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Synthesis and discovery of highly potent agents, trifluoromethyl containing heterocycles against influenza virus

Satoshi Mizuta
Nagasaki University, Japan

Trifluoromethyl heterocycles have been an important motif of pharmaceutical drugs and agrochemicals because the presence of a CF_3 group can cause the improved metabolic stability, lipophilicity and bioavailability. Nowadays, numerous CF_3 substituted heterocycle-containing pharmaceuticals on the market can be witnessed, with examples such as trifluridine, efavirenz, celecoxib and mefloquin. Over the past decades, there has been an increasing interest in the development of method for the efficient synthesis of such fluorinated heterocyclic molecules as potential biological targets. Nevertheless, synthetic method accessing an array of CF_3-containing heterocycles remains underdeveloped, in particular for nonaromatic heterocycles. Considering the difficulty of introducing CF_3 moiety in nonaromatic ring systems, divergent synthesis using a simple and readily available CF^3-containing precursor to convert into the diverse set of trifluoromethyl heterocyclic compounds may be one of the versatile and straightforward strategies for drug discovery. In this study, a series of α-trifluoromethyl α,β-unsaturated lactones and trifluoromethyl pyrazolinones were designed and synthesized. These two structural motifs of trifluoromethyl heterocycles were synthesized based on the synthetic pathway including a tandem stereoselective functionalization of the key precursor 3,3-dibromo-2-trifluoromethyl acrylic acid ethyl ester and intramolecular cyclization reaction. Further modification by Suzuki-Miyaura cross-coupling reaction provided a set of multi-functionalized α,β-unsaturated lactones and pyrazolinones. All synthesized compounds were bioassayed *in vitro* to determine their inhibitory activity against influenza A virus. We further modified a few potent hits in a viral inhibition assay and cunducted SAR studies on these scaffolds. The results showed that CF_3-containing spirolactones possessed promising inhibitory activity being nearly active as oseltamivir.

Biography

Satoshi Mizuta received his PhD at Nagoya Institute of Technology in 2008. He worked with Prof. Carlos F BarbasIII at The Scripps Research Institute. Then he went back to Japan to work at the Sagami Chemical Research Institute in 2010-2011. He joined the VG group as a Marie-Curie Fellow in September 2011 until May 2013, to work on the catalytic trifluoromethylation and the development of synthetic method for [18F]labelling. He is working at Nagasaki University, Japan. His current research interest is the drug design for antivirus.

s-mizuta@nagasaki-u.ac.jp

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