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# CONFORMATIONAL PREFERENCE OF THE 6-ACETYL GROUP IN NOVEL ANTICONVULSANT *trans* 4*S*-BENZAMIDO-BENZO[b]PYRAN-3*R*-OLS

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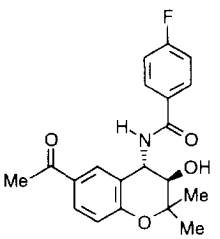
**Abstract**: Conformationally restricted ketones derived from the novel anticonvulsant 4*S* (4-fluorobenzoyl-amino)benzopyran SB-204269 **1** have revealed a preferred "in plane" conformation which is essential for optimal potency at a unique receptor site. © 1997 Elsevier Science Ltd.

In an earlier communication,[1] we reported that novel *trans* 4*S*-(substituted benzamido)-3,4-dihydro-2*H*-benzo[b]pyran-3*R*-ols showed good anticonvulsant activity in the mouse maximal electroshock seizure threshold (MEST) model. More recently, subsequent exploration of structure-activity relationships (SAR) led to the identification of the 4-fluorobenzamide SB-204269 **1** as a potent anticonvulsant which is currently undergoing clinical evaluation as a pioneer treatment for epilepsy disorders. We demonstrated [2,3] that *trans* 4*S*-benzamides of this type interact at a unique novel binding site in the brain of several species including man, which was revealed by high affinity for [$^3$H] SB-204269.




**1 SB-204269**

Examination of the SAR revealed that both the 4*S* stereochemistry of the benzamide and the 6-acetyl group were crucial requirements for maximum potency.[2] We also speculated that the 6-acetyl moiety was involved in a key interaction with a hydrogen bond donor group in the putative receptor site.

In order to investigate this hypothesis and obtain further information on the structural requirements of the binding site, we have examined the effect of conformational restriction of the 6-acetyl group. This was achieved by both introduction of a neighbouring methyl substituent (5-methyl **2** and 7-methyl **3**)and by cyclisation (**4, 5**).

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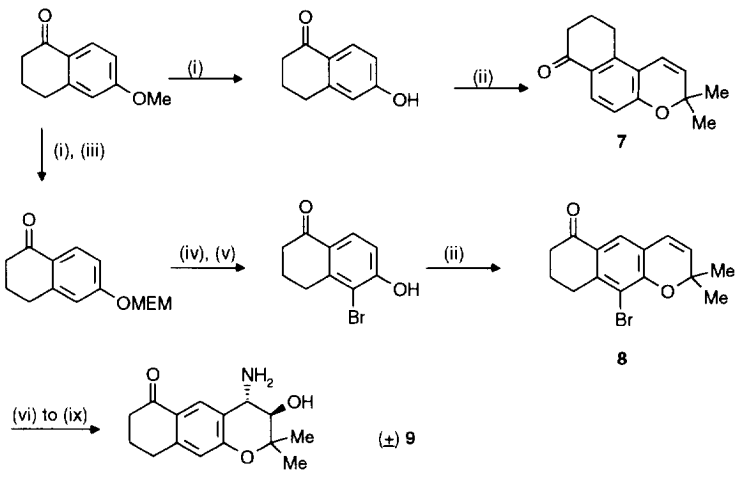
Some of this work was carried out with a 3-chloro, 4-fluoro disubstituted benzamide since the introduction of a 3-chloro group as in (**6**, pKi 7.91) was found to enhance the *in vitro* affinity of benzamides such as **1.**

## Chemistry and Discussion

The conformationally restricted compounds 5-methyl **2**, 7-methyl **3** and the cyclic analogues **4** and **5** were prepared as racemic *trans*-benzamides for ease of synthesis (Scheme). Since it has been demonstrated earlier[1,2] that potent anticonvulsant activity of the *trans* benzamides is associated virtually exclusively with the 4*S* enantiomers, it can be assumed that the 3*R*, 4*S* enantiomers of all racemates shown in the Table would have twice the potency.

## Scheme



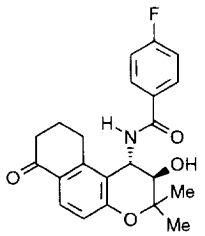

**Reagents and Conditions**

(i) aq HBr; 90% yield
(ii) aq NaOH, 3-chloro-3-methyl-but-1-yne, xylene, Δ followed by $PhNEt_2$, DMF, Δ; 58% yield
(iii) NaH, methoxyethoxymethylchloride, DMF, RT; 98% yield
(iv) $Br_2$, HOAc, NaOAc, 50% yield
(v) TFA, $CH_2Cl_2$, 0→25°C, 100% yield
(vi) DMSO, $H_2O$, NBS; 96% yield
(vii) 1,4-dioxan, aq NaOH, RT; 100% yield
(viii) $NH_4OH$, EtOH, RT; 90% yield
(ix) 10% Pd/C, $H_2$, EtOH, 85% yield

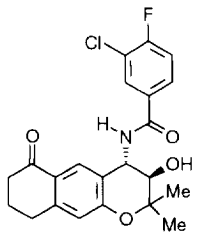
The synthesis of the benzamides was *via* acylation of the corresponding amino alcohols, which were prepared by established procedures,[2,4] already described for **1** and related compounds. The respective amino alcohols required for the synthesis of the conformationally restricted ketones (**4** and **5**) were made from chromene intermediates **7** and **8**, available from 6-methoxy-1-tetralone as depicted in the Scheme. The bromine substituted intermediate was prepared in order to direct the Claisen rearrangement of the propargyl ether to give **8**. Final removal of the bromo substituent by hydrogenolysis over 10% palladium on carbon in ethanol afforded the linear amino alcohol (**9**).

Examination of the binding affinities (Table) revealed important information on the structural requirements of this novel binding site. Introduction of either a 5- or 7-methyl group (**2** and **3** respectively) resulted in 10 to 100 fold loss in binding affinity, possibly due to an "out of plane" low energy conformation being favoured which is inappropriate for good receptor binding. Interestingly, the angular tetralone **4** was essentially devoid of activity whereas the equivalent linear compound **5** (pKi 7.6) maintained the level of affinity of the corresponding 6-acetyl benzopyran (**6**). This suggests strongly that the conformation fixed in tetralone **5** represents the low energy conformation adopted by 6-acetyl benzopyrans at the anticonvulsant binding site.

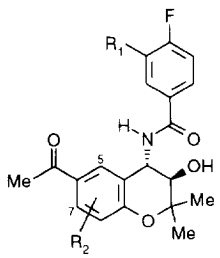
However, it was disappointing to find that on examination *in vivo* in the mouse MEST test, **5** showed a poorer level of activity (+98% at 30mg/kg p.o.) than expected when compared to the level observed with **6** (+138% at 10mg/kg p.o.).[6]




(±) **4**




(±) **5**




**1-3, 6**

**Table: Data for compounds 1 to 6**

| Cpd[a] | m.p.°C | $R_1$ | $R_2$ | Stereochem | [$^3$H] SB 204269 Binding[b] pKi |
|---|---|---|---|---|---|
| **1** | 163-4 | H | H | 3R, 4S | 7.32 ± 0.03 |
| **2** | 192-4 | H | 5-Me | (±) | 5.02 ± 0.08 |
| **3** | 162-3 | H | 7-Me | (±) | 6.15 ± 0.02 |
| **4** | >250 dec | - | - | (±) | <5.0 |
| **5** | 222-6 | - | - | (±) | 7.60 ± 0.06 |
| **6** | 160-1 | Cl | H | 3R, 4S | 7.91 ± 0.01 |

[a] All compounds gave satisfactory elemental analyses (CHN ± 0.4%) and spectroscopic data in accordance with their structures. For further details and data on **4** and **5** see ref. 5.

[b] Procedure as detailed in ref. 3.

In summary, we had shown earlier that the 6-acetyl group played an important role in conferring high anticonvulsant potency in the series of *trans* benzamidobenzopyrans. We have now demonstrated that the orientation of this 6-acetyl group is crucial for optimal activity and lends further support to the hypothesis that it is intimately involved in a key specific interaction with the binding site.

**Acknowledgement**

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**References and Notes**

1. Blackburn, T.P., Buckingham, R.E., Chan, W.N., Evans, J.M., Hadley, M.S., Thompson, M; Upton, N., Stemp, G. and Vong, A.K. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 1163.

2. Chan, W.N., Evans, J.M., Hadley, M.S., Herdon, H.J., Jerman, J.C., Morgan, H.K.A., Stean, T.O., Thompson, M., Upton, N., and Vong, A.K. *J. Med. Chem.*, **1996**, *39*, 4537.

3. (a) Preliminary results are reported in: Herdon, H., Jerman, J., Stean, T.O., Chan, W., Middlemiss, D.N. and Upton, N. *Eur. J. Pharmacol.*, **1996**, 314, R7

   (b) *Patent Cooperation Treaty Application*, **1996**, WO96/18650.

4. (a) Ashwood, V.A., Buckingham, R.E., Cassidy, F., Evans, J.M., Faruk, E.A., Hamilton, T.C., Nash, D.J., Stemp, G. and Willcocks, K. *J. Med. Chem.*, **1986**, *29*, 2194.

5. Prepared as described in Vong, A.K., Thompson, M., Evans, J.M. and Morgan, H.K.A. *Patent Cooperation Treaty Application,* **1995**, WO95/34547. Data for tetralones **4** and **5** are given below.

   Compound **4**
   (±)-2,2-Dimethyl-*trans*-4-(4-fluorobenzoylamino)-3,4,5,6,7,8-hexahydro-8-oxo-naphthaleno[2,1-b]pyran-3-ol. Cream crystals from ethyl acetate $\delta_H$ (270MHz, d$^6$DMSO): 1.28 (3H, s); 1.39 (3H, s); 1.80 - 2.09 (2H, m); 2.38 - 2.53 (2H, m, overlapping DMSO signal); 2.59 - 2.87 (2H, m); 3.80 (1H, t); 5.05 (1H, t); 5.60 (1H, d), 6.80 (1H, d); 7.30 (2H, t); 7.80 (1H, d); 7.98 (2H, m) and 8.66 (1H, d).

   Compound **5**
   (±)-2,2-Dimethyl-*trans*-4-(3-chloro-4-fluorobenzoylamino-3,4,6,7,8,9-hexahydro-6-oxo-naphthaleno[3,2-b]pyran-3-ol. Off-white powder from ethyl acetate/hexane $\delta_H$ (250 MHz; $CDCl_3$) 1.30 (3H, s), 1.53 (3H, s), 1.98 (2H, m), 2.20 (1H, m), 2.48 (1H, m), 2.78 (2H, m), 3.75 (1H, dd), 4.32 (1H, d), 5.22 (1H, t), 6.66 (1H, s), 7.13 (1H, s), 7.45 (1H, d), 7.82 (1H, m), 7.88 (1H, s) and 8.07 (1H, dd).

6. 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. 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. In all experiments, the $CC_{50}$ values for vehicle-treated controls fell within the range of 12-14mA.

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