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Original scientific paper

Synthetic route towards potential bivalent ligands possessing opioid and D_2/D_3 pharmacophores

IVANA I. JEVTIĆ[1], JELENA Z. PENJIŠEVIĆ[1], MILOVAN D. IVANOVIĆ[2] and SLAĐANA V. KOSTIĆ-RAJAČIĆ[1]*

[1]*ICTM – Department of Chemistry, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia and* [2]*Faculty of Chemistry, University of Belgrade, Studentski trg 12–16, 11000 Belgrade, Serbia*

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Abstract: A scalable, cost-efficient and simple synthetic pathway towards potential bivalent opioid/dopamine receptor ligands was developed and optimized. Three novel compounds that contain both opioid and dopamine pharmacophores linked by the four methylene group chain were synthesized in 33, 35 and 39 % overall yield after a four-step synthetic route starting from three commercially available *N*-aryl piperazines. The anilino piperidine precursor was easily prepared in three steps, as previously published, starting from 4-piperidone. The synthesis presented in this paper could be of interest for heterocyclic and general organic chemistry. The newly designed compounds possessing two pharmacophores, opioid and D_2/D_3, are potentially useful pharmacological probes. Of particular interest would be the simultaneous binding to both opioid and D_2/D_3 receptors, and the resulting pharmacological responses may be useful for the further understanding of tolerance and dependence phenomena in opioid clinical use and/or abuse.

Keywords: piperidine; piperazine; heterocycles; *N*-alkylation; analgesics; dopaminergic.

INTRODUCTION

4-Anilido-piperidines and *N*-aryl piperazines are pharmacologically important moieties.[1–6] Both of these pharmacophores are seen separately in numerous compounds possessing high pharmacological activities, many of which have found their way into clinical use. 4-Anilido-piperidines are best known for their analgesic activity since many of them act as μ-opioid receptor agonists in the central nervous system (CNS).[1–4] Opioid analgesics are especially effective for the treatment of strong chronic and acute pain, when other standard analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) are ineffective. There

* Corresponding author. E-mail: srkostic@chem.bg.ac.rs
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are several highly potent opioid analgesics with a 4-anilido-piperidine core in clinical use, including fentanyl (Actiq® and Abstral®), sufentanil (Sufenta®), alfentanil (Alfenta®) and remifentanil (Ultiva®). The serious drawback when opioid usage is considered are side effects, among which the most important are tolerance and dependence due to prolonged treatment of chronic pain, with the most dangerous outcome being respiratory arrest due to CNS depression as a result of overdosing with opioids. The *N*-aryl piperazine scaffold is present in many compounds that are active towards the dopaminergic signalling system in the CNS, especially D_2 and D_3 receptor subtypes.[5] Several antipsychotic drugs that are used in clinical practice for treatment of schizophrenia and bipolar disorders are compounds that contain the piperazine moiety that act as D_2 antagonists, such as Geodon®, Clozaril®, or partial agonists, such as Abilify®. D_2 and D_3 agonists however are clinically used for the treatment of Parkinson's disease, for example Pronoran®.

Recently it was discovered that activation of μ-opioid receptors influences the dopaminergic signal pathway, which in turn is believed to have a reinforcing effect on some psychoactive drugs. It was found that the drugs affecting the dopaminergic system can also influence the effect of opioid agonists on cognitive functions in animal models.[7–14] These results are expected to be useful for further understanding of the tolerance and dependence phenomena in opioids addiction.

In the past several decades, a large number of anilido piperidines have been prepared, particularly analogues with diverse substituents on the piperidine nitrogen. Interestingly, it seems that none of the substituents included a piperazine moiety.[15,16] In view of the fact that many piperazines are significant D_2/D_3 receptor pharmacophores, the aim of this study was to develop a synthetic route towards novel compounds as potential bivalent, opioid–dopaminergic ligands, having the general structure **1** (Fig. 1). Apparently, none of the bivalent, opioid–dopaminergic ligands have hitherto been reported.

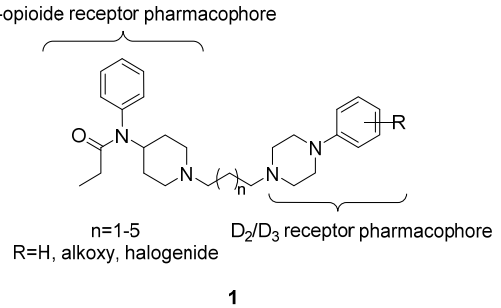

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Fig. 1. The general structure of bivalent ligand containing 4-anilido-piperidine and *N*-aryl piperazine moieties.

Designing multi-target drugs has become a growing area of medicinal chemistry in recent years. The aim of such drug design is to provide the structures that will be superior in efficacy and safety, relative to single target drugs. Introducing two pharmacophores, such 4-anilido-piperidine and *N*-aryl piperazine in one molecule could lead to interesting results in the pharmacological testing of such compounds, regarding their opioid and dopamine receptor activity. Therefore, the development of a synthetic pathway towards bivalent opioid/dopamine receptor ligands could be of interest to synthetic, heterocyclic and medicinal chemistry in general.

EXPERIMENTAL

General information

Unless otherwise stated all solvents were freshly distilled under argon prior to use. All reagents purchased from a commercial vendor were used as supplied.

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance III spectrometer, at 500 MHz for protons (^{1}H) and at 126 MHz for carbons (^{13}C). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as the internal standard in $CDCl_3$. The 2D NMR spectra (HSQC) were recorded at 500 MHz. Coupling constants (*J*) are reported in Hz. Unless otherwise stated, all spectra were recorded at 25 °C. High resolution mass spectra (HRMS) were obtained with a heated ESI (HESI)-Orbitrap spectrometer. Spectral and analytical data are given in Supplementary material to this paper.

All reactions were monitored by thin layer chromatography (TLC). Flash and dry--column flash chromatography[17,18] were performed using silica gel (10−18 or 18–32 μm, ICN-Woelm). Melting points were obtained at a heating rate of 4 °C min^{-1} and are uncorrected. IR spectra were recorded using a Thermo Scientific Nicolet 6700 Fourier-transform spectrometer operated in the ATR mode.

Structures of all new compounds were determined by methods of 1D, 2D NMR and IR spectroscopy. Structures of the three final compounds were additionally confirmed by high resolution mass spectrometry (HRMS).

Syntheses

*General procedure for the synthesis of anilido-piperidines **8a** and **b**.* To a magnetically stirred solution of norfentanyl **4** (300 mg, 1.3 mmol) and K_2CO_3 (360 mg, 2.6 mmol) in MeCN (12 mL) was added bromochloro alkane (13 mmol). The mixture was allowed to stir at 25 °C. The reaction was monitored by TLC with a mixture of CH_2Cl_2/MeOH = 95:5 as the eluent. After 24 h, Et_2O was added, and the mixture was filtered, then concentrated by rotary evaporator. 10 % HBr (0.4 mL) was added, and mixture was extracted with 2×20 mL of *n*-hexane. Aqueous layer was then neutralised with 1.5 M solution of K_2CO_3 (pH ≈11) and extracted with 2×20 mL of CH_2Cl_2. The organic layers were combined and concentrated on a rotary evaporator. The crude product was purified by dry-column flash chromatography (SiO_2; CH_2Cl_2/MeOH = 8:2 to 0:10).

*General procedure for the synthesis of aryl piperazino carboxamides **7a**–**c**.* To a magnetically stirred solution of aryl piperazine hydrochloride **12a–c** (3.5 mmol) in CH_2Cl_2 (10 mL), were added Et_3N (425 mg, 4.2 mmol) and 4-chloro-butyrilchloride (740 mg, 5.25 mmol) at 0 °C. The mixture was then allowed to stir. The reaction was monitored by TLC, with mixture of CH_2Cl_2/MeOH = 95:5 as the eluent. After 40 min stirring at 0 °C and an additional 20 min

at 25 °C, the reaction was complete. MeOH (10 mL) was then added, and the mixture was concentrated on a rotary evaporator. A solution of K_2CO_3 (1.5 M) was added (pH ≈11) and the mixture was extracted with 2×25 mL of CH_2Cl_2. The organic layers were collected and concentrated on a rotary evaporator. The crude product was used in the next step without further purification.

*General procedure for the synthesis of the aryl piperazino carboxamide-anilino-piperidine adducts (**13a**–**c**).* To a magnetically stirred solution of anilino-piperidine **6** (300 mg, 1.7 mmol) and K_2CO_3 (2 equiv.) in MeCN (12 mL), was added aryl piperazino carboxamide **7a**–**c** (2.5 mmol). The mixture was stirred at 70 °C. The reaction was monitored by TLC, with mixture of CH_2Cl_2/MeOH = 95:5 as the eluent. The reaction was completed after 8 h of reflux and additional stirring for 10 h at 25 °C. The mixture was then concentrated on a rotary evaporator and then 50 mL of CH_2Cl_2 was added and the mixture extracted with 2×25 mL of brine. The organic phase was concentrated on a rotary evaporator. The crude product was purified by dry-column flash chromatography (SiO_2; CH_2Cl_2/MeOH = 1:0 to 95:5).

*General procedure for the synthesis of the aryl piperazino-anilino-piperidine adducts (**5a**–**c**).* To a magnetically stirred suspension of aryl piperazino-anilino-piperidine adduct **13a**–**c** (1.0 mmol) in dry THF (12 mL) was added 1M solution of BH_3 in dry THF (34 mg, 2.5 mmol) at 0 °C. Mixture was allowed to stir at 25 °C. After the spontaneous boiling stopped, the mixture was heated at 70 °C. The reaction was monitored by TLC with mixture of CH_2Cl_2/MeOH = 95:5 as the eluent. After 4 h of reflux, water (1 mL) was added dropwise, followed by the addition of 5.5 M HCl (2 mL) at 25 °C. Reflux was continued for an additional 4 h. Mixture was then concentrated on a rotary evaporator, 50 mL of CH_2Cl_2 was added, the layers were separated, and the organic phase was washed with 2×25 mL of brine. The organic phase was concentrated on a rotary evaporator. The crude product was purified by dry-column flash chromatography (SiO_2; CH_2Cl_2/MeOH = 1:0 to 95:5).

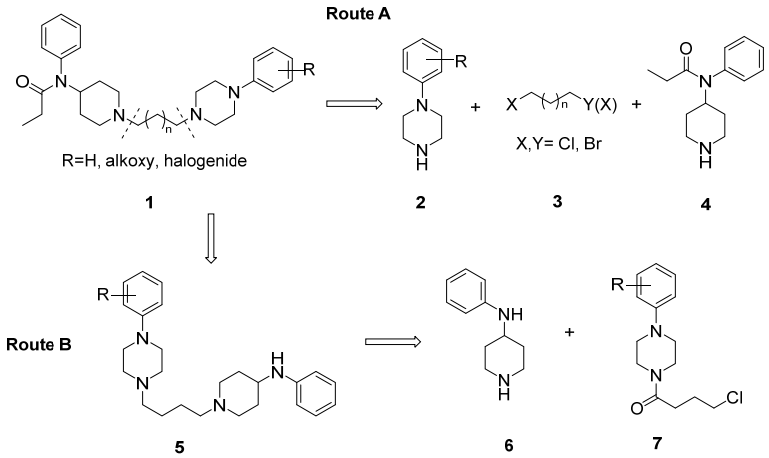
*General procedure for the synthesis of aryl piperazino-anilido-piperidine adducts (**1a**–**c**).* To a magnetically stirred solution of aryl piperazino-anilino-piperidine adduct **5a**–**c** (0.6 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (91 mg, 0.9 mmol) followed by the addition of propionyl chloride (EtCOCl, 166 mg, 1.8 mmol). The mixture was then allowed to stir at 25 °C. The reaction was monitored by TLC with a mixture of CH_2Cl_2/MeOH = 95:5 as the eluent. After 3.5 h, MeOH (10 mL) was added, and the mixture was concentrated on a rotary evaporator. A solution of K_2CO_3 (1.5 M) was added (pH ≈11) and the mixture was extracted with 2×25 mL of CH_2Cl_2. The organic layers were collected, washed with 2×25 mL of brine, and concentrated on a rotary evaporator. The crude product was purified by dry-column flash chromatography (SiO_2; CH_2Cl_2/MeOH = 1:0 to 95:5).

RESULTS AND DISCUSSION

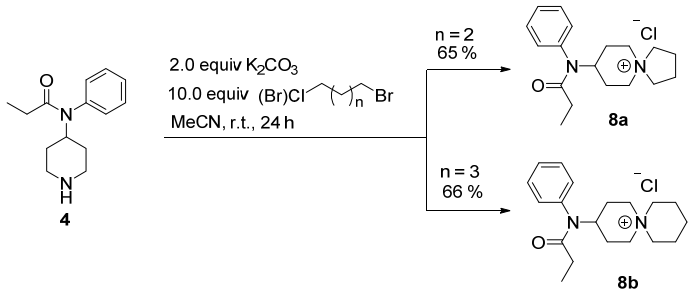
The synthesis of bivalent ligands of the general structure **1** was initially attempted according to the retrosynthetic route A presented in Scheme 1. This approach was anticipated to include two simple alkylation steps of readily available piperazine and piperidine derivatives.

While *N*-aryl piperazines are commercially available, the norfentanyl **4** was obtained according to a known literature procedure.[19–22] For the starting material in the first alkylation step, norfentanyl **4** was selected as it was more readily available than the *N*-aryl piperazine **2**. However, it was expected that both secondary amines would react similarly in this reaction. The alkylating agents were

linear α,ω-bromochloroalkanes having 3–6 methylene groups. Unexpectedly, 1,4-bromochlorobutane and 1,5-bromochloropentane mainly gave the respective spiro-bicyclic quaternary ammonium salts **8a** and **b**. Apparently, the entropic factor favoured the formation of five and six member rings, rather than the linear alkylation products. Since the spiro-bicyclic products were obtained under all attempted conditions, an alternative approach was sought. For further investigation of the synthetic route target compound of general formula **1**, it was selected to have four methylene groups in the alkyl chain, since it could not be prepared by the previous method (Scheme 2) because of quaternary ammonium ion **8a** formation.



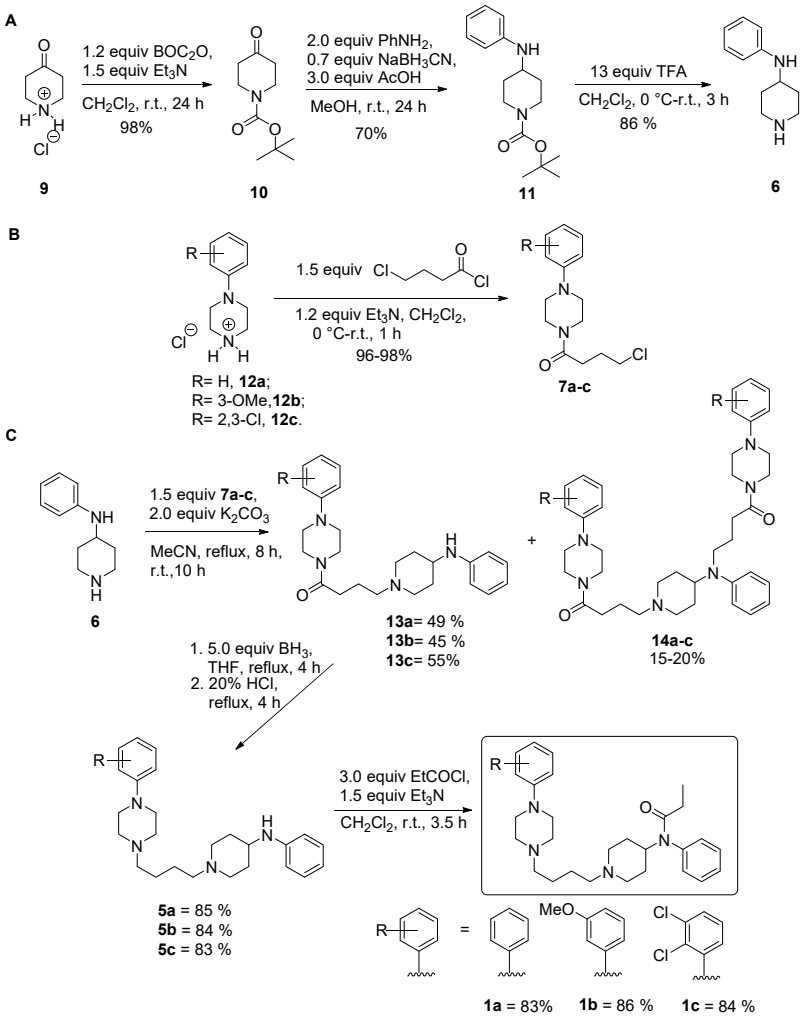
Scheme 1. Initial retrosynthetic route (Route A) and optimized retrosynthetic route (Route B) for the synthesis of 4-anilido-piperidine and *N*-aryl piperazine containing bivalent ligands.



Scheme 2. Initial synthetic route towards bivalent ligands **1**: alkylation of **4** with alkylating agents of different chain lengths.

According to the retrosynthetic route B, replacing the two successive alkylation steps of the previous synthetic route with acylation and alkylation steps seemed to be a promising alternative for connecting the two pharmacophores as

no quaternisation is possible with an amide nitrogen. Indeed, this approach gave the desired ligands of general structure **1** (Scheme 3).



Scheme 3. Synthesis of 4-anilido-piperidine/*N*-aryl piperazine adducts **1a**–**c**.

As a synthon for a four methylene linker, 4-chlorobutyryl chloride was selected.[23] Acylation of *N*-aryl piperazine hydrochloride **12a**–**c** with 4-chlorobutyryl chloride under standard acylation conditions[24] successfully provided carboxamides **7a**–**c** in almost quantitative yields (Scheme 3B). The required anilinopiperidine **6**, was prepared according to Scheme 3A using a known protocol.[25,26] Subsequent alkylation of **6** with carboxamides **7a**–**c** provided intermediates **13a**–**c** in moderate yields (45–55 %). The reaction was slow, requiring

refluxing acetonitrile for several hours. Higher temperatures and longer reaction times were necessary for completion of the alkylation reaction, due to the relatively low alkylation reactivity of alkyl chlorides compared to other alkylating reagents. A significant amount of side product **14a**–**c**, which originated from alkylation of the aniline nitrogen, was detected in all three examples, while no quarterisation was observed. The aniline nitrogen is less nucleophilic than that of alkyl amines, however not sufficiently to afford chemoselective alkylation of just the secondary amino group in **6**. Since there is no efficient way to selectively protect the aniline nitrogen in the presence of other amino groups, the moderate yields of the desired alkylation products **13a**–**c** made this step the least effective in this reaction route. The structure of the dialkylated side product was confirmed in the case of **14b** as a representative, and the spectra are presented in the Supplementary material.

Clean and complete reduction of the amide bond with borane afforded **5a**–**c** in high yields. The final products **1a**–**c** were obtained by propionylation of the aniline nitrogen and isolated in high yields, after purification and in overall yields of nearly 35 % starting from **12** (Scheme 3B and C). Compounds **1a**–**c** may have significant potential in pharmacological testing and docking studies as novel bivalent ligands for opioid and dopamine D_2/D_3 receptors. Synthesis of analogues with different chain lengths as well as their pharmacological testing and theoretical modelling, is part of ongoing research.

CONCLUSIONS

Three novel compounds that contain both opioid and D_2/D_3 receptors pharmacophores connected by four methylene group linkers were synthesized *via* a scalable, cost-efficient and simple synthetic pathway. Starting from three different *N*-aryl piperazines **12a**–**c** and anilino-piperidine **6**, the final products **1a**–**c** were obtained in nearly 35 % overall yield after four steps employing two acylation as well as alkylation and reduction steps. The actual pharmacological activity of the synthesized bivalent ligands cannot be predicted. However, there is a significant possibility that opioid and/or dopamine receptor activity will be revealed in various pharmacological tests. Potentially, these results may help advance the understanding of the interaction between dopaminergic and opioid signal pathways as well as related phenomena. Therefore, the development of the synthetic pathway towards bivalent opioid/dopamine receptor ligands could be of interest to synthetic, heterocyclic and medicinal chemistry in general.

SUPPLEMENTARY MATERIAL

Spectral and analytical 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

СИНТЕТИЧКИ ПУТ ЗА СИНТЕЗУ ПОТЕНЦИЈАЛНИХ, БИВАЛЕНТНИХ ЛИГАНАДА КОЈИ ПОСЕДУЈУ ОПИОИДНУ И ДОПАМИН $Д_2/Д_3$ ФАРМАКОФОРУ

ИВАНА И. ЈЕВТИЋ[1], ЈЕЛЕНА З. ПЕЊИШЕВИЋ[1], МИЛОВАН Д. ИВАНОВИЋ[2] и СЛАЂАНА В. КОСТИЋ-РАЈАЧИЋ[1]

[1]ИХТМ – Центар за хемију, Универзитет у Београду, Његошева 12, 11000 Београд и [2]Хемијски факултет, Универзитет у Београду, Студентски трг 12–16, 11000 Београд

Три нова једињења, која садрже опиоидну и допаминску фармакофору, спојене преко четири метиленске групе, синтетисана су у четири фазе у укупном приносу од приближно 35 %, полазећи од три комерцијално доступна *N*-арилпиперазина. Анилинопиперидински прекурсор је добијен у три једноставне реакционе фазе, полазећи од 4-пиперидона, према познатој литературној методи. Синтеза приказана у овом раду може бити од значаја за хетероцикличну и органску хемију у целини. Новосинтетисана једињења која поседују две фармакофоре, опиоидну и $Д_2/Д_3$, су потенцијално корисни супстрати за фармаколошка испитивања. Од посебног интереса може бити истовремено везивање за опиоидне и $Д_2/Д_3$ рецепторе, а резултујући фармаколошки одговор био би користан у даљем разумевању толеранције и зависности, као феномена везаних за клиничку употребу и/или злоупотребу опијата.

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