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Novel 2-*N*,*N*-dimethylaminomethyl-2,3,3a,12b-tetrahydrodibenzo[*b*,*f*]furo[2,3-*d*]oxepin derivatives displaying combined norepinephrine reuptake inhibition and 5-$HT_{2A/2C}$ receptor antagonism

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Abstract—A novel series of *cis*-fused 2-*N*,*N*-dimethylaminomethyl-2,3,3a,12b-tetrahydrodibenzo[*b*,*f*]furo[2,3-*d*]oxepin derivatives modified at position C-11 was prepared and evaluated for its potential antidepressant/anxiolytic properties. In vitro affinities for the norepinephrine transporter and for 5-HT_{2A} and 5-HT_{2C} receptors, as well as the ED_{50} values obtained in some in vivo assays predictive for antidepressant and anxiolytic potential are reported.

1. Introduction

We have recently reported the discovery of a series of tetracyclic tetrahydrofuran derivatives possessing combined 5-$HT_{2A/2C}$ antagonistic activity.[1,2] These tetracycles, represented by prototype **1** (Fig. 1), have been considered as potential leads in our search for novel compounds with antidepressant/anxiolytic properties. A broader screening of compounds **1** toward a panel of selected CNS receptors, including adrenergic (α_1 and α_2), serotonergic (5-HT_{1A}, 5-HT_6 and 5-HT_7), histaminergic (H_1) and dopaminergic (D_1, D_2, D_3, and D_4) receptors and norepinephrine (NE), serotonin (SER), and dopamine (DA) transporters resulted in the finding that the corresponding *cis*-fused tetrahydrodibenzo[*b*,*f*]-furo[2,3-*d*]oxepine derivatives **2a** and **2b**, in addition to the 5-$HT_{2A/2C}$ antagonism, presented an additional and predominant component of NE reuptake inhibition. This new interaction could contribute positively to their potential antidepressant activity.[3]

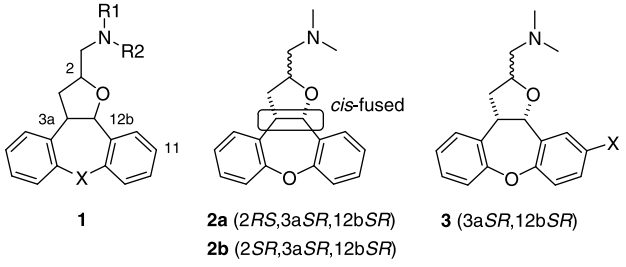

Figure 1.

As this dual activity was confined solely to the *cis*-fused derivatives **2a**,**b** (the corresponding *trans*-fused isomers were much less active as norepinephrine reuptake blockers)[4] we decided to further explore these *cis*-fused tetracyclic systems in order to optimize their combined activities. We report herein the results on the synthesis and pharmacological characterization of a novel series of C-11 substituted *cis*-fused tetrahydrodibenzo[*b*,*f*]-furo[2,3-*d*]oxepine derivatives, represented by formula **3** (Fig. 1) showing combined NE reuptake inhibition and 5-$HT_{2A/2C}$ receptor antagonism. This novel combination of activities has not been previously reported to the best of our knowledge.

Keywords: Antidepressant; Anxiolytic; Norepinephrine; Serotonin.
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2. Chemistry

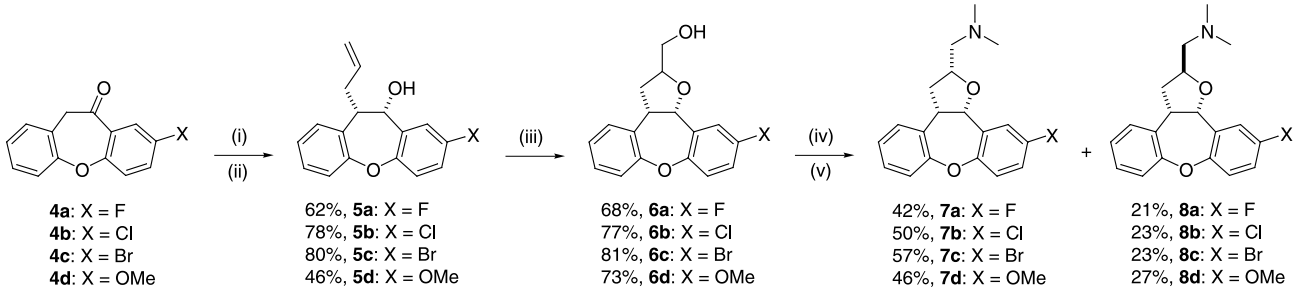
The synthesis of the target compounds **7** and **8** was achieved by the general method shown in Scheme 1. First, the reaction of the corresponding tricyclic ketones **4a**–**d**[5] with sodium hydride, followed by the addition of allylbromide afforded the corresponding α-allylated ketones, which were reduced with Red-Al at −30 °C in THF to give the expected *cis*-alcohols **5a**–**d** with complete diastereoselectivity and excellent yields, as it is shown in Scheme 1.

The determination of the relative configuration of the alcohols **5a**–**d** was carried out by mean of NOE difference experiments. The epoxidation/cyclization of the *cis* β-allylic alcohols **5a**–**d** with *m*-chloroperbenzoic acid (MCPBA) occurred with almost no selectivity, affording the corresponding *cis*-fused tetrahydrofuran derivatives **6a**–**d** as 3:2 mixtures of diastereoisomers. Finally, transformation of the tetracycles **6** into the *cis*-fused target compounds **7a**–**d** and **8a**–**d** was carried out by reaction of the alcohol group with tosyl chloride in dichloromethane, and subsequent thermal displacement of the tosyl group by dimethylamine in THF at 120 °C, conducted in a standard Parr pressure reaction apparatus.

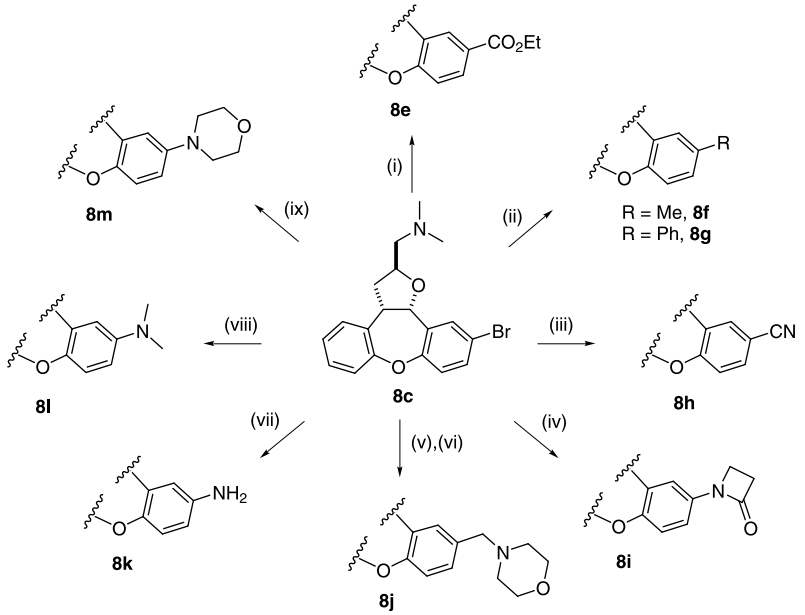
Compound **8c**, which presents a bromine atom at position C-11, was selected for further chemical modifications that led to the new analogues **8e**–**m**. The performed chemical transformations are shown in Scheme 2 and comprise carbonylation, Suzuki-type couplings and Buchwald–Hartwig palladium chemistry under standard reaction conditions.

3. Biological results and discussion

The affinities of the compounds for the NE transporter (NET) were measured by means of radioligand binding studies conducted with rat brain tissues homogenates



Scheme 1. Reagents and conditions: (i) NaH, THF, 0 °C to rt, 3 h then allylbromide 0 °C to rt, 12 h; (ii) Red-Al, THF, −30 °C to rt, 12 h; (iii) MCPBA, hydroquinone (cat.), CH_2Cl_2, rt, 12 h; (iv) Tosyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h; (v) $NHMe_2$, CaO, THF, 120 °C, 8 h.



Scheme 2. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 45 min, then $ClCO_2Et$, −78 °C to rt, 8 h, 60%; (ii) $RB(OH)_2$, $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl, KF, THF, 100 °C, 16 h, R = Me, 22% and R = Ph, 77%; (iii) $Pd(PPh_3)_4$, $Zn(CN)_2$, CH_3CN, 120 °C, 20 min, microwave irradiation, 85%; (iv) azetidine-1-one, CuI, *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine, K_2CO_3, 1,4-dioxane, 110 °C, 16 h, 21%; (v) *n*-BuLi, THF, −78 °C, 45 min, then DMF, −78 °C to rt, 8 h, 53%; (vi) morpholine, $NaB(OAc)_3H$, CH_2Cl_2, rt, 8 h, 88%; (vii) $^tBuOCONH_2$, $Pd(dba)_3$, Xantphos, Cs_2CO_3, 1,4-dioxane, 110 °C, 24 h, then TFA/CH_2Cl_2, rt, 3 h, 66%; (viii) $NHMe_2$ (2 M in THF), $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, sealed tube, 120 °C, 48 h, 41%; (ix) morpholine, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, reflux, 48 h, 53%.

using [^{3}H]nisoxetine as radioligand.[6] The corresponding experiments to measure the affinities for the 5-HT$_2$ receptors were conducted with: (a) human cloned 5-HT$_{2A}$ receptor, expressed in L929 cells using [^{125}I]R91150 as radioligand[7] and (b) human cloned 5-HT$_{2C}$ receptor, expressed in CHO cells using [^{3}H]mesulergine as radioligand.[8]

The binding affinities of previously reported compounds **2a**,**b** and of the new compounds **7** and **8** for the NET and 5-HT$_{2A}$, 5-HT$_{2C}$ receptors are shown in Table 1. Structure–activity relationships were first studied to determine the optimal relative configuration at position C-2 of this new series of *cis*-fused tetracyclic tetrahydrofuran derivatives. For this purpose the corresponding pairs of 2*RS* and 2*SR* isomers, **7a**–**d** and **8a**–**d**, respectively, were synthesized. In contrast to the unsubstituted compounds **2a** and **2b**, in which the most remarkable difference was that the 2*SR* isomer **2b** showed about six-fold higher affinity for the 5-HT$_{2A}$ receptor, in the case of compounds modified at 11-position the 2*SR* isomers **8a**–**d** showed higher affinities for both NET and serotonergic receptors than their corresponding C-2 epimers **7a**–**d**. Based on these findings a broader exploration of the effect of the C-11 substituent was performed maintaining the optimal configuration 2*SR*. For this purpose the chemically diverse set of compounds **8e**–**m** was prepared. Analysis of the data revealed that the most interesting results were obtained for halogen-substituted compounds in which the binding affinities were highly dependent on the halogen nature. Thus, the introduction of a fluorine atom at position C-11 (**7a** and **8a**) resulted in a clear improvement of the affinity for both the NET and the 5-HT$_{2C}$ receptors, but was detrimental for the 5-HT$_{2A}$ receptor affinity. The substitution by a chlorine (**7b** and **8b**) or a bromine atom in the 2*SR* isomer **7c** translated in a clear increase of the affinity for the three transporter/receptors. From this set of derivatives the 11-chloro 2*SR* derivative **8b** was identified as the most potent and balanced compound within the series. The substitution by other electron-withdrawing groups different from halogens, such as cyano (**8e**) and ethoxycarbonyl (**8h**) resulted in a pronounced decrease of the binding affinity for the NET. The influence of electron-donating groups was also studied by the introduction of alkoxy and amino groups at the C-11 position. Only the 2*RS* 11-methoxy isomer **8d** possessed comparable affinity to that of **2a**,**b** for the three targets while its corresponding 2*SR* isomer **7d** and all the nitrogen-substituted derivatives **8i**, **k**, **l**, **m** showed a significant decrease in affinity. The introduction of a small alkyl group (methyl-, **8f)** resulted in binding affinities in the same range to those of **2a** and **2b**. Finally the introduction of bulkier lipophilic- (phenyl-, **8g**) or polar- (*N*-morpholylmethyl-, **8j**) groups led to nearly inactive compounds.

Table 1. NET, 5-HT$_{2A}$, and 5-HT$_{2C}$ affinities of tetracyclic tetrahydrofurans **2a**,**2b**, **7a**–**c**, and **8a**–**m**[a]

Compds	Stereochemistry C-2	NET K_i, nM	5-HT$_{2A}$ K_i, nM	5-HT$_{2C}$ K_i, nM
2a	2*RS*	69	92	183
2b	2*SR*	88	16	179
7a	2*RS*	41	423	63
8a	2*SR*	8	104	41
7b	2*RS*	30	11	21
8b	2*SR*	12	5	12
7c	2*RS*	125	65	87
8c	2*SR*	54	3	6
7d	2*RS*	116	193	235
8d	2*SR*	75	22	72
8e	2*SR*	>5454	97	246
8f	2*SR*	96	36	58
8g	2*SR*	4062	307	183
8h	2*SR*	142	185	183
8i	2*SR*	2458	306	356
8j	2*SR*	3111	189	4105
8k	2*SR*	620	255	270
8l	2*SR*	2254	95	157
8m	2*SR*	4105	306	>5454

[a] The activity of compounds was confirmed in an independent experiment. A difference in pIC$_{50}$ up to 0.6 (SD < 0.5) was considered as reproducible and therefore accepted.

The reference compounds **2a**,**b** and some of the in vitro most active compounds were tested in several animal behavioral models to further evaluate their therapeutic potential. Thus, the antidepressant properties of the compounds (due to their affinity for the NET), were evaluated by measuring their ability to reverse RO-4-1284-induced hypothermia in mice.[9] Additionally, the compounds were studied in rats for their ability to (a) reverse tryptamine-induced cyanosis and bilateral convulsions (predictable for peripheral and central 5-HT$_{2A}$ antagonism, respectively),[10] (b) reverse *m*-chlorophenylpiperazine (*m*CPP)-induced anxiety, thought to reflect central 5-HT$_{2C}$ antagonism and potential anxiolytic properties.[11] The results obtained are summarized in Table 2.

In the case of unsubstituted analogues only the 2*RS* isomer **2a** presented a moderate activity in the RO-4-1284 test and against tryptamine-induced convulsions but not against the tryptamine-induced cyanosis. On the other hand, as a general trend, the introduction of substituents on C-11 resulted in an increase of potency especially against both the RO-4-1284 and tryptamine-induced phenomena. Surprisingly no in vivo activity in the mCPP challenge test was found for derivatives **7b**, **8b**, and **8c** despite having a potent in vitro affinity for the 5-HT$_{2C}$ receptor. The reason for this discrepancy is not well understood yet. Finally, the 2*SR* 11-fluoro- and 11-methyl-substituted derivatives (**8a** and **8f**, respectively) were active in all the in vivo models investigated, compound **8a** being the more potent and balanced member of this series. Its activity in the RO-4-1284-induced hypothermia test (ED$_{50}$ = 0.020 mg/kg, s.c.) was remarkable.

In conclusion, we have discovered a new series of 11-substituted *cis*-fused 2-*N*,*N*-dimethylaminomethyl-2,3,3a,12b-tetrahydrodibenzo[*b*,*f*]furo[2,3-*d*]oxepin derivatives disclosing a unique pharmacological profile combining NE reuptake inhibition and 5-HT$_{2A/2C}$ receptor antagonism. This previously undescribed combination of activities makes them potential antidepressant/anxiolytic agents with a novel mechanism of action.

Table 2. In vivo pharmacological profile of selected 11-substituted *cis*-fused 2-*N*,*N*-dimethylaminomethyl-2,3,3a,12b-tetrahydrodibenzo[*b*,*f*]furo-[2,3-*d*]oxepin derivatives[a]

Compds	X	Stereochemistry C-2	RO-4-1284[b]	Tryptamine cyanosis[c]	Tryptamine convulsions[d]	mCPP[e]
2a	H	2*RS*	1.25 (0.44–3.55)	>2.5[f]	3.15 (–)	>2.5[f]
2b	H	2*SR*	>2.5[f]	>2.5[f]	>2.5[f]	n.t.
7a	F	2*RS*	0.13 (0.058–0.27)	5.0 (2.87–8.71)	1.98 (–)	>2.5[f]
8a	F	2*SR*	0.020 (0.0058–0.069)	0.50 (0.23–1.09)	0.50 (0.23–1.09)	0.50 (0.23–1.09)
7b	Cl	2*RS*	0.050 (0.023–0.11)	0.80 (0.37–1.74)	0.32 (0.18–0.55)	>2.5[f]
8b	Cl	2*SR*	0.50 (0.15–1.72)	0.20 (0.092–0.44)	0.080 (0.028–0.22)	>2.5[f]
8c	Br	2*SR*	3.15 (–)	0.79 (0.36–1.73)	0.32 (0.18–0.55)	>2.5[f]
8d	OMe	2*SR*	0.79 (0.23–2.72)	1.26 (0.73–2.18)	0.32 (0.18–0.55)	>2.5[f]
8f	Me	2*SR*	1.99 (0.91–4.33)	0.50 (–)	0.50 (–)	0.80 (0.36–1.73)

[a] Results expressed as ED_{50} values in mg/kg after subcutaneous administration of the tested compounds. ED_{50} values and corresponding 95% confidence limits were determined according to the modified Spearman–Kaerber estimate using theoretical probabilities instead of empirical ones; this modification allows tabulation the ED_{50} and its confidence interval as a function of the slope of the log dose–response curve.
[b] Reversal of RO-4-1284 induced hypothermia in mice.
[c] Reversal of tryptamine-induced cyanosis in rats.
[d] Reversal of tryptamine-induced bilateral convulsions in rats.
[e] Antagonism of *m*-chlorophenylpiperazine induced anxiety in rats.
[f] Highest tested dose expressed in mg/kg.

In vivo testing of the most promising members of the series led to the identification **8a** and **8f**, which showed activity at relevant doses in animal models predictive for antidepressant/anxiolytic activity. Further SAR and pharmacological investigation of the series are currently in progress and will be reported elsewhere.

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