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# 3-Benzo[*b*]furyl- and 3-benzo[*b*]thienylaminobutyric acids as $GABA_B$ ligands. Synthesis and structure–activity relationship studies

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**Summary** — Baclofen (β-*p*-chlorophenyl GABA) is one of the selective agonists for the bicuculline-insensitive $GABA_B$ receptors. In the search for new compounds that bind to $GABA_B$ receptors it is very important to clarify the structural requirements. We report the syntheses of and binding studies on various 3-heteroaromatic (benzo[*b*]furan and benzo[*b*]thiophen)aminobutyric acids. The 4-amino-3-(7-methyl-benzo[*b*]furan-2-yl)butanoic acid **8g** is a potent and specific ligand for $GABA_B$ receptors, with an $IC_{50}$ value of 5.4 μM in the displacement of [$^3$H]GABA.

**3-heteroaromatic baclofen analogue / benzo[*b*]furan / benzo[*b*]thiophen / $GABA_B$ ligand / structure–activity relationship**

## Introduction

The neutral amino acid 4-aminobutyric acid (GABA) is an inhibitory neurotransmitter concerned with the control of neuronal activity in the mammalian central nervous system and with the regulation of many physiological mechanisms [1, 2].

Within the central and peripheral nervous system, GABA has been shown to act through at least two distinctly different receptor sites [3]. These are termed $GABA_A$ and $GABA_B$ receptors, and have different binding properties [4, 5]. Accumulating evidence suggests that $GABA_B$ receptors are predominantly located presynaptically [6]. However, in a previous report [1], postsynaptically located $GABA_B$ receptors have been described and the postsynaptic location of $GABA_B$ receptors has been confirmed in recent reports [7, 8]. $GABA_B$ receptors have also been detected and characterized in a variety of tissue preparations of peripheral origin [1, 9]. In recent years, some authors have considered the hypothesis of a third receptor class in connection with the design of analogues of GABA. This hypothesis has appeared with the *cis*-4-aminopent-2-enoic acid. This compound is a GABA-like neuronal depressant, that is not sensitive to bicuculline, and that binds to a class of GABA receptor sites which do not recognize isoguvacine or baclofen. This receptor has been termed a $GABA_C$ receptor or a 'non $GABA_A$, non $GABA_B$' receptor for GABA [10, 11].

Until recently, β-*p*-chlorophenyl-GABA (baclofen) was the only selective agonist for the $GABA_B$ receptor. Analogues of baclofen, saturated and unsaturated, have been synthesized and tested for $GABA_B$ receptor affinity. These compounds showed any selective effect on $GABA_B$ receptor sites in vitro [12].

In the last decade, the phosphonic analogue of baclofen (phaclofen) has been shown to be an antagonist at $GABA_B$ receptors [13]. The same workers went on to produce the selective antagonist saclofen and its 2-hydroxy derivative [14]. We recently described the synthesis of furyl, thienyl and benzo[*b*]furan analogues of baclofen, new discriminating ligands for $GABA_B$ sites [15, 16].

In the course of our attempts to elucidate the structural requirements for access to $GABA_B$ receptors, we

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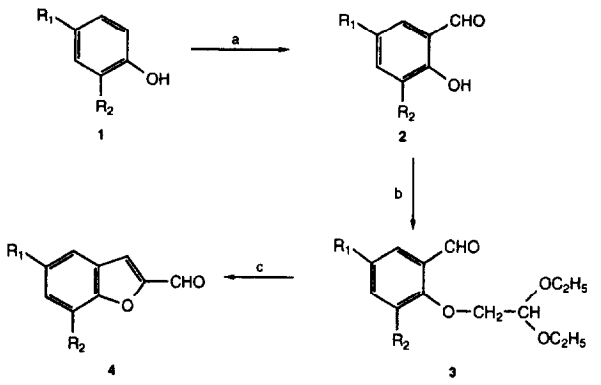
report here the synthesis and binding studies of new 3-benzo[*b*]furan-2-yl and 3-benzo[*b*]thien-2-yl-GABA. These racemic compounds, especially **8g** and **8p**, are potent and specific ligands for the $GABA_B$ receptors, with better $IC_{50}$ values than our previous results [15, 16].

## Chemistry

Scheme 1 illustrates the synthetic route for preparation of the starting aldehydes **4**, which are not commercially available. These starting compounds were synthesized in three steps via Reimer Tieman [17] formylation of the appropriate substituted phenol **1** with $CHCl_3$ and NaOH, or in two steps from commercially-available salicylaldehydes. Aldehydes **2g–i** and **2r** have been previously synthesized with very low yields [18, 19]. The resulting salicylaldehydes **2** were reacted with bromoacetaldehyde diethyl acetal in DMF (dimethylformamide) to give compounds **3**. These compounds **3** were cyclized to benzo[*b*]furan-2-yl carboxaldehydes **4** by heating in concentrated acetic acid. Benzo[*b*]furan aldehydes **4a,j,n,p,q** and benzo[*b*]thiophen aldehydes **4v–x** were prepared according to the methods described in the literature [20–22].

The amino acids **8a–x** were prepared as described in scheme 2 except for compound **8q**. Treatment of substituted aldehydes **4a–x** with (carbethoxymethylene)triphenylphosphorane in benzene at reflux temperature gave adducts **5a–x**, which were treated by nitromethane at 85 °C to afford the nitroesters **6a–x**. The catalytic reduction of compounds **6a–x** at atmospheric pressure led to a mixture of aminoesters and lactams. On heating at 100 °C these mixtures furnished exclusively the lactams **7a–x**. The hydrolysis of the lactams by heating with excess sodium hydroxide in aqueous ethanol gave the acids **8a–x**.




**Scheme 1.** Reagents: (a) $CHCl_3$/NaOH; (b) $BrCH_2CH(OC_2H_5)_2/K_2CO_3$/DMF; (c) $CH_3COOH/\Delta$.

Scheme 3 shows the conditions used for the preparation of compound **8q**. Indeed, the lactam **7q** is rather sensitive (in the elimination of the bromine atom) to the conditions used to hydrolyze the other lactams. An alternative route to avoid this side reaction is the use of milder conditions to cleave the lactam ring [23]. As a first step, the lactam **7q** was treated with Boc-anhydride to furnish the N-Boc derivative. In a second step, this protected lactam was cleaved under milder conditions and the Boc protecting group removed by treatment with TFA (trifluoroacetic acid) to afford the amino acid **8q**.

Tables I–VII list the physical data of the synthesized compounds.

## Pharmacology

All compounds **8a–x** were tested for their ability to displace [$^3$H]muscimol ($GABA_A$ sites) and [$^3$H]GABA ($GABA_B$ sites) from rat brain membranes according to previously described procedures [24]. The pharmacological data obtained are summarized in table VIII.

### *$GABA_A$ sites*

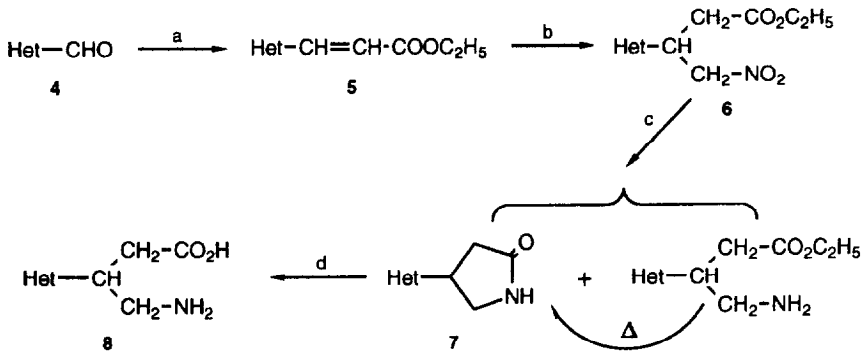
The compounds tested (at concentrations up to 100 μM) failed to displace more than 20% of the tritium-labelled ligand specifically bound to $GABA_A$ receptors. The addition of increasing concentrations of unlabelled GABA and muscimol produced a dose-dependent reduction in binding. The $IC_{50}$ values for GABA and muscimol were 0.03 and 0.01 μM respectively.

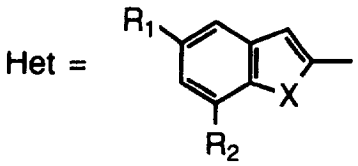
### *$GABA_B$ sites*

Two compounds, **8g** and **8p**, displaced binding of [$^3$H]-GABA to $GABA_B$ sites on rat whole-brain synaptic membranes. The degree of displacement was dependent on the concentration of the compounds; **8g** and **8p** displace [$^3$H]GABA with $IC_{50}$ values of 5.4 and 17 μM respectively.

## Results and discussion

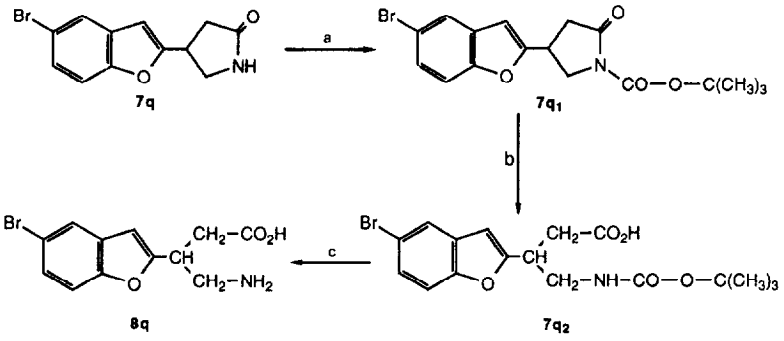
The therapeutic effects of baclofen (Lioresal®) on certain types of spasticity, and in the treatment of multiple sclerosis and trigeminus neuralgia, have prompted synthesis of a variety of structurally-related compounds. However, these compounds have shown little or no effect on the $GABA_B$ receptor in vitro. In fact, for almost one decade, baclofen was the only known selective agonist for the $GABA_B$ receptor. Recently, several phosphinic acid derivatives of GABA that are selective agonists at $GABA_B$ sites have been intro-




| Compd. | $R_1$ | $R_2$ | X |
|---|---|---|---|
| **a** | H | H | O |
| **b** | 5-$CH_3$ | H | O |
| **c** | 5-$C_2H_5$ | H | O |
| **d** | 5-$C_3H_7$ | H | O |
| **e** | 5-$CH(CH_3)_2$ | H | O |
| **f** | 5-$CH(CH_3)C_2H_5$ | H | O |
| **g** | H | 7-$CH_3$ | O |
| **h** | H | 7-$C_2H_5$ | O |
| **i** | H | 7-$CH(CH_3)_2$ | O |
| **j** | 5-$OCH_3$ | H | O |
| **k** | 5-$OC_2H_5$ | H | O |
| **l** | 5-$OC_3H_7$ | H | O |
| **m** | 5-$OC_4H_9$ | H | O |
| **n** | 5,6-O-$CH_2$-O | H | O |
| **o** | 5-F | H | O |
| **p** | 5-Cl | H | O |
| **q** | 5-Br | H | O |
| **r** | H | 7-Cl | O |
| **s** | 5-Cl | 7-Cl | O |
| **t** | 5-Cl | 7-$CH_3$ | O |
| **u** | 5-$CH_3$ | 7-Cl | O |
| **v** | H | H | S |
| **w** | 5-$CH_3$ | H | S |
| **x** | 5-Cl | H | S |

**Scheme 2.** Reagents: (a) $(C_6H_5)_3PCHCO_2C_2H_5/C_6H_6$; (b) $CH_3NO_2$/Triton B; (c) $H_2$/Ni Raney/EtOH; (d) $NaOH/H_2O$/EtOH.



**Scheme 3.** Reagents: (a) $(Boc)_2O$/DMAP/TEA/$CH_2Cl_2$; (b) LiOH/THF; (c) TFA/$CH_2Cl_2$.

duced [25, 26]. Surprisingly, it took 25 years before the first selective $GABA_B$ antagonists, the phosphonic and sulfonic acid analogues of baclofen (phaclofen, saclofen and 2-hydroxysaclofen), were described by Kerr and coworkers [13, 14]. In recent years, Ciba-Geigy Laboratories have discovered a new class of $GABA_B$ ligands by systematic variations of the substituents on the phosphonous moiety and the amino group and in the number of carbon atoms of γ-aminopropylphosphinic acid [26, 27]. Unfortunately, their radioligand binding studies were achieved by displacing [$^3$H]3-aminopropylphosphinic acid or [$^3$H]baclofen, whereas our binding results were obtained by displacement of the endogenous neurotransmitter GABA. Table VIII shows the affinities of our compounds to $GABA_B$ receptors by the displacement of [$^3$H]GABA. Therefore, comparisons between the different classes of compounds are very difficult.

Considerable efforts have been directed toward structure–activity relationships in order to develop more potent $GABA_B$ agonists and antagonists. In previous reports [15, 16] we have proposed some structural requirements for binding to the $GABA_B$ receptor. In order to optimize the prototype (benzo[*b*]furan-2-yl)-

**Table I.** Physical data for compounds **2**.

| *Compound* | $R_1$ | $R_2$ | *Yield (%)* | *Mp (solvent) or Bp (pressure) (°C)* | *Formula* | *Analysis* | *Method* |
|---|---|---|---|---|---|---|---|
| **2b** | $CH_3$ | H | 35 | 48–50 (petroleum ether) | $C_8H_8O_2$ | C, H, O | A |
| **2c** | $C_2H_5$ | H | 36 | 74–76 (0.3 mmHg) | $C_9H_{10}O_2$ | C, H, O | A |
| **2d** | $C_3H_7$ | H | 38 | 80–82 (1.25 mmHg) | $C_{10}H_{12}O_2$ | C, H, O | A |
| **2e** | $CH(CH_3)_2$ | H | 32 | 78–80 (0.3 mmHg) | $C_{10}H_{12}O_2$ | C, H, O | A |
| **2f** | $CH(CH_3)CH_2CH_3$ | H | 30 | 82–84 (0.5 mmHg) | $C_{11}H_{14}O_2$ | C, H, O | A |
| **2g** | H | $CH_3$ | ref [18] | | | | |
| **2h** | H | $C_2H_5$ | ref [18] | | | | |
| **2i** | H | $CH(CH_3)_2$ | ref [19] | | | | |
| **2k** | $OC_2H_5$ | H | 44 | 53–57 (cyclohexane) | $C_9H_{10}O_3$ | C, H, O | A |
| **2l** | $OC_3H_7$ | H | 43 | 35–37(EtOH 95°) | $C_{10}H_{12}O_3$ | C, H, O | A |
| **2m** | $OC_4H_9$ | H | 40 | 34–36 (EtOH 95°) | $C_{11}H_{14}O_3$ | C, H, O | A |
| **2o** | F | H | 30 | 56 (1 mmHg) | $C_7H_5O_2F$ | C, H, O, F | A |
| **2r** | H | Cl | ref [18] | | | | |
| **2t** | Cl | $CH_3$ | 26 | 59 (cyclohexane) | $C_8H_7O_2Cl$ | C, H, O[a], Cl | A |
| **2u** | $CH_3$ | Cl | 13 | 57 (pentane/diisopropyl ether 1:1) | $C_9H_7O_2Cl$ | C, H, O, Cl | A |

[a]Anal: O calc 18.75, found 18.31.

**Table II.** Physical data for compounds **3**.

| *Compound* | $R_1$ | $R_2$ | *Yield (%)* | *Mp (solvent) or Bp (pressure) (°C)* | *Formula* | *Analysis* | *Method* |
|---|---|---|---|---|---|---|---|
| **3b** | $CH_3$ | H | 80 | 192–193 (5 mmHg) | $C_{14}H_{20}O_4$ | C, H, O | B |
| **3c** | $C_2H_5$ | H | 80 | 198 (5 mmHg) | $C_{15}H_{22}O_4$ | C, H, O | B |
| **3d** | $C_3H_7$ | H | 86 | 164 (0.3 mmHg) | $C_{16}H_{24}O_4$ | C, H, O | B |
| **3e** | $CH(CH_3)_2$ | H | 80 | 160 (0.3 mmHg) | $C_{16}H_{24}O_4$ | C, H, O | B |
| **3f** | $CH(CH_3)CH_2CH_3$ | H | 75 | 168 (0.3 mmHg) | $C_{17}H_{26}O_4$ | C, H, O | B |
| **3g** | H | $CH_3$ | 80 | 130 (2 mmHg) | $C_{14}H_{20}O_4$ | C, H, O | B |
| **3h** | H | $C_2H_5$ | 78 | 145 (0.8 mmHg) | $C_{15}H_{22}O_4$ | C, H, O | B |
| **3i** | H | $CH(CH_3)_2$ | 75 | 136–140 (0.4 mmHg) | $C_{16}H_{24}O_4$ | C, H, O | B |
| **3k** | $OC_2H_5$ | H | 68 | 154–160 (0.3 mmHg) | $C_{15}H_{22}O_5$ | C[a], H, O | B |
| **3l** | $OC_3H_7$ | H | 67 | 180 (0.5 mmHg) | $C_{16}H_{24}O_5$ | C, H, O | B |
| **3m** | $OC_4H_9$ | H | 59 | 174–176 (0.3 mmHg) | $C_{17}H_{26}O_5$ | C, H, O | B |
| **3o** | F | H | 78 | 150 (0.5 mmHg) | $C_{13}H_{17}O_4F$ | C, H, O, F | B |
| **3r** | H | Cl | 82 | 140 (0.3 mmHg) | $C_{13}H_{17}O_4Cl$ | C, H, O, Cl | B |
| **3s** | Cl | Cl | 75 | 172–174 (5 mmHg) | $C_{13}H_{16}O_4Cl$ | C, H, O, Cl | B |
| **3t** | Cl | $CH_3$ | 67 | 150 (0.3 mmHg) | $C_{14}H_{19}O_4Cl$ | C, H, O, Cl | B |
| **3u** | $CH_3$ | Cl | 90 | 132 (0.4 mmHg) | $C_{14}H_{19}O_4Cl$ | C, H, O, Cl | B |

[a]Anal: C calc 63.80, found 63.37.

GABA, structural variations were systematically carried out in order to determine (a) the importance of the substituents (position and/or nature) on the heteroaromatic ring, and (b) the role of the heteroatom (benzo[*b*]furan or benzo[*b*]thiophen). In the same way, polysubstitutions on the benzo[*b*]furan ring were also studied.

The present biological data (table VIII) show the specificity of our baclofen analogues for the $GABA_B$ receptor, since compounds **8a–x** discriminate perfectly against $GABA_A$ and $GABA_B$ receptors. In the binding test, compounds **8g** and **8p** displace [$^3$H]-GABA with $IC_{50}$ values of 5.4 and 17 μM respectively. It should be noted that these two compounds are much more potent than **8j** ($IC_{50}$ = 180 μM). This must be compared to the binding results obtained previously with compound **8j** for the displacement of *RS*-[$^3$H]baclofen: $IC_{50}$ = 5.6 μM [13]. **8j** was one of our best compounds, is still marketed by Tocris-Cookson (Bristol, UK) and constituted a reference product [7, 25].

It appears (see the percent of displacement, table VIII) that the 5-position on the heteroaromatic ring (5-alkyl, 5-alkoxy or 5-halogeno) is sensitive to optimum steric bulk and that substituents of this region should be of lipophilic nature: halogen **8p** > **8q** ≫ **8o** ≫ **8a** (as baclofen); alkyl **8b** > **8c** ≫ **8a**; alkoxy **8j** > **8k** ≫ **8a** and **8p** ≫ **8j**. These results are in good agreement with our previous works. For the 7-position also, this region seems to require a lipophilic substituent with an optimum steric bulk: **8g** ≫ **8h** ≫ **8i**. Compound **8g** shows a good affinity ($IC_{50}$ = 5.4 μM), however the result obtained with compound **8r** is inconsistent: surprisingly the 7-position is favourable for methyl substitution: **8g** ≫ **8b**, but unfavourable for chlorine substitution: **8r** ≪ **8p**. Moreover, when the heteroaromatic ring is polysubstituted, these structural modifications (compounds **8s–u**) result in a dramatic decrease in affinity for $GABA_B$ receptors even with **8t** which combines the substitutions of the more potent compounds **8g** and **8p**.

The higher activity of benzo[*b*]furan analogues in comparison with benzothiophen (**8a** ≫ **8v**, **8b** ≫ **8w** and **8p** ≫ **8x**) might be explained by the higher electronegativity of the oxygen atom in comparison with that of the sulfur atom. The electrostatic interactions between the ammonium group and the ring heteroatom (oxygen or sulfur) govern the GABA chain conformation [28]. As a result, this chain can adopt two different conformations: folded for benzo[*b*]furan analogues, and extended for benzo[*b*]thiophen analogues. The folding of the ammonium group towards the benzofuranic oxygen has enabled us to superpose the anionic, cationic and aromatic moieties of benzo[*b*]furanic compounds (**8g** or **8p**) with baclofen, despite the larger size of the benzo[*b*]furan ring. On the other hand, the ammonium group of compounds **8v–x** cannot fold towards the benzo[*b*]thiophen sulfur atom [29].

**Table III.** Physical data for compounds **4**.

| *Compound* | $R_1$ | $R_2$ | *X* | *Yield (%)* | *Mp (solvent) or Bp (pressure) (°C)* | *Formula* | *Analysis* | *Method* |
|---|---|---|---|---|---|---|---|---|
| **4a** | H | H | O | ref [15, 20] | | | | |
| **4b** | $CH_3$ | H | O | 66 | 26 ($EtOH/H_2O$; 9/1) | $C_{10}H_8O_2$ | C, H, O | C |
| **4c** | $C_2H_5$ | H | O | 80 | 130 (3 mmHg) | $C_{11}H_{10}O_2$ | C, H, O | C |
| **4d** | $C_3H_7$ | H | O | 78 | 117–119 (0.2 mmHg) | $C_{12}H_{12}O_2$ | C, H, O | C |
| **4e** | $CH(CH_3)_2$ | H | O | 56 | 131–133 (3 mmHg) | $C_{12}H_{12}O_2$ | C, H, O | C |
| **4f** | $CH(CH_3)C_2H_5$ | H | O | 80 | 124 (0.5 mmHg) | $C_{13}H_{14}O_2$ | C, H, O | C |
| **4g** | H | $CH_3$ | O | 85 | 56–58 (petroleum ether) | $C_{10}H_8O_2$ | C, H, O | C |
| **4h** | H | $C_2H_5$ | O | 58 | 72–73 (diisopropyl ether) | $C_{11}H_{10}O_2$ | C, H, O | C |
| **4i** | H | $CH(CH_3)_2$ | O | 73 | 90–92 (diisopropyl ether) | $C_{12}H_{12}O_2$ | C[a], H, O | C |
| **4j** | $OCH_3$ | H | O | ref [15, 20] | | | | |
| **4k** | $OC_2H_5$ | H | O | 76 | 62–65 (cyclohexane) | $C_{11}H_{10}O_3$ | C, H, O | C |
| **4l** | $OC_3H_7$ | H | O | 85 | 65–67 (diisopropyl ether) | $C_{12}H_{12}O_3$ | C, H, O | C |
| **4m** | $OC_4H_9$ | H | O | 58 | 63–65 (diisopropyl ether) | $C_{13}H_{14}O_3$ | C, H, O | C |
| **4n** | 5,6-O-$CH_2$-O | H | O | ref [21] | | | | |
| **4o** | F | H | O | 56 | 68 (hexane) | $C_9H_5O_2F$ | C, H, O, F | C |
| **4p** | Cl | H | O | ref [20] | | | | |
| **4q** | Br | H | O | ref [20] | | | | |
| **4r** | H | Cl | O | 70 | 82–84 (diisopropyl ether) | $C_9H_5O_2Cl$ | C, H, O, Cl | C |
| **4s** | Cl | Cl | O | 60 | 126–127 (AcOEt) | $C_9H_4O_2Cl$ | C, H, O, Cl | C |
| **4t** | Cl | $CH_3$ | O | 63 | 112 (diisopropyl ether) | $C_{10}H_7O_2Cl$ | C, H, O, Cl | C |
| **4u** | $CH_3$ | Cl | O | 58 | 96–98 (diisopropyl ether) | $C_{10}H_7O_2Cl$ | C, H, O, Cl | C |
| **4v** | H | H | S | ref [22] | | | | |
| **4w** | $CH_3$ | H | S | ref [22] | | | | |
| **4x** | Cl | H | S | ref [22] | | | | |

[a]Anal: C calc 76.57; found 76.02.

From the present and previous results, the following pharmacophoric pattern for 3-heteroaromatic analogues of baclofen can be proposed. Five moieties are mandatory for $GABA_B$ affinity: (a) a carboxylate group; (b) a primary ammonium group, the distance between the ionized moieties being well-defined; (c) an aromatic or heteroaromatic ring bound to the C3 carbon of the GABA chain; (d) a lipophilic substituent in the *para* position (baclofen) or in position 5 (benzo[*b*]furan); this region is sensitive to steric bulk; and (e) another lipophilic group in position **7** (benzo[*b*]furan) [30].

## Experimental protocols

*Chemistry*

Melting points were determined on a Büchi SMP 20 apparatus and are not corrected. IR spectra were recorded on a Beckman Acculab IV spectrometer. $^1H$ NMR were recorded with a Bruker WP 80 or AC 300 pulsed Fourier transform spectrometer using $(CH_3)_4Si$ as an internal standard, except for the compounds dissolved in $D_2O$, where sodium 3-(trimethylsilyl)-propanesulfonate was used. (Laboratoire d'application RMN de l'Université de Lille-II, France). Mass spectra were recorded on a RIBERMAG R10-10 C apparatus (70 eV). The preparative separations were performed on a Jobin-Yvon Modulprep HPLC system with an RI (refractive index) Iota detector and a Spectro Monitor D variable wavelength detector with a 40 mm id column of silica gel (5–40 μm). Elemental analyses were performed by CNRS, Vernaison, and were in agreement with the proposed structures. UV spectral characteristics have been exploited by HPLC-DAD (diode array detector) to confirm peak homogeneity and purity of final amino acids. Analytical HPLC was carried out on an LKB metering pump. The detection was performed with a DAD HP 1040 connected to an HP 9000 computer on a Lichrospher 100 Merck RP 18 column.

*General procedures for the formylation of phenols 2. Method A*
A solution of the substituted phenol **1** (0.5 mol) in 300 mL of 10 N NaOH (3 mol) was heated to 65 °C. Then 80 mL of $CHCl_3$ was added in three portions over 15 min. The mixture was heated at reflux in chloroform for 2 h. After cooling, the

**Table IV.** Physical data for compounds **5**.

| *Compound* | *$R_1$* | *$R_2$* | *X* | *Yield (%)* | *Mp (solvent) or Bp (pressure) (°C)* | *Formula* | *Analysis* | *Method* |
|---|---|---|---|---|---|---|---|---|
| **5a** | H | H | O | ref [20] | | | | |
| **5b** | $CH_3$ | H | O | 52 | 72–73 (hexane) | $C_{14}H_{14}O_3$ | C, H, O | D |
| **5c** | $C_2H_5$ | H | O | 85 | 52 (hexane) | $C_{15}H_{16}O_3$ | C, H, O | D |
| **5d** | $C_3H_7$ | H | O | 85 | 71–72 (hexane) | $C_{16}H_{18}O_3$ | C, H, O | D |
| **5e** | $CH(CH_3)_2$ | H | O | 78 | 186 (3 mm Hg) | $C_{16}H_{18}O_3$ | C, H, O | D |
| **5f** | $CH(CH_3)C_2H_5$ | H | O | 90 | 165–167 (0.5 mmHg) | $C_{17}H_{20}O_3$ | C, H, O | D |
| **5g** | H | $CH_3$ | O | 86 | 136–138 (0.8 mmHg) | $C_{14}H_{14}O_3$ | C, H, O | D |
| **5h** | H | $C_2H_5$ | O | 95 | preparative HPLC | $C_{15}H_{16}O_3$ | C, H, O | D |
| **5i** | H | $CH(CH_3)_2$ | O | 96 | preparative HPLC | $C_{16}H_{18}O_3$ | C, H, O | D |
| **5j** | $OCH_3$ | H | O | ref [20] | | | | |
| **5k** | $OC_2H_5$ | H | O | 90 | 96–99 (cyclohexane) | $C_{15}H_{16}O_4$ | C, H, O | D |
| **5l** | $OC_3H_7$ | H | O | 83 | preparative HPLC | $C_{16}H_{18}O_4$ | C, H, O | D |
| **5m** | $OC_4H_9$ | H | O | 58 | 96–97 (diisopropyl ether) | $C_{17}H_{20}O_4$ | C, H, O | D |
| **5n** | 5,6-O-$CH_2$-O | H | O | 57 | 151 (diisopropyl ether) | $C_{14}H_{12}O_5$ | C, H, O | D |
| **5o** | F | H | O | 80 | 112 (hexane) | $C_{13}H_{11}O_3F$ | C, H, O, F | D |
| **5p** | Cl | H | O | ref [20] | | | | |
| **5q** | Br | H | O | ref [20] | | | | |
| **5r** | H | Cl | O | 80 | 56–57 (hexane) | $C_{13}H_{11}O_3Cl$ | C, H, O, Cl | D |
| **5s** | Cl | Cl | O | 75 | 112 (diisopropyl ether) | $C_{13}H_{10}O_3Cl_2$ | C, H, O, Cl | D |
| **5t** | Cl | $CH_3$ | O | 75 | 95 (diisopropyl ether) | $C_{14}H_{13}O_3Cl$ | C[a],H, O, Cl | D |
| **5u** | $CH_3$ | Cl | O | 95 | 80 (diisopropyl ether) | $C_{14}H_{13}O_3Cl$ | C, H, O, Cl | D |
| **5v** | H | H | S | 92 | 55–56 (hexane) | $C_{13}H_{12}O_2S$ | C, H, O, S | D |
| **5w** | $CH_3$ | H | S | 58 | 83–85 (hexane) | $C_{14}H_{14}O_2S$ | C, H, O, S | D |
| **5x** | Cl | H | S | 82 | 98–99 (diisopropyl ether) | $C_{13}H11O_2SCl$ | C, H, O, S, Cl | D |

[a]Anal: C calcd 63.52; found 63.96.

mixture was acidified to pH 1 with 12 N HCl, the organic layer collected and the aqueous layer extracted with chloroform. The combined chloroform solution was dried and evaporated to give a crude product which was chromatographed on silica gel. An analytical sample was distilled or recrystallized from an appropriate solvent.

*Example 1: 2-hydroxy-5-methylbenzaldehyde* ***2b.*** IR 1650 (C=O); $^1$H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.90 (d, 1H, $J$ = 8.6 Hz), 7.25–7.50 (m, 2H), 9.80 (s, 1H), 10.75 (s, 1H, exch $D_2O$).

*Example 2: 2-hydroxy-3-methyl-5-chlorobenzaldehyde* ***2t.*** IR 1655 (C=O); $^1$H NMR ($CDCl_3$) δ 2.25 (s, 3H), 7.30 (s, 2H), 7.80 (s, 1H, exch $D_2O$), 11.20 (s, 1H).

*General procedures for the syntheses of 2-formyl phenoxyacetaldehyde diethyl acetals* ***3a–p.*** *Method B*

To a stirred suspension containing substituted 2-hydroxybenzaldehydes **2b–m**, **2o**, **2r**, **2t–u** (0.15 mol) and potassium carbonate (28.1 g, 0.16 mol) in 100 mL DMF, bromoacetaldehyde diethyl acetal (31.5 g, 0.16 mol) was added dropwise. The mixture was refluxed for 4 h. After cooling, the precipitate was filtered off and the solvent evaporated under reduced pressure. The oily residue was distilled.

*Example 1: (2-formyl-4-methylphenoxy)acetaldehyde diethyl acetal* ***3b.*** IR 1700 (C=O); $^1$H NMR ($CDCl_3$) δ 1.25 (t, 6H, $J$ = 6.4 Hz), 2.30 (s, 3H), 3.50–4.00 (m, 4H), 4.12 (d, 2H, $J$ = 5.1 Hz), 4.87 (t, 1H, $J$ = 5.1 Hz), 6.90 (d, 1H, $J$ = 8.2 Hz), 7.40 (dd, 1H, $J$ = 2.1 and 8.2 Hz), 7.62 (d, 1H, $J$ = 2.1 Hz), 10.50 (s, 1H).

*Example 2: (2-formyl-6-methylphenoxy)acetaldehyde diethyl acetal* ***3g.*** IR 1700 (C=O); $^1$H NMR ($CDCl_3$) δ 1.12 (t, 6H, $J$ = 6.3 Hz), 2.32 (s, 3H), 3.45–4.00 (m, 4H), 3.95 (d, 2H, $J$ = 4.5 Hz), 4.87 (t, 1H, $J$ = 4.5 Hz), 7.19–7.59 (m, 3H), 10.36 (s, 1H).

*Example 3: (6-chloro-2-formylphenoxy)acetaldehyde diethyl acetal* ***3r.*** IR 1700 (C=O); $^1$H NMR ($CDCl_3$) δ 1.12–1.35 (m, 6H), 3.50–4.01 (m, 4H), 4.18 (d, 2H, $J$ = 4.7 Hz), 4.88 (t, 1H, $J$ = 4.7 Hz), 6.86–7.79 (m, 3H), 10.50 (s, 1H).

*General procedures for the syntheses of heteroaryl-2-aldehydes* ***4a–x.*** *Method C*

A stirred solution of compounds **3a–x** (0.1 mol) in 35 mL of concentrated acetic acid was refluxed for 24 h. After cooling, the solution was evaporated to dryness. The crude product was distilled or recrystallized from an appropriate solvent.

**Table V.** Physical data for compounds **6**.

| *Compound* | $R_1$ | $R_2$ | *X* | *Yield (%)* | *Mp (solvent) or Bp (pressure) (°C)* | *Formula* | *Analysis* | *Method* |
|---|---|---|---|---|---|---|---|---|
| **6a** | H | H | O | ref [20] | | | | |
| **6b** | $CH_3$ | H | O | 46 | Preparative HPLC | $C_{15}H_{17}NO_5$ | C, H, N, O | E |
| **6c** | $C_2H_5$ | H | O | 52 | Preparative HPLC | $C_{16}H_{19}NO_5$ | C, H, N, O | E |
| **6d** | $C_3H_7$ | H | O | 52 | Preparative HPLC | $C_{17}H_{21}NO_5$ | C, H, N, O | E |
| **6e** | $CH(CH_3)_2$ | H | O | 54 | Preparative HPLC | $C_{17}H_{21}NO_5$ | C, H, N, O | E |
| **6f** | $CH(CH_3)C_2H_5$ | H | O | 56 | Preparative HPLC | $C_{18}H_{23}NO_5$ | C, H, N, O | E |
| **6g** | H | $CH_3$ | O | 60 | Preparative HPLC | $C_{15}H_{17}NO_5$ | C, H, N, O | E |
| **6h** | H | $C_2H_5$ | O | 84 | Preparative HPLC | $C_{16}H_{19}NO_5$ | C, H, N, O | E |
| **6i** | H | $CH(CH_3)_2$ | O | 80 | Preparative HPLC | $C_{17}H_{21}NO_5$ | C, H, N, O | E |
| **6j** | $OCH_3$ | H | O | ref [20] | | | | |
| **6k** | $OC_2H_5$ | H | O | 57 | Preparative HPLC | $C_{16}H_{19}NO_6$ | C, H, N, O | E |
| **6l** | $OC_3H_7$ | H | O | 81 | Preparative HPLC | $C_{17}H_{21}NO_6$ | C, H, N, O | E |
| **6m** | $OC_4H_9$ | H | O | 50 | Preparative HPLC | $C_{18}H_{23}NO_6$ | C, H, N, O | E |
| **6n** | 5,6-O-$CH_2$-O | H | O | 82 | Preparative HPLC | $C_{15}H_{15}NO_7$ | C, H, N, O | E |
| **6o** | F | H | O | 50 | Preparative HPLC | $C_{14}H_{14}NO_5F$ | C, H, N, O, F | E |
| **6p** | Cl | H | O | ref [20] | | | | |
| **6q** | Br | H | O | ref [20] | | | | |
| **6r** | H | 7Cl | O | 70 | Preparative HPLC | $C_{14}H_{14}NO_5Cl$ | C, H, N, O, Cl | E |
| **6s** | Cl | Cl | O | 70 | Preparative HPLC | $C_{14}H_{13}NO_5Cl_2$ | C, H, N, O, Cl | E |
| **6t** | Cl | $CH_3$ | O | 56 | Preparative HPLC | $C_{15}H_{16}NO_5Cl$ | C, H, N, O, Cl | E |
| **6u** | $CH_3$ | Cl | O | 60 | Preparative HPLC | $C_{15}H_{16}NO_5Cl$ | C, H, N, O[a], Cl | E |
| **6v** | H | H | S | 70 | Preparative HPLC | $C_{14}H_{15}NO_4S$ | C, H, N, O, S | E |
| **6w** | $CH_3$ | H | S | 58 | Preparative HPLC | $C_{15}H_{17}NO_4S$ | C[b], H, N, O, S | E |
| **6x** | Cl | H | S | 80 | Preparative HPLC | $C_{14}H_{14}NO_4SCl$ | C[c], H, N, O, S, Cl | E |

[a]Anal: O calc 24.55, found 24.10; [b]C calc 58.61, found 59.03; [c]C calc 51.30, found 51.80.

*Example 1: 2-formyl-5-methylbenzo[b]furan* ***4b***. IR 1680 (C=O); $^1$H NMR ($CDCl_3$) δ 2.38 (s, 3H), 7.50 (m, 4H), 9.87 (s, 1H).

*Example 2: 2-formyl-7-methylbenzo[b]furan* ***4g***. IR 1700 (C=O); $^1$H NMR ($CDCl_3$) δ 2.59 (s, 3H), 7.25–7.59 (m, 4H), 9.87 (s, 1H).

*Example 3: 7-chloro-2-formylbenzo[b]furan* ***4r***. IR 1700 (C=O); $^1$H NMR ($CDCl_3$) δ 7.29 (dd, 1H, $J$ = 7.7 and 8.2 Hz, $H_5$), 7.53 (dd, 1H, $J$ = 7.7 and 2.3 Hz, $H_4$), 7.66 (dd, 1H, $J$ = 8.2 and 2.3 Hz, $H_6$), 7.60 (s, 1H, $H_3$), 9.95 (s, 1H).

*General procedures for the syntheses of ethyl 3-substituted prop-2-enoates* ***5a–x***. *Method D*

(Carbethoxymethylene)triphenylphosphorane (34.84 g, 0.1 mol) was added to a stirred solution of the appropriate aldehyde **4a–x** (0.1 mol) in 200 mL of anhydrous $C_6H_6$. The mixture was refluxed for 7 h under nitrogen. After evaporation of $C_6H_6$, the crude residue was stirred for 1 h with diethyl ether, the trimethylphosphine oxide crystallized out and was separated by filtration. The solvent was evaporated. The resulting solid was recrystallized from an appropriate solvent or the oily residue was distilled under reduced pressure. Compounds **5h,i,l** were purified by chromatography (**5h,i** with petroleum ether/ethyl acetate, 95:5; **5l** with toluene) and isolated as oils.

*Example 1: Ethyl 3-(5-methylbenzo[b]furan-2-yl)prop-2-enoate* ***5b***. IR 1720 (C=O); $^1$H NMR ($CDCl_3$) δ 1.36 (t, 3H, $J$ = 7.6 Hz), 2.43 (s, 3H), 4.27 (q, 2H, $J$ = 7.6 Hz), 6.35 (d, 1H, $J$ = 15.8 Hz), 6.85 (s, 1H,), 7.10–7.60 (m, 4H).

*Example 2: Ethyl 3-(7-methylbenzo[b]furan-2-yl)prop-2-enoate* ***5g***. IR 1720 (C=O); $^1$H NMR ($CDCl_3$) δ 1.36 (t, 3H, $J$ = 7.6 Hz), 2.51 (s, 3H), 4.27 (q, 2H, $J$ = 7.6 Hz), 6.58 (d, 1H, $J$ = 15.8 Hz), 6.91 (s, 1H), 7.12–7.50 (m, 4H).

*Example 3: Ethyl 3-(7-chlorobenzo[b]furan-2-yl)prop-2-enoate* ***5r***. IR 1720 (C=O); $^1$H NMR ($CDCl_3$) δ 1.37 (t, 3H, $J$ = 6.9 Hz), 4.78 (q, 2H, $J$ = 6.9 Hz), 6.69 (d, 1H, $J$ = 15.8 Hz), 6.95 (s, 1H), 7.03–7.57 (m, 4H).

*Example 4: Ethyl 3-(5-methylbenzo[b]thiophen-2-yl)prop-2-enoate* ***5w***. IR 1717 (C=O); $^1$H NMR ($CDCl_3$) δ 1.35 (t, 3H, $J$ = 6.9 Hz), 2.45 (s, 3H), 4.28 (q, 2H, $J$ = 6.9 Hz), 6.29 (d, 1H, $J$ = 15.6 Hz), 7.11–7.74 (m, 4H), 7.86 (d, 1H, $J$ = 15.6 Hz).

**Table VI.** Physical data for compounds **7**.

| *Compound* | *$R_1$* | *$R_2$* | *X* | *Yield (%)* | *Mp (solvent) or Bp (pressure) (°C)* | *Formula* | *Analysis* | *Method* |
|---|---|---|---|---|---|---|---|---|
| **7a** | H | H | O | ref [20] | | | | |
| **7b** | $CH_3$ | H | O | 50 | 151 (diisopropyl ether) | $C_{13}H_{13}NO_2$ | C, H, N, O | F |
| **7c** | $C_2H_5$ | H | O | 52 | 126 (diisopropyl ether) | $C_{14}H_{15}NO_2$ | C, H, N, O | F |
| **7d** | $C_3H_7$ | H | O | 58 | 122 (diisopropyl ether) | $C_{15}H_{17}NO_2$ | C, H, N, O | F |
| **7e** | $CH(CH_3)_2$ | H | O | 54 | 158 (diisopropyl ether) | $C_{15}H_{17}NO_2$ | C, H, N, O | F |
| **7f** | $CH(CH_3)C_2H_5$ | H | O | 56 | 111 (diisopropyl ether) | $C_{16}H_{19}NO_2$ | C, H, N, O | F |
| **7g** | H | $CH_3$ | O | 60 | 126 (diisopropyl ether) | $C_{13}H_{13}NO_2$ | C, H, N, O | F |
| **7h** | H | $C_2H_5$ | O | 34 | 137 (AcOEt/diisopropyl ether:1/1) | $C_{14}H_{15}NO2$ | C, H, N, O | F |
| **7i** | H | $CH(CH_3)_2$ | O | 50 | 142–144 (AcOEt) | $C_{15}H_{17}NO_2$ | C[a], H, N, O | F |
| **7j** | $OCH_3$ | H | O | ref [20] | | | | |
| **7k** | $OC_2H_5$ | H | O | 28 | 145–148 (AcOEt) | $C_{14}H_{15}NO_3$ | C, H, N, O | F |
| **7l** | $OC_3H_7$ | H | O | 53 | 150–153 (AcOEt) | $C_{15}H_{17}NO_3$ | C, H, N, O | F |
| **7m** | $OC_4H_9$ | H | O | 69 | 145–148 (AcOEt) | $C_{16}H_{19}NO_3$ | C, H, N, O | F |
| **7n** | 5,6-O-$CH_2$-O | H | O | 59 | 202–204 (AcOEt) | $C_{13}H_{11}NO_4$ | C, H, N, O | F |
| **7o** | F | H | O | 50 | 178 (diisopropyl ether) | $C_{12}H_{10}NO_2F$ | C, H, N, O, F | F |
| **7p** | Cl | H | O | ref [20] | | | | |
| **7q** | Br | H | O | ref [20] | | | | |
| **7r** | H | Cl | O | 50 | 127–129 (AcOEt) | $C_{12}H_{10}NO_2Cl$ | C, H, N, O, Cl | F |
| **7s** | Cl | Cl | O | 45 | 121–122 (AcOEt/diisopropyl ether:2/8) | $C_{12}H_9NO_2Cl_2$ | C, H, N, O, Cl | F |
| **7t** | Cl | $CH_3$ | O | 40 | 165 (diisopropyl ether) | $C_{13}H_{12}NO_2Cl$ | C, H, N, O, Cl | F |
| **7u** | $CH_3$ | Cl | O | 40 | 165 (AcOEt/diisopropyl ether:1/1) | $C_{13}H_{12}NO_2Cl$ | C, H, N, O, Cl | F |
| **7v** | H | H | S | 65 | 173–175 (AcOEt) | $C_{12}H_{11}NOS$ | C, H, N, O, S | F |
| **7w** | $CH_3$ | H | S | G41 | 163–166 (AcOEt/hexane:1/1) | $C_{13}H_{13}NOS$ | C, H, N, O, S | F |
| **7x** | Cl | H | S | 39 | 173 (diisopropyl ether) | $C_{12}H_{10}NOSCl$ | C[b], H, N, O ,S, Cl | F |

[a]Anal: C calc 74.05, found 73.62; [b]C calc 57.25, found 56.50.

*General procedures for the syntheses of ethyl 4-nitro-3-substituted butanoates **6a–x**. Method E*
A stirred solution of esters **5a–x** (0.05 mol) in 100 mL of $CH_3NO_2$ with 4mL of Triton B was heated at 80 °C for 18 h. After cooling, the reaction mediun was acidified to pH 2 with 2 M HCl and 50 mL $H_2O$ was added. The mixture was extracted with diethyl ether. The combined extracts were washed with water, dried and evaporated in vacuo, giving a crude oil which was further purified by preparative HPLC. The resulting oil was used in the next step without further purification.

*Example 1: Ethyl 3-(5-methylbenzo[b]furan-2-yl)-4-nitrobutanoate **6b**.* IR 1740 (C=O); $^1$H NMR ($CDCl_3$) δ 1.25 (t, 3H, $J$ = 6.9 Hz), 2.40 (s, 3H), 2.89 (d, 2H, $J$ = 6.2 Hz), 4.12 (q, 2H, $J$ = 6.9 Hz), 4.25–4.47(m, 1H), 4.80 (d, 2H, $J$ = 6.8 Hz), 6.50 (s, 1H), 7.00–7.48 (m, 3H).

*Example 2: Ethyl 3-(7-methylbenzo[b]furan-2-yl)-4-nitrobutanoate **6g**.* IR 1748 (C=O); $^1$H NMR ($CDCl_3$) δ 1.35 (t, 3H, $J$ = 7.2 Hz), 2.50 (s, 3H), 2.77 (d, 2H, $J$ = 6.5 Hz), 4.00–4.50 (m, 3H), 4.78 (d, 2H, $J$ = 7.1 Hz), 6.52 (s, 1H), 7.00–7.35 (m, 3H).

*Example 3: Ethyl 3-(7-chlorobenzo[b]furan-2-yl)-4-nitrobutanoate **6r**.* IR 1750 (C=O); $^1$H NMR ($CDCl_3$) δ 1.24 (t, 3H, $J$ = 7.3 Hz), 2.88 (d, 2H, $J$ = 6.5 Hz), 4.15 (q, 2H, $J$ = 7.3 Hz), 4.48 (m, 1H), 4.85 (d, 2H), 6.51 (s, 1H), 7.13–7.50 (m, 3H).

*Example 4: Ethyl 3-(5-methylbenzo[b]thiophen-2-yl)-4-nitrobutanoate **6w**.* IR 1734 (C=O); $^1$H NMR ($CDCl_3$) δ 1.22 (t, 3H, $J$ = 7.5 Hz), 2.44 (s, 3H), 2.87 (d, 2H, $J$ = 7.2 Hz), 3.95–4.52 (m, 3H), 4.68–4.88 (m, 2H), 7.00–7.74 (m, 4H).

*General procedures for the syntheses of 4-substituted pyrrolidin-2-one derivatives **7a–x**. Method F*
The nitro esters **6a–x** (0.02 mol) were shaken in 200 mL of ethanol with Raney nickel catalyst at room temperature under an atmospheric pressure of hydrogen. After completion of the

**Table VII.** Physical data for compounds **8**.

| *Compound* | $R_1$ | $R_2$ | *X* | *Yield (%)* | *Mp (solvent) or Bp (pressure) (°C)* | *Formula* | *Analysis* | *Method* |
|---|---|---|---|---|---|---|---|---|
| **8a** | H | H | O | ref [15] | | | | |
| **8b** | $CH_3$ | H | O | 50 | 190 (EtOH 95°) | $C_{13}H_{15}NO_3$ | C, H, N, O | G |
| **8c** | $C_2H_5$ | H | O | 50 | 188–190 (EtOH 95°) | $C_{14}H_{17}NO_3$ | C, H, N, O | G |
| **8d** | $C_3H_7$ | H | O | 50 | 186–188 (EtOH 95°) | $C_{15}H_{19}NO_3$ | C, H, N, O | G |
| **8e** | $CH(CH_3)_2$ | H | O | 45 | 178–180 (EtOH 95°) | $C_{15}H_{19}NO_3$ | C, H, N, O | G |
| **8f** | $CH(CH_3)C_2H_5$ | H | O | 55 | 194–197 (EtOH 95°) | $C_{16}H_{21}NO_3$ | C, H, N, O | G |
| **8g** | H | $CH_3$ | O | 50 | 191 (EtOH 95°) | $C_{13}H_{15}NO_3$ | C, H, N, O | G |
| **8h** | H | $C2_2H_5$ | O | 70 | 161–165 ($EtOH/H_2O$:1/1) | $C_{14}H_{17}NO_3$ | C, H, N, O | G |
| **8i** | H | $CH(CH_3)_2$ | O | 70 | 151–152 (EtOH 95°) | $C_{15}H_{19}NO_3,H_2O$ | C, H, N, O | G |
| **8j** | $OCH_3$ | H | O | ref [15] | | | | |
| **8k** | $OC_2H_5$ | H | O | 53 | 200 (EtOH 95°) | $C_{14}H_{17}NO_4$ | C, H, N, O | G |
| **8l** | $OC_3H_7$ | H | O | 22 | 181–182 (EtOH 95°) | $C_{15}H_{19}NO_4$ | C, H, N, O | G |
| **8m** | $OC_4H_9$ | H | O | 25 | 173–175 (EtOH 95°) | $C_{16}H_{21}NO_4$ | C, H, N, O | G |
| **8n** | 5,6-O-$CH_2$-O | H | O | 25 | 198 (EtOH 95°) | $C_{13}H_{13}NO_5$ | C, H, N, O | G |
| **8o** | F | H | O | 35 | 200–202 (EtOH 95°) | $C_{12}H_{12}NO_3F$ | C, H, N, O, F | G |
| **8p** | Cl | H | O | 60 | 190–192 (EtOH 95°) | $C_{12}H_{12}NO_3Cl$ | C, H, N, O, Cl | G |
| **8q** | Br | H | O | 40 | 200 (EtOH 95°) | $C_{12}H_{12}NO_3Br$ | C, H, N, O, Br | G |
| **8r** | H | Cl | O | 28 | 192–194 (EtOH 95°) | $C_{12}H_{12}NO_3Cl$ | C, H, N, O, Cl | G |
| **8s** | Cl | 7Cl | O | 25 | 198–200 (EtOH 95°) | $C_{12}H_{11}NO_3Cl_2$ | C, H, N, O, Cl | G |
| **8t** | Cl | $CH_3$ | O | 60 | 173 (EtOH 95°) | $C_{13}H_{14}NO_3Cl$ | C, H, N, O[a], Cl | G |
| **8u** | $CH_3$ | Cl | O | 58 | 169–170 (EtOH 95°) | $C_{13}H_{14}NO_3Cl$ | C, H, N, O[b], Cl | G |
| **8v** | H | H | S | 53 | 192–193 (EtOH 95°) | $C_{12}H_{13}NO_2S$ | C, H, N, O, S | G |
| **8w** | $CH_3$ | H | S | 54 | 205 (EtOH 95°) | $C_{13}H_{15}NO_2S$ | C, H, N, O, S | G |
| **8x** | Cl | H | S | 45 | 190–191 (EtOH 95°) | $C_{12}H_{12}NO_2SCl$ | C[c], H, N, O, S, Cl | G |

[a]Anal: O calc 17.95, found 17.24; [b]O calc 17.95, found 17.23; [c]C calc 53.43, found 52.96.

reaction, the catalyst was separated by filtration and the solvent evaporated under vacuum to furnish a mixture of amino esters and lactams. The proportions of the two compounds were estimated to be roughly 50:50 by $^1H$ NMR spectral data. This mixture was heated at 100 °C for 2 h to give exclusively the lactams **7a–x**. The residue was triturated in diethyl ether and the precipitate was filtered and recrystallized from an appropriate solvent.

*Example 1: 4-(5-methylbenzo[b]furan-2-yl)pyrrolidin-2-one* ***7b.*** IR 3300 (CONH), 1690 (C=O); $^1H$ NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.69 (d, 2H, *J* = 7.2 Hz), 3.50–4.00 (m, 3H), 6.00 (ls, 1H), 6.46 (s, 1H), 7.00–7.49 (m, 3H).

*Example 2: 4-(7-methylbenzo[b]furan-2-yl)pyrrolidin-2-one* ***7g.*** IR 3290 (CONH), 1670 (C=O); $^1H$ NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.75 (d, 2H, *J* = 7.7 Hz), 3.50–4.00 (m, 3H), 6.10 (ls, 1H), 6.50 (s, 1H), 7.00–7.50 (m, 3H).

*Example 3: 4-(7-chlorobenzo[b]furan-2-yl)pyrrolidin-2-one* ***7r.*** IR 3280 (CONH), 1670 (C=O); $^1H$ NMR ($CDCl_3$) δ 2.75 (d, 2H, *J* = 7.4 Hz), 3.57–4.13 (m, 3H), 6.10 (ls, 1H), 6.57 (s, 1H), 7.13–7.50 (m, 3H).

*Example 4: 4-(5-methylbenzo[b]thiophen-2-yl)pyrrolidin-2-one* ***7w.*** IR 3245 (CONH), 1675 (C=O); $^1H$ NMR ($CDCl_3$) δ 2.44 (s, 3H), 2.59–2.82 (m, 2H), 3.41–4.17 (m, 3H), 5.90 (ls, 1H), 6.98–7.77 (m, 4H).

*General procedures for the syntheses of 4-amino-3-substituted butanoic acids* ***8a–p*** *and* ***8r–x.*** *Method G*

The lactams **7a–x** (0.01 mol) were refluxed for 1 h in 40 mL of alcohol (95°) and 10 mL of 10 N NaOH. After cooling, the alcohol was evaporated under reduced pressure. The crude product was dissolved in water (50 mL) and acidified to pH 1 with 10% HCl. The aqueous layer was washed with small portions of diethyl ether and evapored under vacuum. The residue was suspended in $CF_3COOH$ (3 mL) and adsorbed on Dowex 50 W 8-200 ion-exchange resin (10 mL), washed with water and eluted with 5% $NH_4OH$. The ammoniacal solution was evaporated to dryness under vacuum and the residue recrystallized from an appropriate solvent. The purity of this compound was controlled by analytical HPLC analysis: Lichrospher 100 RP 18, 5 μm column, 4 mm × 25 cm (Merck), eluent $CH_3OH/H_2O$ 80:20, flow rate 0.7 mL/min.

**Table VIII.** Binding results ($IC_{50}$[a] μM).

| *Compound* | $R_1$ | $R_2$ | *X* | *[³H]GABA binding $GABA_B$* | *Percentage displacement of [³H]GABA at $10^{-5}$ M* | *[³H]Muscimol binding $GABA_A$* |
|---|---|---|---|---|---|---|
| **8a** | H | H | O | > 100 | | ≫ 100 |
| **8b** | $CH_3$ | H | O | 108 | 19 | ≫ 100 |
| **8c** | $C_2H_5$ | H | O | > 100 | 15 | ≫ 100 |
| **8d** | $C_3H_7$ | H | O | > 100 | | ≫ 100 |
| **8e** | $CH(CH_3)_2$ | H | O | > 100 | | ≫ 100 |
| **8f** | $CH(CH_3)C_2H_5$ | H | O | > 100 | | ≫ 100 |
| **8g** | H | $CH_3$ | O | 5.4 | 57 | ≫ 100 |
| **8h** | H | $C_2H_5$ | O | > 100 | 32 | ≫ 100 |
| **8i** | H | $CH(CH_3)_2$ | O | ≫ 100 | | ≫ 100 |
| **8j** | $OCH_3$ | H | O | 180 (5.6)[b] | 25 | ≫ 100 |
| **8k** | $OC_2H_5$ | H | O | > 100 | 20 | ≫ 100 |
| **8l** | $OC_3H_7$ | H | O | > 100 | | ≫ 100 |
| **8m** | $OC_4H_9$ | H | O | > 100 | | ≫ 100 |
| **8o** | F | H | O | > 100 | 14 | ≫ 100 |
| **8p** | Cl | H | O | 17 | 51 | ≫ 100 |
| **8q** | Br | H | O | > 100 | 25 | ≫ 100 |
| **8r** | H | Cl | O | > 100 | 21 | ≫ 100 |
| **8s** | Cl | Cl | O | > 100 | | ≫ 100 |
| **8t** | Cl | $CH_3$ | O | > 100 | 19 | ≫ 100 |
| **8u** | $CH_3$ | Cl | O | ≫ 100 | | ≫ 100 |
| **8v** | H | H | S | ≫ 100 | | ≫ 100 |
| **8w** | $CH_3$ | H | S | ≫ 100 | | ≫ 100 |
| **8x** | Cl | H | S | ≫ 100 | | ≫ 100 |
| *RS*-Baclofen | | | | 0.13 (0.2)[b] | 96 | ≫ 100 |

[a]Results were means of two experiments done in triplicate; [b]in parentheses $IC_{50}$ obtained vs *RS*-[³H]baclofen [15].

*Example 1: 4-amino-3-(5-methylbenzo[b]furan-2-yl)butanoic acid **8b**.* IR 3200–2200 (OH), 1580 (C=O); $^1$H NMR ($D_2O$) δ 2.51 (s, 3H), 2.75 (d, 2H, $J$ = 6.7 Hz), 3.38–3.90 (m, 3H), 6.80 (s, 1H), 7.20–7.60 (m, 3H); MS, *m/e* 233 (M, 2), 215 (24); retention time 3.79 min.

*Example 2: 4-amino-3-(7-methylbenzo[b]furan-2-yl)butanoic acid **8g**.* IR 3200–2200 (OH), 1600 (C=O); $^1$H NMR ($D_2O$) δ 2.56 (s, 3H), 2.80 (d, 2H, $J$ = 6.6 Hz), 3.50–3.75 (m, 3H), 6.83 (s, 1H), 7.25–7.52 (m, 3H); MS, *m/e* 233 (M, 2), 215 (24); retention time 3.77 min.

*Example 3: 4-amino-3-(7-chlorobenzo[b]furan-2-yl)butanoic acid **8r**.* IR 3200–2200 (OH), 1600 (C=O); $^1$H NMR ($D_2O$) δ 3.23 (d, 2H, $J$ = 5.5 Hz), 3.75–4.38 (m, 3H), 6.63 (s, 1H), 7.10–7.53 (m, 3H); MS, *m/e* 235 (M $^{35}$Cl-$H_2O$, 18), 237 (M $^{37}$Cl-$H_2O$, 4); retention time 3.61 min.

*Example 4: 4-amino-3-(5-methylbenzo[b]thiophen-2-yl)butanoic acid **8w**.* IR 3200–2300 (OH), 1570 (C=O); $^1$H NMR ($D_2O$) δ 2.44 (s, 3H), 2.71 (d, 2H, $J$ = 7.3 Hz), 3.27–4.18 (m, 3H), 7.18–7.94 (m, 4H); MS, *m/e* 249 (M, 2), 231 (26); retention time 3.52 min.

*N-tert-Butyloxycarbonyl-4-(5-bromobenzo[b]furan-2-yl)pyrrolidin-2-one **7q**$_1$*

To a stirred solution of 4-(5-bromobenzo[*b*]furan-2-yl)pyrrolidin-2-one (3 g, 0.01 mol), prepared according to [20], in $CH_2Cl_2$ (150 mL) were added, under nitrogen flow, TEA (triethylamine; 1.4 mL, 0.01 mol), Boc-anhydride (4.6 g, 0.02 mol) and 4-dimethylaminopyridin (1.3 g, 0.01 mol). The mixture was stirred for 4 h at room temperature and evaporated to dryness under reduced pressure. Water was added and the mixture was then acidified with 10% acetic acid. The aqueous layer was extracted with chloroform. The organic layer was washed with water, dried, filtered and the solvent evaporated under reduced

pressure. The resulting solid was recrystallized from diisopropyl ether: mp 88–90 °C; IR 1790 (NCOO), 1680 (C=O); $^1$H NMR ($CDCl_3$) δ 1.50 (s, 9H), 3.00 (d, 2H, $J$ = 4.5 Hz), 3.50–4.25 (m, 3H), 6.50 (s, 1H), 7.25–7.63 (m, 3H); anal $C_{16}H_{18}NO_4Br$ (C, H, N, O, Br).

*(5-Bromobenzo[b]furan-2-yl)-4-tert-butyloxycarbonylaminobutanoic acid* **7q**$_2$

A sample of *N*-tert-butyloxycarbonyl-4-(5-bromobenzo[*b*]furan-2-yl)pyrrolidin-2-one (2 g, 0.005 mol) was shaken with 15 mL of 1N LiOH in 200 mL of THF (tetrahydrofuran) at room temperature. The solution was evaporated to dryness. The crude product was dissolved in water (50 mL) and acidified with 10% acetic acid. The mixture was extracted with ethyl acetate portions. The combined extracts were dried and evaporated in vacuo. The residue was recrystallized from hexane: mp 106 °C; IR 1720 (NHCOO), 1675 (C=O); $^1$H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.79 (d, 2H, $J$ = 5.8 Hz), 3.51–3.70 (m, 3H), 4.75 (ls, 1H), 6.50 (s, 1H), 7.25–7.64 (m, 3H); anal $C_{17}H_{20}NO_5Br$ (C, H, N, O, Br).

*4-Amino-3-(5-bromobenzo[b]furan-2-yl)butanoic acid* **8q**

A mixture of 3-(5-bromobenzo[*b*]furan-2-yl)-4-*tert*-butyloxycarbonyl aminobutanoic acid (2 g, 0.005 mol) and 22 mL of TFA in 120 mL of THF was shaken at room temperature. The solution was evaporated to dryness. The residue was dissolved in water (5 mL) and acidified to pH 1 with 1N HCl. The aqueous layer was washed with small portions of chloroform and evaporated to dryness. The residue was suspended in $CF_3COOH$ (3 mL) and adsorbed on Dowex 50 W 8-200 ion-exchange resin (10 mL), washed with water and eluted with 5% $NH_4OH$. The ammoniacal solution was evaporated to dryness under vacum and the residue recrystallized from alcohol (95°): mp 200 °C; IR 3200–2200 (OH), 1580 (C=O); $^1$H NMR ($D_2O$) δ 2.75 (d, 2H, $J$ = 7.1 Hz), 3.40–3.86 (m, 3H), 6.84 (s, 1H), 7.55–7.89 (m, 3H); MS, *m/e* 297 (M $^{79}$Br, 2), 281 (M $^{81}$Br-$H_2O$, 36), 279 (M $^{79}$Br-$H_2O$, 34); retention time 3.93 min.

*Biochemical assays*

Crude synaptic membranes (CSM) were prepared from whole rat brain according to the method of Enna and Snyder [24]. The binding assay procedures were described in a previous paper [15].

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