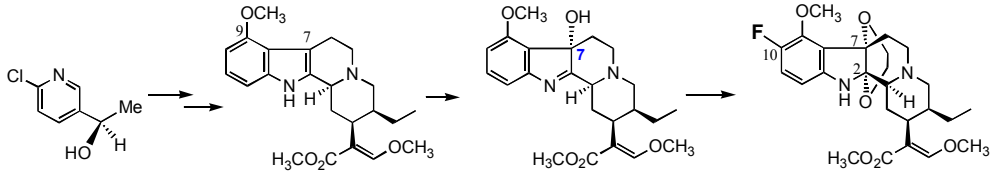
Development of Novel Opioid Ligands Based on the Rubiaceous Indole Alkaloids

Hiromitsu Takayama (Grad. Sch. Pharm. Sci., Chiba Univ.)

The leaves of a tropical rubiaceous plant, *Mitragyna speciosa* Korth., have been traditionally used as a substitute for opium. Phytochemical studies of their constituents have led to the isolation of several 9-methoxy-*Corynanthe* type indole alkaloids including new natural products. The potent opioid agonistic activities of mitragynine (**1**), the major alkaloidal constituent of this plant, and its analogues were found in *in vitro* and *in vivo* experiments. In particular, 7-hydroxymitragynine (**2**) was found to exhibit potent antinociceptive activity in mice. To develop more potent and selective opioid receptor-subtype ligands based on 7-hydroxymitragynine as a lead-compound, several derivatives were prepared. Among the synthetic compounds, an ethylene glycol-bridged derivative (**3**) having a fluorine substituent on the benzene ring revealed the activity as an opioid receptor agonist with potencies higher than that of morphine.



Mitragynine (**1**) 7-Hydroxymitragynine (**2**) F–derivative (**3**)