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A novel series of benzimidazole NR2B-selective NMDA receptor antagonists

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ABSTRACT

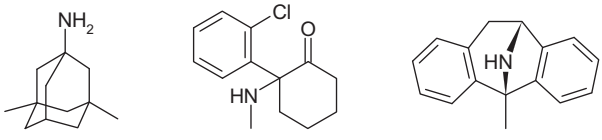
A series of novel benzimidazoles are discussed as NR2B-selective *N*-methyl-D-aspartate (NMDA) receptor antagonists. High throughput screening (HTS) efforts identified a number of potent and selective NR2B antagonists such as **1**. Exploration of the substituents around the core of this template identified a number of compounds with high potency for NR2B (pIC_{50} >7) and good selectivity against the NR2A subunit (pIC_{50} <4.3) as defined by FLIPR-Ca^{2+} and radioligand binding studies. These agents offer potential for the development of therapeutics for a range of nervous system disorders including chronic pain, neurodegeneration, migraine and major depression.

N-methyl-D-aspartate (NMDA) receptors are a molecularly, and pharmacologically, distinct sub-family of glutamate-gated ion channels which are widely distributed throughout the mammalian central nervous system (CNS) where they play key roles in excitatory neurotransmission.[1–3] They are assembled from heteromeric combinations of subunits encoded by distinct NR1, NR2 and NR3 genes. The most common receptor forms in the adult CNS are thought to be heterotetramers of two NR1 and two NR2A or NR2B subunits with alternative (and mixed) combinations with NR2C and NR2D contributing to a diversity of receptors with differing biophysical and pharmacological properties and specific regional distributions.[3,4] The more recently identified NR3A and 3B subunits also contribute to NMDA receptor heterogeneity via formation of ternary complexes, however, the functional roles of these channels are less clear at present.[5,6]

Due to their synaptic and extrasynaptic locations, voltage-dependent block by Mg^{2+} and high Ca^{2+} permeability, NMDA receptors play key roles in a range of mechanisms that underpin physiological processes associated with synaptic plasticity, learning, and memory.[7–9] The ability to elicit high levels of intracellular Ca^{2+} is also an established cause of the NMDA receptor-induced excitotoxicity which has been linked with several CNS disorders and pathologies.[10–12]

NMDA receptor antagonists have, for some time, therefore, been considered as potential therapeutic agents. Non subtype-selective (or pan-) NMDA receptor antagonists such as memantine and MK-801 which act at the pore of the open channel were initially developed for the treatment of stroke, head trauma and neurodegeneration (Fig. 1).[13,14]

Others such as the anaesthetic agent ketamine have been used off-label to treat neuropathic pain and more recently in promising exploratory studies in major depression.[7,15] The therapeutic utility of such agents has however, been severely limited by their CNS side-effects that include cognitive impairment, psychotomimetic effects, hallucinations and even catatonia at higher doses.[8,16]



Memantine Ketamine MK-801

Figure 1. Non subtype-selective NMDA antagonists.

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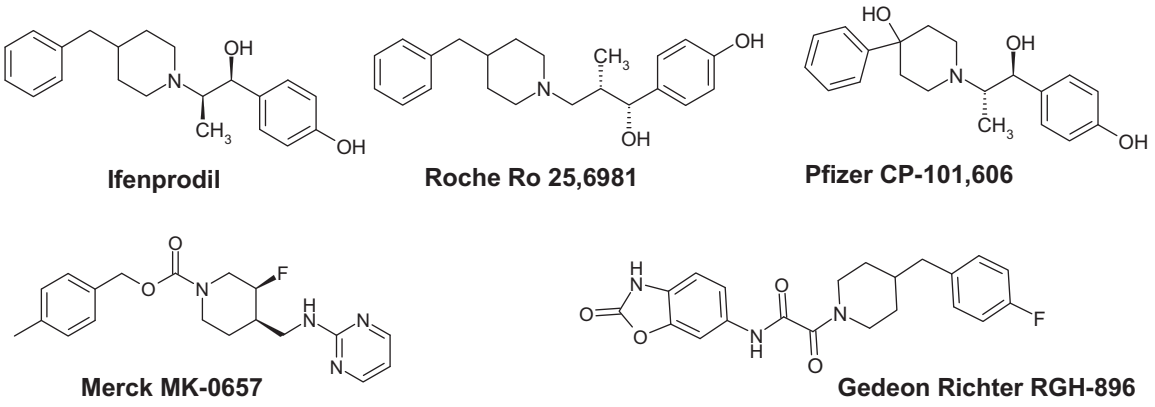


Figure 2. NR2B-selective antagonists.

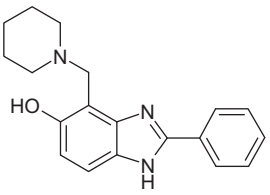
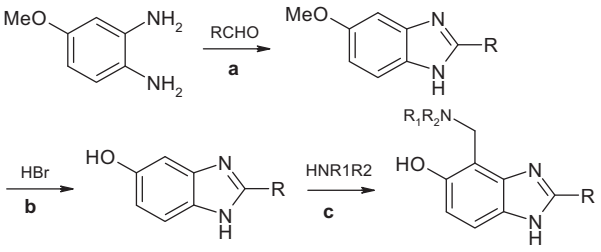


Figure 3. Compound **1**.



Scheme 1. (a) Oxone, rt, DMF:H_2O (97:3) 1–18 h (b) 48% HBr 80 °C, 1–18 h (c) CH_2O, AcOH, R1R2NH, THF, 70 °C, 5 h.

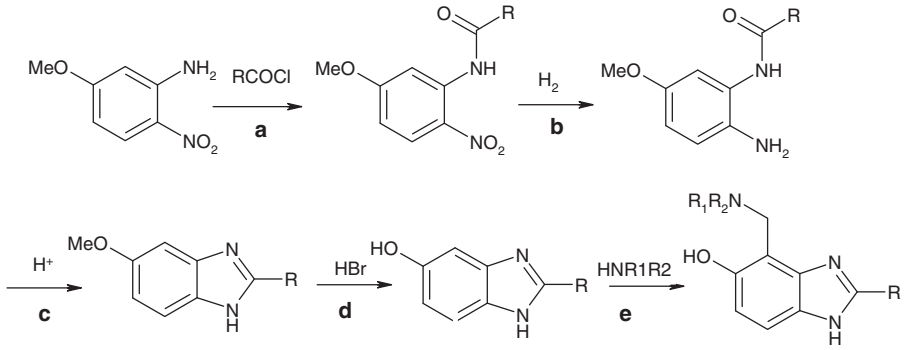
Following on from the discovery of ifenprodil,[17] the first NR2B-selective NMDA antagonist, the potential for a marked improvement in the therapeutic index achievable with respect to the dose-range required for efficacy versus doses resulting in typical NMDA related side effects has been demonstrated.[18,19] Thus, a range of chemotypes which potently and selectively antagonise NR2B-containing NMDA receptors is now available (Fig. 2).[20–25] Where characterized, such NR2B-selective antagonists have shown good activity and side effect profiles in animal models and, encouragingly, in the case of the CP-101,606, have also demonstrated efficacy in clinical studies in patients with chronic pain[26] and treatment-resistant major depressive disorder.[27]

In this Letter we disclose the discovery of a novel series of benzimidazoles as NR2B-selective NMDA antagonists.

High throughput screening identified a benzimidazole (**1**) as a potent inhibitor of NR2B with a sub-micromolar IC_{50} in a plate-based Ca^{2+} flux assay (Fig. 3).

Biological activity was measured in two assay formats. Firstly, a FLIPR (FLuorescent Imaging Plate Reader) based-Ca^{2+} assay, based on a transient transfection protocol with human NR1 and NR2B subunits, was used for primary hit identification. Secondly, the SAR reported herein was generated using a recombinant binding assay employing [^{3}H]-Ro 25,6981 as a specific ifenprodil-site radioligand. More detailed mechanistic studies were performed using whole-cell voltage-clamp electrophysiology using transiently transfected NR1-NR2B HEK-293T cells where NMDA receptor activity was evoked in response to 100 μM glutamate and 10 μM glycine.

The discovery of compound **1** prompted the synthesis of a series of benzimidazoles which were prepared according to the synthetic routes outlined in reaction Schemes 1 and 2. The starting materials were generally commercially available diamines, but where necessary the diamine was prepared by palladium catalysed reduction of the corresponding nitro aniline. In Scheme 1, the diamines were condensed with aldehydes in aqueous DMF in the presence of 'Oxone'. The reaction was often accompanied by a significant degree of di-imine formation but the desired product could be isolated by an acid/base work up procedure. The methoxy benzimidazoles were subsequently demethylated under acidic conditions at elevated temperature to give the corresponding phenols. The phenols were



Scheme 2. (a) TEA, CH_2Cl_2, 2 h (b) Pd(0), EtOH, 1–18 h (c) H_2SO_4, isoamyl alcohol, 18 h (d) 48% HBr 80 °C, 1–18 h (e) CH_2O, AcOH, THF, 70 °C, 5 h.