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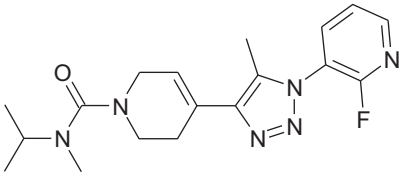
The solution-phase design and synthesis of libraries for the discovery of CNS active substances

Isoindolinone derivatives as metabotropic glutamate receptor 1 antagonists as a potential treatment for psychotic disorders

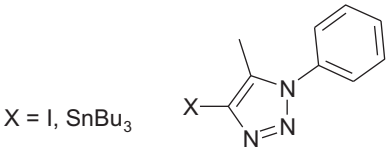
One of the major excitatory neurotransmitters in the central nervous system is glutamate. This neurotransmitter acts on ionotropic glutamate receptors, including NMDA and non-NMDA receptors and on G-protein-coupled metabotropic glutamate receptors (mGluRs). There are eight subtypes (three subclasses) of mGluRs based on sequence homology, coupling mechanisms to G-protein and pharmacological properties. mGluRs as a class are considered to be drug targets for modulating glutamate transmission and so have potential relevance in the treatment of neurological and psychiatric diseases, including epilepsy, Parkinson's disease, cognitive disorders, anxiety and schizophrenia [1,2]. Previously, it has been shown [3] that a potent and selective mGluR1 allosteric antagonist (i) inhibited psychostimulant methamphetamine (MAP)-induced behavioural alterations such as hyperlocomotion. These results suggest that blockage of mGluR1 mimics some effects of antipsychotics and so mGluR1 antagonists could have the potential for the treatment of psychotic disorders. Compound (i) was not progressed into clinical trials because of unacceptable DMPK properties.

To address the liabilities present in (i), recent work [4] has shown that a solution phase library could be constructed where the left-hand portion of (i) was varied. This region represented a metabolic soft-spot of compound (i). The library was constructed either from the iodo- or tributylstannane derivative of compound (ii), which upon coupling with a variety of aryl boronic acids (X = I in compound (ii)) or aryl halides (X = Bu_3Sn in compound (ii)), led to library products of general structure (iii).

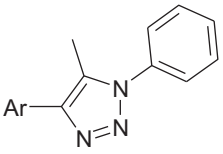
These library compounds were then tested for antagonistic activity on human mGluR1a expressing CHO cells by measuring [Ca^{2+}] with a FLIPR. One of the most potent compounds obtained in this way was (iv), which displayed an IC_{50} of 4.3 nM against the human mGluR1 receptor. This compound was at least 340-fold selective over the related receptors hmGluR5, hmGluR2 and hmGluR8, was brain permeable (mouse brain/plasma concentration were 0.45 nmol/g and 0.17 μM) and an antipsychotic-like effect was observed from an oral dose of 1 mg/kg in rats. These results prompted the mGluR1 allosteric antagonist (iv) to move into pre-clinical phase development as a novel antipsychotic. This work is important because a series of 5-(1-aryl-3-methyl-1,2,3-triazole-4-yl)isoindolin-1-one derivatives were rapidly prepared using parallel synthesis techniques and screened for mGluR1 antagonist activity. These isoindolin-1-one derivatives have the potential for assisting with the elucidation of the functions of mGluR1 in humans and further work is therefore warranted.



(i)



(ii)



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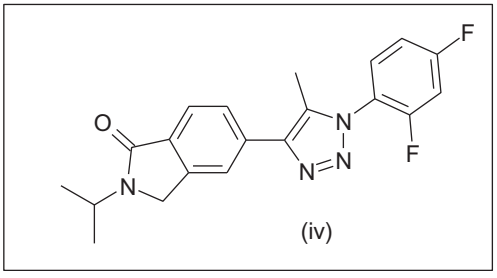


(iv)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2011.06.002

Towards μ-opioid/5-HT4 dual pharmacologically active agents with less GI and respiratory side effects

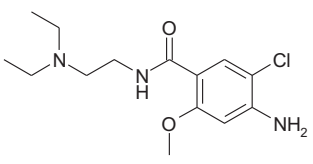
Morphine has been used to treat pain for many years. Although the application of opioids to treat pain remains the most effective therapy and is widespread in its use, the application of opioids therapeutically is not without issue. In particular, work has been on-going for several years to uncouple analgesic potency from the concomitant side effects that occur after chronic use, such as constipation [5]. It is known that opioid-induced constipation is largely peripherally mediated. Mu and delta opioid receptors located on gut smooth muscle play an important role in gastrointestinal motility [6].

The failure of the single therapeutic target approach to properly treat psychiatric diseases such as depression and schizophrenia has led to some drug discovery programs seeking pharmacological activity against multiple targets. Examples of this approach include the triple (5-HT, norepinephrine and dopamine) reuptake inhibitors for depression [7] and D_2/5-HT_{2a} antagonists for schizophrenia [8]. This general concept has been termed 'designed multiple ligands (DML)' [9–11].

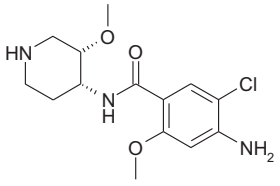
DML can be defined as taking two selective ligands and combining them into a single molecular entity providing for dual activity. DML can provide advantages such as a reduced risk of drug–drug interactions and a less complex PK/PD relationship.

Metoclopramide (v) is used clinically to induce gastric emptying and (+)-Norcisapride (vi), one of the primary de-alkylated metabolites of the now withdrawn drug Cisparide, which was on the market as a prokinetic agent before it was voluntarily withdrawn by Janssen in 2000 because of reports of QT prolongation, are both believed to work via 5-HT_4 agonism. (+)-Norcisapride is additionally a 5-HT_3 antagonist. (±)-*cis* Tramadol (vii) is used for the treatment of moderate to moderately severe pain and its analgesic activity is believed to originate from a dual mechanism: the parent compound (vii) inhibits norepinephrine and serotonin reuptake and its major O-desmethyl metabolite is a potent μ-opioid receptor agonist. Recent work [12] has attempted to take the functionality of both the μ-agonist pharmacophore (contained in Tramadol (vii)) and merge this at the basic nitrogen atom with the prokinetics pharmacophore (Metaclopramide (v) and (+)-Norcisapride (vi)). The approach taken has meant that these researchers could preserve the basic amine functionality for all compounds, but also allow the pharmacophores to be a substitution group for the other. This could offer the best chance to obtain all desired pharmacological activities.

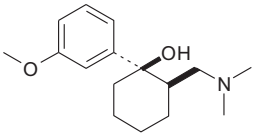
Synthesis of the metoclopramide-designed multiple ligands of general structure (viii) was conducted, in part, on solid-phase (Wang resin), whereas Norcisapride-designed multiple ligands of general structure (ix) was synthesized entirely in solution phase. The designed single enantiomer-DMLs were tested for binding potency at 5-HT_3, 5-HT_4 and μ-opioid receptors. Several of the most potent ligands were also tested in a functional assay, to determine if the compounds were agonists or antagonists. From these tests it was found that the Norcisapride series of compounds were much more potent against the 5-HT_4 receptor. One of the most potent compounds found was (x), which displayed an IC_{50} of 18 nM against 5-HT_4 in a binding assay and an EC_{50} of 90 nM (agonism) against 5-HT_4 in a functional assay. Compound (x) also displayed activity against the μ-opioid receptor (IC_{50} 410 nM; 5-HT_4 binding assay). This series of compounds could therefore provide a reasonable starting point for further optimisation efforts. Further work in this area is warranted, for example in incorporating 5-HT_3 antagonist activity into the series and determining the *in vivo* profile of compounds from this series in models of pain and constipation.



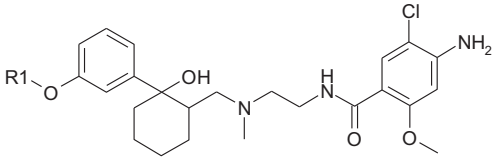
Metoclopramide (v)



(+)-Norcisapride (vi)



(+/-)-Tramadol (vii)



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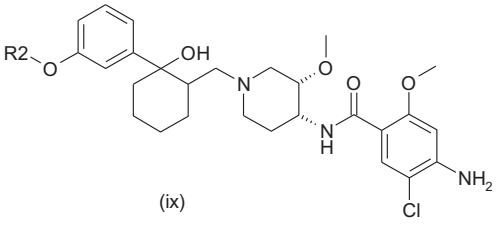

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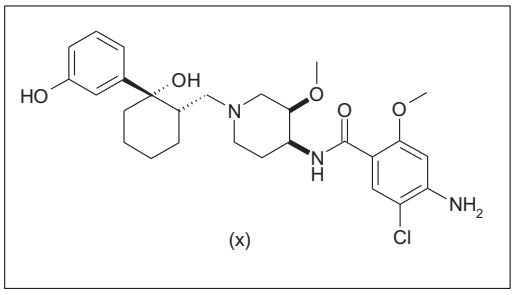

(x)

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