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Molecular docking study and SAR of Triazolopyrimidines fused with Imidazole, Pyrazole and Pyrazine as XO inhibitors

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Allopurinol, a well known drug clinically used for treatment of gout and hyper-uricemia resulting from uric acid,[1] has been reported as a potential inhibitor of xanthine oxidase (XO), which catalyzes the conversion of hypoxanthine and xanthine to uric acid.[2] We have recently discovered that the angular type compounds, 3H-[1,2,4]triazolo[1,5-i]-purin-5(4H)-ones (Ia)[3] and 6,7-dihydro-5H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimi-din-5-ones (Ib)[3], have exhibited more potent bovine milk XO inhibitory activities than that of allopurinol. Herein we fully report the versatile synthesis of the compounds (Ia, b) and their analogs (IV). Furthermore, they are also reported their inhibitory activities as potential XO inhibitors and their docking study into the active site of the bovine milk xanthine dehydrogenase using two scoring functions involved in AutoDock and CAChe. The correlation coefficiency (Fig. 1) obtained between the AutoDock binding energy and IC_{50} of the inhibitors was better than that obtained by the CAChe-PMF docking score. Many ligands exhibited one to four hydrogen bonds within the active site, where the detected hydrogen bonds by CAChe was identified quantitatively in the docked conformation by using MOPAC. These ligands were docked into a long, narrow channel of the enzyme leading to the molybdopterin active moiety, with hydrogen bonding and electrostatic interaction between the planar aromatic moiety of the ligand and the enzyme. The SAR among inhibitors was investigated, which revealed that the oxo group of pyrazolopyrimidine analogs is essential for its activity and the tricyclic derivatives are shown to be more potent than bicyclic ones. References: 1) R. W. Rundles, et al, Trans. Asso. Am. Physicians, 1963, 76, 126. 2) G. B. Elion, Ann. Rheumat. Dis., 1966, 25, 608. 3) T. Nagamatsu, et al, J. Chem. Soc., Perkin Trans. 1, 1999, 3117 and 2000, 33.

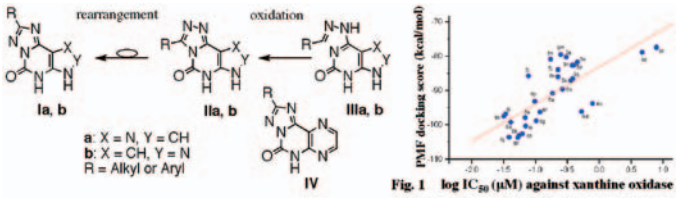

Fig. 1 log IC_{50} (μM) against xanthine oxidase

Biography

Dr. Tomohisa Nagamatsu has completed his Ph.D at the age of 27 years from the John Curtin School of Medical Research in Australian National University and postdoctoral studies from School of Hygiene and Medical Research in Jones Hopkins University. He is an associate professor of Okayama University. He has published more than 110 papers in reputed journals and serving as a reviewer member of many international journals.

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