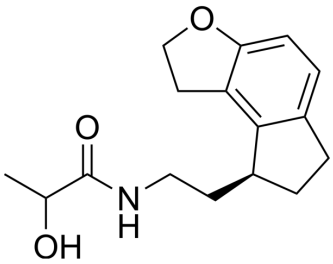
Ramelteon metabolite M-II

Cat. No.:	HY-103005
CAS No.:	896736-21-3
Molecular Formula:	$C_{16}H_{21}NO_3$
Molecular Weight:	275.34
Target:	Melatonin Receptor; Drug Metabolite
Pathway:	GPCR/G Protein; Neuronal Signaling; Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Ramelteon metabolite M-II is the major metabolite of Ramelteon, with IC_{50}s of 208 pM, 1470 pM for human melatonin receptors (MT_1 or MT_2). Ramelteon is a selective melatonin agonist.
In Vitro	The affinity of Ramelteon metabolite M-II (M-II) for MT_1 receptors is 10- and 2.5-fold lower than that of ramelteon and melatonin, respectively. Likewise, the affinity of M-II for MT_2 receptors is approximately 5- and 1.5-fold lower than that of ramelteon and melatonin, respectively. Ramelteon metabolite M-II exhibits no affinity for quinone reductase 2 at concentrations up to 10 μM. Moreover, the selectivity of Ramelteon metabolite M-II for melatonin receptors relative to 215 targets including other receptors, transporters, ion channels and enzymes is investigated. Ramelteon metabolite M-II shows no significant affinities and activities for the other targets, except for the 5-HT_{2B} receptor, for which the Ki value was 1.75±0.23 μM. The potency of Ramelteon metabolite M-II for MT_1 receptors is approximately 17- and 4.3-fold lower than that of ramelteon and melatonin, respectively. Similarly, the potency of Ramelteon metabolite M-II for MT_2 receptors is approximately 28- and 1.6-fold lower than that of ramelteon and melatonin, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Ramelteon metabolite M-II (1 mg/kg) significantly increases NREM sleep ($F_{1,7}$=96.3, p<0.01) and significantly decreases wakefulness ($F_{1,7}$=56.7, p<0.01). Moreover, a lower dose of M-II (0.1 mg/kg) yield similar results (NREM, $F_{1,7}$=121.9, p<0.01; wakefulness, $F_{1,7}$=87.0, p<0.01), and decreased wakefulness is sustained for 6 h after the administration of either dose. After the administration of 0.01 mg/kg Ramelteon metabolite M-II, only NREM sleep is significantly increased ($F_{1,7}$=10.5, p< 0.05). No significant differences in REM sleep are observed after the administration of M-II at any of the doses tested in this study[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Cats[1] Eight adult cats weighing 2.4-5.9 kg are used in each study. The cats are housed individually in rooms maintained at 22-26 °C with a 12-h light-dark cycle (lights on at 7.00 a.m.), fed once daily (9.00 a.m.) and given water ad libitum. The cats are anesthetized, and electrodes are surgically implanted for electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) monitoring. After a recovery period of at least 7 days, the cats are well accustomed to the test chamber (65×35×45 cm). Ramelteon metabolite M-II is orally administered at 0.1 mL/kg to each cat using gelatin capsules. The effects of M-II on sleep are compared with those of the vehicle using a crossover design. The interval between trials is >6

days. The cats are given Ramelteon metabolite M-II (0.001, 0.01, 0.1 or 1 mg/kg) or vehicle between 9.55 and 10.00 a.m. Immediately after the administration, EEG, EOG and EMG recordings are started sequentially and lasted 8 h. The durations of sleep stages are measured after the administration of vehicle or M-II and are presented as mean percentages of time spent in each stage at each 2-hour period after administration[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Nishiyama K, et al. Pharmacological characterization of M-II, the major human metabolite of ramelteon. Pharmacology. 2014;93(3-4):197-201.

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