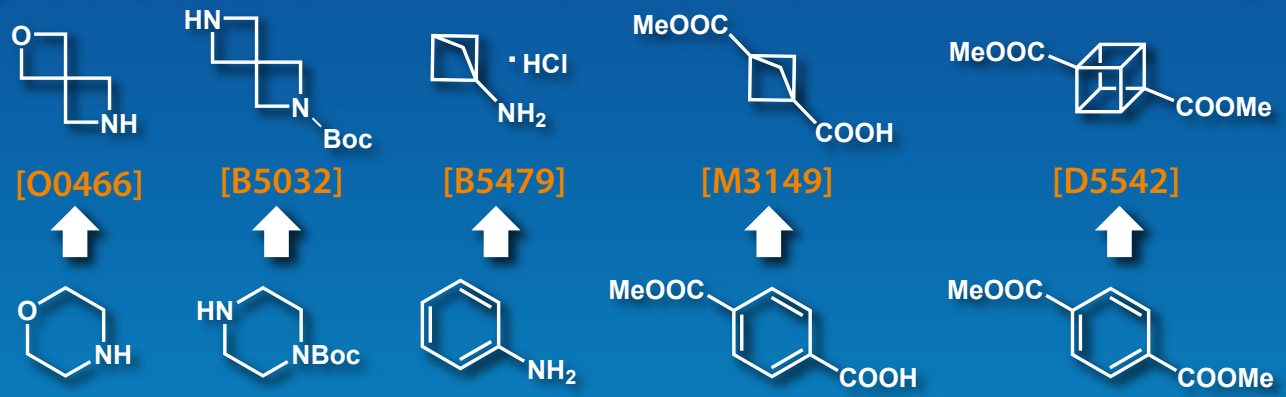
CHEMISTRY

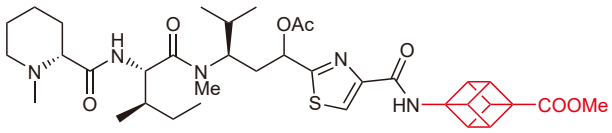
Building Blocks for Bioisosteric Replacement in Medicinal Chemistry



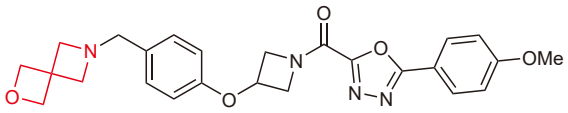
Cross-coupling reactions have become ubiquitous in synthesis and are essential in enabling the expansion of building block libraries. However, reviews of clinical trial data have shown drug candidates with high planarity were more likely to fail.[1)] It was speculated that the planarity of compounds caused unpredictable and undesirable bioavailability and toxicity owing to their insolubility. Spiro type building blocks comprised of an oxetane and azetidine are bioisosteres of morpholine and piperazine respectively.[2,3)] The related bicyclo[1.1.1]pentane or cubane are bioisosteres of benzene rings.[3,4,5)] These building blocks are expected to assist in introducing more sp^3 carbon character to drug candidates, leading to improved solubility, and increasing 3-dimensionality.

Applications

Tubulin polymerization inihibitor (tubulysin analog) [5)]



Melanin concentrating hormone receptor 1 (MCHr1) antagonist [6)]



References
1) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752.
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4) J. M. Lopchuk, P. S. Baran, *et al., J. Am. Chem. Soc.* **2017**, *139*, 3209.
5) T. A. Reekie, C. M. Williams, L. M. Rendina, M. Kassiou, *J. Med. Chem.* **2019**, *62*, 1078.
6) A. Johansson, *et al., J. Med. Chem.* **2016**, *59*, 2497.

2-Oxa-6-azaspiro[3.3]heptane	1g [O0466]
***tert*-Butyl 2,6-Diazaspiro[3.3]heptane-2-carboxylate**	200mg [B5032]
Bicyclo[1.1.1]pentan-1-amine Hydrochloride	200mg / 1g [B5479]
3-(Methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic Acid	200mg / 1g [M3149]
Dimethyl Cubane-1,4-dicarboxylate	100mg / 1g / 5g [D5542]

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