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Synthesis and Preliminary Biological Evaluation of New α-Amino Amide Anticonvulsants Incorporating a Dextromethorphan Moiety

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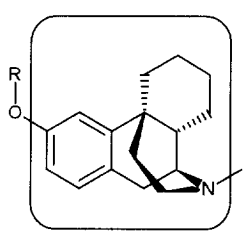
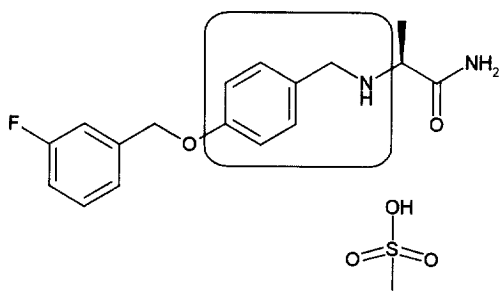
Abstract: Dextromethorphan **1** is an effective neuroprotectant in animal models of epilepsy and ischemia but showed side-effects during clinical trials limiting its potential use in a clinical setting. Here we describe the enantioselective and enantiospecific syntheses and the initial *in vitro* and *in vivo* biological evaluation of new hybrid structures between **1** and a previously disclosed α-amino amide anticonvulsant (**3**).

Keywords: *Amino acids and derivs; Anticonvulsants; Neurologically active compds; Stereospecificity.*

Dextromethorphan **1** and its metabolite dextrorphan **2** belong to the morphinane chemical class and are endowed with a proven activity as neuroprotectants.[1] These compounds are thought to counteract the excitatory amino acid (EAA) action in the Central Nervous System (CNS) during pathological (i.e, ischemia, anoxia, seizures) events, though hypotensive side-effects precluded a further devolopment of **1** in the clinical setting.[2] The precise mechanism through which **1** and **2** protect neurons from excitotoxicity is still unclear. Beside a low micromolar, kinetically favourable interaction with the N-methyl-D-aspartate (NMDA)-receptor associated ion channel,[3] the inhibition of glutamate release, partly mediated by sodium (Na^+) and calcium (Ca^{++}) channel blockade, seems to play an important role.[4]



R = Me (**1**), H (**2**)



PNU-151774E (**3**)

In a program aimed at the discovery of new, potent and safe anticonvulsant agents, various 2-aminopropanamides were evaluated and found highly active in physically- and chemically- induced animal seizure models.[5] PNU-151774E **3** was the lead compound of this new class of anticonvulsants.[6]
These compounds were active at inhibiting glutamate release with a potency comparable to that of **1**, and **3** had high affinity for binding site 2 ot the Na^+ channel receptor.[7]

A benzylamino moiety represents the core aromatic region in compounds like **3** and modeling considerations prompted us to replace this benzylamino group with the morphinane part of **1** in order to

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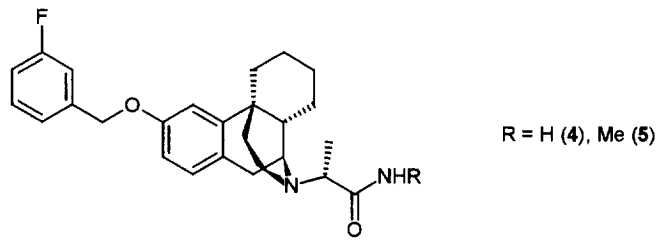
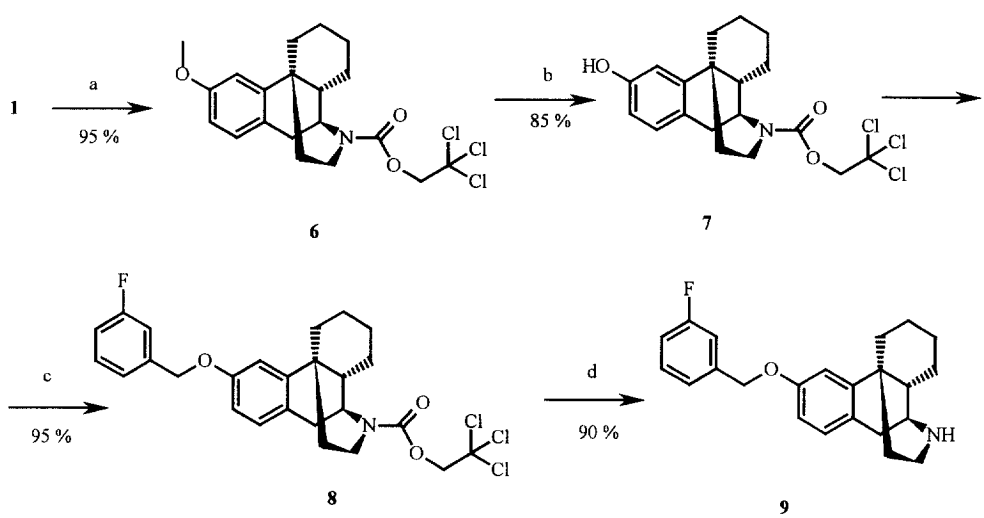
hybridize the two classes and introduce a degree of conformational rigidity into our molecules. Therefore we pursued the synthesis of the two hybrids (**4** and **5**) which was accomplished starting from dextromethorphan itself (Scheme 1).



R = H (**4**), Me (**5**)

Scheme 1

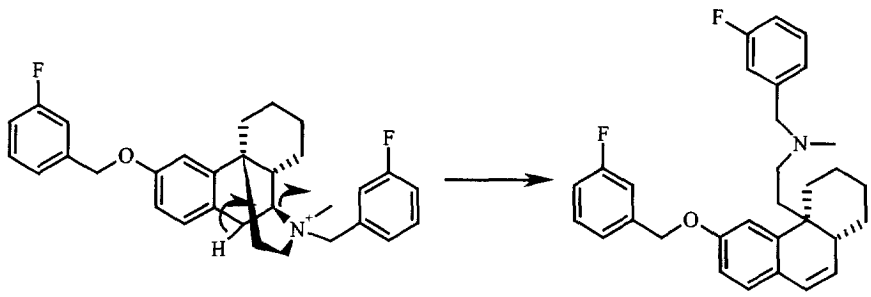


Reagents and conditions: (a) $ClCOOCH_2CCl_3$, toluene, reflux; (b) BBr_3, CH_2Cl_2, r.t.; (c) K_2CO_3, 3-fluorobenzylchloride, EtOH, reflux; (d) Zn dust, AcOH, reflux.

N-demethylation of **1** with trichloroethylchloroformate provided the intermediate **6** which was subsequently O-demethylated with boron tribromide giving rise the phenolic derivative **7**. This was then alkylated with 3-fluorobenzylchloride yielding **8**, that furnished the key intermediate **9** by treatment with zinc dust in acetic acid.

Previous attempts to perform the phenolic group alkylation working on a substrate derived from **1** containing a basic nitrogen furnished only the rearranged product **10**, obtained through tertiary nitrogen quaternarization followed by Hoffman elimination with concomitant opening of the piperidine ring (Scheme 2).

Scheme 2

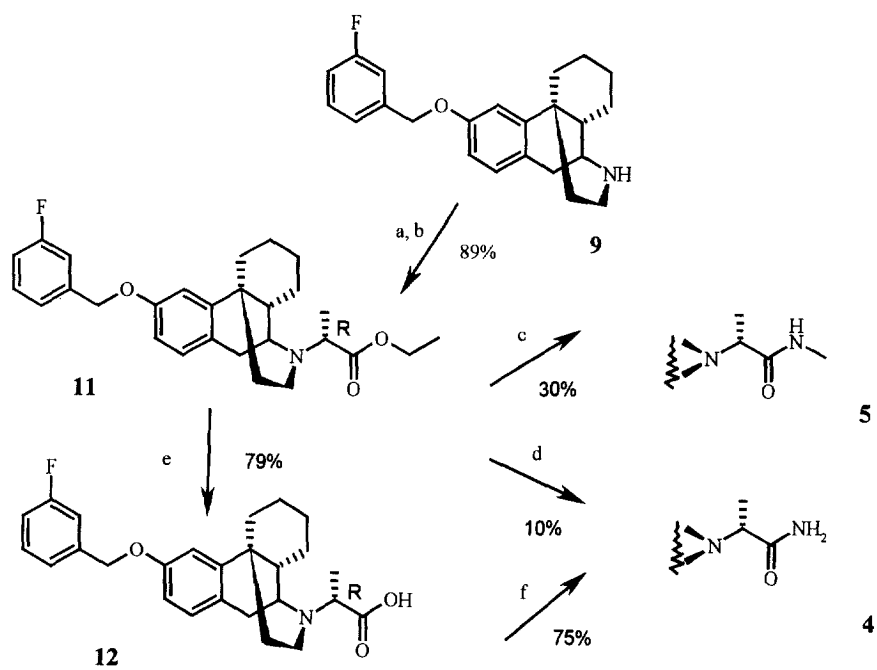


10

Compound **9** is the common precursor for a stereospecific synthesis of **4** and **5** (Scheme 3) and their stereoselective synthesis (Scheme 4). Thus, treatment of **9** with the triflic derivative of (S)-ethyl lactate led to the ester intermediate **11** with complete inversion of the stereochemistry, as previously described for similar reactions.[8] This provided **4** and **5** respectively by treatment with gaseous ammonia in EtOH-DMF and CH_3NH_2 33 % in EtOH. Alternatively **4** was obtained in better yields by hydrolysis to the corresponding acid **12** and subsequent amidation.

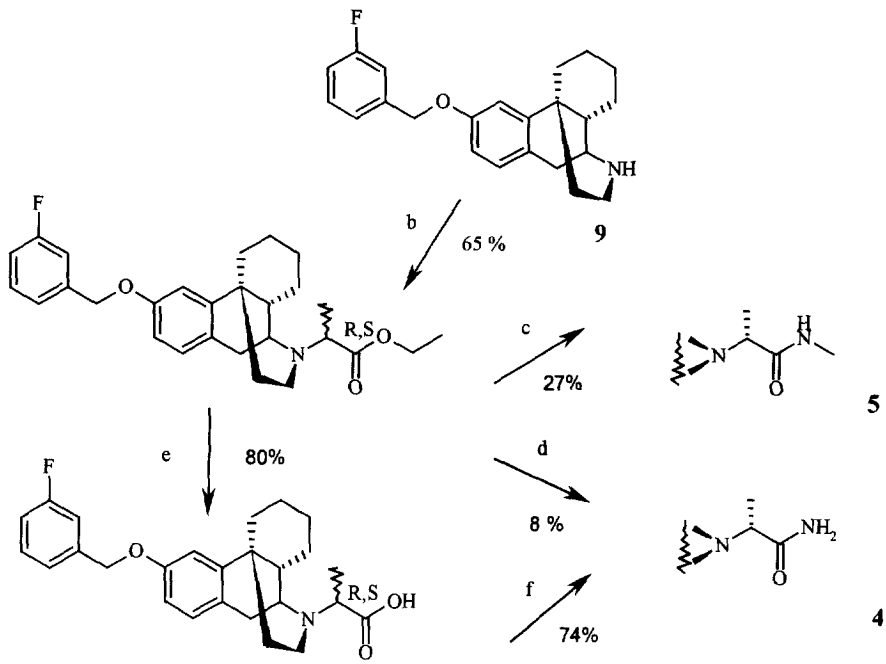
Experimental data for for previously unknown **4** and **5** are reported.[9]

Scheme 3



Reagents and conditions: (a) (S(-)-ethyl lactate, CH_2Cl_2, 0°C, under nitrogen, $(CF_3SO_2)_2O$ in Py; (b) compound (9), Hünig 's base, CH_2Cl_2, r.t; (c) $MeNH_2$ in EtOH 33 %, r.t.; (d) gaseous NH_3 in EtOH-DMF, r.t.; (e) NaOH 2N, MeOH, r.t.; (f) 1) ClCOOEt, $CHCl_3$, Et_3N, 0°C; 2) gaseous NH_3, from 0°C to r.t.;

Scheme 4



Reagents and conditions: as for Scheme 3 except: (b) 2-(R,S)- ethyl bromopropionate, Hünig's base, DMF, 100 °C.

A high degree of stereoselectivity was observed in the outcome of the reaction of 2-bromopropionate with **9**. In fact only the R-α-monoamide having the methyl group **syn** to the cyclohexyl ring was formed. This outcome may likely be ascribed to the constrained morphinane scaffold that can direct the entry of a nucleophile such as ammonia or methylamine.

Compounds **4** and **5** were evaluated *in vitro* (Site-2 Rat Sodium Channel blockade) and *in vivo* (Maximal Electric Seizure (MES)) as potential anticonvulsants, and for their ability to elicit neurological deficits (Rotorod Test)(Table 1). Both compounds displayed sodium channel blocking activity at concentration similar to those of dextromethorphan **1**. *In vivo* activities (both after *po* and *ip* administration) were weaker for **4** with respect to **1**, while **5** clearly is the least active. However, Therapeutic Indexes (TI = Rotorod/MES), suggested that **4** may be safer than dextromethorphan **1** in its action since animals administered with **1** died at the same dosage required for Rotorod impairment by **4** (see Table 1).

An R-configuration at the α-amino amide carbon was chosen because of synthetic constraints in obtaining the triflic derivative of (R)-ethyl lactate. However it was shown earlier[5] that the role of the α-carbon stereochemistry in this anticonvulsant series is seemingly unimportant (e.g., the (R)-derivative of **3** is a comparably active compound in the MES test).

Table 1
Sodium channel binding and anticonvulsant activity of **1**, **3**, **4** and **5**.

Compound	Na^+ channel binding[a] (IC_{50}, μM)		MES, ip, mice[b] (mg/Kg), ED_{50}	MES, po, mice[b] (mg/Kg), ED_{50}	Rotorod, ip, mice[c] (mg/Kg), ED_{50}	TI
	^{3}H-BTX	^{3}H-STX				
4	2.6 ±0.4	>300	18.1 (8.9-26.2)	50.8 (32.9-124)	176 (130-253)	10
5	5.3±1.2	>300	41.6 (18.6-146)	nd	152 (133-183)	4
3	8.2±0.2	>300	6.9 (5.7-8.1)	8.0 (7.0-9.1)	626 (557-703)	78
1	1.3±0.2	>300	10.1 (8.9-11.7)	12.9 (8.4-16.5)	nc[d]	nc[d]

a)[^{3}H]-Batrachotoxin ([^{3}H]-BTX) and [^{3}H]-Saxitoxin ([^{3}H]-STX) binding to rat brain sodium channels were carried out according to Catterall [10]. Rat membranes were incubated with different radioligands in the presence of 9-10 concentrations of the molecules to be tested (10^{-9}-$3x10^{-4}$) b) An Ugo Basile electroconvulsometer (Model ECT UNIT 7801) was used to deliver an electrical stimulus sufficient to produce a hindlimb tonic extensor response in at least 97% of control animals. The stimulus was delivered intra-aurally through clip electrodes in mice (0.7 s of a 28 mA shock, with a pulse train of 80 Hz having a pulse duration of 0.4 ms). The acute effects of compounds administered 60 min orally (po) or 30 min (ip) before MES induction were examined. Complete suppression of the hindlimb tonic extensor component of seizures was taken as evidence of anticonvulsant activity. c) Psychomotor side-effects of the compounds were examined by Rotorod. Mice trained to the rotorod (Ugo Basile; 10 rpm) were used. The compounds were administered 60 min before the test and the number of animals falling over 1-2 min test period were monitored [11]. The toxic dose causing 50% of animals treated to fall from the rotorod (TD_{50}) of each compound was calculated. d) nc = not calculated; Rotorod ED_{50} and TI could not be calculated for dextromethorphan **1** because of significant mortality (LD_{50}: 234 mg/kg) already at doses that did not cause Rotorod impairment of 50% of the animals.

The synthesis and preliminary biological evaluation of two hybrid compounds between the structures of known anticonvulsants dextromethorphan (**1**) and PNU-151774E (**3**) were presented. An interesting stereoselection caused by the benzomorphinane scaffold in the ester and amide formation was observed. Compounds obtained showed a better therapeutic ratio than dextromethorphan (**1**).

References and Notes

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9. Analytical data for compound **4**: ^{1}H NMR (δ, $CDCl_3$): 1.0-1.8 (m, 8H, CH_2-1, CH_2-3, CH_2-2 + H-12eq + H-4ax), 1.83 (d, J = 7.3 Hz, 3H, $\underline{CH_3}CH$), 2.2-2.5 (m, 3H, H-4eq + H-12ax + H-13ax), 2.60 (m, 1H, H-10), 3.13 (s, 2H, CH_2-9), 3.45 (m, 1H, H-13eq), 3.78 (m, 2H, H-10a + CH-14), 5.02 (m, 2H, $Ph\underline{CH_2}O$), 5.70, 8.99 (2xs, 2H, $CO\underline{NH_2}$), 6.8-7.4 (m, 7H, aromatic protons); mp 225°C.
Analytical data for compound **5**: ^{1}H NMR (δ, $CDCl_3$): 1.0-1.7 (m, 8H, CH_2-1, CH_2-3, CH_2-2, H-12eq + H-4ax), 1.79 (d, J = 7.5 (d, J = 7.5 Hz, 3H, $\underline{CH_3}CH$), 2.3-2.5 (m, 3H, H-4eq + H-12ax + H-13ax), 2.56 (m, 1H, H-10), 2.88 (d, J = 4.4 Hz, 3H, $\underline{CH_3}NH$), 3.10 (dd, J = 5.3, 19.7 Hz, 1H, $C\underline{H}(H)9$), 3.17 (d, J = 19.7 Hz, 1H, $CH(\underline{H})9$), 3.45 (m, 1H, H-13eq), 3.58 (m, 1H, H-10a), 3.83 (m, 1H, CH-14), 5.03 (m, 2H, $Ph\underline{CH_2}O$), 6.8-7.4 (m, 7H, aromatic protons), 8.92 (q, J = 4.4 Hz, 1H, $N\underline{H}CH_3$); mp 185°C.
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