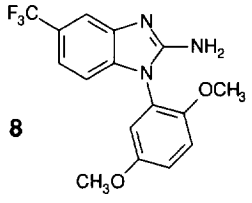
Of the compounds investigated, ziprasidone **7** was found to have affinity for the $D_2$ receptor comparable to that of haloperidol, a typical antipsychotic agent, and a $5\text{-}HT_{2A}$ / $D_2$ ratio comparable to that of clozapine. *In vivo* studies in the rat suggest that this compound will have less tendency to induce extrapyramidal side-effects and the compound has therefore been selected for clinical trials in humans.

## Neuronal calcium channel blocker

The increased levels of free cytoplasmic calcium following stroke may lead to neuronal death. This has been related to the increased levels of glutamate associated with ischemia, which cause the activation of voltage-sensitive calcium channels through the NMDA-subtype of glutamate receptors. Varning, T. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 245–248] describe the synthesis and biological evaluation of 2-amino-1-(2,5-dimethoxyphenyl)-5-trifluoromethyl benzimidazole (NS-649) **8** as a potential neuronal calcium channel blocker.

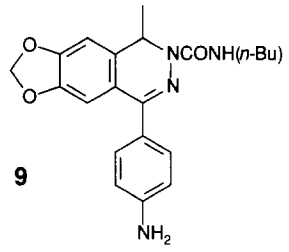



**8**

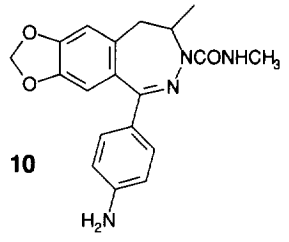
The ability of NS-649 to block neuronal calcium channels was demonstated with patch clamp studies on embryonic chick dorsal root ganglion. NS649 was also shown to inhibit the release of D-aspartate, a nonmetabolizing glutamate analog, from cerebellar granule neurons and to exhibit a neuroprotective effect in both *in vitro* and *in vivo* models of ischemia.

## AMPA receptor inhibitors

α-amino-3-hydroxy-4-methylisooxazolepropionic acid (AMPA) receptors are another subtype of the ionotropic glutamate receptors found in the mammalian CNS. Agents that selectively inhibit these receptor subtypes have also been shown to reduce injury in animal models of stroke and epilepsy. Pelletier, J.C. and coworkers [*J. Med. Chem.* (1996) 39, 353–356] describe the synthesis and biological evaluation of a novel series of potent, selective and noncompetitive AMPA receptor antagonists based on substituted 1,2-dihydrophthalazines. The most potent of the compounds investigated was **9**, which had similar activity to that reported for GYKI 53655 **10**, a 2,3-benzodiazepine which has been previously shown to inhibit AMPA-receptor currents noncompetitively in a similar electrophysiological assay.

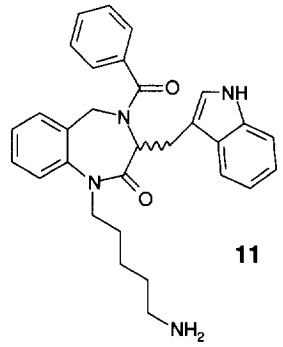



**9**




**10**

## Nonpeptide somatostatin ligand




**11**

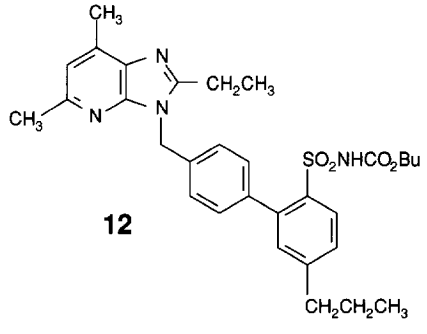
Somatostatin has an important role in inhibiting the release of hormones such as growth hormone, insulin, gastrin and glucagon. This cyclic peptide also acts as a neurotransmitter in the brain. Metabolically stable analogues of somatostatin may therefore have utility in the treatment of endocrine and malignant disorders. Papageorgiou, C. and Borer, X. [*Bioorg. Med. Chem. Lett.* (1996) 6, 267–272] report the synthesis and biological evaluation of the nonpeptide somatostatin mimic 1,3,4-trisubstituted-1,4-benzodiazepin-2-one **11**.

In radioligand binding studies on rat cortex membrane using [$^{125}$I-Tyr$^3$]-octreotide ligand the compound was found to have an $IC_{50}$ of 7 μM.

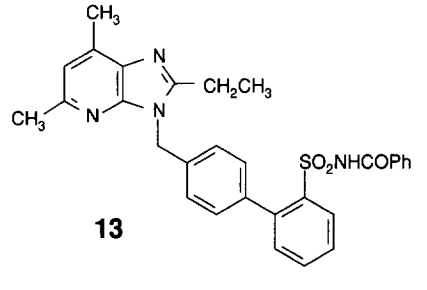
## Balanced angiotensin II receptor antagonist

In recent months there has been increased interest in the development of balanced angiotensin II receptor antagonists with affinity for both $AT_1$ and $AT_2$ receptors to overcome the possible effects of elevated levels of angiotensin II on $AT_2$ receptors that are seen on administration of the existing selective $AT_1$ antagonists [*Drug Discovery Today* (1996) 1, 39–40]. Rivero, R.A. and coworkers [*Bioorg. Med. Chem. Lett.* (1996) 6, 307–310] report the development of a potent angiotensin II receptor antagonist, L162-389 **12**, with affinity for both subtypes, based on the selective orally active $AT_1$ antagonist MK-966 **13**.

L192-389 has been shown to inhibit the pressor response mediated by angiotensin II in conscious normotensive rats and dogs on both intravenous and oral administration.




**12**




**13**