Multitarget Compounds for Bipolar Disorder: From Rational Design to Preliminary Pharmacokinetic Evaluation

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Multitarget compounds for bipolar disorder: from rational design to preliminary pharmacokinetic evaluation

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Abstract: Due to the complex and multifactorial nature of bipolar disorder (BD), single target drugs have traditionally provided limited relief with no disease modifying effects. In line with the polypharmacology paradigm, we attempt to overcome these limitations devising two series of multitarget-directed ligands endowed with both a partial agonist profile at dopamine receptor D3 (D3R) and inhibitory activity against glycogen synthase kinase 3 beta (GSK-3β). These are two structurally unrelated targets that play independent yet connected roles in cognition and mood regulation. Two compounds (**7** and **10**) emerged as promising D3R/GSK-3β multitarget-directed ligands with nanomolar activity at D3R and low micromolar inhibition of GSK-3β, confirming, albeit preliminarily, the feasibility of our strategy. Furthermore, **7** showed promising drug-like properties in stability and pharmacokinetic studies.

Bipolar disorder (BD) is a severe neuropsychiatric condition in which episodes of mania alternate with depression. With an estimated worldwide prevalence up to 4%, BD is one of the leading causes of disability. While molecular details of BD etiopathology remain rather controversial, it has been shown that an increased level of striatal dopamine (DA) D2/3 receptors (D2/3Rs) leads to hyperdopaminergia and in turn to mania; in parallel, elevated levels of striatal DA transporter induce hypo-dopaminergia, which leads to depression. Additionally, faulty homoeostatic mechanisms of DA are likely to play a role in cyclical and marked changes of DA tone, which are at the basis of the bipolar nature of the disorder.[1] Depending on the specific phase, DA antagonists or partial agonists have been employed for the treatment of BD. Some D2/D3Rs partial agonists, namely cariprazine and aripiprazole (**Figure 1**), have been approved as monotherapy for BD.[2] However, the therapeutic outcome of this regimen is hampered by severe side effects caused by

antagonism at D2R. D3R-selective agents could represent a better option.[3] Recently, several selective and potent D3R partial agonists have been reported (e.g. BP-897, **Figure 1**).[4]

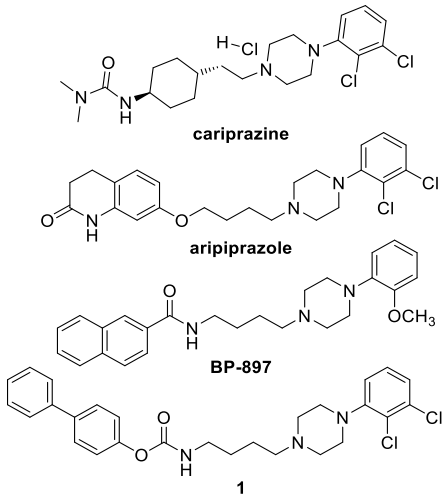


Figure 1. Chemical structures of the D2/D3R partial agonists, the selective D3R partial agonist, and the dual D3R/FAAH modulator mentioned in this study.

In response to persistently elevated extracellular DA levels, the D2-like receptors, through a cAMP-independent mechanism, negatively regulate the Akt/GSK-3β (glycogen synthase kinase 3 beta) intracellular pathway, resulting in GSK-3β activation.[5] This cascade is considered a signal integrator that ensues a fine-tuning of the DA system and that affects several pathways involved in mood regulation, i.e. circadian clock, glutamatergic and serotonergic neurotransmission.[5a] The clinical effects of lithium (Li), a mood stabilizer widely used in BD treatment, could be mediated by either a direct or an indirect GSK-3β inhibition.

Given the multifactorial nature of BD, can we exploit for therapeutic purposes the independent yet connected roles of D3R and GSK-3β in cognition and mood regulation? Multitarget-directed ligands (MTDLs)[6] matching both the pharmacophoric traits of D3R selective partial agonists[7] and the signature H-bond forming pattern of protein kinases inhibitors[8] would be able to concurrently modulate the DA signalling network at two key nodes.

Here, applying a rational multitarget design strategy already employed in the discovery of dual D3R/FAAH modulators (e.g. compound **1**, **Figure 1**),[9] we disclose the first series of D3R partial agonist/GSK-3β inhibitors MTDLs (**Figure 2**). These dual modulators display the following features: a 2,3-di-chlorophenylpiperazine function, widely recognised as a G protein-coupled receptor *(*GPCR) privileged fragment, able to target ASP110 (conserved position 3.32, according to the Ballesteros–Weinstein numeration[10]) in the orthosteric binding pocket (OBP); a four-methylene aliphatic linker; two different ureido/amido-functionalised heterocyclic cores, as dual H-bond systems directed to the D3R specificity binding pocket (SBP) and GSK-3β hinge region. In detail, compounds **5-7** (series I) bear a 2-oxo-2,3-dihydro-1*H*-benzimidazole and **8-10** (series II) a 1*H*-pyrazol-5-amino framework. These heterocyclic cores have previously been exploited for GSK-3β inhibition (compounds **2**, **3** and **4**, **Figure 2**).[11] For the unsubstituted analogues **5** and **8**, bound conformations at both targets were predicted by docking simulations (**Figure 3**). Based on these outcomes, the role of the substituents able to establish additional interactions (van der Waals or H-bond) with the targets was investigated; thus, series I and II scaffolds were decorated with a phenyl or a 3-pyridine moiety, to obtain analogues **6**, **9** and **7**, **10** (**Figure 2**). For series I, to separate the contributions of the 2-oxo-benzimidazole framework and the arylpiperazine function to the affinity for GSK-3β, fragments **11-13** were prepared (**Figure 2**, **Scheme S3** of SI).

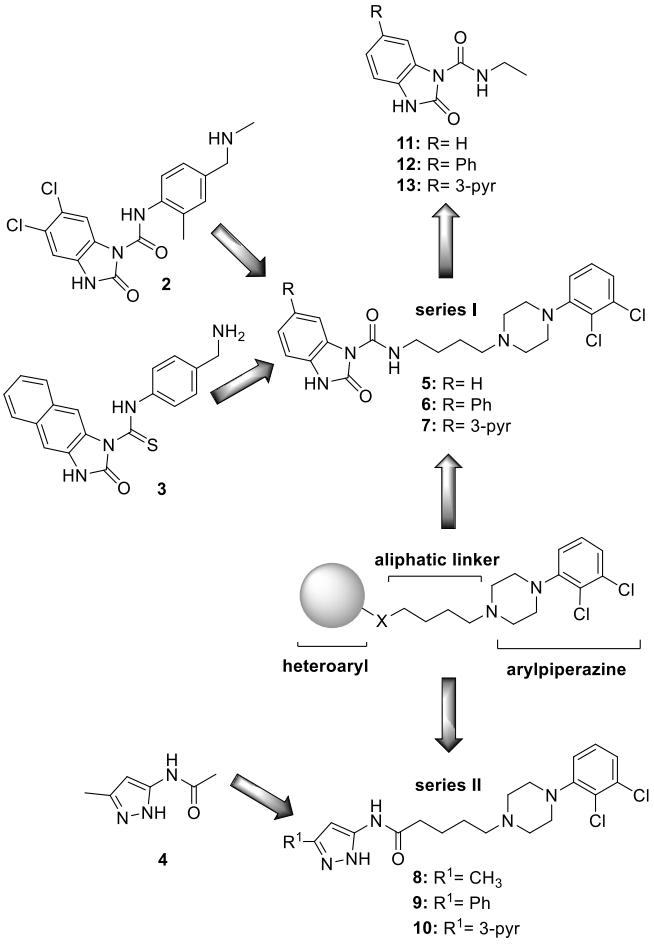
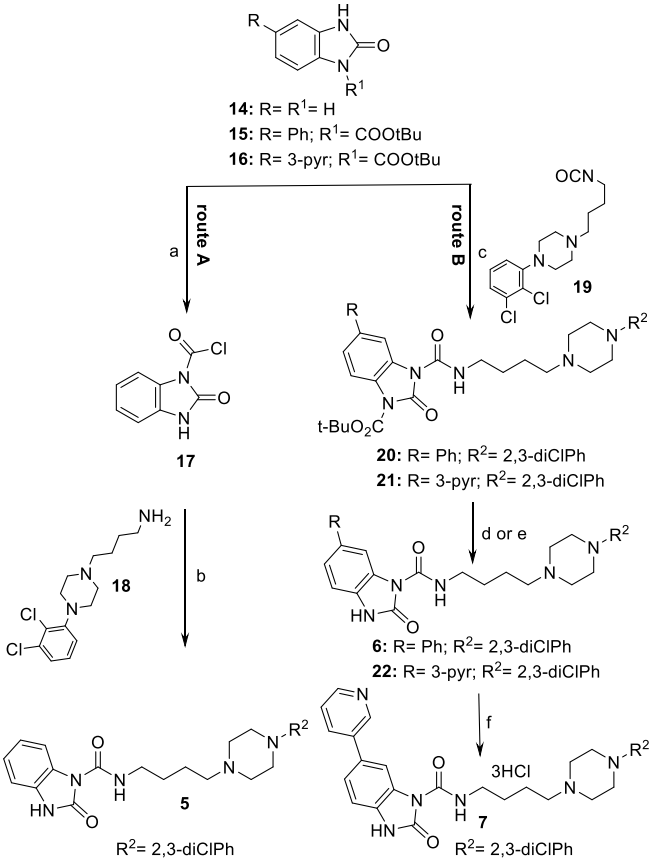


Figure 2. Design strategy for series I and II of dual D3R/GSK-3β modulators and GSK-3β fragments.

The synthetic strategies to prepare derivatives **5-10** are reported in **Schemes 1** (**5-7**) and **2** (**8-10**). In **Scheme 1**, route A, acylation of **14** with trichloromethyl chloroformate afforded **17**, that, reacting with the amine **18**, gave derivative **5**. In route B, reaction of **15** and **16** with the isocyanate **19** yielded the *N*-Boc-protected 2-oxo-

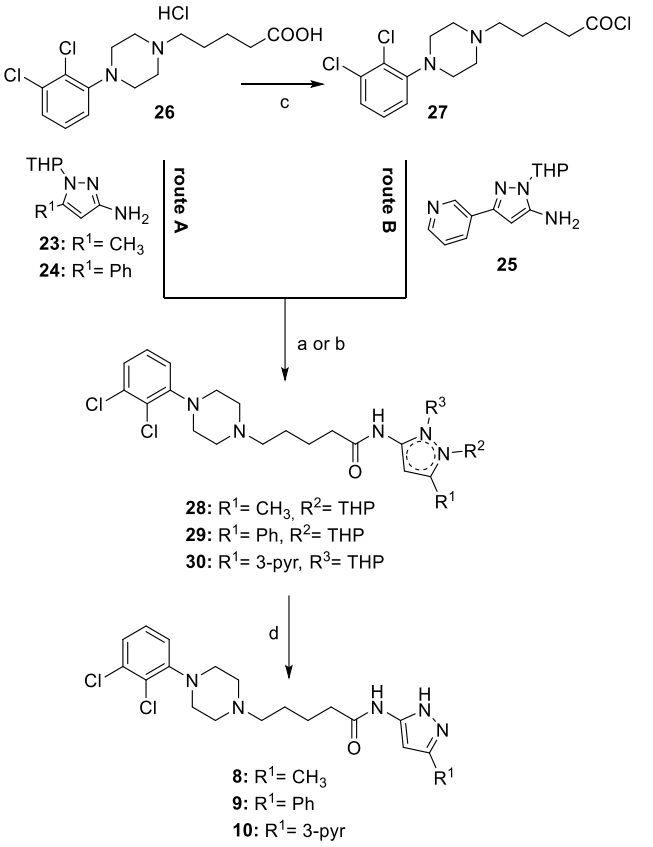
benzimidazoles **20** and **21**, respectively. Analogue **20** underwent HCl treatment to remove the protecting group and gave **6** by basic work-up. Compound **7** was obtained from **21** by TFA treatment, conversion into the free base **22**, and final transformation into HCl salt (**Schemes S1** and **S2** for intermediates synthesis).



Scheme 1. Synthesis of compounds **5-7**. Reagents and conditions: a) trichloromethyl chloroformate, charcoal, dry THF, trap with aq NH_4OH solution (30%), 100 °C, Ar, 30 h, yield: 53%; b) dry CH_2Cl_2/DMF (9:1), rt, Ar, 72 h, yield: 51%; c) dry CH_2Cl_2, rt, Ar, 3 h and 30 min-20 h, yield: 37-50%; d) HCl in 1,4-dioxane (4 M), 1,4-dioxane/CH_3OH (1.5:1), 0 °C to rt, 24 h, (work-up with saturated aq $NaHCO_3$ solution), yield: 66%; e) TFA, dry DCM, 0 °C to rt, 2 h and 30 min, (work-up with saturated aq $NaHCO_3$ solution), yield: 93%; f) HCl in 1,4-dioxane (4 M), 1,4-dioxane, rt, 1 h, yield: 83%.

In **Scheme 2**, route A, an HATU-mediated amide coupling reaction between the key intermediate **26** and the 1*H*-THP-protected-pyrazoles (**23** and **24**) gave **28** and **29**, respectively. In route B, **27**, obtained by oxalyl chloride treatment of **26**, was reacted with **25**, to afford **30**. Treatment of **28-30** with TFA, to remove the protecting group, followed by mild basic work-up, allowed obtaining the final compounds **8-10** (**Schemes S4** and **S5** for intermediates synthesis).

The biological activities of the newly synthesized compounds **7-10** were studied in a HTRF-cAMP functional assay on stably transfected human-D3R expressing CHO-K1 cells and a GSK-3β kinase assay [ULight™-Glycogen Synthase (Ser641/pSer657)



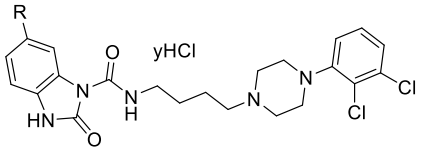
Scheme 2. Synthesis of compounds **8-10**. Reagents and conditions: a) HATU, DIPEA, dry DMF, rt, 5 h, yield: 80-87%; b) TEA, dry 1,4-dioxane, rt, Ar, 48 h, yield: 28%; c) oxalyl chloride, dry DMF, dry CH_2CH_2, 0 °C to rt, 1 h, yield: assumed 100%; d) TFA, dry CH_2Cl_2, 0 °C to rt, 2-18 h, (work-up with saturated aq $NaHCO_3$ solution), yield: 64-88%.

Peptide & Europium-anti-phospho-Glycogen Synthase (Ser641) Antibody, SI for details]. Efficacy at D3R, expressed as a fraction of the effect elicited by 300 nM DA, was also determined. The results obtained are reported in **Tables 1** and **2** for series I and II, respectively. Regarding series I, (**Table 1**) compound **5**, with an unsubstituted 2-oxo-benzimidazole core, was a potent D3R modulator with an EC_{50} value of 7.9 nM; molecular modelling studies showed as it simultaneously engaged both the OBP and the SBP (**Figure 3A**), in line with previously reported simulations.[9b, 12] At GSK-3β, **5** showed an IC_{50} value of 20.1 μM; the 2-oxo-benzimidazole moiety engaged the hinge region of the enzyme, forming the typical H-bond pattern of kinase inhibitors, while the arylpiperazine group projected outside the pocket (**Figure 3B**). A D3R activity similar to that of **5** was observed for analogue **7** (EC_{50} = 10.1 nM), bearing a 3-pyridine group, that possibly engaged the extracellular loop 2 with an additional H-bond (**Figure S1A**). An increased GSK-3β activity up to an IC_{50} of 0.56 μM was also obtained; this effect could be due to the formation of an H-bond between the pyridine nitrogen and LYS85

(**Figure S1B**). The interactions provided by this substituent were of crucial importance, since for **6**, with a phenyl function, a marked decrease in D3R activity (EC_{50} = 42.4 nM) along with no GSK-3β inhibition (up to 5 μM concentration) were observed. This last effect was likely due to poor solubility in buffer (AlogP 5.72).

In series II (**Table 2**), compound **8**, characterized by a methyl group on the pyrazole scaffold, turned out to be a potent D3R modulator (EC_{50} = 8.0 nM), as supported by its proposed binding mode (**Figure 3C**) consistent with that of **5**. When tested on GSK-3β, this derivative showed an IC_{50} of 10.1 μM; its bound conformation confirmed the possibility to form relevant H-bond with the enzyme hinge region while accommodating the arylpiperazine toward the solvent (**Figure 3D**). Interestingly, the presence of a 3-pyridine instead of the methyl moiety improved activities on both targets as derivative **10** exhibited activities of 2.9 nM and 2.6 μM on D3R and GSK-3β, respectively. Binding studies demonstrated that this substituent was likely lodged in the D3R subpocket formed between transmembrane helices 1 and 2 (**Figure S1C**), while for GSK-3β the 3-pyridine ring was favourably lodged toward the conserved salt bridge without, however, directly contacting LYS85 **(Figure S1D)**. These data reinforced the importance of this heterocycle for an optimal modulation of both targets. Indeed, its substitution with a phenyl ring (compound **9**) slightly decreased D3R activity (EC_{50} = 14.1 nM) while no GSK-3β inhibition was observed up to 100 μM. Moreover, series I and II displayed a classical partial agonist profile (efficacies between 21.5% and 56.3%).

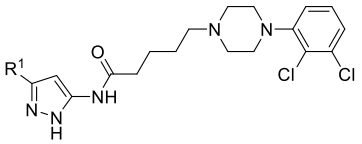
Table 1. Biological results of series I compounds (**5-7**).



Cpd	R	HCl salt	AlogP[13]	D3R[a]		GSK-3β[a]	LELP[14]
				EC_{50} (nM)	Efficacy %	IC_{50} (μM)	
5	H	no	4.20	7.9±1.8	43.4±11.9	20.1±1.4	19.79
6	Ph	no	5.72	42.4±11.9	21.5±6.8	n.i.	37.79
7	3-pyr	yes (y=3)	4.57	10.1±0.4	26.3±2.4	0.6±0.04	19.32

[a] EC_{50} and IC_{50} values are reported as a mean value of three determinations. n.i.= no inhibition up to the concentration of 5 μM (the highest dose tested due to poor solubility of compound **6** in the assay buffer).

Table 2. Biological results of series II compounds (**8-10**).



Cpd	R^1	AlogP	D3R[a]		GSK-3β[a]	LELP
			EC_{50} (nM)	Efficacy %	IC_{50} (μM)	
8	CH_3	2.17	8.0±1.8	47.0±7.5	10.1±2.9	8.40
9	Ph	3.84	14.1±2.5	56.3±7.6	n.i.	
10	3-pyr	2.69	2.9±0.6	43.4±11.1	2.6±0.2	11.00

[a] EC_{50} and IC_{50} values are reported as a mean value of three determinations. n.i.= no inhibition up to the concentration of 100 μM (the highest dose tested).

GSK-3β activity of fragments **11-13** was also investigated and reported in **Table S1**. Consistently with series I, introducing a phenyl ring (**12**) was detrimental for activity, while a 3-pyridine substituent (**13**) greatly increased the activity (IC_{50} = 37.8 nM). Interestingly, **5** and **11** displayed the same potency and **13** was more potent than its counterpart **7**. In line with the results of our docking studies, this behaviour suggested that the 2,3-dichloro-substituted arylpiperazine does not contribute to binding and it is either tolerated or actually detrimental for activity. This is clearly captured by the variation in the ligand efficiency lipophilic price (LELP), which steeply decreases from 19.79 in **5** to 5.45 in **11** and from 19.32 in **7** to 5.53 in **13**. The role of the substituents was further investigated by means of a molecular interaction field (MIF) analysis.[15] As reported in **Figure 4**, the vector projecting from position 6 of the 2-oxo-benzimidazole core points toward a strongly hydrophobic region (green mesh in **Figure 4A**). The 3-pyridine could fit in the hydrophobic region, likely capturing an additional H-bond with LYS85, while causing an only moderate increase in logP (**Figure 4B**). In line with the obtained biological activities on both selected targets, we chose **7** (EC_{50} = 10.1 nM towards D3R and IC_{50} = 561 nM towards GSK-3β) as a dual modulator prototype for generating preliminary pharmacokinetic (PK) data (**Table S2**) and establishing a baseline for further optimisation. This compound displayed stability in *mouse* plasma (over 2 hours). Stability was limited (18 minutes) in *mouse* liver microsomes but increased to over 1 hour in *human* liver microsomes (**Table S2**). PK analysis revealed moderate blood clearance, a low volume of distribution and a $t_{1/2}$ of 0.182 h after intravenous administration (IV) at 2.0 mg/kg. After oral administration (PO) at 10 mg/kg, peak plasma concentration of **7** was observed after 30 minutes (Cmax 482 ng/ml). The compound was detectable up to 8 h post dosing, and systemic exposure

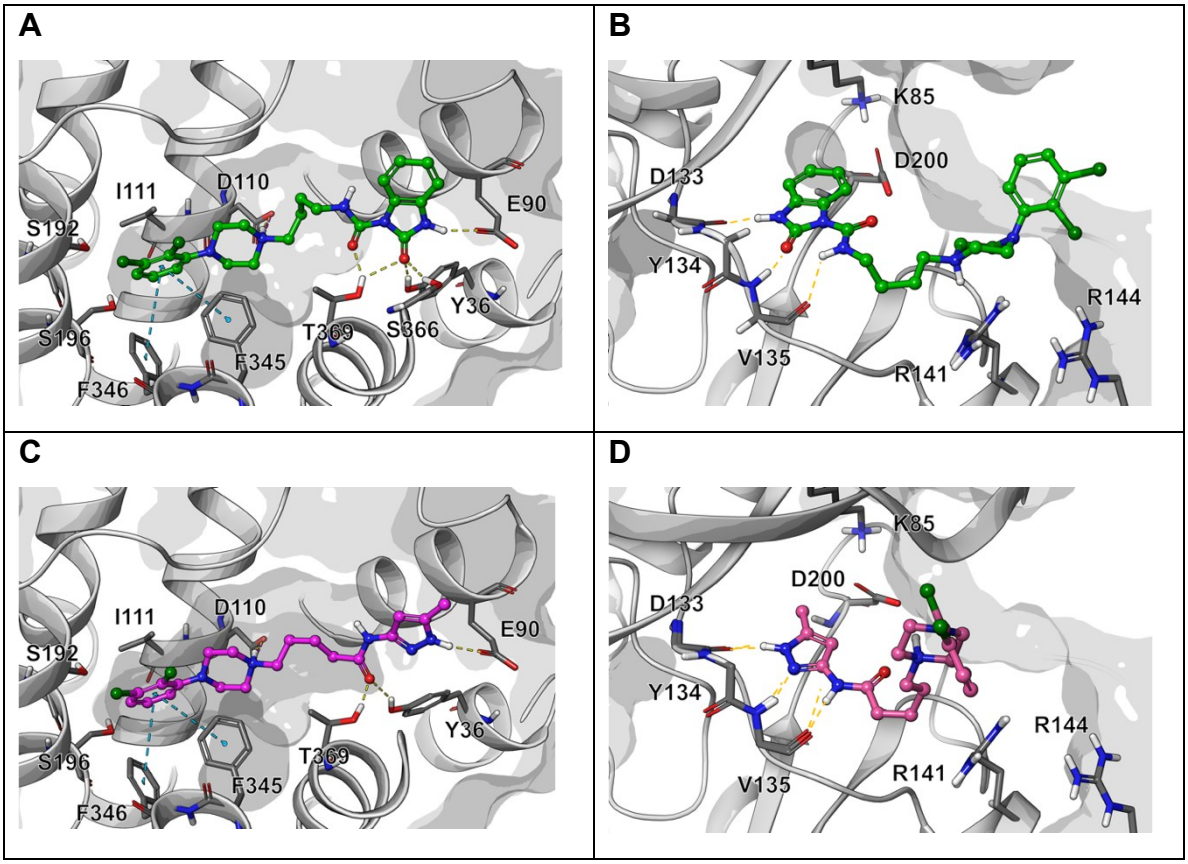


Figure 3. Predicted bound conformations of **5** and **8**. The protein structure is reported in grey ribbons. The binding pocket is highlighted by a transparent grey mesh. Amino acids interacting with the ligand are reported in grey sticks and labelled explicitly. Bound conformation of **5** (green carbon atoms) at A) D3R and B) GSK-3β. Bound conformation of **8** (pink carbon atoms) at C) D3R and D) GSK-3β.

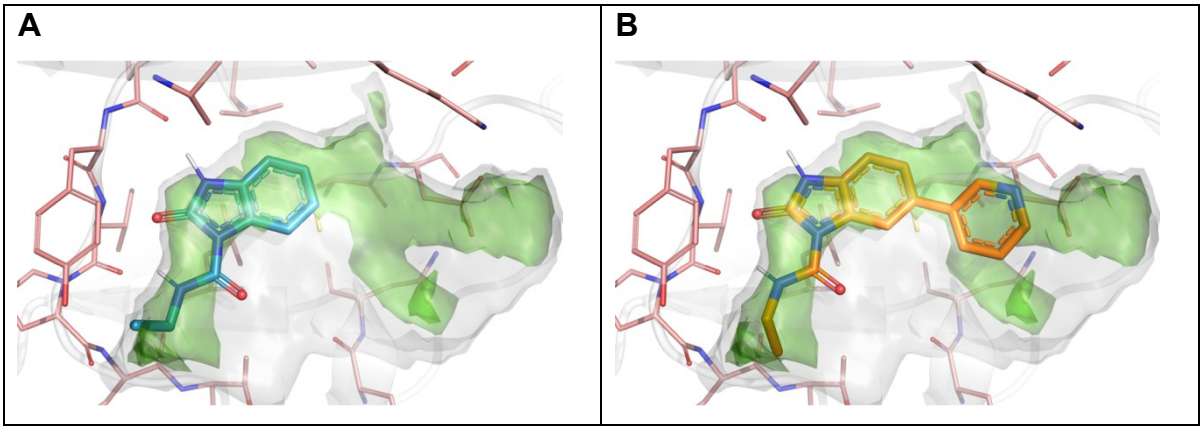


Figure 4. Predicted bound conformations of **11** (A) and **13** (B) at the ATP binding pocket of GSK-3β. MIFs are reported as: C1= probe, transparent green mesh -2.5 kcal/mol isocontour indicating a lipophilic region, and CH3 probe, transparent grey at -1 kcal/mol, defining the pocket shape.

(AUClast) was 488 h*ng/ml. Oral bioavailability was estimated at 16.1%. Central nervous system (CNS) penetration of **7** was also evaluated by quantifying the compound brain concentrations up to 8 h after PO (**Table S2**). Low brain exposure was observed with a maximal brain concentration of 23.1 ng/g and AUClast value of 45.7 h*ng/g. A 17-fold increase in brain penetration was reported after co-administration with P-glycoprotein 1 (P-gp) and breast cancer resistance protein (BCRP) inhibitor Elacridar,[16] suggesting an interaction of **7** with these ATP-dependent efflux transporters. We later confirmed this hypothesis by testing **7** in a P-gp human transporter cell-based antagonist assay.[17] In MDR1-MDCKII cells, the compound inhibited P-gp-mediated acetoxymethyl calcein (calcein-AM) efflux by 47.9% and 69.8% at 1 and 10 μM, respectively (SI for details). Notably, our PK studies were performed on male C57BL/6J mice. While a fully validated *in vivo* model for BD capable of emulating both manic and depressive episodes is still missing, recent models have been generated introducing on the C57BL/6J strain genetic alterations

in the Brain-Derived Neurotrophic Factor (BDNF)–Extracellular Signal-Regulated Kinase-1 (ERK) pathway. Because of the putative role of ERK-MAP kinase cascade in synaptic plasticity and memory formation, as well as the upstream activation of the ERK-MAP kinase pathway by BDNF, these newly proposed models are gaining traction in the community.[18]

Herein, we have reported on the design, synthesis, and biological evaluations of the first series of dual D3R/GSK-3β modulators. This endeavor was undertaken to address the complex and multifactorial features of BD. We sought the concurrent modulation of two targets that contribute to the regulation of the DA signalling pathway and that have both been involved in related neuropsychiatric disorders.[3b, 5a] D3R/GSK-3β MTDLs could potentially turn into innovative therapeutics endowed with improved efficacy and reduced side effects. Our results, albeit preliminarily, confirmed the feasibility of the proposed strategy, and from a more general perspective, the feasibility of modulating simultaneously a GPCR and a kinase, targets rather divergent structurally and genetically. The most promising analogues from the two series, namely **7** and **10**, both bearing a 3-pyridine function, displayed low nanomolar activity on D3R and low micro-molar inhibition of GSK-3β. Moreover, acceptable drug-like properties were observed for **7**, when it underwent *in vitro* stability and PK studies. An optimization campaign on these series of D3R/GSK-3β modulators is currently ongoing, aimed at improving PK properties and at slightly increasing GSK-3β inhibition. While obtaining compounds with balanced affinities towards the selected targets is indeed one of the key tenets of the MTDL paradigm, it should also be noticed how mild GSK-3β inhibitors are usually considered safer than potent ones,[19] since they do not interfere with the physiological activity of the peripheral enzyme. The outcomes of these efforts will be reported in due time.

Acknowledgements

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Keywords: drug discovery • receptors • enzymes • molecular modelling • multitarget

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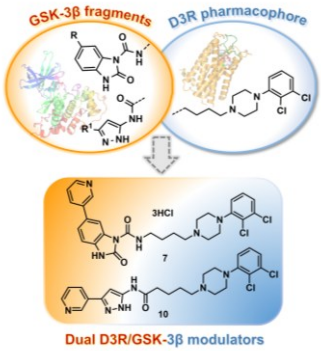

This study describes multitarget-directed ligands combining partial agonist activity at Dopamine Receptor D3 and inhibitory activity at glycogen synthase kinase 3 beta (GSK-3β). Thanks to a seamless integration of key pharmacophore features, these compounds could originate a new wave of therapeutic agents for the treatment of bipolar disorder, endowed with a disease-modifying effect while devoid of severe side effects.