The Synthesis and Use of Certain Pyridine Derivatives as Modulators of the G-protein Coupled Receptors mGlu5 and P2Y\textsubscript{12}

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Avhandlingen kommer att försvaras på engelska.
Abstract

The glutamatergic mGlu5 receptor and the purinergic P2Y12 receptor are two important targets in the development of novel treatments of gastroesophageal reflux disease (GERD) and thrombosis, respectively.

Synthesis was developed to investigate the structure-activity relationships (SAR) of a novel series of 2-alkynylpyridine derivatives as mGluR5 antagonists. This led to the discovery of antagonists with potency in the low-nanomolar range. High microsomal metabolism, possibly due to high lipophilicity, remained an issue.

Further, SAR development for a series of ethyl 6-piperazinylnicotinates, featured by a urea linker, as antagonists of the P2Y12 receptor showed the 3-ethoxycarbonyl substituent as central to binding. The low aqueous solubility was addressed by variation of the linker which led to the discovery of sulfonyleureas as P2Y12 antagonists. The chemical stability of the sulfonyleurea compounds during prolonged storage in solution was found to be related to the sulfonyle urea linker and depended on the type of solvent and the substitution pattern of the sulfonyle urea functionality.

Synthesis was developed to facilitate the replacement of the 2-methyl substituent on pyridine with more electron donating substituents and of the 3-ethoxycarbonyl substituent with 5-ethyl-oxazoles. Both strategies led to compounds with higher metabolic stability, but also with lower potency.

Pair-wise comparison of compounds showed that a correctly positioned alkyl group, like in an ethyl ester or a 5-ethyl-oxazole, and a correctly positioned strong hydrogen bond acceptor both were required for binding.

Chemical design was used to study how the regioselectivity $R_{sel}$ for the 2-position depended on the character of the 3-substituent in the reaction of 3-substituted 2,6-dichloropyridines with 1-methylpiperazine. It was found that $R_{sel}$ depended on neither of the parameters $PI$, $MR$, or $\sigma_p$, but showed a statistically significant correlation with the Verloop steric parameter $B1$ ($R^2 = 0.45$, $p = 0.006$). This implied that 3-substituents that are bulky close to the pyridine ring directed the regioselectivity towards the 6-position. With $R^3 = -CO_2CH_3$ a study of the solvent effect showed that $R_{sel}$ could be predicted by the Kamlet-Taft equation:

$$R_{sel} = 1.28990 + 0.03992\alpha - 0.59417\beta - 0.46169\pi^* \quad (R^2 = 0.95; \ p = 1.9 \times 10^{-10}).$$

The dependency on the solvatochromic $\beta$ parameter meant that the 16:1 regioselectivity for the 2-isomer in DCM ($\beta = 0.10$) could be switched to a 2:1 selectivity for the 6-isomer in DMSO ($\beta = 0.76$).

Keywords: mGluR5, P2Y12, gastroesophageal reflux disease (GERD), thrombosis, ethyl nicotinates, ureas, sulfonyleureas, oxazoles, bioisosteres, regioselectivity, solvent effect.