S50-3 **Design of GPCR ligands based on the three-dimensional diversity-oriented strategy: development of histamine H3 and/or H4 receptor ligands**

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The three-dimensional diversity-oriented conformational restriction (TDCR) strategy (Fig. 1) is an efficient method for developing GPCR ligands. Based on this strategy, in order to develop potent H_3 and/or H_4 receptor antagonists, a series of conformationally restricted analogues of histamine with a chiral *cis*- or *trans*-cyclopropane structure were designed and synthesized. Among these analogues, potent H_3 and/or H_4 receptor agonists and antagonists (Fig. 2) were identified. These results show that, when the structure of the target protein is unknown, the stereochemical diversity-oriented approach can be a powerful strategy in medicinal chemical studies.

Fig. 1

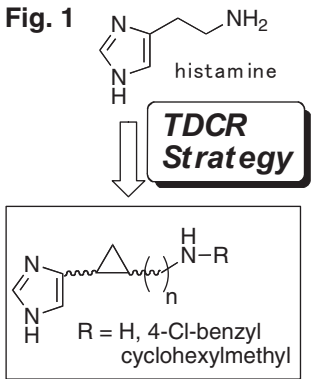

Fig. 2