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Research paper

Synthesis and biological evaluation of magnolol derivatives as melatonergic receptor agonists with potential use in depression

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ABSTRACT

Depression is associated with high mortality and morbidity rates worldwide. By our random screening, it was first revealed that 23 magnolol derivatives were synthesized followed by *in vitro* and *in vivo* evaluation of their antidepressive potential. Compound **7c** was found to be the most promising compound, with EC_{50} values of 396.5 and 383.0 μM agitating on MT_1 and MT_2 receptors, respectively. Additionally, we carried out *in vivo* experiments to confirm the efficacy and safety of compound **7c**; the compound was found to be orally bioavailable and highly effective, leading to a significant reduction of immobility time in a mouse model of depression (forced swimming test and tail suspension test); the acting mechanism was explored by determining its effect on the levels of monoamine neurotransmitters and their metabolites in different mice brain regions; the acute toxicity study showed that the 50% lethal dose (LD50) of **7c** was higher than 2000 mg/kg, p. o. A total of 25 metabolites of **7c** were identified, including 5 metabolites in phase I and 20 metabolites in phase II. Altogether, these results indicate that magnolol derivative **7c** is a promising lead compound for the development of a new chemical class of antidepressant drugs.

1. Introduction

Depression is the leading cause of disability and a major contributor to the overall global burden of disease, with a lifetime prevalence of 17% in the USA, and it is estimated that 300 million people affecting worldwide [1,2]. According to the World Health Organization (WHO), almost 800,000 lives are lost yearly due to suicide, and by the year 2020 is projected to be second only to ischemic heart disease in the amount of disability experienced by sufferers. Current pharmacotherapy is based on monoamine deficiency as the underlying etiology and pathogenesis of depression. There are several drugs on the market which have anti-depressant properties such as inhibitors of the enzyme monoamine oxidase (MAO), selective monoamine reuptake inhibitors, and, more recently, triple anti-depressants [3,4]. Although first-line antidepressants offer therapeutic benefit, the response to antidepressants is not immediate and usually occurs between the second and fourth weeks as well as causing side effects, as sedation and weight gain [5–7]. Furthermore, about 35% of depressed patients are not adequately treated, creating a large unmet medical need [8]. Evidence from preclinical and clinical studies implicates melatonin hypofunction in the pathophysiology of depression, and the potent MT_1 and MT_2 melatonergic agonist agomelatine displayed effective in the treatment of depressed patients [9,10]. Thus, during the past decade, a great number of structurally different MT receptor ligands which range from simple indole derivatives and their bioisosteres to phenylalkyl amides and constrained melatoninergic agents, have been reported in the literature [11]. The above reports clearly confirm that melatonergic agonists are emerging as an important target for the treatment of depression. In an attempt to develop a set of melatonergic agonists inspired by natural products, and magnolol displayed moderate activity on $MT_{1/2}$ receptors (agonistic rates: 40.24% and 20.04%, respectively at a concentration of 1.0 mM) in our earlier study, thus, we have selected magnolol as the parent scaffold. Although simple chemical modifications of the magnolol via the acetylation and methylation reported, their bioactivities only determined with anti-inflammatory activity or activation of cannabinoid receptors [12,13].

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In this report, we designed and synthesized a series of magnolol derivatives via suitable chemical transformation, then these derivatives evaluated for agitating activity on $MT_{1/2}$ receptors. The most potent derivative **7c** was further studied to confirm the efficacy *in vivo* by the behavioral test. Then the safety of compound **7c** was estimated with acute toxicity and its metabolites from urine, plasma and faeces were also detected and identified.

2. Results and discussion

2.1. Chemistry

The synthetic routes for the target compounds outline in Scheme 1. Magnolol treated with corresponding acids in the presence of *N*, *N*-dicyclohexylcarbodiimide and 4-dimethylaminopyridine to afford 1-substituted magnolol derivatives **1a**-**1g** and 1, 2-substituted derivatives **2a**-**2e**. To obtain the epoxides compounds **3**–**4**, magnolol was reacted with meta-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at room temperature. Compounds **5**–**6** prepared by the α-D-glucopyranosyl bromide tetraacetate and magnolol with tetrabutylammonium bromide (TBAB). Stirring compounds **5** or **6** in sodium methoxide-methanol solution for 4–8 h furnished the corresponding derivatives **7a**-**7d**. A mixture of compound **7c** and appropriate carboxylic acid in a solution of DCC and DMAP to get target compounds **8a**-**8c**.

2.2. In vitro agonistic activities on $MT_{1/2}$ receptors

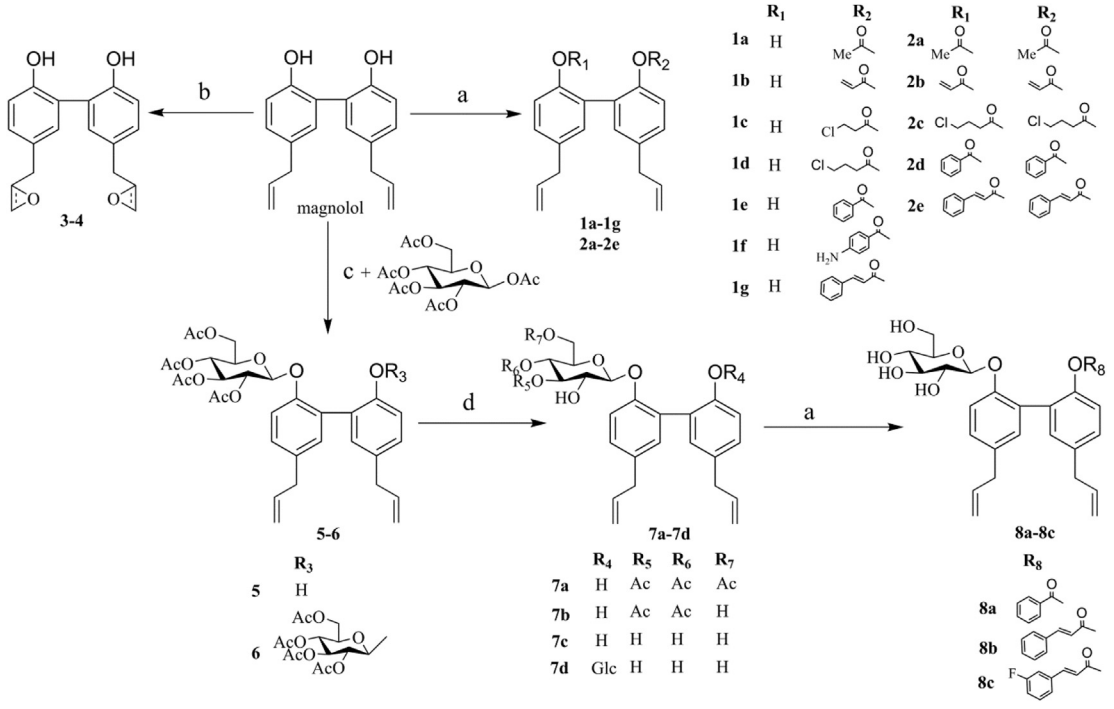
MT_1 and MT_2 melatonin receptors are important targets for the development of novel antidepressants. Thus, all synthesized compounds for their agonistic activities on $MT_{1/2}$ receptors evaluated. The results were summarized, and the details of the bioassay procedures described in the Experimental Section. As shown in Table 1, the mono-acetylated derivative **1a** exhibited stronger agonistic activities on $MT_{1/2}$ receptors compared with magnolol. Interestingly, derivatives **1d** and **7b** can only improve agitating activity on MT_2 (nearly 3.5–4.5 folds compared with magnolol). Compounds **1e**-**1g** showed no activities indicating that different aromatic groups at the position of R_2 were not beneficial because of steric hindrance. Compared mono-substituted (**1a** and **1d**) with bis-substituted (**2a** and **2c**), the agonistic activities decreased dramatically suggesting hydroxyl at the position of R_1 was very much beneficial to the activity. To confirm the role of double bonds, we synthesized compounds **3**–**4**. Unfortunately, the introduction of epoxide groups could not improve their biological activities, indicating the double bond may be the binding site to the receptors.

To develop more potent derivatives, another kind of compound with a glucosyl group was synthesized. Notably, compound **7c** exhibited excellent agonistic activity on $MT_{1/2}$ receptors with the values of 107.95% and 150.67%, respectively at a concentration of 1.0 mM. As shown in Table 1, the result suggested decrement in the

Table 1
Agonistic activities of magnolol and its derivatives on melatonin receptors.

Comp.	Agonistic activities (%)[b]		Comp.	Agonistic activities (%)[b]	
	MT_1	MT_2		MT_1	MT_2
Ago.[a]	100.00 ± 1.98	100.00 ± 3.21	**2e**	28.34 ± 1.80	3.34 ± 0.36
Mag.	40.24 ± 2.17	20.04 ± 0.85	**3**	53.77 ± 3.38	−3.08 ± 0.22
1a	91.43 ± 2.74	77.60 ± 3.06	**4**	2.18 ± 0.35	−3.39 ± 0.41
1b	1.31 ± 0.22	2.93 ± 1.09	**5**	−0.58 ± 0.02	−2.09 ± 0.08
1c	21.01 ± 2.21	30.15 ± 3.18	**6**	7.09 ± 1.33	0.04 ± 1.09
1d	32.05 ± 2.04	69.68 ± 3.41	**7a**	10.98 ± 1.20	19.06 ± 2.16
1e	−6.50 ± 1.35	−0.04 ± 0.42	**7b**	31.03 ± 1.83	89.00 ± 3.52
1f	−1.55 ± 0.33	5.17 ± 0.53	**7c**	107.95 ± 3.12	150.67 ± 2.75
1g	56.78 ± 2.57	25.56 ± 1.79	**7d**	2.97 ± 0.08	10.85 ± 0.96
2a	−1.86 ± 0.30	−2.52 ± 0.59	**8a**	13.24 ± 2.37	−5.71 ± 0.53
2b	0.04 ± 0.14	4.57 ± 0.23	**8b**	50.31 ± 5.36	−10.12 ± 1.67
2c	8.14 ± 0.77	2.11 ± 0.10	**8c**	5.30 ± 1.11	−10.50 ± 1.28
2d	−5.93 ± 0.51	−1.72 ± 3.11			

[a] Agomelatine was as a positive control and 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).



Scheme 1. (A) DMAP, DCC, CH_2Cl_2, rt, 4–6 h; (b) *m*-CPBA, CH_2Cl_2, rt, 4 h; (c) HBr, CH_2Cl_2, ice-bath, 6 h; Bu_4NBr, NaOH, $CHCl_3$, H_2O, rt, 2–4 h; (d) NaOMe, MeOH, rt, 4–8 h.