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Synthesis and SAR studies of novel isoquinoline and tetrahydroisoquinoline derivatives as melatonin receptor ligands

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Abstract: In our constant search for new successors of agomelatine, we report herein another new series of compounds resulting from bioisosteric modulation of the naphthalene ring. New isoquinoline and tetrahydroisoquinoline derivatives were synthesized and pharmacologically evaluated. This isosteric replacement of the naphthalene group of agomelatine has led to potent agonist and partial agonist compounds with nanomolar melatonergic binding affinities. Overall, the presence of a nitrogen atom was accompanied with a decrease in the binding affinity towards both MT₁ and MT₂ and the loss of 5HT_{2C} response, especially for tetrahydroisoquinoline in comparison with the parent compound. Interestingly, due to the presence of this nitrogen atom, a noticeable improvement in the pharmacokinetic properties was observed for all compounds.

Introduction

Due to their physicochemical properties, heteroatoms are keystones in biologically active molecules. Accordingly, more than 85% of biologically active molecules are heterocycle-based entities and more than 75% of the approved drugs by the FDA are nitrogen-based moieties.^[1-2]

In particular, nitrogen-based heterocycles including isoquinoline, a naphthalene bioisoster,

and tetrahydroisoquinoline scaffolds are considered as privileged structures because of their presence in a number of biologically-active chemical entities and drugs.^[2-3] In this sense, isoquinoline alkaloids is the largest group of natural products among alkaloids. Nowadays, almost 2500 isoquinoline alkaloids originated from plants are reported and mostly used for their sedative, analgesic, psychotropic or antispasmodic effects.^[4-5] Moreover, isoquinoline nucleus is increasingly considered as a privileged structure and frequently used in contemporary medicinal chemistry.

In general, conjugated *N*-heterocyclic bases including isoquinoline are very common in nature

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and thanks to their electronic and physicochemical properties they exhibit a strong bioactive effect.^[6-7] Importantly, their basicity is crucial for hydrogen bonding interactions and solubility which lead to the optimization of the ADMET properties of drug candidates.^[7-8] Moreover, due to the advances in synthetic organic methodologies, the rapid access to a wide range of functionalized isoquinolines will expand the druggability of such heterocycles and boost drug discovery programs. For instance, isoquinolines were reported to possess anti-tumor and antiproliferative properties,^[9-10] antimalarial, antibacterial, antifungal, antipsychotic and antidepressant activities.^[11-12] Moreover, several isoquinoline derivatives were found to exhibit anti-oxidant, anti-inflammatory, analgesic and antihypertensive activities.^[13] Additionally, with the rise of neuropsychiatric and neurodegenerative diseases and the related difficulty of passing the hemato-encephalic barrier, access to such a modifiable class of molecules is of utmost importance for the medicinal chemistry community.^[14]

In the central nervous system serotonin and melatonin, two endogenous N-heterocyclic moieties

are well known and studied. Serotonin is a neurotransmitter that is involved in several neuropsychiatric disorders. Melatonin, a neurohormone mainly synthesized by the pineal gland,^[15] is involved in the regulation of number of physiological processes through the activation of its two G protein coupled receptors (GPCRs) class namely MT₁ and MT₂.^[16] This interesting profile of the melatonin system as potential drug target has led to the development of different drug discovery programs to investigate new therapeutic agents and tackle many CNS linked disorders including anxiety, depression, insomnia and sleep disorders. In this regard, different melatonin receptor ligands were developed and many of them put into the market including agomelatine (Valdoxan[®], Melitor[®], Thymanax[®]) and ramelteon (Rozerem[®]). Agomelatine (AGM), a high-affinity non-selective MT₁/MT₂ melatonin agonist and selective 5-HT_{2C} serotonin antagonist dual ligand, has shown a high profile in the treatment of depression with high efficacy on sleep and circadian rhythm disorders.^[17]

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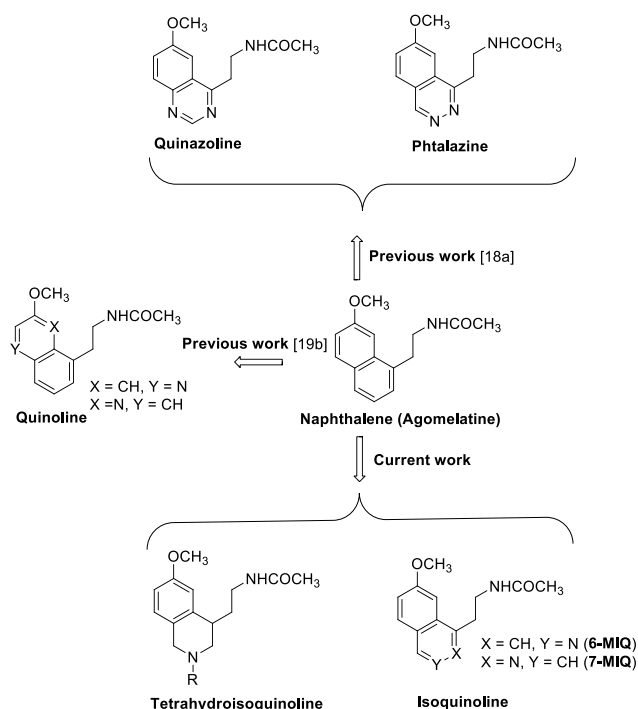


Figure 1. Aza-agomelatine analogues

For decades, our team was involved in the research and development of new melatonin ligands for the treatment of certain CNS disorders including depression, anxiety and insomnia. However, with the discovery of agomelatine the objective was refocused into the design and preparation of dual ligands, successors of the agomelatine, that act concurrently on the serotonin system by blocking its 5-HT_{2C} receptor subtype and activating melatonin system through targeting its MT₁ and MT₂ receptor subtypes. In this scope, several series of new ligands issued from the modulation of the naphthalene scaffold and specially its replacement by different heterocycles

were reported (Figure 1).^[18-19] In the light of the obtained results so far, we report in this paper the design and synthesis of a series of isoquinoline and tetrahydroisoquinoline compounds to explore the relationship between the structure of these ligands on the melatonergic and/or serotonergic binding affinities, and the effect on their pharmacokinetic properties (Figure 2). More importantly, our lab was recently involved in the determination of the crystal structures of the MT₁ and MT₂ receptor subtypes.^[20] This exciting news has given insights into understanding melatonergic ligands interactions with their receptors. Data from this co-crystallization was used herein to construct a 3D model to investigate the binding modes of the new synthesized ligands to the melatonin sites and hence help deciphering the structural component of our structure-activity-relationship (SAR).

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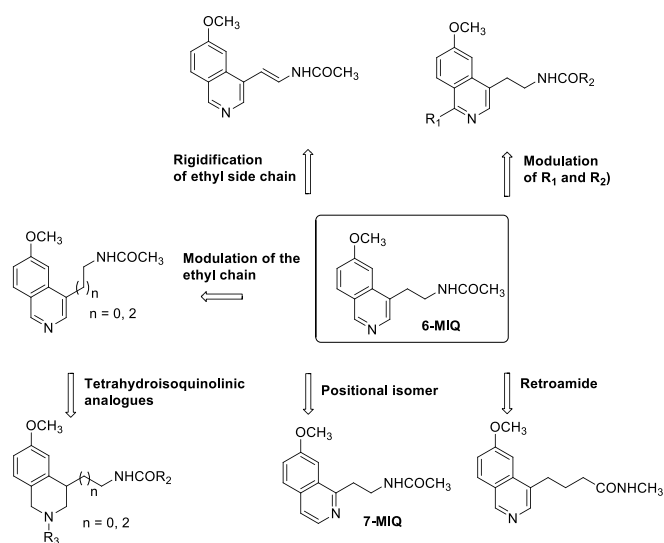


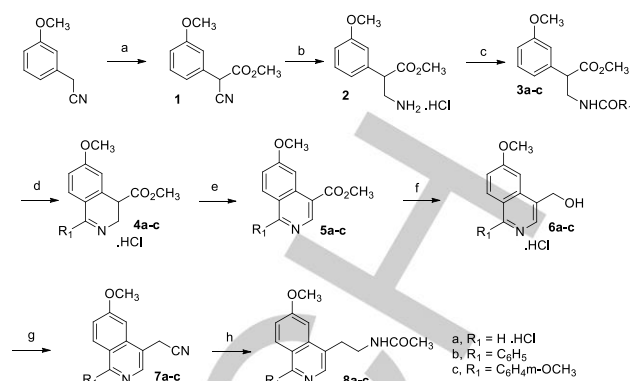
Figure 2. Modulation of isoquinoline analogues

Results and Discussion

Chemical synthesis of isoquinoline and tetrahydroisoquinoline derivatives

Syntheses of target compounds were carried out in the state-of-the-art of medicinal chemistry and outlined in Schemes 1-7. First, 6-methoxy-isoquinoline (6-MIQ) derivatives **8a-c** were prepared in eight steps starting from commercially available 3-methoxyphenyl-acetonitrile as depicted in Scheme 1. Treatment of starting material with dimethyl carbonate in dry THF and the presence of sodium hydride gave cyanoester **1**.^[21] Catalytic hydrogenation of ester **1** in the presence of platinum oxide led to intermediate **2**.^[22] The latter was then transformed into compound **3a** through formylation by reflux in ethyl formate, and into compounds **3b-c** via *N*-acylation in the presence of acyl chloride. Resulting β -arylethylamide **3a-c** were then subjected to a Bischler-Napieralski cyclization under POCl₃ in acetonitrile to produce dihydroisoquinoline precursor **4a-c**.^[23] Aromatization reaction of **4a-c** using Pd/C in dry toluene under reflux has led to isoquinolines **5a-c**.

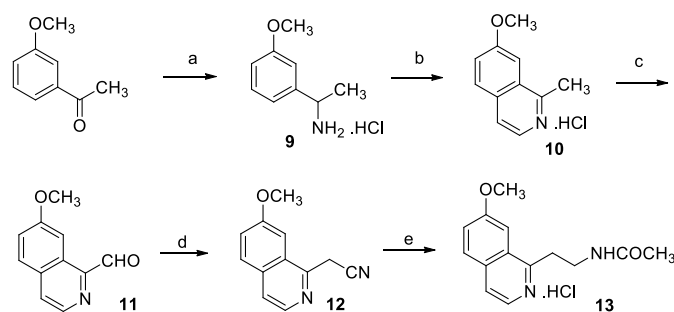
Scheme 1. Synthesis of acetamides **8a-c**.



^aReagents: a) (MeO)₂CO, NaH 60%, THF; b) H₂, PtO₂, CHCl₃/MeOH; c) HCO₂Et reflux for **3a** or R₁COCl, K₂CO₃, DCM/H₂O for compounds **3b-c**; d) POCl₃, MeCN, reflux; e) (i) K₂CO₃, H₂O, rt (ii) Pd/C, toluene, reflux; f) (i) LiAlH₄, THF, (ii) HCl/Et₂O; g) (i) SOCl₂, DCM, (ii) K₂CO₃, KCN, DCM/H₂O TBAB for **7a** or KCN, DMSO for **7b-c**; h) (i) (MeCO)₂O, Raney nickel, H₂, (ii) Pd/C, toluene, reflux.

Compounds **5a-c** were then chemically reduced into alcohols **6a-c** by treatment with lithium aluminum hydride in dry THF. Hydroxy groups of compounds **6a-c** were then activated by treatment with thionyl chloride in dichloromethane into corresponding chloride and then transformed into nitriles **7a-c** over nucleophilic substitution with potassium cyanide. Finally, catalytic hydrogenation of nitriles **7a-c** in acetic anhydride and Raney nickel furnished final acetamides **8a-c**. During the catalytic hydrogenation step, we observed a partial reduction of the isoquinoline cycle into dihydroisoquinoline. To overcome this issue, the obtained mixture was aromatized by reflux in toluene in the presence of Pd/C (Scheme 1).

Scheme 2. Synthesis of acetamide **13**.

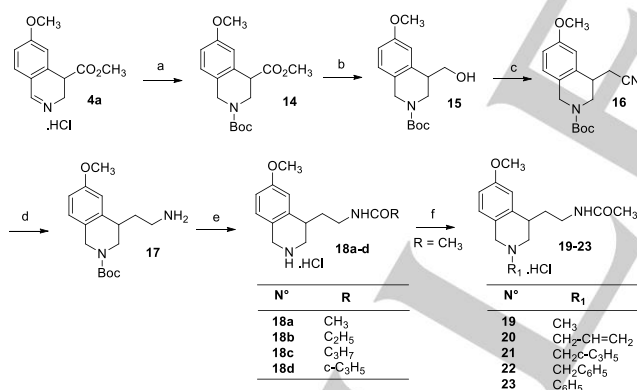


^aReagents: a) (i) NH₂OH.HCl, K₂CO₃, EtOH, (ii) H₂, NH₃(g), Raney nickel; b) (i) 2,2-dimethoxy acetaldehyde-solution 60% Wt. in H₂O, toluene, (ii) H₂SO₄, (iii) HCl(g), diethyl ether; c) SeO₂, 1,4-dioxane; d) (i) NaBH₄, EtOH, (ii) MeSO₂Cl, DCM, TEA, (iii) KCN, DCM, TBAB; e) (i) (MeCO)₂O, H₂, Raney nickel, (ii) Pd/C, toluene, reflux, (iii) HCl (g), diethyl ether.

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7-MIQ derivative **13** was prepared in five steps starting from commercially available 3-acetylanisole as illustrated in Scheme 2. First, starting material condensation with hydroxylamine hydrochloride led to the corresponding oxime. This latter was then reduced into corresponding amine **9** by catalytic hydrogenation in the presence Raney nickel. Submitted to a Pomeranz-Fritsch cyclization, derivative **9** gave isoquinoline **10** in 45% yield.^[24] Next, oxidation of methyl group of **10** by reaction with selenium dioxide in 1,4-dioxane furnished aldehyde **11** in a good yield (90%). The chemical reduction of the formyl group of **11** with sodium borohydride followed by the activation of the obtained primary alcohol into mesylate, and the transformation of this mesylate into nitrile, by treatment with potassium cyanide, led to the key acetonitrile **12** in 60% yield. Finally, catalytic hydrogenation, in acetic anhydride, over Raney nickel followed by reflux in toluene in the presence of Pd/C furnished the desired acetamide **13** in 50% yield (Scheme 2).

Scheme 3. Synthesis of *N*-substituted tetrahydroisoquinolines **18a-18d** and **19-23**.



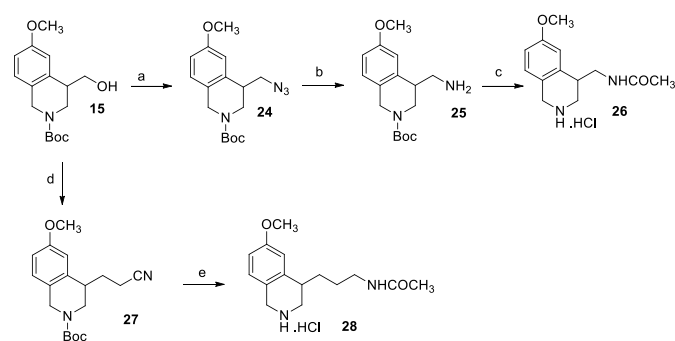
^aReagents: a) (i) H₂, Pd/C, MeOH, (ii) Boc₂O, TEA, DCM; b) LiAlH₄, anhydrous THF; c) (i) MeSO₂Cl, TEA, DCM, (ii) KCN, DMSO, 80 °C; d) H₂, Raney nickel, NH₃(g), MeOH; e) (i) RCOCI, K₂CO₃, ethyl acetate/H₂O, (ii) HCl, MeOH; f) HCO₂H, HCHO 37% for **19**, BrCH₂CH=CH₂, for **20**, BrCH₂C-C₃H₅ for **21**, BrCH₂C₆H₅ for **22** and Bi(C₆H₅)₃, Cu(AcO)₂ for **23**.

Synthetic pathway for tetrahydroquinoline derivatives **18a-d** and **19-23** using dihydroisoquinoline **4a** as starting material is outlined in Scheme 3. First, catalytic hydrogenation in methanol of the double bond in the presence of Pd/C followed by the protection of the amine moiety by *tert*-butyloxycarbonyl (Boc),

produced the key tetrahydroisoquinoline **14** in a good yield (95%). Chemical reduction of the ester group of this compound by treatment with lithium aluminum hydride gave primary alcohol **15**. This latter was then converted into acetonitrile **16** in two steps: first, activation of the hydroxy group into mesylate followed by cyanation using potassium cyanide in DMSO. Finally, key primary amine **17** was obtained in 80% yield by catalytic hydrogenation of acetonitrile **16** in the presence of Raney nickel in a solution of NH₃-saturated methanol (Scheme 3).

Final amides **18a-d** and **19-23** were first prepared by acylation of amine **17** by reaction with the corresponding acyl chloride in the presence of K₂CO₃, in a biphasic medium according to a variant of the Schotten-Baumann conditions.^[25] Then, deprotection of the tetrahydroisoquinoline moiety by treatment with a solution of hydrochloric acid in methanol. *N*-substituted acetamides **19-23** were prepared starting from tetrahydroisoquinoline **18a**. Hence, compound **19** was obtained in 30% yield through *N*-methylation of **18a** with formaldehyde in formic acid using Eschweiler-Clarke reaction.^[26] Next, compounds **20-22** were prepared by *N*-alkylation of **18a** with the adequate halogenated derivative in acetone in the presence of K₂CO₃. Finally, compound **23** was obtained in 75% yield by *N*-arylation of **18a** by reaction with triphenyl bismuth in the presence of copper acetate in dichloromethane.^[27]

Scheme 4. Synthesis of extended chain derivative **28**.

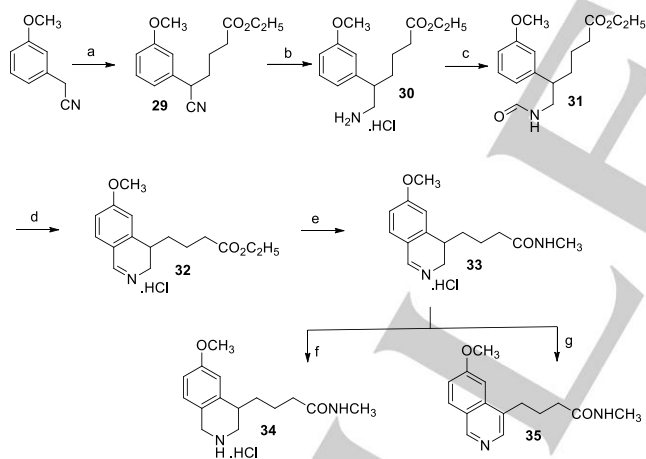


^aReagents: a) (i) MsCl, TEA, DCM, (ii) NaN₃, DMF; b) H₂, Pd/C, MeOH; c) (i) MeCOCl, K₂CO₃, DCM/H₂O, (ii) HCl (g), MeOH; d) (i) MsCl, TEA, DCM, (ii) Na, NCC₂CO₂Et, DMF, 100°C e) (i) (MeCO)₂O, H₂, Raney nickel, (ii) HCl, MeOH.

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Moreover, synthesis of amides **26** and **28**, analogues of compound **18a**, was carried out using key alcohol **15** as shown in Scheme 4. The hydroxy group of **15** was first converted into its corresponding azide **24** through a reaction of mesylation followed by nucleophilic substitution with sodium azide. The azide group was transformed into amine **25** via catalytic hydrogenation in methanol, and the obtained amine was *N*-acetylated by reaction with acetyl chloride. The cyclic *N*-Boc was then deprotected in methanol in the presence of hydrochloric acid leading to the desired acetamide **26**. The higher analogue of **18a** however was prepared in two steps. First, alcohol **15** was converted into its corresponding mesylate, substituted by sodium cyanoacetate and decarboxylated to lead to the key cyano-derivative **27**. A catalytic hydrogenation of **27** in the presence of Raney nickel and acetic anhydride, followed by deprotection of the Boc group in an acidic medium, has led to amide **28** (Scheme 4).

Scheme 5. Synthesis of retroamides **34** and **35**.

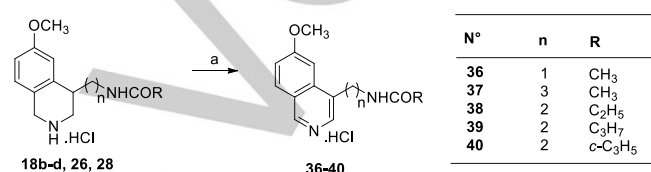


^aReagents: a) NaH, DMF, Br(CH₂)₃CO₂Et; b) H₂, PtO₂, CHCl₃/MeOH; c) (i) K₂CO₃, (ii) HCO₂Et reflux; d) POCl₃, MeCN; e) MeNH₂, 40Wt. % in H₂O, EtOH; f) (i) H₂, Pd/C, MeOH, (ii) HCl(g), MeOH; g) Pd/C, toluene, reflux.

Further, retroamides **34** and **35** were prepared starting from 3-methoxyphenyl-acetonitrile as described in Scheme 5. First, a *C*-alkylation of starting material with ethyl 4-bromobutyrate led to cyanoester **29**. Nitrile group of **29** was then catalytically reduced, in the presence of platinum oxide, into primary amine hydrochloride **30**. Next, reflux of **30** in methyl formate resulted into

β -arylethylamide **31** which was subjected to a Bischler-Napieralski cyclization in the presence of POCl₃ in toluene to afford the dihydroisoquinoline **32** in 54% yield. An acylation reaction of **32** using methylamine 40% in water/ethanol furnished amide **33**. Finally, a catalytic hydrogenation in methanol or a dehydrogenation at reflux in toluene of **33** in the presence of Pd/C gave access respectively to the final amides **34** and **35** in good yields (60% and 80% respectively).

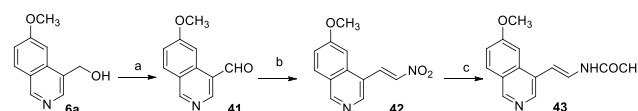
Scheme 6. Preparation of isoquinolines **36-40**.



^aReagents: a) K₂CO₃, Pd/C, toluene, reflux.

Ultimately, isoquinoline derivatives **36-40** were prepared from tetrahydroquinolines **18b-d**, **26** and **28** by dehydrogenation reaction using Pd/C in toluene under reflux. Besides, we report herein a second method for the preparation of acetamide **8a** from **18a** using this aromatization method (Scheme 6). Unsaturated compound **43** was obtained in three steps from alcohol **6a** previously prepared in Scheme 1. First, oxidation of **6a** in the presence of manganese (IV) in DMSO led to aldehyde **41**. Second, condensation of obtained aldehyde **41** with nitromethane following Henry's reaction led to nitro derivative **42** in 68% yield.^[28] Finally, in Scheme 7, selective reduction of nitro group with iron in a mixture of acetic acid/acetic anhydride furnished the desired acetamide **43** in a one-step reaction.^[29] *E/Z* stereochemistry ratio of **43** was not defined herein, and the compound was used in biological testing without any further resolution.

Scheme 7. Synthesis of unsaturated acetamide **43**.



^aReagents: a) MnO₂, DMSO; b) MeNO₂, NH₄OAc; c) Fe, Ac₂O, AcOH.

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Biological activity of isoquinoline and tetrahydroisoquinoline derivatives

Herein we present a new series of prepared azaheterocycle based compounds. Isoquinoline and tetrahydroisoquinoline heterocycles were chosen to improve the pharmacokinetic properties of the AGM. Therefore, prepared compounds were first submitted to binding affinity experiments to the serotonergic 5-HT_{2C} receptor subtype using Chinese Hamster Ovarian (CHO) cell lines stably expressing the human 5-HT_{2C} receptors. Second, binding assays for melatonin MT₁ and MT₂ receptor subtypes consisted of addition of membrane preparations from transfected CHO cells stably expressing the human melatonin MT₁ or MT₂ diluted in binding buffer (50mM Tris-HCl buffer, pH 7.4, containing 5mM MgCl₂) to 2-[¹²⁵I]iodomelatonin (20pM for MT₁ and MT₂ receptors expressed in CHO cells) and the tested compound. Non-specific binding was defined in the presence of 1μM melatonin, and data from the dose-response curves were analyzed using the program PRISM (Graph Pad Software Inc., San Diego, CA, USA) to yield IC₅₀. Results are expressed as pKi (pKi = -Log₁₀ (Ki)) with Ki = IC₅₀/1 + ([L]/KD), where [L] is the concentration of radioligand used in the assay and KD, the dissociation constant of the radioligand characterizing the membrane preparation.^[30] The biological obtained results are depicted in Tables 1-4.

Table 1. Melatonin MT₁/MT₂ binding affinities of isoquinolines.

Cpd	R ₁	R ₂	n	Ki(nM) [I95](n)	
				h-MT ₁	h-MT ₂
AGM	-	-	-	0.1 [0.1;0.1] (2)	0.2 [0.1;0.6] (2)
8a	H	CH ₃	2	22 [12;22] (2)	6 [2.1;5.1] (2)
13	-	-	-	30 [14;11] (2)	6.7 [0.5;0.9] (2)
8b	C ₆ H ₅	CH ₃	2	1520 [863;504] (2)	>10 ⁻⁵

8c	C ₆ H ₄ OCH ₃ (m)	CH ₃	2	>10 ⁻⁵	>10 ⁻⁵
35	-	-	-	3.8 [0.7;0.4] (2)	2.6 [0.5;0.3] (2)
36	H	CH ₃	1	>10 ⁻⁵	>10 ⁻⁵
37	H	CH ₃	3	54 [38;67] (2)	29 [17;42] (2)
38	H	C ₂ H ₅	2	4.3 [1.2;2.3] (2)	1.1[0.4;0.7] (2)
39	H	C ₃ H ₇	2	12.3 [2.5;3.1] (2)	0.9 [1.1;0.7] (2)
40	H	c-C ₃ H ₅	2	23.5 [8.5;5.1] (2)	32.6 [7.5;8.1] (2)
43	-	-	-	4.1 [0.7;0.5] (2)	0.6 [0.2;0.1] (2)

Ki(nM) values are geometric mean values (with 95% confidence limits shown in brackets) of at least n separate experiments performed in duplicate.

E/Z stereochemistry ratio of compound **43** was not defined, and the compound was used in biological testing without any further resolution. Binding affinity experiments on 5-HT_{2C} receptors revealed that all synthesized compounds of the three series were devoid of any binding affinity to this receptor subtype. In contrary, binding affinity experiments of prepared compounds revealed very interesting pharmacological profiles. First, the introduction of a nitrogen atom into the C-3 position of the agomelatine (6-methoxy-isoquinoline (6-MIQ) **8a**) has led to a slight decrease in affinity towards MT₁ and MT₂ by 100 and 10 times respectively (Table 1). However, **8a** maintains a fair nanomolar affinity towards both melatonin receptor subtypes (MT₁: 22 nM, MT₂: 6 nM) with the onset of a slight MT₂-selectivity. The displacement of the nitrogen atom from metabolic position C-3 to position C-2 of the naphthalene nucleus led to 7-methoxy-isoquinoline (7-MIQ) **13**. Binding affinity studies of isoquinoline **13** showed the same decreasing tendency as that observed for its isomer **8a** with a decrease of two logs and one log in binding affinities respectively towards MT₁ and MT₂ receptor subtypes (MT₁: 30 nM, MT₂: 6.7 nM) in comparison with the parent compound AGM (MT₁: 0.1 nM, MT₂: 0.2 nM).

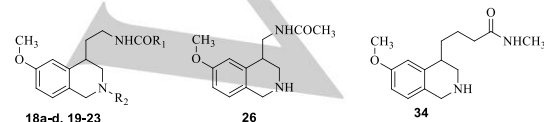
Following these obtained results, 6-MIQ **8a** was considered for further modulations to investigate its pharmacological potential

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towards melatonin receptors. Therefore, to investigate the effect of **8a** C-1 position modulation on both binding affinity and intrinsic activity at MT₁ and MT₂ receptor subtypes, two aromatic groups were inserted. Consequently, the introduction of a phenyl (**8b**) and a methoxy-phenyl (**8c**) have dropped the melatonergic binding affinity from sub-nanomolar to high micromolar (Table 1). The second modulation consisting of **8a** acetamide lateral chain modification through the incorporation of different groups (compounds **38-40**), and the modulation of its length.

Substitution of acetamide methyl for an ethyl or a propyl group (compounds **38-39**) showed no noticeable effect on both MT₁ and MT₂ binding affinities (**38**: MT₁: 4.3 nM, MT₂: 1.1 nM, **39**: MT₁: 12.3 nM, MT₂: 0.9 nM). Moreover, replacement of the methyl group with a cyclopropyl (compound **40**) however showed a more pronounced decrease in MT₂ binding affinity than in MT₁ in comparison with **8a** and the onset of a slight MT₁-selectivity (MT₁: 23.5 nM, MT₂: 32.6 nM). Second, modulation of length and free movement of the ethyl side chain (compounds **35-36** and **43**). The increase of this side chain from an ethyl to a propyl (compound **37**) decreased the binding affinities at MT₁ and MT₂ respectively by 6 and 10 times. In contrary, the contraction of the ethyl side chain (compound **36**) led to the loss of melatonergic binding affinity at both MT₁ and MT₂. Finally, the extension of the ethyl side chain accompanied with the transformation of the acetamide into a retroamide, *N*-methyl amide **35**, exhibited the same melatonergic binding affinity as the parent compound (MT₁: 3.8 nM, MT₂: 2.6 nM). More interestingly, the introduction of a constraint at ethyl side chain through an α,β -unsaturation (compound **43**), improved melatonergic binding affinity at both MT₁ and MT₂ in comparison with **8a**.

Table 2. Melatonin MT₁/MT₂ binding affinities of tetrahydroisoquinoline derivatives.



Cpd	R ₁	R ₂	K _i (nM) [I95](n)	
			<i>h</i> -MT ₁	<i>h</i> -MT ₂
8a	-	-	22 [12;22] (2)	6 [2.1;5.1] (2)
18a	CH ₃	H	>10 ⁻⁵	1030 [764;570] (2)
18b	C ₂ H ₅	H	1430 [357;603] (2)	700 [27;34] (2)
18c	C ₃ H ₇	H	>10 ⁻⁵	132 [33;52] (2)
18d	<i>c</i> -C ₃ H ₅	H	1740 [830;747] (2)	1600 [357;695] (2)
19	CH ₃	CH ₃	1000 [237;158] (2)	130 [38;43] (2)
20	CH ₃	CH ₂ CH=CH ₂	95.5 [9;11] (2)	15.9 [7;6] (2)
21	CH ₃	CH ₂ <i>c</i> -C ₃ H ₅	1060 [466;341] (2)	220 [37;28] (2)
22	CH ₃	CH ₂ C ₆ H ₅	248 [25;31] (2)	19.8 [11;8] (2)
23	CH ₃	C ₆ H ₅	156 [37;24] (2)	3.5 [0.9;1.2] (2)
26	-	-	5140	6630
34	-	-	>10 ⁻⁵	5600

K_i(nM) values are geometric mean values (with 95% confidence limits shown in brackets) of at least n separate experiments performed in duplicate.

Cpd: Compound.

Both 6-MIQ and 7-MIQ isoquinolines showed nanomolar binding affinities at both MT₁ and MT₂ receptor subtypes with better results for 6-MIQ. However, after modulating the C-1 position and the acetamide lateral chain of our lead compound **8a**, our next move was focused in probing the effect of the aromaticity of 6-MIQ heterocycle on both melatonin and serotonin systems. In this regard, 6-MIQ isoquinoline was replaced with its tetrahydroisoquinoline analogue. The biological results of obtained compound **18a**, the equivalent of **8a**, showed a drop of the MT₂ binding affinity and the loss of the MT₁ binding affinity leading the appearance of an MT₂-selectivity. Compound **18a** was then submitted to the same pharmacomodulations as **8a** (compounds **18b-18d**) and the obtained results showed the same profile as compound with butylamide **18c** (MT₁: >10⁻⁵ nM, MT₂: 132 nM) showing a nanomolar binding affinity at MT₂ and hence an important selectivity to this receptor subtype. Moreover, the retraction and extension of ethyl side chain (compounds **26-34**)

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showed a drop of the binding affinity towards both MT₁ and MT₂ in comparison with **8a**.

Finally, to study the effect of the NH position of the tetrahydroisoquinoline **18a**, we decided to block this position through the introduction of different groups (compounds **19-23**). First, the introduction of alky groups (compounds **19-21**) showed an improvement in the melatonergic binding affinity at both MT₁ and MT₂ versus the tetrahydroisoquinoline **18a** and the appearance of an MT₂-selectivity (Table 2). The same pharmacological profile was observed with the introduction of a benzyl or a phenyl (compounds **22** and **23**). Among this series, compounds **20**, **22** and **23** showed a very interesting pharmacological profile in comparison with compound **18a** (Table 2).

Table 3. Intrinsic activity of most interesting synthesized compounds.

Cpd	<i>h</i> -MT ₁		<i>h</i> -MT ₂	
	EC ₅₀ (nM) [I95](n)	E _{max} (%) ± ESM (n)	EC ₅₀ (nM) [I95](n)	E _{max} (%) ± ESM (n)
AGM	.56 [1.12;2.00] (4)	99 ± 6 (4)	0.21 [0.13;0.30] (3)	91 ± 7 (3)
8a	200 [165;216] (2)	72 ± 5 (2)	300 [417;598] (2)	88 ± 2 (2)
13	352 [18;11] (2)	76 ± 6 (2)	5.1 [0.3;0.8] (2)	100 ± 4 (2)
35	135 [23;47] (2)	62 ± 7 (2)	0.5 [0.1;0.4] (2)	82 ± 3 (2)
38	120 [15;17] (2)	95 ± 5 (2)	3.1 [1.2;0.8] (2)	95 ± 2 (2)
39	208 [21;18] (2)	77 ± 6 (2)	0.9 [0.3;0.6] (2)	94 ± 3 (2)
40	320 [28;23] (2)	70 ± 8 (2)	32 [7;10] (2)	74 ± 4 (2)
43	3.1 [0.9;1.2] (2)	99 ± 3 (2)	0.4 [0.1;0.3] (2)	109 ± 4 (2)
20	437 [28;32] (2)	62 ± 6 (2)	274 [38;43] (2)	90 ± 2 (2)
22	>10 ⁻⁵	nd	5215 [269;428] (2)	38 ± 12 (2)
23	>10 ⁻⁵	nd	34 [7;11] (2)	35 ± 8 (2)

EC₅₀(nM) values are geometric mean values (with 95% confidence limits shown in brackets) of at least n separate experiments performed in duplicate.

nd: not determined
Cpd: Compound.

Later, most interesting compounds issued from our pharmacomodulations of the three series were submitted to intrinsic activity experiments towards both MT₁ and MT₂ melatonergic receptor subtypes and the obtained results are depicted in Table 3. Most of the evaluated compounds including **20**, **35**, **38-40** showed partial agonist activities at both MT₁ and MT₂. 7-MIQ compound **13** (MT₁: EC₅₀ = 352 nM, MT₂: EC₅₀ = 3.5 nM) along with 6-MIQ vinylacetamide **43** (MT₁: EC₅₀ = 3.1 nM, MT₂: EC₅₀ = 0.4 nM) however exhibited a full agonist activity at MT₂ and a partial agonist activity at MT₁ thus confirming the interesting pharmacological profile of these series. Tetrahydroisoquinoline derivatives **22** and **23**, however, showed no activity at MT₁ and a partial agonist activity at MT₂ strictly lower than the efficacy of the melatonin, AGM and the parent compound **8a** with an E_{max} lower than 38%.

Table 4. Bioavailability, Caco2 and CYP2B data of prepared compounds.

Compound	Bioavailability		Caco2 %	CYP2B
	Rodent	Human		
AGM	13	11	nd	nd
8a	34	61	100	1
21	6	52	100	nd
35	21	21	100	2
38	11	19	100	2
39	6	12	100	2
40	9	17	100	2

nd: not determined; Values are geometric mean values of 2 experiments.

Pharmacokinetic simulation studies of prepared compounds were performed using the same procedure as was previously described,^[31,36-37] and results are shown in Table 4. The introduction of a nitrogen atom into the naphthalene ring (compound **8a**) improved the bioavailability at both rodent and human in comparison with agomelatine (Table 4). However, this

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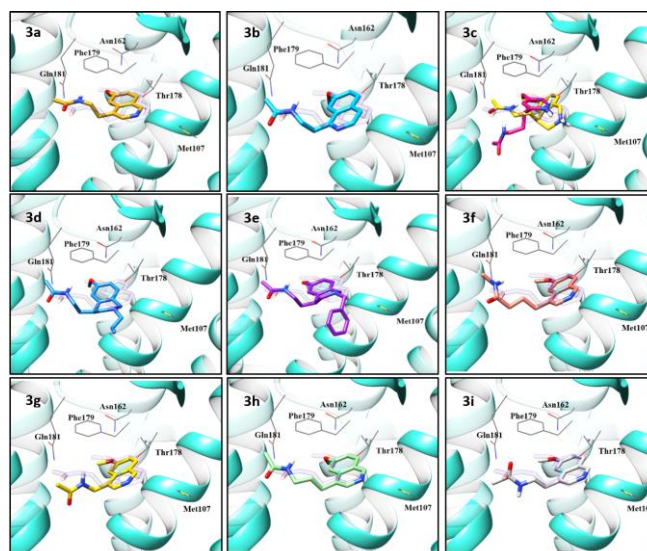
improvement of the availability was again lost with the modulation of the acetamide lateral chain (compounds **35-36** and **38-40**). Along with compound **8a**, tetrahydroisoquinoline *N*-methylcyclopropyl **21** displayed the highest bioavailability of this series (61% versus 52%). Overall, these results confirm that the presence of a nitrogen atom may improve pharmacokinetic properties by granting good solubility and absorption to these compounds. However, this improvement may be counterbalanced by the presence of bulky groups in the lateral amide chain. Drug absorption and permeability experiments (Caco2 test) of the most interesting prepared compounds showed a 100% absorption for the tested compounds confirming the positive effect of the presence of the nitrogen atom. Finally, drug metabolism assays including CYP2B enzymatic activity inhibition (CYP inhibition) assays showed a two-factor inhibition for all prepared compounds except 6-MIQ **8a** (Table 4).

Exploration of the prepared isoquinoline and tetrahydroisoquinoline derivatives through molecular docking experiments

With the determination of the crystal structures of MT₁ and MT₂ receptor subtypes mentioned above, the way is now well paved into the use of efficient computational docking studies to design and prepare new melatonin ligands with new functions.^[32] Accordingly, the available structures of melatonin MT₁ and MT₂ receptor subtypes were used herein to perform docking studies and obtain structural insights underlying our RSA. Due to the high degree of similarity between MT₁ and MT₂ receptor subtypes, where about 20 to 21 residues are identical,^[32] we used a receptor structure with orthosteric binding site for our docking studies.^[33] Obtained results revealed that, in general, the decrease of binding affinities observed with the newly prepared isoquinoline and tetrahydroisoquinoline derivatives in comparison with AGM, is due to electronic repulsion between the nitrogen of the ligand and the oxygen atom of the threonine residues Thr178 for MT₁ and Thr191 for MT₂ (Fig. **3a-b**). Moreover, the decrease in the binding affinities at MT₁ and MT₂ of compound **37** results from a distortion

of the optimal geometry for the H-bond with the Gln194/Tyr281 (Gln194/294 for MT₂), induced by the longer arm with the increase of the lateral side chain (Fig. **3h**) while the contraction of this side chain (compound **36**) led to a total loss of this H-bond (Fig. **3g**). However, we have observed that both the introduction of a retroamide (compound **35**) or the rigidification of the side chain (compound **43**) improved melatonergic binding affinity at both MT₁ and MT₂. Clearly, herein the retroamide allows to bring back the oxygen atom in an optimal position, as in AGM, and hence overcame the distortion of the geometry of the H-bond system phenomena observed with propylamide **37** (Fig. **3f**). The rigidification of the ethyl side chain however might lead to a reduced entropic cost compared to the saturated arm (Fig. **3i**). Finally, in the case of tetrahydroisoquinoline derivatives (**18a**, **20** and **22**), the loss of the melatonergic binding affinity, from a point of view of virtual binding studies, might result from the fact that the formal charge of tetrahydroisoquinoline moiety is localized in the hydrophobic core of the binding pocket. The *N*-alkylation of tetrahydroisoquinoline heterocycle had allowed to bring back a hydrophobic chain in this pocket, more selective for MT₂ which presents a bigger cavity at this position (Fig. **3c-e**).

Figure 3. Molecular docking results of prepared compounds.



Best docking pose of compounds in the orthosteric binding pocket of MT₁, compared with the crystal structure of AGM (in shadow), a: 3-aza analog of AGM **8a**, b: 2-aza analog of AGM **13**, c: tetrahydroisoquinoline analog of AGM **18a**, d,e: compound **18a** *N*-alkylated with propyl **20** or benzyl **22**, f: compound

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8a ethyl to propyl analog **35**, **g**: compound **8a** ethyl to methyl analog **36**, **h**: compound **35** retroamide analog **37**, **i**: compound **8a** vinyl rigidified analog **43**.

Conclusion

Altogether, in this work we investigated the potential of isoquinoline and tetrahydroisoquinoline families as new melatonin receptor ligands. Besides, pharmacological results of prepared derivatives revealed very promising pharmacological profiles of these families despite their lack of serotonergic 5-HT_{2C} binding affinity. 6-Methoxy-isoquinoline (6-MIQ) revealed to be greater melatonin ligand than 7-methoxy-isoquinoline (7-MIQ). 6-MIQ tetrahydroisoquinoline analogues however showed more noticeable decrease of the melatonergic binding affinity specially at MT₁ leading the appearance of an MT₂-selectivity. Besides, compound **18c** showed an important selectivity to this receptor subtype confirming the existence of an eventual role of the aromaticity in maintaining good melatonergic binding affinities for isoquinoline versus tetrahydroisoquinoline series.

Overall, most prepared compounds have shown partial agonist activities at both MT₁ and MT₂, except 7-MIQ compound **13** and 6-MIQ vinylactemide **43** whose showed a full agonist activity at MT₂ and a partial agonist activity at MT₁. Herein compound **43** was used as *E/Z* mixture without any further resolution. Finally, pharmacokinetic studies confirmed that the presence of a nitrogen atom improves in general pharmacokinetic properties by granting good solubility and absorption to these compounds in comparison with agomelatine. However, these pharmacokinetic improvements were counterbalanced by the presence of bulky groups in the lateral amide chain. Finally, a new 3D model of MT₁ and MT₂ receptors is needed to shed lights on the observed phenomena herein and investigate the binding modes and behaviors of these melatonin ligands and their effects on the binding affinity.

Experimental Section

Chemistry

General experimental methods: All reagents and solvents were purchased and used without further purification. Melting points were determined on a BÜCHI B-540 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 Avance 300 spectrometer operating at 300 MHz (¹H) or 75 MHz (¹³C). Chemical shifts are in parts per million (ppm) and were referenced to the residual proton peaks in deuterated solvents. Mass spectra were recorded with an LCMS (Waters Alliance Micromass ZQ 2000) using a Waters XBridge C18 column (5 μm particle size column, dimensions 50 mm × 4.6 mm). A gradient starting from 98% H₂O/formate buffer 5 mM (pH 3.8) and reaching 100% CH₃CN/formate buffer 5 mM (pH 3.8) within 4 min at a flow rate of 2 mL/min was used followed by a return to the starting conditions within 1 min. HRMS experiments were performed on a Q-Exactive Benchtop LC-MS/MS (Thermo Scientific).

Methyl 2-cyano-2-(3-methoxyphenyl)acetate (1): To a solution of 3-methoxyphenylacetonitrile (25.00 g, 0.17 mol) in dry THF (200 mL) was added sodium hydride (60% suspension in paraffin oil) (8.88 g, 0.37 mol). The reaction mixture was refluxed for 30 minutes. Dimethyl carbonate (58 mL, 0.68 mol) was added dropwise over 30 minutes and the reaction mixture was stirred at reflux for another 2h. Thereafter, the mixture reaction was cooled to room temperature and poured in cold and slightly acidified (HCl) water. Aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed two times with an aqueous potassium carbonate solution (47.15 g, 0.34 mol). Combined aqueous layers were acidified and extracted with diethyl ether. The organic phase was washed using a sodium hydrogen carbonate solution (10%), dried over MgSO₄, filtered and concentrated under *vacuum* to afford **1** as an colorless oil (77% yield); IR, ν (cm⁻¹): 2253, 1750; ¹H-NMR (300 MHz, CDCl₃): 7.34 (t, 1H, *J* = 7.9 Hz), 7.08-6.92 (m, 3H), 4.72 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H); LC-MS (ESI): *m/z* = 206 [M-H]⁺.

Methyl 3-amino-2-(3-methoxyphenyl)propanoate hydrochloride (2): A solution of compound **1** (17.16 g, 0.08 mol) in methanol (150 mL) was put in an autoclave. Chloroform (50 mL) and platinum dioxide (10%) were added. The mixture was sealed and stirred at room temperature under H₂ atmosphere (60 bars) for 24 h. Catalyst was filtered off and the solution was concentrated under *vacuum*. Diethyl ether was added to crude product and the resulting solid was filtered. Recrystallization from

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acetonitrile afford **2** as a white solid (50% yield); mp 170-172 °C; IR ν (cm⁻¹): 1727; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.25-8.00 (br s, 3H), 7.31 (t, 1H, *J* = 8.2 Hz), 6.93 (d, 1H, *J* = 8.2 Hz), 6.88-6.83 (m, 2H), 4.00 (m, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.45 (dd, 1H, *J*_{gem} = 12.7 Hz and *J*_{vic} = 8.5 Hz), 3.00 (dd, 1H, *J*_{gem} = 12.7 Hz and *J*_{vic} = 6.2 Hz); LC-MS (ESI): *m/z* = 210 [M-H]⁺.

Methyl 3-formamido-2-(3-methoxyphenyl)propanoate (3a): A solution of **2** (8.37 g, 0.04 mol) in ethyl formate (60 mL) was stirred at reflux for 6h. The reaction mixture was concentrated under *vacuum* and the resulting oil was solubilized in ethyl acetate. Organic layer was washed with a 1M HCl solution and water, dried over MgSO₄, filtered and concentrated under *vacuum* to afford **3a** as a yellow oil (90% yield); IR ν (cm⁻¹): 3240, 1732, 1670; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.18 (br s, 1H), 7.96 (s, 1H), 7.27 (t, 1H, *J* = 7.9 Hz), 6.91-6.80 (m, 3H), 3.85 (t, 1H, *J* = 6.1 Hz), 3.75 (s, 3H), 3.65-3.54 (m, 4H), 3.44 (dd, 1H, *J*_{gem} = 13.3 Hz and *J*_{vic} = 6.1 Hz); LC-MS (ESI): *m/z* = 238 [M-H]⁺.

Methyl 3-benzamido-2-(3-methoxyphenyl)propanoate (3b): To a cold solution of **2** (12.3 g, 0.05 mol) in a mixture of CH₂Cl₂ (100 mL) and water (50 mL) was added potassium carbonate (13.8 g, 0.1 mol). Benzoyl chloride (7 mL, 0.06 mol) in 30 mL of CH₂Cl₂ was added dropwise to the solution. The mixture reaction was stirred at room temperature for 2 h. Aqueous layer was extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Recrystallization from toluene/cyclohexane (1/2) afford **3b** as a white solid (87% yield); mp 87-88 °C; IR ν (cm⁻¹): 3220, 1720, 1650; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.61 (br t, 1H), 7.76 (m, 2H), 7.51 (m, 1H), 7.44 (m, 2H), 7.27 (m, 1H), 6.87 (m, 3H), 4.06 (m, 4H), 3.81 (m, 1H), 3.73 (s, 3H), 3.61 (m, 1H); LC-MS (ESI): *m/z* = 314 [M-H]⁺.

Methyl 2-(3-methoxybenzamido)-3-(2-(3-methoxyphenyl)acetamido)propanoate (3c): This compound was prepared as described for compound **3b** using compound **2** and 3-methoxy benzoyl chloride. Recrystallization from toluene/cyclohexane (1/2) gave **3c** as a white solid (82% yield); mp 92-93 °C; IR ν (cm⁻¹): 3250, 1730, 1654; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.63 (br t, 1H), 7.75 (m, 2H), 7.27 (m, 2H), 7.07 (d, 1H, *J* = 2.3 Hz), 6.90- 6.81 (m, 3H), 4.23 (m, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 3.75 (m, 2H), 3.68 (s, 3H). LC-MS (ESI): *m/z* = 344 [M-H]⁺.

General procedure for synthesis of compound 4: A solution of **3a** (8.03 g, 0.03 mol) in acetonitrile (100 mL) was stirred at 60 °C. Phosphorus oxychloride (14 mL, 0.15 mol) was added, and the solution was stirred at 60 °C for additional 6h. The solution was concentrated under *vacuum*.

Methanol was added to the crude product and evaporated. Acetone was added to the residue and the resulting solid was filtered.

Methyl 6-methoxy-3,4-dihydroisoquinoline-4-carboxylate, hydrochloride (4a): white solid (45% yield); mp 212-215 °C; IR ν (cm⁻¹): 1721; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.10 (d, 1H, *J* = 1.9 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 7.23 (d, 1H, *J* = 2.3 Hz), 7.20 (m, 1H), 4.38 (dd, 1H, *J* = 6.6 Hz and *J* = 2.6 Hz), 4.30 (dd, 1H, *J* = 15.9 Hz and *J* = 2.6 Hz), 4.05 (dd, 1H, *J* = 15.9 Hz, *J* = 6.6 Hz and *J* = 2.3 Hz), 3.95 (s, 3H), 3.64 (s, 3H); LC-MS (ESI): *m/z* = 220 [M-H]⁺.

Methyl 6-methoxy-1-phenyl-3,4-dihydroisoquinoline-4-carboxylate, hydrochloride (4b): recrystallized from acetonitrile as a white solid (70% yield); mp 209-210 °C; IR ν (cm⁻¹): 1710; ¹H-NMR (300 MHz, DMSO-*d*₆): 7.81 (m, 1H), 7.68 (m, 4H), 7.46 (d, 1H, *J* = 8.54 Hz), 7.33 (d, 1H, *J* = 2.45 Hz), 7.15 (dd, 1H, *J* = 8.54 Hz and 2.45 Hz), 4.35-4.32 (m, 2H), 4.11 (m, 1H), 3.94 (s, 3H), 3.78 (s, 3H); LC-MS (ESI): *m/z* = 296 [M-H]⁺.

Methyl-6-methoxy-1-(3-methoxyphenyl)-3,4-dihydroisoquinoline-4-carboxylate, hydrochloride (4c): recrystallized from acetonitrile as a white solid (85% yield); mp 205-207 °C; IR ν (cm⁻¹): 1730; ¹H-NMR (300 MHz, DMSO-*d*₆): 7.88-7.53 (m, 2H), 7.27-7.23 (m, 2H), 7.08-6.88 m, 3H), 4.36 (d, 1H, *J* = 15.90 Hz), 4.11 (d, 1H, *J* = 15.90 Hz), 3.88 (s, 3H), 3.83 (s, 3H), 3.68 (s, 3H), 3.60 (dd, 1H, *J* = 6.61 Hz and 2.56 Hz); LC-MS (ESI): *m/z* = 326 [M-H]⁺.

General procedure for synthesis of compound 5: To a solution of **4a**, **4b** or **4c** under base form (1.31g, 0.006 mmol) in decahydronaphthalene (10 mL) was added Pd/C 10% (160 mg). The mixture was heated at 130 °C for 24h. After cooling to room temperature, catalyst was filtered off and washed with methanol. Solution was concentrated under *vacuum* and the resulting oil was suspended in diethyl ether with HCl gas, and the solid filtered.

Methyl 6-methoxyisoquinoline-4-carboxylate, hydrochloride (5a): recrystallized from acetonitrile as a white solid (88% yield); mp 179-180 °C; IR ν (cm⁻¹): 1724; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.70 (s, 1H), 9.06 (s, 1H), 8.44 (d, 1H, *J* = 9.1 Hz), 8.33 (d, 1H, *J* = 2.3 Hz), 7.64 (dd, 1H, *J* = 9.1 Hz and *J* = 2.3 Hz), 4.04 (s, 3H), 4.01 (s, 3H); LC-MS (ESI): *m/z* = 218 [M-H]⁺.

Methyl 6-methoxy-1-phenylisoquinoline-4-carboxylate (5b): recrystallized from cyclohexane as a white solid (85% yield); mp 95-96 °C; IR ν (cm⁻¹): 1725; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.25 (s, 1H), 8.51 (d, 1H, *J* = 2.5 Hz), 8.05 (d, 1H, *J* = 9.0 Hz), 7.65 (m, 1H), 7.50 (m, 2H), 7.42

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(m, 2H), 7.20 (dd, 1H, $J = 9.0$ Hz and $J = 2.5$ Hz), 4.08 (s, 3H), 4.04 (s, 3H); LC-MS (ESI): $m/z = 294$ [M-H]⁺.

Methyl 6-methoxy-1-(3-methoxyphenyl)isoquinoline-4-carboxylate (5c): recrystallized from cyclohexane as a white solid (82% yield); mp 99-100 °C; IR ν (cm⁻¹): 1720; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.07 (s, 1H), 8.32 (d, 1H, $J = 2.5$ Hz), 8.00 (d, 1H, $J = 9.2$ Hz), 7.50 (m, 1H), 7.34 (dd, 1H, $J = 9.2$ Hz and $J = 2.5$ Hz), 7.13-7.20 (m, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.83 (s, 3H); LC-MS (ESI): $m/z = 324$ [M-H]⁺.

General procedure for synthesis of compound 6: To a solution of **5a**, **5b** or **5c** (0.004 mol) in dry THF (30 mL) was added dropwise to a cold solution of lithium aluminum hydride (0.228 g, 0.006 mol) in dry tetrahydrofuran (20 mL). The mixture reaction was stirred at room temperature for 2h. Few drops of a hydroxide sodium solution (30%) were added. Mineral solid was filtered off and washed with ethyl acetate. Organic phase was dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane 5/5). The resulting oil was suspended in diethyl ether with HCl gas, and the solid filtered.

(6-Methoxyisoquinolin-4-yl)methanol, hydrochloride (6a): recrystallized from acetonitrile as a white solid (60% yield); mp 251-252 °C; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.56 (s, 1H), 8.47 (s, 1H), 8.42 (d, 1H, $J = 9.3$ Hz), 7.62 (dd, 1H, $J = 2.3$ Hz and $J = 9.3$ Hz), 7.52 (d, 1H, $J = 2.3$ Hz), 5.85 (br s, 1H), 5.04 (s, 2H), 4.06 (s, 3H); LC-MS (ESI): $m/z = 190$ [M-H]⁺.

(6-Methoxy-1-phenylisoquinolin-4-yl)methanol, hydrochloride (6b): recrystallized from acetonitrile as a white solid (90% yield); mp 228-229 °C; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.44 (s, 1H), 8.07 (d, 1H, $J = 9.0$ Hz), 8.68-7.24 (m, 5H), 7.58 (m, 2H), 5.80 (br s, 1H), 5.10 (s, 2H), 4.08 (s, 3H); LC-MS (ESI): $m/z = 266$ [M-H]⁺.

(6-Methoxy-1-(3-methoxyphenyl)isoquinolin-4-yl)methanol, hydrochloride (6c): recrystallized from acetonitrile as a white solid (90% yield); mp 215-217 °C; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.40 (s, 1H), 7.87-7.86 (m, 2H), 7.82-7.43 (m, 2H), 7.19-7.01 (m, 3H), 5.82 (br s, 1H), 5.12 (s, 2H), 4.00 (s, 3H), 3.92 (s, 3H); LC-MS (ESI): $m/z = 296$ [M-H]⁺.

2-(6-Methoxyisoquinolin-4-yl)acetonitrile (7a): To a suspension of **6a** (1.13 g, 0.005 mol) in chloroform (50 mL) was added thionyl chloride (1.45 mL, 0.02 mol) dropwise. The solution was stirred at room temperature for 18h and then concentrated under *vacuum*. The residue was solubilized in a mixture of CH₂Cl₂ (40 mL) and a saturated aqueous solution of potassium carbonate (10 mL). To this solution were added tetra-*n*-

butylammonium bromide (2 g, 0.006 mol) and potassium cyanide (0.80 g, 0.012 mol). The mixture was stirred at room temperature for 24h. Aqueous layer was extracted three times with CH₂Cl₂. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. The resulting oil was suspended in acetone and diethyl ether with HCl gas to afford **7a** as a yellow solid (70% yield); mp 114-115 °C; IR ν (cm⁻¹): 2246; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.13 (s, 1H), 8.49 (s, 1H), 7.95 (d, $J = 9.1$ Hz, 1H), 7.33 (dd, 1H, $J = 2.5$ Hz and $J = 9.1$ Hz), 7.09 (d, 1H, $J = 2.5$ Hz), 4.69 (s, 2H), 4.11 (s, 3H); LC-MS (ESI): $m/z = 199$ [M-H]⁺.

2-(6-Methoxy-1-phenylisoquinolin-4-yl)acetonitrile (7b): To a solution of **6b** (1.5 g, 0.005 mol) in CH₂Cl₂ (50 mL) was added thionyl chloride (1.81 mL, 0.025 mol) dropwise. The solution was stirred at room temperature for 18h and then concentrated under *vacuum*. Residue was solubilized in a small amount of DMSO. This solution was added slowly to a suspension of potassium cyanide (1.3 g, 0.02 mol) in DMSO (25 mL). The mixture reaction was stirred at room temperature for 2 h and poured into water (100 mL). Aqueous layer was extracted three times with CH₂Cl₂. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel to afford **7b** as a white solid (75% yield); mp 134-135 °C; IR ν (cm⁻¹): 2246. ¹H-NMR (300 MHz, DMSO-*d*₆): 8.55 (s, 1H), 8.00 (d, 1H, $J = 9.2$ Hz), 7.87 (m, 5H), 7.43 (d, 1H, $J = 2.5$ Hz), 7.33 (d, 1H, $J = 9.2$ and $J = 2.5$ Hz), 4.50 (s, 2H), 4.00 (s, 3H); LC-MS (ESI): $m/z = 275$ [M-H]⁺.

2-(6-Methoxy-1-(3-methoxyphenyl)isoquinolin-4-yl)acetonitrile (7c): This compound was obtained as described for **7a** starting from **6c** to led to compound **7c** as a white solid (85% yield); mp 137-138 °C; IR ν (cm⁻¹): 2245; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.54 (s, 1H), 7.99 (d, 1H, $J = 9.24$ Hz), 7.47 (m, 1H), 7.42 (d, 1H, $J = 2.34$ Hz), 7.33 (dd, 1H, $J = 9.24$ and $J = 2.34$ Hz), 7.18-7.02 (m, 3H), 4.49 (s, 2H), 4.00 (s, 3H), 3.82 (s, 3H); LC-MS (ESI): $m/z = 305$ [M+H]⁺; LC-MS (ESI): $m/z = 305$ [M-H]⁺.

General procedure for synthesis of compound 8: To solution of **7a**, **7b** or **7c** (0.006 mol) in acetic anhydride (50 mL) was put in an autoclave. Raney nickel in a catalytic amount was added. The reaction mixture was sealed and stirred at 60 °C under H₂ atmosphere (60 bars) for 6h. After cooling to room temperature, catalyst was filtered off and the solvent was evaporated under *vacuum*. Crude product was refluxed in toluene in the presence of palladium on activated charcoal for 24h. Catalyst was filtered, and the solvent was evaporated. The obtained residue was purified using chromatography on silica gel (Ethyl acetate/cyclohexane: 7/3). The

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resulting oil was suspended in diethyl ether with HCl(gas), and the solid filtered.

N-[2-(6-Methoxyisoquinolin-4-yl)ethyl]acetamide, hydrochloride (8a): recrystallized from toluene as a white solid (55% yield); mp 212-214 °C; IR ν (cm⁻¹): 3260, 1670; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.62 (s, 1H), 8.47 (s, 1H), 8.45 (d, *J* = 9.1 Hz, 1H), 8.22 (s, 1H), 7.85 (d, 1H, *J* = 2.3 Hz), 7.63 (dd, 1H, *J* = 9.1 Hz and *J* = 2.3 Hz), 4.11 (s, 3H), 3.38 (m, 2H), 3.26 (t, 2H, *J* = 4.5 Hz), 1.79 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.2, 165.7, 144.1, 140.7, 133.6, 133.2, 131.4, 123.5, 122.8, 103.3, 57.1, 38.9, 29.9, 23.0; LC-MS (ESI): *m/z* = 245 [M-H]⁺; HRMS (ESI) [M+H]⁺ [M+H]⁺ calculated for C₁₄H₁₇N₂O₂, 245.12845; found, 245.13124.

N-[2-(6-Methoxy-1-(phenylisoquinolin-4-yl)ethyl]acetamide (8b): recrystallized from toluene as a white solid (58% yield); mp 167-169 °C; IR ν (cm⁻¹): 3220, 1660; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.35 (s, 1H), 8.17 (br t, 1H), 7.92 (d, 1H, *J* = 9.1 Hz), 7.70 (d, 1H, *J* = 2.4 Hz), 7.60-7.50 (m, 5H), 7.25 (dd, 1H, *J* = 9.1 and 2.3 Hz), 4.00 (s, 3H), 3.42 (m, 2H), 3.10 (m, 2H), 1.85 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.7, 161.4, 143.1, 136.9, 135.0, 129.8, 129.5, 129.2, 127.9, 127.6, 127.3, 121.9, 121.2, 119.7, 102.7, 57.6, 55.8, 40.7, 30.1, 23.3; LC-MS (ESI): *m/z* = 321 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₂₀H₂₁N₂O₂, 321.38; found, 320.152477.

N-(2-(6-Methoxy-1-(3-methoxyphenyl)isoquinolin-4-yl)ethyl)acetamide (8c): recrystallized from toluene/cyclohexane (1/1) as a white solid (68% yield); mp 122-123 °C; IR ν (cm⁻¹): 3240, 1670; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.35 (s, 1H), 8.19 (br t, 1H, *J* = 5.7 Hz), 7.95 (d, 1H, *J* = 9.1 Hz), 7.70 (d, 1H, *J* = 2.4 Hz), 7.43 (m, 1H), 7.25 (dd, 1H, *J* = 9.1 and 2.3 Hz), 7.10 (m, 3H), 4.00 (s, 3H), 3.82 (m, 3H), 3.35 (m, 2H), 3.15 (m, 2H), 1.85 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.7, 161.4, 161.1, 157.6, 143.1, 140.7, 136.9, 130.2, 122.9, 121.9, 129.8, 119.9, 119.7, 113.7, 112.9, 102.7, 80.1, 56.8, 55.8, 40.7, 23.3; LC-MS (ESI): *m/z* = 351 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₂₁H₂₃N₂O₃, 351.17032; found, 351.17346.

1-(3-Methoxyphenyl)ethan-1-amine, hydrochloride (9): To a solution of 3-methoxyacetophenone (20g, 0.133 mol) in absolute ethanol (100 mL) were added hydroxylamine hydrochloride (18.5 g, 0.266 mol) and potassium carbonate (46g, 0.332 mol). The mixture reaction was stirred and heated at reflux for 3h. After cooling to room temperature, the mixture reaction was filtered and concentrated under *vacuum*. A solution of the crude product in methanol (150 mL) was put in an autoclave. Raney Nickel (catalytic amount) was added to the solution. The mixture reaction was sealed, saturated with ammonia and stirred at room temperature under H₂

(20 bars) for 24h. Catalyst was filtered off and the solution was concentrated under *vacuum*. Residue was suspended in diethyl ether with HCl gas. Solid was filtered and recrystallized from acetone to afford **9** as a white solid (85% yield); mp 164-165 °C, ¹H-NMR (300 MHz, DMSO-*d*₆): 8.51 (s, 3H), 7.34 (m, 1H), 7.15 (s, 1H), 7.06 (d, 1H, *J* = 7.8 Hz), 6.94 (m, 1H), 4.35 (d, 1H, *J* = 6.8 Hz), 3.78 (s, 3H), 1.50 (d, 3H, *J* = 6.8 Hz); LC-MS (ESI): *m/z* = 152 [M-H]⁺.

7-Methoxy-1-methylisoquinoline, hydrochloride (10): To a solution of **9** (2.25g, 0.012 mol) in toluene (50 mL) was added 2,2-dimethoxyacetaldehyde 60 wt. % in water (1 mL, 0.011 mol) dropwise. The solution was stirred and heated at reflux for 12h using a Dean-Stark apparatus. After cooling to room temperature, the solution was concentrated under *vacuum*. 15 mL of an 80% acid sulfuric solution was added slowly to the crude product under a vigorous stirring. The mixture reaction was alkalized at 0 °C using a 30% sodium hydroxide solution. Aqueous layer was extracted two times with ethyl acetate. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 4/6). The resulting oil was suspended in diethyl ether with HCl gas. Solid was filtered and recrystallized from ethyl acetate to afford **10** as a white solid (45% yield); mp 196-198 °C; ¹H-NMR (300 MHz, DMSO-*d*₆): 16.4 (s, 1H), 8.39 (d, *J* = 6.5 Hz, 1H), 8.29 (d, 1H, *J* = 6.5 Hz), 8.26 (d, 1H, *J* = 9.1 Hz), 7.84 (dd, 1H, *J* = 9.1 Hz and *J* = 2.4 Hz), 7.76 (d, *J* = 2.4 Hz, 1H), 4.04 (s, 3H), 3.21 (s, 3H); LC-MS (ESI): *m/z* = 174 [M-H]⁺.

7-Methoxyisoquinoline-1-carbaldehyde (11): To a solution of **10** (2 g, 0.012 mol) in dioxane (60 mL) was added selenium dioxide (2.0 g, 0.018 mol). The mixture reaction was stirred and heated at reflux for 3 days. After cooling to room temperature, the mixture reaction was concentrated under *vacuum*. Water was added, and the mixture was extracted three times with ethyl acetate. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel and recrystallized from cyclohexane to afford **11** as an orange solid (90% yield); mp 118-120 °C; IR ν (cm⁻¹): 1697; ¹H-NMR (300 MHz, DMSO-*d*₆): 10.28 (s, 1H), 8.71 (d, 1H, *J* = 5.5 Hz), 8.60 (d, *J* = 2.5 Hz, 1H), 8.15 (d, 1H, *J* = 5.5 Hz), 8.10 (d, 1H, *J* = 9.0 Hz), 7.56 (dd, 1H, *J* = 9.0 Hz and *J* = 2.5 Hz), 3.96 (s, 3H), LC-MS (ESI) : *m/z* = 188 [M-H]⁺.

2-(7-Methoxyisoquinolin-1-yl)acetonitrile (12): To a solution of **11** (1.9 g, 0.01 mol) in absolute ethanol (25 mL) was added sodium borohydride

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(0.95 g, 0.025 mol) portion wise. The mixture reaction was stirred at room temperature for 2h. The solution was acidified with acetic acid and concentrated under *vacuum*. Water was added to the residue which was alkalinized using a potassium carbonate solution. Aqueous layer was extracted with CH₂Cl₂. Organic layer was dried over MgSO₄ and filtered. Triethylamine (2.4 mL, 0.017 mol) was added and the solution was cooled to 0 °C and methanesulfonyl chloride (1.3 mL, 0.017 mol) was added dropwise. The solution was stirred at room temperature for 2h and then poured into water. Methylene chloride was dried over MgSO₄ and filtered. A saturated solution of potassium carbonate (10 mL), tetrabutyl ammonium bromide (0.2 g, 0.0006 mol) and potassium cyanide (1.65 g, 0.025 mol) was added. The mixture reaction was stirred at room temperature for 24h. CH₂Cl₂ was added and the organic layer was separated, washed with water, dried over MgSO₄, filtered and concentrated under *vacuum*. The resulting oil was suspended in acetone and diethyl ether with HCl gas. Solid was filtered and recrystallized from toluene and cyclohexane (5/5) to afford **12** as a white solid (60% yield); mp 99-100 °C; IR ν (cm⁻¹): 2252; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.35 (d, 1H, *J* = 5.6 Hz), 7.97 (d, 1H, *J* = 9.1 Hz), 7.78 (d, 1H, *J* = 5.6 Hz), 7.49 (dd, 1H, *J* = 9.1 Hz and *J* = 2.4 Hz), 7.44 (d, 1H, *J* = 2.4 Hz), 4.78 (s, 2H), 3.96 (s, 3H); LC-MS (ESI): *m/z* = 199 [M-H]⁺.

N-(2-(7-Methoxyisoquinolin-1-yl)ethyl)acetamide (13): prepared similarly as compound **8a**. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 7/3) and recrystallized from isopropyl ether to afford **13** as a white solid (50% yield); mp 120-122 °C; IR ν (cm⁻¹): 3230, 1647; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.28 (d, 1H, *J* = 5.5 Hz), 8.09 (br t, 1H, *J* = 5.2 Hz), 7.86 (d, 1H, *J* = 8.9 Hz), 7.65-7.60 (m, 2H), 7.42 (dd, 1H, *J* = 8.9 Hz and *J* = 2.3 Hz), 3.96 (s, 3H), 3.50 (m, 2H), 3.34 (m, 2H), 1.81 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 169.9, 158.4, 157.8, 140.2, 131.4, 129.3, 128.2, 123.1, 119.5, 103.7, 55.9, 38.5, 35.3, 23.1; LC-MS (ESI): *m/z* = 245 [M-H]⁺; HRMS (ESI) [M+H]⁺ [M+H]⁺ calculated for C₁₄H₁₇N₂O₂, 245.12845; found, 245.13092.

2-(Tert-Butyl)-4-methyl-6-methoxy-3,4-dihydroisoquinoline-2,4(1H)-dicarboxylate (14): To a solution of **4a** base (7.89 g, 0.036 mol) in methanol (150 mL) was added palladium on activated charcoal (100 mg). The mixture reaction was stirred at room temperature under H₂ atmosphere for 4h. Catalyst was filtered off and the solution was concentrated under *vacuum*. The resulting oil was solubilized in CH₂Cl₂ (100 mL) and triethylamine (6.27 mL, 0.045 mol) and di-*tert*-butyl dicarbonate (9.6 g, 0.043 mol) were added. The solution was stirred at

room temperature for 3h and poured into water. Aqueous layer was extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 3/7) to afford **14** as a colorless oil (95% yield); IR ν (cm⁻¹): 1730, 1670; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.50 (d, 1H, *J* = 8.5 Hz), 6.85 (dd, *J* = 8.5 Hz and *J* = 2.5 Hz, 1H), 6.75 (d, 1H, *J* = 2.5 Hz), 4.65 (m, 1H), 4.30-4.20 (m, 2H), 3.70 (s, 3H), 3.65-3.60 (m, 2H), 3.35 (s, 3H), 1.40 (s, 9H); LC-MS (ESI): *m/z* = 322 [M-H]⁺.

Tert-butyl-4-(hydroxymethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (15): The same procedure as described for compound **6a** was used starting from **14**. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 5/5) to afford **15** as a yellow oil (70% yield); IR ν (cm⁻¹): 1665; ¹H-NMR (300 MHz, DMSO-*d*₆): 7.05 (d, *J* = 8.0 Hz, 1H), 6.80-6.75 (m, 2H), 4.75 (s, 1H), 4.62 (m, 1H), 4.22 (m, 1H), 4.00 (m, 1H), 3.70 (s, 3H), 3.55 (q, 1H, *J* = 5.0 Hz), 3.35 (m, 1H), 3.20 (dd, 1H, *J* = 3.7 Hz and *J* = 12.7 Hz), 2.83 (m, 1H), 1.24 (s, 9H); LC-MS (ESI): *m/z* = 294 [M-H]⁺.

Tert-butyl-4-(cyanomethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (16): To a solution of **15** (10.5 g, 0.036 mol) in CH₂Cl₂ (150 mL) was added triethylamine (6.95 mL, 0.05 mol). The solution was stirred and cooled at 0 °C and methanesulfonyl chloride (4.8 mL, 0.062 mol) was added dropwise. The mixture reaction was stirred at room temperature for 2 h and then poured into water (150 mL). Aqueous layer was extracted two times with CH₂Cl₂. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was solubilized in DMSO (30 mL) and the solution was added slowly to a suspension of potassium cyanide (11.69 g, 0.180 mol) in DMSO (50 mL) at 80 °C. The mixture reaction was stirred and heated at 80 °C for 30minutes and poured into water (100 mL). Aqueous layer was extracted three times with CH₂Cl₂. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. The resulting oil was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 3/7) to afford **16** as a white solid (70% yield); mp 76 °C; IR ν (cm⁻¹): 2247, 1685; ¹H-NMR (300 MHz, DMSO-*d*₆): 7.15 (d, 1H, *J* = 8.5 Hz), 6.95 (d, 1H, *J* = 2.3 Hz), 6.85 (dd, 1H, *J* = 8.5 Hz and *J* = 2.3 Hz), 4.73 (m, 1H), 4.18 (m, 1H), 3.97 (m, 1H), 3.75 (s, 3H), 3.37 (m, 1H), 3.16 (m, 1H), 2.77 (m, 2H), 1.40 (s, 9H); LC-MS (ESI): *m/z* = 303 [M-H]⁺.

Tert-butyl-4-(2-aminoethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (17): A solution of **16** (6.3 g, 0.021 mol) in methanol

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saturated with ammonia (150 mL) was put in an autoclave. Raney Nickel (catalytic amount) was added. The mixture reaction was stirred and heated at 60 °C under H₂ (50 bars) for 6h. After cooling to room temperature, catalyst was filtered off. Solution was concentrated under *vacuum*. The resulting oil was purified using chromatography on silica gel (CH₂Cl₂/CH₃OH; 9/1) to afford **17** as a colorless oil (80% yield); IR ν (cm⁻¹): 3300-3600, 1670; ¹H-NMR (300 MHz, DMSO-*d*₆): 7.05 (d, 1H, *J* = 8.4 Hz), 6.80-6.70 (m, 2H), 4.67 (m, 1H), 4.13 (m, 1H), 3.87 (m, 1H), 3.72 (s, 3H), 3.15 (m, 2H), 2.64 (m, 1H), 1.45 (s, 9H); LC-MS (ESI): *m/z* = 307 [M-H]⁺.

General procedure for compounds 18a-18d: To a solution of **17** (1 eq.) in a mixture of ethyl acetate and water (3/2) were added potassium carbonate (2 eq.) and the corresponding acid chloride (2 eq.) dropwise. The mixture reaction was stirred at room temperature for 2 h. Ethyl acetate was added, and the organic layer was separated, washed with water, dried over MgSO₄, filtered and concentrated under *vacuum*. The resulting residue was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 5/5). The obtained oil was suspended in methanol with HCl gas and stirred for 1h. The solution was concentrated under *vacuum* and the obtained precipitate was filtered and dried.

N-(2-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)acetamide, hydrochloride (18a): a white solid (80% yield); mp 162-164 °C; IR ν (cm⁻¹): 1685; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.75 (s, 2H), 8.15 (s, 1H), 7.15 (d, 1H, *J* = 8.4 Hz), 6.90 (s, 1H), 6.80 (dd, 1H, *J* = 8.4 Hz and *J* = 2.3 Hz), 4.10 (s, 2H), 3.75 (s, 3H), 3.32 (m, 1H), 3.20-3.10 (m, 4H), 1.95-1.85 (m, 2H), 1.80 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 169.7, 159.1, 137.7, 128.4, 121.2, 113.4, 112.9, 55.6, 44.0, 43.7, 36.2, 33.5, 32.2, 23.1; LC-MS (ESI): *m/z* = 249 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₄H₂₁N₂O₂, 249.15975; found, 249.16249.

N-(2-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)propionamide hydrochloride (18b): a white solid (90% yield); mp 160-161 °C; IR ν (cm⁻¹): 1644; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.50 (br s, 2H), 8.00 (br t, 1H, *J* = 5.6 Hz), 7.15 (d, 1H, *J* = 8.4 Hz), 6.90-6.85 (m, 2H), 4.12 (s, 2H), 3.75 (s, 3H), 3.37 (m, 1H), 3.20-3.00 (m, 4H), 2.10 (q, 2H, *J* = 7.5 Hz), 1.85 (m, 2H), 1.00 (t, 3H, *J* = 7.5 Hz); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.6, 159.4, 137.7, 128.4, 122.2, 113.4, 113.4, 55.3, 44.2, 44.8, 36.8, 34.7, 33.2, 29.5, 10.7; LC-MS (ESI): *m/z* = 263 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₅H₂₃N₂O₂, 263.16812; found, 263.16249.

N-(2-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)butyramide hydrochloride (18c): a white solid (60% yield); mp 155-157 °C; IR ν (cm⁻¹):

1641; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.55 (br s, 2H), 8.02 (br t, 1H), 7.14 (d, 1H, *J* = 8.4 Hz), 6.90-6.80 (m, 2H), 4.13 (m, 2H), 3.75 (s, 3H), 3.37 (m, 1H), 3.25-3.00 (m, 4H), 2.06 (t, 2H, *J* = 7.4 Hz), 1.88 (m, 2H), 1.55 (m, 2H), 0.86 (t, 3H, *J* = 7.4 Hz); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 169.8, 159.8, 137.6, 128.7, 121.4, 113.2, 112.8, 55.7, 44.4, 43.7, 37.5, 36.5, 33.4, 32.2, 18.5, 12.9; LC-MS (ESI) : *m/z* = 277 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₆H₂₅N₂O₂, 277.18377; found, 277.17244.

N-(2-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)cyclopropanecarboxamide, hydrochloride (18d): a white solid (80% yield); mp 215-217 °C; IR ν (cm⁻¹): 1641; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.45 (br s, 2H), 8.27 (br s, 1H), 7.14 (d, 1H, *J* = 8.2 Hz), 6.89 (d, 1H, *J* = 2.7 Hz), 6.85 (dd, 1H, *J* = 8.2 Hz and *J* = 2.7 Hz), 4.14 (s, 2H), 3.75 (s, 3H), 3.40 (m, 1H), 3.25-3.05 (m, 4H), 1.88 (m, 2H), 1.57 (m, 1H), 0.70-0.60 (m, 4H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 169.4, 159.2, 137.5, 128.7, 121.8, 113.5, 112.9, 55.7, 44.2, 43.3, 36.4, 33.4, 32.3, 15.6, 7.6 (2C); LC-MS (ESI): *m/z* = 275 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₆H₂₃N₂O₂, 275.16812; found, 275.16944.

N-(2-(6-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)acetamide hydrochloride (19): to a solution of **18a** (1.8 g, 0.0072 mol) in formic acid (0.55 mL) was added formaldehyde 37% solution (0.6 mL) at 0 °C. The mixture reaction was stirred at 80 °C for 24h. After cooling, the solution was made acid with 2M HCl solution and washed with diethyl ether. The aqueous phase was then made basic with 2M NaOH solution and extracted two times with diethyl ether. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (CH₂Cl₂/CH₃OH: 9.5/0.5). The resulting oil was suspended in diethyl ether with HCl gas. The solid was filtered and dried to afford **19** as a hygroscopic white solid (30% yield); mp 60-63 °C; IR ν (cm⁻¹): 1658; ¹H-NMR (300 MHz, DMSO-*d*₆): 10.5 (br s, 1H), 8.02 (br s, 1H), 7.11 (d, 1H, *J* = 8.5 Hz), 6.95-6.85 (m, 2H), 3.77 (s, 3H), 4.16 (m, 2H), 3.36 (m, 2H), 3.19-2.89 (m, 3H), 2.88 (s, 3H), 2.08-1.76 (m, 5H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 169.9, 158.7, 137.4, 128.2, 122.7, 111.9, 110.9, 55.4, 44.6, 44.0, 43.7, 36.2, 33.4, 31.8, 23.2; LC-MS (ESI): *m/z* = 263 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₅H₂₃N₂O₂, 263.16813; found, 263.16712.

N-(2-(2-Allyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)acetamide hydrochloride (20): a suspension of **18a** (1.03 g, 0.0036 mol) and potassium carbonate (1.75 g, 0.0126 mol) in acetone (50 mL) was stirred at room temperature for 10minutes. Allyl bromide (0.48 mL, 0.0054 mol) was added and the mixture reaction was stirred at room

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temperature for 12h. The mineral solid was filtered, washed with acetone and the filtrate was concentrated under *vacuum*. The residue was suspended in water and aqueous layer was extracted two times with diethyl ether. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (CH₂Cl₂/CH₃OH; 9.5/0.5) and the resulting oil was suspended in diethyl ether with HCl gas. Solid was filtered and dried to afford **20** as a hygroscopic white solid (30% yield); mp 48-50 °C; IR ν (cm⁻¹): 1644; ¹H-NMR (300 MHz, DMSO-*d*₆): 10.6 (br s, 1H), 7.87 (br s, 1H), 6.94 (d, 1H, *J* = 8.3 Hz), 6.72 (m, 1H), 6.68 (d, 1H, *J* = 2.5 Hz), 5.88 (m, 1H), 5.21 (m, 2H), 3.71 (s, 3H), 3.60 (m, 1H), 3.33 (m, 2H), 3.16-2.95 (m, 4H), 2.65 (m, 1H), 2.45 (m, 1H), 1.81 (s, 3H), 1.75 (m, 2H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 169.7, 159.2, 137.8, 133.2, 128.2, 121.3, 117.5, 113.4, 112.9, 60.3, 55.6, 44.0, 43.7, 35.2, 33.5, 32.4, 23.2; LC-MS (ESI): *m/z* = 289 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₇H₂₅N₂O₂, 289.18378; found, 289.18245.

N-(2-(2-(Cyclopropylmethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)-acetamide, hydrochloride (21): the same procedure as described for compound **20** was used using (bromomethyl)cyclopropane (0.36 mL, 0.004 mol) as reagent to afford **21** as a hygroscopic white solid (30% yield); mp 65-68 °C IR ν (cm⁻¹): 1645; ¹H-NMR (300 MHz, DMSO-*d*₆): 10.4 (br s, 1H), 7.99 (br s, 1H), 7.17 (dd, 1H, *J* = 8.5 Hz), 6.96-6.86 (m, 2H), 4.46 (m, 2H), 4.25 (m, 2H), 3.78-3.77 (m, 4H), 3.36-2.90 (m, 4H), 2.10-1.70 (m, 5H), 1.07 (m, 1H), 0.68-0.44 (m, 4H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 169.5, 159.3, 137.4, 128.2, 122.2, 113.7, 113.2, 64.2, 54.6, 44.5, 43.2, 36.3, 33.5, 32.4, 23.21, 10.1, 4.2; LC-MS (ESI): *m/z* = 303 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₈H₂₇N₂O₂, 303.19943; found, 303.197105.

N-(2-(2-Benzyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)acetamide (22): to a suspension of **18a** (740 mg, 0.0025 mol) and potassium carbonate (720 mg, 0.005 mol) in dimethylformamide (20 mL) was added benzyl bromide (0.37 mL, 0.003 mol). The mixture reaction was stirred and heated at 60 °C for 4h. After cooling to room temperature, the mixture reaction was poured into water (50 mL) and acidified (3M HCl) solution. The aqueous layer was washed with diethyl ether, alkalinized with 2M NaOH and extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (CH₂Cl₂/CH₃OH; 9.5/0.5) and recrystallized from toluene/cyclohexane (7/3) to afford **22** as a white solid (42% yield); mp 123-125 °C; IR ν (cm⁻¹): 3230, 1642; ¹H-NMR (300 MHz,

DMSO-*d*₆): 7.80 (br t, 1H), 7.35-7.27 (m, 5H), 6.92 (d, 1H, *J* = 8.5 Hz), 6.72 (d, 1H, *J* = 2.7 Hz), 6.67 (dd, 1H, *J* = 8.9 Hz and *J* = 2.7 Hz), 3.70 (s, 3H), 3.65-3.52 (m, 3H), 3.25 (m, 1H), 3.02 (m, 2H), 2.74 (m, 1H), 2.64 (m, 1H), 2.44 (m, 1H), 1.90-1.82 (m, 5H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.4, 159.2, 138.5, 136.1, 133.3, 128.7, 128.2, 127.4, 127.2, 112.3, 108.3, 62.4, 62.1, 55.4, 53.2, 34.5, 32.8, 29.6, 23.3; LC-MS (ESI): *m/z* = 339 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₂₁H₂₇N₂O₂, 339.19943; found, 339.19932.

N-(2-(6-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)acetamide hydrochloride (23): to a solution of **18a** (460 mg, 0.0018 mol) in CH₂Cl₂ (30 mL) were added under inerte atmosphere (argon), triphenylbismuth (900 mg, 0.002 mol) and copper acetate (II) (190 mg, 0.00095 mol). The reaction mixture was stirred at room temperature for 18h. The mineral was filtered, washed with CH₂Cl₂. The organic layer was washed with water, dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 2/8) and the resulting oil was suspended in diethyl ether with HCl gas. Solid was filtered and dried to afford **23** as a white solid (75% yield); mp 84-85 °C; ¹H-NMR (300 MHz, DMSO-*d*₆): 10.31 (br s, 1H), 8.01 (br s, 1H), 7.42-7.37 (m, 5H), 7.16 (d, 1H, *J* = 8.5 Hz), 6.89-6.82 (m, 2H), 4.48 (m, 2H), 3.76 (s, 3H), 3.73 (m, 1H), 3.58 (m, 1H), 3.22-3.12 (m, 3H), 1.97-1.76 (m, 5H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.2, 159.2, 148.4, 135.2, 128.5, 126.8, 126.6, 122.4, 114.6 (2C), 112.4, 108.5, 67.4, 56.2, 54.7, 35.3, 34.4, 29.2, 23.6; LC-MS (ESI): *m/z* = 325 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₂₀H₂₅N₂O₂, 325.18378; found, 325.18245.

Tert-butyl-4-(azidomethyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (24): to a solution of **15** (5.25 g, 0.018 mol) in CH₂Cl₂ (60 mL) was added triethylamine (4.18 mL, 0.03 mol). The solution was stirred at 0 °C and methanesulfonyl chloride (2.4 mL, 0.03 mol) was added dropwise. The mixture reaction was stirred at room temperature for 2 h and then poured into water. Aqueous layer was extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was solubilized in DMF (50 mL) and sodium azide (1.3 g, 0.02 mol) was added. The mixture reaction was stirred and heated at 80 °C for 3h. After cooling to room temperature, the mixture reaction was poured into water. Aqueous layer was extracted with ethyl acetate. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 2/8 to 5/5) to

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afford **24** as a colorless oil (84% yield); IR ν (cm^{-1}): 2100, 1693; $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.45 (d, 1H, $J = 8.6$ Hz), 6.81 (dd, 1H, $J = 8.6$ Hz and $J = 2.7$ Hz), 6.71 (m, 1H), 4.31 (m, 2H), 3.80 (s, 3H), 3.50-3.34 (m, 3H), 3.18 (dd, 1H, $J = 13.4$ Hz and $J = 3.6$ Hz), 2.90 (m, 1H), 1.52 (s, 9H); LC-MS (ESI): $m/z = 319$ $[\text{M-H}]^+$.

Tert-butyl-4-(aminomethyl)-6-methoxy-3,4-dihydroisoquinoline-

2(1H)-carboxylate (25): to a solution of **24** (1.14 g, 0.0035 mol) in methanol (100 mL) was added palladium on activated charcoal (120 mg).

The mixture reaction was stirred at room temperature under H_2 atmosphere for 3h. Catalyst was filtered off and the solution was concentrated under *vacuum*. Residue was purified using chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$: 9/1) to afford **25** as a colorless oil (77% yield); IR ν (cm^{-1}): 1689 (CO); $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.04 (d, 1H, $J = 8.4$ Hz), 6.78 (dd, 1H, $J = 8.4$ Hz and $J = 2.6$ Hz), 6.70 (m, 1H), 4.30 (m, 2H), 3.79 (s, 3H), 3.12 (m, 1H), 2.86-2.72 (m, 4H), 1.50 (s, 9H); LC-MS (ESI): $m/z = 293$ $[\text{M-H}]^+$.

N-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)acetamide, hydrochloride (26):

to a solution of **25** (0.77 g, 0.0026 mol) in CH_2Cl_2 (25 mL) and water (25 mL) were added potassium carbonate (1.8 g, 0.013 mol) and acetyl chloride (0.47 mL, 0.0065 mol) dropwise. The solution was stirred at room temperature for 2 h. Aqueous layer was extracted with CH_2Cl_2 . Combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under *vacuum*. The resulting oil was suspended in methanol with HCl gas for 2h. The solution was concentrated under *vacuum* and the obtained precipitate was recrystallized from acetonitrile to afford **26** as a white solid (70% yield); mp 246-248 °C; IR ν (cm^{-1}): 1645; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 9.67 (br s, 1H), 9.18 (br s, 1H), 8.24 (m, 1H), 7.18-7.14 (d, 1H, $J = 9.3$ Hz), 6.89-6.86 (m, 2H), 4.15 (s, 2H), 3.76 (s, 3H), 3.52-3.16 (m, 5H), 1.86 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz $\text{DMSO-}d_6$) δ : 170.3, 159.6, 145.1, 126.5, 125.5, 110.2, 106.2, 56.8, 56.6, 46.7, 42.7, 42.2, 23.3; LC-MS (ESI): $m/z = 235$ $[\text{M-H}]^+$; HRMS (ESI) $[\text{M+H}]^+$ calculated for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$, 235.13683; found, 235.13351.

Tert-butyl-4-(2-cyanoethyl)-6-methoxy-3,4-dihydroisoquinoline-

2(1H)-carboxylate (27): to a solution of **15** (10.5 g, 0.036 mol) in CH_2Cl_2 (150 mL), were added triethylamine (8.36 mL, 0.06 mol) and methanesulfonyl chloride (4.64 mL, 0.06 mol) dropwise at 0 °C. The mixture reaction was stirred at room temperature for 2h, poured into water and extracted with ethyl acetate. Organic layer was dried over MgSO_4 , filtered and concentrated under *vacuum* to give a crude mesylate. Sodium (0.92 g, 0.04 at.g) was solubilized in ethanol (50 mL) and ethyl

cynoacetate (5.9 mL, 0.054 mol) was added dropwise. The solution was stirred at room temperature for 30 minutes and then concentrated under *vacuum* to give the sodium salt of ethyl cyanoacetate. The crude mesylate was solubilized in DMF (50 mL) and the sodium salt was added dropwise. The solution was heated at 100 °C under stirring for 4h. After cooling to room temperature, the reaction mixture was poured into water (150 mL). Aqueous layer was extracted with diethyl ether. Organic layer was dried over MgSO_4 , filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane 3/7) to afford **27** as a colorless oil (45% yield); IR ν (cm^{-1}): 2246, 1694; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 7.15 (d, 1H, $J = 8.4$ Hz), 6.95 (d, 1H, $J = 2.7$ Hz), 6.85 (dd, 1H, $J = 8.4$ Hz and $J = 2.7$ Hz), 4.80-4.60 (m, 1H), 4.30-4.10 (m, 1H), 3.74-3.72 (m, 4H), 3.55-3.35 (m, 3H), 3.25-3.10 (m, 1H), 2.95-2.75 (m, 2H), 1.45 (s, 9H); LC-MS (ESI): $m/z = 317.2$ $[\text{M-H}]^+$.

N-(2-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)ethyl)acetamide, hydrochloride (28):

a solution of **27** (1.69 g, 0.0053 mol) in acetic anhydride (50 mL) was put in an autoclave. Raney Nickel was added, and the mixture reaction was heated at 60 °C under H_2 atmosphere (50 bars) for 6 h. After cooling to room temperature, catalyst was filtered off and the solution was concentrated under *vacuum*. Residue was suspended in a 10% sodium hydroxide solution and extracted two times with ethyl acetate. Combined organic layers were dried over MgSO_4 , filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane; 5/5). The resulting oil was suspended in methanol with HCl gas and stirred for 2h. The solution was concentrated under *vacuum* and the obtained precipitate was recrystallized from acetonitrile to afford **28** as a white solid (37% yield); IR ν (cm^{-1}): 1614; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 9.36 (br m, 2H), 8.02 (m, 1H), 7.12 (d, 1H, $J = 8.5$ Hz), 6.93-6.82 (m, 2H), 4.14 (s, 2H), 3.76-3.74 (m, 5H), 3.35 (m, 2H), 3.20-3.05 (m, 5H), 1.82 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz $\text{DMSO-}d_6$) δ : 170.4, 158.5, 136.8, 126.8, 126.3, 111.4, 109.4, 58.7, 54.8, 46.7, 40.4, 39.2, 30.8, 27.2, 23.4; LC-MS (ESI): $m/z = 263$ $[\text{M-H}]^+$; HRMS (ESI) $[\text{M+H}]^+$ calculated for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_2$, 263.15241; found, 263.14482.

Ethyl 5-cyano-5-(3-methoxyphenyl)pentanoate (29): to a solution of 3-methoxyphenylacetone (2 g, 0.013 mol) in dry dimethylformamide (50 mL) were added ethyl 4-bromobutyrate (1.5 mL, 0.01 mol) and sodium hydride suspension (60% suspension in paraffin oil) (600 mg, 0.015 mol) portion wise. The reaction mixture was stirred at room temperature for 4 h and poured into water. Aqueous layer was acidified with 2M HCl solution and extracted with diethyl ether. Organic layer was dried over MgSO_4 ,

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filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 4/6) to afford **29** as a yellow oil (50% yield); IR ν (cm^{-1}): 2240, 1732; $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.31 (t, 1H, $J = 8.0$ Hz), 6.95-6.80 (m, 3H), 4.12 (q, 2H, $J = 7.2$ Hz), 3.82 (s, 3H), 3.78 (t, $J = 7.1$ Hz, 1H), 2.35 (t, 2H, $J = 7.0$ Hz), 1.86 (m, 2H), 1.78 (m, 2H), 1.25 (t, 3H, $J = 7.2$ Hz); LC-MS (ESI): $m/z = 262$ [M-H] $^+$.

Ethyl 6-amino-5-(3-methoxyphenyl)hexanoate, hydrochloride (30): the same procedure as described for compound **2** starting from **29** (11.2 g, 0.043 mol) under H_2 atmosphere (10 bars). The resulting oil was suspended in diethyl ether and the solid was filtered and recrystallized from toluene to afford **30** as a white solid (60% yield); mp 104-105 °C; IR ν (cm^{-1}): 1725; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 7.28 (t, 1H, $J = 7.3$ Hz), 6.88-6.82 (m, 3H), 4.01 (q, 2H, $J = 7.3$ Hz), 3.76 (s, 3H), 3.01 (m, 2H), 2.83 (m, 1H), 2.23 (t, $J = 7.6$ Hz, 2H), 1.60 (m, 2H), 1.32 (m, 2H), 1.15 (t, 3H, $J = 7.3$ Hz); LC-MS (ESI): $m/z = 266$ [M-H] $^+$.

Ethyl 6-formamido-5-(3-methoxyphenyl)hexanoate (31): the same procedure as described for compound **3a** was used starting from **30** (6.4 g, 0.027 mol) to afford **31** as a yellow oil (90% yield); IR ν (cm^{-1}): 3304, 1730, 1666; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 8.07 (s, 1H), 7.26 (t, 1H, $J = 7.9$ Hz), 6.82-6.70 (m, 3H), 5.38 (s, 1H), 4.08 (q, 2H, $J = 8.2$ Hz), 3.84-3.76 (m, 4H), 3.20 (m, 1H), 2.77 (m, 1H), 2.27 (m, 2H), 1.62 (m, 2H), 1.51 (m, 2H), 1.24 (t, 3H, $J = 8.2$ Hz); LC-MS (ESI): $m/z = 294$ [M-H] $^+$.

Ethyl 4-(6-methoxy-3,4-dihydroisoquinolin-4-yl)butanoate, hydrochloride (32): to a solution of **31** (6.8 g, 0.023 mol) in acetonitrile (150 mL) was stirred at 60 °C. Phosphorus oxychloride (9.2 mL, 0.1 mol) was added and the solution was stirred under reflux for 6h. The solution was cooled to room temperature and concentrated under *vacuum*. Water was added, and the aqueous phase was washed with diethyl ether and then alkalinized using a potassium carbonate solution (10%). Aqueous layer was extracted with CH_2Cl_2 and organic layer was dried over MgSO_4 , filtered and concentrated under *vacuum*. The resulting oil was suspended in diethyl ether with HCl gas. Solid was filtered and recrystallized from toluene to afford **32** as a white solid (54% yield); mp 97-99 °C; IR ν (cm^{-1}): 1726; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 13.59 (br s, 1H), 9.08 (s, 1H), 7.94 (d, 1H, $J = 8.3$ Hz), 7.15-7.10 (m, 2H), 4.01 (q, 2H, $J = 7.1$ Hz), 3.92 (s, 3H), 3.86 (m, 2H), 3.16 (m, 1H), 2.30 (m, 2H), 1.52 (m, 2H), 1.41 (m, 2H), 1.15 (t, $J = 7.1$ Hz, 3H); LC-MS (ESI): $m/z = 276$ [M-H] $^+$.

4-(6-Methoxy-3,4-dihydroisoquinolin-4-yl)-N-methylbutanamide, hydrochloride (33): a solution of **32** (1.56 g, 0.0056 mol) in ethanol (20 mL) containing methylamine 40 Wt. % in H_2O (70 mL) was stirred at room

temperature for 12 h and poured in water (50 mL). Aqueous layer was extracted with CH_2Cl_2 and the organic layer was dried over MgSO_4 , filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$: 9/1). The obtained oil was suspended in diethyl ether with HCl gas and the obtained precipitate was filtered, dried and recrystallized from acetonitrile to afford **33** as white solid (85% yield); mp 77-79 °C; IR ν (cm^{-1}): 1644; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 8.23 (s, 1H), 7.71 (s, 1H), 7.33 (d, 1H, $J = 8.3$ Hz), 6.88 (dd, 1H, $J = 8.3$ and $J = 2.5$ Hz), 6.80 (d, 1H, $J = 2.5$ Hz), 3.80 (s, 3H), 3.75 (m, 1H), 3.48 (m, 1H), 2.64 (m, 1H), 2.53 (d, 1H, $J = 4.6$ Hz), 2.02 (m, 2H), 1.56-1.35 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz $\text{DMSO-}d_6$) δ : 172.9, 162.7, 159.5, 140.0, 130.0, 124.0, 112.3, 111.6, 56.8, 55.8, 39.0, 36.5, 32.9, 26.2, 22.7; LC-MS (ESI): $m/z = 261$ [M-H] $^+$.

4-(6-Methoxy-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-methylbutanamide, hydrochloride (34): the same procedure as described for compound **14** was used starting from **33** (1.42 g, 0.0054 mol). Crude product was recrystallized from acetonitrile to afford **34** as a white solid (60% yield); mp 138-140 °C; IR ν (cm^{-1}): 3318, 1668; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 9.28 (s, 2H), 7.81 (m, 1H), 7.14 (d, 1H, $J = 8.0$ Hz), 6.86 (m, 1H), 6.82 (d, 1H, $J = 2.4$ Hz), 4.14 (s, 2H), 3.75 (s, 3H), 3.35 (m, 1H), 3.12 (m, 2H), 2.56 (d, 3H, $J = 4.2$ Hz), 2.11 (m, 2H), 1.73-1.53 (m, 4H); $^{13}\text{C-NMR}$ (75 MHz $\text{DMSO-}d_6$) δ : 172.6, 158.1, 137.1, 126.4, 125.2, 113.4, 111.9, 109.2, 58.6, 55.2, 47.0, 39.7, 36.2, 32.2, 22.3; LC-MS (ESI): $m/z = 265$ [M-H] $^+$; HRMS (ESI) [M+H] $^+$ calculated for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_2$, 263.16213; found, 265.16423.

4-(6-Methoxyisoquinolin-4-yl)-N-methylbutanamide (35): the same procedure as described for compound **5a** was used starting from **33** (1.42 g, 0.0054 mol) to afford **35** (80% yield); mp 117-118 °C; IR ν (cm^{-1}): 3250, 1669; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 9.01 (s, 1H), 8.25 (s, 1H), 8.02 (d, 1H, $J = 9.0$ Hz), 7.81 (s, 1H), 7.42 (d, 1H, $J = 2.3$ Hz), 7.30 (dd, $J = 9.0$ Hz and $J = 2.3$ Hz), 3.97 (s, 3H), 2.92 (t, $J = 7.7$ Hz, 2H), 2.59 (d, $J = 4.9$ Hz, 3H), 2.18 (t, 1H, $J = 7.0$ Hz, 2H), 1.89 (m, 2H); $^{13}\text{C-NMR}$ (75 MHz $\text{DMSO-}d_6$) δ : 172.6, 161.0, 150.5, 143.3, 136.3, 130.4, 130.3, 124.2, 119.9, 110.9, 56.0, 35.1, 29.4, 26.2, 25.9; LC-MS (ESI): $m/z = 259$ [M-H] $^+$; HRMS (ESI) [M+H] $^+$ calculated for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2$, 259.14691; found, 259.14410.

N-((6-Methoxyisoquinolin-4-yl)methyl)acetamide, hydrochloride (36): to a suspension of **26** (0.7 g, 0.003 mol) in toluene (20 mL) were added potassium carbonate (0.414 g, 0.003 mol) and palladium on activated charcoal (100 mg). The mixture reaction was stirred and heated at reflux for 48 h. After cooling to room temperature, catalyst was filtered off and

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the solution was concentrated under *vacuum*. The resulting oil was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 7/3) and suspended in diethyl ether with HCl gas. Solid was filtered and recrystallized from toluene to afford **36** as a white solid (30% yield); mp 203-204 °C; IR ν (cm⁻¹): 1654; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.60 (s, 1H), 8.77 (br t, 1H), 8.43-8.35 (m, 2H), 7.71-7.55 (m, 2H), 4.76 (m, 2H), 4.05 (s, 3H), 1.91 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.2; 165.4, 145.5, 139.4, 133.5, 132.3, 131.7, 123.4, 122.8, 103.2, 57.0, 38.0, 22.9; LC-MS (ESI): *m/z* = 231 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₃H₁₅N₂O₂, 231.11280; found, 231.11528.

N-(3-(6-Methoxyisoquinolin-4-yl)propyl)acetamide, hydrochloride (37): the same procedure as described for compound **36** starting from **28** (0.750 g, 0.0025 mol). After 3h, the resulting precipitate was recrystallized from acetonitrile to afford **37** as a white solid (35% yield); mp 195-198 °C; IR ν (cm⁻¹): 3300, 1654; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.65 (s, 1H), 9.62 (s, 1H), 8.22 (s, 1H), 7.89 (m, 1H), 7.66 (m, 1H), 7.55 (m, 1H), 3.76-3.74 (m, 4H), 3.43 (m, 2H), 3.30 (m, 2H), 3.20-3.05 (m, 1H), 1.79 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 170.2, 161.2, 151.4, 141.9, 134.7, 129.8, 125.2, 123.4, 119.7, 102.4, 55.4, 38.6, 29.4, 27.7, 23.4; LC-MS (ESI): *m/z* = 259 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₅H₁₉N₂O₂, 259.13683; found, 259.12515.

N-(2-(6-Methoxyisoquinolin-4-yl)ethyl)propionamide, hydrochloride (38): the same procedure as described for compound **36** was used starting from **18b** to afford **38** as a white solid (55% yield); mp 233-235 °C; IR ν (cm⁻¹): 3269, 1649; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.60 (s, 1H), 8.50-8.45 (m, 2H), 8.10 (s, 1H), 7.85 (d, 1H, *J* = 1.9 Hz), 7.65 (dd, 1H, *J* = 9.4 Hz and *J* = 1.9 Hz), 4.15 (s, 3H), 3.42 (m, 2H), 3.25 (t, 2H, *J* = 6.6 Hz), 2.05 (q, 2H, *J* = 7.5 Hz), 0.95 (t, 3H, *J* = 7.5 Hz); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 171.2, 166.7, 144.5, 141.7, 133.2, 133.5, 131.7, 123.7, 123.8, 103.3, 57.1, 38.9, 30.5, 29.8, 11.2; LC-MS (ESI): *m/z* = 259.1 [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₅H₁₉N₂O₂, 259.13683; found, 259.12756.

N-(2-(6-Methoxyisoquinolin-4-yl)ethyl)butyramide, hydrochloride (39): the same procedure as described for compound **36** was used starting from **18c** to afford **39** as a white solid (35% yield); mp 195-197 °C; IR ν (cm⁻¹): 3247, 1656; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.63 (s, 1H), 8.50-8.45 (m, 2H), 8.18 (s, 1H), 7.86 (d, 1H, *J* = 1.9 Hz), 7.66 (dd, 1H, *J* = 9.0 Hz and *J* = 1.9 Hz), 4.13 (s, 3H), 3.40 (m, 2H), 3.27 (t, 2H, *J* = 6.8 Hz), 2.00 (t, 2H, *J* = 7.3 Hz), 1.45 (m, 2H), 0.77 (t, 3H, *J* = 7.3 Hz); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 172.5, 162.4, 151.5, 141.9, 134.7, 129.7, 123.4, 119.4, 102.7, 55.4, 42.1, 37.7, 30.4, 19.1, 13.2; LC-MS (ESI): *m/z* = 273.2 [M-H]⁺;

HRMS (ESI) [M+H]⁺ calculated for C₁₆H₂₁N₂O₂, 273.15248; found, 273.15457.

N-(2-(6-Methoxyisoquinolin-4-yl)ethyl)cyclopropanecarboxamide, hydrochloride (40): Same procedure as described for compound **36** was used starting from **18d** to afford **40** as a white solid (30% yield); mp 227 °C; IR ν (cm⁻¹): 3245, 1641; ¹H-NMR (300 MHz, DMSO-*d*₆): 9.54 (s, 1H), 8.55-8.40 (m, 3H), 7.77 (d, 1H, *J* = 2.1 Hz), 7.64 (dd, 1H, *J* = 9.3 Hz and *J* = 2.1 Hz), 4.09 (s, 3H), 3.44 (m, 2H), 3.26 (t, 2H, *J* = 6.7 Hz), 1.45 (m, 1H), 0.65-0.55 (m, 4H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 173.3, 161.4, 150.4, 142.9, 135.7, 129.8, 125.0, 124.4, 119.7, 102.7, 55.8, 41.3, 30.1, 15.3, 7.6; LC-MS (ESI): *m/z* = [M-H]⁺; HRMS (ESI) [M+H]⁺ calculated for C₁₆H₁₉N₂O₂, 271.13683; found, 271.13743.

6-Methoxyisoquinoline-4-carbaldehyde (41): to a solution of **6a** (1 g, 0.0044 mol) in DMSO (40 mL) was added Manganese oxide (200 mg). The mixture reaction was stirred and heated at 150 °C for 48 h. After cooling to room temperature, the crude was poured in water (50 mL). Aqueous layer was extracted with ethyl acetate. Combined organic layers were dried over MgSO₄, filtered and concentrated under *vacuum*. Crude product was purified using chromatography on silica gel (ethyl acetate/cyclohexane : 7/3) to afford after recrystallization from cyclohexane compound **41** as a yellow solid (70% yield); mp 120-122 °C; IR ν (cm⁻¹): 1690; ¹H-NMR (300 MHz, DMSO-*d*₆): 10.34 (s, 1H), 9.27 (s, 1H), 8.88 (s, 1H), 8.62 (d, 1H, *J* = 2.5 Hz), 7.95 (d, 1H, *J* = 9.0 Hz), 7.35 (dd, 1H, *J* = 9.0 and 2.5 Hz), 4.04 (s, 3H). LC-MS (ESI): *m/z* = 188.2 [M-H]⁺.

(E)-6-Methoxy-4-(2-nitrovinyl)isoquinoline (42): to a stirred solution of the aldehyde **41** (0.5 g, 0.0026 mol) in nitromethane (30 mL) was added ammonium acetate (0.23 g, 0.003 mol) at room temperature. The resulting red solution was heated at reflux for 5 h. After removal of nitromethane by evaporation, the residue was diluted with CH₂Cl₂, washed with water twice and brine. The organic layer was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified using chromatography on silica gel (ethyl acetate/cyclohexane: 7/3) to afford **42** as colourless oil (68% yield); ¹H-NMR (300 MHz, DMSO-*d*₆): 9.24 (s, 1H), 8.56 (s, 1H), 8.62 (d, 1H, *J* = 2.6 Hz), 8.15 (d, 1H, *J* = 13.5 Hz), 7.88-7.84 (m, 2H), 7.25 (dd, 1H, *J* = 9.2 and 2.6 Hz), 4.0 (s, 3H). LC-MS (ESI): *m/z* = 231.2 [M-H]⁺.

(E)-N-(2-(6-Methoxyisoquinolin-4-yl)vinyl)acetamide (43): a suspension of iron powder suspension of iron powder (1.6 g, 0.030 mol) in acetic anhydride (5 ml) and acetic acid (0.2 ml) was heated to reflux under an argon atmosphere for 30 minutes and the compound **42** (0.23 g, 0.001

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mol) was then added in portions. After heating for a further 4h, the mixture was cooled, diluted with methanol and filtered. The filtrate was evaporated, and the residue taken up in a little methanol and the pH adjusted to about 12-14 using methanolic KOH. Filtration through celite followed by removal of the solvent and purification of the residue by chromatography on silica gel (ethyl acetate/cyclohexane: 5/5) afford **43** as white solid (10% yield); mp 204-206 °C; IR ν (cm⁻¹): 1635; ¹H-NMR (300 MHz, DMSO-*d*₆): 10.36 (br d, 1H, *J* = 10.2 Hz), 8.99 (s, 1H), 8.47 (s, 1H), 8.02 (d, 1H, *J* = 8.9 Hz), 7.42 (dd, 1H, *J* = 10.2 Hz and *J* = 14.5 Hz), 7.31 (dd, *J* = 2.3 Hz and *J* = 8.9 Hz, 1H), 7.23 (d, 1H, *J* = 2.3 Hz), 6.67 (d, 1H, *J* = 14.5 Hz), 3.94 (s, 3H), 2.01 (s, 3H); ¹³C-NMR (75 MHz DMSO-*d*₆) δ : 167.9, 160.9, 150.1, 139.7, 135.0, 130.4, 126.8, 126.5, 124.0, 120.2, 105.0, 101.2, 55.8, 23.2; LC-MS (ESI): *m/z* = [M-H]⁺. HRMS (ESI) [M+H]⁺[M+H]⁺ calculated for C₁₄H₁₅N₂O₂, 243.11549; found, 243.11280.

Binding and pharmacokinetic studies

Reagents and chemicals: 2-[¹²⁵I]iodomelatonin (2200 Ci/mmol) was purchased from NEN (Boston, MA). Other drugs and chemicals were purchased from Sigma–Aldrich (Saint Quentin, France) and used without further purification.

Cell Culture: HEK (provided by A.D. Strosberg, Paris, France) and CHO cell lines stably expressing the human melatonin MT₁ or MT₂ receptors were grown in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU/mL penicillin and 100 mg/mL streptomycin. Grown at confluence at 37 °C (95%O₂/5%CO₂), 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 5mM (pH 7.5), containing EDTA 2mM and homogenized using a Kinematica polytron. The homogenate was then centrifuged (95000 *g*, 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.

Binding assays for MT₁ and MT₂ receptors subtypes: 2-[¹²⁵I]iodomelatonin competition binding assay conditions were essentially as previously described.^[34] Briefly, binding was initiated by addition of membrane preparations from transfected CHO cells stably expressing the human melatonin MT₁ or MT₂ diluted in binding buffer (50 mM Tris–HCl buffer, pH 7.4, containing 5 mM MgCl₂) to 2-[¹²⁵I]iodomelatonin (20 pM for MT₁ and MT₂ receptors expressed in CHO cells) and the tested drug. Non-specific binding was defined in the presence of 1 μM of 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 (seven concentrations in duplicate) were analyzed using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield IC₅₀ (inhibitory concentration 50). Affinities are expressed as pK_i.^[35] [³⁵S] GTPγS binding assay was performed according to published methodology.^[34] 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 mM and 180 in the presence of GTPγS 10 mM 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 E_{max} (maximal effect) for agonists. Antagonist potencies are expressed as K_B = IC₅₀/1 + ([Ago]/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 ([Ago]) and EC₅₀ ago is the EC₅₀ 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 MT₂ receptor. Serotonin 5-HT_{2C} binding assay was determined according to reported tests.^[35]

cLogP and cytotoxicity: The *n*-octanol-water partition coefficients, which are well established measures of the compounds' hydrophilicity, were calculated for final prepared compounds by use of theoretical procedures previously.^[36] Numerical values of the partition coefficients were obtained as follows using using Data Warrior software: the logP value, which is the logarithm of the partition coefficient of a compound between *n*-octanol and water $\log(C_{\text{octanol}}/C_{\text{water}})$, is calculated as increment system the contributions of every atom based on its atom type. Cytotoxic activities towards standard cancer cell line Caco-2 was performed using the same procedure as was previously described.^[37]

Drug metabolism. Drug metabolism experiments were conducted to better understand the properties of the prepared compounds in terms of pharmacokinetics or drug's cellular penetration. The first experiments were those involving measurement of the behavior of prepared compounds in an in cellulo-blood-brain barrier model, based on co-cultures of bovine brain micro-vessel endothelial cells and rat astrocytes. [38] Permeability surface total (PSt) (filter + collagen + cells) and permeability surface filter (PSf) (filter + collagen without cells) expressed in milliliters per minute were

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measured, and the ratio PSt/PSf (permeability class) was determined for each compound.

Molecular docking experiments

Molecular docking studies were performed using AutodockVina 1.1.2 software,^[33] using the recently disclosed melatonin receptor structures (PDB ID: 6ME5, 6ME6 & 6ME9) with orthosteric binding site agonists (agomelatine, 4-phenylmelatonin and ramelteon). Hydrogens and charges were added then ligands were removed, centering the searching box 10 Å around this region. Binding poses were analyzed for their binding mode and assessed in comparison with crystallized analogs.

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Keywords: agomelatine • melatonin • MT₁/MT₂ • isoquinoline • tetrahydroisoquinoline

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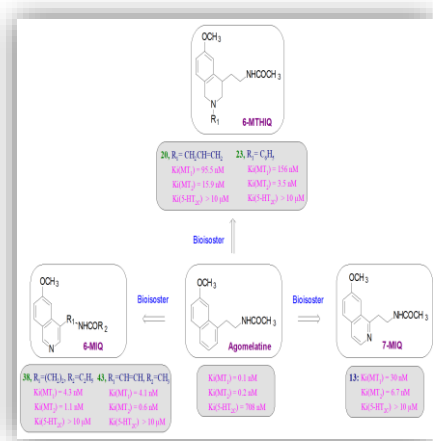
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A new series of isoquinoline and tetrahydroisoquinoline derivatives and showed good melatonergic affinity and no 5-HT_{2C} affinity. Compounds **38** and **43** showed the most interesting binding affinities, while tetrahydroisoquinoline **23** showed a 45 times MT₂-selectivity over MT₁ receptor subtype.

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