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Synthesis and in vivo evaluation of 3,4-disubstituted gababutins

David C. Blakemore [a,*], Justin S. Bryans [a], Pauline Carnell [a], Mark J. Field [a], Natasha Kinsella [a], Jack K. Kinsora [b], Leonard T. Meltzer [b], Simon A. Osborne [a], Lisa R. Thompson [a], Sophie C. Williams [a]

[a] Sandwich Laboratories, Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK
[b] Groton Laboratories, Eastern Point Road, Groton, CT 00340, USA

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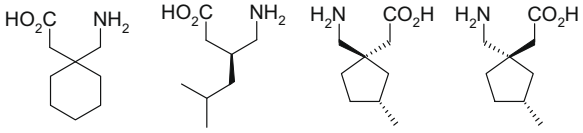
ABSTRACT

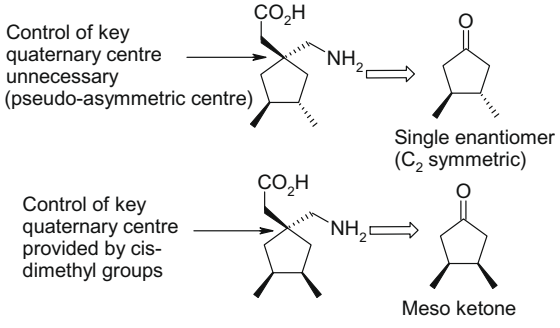
A range of 3,4-alkylated five-membered ring derivatives of gabapentin were synthesised. One compound (**21**) had an excellent level of potency against $\alpha_2\delta$ and was profiled in in vivo models of pain and anxiety.

Gabapentin (Neurontin®) (**1**)[1] was launched as an add-on therapy for epilepsy in 1994. Utility against neuropathic pain[2,3] and anxiety[4,5] have been reported preclinically and efficacy against neuropathic pain has been demonstrated clinically in humans.[6] Pregabalin[7,8] (Lyrica®) (**2**), has superior potency and pharmacokinetics[9] to gabapentin and has been approved for the management of neuropathic pain associated with diabetic peripheral neuropathy, post-herpetic neuralgia, adjunctive treatment of partial seizures, and fibromyalgia in the US.



Gabapentin and pregabalin are thought to mediate their pharmacological actions through binding to the $\alpha_2\delta$ subunit of a voltage gated calcium channel[10,11] and it has been shown that gabapentin and pregabalin bind to this $\alpha_2\delta$ subunit with IC_{50} values of 140 nM and 80 nM, respectively. We have recently disclosed our initial SAR investigations around five-membered ring gabapentin analogues, which we have termed gababutins.[12] In that Letter, we investigated a range of 3-substituted gababutin analogues and identified the 3-(*R*)-methyl gababutins (**3**) and (**4**). Both (**3**) and (**4**) bind to the gabapentin binding site with high affinity but have different in vivo profiles, with (**3**) being effective on oral dosing in models of anxiety and (**4**) being effective on oral dosing in models of neuropathic pain. We now wish to report an extension to this study which has focused on the synthesis and biological evaluation of 3,4-disubstituted gababutins.

The synthesis of 3,4-dialkyl gababutins presents a different set of challenges to the 3-alkyl gababutins.



The two alkyl groups can be *cis* or *trans* to one another. In the case of the 3,4-dimethyl gababutin, if the methyl groups are *trans*, then the stereochemistry of the quaternary centre carrying the aminomethyl group is irrelevant as this centre is *pseudo*-asymmetric; the key problem is synthesis of the C_2 symmetric chiral ketone precursor. If the methyl groups are *cis*, then the starting ketone is

* Corresponding author. Tel.: +44 1304 644573.
E-mail address: david.blakemore@pfizer.com (D.C. Blakemore).

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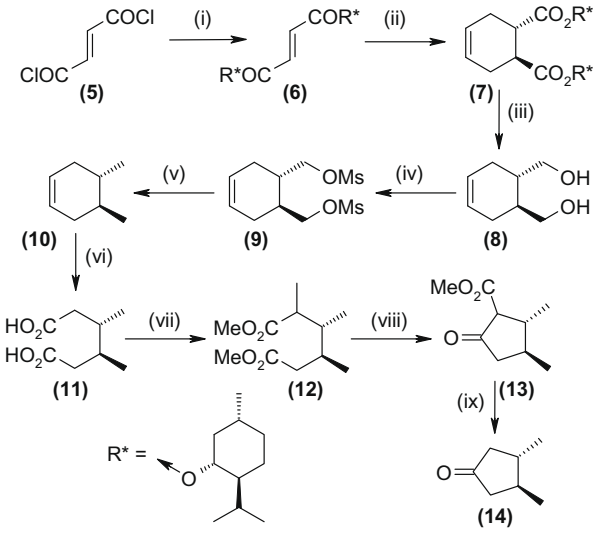
not chiral but introduction of the stereogenic quaternary centre carrying the aminomethyl group must be controlled (by making use of the steric impact of the two *cis*-dimethyl groups).

A number of different methods were utilised to synthesise the starting cyclopentanones. The synthesis of 3,4-*trans*-dimethyl cyclopentanone (**14**), is detailed in Scheme 1.

Fumaryl chloride (**5**) was converted to the diester (**6**) by reaction with (−)-menthol in good yield. The ratio of diastereoisomers of (**7**) obtained in the Diels–Alder reaction with butadiene varied according to the choice of Lewis acid with the auxiliary setting the facial selectivity.[13–15] Diethylaluminium chloride at −60 °C gave an excellent ratio of diastereoisomers (9:1), with diisobutylaluminium chloride giving an even better ratio (94:6) (as measured by ^{1}H NMR).[16] Titanium tetrachloride at −10 °C gave a poorer diastereoselectivity (83:17) but was the preferred Lewis acid for this reaction because of its ease of handling in large scale (>1 mol) reactions. Attempts to increase the diastereoselectivity by lowering the reaction temperature were unsuccessful as the dienophile–$TiCl_4$ complex would precipitate from solution. The lower diastereoselectivity did not prove to be a hindrance, as the diol (**8**) is highly crystalline. Therefore, reduction of diester (**7**) with lithium aluminium hydride afforded diol (**8**) as a 83:17 mixture of enantiomers which could be recrystallised to give the (3*S*,4*S*)-diol as a single enantiomer (the optical purity was confirmed by chiral HPLC and chiral GC at >99.5%). The diol was then mesylated and reduced with lithium aluminium hydride/NaH to give the volatile (bp 110 °C) alkene (**10**). The alkene was oxidatively cleaved with $KMnO_4$ under phase transfer conditions to give diacid (**11**) as a white solid. This was then esterified and a Dieckmann cyclisation with potassium *tert*-butoxide gave cyclopentanone ester (**13**). Hydrolysis and decarboxylation was carried out using water in DMSO to give the desired (3*S*,4*S*)-3,4-dimethyl cyclopentanone (**14**). The optical integrity was confirmed by chiral GC. The pure (3*R*,4*R*)-3,4-dimethyl cyclopentanone could be produced in a similar manner by utilising (+)-menthol as the chiral auxiliary. The 3,4-*cis*-dimethyl cyclopentanone was also synthesised in a similar manner starting from the Diels–Alder adduct, *cis*-1,2,3,6-tetrahydrophthalic anhydride.



Scheme 1. Reagents and conditions: (i) (−)-menthol, pyridine, CH_2Cl_2; (ii) butadiene, $TiCl_4$, toluene, −10 °C (100% yield, 65% de) or butadiene, Et_2AlCl, toluene, −60 °C (64% yield, 95% de); (iii) $LiAlH_4$, THF; recrystallisation from acetone; (iv) pyridine, MsCl, 0 °C, 18h (82%); (v) $LiAlH_4$, diethyl ether, 40 °C, 2h (98%); (vi) $KMnO_4$, ^{n}Bu$_4$NBr, H_2O–CH_2Cl_2, rt, 18h; then SO_2, 0 °C (82%); (vii) methanol, cH_2SO_4, rt, 18h (90%) (viii) KO^{t}Bu, THF, 75 °C, 3h (100%); (ix) DMSO, H_2O, 140 °C, 4 h (86%).

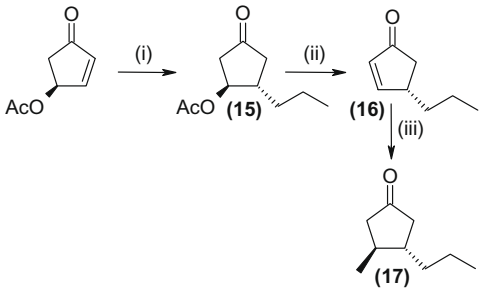
An alternative approach towards the 3,4-*trans*-cyclopentanones made use of 3-acetoxy cyclopent-2-en-1-one. Conjugate addition of an alkyl Grignard reagent to the acetoxy-cyclopentenone[17–19] (made with enantiomeric excess of >99%) followed by elimination and a further conjugate addition gave the 3,4-*trans*-dialkyl cyclopentanone without loss of stereochemical integrity (Scheme 2).

For example, conjugate addition of the *n*-propyl zincate (generated from *n*-propyl magnesium chloride and dimethylzinc) occurred exclusively on the least hindered face of the cyclopentenone (the acetoxy group forcing the *n*-propyl group onto the opposite face) to generate propyl cyclopentanone (**15**). Low temperature elimination with DBU followed by conjugate addition of the methyl zincate occurred without any epimerisation to give the 3,4-dialkyl cyclopentanone (**17**) in >98% enantiomeric excess (as determined by chiral GC).

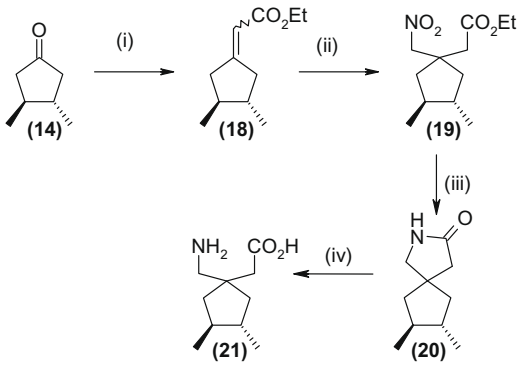
Conversion of the ketones through to the gababutin analogues is detailed in Scheme 3. Ketone (**14**) was converted to α,β-unsaturated ester (**18**) via a Horner–Wadsworth–Emmons reaction. Subsequent nitromethane anion addition gave the nitroester (**19**). Hydrogenation to the lactam (**20**) and then acid hydrolysis gave the final amino acid (**21**).

For 3,4-*cis*-dimethyl cyclopentanone, two possible diastereoisomers of the final gababutin are possible and control of the stereochemistry was obtained by making use of the steric impact of the two methyl groups.

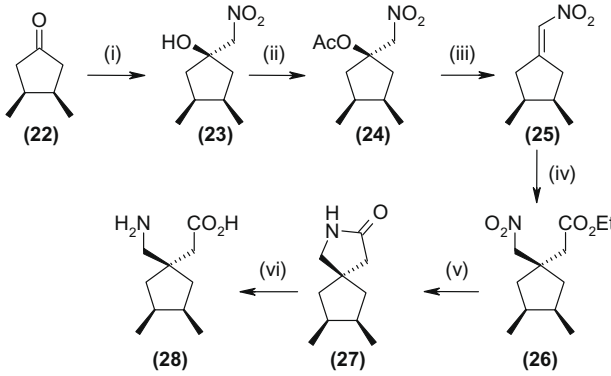
For synthesis of (**28**), a nitroalkene route was employed (Scheme 4). Here, ketone (**22**) was reacted with the dianion of nitromethane utilising 2 equiv of butyl lithium to generate alcohol (**23**). Acetylation and base-catalysed elimination gave the nitroalkene (**25**). Low temperature conjugate addition of the ethyl acetate anion gave nitro ester (**26**) as a 9:1 mixture of diastereoisomers, addition occurring from the face opposite to the two methyl groups



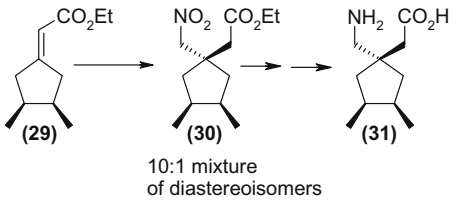
Scheme 2. Reagents and conditions: (i) *n*-PrMgCl, Me_2Zn, THF, −78 °C; (ii) DBU, Et_2O, −40 °C (68% over two steps); (iii) MeMgCl, Me_2Zn, THF, −78 °C (63%).



Scheme 3. Reagents and conditions: (i) triethylphosphonoacetate, NaH, THF, 0 °C to rt (95%); (ii) $MeNO_2$, TBAF, THF, reflux (65%); (iii) H_2, Ni, MeOH; (iv) 6 N HCl, 1,4-dioxane, reflux (69% from nitroester).



Scheme 4. Reagents and conditions: (i) BuLi (2 equiv), $MeNO_2$, THF, HMPA, −78 °C (40%); (ii) Ac_2O, H_2SO_4, reflux (98%); (iii) KOH, MeOH, 0 °C (53%); (iv) AcOEt, LHMDS, THF, −78 °C (45%); (v) H_2, Raney Ni, MeOH; (vi) 6 N HCl, 1,4-dioxane, reflux (45% from nitroester).

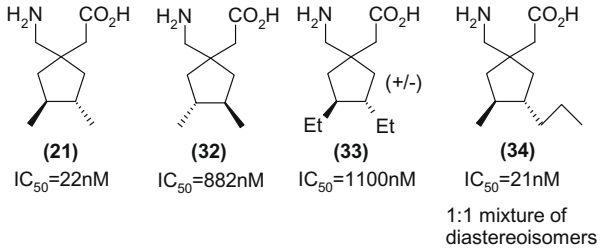


Scheme 5.

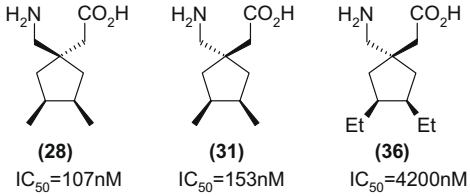
(^{1}H NMR, 2D NMR and HPLC confirmed ratio and relative stereochemistry). Reduction and spontaneous cyclisation gave the lactam (**27**) which was hydrolysed without purification in 6 N HCl to give the amino acid (**28**). A single recrystallisation from ethyl acetate/methanol/heptane gave (**28**) as a single diastereoisomer as confirmed by ^{1}H NMR and HPLC analysis.

Utilising a nitromethane conjugate addition route from (**29**) gave the alternative diastereoisomer (**31**) (Scheme 5).

As with the 3-alkyl gababutins, chirality proved to have a significant impact on binding affinity at $\alpha_2\delta$ (a radioligand binding assay incorporating [^{3}H]gabapentin at the $\alpha_2\delta$ subunit of a calcium channel was utilised in this work, as previously described[10]), with one enantiomer of 3,4-*trans*-dimethyl gababutin, (**21**), having excellent levels of potency while the other enantiomer, (**32**), bound weakly. The racemic 3,4-*trans*-diethyl gababutin, (**33**) also had weak binding affinity at $\alpha_2\delta$ proving consistent with our 3-alkyl gababutin hypothesis that space in the binding pocket is limited; however, replacement of one methyl group of (**21**) by a propyl group to give (**34**) (as a mixture of diastereoisomers) was not detrimental to binding affinity.



The 3,4-*cis*-dimethyl gababutins (**28**) and (**31**) both had reasonable levels of potency against $\alpha_2\delta$ but were considerably less potent than the *trans*-dimethyl analogue (**21**). As with the *trans* analogues, the diethyl analogue (**36**) bound weakly to $\alpha_2\delta$.



Compound (**21**) was evaluated in in vivo models of pain and anxiety. The compound proved to have a similar profile to pregabalin in anxiety models as illustrated for the water-lick (Vogel) conflict model of anxiety (Fig. 1). In this model, a group of rats were dosed orally with compound and were then placed in a cage containing a drinking tube from which they received a shock each time they drank. The mean number of shock episodes received per rat over 10 min was measured at different doses. The more anxiety that the animals feel, the less they drink and the less shocks they receive. For an effective compound, as the dose of compound increases then the number of shocks received by the animals should also increase.

The minimum effective dose (MED) for activity for compound (**21**) in this model was identical to that of pregabalin at 10 mg/kg. It was noted, however, that at higher doses of compound (**21**), sedation of the animals was occurring.

Compound (**21**) was also evaluated in the carageenan induced thermal hyperalgesia model of pain (Fig. 2). In this model, the

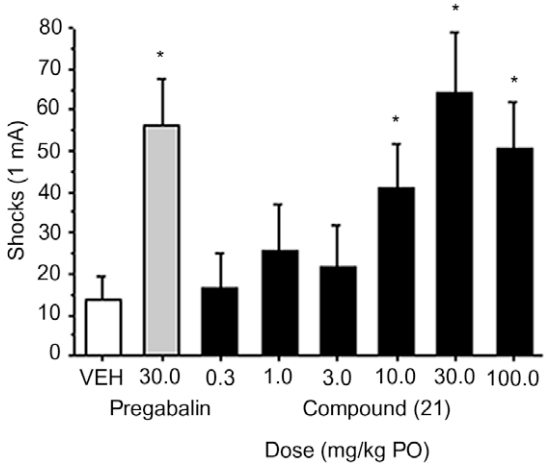


Figure 1. * = P <0.05, significantly different compared to vehicle.

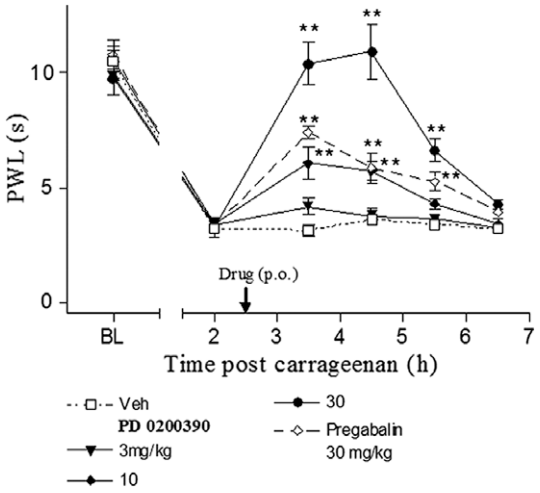


Figure 2. * = P <0.05, ** = P <0.01, significantly different compared to vehicle.

pro-inflammatory agent carrageenan was administered via intraplantar injection into the paw of a rat. Within 2 h of injection, the paw became inflamed and hyperalgesia had been induced. An infra-red light source was shone on the paw and the time it took the animal to withdraw its paw from the heat-source was measured. Before treatment, baseline measurements were taken giving a reading of 10 s to paw withdrawal. After 2 h, once the hyperalgesia had fully formed the time to paw withdrawal had reduced to 2.5 s. At this point the compound to be assessed was dosed orally and any reversal of the hyperalgesia was assessed by measuring the time to paw withdrawal.

Compound (**21**) showed excellent levels of efficacy in this model with a 30 mg/kg dose fully reversing the hyperalgesia and giving a similar effect to that of pregabalin. Again, sedation of the animals was noted at higher dosing.

The pharmacokinetic profile of compound (**21**) in the rat is shown below:

Compound	*F* (%)	Elimination half-life (h)	Clearance (mL/min/Kg)
(**21**)	87	2.4	4

Compound (**21**) is a highly polar ($\log D_{7.4} = -1.0$), low molecular weight zwitterionic molecule; it has a pharmacokinetic profile that is similar to pregabalin with high bioavailability (driven by active transport from the gut combined with negligible first pass metabolism) and a short half-life in rat. The compound is renally cleared at just under glomerular filtration rate with no noticeable reabsorption in the proximal tubule. The short half-life coupled with a t_{max} of 1.2 h makes the compound ideal as a fast-acting agent that is removed from the system rapidly. Compound (**21**) has been progressed for further studies.

Acknowledgements

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References and notes

1. Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149.
2. Pan, H. L.; Eisenach, J. C.; Chen, S. R. J. *Pharmacol. Exp. Ther.* **1999**, *288*, 1026.
3. Hunter, J. C.; Gogas, K. R.; Hedley, L. R.; Jacobsen, L. O.; Kassotakis, L.; Thompson, J.; Fontana, D. J. *Eur. J. Pharmacol.* **1997**, *324*, 153.
4. Singh, L.; Field, M. J.; Ferris, P.; Hunter, J. C.; Oles, R. J.; Williams, R. G.; Woodruff, G. N. *Psychopharmacology* **1997**, *127*, 1.
5. de-Paris, F.; Busnello, J. V.; Vianna, M. R. M.; Salgueiro, J. B.; Quevedo, J.; Izquierdo, I.; Kapczinski, F. *Behav. Pharmacol.* **2000**, *11*, 169.
6. Rice, A. S. C.; Maton, S. *Pain* **2001**, *94*, 215.
7. Dworkin, R. H.; Kirkpatrick, P. *Nat. Rev. Drug Disc.* **2005**, *4*, 455.
8. Zareba, G. *Drugs Today* **2005**, *41*, 509.
9. Guay, D. R. P. *Am. J. Geriatr. Pharmacother.* **2005**, *3*, 274.
10. Gee, N. S.; Brown, J. P.; Dissanayake, V. U. K.; Offord, J.; Thurlow, R.; Woodruff, G. N. *J. Biol. Chem.* **1996**, *271*, 5768.
11. Stahl, S. M. *J. Clin. Psychiat.* **2004**, *65*, 1033. and references cited therein.
12. Blakemore, D. C.; Bryans, J. S.; Carnell, P.; Chessum, N. E. A.; Field, M. J.; Kinsella, N.; Kinsora, J. K.; Osborne, S. A.; Williams, S. C. *Bioorg. Med. Chem. Lett.* **2009**. doi:10.1016/j.bmcl.2009.10.089.
13. Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1996**, *27*, 4507.
14. Corey, E. J.; Su, W.-G. *Tetrahedron Lett.* **1988**, *29*, 3423.
15. Solladie, G.; Lohse, O. *J. Org. Chem.* **1993**, *58*, 4555.
16. Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507.
17. Deardorff, D. R.; Myles, D. C. *Org. Synth.* **1989**, *67*, 114.
18. Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth.* **1995**, *73*, 25.
19. Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287.