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Viewpoint

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The σ_1 Receptor Antagonist S1RA Is a Promising Candidate for the Treatment of Neurogenic Pain

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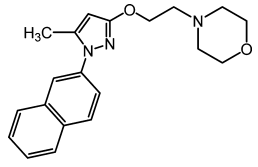
The σ_1 receptor represents a unique ligand-regulated chaperone that modulates the activity of several proteins including various receptors (e.g., NMDA receptor, IP_3 receptor) and ion channels (e.g., K^+ or Ca^{2+} channels). Despite the huge potential of σ_1 ligands for the treatment of various neurological disorders, a selective σ_1 receptor ligand has not been introduced into the market. The newly developed σ_1 receptor antagonist S1RA represents the first σ_1 receptor antagonist with promising antinociceptive properties in different neurogenic pain models. Single and multiple dose phase I clinical studies with S1RA have been completed, and the proof of concept phase II clinical studies for the treatment of neuropathic pain of different etiologies are currently ongoing.

In the study of Diaz et al.[1] the 1-arylpyrazole system was extensively modified at all ring positions in order to achieve high σ_1 affinity and high σ_1/σ_2 selectivity. The 2-naphthyl and the 3,4-dichlorophenyl groups were identified as promising substituents at the 1-position. Whereas a methyl moiety at the 4-position was detrimental for σ_1 affinity, a methyl moiety at the 5-position increased the σ_1/σ_2 selectivity compared to C-5 unsubstituted analogues. Only a 2-aminoethoxy group with a cyclic amine containing an additional heteroatom (morpholine, piperazine) fulfilled the criteria of high σ_1 affinity (IC_{50} < 50 nM) and high σ_1/σ_2 selectivity ($IC_{50}(\sigma_2)$ > 1000).

Sufficient metabolic stability and interaction with the hERG channel in the heart served as further filters in the decision process leading to S1RA (**1**, Figure 1) as most promising



S1RA (**1**)

Figure 1. Because of good in vitro and in vivo properties in several neuropathic pain models, S1RA (**1**) was selected as clinical candidate.

candidate. In the mouse model of neurogenic pain induced by intraplantar injection of capsaicin the 2-naphthyl substituted pyrazole **1** showed the highest activity of all tested 1-arylpyrazoles. **1** revealed high selectivity against more than 170 molecular targets. Addition of phenytoin, an allosteric modulator that shifts the affinity of σ_1 agonists to significantly higher affinities, did not lead to changed affinity, indicating that **1** represents a σ_1 antagonist.

Moderate to high analgesic activity of **1** was found in different pain models. In particular in the partial sciatic nerve ligation model, **1** inhibited dose-dependently mechanical allodynia and thermal hypersensitivity. Compared to pregabalin, the gold standard for neuropathic pain treatment, **1** showed increased analgesic potency (Figure 2).

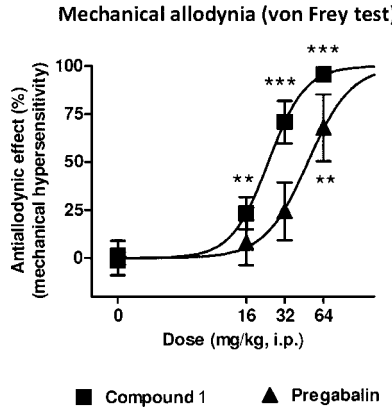


Figure 2. Dose response effect of **1** and pregabalin on mechanical allodynia (von Frey test) in the partial sciatic nerve ligation model of neuropathic pain showing that **1** is superior to pregabalin.

After oral administration (mouse) the pharmacokinetic profile of **1** was characterized. Because of the good physicochemical and ADME properties, **1** was selected as candidate for clinical studies.

During the past years several pharmacophore models for σ_1 ligands have been published. All these models postulate a basic amino group and at least two hydrophobic substituents at the N-atom.[2] In case of **1** the 2-[1-(2-naphthyl)pyrazol-3-yloxy]-ethyl moiety meets nicely the requirements of the first hydrophobic N-substituent. However, the second hydrophobic substituent is represented only by the morpholine ring. According to the reported models, the high affinity of **1** is unexpected, since the morpholine ring alone is usually not sufficient to fill the second hydrophobic pocket of the binding site of the σ_1 receptor.

Very recently σ_1 ligands with a benzoxazolone scaffold have been docked into the hypothetical binding site of the σ_1 receptor. These docking experiments led to the interaction of these ligands with the receptor protein on the molecular level. In particular it was shown that Asp126 forms an ionic interaction with the basic amino moiety.[3] The importance of Asp126 for ligand binding has already been shown by site directed mutagenesis experiments. Docking of the naphthylpyr-

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azole **1** into the binding site of the σ_1 receptor would be of high interest.

Some years ago σ_1 receptor knockout mice were generated, which are viable and fertile. With the exception of a reduced mobility they do not show any behavioral anomalies. These mice were used for the validation of the σ_1 receptor as target for the treatment of neuropathic pain. Capsaicin was completely unable to induce mechanical hypersensitivity in σ_1 receptor knockout mice. High affinity and selective σ_1 receptor antagonists dose-dependently inhibited mechanical allodynia induced by capsaicin in wild type mice. This analgesic effect was reversed completely by application of a selective σ_1 agonist.[4]

The σ_1 receptor is highly expressed in the central nervous system and in some organs and tissues in the periphery (e.g., kidney, lung, liver, heart). Several drugs in clinical use for different neurological indications bind in addition to their known mode of action toward σ_1 receptors. Some examples are the antipsychotic dopamine D_2 receptor antagonist haloperidol, the opioid analgesic (±)-pentazocine, the selective serotonin reuptake inhibitor fluvoxamine, the tricyclic antidepressant opipramol, and the acetylcholine esterase inhibitor donepezil. However, these compounds have another main mechanism of action that is responsible for their pharmacological action. It is assumed that the σ_1 affinity contributes to the overall pharmacological effects. Selective σ_1 receptor ligands have been investigated in clinical trials as antidepressants and antipsychotics. The new class of arylpyrazoles represents the first example of selective σ_1 receptor antagonists for the treatment of neuropathic pain. It was shown that the naphthylpyrazole **1** exceeds the analgesic activity of pregabalin, the gold standard for the treatment of neuropathic pain. The promising pharmacological properties makes the selective σ_1 receptor antagonist **1** a promising candidate for phase II clinical studies. The naphthylpyrazole **1** could become the first σ_1 selective drug in clinical use.

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