Synthesis and biological evaluation of new naphtho- and quinolinocyclopentane derivatives as potent melatoninergic (MT 1 /MT 2 ) and serotoninergic (5-HT 2C ) dual ligands

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Synthesis and biological evaluation of new naphtho- and quinolinocyclopentane derivatives as potent melatonergic (MT₁/MT₂) and serotoninergic (5-HT₂C) dual ligands

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Ki ($M_{T1}$) = 0.1 nM  
Ki ($M_{T2}$) = 0.2 nM  
Ki ($5HT_{2c}$) = 708 nM  

Ki ($M_{T1}$) = 0.3 nM  
Ki ($M_{T2}$) = 0.2 nM  
Ki ($5HT_{2c}$) = 61 nM  

Ki ($M_{T1}$) = 0.4 nM  
Ki ($M_{T2}$) = 0.2 nM  
Ki ($5HT_{2c}$) = 160 nM
Synthesis and Biological Evaluation of new Naphtho- and Quinolinocyclopentane Derivatives as Potent Melatonergic (MT₁/MT₂) and Serotonergic (5-HT₂C) Dual Ligands

Romain Duroux, a Marouan Rami, a Elodie Landagaray, a Mohamed Ettaoussi, a, * Daniel-Henri Caignard, b Philippe Delagrange, b Patricia Melnyk, a Said Yous, a, *

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ABSTRACT

We recently reported a series of naphthofuranic compounds as constrained agomelatine analogues. Herein, in order to explore alternative ethyl amide side chain rigidification, naphthocyclopentane and quinolinocyclopentane derivatives with various acetamide modulations were synthesized and evaluated at both melatonin (MT₁, MT₂) and serotonin (5-HT₂C) receptors. These modifications has led to compounds with promising dual affinity and high MTs receptors agonist activity. Enantiomeric separation was then performed on selected compounds allowing us to identify levogyre enantiomers (-)\textsuperscript{17g} and (-)\textsuperscript{17k} as the highest (MT₁, MT₂) / 5-HT₂C dual ligands described nowadays.

Key Words: Melatonin, serotonin, agomelatine, levogyre, dextrogyre
1. Introduction

Since its discovery [1], melatonin remains one of the most studied neurohormones by the scientific community due to its therapeutic perspectives and physio-pathological implications. In fact, during the last half century, melatonin has attracted an extensive campaign of research to fully study its physiological and pathological processes. Overall, however, it is clear that the melatoninergic system still haven't delivered all its secrets! To date, the available evidences indicate that this neurohormone, that is mainly synthesized by the pineal gland following a circadian rhythm [2], is one of the most promising therapeutic targets considering its physiological implications. Interestingly, and consistent with reported findings, melatonin is a key player in several physiological processes such as hormonal secretion, core body temperature regulation and immune system control [3-5] but also participates in several pathological processes including depression and anxiety [6-7]. Although, despite the consented efforts, the melatonin mechanisms of action have not yet been fully resolved. Moreover, it has been demonstrated that, through its signalling pathways, melatonin contributes to the control of replication and survival of many parasites such as *Plasmodium falciparum, Plasmodium knowlesi, Trypanosoma cruzi, Toxoplasma gondii,* and *Leishmania infantum* [8-9]. In this context, several *in vitro* and *in vivo* studies have shown that melatonin receptor antagonists such as luzindole were able to inhibit the *Plasmodium falciparum* growth [10-11]. These findings may constitute a new promising approach to research and development of new efficient anti-parasitic agents with rapid action and low toxicity.

The aforementioned physiological and pathological effects of melatonin are attributed to the activation of its binding sites, two major receptors (MT$_1$ and MT$_2$) belonging to the superfamily of high-affinity G protein-coupled receptors (GPCRs) [12], and the enzyme quinone reductase 2 (QR2 previously known as MT$_3$) [6a]. The design and synthesis of
melatoninergic ligands has led to a large number of derivatives with different pharmacological profiles. However, only very few melatoninergic ligands (ramelteon, tasimelteon and agomelatine) are commercialized up to now [13-14]. Agomelatine marketed nowadays for the treatment of major depression behaves as a dual ligand acting as a full agonist at melatonin MT$_1$ and MT$_2$ receptor subtypes and an antagonist for serotonin 5-HT$_{2C}$ receptor subtype [15]. The mechanism of action of this new antidepressant is not yet fully elucidated but appears to be caused by the synergy between this combination MT$_{1}$/MT$_{2}$ activation and 5-HT$_{2C}$ deactivation [16]. Research for new successors has led our lab to perform a number of pharmacomodulations of agomelatine. Besides, different positions of the aromatic nucleus, the lateral acetamide chain and the methoxy group were targeted. One of the strategies adopted for the agomelatine analogues was based on the blockade of its major metabolic sites [17-18]. Recently, we also described compounds issued from constrained naphthalenic-like structures especially the (8,9-dihydro-7H-furo[3,2-f]chromen-1-yl) derivatives [19] and naphthofuranic ligands [20]. This later modulation has led to compounds with an interesting pharmacological profile and a sub-nanomolar binding affinity especially at melatonin receptors. Insofar, we chose to extent this successful concept into a new conformationally restricted structure. Subsequently, herein we describe the synthesis and pharmacological evaluation of a new series of naphthocyclopentane derivatives as new dual ligands analogues of agomelatine.

**Figure 1.** Melatonin, Agomelatine and its quinolinic analogue.
2. Results and discussion

2.1. Chemistry

Synthetic routes to the designed compounds are depicted in Schemes 1-5. The synthesis of key intermediate ketones 10 and 11 was accomplished as shown in Scheme 1. Compound 10 was prepared from commercially available 2-hydroxy-7-methoxy-naphthalene (1), which was converted to the triflate 2 by action of triflic anhydride. Heck reaction [21] was then realized using ethyl acrylate in the presence of bis(triphenylphosphine)palladium(II) dichloride to give compound (4). Catalytic hydrogenation and subsequent basic hydrolysis gave propionic acid 8. Finally, intramolecular Friedel-Crafts acylation with methanesulfonic acid [22] afforded ketone 10. The same procedure was used starting from commercial 2-methoxy-8-bromo-quinoline (3) to get compound 9. Intramolecular Friedel-Crafts acylation on the latter was then realized using chlorosulfonic acid [23] to obtain compound 11.

![Scheme 1](image)

**Scheme 1**. Synthesis of key intermediates 10 and 11.

*Reagents and conditions: (a) Tf₂O, Et₃N, CH₂Cl₂, -20 °C to rt, 100%; (b) ethyl acrylate, PdCl₂(PPh₃)₂, Et₃N, DMF, 120 °C, 77% for 4 and 93% for 5; (c) Pd/C, H₂, CH₂Cl₂/EtOH, rt,
96% for \textit{6} and 80% for \textit{7}; (d) (i) 6M NaOH, EtOH, rt, (ii) 6M HCl, 93% for \textit{8} and 73% for \textit{9}; (e) CH$_3$SO$_2$H, 90°C, 70%; (f) ClSO$_3$H, 0°C to rt, 84%.

Naphthocyclopentane derivatives \textit{17-19} were synthesized according to the general route outlined in Scheme 2. On one hand, ketone \textit{10} was first cyanated using trimethylsilyl cyanide [24] followed by a dehydration reaction to afford cyanoindene \textit{12}. Alkene was then selectively reduced under H$_2$ atmosphere to give compound \textit{13}. The later was C-methylated by action of methyl iodide in the presence of sodium hydride afforded compound \textit{14}. On the other hand, a Horner-Emmons olefination [25] on ketone \textit{10} with diethyl cyanomethylphosphonate was realized to afford cyanomethylenated compound \textit{15} which was selectively hydrogenated to afford its saturated analogue (\textit{16}). Finally, catalytic hydrogenation of cyano derivatives \textit{13, 14} and \textit{16} with Raney-nickel provided aminoalkyl derivatives \textit{17-19}. 

Reagents and conditions: a) (i) Trimethylsilyl cyanide, zinc iodide, CH₂Cl₂, rt (ii) Acetyl chloride, acetic acid, rt, 83%; b) Pd/C, H₂, CH₂Cl₂/EtOH, rt, 72%; c) CH₃I, NaH, DMF, 0 °C to rt, 91%; d) NaH, diethyl cyanomethylphosphonate, THF, -10 °C to rt, 50%; e) Raney Ni, H₂, EtOH, 50 bars, 60°C, 79% for 17, 93% for 18 and 30% for 19.

Preparation of amines 24-25 is depicted in scheme 3. To obtain the amine 24, hydrocyanation of ketone 11 using trimethylsilyl cyanide followed by dehydration to afford cyanoindene 20 was attempted unsuccessfully. Thus, ketone 11 was cyanomethylated by a Horner-Emmons olefination with diethyl cyanomethylphosphonate to give, after (selective)
hydrogenation, the nitrile 21. Then, a Curtius reaction was realized where 21 was first treated under basic condition to afford acid 22 before being activated to react with sodium azide. The resulting carboxylic azide 23, not isolated was treated with NaOH to provide amine 24 with one-methylene linker. To get amine 25 (two-methylene linker), reduction of cyano function 21 using Raney-nickel as catalyst was realized.


Reagents and conditions: a) (i) trimethylsilyl cyanide, zinc iodide, CH₂Cl₂, rt, (ii) acetyl chloride, acetic acid, rt; b) (i) NaH, diethyl cyanomethylphosphonate, THF, -10 °C to rt, (ii) Pd/C, H₂, CH₂Cl₂/EtOH, rt, 55%; c) LiAlH₄, AlCl₃, Et₂O/CH₂Cl₂, 0 °C to rt, 90%; d) (i) 6M NaOH, (ii) 6M HCl; e) ClCO₂Et, Et₃N, NaN₃, 0 °C to rt; f) 1M NaOH, THF, rt, 66% over two steps.

The synthesis of final compounds is illustrated Scheme 4. First, amides ligands (17a-19a, 24a-25a, and 17b) were synthesized from corresponding amines (17-19 and 24-25), according to a variant of the Schotten-Baumann procedure, by reaction with the appropriate acid chloride. Carbamate 17c and sulfonamides 17d, 17e and 19b were obtained respectively.
by reaction of amine 17 and 19 with methyl chloroformate or methanesulfonyl chloride. To synthesize primary urea 17f and thiourea 17j, reaction between corresponding amine 17 and potassium cyanate in acidic medium or potassium thiocyanate in dioxane was performed. For the alkylureas (17h-i, 19c-d and 24c) and alkylthioureas (17k-m, 18b and 19e-f) series, treatment of corresponding amines with alkyl isocyanate or alkyl isothiocyanate was realized. Finally, reaction between amines 17 and 19 with methyl-N-phenylcarbamate in dimethylsulfoxide allowed to get methyl urea (17g and 24b) molecules.

**Compounds**

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<td>S</td>
<td>NHCH₂H₇</td>
<td>e</td>
<td>41%</td>
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**Scheme 4.** Synthesis of finals compounds 17a-m, 19a-g, 24a-c, 25a.

*aReagents and conditions:* a) R₂COCl, K₂CO₃, EtOAc/H₂O, 0°C to rt; b) R₂SO₂Cl, Et₃N, CH₂Cl₂, 0°C to rt; c) KNCO, H₂O/HCl, rt; d) N-methylphenylcarbamate, Et₃N, DMSO, 60°C; e) R₁NCX, Et₃N, CH₂Cl₂, 0°C to rt; f) KSCN, Dioxane, THF, 60°C.

**2.2. Pharmacology**

*Biological Results.* Synthesized compounds were assayed at human MT₁ and MT₂ receptors stably transfected in Chinese Hamster Ovarian (CHO) cells, using 2-[¹²⁵I]iodomelatonin as radioligand [26]. Serotoninergic 5-HT₂C binding affinity was performed using Chinese Hamster Ovarian (CHO) cell lines stably expressing the human 5-HT₂C receptors. In Tables 1-2 are depicted the chemical structures, binding affinities and intrinsic activity of the synthesized ligands.

The actual reported work focuses on the design and synthesis of new constrained naphtho- and quinolinocyclopentane derivatives as dual ligands for melatonin MT₁/MT₂ and serotonin 5-HT₂C receptor subtypes as successors of agomelatine. This new modulation of the agomelatine structure concerned the inclusion of carbon C2 of the amide lateral chain into a cyclopentane moiety (Chart 1). This free movement restriction of the lateral chain has already been performed as naphthofuranic derivatives and had shown no marked effect at melatonin binding affinity at both MT₁ and MT₂ in comparison with agomelatine [20]. The same effect was actually observed with synthesized acetamide 17a, however this modulation exhibited a noticeable improvement of the serotoninergic 5-HT₂C binding affinity by a factor 10 (Table 1). This pharmacological effect confirms our previous findings. At this point, we
have no confirmed explanations for such effect and further investigations are in course in order to find out the basis of these results.

**Chart 1: Rigidification of Agomelatine**

![Chart 1: Rigidification of Agomelatine](image)

To further investigate the effect of the acetamide function modulation, 17a was considered as a lead compound. Thus, different amides, ureas, thioureas known for their positive effect at both melatonin and serotonin binding affinities were introduced (compounds 17b-17m). The resulted compounds were then tested for their binding affinities at MT\(_1\), MT\(_2\) and 5-HT\(_{2C}\). The obtained results are shown in Table 1 and reveal that these modulations had no or a slight effect at both MT\(_1\) and MT\(_2\) receptor subtypes (compare to 17a) except for thioureas 17l and 17m. Indeed, substitution of the acetamide group of 17a with ethyl (17l) or propyl (17m) thiourea led to a loss of two logs at the MT\(_1\) affinity and one log at MT\(_2\), showing a slight MT\(_2\) selectivity. This effect was already reported but we haven’t been able to explain the reason yet. In light of the results obtained with acetamide 17a, we also extended the length of the ethyl amide lateral chain from two to three carbons (18a). This extension was
performed to further investigate the role of this lateral chain on the binding affinities especially at 5-HT$_{2C}$. However, resulting compound 18a had shown the same profile as 17a with a slight decrease of the binding affinities at both melatonin and serotonin 5-HT$_{2C}$ receptor subtypes.

To block one of the metabolic site caused by the oxidation of the lateral amide chain observed with agomelatine derivatives, we introduced an angular methyl group attached to carbon-C1 of the naphthocyclopentane ring (19a-g). Indeed, angular methyl groups are known for their resistance to metabolic oxidation, probably due to local steric hindrance. Interestingly, this modulation led to a same good binding affinities at both MT$_1$ and MT$_2$ and a loss of the serotoninergic 5-HT$_{2C}$ binding affinity. Additional investigations are necessary to understand such an effect with this constrained structure. Concerning the introduction of a nitrogen atom through the bioisosteric replacement of naphthalene with quinoline (compound 24a), a similar melatoninergic binding affinity to 17a with a very slight decrease at the at 5-HT$_{2C}$ binding affinity is observed. Instead, 25a showed an increase in MT$_2$ binding affinity and a decrease towards 5-HT$_{2C}$ compared to its quinolic analogue (18a). Moreover, a pronounced decrease in both MT$_1$ and 5-HT$_{2C}$ receptors is observed comparing 25a and its inferior homologue (24a).

Table 1. MT$_1$ and MT$_2$ binding affinity data of synthesized analogues of melatonin

<table>
<thead>
<tr>
<th>Compound</th>
<th>h-MT$_1$</th>
<th>h-MT$_2$</th>
<th>h-5HT$_{2C}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag (I)</td>
<td>0.1 [0.1; 0.1] (2)</td>
<td>0.2 [0.1; 0.6] (2)</td>
<td>708 [46; 895] (2)</td>
</tr>
<tr>
<td>17a</td>
<td>0.3 [0.2; 1.3] (2)</td>
<td>0.2 [0.02; 0.6] (2)</td>
<td>61 [35; 129] (2)</td>
</tr>
<tr>
<td>18a</td>
<td>4 [3.0; 5.2] (2)</td>
<td>2 [0.9; 2.1] (2)</td>
<td>180 [102; 335] (2)</td>
</tr>
<tr>
<td>19a</td>
<td>0.1 [0.07; 0.7] (2)</td>
<td>0.1 [0.05; 0.7] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>17b</td>
<td>0.6 [0.4; 1.1] (2)</td>
<td>0.1 [0.07; 0.3] (2)</td>
<td>200 [123; 302] (2)</td>
</tr>
<tr>
<td>24a</td>
<td>0.4 [0.2; 0.8] (2)</td>
<td>0.2 [0.1; 0.4] (2)</td>
<td>160 [125; 212] (2)</td>
</tr>
</tbody>
</table>
Finally, replacement of the amide function of 17a by a methylurea (17g) and a methylthiourea (17k) led to the most interesting compounds profiles that we are looking for with a good balance between the melatoninergic and serotoninergic binding affinities. Compounds 17g and 17k were then submitted to enantiomeric resolution leading to two pairs of compounds: (+)-17g, (-)-17g, (+)-17k and (-)-17k. Evaluation of these four compounds revealed that binding to melatoninergic MT1, MT2 and serotoninergic 5-HT2C receptors is

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MT1 affinity</th>
<th>MT2 affinity</th>
<th>5-HT2C affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>17g (+)</td>
<td>32 [28 ; 41] (2)</td>
<td>970 [734 ; 1120] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>17g (-)</td>
<td>0.4 [0.1 ; 0.9] (2)</td>
<td>0.07 [0.02; 0.1] (2)</td>
<td>15 [7 ; 26] (2)</td>
</tr>
<tr>
<td>17k (+)</td>
<td>99 [43 ; 127] (2)</td>
<td>9 [2; 14] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>17k (-)</td>
<td>3 [1.6 ; 4.2] (2)</td>
<td>0.1 [0.08; 0.17] (2)</td>
<td>9 [3 ; 11] (2)</td>
</tr>
<tr>
<td>17l</td>
<td>29 [15 ; 47] (2)</td>
<td>2 [1.1; 3.1] (2)</td>
<td>8 [3 ; 16] (2)</td>
</tr>
<tr>
<td>17m</td>
<td>63 [48 ; 79] (2)</td>
<td>3 [1.6; 5.1] (2)</td>
<td>42 [23 ; 75] (2)</td>
</tr>
<tr>
<td>19e</td>
<td>1 [0.3 ; 2.5] (2)</td>
<td>0.2 [0.1; 0.4] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>19f</td>
<td>4 [2.1 ; 6.2] (2)</td>
<td>3 [1.3; 5.7] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>19g</td>
<td>9 [6.2 ; 13] (2)</td>
<td>0.3 [0.1; 0.7] (2)</td>
<td>&gt;10000</td>
</tr>
</tbody>
</table>

Carbamate

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MT1 affinity</th>
<th>MT2 affinity</th>
<th>5-HT2C affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>17c</td>
<td>2 [0.9 ; 2.3] (2)</td>
<td>0.4 [0.1; 0.7] (2)</td>
<td>100 [83 ; 133] (2)</td>
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Sulfonamides

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MT1 affinity</th>
<th>MT2 affinity</th>
<th>5-HT2C affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>17d</td>
<td>0.8 [0.2 ; 1.3] (2)</td>
<td>0.1 [0.07; 0.4] (2)</td>
<td>580 [437 ; 723] (2)</td>
</tr>
<tr>
<td>19b</td>
<td>0.6 [0.3 ; 1.1] (2)</td>
<td>0.2 [0.09; 0.4] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>17e</td>
<td>7 [4.3 ; 9.2] (2)</td>
<td>0.4 [0.1; 0.6] (2)</td>
<td>400 [277 ; 578] (2)</td>
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</tbody>
</table>

Ureas

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MT1 affinity</th>
<th>MT2 affinity</th>
<th>5-HT2C affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>17f</td>
<td>0.3 [0.1 ; 0.5] (2)</td>
<td>0.1 [0.08; 0.4] (2)</td>
<td>145 [97 ; 223] (2)</td>
</tr>
<tr>
<td>17g</td>
<td>0.6 [0.5 ; 0.8] (2)</td>
<td>0.2 [0.07; 0.5] (2)</td>
<td>170 [135 ; 217] (2)</td>
</tr>
<tr>
<td>(+)-17g</td>
<td>32 [28 ; 41] (2)</td>
<td>970 [734 ; 1120] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>(-)-17g</td>
<td>0.4 [0.1 ; 0.9] (2)</td>
<td>0.07 [0.02; 0.1] (2)</td>
<td>15 [7 ; 26] (2)</td>
</tr>
</tbody>
</table>

Thioureas

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MT1 affinity</th>
<th>MT2 affinity</th>
<th>5-HT2C affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>17j</td>
<td>6 [4.7 ; 8.3] (2)</td>
<td>0.4 [0.1; 0.9] (2)</td>
<td>72 [43 ; 117] (2)</td>
</tr>
<tr>
<td>17k</td>
<td>4 [2.7 ; 7.1] (2)</td>
<td>0.3 [0.1; 0.7] (2)</td>
<td>30 [18 ; 54] (2)</td>
</tr>
<tr>
<td>(+)-17k</td>
<td>99 [43 ; 127] (2)</td>
<td>9 [2; 14] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>(-)-17k</td>
<td>3 [1.6 ; 4.2] (2)</td>
<td>0.1 [0.08; 0.17] (2)</td>
<td>9 [3 ; 11] (2)</td>
</tr>
<tr>
<td>17l</td>
<td>29 [15 ; 47] (2)</td>
<td>2 [1.1; 3.1] (2)</td>
<td>8 [3 ; 16] (2)</td>
</tr>
<tr>
<td>17m</td>
<td>63 [48 ; 79] (2)</td>
<td>3 [1.6; 5.1] (2)</td>
<td>42 [23 ; 75] (2)</td>
</tr>
<tr>
<td>19e</td>
<td>1 [0.3 ; 2.5] (2)</td>
<td>0.2 [0.1; 0.4] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>19f</td>
<td>4 [2.1 ; 6.2] (2)</td>
<td>3 [1.3; 5.7] (2)</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>19g</td>
<td>9 [6.2 ; 13] (2)</td>
<td>0.3 [0.1; 0.7] (2)</td>
<td>&gt;10000</td>
</tr>
</tbody>
</table>
enantioselective. Indeed, levogyre enantiomers (-)-17g and (-)-17k were more potent than their dextrogyre counterpart and their mixtures (Table 1). These two compounds represent the most interesting dual ligands for described nowadays. However, further investigations are needed in order to determine the enantioselectivity effect on the ADME properties. Intrinsic activity evaluation for all compounds towards melatonin MT\(_1\) and MT\(_2\) receptors was performed and the results are depicted in Table 2. In general, two intrinsic activity profiles were observed. A first group with MT\(_1\)/MT\(_2\) partial agonist/full agonist profile including compounds 17a, 17b, 17h, 17g, 17i, 17k, 19c, 19d and (-)-17g. A second group with an MT\(_1\)/MT\(_2\) partial agonist profile was reported and includes compounds 17c, 17d, 17f, 17j, 17l, 17m, 19a, 19e, 19f, 19g, 24b and 24c. Evaluation of intrinsic activity of these compounds at 5-HT\(_{2C}\) showed an antagonist activity profile (data not shown).

### Table 2. Intrinsic activity of most interesting synthesized compounds.

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>EC(_{50}) (nM) [95] (n)</th>
<th>(E_{\text{max}}) (%) ± ESM (n)</th>
<th>EC(_{50}) (nM) [95] (n)</th>
<th>(E_{\text{max}}) (%) ± ESM (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.4 [0.7;2.5] (4)</td>
<td>99 ± 6 (4)</td>
<td>0.18 [0.1;0.39] (3)</td>
<td>91 ± 7 (3)</td>
</tr>
<tr>
<td>17a</td>
<td>0.9 [0.9;2.4] (2)</td>
<td>78 ± 1 (2)</td>
<td>0.2 [0.1;0.5] (2)</td>
<td>118 ± 37 (2)</td>
</tr>
<tr>
<td>19a</td>
<td>0.2 [0.1;0.4] (2)</td>
<td>79 ± 3 (2)</td>
<td>0.2 [0.09;0.42] (2)</td>
<td>87 ± 3 (2)</td>
</tr>
<tr>
<td>17b</td>
<td>5 [3.1;6.4] (2)</td>
<td>81 ± 3 (2)</td>
<td>0.4 [0.1;0.8] (2)</td>
<td>99 ± 2 (2)</td>
</tr>
<tr>
<td>24a</td>
<td>0.05 [0.02;0.08] (2)</td>
<td>53 ± 4 (2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17d</td>
<td>4 [2.2;6.8] (2)</td>
<td>30± 1 (2)</td>
<td>1 [0.4;2.8] (2)</td>
<td>63 ± 2 (2)</td>
</tr>
<tr>
<td>17e</td>
<td>10000</td>
<td>-</td>
<td>1000</td>
<td>-</td>
</tr>
<tr>
<td>17c</td>
<td>-</td>
<td>-</td>
<td>5 [2.3;7.9] (2)</td>
<td>71 ± 2 (2)</td>
</tr>
<tr>
<td>17f</td>
<td>2 [0.7;4.1] (2)</td>
<td>53 ± 3 (2)</td>
<td>0.9 [0.5;1.8] (2)</td>
<td>56 ± 1 (2)</td>
</tr>
<tr>
<td>17g</td>
<td>5 [2.9;8.4] (2)</td>
<td>66 ± 4 (2)</td>
<td>3 [1.7;5.4] (2)</td>
<td>95 ± 5 (2)</td>
</tr>
<tr>
<td>(-)-17g</td>
<td>3 [1.7;4.4] (2)</td>
<td>51± 5 (2)</td>
<td>0.6 [0.4;0.7] (2)</td>
<td>133± 21 (2)</td>
</tr>
<tr>
<td>17h</td>
<td>20 [14;27] (2)</td>
<td>64 ± 2 (2)</td>
<td>3 [1.7;4.3] (2)</td>
<td>103 ± 2 (2)</td>
</tr>
<tr>
<td>19c</td>
<td>5 [2.3;9.1] (2)</td>
<td>66 ± 3 (2)</td>
<td>0.3 [0.1;0.6] (2)</td>
<td>109 ± 4 (2)</td>
</tr>
<tr>
<td>17i</td>
<td>30 [13;68] (2)</td>
<td>76± 6 (2)</td>
<td>20 [10;50] (2)</td>
<td>96 ± 10 (2)</td>
</tr>
</tbody>
</table>
EC$_{50}$ values are geometric mean values (with 95% confidence limits in parentheses) Emax values are arithmetic mean ± S.E.M. ND: Not determined

3. Conclusions

The present work deals with the optimization of a new series of constrained agomelatine analogues. Indeed, constrained structures revealed to be of interest in our case and the inclusion of the ethyl amide side chain into a naphthocyclopentane structure seems to confirm our actual strategy. Obtained acetamide 17a exhibited a very interesting pharmacological profile in comparison to agomelatine. Modulation of the acetamide group of 17a revealed once again that the nature of this group is important to the melatonin binding affinity but critical to the serotonin 5-HT$_{2C}$ receptor. Among prepared derivatives, methyl urea 17g and methyl thiourea 17k exhibited the most interesting profiles and showed the enantioselective character of the binding affinity at these three receptors. Thus, this enantiomeric separation allows us to describe the levogyre enantiomers (-)-17g and (-)-17k as the highest (MT$_1$, MT$_2$)/5HT$_{2C}$ dual ligands found nowadays.
4. Experimental section

4.1. Chemistry

Chemicals and solvents were obtained from commercial sources, and used without further purification unless otherwise noted. Reactions were monitored by TLC performed on Macherey–Nagel Alugram® Sil 60/UV_254 sheets (thickness 0.2 mm). Purification of products was carried out by recrystallization or column chromatography. Column chromatography was carried out using Macherey–Nagel silica gel (230–400 mesh). Melting points were determined on a Büchi SMP-20 capillary apparatus and are uncorrected. FT-IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. NMR spectra were recorded on a Bruker DRX 300 spectrometer (operating at 300 MHz for 1H and 75 MHz for 13C). Chemical shifts are expressed in ppm relative to either tetramethylsilane (TMS). Chemical shifts are reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = double doublet, br = broad and m = multiplet), coupling constant (J in Hz), relative integral and assignment. Mass spectra were recorded on a Varian triple quadrupole 1200W mass spectrometer equipped with a non-polar C18 TSK-gel Super ODS (4.6 × 50 mm) column, using electrospray ionization and a UV detector (diode array). HRMS-ESI spectra were recorded on a Thermo Scientific Exactive spectrometer.

4.2. (7-Methoxy-2-naphthyl)trifluoromethanesulfonate (2).

A solution of trifluoromethane sulfonic anhydride (19.92 mL, 120 mmol) in methylene chloride (20 mL) was added dropwise to a stirred solution of 7-methoxy-2-naphthol 1 (17.42 g, 100 mmol) and triethylamine (20.85 mL, 150 mmol) in methylene chloride (320 mL) at -70 °C. The reaction mixture was stirred for 20 min at room temperature, hydrolyzed with water and extracted with methylene chloride. The combined organic layers were washed with water, brine, dried over MgSO₄, filtered and concentrated under vacuum. The product was obtained quantitatively without further purification as a yellow oil; 1H NMR (300 MHz, CDCl₃) δ: 7.84
(d, 1H, 9.0 Hz), 7.78 (d, 1H, 9.0 Hz), 7.65 (d, 1H, 2.4 Hz), 7.25-7.21 (m, 2H), 7.15 (d, 1H, 2.7 Hz), 3.94 (s, 3H); LC-MS: m/z = 275 (MH⁺).

4.3. Ethyl (E)-3-(7-methoxynaphtalen-2-yl)prop-2-enoate (4).

To a solution of 2 (30.63 g, 100 mmol) in DMF (150 mL) under an inert atmosphere, were added ethyl acrylate (11.97 mL, 110 mmol), bis(triphenylphosphine) palladium chloride (7.72 g, 11 mmol) and triethylamine (15.29 mL, 110 mmol). The reaction mixture was refluxed at 120 °C for 15 h, cooled to room temperature, hydrolyzed with water and then extracted twice with ethyl acetate. The combined organic layers were washed with a 1 M solution of HCl, water and brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, cyclohexane/ EtOAc: 7/3) to give 4 (77%) as a white solid; mp 90-92 °C; ¹H NMR (300 MHz, CDCl₃) δ: 7.87-7.72 (m, 2H), 7.77 (d, 1H, 8.4 Hz), 7.74 (d, 1H, 8.7 Hz), 7.54 (dd, 1H, 8.4 Hz and 1.5 Hz), 7.19 (dd, 1H, 8.7 Hz and 2.4 Hz), 7.16 (d, 1H, 2.4 Hz), 6.55 (d, 1H, 15.9 Hz), 4.30 (q, 2H, 7.2 Hz), 3.95 (s, 3H), 1.37 (t, 3H, 7.2 Hz); IR (υ, cm⁻¹): 1705 (CO); LC-MS: m/z = 257 (MH⁺).

4.4. Ethyl 3-(7-methoxynaphtalen-2-yl)propanoate (6).

A solution of 4 (10 g, 40 mmol) in 60 mL of ethanol/ methylene chloride (1/1) with palladium 10% on charcoal was stirred under hydrogen atmosphere at room temperature for 6h. The mixture was then filtered and concentrated under reduced pressure. The crude product was recrystallized from petroleum ether to give 6 (96%) as a white solid; mp 82-84 °C; ¹H NMR (300 MHz, CDCl₃) δ: 7.72-7.69 (m, 2H), 7.56 (s, 1H), 7.21 (dd, 1H, 8.4 Hz and 1.5 Hz), 7.12-7.09 (m, 2H), 4.15 (q, 2H, 6.9 Hz), 3.93 (s, 3H), 3.10 (t, 2H, 7.5 Hz), 2.71 (t, 2H, 7.5 Hz), 1.24 (t, 3H, 6.9 Hz); IR (υ, cm⁻¹): 1720 (CO); LC-MS: m/z = 259 (MH⁺).

4.5. 3-(7-Methoxynaphtalen-2-yl)propionic acid (8).

Compound 6 (9 g, 34.85 mmol) was dissolved in ethanol (40 mL), followed by the addition of 6M solution of NaOH (40 mL). The reaction mixture was stirred at room
temperature, for 3 h, hydrolyzed with a 2 M solution of HCl and extracted twice with methylene chloride. The combined organic layers were washed with water, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was recrystallized from methanol to afford 8 (93%) as a white solid; mp 175-177 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 10.2 (br s, 1H), 7.73-7.70 (m, 2H), 7.57 (s, 1H), 7.21 (dd, 1H, 8.4 Hz and 1.8 Hz), 7.13-7.10 (m, 2H), 3.93 (s, 3H), 3.12 (t, 2H, 7.5 Hz), 2.79 (t, 2H, 7.5 Hz); IR (v, cm$^{-1}$): 2833 (OH), 1694 (CO); LC-MS: m/z = 231 (MH$^+$).

4.6. 8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-one (10).

Methanesulfonic acid (20 mL) was added dropwise to the acid 8 (6.20 g, 26.90 mmol). Stirring was maintained for 2 h at 90 °C, and then the mixture was poured into water and extracted twice with diethyl ether. The combined organic phases were washed with water, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was recrystallized from acetonitrile to afford 10 (70%) as a white solid; mp 122-124 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.60 (d, 1H, 2.4 Hz), 7.97 (d, 1H, 8.4 Hz), 7.79 (d, 1H, 9.0 Hz), 7.38 (d, 1H, 8.4 Hz), 7.20 (dd, 1H, 9.0 Hz and 2.4 Hz), 4.00 (s, 3H), 3.23-3.20 (m, 2H), 2.83-2.79 (m, 2H); IR (v, cm$^{-1}$): 1681 (CO); LC-MS: m/z = 213 (MH$^+$).

4.7. (8-Methoxy-3H-cyclopenta[a]naphthalen-1-yl)carbonitrile (12).

Step 1: To a solution of 10 (4.74 g, 22.33 mmol) in DCM (70 mL), was added zinc iodide (142 mg, 0.45 mmol) trimethylsilyl cyanide was then added dropwise at 0 °C (7 mL, 55.83 mmol). The mixture was stirred at room temperature during 3 h and a saturated solution of NaHCO$_3$ was added. Extraction was realized with methylene chloride and the organic layer was washed with water, dried over MgSO$_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO$_2$, cyclohexane/EtOAc: 9/1) and recrystallized from cyclohexane to afford 8-Methoxy-1-(((trimethylsilyl)oxy)-2,3-dihydro-1H-cyclopenta[a] naphthalen-1-yl) carbonitrile (83%) as a yellow solid; mp 67-69 °C; $^1$H
NMR (300 MHz, CDCl$_3$) $\delta$: 7.80-7.78 (m, 2H), 7.68 (d, 1H, 2.7 Hz), 7.22 (d, 1H, 8.4 Hz), 7.16 (dd, 1H, 9.0 Hz and 2.7 Hz), 3.98 (s, 3H), 3.30-2.99 (m, 3H), 2.58 (m, 1H). 0.29 (s, 9H); IR ($\nu$, cm$^{-1}$): 2230 (CN); LC-MS: $m/z = 312$ (MH$^+$).

**Step 2:** To a solution of this compound (3 g, 9.63 mmol) in acetic acid (3 mL) was added dropwise at 0 °C acetyl chloride (2.05 mL, 28.9 mmol). The mixture was stirred at room temperature during 1 h, hydrolyzed and extracted with methylene chloride. The organic layer was washed with water, dried over MgSO$_4$, filtered and concentrated under vacuum. The residue was recrystallized from toluene to afford 12 (83%) as a white solid; mp 111-112 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.22 (d, 1H, 2.4 Hz), 7.83 (d, 1H, 9.0 Hz), 7.76 (d, 1H, 8.1 Hz), 7.51-7.48 (m, 2H), 7.20 (dd, 1H, 9.0 Hz and 2.4 Hz), 4.01 (s, 3H), 3.75 (d, 2H, 1.5 Hz); IR ($\nu$, cm$^{-1}$): 2229 (CN); LC-MS: $m/z = 222$ (MH$^+$).

**4.8. (8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)carbonitrile (13).**

A solution of 12 (1.10 g, 5 mmol) in 60 mL of ethanol/dichloromethane (1/2) with palladium 10% on charcoal was stirred under hydrogen atmosphere at room temperature for 6 h. The mixture was filtered, concentrated under reduced pressure. The crude product was recrystallized from toluene to give 13 (72%) as a white solid; mp 103-105 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.80 (d, 1H, 9.0 Hz), 7.75 (d, 1H, 8.1 Hz), 7.28 (d, 1H, 8.1 Hz), 7.21 (d, 1H, 2.4 Hz), 7.17 (dd, 1H, 9.0 Hz and 2.4 Hz), 4.47 (dd, 1H, 8.4 Hz and 5.4 Hz), 3.98 (s, 3H), 3.36 (m, 1H), 3.16 (m, 1H), 2.77-2.70 (m, 2H); IR ($\nu$, cm$^{-1}$): 2227 (CN); LC-MS: $m/z = 224$ (MH$^+$).

**4.9. (8-Methoxy-1-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)carbonitrile (14).**

To a solution of 13 (0.86 g, 3.85 mmol) in DMF (30 mL) under argon atmosphere was added at 0 °C sodium hydride (185 mg, 7.7 mmol). The mixture was stirred at 0 °C during 15 min, then methyl iodide (820 mg, 5.78 mmol) was added and stirring was continued for additional 45 min. The mixture was hydrolyzed with water and extracted with ethyl acetate.
The organic layer was washed with water, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, cyclohexane/EtOAc: 5/5) and recrystallized from cyclohexane to afford 14 (91%) as a white solid; mp 95-97 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.79 (d, 1H, 9.0 Hz), 7.74 (d, 1H, 8.1 Hz), 7.54 (d, 1H, 2.4 Hz), 7.22 (d, 1H, 8.1 Hz), 7.15 (dd, 1H, 9.0 Hz and 2.4 Hz), 3.99 (s, 3H), 3.22-3.10 (m, 2H), 2.85 (m, 1H), 2.45 (m, 1H), 1.78 (s, 3H); IR ($\nu$, cm$^{-1}$): 2231 (CN); LC-MS: $m/z = 238$ (MH$^+$).

4.10. 2-(8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-ylidene)acetonitrile (15).

Dry THF (5 mL) was added at -10 °C to sodium hydride 60% (1.8 g, 4.4 mmol) under argon. A solution of diethyl cyanomethylphosphonate (7.1 mL, 44 mmol) in dry THF (10 mL) was then added dropwise. The mixture was stirred under argon until precipitation of the ylure and the solution of compound 10 (2.13 g, 10.04 mmol) in THF (10 mL) was added dropwise. The mixture was stirred for 16 h, and then hydrolyzed. The formed solid was filtered, dissolved in diethyl ether, dried over MgSO$_4$, filtered and concentrated under reduced pressure. Recrystallization from toluene afford 15 (50%) as a white solid; mp 135-137 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.83 (d, 1H, 9.0 Hz), 7.81 (d, 1H, 8.1 Hz), 7.49 (d, 1H, 2.4 Hz), 7.32 (d, 1H, 8.1 Hz), 7.20 (dd, 1H, 9.0 Hz and 2.4 Hz), 6.02 (m, 1H), 3.98 (s, 3H), 3.31-3.19 (m, 4H); IR ($\nu$, cm$^{-1}$): 2228 (CN); LC-MS: $m/z = 236$ (MH$^+$).

4.11. 2-(8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)acetonitrile (16).

This compound was obtained from 15 in 75% yield as described for 13; mp 82-84 °C (methanol); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.79 (d, 1H, 9.0 Hz), 7.69 (d, 1H, 8.1 Hz), 7.27 (d, 1H, 8.1 Hz), 7.13 (dd, 1H, 9.0 Hz and 2.4 Hz), 7.02 (d, 1H, 2.4 Hz), 4.01 (m, 1H), 3.96 (s, 3H), 3.29 (m, 1H), 3.06 (m, 1H), 2.83 (m, 1H), 2.61-2.45 (m, 2H), 2.31 (m, 1H); IR ($\nu$, cm$^{-1}$): 2241 (CN); LC-MS: $m/z = 238$ (MH$^+$).
4.12. 8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methylamine hydrochloride (17).

An NH$_3$-saturated solution of 13 (1.12 g, 5 mmol) in 60 mL of ethanol was hydrogenated over Raney nickel under pressure (50 bars) at 60 °C for 16 h. After filtration and evaporation of ethanol, the oil was dissolved in ether, washed with water, dried over MgSO$_4$ and treated with gaseous HCl. The obtained solid was filtered to give 17 (79%) as a white solid; mp 247-248 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.42 (br s, 3H), 7.82 (d, 1H, 9.0 Hz), 7.70 (d, 1H, 8.20 Hz), 7.25 (d, 1H, 2.4 Hz), 7.18 (d, 1H, 2.4 Hz), 7.10 (dd, 1H, 9.0 Hz and 2.4 Hz), 3.99 (m, 1H), 3.93 (s, 3H), 3.15-3.06 (m, 2H), 2.92 (m, 1H), 2.72 (m, 1H), 2.39 (m, 1H), 2.18 (m, 1H); IR (v, cm$^{-1}$): 3200-2800 (NH$_3$+Cl$-$); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 163.1, 146.8, 142.2, 135.8, 135.4, 133.0 (2C), 126.0, 122.5, 107.8, 61.1, 46.7, 46.0, 36.1, 33.5; LC-MS: m/z = 228 (MH$^+$).

4.13. 2-(8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl) ethylamine (18).

Amine 18 was obtained from 16 in 65% yield as described for compound 17; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.52 (br s, 2H), 7.75 (d, 1H, 8.7 Hz), 7.61 (d, 1H, 8.1 Hz), 7.24 (d, 1H, 8.1 Hz), 7.20 (d, 1H, 2.4 Hz), 7.08 (dd, 1H, 8.7 Hz and 2.4 Hz), 3.93 (s, 3H), 3.76 (m, 1H), 3.41-2.85 (m, 6H), 2.42-2.07 (m, 2H); LC-MS: m/z = 242 (MH$^+$).


Amine 19 was obtained from 14 in 93% yield as described for compound 17; mp 70-72 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.42 (br s, 2H), 7.76 (d, 1H, 9.0 Hz), 7.62 (d, 1H, 8.2 Hz), 7.40 (d, 1H, 2.4 Hz), 7.21 (d, 1H, 8.2 Hz), 7.09 (dd, 1H, 9.0 Hz and 2.4 Hz), 3.93 (s, 3H), 3.11-2.98 (m, 4H), 2.34 (m, 1H), 1.97 (m, 1H), 1.54 (s, 3H); IR (v, cm$^{-1}$): 3290 (NH$_2$); LC-MS: m/z = 242 (MH$^+$).

4.15. (E)-Ethyl-3-(2-methoxyquinolin-7-yl)prop-2-enooate (5).
This product was obtained from commercially 7-bromo-2-methoxyquinoline (3) as described for compound (4). The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) to afford 5 (93%) as a white solid; mp 105-107 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.99 (s, 1H), 7.96 (d, 1H, 8.7 Hz), 7.84 (d, 1H, 16.2 Hz), 7.71 (d, 1H, 8.4 Hz), 7.55 (d, 1H, 8.4 Hz), 6.93 (d, 1H, 8.7 Hz), 6.60 (d, 1H, 16.2 Hz), 4.30 (q, 2H, 7.2 Hz), 4.09 (s, 3H), 1.37 (t, 3H, 7.2 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 166.9, 162.9, 146.7, 144.3, 138.2, 135.5, 128.1, 128.0, 126.1, 122.3, 119.4, 114.1, 60.6, 53.5, 14.3; IR (v, cm$^{-1}$): 1700 (C=O); LC-MS: $m/z$ = 258 (MH$^+$).

4.16. Ethyl 3-(2-methoxyquinolin-7-yl)propanoate (7).

This product was obtained from 5 as described for compound 6. The crude product was purified by flash chromatography (cyclohexane/CH$_2$Cl$_2$: 9/1) to afford 7 (80%) as a white solid; mp 91-93 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.94 (d, 1H, 8.7 Hz), 7.70 (d, 1H, 2.4 Hz), 7.64 (d, 1H, 8.1 Hz), 7.25 (dd, 1H, 8.7 Hz and 2.4 Hz), 6.86 (d, 1H, 8.1 Hz), 4.15 (q, 2H, 7.2 Hz), 4.08 (s, 3H), 3.13 (t, 2H, 7.5 Hz), 2.73 (t, 2H, 7.5 Hz), 1.25 (t, 3H, 7.2 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 172.3, 162.8, 146.2, 140.3, 137.2, 128.8, 128.1, 126.3, 122.3, 113.4, 61.6, 53.6, 34.1, 30.5, 14.3; IR (v, cm$^{-1}$): 1715 (CO); LC-MS: $m/z$ = 260 (MH$^+$).

4.17. 3-(2-Methoxyquinolin-7-yl)propanoic acid (9).

This product was obtained from 7 as described for compound (8). The crude product was purified by flash chromatography (DCM/MeOH : 9/1) to afford 9 (73%) as a white solid; mp 185-187 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 10.3 (br s, 1H), 7.95 (d, 1H, 9.0 Hz), 7.72 (d, 1H, 9.0 Hz), 7.65 (d, 1H, 8.1 Hz), 7.26 (dd, 1H, 9.0 Hz and 2.4 Hz), 6.87 (d, 1H, 8.1 Hz), 4.08 (s, 3H), 3.14 (t, 2H, 7.5 Hz), 2.81 (t, 2H, 7.5 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 174.3, 162.2, 146.1, 139.3, 136.2, 128.8, 127.5, 126.7, 121.6, 112.4, 53.2, 35.1, 30.4; IR (v, cm$^{-1}$): 1695 (C=O); LC-MS: $m/z$ = 232 (MH$^+$).

4.18. 2-Methoxy-7,8-dihydrocyclopenta[h]quinolin-9-one (11).
Chlorosulfonic acid (20 mL) was added dropwise at 0 °C to acid 9 (2.31 g, 1 mmol). Stirring was maintained for 24 h at room temperature, and then the mixture was poured into ice and extracted twice with diethyl ether. The combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, cyclohexane/EtOAc: 7/3) to give 11 (84%) as a white solid; mp 155-157 °C; ¹H NMR (300 MHz, CDCl₃) δ: 7.99 (d, 1H, 8.9 Hz), 7.88 (d, 1H, 8.4 Hz), 7.39 (d, 1H, 8.4 Hz), 6.94 (d, 1H, 8.9 Hz), 4.19 (s, 3H), 3.20 (m, 2H), 2.78 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 205.0, 164.4, 160.9, 143.5, 138.6, 134.7, 130.6, 124.2, 122.2, 113.1, 53.8, 37.1, 26.1; IR (υ, cm⁻¹): 1645 (C=O); LC-MS: m/z = 214 (MH⁺).

4.19. 2-(2-Methoxy-8,9-dihydro-7H-cyclopenta[h]quinolin-9-yl)acetonitrile (21).

Dry THF (5 mL) was added at -10 °C to sodium hydride 60% (0.88 g, 22 mmol) under argon. A solution of diethyl cyanomethylphosphonate (7.1 mL, 44 mmol) in dry THF (10 mL) was then added dropwise. The mixture was stirred under argon until precipitation of the ylure and the solution of compound 11 (2.13 g, 10.0 mmol) in THF (10 mL) was added dropwise. The mixture was stirred for 16 h, and then hydrolyzed with water. The formed solid was filtered, dried and used without further purification for the next step. A solution of this crude product in 60 mL of ethanol/dichloromethane (1/2) was stirred with palladium 10% on charcoal under hydrogen atmosphere at room temperature for 6 h. The mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc: 9/1) to afford 21 (55%) as a white solid; mp 66-67 °C; ¹H NMR (300 MHz, CDCl₃) δ: 7.99 (d, 1H, 8.9 Hz), 7.61 (d, 1H, 7.8 Hz), 7.29 (d, 1H, 7.8 Hz), 6.87 (d, 1H, 8.9 Hz), 4.08 (m, 1H), 4.04 (s, 3H), 3.42 (dd, 1H, 16.5 Hz and 3.9 Hz), 3.29 (m, 1H), 3.09 (m, 1H), 2.99 (dd, 1H, 16.5 Hz and 8.4 Hz), 2.60 (m, 1H), 2.20 (m, 1H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 161.1, 155.4, 138.5, 137.2, 132.7, 127.6, 125.2, 122.1, 117.1, 111.2, 53.8, 36.1, 31.2, 30.7, 24.6; IR (υ, cm⁻¹): 2225 (CN); LC-MS: m/z = 239 (MH⁺).
4.20. 2-(2-Methoxy-8,9-dihydro-7H-cyclopenta[h]quinolin-9-yl)acetic acid (22).

Compound 21 (1.2 g, 5 mmol) was dissolved in ethanol (20 mL), followed by the addition of 6M solution of NaOH (10 mL). The reaction mixture was refluxed during 24 h. After cooling to room temperature, water was added and the solution was extracted twice with diethyl ether. The aqueous solution was acidified with a 6M solution of HCl. The formed solid was filtered and dried to afford 22 (85%) as a white solid; mp 149-150 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.00 (d, 1H, 8.8 Hz), 7.59 (d, 1H, 8.4 Hz), 7.29 (d, 1H, 8.4 Hz), 6.87 (d, 1H, 8.7 Hz), 4.20 (m, 1H), 4.08 (s, 3H), 3.66 (dd, 1H, 15.8 Hz and 4.0 Hz), 3.17 (m, 1H), 3.05 (m, 1H), 2.62-2.53 (m, 2H), 2.08 (m, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 177.9, 162.1, 145.6, 143.2, 139.8, 139.3, 127.0, 124.0, 121.3, 111.6, 53.5, 40.64, 38.8, 32.1, 31.5; IR ($\nu$, cm$^{-1}$): 1680 (C=O); LC-MS: $m/z$ = 258 (MH$^+$).


To a solution of 22 (0.5 g, 2 mmol) in THF (20 mL) was added at 0 °C triethylamine (0.42 mL, 3 mmol) and ethyl chloroformate (0.28 mL, 3 mmol). After 1 h stirring, sodium azide (195 mg, 3 mmol) was added at 0 °C and the reaction mixture was stirred for an additional 2 h. The mixture was hydrolyzed with water and extracted with CH$_2$Cl$_2$. The organic layer was washed with water, dried over MgSO$_4$, filtered and concentrated under reduced pressure at cold condition. The crude product (23) was dissolved in THF (10 mL), followed by the addition of 1 M solution of NaOH (5 mL). The reaction mixture was refluxed during 2 h. A solution of 1 M HCl was added and the reaction mixture was extracted twice with diethyl ether. The aqueous phase was then basified with 2 M solution of NaOH and extracted with diethyl ether. The organic layer was dried over MgSO$_4$, filtered and treated with gaseous HCl. The obtained solid was filtered to give 24 (66%) as a white solid; mp 218-220 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.54 (br s, 3H), 8.00 (d, 1H, 8.94 Hz), 7.62 (d, 1H,
7.60 Hz), 7.32 (d, 1H, 7.60 Hz), 6.85 (d, 1H, 8.94 Hz), 4.00-3.93 (m, 4H), 3.12-3.04 (m, 2H), 2.90 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H), 2.16 (m, 1H); IR (υ, cm⁻¹) : 3210-2800 (NH⁺Cl⁻); ¹³C NMR (75 MHz, DMSO-d⁶) δ: 158.4, 147.6, 142.5, 138.2, 139.2, 126.1, 124.2, 121.7, 111.5, 53.8, 45.5, 43.1, 41.5, 32.4; LC-MS : m/z = 229 (MH⁺).

4.22. 2-(2-Methoxy-8,9-dihydro-7H-cyclopenta[h]quinolin-9-yl)ethanamine hydrochloride (25).

To a suspension of LiAlH₄ (0.38 g, 10 mmol) in Et₂O (10 mL) at 0 °C was added a solution of AlCl₃ (1.33 g, 10 mmol) in Et₂O (10 mL). After 5 min stirring, a solution of 21 (0.6 g, 2.5 mmol) in CH₂Cl₂ (10 mL) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature during 1 h. An aqueous solution of sodium hydroxide 10% was added carefully and the mineral solid was filtered and washed with Et₂O. The filtrate was washed with water, dried over MgSO₄ and treated with gaseous HCl. The obtained solid was filtered to give 25 (90%) as a white solid; mp 228-229 °C; ¹H NMR (300 MHz, CD₃OD-d₆) δ: 8.10 (d, 1H, 8.9 Hz), 7.65 (d, 2H, 7.8 Hz), 7.31 (d, 1H, 7.8 Hz), 6.89 (d, 1H, 8.9 Hz), 4.90 (brs, 3H), 4.07 (s, 3H), 3.88 (m, 1H), 3.21 (m, 1H), 3.12-2.95 (m, 3H), 2.38 (m, 2H), 2.00 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 162.2, 145.4, 143.2, 139.9, 139.3, 127.0, 124.1, 121.0, 111.0, 52.5 40.6, 38.4, 32.1, 31.6, 30.9; IR (υ, cm⁻¹) : 3200-2820 (NH⁺Cl⁻); LC-MS : m/z = 243 (MH⁺).

4.23. General procedure for synthesis of amides 17a-b, 18a, 19a, 24a, 25a and carbamate 17c.

To a solution of corresponding amine 17, 19, 24, 25 (2 mmol) in EtOAc (30 mL) and water (10 mL) were added K₂CO₃ (4 mmol) and the corresponding acid chloride (2.2 mmol) at 0 °C. The mixture was stirred at room temperature during 2 h and the layers were separated. The organic layer was washed with 1 M solution of HCl, water, dried over MgSO₄, filtered and concentrated under reduced pressure.

The crude product was recrystallized from toluene to afford 17a (86%) as a white solid; mp 130-132 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 8.28 (br t, 1H), 7.79 (d, 1H, 9.0 Hz), 7.64 (d, 1H, 8.4 Hz), 7.56 (d, 1H, 2.1 Hz), 7.22 (d, 1H, 8.4 Hz), 7.08 (dd, 1H, 9.0 Hz and 2.1 Hz), 3.92 (s, 3H), 3.68-3.59 (m, 2H), 3.12 (m, 1H), 2.90 (m, 1H), 2.73 (m, 1H), 2.19-2.13 (m, 2H), 1.88 (s, 3H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 170.1, 158.0, 141.5, 139.2, 131.4, 130.4, 128.2, 127.5, 121.3, 117.6, 103.3, 55.7, 44.7, 42.0, 31.5, 29.3, 23.2; IR (\(\nu\), cm\(^{-1}\)) : 3284 (NH), 1639 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]\(^+\), 270.15. HRMS (ESI\(^+\)): \(m/z\) = calcd. for C\(_{17}\)H\(_{20}\)NO\(_2\) [M+H]\(^+\) 270.14886 found: 270.14868.


The crude product was recrystallized from toluene to afford 18a (76%) as a white solid; mp 141-142 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 8.35 (br t, 1H), 7.78 (d, 1H, 9.0 Hz), 7.58 (d, 1H, 8.6 Hz), 7.52 (d, 1H, 2.0 Hz), 7.22 (d, 1H, 8.6 Hz), 7.08 (dd, 1H, 9.0 Hz and 2.0 Hz), 3.95 (s, 3H), 3.82 (m, 1H), 3.42 (m, 1H), 3.23-3.14 (m, 2H), 3.05 (m, 1H), 2.42 (m, 1H), 2.27 (m, 1H), 2.00-1.92 (m, 2H), 1.82 (s, 3H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 170.1, 158.0, 141.5, 139.2, 131.4, 130.4, 128.2, 127.5, 121.3, 117.6, 103.3, 54.0, 46.2, 43.0, 33.5, 32.5, 30.8, 23.4; MS (APCI, pos. 30 V) m/z: [M+H]\(^+\), 284.34. HRMS (ESI\(^+\)): \(m/z\) = calcd. for C\(_{18}\)H\(_{22}\)NO\(_2\) [M+H]\(^+\) 284.16092 found: 284.16034.


The crude product was recrystallized from cyclohexane to afford 19a (80%) as a white solid; mp 84-86 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 7.92 (br t, 1H), 7.69 (d, 1H, 9.0 Hz), 7.45 (d, 1H, 8.7 Hz), 7.36 (d, 1H, 2.1 Hz), 7.22 (d, 1H, 8.7 Hz), 7.10 (dd, 1H, 9.0 Hz and 2.1 Hz), 3.91 (s, 3H), 3.69 (dd, 1H, 13.3 Hz and 6.3 Hz), 3.41 (dd, 1H, 13.3 Hz and 6.3 Hz), 3.11-
3.03 (m, 2H), 2.23 (m, 1H), 1.78 (m, 1H), 1.88 (s, 3H), 1.47 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 171.0, 157.6, 142.1, 140.2, 131.4, 129.5, 128.2, 128.0, 121.3, 117.3, 102.9, 55.6, 47.0, 45.2, 38.5, 29.8, 24.9, 23.2; IR (u, cm$^{-1}$): 3251 (NH), 1624 (C=O); MS (APCI, pos. 30 V) $m/z$: [M+H]$^+$, 284.25. HRMS (ESI$^+$): $m/z = $ calcd. for C$_{18}$H$_{22}$NO$_2$ [M+H]$^+$ 284.12337 found: 284.12259.


The crude product was recrystallized from toluene to afford 24a (85%) as a white solid; mp 110-111 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.03 (d, 1H, 8.9 Hz), 7.61 (d, 1H, 8.0 Hz), 7.36 (br s, 1H), 7.33 (d, 1H, 8.0 Hz), 6.88 (d, 1H, 8.9 Hz), 4.12 (s, 3H), 4.06 (m, 1H), 3.69 (m, 1H), 3.59 (m, 1H), 3.23 (m, 1H), 3.00 (m, 1H), 2.41 (m, 1H), 2.06 (m, 1H), 1.86 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 170.1, 162.4, 146.6, 143.5, 139.9, 139.8, 127.2, 124.0, 121.8, 111.7, 53.5, 45.0, 42.4, 32.2, 30.6, 23.2; IR (u, cm$^{-1}$): 3290 (NH), 1626 (C=O); MS (APCI, pos. 30 V) $m/z$: [M+H]$^+$, 271.26. HRMS (ESI$^+$): $m/z = $ calcd. for C$_{16}$H$_{19}$N$_2$O$_2$ [M+H]$^+$ 271.1441 found: 271.14364.


The crude product was recrystallized from toluene to afford 25a (84%) as a white solid; mp 119-120 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.98 (d, 1H, 8.9 Hz), 7.56 (d, 1H, 8.0 Hz), 7.28 (d, 1H, 8.0 Hz), 6.85 (d, 1H, 8.9 Hz), 5.81 (br s, 1H), 4.08 (s, 3H), 3.84 (m, 1H), 3.46 (m, 1H), 3.33-3.16 (m, 2H), 3.00 (m, 1H), 2.40 (m, 1H), 2.25 (m, 1H), 2.07-1.92 (m, 2H), 1.89 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 170.5, 161.4, 145.6, 142.5, 139.8, 139.2, 127.2, 124.2, 122.4, 111.5, 53.5, 45.0, 42.4, 32.2, 31.5, 30.6, 23.2; IR (u, cm$^{-1}$): 3290 (NH), 1626 (C=O); MS (APCI, pos. 30 V) $m/z$: [M+H]$^+$, 285.24. HRMS (ESI$^+$): $m/z = $ calcd. for C$_{17}$H$_{21}$N$_2$O$_2$ [M+H]$^+$ 285.15975 found: 285.15932.

4.29. 2-Methoxy-N-[(8-methoxy-2,3-dihydro-1H-cyclopenta[a]naphtalen-1-yl)methyl]acetamide (17b).
The crude product was purified by flash chromatography (cyclohexane / EtOAc : 5/5) and recrystallized from toluene to afford 17b (73%) as a white solid; mp 103-104 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.72 (d, 1H, 8.9 Hz), 7.66 (d, 1H, 8.5 Hz), 7.40 (d, 1H, 2.4 Hz), 7.26 (d, 1H, 8.5 Hz), 7.11 (dd, 1H, 8.9 Hz and 2.4 Hz), 6.76 (br s, 1H), 4.00 (s, 3H), 3.94-3.86 (m, 4H), 3.38 (s, 3H), 3.24-3.15 (m, 2H), 3.00 (m, 1H), 2.35 (m, 1H), 2.13 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 169.9, 158.1, 141.6, 138.0, 131.3, 130.0, 128.2, 127.6, 120.8, 117.5, 102.5, 72.0, 59.1, 55.4, 44.0, 41.8, 31.7, 29.3; IR (υ, cm$^{-1}$): 3318 (NH), 1635 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 300.24. HRMS (ESI$^+$): m/z = calcd. for C$_{18}$H$_{22}$NO$_3$ [M+H]$^+$ 300.15214 found: 300.15259.


The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 17c (88%) as a white solid; mp 76-78 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.80 (d, 1H, 9.0 Hz), 7.65 (d, 1H, 8.1 Hz), 7.55 (t, 1H, 5.7 Hz), 7.46 (d, 1H, 2.4 Hz), 7.23 (d, 1H, 8.1 Hz), 7.09 (dd, 1H, 9.0 Hz and 2.4 Hz), 3.91 (s, 3H), 3.69 (m, 1H), 3.58 (s, 3H), 3.45 (m, 1H), 3.08 (m, 1H), 2.90 (m, 1H), 2.75 (m, 1H), 2.19-2.15 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 158.0, 157.6, 141.6, 139.0, 131.4, 130.4, 128.2, 127.6, 121.3, 117.5, 103.1, 55.6, 51.8, 44.9, 43.4, 31.4, 29.0; IR (υ, cm$^{-1}$): 3296 (NH), 1722 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 286.24. HRMS (ESI$^+$): m/z = calcd. for C$_{17}$H$_{20}$NO$_3$ [M+H]$^+$ 286.12337 found: 286.12359.


To a solution of corresponding amine 17 or 19 (404 mg, 2 mmol) in CH$_2$Cl$_2$ (50 mL) were added at 0 °C triethylamine (0.70 mL, 5 mmol) and the corresponding alkyl sulfonyl chloride (2.6 mmol). The mixture was stirred at room temperature for 2 h and hydrolyzed with
water. The organic layer was washed with 1 M solution of HCl, water, dried over MgSO$_4$, filtered and concentrated under reduced pressure.


The crude product was treated with diisopropyl ether and recrystallized from cyclohexane to afford **17d** (70%) as a white solid; mp 110-112 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.82 (d, 1H, 9.0 Hz), 7.68 (d, 1H, 8.4 Hz), 7.36 (t, 1H, 6.3 Hz), 7.26 (d, 1H, 2.1 Hz), 7.25 (d, 1H, 8.4 Hz), 7.09 (dd, 1H, 9.0 Hz and 2.1 Hz), 3.89 (s, 3H), 3.72 (m, 1H), 3.31 (m, 1H), 3.11 (m, 1H), 2.93 (m, 1H), 2.87 (s, 3H), 2.82 (m, 1H), 2.25-2.21 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 158.0, 142.0, 138.5, 131.2, 130.5, 128.2, 127.8, 121.4, 117.6, 103.0, 55.6, 45.4, 45.3, 40.1, 31.5, 28.9; IR ($\nu$, cm$^{-1}$): 3294 (NH); LC-MS: $m/z$ = 306 (MH$^+$). MS (APCI, pos. 30 V) $m/z$: [M+H]$^+$, 306.27. HRMS (ESI$^+$): $m/z$ = calcd. for C$_{16}$H$_{20}$NO$_3$S [M+H]$^+$ 306.14312 found: 306.14372.


The crude product was recrystallized from cyclohexane to afford **17e** (70%) as a white solid; mp 109-110 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.82 (d, 1H, 9.0 Hz), 7.67 (d, 1H, 8.4 Hz), 7.41 (t, 1H, 6.3 Hz), 7.26 (d, 1H, 2.7 Hz), 7.25 (d, 1H, 8.4 Hz), 7.09 (dd, 1H, 9.0 Hz and 2.7 Hz), 3.89 (s, 3H), 3.71 (m, 1H), 3.27 (m, 1H), 3.16-2.74 (m, 5H), 2.23-2.17 (m, 2H), 1.16 (t, 3H, 7.5 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 158.0, 142.0, 138.5, 131.2, 130.5, 128.2, 127.8, 121.4, 117.6, 103.0, 55.6, 46.1, 45.6, 45.3, 31.4, 28.8, 8.6; IR ($\nu$, cm$^{-1}$): 3298 (NH); MS (APCI, pos. 30 V) $m/z$: [M+H]$^+$, 320.27. HRMS (ESI$^+$): $m/z$ = calcd. for C$_{17}$H$_{22}$NO$_3$S [M+H]$^+$ 320.15232 found: 320.15254.

The crude product was recrystallized from cyclohexane to afford 19b (50%) as a white solid; mp 98-100 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 7.82 (d, 1H, 9.0 Hz), 7.68 (d, 1H, 8.1 Hz), 7.39 (d, 1H, 1.8 Hz), 7.21 (d, 1H, 8.1 Hz), 7.11 (dd, 1H, 9.0 Hz and 1.8 Hz), 7.03 (t, 1H, 6.9 Hz), 3.88 (s, 3H), 3.42 (dd, 1H, 13.2 Hz and 6.9 Hz), 3.26 (dd, 1H, 13.2 Hz and 6.9 Hz), 2.97-2.94 (m, 2H), 2.77 (s, 3H), 2.38 (m, 1H), 1.83 (m, 1H), 1.56 (s, 3H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 157.4, 142.7, 140.8, 131.3, 131.0, 129.0, 128.3, 121.6, 116.9, 103.1, 55.4, 50.5, 50.2, 39.8, 38.1, 30.6, 25.0; IR (\(\nu\), cm\(^{-1}\)) : 3297 (NH); MS (APCI, pos. 30 V) m/z: [M+H]\(^+\), 320.24. HRMS (ESI\(^+\)): \(m/z\) = calcd. for C\(_{17}\)H\(_{22}\)NO\(_3\)S [M+H]\(^+\) 320.12328 found: 320.12247.

4.35. N\(^1\)-[(8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methyl]urea (17f).

To a solution of amine 17 (0.45 g, 2 mmol) in water (10 mL) and 1 M solution of HCl (1 mL) was added potassium cyanate (0.2 g, 2.5 mmol). The mixture was stirred at room temperature during 24 h). The solid was filtered, washed with water and recrystallized from acetonitrile to afford 17f (84%) as a white solid; mp 173-175 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 7.79 (d, 1H, 8.97 Hz), 7.64 (d, 1H, 8.20 Hz), 7.64 (d, 1H, 2.4 Hz), 7.23 (d, 1H, 8.2 Hz), 7.00 (dd, 1H, 8.97 Hz and 2.4 Hz), 6.26 (br t, 1H, 6 Hz), 5.51 (br s, 2H), 3.90 (s, 3H), 3.67 (m, 1H), 3.49 (m, 1H), 3.11 (m, 1H), 2.89 (m, 1H), 2.76 (m, 1H), 2.19-2.09 (m, 2H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 160.5, 155.7, 141.1, 138.5, 130.5, 130.0, 127.1, 128.5, 121.4, 118.2, 102.5, 55.8, 46.2, 44.2, 31.4, 29.1; IR (\(\nu\), cm\(^{-1}\)) : 3425 (NH\(_2\)), 3340 (NH), 1625 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]\(^+\), 271.23. HRMS (ESI\(^+\)): \(m/z\) = calcd. for C\(_{16}\)H\(_{19}\)N\(_2\)O\(_2\) [M+H]\(^+\) 271.12418 found: 320.12357.

4.36. N\(^1\)-[(8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methyl]-N\(^3\)-methyl-urea (17g).

To a solution of amine 17 (1.93 g, 8.49 mmol) in DMSO (50 mL) were added triethylamine (1.77 mL, 12.74 mmol) and then N-methylphenylcarbamate (1.92 g, 12.74 mmol). The mixture was stirred at 60 °C during 3 h then, hydrolyzed and extracted with ethyl
acetate. The organic layer was washed with 1 M solution of HCl, water, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was recrystallized from toluene to afford 17g (68%) as a white solid; mp 160-161 °C; ¹H NMR (300 MHz, DMSO-d₆) δ: 7.79 (d, 1H, 9.0 Hz), 7.64 (d, 1H, 8.1 Hz), 7.53 (d, 1H, 2.1 Hz), 7.22 (d, 1H, 8.1 Hz), 7.07 (dd, 1H, 9.0 Hz and 2.1 Hz), 6.23 (br t, 1H), 5.79 (q, 1H, 5.4 Hz), 3.91 (s, 3H), 3.69 (m, 1H), 3.52 (m, 1H), 3.11 (m, 1H), 2.91-2.74 (m, 2H), 2.59 (d, 3H, 4.5 Hz), 2.14-2.10 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆) δ: 159.5, 157.9, 141.6, 139.5, 131.5, 130.3, 128.2, 127.4, 121.3, 117.5, 103.5, 55.6, 45.3, 42.8, 31.6, 29.2, 26.9; IR (υ, cm⁻¹): 3333 (NH), 1624 (C=O); LC-MS: m/z = 285 (MH⁺). MS (APCI, pos. 30 V) m/z: [M+H]⁺, 285.23. HRMS (ESI⁺): m/z = calcd. for C₁₇H₂₁N₂O₂ [M+H]⁺ 285.12416 found: 285.12346.

4.37. General procedure for synthesis of alkyl urea 17h-i, 19c-d, 24b-c and thiourea 17k-m, 19e-g and 24b.

To a solution of corresponding amine 17, 18, 19 or 24 (1 mmol) in CH₂Cl₂ (10 mL) were added triethylamine (2 mmol) and the corresponding alkyl isocyanate or isothiocyanate (1.2 mmol) at 0 °C. The mixture was stirred at room temperature during 2 h and hydrolyzed. CH₂Cl₂ was added and the organic layer was washed with a 1 M solution of HCl and water, dried over MgSO₄, filtered and concentrated under reduced pressure.


The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 17h (57%) as a white solid; mp 148-150 °C; ¹H NMR (300 MHz, DMSO-d₆) δ: 7.79 (d, 1H, 9.0 Hz), 7.65 (d, 1H, 8.1 Hz), 7.51 (d, 1H, 2.4 Hz), 7.23 (d, 1H, 8.1 Hz), 7.08 (dd, 1H, 9.0 Hz and 2.4 Hz), 6.11 (t, 1H, 6.0 Hz), 5.84 (t, 1H, 5.4 Hz), 3.91 (s, 3H), 3.67 (m, 1H), 3.51 (m, 1H), 3.13-3.00 (m, 3H), 2.93-2.74 (m, 2H), 2.15-2.10 (m, 2H), 1.00 (t, 3H, 7.2 Hz); ¹³C NMR (75 MHz, DMSO-d₆) δ: 158.8, 157.9,
141.6, 139.5, 131.5, 130.3, 128.2, 127.4, 121.3, 117.5, 103.6, 55.6, 45.3, 42.7, 34.6, 31.6, 29.2, 16.2; IR (υ, cm⁻¹): 3317 (NH), 1622 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]^+, 300.21. HRMS (ESI⁺): m/z = calcd. for C_{18}H_{23}N_{2}O_{2} [M+H]^+ 300.16812 found: 300.16734.


The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 17i (77%) as a white solid; mp 139-141 °C; ¹H NMR (300 MHz, DMSO-d_6) δ: 7.79 (d, 1H, 9.0 Hz), 7.64 (d, 1H, 8.1 Hz), 7.50 (d, 1H, 2.4 Hz), 7.23 (d, 1H, 8.1 Hz), 7.08 (dd, 1H, 9.0 Hz and 2.4 Hz), 6.10 (t, 1H, 6.0 Hz), 5.90 (t, 1H, 5.7 Hz), 3.91 (s, 3H), 3.68 (m, 1H), 3.51 (m, 1H), 3.08 (m, 1H), 2.96 (q, 2H, 6.6 Hz), 2.92-2.76 (m, 2H), 2.16-2.10 (m, 2H), 1.38 (m, 2H), 0.84 (t, 3H, 6.6 Hz); ¹³C NMR (75 MHz, DMSO-d_6) δ: 158.8, 158.0, 141.8, 139.3, 131.7, 130.3, 128.2, 127.5, 121.3, 117.8, 103.8, 56.0, 46.2, 45.6, 44.0, 31.4, 28.8, 22.5, 11.9; IR (υ, cm⁻¹): 3294 (NH), 1623 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]^+, 313.25. HRMS (ESI⁺): m/z = calcd. for C_{19}H_{25}N_{2}O_{2} [M+H]^+ 313.18377 found: 313.18334.


The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 19c (67%) as a white solid; mp 143-145 °C; ¹H NMR (300 MHz, DMSO-d_6) δ: 7.82 (d, 1H, 9.0 Hz), 7.66 (d, 1H, 8.1 Hz), 7.40 (d, 1H, 2.4 Hz), 7.20 (d, 1H, 8.1 Hz), 7.09 (dd, 1H, 9.0 Hz and 2.4 Hz), 5.83 (br t, 1H, 5.4 Hz), 5.64 (br t, 1H, 6.3 Hz), 3.88 (s, 3H), 3.71 (dd, 1H, 13.5 Hz and 6.3 Hz), 3.36 (dd, 1H, 13.5 Hz and 6.3 Hz), 3.01-2.98 (m, 4H), 2.24 (m, 1H), 1.78 (m, 1H), 1.47 (s, 3H), 0.92 (t, 3H, 7.2 Hz); ¹³C NMR (75 MHz, DMSO-d_6) δ: 158.8, 157.4, 142.6, 141.2, 131.4, 131.0, 129.0, 128.0, 121.6, 116.9, 102.9, 55.5, 47.1, 45.9, 38.2, 34.5, 30.7, 24.9, 16.1; IR (υ, cm⁻¹): 3279 (NH),
1623 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 313.26. HRMS (ESI$^+$): m/z = calcd. for C$_{19}$H$_{25}$N$_2$O$_2$ [M+H]$^+$ 313.18377 found: 313.18344.

4.41. N$^1$-[{(8-Methoxy-1-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methyl]-N$^3$ propylurea (19d).

The crude product was recrystallized from toluene to afford 19d (70%) as a white solid; mp 115-117 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.82 (d, 1H, 9.0 Hz), 7.66 (d, 1H, 8.1 Hz), 7.40 (d, 1H, 2.4 Hz), 7.20 (d, 1H, 8.1 Hz), 7.09 (dd, 1H, 9.0 Hz and 2.4 Hz), 5.83 (br t, 1H, 5.7 Hz), 5.59 (br t, 1H, 6.0 Hz), 3.87 (s, 3H), 3.71 (dd, 1H, 13.8 Hz and 6.0 Hz), 3.38 (dd, 1H, 13.8 Hz and 6.0 Hz), 2.94-2.87 (m, 4H), 2.23 (m, 1H), 1.79 (m, 1H), 1.46 (s, 3H), 1.30 (m 2H), 0.78 (t, 3H, 7.2 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 158.9, 157.4, 142.6, 141.1, 131.3, 131.0, 129.0, 128.0, 121.6, 116.9, 102.9, 55.5, 51.4, 47.2, 41.5, 38.1, 30.7, 24.9, 23.6, 16.1; IR (υ, cm$^{-1}$): 3313 (NH), 1624 (C=O); LC-MS: m/z = 327 (MH$^+$). MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 327.26. HRMS (ESI$^+$): m/z = calcd. for C$_{20}$H$_{27}$N$_2$O$_2$ [M+H]$^+$ 327.19942 found: 327.19834.

4.42. N$^1$-{(8-methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methyl]-N$^3$-methyl-thiourea (17k).

The crude product was purified by flash chromatography(cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 17k (87%) as a white solid; mp 159-161 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.75 (d, 1H, 9.0 Hz), 7.65 (d, 1H, 8.1 Hz), 7.40 (d, 1H, 8.1 Hz), 7.10 (dd, 1H, 9.0 Hz and 2.4 Hz), 5.90 (br s, 2H), 4.23-4.04 (m, 2H), 3.99 (s, 3H), 3.53 (m, 1H), 3.20 (m, 1H), 3.00 (m, 1H), 2.83 (s, 3H), 2.38 (m, 1H), 2.14 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 183.6, 158.0, 141.8, 139.3, 131.7, 130.3, 128.2, 127.5, 121.3, 117.8, 103.9, 56.0, 46.4, 44.0, 31.4, 30.8, 28.8; IR (υ, cm$^{-1}$): 3392 (NH), 1213 (C=S); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 301.26. HRMS (ESI$^+$): m/z = calcd. for C$_{17}$H$_{21}$N$_2$OS [M+H]$^+$ 301.13691 found: 301.13648.

The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 17l (64%) as a white solid; mp 200-202 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.80-7.77 (m, 2H), 7.72 (br s, 1H), 7.65 (d, 1H, 8.4 Hz), 7.46 (s, 1H), 7.24 (d, 1H, 8.4 Hz), 7.06 (dd, 1H, 9.0 Hz and 2.4 Hz), 4.09-3.98 (m, 2H), 3.91 (s, 3H), 3.35 (m, 2H), 3.20-2.86 (m, 3H), 2.15-2.12 (m, 2H), 1.08 (t, 3H, 6.9 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 182.6, 158.0, 141.8, 139.3, 131.7, 130.3, 128.2, 127.5, 121.3, 117.8, 103.8, 56.0, 46.2, 44.0, 38.5, 31.4, 28.8, 14.9; IR (υ, cm$^{-1}$): 3245 (NH), 1213 (C=S); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 315.22. HRMS (ESI$^+$): m/z = calcd. for C$_{18}$H$_{23}$N$_2$OS [M+H]$^+$ 315.19942 found: 315.19834.

4.44. $N^1$-[(8-Methoxy-2,3-dihydro-1H-cyclopenta[a]napthalen-1-yl)methyl]-$N^3$-propylthiourea (17m).

The crude product was recrystallized from toluene to afford 17m (56%) as a white solid; mp 137-139 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.80-7.77 (m, 2H), 7.73 (br s, 1H), 7.65 (d, 1H, 8.1 Hz), 7.50 (s, 1H), 7.24 (d, 1H, 8.1 Hz), 7.07 (dd, 1H, 9.0 Hz and 2.4 Hz), 4.15-3.98 (m, 2H), 3.91 (s, 3H), 3.33 (m, 2H), 3.17-2.86 (m, 3H), 2.15-2.11 (m, 2H), 1.50 (m, 2H), 0.87 (t, 3H, 6.6 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 184.1, 158.0, 141.8, 139.3, 131.7, 130.3, 128.2, 127.5, 121.3, 117.8, 103.8, 56.0, 46.2, 44.0, 38.5, 31.4, 26.8, 14.9; IR (υ, cm$^{-1}$): 3295 (NH), 1213 (C=S); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 329.22. HRMS (ESI$^+$): m/z = calcd. for C$_{19}$H$_{25}$N$_2$OS [M+H]$^+$ 329.16092 found: 329.16034.


The crude product was recrystallized from toluene to afford 19e (57%) as a white solid; mp 144-146 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.82 (d, 1H, 9.0 Hz), 7.68 (d, 1H, 8.2 Hz),
7.52 (d, 1H, 2.4 Hz), 7.43 (br s, 1H), 7.22 (d, 1H, 8.2 Hz), 7.19 (br s, 1H), 7.08 (dd, 1H, 9.0 Hz and 2.4 Hz), 4.41 (m, 1H), 3.89 (s, 3H), 3.61 (m, 1H), 2.96-2.93 (m, 2H), 2.82 (d, 3H, 3.6 Hz), 2.34 (m, 1H), 1.80 (m, 1H), 1.54 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$: 182.3, 157.5, 142.5, 140.9, 131.3, 131.0, 129.0, 128.2, 121.6, 117.2, 102.8, 55.6, 51.3, 51.1, 38.2, 31.0, 30.6, 24.7; IR ($\nu$, cm$^{-1}$): 3297 (NH), 1212 (C=S); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 315.23. HRMS (ESI$^+$): m/z = calcd. for C$_{18}$H$_{23}$N$_2$O$_5$ [M+H]$^+$ 315.14528 found: 315.14434.


The crude product was recrystallized from toluene to afford 19f (51%) as a white solid; mp 125-127 °C; $^1$H NMR (300MHz, DMSO-$d_6$) $\delta$: 7.2 (d, 1H, 9.0 Hz), 7.67 (d, 1H, 8.1 Hz), 7.52 (d, 1H, 2.4 Hz), 7.44 (br s, 1H), 7.21 (d, 1H, 8.1 Hz), 7.11-7.07 (m, 2H), 4.44 (m, 1H), 3.90 (d, 1H), 3.64 (m, 1H), 3.36 (q, 2H, 7.5 Hz), 2.99-2.94 (m, 2H), 2.33 (m, 1H), 1.82 (m, 1H), 1.54 (s, 3H), 1.03 (t, 3H, 7.5 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 183.7, 157.5, 142.6, 140.8, 131.3, 131.0, 129.0, 128.2, 121.6, 117.2, 102.7, 55.6, 51.2, 51.0, 38.8, 38.2, 30.7, 24.8, 14.8; IR ($\nu$, cm$^{-1}$): 3294 (NH), 1223 (C=S); MS (APCI, pos. 30 V) m/z: [M+H]$^+$, 329.27. HRMS (ESI$^+$): m/z = calcd. for C$_{19}$H$_{25}$N$_2$O$_5$ [M+H]$^+$ 329.16094 found: 329.16023.

4.47. $N^1$-[(8-Methoxy-1-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methyl]-$N^3$-propylthiourea (19g).

The crude product was recrystallized from toluene to afford 19g (41%) as a white solid; mp 109-111 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.82 (d, 1H, 9.0 Hz), 7.67 (d, 1H, 8.1 Hz), 7.50-7.46 (m, 2H), 7.22 (d, 1H, 8.1 Hz), 7.11-7.07 (m, 2H), 4.43 (m, 1H), 3.89 (d, 1H), 3.63 (m, 1H), 3.31 (q, 2H, 7.2 Hz), 2.98-2.95 (m, 2H), 2.32 (m, 1H), 1.80 (m, 1H), 1.52 (m, 1H), 1.43 (m, 1H), 0.82 (t, 3H, 7.2 Hz); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 182.6, 157.5, 142.6, 140.8, 131.3, 131.0, 129.0, 128.3, 121.6, 117.2, 102.7, 55.6, 51.2, 51.1, 45.4, 38.2, 30.7, 24.8,
22.5, 11.8; IR (ν, cm\(^{-1}\)) : 3213 (NH), 1223 (C=S); MS (APCI, pos. 30 V) m/z: [M+H]+, 342.32. HRMS (ESI\(^{+}\)) : m/z = calcd. for C\(_{20}\)H\(_{27}\)N\(_2\)O\(_5\) [M+H]+ 342.17658 found: 342.176223.

4.48. (8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methylthiourea (17j).

To a solution of 17 (0.50 g, 2.20 mmol) in a mixture of dioxane/THF (6/1) (35 mL) was added 12 M HCl (0.2 mL) and potassium thiocyanate (427 mg, 4,40 mmol). The mixture was stirred at 60 °C during 16 h then hydrolyzed and extracted with EtOAc. The organic layer was washed with water, dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/ EtOAc : 5/5) to afford 17j (25%) as a white solid; mp 86-87 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) δ: 7.94 (br s, 1H), 7.79 (d, 1H, 9.0 Hz), 7.75 (d, 1H, 2.4 Hz), 7.66 (d, 1H, 8.1 Hz), 7.24 (d, 1H, 8.1 Hz), 7.09 (dd, 1H, 9.0 Hz and 2.4 Hz), 7.04 (br s, 2H), 4.00 (m, 1H), 3.91 (s, 3H), 3.60 (m, 1H), 3.20-2.86 (m, 3H), 2.13-2.08 (m, 2H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) δ: 183.0, 157.7, 141.6, 139.5, 131.7, 130.0, 128.1, 127.5, 121.3, 118.0, 102.1, 55.9, 46.3, 44.1, 31.3, 28.8; IR (ν, cm\(^{-1}\), KBr): 3291 (NH), 1213 (C=S); MS (APCI, pos. 30 V) m/z: [M+H]+, 287.22. HRMS (ESI\(^{+}\)) : m/z = calcd. for C\(_{16}\)H\(_{19}\)N\(_2\)O\(_5\) [M+H]+ 287.17658 found: 287.176253.

4.49. \(N^1\)-[(2-Methoxy-8,9-dihydro-7H-cyclopenta[h]quinolin-9-yl)methyl]-\(N^3\)-methylurea (24b).

The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 24b (55%) as a white solid; mp 142-143 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ: 8.00 (d, 1H, 8.9 Hz), 7.58 (d, 1H, 7.7 Hz), 7.31 (d, 1H, 7.7 Hz), 6.87 (d, 1H, 8.9 Hz), 5.78 (br s, 1H), 4.25 (br s, 1H), 4.13 (s, 3H), 4.0 (m, 1H), 3.61 (m, 2H), 3.20 (m, 1H), 3.00 (m, 1H), 2.69 (d, 2H, 4.3 Hz), 2.40 (m, 1H), 2.10 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ: 162.4, 159.2, 146.6, 143.5, 139.67, 139.5, 127.2, 123.9, 121.6, 111.7, 53.6, 45.2, 43.6, 42.2, 32.3, 30.2, 27.1; IR (ν, cm\(^{-1}\)) : 3290 (NH), 1626 (C=O); MS (APCI, pos. 30
V) \( m/z: [M+H]^+ \), 286.25. HRMS (ESI\(^+\)): \( m/z = \text{calcd. for C}_{16}\text{H}_{20}\text{N}_3\text{O}_2 [M+H]^+ \) 286.155 found: 286.15461.

4.50. \( N^1\)-\((2\text{-Methoxy-8,9-dihydro-7H-cyclopenta[h]quinolin-9-yl})\text{methyl\}-N^3\text{-propylurea (24c).} \)

The crude product was purified by flash chromatography (cyclohexane/EtOAc : 5/5) and recrystallized from toluene to afford 24c (78%) as a white solid; mp 167-168 °C; \( ^1\text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \): 8.00 (d, 1H, 8.8 Hz), 7.59 (d, 1H, 8.3 Hz), 7.31 (d, 1H, 8.3 Hz), 6.87 (d, 1H, 8.8 Hz), 5.75 (br t, 1H), 4.19 (br t, 1H), 4.13 (s, 3H), 4.0 (m, 1H), 3.63 (m, 2H), 3.35 (m, 1H), 3.10-2.95 (m, 3H), 2.40 (m, 1H), 2.12 (m, 1H), 1.41 (q, 2H, 7.5 Hz), 0.85 (t, 3H, 7.53 Hz); \( ^{13}\text{C} \) NMR (75 MHz, CDCl\(_3\)) \( \delta \): 162.4, 158.5, 146.6, 143.6, 139.5 (2C), 127.2, 123.9, 121.6, 111.7, 53.6, 45.2, 43.6, 42.2, 32.3, 30.2, 23.4, 11.2; IR (\( \nu, \text{cm}^{-1} \)): 3325 (NH), 1613 (C=O); MS (APCI, pos. 30 V) \( m/z: [M+H]^+ \), 314.35. HRMS (ESI\(^+\)): \( m/z = \text{calcd. for C}_{18}\text{H}_{24}\text{N}_3\text{O}_2 [M+H]^+ \) 313.17902 found 313.17743.

5. Pharmacological methods

5.1. Reagents and Chemicals.

2-[\(^{125}\text{I}\)]-Iodomelatonin (2200 Ci/mmol) was purchased from NEN (Boston, MA). Other drugs and chemicals were purchased from Sigma-Aldrich (Saint Quentin, France).

5.2. Cell Culture.

HEK (provided by A.D. Strosberg, Paris, France) and CHO cell lines stably expressing the human melatonin MT\(_1\) or MT\(_2\) receptors were grown in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/mL penicillin and 100 \( \mu \)g/ml streptomycin. Grown at confluence at 37 °C (95%\( \text{O}_2/5\%\text{CO}_2\)), they were harvested in PBS containing EDTA 2 mM and centrifuged at 1000 x g for 5 min (4 °C). The resulting pellet was suspended in TRIS 5 mM (pH 7.5), containing EDTA 2 mM and homogenized using a
Kinematica polytron. The homogenate was then centrifuged (95,000g, 30 min, 4 °C) and the resulting pellet suspended in 75 mM TRIS (pH 7.5), 12.5 mM MgCl₂ and 2 mM EDTA. Aliquots of membrane preparations were stored at -80 °C until use.

5.3. Binding Assays.

2-[¹²⁵I]iodomelatonin binding assay conditions were essentially as previously described [27]. Briefly, binding was initiated by addition of membrane preparations from stable transfected HEK or CHO cells diluted in binding buffer (50 mM Tris-HCl buffer, pH 7.4 containing 5 mM MgCl₂) to 2-[¹²⁵I]-iodomelatonin (25 or 200 pM for MT₁ and MT₂ receptors, respectively, expressed in HEK cells or 20 pM for MT₁ and MT₂ receptors expressed in CHO cells) and the tested drug. Nonspecific binding was defined in the presence of 1 µM melatonin. After 120 min incubation at 37 °C, reaction was stopped by rapid filtration through GF/B filters presoaked in 0.5% (v/v) polyethylenimine. Filters were washed three times with 1 ml of ice-cold 50 mM Tris-HCl buffer, pH 7.4.

Data from the dose-response curves (7 concentrations in duplicate) were analysed using PRISM program (Graph Pad Software Inc., San Diego, CA) to yield IC₅₀ (inhibitory concentration 50). Results are expressed as $K_i = IC_{50} / (1 + ([L]/K_D))$, where [L] is the concentration of radioligand used in the assay and $K_D$, the dissociation constant of the radioligand characterising the membrane preparation [28].

[³⁵S]GTPγS binding assay was performed according to published methodology [27]. Briefly, membranes from transfected CHO cells expressing MT₁ or MT₂ receptor subtype and compounds were diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3 µM GDP, 3 mM MgCl₂, and 20 µg/mL saponin). Incubation was started by the addition of 0.2 nM [³⁵S]GTPγS to membranes (20 µg/ml) and drugs, and further followed for 1 h at room temperature. For experiments with antagonists, membranes were pre-incubated with both the melatonin (3 nM) and the antagonist for 30 min prior the addition of [³⁵S]GTPγS. Non
specific binding was defined using cold GTPγS (10 µM). Reaction was stopped by rapid filtration through GF/B filters followed by three successive washes with ice cold buffer.

Usual levels of [35S]GTPγS binding (expressed in dpm) were for CHO-MT1 or MT2 membranes: 2000 for basal activity, 8000 in the presence of melatonin 1 µM and 180 in the presence of GTPγS 10 µM which defined the non specific binding. Data from the dose-response curves (7 concentrations in duplicate) were analyzed by using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield EC50 (Effective concentration 50 %) and Emax (maximal effect) for agonists. Antagonist potencies are expressed as Kᵦ = IC50 / 1 + ([Ag]/EC50 ago), where IC50 is the inhibitory concentration of antagonist that gives 50% inhibition of [35S] GTPγS binding in the presence of a fixed concentration of melatonin ([Ag]) and EC50 ago is the EC50 of the molecule when tested alone. Imax (maximal inhibitory effect) was expressed as a percentage of that observed with melatonin at 3 nM for MT2 receptor.

Serotonin 5-HT2C binding assay was determined according to reported tests [29]. First incubation of 200 µl solution from membrane CHO cell lines, stably expressing the human 5-HT2C receptors, for 60 min at 37 °C in binding buffer (50 mM Tris–HCl buffer, pH 7.4, containing 10 mM MgCl2 and 0.1% BSA) containing the radioligand [3H]-mesulergine (1 nM). Non-specific binding was defined in the presence of 10 µM mianserine. Dose–response curves are obtained by displacement of the radioligand. Reaction was stopped by rapid filtration through GF/B filters presoaked in 0.1% (v/v) polyethylenimine. Filters were washed three times with 1 mL of ice-cold 50 mM Tris–HCl buffer, pH 7.4. Residual radioactivity was revealed by addition of Microscint 20 and measured by using TopCount calculator (Packard). IC50 was determined from dose–response curves and results are expressed as Kᵦ = IC50/1 + ([L]/KD), where [L] is the concentration of radioligand used in the assay and KD, the dissociation constant of the radioligand characterising the membrane preparation.
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HIGHLIGHTS

- New constrained analogues of agomelatine were designed and synthesized
- Prepared compounds showed good affinities at melatonin and 5HT\textsubscript{2C} receptors
- Naphthocyclopentane derivative \textit{17a} was considered as the lead
- (-)-\textit{17k} represents one of the highest dual MT and 5HT\textsubscript{2C} derivative