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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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 serotonergic drugs for the treatment of migraine and Parkinson's disease. The proposed target profile includes receptor activities beneficial to migraine treatment while eliminating or modifying receptor activities associated with deleterious effects. In this poster, 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 neurology drugs have polypharmaceutical attributes: 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 migraine), and pergolide (for Parkinson's disease therapy), represent one such class, having broad activity at adrenergic, dopaminergic and serotonergic receptors. In each of these cases, while the compounds' broad activity likely augments their therapeutic efficacy, which depends primarily on activity at the serotonergic 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 neurological indications. The focus of this evaluation was on serotonergic agents known to be effective in acute treatments of migraine, migraine prevention, and Parkinson's disease maintenance. Xoc determined accurate receptor activity profiles using modern human-cloned cell assays. Xoc then correlated the established receptor activity with the observed clinical effects to elucidate receptor interactions that were likely responsible for the desired activity and undesired side effects. Based on the correlations, a prospective target receptor activity profile was developed for compounds suitable for migraine prevention. A similar approach was used to develop target profile 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 targeted 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's molecules, XC101-D13H, 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 researched through the clinical and scientific literature for clinical behaviors.

Ergolines	Isoergolines	Non-Ergots
Methysergide	Pergolide	Cyproheptadine
Dihydromethysergide	Cabergoline	Topiramate
Methylergometrine	Lisuride	Pizotifen
Dihydroergotamine	2-Bromolisuride	Quetiapine
Ergotamine	Terguride	
2-Bromocriptine		

Accurate serotonergic receptor activity profiles for the migraine compounds were determined and a desired target profile for migraine treatment (Table 1) was developed. The 5-HT_{1E} and 5-HT_{5A} receptors were determined to have no relation to migraine treatment or therapeutic side effects.

Table 1. Xoc-Developed Target Receptor Activity Profile for Migraine Prevention

Receptor Type	Target Activity	Desired Effects
5-HT_{1A}	Inactive or Agonist	Potential migraine preventative, agonism attenuates 5-HT_{2A} agonism effects[1-5]
5-HT_{1B}	Agonist High 1D/1B Ratio Preferred	Acute migraine effect may be beneficial, avoid vasoconstriction[1, 3-4, 7-10]
5-HT_{1D}	Agonist	Acute migraine effect may be beneficial[1, 3-4, 7-10]
5-HT_{1F}	Agonist	Acute migraine effect may be beneficial[1, 3-4, 7-10]
5-HT_{2A}	Antagonist	Avoid cognition and psychotic effects[6,11]
5-HT_{2B}	Antagonist	Prevent migraine and avoid fibrogenesis[12-22]
5-HT_{2C}	Antagonist	Prevent migraine[23]
5-HT_3	No activity	Avoid cardiovascular side effects (prolonged QT)
5-HT_{4E}	No activity	Therapeutic and side effect profile unclear[2,22]
5-HT_6	No activity	Therapeutic and side effect profile unclear[24]
5-HT_7	Antagonist	Potentially beneficial for migraine prevention, may reduce CGRP generation[2, 7, 9, 24-31]

Xoc evaluated more than 250 unique molecules for migraine prevention and other indications. The receptor activity profiles of the new compounds were compared and contrasted with those of the "known" molecules and with the Xoc-determined target receptor activity profile for migraine prevention.

Xoc produced several structures with profiles that closely matched the target receptor activity profile for migraine treatment. Table 2 shows the target profile overlap for two historical ergot alkaloid migraine compounds and the lead Xoc candidate for migraine prevention, XC101-D13H, which is scheduled to enter human clinical trials in 2019. The receptor profile for XC101-D13H closely follows the derived migraine prevention target activity profile. XC101-D13H is also very similar to methysergide at the migraine efficacy-specific receptors, but, based on this profile, would not be expected to have the undesirable side effects vasoconstriction, psychotic effects, and fibrotic complications common to the historical compound.

Table 2. Compound Receptor Activity Assessment Relative to Target Receptor Activity Profile for Migraine Prevention

Receptor Type	XC101-D13H	Methysergide	Dihydroergotamine
5-HT_{1A}	Inactive	Agonist	Agonist
5-HT_{1B}	Agonist (1D/1B >10)	Agonist (1D/1B = 0.06)	Agonist (1D/1B = 1)
5-HT_{1D}	Partial Agonist	Agonist	Agonist
5-HT_{1F}	Partial Agonist	Agonist	Partial Agonist
5-HT_{2A}	Antagonist	Agonist	Agonist
5-HT_{2B}	Antagonist	Silent Antagonist	Partial Agonist
5-HT_{2C}	Antagonist	Antagonist	Agonist
5-HT_3	Inactive	Inactive	N/A
5-HT_{4E}	Inactive	Inactive	N/A
5-HT_6	Inactive	Inactive	N/A
5-HT_7	Partial agonist	Inactive	Antagonist

Profile Legend:
Green – receptor activity consistent with target
Yellow – receptor activity inconsistent with target, but tolerable effect
Red – receptor activity unacceptable

N/A = receptor not evaluated

CONCLUSIONS

- Xoc developed a target receptor profile for serotonergic migraine preventive treatment.
- Based on the profile, novel Xoc compounds were synthesized and assayed for receptor binding and functional activity.
- A lead clinical-stage candidate, XC101-D13H, was selected based on a close match with the target profile for migraine prevention. XC101-D13H is expected to be effective for migraine prevention but lack common serotonergic agonist-driven side effects.

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