

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2903-2906

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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

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Received 11 May 1998; accepted 8 September 1998

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. © 1998 Elsevier Science Ltd. All rights reserved.

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

In an earlier publication,¹ we reported that novel *trans 4S* 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 4S* 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 [³H] 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 forebrain⁴ 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.



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Chemistry and SAR



Scheme 1: Reagents and Conditions

(iii) ArCO₂H, 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





17 - 18

Cpda		R	[³ H] SB-204269 Binding ^b pKi	rodent MEST ^c , % increase in	
				Mouse at 1h	Rat at 4h post-dose
	SB-204209	-	1.3	100***	5/0****
2	5	н	5.8	ND	ND
3	5	4-Et	7.3	60**	ND
4	5	4-But	7.7	140***	330***
5	5	4-Ci	6.1	ND	ND
6	5	5-CI	7.0	20*	ND
7	5	3,5-diCl	5.4	ND	ND
8	5	4-NO2, 5-Ci	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-NH2, 5-Cl	7.8	25*	ND
13	6	4-But	6.4	4NS	ND
14	7	4-Bu ^t	7.6	130***	110***
15	7	5-CI	7.2	4NS	ND
16	8	4-NH2, 5-Cl	6.1	ND	ND
17	5	4-Bu ^t	6.0	ND	ND
18	5	3-C1	<5.0	ND	ND

a All compounds gave satisfactory spectroscopic data [¹H 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.

⁽i) 10% PdC, H₂, ethanol, 4h; (ii) ArCOCI, Et₃N, CH₂Cl₂, 6h, 25°C;

In the 5-substituted THIQs, removal of the 4-amino-5-chloro substituents from the potent lead 12 gave the 2methoxybenzamide 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 4chloro substituent (compound 5) had little effect on affinity (pKi 6.1), whereas moving the chloro to the 5position (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 4nitro, 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 SYBYL⁹ (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

We thank Anna Wright for technical assistance in the preparation of compounds 2 and 18, Vicky Holland for cross-screening information and Kellie Darker for manuscript preparation.

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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 drugtreated 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 CH₂Cl₂ (2 ml) was added and the mixture kept at 25°C for 18 h. Work-up with CHCl₃ followed by flash chromatography gave 4 (253mg, 75%) which was converted into a hydrochloride salt. ¹H NMR (270MHz, DMSO-d⁶) 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 C₂₂H₂₈N₂O₂ 352.21666.
- 9. SYBYL, Tripos Associates, Inc., 1699 S. Hanley Rd, Suite 303, St. Louis, MO 63144, USA.