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Synthesis and Biological Activity of Allosteric Modulators of $GABA_B$ Receptors, Part 1. *N*-(Phenylpropyl)-1-arylethylamines*

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A series of 15 analogues of fendiline, and 34 derivatives of *N*-(3-phenylpropyl)-1-arylethylamine have been prepared for evaluation as positive allosteric modulators of $GABA_B$ receptors. The most active (EC_{50}, 10 nM) was *N*-(3,3-diphenylpropyl)-1-(3-chloro-4-methoxyphenyl)ethylamine **6g**.

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Introduction

The flow of information along nerve fibres requires transmission of the signals across the synapse to the adjacent cell.[1] γ-Aminobutyric acid (GABA, **1**, Fig. 1) is one of the major inhibitory neurotransmitters which regulates synaptic transmission and neuronal excitability in the mammalian central and peripheral nervous system.[2–4] Defects in GABA-ergic transmission can cause a variety of neurological and psychiatric diseases such as spasticity,[5] epilepsy,[6] and Huntington's[7] and Parkinson's[8] diseases. $GABA_B$ receptors are also implicated in drug addiction related to alcohol[9,10] and cocaine.[11]

GABA has been implicated in the regulation of many physiological processes and it activates three pharmacologically distinct classes of receptors, $GABA_A$, $GABA_B$, and $GABA_C$.[12] $GABA_A$ and $GABA_B$ receptors can be further sub-divided into three categories, presynaptic, postsynaptic, and autoreceptors.[12,13] The $GABA_B$ receptor was originally defined on the basis that it is sensitive to the agonist baclofen **2** and insensitive to the antagonist bicuculline.[14–16]

$GABA_B$ receptors are coupled to G-proteins, which when activated induce either a decrease in calcium (Ca^{2+}) influx or an increase in potassium (K^+) membrane conductance, the latter leading to inhibitory postsynaptic potentials mediating membrane hyperpolarizations.[17] Metabotropic $GABA_B$ receptors belong to Family 3 of G-protein-coupled receptors (GPCRs), which show extensive similarities in sequence structure to metabotropic glutamate receptors (mGluRs), extracellular Ca^{2+} sensing receptors (CaSRs), and some pheromone as well as taste receptors.[18,19] They all possess

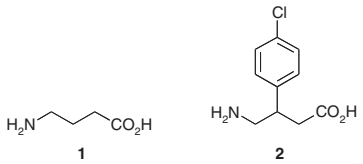

Fig. 1.

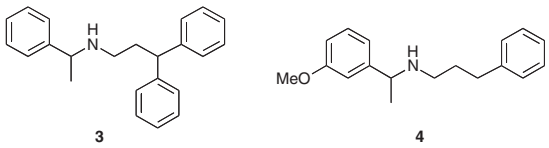

Fig. 2.

a molecular structure that is characterized by its seven transmembrane-spanning domain and a large extracellular N-terminal ligand binding domain, which contains a so-called 'Venus flytrap' ligand-binding site.[20]

Allosteric (other shape) modulation of GPCR function is now well recognized as an important feature of their pharmacology, particularly among receptors of Family 1 and Family 3.[21] Such compounds, unrelated in structure to the orthosteric ligand, have been found most often by screening techniques, and embrace negative and positive modulators of receptor function. At the molecular level, allosteric ligands are considered to combine at a site on the receptor molecule, other than that occupied by the true orthosteric ligand, and often may induce an alteration of the receptor's molecular structure in such a way as to change the

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binding of the orthosteric ligand.[22] In Family 3 receptors most, if not all, allosteric modulators bind at the heptahelical domain.

Nemeth et al.[23,24] showed that a variety of phenylalkylamines are potent allosteric modulators at extracellular CaSRs. These amines include the lead compound fendiline (*N*-[3,3-diphenylpropyl]-α-methylbenzylamine **3**; Fig. 2) and several *N*-[3-phenylpropyl]-α-methyl benzylamines, such as (**4**, NPS 467).

The ability of these new positive and negative modulators led to modelling of their binding sites at the CaSRs.[25] There is some disagreement as to the precise structure of the TM1–7 domains in the calcium-sensing receptor, but the pivotal role of the glutamate residue E837 near the top of TM7 of the heptahelical domain is generally recognized, since this acidic residue provides ionic bonding with the amine nitrogen of the phenylalkylamines. In addition, there are two hydrophobic pockets which accept the benzyl or naphthyl ring of the *N*-α-benzyl moiety and the aromatic terminal of the phenylpropyl moiety, respectively.

We have recently found that the compounds reported by Nemeth et al.[23,24] are also extremely potent positive allosteric modulators of the $GABA_B$ receptor.[26] This project aims to develop further positive allosteric modulators with high potencies and selectivity for $GABA_B$ receptors by exploring the structure–action profile of phenylalkylamines.

Results and Discussion

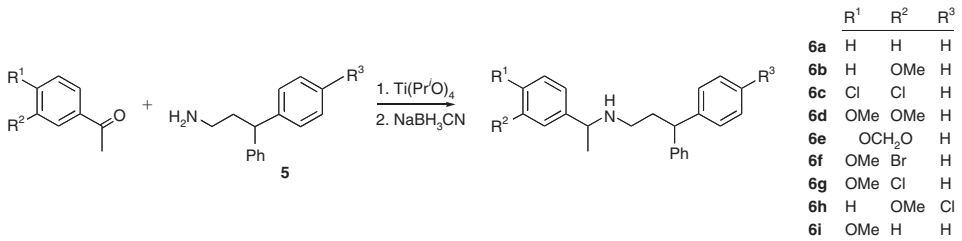
Synthesis of Analogues of N-*[3,3-Diphenylpropyl]-α-methylbenzylamine (Fendiline)*

The general synthetic procedure is essentially that of Nemeth et al.,[23,24] involving condensation of 3,3-diphenylpropylamine **5** ($R^3 = H$) with a substituted acetophenone in the presence of excess titanium isopropoxide, followed by reduction with sodium cyanoborohydride, which afforded the compounds **6a**–**6i** (Scheme 1).

The synthesis of compound **6h** required access to 3-(4-chlorophenyl)-3-phenylpropylamine **7**, and was carried out as summarized in Scheme 2. While catalytic hydrogenation of the intermediate nitrile **8** gave **7**, accompanied by partially reduced products, lithium aluminium hydride reduction was more satisfactory. Reductive alkylation of **7** with the appropriate acetophenone gave **6h** as a mixture of two diastereoisomers (13:87 ratio).

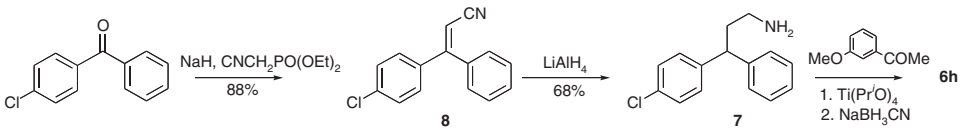
The short-chain analogues **9a** and **9b** were prepared by the general method of Barmore et al.[27] using addition of amines to the diisobutylaluminium complex derived from the nitrile **10** (Scheme 3). The required nitrile **10** was made from the corresponding chloro compound by the method of Zieger and Wo;[28] substitution with sodium cyanide was unsuccessful.

Similarly, the 'abnormal' chain length compounds **11** and **12** (Fig. 3)[24] were prepared for comparison.

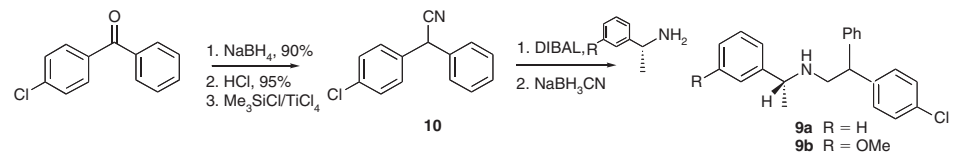


	R^1	R^2	R^3
6a	H	H	H
6b	H	OMe	H
6c	Cl	Cl	H
6d	OMe	OMe	H
6e	OCH_2O		H
6f	OMe	Br	H
6g	OMe	Cl	H
6h	H	OMe	Cl
6i	OMe	H	H

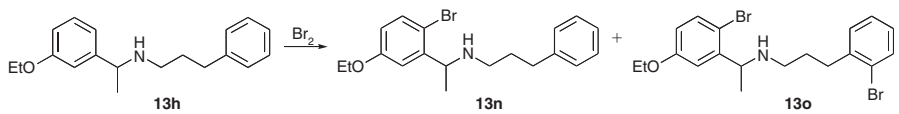
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

Synthesis of 3-Phenylpropylamine Analogues

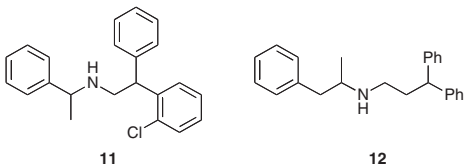
A series of compounds **13a**–**13p** (Fig. 4) was prepared as above, mostly by reductive alkylation of the 3-arylpropylamine with the corresponding acetophenone. With a view to synthesizing the brominated analogue, the corresponding acetophenone was required. Bromination of 3-methoxybenzaldehyde surprisingly gave only a single mono bromination product which was assigned the structure **14**, confirmed by a NOESY experiment which showed a correlation between the methoxy signal and H2 and H4. Alkylation of **14** with methyl lithium followed by oxidation with Jones' reagent gave 6-bromo-3-methoxyacetophenone which was used to prepare **13m**.

Interestingly, bromination of **13h** gave a mixture of **13n** and **13o** (Scheme 4); the structures were established by ^{1}H NMR analysis, COSY, NOESY, and accurate mass data. In particular, the NOESY spectrum of **13n** showed a nuclear Overhauser effect between H4 and OCH_2, H2 and OCH_2, and H2 and CH_3.

Two of the analogues in this series, fendiline **15** (Fig. 5) and the 1-naphthyl analogues **16** were prepared in both enantiomeric forms by reductive alkylation of hydrocinnamaldehyde with (*R*)-(+)- and (*S*)-(−)-α-methylbenzylamine and (*R*)-(+)- and (*S*)-(−)-1-(1-naphthyl)ethylamine respectively. Attempts to resolve the racemic **13a** with camphorsulfonyl chloride[29] were not successful; the resulting sulfonamides could not be adequately separated by chromatography. The resolution of **13a** in small quantities has been reported using chiral HPLC.[23,30]

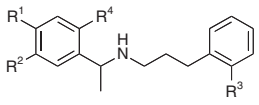
Synthesis of N-*[3-Phenylpropyl]-α-methylbenzylamines Substituted on the Nitrogen Atom*

Kerr and Ong[31] suggest that, in the $GABA_B$ receptor, an aspartic acid group at the top of transmembrane TM7 replaces the glutamic acid present in the CaSR. This acidic group would bind to the basic group of arylalkylamine, either electrostatically if it is protonated, or through hydrogen bonding.



11 **12**

Fig. 3.



	R^1	R^2	R^3	R^4
13a	H	OMe	H	H
13b	HH	Cl	H	H
13c	Cl	Cl	H	H
13d	OMe	OMe	H	H
13e	-OCH_2-		H	H
13f	H	OH	H	H
13g	OH	OMe	H	H
13h	H	OEt	H	H
13i	OMe	Cl	H	H
13j	OMe	Br	H	H
13k	H	OMe	Cl	H
13l	OMe	Cl	Cl	H
13m	Br	OMe	Cl	H
13n	H	OEt	H	Br
13o	H	OMe	Br	H
13p	H	OMe	Cl	Br

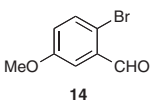


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Fig. 4.

The adjacent phenylalanine (F832, 765, or 720) could provide π-stacking for the α-methylbenzylamine (Fig. 6). The analogous CaSR site has been modelled,[32] and assumes the importance of the glutamic carboxyl group and two hydrophobic pockets, which bind to the α-methylbenzyl and phenylpropyl group.

It was noticed that potentiation of GABA by several of the above compounds was sensitive to protonation of the amino group, namely whether they were administered as the free base or hydrochloride salt, the latter being about one-third as active as the free base (see Table 1). Therefore, the environment around the nitrogen was modified to determine whether it needed an attached hydrogen atom for hydrogen bonding. This led to the synthesis of compounds **17**–**20** (Fig. 7).

Analogues with Additional Hydrogen-Bonding Potential

We have synthesized a small group of urea or amide-based analogues with the potential to bind strongly to the (aspartic) acid carboxyl group of TM7, and which would also restrict the conformation of the spacer group. Since the 1-(1-naphthyl)ethylamine and the 2-chlorophenylpropyl groups appeared to be among the most active sub-groups for the calcium modulator,[24] the ureas **21**–**23** (Fig. 8) were synthesized by the reaction of the amine with either 2-chlorophenyl isocyanate or isothiocyanate, respectively.

While **21**–**23** contained two hydrogen-bonding groups, they contained only two atoms in the spacer group, which we found to be considerably less active than three atoms.[33] Accordingly, the amides **24** and **25** appeared suitable substrates to test whether a basic nitrogen was necessary in addition to the chain length, and a comparison of the conformationally more rigid cinnamide **25** with the conformationally more mobile dihydro compound **24** would be instructive before embarking on the synthesis of more conformationally restricted analogues.

Synthesis of Shorter and Elongated Alkyl Chain Analogues of N-*[3-Phenylpropyl]-α-methylbenzylamine*

The spacing between the two aryl groups was probed by the synthesis of the higher homologues **26** and **27**, the shorter analogue **28**, and the des-methyl compounds **29** and **30** (Fig. 9).

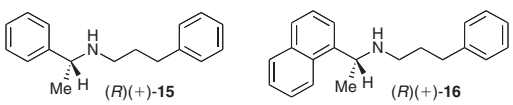

Fig. 5.

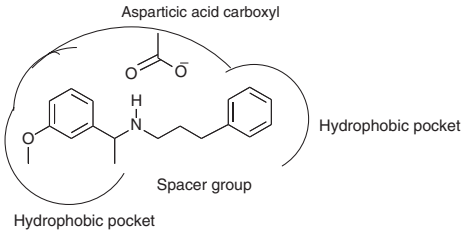

Fig. 6.

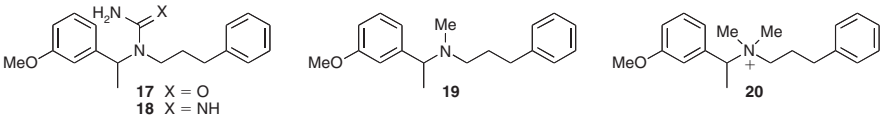

Fig. 7.

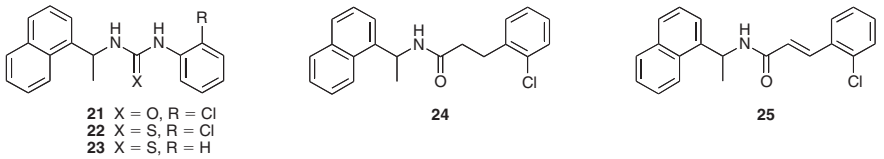

Fig. 8.

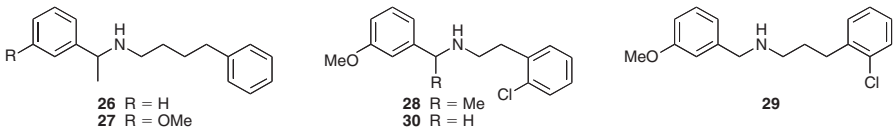

Fig. 9.

Biological Evaluation

A standard electrophysiological recording on rat brain slices was routinely used in evaluating the activities and potencies of putative allosteric modulators at $GABA_B$ receptors. The method has been previously described.[26,33,34] The compounds described above were examined for their pharmacological effects in enhancing baclofen-induced hyperpolarizing responses at $GABA_B$ post-synaptic receptors. Baclofen is a classical selective agonist at $GABA_B$ receptor sites,[15,16] and is commonly used in rat brain preparations to stimulate these receptors to induce a neuronal response. Herein we summarize the results of the effects of the test compounds in modulating baclofen-mediated function using grease gap recording in rat neocortical slices.[33–35]

Our results on the potentiating effects of the test compounds on baclofen-induced hyperpolarizing responses in rat brain slices are summarized in Tables 1–3. The responses induced by baclofen are dose-dependent, with baclofen generating an EC_{50} value of $\sim$10 μM.[34] The potencies of the various compounds are measured as their respective EC_{50} values where the EC_{50} is defined as the concentration of the drug giving a response equal to 50% of the maximally effective concentration in potentiating the baclofen response.

The results summarized in Tables 1–3 show that among all the compounds tested, 3-Cl-4-MeO-fendiline **6g** (Table 1) is still by far the most effective potentiator of $GABA_B$ receptor-mediated actions in rat brain slices, with an EC_{50} of 10 nM for the free base and an EC_{50} of 30 nM for the HCl salt. Indeed, this is the most potent and active modulator reported.[30] The potentiating actions were mediated by $GABA_B$ receptors, as the responses to baclofen were reversibly antagonized by specific $GABA_B$ receptor antagonists such as Sch 50911, and the responses to $GABA_A$ receptor agonists were not affected by the modulators examined (data not shown). The modulators when applied alone had no detectable effect on the tissues, indicating that they had no intrinsic activity at the receptor sites. In the presence of the modulators, the hyperpolarization generated by a given baclofen concentration was not only increased in amplitude, but the duration also became prolonged. This suggests that the modulators in some way prevented desensitization, and that the dissociation of the agonist was delayed by the modulator, or that the activation of the G-proteins was prolonged. In our studies, the modulator also potentiates the inhibitory effects of baclofen on the release of GABA and glutamate, through their actions at presynaptic auto and hetero-receptors. It is most probable that these effects on receptors are due to an increase in G-protein coupling, as a result of an action at the seven-transmembrane region. A most important observation, if these compounds are ever to have any clinical applications, is that they are acting as $GABA_B$-receptor potentiators at much lower concentrations than that required to modulate extracellular CaSRs.

Effect of Oxygen Substituents on Phenylethylamine Ring

Comparison of fendiline (**3** $\equiv$ **6a**) (EC_{50} 20 μM; Table 1) and its methoxylated derivative **6b** (EC_{50} 3 μM) indicates that incorporation of a *meta*-methoxy group in the phenylethylamine ring markedly increases the activity. A second methoxyl, as in 3,4-$(OMe)_2$ **6d** slightly improved the activity (EC_{50} $\sim$2 μM). However, the 3,4-OCH_2O substituent **6e** decreases the activity (EC_{50} $\sim$15 μM). This result suggests that the second alkoxy group is required mainly for the hydrophobic interaction of its alkyl group, as seen with halogen substitution (see below).

This finding is supported by comparing the activity (Table 2) of the unsubstituted phenylpropylamine (*R*-**15**; Table 2; EC_{50} 3 μM) with its hydroxylated derivative **13f** (EC_{50} > 100 μM), which suggested that introduction of a hydrophilic hydroxyl group at the *meta* position considerably decreases the activity. The 3,4-$(OMe)_2$ substituents (**13d**) again increase the activity (EC_{50} 1 μM) while the 3,4-OCH_2O group **13e** decreases the activity (EC_{50} 10 μM). The incorporation of the 3-OMe into the benzylamine ring, **13a** markedly increases the activity (EC_{50} 0.6 μM,) as was seen

Table 1. Pharmacological activity (EC_{50}) of fendiline derivatives as $GABA_B$ potentiators

All numerical data on the concentration–response curves were expressed as approximate EC_{50} values ($n = 6$–12)

Compound	Activity
6a	20 μM
6b	3 μM
6c	1 μM
6d	2 μM
6e	15 μM
6f	2 μM
6f·HCl	10 μM
6g	10 nM (0.01 μM)
6h	25 μM
6i	5 μM

Table 2. Pharmacological activity (EC_{50}) of 3-arylpropyl-1-arylethylamines as $GABA_B$ potentiators

All numerical data on the concentration–response curves were expressed as approximate EC_{50} values ($n = 6$–12)

Compound	Activity	Compound	Activity
13a	0.6 μM	**13m**	10 μM
13b	20 μM	**13n**	20 μM
13c	100 μM	**13o**	Not tested
13d	1 μM	**13p**	10 μM
13e	10 μM	(*R*)-**15**	3 μM
13f	>100 μM	(*S*)-**15**	Inactive
13g	50 μM	(*R*)-**16**	0.6 μM
13h	20 μM	(*S*)-**16**	Inactive
13i	100 nM (0.1 μM)	**17**	Inactive
13j	3 μM	**18**	Inactive
13k	0.3 μM	**19**	Inactive
13l	1 μM	**20**	ca 100 μM

Table 3. Pharmacological activity (EC_{50}) of chain-modified arylethylamines as $GABA_B$ potentiators

All numerical data on the concentration–response curves were expressed as approximate EC_{50} values ($n = 6$–12)

Compound	Activity
9a	300 μM
9b	25 μM
11	300 μM
12	50 μM
21	>100 μM
22	>100 μM
23	70 μM
26	100 μM
27	10 μM
28	30 μM
29	Inactive
30	Inactive

in the fendiline series. The further addition of a 4-hydroxyl group **13g** again leads to decrease in activity (EC_{50} 50 μM). Replacement of 3-OMe **13a** (EC_{50} 0.6 μM) with the bulkier 3-OEt group in **13h** also reduces the activity (EC_{50} 20 μM).

Effect of Introduction of Halogens

Comparison of fendiline derivatives **6b** (EC_{50} 3 μM) and **6h** (EC_{50} 25 μM) shows that the presence of a *para* chloro group in the diphenylpropyl group considerably decreases the activity, probably because of congestion in the hydrophobic pocket (Fig. 6). However, the presence of an *ortho* chloro substituent in the phenylpropylamine moiety (Table 2), as seen in comparing phenylpropylamines **13a** (EC_{50} 0.6 μM) and **13k** (EC_{50} 0.3 μM), leads to an *increase* in activity. Again, the presence of halogens in the methylbenzylamine ring generally leads to increase in activity. While bromination reduces the activity (phenylpropylamine **13j** is six times less active than phenylpropylamine **13a**, and the presence of a Br *ortho* to the alkyl group as in **13n** lead to a further reduction in activity), chlorination appears to *increase* the activity.

Fendiline itself **6a** (Table 1) has an EC_{50} of 20 μM, but the 3,4-dichloro derivative **6c** has an EC_{50} of 1 μM. The EC_{50} of 4-methoxyfendiline **6i** is 5 μM, but its 3-chloro derivative **6g** has an EC_{50} of 10 nM, and is one of the two most potent potentiators. In the phenylpropylamine series (Table 2), chlorination at C4 **13b** markedly reduces the activity (EC_{50} of 20 μM for free base and EC_{50} of 50 μM for HCl salt), as does 3,4-dichlorination **13c** (EC_{50} 100 μM), but again the most active compound was the 3-Cl 4-MeO analogue **13i**, with an EC_{50} ~100 nM.

Conformational Modelling

The lower activity of compound with the Br *ortho* to the alkylamine, **13n**, compared to that with Br *meta*, **13j**, could be considered in terms of their most favoured conformations. A conformational search of the active **13j** and less active **13n** was carried out using *Spartan* at the AM 1 level. We have arbitrarily compared the five lowest energy conformations for each compound. Two differences were apparent which might have some bearing on the differences in activity of the two isomers. Modelling of the active **13j** shows that the lone pair of the amino group was directed at right angles to the plane of the methylbenzyl ring, and the phenylpropyl group was essentially linear in the lowest five conformations. Therefore the lone pair on the nitrogen would be in the correct position for receptor (CO_2H) binding (see Fig. 6). However, the nitrogen lone pair was in the plane of the methylbenzyl ring, and the phenylpropyl chain was folded in the five lowest conformations for the less active **13n**, and these conformations might not allow for correct positioning for good receptor binding. A suitable linear conformer was significantly higher in energy. The *ortho* bromo analogue (**13p**), which has intermediate activity, but contain an *ortho* chlorine in the phenylpropylamine ring, has also been modelled in the hope that the chlorine would induce a conformational change in the lower energy conformers; however, calculations showed that **13p** has a similar conformational distribution to that of **13n**. While at this stage our analysis is not comprehensive, we propose it as a working hypothesis (see Fig. 6).

Comparison of Fendiline and Phenylpropylamine Series

Comparing 3-OMe-fendiline **6b** (EC_{50} 3 μM) with the 3-OMe-propylamine **13a** (EC_{50} 0.6 μM), and fendiline **6a** (EC_{50} 20 μM; Table 1) with the unsubstituted phenylpropylamine **15** (EC_{50} 3 μM; Table 2), clearly suggests that the phenylpropylamine series fits better at the receptor than those with two phenyl groups. However, in the two most active

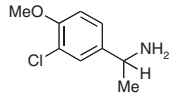

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Fig. 10.

compounds, the 3-chloro-4-methoxy derivatives, it is the fendiline **6g** (EC_{50} 10 nM) which is the more active (**13i**, EC_{50} 100 nM). The compound **13l**, bearing the best substitution pattern in the methylbenzylamine ring, and the preferred *ortho* chlorination in the phenylpropylamine ring was highly active, but its Ca^{2+} modulation now became comparable to its $GABA_B$ modulation.

Effect of Chain Length

Changing the chain length in the phenylpropyl chain in the fendiline series from three methylenes to only two as in **11** (EC_{50} 300 μM), or insertion of an extra methylene group into the α-methylbenzyl group, as in **12** (EC_{50} 50 μM) both resulted in decreasing the activity (Table 3). Likewise in the phenylpropylamine series, the addition of one methylene chain into the phenylethylamine ring as in **26** and **27** (Table 3) reduced the activity from 0.6 μM to 10 μM in the 3-methoxy series, and from 3 μM to 100 μM in the unsubstituted series. The presence of the α-methyl group was clearly desirable, as its removal in **29** and **30** (Table 3) greatly decreased activity. When the phenyl ring was replaced by a 1-naphthyl, as in **16**, the activity generally increased (Ph EC_{50} 3 μM, Naphth EC_{50} 0.6 μM), but **16** induced an oscillatory response (Table 2). A urea linkage was now introduced, resulting in a shorter chain length but a more rigid conformation (Table 3, **21**–**23**). The activity was essentially abolished, but we cannot ascertain whether this is due to the low solubility of the compounds, or that H-bonding induced binding to other sites on the protein molecule.

Effect of Substitution on Nitrogen

The simplest modification of the compounds was to compare the activity of the free base with that of its hydrochloride salt. Considering that the pH of the Krebs solution was 7.2–7.4, we had anticipated that all amines would be present as the free bases, but in all cases where both free base and hydrochloride were independently tested, there was a difference, and the hydrochloride routinely was approximately half to one third as active as the free base (Table 1, **6f**). Substitution on the nitrogen atom also had considerable bearing on activity (Table 2). Replacement of NH by NMe, N–$CONH_2$, or N–$C(NH_2)$=NH abolished the activity completely. The last two moieties were designed to possibly increase binding with an acidic group (of a Glu or Asp amino acid), assumed to be at the binding site. Surprisingly, the methiodide of the *N*-methyl derivative **20** showed some, but decreased activity.

Stereochemistry of the α-Methylbenzyl Moiety

As can be seen from Table 2, the modulatory activity of $GABA_B$ potentiators was stereoselective, *R*-isomers **15** and **21** being active while the *S*-isomers were inactive. At this stage we have not resolved the amine **31** (Fig. 10), required for the synthesis of (*R*)-**6g** or (*R*)-**13i**. However, we believe the test results for the racemic mixtures, particularly for **6g**, are indicative of activity of the *R*-enantiomers as suggested by the lack of activity of (*S*)-**15** and (*S*)-**16**.

Conclusions

The 3,3′-diarylpropyl-1-arylethylamines and 3-arylpropyl-1-arylethylamines reported herein represent a novel class of $GABA_B$ receptor modulators where they potentiate baclofen-induced responses in the brain. 3-Chloro-4-methoxyfendiline appears to be the most potent, acting at nanomolar levels (EC_{50} 10 nM). These $GABA_B$ modulators may represent a novel therapeutic strategy for the treatment of various neurological and pathological diseases mentioned previously without the side effects of full $GABA_B$ receptor agonists.

Experimental

All solvents used were freshly distilled and dried according to the methods of Perrin et al.[36] Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^1H (200 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Gemini Varian 300 spectrometer in deuterated chloroform with tetramethylsilane as internal standard, unless otherwise stated. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-infrared spectrophotometer, using fused sodium chloride cells, measured as Nujol mulls or films. Optical rotations were measured on a Polaar 21 instrument (Optical Activity) at 589.44 nm and 18°C, unless otherwise noted, and are reliable to ±1°. Reidel–de Haen Silica gel S (pH 7, granulation 32–63 mm) was used for all column chromatography. Merck silica gel 60 F 254 aluminium-backed sheets were used for analytical thin-layer chromatography. GC-MS analysis was carried out with a Varian Saturn 4D instrument using a Zebron ZB-5 5% phenyl polysiloxane column (30 m, 0.25 mm ID). Electrospray ionization mass spectra (EIMS), using a Bruker 4.7T FTMS ultra high-resolution spectrometer, reporting the $(MH)^{+\bullet}$ and some fragmentation ions, were determined at Monash University, Melbourne.

Compound **23** was prepared by a literature procedure.[37] Methods for obtaining the data in Tables 1–3 have been detailed elsewhere.[26]

*(*R,S*)-*N*-(3,3-Diphenylpropyl)-1-(3-methoxyphenyl)ethylamine* ***6b***

A mixture of 3-methoxyacetophenone (1.5 g, 10 mmol), *N*-3,3-diphenylpropylamine (2.11 g, 10 mmol), and titanium isopropoxide (2.1 g, 12.5 mmol) was stirred at room temperature under nitrogen overnight. Subsequently, sodium cyanoborohydride (0.60 g, 10 mmol) in ethanol (10 mL) was added dropwise over 2 min. The reaction mixture was stirred overnight at room temperature. Water (100 mL) was added followed by ether (250 mL). The inorganic salts were filtered off and the ether extract was collected. The aqueous phase was extracted thoroughly with ether (3 × 250 mL). The combined ether extract was dried over K_2CO_3 then concentrated under vacuum to yield a thick oil (2.85 g). The oil then was converted into the corresponding hydrochloride salt by solution in the minimum volume of ethanol, followed by the addition of concentrated hydrochloric acid and ether. The white solid hydrochloride salt was collected by vacuum filtration (2.36 g, 62%), mp. 165–168°C. (Found: $[M+H]^+$ 346.2190; $C_{24}H_{28}NO$ requires $[M]^+$ 346.2173). Hydrochloride salt: δ_H 1.68 (d, *J* 6.9, 3H), 2.63 (m, 4H), 3.85 (s, 3H), 3.93 (q, *J* 6.9, 1H), 4.06 (t, *J* 7.2, 1H), 6.86 (dd, *J* 2.2, 10.2, 1H), 7.00 (d, *J* 7.6, 1H), 7.03–7.30 (m, 12H), 9.78 (s, 1H, NH), 10.30 (s, 1H, NH). δ_C 20.6 (CH_3), 31.0 (CH_2), 44.1 (CH_2), 48.3 (CH), 55.6 (CH), 58.8 (CH_3), 112.2 (CH), 115.6 (CH), 119.9 (CH), 126.7 (CH), 126.8 (CH), 127.8 (CH), 127.9 (CH), 128.7 (CH), 128.8 (CH), 130.5 (CH), 137.4 (CH), 142.8 (C), 143.2 (C), 160.6 (C).

*(*R,S*)-*N*-(3,3-Diphenylpropyl)-1-(3,4-dichlorophenyl)ethylamine* ***6c***

A mixture of 3,4-dichloroacetophenone (1.89 g, 10 mmol), *N*-3,3-diphenylpropylamine (2.11 g, 10 mmol), and titanium isopropoxide

(3.55 g, 12.5 mmol) was reacted as above to give **6c** as a yellow oil (2.05 g, 53%) characterized as the hydrochloride salt, mp. 168–172°C. (Found: $[M+H]^+$ 384.1281; $C_{23}H_{24}{}^{35}Cl_2N$ requires $[M]^+$ 384.1280). Free base: δ_H 1.27 (d, *J* 6.4, 3H), 2.23 (m, 2H), 2.41 (m, 4H), 3.65 (q, *J* 6.4, 1H), 4.02 (t, *J* 7.6, 1H), 7.05–7.39 (m, 13H). δ_C 24.3 (CH_3), 35.9 (CH_2), 45.9 (CH_2), 48.9 (CH), 57.3 (CH), 125.9 (CH), 126.1 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 128.5 (CH), 130.2 (CH), 130.3 (CH), 132.2 (CH), 144.5 (C), 144.8 (C), 146.2 (C).

*(*R,S*)*-N-*(3,3-Diphenylpropyl)-1-(3,4-dimethoxyphenyl)ethylamine* ***6d***

A mixture of 3,4-dimethoxyacetophenone (0.90 g, 5 mmol), *N*-3,3-diphenylpropylamine (1.05 g, 5 mmol) and titanium isopropoxide (1.8 g, 6.25 mmol) was reacted as above to give **6d** as a yellow oil (0.52 g, 50%). Hydrochloride salt mp. 168–170°C. (Found: $[M+H]^+$ 376.2277; $C_{25}H_{30}NO_2$ requires $[M]^+$ 376.2271). Free base: δ_H 1.34 (d, *J* 6.4, 3H), 2.29 (m, 2H), 2.51 (m, 4H), 3.69 (q, *J* 6.4, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 4.01 (t, *J* 7.6, 1H), 6.80 (s, 1H), 6.89–7.28 (m, 12H). δ_C 24.0 (CH_3), 35.6 (CH_2), 45.7 (CH_2), 48.8 (CH), 55.6 (2 × CH_3), 57.7 (CH), 109.2 (CH), 110.7 (CH), 125.9 (CH), 127.5 (CH), 128.2 (CH), 137.7 (C), 144.4 (C), 144.6 (C), 147.6 (C), 148.7 (C).

*(*R,S*)*-N-*(3,3-Diphenylpropyl)-(3,4-methylenedioxyphenyl)-ethylamine* ***6e***

A mixture of 3,4-methylenedioxyacetophenone (0.82 g, 5 mmol), *N*-3,3-diphenylpropylamine (1.05 g, 5 mmol), and titanium isopropoxide (1.8 g, 6.25 mmol) was reacted as above to give **6e** as a yellow oil (0.59 g, 53%). Hydrochloride salt mp. 220–224°C. (Found: $[M+H]^+$ 360.1954; $C_{24}H_{26}NO_2$ requires $[M]^+$ 360.1958). Free base: δ_H 1.29 (d, *J* 6.6, 3H), 2.27 (m, 2H), 2.48 (m, 4H), 3.63 (q, *J* 6.6, 1H), 4.00 (t, *J* 7.6, 1H), 5.93 (s, 2H), 6.69 (dd, *J* 1.4, 6.8, 1H), 6.72 (d, *J* 6.8, 1H), 6.81 (d, *J* 1.2, 1H), 7.16–7.28 (m, 10H). δ_C 24.2 (CH_3), 35.8 (CH_2), 45.8 (CH_2), 48.9 (CH), 57.9 (CH), 100.8 (CH_2), 106.7 (CH), 107.9 (CH), 119.7 (CH), 126.1 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 139.4 (C), 144.5 (C), 144.8 (C), 146.3 (C), 147.6 (C).

*(*R,S*)*-N-*(3,3-Diphenylpropyl)-1-(3-bromo-4-methoxyphenyl)-ethylamine* ***6f***

A mixture of 3-bromo-4-methoxyacetophenone[38] (0.69 g, 3 mmol), 3,3-diphenylpropylamine (0.63 g, 3 mmol) and titanium isopropoxide (1.3 mL, 12.5 mmol) was reacted as above to give **6f**, isolated as the hydrochloride, mp. 132–136°C (350 mg, 26%). (Found: $[M+H]^+$ 424.1269; $C_{24}H_{27}{}^{79}BrNO$ requires $[M]^+$ 424.1271). Free base: δ_H 1.37 (d, *J* 6.6, 3H), 2.25 (m, 2H), 2.46 (m, 2H), 3.63 (q, *J* 6.6, 1H), 3.91 (s, 3H), 3.98 (t, *J* 7.2, 1H), 6.81 (d, *J* 8.4, 1H), 7.12–7.33 (m, 11H), 7.49 (d, *J* 2.0, 1H). Hydrochloride salt: δ_H 1.62 (d, *J* 6.6, 3H), 2.60 (m, 4H), 3.85 (s, 3H), 4.01 (q, *J* 7.2, 1H), 4.15 (s, 1H), 6.82 (d, *J* 8.4, 1H), 7.02–7.20 (m, 11H), 7.61 (d, *J* 2.0, 1H), 9.79 (br s, 1H, NH), 10.21 (br s, 1H, NH). δ_C 20.4 (CH_3), 31.2 (CH_2), 44.0 (CH_2), 48.3 (CH), 56.4 (CH), 57.7 (CH_3), 112.1 (C), 112.7 (CH), 126.5 (CH), 127.6 (CH), 128.1 (CH), 128.7 (CH), 129.2 (CH), 133.0 (CH), 142.7 (C), 143.2 (C), 156.6 (C).

*(*R,S*)*-N-*(3,3-Diphenylpropyl)-1-(3-chloro-4-methoxyphenyl)-ethylamine* ***6g***

A mixture of 3-chloro-4-methoxyacetophenone[38] (0.80 g, 4.33 mmol), 3,3-diphenylpropylamine (0.91, 4.33 mmol) and titanium isopropoxide (1.6 mL, 5.25 mmol) was reacted in the usual way to give **6g**, isolated as the hydrochloride salt (850 mg, 46%), mp. 192–195°C. (Found: $[M+H]^+$ 380.1774; $C_{24}H_{27}{}^{35}ClNO$ requires $[M]^+$ 380.1776). Free base: δ_H 1.30 (d, *J* 6.4, 3H), 2.27 (m, 2H), 2.46 (m, 2H), 3.66 (q, *J* 6.4, 1H), 3.86 (s, 3H), 4.05 (t, *J* 7.2, 1H), 6.85 (d, *J* 8.4, 1H), 7.09–7.35 (m, 12H). δ_C 24.2 (CH_3), 35.9 (CH_2), 45.7 (CH_2), 48.8 (CH), 55.9 (CH), 57.1 (CH_3), 111.8 (CH), 122.1 (CH), 125.6 (CH), 126.0 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 139.0 (C), 144.5 (C), 144.8 (C), 153.6 (C). Hydrochloride salt: δ_H 1.66 (d, *J* 5.6, 3H), 2.61 (br, 4H), 3.90 (s, 3H), 3.96 (br, 2H), 6.92 (d, *J* 8.0, 1H), 7.11–7.55 (m, 12H), 9.79 (br s, 1H, NH), 10.20 (br s, 1H, NH). δ_C 20.3 (CH_3), 31.1 (CH_2), 44.0 (CH_2), 48.3 (CH), 56.2 (CH), 57.8 (CH_3), 112.8 (CH), 123.0 (CH), 126.5 (CH), 126.6 (CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 128.6 (CH), 128.7 (CH), 129.9 (C), 142.7 (C), 143.2 (C), 155.7 (C).

*(*R,S*)*-N-*[3-(4-Chlorophenyl)-3-phenylpropyl]-1-(3-methoxyphenyl)-ethylamine* ***6h***

3-(4-Chlorophenyl)-3-phenylpropenonitrile ***8***

To a suspension of sodium hydride (0.72 g, 29 mmol) in dry *N*,*N*-dimethylformamide (15 mL) was added dropwise diethyl cyanomethylphosphonate (2.25 mL, 14 mmol) followed by 4-chlorobenzophenone (3 g, 14 mmol) in dry DMF (10 mL). The mixture was stirred for 10 h. Water (20 mL) was added, and the mixture was extracted with ether (3 × 25 mL). The ether extract was dried over $MgSO_4$ and then concentrated to yield a brown liquid (3.5 g) which was purified by flash silica gel column chromatography using *n*-hexane/chloroform (1/1) as eluent to give a yellow oil (2.9 g, 88%) which was shown by NMR analysis to be a 1:1 mixture of (*E*) and (*Z*) isomers of 3-(4-chlorophenyl)-3-phenylpropenonitrile.[39] (Found: $[M+1]^+$ 239.0512; $C_{15}H_{10}ClN$ requires $[M]^+$ 239.0502). δ_H 5.72 (s, 1H), 5.75 (s, 1H), 7.26–7.46 (m, 18H). δ_C 95.7 (CH), 117.9 (C), 128.7 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 129.8 (CH), 130.1 (CH), 130.5 (CH), 131.0 (CH), 131.2 (CH), 135.8 (C), 136.4 (C), 136.9 (C), 137.6 (C), 137.7 (C), 161.9 (C), 162.0 (C).

3-(4-Chlorophenyl)-3-phenylpropylamine ***7***

The nitrile **8** (1.2 g, 5.1 mmol) in ether (5 mL) was added dropwise to a stirred solution of lithium aluminium hydride (0.5 g, 13 mmol) in dry ether (30 mL) at 0°C. The mixture was refluxed for 3 h, and then was quenched cautiously with 1 M HCl. The aqueous layer was collected, neutralized with 1 M NaOH, and then extracted with ether. The ether extract was dried over Na_2SO_4 and concentrated to afford **7**, isolated as a colourless oil (450 mg, 30%). δ_H 1.79 (s, 2H, NH_2), 2.19 (q, *J* 7.8, 2H), 2.64 (t, *J* 7.6, 2H), 3.97 (t, *J* 8.0, 1H), 7.14–7.29 (m, 9H).

A mixture of 3-methoxyacetophenone (0.08 g, 0.5 mmol), amine **7** (0.13 g, 0.5 mmol), and titanium isopropoxide (0.19 g, 0.64 mmol) was reacted as above to yield a yellow oil (250 mg), which was subjected to flash silica gel column chromatography using dichloromethane/methanol (9.5/0.5) as eluent to give **6h** as a mixture (87:13) of diastereoisomers (75%). (Found $[M]^+$ 379.1707; $C_{24}H_{26}{}^{35}ClNO$ requires $[M]^+$ 379.1706). Major isomer: δ_H 1.31 (d, *J* 6.6, 3H), 2.18 (m, 2H), 2.44 (m, 2H), 3.66 (q, *J* 6.6, 1H), 3.80 (s, 3H), 3.98 (t, *J* 2.2, 1H), 6.65–6.68 (m, 3H), 7.13–7.27 (m, 10H). δ_C 24.2 (CH_3), 35.9 (CH_2), 45.8 (CH_2), 48.2 (CH), 55.2 (CH), 112.1 (CH), 118.9 (CH), 126.3 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 129.2 (CH), 131.8 (C), 143.2 (C), 143.4 (C), 144.1 (C), 144.4 (C), 147.2 (C), 159.8 (C).

*(*R,S*)*-N-*(3,3-Diphenylpropyl)-1-(4-methoxyphenyl)ethylamine* ***6i***

A mixture of 4-methoxyacetophenone (0.82 g, 5 mmol), *N*-3,3-diphenylpropylamine (1.05 g, 5 mmol), and titanium isopropoxide (5 g, 20 mmol) was reacted as above to give **6i** as a yellow oil (0.57 g, 33%). Hydrochloride salt mp. 180°C. (Found: $[M+H]^+$ 346.2198; $C_{24}H_{28}NO$ requires $[M]^+$ 346.2173). Free base: δ_H 1.34 (d, *J* 6.6, 3H), 2.30 (m, 2H), 2.48 (m, 2H), 3.72, (q, *J* 6.6, 1H), 3.80 (s, 3H), 3.95 (t, *J* 7.6, 1H), 6.86 (d, *J* 8.8, 2H), 7.21 (m, 10H),7.40 (d, *J* 8.4). δ_C 20.5 (CH_3), 31.0 (CH_2), 43.9 (CH_2), 48.3 (CH), 55.3 (CH), 58.1 (CH_3), 114.6 (CH), 126.4 (CH), 127.6 (CH), 127.7 (CH), 128.6 (CH), 129.2 (CH), 142.8 (C), 143.3 (C), 160.1 (C).

N-*[2-(4-Chlorophenyl)-2-phenylethyl]-1-(*R*)-methylbenzylamine* ***9***

1-(4-Chlorophenyl)benzyl Chloride

To a solution of 1-(4-chlorophenyl)benzyl alcohol[40] (9.9 g, 45 mmol) in ethanol (100 mL) was added concentrated hydrochloric acid (12.5 mL). The reaction mixture was refluxed overnight. The two phases were separated and the bottom layer was diluted with ether, washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and then concentrated to yield 1-(4-chlorophenyl)benzyl chloride, isolated as yellow oil (10.09 g, 95%). δ_H 5.33 (bs, 1H), 7.28–7.34 (m, 9H).

1-(4-Chlorophenyl)phenylacetonitrile

To a stirred solution of 1-(4-chlorophenyl)benzyl chloride (1.19 g, 5 mmol) and trimethylsilyl cyanide (0.50 g, 5 mmol) in dry dichloromethane (25 mL) was added titanium tetrachloride (0.5 mL) dropwise at 0°C. After 2 h, the reaction mixture was quenched with methanol (10 mL) and the product was extracted with dichloromethane. The organic phase was washed with water, 10% $NaHCO_3$, water, dried over Na_2SO_4, and then concentrated to yield an orange oil (0.92 g, 81%) which was purified by silica gel column chromatography with *n*-hexane/chloroform (50/50) as eluent to yield 1-(4-chlorophenyl)phenylacetonitrile as a white solid (0.53 g), mp. 70°C (lit[41] mp. 74–75°C). δ_H 5.12 (s, 1H), 7.29–7.39 (m, 9H). δ_C 41.9 (CH), 119.2 (C), 127.6 (CH), 128.5 (CH), 129.1 (CH), 129.3 (CH), 129.3 (C), 134.4 (C), 135.4 (C).

To a solution of 1-(4-chlorophenyl)phenylacetonitrile (0.11 g, 0.5 mmol) in dry dichloromethane (1 mL) was added dropwise 1.5 M diisobutylaluminium hydride (0.4 mL) at −78°C. The mixture was stirred at room temperature for 3 h and then cooled to 0°C. (*R*)-(+)-α-methylbenzylamine (0.26 mL, 1 mmol) was added and the reaction mixture was stirred at 0°C for 3 h, then added to a solution of sodium borohydride (0.03 g, 5 mmol) in ethanol (0.5 mL) and the reaction mixture was stirred at room temperature for 1 h. The solution then was quenched with 10% hydrochloric acid (0.5 mL), neutralized with 1 M sodium hydroxide (0.5 mL) and then extracted with ether (3 × 5 mL). The combined organic extracts were washed with water (3 × 1 mL), dried over $MgSO_4$, and concentrated to yield a yellow oil (0.3 g) which was purified by preparative thin layer chromatography on alumina using *n*-hexane/chloroform (1/9) as eluent to give compound (**9**) (0.15 g) as a yellow oil. (Found: $[M + H]^+$ 336.1515; $C_{22}H_{22}{}^{35}ClN$ requires $[M + H]^+$ 336.1519). δ_H 1.29 (d, *J* 7.8, 3H), 1.40 (bs, 1H, NH), 3.06 (m, 2H), 3.77 (q, *J* 7.8, 1H), 4.13 (t, *J* 7.2, 1H), 7.02–7.38 (m, 13H). δ_C 24.3 (CH_3), 50.7 (CH_2), 52.2 (CH), 58.4 (CH), 57.7 (CH), 132.2 (CH), 141.3 (CH), 141.7 (C), 142.2 (C), 142.7 (C), 145.4 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(3-methoxyphenyl)ethylamine* ***13a***

A mixture of 3-methoxyacetophenone (1.50 g, 10 mmol), 3-phenylpropylamine (1.35 g, 10 mmol), and titanium isopropoxide (3.55 g, 12.5 mmol) was reacted in the usual way to yield **13a** as a colourless oil (1.58 g, 59%). Free base: δ_H 1.37 (d, *J* 6.6, 3H), 1.82 (m, 2H), 2.60 (m, 4H), 3.75 (q, *J* 6.6, 1H), 3.81 (s, 3H), 6.79 (qd, *J* 1.8, 4.6, 1H), 6.90–6.93 (m, 2H), 7.17–7.32 (m, 6H). δ_C 24.2 (CH_3), 31.8 (CH_2), 33.6 (CH_2), 47.3 (CH_2), 55.1 (CH), 58.3 (CH_3), 112.2 (CH), 119.0 (CH), 125.7 (CH), 128.2 (CH), 128.3 (CH), 129.3 (CH), 142.1 (C), 147.5 (C), 159.8 (C).

The free base was converted to its hydrochloride salt, isolated as a white solid, mp. 118°C. (Found: $[M + 1]^+$ 270.1845; $C_{18}H_{24}NO$ requires $[M]^+$ 270.1858). Hydrochloride salt: δ_H 1.82 (d, *J* 6.6, 3H), 2.20 (m, 2.51, t, *J* 7, 2H), 2.64 (t, *J* 7, 2H), 3.86 (s, 3H), 4.11 (t, *J* 6.6,1H), 6.88 (dd, *J*, 1H), 7.04–7.33 (m, 8H), 9.78 (s, 1H, NH), 10.17 (s, 1H, NH). δ_C 20.5 (CH_3), 27.2 (CH_2), 32.6 (CH_2), 45.1 (CH_2), 55.6 (CH), 59.1 (CH_3), 112.3 (CH), 115.6 (CH), 119.9 (CH), 126.1 (CH), 128.3 (CH), 130.3 (CH), 137.5 (C), 139.9 (C), 160.4 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(4-chlorophenyl)ethylamine* ***13b***

A mixture of 4-chloroacetophenone (1.54 g, 10 mmol), 3-phenylpropylamine (1.35 g, 10 mmol), and titanium isopropoxide (3.55 g, 12.5 mmol) was reacted as above to yield **13b** as a yellow oil (1.20 g, 44%). The corresponding hydrochloride salt was obtained as a white solid, mp. 160–164°C. (Found: $[M + 1]^+$ 274.1369; $C_{17}H_{21}ClN$ requires $[M]^+$ 274.1363). Free base: δ_H 1.32 (d, *J* 6.8, 3H), 1.78 (q, *J* 7.8, 2H), 2.55 (m, 4H), 3.73 (q, *J* 6.8, 1H), 7.10–7.28 (m, 9H). δ_C 24.3 (CH_3), 31.8 (CH_2), 33.6 (CH_2), 47.2 (CH_2), 57.7 (CH), 125.7 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 132.3 (C), 142.0 (C), 144.3 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(3,4-dichlorophenyl)ethylamine* ***13c***

A mixture of 3,4-dichloroacetophenone (1.89 g, 10 mmol), 3-phenylpropylamine (1.35 g, 10 mmol), and titanium isopropoxide (3.55 g, 12.5 mmol) was reacted as above to give **13c** as a yellow oil (1.70 g, 55%). The corresponding hydrochloride salt was obtained as a white solid, mp. 128–130°C. (Found: $[M + H]^+$ 308.0968; $C_{17}H_{20}{}^{35}Cl_2N$ requires $[M]^+$ 308.0967). Free base: δ_H 1.33 (d, *J* 6.6, 3H), 1.81 (quin, *J* 7.4, 2H), 2.51 (m, 2H), 2.66 (m, 2H), 3.73 (q, *J* 6.6, 1H), 7.15–7.47 (m, 8H). δ_C 24.3 (CH_3), 31.7 (CH_2), 33.4 (CH_2), 47.1 (CH_2), 57.4 (CH), 125.7 (CH), 126.0 (CH), 128.2 (2 × CH), 128.5 (CH), 130.2 (C), 132.2 (C), 141.9 (C), 146.4 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(3,4-dimethoxyphenyl)ethylamine* ***13d***

A mixture of 3,4-dimethoxyacetophenone (1.80 g, 10 mmol), 3-phenylpropylamine (1.35 g, 10 mmol), and titanium isopropoxide (3.55 g, 12.5 mmol) was reacted as above to give **13d** as a pale yellow oil (1.72 g, 58%). The corresponding hydrochloride salt was obtained as a white solid, mp. 176–177°C. (Found: $[M + H]^+$ 300.1955; $C_{19}H_{26}NO_2$ requires $[M]^+$ 300.1958). Free base: δ_H 1.34 (d, *J* 6.4, 3H), 1.81 (quin, *J* 7.8, 2H), 2.55 (m, 4H), 3.70 (q, *J* 6.4, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 6.80 (d, *J* 1.0, 2H), 6.87 (s, 1H), 7.11–7.26 (m, 5H). δ_C 23.9 (CH_3), 31.3 (CH_2), 33.5 (CH_2), 47.0 (CH_2), 55.8 (2 × CH_3), 58.1 (CH), 109.4 (CH), 110.8 (CH), 118.8 (CH), 125.7 (CH), 128.2 (CH), 137.4 (C), 141.9 (C), 147.9 (C), 149.0 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(3,4-methylenedioxyphenyl)-ethylamine* ***13e***

A mixture of 3,4-methylenedioxyacetophenone (1.64 g, 10 mmol), 3-phenylpropylamine (1.35 g, 10 mmol), and titanium isopropoxide (3.55 g, 12.5 mmol) was reacted as above to yield **13e** as a pale yellow oil (1.10 g, 39%). The corresponding hydrochloride salt was obtained as a white solid, mp. 188–190°C. (Found: $[M + H]^+$ 284.1641; $C_{18}H_{22}NO_2$ requires $[M]^+$ 284.1645). Free base: δ_H 1.36 (d, *J* 6.4, 3H), 1.83 (quin, *J* 7.4, 2H), 2.53 (m, 2H), 2.66 (m, 2H), 3.72 (q, *J* 6.4, 1H), 5.93 (s, 2H), 6.78 (d, *J* 1.0, 2H), 6.91 (s, 1H), 7.17–7.30 (m, 5H). δ_C 24.1 (CH_3), 31.5 (CH_2), 33.4 (CH_2), 46.9 (CH_2), 57.9 (CH), 100.6 (CH_2), 106.5 (CH), 107.8 (CH), 119.6 (CH), 125.5 (CH), 128.1 (CH), 139.4 (C), 141.9 (C), 146.2 (C), 147.6 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(3-hydroxyphenyl)ethylamine* ***13f***

A mixture of 3-hydroxyacetophenone (0.68 g, 5 mmol), 3-phenylpropylamine (0.70 g, 5 mmol), and titanium isopropoxide (1.85 mL, 6.25 mmol) was reacted as above to yield **13f** as a white solid (0.69 g, 47%), mp. 90–94°C. (Found $[M + H]^+$ 256.1696; $C_{17}H_{22}NO$ requires $[M]^+$ 256.1696). δ_H 1.35 (d, *J* 6.6, 3H), 1.81 (quin, *J* 7.2, 2H), 2.56 (m, 4H), 3.72 (q, *J* 6.6, 1H), 4.99 (bs, OH), 6.71–6.84 (td, *J* 7.4, 4.4, 3H), 7.10 (m, 6H). δ_C 22.9 (CH_3), 30.7 (CH_2), 33.4 (CH_2), 46.9 (CH_2), 58.2 (CH), 113.3 (CH), 115.1 (CH), 119.0 (CH), 125.8 (CH), 128.3 (CH), 129.7 (CH), 141.6 (C), 145.3 (C), 157.0 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(4-hydroxy-3-methoxyphenyl)-ethylamine* ***13g***

A mixture of 4-hydroxy-3-methoxyacetophenone (0.83 g, 5 mmol), 3-phenylpropylamine (0.70 g, 5 mmol), and titanium isopropoxide (1.85 mL, 6.25 mmol) was reacted as above to obtain **13g** as a white solid (0.65 g, 45%), mp. 142–143°C. (Found: $[M + 1]^+$ 286.1810; $C_{18}H_{24}NO_2$ requires $[M]^+$ 286.1807). δ_H 1.36 (d, *J* 6.6, 3H), 1.81 (quin, *J* 7.2, 2H), 2.56 (m, 4H), 3.71 (q, *J* 6.6, 1H), 3.89 (s, 3H), 6.75 (dd, *J* 1.8, 8.0, 1H), 6.85 (d, *J* 8.0, 1H), 7.11–7.27 (m, 5H). δ_C 23.9 (CH_3), 31.3 (CH_2), 33.6 (CH_2), 47.1 (CH_2), 55.9 (CH), 58.2 (CH_3), 108.8 (CH), 114.1 (CH), 119.6 (CH), 125.8 (CH), 128.3 (CH), 136.6 (C), 141.9 (C), 144.7 (C), 146.7 (C).

*(*R,S*)*-N-*(3-Phenylpropyl)-1-(3-ethoxyphenyl)ethylamine* ***13h***

A mixture of 3-ethoxyacetophenone[24] (0.70 g, 5 mmol), 3-phenylpropylamine (0.70 g, 5 mmol), and titanium isopropoxide (1.85 mL, 6.25 mmol) was reacted as above to afford **13h** as a yellow oil (0.62 g, 44%). (Found: $[M + 1]^+$ 284.2018; $C_{19}H_{26}NO$ requires $[M]^+$ 284.2014). δ_H 1.39 (d, *J* 6.6, 3H), 1.46 (t, *J* 7.2, 3H), 1.84 (m, 2H), 2.62 (m, 4H), 3.76 (q, *J* 6.6, 1H), 4.08 (q, *J* 7.2, 2H), 6.81–6.86 (m, 1H),

6.91–6.95 (m, 2H), 7.18–7.31 (m, 6H). δ_C 14.8 (CH_3), 24.2 (CH_3), 31.8 (CH_2), 33.5 (CH_2), 47.2 (CH_2), 58.2 (CH), 63.1 (CH_2), 112.5 (CH), 112.6 (CH), 118.7 (CH), 125.6 (CH), 128.2 (CH), 129.2 (CH), 142.1 (C), 147.4 (C), 159.0 (C).

*(*R,S*)-*N*-(3-Phenylpropyl)-1-(3-chloro-4-methoxyphenyl)-ethylamine* ***13i***

A mixture of 3-chloro-4-methoxyacetophenone (0.76 g, 4.11 mmol), 3-phenylpropylamine (0.55 g, 4.11 mmol), and titanium isopropoxide (0.57 g, 5.25 mmol) was reacted as above to produce **13i** as a yellow oil (0.58 g, 48%). The corresponding hydrochloride salt was obtained as a white solid, mp. 145–148°C. (Found: $[M + H]^+$ 304.1460; $C_{18}H_{23}{}^{35}ClNO$ requires $[M]^+$ 304.1463). Free base: δ_H 1.31 (d, *J* 6.6, 3H), 1.78 (m, 2H), 2.57 (m, 4H), 3.68 (q, *J* 6.6, 1H), 3.89 (s, 3H), 6.88 (d, *J* 8.4, 1H), 7.13–7.33 (m, 8H). δ_C 24.1 (CH_3), 31.6 (CH_2), 33.6 (CH_2), 47.1 (CH_2), 56.2 (CH), 57.4 (CH_3), 112.1 (CH), 122.4 (CH), 125.8 (CH), 128.3 (CH), 128.5 (CH), 138.8 (C), 141.1 (C), 142.1 (C), 153.9 (C).

*(*R,S*)-*N*-(3-Phenylpropyl)-1-(3-bromo-4-methoxyphenyl)-ethylamine* ***13j***

A mixture of 3-bromo-4-methoxyacetophenone (0.68 g, 3.0 mmol), 3-phenylpropylamine (0.40 g, 3.0 mmol), and titanium isopropoxide (1.3 mL, 4.25 mmol) was reacted as above to yield **13j** as a colourless oil (0.55 g, 53%). The corresponding hydrochloride salt was obtained as a white solid, mp. 157–160°C. (Found: $[M + H]^+$ 348.0958; $C_{18}H_{23}{}^{79}BrNO$ requires $[M]^+$ 348.0958). Free base: δ_H 1.31 (d, *J* 6.6, 3H), 1.78 (m, 2H), 2.57 (m, 4H), 3.68 (q, *J* 6.6, 1H), 3.89 (s, 3H), 6.88 (d, *J* 8.4, 1H), 7.13–7.33 (m, 8H). δ_C 24.1 (CH_3), 31.6 (CH_2), 33.6 (CH_2), 47.1 (CH_2), 56.2 (CH), 57.4 (CH_3), 112.1 (CH), 122.4 (CH), 125.8 (CH), 128.3 (CH), 128.5 (CH), 138.8 (C), 141.1 (C), 142.1 (C), 153.9 (C).

*(*R,S*)-*N*-[3-(2-Chlorophenyl)propyl]-(3-methoxyphenyl)-ethylamine* ***13k***

N-3-(2-Chlorophenyl)propylamine

To a stirred solution of aluminium hydride (1.0 g, 26 mmol) in dry ether (50 mL) at 0°C was added dropwise 2-chlorocinnamonitrile (2.0 g, 12 mmol) in ether (10 mL). The reaction mixture was refluxed for 4 h. The mixture was cooled to 0°C and 1 M hydrochloric acid was added slowly. The aqueous layer was neutralized with 1 M NaOH and extracted with ether. The ether layer was dried over Na_2SO_4 and concentrated to yield *N*-3-(2-chlorophenyl)propylamine as a pale yellow oil (2.01 g, 98%). δ_H 1.54 (bs, 2H, NH_2), 1.72 (m, 2H), 2.72 (m, 4H), 7.04–7.30 (m, 4H). δ_C 30.7 (CH_2), 33.3 (CH_2), 41.7 (CH_2), 126.6 (CH), 127.0 (CH), 129.2 (CH), 130.1 (CH), 133.7 (C), 139.6 (C).

A mixture of 3-methoxyacetophenone (0.75 g, 5.0 mmol), 3-(2-chlorophenyl)propylamine (0.85 g, 5.0 mmol), and titanium isopropoxide (1.80 g, 6.25 mmol) was reacted as above to yield **13k** as a yellow oil (250 mg, 24%). The corresponding hydrochloride salt was obtained as a white solid, mp. 135–140°C. (Found: $[M + 1]^+$ 304.1473; $C_{18}H_{23}ClNO$ requires $[M]^+$ 304.1468). Free base: δ_H 1.36 (d, *J* 6.6, 3H), 1.80 (m, 2H), 2.54 (m, 2H), 2.75 (m, 2H), 3.78 (q, *J* 6.6, 1H), 3.81 (s, 3H), 6.77 (dd, *J* 1.2, 3.4, 1H), 6.90 (dd, *J* 2.4, 5.6, 2H), 7.11–7.33 (m, 5H). δ_C 23.6 (CH_3), 29.3 (CH_2), 31.1 (CH_2), 46.8 (CH_2), 55.2 (CH), 58.4 (CH_3), 112.1 (CH), 119.2 (CH), 126.7 (CH), 127.3 (CH), 129.5 (CH), 130.3 (CH), 133.9 (C), 139.4 (C), 145.8 (C), 159.8 (C).

*(*R,S*)-*N*-[3-(2-Chlorophenyl)propyl]-1-(3-chloro-4-methoxyphenyl)-ethylamine* ***13l***

A mixture of 3-chloro-4-methoxyacetophenone (0.37 g, 2.0 mmol), 3-(2-chlorophenyl)propylamine (0.34 g, 2.0 mmol), and titanium isopropoxide (0.9 mL, 3 mmol) was reacted as above to yield **13l** as a pale yellow oil (250 mg, 37%). The corresponding hydrochloride salt was obtained as a white solid, mp. 198–200°C. (Found: $[M + H]^+$ 338.1072; $C_{18}H_{22}{}^{35}Cl_2NO$ requires $[M]^+$ 338.1073). Free base: δ_H 1.34 (d, *J* 6.6, 3H), 1.79 (m, 2H), 2.51 (m, 2H), 2.72 (m, 2H), 3.71 (q, *J* 6.6, 1H), 3.89 (s, 3H), 6.88 (d, *J* 8.4, 1H), 7.11–7.30 (m, 5H), 7.34 (d, *J* 2.2, 1H). δ_C 24.1 (CH_3), 29.8 (CH_2), 31.2 (CH_2), 47.0 (CH_2), 56.1 (CH), 57.3 (CH_3), 112.0 (CH), 122.3 (C), 125.9 (CH), 126.7 (CH), 127.2 (CH), 128.4 (CH), 129.4 (CH), 130.3 (CH), 133.8 (C), 138.5 (C), 139.5 (C), 153.8 (C).

*(*R,S*)-*N*-[3-(2-Chlorophenyl)propyl]-1-(6-bromo-3-methoxyphenyl)-ethylamine* ***13m***

A mixture of 6-bromo-3-methoxyacetophenone (0.69 g, 3.0 mmol), 3-(2-chlorophenyl)propylamine (0.51 g, 3.0 mmol), and titanium isopropoxide (1.3 mL, 4.25 mmol) was reacted as above to yield **13m** as a yellow oil (0.47 g, 43%). The corresponding hydrochloride salt was obtained as a white solid, mp. 144–146°C. (Found: $[M + H]^+$ 382.0571; $C_{18}H_{22}{}^{79}BrNO^{35}Cl$ requires $[M]^+$ 382.0568). Free base: δ_H 1.39 (d, *J* 6.6, 3H), 1.87 (m, 2H), 2.65 (m, 4H), 3.81 (s, 3H), 4.30 (q, *J* 6.6, 1H), 6.69 (dd, *J* 3.2, 12.1, 1H), 7.10–7.33 (m, 5H), 7.40 (d, *J* 8.8, 1H). δ_C 22.6 (CH_3), 29.8 (CH_2), 31.1 (CH_2), 46.9 (CH_2), 55.3 (CH), 56.7 (CH_3), 112.7 (CH), 113.8 (C), 114.2 (CH), 126.6 (CH), 129.2 (CH), 130.1 (CH), 133.2 (CH), 133.7 (C), 139.5 (C), 144.8 (C), 159.3 (C).

Bromination of ***13h***

A solution of bromine (25 μL) in carbon tetrachloride (1 mL) was added slowly with stirring to a solution of **13h** (141 mg) in carbon tetrachloride (1 mL) at room temperature. After 2 h, the solvent was evaporated, 1 M NaOH (2 mL) was added, and the mixture extracted with ether (3 × 10 mL), and the dried extract evaporated to give a yellow oil (240 mg) which was purified by chromatography (hexane/dichloromethane) to give three fractions. The first (40 mg) was identified as the reactant. The second fraction was a yellow oil (50 mg), identified as the mono brominated product **13n**. (Found: $[M + 1]^+$ 362.1114; $C_{19}H_{25}{}^{79}BrNO$ requires $[M]^+$ 362.1120). δ_H 1.45 (t, *J* 7, 3H), 1.85 (d, *J* 6, 3H), 2.4 (m, 6H), 4.05 (q, *J* 7, 2H), 4.31 (q, *J* 6, 1H), 6.68 (dd, *J* 3, 8, 1H), 7.00 (d, *J* 3, 1H), 7.1–7.3 (m, 5H), 7.40 (d, *J* 8, 1H). A nOe was observed between the quartet at δ 4.05 and the triplet at δ 1.45, and the doublets at δ 6.68 and 7.00.

The third fraction (20 mg) was the dibromo compound **13o**, isolated as a yellow oil. (Found: $[M + 1]^+$ 440.0228; $C_{19}H_{24}{}^{79}Br_2NO$ requires 440.0225).

*(*R*)-*N*-(3-Phenylpropyl)-1-phenylethylamine* ***15***

A mixture of (*R*)-α-methylbenzylamine (0.60 g, 5 mmol), 3-phenylpropanal (0.67 g, 5 mmol), and titanium isopropoxide (1.065 g, 6.25 mmol) was reacted as above to yield (*R*)-**15** as yellow oil (0.50 g, 49%). δ_H 1.40 (d, *J* 6.8, 3H), 1.83 (quin, *J* 7.2, 2H), 2.58 (m, 4H), 3.80 (q, *J* 6.8, 1H), 7.15–7.36 (m, 10H). δ_C 23.2 (CH_3), 30.5 (CH_2), 33.8 (CH_2), 46.7 (CH_2), 58.5 (CH), 125.8 (CH), 126.9 (CH), 127.5 (CH), 128.3 (CH), 128.7 (CH), 141.5 (C), 145.2 (C).

The (*S*)-enantiomer was obtained in the same way from (*S*)-α-methylbenzylamine.

*(*R*)-*N*-(3-Phenylpropyl)-1-(1-napthyl)ethylamine* ***16***

A mixture of *R*-α-(1-naphthyl)ethylamine (0.40 mL, 2.5 mmol), 3-phenylpropanal (0.33 mL, 2.5 mmol), and titanium isopropoxide (0.53 g, 3.25 mmol) was reacted as above to yield pure (*R*)-**16** as a yellow oil (650 mg, 90%). The free base was converted to the corresponding hydrochloride salt, mp. 130–138°C. (Found: $[M + 1]^+$ 290.1920; $C_{21}H_{24}N$ requires $[M]^+$ 290.1909). Free base: δ_H 1.56 (d, *J* 6.8, 3H), 1.90 (quin, *J* 7.4, 2H), 2.63 (m, 4H), 4.71 (q, *J* 6.8, 1H), 7.10–7.28 (m, 3H), 7.46–7.56 (m, 4H), 7.72–7.79 (m, 2H), 7.86–7.91 (m, 2H), 8.12 (d, *J* 9.6, 1H). δ_C 23.2 (CH_3), 31.2 (CH_2), 33.5 (CH_2), 47.2 (CH_2), 53.6 (CH), 122.7 (CH), 123.1 (CH), 125.4 (CH), 125.6 (CH), 125.8 CH), 125.9 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 129.4 (C), 131.2 (C), 133.9 (C), 141.8 (ArC).

The (*S*)-enantiomer was obtained in the same way.

*(*R,S*)-*N*-(3-Phenylpropyl)-N-[1-(3-methoxyphenyl)ethyl]Urea* ***17***

A solution of NPS 467 **13a** (0.27 g, 1 mmol) in glacial acetic acid (0.5 mL) and water (0.5 mL) was treated dropwise with sodium cyanate

(0.13 g, 2 mmol) in water (1 mL) at 35°C. The reaction mixture was stirred overnight, cooled to 0°C and extracted with ether. The extract was washed with saturated aqueous Na_2CO_3, dried over Na_2SO_4, and concentrated to yield a glass (0.14 g, 45%), which could not be induced to crystallize. (Found: $[M + H]^+$ 313.1906; $C_{19}H_{25}N_2O_2$ requires $[M]^+$ 313.1911). δ_H 1.49 (d, *J* 7.2, 3H), 1.74 (dd, *J* 2.0, 6.1, 2H), 2.49 (t, *J* 7.2, 2H), 2.98 (m, 2H), 3.79 (s, 3H), 5.44 (q, *J* 7.2, 1H), 6.82 (m, 3H), 7.08 (dd, *J*, 2H), 7.26 (m, 4H). δ_C 17.3 (CH_3), 30.9 (CH_2), 33.2 (CH_2), 43.3 (CH_2), 53.0 (CH), 55.3 (CH_3), 112.5 (CH), 113.2 (CH), 112.1 (CH), 119.4 (CH), 126.1 (CH), 128.3 (CH), 128.5 (CH), 129.5 (CH), 140.9 (C), 143.1 (C), 158.6 (C), 159.8 (CO). ν_{max} (KBr/cm^{-1}) 3359 (br), 1650, 1257.

N-*[1-(3-Methoxyphenyl)ethyl]*-N-*(3-phenylpropyl)guadinium Sulfate* ***18***

A mixture of **13a** (0.27 g, 1 mmol), and *S*-methylisothiouronium sulfate (0.14 g, 0.5 mmol) in ethanol (5 mL) and water (5 mL) was refluxed for 3 h. The solvent was then evaporated to give a colourless gel (0.150 g), which was triturated with acetone to yield **18** in the acetone-soluble fraction as a pale yellow gel. (Found: $[M + H]^+$ 312.2080; $C_{19}H_{26}N_3O$ requires $[M]^+$ 312.2143). δ_H 1.91 (d, *J* 6.8, 3H), 2.30 (m, 2H), 2.62 (t, *J* 6.8, 2H), 2.84 (m, 2H), 3.95 (s, 3H), 4.35 (q, *J* 6.6, 1H), 7.05 (dd, *J* 2.2, 2.4, 1H), 7.20–7.38 (m, 7H), 7.39–7.45 (d, *J* 1.2, 1H). δ_C 20.3 (CH_3), 26.7 (CH_2), 32.5 (CH_2), 44.8 (CH_2), 55.3 (CH), 58.1 (CH_3), 113.2 (CH), 114.3 (CH), 119.9 (CH), 125.9 (CH), 128.3 (CH), 130.1 (CH), 138.4 (C), 140.4 (C), 160.1 (C), 161.9 (C), 163.4 (C).

Reaction of ***13a*** *with Methyl Iodide*

A solution of **13a** (0.30 g, 1 mmol) and methyl iodide (0.07 mL, 1.25 mmol) in dichloromethane (5 mL) was stirred at room temperature for 52 h. The solution was diluted with ether to yield a yellow gel (0.33 g). Crystallization from acetone/ether gave a white powder which was found to be a mixture of the *N*-methylated hydroiodide and the *N*,*N*-dimethyl quaternary salt. The two products were separated by addition of aqueous sodium hydroxide followed by extraction with dichloromethane. The dichloromethane extract was evaporated and the residue was extracted with ether to yield **19** as a thick yellow oil (100 mg) and the ether insoluble fraction was found to be the quaternary salt **20**, isolated as a white powder (100 mg), mp. 110–114°C.

N-*Methyl*-N-*(3-phenylpropyl)-1-(3-methoxyphenyl)ethylamine* ***19***

(Found: $[M + 1]^+$ 284.2013; $C_{19}H_{26}NO$ requires $[M]^+$ 284.2009). δ_H 1.39 (d, *J* 6.8, 3H), 1.84 (m, 2H), 2.22 (s, 3H), 2.40 (m, 2H), 2.62 (m, 2H), 3.59 (q, *J* 6.8, 1H), 3.81 (s, 3H), 6.78 (dd, *J* 2.2, 2.2, 1H), 6.90 (m, 2H), 7.10–7.30 (m, 6H). δ_C 18.4 (CH_3), 28.6 (CH_2), 33.5 (CH_2), 38.3 (CH_2), 53.8 (CH_3), 55.2 (CH), 63.6 (CH_3), 112.3 (C), 113.4 (CH), 120.2 (CH), 125.7 (CH), 128.3 (CH), 129.1 (CH), 142.3 (C), 159.6 (C).

N,N-*Dimethyl*-N-*(3-phenylpropyl)-1-(3-methoxyphenyl)-ethylammonium Iodide* ***20***

(Found: $[M]^+$ 298.2167; $C_{20}H_{28}NO$ requires $[M]^+$ 298.2165). δ_H 1.74 (d, *J* 6.8, 3H), 2.14 (quin, *J* 7.2, 2H), 2.77 (q, *J* 7.6, 2H), 3.17 (s, 3H), 3.19 (s, 3H), 3.53 (m, 2H), 3.85 (s, 3H), 3.52 (q, *J* 6.8, 1H), 6.96 (dd, *J* 2.2, 2.2, 1H), 7.09 (d, *J* 12.6, 1H), 7.19–7.39 (m, 7H). δ_C 15.2 (CH_3), 24.8 (CH_2), 32.3 (CH_2), 48.0 (CH_3), 48.7 (CH_3), 55.8 (CH_2), 61.9 (CH), 72.9 (CH_3), 116.1 (CH), 116.8 (CH), 126.8 (CH), 128.5 (CH), 128.9 (CH), 130.5 (CH), 133.4 (C), 139.2 (C), 160.1 (C).

N-*2-Chlorophenyl*-N′-*1-(1-naphthyl)ethyl Urea* ***21***

2-Chlorophenyl isocyanate (460 mg, 3 mmol) was added dropwise to a solution of 1-(1-naphthyl)-ethylamine (473 μL, 3 mmol) in dichloromethane (5.5 mL) at room temperature, and stirred for 1 h. The solvent was removed and the residue recrystallized from ethyl acetate to give **21** as white needles (700 mg, 72%), mp. 195–196°C. (Found: $[M^+]$ 324.1020; $C_{19}H_{17}ClN_2O$ requires $[M]^+$ 324.1029). δ_H (DMSO) 1.60 (d, *J* 6.5, 3H), 5.70 (q, *J* 6.5, 1H), 6.97 (dt, *J* 7.2, 0.9, 1H), 7.25 (dt, *J* 7.2, 0.9, 1H), 7.42 (dt, *J* 8.5, 0.8, 1H), 7.60 (m, 4H), 7.71 (d, *J* 10, 1H), 7.89 (d, *J* 10, 1H), 8.0 (dd, *J* 9.5, 1.0, 1H), 8.20 (d, *J* 9, 1H). δ_C (DMSO) 23.1, 45.7, 121.2, 121.8, 123.0, 123.3, 124.0, 126.5, 126.6, 127.2, 128.3, 128.4, 129.6, 130.0, 131.2, 134.4, 137.6, 141.4, 154.8.

N-*2-Chlorophenyl*-N′-*1-(1-naphthyl)ethyl Thiourea* ***22***

The use of 2-chlorophenyl isothiocyanate, as above, gave **22** as white crystals (61%) from ethyl acetate, mp. 162–164°C. (Found: $[M]^+$ 340.0812; $C_{19}H_{17}ClN_2S$ requires $[M]^+$ 340.0801). δ_H (DMSO) 1.67 (d, *J* 6.6, 3H), 6.28 (m, 1H), 7.22 (t, *J* 8.1, 1H), 7.33 (t, *J* 7.5, 1H), 7.50 (d, *J* 8.1, 1H), 7.55–7.65 (m, 4H), 7.85 (d, *J* 6.9, 1H), 7.92 (d, *J* 7.8, 1H), 8.01 (d, *J* 8.1, 1H), 8.21 (d, *J* 8.1, 1H), 8.64 (d, *J* 8.1, 1H), 9.05 (br s, 1H), 8.64 (d, *J* 8.1, 1H). δ_C (DMSO) 21.4, 50.1, 123.8, 124.9, 126.4, 126.7, 127.3, 127.3, 127.5, 127.8, 128.6, 129.9, 130.2, 131.6, 134.4, 137.6, 139.6, 181.5.

3-(2-Chorophenyl)-N-*1-(1-naphthyl)ethylpropenamide* ***25***

1-(1-Naphthyl)ethylamine (473 mL, 3 mmol) was added to a solution of 2-chlorocinnamoyl chloride (605 mg, 3 mmol) in pyridine (1 mL) and dichloromethane (5 mL), and the mixture stirred overnight at room temperature. The solvents were removed, and the residue was partitioned between ether and 2 M HCl. The ether phase was washed with water, dried and evaporated and the product recrystallized from ethyl acetate as fine pale yellow crystals (742 mg, 74%), mp. 125–126°C. (Found: $[M]^+$ 335.1070; $C_{21}H_{18}ClNO$ requires $[M]^+$ 335.1077). δ_H (DMSO) 1.61 (d, *J* 6.9, 3H), 5.89 (m, 1H), 6.80 (d, *J* 15.9, 1H), 7.42–7.47 (m, 2H), 7.53–7.64 (m, 5H), 7.72–7.75 (m, 1H), 7.78 (d, *J* 15.6, 1H), 7.89 (d, *J* 7.8, 1H), 8.01 (d, *J* 8.7, 1H), 8.19 (d, *J* 8.1, 1H), 8.67 (d, *J* 8.1, 1H). δ_C (DMSO) 27.9, 45.2, 123.5, 124.1, 126.1, 126.4, 126.6, 127.3, 128.4, 128.5, 128.7, 129.6, 130.9, 131.4, 131.9, 133.6, 134.2, 134.4, 135.2, 140.7, 169.4.

*(*R*)*-N-*4-(Phenylbutyl)-1-phenylethylamine* ***26***

A mixture of 4-phenylbutanal[42] (0.74 g, 5 mmol), (*R*)-α-methylbenzylamine (0.60 g, 5 mmol), and titanium isopropoxide (1.86 mL, 6.25 mmol) was reacted as above to give **26** as an oil, characterized as the hydrochloride salt, mp. 140°C. (Found: $[M + 1]^+$ 254.1918; $C_{18}H_{24}N$ requires $[M]^+$ 254.1909). The hydrochloride salt was basified with 1 M NaOH to afford the oily free base (0.66 g). Free base: δ_H 1.35 (d, *J* 6.6, 3H), 1.59 (m, 4H), 2.55 (m, 4H), 3.74 (q, *J* 6.6, 1H), 7.12–7.34 (m, 10H). δ_C 24.3 (CH_3), 29.2 (CH_2), 29.9 (CH_2), 35.8 (CH_2), 47.7 (CH_2), 58.4 (CH), 125.6 (CH), 126.5 (CH), 126.8 (CH), 128.2 (CH), 128.4 (CH), 142.5 (C), 145.9 (C). Hydrochloride salt: δ_H 1.55 (m, 2H), 1.87 (d, *J* 6.8, 3H), 1.95 (m, 2H), 2.52 (t, *J* 8, 2H), 2.66 (t, *J* 8.8, 2H), 4.16 (q, *J* 6.8, 1H), 7.16 (m, 5H), 7.41 (m, 3H), 7.57 (dd, *J* 2.2, 1.4, 2H). δ_C 20.6 (CH_3), 25.6 (CH_2), 28.6 (CH_2), 35.2 (CH_2), 45.5 (CH_2), 58.8 (CH), 125.9 (CH), 127.8 (CH), 128.3 (CH), 128.4 (CH), 129.3 (CH), 129.4 (CH), 136.2 (C), 141.4 (C).

*(*R,S*)*-N-*(4-Phenylbutyl)-1-(3-methoxyphenyl)ethylamine* ***27***

A mixture of 4-phenylbutylamine (0.75 g, 5 mmol), 3-methoxyacetophenone (0.60 g, 5 mmol), and titanium isopropoxide (1.86 mL, 6.25 mmol) was reacted as above to yield **27** as a yellow oil (1.19 g, 75%). (Found: $[M + 1]^+$ 284.1917; $C_{20}H_{30}NO$ requires $[M]^+$ 284.2009). Free base: δ_H 1.35 (d, *J* 6.6, 3H), 1.56 (m, 4H), 2.56 (m, 4H), 3.73 (q, *J* 6.6, 1H), 3.82 (s, 3H), 6.85 (dd, *J* 11.0, 7.2, 1H), 6.90 (dd, *J* 2.2, 1.4, 2H), 7.12–7.34 (m, 6H). δ_C 24.3 (CH_3), 29.1 (CH_2), 29.9 (CH_2), 35.7 (CH_2), 47.6 (CH_2), 55.1 (CH), 58.4 (CH_3), 112.1 (CH), 118.9 (CH), 125.7 (CH), 128.2 (CH), 128.4 (CH), 129.3 (CH), 142.4 (C), 147.6 (C), 159.8 (C).

*(*R,S*)*-N-*[(2-Chlorophenyl)ethyl]-1-(3-methoxyphenyl)ethylamine* ***28***

A mixture of 3-methoxyacetophenone (0.75 g, 5 mmol), 2-(2-chlorophenyl)ethylamine (0.78 g, 5 mmol), and titanium isopropoxide (1.80 g, 6.25 mmol) was reacted as above to yield **28** as a yellow oil (300 mg) which was converted to the white hydrochloride salt (500 mg), mp. 166–170°C. (Found: $[M + H]^+$ 290.1304; $C_{17}H_{21}{}^{35}ClNO$ requires $[M]^+$ 290.1306). Free base: δ_H 1.35 (d, *J* 6.6, 3H), 2.70 (m, 2H), 2.80

(m, 2H), 3.79 (s, 3H), 3.80 (q, *J* 6.6, 1H), 6.76 (dd, *J* 3.6, 3.4, 1H), 6.89 (dd, *J* 2.4, 1.8, 2H), 7.12–7.35 (m, 5H). δ_C 24.3 (CH_3), 34.2 (CH_2), 47.1 (CH_2), 55.1 (CH), 58.0 (CH_3), 111.9 (CH), 112.3 (CH), 119.0 (CH), 126.7 (CH), 127.5 (CH), 129.3 (CH), 129.5 (CH), 130.6 (CH), 134.1 (C), 137.7 (C), 147.5 (C), 159.8 (C).

N-*3-(2-Chlorophenylpropyl)-(3-methoxy)benzylamine* ***29***

A mixture of 3-methoxybenzaldehyde (0.6 mL, 5.0 mmol), 3-(2-chlorophenyl)propylamine (0.85 g, 5.0 mmol), and titanium isopropoxide (1.80 g, 6.25 mmol) was reacted as above to yield **29** as a yellow oil (280 mg, 19%). (Found: $[M + H]^+$ 290.1307; $C_{17}H_{21}{}^{35}ClNO$ requires $[M]^+$ 290.1306). δ_H 1.86 (quin, *J* 7.4, 2H), 2.70 (t, *J* 7.4, 2H), 2.80 (t, *J* 7.4, 2H), 3.80 (s, 2H), 3.81 (s, 3H), 6.82 (dd, *J* 11.2, 9.2, 1H), 6.91 (dd, *J* 2.2, 7.4, 2H), 7.11–7.35 (m, 5H). δ_C 29.6 (CH_2), 31.2 (CH_2), 48.5 (CH_2), 53.6 (CH), 55.2 (CH_3), 112.8 (CH), 113.7 (CH), 126.8 (CH), 127.3 (CH), 129.5 (CH), 130.6 (CH), 133.9 (C), 139.5 (C), 141.0 (C), 159.8 (C).

N-*[(2-Chlorophenyl)ethyl]-3-methoxybenzylamine* ***30***

A mixture of 3-methoxybenzaldehyde (0.6 mL, 5 mmol), 2-(2-chlorophenyl)ethylamine (0.7 mL, 5 mmol), and titanium isopropoxide (1.80 g, 6.25 mmol) was reacted as above to yield **30** as a yellow oil (130 mg). The hydrochloride salt was isolated as a white solid, mp. 118–120°C. (Found: $[M + H]^+$ 276.1145; $C_{16}H_{19}{}^{35}ClNO$ requires $[M]^+$ 276.1150). Free base: δ_H 2.95 (m, 4H), 3.80 (s, 3H), 3.82 (s, 2H), 6.82 (dd, *J* 3.6, 3.4, 1H), 6.97 (m, 2H), 7.10–7.34 (m, 5H). δ_C 34.1 (CH_2), 48.7 (CH_2), 53.6 (CH_2), 55.2 (CH_3), 112.6 (CH), 113.4 (CH), 120.3 (CH), 126.7 (CH), 127.6 (CH), 129.3 (CH), 129.5 (CH), 130.8 (CH), 134.1 (C), 137.6 (C), 141.8 (C), 159.8 (C).

Biological Assay

The biological assay used in this study was as previously described in our laboratory.[26] Rat neocortical slices were prepared from halothane anaesthetized outbred male adult Sprague–Dawley rats and equilibrated in gassed Krebs solution at room temperature (20–23°C) for 1 h before experimentation. Following the equilibration period, wedge-shaped slices from the neocortex were placed in a two-compartment Perspex perfusion chamber, where each wedge was placed across a septum, separating pools containing the cortex and white matter by a grease seal, using a superfusion method based on a grease-gap system. The grey matter was then continuously superfused with gassed Krebs medium at 25°C delivered by a peristaltic pump at 1 mL min^{-1}. The white matter was immersed in a chamber containing Krebs solution. Potential changes induced by $GABA_B$ receptor agonists were recorded during 3 min applications of each agonist. Differential recordings [mV] between the cortex and white matter were measured with Ag|AgCl electrodes, and the DC potentials were monitored on a chart recorder using a high input-impedance DC amplifier.

After 60 min equilibration, the $GABA_B$ receptor agonist baclofen was added to the superfusing medium, and applied to the cortical side of the tissue for 3 min, to achieve steady-state concentrations within the recording chamber. Each preparation was allowed a minimum of 30–60 min recovery between drug applications. When examining the potentiating effects of a compound, the latter was first superfused for 5 min and then added together with the agonist for a further 3 min before tissue wash-out. In each experiment, the responses to the agonist were re-established after drug application to control for the stability of the preparation. Results were quantified, and values expressed as a percentage of the maximum hyperpolarization obtained with the agonist alone. Concentration–response curves were constructed, in the absence and presence of the test agent. To test the potentiating activity of the compound, it was applied at ascending concentrations with a fixed agonist concentration. The concentration–response profile for the potentiator was constructed by measuring the peak amplitude during application of the compound and a standard concentration of agonist (EC_{50} of the agonist), calculating the percent increase relative to the agonist (alone) response, and plotting the data as a function of potentiator concentration.

All numerical data on the concentration-response curves were expressed as means ± standard error. Each experiment was repeated on 6–12 slices obtained from at least six different animals. Comparison of the data was made using a Student's *t*-test with $P < 0.05$ being significant.

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