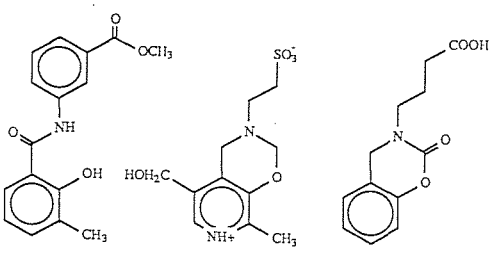
03.1-1 CRYSTAL STRUCTURES OF TRANSITION-STATE ANALOGUES OF GABA-TRANSAMINASE INHIBITORS. By J.M. Gulbis and M.F. Mackay, Department of Chemistry, La Trobe University, Bundoora, Victoria, Australia 3083.

Compounds that inhibit the conversion of the neurotransmitter γ-aminobutyric acid (GABA) into its metabolite succinic semialdehyde by the enzyme GABA-transaminase increase brain levels of GABA, and may cause an anticonvulsant reaction in the central nervous system. The reaction catalyzed by GABA-transaminase involves the initial formation of a Schiff base (the transition-state) between the coenzyme pyridoxal phosphate and GABA. A number of inhibitors based on the transition-state structure (Andrews, Iskander, Jones and Winkler, *Int. J. Quantum Chem., Quantum Biol. Symp.*, 1982, **9**, 345-353) are being designed as potential anticonvulsant drugs by Professor P.R. Andrews, group at the Victorian College of Pharmacy Ltd. In collaboration with this group, the X-ray structures of some of these inhibitors are being determined and include the three structures presented below.



(1) (2) (3)

Crystal data: (1) $C_{16}H_{15}NO_4$, *Pbca*, a = 6.136(1), b = 13.623(2), c = 33.839(5) Å, Z = 8, R = 0.066 for 1271 data ($I \geq \sigma I$); (2) $C_{11}H_{16}N_2O_5S$, $P\bar{1}$, a = 7.818(1), b = 8.504(1), c = 10.214(1) Å, α = 107.76(2), β = 94.89(1), γ = 98.42(1)°, Z = 2, R = 0.048 for 1993 data ($I \geq 1.5\sigma I$); (3).H_2O, $C_{12}H_{15}NO_5$, $P2_1/c$, a = 15.359(2), b = 6.100(1), c = 14.392(2) Å, β = 113.72(1)°, Z = 4, R = 0.050 for 1352 data ($I \geq 3\sigma I$).

Structure (3), with the oxazone ring planar, most closely resembles that of the calculated transition-state (Andrews, Iskander, Jones and Winkler submitted for publication) whereas in (2), the oxazine ring is in a sofa form with the nitrogen lying 0.57(1) Å from the plane of the other ring atoms. Although (1) is virtually planar (dihedral angle between the phenyl rings 4.8(3)°), an intramolecular hydrogen bond between the amide oxygen and phenol hydroxyl precludes interaction of the latter with the amide nitrogen.

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03.1-2 STUDIES OF POTENT BENZAMIDE ANTICONVULSANTS: THE IMPORTANCE OF CHIRALITY TO TOXICITY AND ACTIVITY. By Norma E. Duke and Penelope W. Codding, Departments of Chemistry and of Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, Canada.

Because epileptic disorders are not adequately managed by the currently available anticonvulsant drugs, there is still a need for new drugs with greater selectivity and lower toxicity. One promising new series of compounds is based on the 4-amino-N-benzamide molecular backbone. This series is particularly interesting since chiral analogues show differences in activity and even greater differences in toxicity.

A chiral benzamide, 4-amino-N-(α-methylbenzyl)benzamide, is a potent drug in the two tests commonly used to screen compounds for anticonvulsant activity, the MES test (clonic-tonic seizures) and the scMET test (myoclonic seizures). Furthermore, the protective indices for both isomers are either superior to or equal to those of phenobarbital and phenytoin. The R isomer, however, is preferred as it has an extremely low toxicity[1] (TD_{50} = 640 mg/kg). This analogue is active against bicuculline-induced seizures, indicating that it might act as an agonist of the inhibitory neurotransmitter, GABA.

An achiral structural isomer, 4-amino-N-(2,6-dimethylphenyl)benzamide, has a different activity profile. This compound displays higher MES activity than the chiral compound, but no scMET activity[2]; and, this achiral analogue has significant and long-lasting toxicity. It is, as well, inactive against biculline-, picrotoxin-, and strychine-induced seizures, indicating it is not an agonist for either GABA or glycine.

The conformations of these drugs will be compared to probe the structural bases for toxicity. In addition, the structures of these compounds will be compared to known MES- and scMET-active anticonvulsants to identify the molecular features that discriminate between these two types of activities.

Crystal data: 4-amino-N-(α-methybenzyl)benzamide, $C_{15}H_{16}N_2O$, $P2_12_12_1$, a = 11.3497(5), b = 22.223(2), c = 5.107(3)Å, Z = 4, present R = 0.055. 4-amino-N-(2,6-dimethylphenyl)benzamide, $C_{15}H_{16}N_2O$, $P2_1/c$, a = 8.9013(5), b = 16.722(2), C = 18.390 (2)Å, β = 95.364(5)°, Z = 8, present R = 0.077.

1 D.W. Robertson, et al., ASPET, Abst. 112, p. 231, Boston, 1985.
2 C.R. Clark, et al., J. Med. Chem., 28, 1259 (1985).