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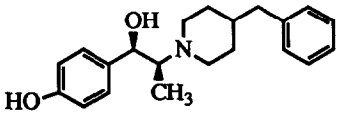
OXINDOLE N-METHYL-D-ASPARTATE (NMDA) ANTAGONISTS

B. L. Chenard,* T. W. Butler, I. A. Shalaby, M. A. Prochniak, B. K. Koe, C. B. Fox
Central Research Division, Pfizer Inc., Groton, CT 06340

Abstract: Replacement of the phenol group in non-competitive NMDA antagonist ifenprodil with oxindole results in a new series of 'non-traditional' NMDA antagonists. In combination with threo relative stereochemistry, improved NMDA antagonist potency and selectivity may be achieved.

Introduction: There is now substantial evidence that excessive release of glutamate in the central nervous system may contribute to the neurodegeneration found in many clinical conditions. The N-Methyl -D-Aspartate (NMDA) subtype of glutamate receptors has been strongly linked to the degenerative processes.[1] Thus it has been suggested that NMDA antagonists may find use in the treatment of diseases ranging from stroke[2] to Alzheimer's disease.[3] Conventional NMDA antagonists (competitive agents such as 2-amino-5-phosphono-valeric acid, ion channel blockers such as phencyclidine and MK-801, antagonists of the glycine modulatory site such as 7-chlorokynurenic acid) suffer from a number of liabilities which may make clinical development difficult (poor brain penetration, neuronal vacuolization,[4] stimulant[5] and psychotomimetic[6] effects).

Ifenprodil is the first example of a new class of NMDA antagonist which interacts with the receptor via a novel mechanism (possibly via the polyamine modulatory site).[7] Thus, ifenprodil may not be subject to the limitations of the 'traditional' NMDA antagonists noted above. Ifenprodil has problems of its own, namely a lack of receptor selectivity (especially affinity for the α1 adrenergic and σ[8] receptors) and poor oral bioavailability. If these limitations could be overcome, a useful NMDA antagonist might emerge. One approach to solve these problems replaced the phenolic hydroxyl with chlorine (SL 82.0715).[9] This substitution however, greatly reduces the NMDA antagonist potency and does little to improve the receptor selectivity (see Table 1 below).



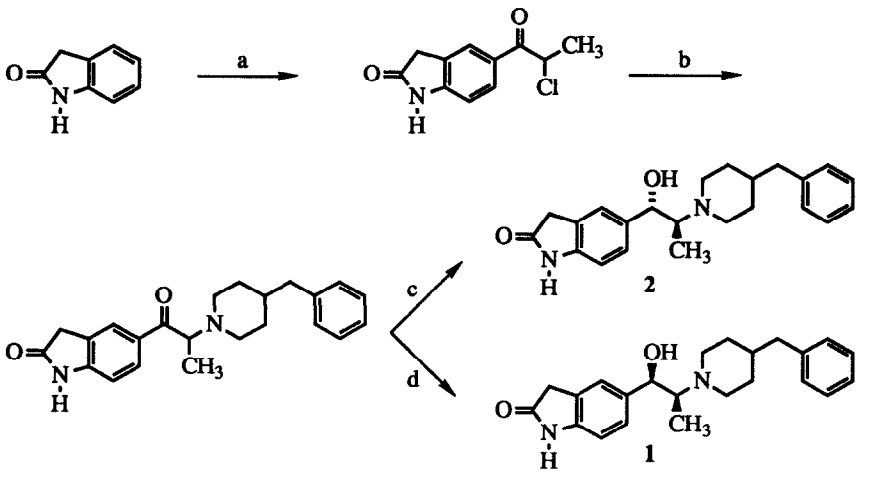
Ifenprodil

In a previous report, we dissected the ifenprodil structure to define the key features responsible for NMDA and α1 adrenergic receptor affinity.[10] From this work it was clear that potent and selective NMDA antagonists could be designed from the series. Herein we continue our studies of this class of coupounds seeking replacements for the phenolic hydroxyl group. We find that oxindole may replace the phenolic group of ifenprodil resulting in potent NMDA antagonists. Furthermore, we highlight some key SAR features which nicely parallel the phenol series and compare these new NMDA antagonists with ifenprodil, its threo diastereomer, and SL 82.0715.

Chemistry: The preparation of the compounds for this study is illustrated in Scheme 1 with the synthesis of **1** and **2**. Briefly, Friedel-Crafts acylation of oxindole with 2-chloropropionyl chloride gave the 5-(2-

chloropropionyl)oxindole in 90 % yield. Nucleophilic substitution with the appropriate piperidine nucleophile gave the corresponding ketones in good yields (50-60 %). Sodium borohydride reduction of the ketones gave the desired alcohol products (50-75 %). Reasonable diastereoselectivity (up to about 10:1) in the reduction step could be easily obtained by carrying out the reaction under acidic[11] (erythro selective) or basic (threo selective, ketone added to the reaction mixture last) conditions.[12]

Scheme 1 Synthesis of 1 and 2

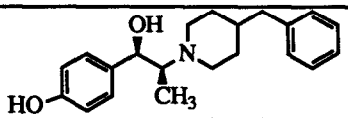
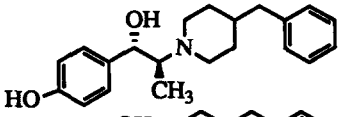
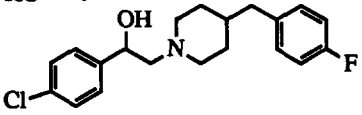
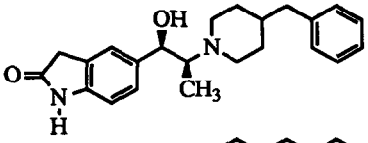
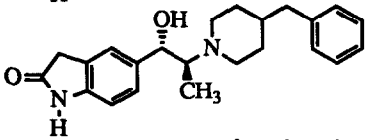
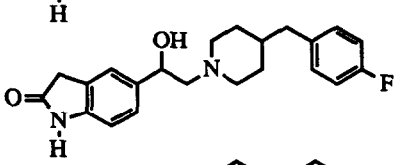
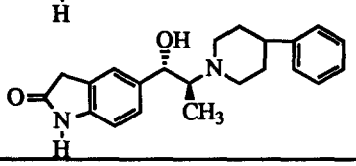


a. 2-chloropropionyl chloride, $AlCl_3$ b. 4-benzylpiperidine, ethanol, reflux
c. $NaBH_4$, ethanol d. $NaBH_4$, acetic acid, ethanol.

Biology: NMDA antagonist activity was assessed using a functional assay - protection of cultured hippocampal neurons from the toxic effects of extracellularly applied glutamate (glutamate toxicity, GT). The details of this procedure have already been described.[13] As a measure of selectivity, we evaluated $\alpha 1$ adrenergic receptor affinity in a standard radioligand binding assay with [^{3}H] prazosin.[14] The ratio of the IC_{50}s of these two assays ($\alpha 1$ / GT) was used as an estimate of selectivity (TI).

Our results are summarized in Table 1. Simple replacement of the phenol group of ifenprodil with oxindole while maintaining the erythro relative stereochemistry results in a compound (**1**) with a nearly identical biological profile. This is in contrast to the hydroxyl - chloride substitution of SL 82.0715 which results in a fourfold reduction in NMDA antagonist activity. Since SL 82.0715 can be further distinguished structurally from ifenprodil due to a para fluorine atom in its phenyl ring and the absence of the pendent methyl group, it was desirable to compare the oxindole and chlorine replacements for the phenolic hydroxyl on more closely related structures. Thus, we prepared **3**, the direct oxindole analog of SL 82.0715. Comparison of **3** and SL 82.0715 confirms that the oxindole functions more effectively as a phenol replacement in this series. Additionally, it appears that the SL 82.0715 structure imparts weaker NMDA antagonist activity.

Table 1 Biological Profile of Oxindole Compounds

Compound	Structure	GT IC_{50} nM ±SEM(n)	α_1 IC_{50} nM ±SEM(n)	TI
Ifenprodil (Erythro)		263 ± 63(4)	100 ± 36(3)	0.38
Ifenprodil Diastereomer (Threo)		55 ± 13 (3)	843 ± 137(3)	15.3
SL 82.0715		1000 ± 180(3)	800 ± 39(3)	0.8
1		231 ± 39(3)	100 ± 66(3)	0.4
2		111 ± 44(4)	710 ± 239(3)	6.4
3		600 ± 115(3)	183 ± 37(3)	0.3
4		40 ± 11(3)	349 ± 54(3)	8.7

Incorporation of the threo relative stereochemistry into this new series yields **2**, a compound with improved NMDA antagonist potency and selectivity over ifenprodil (TI = 6.4 versus 0.38, respectively). The improved selectivity of the threo diastereomer has been previously observed in the parent phenol series.[10] In this case however, the magnitude of the separation (TI) is only about half that seen with the phenols (compare the threo diastereomer of ifenprodil in Table 1). We presently have no explanation for this difference in selectivity.

The presence of the 4-benzyl group on the piperidine ring was previously found to be vital to NMDA antagonist activity.[10] We now find that the location of this aromatic ring may not be optimized with a methylene spacer separating the phenyl and piperidine moieties. This suggestion is supported by the finding that **4**, with the phenyl group directly attached to the piperidine ring, has both improved NMDA antagonist potency (IC_{50} = 40

nM) and is more selective (TI = 8.7). It may be appropriate to reevaluate the SAR of the parent ifenprodil series in light of this result.

In conclusion, we have found that oxindole functions as an excellent replacement for phenol in the ifenprodil class of non-traditional NMDA antagonists. The combination of threo relative stereochemistry, phenylpiperidine substitution for benzylpiperidine, and oxindole incorporation for phenol leads to a new series of potent and selective NMDA antagonists. We are presently testing these and related oxindole NMDA antagonists to see if improved oral bioavailability can be realized from this series of phenol bioisosteres.

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12 All new compounds gave acceptable elemental analysis and / or exact mass measurement. All compounds described in this manuscript are racemic. The structures depict relative stereochemistry.

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