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Design and synthesis of novel indole-chalcone fibrates as lipid lowering agents☆

Koneni V. Sashidhara [a,*], Ranga Prasad Dodda [a], Ravi Sonkar [b], Gopala Reddy Palnati [a], Gitika Bhatia [b]

[a] Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow, Uttar pradesh 226031, India
[b] Biochemistry Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, India

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ABSTRACT

A series of novel indole-chalcone fibrates were synthesized and their hypolipidemic activity was evaluated in triton WR-1339 induced hyperlipidemic rat model. Preliminary studies indicated that the hybrids **19**, **24** and **29** exhibited potent in vitro antioxidant and significant in vivo antidyslipidemic effects. Our results suggest that these new hybrid architectures may serve as promising leads for the development of next generation lipid lowering agents.

1. Introduction

Coronary heart disease (CHD) is the dominant cause of morbidity and mortality in the industrialized nations [1,2]. Among the predominant risk factors for CHD are high levels of low-density lipoprotein cholesterol (LDL-C), triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C) [3]. An improvement in the levels of these risk factors would reduce the risk for developing CHD. Currently, the most common method to treat dyslipidemia is the use of statins, which are HMG-CoA reductase inhibitors. The widespread clinical use of the statins is accompanied by potential dose-limiting hepatotoxicity and myotoxicity, which may be the consequence of reduced levels of essential isoprenoid precursors, the antioxidant ubiquinone, or dolichols [4]. Cerivastatin, one of the second generation statins, was withdrawn from the world market in 2001, due to its adverse effects [5]. The fibrate class of lipid-lowering drugs such as fenofibrate and gemfibrozil (Fig. 1) are selective activators of alpha-isotype of the receptors peroxisome proliferator activated receptor (PPAR) [6,7]. These drugs lower triglyceride levels and increase HDL cholesterol levels in hyperlipidemic patients [8] and reduce the risk of coronary heart disease in patients with low HDL cholesterol levels [9]. In recent years the design of dual-target hypoglycemic agents that activate glucokinase and PPARγ have also been reported for treating Type 2 diabetes mellitus [10]. Recent studies outline the role of oxidative stress in the pathogenesis and development of various diseases including atherosclerosis, diabetes mellitus, hypertension, and coronary heart disease [11]. Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS) and antioxidant systems [12]. So a single-targeted therapeutic approach in multifactorial disorders such as those mentioned above is mostly considered inadequate [13,14]. Thus molecules endowed with both antidyslipidemic and antioxidant properties are in great demand.

Molecular hybridization is a strategy of rational design of new ligands or prototypes based on the recognition of pharmacophoric subunits in the molecular structure of two or more known bioactive derivatives [15]. Owning to its wide range of pharmacological activities, indole and their derivatives has been a subject of intense investigations [16–20]. Fluvastatin (Fig. 1), which includes an indole moiety, is a synthetic member of the statin class of drug, used to lower cholesterol and prevent cardiovascular disease. Our group recently reported a series of coumarin-bisindole hybrids, which have shown significant antihyperlipidemic activity [21]

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* Corresponding author.
E-mail addresses: sashidhar123@gmail.com, kv_sashidhara@cdri.res.in (K.V. Sashidhara).

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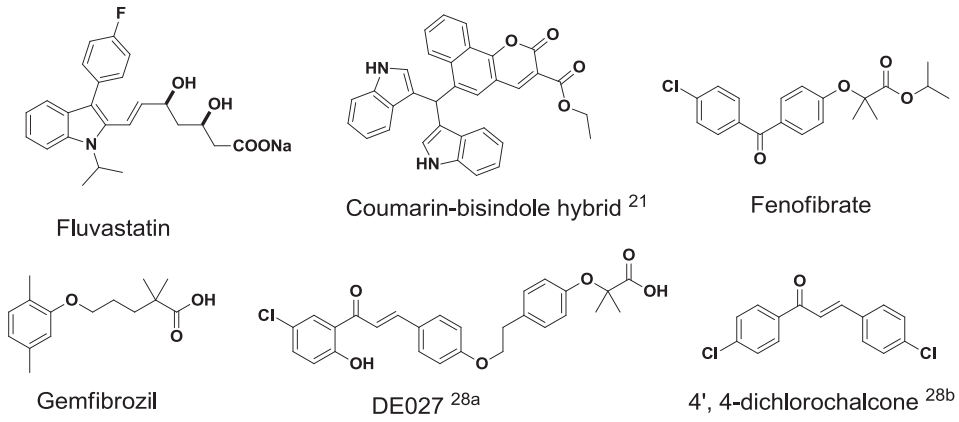

Fig. 1. Chemical structures of some representative indoles, fibrates and chalcones possessing lipid lowering activities.

(Fig. 1). On the other hand, chalcones are important compounds that are present in many naturally occurring products. Their pharmaceutical potential is due to their radical-scavenging [22,23], antitumor [24,25], anti-inflammatory [26] and neuro-protective properties [27]. Furthermore, recent literature survey revealed that synthetic chalcone derivatives, DE027 and 4′, 4-dichlorochalcone (Fig. 1), exhibited potential hypolipidemic activities [28]. In our previous reports, we disclosed the indole based fibrates and coumarin-chalcone fibrates as potent antidyslipidemic agents [29,30] (Fig. 2).

These above interesting findings and our continuous quest to identify more potent analogues, led to the molecular hybridization of indole, chalcone and fibrate to integrate them in one molecular platform to generate a new hybrid architecture with the aim of exploring the impact of such modification on the hypolipidemic profile [21,31,32] (Fig. 2). In this paper we report the synthesis and evaluation of novel indole-chalcone fibrates as new class of antidyslipidemic agents. Fig. 1 shows some representative chemical structures of compounds possessing indole, fibrate and chalcone framework with lipid lowering activities.

2. Chemistry

The synthesis of the designed compounds is outlined in Scheme 1. The commercially available indole and substituted indoles (**1**–**4**) underwent Vilsmeier Haack reaction [33] in presence of $POCl_3$ and DMF to afford corresponding indole-3-carbaldehydes (**5**–**8**). On the other hand, the reaction of 4-hydroxy acetophenone with the appropriate bromo esters in the presence of K_2CO_3 in acetonitrile under reflux conditions furnished substituted acetophenones (**9**–**12**) in quantitative yield. The subsequent Claisen–Schmidt condensation of these acetophenones (**9**–**12**) with indole-3-carbaldehydes (**5**–**8**) in the presence of catalytic amount of piperidine in MeOH or EtOH under reflux conditions [34] yielded the desired indole-chalcone fibrates **13**–**21** and **22**–**30**, respectively and the trans double bond was obtained exclusively (J = 15–16 Hz). When

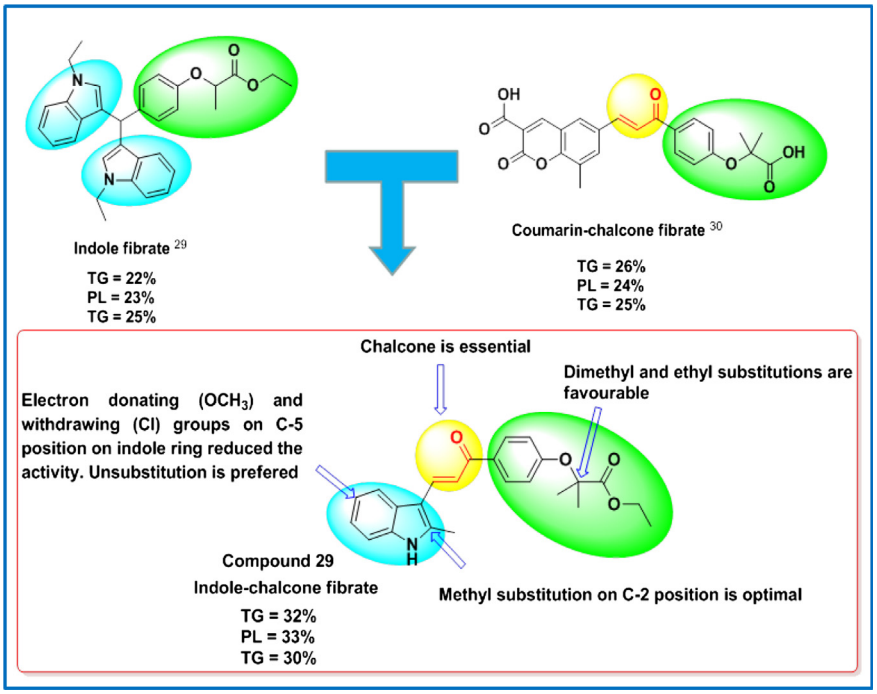

Fig. 2. Rational designing and preliminary SAR of indole-chalcone fibrates.