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Bioactivity-guided synthesis of tropine derivatives as new agonists for melatonin receptors

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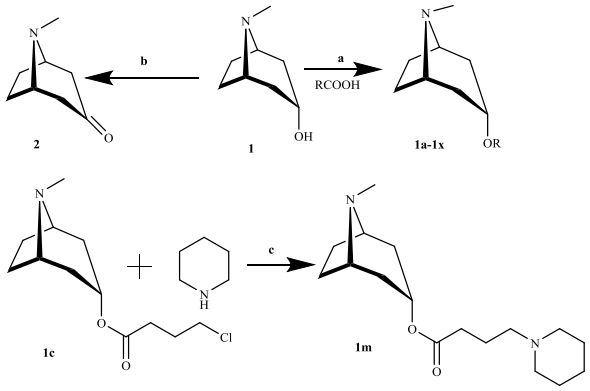
Twenty-three tropine derivatives as new melatonin receptors (MT_1 and MT_2) agonists were synthesized and evaluated on HEK293 cells *in vitro*. Derivatives **1f**, **1i**, **1j**, **1m-1s** and **1t** exhibited increased agonisting activities on MT_1 and MT_2 receptors compared to the substrate tropine. Particularly, compound **1r** showed significantly agonistic activities on MT_1 and MT_2 receptors with EC_{50} values of 0.20 and 0.24 mM, respectively. The preliminary structure-activity relationships (SARs) of tropine derivatives were summarized for further investigation on melatonin receptor agonists.

Melatonin (MT), 5-methoxy-*N*-acetyltryptamine, released from the pineal gland at night, can regulate a variety of physiology and behavior by targeting MT_1 and MT_2 receptors.[1] MT_1 and MT_2 receptors belonging to the G-protein-coupled receptor (GPCR) superfamily are widely distributed in brain and peripheral nervous systems of mammals,[2-7] which are fascinating targets for drug discovery due to their multiply regulatory functions.[8-10] MT_1 receptor, generally expressed in the central nervous system and many peripheral tissues,[11] modulates neuronal firing. MT_2 receptor is observed in brain and lung, closely related to circadian rhythms of neuronal firing in the suprachiasmatic nucleus and dopamine release in retina.[12] In recent years, different types of MT_1 and MT_2 receptors agonistic ligands were reported, some of which had been used for psychiatric purposes.[13-14] For example, TAK-375 and VEC-162 were marketed for the treatment of insomnia,[15] and circadian rhythm sleep disorders.[16] However, most of the MT_1 and MT_2 receptors agonists are synthetic compounds possessing high similarity with melatonin, [17] and exploring novel types of agonists is still needed.

In the 19th and early 20th centuries, tropane alkaloids attracted particular interest due to their potent and extensive biological activities,[18] such as regulating secretion of the monoamine neurotransmitter, [19-22] influencing expression of the glycine receptor,[23] and modulating activation of the acetylcholine receptor.[24-26] Tropine as a natural tropane alkaloid mainly distributed in *Solanaceae* plants, showed pleiotropic physiological effects in humans and animals,[27] however, its agonistic effects on MT receptors have not been revealed.

Within the G-protein coupled receptor family of proteins, the MT_1 and MT_2 receptors can couple to multiple and distinct signal transduction cascades whose activation lead to unique cellular response. [28] MT_1 (or MT_2)-expressing cell line was made in the HEK 293-G_α15 host cells, which supported high levels of recombinant MT_1 (or MT_2) expression on the cell surface and contained high levels of the promiscuous G protein G_α15 to enhance coupling of the receptor to the calcium signaling pathway. Based on the Ca^{2+} influx , the receptor channel pore could be controlled by agonists using fluorimetric techniques, monitored by Ca^{2+}-sensitive dyes.[29] Test data for detecting changes in intracellular calcium was the transient calcium flux observed after activation of G-coupled protein receptors .[30] The details of Fluo-8 calcium assay were



Scheme 1. Reagents and conditions: (a) DMAP, DCC, CH_2Cl_2, r.t., 60-70% for compounds **1a-1x.** (b) PCC, CH_2Cl_2, r.t., 95% for compound **2**. (c) CH_3CN, reflux, 50-65% for compounds **1m.**

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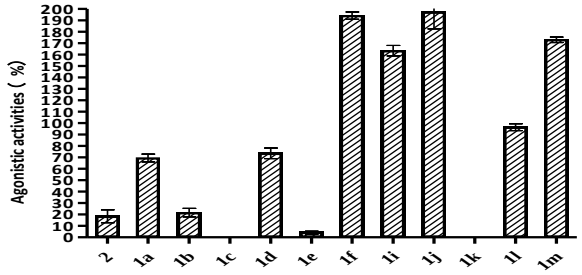
listed.[31] Our previous bio-assay evaluation suggested that tropine exhibited moderate agonistic activities on MT_1 and MT_2 receptors with the values of 90.50% and 77.48% at 1mM. Thus, a series of tropine derivatives were synthesized for developing new MT receptors agonists. The preliminary structure-activity relationships (SARs) were also discussed based on the bioassay on HEK293 cells *in vitro*.

With an objective to obtain target compounds which have agonistic activities on HEK293 cells *in vitro,* the synthetic strategies for target compounds are flexible. Tropine was reacted with various organic acids by Steglich esterification in the mixed solution of a catalytic amount of 4-dimethylaminopyridine (DMAP), dehydrating agent *N*,*N*-dicyclohexylcarbodiimide (DCC) and anhydrous CH_2Cl_2 to generate compounds **1a-1f** and **1i-1l** (Scheme 1).

The results of preliminary bioassay on MT_1 receptor showed that introduction of a benzoyl group and a cinnamoyloxy group



Compounds were tested at the concentration of 1.00 mM. The agonistic activities expressed as $\overline{X} \pm SD$ (n = 3) were obtained by comparing to the highest agonistic activity that was achieved for melatonin at the highest concentration and was set as 100%.

Figure 1. Agonistic activities of derivatives **2**, **1a-1f** and **1i-1m** on MT_1 receptor.

improved agonistic activity compared with that of tropine (Figure 1), and thus, derivatives **1g-1h** and **1n-1x** were gained for further study. Derivative **2** was synthesized starting from tropine with the oxidizing agent pyridinium chlorochromate (PCC) by oxidation reaction, which was no activity on MT_1 receptor. Derivative **1c** and piperazine were dissolved in CH_3CN with reflux condition to give derivative **1m**, and agonistic activity of derivative **1m** on MT_1 receptor increased . The structure of target compounds were identified by ^{1}H-NMR, ^{13}C-NMR, MS, HRMS and physicochemical properties (including clog P – calculated logarithm of partition coefficient between n-octanol and water, TPSA-polar surface area, logS – a unit stripped logarithm of the solubility measured in mol/liter and toxicity profiles (including mutagenic effect, tumorigenic effect, irritating effect and reproductive effect). Physicochemical properties of these compounds were calculated and predicted using OSIRIS Property Explorer software at URL

http://www.organic-chemistry.org/prog/peo/.[32, 33] The calculated data were shown in Table 1.

As shown in Table 2, tropine displayed moderate agonistic activities on MT_1 and MT_2 receptors with the values of 90.50% and 77.48% at 1mM. When the hydroxyl group was changed to be a carbonyl group, derivative **2** obviously reduced activities on MT_1 and MT_2 receptors with the values of 18.42% and 26.73% at 1mM respectively, suggesting C=O group was unfavorable activity for maintaining activities (Figure 2). In an effort to gain more information of the SARs of tropine derivatives, the esterified products were further obtained.

Table 1 Calculated physicochemical properties and predicted toxicity of compounds **2** and **1a-1x**.

Compd	Clog p^a	TPSA^b (Å^2)	logS^c	Toxicity risks^d M/T/I/R
2	0.65	20.31	-1.26	L/L/L/L
1a	0.99	29.54	-1.62	L/L/L/L
1b	1.89	29.54	-2.16	L/L/L/L
1c	2.12	29.54	-2.56	M/H/L/H
1d	2.57	29.54	-2.92	L/L/H/L
1e	6.44	29.54	-4.86	L/L/L/L
1f	2.43	29.54	-2.79	L/L/L/L
1g	3.04	29.54	-3.52	L/L/L/L
1h	3.16	29.54	-3.62	L/L/L/L
1i	2.25	29.54	-2.05	L/L/H/L
1j	2.76	29.54	-3.16	L/L/H/L
1k	2.46	38.77	-2.84	L/L/H/L
1l	1.42	67.87	-2.49	L/L/L/L
1m	2.32	32.78	-2.24	L/L/L/L
1n	3.10	29.54	-3.50	L/L/L/L
10	3.10	29.54	-3.50	L/L/L/L
1p	2.86	29.54	-3.47	L/L/L/M
1q	2.86	29.54	-3.47	L/L/L/L
1r	2.86	29.54	-3.47	L/L/L/L
1s	3.37	29.54	-3.89	L/L/L/L
1t	2.69	38.77	-3.17	L/L/H/M
1w	3.97	29.54	-4.63	L/L/L/L
1x	2.62	48.00	-3.19	L/L/L/L

[a] clog P, calculated logarithm of partition coefficient between n-octanol and water. [b] TPSA, polar surface area. [c] S, Solubility. [d]Toxicity risks: M, mutagenic effect; T, tumorigenic effect; I, irritating effect; R, reproductive effect; L, low; M,medium; H, high.

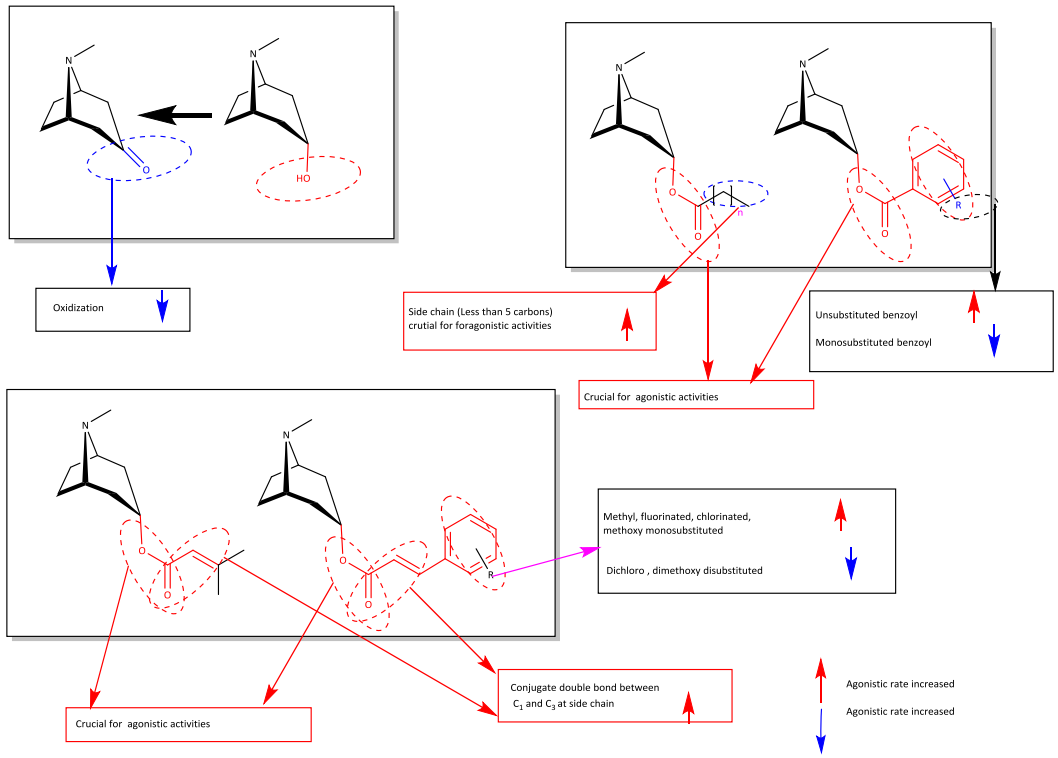


Figure 2. Structure–activity relationships of tropane derivatives.

Most of esterified derivatives showed attractively agonistic activities on MT_1 and MT_2 receptors (Table 2). The acetylated derivative **1a** displayed similar agonistic activities compared with tropine. Derivative **1b**, with a butyryl group at C-3 position, exhibited increased agonistic activity on MT_2 receptor. Derivative **1c** with a chlorinated group at the C-4 position of the butyryl group showed similar agonistic activity with derivative **1b**. Derivative **1d** with a 2-methyl-valeryl group owned an approximately 2-fold agonistic activity on MT_2 receptor and similar agonistic activity on MT_1 receptor compared to tropine. However, the myristoyl derivative **1e** resulted in a significantly decreased activities on MT_1 and MT_2 receptors. The above analyses suggested that bearing -OCO- ester group at C-3 position and a side chain (Less than 5 carbons) are crutial for agonistic activities(Figure 2). Followingly, the effect of some bulky aromatic groups at C-3 position was investigated. As shown in Table 2, introduction of a benzoyl group improved agonistic activities on both receptors. Derivative **1f** endowed significantly agonistic activities on MT_1 (194.22% at 1.00 mM) and MT_2 (219.61%, at 1.00 mM) receptors. These results encouraged us to further explore derivatives **1g** and **1h** by introducing diverse substitutions on a phenyl group. Interestingly, the unsubstituted benzoyl derivative **1f**, showed higher agonistic

Table 2. Agonistic activities of tropine derivatives (General molecular formula **1**, Figure 3) on melatonin receptors[a].

Comp.	R	Agonistic activities (%)	
		MT_1[b]	MT_2[c]
Ago.	-	100.00 ± 3.54	100.00± 2.00
2	-	18.42 ± 5.72	26.73 ± 1.84
Tropine	H	90.50 ± 3.33	77.48 ± 5.67
1a	Acetyl	69.51 ± 3.43	98.45 ± 4.35
1b	Butyryl	21.63 ± 3.70	149.97 ± 33.86
1c	4-Chloro butyryl	-3.06 ± 0.45	106.34 ± 8.71
1d	2-Methylvaleryl	73.52 ± 4.62	141.05 ± 13.91
1e	Myristoyl	4.20 ± 1.26	88.60 ± 14.28
1f	Benzoyl	194.22 ± 3.15	219.61 ± 7.28
1g	4-Chlorlbenzoyl	100.44 ± 3.50	127.05 ± 15.81
1h	4-Bromoxybenzoyl	47.65 ± 1.74	88.69 ± 2.03
1i	Senecioyl	163.13 ± 5.70	173.01 ± 50.85
1j	Cinnamoyl	197.18 ± 14.55	215.67 ± 14.01
1k	3-Phenoxy-propionyl	-2.55 ± 0.24	193.87 ± 7.35
1l	Boc-glycyl	96.37 ± 2.97	95.64 ± 1.91
1m	4-(*N*-piperidyl)butyryl	173.02 ± 2.35	217.84 ± 12.70

[a] Agomelatine was tested at the concentration of 3.33 μM.and Other compounds were tested at the concentration of 1.00 mM.[b]The agonistic activities expressed as $\bar{X} \pm SD$ (n = 3) were obtained by comparing to the highest agonistic activity that was achieved for melatonin at the highest concentration and was set as 100%.

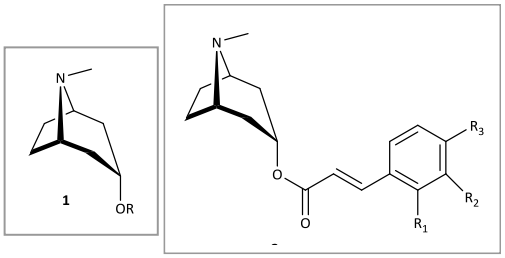


Figure 3. General molecular formula **1** and **2** .

activities than derivatives **1g** and **1h** with *para*-substituted at the phenyl ring. Agonistic activities of derivative **1i** with a conjugate double bond was two times higher than that of the tropine on both receptors. Cinnamoyloxy substituted derivatives **1j** with a conjugate double bond exhibited excellent agonistic activities on both receptors(Figure 2), which encouraged us to further explore derivatives **1o-1x**. Derivative **1k** with a phenoxylpropionyl group showed a 3-fold agonistic activity on MT_2 receptor but no activity on MT_1 receptor. Derivative **1i** with a *N*-(*tert*-butoxycarbonyl)-glycinyl group had similar agonistic activities compared with that of tropine. Derivative **1m** with a 4-butyryl piperidyl group at C-4 position, displayed an approximately 2-fold agonistic activity on MT_1 receptor and 3-fold on MT_2 receptor compared with tropine.

Derivative **1j** with a cinnamoyloxy group at C-3 position exhibited excellent agonistic activities on MT_1 (197.18%, at 1.00 mM) and MT_2 (215.67%, at 1.00 mM) receptors, suggesting that the cinnamoyl group is preferable for gaining high agonistic activity. Followingly, derivatives with diverse substitutions on the cinnamoyl group were synthesized in the following investigation. Derivatives **1n-1x**, with different substituents on the cinnamoyl ring, displayed agonistic activities from 56.65 to 190.04% on MT_1, and from 30.53% to 255.23% on MT_2, respectively (Table 3). Agonistic activities of methyl substituted analogues at *ortho*- and *para*- positions of phenyl ring (**1n**, **1o**) resulted in a significantly decreased activity on MT_1 receptor and maintained almost no change on MT_2 receptor compared with derivative **1j**. Fluorinated analogoues (**1p**, **1q**, **1r**) with *ortho*-, *meta*-, and *para*-substituted patterns at the phenyl ring, displayed agonistic potency on MT_2 receptor with the values of 177.57%, 196.72% and 255.23%, respectively. Agonistic activity of fluorinated analogue at *para*-position of phenyl ring exhibited higher activity than derivative **1j** on MT_2 receptor. Chlorinated derivative (**1s**) at *meta*-position of phenyl ring displayed slightly lower activity than derivative **1j** on both receptors. Derivative **1t** with a methoxy group at the C-3 position of the phenyl ring showed similar agonistic activities on both receptors compared with derivative **1j**. The dichloro substituted analogue (**1w**) and the dimethoxy substituted analogue (**1x**) resulted in remarkably reduced activity on both receptors compared with derivative **1j**.

Table 3. Agonistic activities of cinnamoyloxytropane derivatives (General molecular formula **2** , Figure 3) on melatonin receptors[a].

Comp.	R_1	R_2	R_3	Agonistic activities (%)	
				MT_1[b]	MT_2[c]
Ago.	-	-	-	100.00 ± 3.54	100.00± 2.00
1n	Me	H	H	158.60 ± 9.63	200.66 ± 4.50
1o	H	H	Me	145.56 ± 2.76	223.44 ± 10.94
1p	F	H	H	142.46 ± 6.25	177.57 ± 12.79
1q	H	F	H	160.17 ± 9.02	196.72 ± 3.75
1r	H	H	F	190.04 ± 9.13	255.23 ± 10.01
1s	H	Cl	H	125.35 ± 2.64	183.36 ± 2.35
1t	H	H	OMe	146.35 ± 10.32	193.24 ± 8.02
1w	Cl	H	Cl	56.65 ± 8.75	36.56 ± 10.02
1x	H	OMe	OMe	63.00 ± 6.26	30.53 ± 2.81

[a] Agomelatine was tested at the concentration of 3.33 μM.and Other compounds were tested at the concentration of 1.00 mM.[b]The agonistic activities expressed as $\overline{X}$ ± SD (n = 3) were obtained by comparing to the highest agonistic activity that was achieved for melatonin at the highest concentration and was set as 100%.

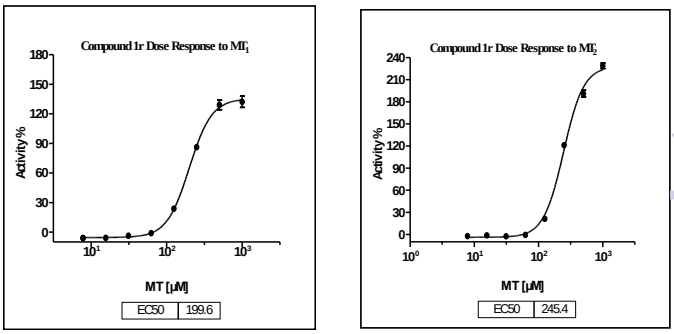


Figure 4. The dose-dependent effects of derivative **1r** on MT_1 and MT_2 receptors.

The dose-response curves for the most potent derivative **1r** was investigated to provide EC_{50} values of 0.20 and 0.24 mM on MT_1 and MT_2 receptors, respectively (Figure 4). Dose-response of calcium activity was performed in triplicate and monitored with FlexStation plate reader. EC_{50} values for the derivative **1r** were determined from the dose-response curves obtained with eight concentrations from the range of 7.81 to 1000 μM for MT_1 and MT_2 receptors, and calculated by the software of Graphpad Prism 5.0.

Conclusions

In conclusion, twenty-three derivatives of tropine were synthesized and evaluated on MT_1 and MT_2 receptors, of which, derivatives **1f**, **1j** and **1r** exhibited promising agonistic activities. The preliminary SARs suggested that the hydroxyl group at C-3 position was crucial for maintaining agonistic activities, and esterification on the hydroxyl group will generate different activities. This investigation will provide valuable insights for further developing tropine derivatives as potential melatonin receptors agonists.

Author contributions

Xiu-juan Yin and Ji-jun Chen contributed to the design of experiments and the manuscript preparation. Xiu-juan Yin, Chang-an Geng, Xiao-yan Huang, Yun-bao Ma and Ji-jun Chen performed the experimental studies and analyzed the data. Xiao-yan Huang and Yun-bao Ma contributed to the design and test of biological activity. Xing-long Chen was responsible for data testing of HRMS. Chang-li Sun, Tong-hua Yang, Jun Zhou and Xue-mei Zhang contributed in critical reading and discussion on the manuscript. All the authors approved the final version.

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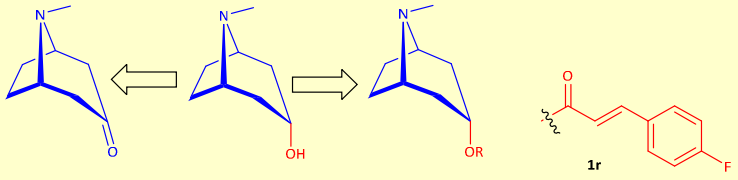
Notes and references

1. D. Sugden, K. Davidson, K. A. Hough, M. T. Teh. *Pigm. Cell Res*. 2004, **17**, 454.
2. A. Ghanemi. *Saudi Pharm. J*. 2015, **23**, 115.
3. J. M. Karasinska, S. R. George, B. F. O'Dowd. *Brain Res. Rev*. 2003, **41**, 125.
4. B. L. Roth, D. L. Willins, W. K. Kroeze. *Drug Alcohol Depen*. 1998, **51**, 73.
5. J. A. Salon, D. T. Lodowski, K. Palczewski. *Pharmacol. Rev*. 2011, **63**, 901.
6. R. Jockers, P. Maurice, J. A. Boutin, P. Delagrange. *Brit. J. Pharmacol*. 2008, **154**, 1182.
7. V. Audinot, F. Mailliet, C. Lahaye-Brasseur, A. Bonnaud, A. Le Gall, C. Amossé, S. Dromaint, M. Rodriguez, N. Nagel, J. P. Galizzi, B. Malpaux, G. Guillaumet, D. Lesieur, F. Lefoulon, P. Renard, P. Delagrange, J. A. Boutin. *N-S. Arch. Pharmacol.* 2003, **367**, 553.
8. Dubocovich, M. L.; Delagrange, P.; Krause, D. N.; Sugden, D.; Cardinali, D. P.; Olcese, J. *Pharmacol. Rev*. 2010, **62**, 343.
9. M. A. Shehata, H. B. Christensen, V. Isberg, D. S. Pedersen, A. Bender, H. Bräuner-Osborne, D. E. Gloriam. *RSC Adv.* 2015, **5**, 48551.
10. S. M. Reppert, C. Godson, C. D. Mahle, Weaver, D. R.; Slaugenhaupt, S. A.; Gusella, J. F. *Proc. Natl. Acad. Sci.* 1995, **92**, 8734.
11. K. H. Chan, Y. H. Wong. A. *Int. J. Mol. Sci.* 2013, **14**, 18385.
12. M. L. Dubocovich, M. Markowska. *Endocrine*. 2005, **27**, 101.
13. D. P. Zlotos. *Arch. Pharm.* 2005, **338**, 229.
14. L. Naji, A. Carrillo-Vico, J. M. Guerrero, J. R. Calvo. *Life Sci*. 2004, **74**, 2227.
15. K. Kato, K. Hirai, K. Nishiyama, O. Uchikawa, K. Fukatsu, S. Ohkawa, Y. Kawamata, S. Hinuma, M. Miyamoto. *Neuropharmacology*. 2005, **48**, 301.
16. S. M. W. Rajaratnam, M. H. Polymeropoulos, D. M. Fisher, T. Roth, C. Scott, G. Birznieks, E. B. Klerman. *Lancet*. 2009, **373**, 482.
17. D. P. Zlotos. *Curr. Med. Chem.* 2012, **19**, 3532.
18. J. W. Medley, M. Movassaghi. *Chem. Commun*. 2013, **49**, 10775.
19. L. Melzig, A. Gavryushin, P. Knochel. *Org. Lett.* 2007, **26**, 5529.
20. K. C. Schmitt, J. Zhen, P. Kharkar, M. Mishra, N. Chen, A. K. Dutta, M. E. A. Reith. *J. Neurochem*. 2008, **107**, 928.
21. R. H. Kline, S. Izenwasser, J. L. Katz, D. B. Joseph, W. D. Bowen, A. H. Newman. *J. Med. Chem*. 1997, **40**, 851.
22. J. L. Katz, G. E. Agoston, K. L. Alling, R. H. Kline, M. J. Forster, W. L. Woolverton, T. A. Kopajtic, A. H. Newman. *Psychopharmacology.* 2001, **154**, 362.
23. G. Maksay, P. Nemes, Z. Vincze, T. Bíró. *Bioorg. Med. Chem.* 2008, **16**, 2086.
24. R. L. Papke, H. C. Schiff, B. A. Jack, N. A. Horenstein. *Neurosci. Lett*. 2005, **378**, 140.
25. K. Sun, Z. D. Guo. *Int. J. Pharm. Res.* 2008, **35**, 87.
26. D. I. Lainé, H. B. Xie, N. Buffet, J. J. Foley, P. Buckley, E. F. Webb, K. L. Widdowson, M. R. Palovich, K. E. Belmonte. *Bioorg. Med. Chem. Lett*. 2007, **17**, 6066.
27. W. J. Griffin, G. D. Lin. *Phytochemistry*. 2000, **53**, 623.
28. P. A. Witt-Enderby, J. Bennettb, M. J. Jarzynkaa, S. Firestinea, M. A. Melan. Life Sci. 2003, 72, 2183.
29. J. Walstab, S. Combrink, M. Brüss, M. Göthert, B. Niesler, H. Bönisch. *Anal. Biochem*. 2007, **368**, 185.
30. P. Gribbon, C. Chambers, K. Palo, J. Kupper, J. Mueller, A. Sewing. *J. Biomol. Screen.* 2006 , **11**, 511.
31. *In vitro* agonist activity: The Fluo-8 Calcium Assay could provide a fast, simple and reliable fluorescence-based assay for detecting changes in intracellular calcium. HEK293 cell lines stably expressing the human melatonin MT_1 or MT_2 receptor was grown in Dubecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), and cultured with 95% O_2/5% CO_2 at 37℃. The cells were seeded in a Matrigel coated 96-well black plate with a plating volume of 100 µL / well at a density of 4×104/well, and incubated in CO_2 incubator (Thermo Forma 3310, US) for overnight. Then the cells were dyed by HDB Wash Free Calcium Assay Kit, and placed in CO_2 incubator for 1h. Tested compounds and positive drug were dissolved in 10 µL dimethyl sulfoxide (DMSO) and 990 µL HBSS Buffer respectively, and extracted a plating volume of 100 µL/well in a Matrigel coated 96-well plate. Two 96-well plates were put into Flexstation 3 Benchtop Multi-Mode Microplate Reader (Molecular Devices, Sunnyvale, California, USA). The absorption values were readed by Flexstation 3 Benchtop Multi-Mode Microplate Reader at room temperature with wavelength (Excitation: 485 nm; Emissiom: 525 nm; Emission cut-off: 515 nm). The agonistic activities expressed as $\overline{X} \pm$ SD (n = 3) were obtained by comparing to the highest agonistic activity that was achieved for melatonin at the highest concentration and was set as 100%. The results were calculated by the software of Graphpad Prism 5.0.
32. S.Y. Wang, L. J. Wang, B. Jiang, N. Wu, X. Q. Li, J. Luo, B. C. Wang, R. S. Zhang, Q. Xu , D. Y. Shi. *RSC Adv.* 2015, **5**, 91795.
33. OSIRIS Property Explore, http://www.organic-chemistry.Org /prog/peo/, accessed 23-11-2015.



HEK293 cells *in vitro*, MT_1: EC_{50} = 0.20 μM; MT_2: EC_{50} = 0.24 μM.