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Short communication

Synthesis of Abyssinone II and related compounds as potential chemopreventive agents

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Abstract

A facile and efficient approach to the synthesis of prenylated flavonoids as potential chemopreventive agents has been described. This features the synthesis of prenyl halide, prenylation of *p*-hydroxybenzaldehyde, formation of prenylated polyhydroxychalcone and cyclization of prenylated polyhydroxychalcone to flavanones (**15**) and (**16**), and flavonol (**17**) starting from isoprene (**1**). The structures of all three compounds have been characterized by NMR, IR and mass spectroscopy.

Keywords: Flavonoids; Abyssinone II; Prenylation; Chemoprevention; Polyhydroxychalcone; Prenylated chalcone

1. Introduction

Flavonoids constitute an important class of naturally occurring compounds exhibiting a wide spectrum of biological activities, which include anti-carcinogenic, anti-viral, anti-inflammatory and anti-fungal properties [1]. The remarkable biological effect of hydroxy flavonoids is mainly attributed to the presence of phenolic groups, which have high affinity for proteins and therefore act as inhibitors of microbial enzymes [2] as well as through their effect on uncoupling oxidative phosphorylation [3] and inhibition of NADH dehydrogenase of mitochondrial inner membranes [4].

In addition, substitution on the flavonoid ring system with prenyl groups is thought to increase their lipophilicity and consequently enhance their lipophilicity through interaction with cellular membranes [5].

It is generally agreed that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonoid compounds [6]. In spite of the diversity of biological activity exhibited by the prenylated flavonoids, there is little information as to the structure–activity relationship. However, it appears that the position of prenylation rather than the number of prenyl groups, determines the biological activity of the compounds [7].

Notably, there is substantial evidence that a high intake of flavonoids lowers cancer risk [8,9]. Last decade has witnessed an explosion of research publication on the use of flavonoids as cancer chemopreventive agents [8,9]. A large number of flavonoids have been used for the chemopreventive studies in vivo, in vitro and in human clinical trials [8,9]. Flavonoids have shown promise to inhibit carcinogenesis by acting via a series of mechanisms by affecting the molecular events at the initiation and progression stages [8,9]. Hydroxy flavonoids with prenyl group have been shown to be aromatase inhibitors. The enzyme aromatase catalyses the final and rate-limiting step in estrogen biosynthesis. The overall hypothesis is that these compounds will be safe and effective inhibitors of estrogen-dependent tumor formation.

2. Results and discussion

In continuation of our ongoing research in the area of cancer chemoprevention, we have synthesized Abyssinone II, 7-hydroxy-2-[4-hydroxy-3-(methyl-but-2-enyl) phenyl] chroman-4-one (**15**) and its derivatives. Abyssinone (II) has been isolated from the Chinese medical plant *Broussonetia papyfera.* It has

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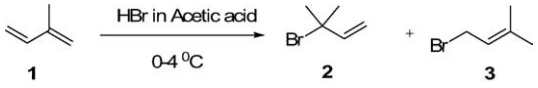
been found to be one of the most active naturally occurring aromatase inhibitors and has exhibited higher potency than aminoglutethinide [10]. The National Cancer Institute selected Abyssinone (II) considering its plant origin and potency for further development through the Rapid Access to Preventive Intervention Development (RAPID) [11]. Owing to its limited availability from natural sources and its excellent potency, synthesis of Abyssinone II was undertaken.

± Abyssinone (II) was accomplished using the route shown in Scheme 3. Lack of a general, efficient, regioselective method for the introduction of prenylated side chain and appropriate protection for the phenoxy group presented a major challenge. The first step involved synthesis of 1-bromo-3-methyl-but-2-ene (**3**) using isoprene (**1**). The reaction of HBr in acetic acid with isoprene at 0–4 °C resulted in formation of desired (**3**) 1,4-addition product along with minor amounts of undesired (**2**) 1,2-addition product and the unreacted starting material (Scheme 1) [12]. Separation of the desired compound was accomplished by vacuum distillation in about 45% yield.

The key step was the introduction of the prenyl group to 4-hydroxybenzaldehyde, which proceeded into an unsatisfactory yield. The different methods for the prenylation on the phenyl group were tried without much success. The synthesis of 4-hydroxy-3-(3-methyl-but-2-enyl)-benzaldehyde (**8**) was achieved by treatment of 1-bromo-3-methyl-but-2-ene (**3**) with *p*-hydroxy benzaldehyde in 10% aqueous KOH solution for 48 h at r.t. [13]. The reaction gave a mixture of prenylated compounds (Scheme 2).



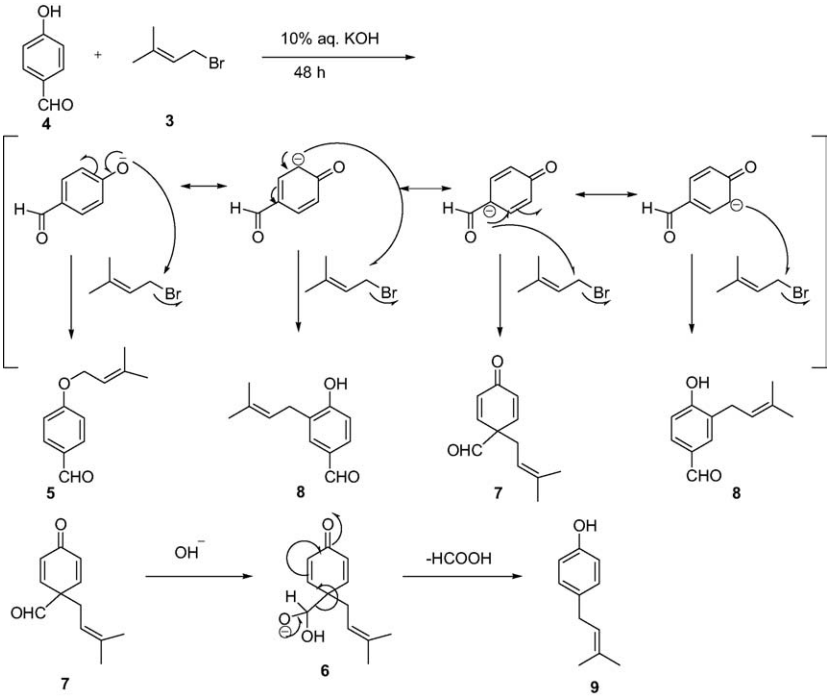
Scheme 1.

The product contained multiple C- and O-prenylated products, which can be explained by the delocalization of phenoxide anion within the aromatic ring. Interestingly, compound (**9**) was obtained where the carbonyl group of the benzaldehyde was replaced by a prenyl moiety. The formation of this compound can be explained by the proposed mechanism that goes via the elimination of the formic acid from the aromatic ring. The desired product (**8**) was obtained by employing silica gel column chromatography (hexane/acetone 12:1) followed by crystallization as a white solid (m.p. 57–60 °C) in a low yield of 6–8% [13].

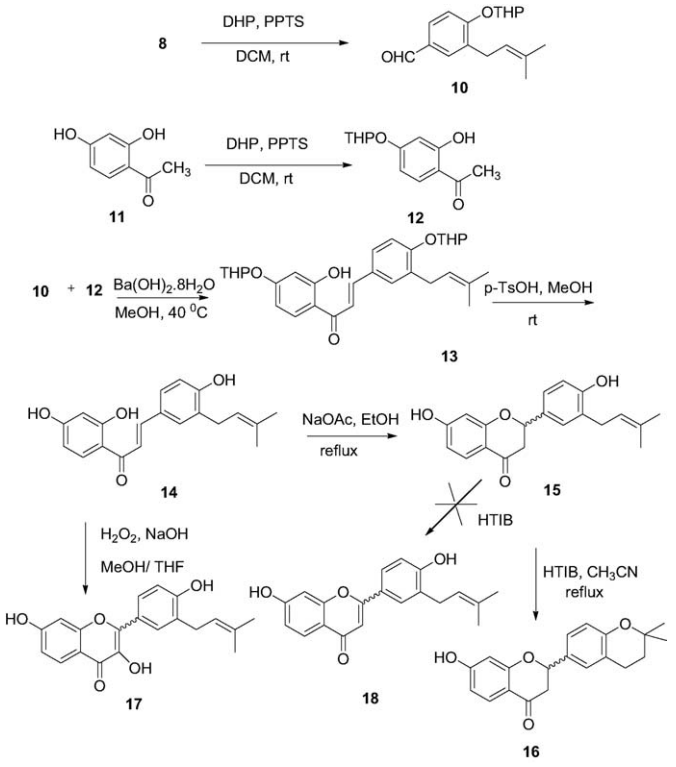
The hydroxyl group of the *para*-hydroxybenzaldehyde was protected by converting to the –OTHP derivative (**10**) in quantitative yields. Similarly, 2,4- dihydroxyacetophenone (**11**) was also protected in an analogous manner to yield 1-[2-hydroxy-4-(tetrahydropyran-2-yloxy)-phenyl] ethanone (**12**).

Treatment of (**10**) and (**12**) with $Ba(OH)_2.H_2O$/methanol yielded 1-[2-hydroxy-4-(tetrahydro-pyran-2-yloxy)phenyl]-3-[3-methyl-but-2-enyl)-4-(tetrahydro-pyran-2-yloxy)-phenyl] propenone (**13**) in about 40% yield. The deprotection of the –OTHP group was achieved by using para-toluenesulfonic acid to yield 1-(2, 4-dihydroxyphenyl)-3-[4-hydroxy-3-(3-methyl-but-2-enyl-phenyl] propenone (**14**).

The cyclization was carried out in NaOAc/methanol to yield 7-hydroxy-2-[4-hydroxy-3-(3-methyl-but-2-enyl)-phenyl] chroman-4-one (**15**) as a slightly yellow solid after silica gel chromatography. The synthetic **15** was confirmed to be identical with data reported for natural Abyssinone II by ^{1}H, ^{13}C-NMR and mass spectra. In an attempt to convert flavanone **15** to flavone **18**, we tried employing hypervalent iodine oxidation using HTIB



Scheme 2.



Scheme 3.

in acetonitrile. However, instead of getting flavone, we got cyclization of the prenyl group at the hydroxy resulting in the formation of **16** along with the starting material (**15**). The compound showed an absence of characteristic triplet at δ 5.2 ppm responsible for = $CH(CH_3)_3$ of the isoprenyl group of **15.**

Synthesis of the flavonol **17** was carried out by treating **16** with H_2O_2 and sodium hydroxide. The structure of the compound **16** was confirmed by NMR (absence of peaks for methylene protons (C_3–H_aH_b) of compound **15** and mass spectra (HRMS: *m/z* $[M + H]^+$ at 338).

2.1. Activity of Abyssinone II in aromatase assay

The synthetic racemic mixture of Abyssinone II was tested for aromatase assay using the radiometric method developed by Thompson and Sitteri [14a] and human placental microsomes as source of aromatase enzyme. The briefly tested compound was incubated with ^{3}H-androstenedione, unlabeled androstenedione and human placental microsomes as the source of aromatase. The amount of released tritiated water (^3H_2O) was measured to determine the amount of converted substrate. The radiometric assay was later replaced by a highly developed new fluorimetric high-throughput assay [14b].

Briefly, the test compound was incubated with aromatase enzyme, NADPH regenerating system and dibenzylfluorescein (DBF) for 30 min. The reaction was then quenched and after standing at room temperature for 2 hours, fluorescence of fluorscein (converted from DBF by aromatase) was measured at 485 nm (excitation) and 530 nm (emission). Initial screening was done at 10 μg/ml and since this significantly inhibited aromatase (more than 90%) it was tested for dose–response and the IC_{50} values were calculated where IC_{50} represents the concentration of the test compound that inhibits 50% of the enzyme activity. All experiments were performed in duplicate and the mean was used for calculation of IC_{50}. The reaction was then quenched. The compound was tested in comparison to aminoglutethimide, which was used as a positive control.

Name of the compound	IC_{50} (μM) radiometric method	IC_{50} (μM) fluorimetric high through put assay
Abyssinone II	**0.6**	**62**
Aminoglutethimide	**6.4**	**0.27**

IC_{50} represents the concentration of the test compound that inhibits 50% of enzyme activity.

3. Experimental

All moisture-sensitive reactions were carried out under an argon atmosphere in flame-dried glassware. Solvents and reagents were purchased from Aldrich. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane (DCM) and triethylamine were distilled from calcium hydride. Thin layer chromatography (TLC) was carried out on Aldrich silica gel glass plates with UV indicator. Flash column chromatography was performed on Merck silica gel 60 (mesh 230–400). ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker Avance (400 MHz) or Avance (500 MHz) spectrometers. All melting points were recorded on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on ATI Mattson Genesis series FTIR spectrometer. The Midwestern Microlab, Indianapolis, IN performed elemental analyses. Mass spectra were obtained at the Mass Spectroscopy Service Laboratory, University of Illinois at Chicago.

3.1. 1-Bromo-3-methylbut-2-ene (*3*)

A solution of hydrogen bromide in acetic acid (45% W/V HBr, 136 ml) was added drop-wise to isoprene (50 g, 0.734 mol) at 0 °C (ice salt bath). After stirring at 0–4 °C for 48 h, the pale yellow solution was poured into ice (400 g) and an oily product separated, which was dissolved in dichloromethane and washed with water (2 × 100 ml). The organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give pale yellow oil. Distillation gave 1-bromo-3-methylbut-2-ene (**3**) as a colorless liquid b.p. 36–38 °C at 15 mmHg (Ref. [12], b.p. 26–33 °C at 12 mmHg). Yield 50 g, 45.8%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.55 (m, 1H, = CH), 4.01 (d, 2H, CH_2Br), 1.80 (s, 3H, CH_3), 1.75 (s, 3H, CH_3).

3.2. 4-Hydroxy-3-(3-methyl-but-2-enyl)-benzaldehyde (*8*)

4-Hydroxybenzaldehyde (4.01 g, 32.8 mmol) was dissolved in 10% (w/v) aqueous KOH solution (48 ml) and 1-bromo-2-methyl-but-2-ene (**3**) (10.0 g, 67.1 mmol) was added drop-wise with stirring over 1 h at r.t. The reaction mixture was stirred at r.t. for 48 h, and then acidified with 1 N aqueous HCl solution

to pH 2 and extracted with diethyl ether (3 × 100 ml). The combined ether layers were washed with 2% aqueous Na_2CO_3 solution (2 × 100 ml), water and brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a dark brown oil. The resulting oil was purified by flash chromatography over silica gel (acetone/hexane, 1:12) to afford **8** (458 mg, 2.41 mmol, yield 7.5%): white solid, m.p. = 58–61 °C (Ref. [13] m.p. = 61 °C); *Rf* = 0.13 (acetone/hexane, 1:9); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.73 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.41 (d, J = 7.3 Hz, 2H, CH_2), 5.35 (t, J = 7.5 Hz, 1H, = CH), 7.00 (dd, J = 8.2, 1.4 Hz, 1H), 7.67 (dd, J = 8.3, 1.8 Hz, 1H), 7.71 (s, 1H), 8.32 (br s, 1H, OH), 9.79 (s, 1H, CHO); ^{13}C-NMR (500 MHz, $CDCl_3$): 18.29, 26.23, 29.01, 116.34, 121.33, 129.22, 129.47, 131.19, 132.61, 135.41, 161.60, 192.92; FTIR (neat) υ_{max}: 3305 (OH), 1665 (C = O), 1591 (C = C, aromatic) cm^{-1}.

The combined aqueous Na_2CO_3 extracts were acidified with 1 N aqueous HCl to pH 4, extracted with ether (3 × 100 ml), dried (Na_2SO_4) and evaporation of solvent under reduced pressure gave 1.66 g of starting 4-hydroxybenzaldehyde.

3.3. 3-(3-Methyl-but-2-enyl)-4(tetrahydro-pyran-2-yloxy)-benzaldehyde (**10**)

4-Hydroxy-3-(3-methyl-but-2-enyl)-benzaldehyde (**8**) (3.30 g, 17.8 mmol) and pyridinium *p*-toluene-sulfonate (110 mg, 0.4 mmol) were dissolved in DCM (7 ml), and 3,4-dihydro-2H-pyran (4.60 g, 5 ml, 54 mmol) was added drop-wise under flow of argon, at r.t. The resulting reaction mixture was stirred at r.t. for 24 h, and then water (20 ml) was added. The organic layer was separated and washed with water (2 × 20 ml), brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give yellow oil. The resulting oil was purified by flash chromatography over silica gel (EtOAc/hexane, 5:95) to afford **10** as colorless oil (3.02 g, 11 mmol, yield 62%): *Rf* = 0.75 (30% EtOAc/hexane); FTIR (neat): υ_{max} = 1687 (C = O), 1594 (C = C, aromatic), 1245 (C–O–C) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.58 (m, 2H, CH_2), 1.68 (s, 3H), 1.71 (s, 3H), 1.87 (m, 2H, CH_2), 1.96 (m, 2H, CH_2), 3.36 (d, J = 6.8 Hz, 2H, CH_2), 3.58 (m, 1H), 3.77 (m, 1H), 5.28 (t, J = 7.0 Hz, 1H, = CH), 7.16 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.5, 2.1 Hz, 1H), 9.80 (s, 1H, CHO); ^{13}C-NMR (500 MHz, $CDCl_3$): 17.78, 18.50, 19.68, 25.06, 25.75, 28.61, 30.14, 30.63, 61.90, 95.84, 113.63, 121.74, 130.11, 130.49, 131.33, 159.74, 191.13; HRMS: *m/z* $[M + H]^+$ calcd. for $C_{17}H_{23}O_3$: 275.1647, found 275.1650.

3.4. 1-[2-Hydroxy-4-(tetrahydro-pyran-2-yloxy)-phenyl]-ethenone (**11**)

2,4-Dihydroxyacetophenone (4.43 g, 29.1 mmol) and pyridinium *p*-toluene-sulfonate (180 mg, 0.7 mmol) were dissolved in DCM (70 ml), and 3,4-dihydro-2H-pyran (14.8 g, 16 ml, 176 mmol) was added drop-wise under flow of argon, at r.t. The resulting reaction mixture was stirred at r.t. for 20 h, and then water was added (100 ml). The organic layer was separated and washed with water (2 × 100 ml) and brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a colorless oil. The resulting oil was purified by flash chromatography over silica gel (EtOAc/hexane, 5:95) to afford **11** (4.35 g, 18.9 mmol, yield 65%): white solid, m.p. = 66–68 °C (Ref. [15] m.p. = 67–9 °C); *Rf* = 0.54 (EtOAc/hexane, 3:7); FTIR (neat): υ_{max} = 1632 (C = O), 1256 (C–O–C) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.57 (m, 1H), 1.65 (m, 2H), 1.83 (m, 2H), 1.95 (m, 2H), 2.5 (s, 3H, CH_3), 3.59 (m, 1H), 3.79 (m, 1H), 5.45 (t, J = 3.1 Hz, 1H), 6.52 (dd, J = 8.9, 2.4 Hz, 1H, 5-CH), 6.57 (d, J = 2.4 Hz, 1H, 3-CH), 7.60 (d, J = 8.9 Hz, 1H, 6-CH); ^{13}C-NMR (500 MHz, $CDCl_3$): 18.89, 25.37, 26.63, 30.36, 62.54, 96.46, 104.35, 108.87, 114.895, 132.67, 163.94, 165.23, 203.11.

3.5. 1-[2-Hydroxy-4-(tetrahydro-pyran-2-yloxy)-phenyl]-3-[3-(3-methyl-but-2-enyl)-4-(tetrahydro-pyran-2-yloxy)-phenyl]-propenone (**13**)

3-(3-Methyl-but-2-enyl)-4(tetrahydro-pyran-2-yloxy)-benzaldehyde (**12**) (2.61 g, 13.3 mmol) and 1-[2-hydroxy-4-(tetrahydro-pyran-2-yloxy)-phenyl]-ethenone (**10**) (3.14 g, 13.3 mmol) were dissolved in MeOH (55 ml) and $Ba(OH)_2.H_2O$ (2.51 g, 13.3 mmol) was added. The resulting mixture was heated at 50 °C for 1 h and allowed to reach r.t. and stirred for another 24 h. The solvent was then evaporated under reduced pressure, water (60 ml) was added and the mixture was acidified with 1 N aqueous HCl to pH 4. The resulting mixture was then extracted with DCM (3 × 45 ml). The combined extracts were washed with brine, dried Na_2SO_4 and solvent evaporated under reduced pressure to give orange oil. The resulting solution was purified by flash chromatography over silica gel (EtOAc/hexane 1:9) to afford **13** (3.69 g, 7.5 mmol, yield 56%): yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.61 (m, 3H), 1.71 (m, 3H), 1.74 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.89 (m, 4H, CH_2), 2.00 (m, 4H, CH_2), 3.39 (d, J = 5.7 Hz, 2H, CH_2), 3.63 (d, J = 5.7 Hz, 1H), 3.85 (t, J = 5.7 Hz, 2H, CH_2), 5.28 (t, J = 6.0 Hz, 1H, = CH), 5.52 (t, J = 3.3 Hz, 2H, O-CH), 6.60 (dd, J = 9.0, 2.4 Hz, 1H, 5′-H), 6.66 (d, J = 8.9, 2.3 Hz, 1H, 3′-H), 7.13 (d, J = 8.4 Hz, 1H, 5-H), 7.46 (m, 3H), 7.84 (m, 2H); ^{13}C-NMR (500 MHz, MeOH-d_4): 17.90, 18.52, 18.62, 24.99, 25.17, 25.82, 28.76, 29.99, 30.28, 61.95, 62.19, 95.87, 96.08, 104.21, 108.37, 114.17, 117.73, 122.18, 127.86, 127.94; 130.18, 131.25, 132.87, 144.86, 156.99,2 163.40, 166.14, 192.10; FTIR (neat): υ_{max} = 1632 (C = O), 1566 (C = C aromatic) , 1241 (C–O–C) cm^{-1}; HRMS: *m/z* $[M + K]^+$ calcd. for $C_{30}H_{36}O_6K$: 531.2149, found 531.2144.

3.6. 1-(2,4-Dihydroxy-phenyl)-3-[4-hydroxy-3-(3-methyl-but-2-enyl)-phenyl]-propenone (**14**)

1-[2-Hydroxy-4-(tetrahydro-pyran-2-yloxy)-phenyl]-3[3-(3-methyl-but-2-enyl)-4-(tetrahydro-pyran-2-yloxy)-phenyl]-propenone (**13**) (8.61 g, 17.5 mmol) and *p*-toluenesulfonic acid monohydrate (122 mg, 0.6 mmol) were dissolved in methanol (90 ml) and stirred for 24 h at r.t. Solvent was then evaporated under reduced pressure and water was added (150 ml). The aqueous mixture was neutralized with saturated aqueous $NaHCO_3$ solution to

pH 7 and extracted with EtOAc (3 × 50 ml). The combined organic phases were washed with water (15 ml) and brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a viscous, yellow oil. The resulting oil was purified by flash chromatography over silica gel (EtOAc/hexane, 2:8) to afford **14** (3.27 g, 10.1 mmol, yield 58%): yellow solid, m.p. = 166–168 °C; *Rf* = 0.13 (EtOAc/hexane, 2:8); ^{1}H-NMR (400 MHz, MeOH-d_4) δ (ppm): 1.74 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.31 (dd, J = 6.8, 3.8 Hz, 2H, CH_2), 5.35 (t, J = 3.8 Hz, 1H, = CH), 6.28 (d, J = 2.4 Hz, 1H, 3′-H), 6.40 (dd, J = 8.9, 2.4 Hz, 1H, 5′-H), 6.80 (d, J = 8.3 Hz, 1H, 5–H), 7.44 (m, 2H, 2, 6-H), 7.54 (d, J = 15.0 Hz, 1H, α-H), 7.69 (d, J = 15.0 Hz, 1H, β-H), 7.93 (d, J = 9.0 Hz, 1H, 6′-H); ^{13}C-NMR (500 MHz, MeOH-d_4): 16.89, 24.95, 28.30, 102.81, 108.13, 113.70, 115.29, 116.92, 122.61, 126.74, 128.11, 129.17, 130.90, 132.33, 145.15, 158.46, 158.58, 160.05, 166.51, 192.54; FTIR (neat): υ_{max} = 3375 (OH), 1628 (C = O), 1556 (C = C aromatic) cm^{-1}; elemental analysis calcd. for $C_{20}H_{20}O_4$: C, 73.06; H, 6.21, found: C, 73.01; H, 6.14.

*3.7. 7-Hydroxy-2-[4-hydroxy-3-(3-methyl-but-2-enyl)-phenyl]-chroman-4-one [Abyssinone II] (**15**)*

1-(2,4-Dihydroxy-phenyl)-3-[4-hydroxy-3-(3-methyl-but-2-enyl)-phenyl]-propenone (**14**) (1.01 g, 3.11 mmol) and sodium acetate (4.65 g, 56.7 mmol) were mixed in ethanol and heated under reflux for 46 h. The mixture was then allowed to reach r. t., poured into ice water (15 ml) and extracted with methylene chloride (3 × 20 ml). The combined organic phase was washed with water (10 ml) and brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a pale yellow solid. The resulting mixture was purified by preparative HPLC (water/MeOH, 2:8) to afford **15** (580 mg, 1.71 mmol, yield 58%): white solid, m.p. = 76–78 °C, *Rf* = 0.59 (EtOAc/hexane/MeOH, 3/7/0.08); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.76 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.79 (dd, J = 17, 2.9 Hz, 1H, 3-H), 3.07 (dd, J = 13.3, 3.7 Hz, 1H, 3-H), 3.37 (d, J = 7.2 Hz, 2H, CH_2), 5.31 (t, J = 7.2 Hz, 1H, = CH), 5.36 (dd, J = 13.4, 2.8 Hz, 1H, 2-H), 5.66 (br s, 1H, OH), 6.47 (d, J = 2.3 Hz, 1H, 8-H), 6.56 (dd, J = 8.7, 2.3 Hz, 1H, 6-H), 6.84 (d, J = 8.8 Hz, 1H, 3′-H), 7.19 (m, 2H, 2′,6′-H), 7.35 (br s, 1H, OH), 7.84 (d, J = 8.7 Hz, 1H, 5-H); ^{13}C-NMR (500 MHz, $CDCl_3$): 18.33, 26.22, 30.14, 44.36, 80.19, 103.89, 111.27, 115.03, 116.39, 121.72, 126.14, 127.85, 128.69, 129.87, 130.99, 135.61, 155.27, 164.10, 164.42, 192.67; FTIR (neat): υ_{max} = 3282 (OH), 1653 (C = O), 1601 (C = C, aromatic) cm^{-1}; HRMS [M – H]$^+$ calcd. for $C_{20}H_{19}O_4$: 323.1283, found 323.1298.

*3.8. 2-(2,2-Dimethyl-3,4-dihydro-2-H-chromen-6-yl)-7-hydroxy-2,3-dihydrochromen-4-one (**16**)*

To a solution of 7-hydroxy-2-[4-hydroxy-3-(3-methyl-but-2-enyl)-phenyl]-chroman-4-one [Abyssinone II] (**15**) (200 mg, 0.6 mmol) in acetonitrile (30 ml) was added HTIB (241 mg, 0.6 mmol) and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated, washed with water and extracted with DCM. The resulting oil was purified by flash chromatography over silica gel (EtOAc/hexane, 2:8) to afford **16** (60 mg, 0.18 mmol, yield 30%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.76 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.79 (dd, J = 17, 2.9 Hz, 1H, 3-H), 3.07 (dd, J = 13.3, 3.7 Hz, 1H, 3-H), 3.37 (d, J = 7.2 Hz, 2H, CH_2), 5.31 (t, J = 7.2 Hz, 1H, = CH), 5.36 (dd, J = 13.4, 2.8 Hz, 1H, 2-H), 5.66 (br s, 1H, OH), 6.47 (d, J = 2.3 Hz, 1H, 8-H), 6.56 (dd, J = 8.7, 2.3 Hz, 1H, 6-H), 6.84 (d, J = 8.8 Hz, 1H, 3′-H), 7.19 (m, 2H, 2′,6′-H), 7.35 (br s, 1H, OH), 7.84 (d, J = 8.7 Hz, 1H, 5-H); FTIR (neat): υ_{max} = 3282 (OH), 1653 (C = O), 1601 (C = C, aromatic) cm^{-1}.

*3.9. 3,7-Dihydroxy-2,(4-hydroxy-3-(3-methylbut-2-enyl)-4H-chromen-4-one (**17**)*

To a stirring solution of chalcones (**13**) (246 mg, 0.5 mmol) in MeOH–THF (5 ml each) was added NaOH 16% at 0 °C. A solution of 15% H_2O_2 was added. The reaction mixture was stirred till starting material gets consumed. Reaction was acidified with 2 N HCl and extracted with DCM, washed with water, brine, dried over anhydrous Na_2SO_4. Purification was done using silica gel column chromatography (EtOAc/hexane, 3:7) to afford **17** (66 mg, 0.19 mmol, 39%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (d, J = 7.28 Hz, 6H, 2CH_3), 1.78–1.86 (m, 2H, 4′-CH_2), 2.76–2.83 (m, 3H, 3, 3′, 4′-H), 3.03–3.12 (dd, J = 13.48, 13.48 Hz, 1H, 3-H), 5.35 (d, J = 13.38 Hz, 1H, 2-H), 5.77 (br s, OH), 6.44 (s, 1H, 8-H), 6.53 (d, J = 8.68 Hz, 1H, 6-H), 6.82 (d, J = 8.6 Hz, 1H, 7′-H), 7.17 (m, 2H, 2′, 8′-H), 7.86 (d, 1H, 5-H); HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}O_4$: 346.1181, found: 347.1266.

References

[1] D. Carlo, N. Mascolo, A.A. Izzo, F. Capasso, Life Sc. 65 (1999) 337–353.
[2] D. Prusky, N.T. Keen, Plant Dis. 77 (1993) 114.
[3] P. Ravanel, M. Tissut, R. Douce, Phytochemistry 21 (1982) 2865.
[4] P. Ravanel, S. Creuzet, M. Tissut, Phytochemistry 29 (1990) 441.
[5] D. Baron, K.I. Ragai, Phytochemistry 43 (1996) 921.
[6] P.E. Laks, M.S. Pruner, Phytochemistry 27 (1989) 87.
[7] Y. Hano, Y. Yamagami, M. Kobayashi, R. Isohata, T. Nomura, Heterocycles 31 (1990) 77.
[8] C.S. Yang, J.M. Landau, M.T. Huang, H.L. Newmark, Ann, Reviews Nutrition 21 (2001) 381.
[9] W. Ren, Z. Qiao, H. Wang, L. Zhu, L. Zhang, Med. Res. Rev. 23 (2003) 519.
[10] A.D. Kinghorn, J.M. Pezzuto, D. Lee, K.P.L. Bhat, P.C.T. Int. Appl. WO 2003013554 (2003) 79.
[11] D. Lee, K.P. Bhat, H.H. Fong, N.R. Farnsworth, J.M. Pezzuto, A.D. Kinghorn, J. Nat. Prod. 64 (2001) 1286.
[12] D.B. Anthony, S.J. Warren, Chem. Soc. Perkin Trans. 1 (1985) 2307.
[13] K. Kyogoku, K. Hatayama, S. Yokomori, T. Sek, I. Tanaka, Agric. Biol. Chem. 1 (1975) 133.
[14] (a) E.A. Thompson, P.K. Sitteri, J. Biol. Chem. 249 (2000) 5364.(b) D.M. Stresser, S.D. Turner, J. McNamara, P. Strocker, V.P. Miller, C.L. Crespi, C.J. Patten, Anal. Biochem 284 (1974) 427.
[15] M. Artico, R.D. Santo, R. Costi, E. Novellino, G. Greco, S. Mars, E. Tramontano, M.E. Marongive, A. De Montis, A.P. Lacolla, J. Med. Chem. 41 (1990) 3948.