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Synthesis, biological evaluation and docking analysis of substituted piperidines and (2-methoxyphenyl)piperazines

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Abstract: A series of sixteen novel substituted piperidines and (2-methoxyphenyl)piperazines were synthesized, starting from the key intermediates 1-(2-methoxyphenyl)-4-(piperidin-4-yl)piperazine and 1-(2-methoxyphenyl)-4-(piperidin-4-ylmethyl)piperazine. Biological evaluation of the synthesized compounds was pointed out for seven compounds, of which 1-(2-methoxyphenyl)-4-{[1-(2-nitrobenzyl)piperidin-4-yl]methyl}piperazine had the highest affinity for the dopamine D_2 receptor. For all seven selected compounds docking analysis was performed in order to establish their structure-to-activity relationship.

Keywords: dopamine D_2 receptor, docking analysis, allosteric, orthosteric bind site

INTRODUCTION

G-protein-coupled receptors (GPCRs) are transmembrane receptors that mediate most of their intracellular actions through pathways involving an activation of G-protein[1]. D_2 dopamine receptors (D_2DAR) are member of this large protein family. Dysfunction of dopaminergic system in CNS can lead to a number of diseases, such as Parkinson's disease, schizophrenia, some neurohumoral disturbances, etc[2,3]. Therefore it is not surprising that the design and synthesis of new potential dopaminergic drugs is one of the main objectives of organic and medicinal chemistry.

Arylpiperazines are a common structural motif included in various compounds that interacts in specific manor with various GPCRs[4]. Within the scope of the program aimed at the discovery of new dopaminergic (DA-ergic)

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ligands and in order to further explore our previously published data, a series of sixteen novel arylpiperazines have been synthesized[5]. All synthesized ligands were estimated for their *in vitro* binding affinities at the rat D_2DAR and compared with results obtained trough docking analysis, using available D_2DAR molecular model.

EXPERIMENTAL

General

M.p.: Boetius PHMK apparatus (VEB Analytic, Dresden, Germany) - uncorrected. ^{1}H-NMR and ^{13}C-NMR (200 and 50 MHz): Gemini 2000 (Varian, Oxford); solvent deuterochloroform, unless otherwise stated; ppm (δ) downfield from the internal standard tetramethylsilane as the internal standard. LC/MS: 6210 Time-of-Flight LC-MS system (Agilent Technologies, Germany); for data analysis MassHunter Workstation Software was used. IR spectra: Thermo Scientific spectrometer. Microwave: MicroSYNTH Milestone and a Biotage Initiator 2.5 EXP. Analytical TLC: POLYGRAM SIL G/UV254 plastic-backed thin-layer silica gel plates (Macherey-Nagel, Germany). Chromatographic purifications: Merck-60 silica gel columns (diameter 70 mm, h = 45 mm; the same for all compounds), 230–400 mesh ASTM, medium pressure (dry column flash chromatography). Reagents and solvents were used without purification: Alfa–Aesar and Sigma Aldrich. Solutions: routinely dried over anhydrous Na_2SO_4 prior to evaporation.

Chemistry

Ethyl 4-[4-(2-metoxyphenyl)piperazin-1-yl]piperidine-1-carboxylate (**3**): To a stirring solution of *N*-carbethoxy-4-piperidone (**1**) (1.7 g, 0.01 mol) in methanol (25 ml) (pH value of solution was adjusted to 7 by addition of CH_3CO_2H), 1-(2-methoxyphenyl)piperazine (**2**) (3.24 g, 0.02 mol) was added, followed by the addition of $NaBH_3CN$ (0.4 g, 0.0072 mol) in portions. Stirring was continued at r.t. for 24h. The pH value of resulting solution was adjusted to 2 by the addition of 10% HCl solution and the excess of the methanol was removed in vacuum. The pH value of the residue was adjusted to 9 by the addition of 10% NaOH solution, extracted with dichloromethane. Organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuum*. The product was purified by dry-flash chromatography using a gradient of CH_3OH (0-10%) in dichloromethane as a solvent. Yield: 88%.

*General procedure for the hydrolysis of the carbamates **3** and **9***

Carbamates **3** or **9** (0.02 mol) was suspended in ccHCl (60 ml), transferred into a sealed tube, placed into microwave. Irradiation at 130 °C was completed after 90 min at an initial power of 300 W. The reaction mixture was poured into water, pH value adjusted to 9 by addition of 10% NaOH solution and extracted with dichloromethane. Organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuum*. The product was purified by dry-flash chromatography using a gradient of methanol (0-10%) in dichloromethane as a solvent.

1-(Ethoxycarbonyl)piperidine-4-carboxylic acid (**6**): To a solution of piperidine-4-carboxylic acid (**5**) (20 g, 0.155 mol) in water (200 ml), Na_2CO_3 (20 g) was added, mixture was stirred at room temperature for 30 min. and solution of ethyl chloroformate (25.5 g, 0.28 mol) in toluene (240 ml) was added dropwise. Stirring was continued at room temperature for 20h. After separation of the layers, in the aqueous layer ccHCl was added until pH~2, extracted with dichloromethane, organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuum*. Yield: 78%.

Ethyl 4-(chlorocarbonyl)piperidine-1-carboxylate (**7**): Solution of 1-(ethoxycarbonyl) piperidine-4-carboxylic acid (**6**) (7.5 g, 0.0375 mol), thionyl chloride (5.35 g, 0.045 mol) and chloroform (200 ml) was stirred for 2h at 0°C. The reaction mixture was evaporated *in vacuum* and product was used immediately, without further purification. Yield: 67%.

Ethyl 4-[4-(2-methoxyphenyl)piperazine-1-carbonyl]piperidine-1-carboxylate (**8**): The solution of chloride **7** in chloroform (50 ml) was added dropwise to a solution of triethylamine (3.78 g, 0.0375 mol), 1-(2-methoxyphenyl)piperazine (**2**) (6.07 g, 0.0375 mol) in chloroform (150 ml) at 5°C. Reaction mixture was stirred at room temperature for 20 h. The resulting mixture was extracted with 10% Na_2CO_3, organic layer was extracted with 10% HCl solution. Organic layer was dried over anhydrous Na_2SO_4, and evaporated in *vacuum*. The product was purified by dry-flash chromatography eluting with dichloromethane containing increasing amounts of methanol (0-10%). Yield: 85%.

Ethyl 4-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}piperidine-1-carboxylate (**9**): Mixture of compound **8** (0.01 mol) and $NaBH_4$ (1 g, 0.025 mol) in diglyme (25 ml) was stirred for 40 min at -5 °C under argon. During that time, boron trifluoride diethyl etherate (3.9 g, 3.4 ml, 0.025 mmol) was added dropwise. After stirring for 1h at 5 °C reaction mixture was heated to 80-90 °C, followed by stirring for additional one hour. The mixture was cooled at room temperature, carefully poured into 10 ml of water and then 20 ml cc HCl was added. Mixture was heated at 60-80 °C on aqueous bathroom for 3h and concentrated on *vacuum*. In the residue 10% NaOH solution was added until pH 9, extracted with CH_2Cl_2, organic layer dried over anhydrous Na_2SO_4 and evaporated *in vacuum*. Product was purified by dry-flash chromatography using dichloromethane/methanol system as eluent. Yield: 85%.

*General procedure for alkylation of compounds **4** and **10***

Mixture of compound **4** or **10** (0.0018 mol), benzyl halides **11-14** (0.0018 mol), K_2CO_3 (0.0036 mol) and acetonitrile (25 ml) was stirred at room temperature for 48h, poured into water, extracted with dichloromethane. Organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuum*. Product was purified by dry-flash chromatography using a gradient of methanol (0-10%) in dichloromethane as a solvent.

*General procedure for the synthesis of compounds (**27-30**) and (**31-34**)*

Solution of benzoyl or nitrobenzoyl chloride **23-26** (0.0017 mol) and CH_2Cl_2 (0.34 ml) was added dropwise to a solution of **4** or **10** (0.0017 mol), CH_2Cl_2 (1.7 ml) and Et_3N (0.24 ml, 0.0017 mol) at 0°C. The reaction mixture was stirred at room temperature for 72 h. The resulting mixture was extracted with 10% Na_2CO_3 solution, separated organic layer was washed with 10% K_2CO_3 solution, dried over anhydrous Na_2SO_4 and evaporated *in vacuum*. The product was purified by dry-flash chromatography eluting with CH_2Cl_2 containing increasing amounts of MeOH (0-10%).

Analytical and spectral data for the synthesized compounds are given in the Supplementary material to this paper.

Membrane preparation, radio ligand binding assays and data analysis

Synaptosomal membranes from rat striatal were prepared for radioligand binding assays as previously described[6]. [^{3}H]Spiperone (spec. act.73.36 Ci mmol–1) used to label D_2DAR were purchased from Perkin Elmer LAS GmbH, Rodgau, Germany).

[^{3}H]Spiperone-receptor binding assay

[^{3}H]Spiperone binding was assayed in 4 mM $MgCl_2$, 1.5 mM $CaCl_2$, 5 mM KCl, 120 mM NaCl, 25 mM Tris–HCl solution, pH 7.4, at a membrane protein concentration of 0.7

mgmL^{-1}at 37°C for 10 min. in a total volume of 0.4 mL of the incubation mixture. Binding of the radioligand to the 5-HT$_2$ receptors was prevented by 50 μM ketanserin. The Ki values of the tested compounds were determined by competition binding at 0.2 nM of the radio ligand and eight to ten different concentrations of each compound (10^{-4} to 10^{-10} M). Nonspecific binding was measured in the presence of 1.0 mM spiperone. The reaction was terminated by rapid filtration through Whatman GF/C filters, which were further washed three times with 5.0 mL of ice-cold incubation buffer. Each point was determined in triplicate. Retained radioactivity was measured by introducing of dry filters into 10 mL of toluene-based scintillation liquid and counting in a 1219 Rackbeta Wallac scintillation counter (EG&G Wallac, Turku, Finland) at an efficiency of 51–55% for tritium. The results were analyzed by nonlinear curve fitting of the inhibition curves of the compounds utilizing the Graph-Pad Prism program[7]. Hill slope coefficients were fixed to unity during calculation.

Docking analysis

Docking analysis was done with already available D$_2$DAR model based on a crystal D$_3$DAR structure[8]. The receptors' binding site was determined by combining results from experimental data[9,10] and the Schrödinger Maestro receptor grid generation module[11]. Amino acid residue charges were adjusted where needed, assuming physiological conditions.

Selected ligands were prepared with ligprep Maestro module and docked using Glide module from Schrödinger Suite 2011[11]. All ligands were docked as protonated, using the OPLS_2005 force field. The initial position of the ligand in the binding site, was arbitrary, while the protonated nitrogen on the ligand part was kept in close proximity of the Asp 114 of the D$_2$DAR. After initial ligand placement, no further constraints were applied and the docking procedure was carried out. Obtained structures were examined and those meeting the following criteria were selected: best docking score of the complex, shortest salt bridge formed between Asp 114 of the D$_2$DAR and ligand, chair conformation of arylpiperazine ring and aryl part of the molecule positioned in the rear hydrophobic pocket of the receptor (Phe 386, Trp 390 and Tyr 420)[12]. After an initial criterion was satisfied, the second step was the examination of different interactions that can be formed between receptor and ligand (hydrogen bonds, aromatic–aromatic interactions, etc.). In that way, the best possible docking structures were selected. Structures were visualized using DS Visualize v2.5.1[13] and the obtained images were rendered using PovRay Raytracer v3.6 [14].

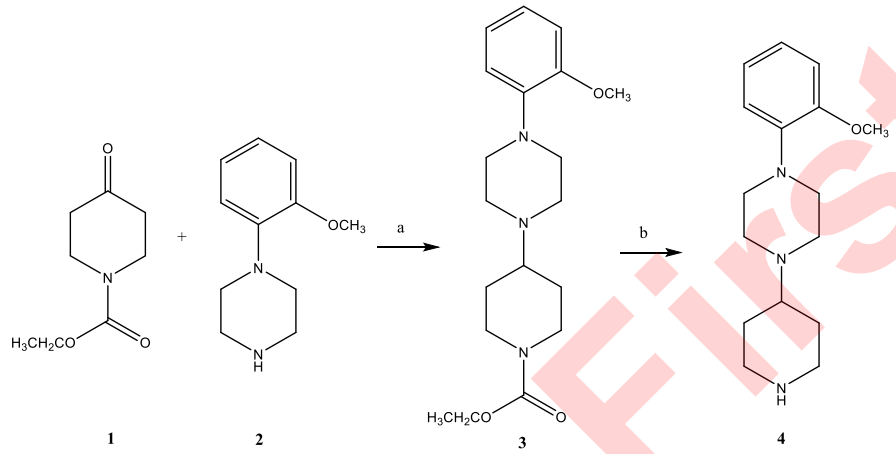
RESULT AND DISCUSSION

The general synthetic route and chemical structures of the novel substituted piperidine and (2-methoxyphenyl)piperazine are summarized in Schemes 1-3.

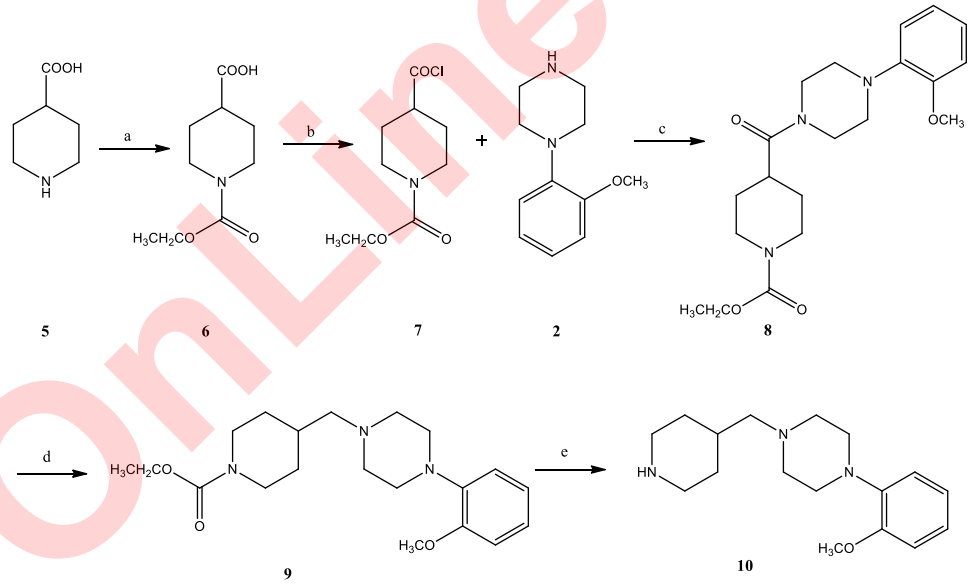
Preparation of the key intermediates, 1-(2-methoxyphenyl)-4-(piperidin-4-yl)piperazine (**4**) and 1-(2-methoxyphenyl)-4-(piperidin-4-ylmethyl)piperazine (**10**) are described in Schemes 1 and 2. Ethyl 4-[4-(2-metoxyphenyl)piperazin-1-yl]piperidine-1-carboxylate (**3**), produced by reductive amination of the commercially available ketone **1** was further hydrolyzed, under microwave conditions, and intermediate **4** was obtained (Scheme 1).

Commercially available piperidine-4-carboxylic acid (**5**) was transformed into carbamate **6** and further into chloride **7** by reacting with thionyl chloride. Acylation of (2-methoxyphenyl)piperazine with chloride **7** gave amide **8**, which provide compound **9** by the reduction with NaBH$_4$/boron trifluoride ethyl

etherate. The carbamate **9** was converted to secondary amine **10** by hydrolysis with ccHCl under MW conditions (Scheme 2).

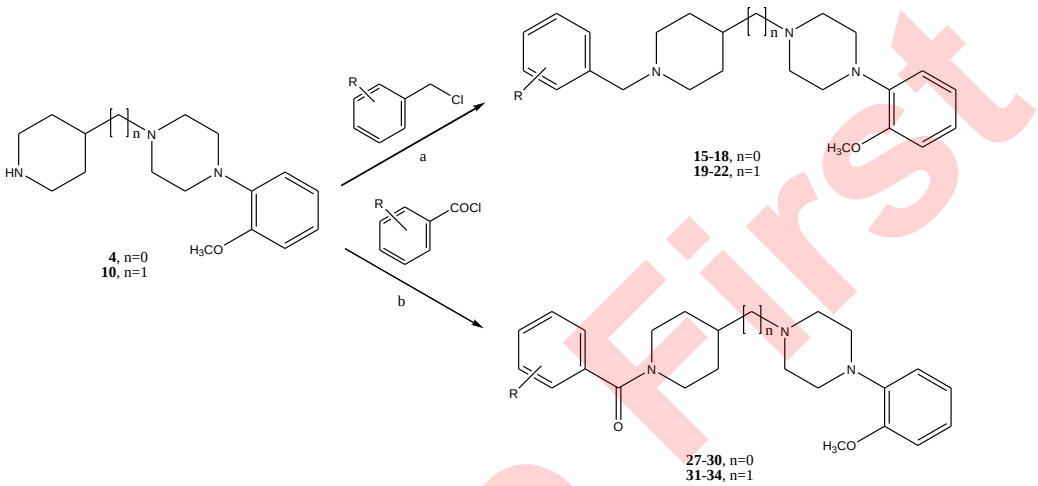


Scheme 1. Synthesis of 1-(2-methoxyphenyl)-4-(piperidin-4-yl)piperazine (**4**); reagents: a) $NaBH_3CN$, MeOH, pH 7, r.t; b) cc HCl, MW, 180 °C, 300 W.



Scheme 2. Synthesis of 1-(2-methoxyphenyl)-4-(piperidin-4-ylmethyl)piperazine (**10**); reagents: a) Na_2CO_3, ethyl chloroformate, toluene, r.t; b) thionyl chloride, CH_2Cl_2, 0°C; c) triethyl amine, chloroform, 5°C; d) $NaBH_4$, boron trifluoride diethyl etherate, diglyme, -5 °C; e) cc HCl, MW, 180 °C, 300 W.

Both intermediates, **4** and **10**, were alkylated with benzyl or nitro benzyl halogenide to give final ligands **15-18** and **19-22**. Ligands **27-30** and **31-34** were obtained by acylation with corresponding acyl chloride (Scheme 3).



Scheme 3. Synthetic route and chemical structures of the (2-methoxyphenyl)piperazine dopaminergic ligands; reagents: a) compounds **11-14** (R = H, 2-NO_2, 3-NO_2, 4-NO_2), K_2CO_3, CH_3CN, r.t; b) compounds **23-26** (R = H, 2-NO_2, 3-NO_2, 4-NO_2), triethyl amine, CH_2Cl_2, 0°C; c) DCC, CH_3CN, 0°C; d) $NaBH_4$, boron trifluoride diethyl etherate, diglyme, -5 °C; yields for 15-22 and 27-34 (68-89%).

Final products **15-22** and **27-34** were evaluated for their affinity to D_2DAR *in vitro* competitive displacement assay of the [^{3}H]-spiperone (***Table I***). As a source of D_2DAR synaptosomal membranes prepared from rat striatum were used.

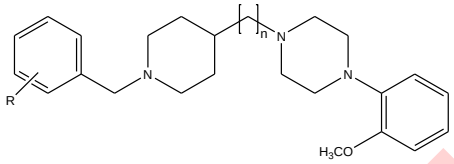
The compound with the highest affinity for D_2DAR was 1-(2-methoxyphenyl)-4-{[1-(2-nitrobenzyl)piperidin-4-yl]methyl}piperazine (**20**, Ki=30.6 nM). Compounds **19**, **21**, **22** and **31-34**, expressed moderate binding affinity for D_2DAR, while **15-18** and **27-30** were completely inactive competitors of bound [^{3}H]-spiperone.

Compounds **20-22** and **31-34** were selected for docking analysis in order to establish their structure-to-activity relationship.

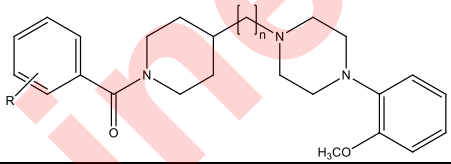
D_2DAR model and selected compound were prepared as described and docking analysis was carried out. Obtained result show that compound **20** bind to D_2DAR via salt bridge with Asp 114 on TM3. This is followed by multiple aromatic interactions between aryl part of the ligand and hydrophobic pocket (Phe 386, Trp 390 and Tyr 420)[8,15,16]. In this way ligand establish favorable orientation inside the receptor binding cavity that is prerequisite for forming of hydrogen bonds with Ser 193 on TM5. Stated interactions are formed with

D_2DAR inside the orthosteric bind site (OBS). Docking analysis showed possible aromatic interactions with Phe 393 and His 397, both located inside the alosteric bind site (ABS) (Figure 1) and listed interactions lead to high compound activity.

TABLE I. Binding constants of the synthesized compounds for the dopamine D_2 receptor



Compound	n	R	Ki / nM ± S.E.M
15	0	H	736 ± 24
16	0	2-NO_2	521.5±13
17	0	3-NO_2	937.5±35
18	0	4-NO_2	1512± 30
19	1	H	341.5±12
20	1	2-NO_2	30.6±1.2
21	1	3-NO_2	258±11
22	1	4-NO_2	200±12



Compound	n	R	Ki / nM ± S.E.M
27	0	H	1583.5±32
28	0	2-NO_2	1205±19
29	0	3-NO_2	755±21
30	0	4-NO_2	905±28
31	1	H	189.5±12.1
32	1	2-NO_2	219.5±14.4
33	1	3-NO_2	300±16.2
34	1	4-NO_2	334.5±17.8

In the case of compounds **21** and **22**, in contrast to compound **20**, optimal hydrogen bond with serine residues on TM5 cannot be formed. Reduced binding affinity was a clear consequence of unfavorable orientation of the ligands **21** and **22** inside the receptor binding cavity. Compounds **31**-**34** dock, in the same manner, with aryl part oriented inside the hydrophobic pocket (Phe 386, Trp 390 and Tyr 420), salt bridge with Asp 114 and hydrogen bond with Ser 193 (Figure 2). The only difference, compared to compound **20**, is the positioning of the head part of the ligand. Reduced flexibility of the head part leads to suboptimal

positioning of the aromatic part inside the ABS and only observed aromatic interaction is with Phe 394. This leads to reduced binding affinity, in regard to ligand **20**.

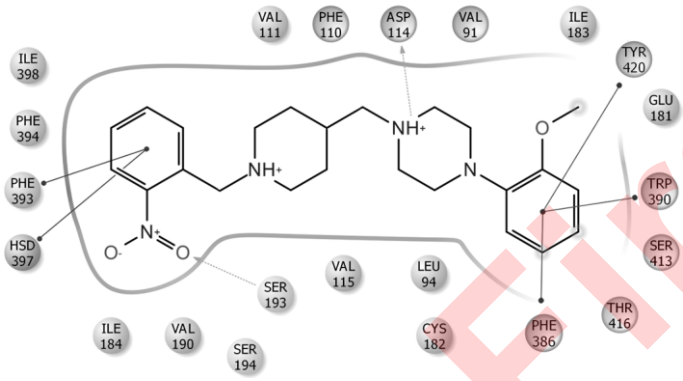


Fig. 1. Docking of compound **20** into D_2DAR binding pocket.

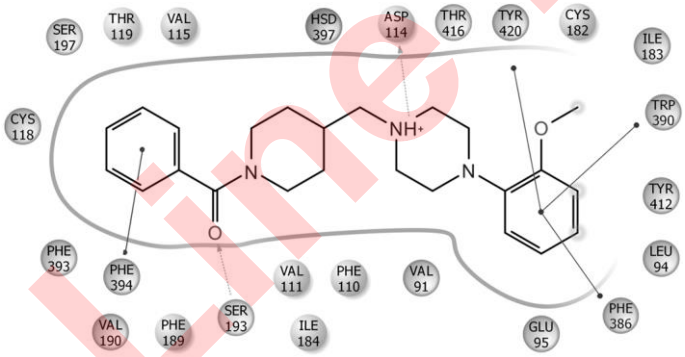


Fig. 2. Docking of compound **31** into D_2DAR binding pocket.

Other compounds cannot form interactions listed above, mostly due to their rigidity. Therefore, they either cannot achieve correct orientation inside the ABS, or cannot form any hydrogen bond to serine residues on TM5.

CONCLUSION

In order to achieve high binding affinity D_2DAR ligand has to fulfill several requirements. Formation of salt bridge with Asp 114 is crucial interaction that starts binding process, followed by orientation of arylpiperazine ligand part into OBS hydrophobic cavity. After those initial requirements are met, ligand has to establish one or more hydrogen bonds with serine residues on TM5. Failing that, ligand can still bind to D_2DAR, but with reduced affinity. In order to establish hydrogen bonds, ligand has to be of considerable length to span entire OBS

between Asp 114 and Ser 193 and/or 197. Since OBS is not linear, ligand has to adopt slightly curved conformation in order to successfully bind. Conformation of arylpiperazine part is fixed at chair conformation of arylpiperazine ring and rest of ligand has to be flexible enough to fit into the OBS space. In case of compounds **15**-**34**, only compounds **21**-**22** and **31**-**34** can adopt described conformation that leads to high affinity receptor binding. Once, conformational requirements are fulfilled, affinity is determined by the number and streght of particular receptor-ligand interactions. Ligand **20** has the best overall fit into D_2DAR, and together with formed interactions, lead to highest affinity in the group.

Obtained results suggest that in future studies special attention should be paid to the synthesis of the ligands with prolonged, flexible bridge that will provide more degree of rotational freedom of the molecules, what allows a proper orientation of the ligands into OBS cavity, what is essential prerequisite for high affinity D_2DAR ligands.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА, БИОЛОШКО ИСПИТИВАЊЕ И ДОКИНГ АНАЛИЗА СУПСТИТУИСАНИХ ПИПЕРИДИНСКИХ И (2-МЕТОКСИФЕНИЛ)ПИПЕРАЗИНСКИХ ЛИГАНАДА

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Синтетисана је серија од шеснаест нових супституисаних пиперидина и (2-метоксифенил)пиперазина, полазећи од кључних интермедијера 1-(2-метоксифенил)-4--(пиперидин-4-ил)пиперазина и 1-(2-метоксифенил)-4-(пиперидин-4-илметил)пиперазина. Биолошко испитивање синтетисаних једињења је истакло седам једињења, од којих 1-(2-метоксифенил)-4-{[1-(2-нитробензил)пиперидин-4-ил]метил}пиперазин има највиши афинитет ка $Д_2$ допаминском рецептору. За свих седам једињења је урађена докинг анализа у циљу утврђивања односа структуре и активности.

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SUPPLEMENTARY MATERIAL TO

Synthesis, biological evaluation and docking analysis of substituted piperidines and (2-methoxyphenyl)piperazines

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ANALYTICAL AND SPECTRAL DATA FOR THE SYNTHESIZED COMPOUNDS

Ethyl 4-[4-(2-metoxyphenyl)piperazin-1-yl]piperidine-1-carboxylate (**3**): Yield: 88%, oil; IR (ATR, cm^{-1}): 1698.2 (C=O), 1590.7, 1501.4 (C=C-), 1236.0 (C-N), 1025.7 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.25 (3H, t, J=6.8 Hz, CH_2-$C\underline{H}_3$), 1.46 (2H, qd, J_1=4 Hz, J_2=12 Hz, ^{3}CH and ^{5}CH piperidine), 1.87 (2H, d, J=12.4 Hz, ^{3}CH and ^{5}CH piperidine), 2.45 (1H, tt, J_1=11.2 Hz, J_2=3.4 Hz, ^{4}CH), 2.76-2.83 (6H, m, ^{2}CH and ^{6}CH piperidine, $^2CH_2$ and $^6CH_2$ piperazine), 3.02-3.15 (4H, m, $^3CH_2$ and $^5CH_2$ piperazine), 3.85 (s, 3H, OCH_3), 4.12 (2H, q, J=6.8 Hz, J=7.2 Hz, CH_3-$C\underline{H}_2$), 4.21-4.24 (2H, m, ^{2}CH and ^{6}CH piperidine), 6.83-7.043 (4H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 14.4 (1C, CH_2-$\underline{C}H_3$), 27.9 (2C, C_3 and C_5 piperidine), 43.1 (2C, C_2 and C_6 piperidine), 49.0 (2C, C_2 and C_6 piperazine), 50.7 (2C, C_3 and C_5 piperazine), 55.1 (1C, OCH3), 61.6 (1C, $\underline{C}H_2$-CH_3), 66.9 (1C, C_4 piperidine), 110.8 (1C, C_3, 2-methoxyphenyl group), 117.9 (1C, C_5, 2-methoxyphenyl group), 120.8 (1C, C_4, 2-methoxyphenyl group), 122.8 (1C, C_6, 2-methoxyphenyl group), 140.9 (1C, C_2, 2-methoxyphenyl group), 152.0 (1C, C_1, 2-methoxyphenyl group), 155.3 (-C=O); MS (m/z): $[M+H]^+$ calculated for $C_{19}H_{29}N_3O_3$ 348.2282; found 348.2284.

1-(2-Methoxyphenyl)-4-(piperidin-4-yl)piperazine (**4**): Yield: 50%, oil; IR (ATR, cm^{-1}): 3254.4 (N-H), 1585.6, 1502.6 (C=C-), 1241.1 (C-N), 1018.0 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.76 (2H, qd, J=3.5 Hz, J= 10,5 Hz, ^{3}CH and ^{5}CH piperidine), 1.98 (2H, d, J=11.5 Hz, ^{3}CH and ^{5}CH piperidine), 2.49 (1H, tt, J=3.5 Hz, J=10.5 Hz, ^{4}CH piperidine), 2.75-2.82 (6H, m, ^{2}CH and ^{6}CH piperidine, $^2CH_2$ and $^6CH_2$ piperazine), 3.09 (4H, s, $^3CH_2$ and $^5CH_2$ piperazine), 3.37 (2H, d,

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J=12.5 Hz, ^{2}CH and ^{6}CH piperidine), 3.86 (3H, s, OCH_3), 6.82-7.02 (4H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 27.2 (2C, C_3 and C_5 piperidine), 44.4 (2C, C_2 and C_6 piperidine), 49.1 (2C, C_2 and C_6 piperazine), 50.8 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 60.2 (1C, C_4 piperidine), 111.0 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 122.9 (1C, C_6, 2-methoxyphenyl group), 141.1 (1C, C_2, 2-methoxyphenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{16}H_{25}N_3O$ 276.2070; found 276.2066.

1-(2-Methoxyphenyl)-4-(piperidin-4-ylmethyl)piperazine (**10**): Yield: 54%, oil; IR (ATR, cm^{-1}): 3432.4 (N-H), 1534.8, 1499.6 (C=C-), 1237.1 (C-N), 1021.9 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.03-1.23 (2H, m, ^{3}CH and ^{5}CH piperidine), 1.62-1.69 (1H, m, ^{4}CH piperidine), 1.78 (2H, d, J=13 Hz, ^{3}CH and ^{5}CH piperidine), 2.24 (2H, d, J=6.8 Hz, CH_2-N), 2.60-2.67 (6H, m, ^{2}CH and ^{6}CH piperidine, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 3.05-3.10 (4H, m, $^{3}CH_2$ and ^{5} CH_2 piperazine), 3.86 (3H, s, OCH_3), 3.38-3.48 (2H, m, ^{2}CH and ^{6}CH piperidine), 6.83-7.02 (4H, m, aromatic); ^{13}C-NMR (50 MHz, $CDCl_3$, δ/ppm): 31.4 (2C, C_3 and C_5 piperidine), 33.3 (1C, C_4 piperidine), 45.9 (2C, C_2 and C_6 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.7 (2C, C_3 and C_5 piperazine), 55.2 (1C, OCH_3), 65.0 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 122.8 (1C, C_6, 2-methoxyphenyl group), 141.5 (1C, C_2, 2-methoxyphenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{17}H_{27}N_3O$ 290.2227; found 290.2222.

1-(Ethoxycarbonyl)piperidine-4-carboxylic acid (**6**): Yield: 78%, oil; IR (ATR, cm^{-1}): 1732.7 (C=O), 1673.5 (C=O), 1033.2 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.26 (3H, t, J=7.4 Hz, CH_2-C$\underline{H_3}$), 1.66 (2H, qd, J=10.4 Hz, J= 4.4 Hz, ^{3}CH and ^{5}CH piperidine), 1.93 (2H, d, J=13.5 Hz, ^{3}CH and ^{5}CH piperidine), 2.51 (1H, tt, J=4 Hz, J=10.6 Hz, ^{4}CH piperidine), 2.85-2.99 (2H, m, ^{2}CH and ^{6}CH piperidine), 4.03-4.19 (4H, m, ^{2}CH and ^{6}CH piperidine, C$\underline{H_2}$-CH_3), 8.43 (s, 1H, COOH); ^{13}C-NMR (50 MHz, δ/ppm): 14.6 (1C, CH_2-$\underline{C}H_3$), 27.6 (2C, C_3 and C_5 piperidine), 40.6 (1C, C_4 piperidine), 43.0 (2C, C_2 and C_6 piperidine), 61.5 (1C, CH_3-$\underline{C}H_2$), 155.6 (1C, -C=O), 179.9 (1C, COOH); MS (m/z): $[M+H]^+$ calculated for $C_9H_{15}NO_4$ 202.1073; found 202.1069.

Ethyl 4-[4-(2-methoxyphenyl)piperazine-1-carbonyl]piperidine-1-carboxylate (**8**): Yield: 85%, oil; IR (ATR, cm^{-1}): 1690.4 (C=O), 1622.2 (C=O), 1503.3, 1430.7 (C=C-), 1243.3 (C-N), 1015.6 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.26 (3H, t, J=7.2 Hz, CH_2-C$\underline{H_3}$), 1.70-1.88 (4H, m, $^{3}CH_2$ and $^{5}CH_2$ piperidine), 2.63-2.90 (3H, m, ^{4}CH, ^{2}CH and ^{6}CH piperidine), 3.00-3.09 (4H, m, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.67-3.83 (4H, m, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 3.88 (3H, s, OCH_3), 4.08-4.24 (4H, m, C$\underline{H_2}$-CH_3, ^{2}CH and ^{6}CH piperidine), 6.83-7.09 (m, 4H, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 14.6 (1C, CH_2-$\underline{C}H_3$), 28.2 (2C, C_3 and C_5

piperidine), 38.1 (1C, C_4 piperidine), 43.2 (2C, C_2 and C_6 piperidine), 50.5 (2C, C_2 and C_6 piperazine), 51.1 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 61.2 (1C, $\underline{C}H_2$-CH_3), 111.2 (1C, C_3, 2-methoxyphenyl group), 118.3 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 123.6 (1C, C_6, 2-methoxyphenyl group), 140.3 (1C, C_2, 2-methoxyphenyl group), 152.1 (1C, C_1, 2-methoxyphenyl group), 155.4 (1C, O-C=O), 172.7 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{20}H_{29}N_3O_4$ 376.2228; found 376.2231.

Ethyl 4-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}piperidine-1-carboxylate (**9**): Yield: 85%, oil; IR (ATR, cm^{-1}): 1691.3 (C=O), 1499.0, 1432.0 (C=C-), 1225.4 (C-N), 1017.0 (C-N); ^{1}H-NMR (200MHz, δ/ppm): 1.00-1.14 (2H, m, ^{3}CH and ^{5}CH piperidine), 1.25 (3H, t, J= 6.6 Hz, CH_2-$C\underline{H}_3$), 1.57-1.81 (3H, m, ^{4}CH, ^{3}CH and ^{5}CH piperidine), 2.24 (2H, d, J= 6.6 Hz, CH_2-N), 2.58-2.63 (4H, m, $^2CH_2$ and $^6CH_2$ piperazine), 2.67-2.80 (2H, m, ^{2}CH and ^{6}CH piperidine), 3.07 (4H, s, $^3CH_2$ and $^5CH_2$ piperazine), 3.86 (3H, s, OCH_3), 4.00-4.17 (4H, m, $C\underline{H}_2$-CH_3, ^{2}CH and ^{6}CH piperidine), 6.84-7.04 (4H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 14.7 (1C, CH_2-$\underline{C}H_3$), 30.7 (2C, C_3 and C_5 piperidine), 33.5 (1C, C_4 piperidine), 43.9 (2C, C_2 and C_6 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 61.1 (1C, $\underline{C}H_2$-CH_3), 64.6 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.8 (1C, C_6, 2-methoxyphenyl group), 141.4 (1C, C_2, 2-methoxyphenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group), 155.7 (1C, O-C=O); MS (m/z): $[M+H]^+$ calculated for $C_{20}H_{31}N_3O_3$ 362.2438; found 362.2437.

1-(1-Benzylpiperidin-4-yl)-4-(2-methoxyphenyl)piperazine (**15**): Yield: 76%, oil; IR (ATR, cm^{-1}): 1590.7, 1450.5 (C=C-), 1237.0 (C-N), 1019.6 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.65 (2H, qd, J=3.2 Hz, J=11.8 Hz, ^{3}CH and ^{5}CH piperidine), 1.86 (2H, d, J=11.2 Hz, ^{3}CH and ^{5}CH piperidine), 2.01 (2H, t, J=11.2 Hz, ^{2}CH and $^6CH_2$ piperidine), 2.36 (1H, tt, J=4Hz, J=11.4 Hz, ^{4}CH piperidine), 2.76-2.81 (m, 4H, $^2CH_2$ and $^6CH_2$ piperazine), 2.97 (d, 2H, J=11.8 Hz, ^{2}CH and ^{6}CH piperidine), 3.09-3.14 (m, 4H, $^3CH_2$ and $^5CH_2$ piperazine), 3.51 (s, 2H, CH_2-N), 3.85 (s, 3H, OCH_3), 6.83-7.04 (m, 4H, aromatic), 7.22-7.33 (m, 5H, aromatic); ^{13}CNMR (50 MHz, δ/ppm): 27.8 (2C, C_3 and C_5 piperidine), 49.2 (2C, C_2 and C_6 piperidine), 50.7 (2C, C_2 and C_6 piperazine), 53.0 (2C, C_3 and C_5 piperazine), 55.2 (1C, OCH_3), 62.1 (1C, CH_2-N), 62.9 (1C, C_4, piperidine), 111.0 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.9 (1C, C_6, 2-methoxyphenyl group), 127.0 (1C, C_4, phenyl group), 128.2 (2C, C_3 and C_5, phenyl group), 129.1 (2C, C_2 and C_6, phenyl group), 138.1 (1C, C_1, phenyl group), 141.2 (1C, C_2, 2-methoxyphenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{31}N_3O$ 366.2540; found 366.2547.

1-(2-Methoxyphenyl)-4-[1-(2-nitrobenzyl)piperidin-4-yl]piperazine (**16**): Yield: 80%, m.p. 145-147°C; IR (ATR, cm^{-1}): 1589.7, 1454.5 (C=C-), 1526.0 (N-O), 1369.8 (N-O), 1237.5 (C-N), 1022.6 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.56 (2H, qd, J=3.2 Hz, J= 11.8 Hz, ^{3}CH and ^{5}CH piperidine), 1.82 (2H, d, J=11.8 Hz, ^{3}CH and ^{5}CH piperidine), 2.01-2.12 (2H, m, ^{2}CH and ^{6}CH piperidine), 2.29 (1H, tt, J=3.4Hz, J=11.2Hz, ^{4}CH piperidine), 2.74-2.78 (4H, m, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.86 (2H, d, J=11.8 Hz, ^{2}CH and ^{6}CH piperidine), 3.1 (4H, s, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.76 (2H, s, CH_2-N), 3.85 (s, 3H, OCH_3), 6.83-7.04 (4H, m, aromatic), 7.37 (1H, t, J=7.8 Hz, aromatic), 7.53 (1H, t, J=7.2 Hz, aromatic), 7.63 (1H, d, J=6.8 Hz, aromatic), 7.81 (1H, d, J=6.8 Hz, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 28.3 (2C, C_3 and C_5 piperidine), 49.3 (2C, C_2 and C_6 piperidine), 50.9 (2C, C_2 and C_6 piperazine), 53.3 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 58.8 (1C, CH_2-N), 61.8 (1C, C_4, piperidine), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.9 (1C, C_6, 2-methoxyphenyl group), 124.3 (1C, C_1, 2-nitrophenyl group), 127.7 (1C, C_3, 2-nitrophenyl group), 130.8 (1C, C_4, 2-nitrophenyl group), 132.4 (1C, C_5, 2-nitrophenyl group), 134.3 (1C, C_6, 2-nitrophenyl group), 141.3 (1C, C_2, 2-methoxyphenyl group), 149.7 (1C, C_2, 2-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{30}N_4O_3$ 411.2391; found 411.2402.

1-(2-Methoxyphenyl)-4-[1-(3-nitrobenzyl)piperidin-4-yl]piperazine (**17**): Yield: 86%, oil; IR (ATR, cm^{-1}): 1588.3, 1499.4 (C=C-), 1530.8 (N-O), 1346.9 (N-O), 1237.5 (C-N), 1027.6 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.63 (2H, qd, J=3.2 Hz, J=10.7 Hz, ^{3}CH and ^{5}CH piperidine), 1.86 (2H, d, J=11.8 Hz, ^{3}CH and ^{5}CH piperidine), 2.05 (2H, t, J=11.8 Hz, ^{2}CH and ^{6}CH piperidine), 2.34 (1H, tt, J=3.8 Hz, J=11.8 Hz, ^{4}CH piperidine), 2.76-2.80 (4H, m, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.92 (2H, d, J=11.2 Hz, ^{2}CH and ^{6}CH piperidine), 3.08-3.11 (4H, m, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.57 (2H, s, CH_2-N), 3.86 (3H, s, OCH_3), 6.83-7.04 (4H, m, aromatic), 7.47 (1H, t, J=7.8 Hz, aromatic), 7.67 (1H, d, J=7.2Hz, aromatic), 8.11 (1H, d, J=8.4 Hz, aromatic), 8.2 (1H, s, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 28.2 (2C, C_3 and C_5 piperidine), 49.3 (2C, C_2 and C_6 piperidine), 50.9 (2C, C_2 and C_6 piperazine), 55.2 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 62.0 (2C, CH_2-N and C_4 piperidine), 111.0 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 120.3 (2C, C_4, 2-methoxyphenyl group and C_4, 3-nitrophenyl group), 122.1 (1C, C_6, 2-methoxyphenyl group), 122.9 (1C, C_2, 3-nitrophenyl group), 123.6 (1C, C_5, 3-nitrophenyl group), 129.1 (1C, C_6, 3-nitrophenyl group), 134.9 (1C, C_1, 3-nitrophenyl group), 141.3 (1C, C_2, 2-methoxyphenyl group), 149.8 (1C, C_3, 3-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{30}N_4O_3$ 411.2391; found 411.2389.

1-(2-Methoxyphenyl)-4-[1-(4-nitrobenzyl)piperidin-4-yl]piperazine (**18**): Yield: 76%, m.p. 144-146°C; IR (ATR, cm^{-1}): 1599.4, 1445.6 (C=C-), 1513.8 (N-O), 1344.2 (N-O), 1236.8 (C-N), 1020.3 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.65 (2H, qd, J=3.4 Hz, J= 12.2 Hz, ^{3}CH and ^{5}CH piperidine), 1.89 (2H, d, J=11,8 Hz, ^{3}CH and ^{5}CH piperidine), 2.00-2.11 (2H, m, ^{2}CH and ^{6}CH piperidine), 2.39 (1H, tt, J=4 Hz, J=11.2 Hz, ^{4}CH piperidine), 2.80-2.84 (4H, m, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.92 (d, 2H, J=11.8 Hz, ^{2}CH and ^{6}CH piperidine), 3.12-3.14 (m, 4H, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.58 (2H, s, CH_2-N), 3.86 (3H, s, OCH_3), 6.84-7.05 (4H, m, aromatic), 7.59 (2H, d, J=9 Hz, aromatic), 8.17 (2H, d, J=8.4 Hz, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 28.1 (2C, C_3 and C_5 piperidine), 49.3 (2C, C_2 and C_6 piperidine), 50.7 (2C, C_2 and C_6 piperazine), 53.2 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 62.0 (2C, CH_2-N and C_4 piperidine), 111.0 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 123.0 (1C, C_6, 2-methoxyphenyl group), 123.5 (2C, C_3 and C_5, 4-nitrophenyl group), 129. 3 (2C, C_2 and C_6, 4-nitrophenyl group), 141.1 (1C, C_2, 2-methoxyphenyl group), 146.8 (2C, C_1 and C_4, 4-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{30}N_4O_3$ 411.2391; found 411.2409.

1-[(1-Benzylpiperidin-4-yl)methyl]-4-(2-methoxyphenyl)piperazine (**19**): Yield: 80%, m.p. 104-105°C; IR (ATR, cm^{-1}): 1588.4, 1447.5 (C=C-), 1238.7 (C-N), 1024.9 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.25 (2H, qd, J=2.8 Hz, J= 12 Hz, ^{3}CH and ^{5}CH piperidine), 1.46-1.59 (1H, m, ^{4}CH piperidine), 1.74 (2H, d, J=13 Hz, ^{3}CH and ^{5}CH piperidine), 1.89-2.00 (2H, m, ^{2}CH and ^{6}CH piperidine), 2.41 (2H, d, J=6.8 Hz, CH_2-N), 2.52 (4H, s, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.89 (2H, d, J=11.8 Hz, ^{2}CH and ^{6}CH piperidine), 3.07 (4H, s, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.50 (2H, s, CH_2-N), 3.86 (3H, s, OCH_3), 6.83-7.04 (4H, m, aromatic), 7.23-7.33 (5H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 31.0 (2C, C_3 and C_5 piperidine), 33.1 (1C, C_4 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.8 (2C, C_2 and C_6 piperidine), 53.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 62.5 (1C, CH_2-N), 64.8 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.8 (1C, C_6, 2-methoxyphenyl group), 126.9 (1C, C_4, phenyl group), 128.1 (2C, C_3 and C_5 phenyl group), 129.2 (2C, C_2 and C_6 phenyl group), 138.5 (1C, C_1, phenyl group), 141.5 (1C, C_2, 2-methoxyphenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{33}N_3O$ 380.2696; found 380.2692.

1-(2-Methoxyphenyl)-4-{[1-(2-nitrobenzyl)piperidin-4-yl]methyl}piperazine (**20**): Yield: 82%, m.p. 99-101°C; IR (ATR, cm^{-1}): 1589.1, 1499.5 (C=C-), 1532.6 (N-O), 1314.2 (N-O), 1236.1 (C-N), 1026.4 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.21 (2H, qd, J_1=11.5 Hz, J_2=3 Hz, ^{3}CH and ^{5}CH piperidine), 1.45-1.58 (1H, m, ^{4}CH piperidine), 1.72 (2H, d, J=11.5 Hz, ^{3}CH and ^{5}CH piperidine),

1.96-2.07 (2H, m, ^{2}CH and ^{6}CH piperidine), 2.23 (2H, d, J=6.8 Hz, CH_2-N), 2.59-2.61 (4H, m, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.78 (2H, d, J=11.2 Hz, ^{2}CH and ^{6}CH piperidine), 3.07 (4H,s, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.76 (2H, s, CH_2-N), 3.86 (3H, s, OCH_3), 6.83-7.03 (4H, m, aromatic), 7.32-7.83 (m, 4H, aromatic)**;** ^{13}C-NMR (50 MHz, δ/ppm): 31.1 (2C, C_3 and C_5 piperidine), 33.1 (1C, C_4 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.9 (4C, C_2, C_6 piperidine and C_3, C_5 piperazine), 55.3 (1C, OCH_3), 63.5 (1C, CH_2-N), 64.9 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.8 (1C, C_6, 2-methoxyphenyl group), 124.3 (1C, C_1, 2-nitrophenyl group), 127.6 (1C, C_3, 2-nitrophenyl group), 130.8 (1C, C_4, 2-nitrophenyl group), 132.4 (1C, C_5, 2-nitrophenyl group), 134.7 (1C, C_6, 2-nitrophenyl group), 141.5 (1C, C_2, 2-methoxyphenyl group), 149.8 (1C, C_2, 2-nitrophenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{32}N_4O_3$ 425.2547; found 425.2540.

1-(2-Methoxyphenyl)-4-{[1-(3-nitrobenzyl)piperidin-4-yl]methyl}piperazine (**21**): Yield: 80%, m.p. 131-133°C; IR (ATR, cm^{-1}): 1594.7, 1444.9 (C=C-), 1534.2 (N-O), 1342.3 (N-O), 1251.5 (C-N), 1030.8 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.32 (2H, qd, J=3.4 Hz, J=12 Hz, ^{3}CH and ^{5}CH piperidine), 1.48-1.64 (1H, m, ^{4}CH piperidine), 1.76 (2H, d, J=12 Hz, ^{3}CH and ^{5}CH piperidine), 1.95-2.06 (2H, m, ^{2}CH and ^{6} CH piperidine), 2.25 (2H, d, J= 7.4 Hz, CH_2-N), 2.60 (s, 4H, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.85 (2H, d, J=11.8 Hz, ^{2}CH and ^{6}CH piperidine), 3.07 (4H, s, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.57 (2H, s, CH_2-N), 3.86 (s, 3H, OCH_3), 6.83-7.04 (4H, m, aromatic), 7.47 (1H, t, J=7.8 Hz, aromatic), 7.67 (1H, d, J=8 Hz, aromatic), 8.10 (1H, d, J=8.4 Hz, aromatic) 8.2 (1H, s, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 31.0 (2C, C_3 and C_5 piperidine), 33.1 (1C, C_4 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.8 (2C, C_2 and C_6 piperidine), 53.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 62.5 (1C, CH_2-N), 64.8 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 120.9 (2C, C_4, 3-nitrophenyl group and C_4, 2-methoxyphenyl group), 122.1 (1C, C_6, 2-methoxyphenyl group), 122.8 (1C, C_2, 3-nitrophenyl group), 123.7 (1C, C_5, 3-nitrophenyl group), 129.1 (1C, C_6, 3-nitrophenyl group), 135.0 (1C, C_1, 3-nitrophenyl group), 141.3 (1C, C_2, 2-methoxyphenyl group), 149.3 (1C, C_3, 3-nitrophenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{32}N_4O_3$ 425.2547; found 425.2552.

1-(2-Methoxyphenyl)-4-{[1-(4-nitrobenzyl)piperidin-4-yl]methyl}piperazine **(22**): Yield: 87%, m.p. 120-121°C; IR (ATR, cm^{-1}): 1598.2, 1447.6 (C=C-), 1507.9 (N-O), 1343.0 (N-O), 1242.9 (C-N), 1026.6 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.26 (2H, qd, J=3.8 Hz, J=10.6 Hz, ^{3}CH and ^{5}CH piperidine), 1.47-1.66 (1H, m, ^{4}CH piperidine), 1.76 (2H, d, J=11.8 Hz, ^{3}CH and ^{5}CH piperidine), 1.95-2.05 (2H, m, ^{2}CH and ^{6}CH piperidine), 2.26 (2H, d, J=6.4 Hz, CH_2-N), 2.60-2.62

(4H, m, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.84 (d, 2H, J=11.2 Hz, ^{2}CH and ^{6}CH piperidine), 3.07 (s, 4H, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.57 (s, 2H, CH_2-N), 3.86 (s, 3H, OCH_3), 6.83-7.04 (4H, m, aromatic), 7.50 (2H d, J=8.4 Hz, aromatic), 8.17 (2H, d, J=8.4 Hz, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 31.0 (2C, C_3 and C_5 piperidine), 33.0 (1 C,C_4 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.8 (4C, C_2, C_6 piperidine and C_3, C_5 piperazine), 55.3 (1C, OCH_3), 62.5 (1C, CH_2-N), 64.8 (1C, CH_2-N), 111.0 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.8 (1C, C_6, 2-methoxyphenyl group), 123.4 (2C, C_3 and C_5, 4-nitrophenyl group), 129.4 (2C, C_2 and C_6, 4-nitrophenyl group), 141.4 (1C, C_2, 2-methoxyphenyl group), 146.9 (2C, C_1 and C_4, 4-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{32}N_4O_3$ 425.2547; found 425.2561.

{4-[4-(2-methoxyphenyl)piperazin-1-yl]piperidin-1-yl}(phenyl)methanone (**27**): Yield: 76%, m.p. 131-132°C; IR (ATR, cm^{-1}): 1626.6 (C=O), 1234.1 (C-N), 1024.3 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.55-2.17 (5H m, $^{3}CH_2$, $^{5}CH_2$ and ^{2}CH piperidine), 2.56 (1H, tt, J=3.4 Hz, J=7.4 Hz, ^{4}CH piperidine), 2.76-2.80 (5H, m, $^{2}CH_2$, $^{6}CH_2$ piperazine and ^{6}CH piperidine), 3.109 (5H, s, $^{3}CH_2$, $^{5}CH_2$ piperazine and ^{2}CH piperidine), 3.86 (s, 3H, OCH_3), 4.75 (1H, s, ^{6}CH piperidine), 6.84-7.05 (4H, m, aromatic), 7.26-7.40 (5H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 28.2 (2C, C_3 and C_5 piperidine), 47.1 (2C, C_2 and C_6 piperidine), 49.4 (2C, C_2 and C_6 piperazine), 50.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 61.8 (1C, C_4 piperidine), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 123.0 (1C, C_6, 2-methoxyphenyl group), 126.8 (2C, C_2 and C_6 phenyl group), 128.4 (2C, C_3 and C_5, phenyl group), 129.5 (1C, C_4, phenyl group), 136.2 (1C, C_1, phenyl group), 141.2 (1C, C_2, 2-methoxyphenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group), 170.2 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{29}N_3O_2$ 380.2333; found 380.2338.

{4-[4-(2-methoxyphenyl)piperazin-1-yl]piperidin-1-yl}(2-nitrophenyl)-methanone (**28**): Yield: 75%, m.p. 159-161°C; IR (ATR, cm^{-1}): 1638.7 (C=O), 1521.1 (N-O), 1341.8 (N-O), 1236.1 (C-N), 1025.4 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.25-1.99 (5H, m, $^{3}CH_2$, $^{5}CH_2$ and ^{2}CH piperidine), 2.61 (1H, tt, J=3.4 Hz, J=10 Hz, ^{4}CH piperidine), 2.78-2.83 (5H, m, $^{2}CH_2$, $^{2}CH_2$ piperazine and ^{6}CH piperidine), 3.10-3.12 (5H, m, $^{3}CH_2$, $^{5}CH_2$ piperazine and ^{2}CH piperidine), 3.78 (1H, s, ^{6}CH piperidine), 3.87 (3H, s, OCH_3), 6.85-7.06 (5H, m, aromatic), 7.58-7.66 (1H, m, aromatic), 7.72-7.78 (1H, m, aromatic), 8.18-8.35 (1H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 28.0 (2C, C_3 and C_5 piperidine), 47.1 (2C, C_2 and C_6 piperidine), 49.3 (2C, C_2 and C_6 piperazine), 50.8 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 61.5 (1C, C_4 piperidine), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 122.1 (1C, C_6, 2-methoxyphenyl group), 124.8 (1C, C_3,

2-nitrophenyl group), 128.0 (1C, C_6, 2-nitrophenyl group), 129.7 (1C, C_4, 2-nitrophenyl group), 133.2 (1C, C_1, 2-nitrophenyl group), 134.3 (1C, C_5, 2-nitrophenyl group), 141.1 (1C, C_2, 2-methoxyphenyl group), 145.4 (1C, C_2, 2-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group), 166.4 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{28}N_4O_4$ 425.2183; found 425.2192.

{4-[4-(2-methoxyphenyl)piperazin-1-yl]piperidin-1-yl}(3-nitrophenyl)-methanone (**29**): Yield: 72%, m.p. 118-119°C; IR (ATR, cm^{-1}): 1621.8 (C=O), 1531.0 (N-O), 1351.3 (N-O), 1244.8 (C-N), 1025.3 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.53-1.63 (2H, m, ^{3}CH and ^{5}CH piperidine), 1.88-2.16 (2H, m, ^{3}CH and ^{5}CH piperidine), 2.62 (1H, tt, J=3.4 Hz, J=11.4 Hz, ^{4}CH piperidine), 2.73-2.83 (5H, m, $^2CH_2$, $^6CH_2$ piperazine and ^{2}CH piperidine), 3.10-3.15 (5H, m, $^3CH_2$, $^5CH_2$ piperazine and ^{6}CH piperidine), 3.50-3.73 (1H, m, ^{2}CH piperidine), 3.82 (s, 3H, OCH_3), 4.74-4.79 (1H, m, ^{6}CH piperidine), 6.82-7.06 (4H, m, aromatic), 7.46-7.68 (2H, m, aromatic), 8.18-8.39 (2H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 27.9 (2C, C_3 and C_5 piperidine), 46.8 (2C, C_2 and C_6 piperidine) 49.3 (2C, C_2 and C_6 piperazine), 50.7 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 61.5 (1C, C_4 piperidine), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 122.1 (1C, C_6, 2-methoxyphenyl group), 123.0 (1C, C_2, 3-nitrophenyl group), 124.4 (1C, C_4, 3-nitrophenyl group), 129.8 (1C, C_5, 3-nitrophenyl group), 132.9 (1C, C_6, 3-nitrophenyl group), 137.7 (1C, C_1, 3-nitrophenyl group), 141.1 (1C, C_2, 2-methoxyphenyl group), 148.0 (1C, C_3, 3-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group), 167.5 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{28}N_4O_4$ 425.2183; found 425.2195.

{4-[4-(2-methoxyphenyl)piperazin-1-yl]piperidin-1-yl}(4-nitrophenyl)-methanone (**30**): Yield: 70%, m.p. 156-157°C; IR (ATR, cm^{-1}): 1630.1 (C=O), 1522.0 (N-O), 1352.0 (N-O), 1233.0 (C-N), 1024.5 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.47-2.07 (5H, m, $^3CH_2$, $^5CH_2$ and ^{2}CH piperidine), 2.57-2.61 (1H, m, ^{4}CH piperidine), 2.79 (s, 4H, $^2CH_2$ and $^6CH_2$ piperazine), 2.87 (1H, s, ^{6}CH piperidine), 3.11 (4H, s, $^3CH_2$ and $^5CH_2$ piperazine), 3.66 (1H, m, ^{2}CH piperidine), 3.86 (3H, s, OCH_3), 4.73-4.76 (1H, m, ^{6}CH piperidine), 6.85-7.02 (4H, m, aromatic), 7.56-7.58 (2H m, aromatic), 8.27-8.29 (2H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 28.1 (2C, C_3 and C_5 piperidine), 47.0 (2C, C_2 and C_6 piperidine), 49.4 (2C, C_2 and C_6 piperazine), 50.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 61.5 (1C, C_4 piperidine), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 123.1 (1C, C_6, 2-methoxyphenyl group), 123.9 (2C, C_3 and C_5, 4-nitrophenyl group), 127.9 (2C, C_2 and C_6, 4-nitrophenyl group), 141.1 (1C, C_2, 2-methoxyphenyl group), 142.29 (1C, C_1, 4-nitrophenyl group), 148.35 (1C, C_4, 4-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group), 167.8 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{23}H_{28}N_4O_4$ 425.2183; found 425.2186.

(4-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}piperidin-1-yl)(phenyl)-methanone (**31**): Yield: 68%, oil; IR (ATR, cm^{-1}): 1629.3 (C=O), 1239.0 (C-N), 1130.4 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.24-125 (2H, m, ^{3}CH, ^{5}CH piperidine), 1.80-1.85 (3H, m, ^{3}CH, ^{5}CH and ^{4}CH piperidine), 2.28-2.29 (2H, m, CH_2-N), 2.62 (5H, s, $^{2}CH_2$, $^{6}CH_2$ piperazine and ^{2}CH piperidine), 3.07 (5H, s, $^{3}CH_2$, $^{5}CH_2$ piperazine and ^{6}CH piperidine), 3.70 (1H, s, ^{2}CH piperidine), 3.86 (3H, s, OCH_3), 4.72 (1H, s, ^{6}CH piperidine), 6.84 (1H, m, aromatic), 6.89 (2H, m, aromatic), 6.94 (1H, m, aromatic), 6.97 (5H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 30.7 (2C, C_3 and C_5 piperidine), 33.7 (1C, C_4 piperidine), 48.0 (2C, C_2 and C_6 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 64.4 (1C, CH_2-N), 111.2 (1C, C_3, 2-methoxyphenyl group), 118.2 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 122.9 (1C, C_6, 2-methoxyphenyl group), 126.8 (2C, C_2 and C_6 phenyl group), 128.4 (2C, C_3 and C_5, phenyl group), 129.4 (1C, C_4, phenyl group), 136.5 (1C, C_1, phenyl group), 141.4 (1C, C_2, 2-methoxyphenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group), 170.3 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{31}N_3O_2$ 394.2489; found 394.2488.

(4-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}piperidin-1-yl)(2-nitrophe-nyl)methanon (**32**): Yield: 73%, m.p. 127-130°C; IR (ATR, cm^{-1}): 1628.4 (C=O), 1524.2 (N-O), 1343.5 (N-O), 1235.7 (C-N), 1114.5 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.06-1.09 (2H,m, ^{3}CH, ^{5}CH piperidine), 1.59 (2H, s, CH_2-N), 1.68-1.72 (3H, m, ^{3}CH, ^{5}CH and ^{4}CH piperidine), 2.24-2.33 (1H, m, ^{2}CH piperidine), 2.61 (4H, s, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.84-2.88 (1H, m, ^{6}CH piperidine), 3.02 (4H, s, $^{3}CH_2$ and $^{5}CH_2$ piperazine), 3.36 (1H, s, ^{2}CH piperidine), 3.85 (s, 3H, OCH_3), 4.73-4.78 (1H, m, ^{6}CH piperidine), 6.84 (1H, d, J=8.5 Hz, aromatic), 6.89-6.94 (2H, m, aromatic), 6.97-7.00 (1H, m, aromatic) 7.38 (1H, s, aromatic), 7.55 (1H, t, J=8.5 Hz, aromatic), 7.69 (1H, t, J=7.5 Hz, aromatic), 8.19 (1H, d, J=8.5 Hz, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 29.9 (2C, C_3 and C_5 piperidine), 33.6 (1C, C_4 piperidine), 46.7 (2C, C_2 and C_6 piperidine), 50.7 (2C, C_2 and C_6 piperazine), 53.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 64.2 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 121.0 (1C, C_4, 2-methoxyphenyl group), 122.9 (1C, C_6, 2-methoxyphenyl group), 124.8 (1C, C_3, 2-nitrophenyl group), 128.0 (1C, C_6, 2-nitrophenyl group), 129.6 (1C, C_4, 2-nitrophenyl group), 133.5 (1C, C_1, 2-nitrophenyl group), 134.4 (1C, C_5, 2-nitrophenyl group), 141.4 (1C, C_2, 2-methoxyphenyl group), 145.3 (1C, C_2, 2-nitrophenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group), 170.3 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{30}N_4O_4$ 439.2340; found 439.2348.

(4-{[4-(2-methoxyphenyl)piperazin-1-yl)methyl]piperidin-1-yl}(3-nitrophe-nyl)methanone (**33**): Yield: 80%, m.p. 116-118°C; IR (ATR, cm^{-1}): 1630.6 (C=O), 1533.1 (N-O), 1351.6 (N-O), 1243.6 (C-N), 1109.9 (C-N); ^{1}H-NMR

(200MHz, δ/ppm): 1.15-1.17 (2H, m, ^{3}CH, ^{5}CH piperidine), 1.82-1.94 (3H, m, ^{3}CH, ^{5}CH and ^{4}CH piperidine), 2.30 (2H, s, CH_2-N), 2.62 (s, 4H, $^{2}CH_2$ and $^{6}CH_2$ piperazine), 2.84 (1H, s, ^{2}CH piperidine), 3.07 (5H, s, $^{2}CH_2$, $^{6}CH_2$ piperazine and ^{6}CH piperidine), 3.64-3.66 (1H, m, ^{2}CH piperidine), 3.86 (3H, s, OCH_3), 4.73 (1H, s, ^{6}CH piperidine), 6.84-6.86 (1H, m, aromatic), 6.89-6.94 (2H, m, aromatic), 6.97-7.00 (1H, m, aromatic), 7.58-7.62 (1H, m, aromatic), 7.74 (1H, m, aromatic), 8.26-8.28 (2H, m, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 30.4 (2C, C_3 and C_5 piperidine), 33.6 (1C, C_4 piperidine), 47.9 (2C, C_2 and C_6 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.8 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 64.2 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.8 (1C, C_6, 2-methoxyphenyl group), 124.2 (1C, C_2, 3-nitrophenyl group), 128.0 (1C, C_4, 3-nitrophenyl group), 129.7 (1C, C_5, 3-nitrophenyl group), 132.9 (1C, C_6, 3-nitrophenyl group), 137.9 (1C, C_1, 3-nitrophenyl group), 141.3 (1C, C_2, 2-methoxyphenyl group), 149.8 (1C, C_3, 3-nitrophenyl group), 152.3 (1C, C_1, 2-methoxyphenyl group), 167.2 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{30}N_4O_4$ 439.2340; found 439.2357.

(4-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}piperidin-1-yl)(4-nitrophenyl)methanone (**34**): Yield: 85%, m.p.119-121°C; IR (ATR, cm^{-1}): 1630.7 (C=O), 1519.0 (N-O), 1347.9 (N-O), 1239.4 (C-N), 1012.9 (C-N); ^{1}H-NMR (200 MHz, δ/ppm): 1.11-1.13 (2H, m, ^{3}CH, ^{5}CH piperidine), 1.79-1.87 (2H, m, ^{3}CH, ^{5}CH piperidine), 1.95 (1H, m, ^{4}CH piperidine), 2.28-2.30 (2H, m, CH_2-N), 2.62 (5H, s, $^{2}CH_2$, $^{6}CH_2$ piperazine and ^{2}CH piperidine), 3.07 (5H, s, $^{3}CH_2$, $^{5}CH_2$ piperazine and ^{6}CH piperidine), 3.59 (1H, d, J=12.5 Hz, ^{2}CH piperidine), 3.86 (3H, s, OCH_3), 4.71 (1H, d, J=12 Hz, ^{6}CH piperidine), 6.84-6.86 (1H, m, aromatic), 6.89-6.94 (2H, m, aromatic), 6.97-7.01 (1H, m, aromatic), 7.55 (2H, d, J=9 Hz, aromatic), 8.26 (2H, d, J=9 Hz, aromatic); ^{13}C-NMR (50 MHz, δ/ppm): 30.4 (2C, C_3 and C_5 piperidine), 33.6 (1C, C_4 piperidine), 47.8 (2C, C_2 and C_6 piperidine), 50.6 (2C, C_2 and C_6 piperazine), 53.9 (2C, C_3 and C_5 piperazine), 55.3 (1C, OCH_3), 64.2 (1C, CH_2-N), 111.1 (1C, C_3, 2-methoxyphenyl group), 118.1 (1C, C_5, 2-methoxyphenyl group), 120.9 (1C, C_4, 2-methoxyphenyl group), 122.9 (1C, C_6, 2-methoxyphenyl group), 123.8 (2C, C_3 and C_5, 4-nitrophenyl group), 127.8 (2C, C_2 and C_6, 4-nitrophenyl group), 141.4 (1C, C_2, 2-methoxyphenyl group), 142.6 (1C, C_1, 4-nitrophenyl group), 148.2 (1C, C_4, 4-nitrophenyl group), 152.2 (1C, C_1, 2-methoxyphenyl group), 167.8 (1C, C=O); MS (m/z): $[M+H]^+$ calculated for $C_{24}H_{30}N_4O_4$ 439.2340; found 439.2360.