

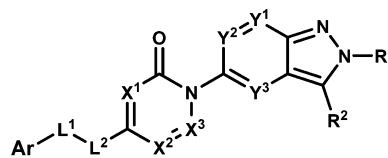
# Melanin-Concentrating Hormone Receptor 1 Antagonists for Treatment of Obesity

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**Title:** Heterocyclic Compound  
**Patent Application Number:** WO 2015/005489 A1  
**Priority Application:** JP 2013-143940  
**Inventors:** Igawa, H.; Takahashi, M.; Kakegawa, K.; Ikoma, M.; Aida, J.  
**Assignee Company:** Takeda Pharmaceutical Company Limited; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410045, Japan  
**Disease Area:** Obesity  
**Biological Target:** Melanin-concentrating hormone receptor 1 (MCHR1)  
**Summary:** The invention in this patent application relates to 2*H*-indazole derivatives represented generally by formula (I). These compounds possess melanin-concentrating hormone receptor antagonistic activities and may be useful for the treatment or prophylaxis of obesity. The melanin-concentrating hormone (MCH) is a cyclic 19-amino acid hypothalamus-derived peptide that shows appetite stimulant activity. Studies have indicated that antagonism of the melanin-concentrating hormone receptor 1 (MCHR1) is a promising therapeutic target for the treatment of obesity. MCH knockout mice behave normally; however, they show significantly decreased food intake and lighter body weights compared to normal mice. In addition, MCHR1-deficient mice have been reported to show lean phenotypes. Therefore, the MCHR1 antagonists such as the compounds described in this patent application may provide a promising treatment for obesity by virtue of their properties as excellent appetite suppressants.

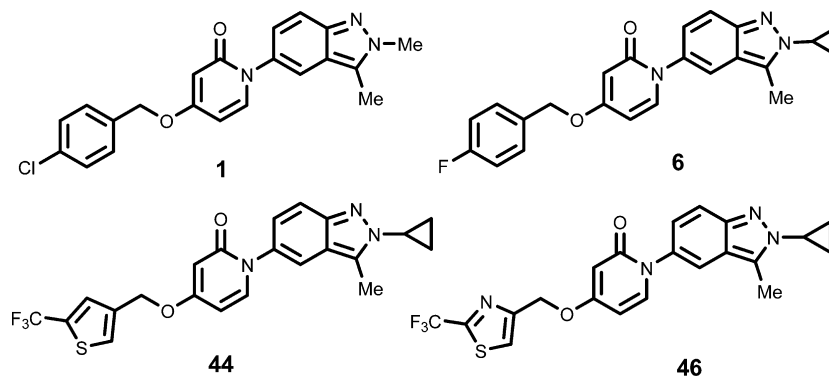
## Important Compound Classes:



Formula (I)

## Key Structures:

The inventors reported the structures of 48 examples of formula (I) including the following four representative examples:



## Biological Assay:

- Determination of human MCH receptor 1 (MCHR1) competitive inhibitory activity using binding assay
- Measurement of MCH receptor 1 antagonistic activity using  $\text{Ca}^{2+}$  mobilization assay
- Evaluation of anorectic effect using male diet-induced obese F344/Jcl rats
- hERG activity measurement by IonWorks Quattro

**Received:** February 16, 2015**Published:** February 26, 2015

**Biological Data:**

The biological data obtained from testing the representative examples (structures shown above) are listed in the following table:

Compound	MCHR1 competitive inhibitory activity Inhibition rate % (0.1 $\mu$ M)	MCHR1 Antagonistic Activity Inhibition rate % (0.1 $\mu$ M)	Anorectic Effect Food intake suppression rate (%)	% hERG inhibition (10 $\mu$ M)
1	72	83	32.1	22.1
6	72	70	26.4	-
44	77	55	30.6	5.7
46	50	78	13.3	16.8

**Recent Review Articles:**

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2. MacNeil, D. J. *Front. Neuroendoc. Sci.* **2013**, *4* (April), 49.
3. Cheon, H. G. *Handb. Exp. Pharmacol.* **2012**, *209* (Appetite Control), 383–403.
4. Johansson, A. *Expert Opin. Ther. Pat.* **2011**, *21* (6), 905–925.

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**Notes**

The authors declare no competing financial interest.