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# Accepted Manuscript

Synthesis and biological evaluation of new naphtho- and quinolinocyclopentane derivatives as potent melatonergic (MT<sub>1</sub>/MT<sub>2</sub>) and serotonergic (5-HT<sub>2C</sub>) dual ligands

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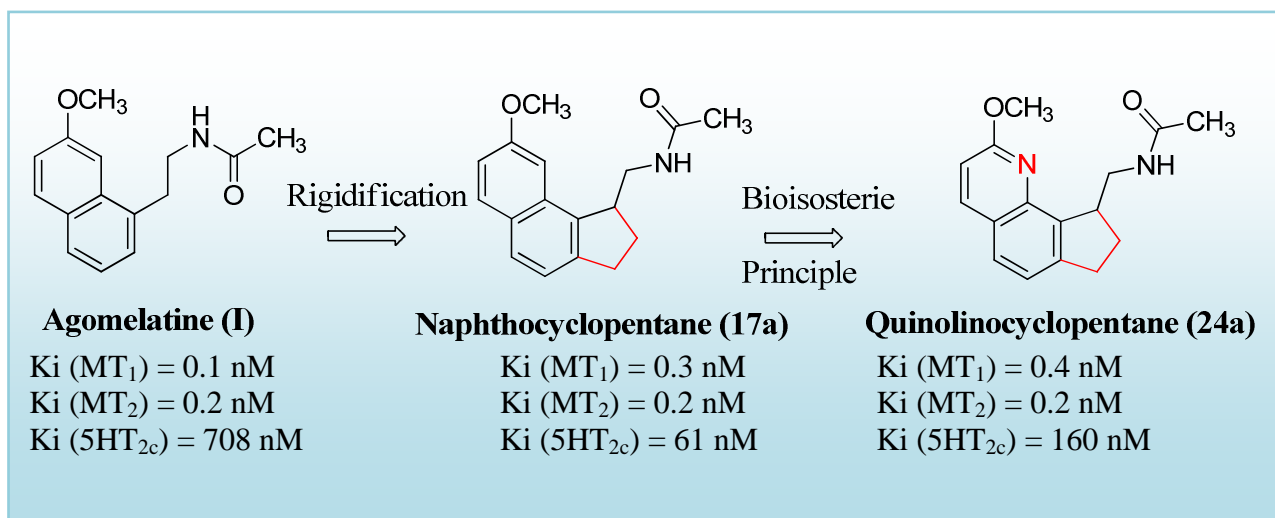
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ACCEPTED MANUSCRIPT

**Synthesis and Biological Evaluation of new Naphtho- and  
Quinolinocyclopentane Derivatives as Potent Melatonergic (MT<sub>1</sub>/MT<sub>2</sub>)  
and Serotonergic (5-HT<sub>2C</sub>) Dual Ligands**

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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 (MT<sub>1</sub>, MT<sub>2</sub>) and serotonin (5-HT<sub>2C</sub>) 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 (-)-**17g** and (-)-**17k** as the highest (MT<sub>1</sub>, MT<sub>2</sub>) / 5-HT<sub>2C</sub> dual ligands described nowadays.

**Key Words:** Melatonin, serotonin, agomelatine, levogyre, dextrogyre

## 1. Introduction

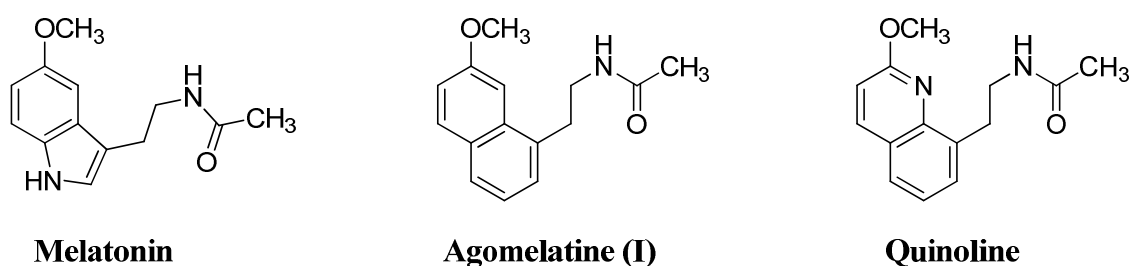
Since its discovery [1], melatonin remains one of the most studied neurohormones by the scientific community due to its therapeutic perspectives and physio-pathological implications. In fact, during the last half century, melatonin has attracted an extensive campaign of research to fully study its physiological and pathological processes. Overall, however, it is clear that the melatonergic 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<sub>1</sub> and MT<sub>2</sub>) belonging to the superfamily of high-affinity G protein-coupled receptors (GPCRs) [12], and the enzyme quinone reductase 2 (QR2 previously known as MT<sub>3</sub>) [6a]. The design and synthesis of

melatonergic ligands has led to a large number of derivatives with different pharmacological profiles. However, only very few melatonergic 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-7*H*-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.

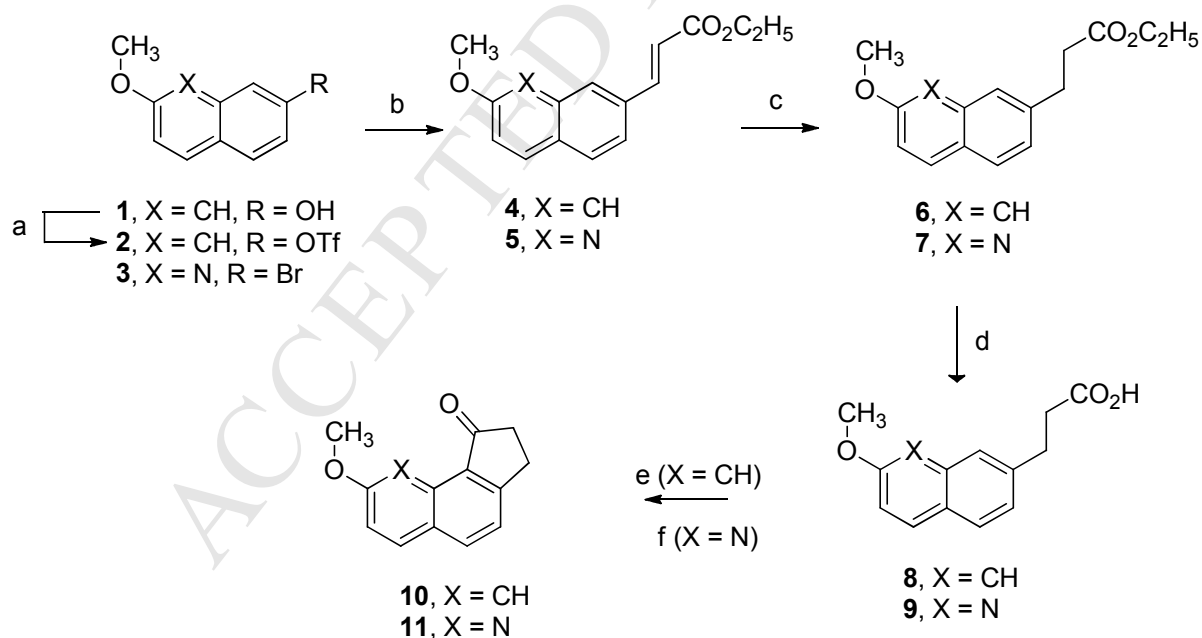
**Figure 1.** Melatonin, Agomelatine and its quinolinic analogue.



## 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**.



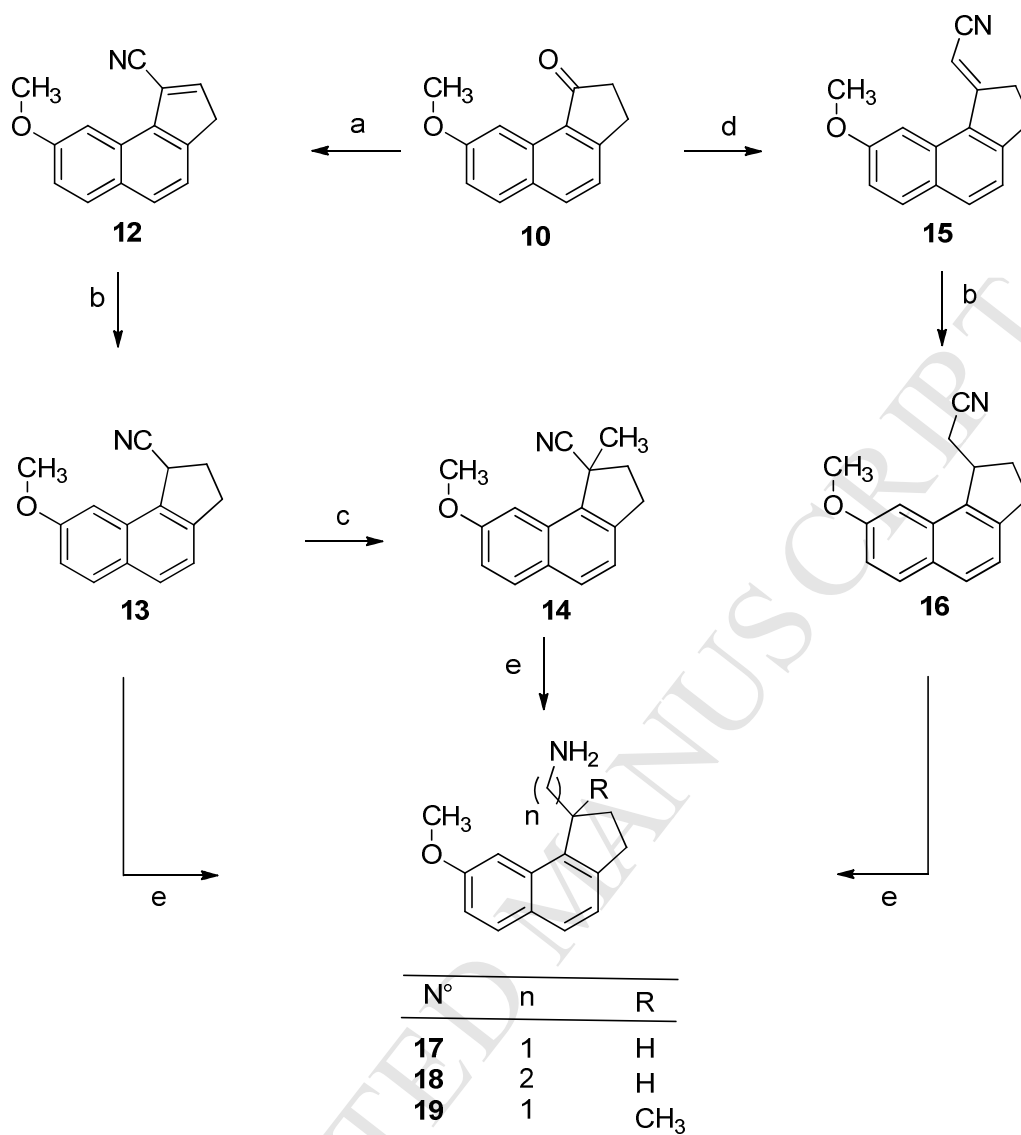
**Scheme 1<sup>a</sup>**. Synthesis of key intermediates **10** and **11**.

<sup>a</sup>*Reagents and conditions:* (a)  $\text{Tf}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-20\text{ }^\circ\text{C}$  to rt, 100%; (b) ethyl acrylate,  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $\text{Et}_3\text{N}$ , DMF,  $120\text{ }^\circ\text{C}$ , 77% for **4** and 93% for **5**; (c) Pd/C,  $\text{H}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{EtOH}$ , rt,



96% for **6** and 80% for **7**; (d) (i) 6M NaOH, EtOH, rt, (ii) 6M HCl, 93% for **8** and 73% for **9**; (e) CH<sub>3</sub>SO<sub>2</sub>H, 90°C, 70%; (f) ClSO<sub>3</sub>H, 0°C to rt, 84%.

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

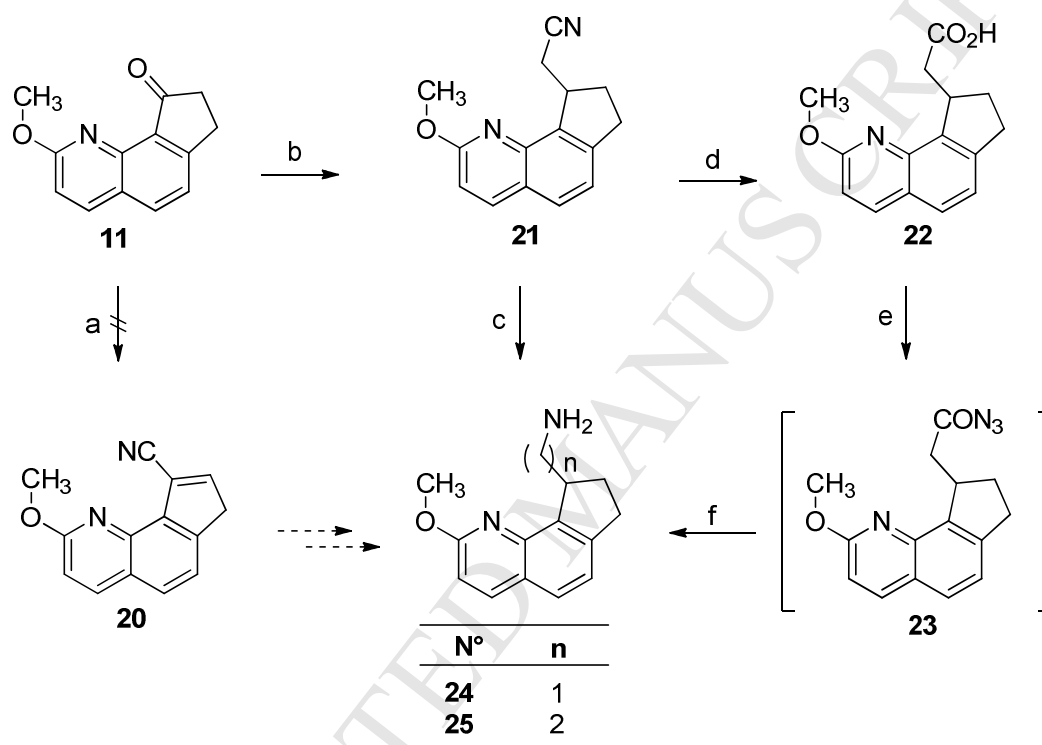


**Scheme 2<sup>a</sup>.** Synthesis of primary amines **17-19**.

<sup>a</sup>*Reagents and conditions:* a) (i) Trimethylsilyl cyanide, zinc iodide, CH<sub>2</sub>Cl<sub>2</sub>, rt (ii) Acetyl chloride, acetic acid, rt, 83%; b) Pd/C, H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOH, rt, 72%; c) CH<sub>3</sub>I, NaH, DMF, 0 °C to rt, 91%; d) NaH, diethyl cyanomethylphosphonate, THF, -10 °C to rt, 50%; e) Raney Ni, H<sub>2</sub>, 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.

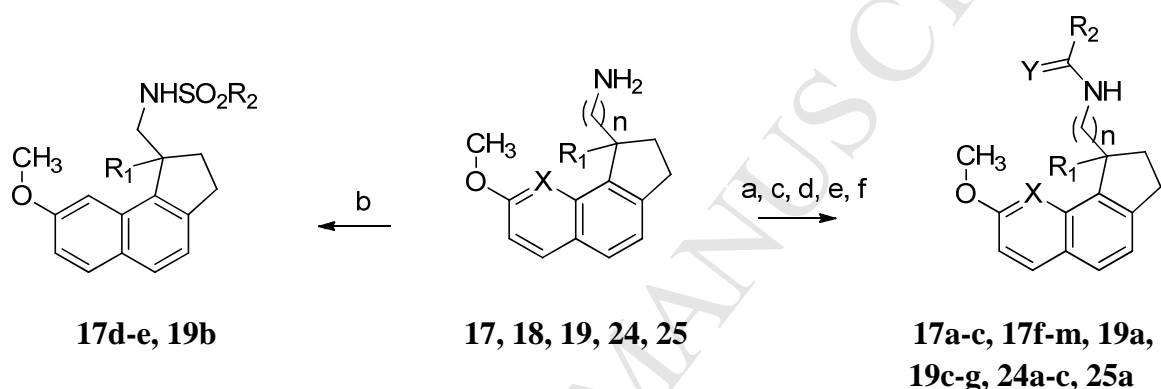


**Scheme 3<sup>a</sup>.** Synthesis of amines **24-25**.

<sup>a</sup>*Reagents and conditions:* a) (i) trimethylsilyl cyanide, zinc iodide, CH<sub>2</sub>Cl<sub>2</sub>, rt, (ii) acetyl chloride, acetic acid, rt; b) (i) NaH, diethyl cyanomethylphosphonate, THF, -10 °C to rt, (ii) Pd/C, H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOH, rt, 55%; c) LiAlH<sub>4</sub>, AlCl<sub>3</sub>, Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 90%; d) (i) 6M NaOH, (ii) 6M HCl; e) ClCO<sub>2</sub>Et, Et<sub>3</sub>N, NaN<sub>3</sub>, 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		n	R <sub>1</sub>	X	Y	R <sub>2</sub>	Conditions	Rdt
Amides	<b>17a</b>	1	H	CH	O	CH <sub>3</sub>	a	86%
	<b>18a</b>	2	H	CH	O	CH <sub>3</sub>	a	76%
	<b>19a</b>	1	CH <sub>3</sub>	CH	O	CH <sub>3</sub>	a	80%
	<b>24a</b>	1	H	N	O	CH <sub>3</sub>	a	85%
	<b>25a</b>	2	H	N	O	CH <sub>3</sub>	a	84%
	<b>17b</b>	1	H	CH	O	CH <sub>2</sub> OCH <sub>3</sub>	a	73%
Carbamate	<b>17c</b>	1	H	CH	O	OCH <sub>3</sub>	a	88%
Sulfonamides	<b>17d</b>	1	H	CH	-	CH <sub>3</sub>	b	70%
	<b>17e</b>	1	H	CH	-	C <sub>2</sub> H <sub>5</sub>	b	70%
	<b>19b</b>	1	CH <sub>3</sub>	CH	-	CH <sub>3</sub>	b	50%
Ureas	<b>17f</b>	1	H	CH	O	NH <sub>2</sub>	c	84%
	<b>17g</b>	1	H	CH	O	NHCH <sub>3</sub>	d	68%
	<b>17h</b>	1	H	CH	O	NHC <sub>2</sub> H <sub>5</sub>	e	57%
	<b>17i</b>	1	H	CH	O	NHC <sub>3</sub> H <sub>7</sub>	e	77%
	<b>19c</b>	1	CH <sub>3</sub>	CH	O	NHC <sub>2</sub> H <sub>5</sub>	e	67%
	<b>19d</b>	1	CH <sub>3</sub>	CH	O	NHC <sub>3</sub> H <sub>7</sub>	e	70%
	<b>24b</b>	1	H	N	O	NHCH <sub>3</sub>	d	55%
	<b>24c</b>	1	H	N	O	NHC <sub>3</sub> H <sub>7</sub>	e	78%
Thioureas	<b>17j</b>	1	H	CH	S	NH <sub>2</sub>	f	25%
	<b>17k</b>	1	H	CH	S	NHCH <sub>3</sub>	e	87%
	<b>17l</b>	1	H	CH	S	NHC <sub>2</sub> H <sub>5</sub>	e	64%
	<b>17m</b>	1	H	CH	S	NHC <sub>3</sub> H <sub>7</sub>	e	56%

	<b>19e</b>	1	CH <sub>3</sub>	CH	S	NHCH <sub>3</sub>	e	57%
	<b>19f</b>	1	CH <sub>3</sub>	CH	S	NHC <sub>2</sub> H <sub>5</sub>	e	51%
	<b>19g</b>	1	CH <sub>3</sub>	CH	S	NHC <sub>3</sub> H <sub>7</sub>	e	41%

**Scheme 4.** Synthesis of final compounds **17a-m**, **19a-g**, **24a-c**, **25a**.

<sup>a</sup>*Reagents and conditions:* a) R<sub>2</sub>COCl, K<sub>2</sub>CO<sub>3</sub>, EtOAc/H<sub>2</sub>O, 0°C to rt; b) R<sub>2</sub>SO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt; c) KNCO, H<sub>2</sub>O/HCl, rt; d) *N*-methylphenylcarbamate, Et<sub>3</sub>N, DMSO, 60°C; e) R<sub>1</sub>NCX, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0°C to rt; f) KSCN, Dioxane, THF, 60°C.

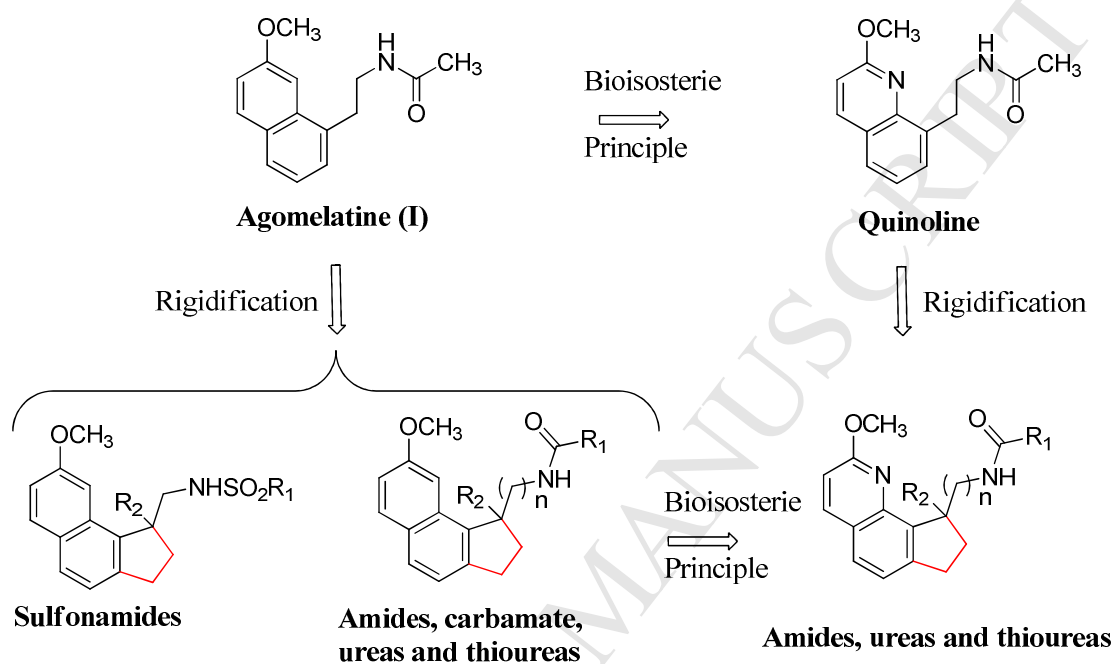
## 2.2. Pharmacology

*Biological Results.* Synthesized compounds were assayed at human MT<sub>1</sub> and MT<sub>2</sub> receptors stably transfected in Chinese Hamster Ovarian (CHO) cells, using 2-[<sup>125</sup>I]iodomelatonin as radioligand [26]. Serotonergic 5-HT<sub>2C</sub> binding affinity was performed using Chinese Hamster Ovarian (CHO) cell lines stably expressing the human 5-HT<sub>2C</sub> 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 MT<sub>1</sub>/MT<sub>2</sub> and serotonin 5-HT<sub>2C</sub> 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 MT<sub>1</sub> and MT<sub>2</sub> in comparison with agomelatine [20]. The same effect was actually observed with synthesized acetamide **17a**, however this modulation exhibited a noticeable improvement of the serotonergic 5-HT<sub>2C</sub> 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**



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<sub>1</sub>, MT<sub>2</sub> and 5-HT<sub>2C</sub>. The obtained results are shown in Table 1 and reveal that these modulations had no or a slight effect at both MT<sub>1</sub> and MT<sub>2</sub> 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<sub>1</sub> affinity and one log at MT<sub>2</sub>, showing a slight MT<sub>2</sub> 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<sub>2C</sub>. 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<sub>2C</sub> 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<sub>1</sub> and MT<sub>2</sub> and a loss of the serotonergic 5-HT<sub>2C</sub> 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 melatonergic binding affinity to **17a** with a very slight decrease at the at 5-HT<sub>2C</sub> binding affinity is observed. Instead, **25a** showed an increase in MT<sub>2</sub> binding affinity and a decrease towards 5-HT<sub>2C</sub> compared to its quinolic analogue (**18a**). Moreover, a pronounced decrease in both MT<sub>1</sub> and 5-HT<sub>2C</sub> receptors is observed comparing **25a** and its inferior homologue (**24a**).

**Table 1.** MT<sub>1</sub> and MT<sub>2</sub> binding affinity data of synthesized analogues of melatonin

Compound	K <sub>i</sub> (nM) [I95 ] (n)			
	h-MT <sub>1</sub>	h-MT <sub>2</sub>	h-5HT <sub>2c</sub>	
<b>Ag (I)</b>	0.1 [0.1; 0.1] (2)	0.2 [0.1; 0.6] (2)	708[46; 895] (2)	
<b>17a</b>	0.3 [0.2 ; 1.3] (2)	0.2 [0.02; 0.6] (2)	61 [35 ; 129] (2)	
<b>Amides</b>	<b>18a</b>	4 [3.0 ; 5.2] (2)	2 [0.9; 2.1] (2)	180 [102 ; 335] (2)
	<b>19a</b>	0.1 [0.07 ; 0.7] (2)	0.1 [0.05; 0.7] (2)	>10000
	<b>17b</b>	0.6 [0.4 ; 1.1] (2)	0.1 [0.07; 0.3] (2)	200 [123 ; 302] (2)
	<b>24a</b>	0.4 [0.2 ; 0.8] (2)	0.2 [0.1; 0.4] (2)	160 [125 ; 212] (2)

	<b>25a</b>	5 [4.3 ; 6.2] (2)	0.8 [0.65; 1.1] (2)	1600
<b>Carbamate</b>	<b>17c</b>	2 [0.9 ; 2.3] (2)	0.4 [0.1; 0.7] (2)	100 [83 ; 133] (2)
<b>Sulfon-</b>	<b>17d</b>	0.8 [0.2 ; 1.3] (2)	0.1 [0.07; 0.4] (2)	580 [437 ; 723] (2)
<b>amides</b>	<b>19b</b>	0.6 [0.3 ; 1.1] (2)	0.2 [0.09; 0.4] (2)	>10000
	<b>17e</b>	7 [4.3 ; 9.2] (2)	0.4 [0.1; 0.6] (2)	400 [277 ; 578] (2)
	<b>17f</b>	0.3 [0.1 ; 0.5] (2)	0.1 [0.08; 0.4] (2)	145 [97 ; 223] (2)
	<b>17g</b>	0.6 [0.5 ; 0.8] (2)	0.2 [0.07; 0.5] (2)	170 [135 ; 217] (2)
	<b>(+)-17g</b>	32 [28 ; 41] (2)	970 [734; 1120] (2)	>10000
	<b>(-)-17g</b>	0.4 [0.1 ; 0.9] (2)	0.07 [0.02; 0.1] (2)	15 [7 ; 26] (2)
<b>Ureas</b>	<b>17h</b>	2 [1 ; 2.7] (2)	0.1 [0.07; 0.3] (2)	60 [53; 69] (2)
	<b>17i</b>	5 [3.5 ; 6.2] (2)	0.2 [0.1; 0.5] (2)	190 [123 ; 218] (2)
	<b>19c</b>	0.8 [0.6 ; 1.3] (2)	0.3 [0.1; 0.5] (2)	>10000
	<b>19d</b>	2 [1.1 ; 3.7] (2)	0.2 [0.09; 0.4] (2)	>10000
	<b>24b</b>	1 [0.7 ; 1.6] (2)	0.2 [0.11; 0.3] (2)	340 [297 ; 394] (2)
	<b>24c</b>	7 [5.2 ; 9.3] (2)	0.4 [0.2; 0.7] (2)	285 [207 ; 410] (2)
	<b>17j</b>	6 [4.7 ; 8.3] (2)	0.4 [0.1; 0.9] (2)	72 [43 ; 117] (2)
	<b>17k</b>	4 [2.7 ; 7.1] (2)	0.3 [0.1; 0.7] (2)	30 [18 ; 54] (2)
	<b>(+)-17k</b>	99 [43 ; 127] (2)	9 [2; 14] (2)	>10000
<b>Thioureas</b>	<b>(-)-17k</b>	3 [1.6 ; 4.2] (2)	0.1 [0.08; 0.17] (2)	9 [3 ; 11] (2)
	<b>17l</b>	29 [15 ; 47] (2)	2 [1.1; 3.1] (2)	8 [3 ; 16] (2)
	<b>17m</b>	63 [48 ; 79] (2)	3 [1.6; 5.1] (2)	42 [23 ; 75] (2)
	<b>19e</b>	1 [0.3 ; 2.5] (2)	0.2 [0.1; 0.4] (2)	>10000
	<b>19f</b>	4 [2.1 ; 6.2] (2)	3 [1.3; 5.7] (2)	>10000
	<b>19g</b>	9 [6.2 ; 13] (2)	0.3 [0.1; 0.7] (2)	>10000

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 melatonergic and serotonergic 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 melatonergic MT<sub>1</sub>, MT<sub>2</sub> and serotonergic 5-HT<sub>2C</sub> receptors is



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<sub>1</sub> and MT<sub>2</sub> receptors was performed and the results are depicted in Table 2. In general, two intrinsic activity profiles were observed. A first group with MT<sub>1</sub>/MT<sub>2</sub> partial agonist/full agonist profile including compounds **17a**, **17b**, **17h**, **17g**, **17i**, **17k**, **19c**, **19d** and (-)-**17g**. A second group with an MT<sub>1</sub>/MT<sub>2</sub> 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<sub>2C</sub> showed an antagonist activity profile (data not shown).

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

Cpd.	<i>h</i> -MT <sub>1</sub>		<i>h</i> -MT <sub>2</sub>	
	EC <sub>50</sub> (nM) [I95] (n)	E <sub>max</sub> (%) ± <i>ESM</i> (n)	EC <sub>50</sub> (nM) [I95] (n)	E <sub>max</sub> (%) ± <i>ESM</i> (n)
<b>I</b>	1.4 [0.7;2.5] (4)	99 ± 6 (4)	0.18 [0.1;0.39] (3)	91 ± 7 (3)
<b>17a</b>	0.9 [0.9;2.4] (2)	78 ± 1 (2)	0.2 [0.1;0.5] (2)	118 ± 37 (2)
<b>19a</b>	0.2 [0.1;0.4] (2)	79 ± 3 (2)	0.2 [0.09;0.42] (2)	87 ± 3 (2)
<b>17b</b>	5 [3.1;6.4] (2)	81 ± 3 (2)	0.4 [0.1;0.8] (2)	99 ± 2 (2)
<b>24a</b>	0.05 [0.02;0.08] (2)	53 ± 4 (2)	-	-
<b>17d</b>	4 [2.2;6.8] (2)	30 ± 1 (2)	1 [0.4;2.8] (2)	63 ± 2 (2)
<b>17e</b>	10000	-	1000	-
<b>17c</b>	-	-	5 [2.3;7.9] (2)	71 ± 2 (2)
<b>17f</b>	2 [0.7;4.1] (2)	53 ± 3 (2)	0.9 [0.5;1.8] (2)	56 ± 1 (2)
<b>17g</b>	5 [2.9;8.4] (2)	66 ± 4 (2)	3 [1.7;5.4] (2)	95 ± 5 (2)
(-)- <b>17g</b>	3 [1.7;4.4] (2)	51 ± 5 (2)	0.6 [0.4;0.7] (2)	133 ± 21 (2)
<b>17h</b>	20 [14;27] (2)	64 ± 2 (2)	3 [1.7;4.3] (2)	103 ± 2 (2)
<b>19c</b>	5 [2.3;9.1] (2)	66 ± 3 (2)	0.3 [0.1;0.6] (2)	109 ± 4 (2)
<b>17i</b>	30 [13;68] (2)	76 ± 6 (2)	20 [10;50] (2)	96 ± 10 (2)

<b>19d</b>	9 [5.3;11.7] (2)	74 ± 1 (2)	0.7 [0.4;1.1] (2)	116 ± 2 (2)
<b>24b</b>	0.2 [0.08;0.5] (2)	42 ± 4 (2)	-	-
<b>24c</b>	0.9 [0.7;1.4] (2)	35 ± 1 (2)	-	-
<b>17j</b>	16 [0.9;2.4] (2)	32 ± 3 (2)	5 [2.9;6.2] (2)	39 ± 3 (2)
<b>17k</b>	8 [6.3;10.5] (2)	52 ± 4 (2)	6 [4.3;8.8] (2)	98 ± 2 (2)
<b>(-)-17k</b>	10 [7.2;13.7] (2)	63 ± 2 (2)	-	-
<b>19e</b>	6 [3.4;9.2] (2)	44 ± 1 (2)	3 [1.4;5.2] (2)	84 ± 5 (2)
<b>17l</b>	70 [63;79] (2)	38 ± 6 (2)	50 [37;67] (2)	67 ± 2 (2)
<b>19f</b>	10 [7.1;14.3] (2)	47 ± 2 (2)	2 [1.3;3.1] (2)	64 ± 1 (2)
<b>17m</b>	20 [15;36] (3)	40 ± 12 (3)	>10000	ND
<b>19g</b>	100 [83;119] (2)	50 ± 1 (2)	4 [2.6;6.3] (2)	83 ± 3 (2)

EC<sub>50</sub> 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<sub>2C</sub> 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<sub>1</sub>, MT<sub>2</sub>)/5HT<sub>2C</sub> 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<sup>®</sup> Sil 60/UV<sub>254</sub> 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 <sup>1</sup>H and 75 MHz for <sup>13</sup>C). Chemical shifts are expressed in ppm relative to either tetramethylsilane (TMS). Chemical shifts are reported as position ( $\delta$  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  $\times$  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 MgSO<sub>4</sub>, filtered and concentrated under vacuum. The product was obtained quantitatively without further purification as a yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 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<sup>+</sup>).

#### 4.3. Ethyl (E)-3-(7-methoxynaphthalen-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 MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/ EtOAc: 7/3) to give **4** (77%) as a white solid; mp 90-92 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 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 ( $\nu$ , cm<sup>-1</sup>): 1705 (CO); LC-MS:  $m/z = 257$  (MH<sup>+</sup>).

#### 4.4. Ethyl 3-(7-methoxynaphthalen-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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 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 ( $\nu$ , cm<sup>-1</sup>): 1720 (CO); LC-MS:  $m/z = 259$  (MH<sup>+</sup>).

#### 4.5. 3-(7-Methoxynaphthalen-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<sub>4</sub>, 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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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 (ν, cm<sup>-1</sup>): 2833 (OH), 1694 (CO); LC-MS: *m/z* = 231 (MH<sup>+</sup>).

#### 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<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was recrystallized from acetonitrile to afford **10** (70%) as a white solid; mp 122-124 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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 (ν, cm<sup>-1</sup>): 1681 (CO); LC-MS: *m/z* = 213 (MH<sup>+</sup>).

#### 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<sub>3</sub> was added. Extraction was realized with methylene chloride and the organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered and concentrated under *vacuum*. The residue was purified by column chromatography (SiO<sub>2</sub>, 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; <sup>1</sup>H

NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 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<sup>-1</sup>): 2230 (CN); LC-MS:  $m/z$  = 312 (MH<sup>+</sup>).

*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<sub>4</sub>, filtered and concentrated under *vacuum*. The residue was recrystallized from toluene to afford **12** (83%) as a white solid; mp 111-112 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 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<sup>-1</sup>): 2229 (CN); LC-MS:  $m/z$  = 222 (MH<sup>+</sup>).

#### 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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 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<sup>-1</sup>): 2227 (CN); LC-MS:  $m/z$  = 224 (MH<sup>+</sup>).

#### 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  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ( $\text{SiO}_2$ , cyclohexane/EtOAc: 5/5) and recrystallized from cyclohexane to afford **14** (91%) as a white solid; mp 95-97 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 2231 (CN); LC-MS:  $m/z = 238$  ( $\text{MH}^+$ ).

#### 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 ylide 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  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Recrystallization from toluene afford **15** (50%) as a white solid; mp 135-137 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 2228 (CN); LC-MS:  $m/z = 236$  ( $\text{MH}^+$ ).

#### 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);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 2241 (CN); LC-MS:  $m/z = 238$  ( $\text{MH}^+$ ).

4.12. *8-Methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methylamine hydrochloride (17).*

An NH<sub>3</sub>-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<sub>4</sub> and treated with gaseous HCl. The obtained solid was filtered to give **17** (79%) as a white solid; mp 247-248 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.42 (br s, 3H), 7.82 (d, 1H, 9.0 Hz), 7.70 (d, 1H, 8.20 Hz), 7.25 (d, 1H, 8.20 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 (ν, cm<sup>-1</sup>): 3200-2800 (NH<sub>3</sub><sup>+</sup>Cl<sup>-</sup>); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ : 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<sup>+</sup>).

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**; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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<sup>+</sup>).

4.14. *(8-Methoxy-1-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methylamine (19).*

Amine **19** was obtained from **14** in 93% yield as described for compound **17**; mp 70-72 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3290 (NH<sub>2</sub>); LC-MS: *m/z* = 242 (MH<sup>+</sup>).

4.15. *(E)-Ethyl-3-(2-methoxyquinolin-7-yl)prop-2-enoate (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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ : 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ : 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 (ν, cm<sup>-1</sup>) : 1700 (C=O); LC-MS : *m/z* = 258 (MH<sup>+</sup>).

#### 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<sub>2</sub>Cl<sub>2</sub>: 9/1) to afford **7** (80%) as a white solid; mp 91-93 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 1715 (CO); LC-MS: *m/z* = 260 (MH<sup>+</sup>).

#### 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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 10.3 (br s, 1H), 7.95 (d, 1H, 9.0 Hz), 7.72 (d, 1H, 2.4 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 1695 (C=O); LC-MS : *m/z* = 232 (MH<sup>+</sup>).

#### 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 MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc: 7/3) to give **11** (84%) as a white solid; mp 155-157 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 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 (ν, cm<sup>-1</sup>): 1645 (C=O); LC-MS: *m/z* = 214 (MH<sup>+</sup>).

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 ylide 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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 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 (ν, cm<sup>-1</sup>): 2225 (CN); LC-MS: *m/z* = 239 (MH<sup>+</sup>).

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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 1680 (C=O); LC-MS: *m/z* = 258 (MH<sup>+</sup>).

4.21. (2-Methoxy-8,9-dihydro-7H-cyclopenta[h]quinolin-9-yl)methylamine hydrochloride (**24**).

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<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water, dried over MgSO<sub>4</sub>, 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<sub>4</sub>, filtered and treated with gaseous HCl. The obtained solid was filtered to give **24** (66%) as a white solid; mp 218-220 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3210-2800 ( $\text{NH}_3^+\text{Cl}^-$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 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 :  $m/z = 229$  ( $\text{MH}^+$ ).

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

To a suspension of  $\text{LiAlH}_4$  (0.38 g, 10 mmol) in  $\text{Et}_2\text{O}$  (10 mL) at 0 °C was added a solution of  $\text{AlCl}_3$  (1.33 g, 10 mmol) in  $\text{Et}_2\text{O}$  (10 mL). After 5 min stirring, a solution of **21** (0.6 g, 2.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{Et}_2\text{O}$ . The filtrate was washed with water, dried over  $\text{MgSO}_4$  and treated with gaseous HCl. The obtained solid was filtered to give **25** (90%) as a white solid; mp 228-229 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}-d_6$ )  $\delta$ : 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 (br s, 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3200-2820 ( $\text{NH}_3^+\text{Cl}^-$ ); LC-MS :  $m/z = 243$  ( $\text{MH}^+$ ).

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  $\text{EtOAc}$  (30 mL) and water (10 mL) were added  $\text{K}_2\text{CO}_3$  (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  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure.

4.24. *N*-[(8-Methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]acetamide (**17a**).

The crude product was recrystallized from toluene to afford **17a** (86%) as a white solid; mp 130-132 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3284 (NH), 1639 (C=O); MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 270.15. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>17</sub>H<sub>20</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 270.14886 found: 270.14868.

4.25. *N*-[2-(8-Methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)ethyl]acetamide (**18a**).

The crude product was recrystallized from toluene to afford **18a** (76%) as a white solid; mp 141-142 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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]<sup>+</sup>, 284.34. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>18</sub>H<sub>22</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 284.16092 found: 284.16034.

4.26. *N*-[(8-Methoxy-1-methyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]acetamide (**19a**).

The crude product was recrystallized from cyclohexane to afford **19a** (80%) as a white solid; mp 84-86 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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);  $^{13}\text{C}$  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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3251 (NH), 1624 (C=O); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 284.25. HRMS (ESI $^+$ ):  $m/z$  = calcd. for  $\text{C}_{18}\text{H}_{22}\text{NO}_2$   $[\text{M}+\text{H}]^+$  284.12337 found: 284.12259.

4.27. *N*-[(2-Methoxy-8,9-dihydro-7H-cyclopenta[*h*]quinolin-9-yl)methyl]acetamide (**24a**).

The crude product was recrystallized from toluene to afford **24a** (85%) as a white solid; mp 110-111 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3290 (NH), 1626 (C=O); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 271.26. HRMS (ESI $^+$ ):  $m/z$  = calcd. for  $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  271.1441 found: 271.14364.

4.28. *N*-[2-(2-Methoxy-8,9-dihydro-7H-cyclopenta[*h*]quinolin-9-yl)ethyl]acetamide (**25a**).

The crude product was recrystallized from toluene to afford **25a** (84%) as a white solid; mp 119-120 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3285 (NH), 1628 (C=O); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 285.24. HRMS (ESI $^+$ ):  $m/z$  = calcd. for  $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  285.15975 found: 285.15932.

4.29. *2-Methoxy-N*-[(8-methoxy-2,3-dihydro-1H-cyclopenta[*a*]naphthalen-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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3318 (NH), 1635 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]<sup>+</sup>, 300.24. HRMS (ESI<sup>+</sup>): m/z = calcd. for C<sub>18</sub>H<sub>22</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 300.15214 found: 300.15259.

4.30. *Methyl-N-[(8-methoxy-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methyl] carbamate (17c).*

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; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3296 (NH), 1722 (C=O); MS (APCI, pos. 30 V) m/z: [M+H]<sup>+</sup>, 286.24. HRMS (ESI<sup>+</sup>): m/z = calcd. for C<sub>17</sub>H<sub>20</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 286.12337 found: 286.12359.

4.31. *General procedure for synthesis of sulfonamide 17d-e and 19b.*

To a solution of corresponding amine **17** or **19** (404 mg, 2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub>, filtered and concentrated under reduced pressure.

4.32. *N*-[(8-Methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]methansulfonamide (**17d**).

The crude product was treated with diisopropyl ether and recrystallized from cyclohexane to afford **17d** (70%) as a white solid; mp 110-112 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3294 (NH); LC-MS : *m/z* = 306 (MH<sup>+</sup>). MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 306.27. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>16</sub>H<sub>20</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> 306.14312 found: 306.14372.

4.33. *N*-[(8-Methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]ethansulfonamide (**17e**).

The crude product was recrystallized from cyclohexane to afford **17e** (70%) as a white solid; mp 109-110 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3298 (NH); MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 320.27. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>17</sub>H<sub>22</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> 320.15232 found: 320.15254.

4.34. *N*-[(8-Methoxy-1-methyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]methane sulfonamide (**19b**).



The crude product was recrystallized from cyclohexane to afford **19b** (50%) as a white solid; mp 98-100 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3297 (NH); MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 320.24. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>17</sub>H<sub>22</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> 320.12328 found: 320.12247.

4.35. *N*<sup>1</sup>-[(8-Methoxy-2,3-dihydro-1*H*-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; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 7.79 (d, 1H, 8.97 Hz), 7.64 (d, 1H, 8.20 Hz), 7.56 (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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3425 (NH<sub>2</sub>), 3340 (NH), 1625 (C=O); MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 271.23. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 271.12418 found: 271.12357.

4.36. *N*<sup>1</sup>-[(8-Methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]-*N*<sup>3</sup>-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 MgSO<sub>4</sub>, 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; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 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 (ν, cm<sup>-1</sup>): 3333 (NH), 1624 (C=O); LC-MS : *m/z* = 285 (MH<sup>+</sup>). MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 285.23. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 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 CH<sub>2</sub>Cl<sub>2</sub> (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. CH<sub>2</sub>Cl<sub>2</sub> was added and the organic layer was washed with a 1 M solution of HCl and water, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure.

**4.38. N<sup>1</sup>-Ethyl-N<sup>3</sup>-[(8-methoxy-2,3-dihydro-1H-cyclopenta[*a*]naphthalen-1-yl)methyl]urea (**17h**).**

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; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3317 (NH), 1622 (C=O); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 300.21. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  300.16812 found: 300.16734.

4.39. *N*<sup>1</sup>-[(8-Methoxy-2,3-dihydro-1H-cyclopenta[*a*]naphthalen-1-yl)methyl]-*N*<sup>3</sup>-propylurea (**17i**).

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; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ) : 3294 (NH), 1623 (C=O); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 313.25. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for  $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  313.18377 found: 313.18334.

4.40. *N*<sup>1</sup>-Ethyl-*N*<sup>3</sup>-[(8-methoxy-1-methyl-2,3-dihydro-1H-cyclopenta[*a*]naphthalen-1-yl)methyl]urea (**19c**).

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; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 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, 5.4 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3279 (NH),

1623 (C=O); MS (APCI, pos. 30 V)  $m/z$ :  $[M+H]^+$ , 313.26. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>  $[M+H]^+$  313.18377 found: 313.18344.

4.41. *N*<sup>1</sup>-[(8-Methoxy-1-methyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]-*N*<sup>3</sup>propylurea (**19d**).

The crude product was recrystallized from toluene to afford **19d** (70%) as a white solid; mp 115-117 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) 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, 5.7 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3313 (NH), 1624 (C=O); LC-MS :  $m/z$  = 327 (MH<sup>+</sup>). MS (APCI, pos. 30 V)  $m/z$ :  $[M+H]^+$ , 327.26. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>  $[M+H]^+$  327.19942 found: 327.19834.

4.42. *N*<sup>1</sup>-[(8-methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]-*N*<sup>3</sup>-methyl-thio-urea (**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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.75 (d, 1H, 9.0 Hz), 7.65 (d, 1H, 8.1 Hz), 7.48 (s, 1H), 7.26 (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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3392 (NH), 1213 (C=S); MS (APCI, pos. 30 V)  $m/z$ :  $[M+H]^+$ , 301.26. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>OS  $[M+H]^+$  301.13691 found: 301.13648.

4.43. *N*<sup>1</sup>-Ethyl-*N*<sup>3</sup>-[(8-methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]thiourea (**17l**).

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; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3245 (NH), 1213 (C=S); MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 315.22. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>18</sub>H<sub>23</sub>N<sub>2</sub>OS [M+H]<sup>+</sup> 315.19942 found: 315.19834.

4.44. *N*<sup>1</sup>-[(8-Methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]-*N*<sup>3</sup>-propylthiourea (**17m**).

The crude product was recrystallized from toluene to afford **17m** (56%) as a white solid; mp 137-139 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ: 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, 45.6, 44.0, 31.4, 28.8, 22.5, 11.9; IR (ν, cm<sup>-1</sup>): 3295 (NH), 1213 (C=S); MS (APCI, pos. 30 V) *m/z*: [M+H]<sup>+</sup>, 329.22. HRMS (ESI<sup>+</sup>): *m/z* = calcd. for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>OS [M+H]<sup>+</sup> 329.16092 found: 329.16034.

4.45. *N*<sup>1</sup>-Methyl-*N*<sup>3</sup>-[(8-methoxy-1-methyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)methyl]thiourea (**19e**).

The crude product was recrystallized from toluene to afford **19e** (57%) as a white solid; mp 144-146 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ: 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);  $^{13}\text{C}$  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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3297 (NH), 1212 (C=S); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 315.23. HRMS (ESI $^+$ ):  $m/z$  = calcd. for  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{OS}$   $[\text{M}+\text{H}]^+$  315.14528 found: 315.14434.

4.46.  $N^1$ -Ethyl- $N^3$ -[(8-methoxy-1-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl)methyl]thiourea (**19f**).

The crude product was recrystallized from toluene to afford **19f** (51%) as a white solid; mp 125-127 °C;  $^1\text{H}$  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 (s, 3H), 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);  $^{13}\text{C}$  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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3294 (NH), 1223 (C=S); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 329.27. HRMS (ESI $^+$ ):  $m/z$  = calcd. for  $\text{C}_{19}\text{H}_{25}\text{N}_2\text{OS}$   $[\text{M}+\text{H}]^+$  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;  $^1\text{H}$  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 (s, 3H), 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 (s, 3H), 1.43 (m, 2H), 0.82 (t, 3H, 7.2 Hz);  $^{13}\text{C}$  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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3213 (NH), 1223 (C=S); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 342.32. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{OS}$   $[\text{M}+\text{H}]^+$  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  $\text{MgSO}_4$ , 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;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ , KBr): 3291 (NH), 1213 (C=S); MS (APCI, pos. 30 V)  $m/z$ :  $[\text{M}+\text{H}]^+$ , 287.22. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for  $\text{C}_{16}\text{H}_{19}\text{N}_2\text{OS}$   $[\text{M}+\text{H}]^+$  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;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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 ( $\nu$ ,  $\text{cm}^{-1}$ ): 3290 (NH), 1626 (C=O); MS (APCI, pos. 30

V)  $m/z$ :  $[M+H]^+$ , 286.25. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for C<sub>16</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub>  $[M+H]^+$  286.155 found: 286.15461.

4.50. *N*<sup>1</sup>-[(2-Methoxy-8,9-dihydro-7H-cyclopenta[*h*]quinolin-9-yl)methyl]-*N*<sup>3</sup>-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; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 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 (ν, cm<sup>-1</sup>): 3325 (NH), 1613 (C=O); MS (APCI, pos. 30 V)  $m/z$ :  $[M+H]^+$ , 314.35. HRMS (ESI<sup>+</sup>):  $m/z$  = calcd. for C<sub>18</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>  $[M+H]^+$  313.17902 found 313.17743.

## 5. Pharmacological methods

### 5.1. Reagents and Chemicals.

2-[<sup>125</sup>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<sub>1</sub> or MT<sub>2</sub> receptors were grown in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/mL penicillin and 100 µg/ml streptomycin. Grown at confluence at 37 °C (95%O<sub>2</sub>/5%CO<sub>2</sub>), 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 MgCl<sub>2</sub> and 2 mM EDTA. Aliquots of membrane preparations were stored at -80 °C until use.

### 5.3. Binding Assays.

2-[<sup>125</sup>I]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 MgCl<sub>2</sub>) to 2-[<sup>125</sup>I]-iodomelatonin (25 or 200 pM for MT<sub>1</sub> and MT<sub>2</sub> receptors, respectively, expressed in HEK cells or 20 pM for MT<sub>1</sub> and MT<sub>2</sub> 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 IC<sub>50</sub> (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<sub>D</sub>, the dissociation constant of the radioligand characterising the membrane preparation [28].

[<sup>35</sup>S] GTPγS binding assay was performed according to published methodology [27]. Briefly, membranes from transfected CHO cells expressing MT<sub>1</sub> or MT<sub>2</sub> receptor subtype and compounds were diluted in binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 3 μM GDP, 3 mM MgCl<sub>2</sub>, and 20 μg/mL saponin). Incubation was started by the addition of 0.2 nM [<sup>35</sup>S]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 [<sup>35</sup>S]GTPγS. Non

specific binding was defined using cold GTP $\gamma$ S (10  $\mu$ M). Reaction was stopped by rapid filtration through GF/B filters followed by three successive washes with ice cold buffer.

Usual levels of [ $^{35}$ S]GTP $\gamma$ S binding (expressed in dpm) were for CHO-MT $_1$  or MT $_2$  membranes: 2000 for basal activity, 8000 in the presence of melatonin 1  $\mu$ M and 180 in the presence of GTP $\gamma$ S 10  $\mu$ M 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 EC $_{50}$  (Effective concentration 50 %) and E $_{max}$  (maximal effect) for agonists. Antagonist potencies are expressed as  $K_B = IC_{50} / 1 + ([Ago]/EC_{50} ago)$ , where IC $_{50}$  is the inhibitory concentration of antagonist that gives 50% inhibition of [ $^{35}$ S] GTP $\gamma$ S binding in the presence of a fixed concentration of melatonin ([Ago]) and EC $_{50} ago$  is the EC $_{50}$  of the molecule when tested alone. I $_{max}$  (maximal inhibitory effect) was expressed as a percentage of that observed with melatonin at 3 nM for MT $_2$  receptor.

Serotonin 5-HT $_{2C}$  binding assay was determined according to reported tests [29]. First incubation of 200  $\mu$ l solution from membrane CHO cell lines, stably expressing the human 5-HT $_{2C}$  receptors, for 60 min at 37  $^{\circ}$ C in binding buffer (50 mM Tris-HCl buffer, pH 7.4, containing 10 mM MgCl $_2$  and 0.1% BSA) containing the radioligand [ $^3$ H]-mesulergine (1 nM). Non-specific binding was defined in the presence of 10  $\mu$ M 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). IC $_{50}$  was determined from dose-response curves and results are expressed as  $K_i = IC_{50} / 1 + ([L]/KD)$ , 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<sub>2C</sub> receptors
- Naphthocyclopentane derivative **17a** was considered as the lead
- (-)-**17k** represents one of the highest dual MT and 5HT<sub>2C</sub> derivative