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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of a neuroprotective and orally active *N*-methyl-D-aspartate receptor ion-channel blocker, CNS 5788†

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Abstract

Asymmetric synthesis of *N*-(2-chloro-5-methylthiophenyl)-*N′*-(3-methylsulfinylphenyl)-*N′*-methylguanidine (CNS 5788) was achieved in high enantiomeric excess through condensation of the cyanamide derivative, **6** and the sulfinylaniline hydrochloride, **5**. The key step involved the asymmetric oxidation of *N*-methyl-3-methylthioaniline using a Davis reagent.

A number of guanidine derivatives containing sulfoxide groups were synthesized to determine whether the target sulfoxides afford neuroprotection with a potentially improved safety profile over conventional NMDA (*N*-methyl-D-aspartate) channel blockers. It was hypothesized that sulfoxide derivatives could be preferentially reduced in the hypoxic environment of ischemic tissue to generate a sulfide-containing potent NMDA ion-channel blocker. Among the compounds studied, the racemic sulfoxide *N*-(2-chloro-5-methylthiophenyl)-*N′*-(3-methylsufinylphenyl)-*N′*-methylguanidine **2** (CNS 5655), a sulfoxide derived from the potent NMDA channel blocker CNS 5161[1] **1**, showed good activity in various animal models including the rat middle cerebral artery occlusion (MCAO) model for stroke. In the rat MCAO model CNS 5655 showed good neuroprotection (32% at 4.5 mg/kg), and in the DBA/2 audiogenic mouse antiseizure test showed good activity following oral administration (76% inhibition at 60 mg/kg, p.o. compared to 72% at 20 mg/kg, i.p.). Both the enantiomers of CNS 5655, obtained through preparative chiral resolution (Chiral Technologies, Exton, PA) of the racemic compound as the free base, were evaluated in several animal models for neuroprotection and for side effects. The (+)-enantiomer **8**[2] (CNS 5788) was found to be at least as neuroprotective as the racemic compound **2** whereas the (−)-enantiomer did not show significant neuroprotection (1% at 4.5

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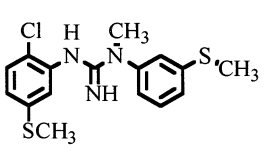
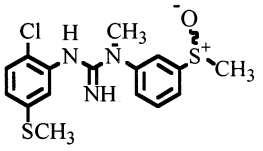
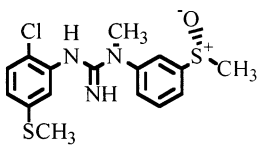
mg/kg) in the rat MCAO model. This good pharmacological profile combined with oral activity led us to explore the asymmetric synthesis of CNS 5788, which is the focus of this report.



1
CNS 5161



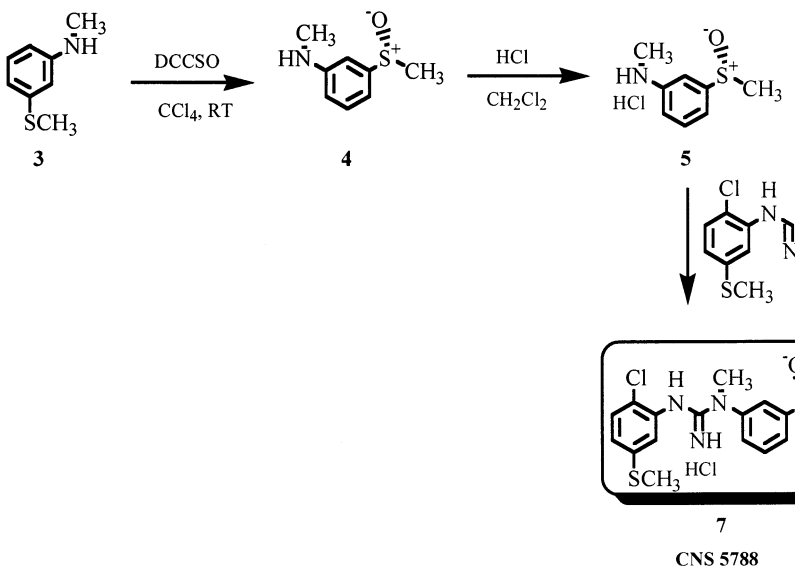
2
CNS 5655



8
CNS 5788

The absolute configuration of CNS 5788 as (*R*) was initially determined by NMR studies following the method developed by the addition of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol[3] and was unambiguously established through X-ray crystallography.[4]

Among the various methods reported, chiral oxidation of *N*-methyl-3-methylthioaniline[1] **3** for the preparation of the key sulfoxide intermediate, **4** was pursued. Three different Davis oxidizing agents, viz. (1*R*)-(−)-(10-camphorsulfonyloxaziridine),[5] (1*R*)-(8,8-dichloro-10-camphorsulfonyl-oxaziridine)[6] (DCCSO) and (1*R*)-8,8-dimethoxy-10-camphorsulfonyloxaziridine)[6] were studied under various reactions conditions and in each case the enantiomeric excess of the resulting sulfoxide was determined by NMR experiments involving the addition of the chiral shift reagent, [(+)-Eu(hfc)$_3$] [tris-3-(heptafluoropropylhydroxymethylene)-(+)-camphorato europium(III)]. Best results were obtained using the Davis reagent DCCSO in carbon tetrachloride at room temperature leading to the desired sulfoxide in ~95% yield and in moderate enantiomeric excess (~75% ee by NMR).



3 **4** **5** **6**

7
CNS 5788

The chiral sulfoxide, **4** was converted to the hydrochloride salt **5** using methanolic hydrogen chloride (1 M) using dichloromethane as solvent in almost quantitative yield. Subsequent condensation of the chiral sulfoxide, **5**, with 2-chloro-5-methylthiophenylcyanamide[1] **6** in a mixture of dichloromethane and toluene (1:1) in an oil bath at 115–120°C for 90 min led to the isolation of CNS 5788 as hydrochloride salt, **7**, in 51% yield (72% ee by NMR).

The hydrochloride salt, **7** was converted to the free base **8** in 73% yield using aqueous sodium hydroxide (1N) and the enantiomeric purity was determined by chiral HPLC as 76.5%. Chiral

HPLC analysis was carried out using a Chiralpak AD analytical column (4.6×250 mm) with 100% EtOH as the mobile phase using a Beckman system with a photodiode array (PDA) detector (flow rate = 0.4 mL/min; ambient temperature) with detection at 254 nm.

The enantiomeric purity of CNS 5788 was enhanced to 98% through two crystallizations of the free base from a mixture of hexanes and dichloromethane in 31% yield (mp 122–124°C). The specific rotation of CNS 5788 free base, $[\alpha]_D^{22} = +74.87$ (*c* 0.31, EtOH) was found to be in good agreement with that of the preparative chiral HPLC sample, $[\alpha]_D^{22} = +74.03$ (*c* 0.31, EtOH).

In conclusion, asymmetric synthesis of CNS 5788, a good neuroprotective agent with oral activity, was achieved in high enantiomeric purity following two crystallizations after the initial asymmetric oxidation. This procedure was followed for synthesis of CNS 5788 in gram quantities (~4 g) for further evaluation in various efficacy and safety animal models.

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