

Expert Opinion

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New H₁/H₃ antagonists for treating allergic rhinitis: WO2010094643

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This application claims dual receptor specificity antihistamines, active as H₁ and H₃ antagonists, which additionally have a long duration of action that renders them suitable for once daily administration via inhalation for the treatment of allergic rhinitis. The compounds lack CNS penetration and have a high affinity for both histamine receptors.

Keywords: allergic rhinitis, GlaxoSmithKline, H₁ antagonist, H₃ antagonist, histamine

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1. Introduction

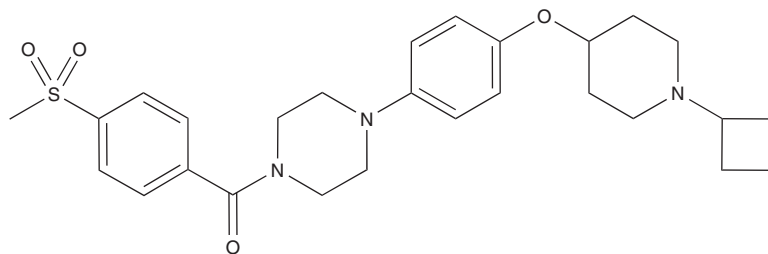
Histamine receptors have proved very valuable targets for the pharmaceutical industry. Antihistamines (H₁ antagonists) have been a mainstay of treatment of allergic rhinitis for many years, with progressive improvements eliminating any central activity, while the identification of the H₂ receptor led to the very useful class of H₂ antagonists for the treatment of ulcers. The histamine H₃ receptor was first described in 1985 as a presynaptic receptor [1,2] and has since been shown to primarily be expressed in the brain although it is also expressed peripherally. The H₃ receptor is primarily regarded as a target for the development of drugs for the treatment of cognitive disorders, sleep disorders and obesity [3-5].

However, the report that H₃ receptors are involved in the nasal blockage response of the human nose [6] indicated that H₃ antagonists might have potential in the treatment of rhinitis, provided that central absorption could be avoided. This clearly underlies GlaxoSmithKline's decision to develop such antagonists for the treatment of rhinitis. This has led to a number of development candidates, such as (1) [7]. There is now an increasing interest in the development of dual acting agents for the treatment of allergic rhinitis acting on the H₁ receptor and a second (relevant) GPCR [8]. GlaxoSmithKline has chosen to focus its efforts on dual H₁/H₃ antagonists that lack brain penetration [9-11].

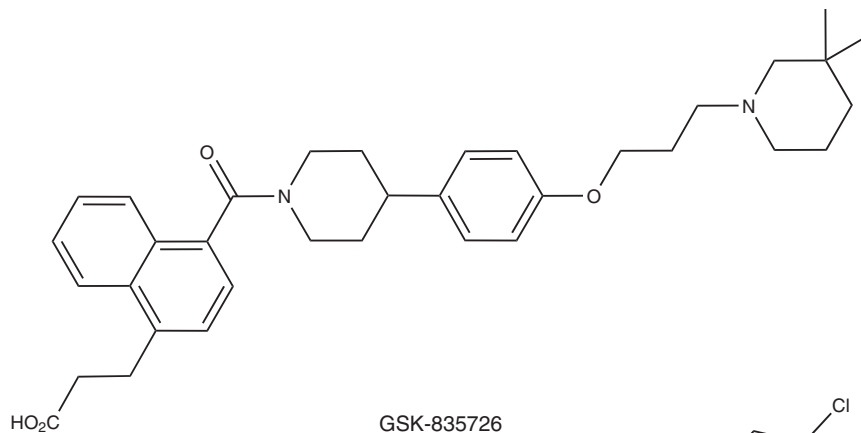
In 2008, it progressed two dual acting antagonists to Phase II development, the intranasally delivered GSK-1004723 and the orally administered GSK-835726, both of which were in Phase I studies in February 2008. Although in active development in February 2009, development of both appears to have been terminated as neither was mentioned in the company's 2009 Annual report (published in February 2010), but details of their preclinical activity were reported in 2009. GSK-835726 displayed comparable affinity for both receptor types (~ 10 nM) and was orally active in animal models [12,13] while GSK-1004723 had a long duration of action and 0.1 nM affinity for the H₁ receptor [14,15].

The application that forms the basis of this evaluation claims H₁/H₃ antagonists (2), some of which are indicated to have high affinity for both receptors.

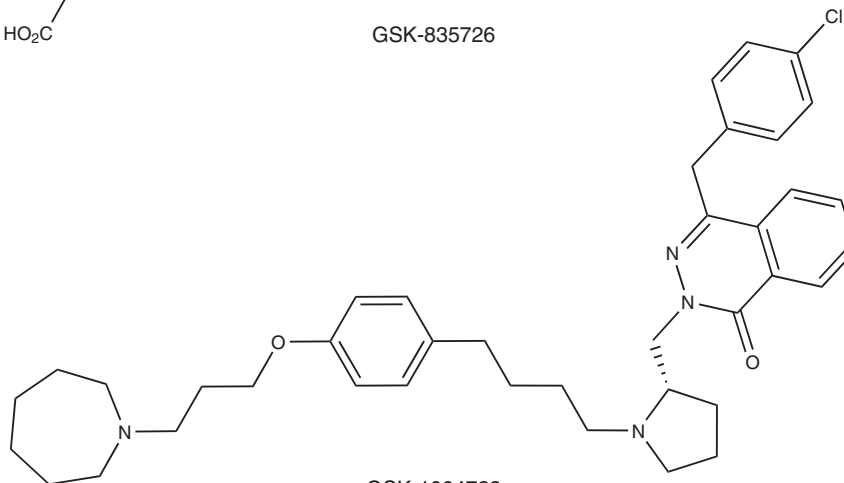
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GSK-835726



GSK-1004723

2. Chemistry

The claimed Markush structure (3) is remarkably simple. 1-Substituted cyclic amines bear an optionally substituted quinolin-8-yloxy substituent, where the 1-substituent is a ring substituted arylalkyl group, with the substituent a cyclic amine attached via an alkoxy or alkylene chain. A total of 26 compounds are specifically claimed, almost all of them incorporating a chain terminated by a hexahydroazepine ring, and the syntheses of all 26 are exemplified. One of these compounds (2) appears to be preferred being the subject of two separate individual claims.

A number of alternative routes are described as methods of preparing the claimed compounds, reflecting the alternative order in which the multiple rings may be connected to each

other. One of the two exemplified routes to compound (2) is shown in Figure 1.

Alkylation of 2-(4-hydroxyphenyl)ethanol with 1-bromo-3-chloropropane was followed by amination with hexahydroazepine. Mesylation of the primary alcohol followed by reaction with quinolinylloxypiperidine gave (2).

3. Biology

The compounds' affinity for H₁ and H₃ receptors was determined using cloned CHO cells transfected with either human H₁ or H₃ receptors. Antagonist affinity for the H₁ receptor was determined using fluo-4 loaded cells, in a FLIPR device, by measuring the inhibition of histamine-induced responses in the presence of increasing concentrations of antagonist.

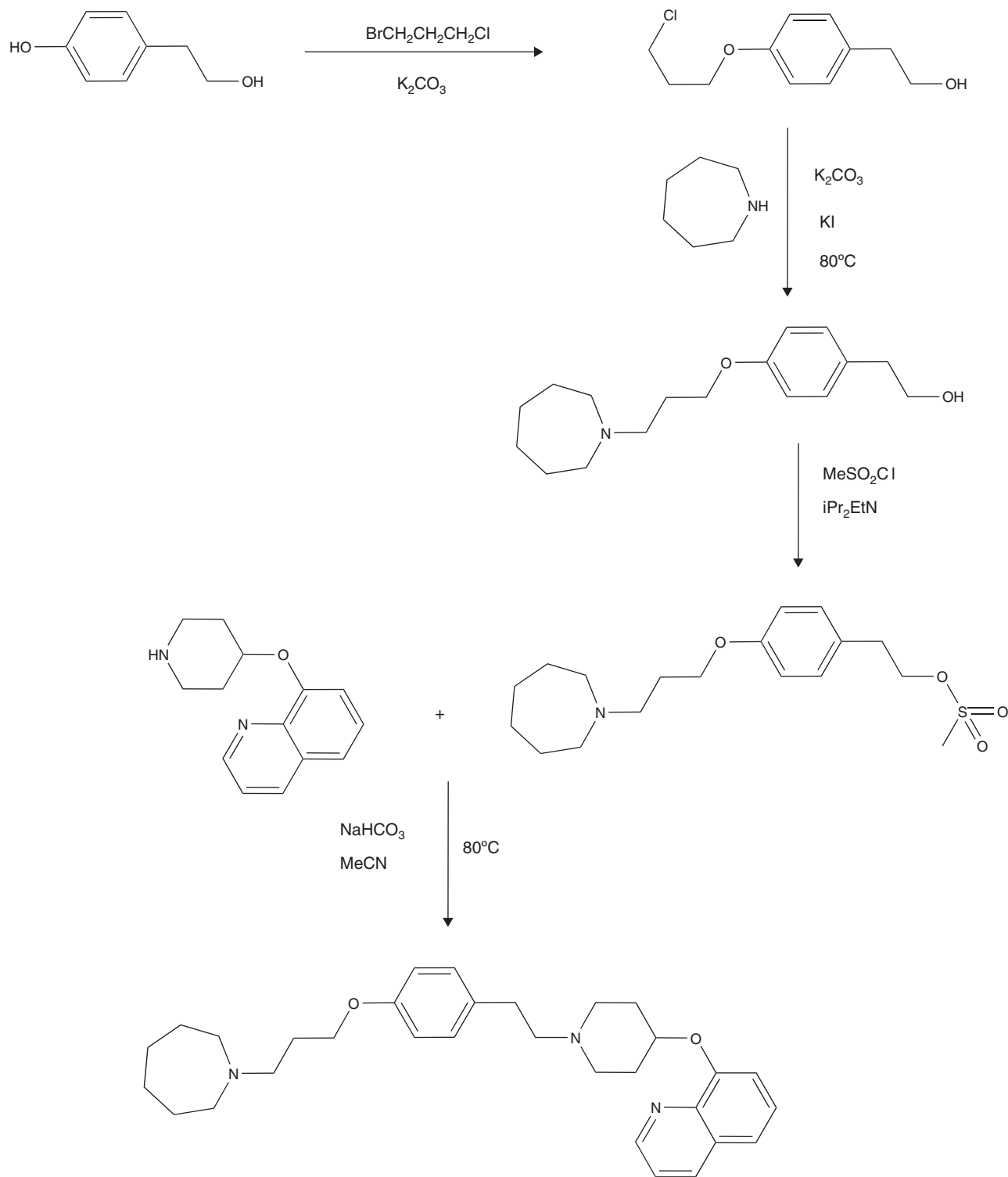
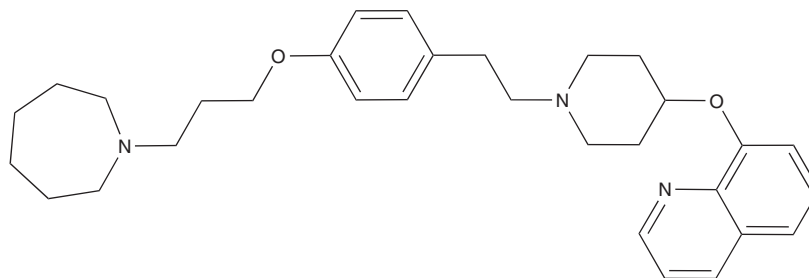
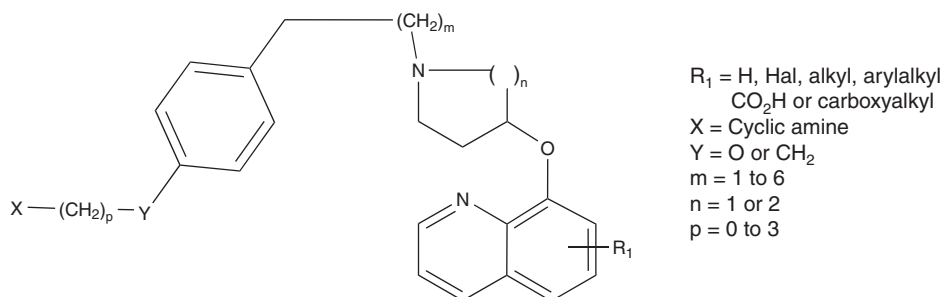


Figure 1. One of the exemplified preparations of compound (2).



2



3

pA₂ values were then calculated from the resulting dose-response curves. For H₃ receptor affinity, the inhibition of histamine-induced [³⁵S]-GTPγS responses were measured in a membrane preparation using a scintillation proximity assay to quantify the amount of label released.

All the exemplified compounds are reported as showing pK_b values > 6.5 at H₁ receptors and > 8 at the H₃ receptor. Compound (2) is one of 10 indicated to have pK_b values > 7 at H₁ receptors and one of five to show a longer duration of action at this receptor than azelastine.

4. Expert opinion

The claimed compounds represent an interesting progression from earlier compounds, clearly combining features of both GSK-835726 and GSK-1004723. The data presented appear to indicate that compounds such as (2) retain the long duration of action seen with GSK-1004723. What is uncertain is whether or not some of the compounds have sufficient bioavailability to permit oral absorption. It may be the case that this requires the presence of an acidic substituent on the quinoline ring, and three examples of such compounds are provided.

Clinical studies with both GSK-835726 and GSK-1004723 appear to have been completed, although no results have yet

been published. The details of these studies available on GlaxoSmithKline's clinical trial register make it clear that one of the key aims of these studies was the comparison of the efficacy of the two compounds and their different routes of administration [16]. This study, completed in August 2009, also compared their efficacy to the widely used anti-histamine ceterizine and found that GSK-1004723 was ineffective in alleviating nasal symptoms and also caused nasal irritation whilst the two oral agents were both effective [17]. These data suggest that any future intranasally delivered compound, for example, such as one of those claimed in this application, will need to have superior efficacy to GSK-1004723 as well as a superior duration of action to azelastine if it is to be useful in the treatment of rhinitis. It is unclear whether the compounds claimed in the application under evaluation do contain a development compound but the appearance of the application does suggest that GlaxoSmithKline felt further improvements might be achievable from this programme.

Declaration of interest

The author has received an honorarium for the preparation of this manuscript. He declares no other conflict of interest.

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