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Synthesis and Structure–Activity Relationship of 2-(Aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine Derivatives: A Novel Series of 5-HT$_{2A/2C}$ Receptor Antagonists. Part 2

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Abstract—Following the programme started at Janssen Research Foundation searching for 5-HT$_{2A/2C}$ antagonists, we now report on the synthesis of a series of substituted 2-(Dimethylaminomethyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine derivatives. The 5-HT$_{2A}$, 5-HT$_{2C}$ and H$_1$ receptor affinities as well as the mCPP antagonistic activity of the compounds synthesised is described.

Introduction

The neurotransmitter serotonin (5-HT) induces a variety of effects that are mediated by specific receptors, which can be subdivided in seven families, 5-HT$_{1-7}$. The 5-HT$_{2A}$ receptor is widely distributed, both in peripheral tissues and in the CNS, while the 5-HT$_{2C}$ receptor has been found only in the CNS.[1] The 5-HT agonist *m*-chlorophenylpiperazine (mCPP) is often used as a probe in clinical studies to challenge brain 5-HT functions in humans.[2] In animals, mCPP also induces symptoms of anxiety in various animal models.[3–7] As this mCPP-induced anxiety seems to be mediated via the 5-HT$_{2C}$ receptor, it has been hypothesised that 5-HT$_{2C}$ antagonists might be potential drugs for the treatment of anxiety and depression.[8,9]

In recent years, we started a programme at Janssen Research Foundation searching for potent, centrally active 5-HT$_{2C}$ receptor antagonists as potential anxiolytic/antidepressant agents. As a result of our synthesis program, R95292 (**1**) was found to display high affinity for both 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors,[10a] but was devoid of in vivo activity in our mCPP challenge test. In our previous paper, we described a series of 2-(aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]-azepine derivatives as novel 5-HT$_{2A/2C}$ antagonists, that also showed high affinity for histamine-H$_1$ receptors.[11] One of those compounds, the dimethylaminomethyl derivative **2**, was a potent mCPP antagonist as shown in our in vivo mCPP challenge test.[5,11] We decided to explore the influence of the presence of substituents at different positions of the tetracyclic system, both for the 5-HT$_{2A/2C}$ receptor affinities as well as for the mCPP antagonistic activity. We also wanted to study the influence of those substituents on the antagonistic effect on the H$_1$ receptor, which may contribute to potential sedative effects of the compounds.[12] This paper describes the synthesis and structure–activity relationship of differently substituted 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine derivatives (**3**) (Fig. 1).[10b]

Chemistry

The synthesis of the target compounds was carried out by cycloaddition of *N*-allyldimethylamine to differently

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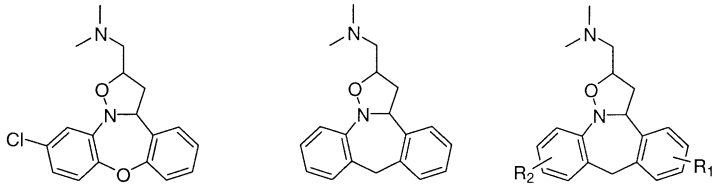


Figure 1.

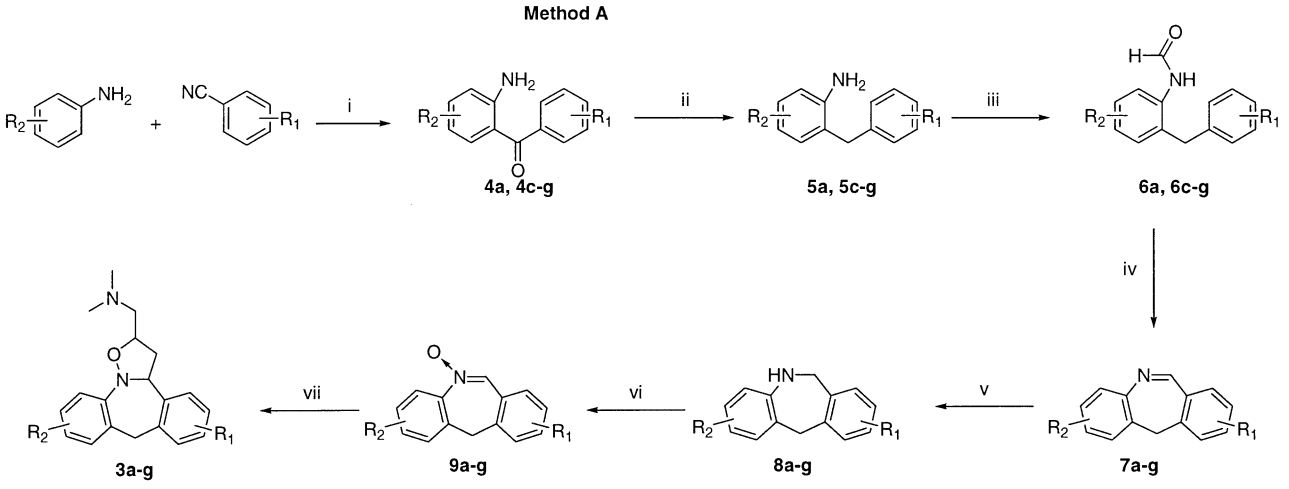
substituted 11*H*-dibenzo[*b*,*e*]azepine-5-oxides (morphanthridine-5-oxides, **9a**–**9t**). The synthesis of the needed tricyclic precursors, substituted 6,11-dihydro-5*H*-dibenzo[*b*,*e*]azepines (5,6-dihydromorphanthridines), was achieved mainly by two general methods, A or B, depending on the availability of the required starting materials.

Method A (Scheme 1)

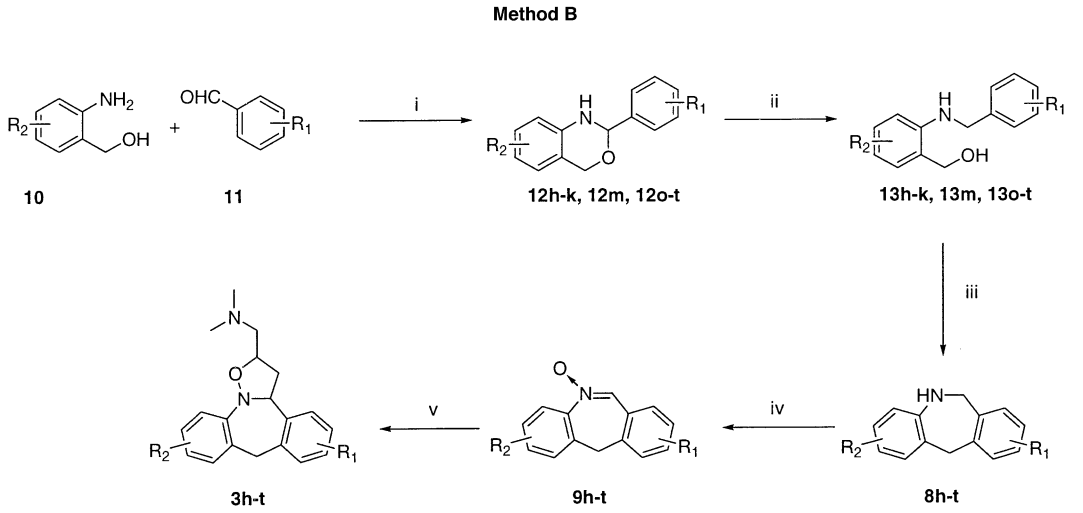
At first we essentially followed one of the methods described in literature for the synthesis of morphanthridines.[13] The starting substituted *o*-aminobenzophenones, **4a** and **4c**–**g**, are commercially available or were prepared by conventional methods described in literature, such as Friedel–Crafts type reaction of substituted anilines with substituted benzonitriles.[14] Wolf–Kishner reduction of compounds **4** afforded the corresponding substituted 2-benzylanilines **5a** and **5c**–**g**. Formylation of the amino groups with formic acid, followed by ring closure by the Bischler–Napieralski reaction afforded the morphanthridines **7a**–**g** (CAUTION: skin irritants). Catalytic hydrogenation of compounds **7a**–**g** yielded the desired 5,6-dihydromorphanthridines **8a**–**g**, which were oxidised using 3-phenyl-2-(phenylsulfonyl)oxaziridine (Davis' reagent)[15] to their corresponding *N*-oxides **9a**–**g**. Finally cycloaddition with *N*-allyldimethylamine, heating in a sealed tube using toluene as solvent, gave the desired target compounds **3a**–**g**. Ring closure of *N*-formyl-2-(3′-methylbenzyl)aniline (**6a**) yielded a mixture of the two possible regioisomers **7a** and **7b**, which was used as such in further synthesis steps and separated into its single isomers **3a** and **3b** at the final step.

Method B (Scheme 2)

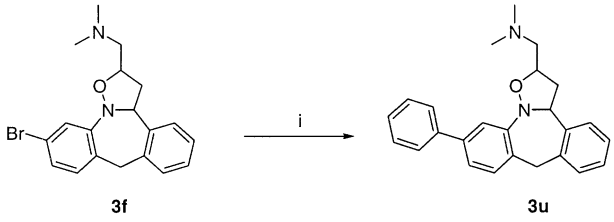
As we described in our previous article in this series we had developed a new and efficient method for the synthesis of 5,6-dihydromorphanthridine.[11] That method has been applied as well to the synthesis of differently substituted 5,6-dihydromorphanthridines. This new method has proved to be a better alternative than the general methods previously described in literature,[16–20] whenever the needed starting benzaldehydes and 2-aminobenzylalcohols were easily available. Condensation of 2-aminobenzylalcohols **10** with benzaldehydes **11** smoothly gave the unreported benzoxazine derivatives **12** in excellent yields. Reductive cleavage of these compounds by means of $NaBH_4$ in ethanol afforded the corresponding *N*-benzyl open analogues **13**, which were cyclised to the desired 5,6-dihydromorphanthridines **8h**–**t** in the presence of sulphuric acid in good yields and after only three steps from the available starting materials. The next two reactions were analogous to those described above in Method A, yielding final compounds **3h**–**t**. Cyclisation of **13k** and



Scheme 1. Reagents and conditions: (i) BCl_3, $AlCl_3$, xylene/CH_2Cl_2, 120 °C, overnight, 35–52%; (ii) $NH_2NH_2{\cdot}H_2O$, HOH_2CCH_2OH, KOH, 200 °C, 12 h, 80–97%; (iii) HCOOH, reflux, 2 h, 75–85%; (iv) PPA, $POCl_3$, xylene, 100 °C, overnight, 57–66%; (v) H_2, Pd/C (10%), CH_3OH/THF, rt, 53–90%; (vi) 3-phenyl-2-(phenylsulfonyl)oxaziridine, CH_2Cl_2, rt, 2 h, 82–93%; (vii) *N*-allyldimethylamine, toluene, 100 °C, sealed tube, overnight, 46–65%.



Scheme 2. Reagents and conditions: (i) $ClCH_2COOH$ (cat), CH_3OH or $(CH_3)_2CHOH$, rt, overnight, 95–100%; (ii) $NaBH_4$, CH_3CH_2OH, reflux, 1 h, 90–95%; (iii) H_2SO_4, CH_2Cl_2, −20 °C, then rt, overnight, 65–86%; (iv) Davis' reagent, CH_2Cl_2, rt, 1–2 h, 90–98%; (v) *N*-allyldimethylamine, toluene, 100 °C, sealed tube, 16 h, 30–65%.



Scheme 3. Reagents and conditions: (i) $PhSn(CH_3)_3$, $Pd(PPh_3)_4$, toluene, reflux, 24 h, 42%.

13m yielded both regioisomers **8k**, **8l** and **8m**, **8n**, respectively. Both isomeric mixtures were used in further steps and separated by preparative HPLC into their single products **3k**, **3l** and **3m**, **3n**, respectively, after the last reaction of this synthetic pathway.

The 11-phenyl derivative **3u** was synthesised by Stille coupling of the 11-bromo analogue **3f** with phenyltrimethyltin in the presence of tetrakis(triphenylphosphine)palladium (0) (Scheme 3).

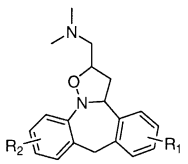
The cycloaddition of the substituted morphanthridine-5-oxides with *N*-allyldimethylamine afforded in all cases the *cis* isomers, and only traces of the corresponding *trans* isomers were occasionally detected. The determination of the relative configuration of the chiral centres was carried out by means of NOE difference experiments on the protons of the isoxazolidine ring.

Biological Results and Discussion

The affinities of the compounds for the 5-HT_2 receptors were measured by means of radioligand binding studies conducted with: (a) human cloned 5-HT_{2A} receptor, expressed in L929 cells using [^{125}I]R91150 as radioligand[21] and (b) human cloned 5-HT_{2C} receptor, expressed in CHO cells using [^{3}H]mesulergine as radioligand.[22] The experiments to measure the affinities for the H_1 receptor were conducted with human cloned H_1 receptors expressed in CHO cells, using [^{3}H]pyrilamine as radioligand.[21] The affinities of the compounds for other serotonergic as well as dopaminergic and adrenergic receptors were also measured. The experiments to measure the in vivo activity of the compounds in our mCPP challenge test were performed in male Wistar rats, weighing between 200 and 220 g, following the method described by Meert and co-workers.[5] The test compounds were administered subcutaneously or orally or both, depending on the availability and solubility of the compounds as well as on the preliminary activity found. Table 1 shows the affinities for the 5-HT_{2A}, 5-HT_{2C} and H_1 receptors of the synthesised compounds as well as their activity in our mCPP challenge test.

As can be deduced from the data shown in Table 1, the introduction of substituents at different positions of the core tetracyclic structure **2** had remarkable influence on the affinity for both 5-HT_2 as well as for the H_1 receptors. Introduction of a halogen atom at 4 position of the tetracycle resulted in complete loss of affinity for receptors (**3h**). But the presence of a methyl or a trifluoromethyl group at that same position gave compounds with comparable receptor binding profile as that of the unsubstituted lead **2**. Even more, the 4-trifluoromethyl derivative **3i** showed the highest selectivity for 5-HT_{2C} receptor. On the other hand, the 5-trifluoromethyl substituted compound completely lost the affinity for all receptors, while the 5-fluoro derivative **3k** showed a quite similar receptor profile to **2**. Introduction of a strong electron donor group such as methoxy at that same position resulted in a significant decrease of affinity for the 5-HT_{2A} receptor. The effect of a fluorine atom at the 7-, 9- and 10-positions on the binding affinity is also noteworthy. While the 7-fluoro derivative **3l** showed a significant increase only in its H_1 affinity, the 9-fluoro analogue **3q** improved its affinity for the 5-HT_{2C} receptor as well, and the 10-fluoro compound **3c** showed increased affinity for the three receptors. Surprisingly the 7-chloro analogue **3p** was completely devoid of in vitro affinity, while the 7-trifluoromethyl

Table 1. 5-$HT_{2A/2C}$ and H_1 affinities and activity in mCPP challenge test of 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine derivatives



Compd	R_1, R_2	Synthetic Method	$5HT_{2A}$ pIC_{50}	$5HT_{2C}$ pIC_{50}	H_1 pIC_{50}	mCPP (sc) ED_{50} (mg/kg)	mCPP (po) ED_{50} (mg/kg)
2	H, H		7.64	7.91	8.17	0.04	0.63
3a	4-CH_3	A	7.32	7.52	7.93	n.t.	>2.5
3b	6-CH_3	A	7.98	8.20	7.80	n.t.	2.5
3c	10-F	A	8.16	8.33	8.89	n.t.	2.5
3d	11-Cl	A	8.46	8.98	8.63	0.16	0.63
3e	11-CH_3	A	8.51	8.52	8.23	0.16	2.5
3f	11-Br	A	n.t.	n.t.	n.t.	n.t.	2.5
3g	12-Cl	A	7.49	7.99	7.81	n.t.	>2.5
3h	4-F	B	<6	<6	<6	>2.5	n.t.
3i	4-CF_3	B	7.17	8.12	7.32	2.5	>2.5
3j	5-CH_3O	B	6.52	7.71	7.84	n.t.	>2.5
3k	5-F	B	7.27	7.97	8.42	>2.5	>2.5
3l	7-F	B	7.50	7.93	8.64	2.5	2.5
3m	5-CF_3	B	<6	<6	<6	2.5	>2.5
3n	7-CF_3	B	6.00	6.36	7.43	n.t.	>2.5
3o	6-Cl	B	n.t.	n.t.	n.t.	>2.5	n.t.
3p	7-Cl	B	<6	<6	<6	n.t.	>2.5
3q	9-F	B	7.62	8.30	8.76	n.t.	2.5
3r	9-CH_3	B	7.04	8.41	8.22	n.t.	>2.5
3s	11-F	B	8.94	8.94	8.59	0.04	2.5
3t	5,11-diF	B	7.97	8.21	7.77	0.04	0.63
3u	11-Ph		7.65	7.95	8.10	>2.5	>2.5

n.t., not tested.

derivative **3n** retained some H_1 activity. The 9-methyl substituted compound **3r** presented a comparable behaviour to that of **3q**.

The most interesting results were obtained with the introduction of substituents at the 11-position of the tetracyclic structure. The presence of a halogen atom or a methyl group at that position resulted in compounds with significant increase in 5-HT_2 and H_1 receptor binding affinity. The 11-chloro derivative **3d** showed a slightly better selectivity for 5-HT_{2C} receptor than the corresponding 11-fluoro analogue **3s**, while both compounds showed a 10-fold increase in potency for 5-HT_2 receptors when compared to the unsubstituted lead compound **2**. We also introduced a bulkier group in that position such as phenyl, exemplified by compound **3u**, but its in vitro profile was almost the same as the one showed by **2**. As can be deduced from the data of compound **3t**, the introduction of two halogen atoms in the 5- and 11-positions proved to increase the affinity for both 5-HT_2 receptors, with a slight decrease of the affinity for the H_1 receptor.

Although quite potent in vitro compounds were synthesised, only those derivatives bearing some substituent in the 11-position were found to show interesting in vivo activity in our mCPP challenge test. The 5,11-difluoro substituted compound **3t** showed the same activity as the unsubstituted reference compound **2**, both subcutaneously and orally, while the monosubstituted 11-fluoro analogue **3s** was equally active subcutaneously but less potent after oral administration. The 11-chloro analogue **3d** and the 11-methyl derivative **3e** showed slightly less activity than **2** after subcutaneous administration, but **3d** was as active as **2** when orally administered. In contrast, the 11-phenyl substituted compound **3u** was not active in our challenge test. The reason why some compounds which showed quite potent affinity for the 5-HT_{2C} receptor did not show high activity in our mCPP in vivo model is not well understood. In this respect it could be hypothesised that metabolic stability, absorption and/or distribution of the compounds might play a vital role. There are also substantial species differences for 5-HT_2 receptors, which might explain as well the apparent discrepancies between the high binding affinity of some compounds and their lack of in vivo activity.

Table 2 shows the binding affinity for several other serotonergic, dopaminergic and adrenergic receptors of compounds **3d**, **3e**, **3s** and **3t** which bear substituents in the 11-position. It is noteworthy that the presence of halogen atoms in that position enhanced the affinity for the dopamine receptors, especially in the case of the 11-chloro derivative **3d**, and more moderately when the halogen is a fluorine atom. However, when a second fluorine atom was introduced in position 5, the affinity for dopaminergic receptors dropped again, as can be deduced from the binding affinities of compound **3t**. These combined data suggest that the activity found in our mCPP challenge test is indeed due to their affinity for the 5-$HT_{2A/2C}$ receptors, so that the anxiolytic

Table 2. Other receptor binding affinities of compounds **3d**, **3e**, **3s**, **3t**, **2** and mianserin (pIC_{50} values)[a]

Compd	α_{1A}	α_{2A}	α_{2C}	5-HT_{1A}	5-HT_{1D}	5-HT_3	D_2 (rat)	D_{2L}	D_3	D_4
Mianserin	6.39	7.68	7.37	6.40	6.42	5.85	5.45	5.15	5.41	5.48
2	6.27	6.43	5.73	6.01	6.18	5.92	6.71	6.06	6.77	6.88
3d	7.84	6.32	6.06	6.7	6.87	6.32	8.05	8.06	9.26	8.58
3e	7.37	<6	<6	<6	<6	<6	<6	7.26	<6	<6
3s	7.35	6.30	5.93	5.80	6.52	<6	<6	7.44	7.85	7.84
3t	6.79	<6	<6	<6	<6	<6	n.t.	6.35	<6	<6

[a]All assays were performed with human cloned receptors (D_2 also with rat receptor) following standard procedures.

effects should be mediated by one of the 5-HT_2 receptors or by both of them.

In conclusion, we have found that the introduction of diverse substituents at different positions on the phenyl rings of the 2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine structure of **2** afforded several compounds with potent 5-$HT_{2A/2C}$ as well as H_1 receptors affinity. Some of the 11-substituted derivatives were also orally potent mCPP antagonists. Separation of compounds **3d** and **3t** into their corresponding enantiomers as well as further pharmacological results will be published elsewhere.

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