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SYNTHESIS AND BIOLOGICAL EVALUATION OF CONFORMATIONALLY RESTRICTED GABAPENTIN ANALOGUES

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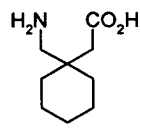
Abstract: A series of conformationally restricted Gabapentin analogues has been synthesised. The pyrrolidine analogue (R)-2-Aza-spiro[4.5]decane-4-carboxylic acid hydrochloride (3a) had an IC_{50} of 120nM, similar to that of Gabapentin (IC_{50} = 140nM), at the Gabapentin binding site on the $\alpha_2\delta$ subunit of a calcium channel. Compound (3a) also reversed carrageenan induced hyperalgesia in rats.

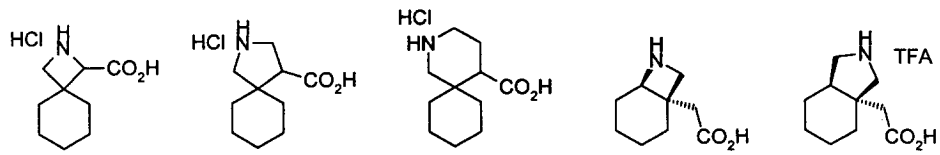
Gabapentin (Neurontin®) (1) is an anticonvulsant with, as yet, an unknown mechanism of action.[1,2] Structurally related to the neurotransmitter GABA (γ-aminobutyric acid), Gabapentin does not interact with any of the GABA receptors, nor is it an inhibitor of GABA uptake or degradation.[3] It is excreted unchanged via the kidneys.

Recently, a high affinity binding site for the Gabapentin, located on the $\alpha_2\delta$ subunit of a calcium channel, has been reported[4] and it has been suggested that this site may be involved in the mediation of the pharmacological actions of Gabapentin[5].



(1)

A series of Gabapentin analogues in which the GABA portion was subjected to conformational constraints was synthesised in order to investigate the preferred binding conformation of the GABA moiety of Gabapentin. The spiro molecules (2), (3), (4) and the fused bicyclic compounds (5) and (6) were chosen as target compounds.



(+/-)-(2) (+/-)-(3) (+/-)-(4) (+/-)-(5) (+/-)-(6)

The analogue (2) was synthesised[6,7] (scheme 1) via aldol condensation of cyclohexane carbonitrile with benzyloxyacetaldehyde. The nitrile (8) was reduced with lithium aluminium hydride to give the free amine (9)

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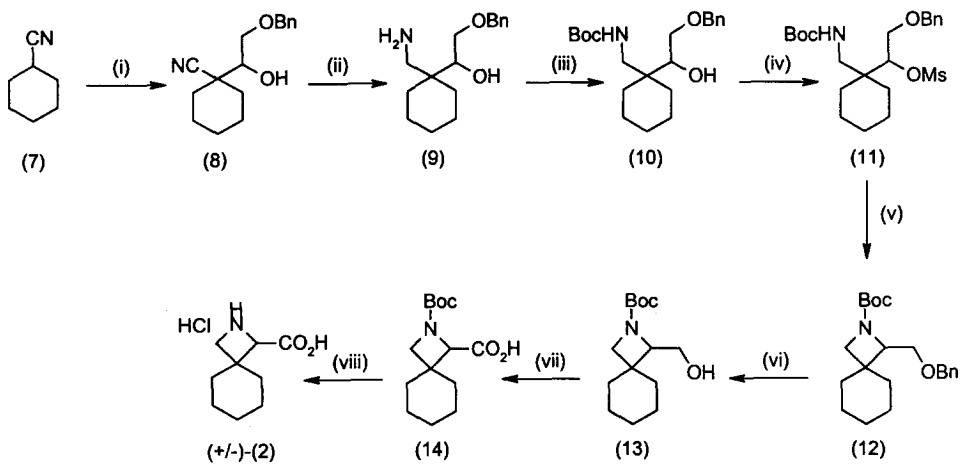
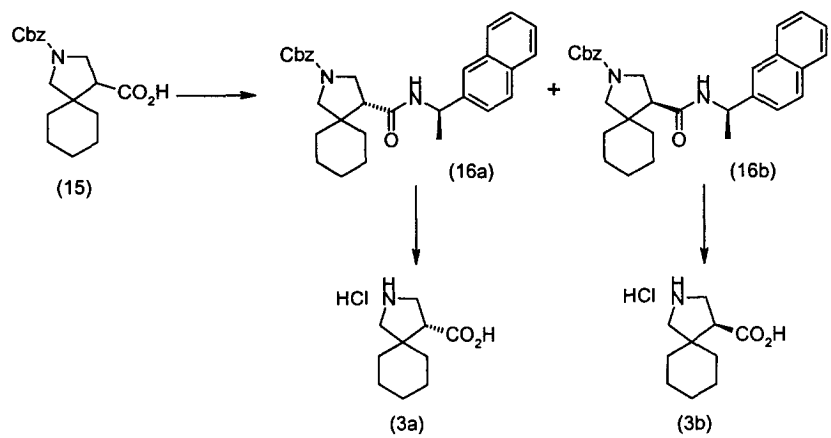
which was protected with a *tert*-butyloxycarbonyl (BOC) group. The primary alcohol (10) was mesylated to obtain (11) which was cyclised to the azetidine (12) using sodium hydride in dimethylformamide. Successive deprotection and oxidation of the primary hydroxyl group led to the carboxylic acid (14).[8] Treatment of (14) with 1N HCl gas in ethyl acetate gave the amino acid hydrochloride (2) in a crystalline form.[9]



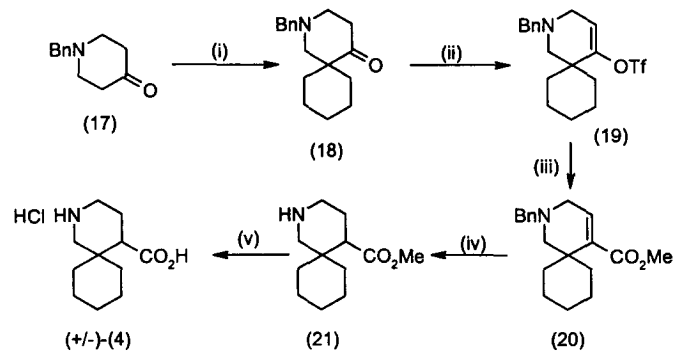
Scheme 1. Reagents: (i) $BnOCH_2CHO$, LDA, THF, -78°C (74%); (ii) $LiAlH_4$, $AlCl_3$, Et_2O (85%); (iii) $(BOC)_2O$, CH_2Cl_2 (96%); (iv) MsCl, Et_3N, CH_2Cl_2 (65%); (v) NaH, DMF 45°C (59%); (vi) Pd/C, H_2, MeOH (90%); (vii) $NaIO_4$, $RuCl_3$, CCl_4, H_2O, MeCN (83%); (viii) HCl, EtOAc (90%).

The synthesis of the racemic analogue (3) was previously reported.[10] Derivatisation of the racemic carboxylic acid (15) (Scheme 2) using (R)-(+)-1-(2-naphthyl) ethylamine led to a mixture of two diastereoisomers (16a and 16b) which could be separated over silica gel chromatography. Hydrolysis of (16a) in refluxing 6N hydrochloride acid gave the R isomer (3a).[9,11] Hydrolysis of (16b) gave the S isomer (3b).[9,12]



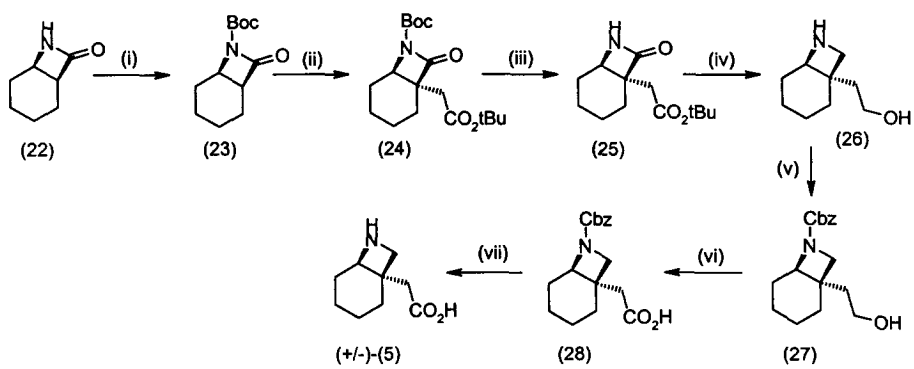
Scheme 2. Reagents: (i) 1) $(COCl)_2$, DMF, THF 2) (R)-(+)-1-(2-naphthyl)ethylamine, Et_3N, CH_2Cl_2 (80%); (ii) HCl, THF, reflux (70%).

The analogue (4) was synthesised[13] (scheme 3) via condensation of 1,5-dibromopentane with 1-N benzyl-4-piperidinone. The spiro ketone (18) was converted to the corresponding vinyl triflate (19)[14] which, upon a palladium-mediated carbonylation-methoxylation[15], gave the α-β unsaturated methyl ester (20). Simultaneous hydrogenation of the double bond and deprotection of the amine with Pearlman's catalyst led to the methyl ester (21). Hydrolysis of (21) in 6N hydrochloride acid gave the desired amino acid hydrochloride (4).[9]

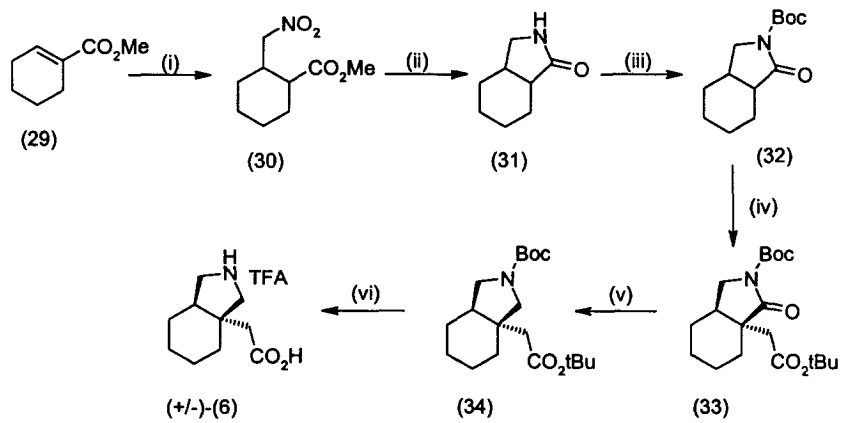


Scheme 3. Reagents: (i) 1-N-benzyl-4-piperidinone, $Br(CH_2)_5Br$, tBuOK, benzene, 70°C (60%); (ii) LDA, N-phenyltriflimide, DME, 5°C (55%); (iii) CO, $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF (61%); (iv) $Pd(OH)_2/C$, H_2, MeOH (75%); (v) HCl, reflux (94%).

The synthesis of (5) (scheme 4) was achieved from the racemic *cis*-β-lactam (22).[16] Protection of the amine with a BOC group and subsequent alkylation with *tert*-butyl bromoacetate gave the *cis*-alkylated β-lactam (24). Selective removal of the Boc protecting group using neutral conditions[17] afforded the free β-lactam which was reduced into the azetidine (26) with lithium aluminium hydride. Protection of (26) with benzyl chloroformate followed by a sodium periodate oxidation of the primary alcohol gave the carboxylic acid (28). The racemic amino acid (5) was isolated after deprotection of the amine by catalytic hydrogenation.[9]



Scheme 4. Reagents: (i) $(BOC)_2O$, DMAP, Et_3N, THF (60%); (ii) LDA, $BrCH_2CO_2tBu$, THF, -78°C (61%); (iii) CAN, CH_3CN, reflux (43%); (iv) $LiAlH_4$, Et_2O; (v) ZCl, pyridine, CH_2Cl_2 (2 steps, 51%); (vi) $NaIO_4$, $RuCl_3$, CCl_4, H_2O, CH_3CN (65%); (vii) Pd/C, H_2, MeOH (77%).



Scheme 5. Reagents: (i) $MeNO_2$, $(Bu)_4N^+F^-$, THF, reflux (73%); (ii) Ni sponge, H_2, MeOH (98%); (iii) $(BOC)_2O$, DMAP, Et_3N, THF (70%); (iv) 1) LDA, $BrCH_2CO_2tBu$, THF, -78°C 2) DMPU, 75°C (70%); (v) 1) $LiBHEt_3$, THF, -78°C 2) Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2, -78°C (48%); (vi) TFA, CH_2Cl_2 (69%).

The analogue (6) was synthesised (scheme 5) via 1-4 Michael addition of nitromethane on methyl-1-cyclohexene-1-carboxylate. Catalytic hydrogenation of the nitro derivative (30) led to the in situ formation of a cis/trans mixture of the lactam (31).[18] Alkylation of the N-Boc protected lactam (32) with tert-butyl bromoacetate gave the cis compound (33).[19] Reduction of the lactam with super hydride and triethylsilane[20] afforded the pyrrolidine (34) which was converted to the desired amino acid TFA salt (6) after treatment with trifluoroacetic acid.

Biological evaluation

The affinities of the conformationally restricted Gabapentin analogues for the Gabapentin binding site located on the $\alpha_2\delta$ subunit of a calcium channel were determined using a radioligand binding assay incorporating [^{3}H]Gabapentin as described previously.[4] The results are summarised in table 1.

Table 1 : In vitro data for compounds 1-6. Values shown are the geometric mean of at least 3 experiments.

Compound	IC_{50} μM (SEM)
(1)	0.14 (0.01)
(2)	1.5 (0.37)
(3a)	0.12 (0.01)
(3b)	>10
(4)	>10
(5)	>10
(6)	>10

As can be seen from table 1, compound (3a) and Gabapentin (1) had similar binding affinity for the Gabapentin binding site, whereas, compounds (3b), (4), (5) and (6) all had significantly lower affinity. These results suggested that the restriction of the nitrogen atom and carboxylic acid group in the pyrrolidine moiety of (3a)

could mimic the biologically active binding conformation of the GABA portion of Gabapentin.

The anti-hyperalgesic action of compound (3a) was evaluated in the rat carrageenan-induced thermal hyperalgesia (CITH) model of pain.[5]

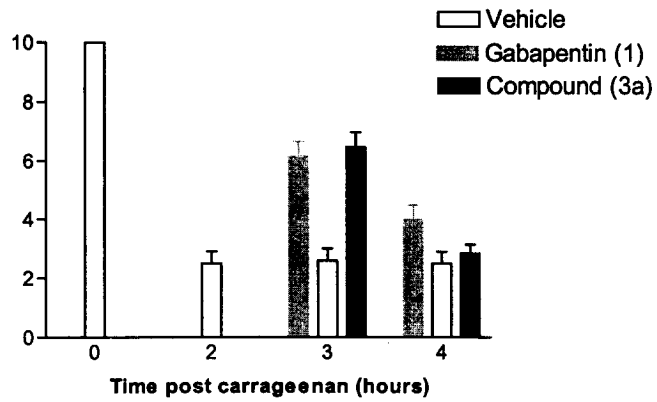


Figure 1: Evaluation of Gabapentin (1) and compound (3a) in the CITH model. Both compounds were dosed at 30mg/kg p.o. at 2h post carrageenan administration.

The administration of carrageenan (10μl of 20mg/ml solution) into the planter surface of a rat hindpaw reduced paw withdrawal latency to the thermal stimulus from approximately 10 seconds to three seconds. This indicated the development of hyperalgesia. The maintenance of this hyperalgesic response was attenuated by both Gabapentin and compound (3a) (Figure 1).[5]

Conclusion

Conformationally constrained analogue (3a) and Gabapentin (1) have similar in vitro and in vivo biological activities at the Gabapentin binding site and in the carrageenan-induced thermal hyperalgesia model respectively. These results suggest that the GABA portion of Gabapentin (1) may adopt a binding conformation close to that attained by the pyrrolidine moiety of the restricted analogue (3a).

Acknowledgements

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References and notes

[1] Taylor, C.P. In New Trends in Epilepsy Management: The role of Gabapentin; Chadwick D, Ed.; Royal Society of Medicine Services Ltd: London, **1993**, 13-40.
[2] Taylor, C.P. *Neurology*. **1994**, *44*, S10-16.
[3] Satzinger, G. *Arzneimittelforschung*. **1994**, *44*, 261-6

[4] Gee, N.S.; Brown, J.P.; Dissanayake, V.U.K.; Offord, J.; Thurlow, R.; Woodruff, G.N. *J.Biol. Chem.* **1996**, *271*, 5768-76.

[5] Field, M.J.; Oles, R.J.; Lewis, A.S.; McCleary, S.; Hughes, J.; Singh, L. *Br. J. Pharmacol.* **1997**, *121(8)*, 1513-22

[6] Nuhrich, A.; Moulines, J. *Tetrahedron.* **1991**, *47*, 3075-88.

[7] Moulines, J.; Bats, J-P.; Hautefaye, P.; Nuhrich. A.; Lamidey, A-M. *Tetrahedron Lett.* **1993**, *34*, 2315-18.

[8] Carlsen, P.H.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, *46*, 3936-9.

[9] All intermediates and final compounds gave satisfactory ^{1}H NMR, infra-red and mass spectra, as well as a satisfactory elemental analysis.

[10] Bryans, J.S.; Horwell, D.C.; Ratcliffe, G.S.; Receveur, J-M.; Rubin, J.R. *Bioorg. Med. Chem.* **1999**, *7*, 715-721.

[11] Compound (3a) gave $[\alpha]_D$ +39.3° (c=1, MeOH). It also gave a single peak with a retention time of 26 minutes on chiral HPLC analysis: Chirabiotic T 250x4.6mm column, eluting with 20% MeOH, 80% water at a flow rate of 1ml/min. Detection was via a Sedex55 light scattering detector.

[12] Compound (3b) gave $[\alpha]_D$ -39.0° (c=1, MeOH). It also gave a single peak with a retention time of 18 minutes on chiral HPLC analysis: Chirabiotic T 250x4.6mm column, eluting with 20% MeOH, 80% water at a flow rate of 1ml/min. Detection was via a Sedex55 light scattering detector.

[13] Mousseron, M.; Jacquier, R.; Christol, H. *Bull. Soc. Chim. Fr.* **1957**, 1027-35.

[14] McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* **1983**, *24*, 979-82.

[15] Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron.* **1997**, *53*, 1391-1402.

[16] Singh, R.; Cooper, R.D.G. *Tetrahedron.* **1994**, *50*, 12049-64.

[17] Hwu, J.R.; Jain, M.L.; Tsay, S.C.; Hakimelahi, G.H. *Tetrahedron Lett.* **1996**, *37*, 2035-38.

[18] Bryans, J.S.; Davies, N.; Gee, N.S.; Dissanayake, V.U.K.; Ratcliffe, G.S.; Horwell, D.C.; Kneen, C. O.; Morrell, A.I.; Oles, R.J.; O'Toole, J.C.; Perkins, G. M.; Singh, L.; Suman-Chauhan, N.; O'Neill, J.A. *J. Med. Chem.* **1998**, *41*, 1838-45.

[19] Clive, D.L.J.; Postema, M.H.D. *J. Chem. Soc. Chem. Commun.***1993**, *5*, 429-30

[20] Pedregal, C.; Ezquerra, J. *Tetrahedron Lett.* **1994**, *35*, 2053-56.