BTS 72664 — a Novel CNS Drug with Potential Anticonvulsant, Neuroprotective, and Antimigraine Properties

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ABSTRACT

BTS 72664, (R)-7-[1-(4-chlorophenoxy)ethyl]-1,2,4-triazolo(1,5-α)pyrimidine, was identified as a drug development candidate from a research program designed to discover novel, broad-spectrum, non-sedative anticonvulsant drugs. BTS 72664 antagonized bicuculline (BIC)- and maximal electroshock (MES)-induced convulsions with ED50 values of 1.9 and 47.5 mg/kg p.o., respectively. In rodents, it has a wide spectrum of activity preventing seizures induced by picrotoxin, pentyleneetrazol, i.e.v. 4-aminopyridine or NMDA, and audiogenic seizures in DBA-2 mice and GEPR-9 rats. BTS 72664 was also effective in preventing convulsions in amygdala-kindled rats. The lack of sedative potential was predicted on the basis of wide separation between ED50 in anticonvulsant models and TD50 for motor impairment in mice in rotating rod and inverted horizontal grid tests. BTS 72664 is likely to produce its anticonvulsant effect by enhancing chloride currents through picrotoxin-sensitive chloride channels, and by weak inhibition of Na+ and NMDA channels. It does not act, however, at the benzodiazepine binding site. In addition to its potential use in the treatment of epilepsy BTS 72664 may be useful in the treatment of stroke. At 50 mg/kg p.o. × 4, given to rats at 12 hourly intervals, starting at 15 min after permanent occlusion of middle cerebral artery (MCA), it reduced cerebral infarct size by 31% (measured at 2 days after insult) and accelerated recovery in a functional behavioral model. BTS 72664 prevented increases in extraneuronal concentrations of glutamate, glycine and serine brain levels induced by a cortical insult to rats (cf. cortical spreading depression). It may, therefore, have also antimigraine activity.