4CO_2Me$	C_6H_4–NO_2-*o*	H	**2**	**16**
32	$(CH_2)_4CO_2Me$	C_7H_{15}	H	**2**	**4**
33	$(CH_2)_4CO_2Me$	C_8H_{17}	H	**2**	**5**
34	$(CH_2)_5CO_2Me$	R_2=R_3=–$(CH_2)_4$–	3	**6**	
35	$(CH_2)_4CO_2Me$	C_6H_4–Ome-*p*	H	**2**	**14**

ture, however, the rate of the reaction was low. Several days were needed for completion of the process. The addition of heptylamine (**4**), octylamine (**5**), pyrrolidine (**6**) and pyperydine (**7**) was completed in 12 h in boiling benzene. Eighteen hours were required for the addition of morpholine (**8**), 3,4-dimethoxyphenethylamine (**9**) and α-methylbenzylamine (**10**). The decrease of the reaction rate with amines **8–10** may be explained by reduction of amine nucleophility owing to the presence of the bulky substituents (compounds **9–10**) and electron-withdrawing oxygen at the position 4 in their structure. The presence of the latter causes inductive migration of electron density from nitrogen to oxygen in the system of bonds N→C→C→O (compound **8**). The addition of alkyl amines to enones **1–3** was completed in 6 h in the triethylamine presence. In case of using 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) catalyst, the reaction time was reduced to 1–2 h.

Aryl amines were less reactive nucleophiles. The rate of the reaction in this case depended on the type and position of the substituents in the aromatic moiety. Electron-donating substituents increased electron density on nitrogen in amine and promoted acceleration of the reaction. Electron-withdrawing groups inhibited nucleophilic addition of amines. The substituents promoting mesomeric delocalization of electron pair of nitrogen of amino group resulted in the greatest deceleration of the reaction. The influence of the *para*-substituents was a little bigger. It was so because, the conjugation effect of substituent reducing basicity of nucleophile was as much as possible expressed in this position and resulted in the difficulty of the new bond formation. The influence of the *ortho*-substituents was complicated by specific intramolecular interaction. Higher nucleophility of *ortho*-aminophenol (**15**) is outweighed by specific effects, which counteract the reaction.

So it was necessary to use stronger bases such as 1,1,3,3-tetramethylguanidine (TMG), DBU or sodium hydride as the catalysts in the addition reaction of aromatic amines with electron-withdrawing or *ortho*-substituent in the aromatic moiety to bicycloheptenones. Only aniline (**11**) and *p*-anisidine (**14**) completed reaction in 6 h in the presence of TMG forming 13-azaprostanoids **25–26, 29** and **35**. The yield of the reaction with *p*-anisidine was low because of



Scheme 1.

resinification of the reaction mixture. In case of using sodium hydride the process was completed in 1 h in higher yield. Azaprostanoids **28, 30–31** were formed only in the presence of sodium hydride.

Furthermore, the behavior of *p*-aminothiophenol (**12**) in the nucleophilic addition reaction to the activated double bond of bicycloheptenone was investigated. There are two competing nucleophilic centers capable to enter the reaction, namely, mercapto and amino group in this molecule. It was expected that the interaction with sulfur as with the atom-donor possessing lower electronegativity, large ionic radius, high polarizability and easy oxidability should proceed faster than with nitrogen of amino group. And it occurred so. Interaction of bicycloheptenone **2** with *p*-aminothiophenol (**12**) in benzene without any catalyst within 30 min resulted in the formation of 13-thiaprostanoid 7-Oxo-9,11-ethano-13-thia-13-(4-aminophenyl)-1,14,15,16,17,18,19,20-octanor prostanoic acid methyl ester **27** in 96% yield [8].

The best solvent for the 1,4-addition reaction of amines to bicycloheptenones **1–3** described above was benzene. It was very convenient from the point of view of experimental practice.

In all cases the formation of only one adduct with the "natural" *trans* configuration of side chains was observed. The addition of amine took place to the *exo*-face of bicycloheptane.

2.1. ^1H NMR spectroscopy

The ^{1}H NMR spectra for obtained azaprostanoids provided the detailed information on their structure. The multiplicity of the appropriate proton signals and values of coupling spin–spin constants were found to confirm the *endo,exo*-stereochemistry of the substituents at positions 8 and 12 of a prostan skeleton, respectively. The type of the signal and the values of chemical shift from *endo*-proton H-12 are characteristic. This proton appears as a double doublet at δ 2.64–3.77 ppm with coupling constants $^3J_{12,8}$ ~ 2.8–5.2 Hz and $^4J_{12,10}$ ~ 1.18–1.8 Hz. Such image of a signal is caused by spin–spin coupling with bicycloheptane *exo*-proton H-8 and by long-range W-coupling with the *anti*-proton of the bicycloheptane methylene bridge H-10. The bicycloheptane *endo*-protons do not couple with bridge-head protons H-9 and H-11. The N-substituent influences on the value of chemical shift of proton H-12. So, proton H-12 resonates at δ ~ 3.00 ppm in compounds **17–19, 32–33** possessing *n*-heptyl and *n*-octyl radical at position 13. Phenyl substituents cause strong deshielding of this proton and low-field shift of its resonant signal on 0.7 ppm. Small high-field shift of a *endo*-proton H-12 signal on 0.3 ppm in prostanoids with a cyclic radical at nitrogen is observed. The image of the signal and the value of coupling constant in this case do not practically vary.

Unlike *endo*-protons, *exo*-protons in the bicycloheptane ring are characterized by a wide spectrum of couplings and have a complex signal in ^{1}H NMR spectrum. The signal from *exo*-H-8 appears as triple doublets at δ 2.48–3.06 ppm with vicinal coupling constant $^3J_{8,12}$ ~ 2.8–5.2 Hz and long-range W-coupling constant $^4J_{8,9'}$ ~ 1–2 Hz. The substituents in ω-chain do not essentially influence on deshielding of this proton.

In spectra of all compounds the proton H-9 appears as broadened singlet since it possesses several coupling spin–spin constants similar in their values and consequently signals superposition takes place. The H-11 proton signals are observed at δ 2.13–2.42 ppm. Proton resonates as broadened doublet. Such image of a signal is caused by vicinal coupling with two bicycloheptane protons H-10, by coupling with an *exo*-H-11′ and by long-range coupling with another bridge-head proton. Using the double resonance technique has allowed us to show the relationship between the protons described above.

The signal from H-5 is observed as triplet at δ ~ 1.05 ppm with vicinal coupling $^3J_{5,6}$ ~ 7.33 Hz in spectra of compounds **18, 20** and **29** having 1-oxopropyl as α side chain. The signals from H-6 appear as a quartet with the same coupling constant in consequence of their coupling with three protons of neighboring methyl.

The signals from protons of CH_2 groups neighboring with keto or ester carbonyl groups appear as triplet at δ 2.38–2.47 and 2.30–2.33 ppm, respectively, with J ~ 6.2–7.9 Hz in compounds **17, 19, 21–28** and **30–35** having methoxycarbonyl group in the structure of α-chain. These protons are magnetic equivalent. Methylene protons of a ω-chain neighboring with amino group are not magnetic equivalent and their signal is a complex multiplet, which is observed at δ 2.33–2.55 ppm for azaprostanoids **17–22** and **32–34**.

The signal from the NH group protons is observed as broadened singlet at δ ~ 3.50 ppm only for compounds with phenyl substituent at nitrogen. It is not characteristic for others azaderivatives of this series.

2.2. Infrared spectroscopy

There are characteristic absorptions of valence oscillations of keto and ester groups at ~1710 and ~1740 cm^{-1}, respectively, in IR spectra of azaprostanoids. The intensity of amino group valence oscillations is very low in alkyl substituted PGH azaanalogues.

An intensive absorption bands at 3400–3450 cm^{-1} are only in spectra of compounds **25–31, 35** with aryl radical at amino group. At the same time the deformation oscillations of NH group are covered by the bands of skeleton oscillations of aromatic carbon–carbon bonds in spectra for compounds with aryl radical. Thus, two overlapped bands are observed at 1594–1606 cm^{-1} in a spectrum. These bands of low intensity are observed at ~1600 cm^{-1} in alkyl amines.

Table 2
Immunomodulating activities of 7-oxo-9,11-ethano-13-azaprostanoids on the model of the B-cellular (humoral) immune response

Compound	ED[a] (μg kg^{-1} per os)	AFC amount per 10^6 spleen cells[b]	Relative activities [c]	P [*]
17	2.5	874.5 ± 44.3	1.9	<0.001
18	2.5	417.3 ± 23.8	0.85	>0.05
19	2.5	638.4 ± 34.4	1.4	<0.02
20	2.5	838.2 ± 39.4	1.6	<0.001
21	2.5	485.4 ± 31.6	0.5	<0.001
22	10.0	881.7 ± 46.4	1.6	<0.001
23	2.5	507.5 ± 21.3	1.0	>0.05
24	5.0	703.2 ± 43.4	1.9	<0.001
25	2.5	361.9 ± 37.2	0.8	>0.05
26	5.0	582.4 ± 34.1	1.5	<0.001
27	2.5	408.4 ± 22.5	0.8	>0.05
28	5.0	388.8 ± 21.5	1.2	<0.05
29	10.0	528.2 ± 29.7	0.7	<0.001
30	2.5	241.6 ± 11.2	0.5	<0.001
31	2.5	766.7 ± 62.4	1.5	<0.002

The compounds were studied on CBA female mice immunized intraperitoneally with SRBC at a dose of 1.5×10^7 SRBC per mouse. Each value is the mean of six mice.

[a] ED, saturation dose.

[b] In control animals the parameter ranged from 324.5 ± 23.4 to 753.7 ± 38.4.

[c] The value of immunization effect was considered to be 1.0.

[*] P, Trustworthiness.

3. Pharmacology

In terms of their effect on the B-cellular immunity, eight (compounds **17, 19, 20, 22, 24, 26, 28, 31**) of the 15 prostanoids studied were shown to be stimulating agents; prostanoids **21, 29, 30** were immunosuppressors whereas compounds **18, 23, 25, 27** had no effect on the immune response (see Table 2).

4. Results and discussion

The prostanoids studied displayed their immunomodulating activities in a dose-dependent manner characterized by a saturation effect. Though saturation doses of the compounds were low and kept within the above-mentioned range of 2.5–10 μg kg^{-1}, they made it possible for the prostanoids to achieve their maximum effects. That is why the saturation doses were referred to as effective doses (ED), which enabled to compare the efficiencies of the prostanoids tested. Thanks to this phenomenon, saturation doses were referred to as ED values, which made it possible to compare the efficiencies of the prostanoids tested.

In the group of alkylamines particular attention should be paid to compound **17**. The administration of the compound (2.5–5.0 μg kg^{-1} perorally) resulted in the increase in antibody-forming cells (AFC) amount per 10^6 spleen cells in immunized CBA mice by 1.9 times in comparison with the respective parameter in control animals. It is obvious that compound **17**, having natural alkyl α-chain, displays high immunomodulating activity. The ω-chain elongation by one methylenic link, taking place in case of alkylamine **19**, resulted in a slight fall of the immunoenhancing activity. At the same time, compound **18**, containing C_2H_5-fragment in the formed α-chain, has no immunomodulating effect. Meanwhile, analogues precursor of prostanoid **20**, characterized by the presence of pyrrolidinyl fragment in ω-chain, increases the B-cellular immune response to sheep red blood cells (SRBC) by 1.6 times.

As a rule, in case of profound ω-chain modification there were no substantial changes of immunomodulating activities (compare prostanoids **22, 24** and **26**). At the same time, PG effect on the immune system may be dependent on the types of cyclic and heterocyclic fragments in ω-chain. For instance, prostanoid **22** having morpholinyl fragment in ω-chain enhanced the B-cellular immune response by 1.6 times, whereas its analogue **21** characterized by the presence of piperidyl fragment in this chain suppressed the immunity. The change of immunomodulating activity direction also takes place in case of the replacement of 2-nitrophenyl fragment in ω-chain by hydroxyphenyl group (compare compounds **30** and **31**).

5. Conclusions

Thus, most of the synthesized prostanoids displayed dose-dependent specific effect on the B-cellular immunity in the range of micromolar doses. This fact enables to suggest that their immunobiological effects are carried out due to specific receptors. Compounds **21** and **22** as well as **30** and **31**, characterized by opposite effects on the immune response, may be considered as agonists or antagonists of the specific prostanoid receptors.

6. Experimental protocols

6.1. Chemistry

^{13}C NMR spectra were measured at 60 MHz on a Bruker AC-200 instrument. ^{1}H NMR spectra were measured at 200 MHz on a Bruker AC-200 and at 400 MHz on a Bruker AC-400 instrument. All NMR spectra were recorded in deuteriochloroform as solvent. Infrared spectra were recorded on UR-20 infrared spectrophotometer. Mass spectra were measured with use of a Varian-MAT-311A mass spectrometer. All new compounds exhibited ^{1}H NMR, IR and MS spectra consistent with their assigned structure.

All reactions were conducted in oven-dried glassware. All solvents were purified before use; benzene was distilled from P_2O_5. The starting reagent bicyclo[2.2.1]heptene was obtained commercially and used without further purification.

The purity of the synthesized compounds was checked by means of TLC. All TLC were performed on Merck DC-Plastikfolien Kieselgel 60 F_{254} and Merck DC-Alufolien Kieselgel 60 F_{254} plates with the following solvent systems: hexane/diethyl ether 50:50 (system 1); diethyl ether (system 2); diethyl ether/ethyl acetate 80:20 (system 3). Column chromatography was performed on silica gel 60 (Merck, 230–400 mesh).

6.1.1. General procedures for the preparation of 7-oxo-9,11-ethano-13-azaprostanoids

*6.1.1.1. General method for the synthesis of compounds **17–24** and **32–34**.* To the solution of **1–3** (0.5 mmol) in 3 ml of dry benzene was added amine **4–10** (0.55 mmol) and three to four drops of triethylamine. This mixture was stirred at room temperature for 6 h before disappearance of initial enone. A solvent was removed by distillation. The product was obtained as pale yellow oil. Purification was effected by column chromatography on silica gel 60 with hexane/diethyl ether (for compounds **17–19** and **32–33**) and diethyl ether/ethyl acetate (compounds **20–24** and **34**) as eluent using gradient eluting method.

6.1.1.1.1. endo-*2-(1-Oxo-7-methoxycarbonylheptyl)*-exo-*3-heptylaminobicyclo[2.2.1]heptane (**17**)*[2]. Yield: 52 mg (96%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.87 (t, 3H, CH_3, ω-chain, $^{3}J_{20,19}$ 6.3 Hz), 0.97–1.08 (m, 1H, H-11′-*endo*), 1.08–1.74 (m, 21H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; H-10-*syn*; H-11′-*exo*; 5CH_2, ω-chain; 3CH_2, α-chain), 2.16 (br d, 1H, H-11, $^{3}J_{11,11'}$ 4.2 Hz), 2.30 (t, 2H, CH_2, α-chain, $^{3}J_{2,3}$ 7.5 Hz), 2.42 (t, 2H, $CH_2C(O)$, $^{3}J_{5,6}$ 7.1 Hz), 2.40–2.56 (m, 3H: H-9, $NHCH_2$), 2.58 (m, 1H, H-8-*exo*), 3.04 (br d d, 1H, H-12-*endo*, $^{3}J_{12,8}$ 4.2 Hz, $^{4}J_{12,10}$ 1.2 Hz), 3.66 (s, 3H, CH_3O). IR (ν_{max}) cm^{-1}: 3400 (νNH), 1604 (δNH), 1706 (ketone C=O), 1740 (ester C=O), 2931, 2958 ($\nu_{as}CH_2$), 2870, 2878 (ν_sCH_2). M/S (M^+): 365.

6.1.1.1.2. endo-*2-(1-Oxopropyl)*-exo-*3-octylaminobicyclo[2.2.1]heptane (**18**).* Yield: 46 mg (96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.88 (t, 3H, CH_3, ω-chain, $^{3}J_{21,20}$ 6.56 Hz), 0.97–1.08 (m, 1H, H-11′-*endo*), 1.05 (t, 3H, CH_3, α-chain, $^{3}J_{5,6}$ 7.33 Hz), 1.11–1.37 (m, 13H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; 1.30, m, 5CH_2, ω-chain), 1.43 (m, 2H, H-15), 1.45–1.55 (m, 1H, H-11′-*exo*), 1.69 (d m, 1H, H-10-*syn*, $^{2}J_{10,10}$ 9.87 Hz), 2.16 (br d, 1H, H-11, $^{3}J_{11,11'}$ 4.27 Hz), 2.39–2.48 (m, 3H: H-8-*exo*; 2CH_2, α-chain), 2.48–2.55 (m, 2H, $NHCH_2$), 2.58 (br s, 1H, H-9), 3.04 (br d, 1H, H-12-*endo*, $^{3}J_{12,8}$ 4.04 Hz). IR (ν_{max}) cm^{-1}: 3400 (νNH), 1600 (δNH), 1711 (ketone C=O), 2960 ($\nu_{as}CH_2$), 2878 (ν_sCH_2). M/S (M^+): 279.

6.1.1.1.3. endo-*2-(1-Oxo-7-methoxycarbonylheptyl)*-exo-*3-octylaminobicyclo[2.2.1]heptane (**19**).* Yield: 53 mg (96%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, 3H, CH_3, $^{3}J_{21,20}$ 6.9 Hz), 0.97–1.08 (m, 1H, H-11′-*endo*), 1.08–1.74 (m, 18H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; H-11′-*exo*; 6CH_2, ω-chain, CH_2, α-chain), 1.62 (m, 4H, 2CH_2, α-chain), 1.71 (d m, 1H, H-10-*syn*, $^{2}J_{10,10}$ 10.0 Hz), 1.90 (br s, 1H, NH), 2.19 (br d, 1H, H-11, $^{3}J_{11,11'}$ 4.2 Hz), 2.33 (t, 2H, CH_2, α-chain, $^{3}J_{2,3}$ 7.0 Hz), 2.39–2.56 (m, 5H: H-9; $NHCH_2$; $CH_2C(O)$), 2.60 (m, 1H, H-8-*exo*), 3.04 (br d d, 1H, H-12-*endo*, $^{3}J_{12,8}$ 3.7 Hz, $^{4}J_{12,10}$ 1.0 Hz), 3.66 (s, 3H, CH_3O). IR (ν_{max}) cm^{-1}: 3350 (νNH), 1600 (δNH), 1706 (ketone C=O), 1740 (ester C=O), 2931, 2958 ($\nu_{as}CH_2$), 2860, 2878 (ν_sCH_2). M/S (M^+): 379.

6.1.1.1.4. endo-*2-(1-Oxopropyl)*-exo-*3-(1-pirrolidinyl)bicyclo[2.2.1]heptane (**20**).* Yield: 33 mg (92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97–1.03 (m, 1H, H-11′-*endo*), 1.06 (t, 3H, CH_3, α-chain, $^{3}J_{5,6}$ 7.33 Hz), 1.15–1.23 (m, 1H, H-9′-*endo*), 1.29 (d m, 1H, H-10-*anti*, $^{2}J_{10,10}$ 9.6 Hz, $^{3}J_{10,12}$ 1.44 Hz), 1.31–1.37 (m, 1H, H-9′-*exo*), 1.46–1.56 (m, 1H, H-11′-*exo*), 1.75 (m, 4H, 2CH_2, H_B pyrrolidine), 1.93 (d m, 1H, H-10-*syn*, $^{2}J_{10,10}$ 9.83 Hz), 2.33 (br d, 1H, H-11, $^{3}J_{11,11'}$ 4.03 Hz), 2.39–2.48 (m, 4H, 2CH_2, H_A pyrrolidine), 2.48–2.55 (m, 2H, CH_2, α-chain), 2.61 (br s, 1H, H-9), 2.66 (br d d, 1H, H-12-*endo*, $^{3}J_{12,8}$ 4.29 Hz, $^{4}J_{12,10}$ 1.27 Hz), 2.81 (m, 1H, H-8-*exo*, $^{3}J_{8,12}$ 4.6 Hz). IR (ν_{max}) cm^{-1}: 3410 (νNH), 1718 (ketone C=O), 2970 ($\nu_{as}CH_2$), 2880 (ν_sCH_2), 2795. M/S (M^+): 221.

6.1.1.1.5. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-(1-piperidyl)bicyclo[2.2.1]heptane (**21**).* Yield: 35 mg (92%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.87–1.08 (m, 1H, H-11′-*endo*), 1.08–1.46 (m, 3H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*), 1.62 (m, 5H: H-11′-*exo*; 4CH_2, α-chain), 1.78 (d m, 1H, H-10-*syn*, $^{2}J_{10,10}$ 10.0 Hz), 2.19–2.56 (m, 11H: H-11; 2H, CH_2, α-chain; 2H, $CH_2C(O)$; 3CH_2, H_B, H_C pyperidine), 2.64 (m, 2H: H-9; H-12-*endo*), 2.70 (m, 1H, H-8-*exo*), 3.66 (m, 7H: 4H, 2CH_2, H_A pyperidine; 3H, CH_3O). ^{13}C NMR

[2] The names of substances are given according to the convention recommended by the International Union of Pure and Applied Chemistry (IUPAC).

($CDCl_3$, 60 MHz), δ: 23.08, 23.77, 24.08, 24.55, 25.09, 25.91, 27.84, 33.87, 37.99, 38.72, 40.44, 41.66, 51.48, 51.71, 59.73, 68.81, 173.80, 210.24. IR (ν_{max}) cm^{-1}: 3400 (νNH), 1655 (δNH), 1709 (ketone C=O), 1739 (ester C=O), 2955 ($\nu_{as}CH_2$), 2880 (ν_sCH_2). M/S (M^+): 321.

6.1.1.1.6. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-(4-morpholinyl)bicyclo[2.2.1]heptane* (***22***). Yield: 44 mg (92%). ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.92–1.09 (m, 1H, H-11′-*endo*), 1.09–1.48 (m, 3H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*), 1.48–1.64 (m, 5H: H-11′-*exo*; $4CH_2$, α-chain), 1.80 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.0 Hz), 2.24–2.62 (m, 9H: H-11; 2H, CH_2, α-chain; 2H, $CH_2C(O)$; $2CH_2$, H_A morpholine), 2.65 (br s, 1H, H-9), 2.74 (br d d, H-12-*endo*, $^3J_{12,8}$ 4.0 Hz, $^4J_{12,10}$ 1.1 Hz), 2.84 (m, 1H, H-8-*exo*), 3.67 (s, 3H, CH_3O) 3.72 (t, 4H, $2CH_2$, H_B morpholine, $^3J_{BA}$ 4.8 Hz). ^{13}C NMR ($CDCl_3$, 60 MHz), δ: 22.99, 23.81, 24.50, 27.37, 33.80, 37.71, 38.10, 40.41, 41.51, 51.18, 51.50, 59.66, 66.59, 68.57, 173.77, 209.84. IR (ν_{max}) cm^{-1}: 3400 (νNH), 1660 (δNH), 1712 (ketone C=O), 1742 (ester C=O), 2960 ($\nu_{as}CH_2$), 2880 (ν_sCH_2). M/S (M^+): 323.

6.1.1.1.7. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-[2-(3,4-dimethoxyphenyl)ethylamino]bicyclo-[2.2.1]heptane* (***23***). Yield: 82 mg (95%). ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.90–1.06 (m, 1H, H-11′-*endo*), 1.06–1.43 (m, 3H: H-9′-*exo*; H-9′-*endo*; 1.30, d m, H-10-*anti*, $^2J_{10,10}$ 10.1 Hz), 1.58 (m, 5H: H-11′-*exo*; $2CH_2$, α-chain), 1.74 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.1 Hz), 2.21 (br d, 1H, H-11, $^3J_{11,11'}$ 4.2 Hz), 2.32 (br t, 2H, CH_2, α-chain, $^3J_{3,4}$ 6.5 Hz), 2.44 (br t, 2H, $CH_2C(O)$, $^3J_{5,6}$ 6.5 Hz), 2.53 (m, 1H, H-8-*exo*), 2.61 (br s, 1H, H-9), 2.78 (s, 4H, $2CH_2$, ω-chain), 3.16 (br d, 1H, H-12-*endo*, $^3J_{12,8}$ 3.7 Hz), 3.66 (s, 3H, CH_3O), 3.87 (s, 3H, OCH_3), 3.88 (s, OCH_3), 6.68–6.84 (m, 3H, phenyl). ^{13}C NMR ($CDCl_3$, 60 MHz), δ: 22.92, 23.65, 24.44, 26.63, 33.74, 35.12, 37.45, 40.02, 41.51, 41.61, 48.78, 51.38, 55.73, 55.80, 60.67, 63.12, 111.32, 111.97, 120.52, 132.09, 147.44, 148.89, 173.58, 209.64. IR (ν_{max}) cm^{-1}: 3350 (νNH), 1595 (δNH), 2842 (νCH_3), 1710 (ketone C=O), 1741 (ester C=O), 2962 ($\nu_{as}CH_2$), 2880 (ν_sCH_2). M/S (M^+): 417.

6.1.1.1.8. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-(α-methylbenzylamino)bicyclo[2.2.1]heptane* (***24***). Yield: 22 mg (90%). ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.88–1.54 (m, 9H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; H-10-*syn*; H-11′-*endo*; H-11′-*exo*; 1.31, d, 3H, $CHCH_3$, $^3J_{15,14}$ 6.8 Hz), 1.54–1.71 (m, 4H, $2CH_2$, α-chain), 2.00 (br d, 1H, H-11, $^3J_{11,11'}$ 4.1 Hz), 2.15–2.40 (m, 4H, CH_2, α-chain; $CH_2C(O)$), 2.46 (m, 1H, H-8-*exo*), 2.56 (br s, 1H, H-9), 2.28 (br d d, 0.5H, H-12-*endo*, $^3J_{12,8}$ 4.0 Hz, $^4J_{12,10}$ 1.2 Hz), 3.04 (br d d, 0.5H, H-12-*endo*, $^3J_{12,8}$ 4.0 Hz, $^4J_{12,10}$ 1.2 Hz), 3.66 (s, 3H, CH_3O), 3.72 (q, 1H, CHMe, $^3J_{14,15}$ 6.8 Hz), 7.10–7.42 (m, 5H, phenyl). IR (ν_{max}) cm^{-1}: 3330 (νNH), 1604 (δNH), 1707 (ketone C=O), 1739 (ester C=O), 2959 ($\nu_{as}CH_2$), 2879 (ν_sCH_2). M/S (M^+): 357.

6.1.1.1.9. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-heptylaminobicyclo[2.2.1]heptane* (***32***). Yield: 34 mg (96%). ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, 3H, CH_3, ω-chain, $^3J_{20,19}$ 6.1 Hz), 0.97–1.09 (m, 1H, H-11′-*endo*), 1.09–1.54 (m, 14H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; H-11′-*exo*; $5CH_2$, ω-chain), 1.60 (m, 4H, $2CH_2$, α-chain), 1.70 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 9.6 Hz), 2.17 (br d, 1H, H-11, $^3J_{11,11'}$ 4.0 Hz), 2.34 (t, 2H, CH_2, α-chain, $^3J_{3,4}$ 7.0 Hz), 2.38–2.54 (m, 5H: H-9; $CH_2C(O)$; $NHCH_2$), 2.59 (m, 1H, H-8-*exo*), 3.03 (br d, 1H, H-12-*endo*, $^3J_{12,8}$ 3.9 Hz), 3.67 (s, 3H, CH_3O). IR (ν_{max}) cm^{-1}: 3400 (νNH), 1660, 1600 (δNH), 1715 (ketone C=O), 1740 (ester C=O), 2935, 2958 ($\nu_{as}CH_2$), 2865, 2879 (ν_sCH_2). M/S (M^+): 351.

6.1.1.1.10. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-octylaminobicyclo[2.2.1]heptane* (***33***). Yield: 91 mg (96%). ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.89 (t, 3H, CH_3, $^3J_{21,20}$ 6.0 Hz), 0.94–1.10 (m, 1H, H-11′-*endo*), 1.10–1.54 (m, 16H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; H-11′-*exo*; $6CH_2$, ω-chain), 1.60 (m, 4H, $2CH_2$), 1.71 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.0 Hz), 2.13 (br d, 1H, H-11, $^3J_{11,11'}$ 3.9 Hz), 2.30 (t, 2H, CH_2, α-chain, $^3J_{3,4}$ 7.0 Hz), 2.34–2.50 (m, 5H: H-9; $NHCH_2$; $CH_2C(O)$), 2.55 (m, 1H, H-8-*exo*), 3.00 (br d, 1H, H-12-*endo*, $^3J_{12,8}$ 3.9 Hz), 3.66 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$, 60 MHz), δ: 14.07, 22.88, 23.59, 24.46, 26.82, 27.21, 27.93, 29.20, 29.31, 31.77, 33.81, 40.37, 41.07, 41.47, 47.20, 51.48, 60.82, 62.10, 209.06. IR (ν_{max}) cm^{-1}: 3400 (νNH), 1604 (δNH), 1717 (ketone C=O), 1749 (ester C=O), 2960, 2933 ($\nu_{as}CH_2$), 2880, 2862 (ν_sCH_2). M/S (M^+): 365.

6.1.1.1.11. endo-*2-(1-Oxo-7-methoxycarbonylheptyl)*-exo-*3-(1-pyrrolidinyl)bicyclo[2.2.1]heptane* (***34***). Yield: 30 mg (92%). ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.90–1.06 (m, 1H, H-11′-*endo*), 1.10–1.46 (m, 5H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; 2H, CH_2), 1.46–1.75 (m, 6H: $2CH_2$, H_B pyrrolidine, CH_2, α-chain), 1.80 (m, 3H: H-11′-*exo*; CH_2, α-chain), 2.02 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.0 Hz), 2.30 (t, 2H, CH_2, α-chain, $^3J_{2,3}$ 7.9 Hz), 2.38 (br d, 1H, H-11, $^3J_{11,11'}$ 4.9 Hz), 2.45 (t, 2H, $CH_2C(O)$, $^3J_{6,5}$ 7.5 Hz), 2.66 (m, 5H: $2CH_2$, H_A pyrrolidine, $^3J_{6,5}$ 3.2 Hz; H-9), 2.81 (d d, 1H, H-12-*endo*, $^3J_{12,8}$ 4.6 Hz, $^4J_{12,10}$ 1.8 Hz), 3.06 (m, 1H, H-8-*exo*, $^3J_{8,12}$ 4.6 Hz), 3.66 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$, 60 MHz), δ: 22.96, 23.17, 23.57, 24.54, 27.26, 28.58, 33.59, 37.60, 40.57, 41.45, 51.24, 52.19, 60.09, 68.42, 173.39, 209.22. IR (ν_{max}) cm^{-1}: 3440 (νNH), 1715 (ketone C=O), 1748 (ester C=O), 2959 ($\nu_{as}CH_2$), 2880 (ν_sCH_2), 2795. M/S (M^+): 321.

6.1.1.2. General method for the synthesis of compounds ***25–26, 28–31*** *and* ***35***. Compounds **1–3** (1 mmol) were dissolved in dry benzene (5 ml). To the solution amine **11, 13–16** (1.1 mmol) and three to four drops of sodium hydride (1–5 mg) suspended by stirring in dry benzene (5–10 ml) were added. The mixture was stirred at room temperature for 1 h (for compounds **25–26, 29** and **35**) or 4 h (for compounds **28, 30–31**). Washing with 1% aqueous HCl solution (3–5 ml), extraction with chloroform, drying over $MgSO_4$ and removal of the solvent gave the product as pale yellow oil. Purification was effected by column chromatography on silica gel 60 with hexane/diethyl ether as eluent using gradient eluting method or by a preparative TLC method with hexane/diethyl ether (90:10) as eluent.

6.1.1.2.1. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-anilinobicyclo[2.2.1]heptane* (***25***). Yield: 40 mg (90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.00–1.18 (m, 1H, H-11′-*endo*), 1.22–1.40 (m, 4H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; H-11′-*exo*), 1.48–1.65 (m, 4H, $2CH_2$, α-chain), 1.72 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.0 Hz), 2.29 (br d, 1H, H-11, $^3J_{11,11'}$ 3.1 Hz), 2.31 (t, 2H, CH_2, α-chain, $^3J_{3,4}$ 7.3 Hz), 2.42 (m, 2H, $CH_2C(O)$), 2.56 (m, 1H, H-8-*exo*), 2.62 (br s, 1H, H-9), 3.65 (s, 3H, CH_3O), 3.76 (br d d, 1H, H-12-*endo*, $^3J_{12,8}$ 3.5 Hz, $^4J_{12,10}$ 1.4 Hz), 6.50 (d, 2H, H_A phenyl, $^3J_{AB}$ 8.0 Hz), 6.65 (m, 1H, H_C phenyl, ^3J 7.5 Hz), 7.12 (m, 2H, H_B phenyl, ^3J 7.5 Hz). IR (ν_{max}) cm^{-1}: 3450 (νNH), 1606 (δNH), 3100, 3065, 3035 (νPh), 1706 (ketone C=O), 1740 (ester C=O), 2955 ($\nu_{as}CH_2$), 2880 (ν_sCH_2). M/S (M^+): 329.

6.1.1.2.2. endo-*2-(1-Oxo-7-methoxycarbonylheptyl)*-exo-*3-anilinobicyclo[2.2.1]heptane* (***26***). Yield: 44 mg (90%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.00–1.18 (m, 1H, H-11′-*endo*), 1.23–1.46 (m, 5H: H-9′-*exo*; H-9′-*endo*; H-10-*anti*; CH_2, α-chain), 1.46–1.69 (m, 5H: H-11′-*exo*; $2CH_2$, α-chain), 1.72 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.0 Hz), 2.27 (br d, 1H, H-11, $^3J_{11,11'}$ 3.1 Hz), 2.30 (t, 2H, CH_2, α-chain, $^3J_{3,4}$ 7.5 Hz), 2.40 (m, 2H, $CH_2C(O)$), 2.56 (m, 1H, H-8-*exo*), 2.62 (br s, 1H, H-9), 3.65 (s, 3H, CH_3O), 3.77 (br d d, 1H, H-12-*endo*, $^3J_{12,8}$ 3.2 Hz, $^4J_{12,10}$ 1.4 Hz), 6.50 (d, 2H, H_A phenyl, $^3J_{AB}$ 8.0 Hz), 6.65 (m, 1H, H_C phenyl, ^3J 7.5 Hz), 7.12 (m, 2H, H_B phenyl, ^3J 7.5 Hz). IR (ν_{max}) cm^{-1}: 3400 (νNH), 1604 (δNH), 3090, 3060, 3020 (νPh), 1704 (ketone C=O), 1735 (ester C=O), 2957 ($\nu_{as}CH_2$), 2879 (ν_sCH_2). M/S (M^+): 343.

6.1.1.2.3. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-(4-chlorophenyl)aminobicyclo[2.2.1]heptane* (***28***). Yield: 25 mg (65%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.05–1.19 (m, 1H, H-11′-*endo*), 1.19–1.50 (m, 4H: H-9′-*endo*; H-10-*anti*; CH_2, α-chain), 1.62 (m, 4H: H-9′-*exo*; H-11′-*exo*; CH_2, α-chain), 1.74 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.2 Hz), 2.29 (br d, 1H, H-11, $^3J_{11,11'}$ 4.0 Hz), 2.32 (br t, 2H, CH_2, α-chain, $^3J_{3,4}$ 6.8 Hz), 2.44 (br t, 2H, $CH_2C(O)$, $^3J_{5,6}$ 6.1 Hz), 2.55 (m, 1H, H-8-*exo*; $^3J_{8,12}$ 3.8 Hz), 2.66 (br s, 1H, H-9), 3.68 (s, 3H, CH_3O), 3.75 (br d, 1H, H-12-*endo*, $^3J_{12,8}$ 3.2 Hz), 6.41 (d, 2H, H_A phenyl, $^3J_{AB}$ 8.8 Hz), 7.10 (d, 2H, H_B phenyl, $^3J_{BA}$ 8.8 Hz). IR (ν_{max}) cm^{-1}: 3390 (νNH), 1609 (δNH), 1715 (ketone C=O), 1738 (ester C=O), 2963 ($\nu_{as}CH_2$), 2881 (ν_sCH_2). M/S (M^+): 363.

6.1.1.2.4. endo-*2-(1-Oxopropyl)*-exo-*3-anisidinoaminobicyclo[2.2.1]heptane* (***29***). Yield: 22 mg (65%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.04 (t, 3H, CH_3, α-chain, $^3J_{5,6}$ 7.35 Hz), 1.07–1.14 (m, 1H, H-11′-*endo*), 1.30–1.37 (m, 2H, H-9′-*exo*; H-9′-*endo*), 1.39 (d m, 1H, H-10-*anti*, $^2J_{10,10}$ 10.12 Hz, $^3J_{10,12}$ 1.55 Hz), 1.57 (m, 1H, H-11′-*exo*), 1.71 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.12 Hz), 2.27 (br d, 1H, H-11, $^3J_{11,11'}$ 4.77 Hz), 2.40 (q, 2H, $CH_2C(O)$, $^3J_{6,5}$ 7.35 Hz), 2.55 (m, 1H, H-8-*exo*, $^3J_{8,12}$ 4.30 Hz, $^4J_{8,9'}$ 1.45 Hz), 2.61 (br s, 1H, H-9), 3.73 (s, 3H, OCH_3), 3.76 (br d d, 1H, H-12-*endo*, $^3J_{12,8}$ 4.30 Hz, $^3J_{12,10}$ 1.55 Hz),6.50 (d, 2H, H_A phenyl, $^3J_{AB}$ 8.81 Hz), 6.74 (d, 2H, H_B phenyl, $^3J_{BA}$ 8.81 Hz). IR (ν_{max}) cm^{-1}: 3400 (νNH), 1630 (δNH), 1717 (ketone C=O), 2840 (νCH_3), 2963 ($\nu_{as}CH_2$), 2880 (ν_sCH_2). M/S (M^+): 273.

6.1.1.2.5. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-(2-hydroxyphenyl)aminobicyclo[2.2.1]heptane* (***30***). Yield: 12 mg (40%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.98–1.20 (m, 1H, H-11′-*endo*), 1.20–1.49 (m, 4H: H-9′-*endo*; H-10-*anti*; CH_2, α-chain), 1.58 (m, 4H: H-9′-*exo*; H-11′-*exo*; CH_2, α-chain), 1.79 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.7 Hz), 2.31 (m, 3H: H-11; CH_2, α-chain), 2.38 (m, 2H, $CH_2C(O)$), 2.60 (m, 2H: H-9; H-8-*exo*), 3.67 (s, 3H, CH_3O), 3.77 (m, 1H, H-12-*endo*), 6.53 m (2H, phenyl), 6.73 (m, 2H, phenyl). IR (ν_{max}) cm^{-1}: 3415 (νNH), 1601 (δNH), 1720 (ketone C=O), 1749 (ester C=O), 2960 ($\nu_{as}CH_2$), 2880 (ν_sCH_2). M/S (M^+): 345.

6.1.1.2.6. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-(2-nitrophenyl)aminobicyclo[2.2.1]heptane* (***31***). Yield: 16 mg (40%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.99–1.20 (m, 1H, H-11′-*endo*), 1.20–1.58 (m, 4H: H-9′-*endo*; H-10-*anti*; CH_2, α-chain), 1.64 (m, 4H: H-9′-*exo*; H-11′-*exo*; CH_2, α-chain), 1.88 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.5 Hz), 2.33 (m, 2H, CH_2, α-chain), 2.42 (br d, 1H, H-11, $^3J_{11,11'}$ 4.2 Hz), 2.48 (br t, 2H, $CH_2C(O)$, $^3J_{5,6}$ 7.0 Hz), 2.74 (m, 2H: H-9; H-8-*exo*), 3.68 (s, 3H, CH_3O), 4.02 (br d d, 1H, H-12-*endo*, $^3J_{12,8}$ 4.0 Hz, $^4J_{12,10}$ 1.8 Hz), 6.65 (m, 1H, H_B phenyl), 6.80 (m, 1H, H_D phenyl), 7.38 (m, 1H, H_C phenyl), 8.06 (m, 1H, H_A phenyl). IR (ν_{max}) cm^{-1}: 3496, 3379 (νNH), 1720 (ketone C=O), 1751 (ester C=O), 2962 ($\nu_{as}CH_2$), 2882 (ν_sCH_2). M/S (M^+): 374.

6.1.1.2.7. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-anisidinoaminobicyclo[2.2.1]heptane* (***35***). Yield: 28 mg (65%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00–1.09 (m, 1H, H-11′-*endo*), 1.18–1.49 (m, 4H: H-9′-*endo*; H-9′-*exo*; H-10-*anti*; H-11′-*exo*), 1.56 (m, 4H: $2CH_2$, α-chain), 1.72 (d m, 1H, H-10-*syn*, $^2J_{10,10}$ 10.2 Hz), 2.32 (br t, 2H, CH_2, α-chain, $^3J_{3,4}$ 7.3 Hz), 2.42 (br d, 1H, H-11, $^3J_{11,11'}$ 4.8 Hz), 2.42 (br t, 2H, $CH_2C(O)$, $^3J_{6,5}$ 7.0 Hz), 2.58 (m, 1H, H-8-*exo*, $^3J_{8,12}$ 5.2 Hz), 2.64 (br s, 1H, H-9), 3.67 (s, 3H, CH_3O), 3.73 (s, 3H, OCH_3), 3.75 (d d, 1H, H-12-*endo*, $^3J_{12,8}$ 4.2 Hz, $^4J_{12,10}$ 1.5 Hz), 6.50 (d, 2H, H_A phenyl, $^3J_{AB}$ 8.8 Hz), 6.72 (d, 2H, H_B phenyl, $^3J_{BA}$ 8.8 Hz). IR (ν_{max}) cm^{-1}: 3400 (νNH), 1610 (δNH), 1712 (ketone C=O), 1740 (ester C=O), 2845 (νCH_3), 2962 ($\nu_{as}CH_2$), 2880 (ν_sCH_2). M/S (M^+): 391.

6.1.1.2.8. endo-*2-(1-Oxo-6-methoxycarbonylhexyl)*-exo-*3-(4-aminophenylthio)bicyclo[2.2.1]-heptane* (***27***). The titled compound was prepared according to Ref. [8] as colorless oil.

6.2. Pharmacology

6.2.1. B-cellular (humoral) immune response

CBA female mice having the weight of 18–22 g were immunized intraperitoneally with SRBC suspended in Hanks solution (1.5×10^7 SRBC per mouse), each group of animals consisting of six mice in every experimental set. The compounds tested, dissolved in 0.9% NaCl, were administered per os at doses of 1.0, 2.5, 5.0, 10.0 mg kg^{-1} simultaneously

with immunization of the mice. On the fifth day after the immunization the mice were decapitated, their spleens were isolated and homogenized in Hanks solution to be analyzed in terms of AFC amounts according to Cunningham method [9]. Spleen cell concentration in the suspension was adjusted to 10^6 ml^{-1}. 0.5 ml of spleen cell suspension (1×10^6 cells ml^{-1}), 0.5 ml of SRBC suspension (1×10^9 SRBC ml^{-1}) and 0.5 ml of complement solution (1:5) were mixed. Cunningham chambers were filled with the mixture and incubated at 37 °C. In 60 min the number of lysis zones was determined and AFC amounts per 10^6 spleen cells were calculated. The results were obtained from a minimum of six experiments for each one of the compounds and were expressed as the mean ± S.E. mean. Statistical analysis of results was performed by unpaired two-tailed Student's *t*-test. Probability levels of <0.05 were taken to indicate statistical significance.

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