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SYNTHESIS OF A SERIES OF SULFINIC ACID ANALOGS OF GABA AND EVALUATION OF THEIR GABA$_B$ RECEPTOR AFFINITIES

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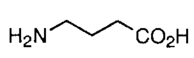
Abstract: A series of γ-aminobutyric acid (GABA) **1** analogs was prepared in which the carboxylic acid group of GABA was replaced with a sulfinic acid group and their affinity for the GABA$_B$ receptor investigated.

γ-Aminobutyric acid (GABA) **1** is a major inhibitory neurotransmitter in the mammalian central nervous system (CNS) mediating effects via at least two distinct receptors,[1] GABA$_A$ and GABA$_B$. The GABA$_B$ receptor was first described by Bowery in 1980[2] and was subsequently shown to be implicated in many different pharmacological situations in both the central and peripheral nervous system. GABA$_B$ agonists exert a role in gastric acid secretion and neuropeptide release from sensory C-fibers while GABA$_B$ antagonists exert a role in petit-mal seizures and cognitive disorders. In an earlier publication,[3] we described the synthesis of a series of 3-amino-N-hydroxypropanesulfonamides **2** and found that they fragmented under physiological conditions to afford the corresponding sulfinic acid **3**, which is a potent GABA$_B$ agonist. Noting that **3** also possessed significant GABA$_A$ affinity, the synthesis and biological evaluation of siclofen (**4**), the sulfinic acid analog of the first selective GABA$_B$ agonist baclofen (**5**), was undertaken.[4] Thus, **4** was prepared and found to be a selective GABA$_B$ agonist also. Given these results we wished to explore the effects of other substituents and adjust the length of the backbone of **3** to determine whether improvements in biological activity and receptor selectivity could be made.



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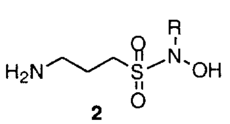

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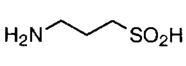

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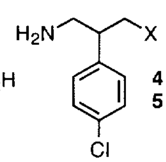

4 X = SO_2H
5 X = CO_2H

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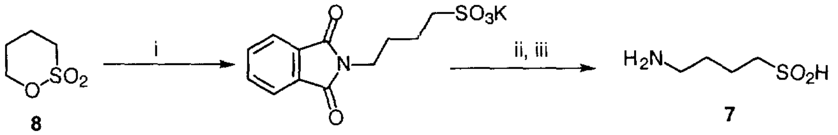
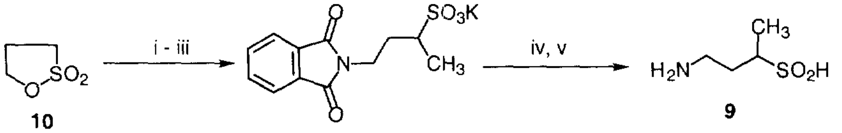
Chemistry.[5]

The lower homolog **6** (Table 1) was obtained commercially,[6] and the higher homolog **7** was synthesized from 1,4-butane sultone (**8**). The sultone **8** was treated with potassium phthalimide to afford the corresponding acyclic sulfonic acid. Conversion of the sulfonic acid to the sulfonyl chloride followed by treatment with hydrazine effected removal of the phthalimido group and reduction of the acid chloride to give **7**.[7]



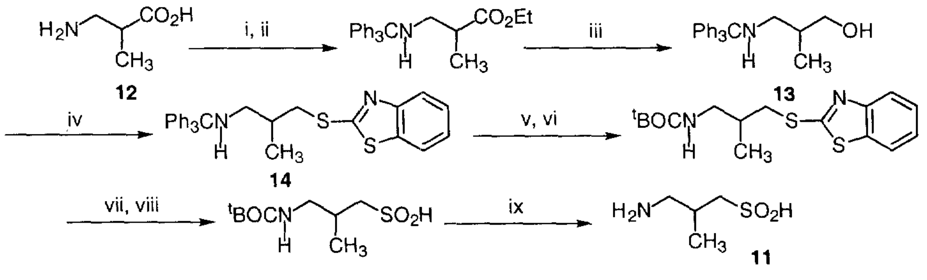
Reagents: (i) Potassium phthalimide, EtOH, reflux, 18 h, (66%); (ii) PCl_5, PhH, reflux, 3 h, (82%); (iii) H_2NNH_2, EtOH, reflux, 1 h, (66%).

The α-methyl analog **9** was synthesized in an analogous manner from 1,3-propane sultone (**10**), which was first alkylated with MeI,[8] and then subjected to the sequence above.



Reagents: (i) ^{n}BuLi, THF, -78 ° C; (ii) MeI, (72%); (iii) Potassium phthalimide, EtOH, reflux, 18 h, (78%); (iv) PCl_5, PhH, reflux, 3 h, (82%); (v) H_2NNH_2, EtOH, reflux, 1 h, (56%).

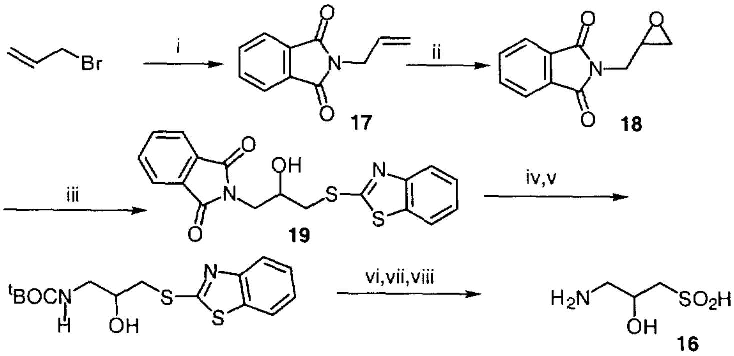
Preparation of the β-methyl analog **11** was achieved as shown in Scheme 1. 3-Aminoisobutyric acid (**12**) was transformed to alcohol **13**, which was converted to the benzothiazole derivative **14**, thus providing a latent sulfinic acid.[9] Manipulation of the nitrogen protecting group was followed by an oxidation/reduction sequence that unmasked the sulfinic acid to afford **11**.



Reagents: (i) HCl, EtOH, (100%); (ii) Ph_3CCl, Et_3N, CH_2Cl_2, (100%); (iii) $LiAlH_4$, THF, (61%); (iv) PBu_3, 2,2'-dithiobis(benzothiazole), THF, (98%); (v) CF_3CO_2H, (100%); (vi) $^{t}BOC_2O$, Et_3N, DMF (59%); (vii) mCPBA, CH_2Cl_2, (90%); (viii) $NaBH_4$, EtOH; (ix) CF_3CO_2H, (43%, two steps).

Scheme 1.

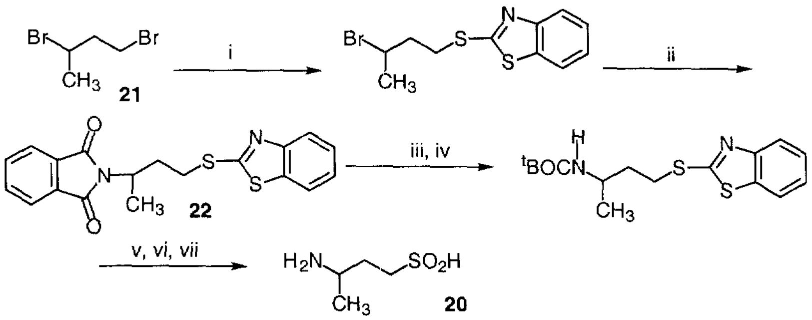
Similar tactics were used to obtain the β-hydroxy analog **16**, Scheme 2. Allylation of potassium phthalimide gave **17**, which was epoxidized to **18**. The epoxide was readily opened with mercaptobenzothiazole anion giving **19**, which was elaborated to **16**.



Reagents: (i) Potassium phthalimide, 18-crown-6, $PhCH_3$, (82%); (ii) mCPBA, CH_2Cl_2, (99%); (iii) NaOMe, 2-mercaptobenzothiazole, MeOH, (70%); (iv) H_2NNH_2 EtOH, 50 °C; (v) $^tBOC_2O$, CH_2Cl_2, (86%, two steps); (vi) mCPBA, CH_2Cl_2, (99%); (vii) $NaBH_4$, EtOH; (viii) CF_3CO_2H, (63%, two steps).

Scheme 2.

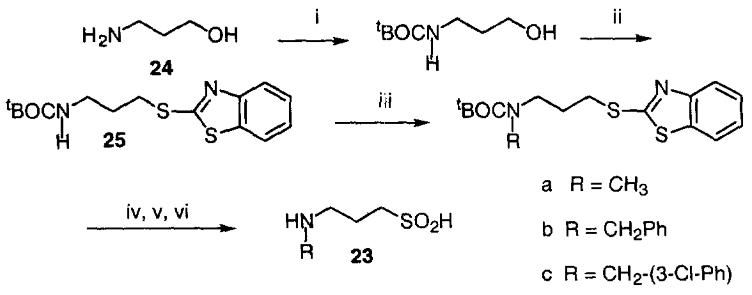
The γ-methyl analog **20** was prepared from 1,3-dibromobutane (**21**), which was condensed first with 2-mercaptobenzothiazole, then potassium phthalimide to yield **22**. Further transformations of **22** gave target **20**, as shown in Scheme 3.



Reagents: (i) NaOEt, EtOH, 2-mercaptobenzothiazole, (100%); (ii) Potassium phthalimide, DMF, Cs_2CO_3, $^nBu_4NHSO_4$, (30%); (iii) H_2NNH_2, EtOH, 50 °C, (87%); (iv) $^tBOC_2O$, CH_2Cl_2 (70%); (v) mCPBA, CH_2Cl_2, (68%); (vi) $NaBH_4$, EtOH; (vii) CF_3CO_2H, CH_2Cl_2 (55%, two steps).

Scheme 3.

N-Substituted analogs **23** were prepared as diagrammed in Scheme 4, from 3-aminopropanol (**24**) that was initially converted to intermediate **25**. N-Alkylation of **25** was followed by generation of a sulfinic acid moiety and removal of the BOC group to yield N-substituted analogs **23**.



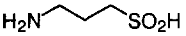
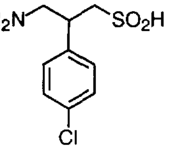
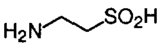
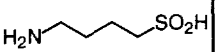
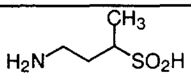
Reagents: (i) $^tBOC_2O$, CH_2Cl_2, (100%); (ii) PBu_3, 2,2'-dithiobis(benzothiazole), THF, (83%); (iii) NaH, THF, RX, (R = CH_3, 53%; R = benzyl, 34%; R = 3-Cl-benzyl, 85%); (iv) mCPBA, CH_2Cl_2, (R = CH_3, 97%; R = benzyl, 66%; R = 3-Cl-benzyl, 65%); (v) $NaBH_4$, EtOH; (vi) CF_3CO_2H, (R = CH_3, 100%; R = benzyl, 63%; R = 3-Cl-benzyl,64% , two steps).

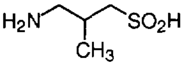
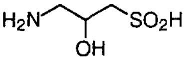
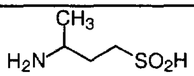
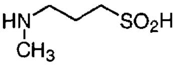
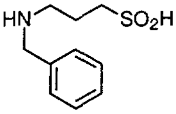
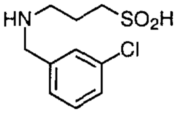
Scheme 4.

Biological Results and Discussion.

The in vitro binding data for the sulfinic acid analogs is summarized below in Table 1 These results confirm that the carboxylic acid functionality of GABA may be replaced with a sulfinic acid moiety to afford potent GABA$_B$ ligands. However, unlike phosphinic acids[10, 11] which show only very weak GABA$_A$ binding, the sulfinic acids retain considerable affinity for the GABA$_A$ receptor, compounds **3**, **9**, **11** and **16** exhibited GABA$_A$ IC$_{50}$'s of 0.47, 2.2, 50 and 13.1 μM respectively.[12] Therefore, the sulfinic acid moiety alone is not responsible for the selectivity of siclofen. Shortening the backbone to two carbons as in analog **6** completely abolishes GABA$_B$ affinity. In contrast, lengthening the backbone to four carbons, as in analog **7** retains good GABA$_B$ binding affinity. The addition of a simple methyl group along the GABA backbone in both the phosphinic acid[10] and sulfinic acid series leads to reduced GABA$_B$ affinity-indicating poor tolerance for any steric bulk. Methylation of the amino moiety is acceptable as evident by the reasonable binding activity of **23a**. However, larger substituents such as the benzyl group in **23b** or the 3-chlorobenzyl group in **23c** decrease biological activity 60 fold. The introduction of a β-hydroxyl substituent, **16**, does confer modest receptor selectivity (**16**, IC$_{50}$ = 13.1 μM GABA$_A$). As noted previously[4] a β-(4-chlorophenyl) substituent (**4**, IC$_{50}$ = >100 μM GABA$_A$) also confers receptor selectivity for the GABA$_B$ receptor over the GABA$_A$ receptor. In this respect sulfinic acids parallel their carboxylic acid anaogs, where β-hydroxyl and β-(4-chlorophenyl)substituents also impart receptor selectivity.

Table 1: $GABA_B$ Binding Affinity[13] for Sulfinic Acid Analogs of GABA.

Structure	$GABA_B$ IC_{50} (μM)
3 	0.04
4 	1.2
6 	> 100
7 	0.72
9 	3.8

Structure	$GABA_B$ IC_{50} (μM)
11 	> 100
16 	0.82
20 	11.0
23a 	0.52
23b 	32
23c 	38

In a functional assay[14] compounds **3**, **4**, **16** and **23a** exhibited pD_2 values of 5.8, 4.7, 4.7 and 5.3 respectively, indicating that the compounds are, albeit weak, $GABA_B$ agonists. In summary, these observations indicate that a sulfinic acid more closely resembles a carboxylic acid than a phosphinic acid in this system and may find further applications in other areas of biology as a bioisosteric replacement for a carboxyl group.

References and Footnotes.

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