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IDENTIFICATION OF A SERIES OF 1,2,3,4-TETRAHYDROISOQUINOLINYL-BENZAMIDES WITH POTENTIAL ANTICONVULSANT ACTIVITY

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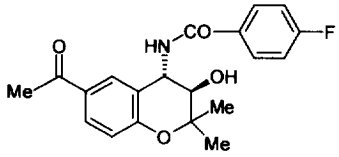
Abstract: A series of *N*-(tetrahydroisoquinolinyl)-2-methoxybenzamides was identified by high-throughput screening at the novel SB-204269 binding site. SAR studies have provided compounds **4** and **14** with high affinity and good anticonvulsant activity in animal models.

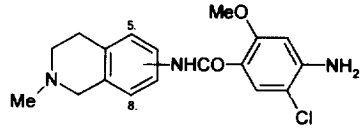
Keywords: Anticonvulsant activity, molecular modelling, heterocyclic compounds, SB-204269 binding site.

In an earlier publication,[1] 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 4-fluorobenzamide **1** SB-204269, as a potent anticonvulsant agent which is currently undergoing clinical evaluation as a pioneer treatment for epilepsy disorders.[2] We demonstrated[2,3,4] that *trans* 4*S* benzamides of this type interact selectively at a novel unique binding site in the brain of several species, including man, which was revealed by high affinity for [^{3}H] SB-204269. It was also shown that there was a good correlation between *in vitro* and *in vivo* potency.[4]

We wished to identify alternative structural classes in order to fully exploit this novel 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[4] revealed the two isomeric tetrahydroisoquinolinyl (THIQ) benzamides, 8-substituted **16** (pKi 6.1) and 5-substituted **12** (pKi 7.8) . The latter already has a 3-fold higher affinity than SB-204269 but, unfortunately, only gave a moderate increase in the level of induced seizure threshold when examined *in vivo* in mouse MEST at a dose of 10 mg/kg p.o. In order to exploit these leads and produce compounds (see Scheme 1) with an improved *in vivo* profile, a preliminary SAR analysis was carried out and the results of that study (see Table 1) are summarised here.



1 SB-204269



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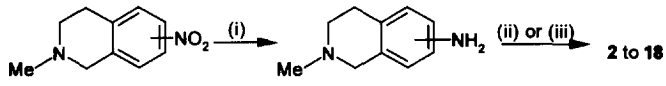
Chemistry and SAR



19 20

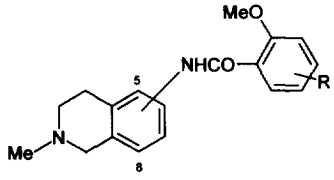
Scheme 1: Reagents and Conditions

(i) 10% PdC, H_2, ethanol, 4h; (ii) ArCOCl, Et_3N, CH_2Cl_2, 6h, 25°C;

(iii) $ArCO_2H$, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide, HOBT, DMF, 18h, 25°C; [see ref. 8 for 4].

The appropriate nitro-1,2,3,4-tetrahydroisoquinolines **19** were prepared according to literature procedures.[5] Catalytic hydrogenation gave the corresponding amines **20** which were converted into the THIQ benzamides **2** to **18**, using standard procedures, in good overall yields from **19**. Any necessary purification was carried out by flash chromatography through silica gel using dichloromethane: methanol: ammonia (95:4.5:0.5) as eluent.

Table 1: Biological Data for Compounds 1 - 18



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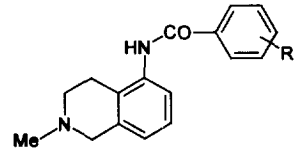


17 - 18

Cpd[a]	Isomer	R	[^{3}H] SB-204269 Binding[b] pKi	rodent MEST[c], % increase in seizure threshold at 10mg/kg p.o. Mouse at 1h post-dose	Rat at 4h post-dose
1	SB-204269	-	7.3	100***	570***
2	5	H	5.8	ND	ND
3	5	4-Et	7.3	60**	ND
4	5	4-Bu^t	7.7	140***	330***
5	5	4-Cl	6.1	ND	ND
6	5	5-Cl	7.0	20*	ND
7	5	3,5-diCl	5.4	ND	ND
8	5	4-NO_2, 5-Cl	6.8	ND	ND
9	5	4-Me, 5-Cl	7.6	50***	ND
10	5	4-Et, 5-Cl	7.9	100***	ND
11	5	4-Bu^t, 5-Cl	6.9	ND	ND
12	5	4-NH_2, 5-Cl	7.8	25*	ND
13	6	4-Bu^t	6.4	4NS	ND
14	7	4-Bu^t	7.6	130***	110***
15	7	5-Cl	7.2	4NS	ND
16	8	4-NH_2, 5-Cl	6.1	ND	ND
17	5	4-Bu^t	6.0	ND	ND
18	5	3-Cl	<5.0	ND	ND

[a] All compounds gave satisfactory spectroscopic data [^{1}H NMR (250MHz) and $^m/_z$] in accordance with their structures.

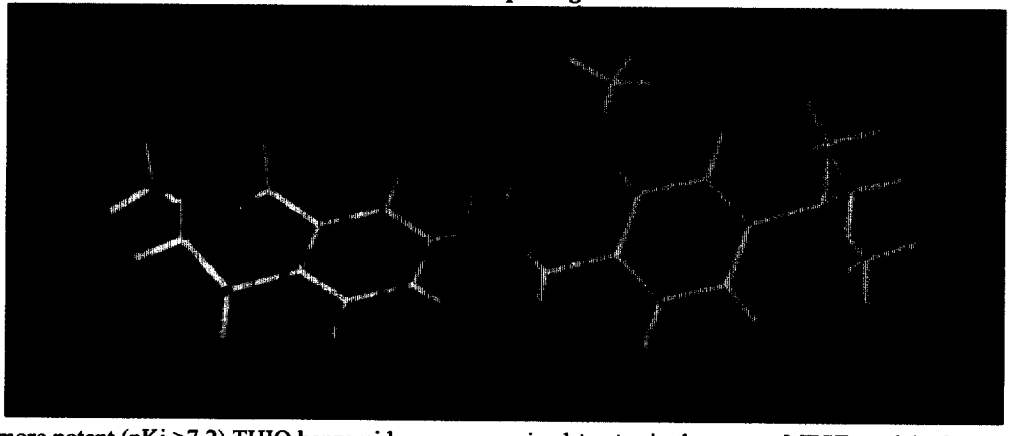
[b] Procedures as detailed in ref 3 and 4; all determinations were carried out in triplicate, s.e.m. < ± 0.05.

[c] Procedures as detailed in ref 6 and 7; * $p<0.05$, ** $p<0.01$, *** $p<0.005$, compared to vehicle-treated controls by (two-tail) Mann Whitney U test following Kruskal-Wallis one way analysis of variance. NS: not significant ND: not determined.

In the 5-substituted THIQs, removal of the 4-amino-5-chloro substituents from the potent lead **12** gave the 2-methoxybenzamide **2** with only modest affinity (pKi 5.8). However, incorporation of an alkyl substituent at the 4-position of **2** restored potency as seen for 2-methoxy, 4-ethyl **3** (pKi 7.3) and more so for 2-methoxy-4-*t*-butyl **4** (pKi 7.7), suggesting an interaction with a lipophilic pocket at the binding site. Introduction of a 4-chloro substituent (compound **5**) had little effect on affinity (pKi 6.1), whereas moving the chloro to the 5-position (compound **6**), as in the lead **12**, had a marked effect (pKi 7.0). The combination of a 5-chloro with a 4-alkyl substituent led to a further increase in potency for small alkyl (e.g. **9** and **10**) but was actually detrimental in the case of the more bulky 4-*t*-butyl **11** (pKi 6.9). Introduction of a second halogen atom at the 3-position of **6** to give the 3,5-dichloro **7** resulted in a marked reduction in affinity (pKi 5.4). In contrast the 4-nitro, 5-chloro **8** had similar affinity (pKi 6.8).

The affinities of the initial leads **12** and **16** showed that attachment of the benzamide moiety at the 5-position was much preferred over attachment at the 8-position of the THIQ nucleus. Further exploration of the location of the point of attachment using the preferred 2-methoxy-4-*t*-butyl substitution pattern showed that whereas 6-substitution (compound **13**) resulted in low affinity, 7-substitution (compound **14**) was indistinguishable from 5-substitution (compound **4**). This was also true for the 2-methoxy-5-chloro analogues (**6**, **15**). For the 5-substituted isomers, the substantial loss of affinity seen with the 3-chloro **18** and the 4-*t*-butyl **17** (pKi 6.0) demonstrated that the 2-methoxy substituent is essential for optimum potency. Molecular modelling overlap studies using SYBYL[9] (see Figure 1) were used to rationalise the equivalent affinities of the 5- and 7-substituted isomers **4** and **14**. These were carried out on the charged molecules and show good overlap of the THIQ nitrogen and lipophilic benzamide groups. 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.

Figure 1 Overlapped energy minimised conformations of 4 (green) and 14 (yellow) generated using the SYBYL package.



The more potent (pKi >7.2) THIQ benzamides were examined *in vivo* in the mouse MEST model. Compounds **4**, **10** and **14** exhibited a similar level of activity to SB-204269. Further evaluation of **4** in the rat MEST model at 4h post-dose confirmed its high anticonvulsant activity and a good duration of action. The potential for

THIQ benzamides in the treatment of epilepsy disorders is encouraging since this profile is comparable to the early *in vivo* data observed for SB-204269 (see Table). Also, **4** was selective (>30 fold) over a range of other receptors which are thought to modulate neurotransmission. Further detailed SAR analysis and the full anticonvulsant profile of these and related THIQ benzamides will be published elsewhere.

Acknowledgement

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7. Compounds were evaluated for oral anticonvulsant activity in groups of 12 naive mice (male CD1-Charles River, 25-30g) in the mouse MEST test using an "up and down" method of shock titration as described in Upton, N. *Trends Pharmacol. Sci.* **1994**, *15*, 456. 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.
8. Synthesis of **4**: 4-*t*-Butyl-2-methoxybenzoic acid (208mg, 1.0 mmol) in DMF (8 ml) was stirred with 1 eq of EDC and HOBT at 25°C for 30 min. A solution of 5-amino **20** (163mg, 1.0 mmol) in CH_2Cl_2 (2 ml) was added and the mixture kept at 25°C for 18 h. Work-up with $CHCl_3$ followed by flash chromatography gave **4** (253mg, 75%) which was converted into a hydrochloride salt. ^1H NMR (270MHz, 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 (CI): 353 (MH^+, 80%), Found: M^+ 352.21549 Calc for $C_{22}H_{28}N_2O_2$ 352.21666.
9. SYBYL, Tripos Associates, Inc., 1699 S. Hanley Rd, Suite 303, St. Louis, MO 63144, USA.