**OBJECTIVES**

Xoc Pharmaceuticals (Xoc) developed a target receptor activity profile for novel small molecules for migraine prevention based on compiled literature information published in scientific journals for marketed serotonin drugs for the treatment of migraine and Parkinson’s disease. The proposed target profiles include receptor activities beneficial to migraine treatment while eliminating or modifying receptor activities associated with deleterious effects. In this post, the receptor profiles of two migraine drugs and a novel compound discovered by Xoc Pharmaceuticals using a targeted medicinal chemistry design approach are compared and contrasted against the developed target receptor profile.

**BACKGROUND**

Many classes of neurologic drugs have polypharmacological activities; they affect multiple receptors, resulting in both targeted beneficial effects as well as undesired effects. Ergot alkaloids, such as methysergide (for migraine prevention), dihydroergotamine (for the acute treatment of migraines), and pergolide (for Parkinson’s disease therapy), represent only one such class, having broad activity at atherothrombotic, dopaminergic and serotoninergic receptors. In each of these cases, while the compounds/compound class likely augments their therapeutic efficacy, which depends primarily on activity at the serotoninergic receptors for the migraine compounds and the dopaminergic receptors for the Parkinson’s disease, it also results in undesirable side effects caused by off-target receptor interactions.

**METHODS**

Xoc reviewed clinical and scientific literature to determine the commonly observed efficacy and side effects and the receptor binding and functional activity of drugs used for neurologic indications. The focus of this evaluation was on serotoninergic agents known to be effective in acute treatments of migraines, migraine prevention, and Parkinson’s disease management. Xoc determined accurate receptor activity profiles using modern homology modeling and receptor binding predictions that were independently validated with the observed clinical trial data. The incorporation of a prospective target receptor activity profile was developed for compounds suitable for migraine prevention. A similar approach was used to develop target profiles for Parkinson’s disease, psychosis and other indications. Using the target profile as a guide, Xoc designed novel molecules based on ergot alkaloid structures that retained features considered responsible for efficacy while eliminating undesired activity. Xoc synthesized proprietary compounds with tailored structural changes that, based on the information from newly acquired receptor activity data for the known compounds and the literature background, had high probability of the desired receptor activity. One of the Xoc molecules, XC101-D134, is summarized herein as a specific example of a novel molecule with a unique receptor activity profile suitable for migraine prevention with low likelihood of significant side effects.

**RESULTS**

Fifteen ‘known’ compounds that were either historically marketed for migraine treatment or are known to be active on serotonin receptors were reviewed through the clinical and scientific literature for their behaviors.

<table>
<thead>
<tr>
<th>Ergolines</th>
<th>Ergolines Non-Ergolines</th>
<th>Ergolines Non-Ergolines</th>
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<tbody>
<tr>
<td>Methysergide</td>
<td>Dihydroergotamine</td>
<td>Dihydroergotamine</td>
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<tr>
<td>Pergolide</td>
<td>Cyproheptadine</td>
<td>Cabergoline</td>
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<td>Cabergoline</td>
<td>Topirimate</td>
<td>Lisinopril</td>
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<td>Quinapril</td>
<td>Lisinopril</td>
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<tr>
<td>Dihydroergotamine</td>
<td>Ergotamine 2-Bromolaudanosine</td>
<td>Ergotamine</td>
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<td>Ergotamine</td>
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**Development of a novel clinical-stage drug for the prevention of migraine based on receptor activity mapping and achievement of a target receptor profile**

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Xoc Pharmaceuticals, Inc.

**CONCLUSIONS**

Xoc developed a target receptor profile for serotoninergic migraine prevention treatment.

Based on the profile, novel Xoc compounds were synthesized and assayed for receptor binding and functional activity.

A lead clinical-stage candidate, XC101-D134, was selected based on a close match with the target profile for migraine prevention. XC101-D134 is expected to be effective for migraine prevention but lack common serotoninergic-driven side effects.

**REFERENCES**