

Synthesis and biological evaluation of 2-aryloxybenzofurans, rugchalcones A, B and their derivatives as potent *anti-inflammatory* agents



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ARTICLE INFO

Article history:

Received 24 October 2015

Revised 28 January 2016

Accepted 10 February 2016

Available online 10 February 2016

Keywords:

2-Aryloxybenzofuran

Rugchalcones

Rap–Stoermer reaction

Nitric oxide

anti-inflammatory

ABSTRACT

An efficient synthesis of 2-aryloxybenzofurans, rugchalcones A, B and their derivatives was accomplished in excellent yields by the Rap–Stoermer reaction between substituted salicylaldehydes and phenacyl bromides. Later their *anti-inflammatory* effects were evaluated in lipopolysaccharide (LPS)-induced RAW-264.7 macrophages. The compounds were exhibited exceptional potency against inflammatory mediated NO production with no cytotoxicity at 10 μ M concentration and IC₅₀ values are found in the range from 0.75 to 13.27 μ M. Among the 2-aryloxybenzofurans prepared in this study, compounds **4** (99.6%; IC₅₀ = 0.57), rugchalcone B (**2**) (99.3%; IC₅₀ = 4.13), **7** (96.8%; IC₅₀ = 1.90) and **8** (74.3%; IC₅₀ = 0.99) were showed the maximum inhibitory activity. This study suggests that compounds **2**, **4**, **7** and **8** which are having 4-hydroxyphenyl group and/or hydroxy (–OH) group at 5- and/or 6-position of benzofuran motif could be considered as a promising scaffolds for the further development of iNOS inhibitors for potential *anti-inflammatory* applications.

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In multi-cellular organisms, inflammation is a cardinal host defense response to tissue damage, injury, infectious agents or autoimmune responses and is an integral part of the immune response.¹ Symptoms of inflammation include swelling, redness of the area, pain, and sometimes loss of function.² Based on time and pathological features, it can be either acute or chronic. Inflammation is present in several disorders and diseases like atherosclerosis, diabetes and cancer. Increased blood supply, enhanced vascular permeability and migration of immune cells occur at damaged sites. In this process, activated inflammatory cells (neutrophils, eosinophils, mononuclear phagocytes and macrophages) secrete increased amounts of nitric oxide (NO), prostaglandins (PGs) and cytokines, such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF). Among these, two of the most prominent are PGs and NO. PGs are produced by cyclooxygenase (COX, which mainly having two forms COX-1 and COX-2) by arachidonic acid pathway. NO is a small, lipophilic, diffusible and transient free-radical species generated from L-arginine by three types of nitric oxide synthase (NOS) enzymes. It acts as a double-edged sword. Physiologically vital amount of NO produced by the endothelial (eNOS) and neuronal (nNOS) enzymes which is crucial for signaling,

including vasodilatation, thermoregulation, and neuromodulation. High levels of NO is produced 'on-demand' by the inducible (iNOS) enzyme, to help kill tumors, viruses and bacteria. Both underproduction and overproduction of NO have been linked to various human pathologies. Insufficient NO production from eNOS and nNOS can lead to hypertension, atherosclerosis, and cardiovascular disease, whereas excess NO production by iNOS can cause inflammation, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, diabetes, stroke, cancer and neurodegenerative disorders.³ Therefore, control of the excess NO production by inhibition of iNOS may exert *anti-inflammatory* effects.

Traditional non-steroidal *anti-inflammatory* drugs (tNSAIDs) and aspirin usage is general practice in the therapeutic approach to alleviate the symptoms associated with both acute and chronic inflammatory diseases. Their activity is most likely mediated through their ability to inhibit COX enzymes. However, their long-term oral administration is restricted because of the high incidence of side effects, particularly those relating to the gastrointestinal (GI) tract, renal and cardiovascular systems due to the inhibition of the housekeeping enzyme COX-1 along with COX-2.⁴ Later, selective COX-2 inhibitors (COXIBs) were introduced to reduce the risks. While these COXIBs did reduce the risk of GI injury, like the tNSAIDs, they are also appeared to increase the risk of cardiovascular events, such as heart attack and stroke. Hence,

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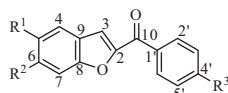
there remains an appeal to search for more effective *anti*-inflammatory drugs with minimal side-effects.

Benzofurans and their derivatives in particular are important scaffolds for drug development.⁵ Several natural and non-natural 2-substituted benzofurans have been noted for their antioxidant,⁶ antifungal,⁷ antimicrobial,⁸ *anti*-inflammatory,⁹ PPAR- δ agonists,¹⁰ antitubercular,¹¹ anti-HIV, anti-tumor and anti-platelet activity.¹² Radiolabeled benzofuran derivatives were used as molecular imaging probes for β -amyloid plaques in Alzheimer's Disease (AD).¹³ Besides this, few derivatives were found application as fluorescent

sensors and organic semiconductors.¹⁴ Their wide range of pharmacological and physical properties created special interest to researchers towards the design and synthesis of these important heterocyclic compounds.

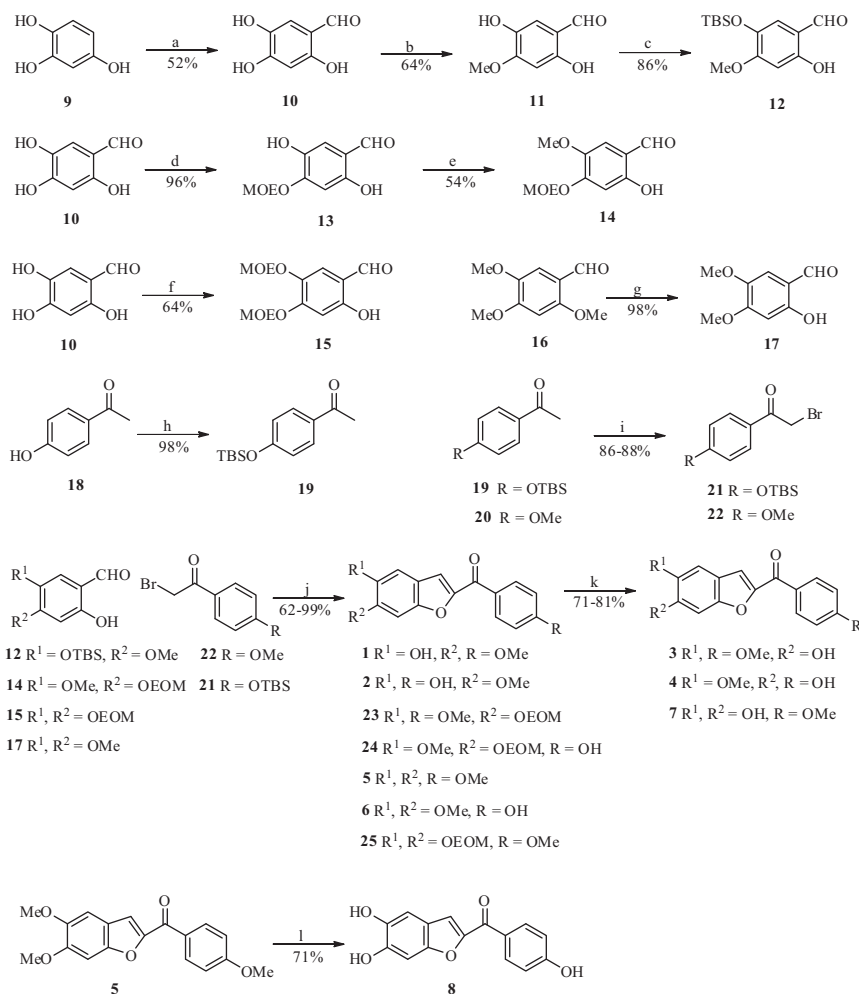
Rugchalcones A and B (Fig. 1) are 2-arylbenzofuran derivatives isolated from the flowers of *Rosa rugosa* and displayed *anti*-tobacco mosaic virus (*anti*-TMV) activities.¹⁵ In continuation of our work¹⁶ on the synthesis of bioactive natural products and their analogs, herein we wish to describe an efficient synthesis and *anti*-inflammatory activity evaluation of rugchalcones A (1), B (2) and their derivatives (3–8).

Our approach for the synthesis of rugchalcones A (1), B (2) and their derivatives (3–8) is outlined in Scheme 1. The synthesis commenced with the preparation of 2,4,5-trihydroxybenzaldehyde (10) from 1,2,4-benzenetriol (9). Regioselective methylation of phenolic 4-OH group of 10 was carried out using equimolar amounts of methyl iodide (MeI) and KOH in *N,N*-dimethylformamide (DMF) to afford compound 11 in 64% yield which was subsequently protected using *tert*-butyldimethylsilyl chloride (TBDMSCl) to furnish substituted salicylaldehyde, 12 in 86% yield. While, phenolic 4-OH group of 10 regioselectively protected with ethoxymethyl (EOM) group using chloromethyl ethyl ether (EOM-Cl), triethylamine (Et₃N) and catalytic tetrabutylammonium iodide (TBAI) in acetone and we were pleased to isolate compound 13 in 96% yield which



- R¹ = OH, R², R³ = OMe; Rugchalcone A (1) R¹, R², R³ = OMe; (5)
 R¹, R³ = OH, R² = OMe; Rugchalcone B (2) R¹, R² = OMe, R³ = OH; (6)
 R¹, R³ = OMe, R² = OH; (3) R¹, R² = OH, R³ = OMe; (7)
 R¹ = OMe, R², R³ = OH; (4) R¹, R², R³ = OH; (8)

Figure 1. Structures of rugchalcones A (1), B (2) and their derivatives (3–8).



Scheme 1. Reagents and conditions: (a) triethyl orthoformate, AlCl₃, benzene, rt, 1 h; (b) MeI, KOH, anhyd DMF, 0–40 °C, 8 h; (c) TBDMSCl, imidazole, DMF, 40 °C, 2.5 h; (d) chloromethyl ethyl ether, Et₃N, TBAI, acetone, 0 °C–rt, 4 h; (e) dimethyl sulfate, K₂CO₃, acetone, 0 °C–rt, 12 h; (f) chloromethyl ethyl ether, K₂CO₃, TBAI, acetone, 0 °C–rt, 2.5 h; (g) BCl₃, CH₂Cl₂, –78 °C to rt, 12 h; (h) TBDMSCl, imidazole, DMF, 40 °C, 12 h; (i) CuBr₂, EtOAc, reflux, 2 h; (j) K₂CO₃, acetonitrile, reflux, 1–2 h; (k) Dowex® resin, MeOH, THF, rt, 2–4 days; (l) BBr₃, CH₂Cl₂, 0 °C–rt, 28 h.

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