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Catalytic asymmetric synthesis of indole derivatives as novel α-glucosidase inhibitors *in vitro*

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ABSTRACT

Indole containing compounds have acquired conspicuous significance due to their wide spectrum of biological activities. Synthesis of a series of enantiomerically pure indole derivatives **3a-r** *via* Friedel–Crafts alkylation of indole **1** with enones **2a-r** were described here. The products were isolated in a moderate to excellent yields (upto 89%) with excellent enantioselectivities (upto 99.9% *ee*). These compounds **3a-r** were evaluated for their *in vitro* α-glucosidase inhibitory activity and some of them were identified as potent inhibitors (IC_{50} = 4.3 ± 0.13–43.9 ± 0.51 μM) with several fold higher activity than the clinically used α-glucosidase inhibitor, acarbose (IC_{50} = 840 ± 1.73 μM). To the best of knowledge, this is the first report of the propanone substituted indole ring containing compounds by *in vitro* α-glucosidase enzyme inhibition.

1. Introduction

Indoles form a large class of heterocyclic compounds, found in many natural products, such as the alkaloids, fungal metabolites, and marine natural products [1,2]. Indole myriad derivatives have, therefore captured the attention of organic synthetic and medicinal chemists. Indole, and its analogs are known to possess a wide spectrum of biological activities. Several indole derivatives were reported as anticancer [3], antibacterial [4], antiulcerative [5], antiplatelet [6], antimalarial [7], antileishmanial [8], antiviral [1], antioxidant [9], antirheumatoidal [10], anti-HIV [11], immunomodulator, antitubercular, and inhibitors of chemical mediator's release, and leukotriene B4 tyrosinase and aldose (reductase activity) [12,13].

Some of these compounds also possess anti- inflammatory and analgesic properties. They play a vital role in the immune system [14,15]. Many indole derivatives are potent scavengers of free radicals [16]. The immense modulating activities of indole derivatives led to the development and optimization of highly efficient and economical synthetic routs towards the synthesis of novel biologically active indole substances [17]. In this regard, asymmetric synthesis is a promising approach for accessing enantio-pure compounds, including diverse indole derivatives [18,19].

The Lewis acid-catalyzed enantioselective Friedel-Crafts alkylation of prochiral α,β-unsaturated enones is a key method towards the synthesis of various classes of compounds, including indole containing enones moieties. Therefore, it was envisaged that the novel pharmacophore would generate novel molecular entities, which are likely to exhibit interesting biological properties in bioassay models. Based on the importance of indoles and in continuation of our work on the synthesis of biologically active compounds, we successfully synthesized a series of pharmacologically active compounds, and evaluated their *in vitro* α-glucosidase inhibitory activity.

α-Glucosidase (EC 3.2.1.20) is a small intestinal membrane bound enzyme that catalyzes the hydrolysis of disaccharides to absorbable monosaccharide, i.e. glucose, and its inhibition suppresses the hyperglycemia in diabetes [20]. Inhibition of α-glucosidase can effectively overcomes the risk of postprandial hyperglycemia, an independent risk factor of cardiovascular diseases [21–23].

Glucosidases are also involved in several of the important biological processes, such as the synthesis of glycoproteins and the lysosomal catabolism of glycol conjugates. α-Glucosidase inhibitors have been also used as inhibitors of tumor metastasis, and as anti-obesity drugs, fungistatic compounds, insect's anti-feedants, anti-viral, and immune modulators [24].

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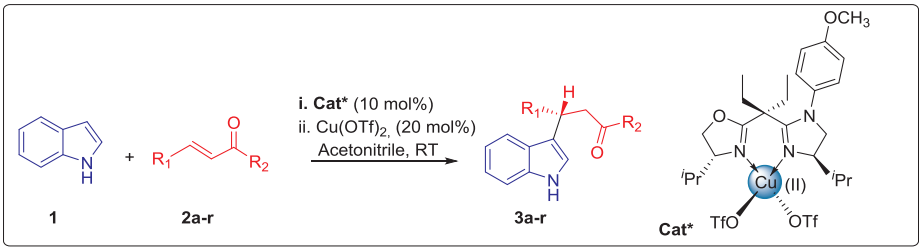
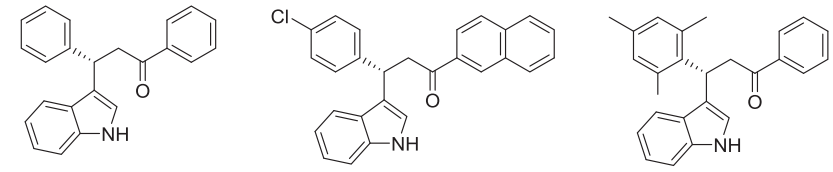
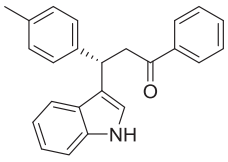




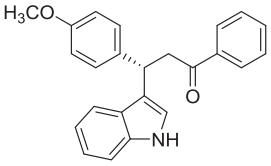
3a 99.9% *ee*
86% yield

3b 95.6% *ee*
81% yield

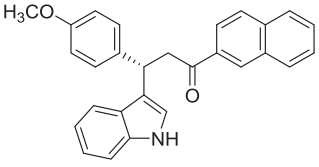
3c 96% *ee*
40% yield



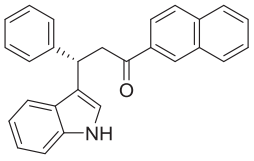
3d 95.8% *ee*
73% yield



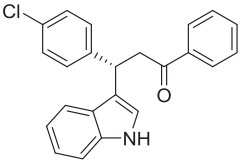
3e 96.4% *ee*
89% yield



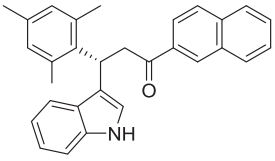
3f 90.8% *ee*
66% yield



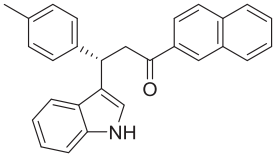
3g 95.5% *ee*
47% yield



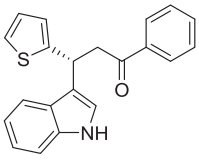
3h 93.85% ee
84% yield



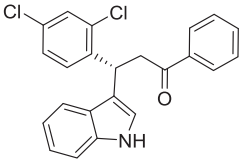
3i 97.8% *ee*
22% yield



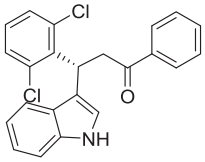
3j 93.4% *ee*
27% yield



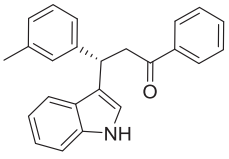
3k 89.8% *ee*
65% yield



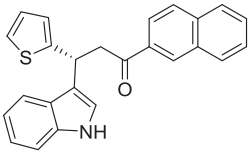
3l 97.55% *ee*
84% yield



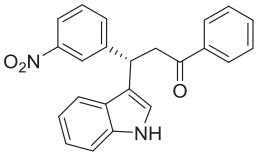
3m 81.7% *ee*
78% yield



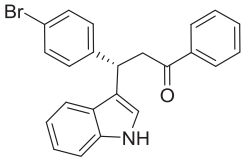
3n 72.4% *ee*
79% yield



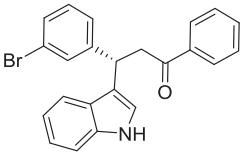
3o 93.2% *ee*
89% yield



3p 97.2 *ee*
86% yield



3q 87.2% *ee*
82% yield



3r 89.1% *ee*
84% yield

Scheme 1. Schematic representation of the synthesis of indole derivatives **3a-r**.

The inhibition of *α*-glucosidase enzyme is consider as the most promising approach to overcome the condition of hyperglycemia, and associated health disorders in diabetic patients. Recently, M. Taha and his team synthesized a series of indole hybrid analogs as a novel *α*-glucosidase inhibitors [25]. Many of the clinically used as *α*-glucosidase inhibitors are associated with adverse effects [26]. Therefore, this is