Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 3573–3577

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# 2-(Dimethylaminomethyl)-tetrahydroisoxazolopyridobenzazepine Derivatives. Synthesis of a New 5-$HT_{2C}$ Antagonist with Potential Anxiolytic Properties

J. Ignacio Andrés,[a,*] José M. Alonso,[a] Javier Fernández,[a] Laura Iturrino,[a] Pedro Martínez,[a] Theo F. Meert[b] and Victor K. Sipido[b]

[a]*Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen-Cilag, Medicinal Chemistry Department, Jarama s/n, 45007 Toledo, Spain*

[b]*Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica N.V., Turnhoutseweg 30, B2340 Beerse, Belgium*

Received 24 May 2002; revised 28 August 2002; accepted 16 September 2002

**Abstract**—Following the program started at Johnson & Johnson Pharmaceutical Research & Development searching for 5-$HT_{2A/2C}$ antagonists, we now report on the synthesis of 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydroisoxazolo[3,2-*a*]pyrido[3,4-*c*]-[2]benzazepine and 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydroisoxazolo[3,2-*a*]pyrido[3,2-*c*]-[2]benzazepine. A new method for the synthesis of pyridobenzazepines is described as well. The affinities for several receptors as well as the mCPP antagonistic activity of the compounds synthesised are 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.[8,9]

In recent years, we started a program at Johnson & Johnson Pharmaceutical Research & Development searching for potent, centrally active 5-$HT_{2C}$ receptor antagonists as potential anxiolytic/antidepressant agents. As a result of our synthesis program we discovered a series of 2-(aminoalkyl)-2,3,3a,8-tetrahydrodibenzo[*c*,*f*]isoxazolo[2,3-*a*]azepine derivatives (**1**) as novel 5-$HT_{2A/2C}$ antagonists, some of which also showed a potent mCPP antagonistic activity as shown in our in vivo mCPP challenge test.[10] Those compounds showed high affinity for histamine-$H_1$ receptors as well, what might contribute to potential undesirable side effects such as sedation[11] and/or weight gain,[12] if any of them were selected for further clinical development. Following with the exploration of this new tetracyclic system, we decided to work on the replacement of one of the phenyl rings of compounds **1** by different pyridyl rings, with the aim of synthesising new heterocyclic systems with comparable or better affinity for 5-$HT_{2A/2C}$ receptors, but with decreased affinity for histamine-$H_1$ receptor than the former compounds.[13] This paper describes the synthesis and biological activity of two different 2-(dimethylaminomethyl)-isoxazolopyridobenzazepines, as well as the chemical approaches used trying to prepare others (Fig. 1).

## Chemistry

**2-(Dimethylaminomethyl)-2,3,3a,8-tetrahydroisoxazolo[3,2-*a*]pyrido[3,4-*c*]-[2]benzazepine (2).** The synthesis of

*Corresponding author. Fax: +34-925-245771; e-mail: iandres@prdes.jnj.com

0960-894X/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(02)00796-5

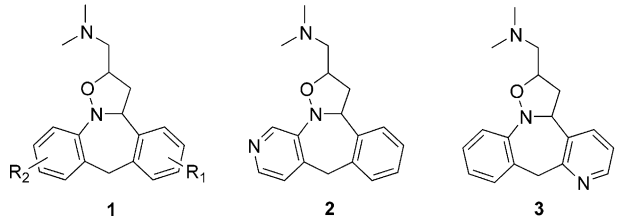
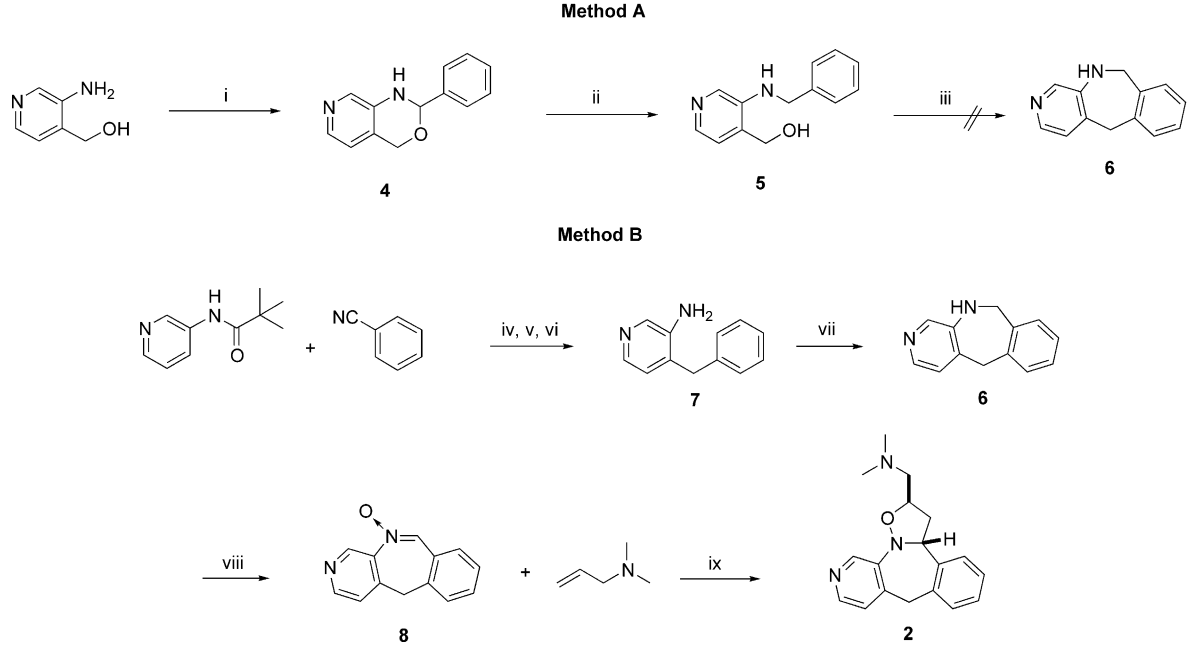


**Figure 1.**

the required tricyclic intermediate 5*H*-pyrido[3,4-*c*]-[2]benzazepine (**6**) was initially tried following the method that we have previously described for the synthesis of substituted 5,6-dihydromorphanthridines.[10] 3-amino-4-pyridylmethanol (obtained by reduction with $LiAlH_4$ of 3-aminoisonicotinic acid[14] ethyl ester) was reacted with benzaldehyde in the presence of a catalytic amount of chloroacetic acid using isopropyl alcohol as solvent, yielding the pyridooxazine derivative **4** in 94% yield. Reductive cleavage of **4** with $NaBH_4$ led to the *N*-benzyl open analogue **5** in 95% yield. Unfortunately all attempts to cyclise compound **5** to the azadihydromorphanthridine analogue **6**, using $H_2SO_4$ as well as other organic and Lewis acids, such as $CH_3SO_3H$, $CF_3SO_3H$ or $SnCl_4$ were unsuccessful (Scheme 1, method A).

After a thorough literature review, we found that some aromatic amines gave intramolecular cyclisations generating benzazepine like rings, in the presence of paraformaldehyde and an acidic medium such as $CF_3COOH$, in a modification of the Pictet–Spengler reaction.[15] We decided to apply these reaction conditions to the intermediate **7**. Thus, treatment of this compound with paraformaldehyde in $CF_3COOH$ at 50 °C for 3 h afforded directly the azadihydromorphanthridine **6**, in 80% yield. Oxidation of **6** with 3-phenyl-2-(phenylsulfonyl)-oxaziridine (Davis' reagent), using the conditions described in our previous articles, afforded the corresponding *N*-oxide **8**, which after 1,3-dipolar cycloaddition with *N*-allyldimethylamine yielded the target compound **2**, in 70% yield. This cycloaddition afforded only the *cis* isomers, in a similar manner as it was observed in the case of the dibenzoisoxazoloazepine analogues,[10] as could be determined by means of NOE difference experiments on the protons of the isoxazolidine ring (Scheme 1, method B).

**2-(Dimethylaminomethyl)-2,3,3a,8-tetrahydroisoxazolo [3,2-*a*]pyrido[3,2-*c*]-[2]benzazepine (3).** We used a different approach towards the synthesis of this compound. Reaction of 2-bromomethyl-*N*-*tert*-butoxycarbonyl-aniline[16] with zinc activated with chlorotrimethylsilane and 1,2-dibromoethane following a procedure described in literature[17] led to the formation of the corresponding organozinc derivative, which reacted in situ with 2-bromo-3-(1,3-dioxolan)pyridine[18] in presence of palladiumtetrakistriphenylphosphine as catalyst, yielding intermediate **9** in 60% yield. Deprotection of the *tert*-butoxycarbonyl group with $CF_3COOH$ gave the aniline derivative **10**. Reaction of this compound with aqueous acetic acid at 65 °C allowed the deprotection of the aldehyde function and subsequent in situ intramolecular cyclisation to the tricyclic structure **11**, in 95% yield. Catalytic hydrogenation afforded the corresponding azadihydromorphanthridine **12**, which in this case was oxidised to the desired *N*-oxide derivative **13** with our usual Davis' reagent procedure, in 90% yield. Finally 1,3-dipolar cycloaddition with *N*-allyldimethylamine

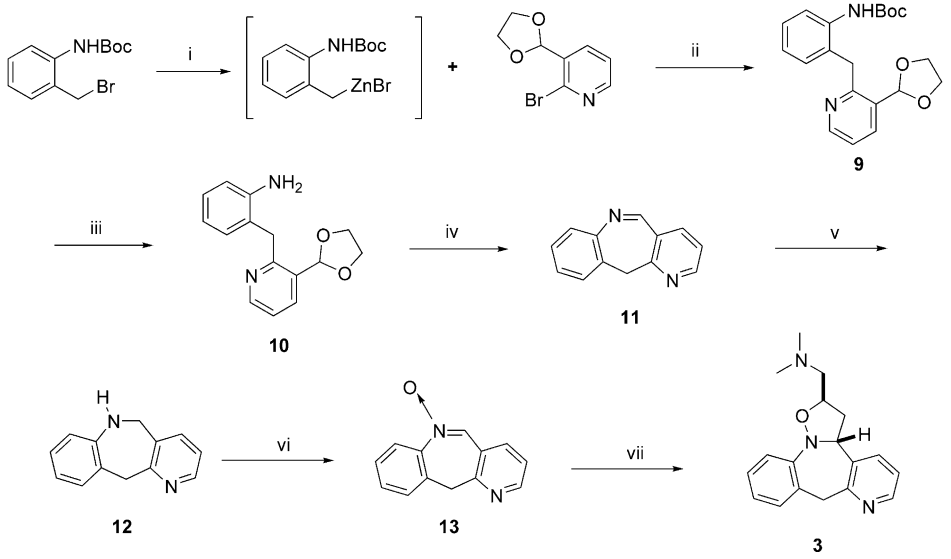


**Scheme 1.** Reagents and conditions: (i) PhCHO, $ClCH_2COOH$ (cat.), $(CH_3)_2CHOH$, rt, 3 h, 94%; (ii) $NaBH_4$, $CH_3CH_2OH$, rt, 2 h, 95%; (iii) $H_2SO_4$, $CH_2Cl_2$, −20 °C, then rt, overnight, or $CH_3SO_3H$, $CF_3SO_3H$ or $SnCl_4$; (iv) *n*BuLi-TMEDA, $Et_2O$, −78 °C to −10 °C, 2 h, then THF, 0 °C, 2 h and rt, overnight; (v) 3N HCl, 90 °C, overnight, 44% (two steps); (vi) $NH_2NH_2{\cdot}H_2O$, $HOH_2CCH_2OH$, KOH, 200 °C, 2 h, 94%; (vii) $(CH_2O)n$, $CF_3COOH$, 50 °C, 3 h, 80%; (viii) 3-phenyl-2-(phenylsulfonyl)oxaziridine, $CH_2Cl_2$, rt, 16 h, 69%; (ix) *N*-allyldimethylamine, THF, 80 °C, sealed tube, overnight, 70%.

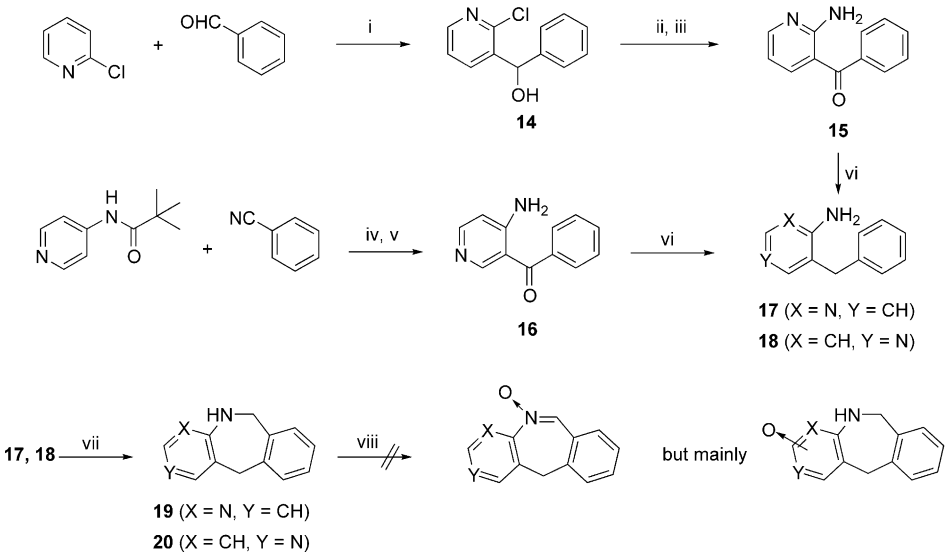
yielded the target compound **3**, in 52% yield, and once again exclusively as the pair of *cis* isomers (Scheme 2).

**Attempts to prepare 5H-pyrido[2,3-*c*]-[2]benzazepine-11-oxide and 5H-pyrido[4,3-*b*]-[2]benzazepine-5-oxide.** Reaction of 2-chloropyridine with phenyllithium in presence of a catalytic amount of diisopropylamine[19] followed by quenching with benzaldehyde afforded compound **14**, which was oxidised to the corresponding ketone. Nucleophilic substitution of the chlorine atom by $NH_2$ was performed by reaction with aqueous $NH_4OH$ in a Parr pressure reaction vessel affording 2-amino-3-benzoylpyridine (**15**). Subsequent Wolf–Kishner reduction of **15** afforded compound **17**, which was the required intermediate to be reacted with paraformaldehyde under the reaction conditions described above. The metalation of 4-pivaloylaminopyridine following the reaction conditions described by Queguiner,[20] subsequent reaction with benzonitrile and further hydrolysis with hydrochloric acid afforded 4-amino-3-benzoylpyridine (**16**) in 45% yield, which after Wolf–Kishner reduction led to compound **18**.

Once again, the reaction of intermediates **17** and **18** with paraformaldehyde in $CF_3COOH$ afforded the tricyclic derivatives **19** and **20**, in 89 and 96% yields, respectively. However all attempts to oxidise **19** and **20** to the desired nitrones, by means of Davis' reagent, *m*-chloroperbenzoic acid (MCPBA) or other oxidising agents were unsuccessful, leading only to oxidation on the nitrogen of the pyridine ring (Scheme 3).




**Scheme 2.** Reagents and conditions: (i) Zn, $BrCH_2CH_2Br$ (cat.), $ClSi(CH_3)_3$ (cat.), THF, rt, 5 h; (ii) $Pd(PPh_3)_4$, THF, 80 °C, overnight, 60%; (iii) $CF_3COOH$, $CH_2Cl_2$, rt, overnight, 100%; (iv) 80% AcOH, 65 °C, 2 h, 95%; (v) $H_2$, Pd/C (10%), $CH_3OH$, rt, 98%; (vi) 3-phenyl-2-(phenylsulfonyl)oxaziridine, $CH_2Cl_2$, rt, 5 h, 90%; (vii) *N*-allyldimethylamine, THF, 65 °C, sealed tube, 5 h, 52%.




**Scheme 3.** Reagents and conditions: (i) (a) 1.8 M PhLi, $iPr_2NH$, THF, −40 °C, 1 h; (b) PhCHO, −70 °C, 45 min, 75%; (ii) $CrO_3$, acetone, −30 °C to rt, 3 h, 86%; (iii) aq $NH_4OH$, Parr pressure vessel, 110 °C, overnight, 56%; (iv) *n*BuLi-TMEDA, $Et_2O$, −78 to −10 °C, 2 h, then THF, 0 °C, 2 h and rt, overnight; (v) 3 N HCl, 90 °C, overnight, 45% (two steps); (vi) $NH_2NH_2{\cdot}H_2O$, $HOH_2CCH_2OH$, KOH, 200 °C, 2 h, 96 and 60%; (vii) $(CH_2O)n$, $CF_3COOH$, 50 °C, 3 h, 89 and 96%; (viii) 3-phenyl-2-(phenylsulfonyl)oxaziridine or MCPBA, $CH_2Cl_2$, rt, overnight.

**Table 1.** Receptor binding affinities of compounds **2**, **3**, and comparison with compounds **1a** and **1b** ($pIC_{50}$ values)

| Compd | 5-$HT_{2A}$ | 5-$HT_{2C}$ | $H_1$ | $\alpha_{1A}$ | $\alpha_{2A}$ | $\alpha_{2C}$ | 5-$HT_{1A}$ | 5-$HT_{1D}$ | $D_{2L}$ | $D_3$ | $D_4$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | 7.64 | 7.91 | 8.17 | 6.27 | 6.43 | 5.73 | 6.01 | 6.18 | 6.06 | 6.77 | 6.88 |
| **1b** | 8.46 | 8.98 | 8.63 | 7.84 | 6.32 | 6.06 | 6.7 | 6.87 | 8.06 | 9.26 | 8.58 |
| **2** | **6.41** | **7.90** | **<6** | 6.4 | <6 | <6 | <6 | <6 | 5.72 | 5.78 | 6.60 |
| **3** | <6 | 6.04 | **7.78** | <6 | <6 | <6 | <6 | <6 | <6 | <6 | <6 |

## Biological Results and Discussion

The affinities for histamine-$H_1$ receptor as well as for different human serotonergic, dopaminergic and adrenergic receptors of the two target compounds that could be synthesised were measured by means of radioligand binding assays as it was described in our previous articles.[10] 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 45 min after intravenous injection of mCPP. Two activity criteria were measured: disinhibition (partial antagonism of mCPP) and exploration (full antagonism of mCPP).[5] Table 1 shows the binding affinity of compounds **2**, **3** and reference compounds **1a** ($R_1 = R_2 = H$) and **1b** ($R_1 = H$, $R_2 = 11$-Cl) for several receptors.

As can be seen in Table 1, compound **2** showed a quite remarkable selectivity for the human 5-$HT_{2C}$ receptor over 5-$HT_{2A}$ receptor. Furthermore, and most interesting, is its lack of affinity for $H_1$ receptor and other serotonergic receptors. Only weak affinity was observed for $D_4$ and $\alpha_1$ receptors. Comparing the receptor binding data of compound **2** with compounds **1a** and **1b** it can be deduced that the replacement of the carbon atom present in the 11-position by a nitrogen atom dropped the affinity for $H_1$ receptors, which was of the same order of magnitude as that for 5-$HT_2$ receptors in the dibenzoisoxazoloazepine series. Even more all compounds from those series were proved to be indeed new 5-$HT_{2A/2C}$ receptor antagonists, while **2** might be defined as a rather selective 5-$HT_{2C}$ antagonist. It is noteworthy as well that the presence of halogen atoms in the 11-position enhanced the affinity for the dopamine receptors, but on the contrary replacement of that CH by nitrogen even decreased this affinity. The 5-$HT_{2C}$ antagonistic activity of compound **2** was confirmed in our in vivo mCPP challenge test (Table 2). It was quite potent in the disinhibition test and moderately potent in the exploration test. On the other hand, compound **3**, with the nitrogen atom in the 7-position of the tetracyclic system, did not show high or moderate affinity for any receptor except for $H_1$. As it was expected from those binding data **3** was inactive in our mCPP test.

**Table 2.** Activity in our mCPP challenge test, disinhibition and exploration measurements after sc administration,[5] of compounds **2** and **3**

| Compd | mCPP (disin.) $ED_{50}$ (mg/kg) | mCPP (expl.) $ED_{50}$ (mg/kg) |
|---|---|---|
| **1a** | 0.01 | >2.5 |
| **1b** | 0.16 | >2.5 |
| **2** | 0.16 | 2.5 |
| **3** | >2.5 | >2.5 |

In conclusion, we have synthesised two new tetracyclic structures, namely 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydroisoxazolo[3,2-*a*]pyrido[3,4-*c*]-[2]benzazepine (**2**) and 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydroisoxazolo[3,2-*a*]pyrido[3,2-*c*]-[2]benzazepine (**3**). In addition we have described a new method for the synthesis of pyridobenzazepines. Compound **2** showed quite remarkable selectivity for 5-$HT_{2C}$ receptor, but did not show affinity for $H_1$ receptor in contrast to its tetrahydrodibenzoisoxazoloazepine analogues. Compound **2** was active subcutaneously in our mCPP challenge test as well, what indicates it could be considered as a 5-$HT_{2C}$ antagonist. Larger scale resynthesis and separation of **2** into its enantiomers is currently in progress, our hope being to be able to identify one of them as a new potent and selective 5-$HT_{2C}$ antagonist. Pharmacological results of those pure enantiomers will be the subject for further publications.

## Acknowledgements

The authors would like to thank Ms. Valle Ancos, Alcira Del Cerro and Victoria Pérez for their experimental work performed. They would also like to thank Mr. Willy Van Gorp for his help in management and coordination of all data generated.

## References and Notes

1. Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. P. A. *Pharmacol. Rev.* **1994**, *46*, 157.
2. Sanders-Bush, E. and Mayer, S. E. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Goodman, L. S., Gilman, A. G., Eds.; McGraw-Hill: New York, 1996; p 249.
3. Gibson, E. L.; Barnfield, A. M. C.; Curzon, G. *Neuropharmacology* **1994**, *33*, 457.
4. Kennett, G. A.; Whitton, P.; Shah, K.; Curzon, G. *Eur. J. Pharmacol.* **1989**, *164*, 445.
5. Meert, T. F.; Melis, W.; Aerts, N.; Clincke, G. *Behav. Pharmacol.* **1997**, *8*, 353.
6. Whitton, P.; Curzon, G. *Psychopharmacology* **1990**, *100*, 138.
7. Rodgers, R. J.; Cole, J. C.; Cobain, M. R.; Daly, P.; Doran, P. J.; Eells, J. R.; Wallis, P. *Behav. Pharmacol.* **1992**, *3*, 621.
8. Di Matteo, V.; Di Giovanni, G.; Esposito, E. *CNS Drug Rev.* **2000**, *6*, 195.

9. Bagdy, G.; Graf, M.; Anheuer, Z. E.; Modos, E. A.; Kantor, S. *Int. J. Neuropsychopharmacol.* **2001**, *4*, 309.
10. Andrés, J. I.; Alcázar, J.; Alonso, J. M.; Díaz, A.; Fernández, J.; Gil, P.; Iturrino, L.; Matesanz, E.; Meert, T. F.; Megens, A.; Sipido, V. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 243 249.
11. Hall, H.; Oegren, S. O. *Life Sci.* **1984**, *34*, 597.
12. Wirshing, D. A. *J. Clin. Psychiatry* **2001**, *62* (Suppl. 21), 7 and references cited therein.
13. Andrés-Gil, J. I., Martínez, P., Fernández-Gadea, F. J., Sipido, V. K. WO 9739001, 1997, Chem. Abstr. **1997**, 127, 346383.
14. Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290.
15. (a) Zhang, L.; Meier, W.; Wats, E.; Costello, T. D.; Ma, P.; Ensinger, C. L.; Rodgers, J. M.; Jacobson, I. C.; Rajagopalan, P. *Tetrahedron Lett.*, **1995**, *36*, 8387 (b) Sotomayor, N.; Domínguez, E.; Lete, E. *Tetrahedron* **1995**, *51*, 12159.
16. Liu, J.; Dodd, R. H. *J. Heterocycl. Chem.* **1995**, *35*, 523.
17. Reich, H. J.; Jasperse, C. P. *J. Org. Chem.* **1988**, *53*, 2390.
18. (a) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187. (b) Marsais, F.; Laperdrix, B.; Gungor, T.; Mallet, M.; Queguiner, G. *J. Chem. Res. Synop.* **1982**, 278.
19. Trecourt, F.; Marsais, F.; Gungor, T.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409.
20. (a) Marsais, F.; Rovera, J. C.; Turck, A.; Godard, A.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2611. (b) Estel, L.; Linard, F.; Marsais, F.; Godard, A.; Queguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 105. (c) Gungor, T.; Marsais, F.; Queguiner, G. *Synthesis* **1982**, 499.