The Synthesis and Use of Certain Pyridine Derivatives as Modulators of the G-protein Coupled Receptors mGlu5 and $P2Y_{12}$

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Abstract

The glutamatergic mGlu5 receptor and the purinergic $P2Y_{12}$ 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 $P2Y_{12}$ 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 sulfonylureas as $P2Y_{12}$ antagonists. The chemical stability of the sulfonylurea compounds during prolonged storage in solution was found to be related to the sulfonyl urea linker and depended on the type of solvent and the substitution pattern of the sulfonyl 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 σ_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: $R_{sel} = 1.28990 + 0.03992\alpha - 0.59417\beta - 0.46169\pi^*$ ($R^2 = 0.95$; $p = 1.9 \times 10^{-10}$). The dependency on the solvatochromic β 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, $P2Y_{12}$, gastroesophageal reflux disease (GERD), thrombosis, ethyl nicotinates, ureas, sulfonylureas, oxazoles, bioisosteres, regioselectivity, solvent effect.

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