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The synthesis and synergistic antifungal effects of chalcones against drug resistant *Candida albicans*

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ABSTRACT

To identify effective and low toxicity synergistic antifungal compounds, 24 derivatives of chalcone were synthesized to restore the effectiveness of fluconazole against fluconazole-resistant *Candida albicans*. The minimal inhibitory concentration (MIC_{80}) and the fractional inhibitory concentration index (FICI) of the antifungal synergist fluconazole were measured against fluconazole-resistant *Candida albicans*. This was done via methods established by the clinical and laboratory standards institute (CLSI). Of the synthesized compounds, 2′-hydroxy-4′-methoxychalcone (**8**) exhibited the most potent in vitro (FICI = 0.007) effects. The structure activity relationship of the compounds are then discussed.

Candida albicans is the most common pathogenic fungus and is frequent in persons with weaker immunity or bacterial flora imbalance including those with cancer, chronic wasting disease, or excessive use of broad-spectrum antibiotics, immunosuppressive agents, and hormones. Fluconazole is the most commonly used drug to treat *C. albicans* in prophylaxis and therapy; however, widespread and repeated use of fluconazole resulted in resistance to or failure of fluconazole therapy.[1]

One promising approach aimed at overcoming azole resistance has been sensitizing *C. albicans* toward fluconazole via small molecules such as berberine,[2,3] caffeic acid amides[4] and minocycline.[5] Recently, natural flavonoids have been reported that have synergistic antifungal activity[6,7] such as baicalein and quercetin—this encouraged us to study new flavonoids with synergistic antifungal activity. Chalcones are naturally occurring flavonoids composed of two aromatic rings connected by a three-carbon unit to form an α,β unsaturated carbonyl group. Some research has demonstrated that chalcones have antitumor, anti-fungal and anti-inflammatory activities,[8–10] but to the best of our knowledge, no study has yet described the synergistic antifungal activity of chalcones against drug-resistant *C. albicans*. This current work is motivated by a recent study describing new active scaffolds containing an α,β unsaturated carbonyl group against drug-resistant *C. albicans*.[4] Inspired by these, we designed and synthesized some chalcones—most of which, as expected, exhibited activity. Herein, we report the results and the SAR (structure activity relationship) is investigated and discussed.

Previous studies have reported that baicalein (BE, Fig. 1) and caffeic acid amides (CAA, Fig. 1) exert synergistic antifungal activity on fluconazole-resistant *C. albicans*. Bitencourt's study reported non-substituted chalcone (NSC, Fig. 1) that was effective against *Trichophyton rubrum*. In the structures of BE, CAA and NSC, all contain the an α,β unsaturated carbonyl and catechol moiety, but the catechol moiety was believed to be a pan assay interference compounds (PAINS)[11] and thus should be avoided in compound design. Thus, we designed the structure of chalcone to exclude the catechol moiety and keep the BE moiety (1-alkoxyl and 5-hydroxyl structure (Compd **1**–**6**, Fig. 1 and Table 1)). We also kept only the 5-hydroxyl and/or introduced other groups (Compd **6**–**24**, Fig. 1 and Table 1) to investigate SAR.

The synthetic route to target compounds is outlined in Scheme 1. The chalcones were synthesized by aldol condensation catalyzed by 30% NaOH. The 2′,6′-dihydroxyacetophenone was used as a starting material for the synthesis of compounds **1**–**6**. First, 2′,6′-dihydroxyacetophenone was treated with CH_3I and K_2CO_3 in dry DMF to give 2′-hydroxy-6′-methoxyacetophenoe, which then reacted with a series of aromatic aldehydes to achieve

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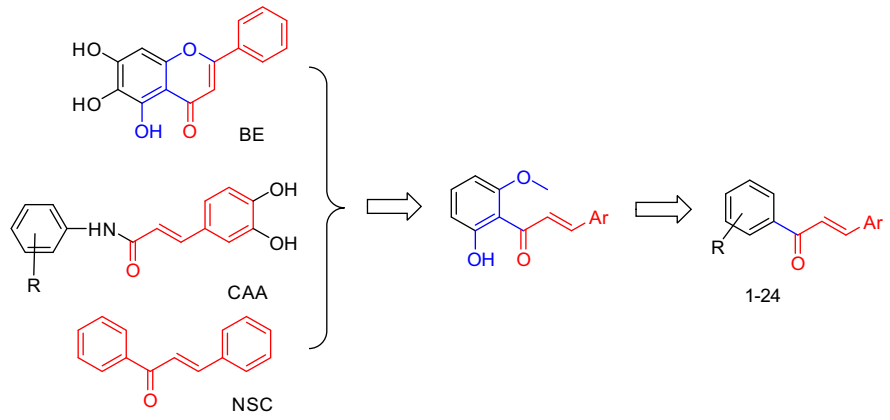
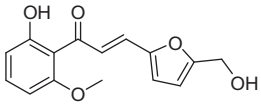
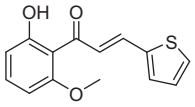
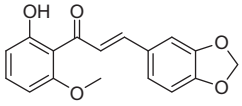
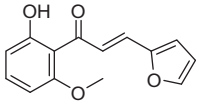
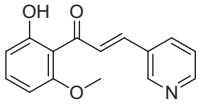
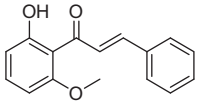
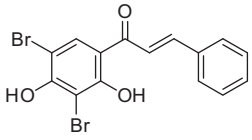
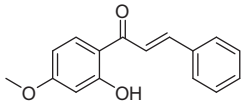
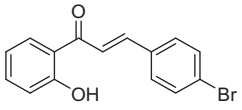
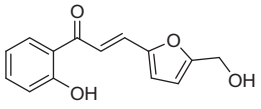


Figure 1. The design of title compounds.

Table 1
Structures and interaction modes of the title compounds and their MIC_{80} and FICI values

No.	Structure	MIC_{80} (μg mL^{-1})		FICI	Mode of interaction
		Alone	With FLC[a]		
1*		>64	8	0.125	Synergy
2*		>64	4	0.094	Synergy
3		>64	4	0.094	Synergy
4		>64	4	0.094	Synergy
5*		>64	8	0.125	Synergy
6		>64	16	0.188	Synergy
7		64	4	0.125	Synergy
8		>64	1	0.007	Synergy
9		>64	16	0.188	Synergy
10		>64	8	0.125	Synergy

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