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Laboratory note

New isoxazole derivatives designed as nicotinic acetylcholine receptor ligand candidates

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Abstract

In this work we report the synthesis and evaluation of the analgesic properties of new isosteric heterocyclic derivatives, presenting the isoxazole nucleus, designed as nicotinic acetylcholine receptor ligand candidates, analogues to alkaloid epibatidine. Compound 2-(3-methyl-5-isoxazolyl)pyridine (**3**) presented the best analgesic profile of this series in hot plate test, which was partially prevented by pretreatment with nicotinic receptor antagonist mecamylamine. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Isoxazole derivatives; Nicotinic receptor ligand; Analgesic activity; Molecular hybridization; Epibatidine

1. Introduction

Acetylcholine is an important neurotransmitter molecule, which is associated to parasympatic pre-ganglionar and sympatic post-ganglionar synapses as well as displaying several functions in central nervous system (CNS), e.g. in the cognitive processes [1].

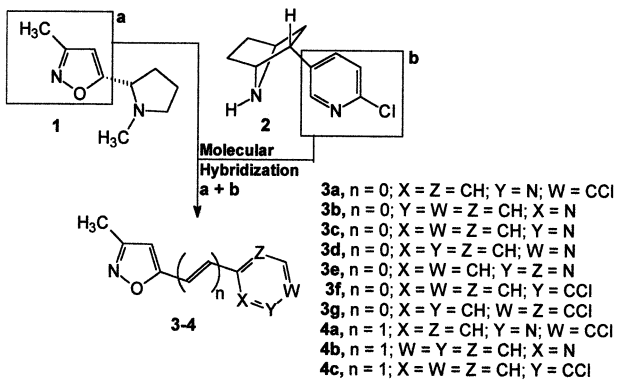

Fig. 1. Design concept of new isoxazole derivatives **3**–**4**.

The receptors modulated by acetylcholine stimulation comprehended two principal types, i.e. muscarinic (mAchR) and nicotinic (nAchR), defined by action of the specific alkaloid ligands muscarine and nicotine (Fig. 1) [2].

The current interest in the medicinal chemistry aspects of nAchR ligands is due, in part, to perceived beneficial effects of nicotine in CNS disorders, such as Alzheimer disease [3,4], Parkinson disease [5,6] or pain reflexes [7,8]. Indeed, recently ABT-418 [9,10] (**1**) and epibatidine [11,12] (**2**) were described as nicotinic receptor agonists which presented potent analgesic profile.

In the scope of a research programme aiming at the synthesis of new nicotinic receptor ligands candidates, we described in this paper the preparation and evaluation of the analgesic profile of two series of substituted isoxazole derivatives **3a**–**g** and **4a**–**c** (Fig. 1) [13]. The compound **3a** was planned by molecular hybridization

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between ABT-418 (**1**) and epibatidine (**2**), by association of the pharmacophoric 3-methylisoxazolyl sub-unit (*a*) from **1** with 2-chloropyridinyl framework (*b*) of **2** (Fig. 1).

Compounds **3b**–**e** were structurally designed in order to investigate the eventual contribution of the isosteric substitution [14] of the pharmacophoric nitrogen-containing six member ring (*b*), e.g. 2-, 3-, 4-pyridine and pyridazine nucleus in the analgesic activity (Fig. 1). Additionally, we promoted the isosteric replacement of the aromatic nitrogen of this sub-unit (*b*) by carbahalogenated framework as in the compounds **3f** and **3g** (Fig. 1).

In addition, we decided to investigate the contribution of the distance between both heteroaromatic rings, by introduction of unsaturated C_2 spacer unit in the derivatives of the (*E*)-vinylogous series **4**, in the anticipated analgesic profile (Fig. 1).

The fit of the new isoxazole derivative **3a** in the nicotinic acetylcholine pseudo-receptor model developed in our laboratory [15] indicated the presence of all minimal structural requirements envisioned to a nicotinic receptor ligand [16].

2. Chemistry

The new substituted isoxazole derivatives **3a**–**g** and **4a**–**c** were synthesised exploring Beam's method [17], involving the condensation of 1,4-dilithium salts of acetone oxime with the corresponding methyl ester derivative (Fig. 2).

The esters precursors of the series **3** and **4** were obtained commercially or prepared from corresponding aromatic aldehyde or carboxylic acid derivative, as shown in Figs. 3 and 4.

Employing the oxidative Yamada's procedure [18], the esters **5**, **6** and **8** were obtained from the respective aldehyde derivative **12**–**14**, in yields ranging from 75 to 85%, by treatment with 2.6 equiv. of KOH and 1.3 equiv. of iodine in methanol at 0 °C (Fig. 3). Additionally, methyl 2-pyrazinecarboxylate (**9**) was prepared quantitatively by diazomethane esterification of the 2-pyrazine carboxylic acid (**15**). Finally, Fisher esterification of 3-chlorobenzoic acid (**16**) and 2,4-dichlorobenzoic acid (**17**) by treatment with MeOH using catalytic amounts of sulphuric acid furnished the desired methyl benzoate derivatives **10** and **11**, in 90 and 85% yield, respectively.

The diastereoselective synthesis of the α,β-unsaturated ester precursors **18**–**20** was achieved, in yields that varied from 81 to 98%, through Knovenagel condensation of corresponding aromatic aldehydes **21**–**23** with malonic acid monomethyl ester, using catalytic amount of piperidine and pyridine as solvent, followed by in situ descarboxylation (Fig. 4) [19]. The ^{1}H-NMR

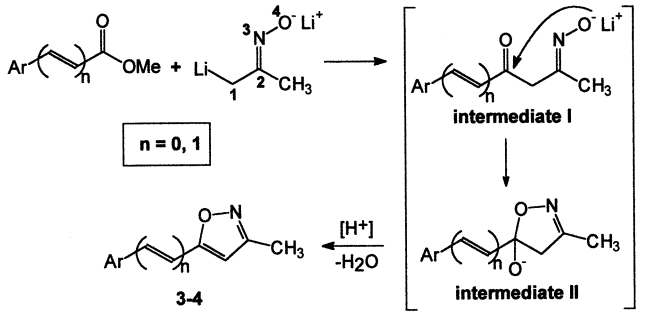


Fig. 2. General method for synthesis of isoxazole derivatives **3**–**4** from carboxylic esters.

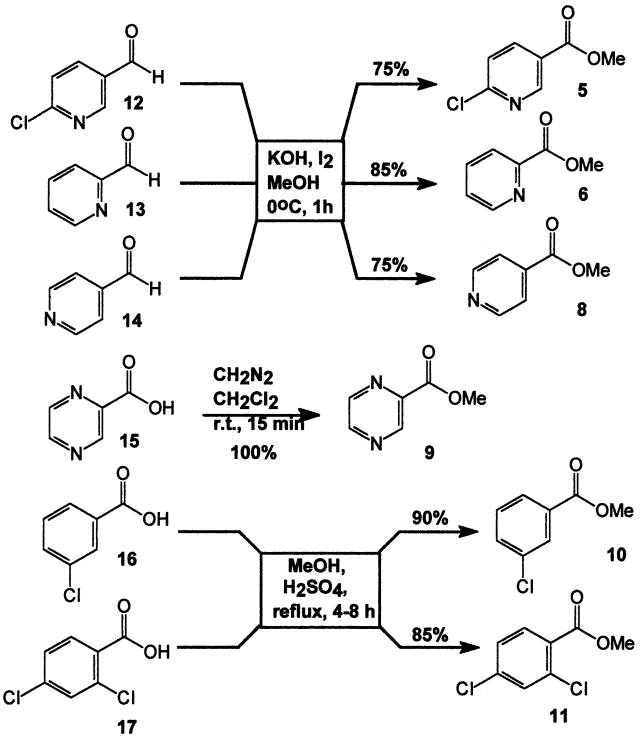


Fig. 3. Synthesis of aromatic or heteroaromatic methyl esters **5**–**6**, **8**–**11** from the corresponding aldehydes or carboxylic acid derivatives.

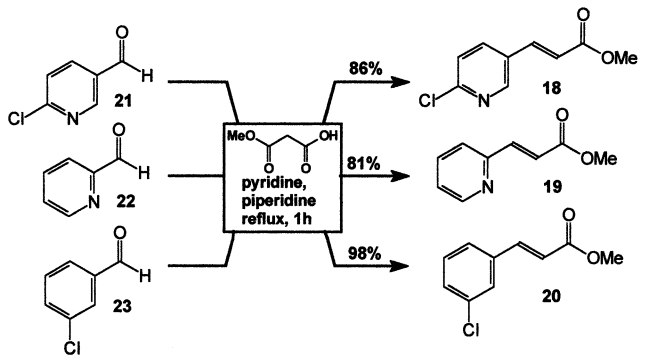
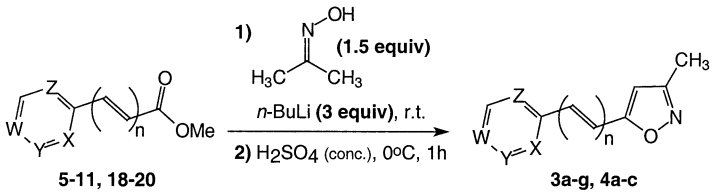


Fig. 4. Synthesis of α,β-unsaturated aromatic or heteroaromatic methyl esters **18**–**20**.

Table 1
Chemical yields and physical data of new substituted isoxazole derivatives **3a–g** and **4a–c**



Starting material	N	X	W	Y	Z	Isoxazole derivative	*t* (h)	Molecular formula [b]	Yield (%)	Melting point (°C)
5	0	CH	CCl	N	CH	**3a**	2	$C_9H_7N_2OCl$	40	122–4
6	0	N	CH	CH	CH	**3b**	2	$C_9H_8N_2O$	20	55–7
7 [a]	0	CH	CH	N	CH	**3c**	5	$C_9H_8N_2O$	65	66–8
8	0	CH	N	CH	CH	**3d**	3	$C_9H_8N_2O$	30	54–6
9	0	CH	CH	N	N	**3e**	1	$C_8H_7N_3O$	35	113–5
10	0	CH	CH	CCl	CH	**3f**	2	$C_{10}H_8NOCl$	47	42–4
11	0	CH	CCl	CH	CCl	**3g**	5	$C_{10}H_7NOCl_2$	37	75–7
12	1	CH	CCl	N	CH	**4a**	1	$C_{11}H_9N_2OCl$	45	145–7
13	1	N	CH	CH	CH	**4b**	2	$C_{11}H_{10}N_2O$	35	64–6
14	1	CH	CH	CCl	CH	**4c**	3	$C_{12}H_{10}NOCl$	40	62–4

[a] Purchased from Aldrich Co, Milwaukee, USA.
[b] The analytical results for C, H, N were within ±0.4% of calculated values.

spectra of methyl esters **18**, **19** and **20** showed a typical AB pattern ($J \sim 16$ Hz) for the vinyl protons with the expected (*E*)-configuration.

The key-step to synthesize desired isoxazole derivatives **3a–g** and **4a–c** was accomplished by treatment of 1.5 equiv. of dilithium salt of acetone oxime, prepared from reaction of acetone oxime with *n*-BuLi in THF at room temperature [17,20], with respective methyl ester derivatives **5–11** and **18–20** as described in Table 1. Compound **3b** was obtained in poor yield, due to the formation in 30% yield of the undesirable bipyridine-*N*-oxide derivative **21** (Fig. 5), resulting from addition of a second molecule of dilithium salt of acetoxime to the keto-carbonyl intermediate I (Fig. 2), followed by cyclization and dehydratation, as previously described by Elliot et al. [21], during the synthesis of isoxazole derived from L-proline methyl ester. Despite several experimental variations in the number of equivalents of dilithium salt used, we are not able to improve the formation of the isoxazole derivative **3b** in this process.

All new isoxazole derivatives described herein (**3a–g** and **4a–c**) were completely structurally characterized by ^{1}H- and ^{13}C-NMR (Tables 2 and 3, respectively) to be subsequently submitted to pharmacological evaluation.

3. Results and discussion

The preliminary evaluation of the central analgesic profile of isoxazole derivatives **3a–g** and **4a–c** in hot plate test [22] showed that only compound **3b** (250 μmol kg^{-1}; i.p.) promotes a significant elevation of latency time of the animals, similar to that obtained for morphine (39.5 μmol kg^{-1}), used as a positive control (Fig. 6A). This effect seems to be dose-dependent in view that it was diminished, but even significant, when compound **3b** was tested at a dose of 100 μmol kg^{-1}. The antinociceptive effect for both doses peaked at 40 min and still present at 80 min after i.p. administration (Fig. 6A). In addition, after oral administration, compound **3b** was effective only at the first's 20 min, probably due to differences in bioavailability between these two routes of administration (data not shown).

Moreover, the antinociceptive effect of compound **3b**, at 100 μmol kg^{-1} but not at 250 μmol kg^{-1}, was slightly but significantly prevented by pretreatment with the noncompetitive neuronal nicotinic acetylcholine receptor antagonist mecamylamine (5 μmol kg^{-1}; i.p.) (Fig. 6B).

The antinociceptive effects of epibatidine (**2**) and other nAChR ligands such ABT-594 (**1**) are also prevented by mecamylamine [23,24], suggesting the involvement of neuronal AChRs in these effects.

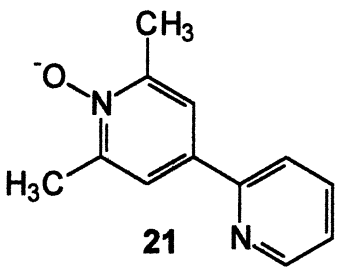
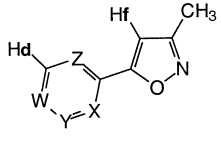
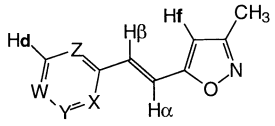


Fig. 5. Bipyridine-*N*-oxide derivative **21**.

Table 2
^{1}H-NMR data at 200 MHz ($CDCl_3$) of substituted isoxazole derivatives **3a–g** and **4a–c**



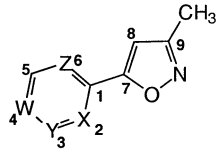
3a-g



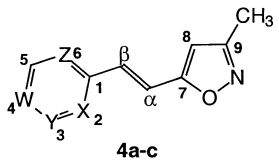
4a-c

Isoxazole derivative	X	Y	W	Z	Há	Hb	Hc	Hd	He	Hf	Hα	Hβ	CH_3
3a	C–H**a**	N	C–Cl	C–H**e**	8.74 (dd) $J = 2.5/0.7$	–	–	7.42 (dd) $J = 8.4/0.8$	8.00 (dd) $J = 8.4/2.5$	6.47 (s)	–	–	2.38 (s)
3b	N	C–H**b**	C–H**c**	C–H**e**	–	8.67 (dt) $J = 4.7/1.3/1.3$	7.33 (ddd) $J = 7.2/5.0/1.8$	7.81 (td) $J = 7.6/7.5/1.7$	7.89 (dt) $J = 7.6/1.3/1.3$	6.76 (s)	–	–	2.40 (s)
3c	C–H**a**	N	C–H**c**	C–H**e**	9.00 (d) $J = 1.7$	–	8.66 (dd) $J = 4.8/1.4$	7.42 (ddd) $J = 8.0/4.9/0.7$	8.08 (dt) $J = 8.0/2.2/1.7$	6.49 (s)	–	–	2.39 (s)
3d	C–H**a**	C–H**b**	N	C–H**e**	7.61 (dd) $J = 4.6/1.6$	8.73 (dd) $J = 4.6/1.6$	–	8.73 (dd) $J = 4.6/1.6$	7.61 (dd) $J = 4.6/1.6$		–	–	
3e	C–H**a**	N	C–H**c**	N	9.11 (d) $J = 1.4$	–	8.61 (m)		–	6.83 (s)	–	–	2.42 (s)
3f	C–H**a**	C–Cl	C–H**c**	C–H**e**	7.73 (t) $J = 1.7/1.6$	–	7.38 (m)		7.63 (m)	6.39 (s)	–	–	2.38 (s)
3g	C–Cl	C–H**b**	C–Cl	C–H**e**	–	7.52 (d) $J = 2.1$	–	7.37 (dd) $J = 8.5/2.1$	7.88 (d) $J = 8.6$	6.79 (s)	–	–	2.39 (s)
4a	C–H**a**	N	C–Cl	C–H**e**	8.51 (d) $J = 2.5$	–	–	7.37 (d) $J = 8.4$	7.81 (dd) $J = 8.4/2.5$	6.18 (s)	6.97 (d) $J = 16.5$	7.26 (d) $J = 16.6$	2.35 (s)
4b	N	C–H**b**	C–H**c**	C–H**e**	–	8.63 (d) $J = 4.0$	7.21 (dd) $J = 7.6/4.9$	7.70 (td) $J = 7.7/7.7/1.7$	7.36 (d) $J = 7.7$	6.19 (s)	7.32 (d) $J = 16.0$	7.52 (d) $J = 15.9$	2.35 (s)
4c	C–H**a**	C–Cl	C–H**c**	C–H**e**	7.49 (s)	–	7.30 (m)		7.36 (m)	6.12 (s)	6.91 (d) $J = 16.4$	7.23 (d) $J = 16.6$	2.32 (s)

Table 3
^{13}C-NMR data at 50 MHz ($CDCl_3$) of substituted isoxazole derivatives **3a–g** and **4a–c**



3a-g



4a-c

Isoxazole derivative	X	Y	W	Z	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	Cα	Cβ	CH_3
3a	CH	N	CCl	CH	122.6	146.6	–	152.4	124.4	135.2	165.5	101.4	160.4	–	–	11.2
3b	N	CH	CH	CH	146.6	–	149.8	124.1	136.8	120.6	168.9	102.7	160.5	–	–	11.3
3c	CH	N	CH	CH	123.4	146.6	–	150.4	123.6	132.7	166.5	101.0	160.2	–	–	11.2
3d	CH	CH	N	CH	134.0	119.3	150.5	–	150.5	119.3	166.8	102.6	160.4	–	–	11.3
3e	CH	N	CH	N	142.3	141.9	–	144.3	144.9	–	166.5	104.4	160.5	–	–	11.3
3f	CH	CCl	CH	CH	129.0	129.8	134.8	130.1	125.6	123.6	168.0	100.8	160.3	–	–	11.3
3g	CCl	CH	CCl	CH	124.8	132.1	129.9	135.9	127.5	130.4	164.7	105.1	160.2	–	–	11.4
4a	CH	N	CCl	CH	130.2	148.3	–	151.1	124.2	135.5	166.7	103.3	160.0	115.4	128.9	11.2
4b	N	CH	CH	CH	153.5	–	149.7	123.0	136.6	123.4	167.4	103.8	160.0	116.6	132.8	11.2
4c	CH	CCl	CH	CH	137.3	129.9	134.6	126.5	128.7	125.1	167.3	102.7	160.0	114.2	132.7	11.2

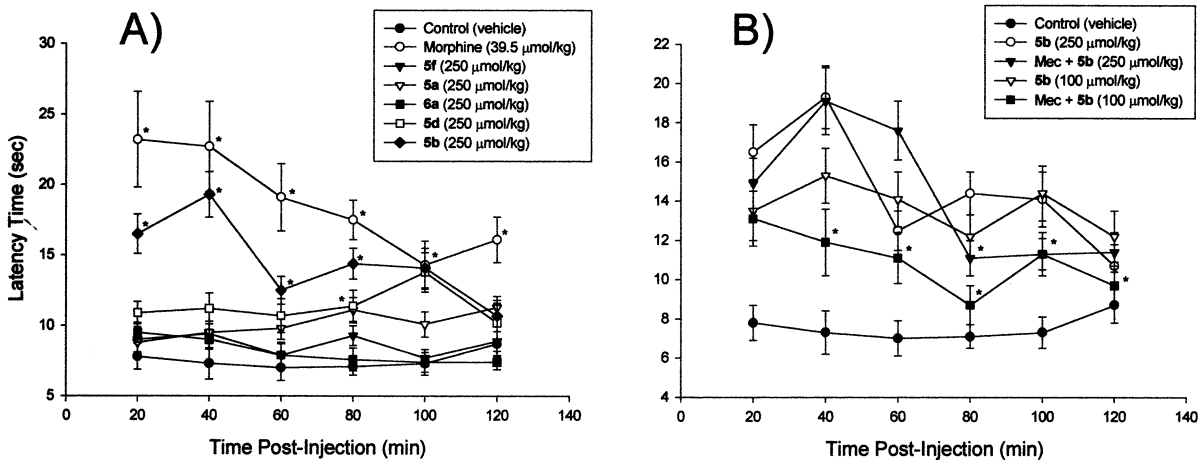


Fig. 6. (A) Effect of i.p. administration of isoxazole derivatives (250 μmol kg^{-1}) on the course of the latency times in the hot plate test in mice. Results are expressed as means ± S.E.M. $N = 8–10$ mice per group. (B) Effect of mecamylamine (Mec) pretreatment (5 μmol kg^{-1}, i.p.) on the antinociceptive effect of compound **3b** at 250 μmol kg^{-1} (i.p.) and 100 μmol kg^{-1} (i.p.), in the hot plate test. Mecamylamine (Mec) was administered 20 min before the test compound. $N = 8–10$ mice per group. *Significantly different from derivative **3b** group ($P < 0.05$).

ABT-594 (**1**) is effective in the hot plate test at 0.62 μmol kg^{-1} (i.p.) [24].

As concluding remarks, our results suggested that isoxazole derivative **3b** showed the best analgesic profile of this series, probable due to its action at nicotinic receptor level, which could be considered as a new heterocyclic template for design of new nAchR ligands.

4. Experimental protocols

4.1. Chemistry

Melting points were determined with a Quimis 340 apparatus and are uncorrected. ^{1}H-NMR spectra were determined in deuterated chloroform containing ca. 1% tetramethylsilane as an internal standard, with Brucker AC 200 or Varian Gemini 200 at 200 MHz. ^{13}C-NMR spectra were determined in the same spectrometers described above at 50 MHz, employing the same solvents. Microanalysis data was obtained with Perkin–Elmer 240 analyser, using Perkin–Elmer AD-4 balance. The usual work-up means that the organic extracts prior to concentration under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred as to brine, dried over anhydrous sodium sulphate and filtered.

4.1.1. General procedure for synthesis of methyl esters *5*, *6* and *8* from corresponding heteroaromatic aldehydes *12*, *13* and *14*

To a solution of the heterocyclic aldehyde derivative **12**, **13** or **14** (9.35 mmol)) in absolute MeOH (10 mL) cooled at 0 °C, were successively added methanolic solutions (each 15 mL) of KOH (1.36 g, 24.31 mmol) and iodine (3.13 g, 12.15 mmol). After stirring for 1 h at 0 °C, small amounts of saturated $NaHSO_3$ solution (ca. 15 mL) were added until the disappearance of the brown colour. Next, the methanol was almost totally evaporated under reduced pressure. The residue was partitioned between water (20 mL) and ethyl ether (30 mL), followed by separation of the organic phase. The aqueous layer was further extracted with ethyl ether (3×10 mL) and the organic extracts were combined and submitted to the usual work-up to give the desired methyl esters **5**, **6** and **8** (see Fig. 3).

4.1.2. General procedure for synthesis of methyl esters *10* and *11* from corresponding benzoic acids *16* and *17*

To a solution of the substituted benzoic acid derivative (**16** or **17**) (8.20 mmol) and sulphuric acid (0.8 mL) in MeOH (14 mL), was refluxed until TLC analysis indicated the total consumption of the starting material. Then, solvent was concentrated and pH was adjusted to 7.0 with 10% aq. $NaHCO_3$ solution, the water phase was extracted with ethyl ether (3×15 mL), and the combined extracts were dried with anhydrous sodium sulphate and concentrated under reduced pressure to give the desired methyl esters, as described in Fig. 3.

4.1.3. Methyl 2-pyrazinecarboxylate *(9)*

To a stirred solution of 2-pyrazine carboxylic acid (**15**) (0.50 g; 4.03 mmol) in CH_2Cl_2 (10 mL) was slowly dropped an ethereal solution of diazomethane until the reaction was finished (TLC). Then glacial acetic acid (ca. 1.0 mL) was added and the organic phase was dried with anhydrous K_2CO_3. The resulting suspension

was filtered and the solvent was concentrated at reduced pressure to afford, quantitatively, the methyl ester **9** as a yellow solid, m.p. 55–56 °C (Fig. 3).

4.1.4. General procedure for synthesis of α,β-unsaturated methyl esters *18*, *19* and *20* from their corresponding aromatic or heteroaromatic aldehydes *21*, *22* and *23*

To a solution of malonic acid monomethyl ester [25] (0.41 g; 3.51 mmol) in pyridine (1.05 mL) containing a catalytic amount of piperidine (0.02 mL) was added 2.34 mmol of the aldehyde derivative (**21**, **22** or **23**). The reaction mixture was refluxed, until TLC analysis indicated total consumption of the aromatic aldehyde (see below). Then, after cooling at room temperature, water (ca. 10 mL) was added, the pH was adjusted to 7.0 with 20% aq. HCl and the aqueous phase was extracted with ethyl ether (4×5 mL). The organic extracts were joined, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a residue, which was purified by flash chromatography (eluent *n*-hexane–ethyl acetate, gradient 95/5 to 50/50 v/v). See yields in Fig. 4.

4.1.5. General procedure for synthesis of new isoxazole derivatives *3a–g* and *4a–c* from corresponding methyl ester derivatives *5–11* and *18–20*

To a solution of acetone oxyme (0.48 g; 6.62 mmol) in dry THF (12 mL) maintained at 0 °C, was added a solution of *n*-butyllithium in hexane (9.5 mL; 13.22 mmol/solution 1.39 M). The ice bath was removed and the mixture was stirred at room temperature for additional 30 min. Then, a solution of aromatic or heteroaromatic methyl ester derivative (4.42 mmol) in dry THF (3 mL) was added and the reaction was stirred at room temperature until TLC analysis indicated the total consumption of the starting material. Next, sulphuric acid (3.6 mL) was added at 0 °C, followed by stirring at room temperature for 1 h. Then, pH was adjusted to 7.0 with 50% aq. NaOH solution and water (15 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (5×15 mL) and combined organic layers were dried under anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue obtained was purified by silica gel column chromatography (eluent *n*-hexane–ethyl acetate, gradient 95/5 to 70/30 v/v) (see Tables 1–3).

4.2. Pharmacological assays

4.2.1. Hot plate test

The central analgesic activity was determined in vivo by the hot plate test according to Kuraishi et al. [22]. Swiss mice of both sexes (18–25 g) were used, maintained with water ad libitum and fasted for 8 h.

Animals were placed on a plate heated at 55 ± 0.1 °C and their responses to thermal stimulation (licking or withdraw of the hindpaw) were timed. Three control measures were done (in the absence of the test drugs) in intervals of 30 min to determine the control latency mean time and the cut-off time (maximum time of permanence of the animal in the plate), calculated as three times the control mean value (25 s). The response time for each mouse was registered at 20 min intervals after drug administration for a total of 120 min. Data are expressed as latency time and the percentage of latency time increase (%LTI)

$$\%\ \mathrm{LTI} = \frac{\text{test latency} - \text{control latency}}{\text{cut-off} - \text{control latency}} \times 100$$

4.2.2. Effect of compounds on the hot plate test

Immediately after the control measures, groups of 10–13 mice were treated intraperitoneally with arabic gum 5% (vehicle control group), isoxazole derivatives **3a–g** and **4a–c** (100 and 250 μmol kg^{-1}) or morphine (39.5 μmol kg^{-1}) in a volume of 5 mL kg^{-1}. Latency times were measured as described above.

4.2.3. Effect of pretreatment with mecamylamine on the hot plate test

Immediately after the control measures, groups of 10 mice were treated with mecamylamine (1 mg kg^{-1}; i.p.), 20 min prior to the administration of test compounds.

4.2.4. Statistical analysis

Differences between responses were statistically analysed by Student *t*-test and analysis of variance (ANOVA), followed by Bonferroni's *t*-test, for a significance level of $^{*}P < 0.05$. Results are expressed as means ± S.E.M. of measurements.

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