Pergamon

Bioorganic & Medicinal Chemistry 8 (2000) 2085–2094

BIOORGANIC & MEDICINAL CHEMISTRY

Evaluation of a Series of Anticonvulsant 1,2,3,4-Tetrahydroisoquinolinyl-benzamides

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Received 10 November 1999; accepted 18 May 2000

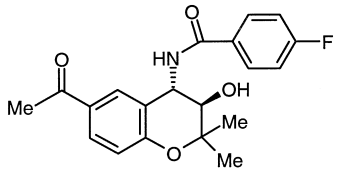
Abstract—SAR studies around a series of *N*-(tetrahydroisoquinolinyl)-2-methoxybenzamides, identified by high-throughput screening at the novel SB-204269 binding site, have provided compounds such as **13**, **29–33** with high affinity and excellent anticonvulsant activity in animal models.

Introduction

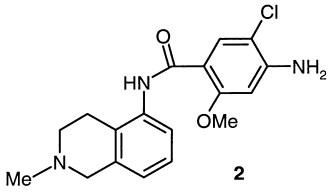
Epilepsy is one of the most serious neurological conditions for which there is a clear major unmet medical need for compounds with enhanced efficacy and safety.[1,2] For example, around 20–30% of sufferers do not have their seizures fully controlled with currently available drugs (many of which also have problems with side effects) and the prognosis for some childhood epileptic syndromes and partial seizures in adults is poor. It was against this background that we embarked upon our studies with novel benzopyrans in an attempt to identify new improved anticonvulsant agents.

In an earlier publication,[3] we reported that novel *trans* 4*S* benzamido-3,4-dihydro-2*H*-benzopyrans showed good anticonvulsant activity in the mouse maximal electroshock seizure threshold (MEST) model. Subsequent exploration of structure–activity relationships (SAR) led to the identification of the novel 4-fluorobenzamide **1** SB-204269 with potent anticonvulsant activity in a range of seizure models and an overall profile indicative of potential utility for the treatment of partial and generalised tonic-clonic seizures.[4]

The compound is currently undergoing clinical evaluation as a pioneer treatment for epilepsy disorders and has progressed to Phase II of clinical development. It was demonstrated[4–6] that *trans* 4*S* benzamides of this type bind enantioselectively at a novel unique site in various regions (e.g., forebrain, hippocampus, cerebellum, cerebral cortex) of the brains of several animal species (mouse, cat, dog, marmoset) and man with similar high affinity for the [^{3}H] SB-204269 site. It was also shown that there was a good correlation between in vitro potency and the level of in vivo activity in anticonvulsant models (e.g., rodent MEST and MES (maximal electroshock seizure) tests).[6]



1 SB-204269



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We wished to identify alternative structural classes to fully exploit this novel CNS binding site and capitalise on the superior anticonvulsant profile afforded by its modulation. High-throughput screening of the SB compound bank in the [^{3}H] SB-204269 assay in rat forebrain[6]

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0968-0896/00/$ - see front matter
PII: S0968-0896(00)00149-8

identified an interesting high affinity 5-benzamido-tetrahydroisoquinoline (THIQ) (**2**) which was actually 3-fold more potent than SB-204269 itself. Preliminary SAR studies revealed that attachment of the benzamide moiety at the 5- or 7-positions was much preferred over attachment at the 6- or 8- positions of the THIQ nucleus.[7] Early molecular modelling overlap studies using SYBYL were used to rationalise the equivalent affinities of the 5- and 7-substituted isomers (see Fig. 1). To further exploit these THIQ leads and optimise the in vivo profile, a full SAR analysis was carried out and the results of this work (see Tables 1 and 2) are reported

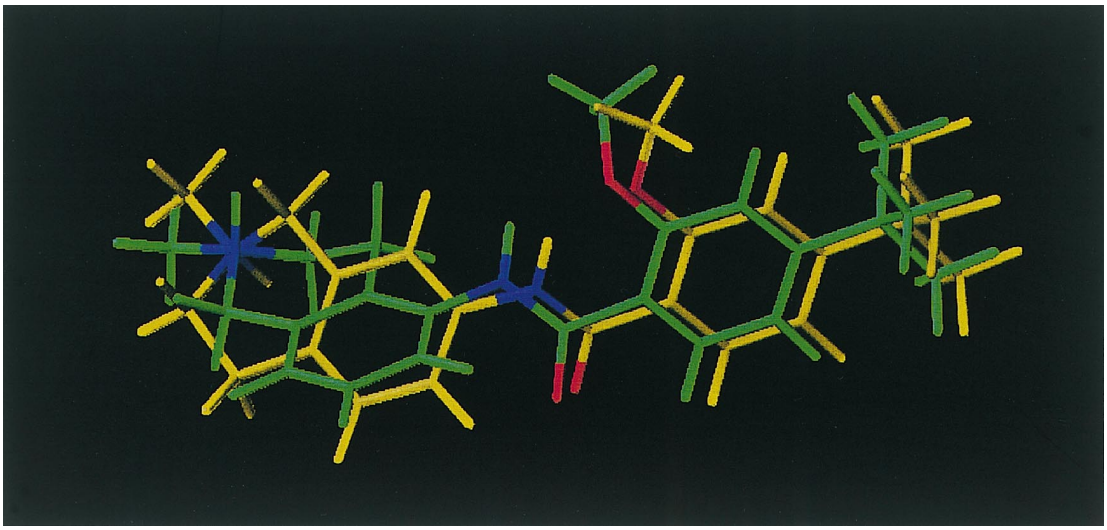
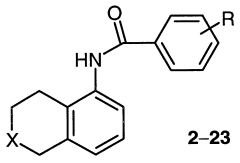


Figure 1. Overlapped energy minimised conformations of **6** (green) and **28** (yellow) generated using the SYBYL package (O = red, N = blue).

Table 1. Biological data for 5-substituted compounds



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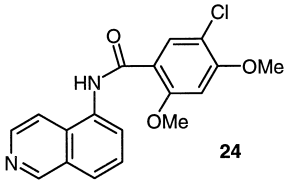

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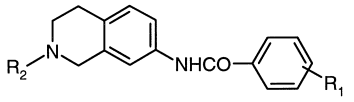
Compound	R	X	[^{3}H]SB-204269 binding[a] pK_i	Mouse MEST[b] % increase in seizure threshold at 10 mg/kg po 1 h post-dose
1	SB-204269	—	7.3	102***
2	2-OMe, 4-NH_2 5-Cl	NMe	7.8	25*
3	2-OMe	NMe	5.8	Nd
4	3-Cl	NMe	< 5.0	Nd
5	4-Bu^t	NMe	6.0	Nd
6	2-OMe, 4-Bu^t	NMe	7.7	140***
7	2-OMe, 5-Cl	NMe	7.0	20*
8	2-OMe, 3,5-diCl	NMe	5.0	Nd
9	2,4-diOMe	NMe	6.5	Nd
10	2,4-diOMe, 6-Me	NMe	5.0	Nd
11	2,4-diOMe, 5-Cl	NMe	7.6	63***
12	2-OMe, 4-OEt, 5-Cl	NMe	8.0	95***
13	2-OMe, 4-OPr^i, 5-Cl	NMe	8.3	120***
14	2-OMe, 4-Bu^t, 5-Cl	NMe	6.8	Nd
15	2-OMe, 4-Pr^i, 5-CF_3	NMe	7.7	128***
16	2,4-diOMe, 5-Cl	NH	7.6	34*
17	2,4-diOMe, 5-Cl	NEt	6.7	Nd
18	2,4-diOMe, 5-Cl	NCH_2Ph	< 6.0	Nd
19	2,4-diOMe, 5-Cl	NCO_2Bu^t	< 5.9	Nd
20	2-OMe, 4-Bu^t	NH	7.5	52**
21	2-OMe, 4-Bu^t	NCO_2Me	6.2	Nd
22	2-OMe, 4-Bu^t	NSO_2Me	6.4	4ns
23	2-OMe, 4-Bu^t	CH_2	< 5.8	Nd
24	—	—	6.1	Nd

[a]Procedures as detailed in refs 5 and 6; all determinations were carried out in triplicate, SEM $< \pm 0.05$.
[b]Procedures as detailed in ref 12; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared to vehicle-treated controls according to analysis following Lichfield and Wilcoxon in ref 17; doses refer to free base. ns: not significant Nd: not determined.

Table 2. Biological data for 7-substituted THIQ benzamides



25–40

Compound	R_1	R_2	[^{3}H]SB-204269 binding[a] pK_i	Mouse MEST[b] % increase in seizure threshold at 10 mg/kg po 1 h post-dose
25	H	Me	6.6	8ns
26	3-Cl	Me	7.5	24***
27	4-Bu^t	Me	8.1	37***
28	2-OMe, 4-Bu^t	Me	7.6	130***
29	3-Cl, 4-OMe	Me	8.6	128***
30	3-Cl, 4-OEt	Me	8.7	195***
31	3-Cl, 4-OPr^i	Me	8.3	192 ***
32	3-Br, 4-OMe	Me	8.8	163***
33	3-CF_3, 4-OMe	Me	8.9	Nd
34	3-CN, 4-OMe	Me	8.3	62**
35	3-OMe, 4-Cl	Me	7.3	Nd
36	2,4-diOMe, 5-Br	Me	7.9	72***
37	3,5-diCl, 4-OMe	Me	7.5	Nd
38	3-CF_3, 4-OMe	H	8.9	Nd
39	3-CF_3, 4-OMe	Et	8.5	Nd
40	3-CF_3, 4-OMe	Pr^i	7.7	Nd

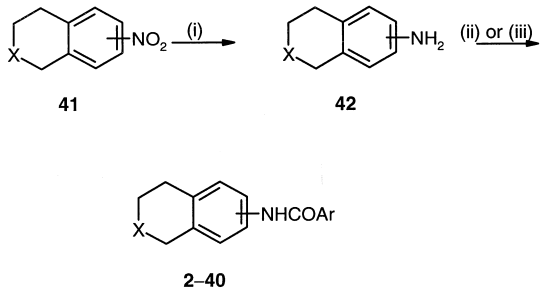
[a]Procedures as detailed in refs 5 and 6; all determinations were carried out in triplicate, SEM $< \pm 0.05$.
[b]Procedures as detailed in ref 12; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, compared to vehicle-treated controls according to analysis following Lichfield and Wilcoxon in ref 17; doses refer to free base. ns: not significant Nd: not determined.

here. The SAR information provided by these latest studies has led to a refinement of the original published[7] pharmacophore model and this is discussed herein.

Results and Discussion

Chemistry

The compounds in Tables 1 and 2 were synthesised as outlined in Scheme 1. The appropriate THIQ amine templates were prepared according to literature procedures[8,9] and consequently only brief details are given in the Experimental. For the 5-substituted isomer, N-2 alkyl templates were made according to the method of Mathison et al.,[8a] (i.e., as for **42e**); N-2 H and N-2 acyl compounds were available using standard methods via the N-2 Boct amine (**42f**). In the case of the 7-substituted isomer, the N-2 trifluoroacetyl amine (**41a**) was prepared in a manner similar to that of Stokker[8b] and base hydrolysis to the NH compound followed by methylation[10] or reductive alkylation[11] and subsequent hydrogenation of the 7-nitro to a 7-amino afforded the desired N-2 alkyl templates (**42b** to **42d**). The required highly functionalised benzoic acids that were not commercially available were prepared as previously described.[9] Coupling of these two precursors, using standard procedures, gave the desired benzamides in good overall yields from **42**. Any necessary purification was carried out by flash chromatography through silica gel using dichloromethane: methanol: ammonia (95:4.5:0.5) as eluent.



Scheme 1. Reagents and conditions: (i) 10% Pd/C, H_2, ethanol, 4 h, >90% yield; or $SnCl_2$, EtOH, 3 h, 50 °C, 40–60% yield; (ii) ArCOCl, Et_3N, CH_2Cl_2, 6 h, 25 °C, 45–85% yield; (iii) $ArCO_2H$, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide, HOBT, DMF, 18 h, 25 °C, 50–85% yield.

Biological Evaluation

Compounds were evaluated in the [^{3}H] SB-204269 binding assay and those which showed a reasonable level of potency (p$K_i > 7.5$) were then examined in vivo in the mouse MEST test at a standard dose of 10 mg/kg po 1 h post-dose. Compounds of interest were further evaluated in the rat model and those which showed good anticonvulsant activity were then examined to determine their duration of action (see Table 3). As the SAR's developed, this led to a refinement of the screening protocol and later compounds (see Table 2) were examined in the rat as the only species of choice.

A large number of compounds was prepared in order to probe the SAR of THIQ benzamides and a selection has been chosen to illustrate key findings (see Tables 1 and 2). Initially, variation of the substitution pattern of the benzamide moiety was investigated, primarily in the 5-substituted isomer series.

Table 3. Rat MEST data for selected compounds

Compound	pK_i	Dose mg/kg po	% Increase in seizure threshold[a] time post-dose (h)					
			0.25	0.5	1	2	4	6
SB-204269	7.3	10	50	90	180	420	570	390
6	7.7	10	190	250	400	580	330	Nd
15	7.6	10	240	420	810	1300	1400	Nd
13	8.3	10	380	640	760	1100	1100	700
		2	50	150	300	520	395	255
28	7.6	10	Nd	Nd	470	340	110	Nd
29	8.6	5	180	400	690	740	700	400
30	8.7	5	105	180	380	620	830	700
31	8.3	2	70	130	225	310	410	190
32	8.8	5	120	260	250	450	650	260
33	8.9	2	70	220	230	850	1200	1100

[a]Procedure as detailed in refs 12 and 16; doses refer to free base; all figures $P < 0.05$; Nd: Not determined.

From our earlier published initial SAR for monosubstituted benzamides in the 5-series, 2-methoxy **3** and 4-*t*-butyl **5** showed modest affinity (pK_i 5.8 and 6.0. respectively) but 3-chloro **4** was inactive (pK_i < 5). The combination of a 2-methoxy with either a 4-*t*-butyl **6** (pK_i 7.7) or 5-chloro **7** (pK_i 7.0) resulted in markedly enhanced potency.[7] Additional analogues have since been prepared to further probe the SAR of this class of THIQ benzamides. In general, for disubstitution in the 5-series the combination of a 2-methoxy with a lipophilic 4-substituent results in optimum potency, although the 2,4-dimethoxy **9** showed a relatively modest level of potency (pK_i 6.5).

Introduction of a 5-chloro into **9** resulted in a trisubstituted compound **11** with a 10-fold increase in potency. Increasing the lipophilic bulk of the 4-alkoxy group (**12**–**13**) was beneficial, the *iso*-propoxy compound **13** (pK_i 8.3) being the most potent 5-series THIQ identified. In contrast, introduction of a 5-chloro into the 2-methoxy 4-*t*-butyl **6** gave compound **14** (pK_i 6.8), which was 10-fold less potent. Interestingly, the 3,5-dichloro 2-methoxy **8** and 2-methoxy 6-methyl **10** were virtually inactive (pK_i 5.0).

On completion of these initial optimisation studies, the effects of changing the nature of the THIQ nucleus were examined, using either the 2-methoxy 4-*t*-butyl or the 2,4-dimethoxy 5-chloro benzamide substitution patterns (**16**–**23**). Comparison of N-2 alkyl substituents revealed that there is steric intolerance with a sharp loss in affinity for substituents larger than methyl (NH = NMe > NEt > NBenzyl). The carbamates **21** (pK_i 6.2) and **19** (pK_i < 5.9) (Again, the size restriction around N-2 was apparent with lower affinity seen for the more bulky *t*-butyl carbamate) and sulfonamide **22** (pK_i 6.4) was also less potent and tetralin **23** (pK_i < 5.8) was inactive, indicating the need for a basic nitrogen for optimum potency. The 30-fold lower potency of the aromatic quinoline **24** (pK_i 6.1) in comparison with its THIQ counterpart **11** (pK_i 7.6) probably reflects its much lower basicity.

Examination of the data for 7-substituted THIQ benzamides, revealed striking differences compared to the 5-substituted series. Firstly, the compounds are generally more potent showing very high affinity at the SB-204269 binding site. Secondly, the 2-methoxy substituent on the benzamide is no longer essential for good binding affinity (e.g. compare 3-chloro **4** (pK_i < 5) and **26** (pK_i 7.5)) and is in fact detrimental (up to 10-fold) to optimum potency (i.e. compare **27/28** (pK_i 8.1, 7.6) and **32/36** (pK_i 8.8, 7.9)). This has been rationalised by molecular modelling (see later). The monosubstituted benzamides (**26** pK_i 7.5, **27** pK_i 8.1) showed potency levels over 100-fold higher than in the 5-substituted series. The disubstituted benzamides (**29**, **30** and **32**–**34**) containing a 3-electron withdrawing group combined with 4-methoxy or 4-ethoxy were of low nanomolar potency. Interestingly, the reversed combination was 20-fold less potent (compare **35** (pK_i 7.3) and **29** (pK_i 8.6)). Introduction of a second chloro group into the 5-position was detrimental (**37**, pK_i 7.5). Another difference from the 5-series THIQs was that increasing the lipophilic bulk of the 4-alkoxy group was slightly detrimental (OMe **29** = OEt **30** > OPr^i **31**). However, in agreement with the 5-series, any increase in the size of the N-2 alkyl on the THIQ was detrimental (compare **33** with **39** and **40**) with NH and NMe being equipotent (**33**, **38** pK_i 8.9).

The most potent compounds from both isomeric series were examined in vivo. Initially, compounds with a pK_i > 7.5 were examined in mouse MEST at 10 mg/kg po for comparison with SB-204269 at the same dose. Three 5-series THIQs (**6**, **13** and **15**) and five 7-series THIQs (**29**–**32**) showed a good level of activity (> 100% increase in seizure threshold) and were further evaluated in the rat MEST model along with the 4-methoxy-3-trifluoromethyl compound **33** (see Table 3).[12] All these compounds showed a rapid onset of activity (good activity at 15 min post-dose) with the peak level of effect being at around 4 h post-dose. The duration of effect was also encouraging with activity maintained at the 6 h time point, especially for (**33**) which was the most potent compound and showed an excellent in vivo profile at the low dose of 2 mg/kg. Unfortunately, the 7-THIQ compound **28** did not exhibit a robust response in the rat in spite of showing good activity in the mouse model. Compound **33**, which showed the best profile in the time-course studies, was further examined in the more stringent MES test and had an ED_{50} of 0.67 mg/kg po. This was some 10-fold lower than the figure for SB-204269 which had an ED_{50} of 6.3 mg/kg po.

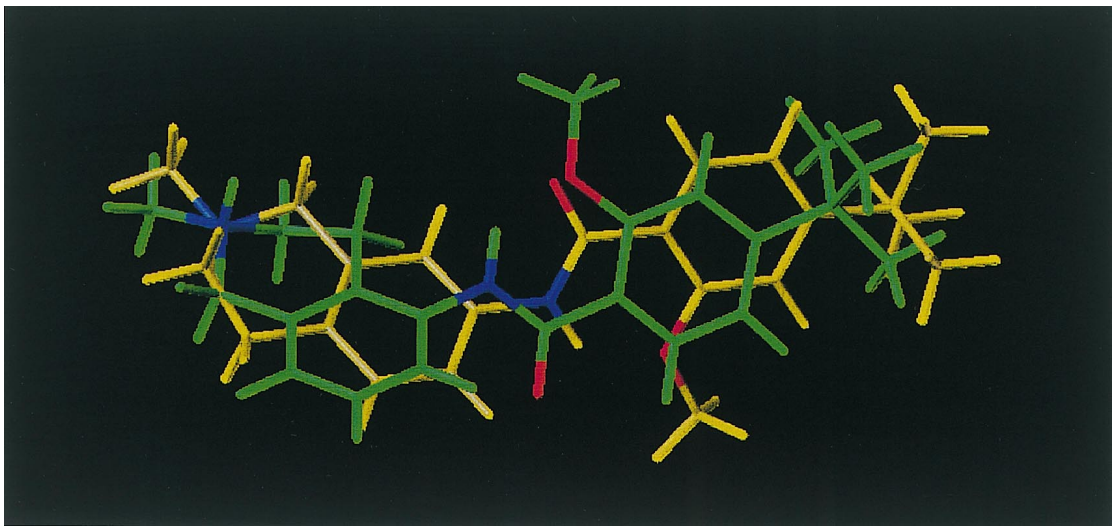


Figure 2. View of the alternative overlapped energy minimised **6** (green) and **28** (yellow) generated using the SYBYL package (O = red, N = blue).

Molecular modelling overlap studies using SYBYL[13] (see Fig. 1) were used to rationalise the equivalent affinities of the 5- and 7-substituted isomers **6** and **28**. These were carried out on the charged molecules, flexibly fitting the 5-isomer onto an energy minimised 7-conformation. Equivalent spring constants were applied to the basic N-2 nitrogens, amide linkages and aromatic carbon atoms bearing the lipophilic *tert*-butyl substituents; resulting in good overlap of the important pharmacophoric elements. If this overlap is correct, the directionality of the THIQ nitrogen lone pair appears to be unimportant for optimum activity. Intramolecular hydrogen bonding between the 2-methoxy and the amide linker gives a virtual 6-membered ring which stabilises a low energy conformation of the compounds. However, this model does not explain why the 2-methoxy group is detrimental in the 7-series.

Further molecular modelling studies suggested an alternative binding mode for 5- and 7-isomers where the essential 2-OMe oxygen of the former overlapped with the carbonyl oxygen of the latter (see Fig. 2). Such an overlap provides a possible explanation of the key SAR finding that the 2-OMe is detrimental in the 7-isomer. Its position in this mode could result in an unfavourable steric interaction at the binding site. The basic THIQ N-2′s overlap well in this alternative model of binding as do the lipophilic 4-substituents on the benzamide moiety, although this extends further in the 7-series. This is consistent with smaller lipophilic groups in the 7-series having greater affinity than would be predicted from the corresponding 5-series SAR as they are able to extend deeper into the presumed lipophilic pocket.

Conclusion

Using [^{3}H] SB-204269 as a ligand, a new chemical series has been discovered with affinities up to 50-fold higher than that of SB-204269 and for a number of these potent compounds, this is reflected in greatly enhanced activity in in vivo anticonvulsant models. The overall pharmacological profile of these compounds suggests a potential therapy for epilepsy with partial seizures (with or without secondary generalisation).[14] In vitro selectivity cross-screening revealed that compounds **6**, **13**, and **33** were selective (> 30-fold) over a range of other receptors (e.g., amino acid receptors) and ion channels (e.g. sodium, potassium and chloride), which are thought to modulate neurotransmission. Further studies around THIQ benzamides and related compounds will be reported in future publications.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Carboxylic acids were prepared as published in ref 9. All extracts were washed with water, brine and dried over anhydrous magnesium sulfate; all solvents were removed with a Buchi rotary film evaporator. Chromatography refers to flash chromatography which was performed on either Merck Kieselgel 60 (0.040–0.063 mm) or Waters Sep-Pak® Vac silica cartridges (5 or 10g). ^{1}H NMR spectra were obtained using either a Bruker AC 250 or a Jeol GX 270 spectrometer. High-resolution electron impact mass spectra were determined on a Jeol JMS DX 303/DA 5000 system operating at 70eV. Atmosperic pressure ionisation mass spectra [*m*/*z* (API)] were obtained using a VG Micromass OpenLynx Platform LCMS system. Melting points (mp) were determined using a Kofler hot stage apparatus and are uncorrected. Biological data for hydrochloride salts refer to the equvalent amount of free base in order to provide a direct comparison.

The full details for the synthesis of all the required THIQ amino templates have been published[9] and the following procedures have been given to illustrate the general principles involved.

7-Nitro-1,2,3,4-tetrahydro-2-trifluoroacetylisoquinoline (41a). The *N*-2-(4-nitrophenyl)ethyl trifluoroacetamide

(2.26 g, 9.15 mmol) and paraformaldehyde (0.45 g, 14.4 mmol) in acetic acid (10 mL) and concd H_2SO_4 (15 mL) were stirred at 25 °C for 20 h and work up according to the procedure of G.E. Stokker, afforded the title compound as a white solid (2.17 g, 86%). ^{1}H NMR ($CDCl_3$) δ 3.10 (2H, m), 3.92 (2H, m), 4.85 + 4.92 (2H, 2xs), 7.38 (1H, t), 8.10 (2H, m); *m*/*z* (EI): 274 (M^+ 11%, $C_{11}H_9F_3N_2O_3$ requires M^+ 274).

2-Methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline (41b). The trifluoroacetamide **41a** (17.22 g; 63 mmol) was hydrolysed at 25 °C using a solution of potassium carbonate (46.6 g) in 10% aqueous methanol (660 mL). After 18 h, extraction with dichloromethane gave the N-2 amine (11 g). A portion of this foregoing N-2 amine (2.08 g, 11.7 mmol) was treated with 88% formic acid (3.45 mL) and 37% aqueous formaldehyde (5.88 mL) at 80 °C for 2 h according to the procedure of G.M. Carrera and D.S. Garvey.[10] Basification with 10% sodium hydroxide followed by extraction with ethyl acetate afforded an orange gum (2.3 g). Chromatography on Kiesegel 60 in 0 to 3% methanol:ethyl acetate gave the title compound as an orange solid (1.7 g). ^{1}H NMR ($CDCl_3$) δ 2.52 (3H, s), 2.75 (2H, t, J = 6 Hz), 3.03 (2H, t, J = 6 Hz), 3.67 (2H, s), 7.28 (1H, d, J = 8 Hz), 7.94 (1H, d, J = 2 Hz), 8.01 (1H, dd, J = 8, 2 Hz); *m*/*z* (API^+): 193 (MH^+; 100%, $C_{10}H_{12}N_2O_2$ requires M^+ 192).

7-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (42b). The 7-nitro compound **41b** (0.25 g; 1.3 mmol) in methanol (40 mL) was hydrogenated over 10% palladium on carbon (100 mg) at atmospheric pressure overnight. The catalyst was removed by filtration through a pad of Kieselguhr and evaporation in vacuo gave the title compound as a cream solid (213 mg; 99%), mp 82–84 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ 2.43 (3H, s), 2.64 (2H, d, J = 7 Hz), 2.79 (2H, d, J = 7 Hz), 3.48 (2H, s), 3.51 (2H, brs), 6.36 (1H, d, J = 2 Hz), 6.50 (1H, dd, J = 8, 2 Hz), 6.89 (1H, d, J = 8 Hz); *m*/*z* (API^+): 163 (MH^+; 90%, $C_{10}H_{14}N_2$ requires M^+ 162).

7-Amino-1,2,3,4-tetrahydro-2-trifluoroacetylisoquinoline (42a). Was prepared from **41a** in a similar manner to the procedure used for (**42b**). ^{1}H NMR ($CDCl_3$) δ 2.84 (2H, m), 3.23 (2H, brs), 3.82 (2H, m), 4.66 (2H, 2s, rotamers), 6.47 (1H, m), 6.57 (1H, m), 6.96 (1H, m); *m*/*z* (API^+): 245 (MH^+; 100%, $C_{11}H_{11}F_3N_2O$ requires M^+ 244).

7-Amino-2-*iso*-propyl-1,2,3,4-tetrahydroisoquinoline (42c). Nitro compound NH *ex* **41a/b** (1.55 g, 8.7 mmol) and acetone (2.52 g, 43.5 mmol) in 1,2-dichloroethane (50 mL) were treated with sodium triacetoxyborohydride (0.28 g, 13.1 mmol) and glacial acetic acid (0.6 mL, 9.0 mmol).[11] The mixture was stirred at 25 °C over 72 h and then diluted with dichloromethane (50 mL). The mixture was washed with saturated $NaHCO_3$, dried (Na_2SO_4) and evaporated in vacuo. Chromatography on Kieselgel 60 in ethyl acetate gave the *N-iso*-propyl compound (0.73 g). This material (0.73 g, 3.32 mmol) in ethanol (100 mL) was heated to 50 °C and treated with a solution of tin (II) chloride (2.52 g, 13.27 mmol) in concd HCl (10 mL) and stirring continued for 3 h. The mixture was basified with 40% NaOH and the product extracted into dichloromethane. Work up and chromatography on Kieselgel 60 in 10% methanol:dichloromethane gave the title compound as a viscous yellow oil (0.26 g; 41%). ^{1}H NMR ($CDCl_3$) δ 1.12 (6H, d, J = 7 Hz), 2.76 (4H, m), 2.84 (1H, m), 3.63 (2H, s), 6.37 (1H, d, J = 7 Hz), 6.48 (1H, dd, J = 7, 1 Hz), 6.86 (1H, d, J = 7 Hz); *m*/*z* (API^+): 191 (MH^+; 80%, $C_{12}H_{18}N_2$ requires M^+ 190).

7-Amino-2-ethyl-1,2,3,4-tetrahydroisoquinoline (42d). The title compound was prepared in 14% overall yield from acetaldehyde using a method similar to that described above. ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, J = 7 Hz), 2.57 (2H, q, J = 7 Hz), 2.74 (4H, m), 3.55 (2H, s), 6.37 (1H, d, J = 7 Hz), 6.50 (1H, dd, J = 7, 1 Hz), 6.87 (1H, d, J = 7 Hz); *m*/*z* (API^+): 177 (MH^+; 100%, $C_{11}H_{16}N_2$ requires M^+ 176).

5-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (42e). 5-Aminoisoquinoline (14.4 g, 100 mmol) in acetone (300 mL) was treated with iodomethane (14.4 mL) and then allowed to stand at 25 °C for 2 h. The yellow precipitate was then filtered, washed with acetone and dried to afford 5-amino-2-methylisoquinolinium iodide (18.8 g, 65 mmol). This was dissolved in methanol (1.5 L) and water (60 mL) with cooling to 0 °C and sodium borohydride (17.8 g, 0.47 mol) was added portionwise over 2 h. The mixture was then allowed to stir at room temperature for 18 h. Concentration in vacuo followed by extraction of the residue into dichloromethane gave the title compound as a beige solid (8.87 g, 54%), mp 51–53 °C (MeOH). ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 2.60 (2H, d, J = 7 Hz), 2.73 (2H, d, J = 7 Hz), 3.53 (2H, s), 3.56 (2H, brs), 6.46–6.57 (2H, m), 6.96 (1H, t, J = 8 Hz).

5-Amino-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (42f). A solution of 5-aminoisoquinoline (10 g, 69 mmol) in glacial acetic acid (150 mL) and concentrated sulfuric acid (1 mL) was hydrogenated over platinum oxide (1 g) at 55 psi for 20 h. Evaporation in vacuo followed by basification of the residue and extraction with dichloromethane gave 5-amino-1,2,3,4-tetrahydroisoquinoline (6.45 g, 44 mmol). This was dissolved in 1,4-dioxane (250 ml) containing 3 M sodium hydroxide (14.7 mL, 44 mmol) and di-*tert*-butyl-dicarbonate (9.57 mL, 44 mmol). The solution was stirred at 25 °C for 18 h. The reaction mixture was then poured into water (400 mL) and extracted with ether. The organic phases were dried and concentrated in vacuo to afford a brown oil which solidified on standing. Recrystallisation from ethanol/petrol gave the title compound as an off-white crystalline solid (5.1 g, 30%). ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.55 (2H, t, J = 7 Hz), 3.60 (2H, brs), 3.70 (2H, t, J = 7 Hz), 4.54 (2H, s), 6.56 (2H, d, J = 8 Hz), 7.01 (1H, t, J = 8 Hz).

The acylation procedure given for **9** was used for the preparation of compounds **2**, **3**, **4**, **5**, **7**, **25**, **26**, **27**, and the remaining benzamides were prepared in a manner similar to that used for **6**. Final compounds were isolated as foams following chromatographic purification and **6**, **9**, **13**, **14**, **15**, **17**, **18**, **20**, **24**, **33** and **36** were converted into monohydrochlorides using 1 M HCl in diethyl ether and methanol mixtures.

5-Series THIQ compounds in Table 1.

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methoxybenzamide, hydrochloride. (3).** ^{1}H NMR (DMSO-d_6) δ 2.90 (3H, s), 3.08 (2H, m), 3.38 (1H, m), 3.75 (1H, m), 4.00 (3H, s), 4.30 (1H, m), 4.50 (1H, m), 7.05 (1H, d, J = 8 Hz), 7.11 (1H, t, J = 8 Hz), 7.23 (1H, d, J = 8 Hz), 7.31 (1H, t, J = 8 Hz), 7.55 (1H, t, J = 8 Hz), 7.85 (2H, m), 9.85 (1H, s), 10.95 (1H, br, s); m/z (API$^+$)$^+$ 297. (MH$^+$; 90%, $C_{18}H_{20}N_2O_2$ requires M$^+$ 296).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3-chlorobenzamide (4).** ^{1}H NMR ($CDCl_3$) δ 2.90–3.50 (7H, m), 4.40 (2H, m), 7.15 (1H, m), 7.36 (2H, m), 7.58 (1H, t, J = 7 Hz), 7.70 (1H, m), 7.97 (1H, d, J = 7 Hz), 8.05 (1H, s), 10.22 (1H, s), 10.85 (1H, brs); m/z (API$^+$): 303, 301 (MH$^+$; 35, 100%, $C_{17}H_{17}ClN_2O$ requires M$^+$ 300).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butylbenzamide (5).** Whitish solid, mp 226 °C (ethyl acetate). ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.31 (9H, s), 2.90 (3H, m), 3.42 (3H, m), 3.62 (1H, m), 4.32 (1H, m), 4.52 (1H, m), 7.11 (1H, m,), 7.31 (2H, m), 7.53 (2H, d, J = 6 Hz), 7.95 (2H, d, J = 6 Hz), 10.98 (1H, brs); m/z (API$^+$): 323 (MH$^+$; 100%, $C_{21}H_{26}N_2O$ requires M$^+$ 322).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide hydrochloride (6).** 4-*t*-Butyl-2-methoxybenzoic acid (208 mg, 1.0 mmol) in DMF (8 mL) was stirred with 1 equiv of 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (192 mg) and 1-hydroxybenzotriazole (135 mg) at 25°C for 30 min. A solution of 5-amino **42e** (163 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added and the mixture kept at 25 °C for 18 h. The mixture was partitioned between chloroform (50 mL) and water (50 mL) and the material in the organic phase was purified by flash chromatography. Combination of appropriate fractions gave a solid (253 mg, 75%) which was converted into a hydrochloride salt, mp 218–220 °C. ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.32 (9H, s), 2.91 (3H, s), 3.06 (2H, m), 3.35 (1H, m), 3.70 (1H, m), 4.02 (3H, s), 4.45 (2H, m), 7.04 (1H, d, J = 10 Hz), 7.15 (2H, m), 7.31 (1H, m), 7.82 (1H, d, J = 12 Hz), 7.90 (1H, d, J = 12 Hz), 9.83 (1H, s), 10.82 (1H, s); m/z (API$^+$): 353 (MH$^+$, 80%), Found: M$^+$ 352.21549, calcd for $C_{22}H_{28}N_2O_2$ 352.21666.

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-benzamide (7).** White crystals, mp 176–178 °C (from ethyl acetate). ^{1}H NMR (DMSO-d_6) δ 2.36 (3H, s), 2.67 (2H, m), 2.73 (2H, m), 3.51 (2H, s), 3.98 (3H, s), 6.92 (1H, d, J = 6 Hz), 7.16 (1H, t, J = 7 Hz), 7.28 (1H, d, J = 8 Hz), 7.61 (1H, dd, J = 3, 10 Hz), 7.71 (1H, d, J = 8 Hz), 7.83 (1H, d, J = 3 Hz), 9.79 (1H, s); m/z (API$^+$): 331. (MH$^+$; 100%, $C_{18}H_{19}ClN_2O_2$ requires M$^+$ 330).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-3,5-dichloro-2-methoxybenzamide (8).** Whitish solid, mp 138 °C (dichloromethane:hexanes). ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 2.58 (2H, m), 2.78 (2H, m), 3.49 (2H, s), 3.88 (3H, s), 6.95 (1H, d, J = 6 Hz), 7.16 (1H, t, J = 6 Hz), 7.40 (1H, d, J = 6 Hz), 7.67 (1H, d, J = 2 Hz), 7.85 (1H, d, J = 2 Hz), 9.87 (1H, s); m/z (API$^+$): 367, 365 (MH$^+$; 65, 100%, $C_{18}H_{18}Cl_2N_2O_2$ requires M$^+$ 365).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxybenzamide, hydrochloride (9).** 2,4-Dimethoxybenzoyl chloride (263 mg 1.54 mmol) was added to a solution of 5-amino **42e** (250 mg, 1.54 mmol) in CH_2Cl_2 (5 mL) containing triethylamine (0.4 mL) and the mixture kept at 25 °C for 18 h. The mixture was partitioned between chloroform (50 mL) and water (50 mL) and work up as above for **6** gave the title compound as a white solid (330 mg, 60%), mp > 200 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.90 (3H, s), 3.05 (2H, br. s), 3.35 (2H,s), 3.85 (3H, s), 4.03 (3H, s), 4.25–4.55 (2H, m), 6.70 (1H, dd, J = 1, 6 Hz), 6.75 (1H, m), 7.00 (1H, d, J = 6 Hz), 7.30 (1H, t, J = 6 Hz), 7.95 (2H, m), 9.75 (1H, s), 11.25 (1H, brs); m/z (API$^+$): 327 (MH$^+$; 100%, $C_{19}H_{22}N_2O_3$ requires M$^+$ 326).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2,4-dimethoxy-6-methylbenzamide (10).** ^{1}H NMR (DMSO-d_6) δ 2.28 (3H, s), 2.31 (3H, s), 2.60 (2H, m), 2.78 (2H, m), 3.48 (2H,s), 3.76 (6H, s), 6.46 (2H, d, J = 7 Hz), 6.92 (1H, d, J = 7 Hz), 7.23 (1H, t, J = 7 Hz), 7.28 (1H, d, J = 7 Hz), 9.46 (1H, s); m/z (API$^+$): 341 (MH$^+$; 100%, $C_{20}H_{24}N_2O_3$ requires M$^+$ 340).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide (11).** White crystals, mp 187–189 °C (from ethyl acetate). ^{1}H NMR (DMSO-d_6) δ 2.34 (3H, s), 2.67 (2H, m), 2.75 (2H, m), 3.49 (2H, s), 3.99 (3H, s), 4.10 (3H, s), 6.87 (1H, d, J = 5 Hz), 6.95 (1H, s) 7.15 (1H, t, J = 5 Hz), 7.89 (1H, d, J = 5 Hz), 7.94 (1H, s), 9.70 (1H, s); m/z (API$^+$)$^+$ 361. (MH$^+$; 70%, $C_{19}H_{21}ClN_2O_3$ requires M$^+$ 360).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-4-ethoxy-2-methoxybenzamide (12).** ^{1}H NMR (DMSO-d_6) δ 1.42 (3H, t, J = 6 Hz), 2.34 (3H, s), 2.70 (4H, m), 3.50 (2H, s), 4.08 (3H, s), 4.28 (2H, m), 6.87 (1H, d, J = 6 Hz), 6.93 (1H, s), 7.15 (1H, t J = 6 Hz), 7.86 (1H, d, J = 6 Hz), 7.94 (1H, s), 9.70 (1H, s); m/z (API$^+$): 375. (MH$^+$; 100%, $C_{20}H_{23}ClN_2O_3$ requires M$^+$ 374).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2-methoxy-4-*iso*-propoxybenzamide, hydrochloride (13).** White crystals, mp 190–193 °C. ^{1}H NMR (DMSO d_6) δ 1.37 (6H, d, J = 6 Hz), 2.92 (3H, s), 3.05 (2H, m), 3.37 (1H, m), 3.73 (1H, m), 4.08 (3H, s), 4.32 (1H, m), 4.51 (1H, m), 4.96 (1H, m), 6.95 (1H, s), 7.06 (1H, d, J = 6 Hz), 7.32 (1H, t, J = 6 Hz), 7.89 (2H, m), 9.27 (1H, s), 11.20 (1H, br s); m/z (API$^+$): 389 (MH$^+$, 80%, $C_{21}H_{25}ClN_2O_3$ requires M$^+$ 388).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxy-5-chlorobenzamide, hydrochloride (14).** ^{1}H NMR (DMSO-d_6) δ 1.49 (9H, s), 2.91 (3H, s), 3.05 (2H, m), 3.18 (2H, s), 3.35 (1H, m), 4.03 (3H, s), 4.42 (1H, m), 7.08 (1H, d, J = 8 Hz), 7.20 (1H, s), 7.33 (1H, m), 7.79 (2H, m), 9.82 (1H, s), 10.66 (1H, br s); m/z (API$^+$): 387 (MH$^+$, 90%, $C_{22}H_{27}ClN_2O_2$ requires M$^+$ 386).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*iso*-propyl-5-trifluoromethyl-2-methoxybenzamide, hydrochloride (15).** White crystals, mp 188–191 °C. ^{1}H NMR (DMSO-d_6) δ 1.30 (6H, d), 2.90 (3H, s), 3.05 (2H, m), 3.30 (1H, m), 3.50 (2H, m), 4.07 (3H, s), 4.39 (2H, m), 7.06 (1H, d, J = 9 Hz), 7.31 (2H, m), 7.74 (1H, d, J = 10 Hz), 8.02 (1H, s), 9.86 (1H, s), 11.00 (1H, br s). m/z (API$^+$): 407 (MH$^+$; 90%, $C_{22}H_{25}F_3N_2O_2$ requires M$^+$ 406).

***N*-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide (16).** To a solution of 5-chloro-2,4-dimethoxy-N-[2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl]benzamide (1 g) in dichloromethane (30 mL) at 0 °C was added trifluoracetic acid (3 mL). The mixture was then stirred at room temperature for 3 h before pouring into saturated aqueous sodium bicarbonate (100 mL) and extracting with dichloromethane. The organic phase was dried and concentrated in vacuo gave the title compound as an off white solid (700 mg). ^{1}H NMR (DMSO-d_6) δ 2.62 (2H, m), 3.06 (2H, m), 3.85 (2H, s), 4.00 (3H, s), 4.10 (3H, s), 6.86 (1H, d, J = 7 Hz), 6.96 (1H, s), 7.13 (1H, t, J = 7 Hz), 7.86 (1H, d, J = 7 Hz), 7.94 (1H, s), 9.70 (1H, s); m/z (API$^+$): 347. (MH$^+$; 100%, $C_{18}H_{19}ClN_2O_3$ requires M$^+$ 346).

***N*-(2-Ethyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide, hydrochloride (17).** ^{1}H NMR (DMSO-d_6) δ 1.36 (3H, t, J = 7 Hz), 3.09 (2H, m), 3.12–3.85 (4H, m), 4.00 (3H, s), 4.10 (3H, s), 4.30 (1H, m), 4.55 (1H, m), 6.94 (1H, s), 7.06 (1H, d, J = 6 Hz), 7.32 (1H, t, J = 6 Hz), 7.89 (2H, m), 9.76 (1H, s), 10.85 (1H, brs); m/z (API$^+$): 375 (MH$^+$; 100%, $C_{20}H_{23}ClN_2O_3$ requires M$^+$ 374).

***N*-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide hydrochloride (18).** ^{1}H NMR (DMSO-d_6) δ 3.08 (2H, m), 3.78 (2H, m), 4.00 (3H, s), 4.09 (3H, s), 4.37 (2H, m), 4.49 (2H, m), 6.95 (1H, s), 7.05 (1H, d, J = 7 Hz), 7.31 (1H, t, J = 7 Hz), 7.50 (3H, m), 7.65 (2H, m), 7.90 (2H, m), 9.75 (1H, s), 10.98 (1H, brs); m/z (API$^+$): 437 (MH$^+$; 100%, $C_{25}H_{25}ClN_2O_3$ requires M$^+$ 436).

***N*-(2-*t*-Butyloxycarbonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide (19).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.51 (9H, s), 2.75 (2H, m), 3.72 (2H, m), 3.97 (3H, s), 4.09 (3H, s), 4.60 (2H, s), 6.54 (1H, s), 6.94 (1H, d, J = 7 Hz), 7.24 (1H, t, J = 7 Hz), 8.11 (1H, m), 8.30 (1H, s), 9.52 (1H, brs).

***N*-(1,2,3,4-Tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide hydrochloride (20).** Whitish crystals, mp 230 °C. ^{1}H NMR (DMSO-d_6) δ .31 (9H, s), 2.97 (2H, m), 3.37 (2H, m), 3.44 (2H, m), 4.06 (3H, s), 4.31 (2H, m), 7.08 (1H, d, J = 9 Hz), 7.16 (2H, m), 7.28 (1H, m), 7.84 (2H, m), 9.55 (2H, br s), 9.83 (1H, s). m/z (API$^+$): 339 (MH$^+$; 80%, $C_{21}H_{26}N_2O_2$ requires M$^+$ 338).

***N*-(2-Methoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide (21).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.39 (9H, s), 2.80 (2H, brt), 3.72 (3H, s), 3.78 (2H, br), 4.10 (3H, s), 4.65 (2H, s), 6.95 (1H, brs), 7.04 (1H, d, J = 2 Hz), 7.18 (1H, dd, J = 8, 2 Hz), 7.25 (1H, m), 8.10 (1H, brs), 8.25 (1H, d, J = 8 Hz), 9.70 (1H, brs); m/z (API$^+$): 397 (MH$^+$; 100%, $C_{23}H_{28}N_2O_4$ requires M$^+$ 396).

***N*-(2-Methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-4-*tert*-butyl-2-methoxybenzamide (22).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (9H, s), 2.88 (3H, s), 2.92 (2H, t, J = 7 Hz), 3.64 (2H, t, J = 7 Hz), 4.09 (3H, s), 4.48 (2H, s), 6.94 (1H, d, J = 8 Hz), 7.0 (1H, d, J = 2 Hz), 7.28 (1H, dd, J = 8, 2 Hz), 7.29 (1H, m), 8.05 (1H, d, J = 8 Hz), 8.23 (1H, d, J = 8 Hz), 9.70 (1H, brs); m/z (API$^+$): 417 (MH$^+$; 100%, $C_{22}H_{28}N_2O_4S$ requires M$^+$ 416).

***N*-(5,6,7,8-Tetrahydronaphthalen-1-yl)-4-*tert*-butyl-2-methoxybenzamide (23).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.39 (9H, s), 1.70–2.00 (4H, m), 2.18 (2H, t, J = 7 Hz), 2.80 (2H, t, J = 7 Hz), 3.98 (3H, s), 6.90 (1H, d, J = 8 Hz), 7.04 (1H, d, J = 2 Hz), 7.08–7.22 (2H, m), 8.10 (1H, d, J = 8 Hz), 8.23 (1H, d, J = 8 Hz), 9.75 (1H, brs); m/z (API$^+$): 338 (MH$^+$; 100%, $C_{22}H_{27}NO_2$ requires M$^+$ 337).

***N*-(Isoquinolin-5-yl)-5-chloro-2,4-dimethoxybenzamide hydrochloride (24).** ^{1}H NMR (DMSO-d_6) δ 4.03 (3H, s), 4.13 (3H, s), 7.00 (1H, s), 7.89 (1H, s), 7.96 (1H, t, J = 7 Hz), 8.15 (2H, m), 8.41 (1H, d, J = 7 Hz), 8.71 (1H, d, J = 7 Hz), 9.78 (1H, s), 10.47 (1H, brs); m/z (API$^+$): 343 (MH$^+$; 100%, $C_{18}H_{15}ClN_2O_3$ requires M$^+$ 342).

7-Series THIQ compounds in Table 2.

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)benzamide (25).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.46 (3H, s), 2.69 (2H, t), 2.91 (2H, t), 3.58 (2H, s), 7.10 (1H, d), 7.30 (1H, dd), 7.40–7.60 (4H, overlapping m), 7.75 (1H, br s), 7.87 (2H, m); m/z (API$^+$): 267 (MH$^+$; 100%, $C_{17}H_{18}ClN_2O$ requires M$^+$ 266).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chlorobenzamide (26).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.46 (3H, s), 2.68 (2H, t), 2.90 (2H, t), 3.57 (2H, s), 7.10 (1H, d), 7.29 (1H, dd, overlapping with $CHCl_3$), 7.39 (1H, s), 7.42 (1H, d), 7.52 (1H, m), 7.73 (1H, m), 7.83 (2H, m).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*t*-butylbenzamide (27).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (9H, s), 2.44 (3H, s), 2.68 (2H, t), 2.89 (2H, t), 3.55 (2H, s), 7.07 (1H, d), 7.29 (1H, dd overlapping with $CHCl_3$ signal), 7.38–7.53 (3H, m, overlapping signals), 7.75–7.90 (3H, m, overlapping signals).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-*tert*-butyl-2-methoxybenzamide (28).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (9H, s), 2.46 (3H, s), 2.68 (2H, t), 2.89 (2H, s), 3.59 (2H, s), 4.06 (3H, s), 7.01 (1H, d), 7.07 (1H, d), 7.15 (1H, dd), 7.31 (1H, dd), 7.50 (1H, d), 8.19 (1H, d), 9.74 (1H, br s); m/z (API$^+$): 353 (MH$^+$; 90%, $C_{22}H_{28}ClN_2O_2$ requires M$^+$ 352).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-methoxybenzamide (29).** ^{1}H NMR ($CDCl_3$) δ 2.47 (3H, s), 2.70 (2H, t, J = 6 Hz), 2.91 (2H, t, J = 6 Hz), 3.59 (2H, s), 3.97 (3H, s), 6.99 (1H, d, J = 9 Hz), 7.09 (1H, d, J = 8 Hz),

7.32 (1H, dd, $J=2$ and 8 Hz), 7.40 (1H, s), 7.79 (2H, m), 7.90 (1H, d, $J=2$ Hz).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-ethoxybenzamide (30).** ^{1}H NMR ($CDCl_3$) δ 1.51 (3H, t, $J=7$ Hz), 2.49 (3H, s), 2.74 (2H, t, $J=6$ Hz), 2.92 (2H, t, $J=6$ Hz), 3.62 (2H, s), 4.18 (2H, q, $J=7$ Hz), 6.96 (1H, d, $J=9$ Hz), 7.09 (1H, d, $J=8$ Hz), 7.31 (1H, dd, $J=2$ and 8 Hz), 7.39 (1H, d, $J=2$ Hz), 7.76 (2H, m), 7.89 (1H, d, $J=2$ Hz); *m*/*z* (API^+): 345 (MH^+; 100%, $C_{19}H_{21}ClN_2O_2$ requires M^+ 344).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-chloro-4-*iso*-propoxybenzamide (31).** ^{1}H NMR ($CDCl_3$) δ 1.42 (6H, d, $J=6$ Hz), 2.49 (3H, s), 2.74 (2H, t, $J=6$ Hz), 2.92 (2H, t, $J=6$ Hz), 3.63 (2H, s), 4.67 (1H, quintet, $J=6$ Hz), 6.98 (1H, d, $J=9$ Hz), 7.09 (1H, d, $J=8$ Hz), 7.28 (1H, dd, $J=2$ and 8 Hz), 7.40 (1H, d, $J=2$ Hz), 7.67–7.81 (2H, bm), 7.88 (1H, d, $J=2$ Hz); *m*/*z* (API^+): 359 (MH^+; 100%, $C_{20}H_{23}ClN_2O_2$ requires M^+ 358).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-bromo-4-methoxybenzamide (32).** White powder, mp 134–136 °C (diethyl ether). ^{1}H NMR ($CDCl_3$) δ 2.47 (3H, s), 2.71 (2H, t), 2.91 (2H, t), 3.60 (2H, s), 3.97 (3H, s), 6.96 (1H, d), 7.10 (1H, d), 7.29 (1H, m), 7.40 (1H, s), 7.67 (1H, s), 7.84 (1H, dd), 8.02 (1H, s), 8.05 (1H, d); *m*/*z* (API^+): 377, 375 (MH^+; 30%, $C_{18}H_{19}BrN_2O_2$ requires M^+ 375).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide (33).** ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 2.72 (2H, t, $J=6$ Hz), 2.92 (2H, t, $J=6$ Hz), 3.60 (2H, s), 3.98 (3H, s), 7.09 (2H, m), 7.32 (1H, dd, $J=2$ and 8 Hz), 7.41 (1H, d, $J=2$ Hz), 7.83 (1H, s), 8.07 (2H, m); *m*/*z* (API^+): 365 (MH^+; 100%, $C_{19}H_{19}F_3N_2O_2$ requires M^+ 364). Converted into a monohydrochloride obtained as white crystals, mp 186–188 °C.

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-cyano-4-methoxybenzamide (34).** ^{1}H NMR ($CDCl_3$) δ 2.47 (3H, s), 2.70 (2H, t, $J=6$ Hz), 2.91 (2H, t, $J=6$ Hz), 3.59 (2H, s), 4.02 (3H, s), 7.09 (2H, t, $J=8$ Hz), 7.29 (1H, dd, $J=2$ and 8 Hz), 7.39 (1H, d, $J=2$ Hz), 7.80 (1H, s), 8.10 (2H, m); *m*/*z* (API^+): 322 (MH^+; 100%, $C_{19}H_{19}N_3O_2$ requires M^+ 321).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-chloro-3-methoxybenzamide (35).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.47 (3H, s), 2.70 (2H, t, $J=6$ Hz), 2.88 (2H, t, $J=6$ Hz), 3.59 (2H, s), 3.98 (3H, s), 7.11 (1H, d), 7.21 (1H, d), 7.30 (2H, m), 7.40 (1H, d), 7.45 (1H, d), 7.75 (1H, s); *m*/*z* (API^+): 331.1 (MH^+; 100%, $C_{18}H_{19}ClN_2O_2$ requires M^+ 330.8).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-bromo-2,4-dimethoxybenzamide, hydrochloride (36).** Off-white solid, mp 190° (dec). ^{1}H NMR (250 MHz, $CDCl_3$ + CD_3OD) δ 2.89–3.19 (4H, m and overlapping s at 2.98 and HOD signal), 3.27 (1H, m), 3.46 (1H, m, overlapping with C*H*D_2OD signal), 3.70 (1H, m), 4.00 (3H, s), 4.11 (4H, overlapping s and d), 4.58 (1H, br d), 6.54 (1H, s), 7.18 (1H, d), 7.38 (1H, d), 7.61 (1H, br s), 8.36 (1H, s), 9.69 (partially exchanged 1H, br s); *m*/*z* (API^+): 407, 405 (MH^+; 80%, $C_{19}H_{21}BrN_2O_3$ requires M^+ 405).

***N*-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-3,5-dichloro-4-methoxybenzamide (37).** ^{1}H NMR ($CDCl_3$) δ 2.46 (3H, s), 2.69 (2H, t, $J=6$ Hz), 2.90 (2H, t, $J=6$ Hz), 3.57 (2H, s), 3.96 (3H, s), 7.09 (1H, d, $J=8$ Hz), 7.30 (1H, dd, $J=2$ and 8 Hz), 7.34 (1H, d, $J=2$ Hz), 7.81 (2H, s), 7.89 (1H, s); *m*/*z* (API^+): 365 (MH^+; 100%, $C_{18}H_{18}Cl_2N_2O_2$ requires M^+ 365).

***N*-(1,2,3,4-Tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethylbenzamide (38).** ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.65 (2H, t, $J=6$ Hz), 3.00 (2H, t, $J=6$ Hz), 3.85 (3H, s), 3.89 (2H, s), 6.95 (2H, d), 7.17 (1H, dd, $J=6$, 2 Hz), 7.25 (1H, s), 7.57 (1H, s), 7.93 (2H, m); *m*/*z* (API^+): 351.1 (MH^+; 100%) $C_{18}H_{17}F_3N_2O_2$ requires M^+ 350).

***N*-(2-Ethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide (39).** ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, $J=7$ Hz), 2.65 (2H, q, $J=7$Hz), 2.80 (2H, d, $J=6$ Hz), 2.92 (2H, t, $J=6$ Hz), 3.67 (2H, s), 3.97 (3H, s), 7.07 (2H, m), 7.30 (1H, m), 7.41 (1H, d, $J=2$ Hz), 7.89 (1H, brs), 8.06 (2H, m); *m*/*z* (API^+): 379 (MH^+; 100%, $C_{20}H_{21}F_3N_2O_2$ requires M^+ 378).

***N*-(2-*iso*-Propyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxy-3-trifluoromethyl benzamide (40).** ^{1}H NMR ($CDCl_3$) δ 1.13 (6H, d, $J=7$ Hz), 2.84 (5H, m), 3.72 (2H, s), 3.97 (3H, s), 7.07 (2H, m), 7.26 (1H, m), 7.43 (1H, d, $J=2$ Hz), 7.83 (1H, brs), 8.04 (2H, m); *m*/*z* (API^+): 393 (MH^+; 100%, $C_{21}H_{23}F_3N_2O_2$ requires M^+ 392).

Pharmacological methods

Mouse MEST model. Compounds were evaluated for oral anticonvulsant activity in groups of 12 naive mice (male CD1-Charles River, 25–30 g) in the mouse MEST test using an 'up and down' method of shock titration as described in Dixon and Mood[15] and Upton et al.[16] Compounds were administered orally by gavage as a fine suspension in 1% methylcellulose in water in a dose volume of 1 mL/kg. Percentage increases for drug-treated groups are devised from studies where standard errors were less than 10% of the CC_{50} values and with $p<0.05$ compared to vehicle control animals; measured at 1 h post-dose. In all experiments, the CC_{50} values for vehicle-treated controls fell within the range of 12–14 mA. Statistical comparisons between vehicle and drug-treated groups were made using the method of Litchfield and Wilcoxon.[17]

Rat MES(T) models. For the MEST test, the threshold for maximal (tonic hindlimb extension) electroshock seizures in male rats (Sprague–Dawley, 80–150 g, 6 weeks old) was determined by a Hugo Sachs Electronik stimulator which delivered a constant current (0.3 s duration; from 1 to 300 mA in steps of 5–20 mA). For the MES test a fixed high-intensity supramaximal current of 120 mA (ca. 5× basal threshold current; 0.3 s duration) was applied. The procedures are similar to that outlined above for mouse and full details are as published by Upton et al.[12,16]

Acknowledgements

We thank Anna Wright and Julie Carlisle for technical assistance in the preparation of compounds **3**, **4**, **10**, **39** and **40**, Vicky Holland and Di Hoult for in vitro screening information and Kellie Darker for manuscript preparation.

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