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SYNTHESIS AND RESOLUTION OF β-(AMINOMETHYL)-4-CHLOROBENZENEETHANESULFINIC ACID A POTENT GABA$_B$ RECEPTOR LIGAND.

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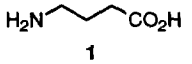
Abstract: The synthesis and resolution of β-(Aminomethyl)-4-chlorobenzeneethanesulfinic acid together with the GABA$_B$ receptor affinity for the racemate and enantiomers is described. In addition the synthesis and GABA$_B$ receptor affinity of the enantiomers of the known GABA$_B$ antagonist (Saclofen) is reported for the first time

GABA (γ-aminobutyric acid) (**1**) is a major inhibitory neurotransmitter in the mammalian central nervous system. Electrophysiological and receptor binding studies have permitted GABA receptors to be divided into two major types;[1] the GABA$_A$ receptor, the classical GABA receptor, which is blocked by the antagonist bicuculline (**2**), and the GABA$_B$ receptor which is insensitive to **2**, but at which *R*-baclofen (**3**) is an agonist. The latter receptor, first described by Bowery[2] in 1980, has received considerable attention to determine its physiological role and to evaluate the therapeutic potential of selective GABA$_B$ receptor agonists and antagonists.[3]



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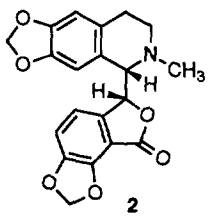

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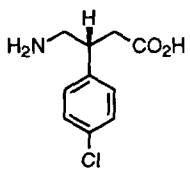

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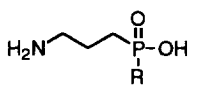
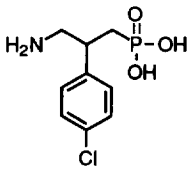
Consequently, in the last few years, series of potent GABA$_B$ agonists and antagonists have been described all of which retain the GABA backbone, but which contain a range of bioisosteric replacements for the carboxyl function of GABA. Replacing the carboxyl function of GABA with a phosphinic acid has led to both potent and selective GABA$_B$ agonists[4] (**4**) and antagonists[5] (**5**) and replacement of the carboxylic acid of baclofen with a phosphonic acid or a sulfonic acid led to the antagonists phaclofen[6] (**6**) and saclofen[7] (**7**), respectively. Thus, compounds which contain a planar carboxylic acid, (**1**) and (**3**), or which contain a singly charged isosteric replacement where the charge is distributed over two heteroatoms, (**4**), are high affinity GABA$_B$ agonists. In contrast when the charge is distributed over more than two heteroatoms, (**6**) and (**7**), or when the acid isostere contains a bulky substituent, (**5**), weakly active antagonists are obtained.[4c] These

observations led us to consider the behavior of sulfinic acids which to our knowledge had not previously been used as bioisosteric replacements for carboxylic acids.



4 R = H, CH_3
5 R = $CH(OEt)_2$, ^nHex



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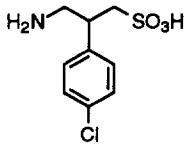

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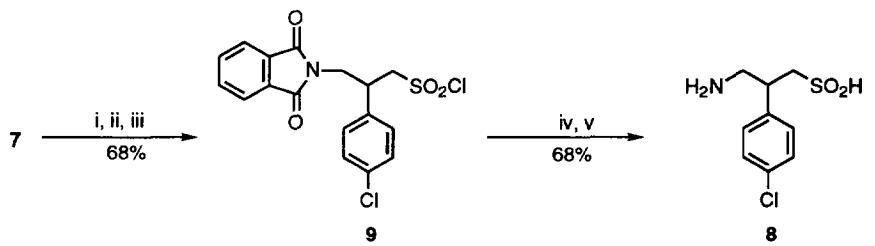
However the apparent similarities between carboxylic and sulfinic acids are deceptive and, unlike the carboxyl group which is planar with a $pK_a \approx 4$, the sulfinyl group is closer to tetrahedral with a $pK_a \approx 1\text{-}2$.[8] We chose as an initial target the analog of baclofen in which the carboxylic acid is replaced with a sulfinic acid to afford "siclofen"† (**8**), with the expectation that if a sulfinic acid behaves like a carboxylic acid then a $GABA_B$ agonist would be obtained.

Racemic and chiral siclofens were prepared from the known $GABA_B$ antagonist saclofen (**7**) which in turn was prepared according to a literature procedure.[9] To obtain racemic siclofen, saclofen was converted to its phthalimido derivative, and without purification to sulfonyl chloride **9**. Noting a literature precedent for the conversion of sulfonyl hydrazides to sulfinic acids,[10] **9** was treated with excess hydrazine to afford **8** directly, Scheme 1.

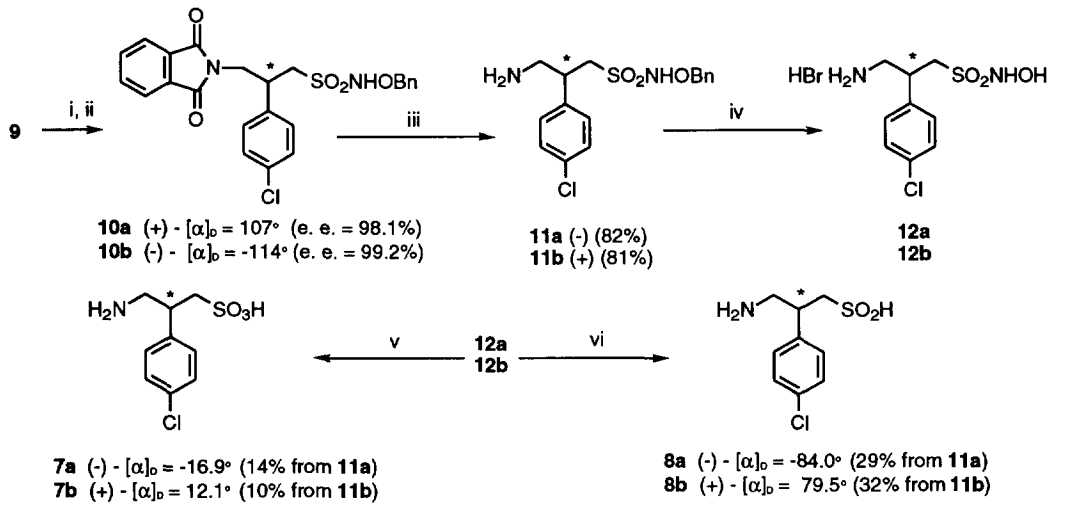


9 **8**

Scheme 1 *Reagents and conditions:* i, Phthalic anhydride, NEt_3, dioxane, room temp, 1.5 h; ii, 1N KOH; iii, PCl_5, benzene, reflux, 45min; iv, H_2NNH_2, 60-65°, 3 h; v, Dowex 50 X 200.

Biological assays demonstrated that **8** was both a selective $GABA_B$ ligand and an agonist.[11]. We next decided to determine if, like baclofen, only one enantiomer of siclofen was active, and as a secondary objective wished to ascertain whether the $GABA_B$ receptor exhibited the same enantioselectivity for agonists and antagonists. To answer these questions we required a common intermediate that could be resolved to provide enantiomerically pure **7** and **8**. Attempts to resolve **7** and **8** by classical methods, or via chiral HPLC, were unsuccessful and therefore several compounds that could be transformed into **7** and **8** were prepared and their HPLC behavior examined. Ultimately we selected the protected N-hydroxysulfonamide **10**, Scheme 2, which was readily resolved using a Daicel Chiralcel OD column. O-Benzyl-N-hydroxysulfonamide **10** was prepared by condensing O-benzylhydroxylamine with sulfonyl

chloride **9**. The resolved enantiomers of **10** were treated with hydrazine to afford amines **11** which upon treatment with boron tribromide gave the N-hydroxysulfonamide enantiomers **12**. We had previously observed[12] that N-hydroxysulfonamides can be selectively converted to either sulfinic acids or sulfonic acids depending on solution pH. Therefore treatment of **12** with aqueous base afforded the enantiomers of siclofen (**8a** and **8b**) and treatment of **12** with aqueous acid gave the enantiomers of saclofen (**7a** and **7b**).



Scheme 2 *Reagents and conditions:* i, $BnONH_2.HCl$, $^iPrNEt_2$, CH_2Cl_2, -5°, 1 h, (72%); ii, Daicel Chiralcel OD; iii, H_2NNH_2, reflux, 1 h; iv, BBr_3, CH_2Cl_2, 0°, 45 min; v, 1N HCl, Dowex 50 X 200, Amberlite IRA-410; vi, 3N NH_4OH, 24 h, Dowex 50 X 200.

Bioassay of the resolved enantiomers demonstrated that biological activity resided in a single enantiomer for both the antagonist saclofen and the agonist siclofen and that the active enantiomers were derived from a single enantiomer of **10**. The active enantiomers **7a** and **8a** exhibited similar CD[13] curves to the active enantiomer of baclofen, *R*-(-)-baclofen, and strongly suggests that the absolute configuration of **7a** and **8a** is the same as that for *R*-(-)-baclofen.[14]

Biological Results and Discussion.

In binding assays racemic siclofen (**8**) exhibited an IC_{50} = 1.2 μM ($GABA_B$)[15] and an IC_{50} >100 μM ($GABA_A$)[16] and behaved as an agonist in an *in vitro* functional assay[17] showing an IC_{30} = 22.0 μM (n = 8, 95% confid. limit 11.5 to 71 μM) for inhibition of electrical field stimulated neuronal cholinergic contractions of guinea pig trachea. The enantiomers **8a** and **8b** had IC_{50} = 0.20 and 90 μM ($GABA_B$) respectively[18] with **8a** exhibiting an IC_{30} = 13.9 μM (n = 8, 95% confid. limit 7.4 to 31.4 μM)) in the functional assay.[19] The enantiomers of saclofen **7a** and **7b** exhibited IC_{50}'s of 33 and > 100 μM ($GABA_B$) respectively. In conclusion we have demonstrated that a sulfinic acid can be a good bioisosteric replacement for a carboxylic acid and that the $GABA_B$ receptor shows

the same enantioselectivity for agonists and antagonists. The SAR of a series of sulfinic acid based GABA analogs will be reported in due course.

Acknowledgements.

The authors are grateful to Mr Charles Rizzo and Ms Susan She for biological determinations and to Mr Joe Lee and Dr Pauline Ting for the preparation of **7**. In addition we thank Drs James J. Kaminski and A. K. Ganguly for fruitful discussions throughout the course of this work.

References and Footnotes.

† Following the naming of phosphonic acid **6** and sulfonic acid **7** as phaclofen and saclofen respectively we chose to name the sulfinic acid **8** as siclofen.

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11. Siclofen was stable under the conditions of bioassay and no decomposition, or oxidation to saclofen was detected by HPLC. During tissue bath experiments substrate concentration was confirmed by HPLC of aliquots at the appropriate time point.
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13. Molar ellipticities were as follows: **3**, $[\theta]_{220.2}$ -8.14 x 10^3; **7a**, $[\theta]_{220.2}$ -4.81 x 10^3; **7b**, $[\theta]_{219.4}$ 4.63 x 10^3; **8a**, $[\theta]_{228.2}$ -1.62 x 10^4; and **8b**, $[\theta]_{228.2}$ 1.76 x 10^4.
14. The resolution of phaclofen (**6**) has recently been described (Frydenvang, K.; Hansen, J. J.; Krogsgaard-Larsen, P.; Mitrovic, A.; Tran, H.; Drew, C. A.; Johnston, G. A. R. *Chirality*, **1994**, 583) and biological activity observed for the R-(-) antipode. We are grateful to a referee for bringing this to our attention.
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18. The weak activity of **8b** is a reflection of the resolution rather than an indication of intrinsic activity.
19. In this assay baclofen exhibited an IC_{30} = 5 μM with maximal inhibition 60 - 70%.

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