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Graphical Abstract

Synthesis and pharmacological properties of naturally occurring prenylated and pyranochalcones as potent anti-inflammatory agents

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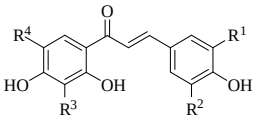
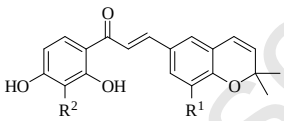


1 R^1, R^3 = prenyl, R^2, R^4 = H (kanzonol C)
2 R^1, R^4= prenyl, R^2, R^3 = H (stipulin)
3 R^1 = OMe, R^3 = prenyl, R^2, R^4 = H (crotaorixin)
4 R^1, R^2 = H, R^3, R^4 = prenyl (medicagenin)
5 R^1 = prenyl, R^2, R^3, R^4 = H (licoagrochalcone A)
6 R^1 = prenyl, R^2 = OMe, R^3, R^4 = H (abyssinone D)



7 R^1 = H, R^2 = prenyl (paratocarpin C)
8 R^1 = prenyl, R^2 = H (anthyllisone)
9 R^1 = OMe, R^2 = H (3-*O*-methylabyssinone A)

A facile approach for the synthesis of naturally occurring prenylated and pyranochalcones is achieved using Claisen-Schmidt condensation as a key step. Subsequently, their anti-inflammatory study revealed that the chalcones bearing the prenyl group at 3- and/or 5-position on ring A (acetophenone moiety), *i.e.*, **1**-**4** and **7** show weak, or no inhibition activity, whereas chalcones having the prenyl group only on ring B (aldehyde part), *i.e.*, **5**, **6** and **8** show significant activity on the production of inflammatory mediated NO with no cytotoxicity.

Original article

Synthesis and pharmacological properties of naturally occurring prenylated and pyranochalcones as potent anti-inflammatory agents

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ABSTRACT

An efficient approach has been developed for the synthesis of naturally occurring prenylated chalcones *viz.* kanzonol C (**1**), stipulin (**2**), crotaorixin (**3**), medicagenin (**4**), licoagrochalcone A (**5**) and abyssinone D (**6**) along with the pyranochalcones paratocarpin C (**7**), anthyllisone (**8**) and 3-*O*-methylabyssinone A (**9**). The key step of the synthesis is a Claisen-Schmidt condensation. Subsequently, their anti-inflammatory effects were investigated in lipopolysaccharides (LPSs)-induced RAW-264.7 macrophages. Of the synthesized chalcones, compounds **5** (IC_{50} = 10.41 µmol/L), **6** (IC_{50} = 9.65 µmol/L) and **8** (IC_{50} = 15.34 µmol/L) show remarkable activity with no cytotoxicity. Compound **9** (IC_{50} = 4.5 µmol/L) exhibits maximum (83.6%) nitric oxide (NO) inhibition, but shows slight cytotoxicity. The results reveal that the chalcones bearing the prenyl group at 3- and/or 5-position on ring A (acetophenone moiety), *i.e.*, **1**-**4** and **7** show weak, or no inhibition activity, whereas chalcones having the prenyl group only on ring B (aldehyde part), *i.e.*, **5**, **6** and **8** show significant activity on the production of inflammatory mediated NO with no cytotoxicity.

1. Introduction

In multi-cellular organisms, inflammation is an early, protective, homeostatic response of a host against a pathogenic challenge [1] and is indicative of either acute or chronic inflammation. In normal conditions, this process is automatically regulated by the limiting expression levels of pro-inflammatory cytokines, but under pathological conditions, macrophage stimulation leads to an increase of nitric oxide (NO) production. NO, short-lived free radical, can regulate various physiological functions in the cardiovascular, nervous and immune system [2]. Its Endogenous secretion from L-arginine is catalyzed by a family of nitric oxide synthase (NOS) enzymes *viz.* neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). The first two are constitutively expressed and can generate physiologically vital amounts of NO involved chiefly in nerve function and blood regulation whereas the later one (*i.e.* iNOS) produces larger amounts (nano molar) in response to various proinflammatory stimuli. Overproduction of NO causes cell damage because of its highly reactive nature. Therefore, effective control of NO accumulation by iNOS inhibition represents a beneficial therapeutic strategy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and classical steroidal anti-inflammatory drugs (SAIDs) are currently used to treat acute inflammation. Treatment of chronic inflammation with these SAIDs and NSAIDs is not absolutely successful due to unexpected side effects associated with these developed compounds. Hence, there is a need for the identification and development of safe, effective and novel anti-inflammatory agents.

Bacterial lipopolysaccharides (LPSs) are the major outer surface membrane components present in almost all Gram-negative bacteria and can induce the production of inflammatory mediators including iNOS in diverse eukaryotic species ranging from insects to humans [3]. Therefore, reducing the expression levels of LPS-inducible inflammatory mediators is a promising method to attenuate a variety of disorders derived from inflammation triggered by activated macrophages. RAW 264.7 is a murine macrophage cell line which has been established as an excellent model to screen anti-inflammatory activity of bioactive compounds.

Chalcones, as members of the flavonoid family, are a distinguished class of naturally occurring, bioactive compounds with 1,3-diaryl-2-propen-1-one skeleton. They are abundantly present in edible plants and are important precursors in the biosynthesis of flavonoids and isoflavonoids [4]. Primitive therapeutic applications of these plant-related, secondary metabolites can be associated with the thousand-year old use of plants and herbs for the treatment of different medical disorders. These small and non-chiral chemical templates possess a conjugated double bond and an entirely delocalized π-electron system on both benzene rings which gives the

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compounds non-linear optical properties [5]. Recently, chalcones have been a subject of great interest around the globe in view of their availability in nature, effortless synthesis, accessible structural modifications and multifarious biological activities. Various natural and non-natural chalcones have been investigated as anti-inflammatory [6], antioxidant [7], anticancer [8], antiprotozoal [9], antimicrobial [10], antiviral [11], antibacterial [12], antihyperglycemic [13], antiplatelet aggregation [14], antiangiogenic [15], antiulcerative [16], antitubercular [17], and antiplasmodial [18] agents. They have also shown inhibitory effects on several enzymes [19].

Continuing our interest on the synthesis and biological evaluation of chalcones as anti-inflammatory agents [20], herein we describe the synthesis of natural prenylated and pyranochalcones using a Claisen–Schmidt condensation as a key step and present the assessment of their anti-inflammatory effects.

Natural prenylated chalcones under the current study *viz*. kanzonol C (**1**) [21], stipulin (**2**) [22], crotaorixin (**3**) [23], medicagenin (**4**) [24], licoagrochalcone A (**5**) [25] and abyssinone D (**6**) [26] were isolated from *Glycyrrhiza eurycarpa*, *Dalbergia stipulacea*, *Crotalaria orixensis*, *Crotalaria medicaginea*, *Glycyrrhiza glabra*, and *Erythrina abyssinica*, respectively (Fig. 1). Pyranochalcones include in this investigation are paratocarpin C (**7**) [27], anthyllisone (**8**) [28] and 3-*O*-methylabyssinone A (**9**) [29] which were isolated from *Paratocarpus Venezosa* Zoll, *Anthyllis hermanniae* and *Lonchocarpus nicou*, respectively (Fig. 1). Synthesis of these interesting compounds was not yet been reported, except for compounds **4** [30] and **5** [31].

2. Experimental

All chemicals were obtained from commercial suppliers and were used without further purification unless noted otherwise. All solvents used for reactions were freshly distilled from proper dehydrating agents under nitrogen gas. All solvents used for chromatography were purchased and directly used without further purification. The ^{1}H NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR and 75 MHz for ^{13}C NMR, with the chemical shift (δ) reported in parts per million (ppm) downfield relative to TMS and the coupling constants (J) quoted in Hz. $CDCl_3/CD_3OD/CD_3COCD_3$ was used as solvent and an internal standard. Mass spectra were recorded using Agilent-5977E spectrometer. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed *silica* gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde. Chromatographic purification was carried out using Kieselgel 60 (60-120 mesh, Merck).

2.1 General procedure for Claisen-Schmidt condensation reaction

To a stirred solution of acetophenone (0.25 mmol) and aromatic aldehyde (0.3 mmol, 1.2 equiv.) in MeOH (2 mL) and H_2O (1 mL) was added KOH (0.309 g, 5.5 mmol, 22 equiv.) and the mixture was stirred at room temperature for 72 h. After completion of the reaction, H_2O (25 mL) was added and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine (2 × 40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography (EtOAc/hexane = 1/20 to 1/5) to obtain the allyl protected chalcone.

2.2 General procedure for allyl group deprotection

To a stirred solution of di- or tri-allyloxy chalcone (0.15 mmol) in anhydrous MeOH (2.5 mL) were added K_2CO_3 (0.124 g, 0.9 mmol, 6 equiv.) and $Pd(PPh_3)_4$ (2 mmol%) at room temperature and degassed for 2 min. The reaction mixture was stirred at 60^{o} C for 1-1.5 h. After completion of the reaction, solvent was removed *in vacuo*. H_2O (15 mL) was added to the crude, neutralized with slow addition of 1 mol/L HCl (1.5 mL) at 0 ^{o}C and then extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (2 × 40 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/5 to 1/1, v/v) to obtain the pure chalcone.

Physical and spectroscopic characterization data of the compounds described in this article were given in Supporting information.

3. Results and discussion

3.1 Chemistry

Our approach for the synthesis of the chalcones **1-9** is outlined in Schemes 1-4. The synthesis commenced with the prenylation of 2,4-dihydroxyacetophenone (**10**) following the literature procedure [31b] (Scheme 1).

Treatment of compound **10** with $BF_3.Et_2O$ followed by 2-methyl-but-3-en-2-ol addition at room temperature afforded compounds **11-13**. Subsequently, allyl protection of **10** along with the prenylated acetophenones **11-13** was accomplished with Cs_2CO_3/NaI and allyl bromide in DMF at 60^{o} C and the resulting products **14-17** were each obtained in high yields.

Next, 4-hydroxybenzaldehyde (**18**) and vanillin (**19**) were transformed to their prenyl derivatives (Scheme 2). Treatment of **18** and **19** with 3,3-dimethylallyl bromide using 1 mol/L NaOH afforded the aldehydes **20** and **21**, respectively. Later, aldehydes **18-21** were reacted with allyl bromide in the presence of Cs_2CO_3/NaI to generate the allyl protected aldehydes **22-25** in high yields, respectively.

Aldehyde part of pyranochalcones **7-9** was obtained from aldehydes **18, 20** and **19** respectively (Scheme 3). Reaction of aldehydes **18-20** with 3-chloro-3-methyl-1-butyne using K_2CO_3/KI and catalytic CuI in acetone under reflux gave compounds **26-28** which were subsequently converted to compounds **29-31**, respectively.

Keeping the allyl protected acetophenones (**14-17**) and aromatic aldehydes (**22-25** and **29-31**) in hand, next we executed the Claisen-Schmidt condensation (Scheme 4). Treatment of the suitable acetophenone with 1.2 equiv. of aromatic aldehyde using excess KOH in MeOH:H_2O (2:1) at room temperature produced the allyl protected chalcones (**32-40**) in good to high yields. Finally, allyl group deprotection was achieved using K_2CO_3 and catalytic $Pd(PPh_3)_4$ (2 mol%) in anhydrous MeOH at 60° C to furnish the desired natural prenylated and pyranochalcones **1-9**. All the products **1-9** were structurally confirmed by their spectral (^{1}H NMR & ^{13}C NMR and MS) data.

3.2. Pharmacology

To examine the anti-inflammatory effect of the synthesized chalcones **1-9**, we selected an *in vitro* model with murine RAW 264.7 macrophage cell line, which is an established model for anti-inflammatory drug screening. We assayed the ability of compounds **1-9** to decrease NO release after LPS stimulation. The RAW 264.7 cells were incubated with LPS and 1 µmol/L & 10 µmol/L concentrations of compounds **1-9** for 24 h. Later, culture media were harvested and the amount of NO was measured. Compounds **1-4** and **7** exhibited weak, or no suppression of NO production at 10 µmol/L level (Table 1). On the other hand, chalcones **5**, **6**, **8** and **9** were shown to exhibit a moderate to good level of activity.

Next, cell viability was analyzed to check whether the inhibitory effect was due to cytotoxicity. All of the prepared chalcones displayed no toxic effects, except compound **9**, which showed a slight cytotoxicity at 10 µmol/L level (Table 1). The IC_{50} values of these natural chalcones **1-9** were evaluated by using GraphPad Prism 4.0 software and the values were 56.75, 35.40, 41.39, 29.09, 10.41, 9.65, 52.71, 15.34 and 4.50 µmol/L, respectively. Based upon the results, it can be concluded that chalcones bearing the prenyl group only on ring B (aldehyde part), *i.e.*, **5**, **6** and **8** are fruitful to show good anti-inflammatory activity by effective inhibition of NO production with no cytotoxicity.

4. Conclusion

We have developed a simple and efficient approach for the synthesis of naturally occurring prenylated and pyranochalcones **1-9** using the Claisen-Schmidt condensation as a key step. Later, their *anti*-inflammatory effects were evaluated in lipopolysaccharides (LPSs)-stimulated RAW-264.7 macrophages. Of the chalcones prepared in this study, compounds **5**, **6** and **8** showed remarkable activities with no cytotoxicity. Compound **9** (IC_{50} = 4.5 µmol/L) exhibited maximum (83.6%) nitric oxide (NO) inhibition, but showed a slight cytotoxicity. The results revealed that the chalcones bearing the prenyl group at 3- and/or 5-position on ring A (acetophenone part), *i.e.*, **1-4** and **7** showed weak or no inhibition activities, whereas chalcones holding prenyl group only on ring B (aldehyde part), *i.e.*, **5**, **6** and **8** showed significant activities on the production of inflammatory mediated NO with no cytotoxicity.

Acknowledgment

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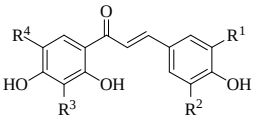

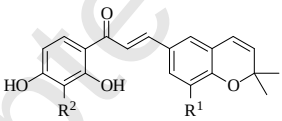

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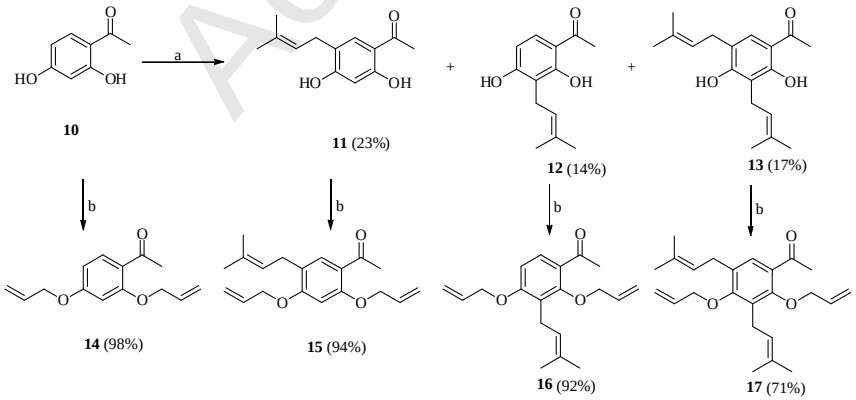
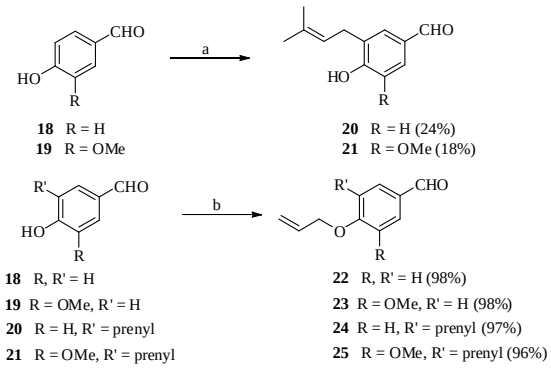
2 R^1, R^4= prenyl, R^2, R^3 = H (stipulin)
3 R^1 = OMe, R^3 = prenyl, R^2, R^4 = H (crotaorixin)
4 R^1, R^2 = H, R^3, R^4 = prenyl (medicagenin)
5 R^1 = prenyl, R^2, R^3, R^4 = H (licoagrochalcone A)
6 R^1 = prenyl, R^2 = OMe, R^3, R^4 = H (abyssinone D)
7 R^1 = H, R^2 = prenyl (paratocarpin C)
8 R^1 = prenyl, R^2 = H (anthyllisone)
9 R^1 = OMe, R^2 = H (3-*O*-methylabyssinone A)

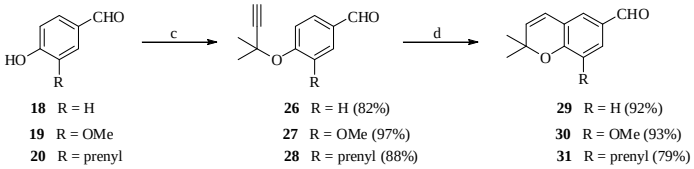
Fig. 1. Structures of naturally occurring prenylated and pyranochalcones (**1**-**9**).



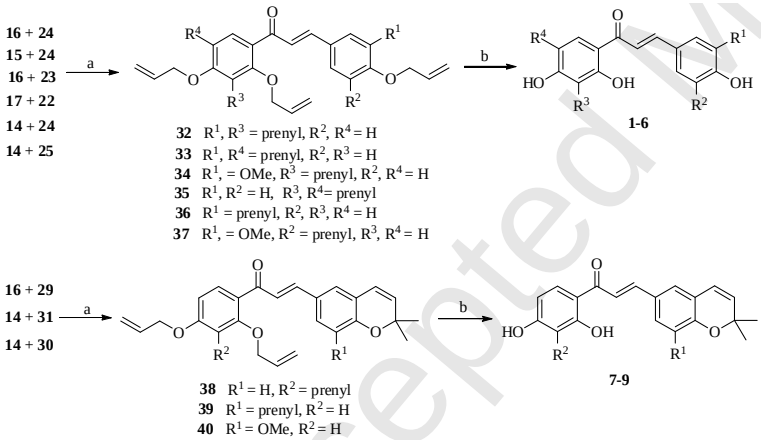
Scheme 1. Synthesis of prenyl substituted acetophenones. Reagents and conditions: (a) 2-methyl-but-3-en-2-ol, $BF_3.Et_2O$, 1,4-dioxane, r.t., 1 h. (b) allyl bromide, Cs_2CO_3/NaI, DMF, 60 °C, 5 h.



Scheme 2. Synthesis of prenyl substituted benzaldehydes. Reagents and conditions: (a) 3,3-dimethylallyl bromide, 1 mol/L NaOH, 0° C – r.t., 2 h. (b) allyl bromide, Cs_2CO_3/NaI, DMF, 60° C, 2 h.



Scheme 3. Synthesis of substituted 2,2-dimethyl-2H-chromene-6-carbaldehydes. Reagents and conditions: (a) 3-chloro-3-methyl-1-butyne, K_2CO_3/KI, acetone, reflux, 4.5 h. (b) *N*, *N*-diethylaniline, sealed tube, 210 °C, 1.5 h.



Scheme 4. Synthesis of naturally occurring prenylated and pyranochalcones.Reagents and conditions: (a) KOH, MeOH/H_2O (2:1), r.t., 72 h, 58%-90%. (b) K_2CO_3, $Pd(PPh_3)_4$, MeOH, 60 °C, 1-1.5 h, 51%-89%.

Table 1.
Anti-inflammatory activities of naturally occurring prenylated and pyranochalcones **1-9**.

Compd	NO Production (% inhibition)[a,b]		Proliferation[c]		IC_{50} (µmol/L)
	1 µmol/L	10 µmol/L	I µmol/L	10 µmol/L	
Medium	1.13 ± 0.87 (98.87)***	1.13 ± 0.87 (98.87)***	99.77 ± 4.23	99.77 ± 4.23	
1	131.54 ± 2.6 (-31.54) ***	124.48 ± 10.29 (-24.48)***	112.35 ± 15.75	93.56 ± 5.91	56.75
2	124.14 ± 1.43 (-24.14) ***	103.13 ± 5.1 (-3.13)	108.03 ± 11.72	157.63 ± 8.06*	35.40
3	124.98 ± 6.49 (-24.98) ***	99.72 ± 11.36 (0.28)	112.35 ± 15.75	113.36 ± 8.80	41.39
4	116.27 ± 2.95 (-16.27) ***	82.26 ± 0.8 (17.74)***	108.03 ± 9.41	99.25 ± 2.71	29.09
5	125.30 ± 4.79 (-25.3)***	53.58 ± 2.41 (46.42)***	99.24 ± 0.63	111.37 ± 11.13	10.41
6	120.10 ± 2.03 (-20.1)***	39.59 ± 4.31 (60.41)***	99.16 ± 3.26	103.85 ± 2.0	9.65
7	124.2 ± 2.91 (-24.2)***	129.9 ± 2.52 (-29.9)***	105.45 ± 6.96	97.43 ± 2.22	52.71
8	119.20 ± 0.64 (-19.2)***	58.09 ± 0.94 (41.91)***	108.47 ± 2.86	98.24 ± 10.12	15.34
9	107.21 ± 3.51 (-7.21)**	16.45 ± 0.89 (83.55)***	106.66 ± 5.82	92.74 ± 1.40*	4.50
LPS	99.99 ± 3.76 (0.01)	99.99 ± 3.76 (0.01)			

[a] The results are reported as mean value ± SEM for n = 3. Statistical significance is based on the difference when compared with LPS-treated groups (**P < 0.01, ***P < 0.001).
[b] Inhibition is based on LPS as shown in parenthesis.
[c] The results are reported as mean value ± SEM for n = 3. Statistical significance is based on the difference when compared with Medium groups (*P < 0.05).