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Bioorganic & Medicinal Chemistry Letters 13 (2003) 1627–1629

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

The Design of 8,8-Dimethyl[1,6]naphthyridines as Potential Anticonvulsant Agents

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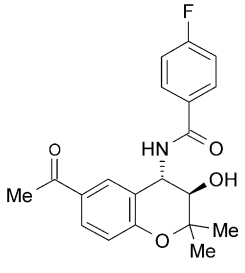
Received 5 February 2003; revised 18 March 2003; accepted 19 March 2003

Abstract—Starting from a series of 7-linked tetrahydroisoquinoline derivatives, as exemplified by SB-270664, a new series of 8,8-dimethylnaphthyridine compounds has been identified. SAR studies around these attractive leads have provided compounds such as **12** which display excellent anticonvulsant activity and an encouraging pharmacokinetic profile in vivo.

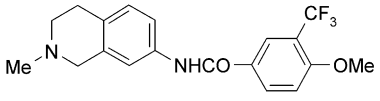
Epilepsy is one of the most prevalent neurological conditions worldwide. Pharmacological therapy remains the cornerstone of epilepsy treatment, however, refractory epilepsy (in 20–30% of sufferers) is still a significant clinical problem despite the discovery of the second generation of anticonvulsant agents.[1,2] Anticonvulsant treatment failures may result from lack of efficacy and the occurrence of significant undesired side-effects. The newer generation of anticonvulsants has taken into account the shortcomings of existing therapies and attempted to improve on the currently available treatments using rational drug design.[3] One such compound with a novel mechanism of action, the benzopyran carabersat (SB-204269), is currently being progressed for the treatment of epilepsy and migraine prophylaxis.[4]



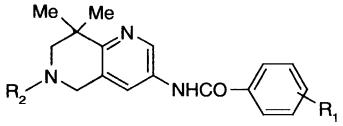
carabersat

SAR Studies and Discussion

In an earlier paper, the 7-substituted tetrahydroisoquinoline (THIQ) SB-270664 was reported as a promising key lead compound.[5] SB-270664 has high affinity at the [^{3}H]-SB-204269 binding site (pK_i 8.9) but was later found to have high in vivo clearance and poor oral bioavailability (Fpo < 2%) in the rat. In-vitro metabolism studies in rat liver microsomes and hepatocytes indicated that the major routes of metabolism were hydroxylation of the THIQ benzo ring, *N*-demethylation and aromatisation to the isoquinolinium species.[6]



SB-270664



(1) and compounds 2-14

Consequently, the aim for medicinal chemistry was to address these issues and improve the overall in vivo profile and properties of SB-270664. Several cycles of

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doi:10.1016/S0960-894X(03)00288-9

target design and SAR analysis provided a series of 8,8-dimethyl[1,6]naphthyridines (**1**) for further exploration. In this series the *gem* dimethyl group is incorporated to prevent aromatisation and replacement of the THIQ benzo ring by pyridyl represents an attempt to reduce hydroxylation. This paper describes the properties and potential of this class of compounds.

Analysis of SAR around the THIQs indicated that the optimal substitution on the benzamide ring was an electron withdrawing group at the 3-position and a bulky lipophilic group at the 4-position. Using this information a limited number of compounds was prepared with the 8,8-dimethylnaphthyridine template. In addition to the parent N-Me analogues, the corresponding N-H compounds were also prepared to address the likely dealkylation previously observed in vivo in the THIQ series.

Compounds were screened in the [^{3}H]-SB-204269 binding assay (Table 1). From primary data, it was apparent that the SAR paralleled that seen in the THIQ series. The nature of the electron withdrawing group at the 3-position (R_1) was crucial for high affinity. The chloro and bromo analogues, **4** and **5**, respectively, showed equivalent affinity and were around 10-fold more active than the fluoro derivative, **3**. The cyano analogue **6** showed reduced affinity compared with the chloro and bromo derivatives but the trifluoromethyl **7** was well tolerated. Lipophilic groups at the 4-position (R_1) were also shown to be a key requirement for high affinity, although increasing the steric bulk of this group was shown to have little effect on activity (cf. **5**, **7** and **8**). From the data obtained on the N-H derivatives (**9**–**14**), it was apparent that this change had little effect on affinity and the SAR followed the existing pattern.

When examined in vivo in the rat MEST test at 2 mg/kg po, compounds **4**, **5**, **7**, **8** and **10**–**12** showed a good level of anticonvulsant activity.

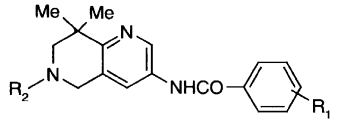
From this investigation, a number of compounds was selected for in vitro and in vivo pharmacokinetic (PK) profiling. The N-H compounds **10**–**12** all showed good oral bioavailability in the rat when dosed at 2 mg/kg (Fpo > 30%). The 3-CF_3, 4-OMe analogue **12** had excellent affinity (pK_i 8.7) and exhibited the optimal in vitro profile. Compound **12** was >100-fold selective across a range of 5-HT and adrenergic receptors. In addition **12** exhibited a clean human cytochrome P450 profile and had low intrinsic clearance in liver microsomes from rodents, dog and man.[10] Following iv/po administration to the rat, **12** showed low clearance and high oral bioavailability (CLb 30 mL/min/kg, Fpo > 50%) and was progressed to the rat supraMES anticonvulsant model.[8]

In contrast, the corresponding N-Me derivative **7** showed only moderate oral bioavailability in the rat (Fpo 20%) but had high in vivo clearance (CLb 82 L/min/kg), presumably due to *N*-demethylation.

Further PK work on **7** and **12** revealed interesting findings. From a rat CNS penetration study, compound **12** was found to have a brain:blood ratio of 0.3:1, while the corresponding N-Me analogue **7** exhibited a much higher level of CNS penetration (brain:blood 1.9:1). This appears to be reflected in the superior performance of **7** in the rat MEST test (see Table 1).

Compound **12** was dosed orally at 1, 10 and 30 mg/kg in the rat supraMES model. Each dose was assessed for the ability to protect the rat from hindlimb tonic seizures following a single shock (180 mA of 0.3 s duration) delivered via corneal electrodes of the HSE shocker, 4 h post dosing. The response to the shock was measured and compared to control. Analysis by 'ALLFITrd-quo;[11] produced an ED_{50} value of 3.9 mg/kg. This figure is comparable to that obtained with carabersat in the same model under identical conditions (ED_{50} of 6.3 mg/kg).

Table 1. Biological data for 8,8 dimethylnaphthyridinyl benzamides



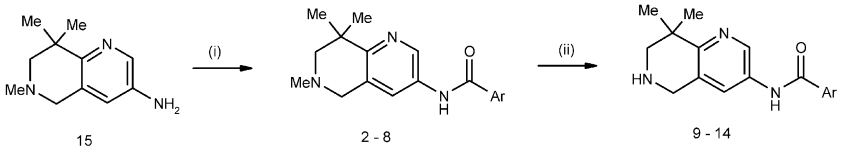
(1) and compounds 2-14

Compd	R_1	R_2	[^{3}H]SB-204269 binding[a] pK_i	Rat MEST[b] % increase in seizure threshold at 2 mg/kg p.o. 2 h post-dose
Carabersat[c]			7.3	120**
2	H	Me	6.2	3ns
3	3-F, 4-OMe	Me	7.3	Nd
4	3-Cl, 4-OMe	Me	8.5	380***
5	3-Br, 4-OMe	Me	8.6	210***
6	3-CN, 4-OMe	Me	7.3	110**
7	3-CF_3, 4-OMe	Me	8.8	570***
8	3-CF_3, 4-OEt	Me	8.5	310***
9	3-F, 4-OMe	H	7.2	Nd
10	3-Cl, 4-OMe	H	8.1	260**
11	3-Br, 4-OMe	H	8.7	260**
12	3-CF_3, 4-OMe	H	8.7	260***
13	3-CF_3, 4-OEt	H	8.6	80**
14	3-CF_3, 4-OiPr	H	8.4	15*

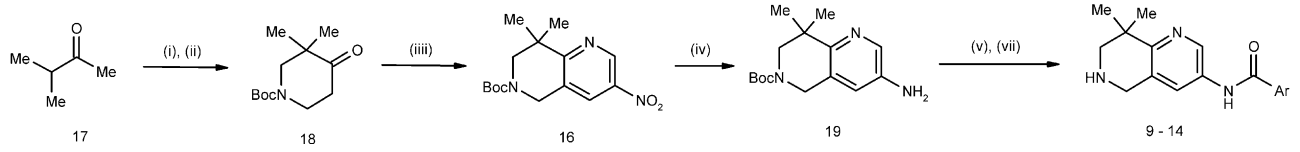
ns: not significant. Nd: not determined.
[a]Procedures as detailed in ref 7; all determinations were carried out in triplicate, sem $< \pm 0.05$.
[b]Procedures as detailed in ref 8; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, compared to vehicle-treated controls according to analysis following Lichfield and Wilcoxon in ref 9; doses refer to free base.
[c]Dosed at 2.5 mg/kg po.

Synthesis

Compounds[12] were prepared according to Schemes 1 and 2. The synthesis of the 3-amino-8,8-dimethyl-*N*-methyl[1,6]naphthyridine template **15** has previously been reported, albeit in low yield.[13] Compounds **2**–**8** were prepared in high yield from **15** via coupling with the requisite carbonyl chloride. The corresponding *des*-methyl analogues were also accessible by this route via demethylation with 1-chloroethyl chloroformate (ACE-Cl)[14] but this step proceeded in variable yields and



Scheme 1. Synthesis of compounds **2**–**8**. Reagents and conditions: (i) ArCOCl, Et_3N, CH_2Cl_2, 6 h, 25 °C (70–94%); (ii) ACE-Cl, CH_2Cl_2, 18 h, 50 °C, then MeOH, 1–24 h (36–97%).



Scheme 2. Synthesis of compounds **9** to **14**. Reagents and conditions: (i) HCHO, $BnNH_2$, EtOH, c.HCl; (ii) 10% Pd/C, H_2, $(Boc)_2O$ EtOH; (iii) 3,5-dinitro-2-pyridone, NH_3, MeOH; (iv) 10% Pd/C, H_2, EtOH, 4 h (25% from **17**); (v) ArCOCl, Et_3N, CH_2Cl_2, 6 h, 25 °C (75–89%); (vi) TFA, CH_2Cl_2 18 h, 25 °C (89–99%).

reproducibility. As it became apparent that the N-H analogues showed superior pharmacokinetic parameters to the N-Me derivatives, the synthesis of larger quantities of key compounds became a requirement. The unpredictable and toxic nature of the demethylation step meant that an alternative synthetic strategy was required. Route optimisation work produced an alternative intermediate **16** which was prepared via **18** and 3,5-dinitro-2-pyridone[15] (Scheme 2). The overall yield to **9**–**14** was high (20%) compared with using the original published route to such benzamides (<4% over nine steps).

Conclusions

A series of novel 8,8-dimethyl[1,6]naphthyridines has been prepared with high affinity in the [^{3}H]-SB-204269 binding assay. Compound **12**[16] has excellent aqueous solubility (>1 mg/mL) and has been shown to have an encouraging pharmacokinetic profile and good in vivo activity in preclinical anticonvulsant models in the rat. A modified synthesis of the naphthyridine core has also been developed allowing this particular series to be amenable to high throughput chemistry and scale-up.

This group of investigational anticonvulsants, from a new structural class, possesses an improvement in drug chemical structure, improved pharmacokinetic properties and as such represents an exciting potential for the treatment of epilepsy and related disorders.

Acknowledgements

The authors would like to thank Ms. G. Espasa-Bosch and Mr. S. P Wright for technical assistance.

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