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STEREOCHEMICAL PREFERENCES AND REQUIREMENT FOR THE 3-HYDROXYL GROUP IN NOVEL ANTICONVULSANT 4-FLUOROBENZOYLAMINO BENZOPYRANS

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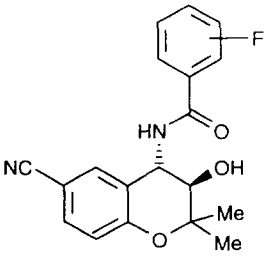
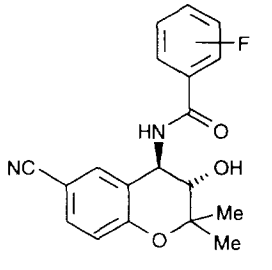
Abstract: A *cis* 3*S*,4*S* isomer, derived stereospecifically from an anticonvulsant *trans* 3*R*,4*S*-(*para*-fluorobenzoylamino)-benzopyran using the DAST reagent, has been shown to possess anticonvulsant properties. In contrast the *cis* 3*R*,4*R* enantiomer did not possess anticonvulsant properties but caused blood pressure to fall.

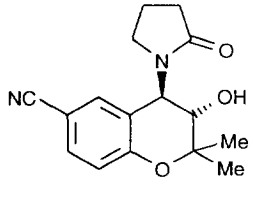
In our earlier communication[1], we reported that the fluorobenzamides **1** and **2** possessing 3*R*,4*S* stereochemistry, showed anticonvulsant activity in the mouse maximal electroshock threshold (MEST) model,[1] while being devoid of blood pressure lowering properties. In contrast, the 3*S*,4*R* enantiomers **3** and **4,** like the K^+ channel activator levcromakalim **5** which has the same absolute stereochemistry, showed potent antihypertensive activity. The anticonvulsant action of **1** and **2** was not thought to involve the modulation of ATP-sensitive K^+ channels.[2]



1, *meta*-F
2, *para*-F



3, *meta*-F
4, *para*-F

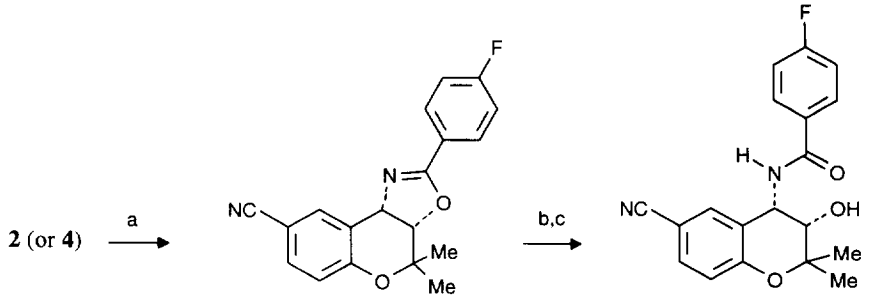


5, levcromakalim (-)-3S,4R

In order to examine further the stereochemical preferences about the benzopyran nucleus at C(3) and C(4) and the requirement for the C(3) hydroxyl group, the *cis* enantiomers **6** and **7** and the chroman **8** were required. In earlier studies[3] we have demonstrated that *trans*-4-benzoylamino-benzopyran-3-ols could be converted into their *cis* counterparts using diethylamino sulphur trifluoride (DAST).[4] Application of DAST (Scheme 1) to the individual *trans* enantiomers, **2** and **4** respectively, followed by acid-catalysed oxazoline ring opening furnished their corresponding *cis* isomers **6** and **7** in high (>99.8% ee) enantiomeric purity.[5] This observation is indicative of a highly stereospecific mechanism of action for the formation of the isomeric oxazolines **9** and **10** and their subsequent hydrolysis (Scheme 1). Oxazoline ring opening

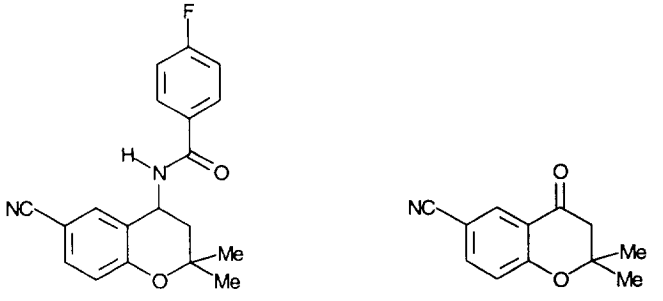
under acidic conditions and acyl transfer from oxygen to nitrogen with base completed the sequence in which the stereochemical integrity of the oxazoline intermediates **9** and **10** is maintained in **6** and **7**.

Scheme 1



Reagents: a) DAST, dichloromethane, room temp. b) aq. dioxan, dil. H_2SO_4 c) aq. dioxan, $NaHCO_3$

Synthesis of the chroman **8**,[5] as the racemate, was achieved by standard methodology from the 4-chromanone **11**. Thus reduction to the chromanol, conversion to the chloride and subsequently the azide, followed by reduction and fluorobenzoylation of the resulting amine, all under standard conditions, furnished the required chroman **8**.



The compounds were evaluated in the previously described[1] mouse MEST test (see Table 1). The *cis* 3*S*,4*S* compound **6** derived from the anticonvulsant 3*R*,4*S* compound **2** was also found to possess anticonvulsant properties, albeit with reduced potency. In contrast, the *cis* 3*R*,4*R* compound **7** derived from the 3*S*,4*R* isomer **4** was devoid of anticonvulsant activity at the administered dose of 10 mg/kg. On i.v. administration of compounds **6** and **7** at a dose of 10 mg/kg infused over 30 minutes to groups of 3 pentobarbitone-anaesthetised Hooded Lister rats, blood pressure falls for the two compounds were recorded as 5 ± 3% and 36 ± 7%, respectively. Thus the 3*R*,4*R* enantiomer **7** caused a significant fall in blood pressure unlike the 3*S*,4*S* enantiomer **6**. Moreover, comparing all four isomers, it can be concluded

that anticonvulsant activity is associated with the presence of an *S* configured fluorobenzoylamino substituent at position C(4), while the hydroxyl group at position C(3) can be of either configuration. In contrast, the presence of an *R* configured fluorobenzoylamino substituent at position C(4) is associated with antihypertensive activity.

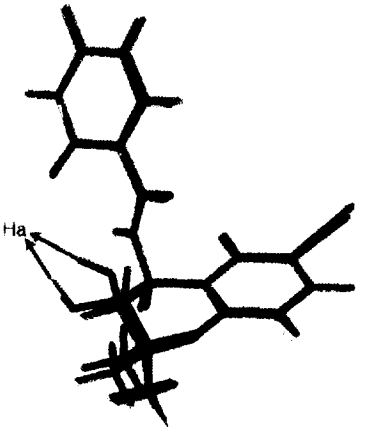
Table 1. Effect of compounds 2, 4 and 6-8 in the mouse MEST model (10 mg/kg po)

Cpd. No.	Stereochemistry	% Increase in Seizure Threshold
2[a]	*3R,4S*	41*
4[a]	*3S,4R*	17
6	*3S,4S*	28*
7	*3R,4R*	0
8	(+)	5

[a] reproduced from ref 1 for comparison. *$p<0.05$ compared to vehicle controls.

The lack of anticonvulsant activity in the racemic chroman **8** is clearly indicative of a requirement for the hydroxyl group. As the C(3) hydroxyl group is acceptable in both configurations with a C(4) *S* orientated substituent, we speculate that each can hydrogen bond to a hydrogen bond acceptor in a putative receptor site for these compounds, which is capable of accepting both configurations. Figure 1 shows overlapped energy-minimised conformations of **2** and **6** generated using the SYBYL package,[6] where the arrows represent such putative hydrogen bonds from the C(3) hydroxyl groups, pointing to a common acceptor location (**Ha**). A rigid systematic search around the C(3) - O bond, showed that these conformations were within 4 Kcal/mol of the absolute minimum. Such an acceptor group could comprise a bifurcate group or be able to freely rotate so as to hydrogen bond in the appropriate direction.

Figure 1 Overlapped energy minimised conformations of 2 and 6 generated using the SYBYL package [putative hydrogen bonds are shown as arrows to a common acceptor location Ha].



In summary, it has been demonstrated that in this series of 4-fluorobenzoylamino benzopyrans, the stereochemistry at C(4) is of crucial importance in determining the pharmacological activity. Those compounds in which the fluorobenzoylamino moiety has *S* stereochemistry show anticonvulsant activity and lack antihypertensive activity. The reverse is true for compounds in which the fluorobenzoylamino group has *R* stereochemistry. The hydroxyl group appears to be essential for anticonvulsant activity, but its stereochemistry is not crucial. Further details of this interesting differentiation of anticonvulsant and antihypertensive activities will form the basis of future reports.

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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. *BioMed. Chem. Letts.*, **1995**, *5*, 1163.
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3. Burrell, G., Evans, J.M., Jones, G.E. and Stemp, G. *Tetrahedron Letts.*, **1990**, *31*, 3649.
4. a) Middleton, W.J. *J. Org. Chem.*, **1975**, *40*, 574.
   b) Mann, J. *Chem. Soc. Rev.*, **1987**, *16*, 381.
5. All new compounds gave satisfactory elemental analyses and mass spectral characteristics in accord with their structures.
   Compound **6** (50%): mp 102-105 °C; NMR (DMSOd_6, 270 MHz) δ 1.32 (Me), 1.42 (Me), 3.74 (narrow m, H-3), 5.47 (dd, J=8, 3Hz, H-4), 5.74 (d, J=5Hz, O*H*), 6.92 (d, J=8Hz, H-8), 7.32 (m, 2 ArH), 7.57 (narrow m, H-5) overlapping 7.60 (m, H-7), 8.10 (m, 2 ArH), 8.57 (d, J=8Hz, N*H*); $[\alpha]_D^{20}$-79.9° (MeOH, c=0.36)
   Compound **7** (36%): mp 105-106 °C; $[\alpha]_D^{20}$ + 86.9° (MeOH, c=1.0)
   Compound **8**: mp 175.5 °C, NMR (DMSOd_6, 400 MHz) δ 1.43(Me), 1.54 (Me), 2.04 (t, J=12 Hz, H-3), 2.37 (dd, J=12, 6Hz, H-3), 5.44 (m, H-4), 2.04 (d, J=8Hz, H-8), 7.43 (m, 2 ArH), 7.20 (irreg m, H-5 & H-7), 8.10 (m, 2 ArH), 8.95 (d, J=7Hz, N*H*).
   Chiral HPLC determinations on a Chiralcel OD, 250 mm x 4.6 mm, P-45SC (Daicel) column using phosphate buffer (pH3)-methanol-acetonitrile as eluent.
6. SYBYL, Tripos Associates, Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO 63144, USA, Version 6.1

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