Medicinal Chemistry on Bioavailability Improvement

○ Hiroharu Matsuoka and Naoki Taka
(Chemistry. Research Dept. I, Chugai Pharm. Co. Ltd.)

So many physicochemical parameters have been reported as metrics for an improvement of bioavailability (BA), such as molecular weight (MW), hydrophobicity (clogP, logD or PSA), number of hydrogen bond donar/acceptor, and number of rotatable bond. I believe most of medicinal chemists have actually felt the benefit of them. However, those parameters are not always chemist-friendly, especially when chemists focus their efforts on modification of substructure or replacement of specific substituent. Because those parameter are measured or calculated based on the whole molecule property. On the other hands, in order to analyze structure-activity relationship (SAR) or design new compounds, medicinal chemists often use not only the whole molecule parameters, but also parameters based on substituent property, such as value (hydrophobicity), value (electron-donating/withdrawing), L value (length) and so on.

Previously we reported the discovery of orally available motilin antagonists from tripeptide lead, GM-109, of which BA was zero %. Motilin is known to be a gastrointestinal peptide hormone (22 amino acids), and its antagonist is considered to be effective for the treatment of irritable bowel syndrome or functional dyspepsia. During a course of this research, we have successfully improved an intestinal permeability and metabolic stability of the peptide lead to find orally available peptidomimetics and realized the importance of use of substituent parameters as well as the whole molecule parameters. In this symposium, I would like to present our examples of BA improvement from research on the motilin antagonist and discuss effective parameters use for the strategy of BA improvement.