Isoprenylated Flavonoids from the Stem Bark of *Erythrina abyssinica*[#]

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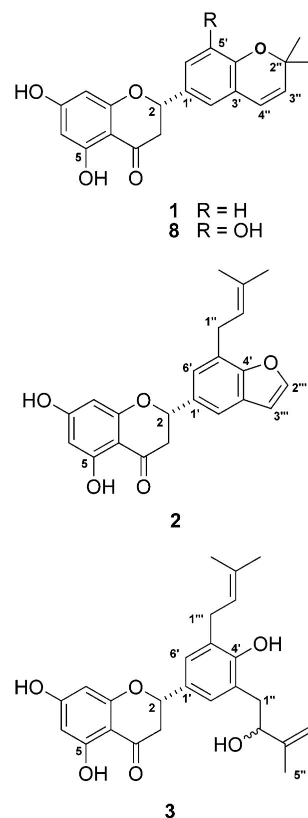
Three new prenylated flavanones, abyssinoflavanones V, VI, and VII (**1**−**3**), together with eight known flavanones (**4**−**11**) and two chalcones (**12**−**13**), were isolated from the stem bark of *Erythrina abyssinica*. Their structures were elucidated on the basis of spectroscopic and physicochemical analyses. All the isolates, with the exception of **1** and **8**, strongly inhibited PTP1B activity in an *in vitro* assay with IC_{50} values ranging from 14.2 ± 1.7 to 26.7 ± 1.2 μM.

Insulin resistance is one of the characteristic pathogenic signs of type-2 diabetes, and several drugs that increase the insulin sensitivity are currently in clinical use. However, these drugs have a number of limitations, which include adverse effects and high rates of secondary failure.[1] Of the various potential drug targets for treatment of type-2 diabetes, protein tyrosine phosphathase-1B (PTP1B) has recently been considered as a major negative regulator in the insulin signaling pathway.[2,3] It has been suggested that compounds reducing PTP1B activity or the genetic expression levels of PTP1B may be useful in the treatment of type-2 diabetes and possibly obesity as well.[2] Although there have been a number of reports on the development of PTP1B inhibitors,[2,4] new types of PTP1B inhibitors having improved pharmacological properties remain to be discovered.

In the course of our screening efforts, we found that an EtOAc extract of the stem bark of *Erythrina abyssinica* greatly inhibited PTP1B activity (>80% inhibition at 30 μg/mL). The *Erythrina* plants are widely distributed in tropical and subtropical regions, with some species in use as indigenous medicines.[5] A number of chemical constituents including alkaloids, pterocarpans, flavonoids, and benzofurans have been isolated from this genus, some of which exhibited antimicrobial, antioxidative, and estrogen-like activities.[6−9] Despite several studies on the chemical constituents and biological activities of the genus *Erythrina*, few investigations have focused specifically on *E. abyssinica*.[10−13] Further investigation on the PTP1B inhibitory compounds from this plant has led to the isolation of a series of prenylated flavonoids including three new ones. This paper describes the isolation, structure elucidation, and evaluation of PTP1B inhibitory properties of these flavonoids.

The EtOAc extract of *E. abyssinica* was subjected to a succession of chromatographic procedures including silica gel chromatography and HPLC to yield three new prenylated flavanones, named abyssinoflavanones V, VI, and VII (**1**−**3**), along with eight known flavanones, sigmoidins A (**7**), B (**5**), C (**8**),[17] and F (**4**),[18] abyssinins I (**11**) and II (**6**),[14] 5-deoxyabyssinin II (**9**),[15] and 3′-prenylnarringenin (**10**),[16] and two chalcones, abyssinone-VI (**12**)[8a] and licoagrochalcone A (**13**).[15] The structures of the known compounds were determined by comparing the physical and spectroscopic data ($[\alpha]_D$, UV, NMR, and MS) with reported values.



Compound **1** was obtained as a white powder, $[\alpha]_D^{25}$ −21.5 (*c* 0.1, MeOH). The molecular formula of **1** was determined as $C_{20}H_{18}O_5$ from a molecular ion peak at *m/z* 338.1157 $[M]^+$ (calcd for 338.1154) in the HREIMS. Its UV spectrum showed absorption bands at λ_{max} 233, 296, and 326 nm. The ^1H NMR displayed an ABX-type spin system at δ 5.45 (1H, dd, *J* = 2.8, 12.8 Hz, H-2), 3.06 (1H, dd, *J* = 12.8, 16.8 Hz, H-3_{ax}), and 2.80 (1H, dd, *J* = 2.8, 16.8 Hz, H-3_{eq}) and another ABX-type aromatic spin system at δ 6.78 (1H, d, *J* = 8.0 Hz), 7.24 (1H, d, *J* = 2.0 Hz), and 7.31 (1H, dd, *J* = 2.0, 8.0 Hz). The ^{13}C NMR showed an oxygenated carbon resonance at δ 79.9 (C-2), a methylene resonance at δ 43.5 (C-3), and a carbonyl resonance at δ 197.2 (C-4). All of these observations were indicative of a flavanone skeleton for **1**.[14,17] In addition, the ^1H and ^{13}C NMR patterns of **1** exhibited the presence of a 2,2-dimethylpyran ring due to the presence of a *gem*-dimethyl resonance [δ_H 1.42 (6H, s, H-5″ and -6″), δ_C 28.3 (C-5″ and -6″)], an olefinic group [δ_H 5.78 (1H, d, *J* = 10 Hz, H-3″) and 6.44 (1H, d, *J* = 10 Hz, H-4″), δ_C 122.8 (C-4″) and 132.3 (C-3″)], and an oxygenated quaternary carbon (δ_C 77.3).[14,17] Accordingly, the ^1H and ^{13}C NMR data of **1** were closely similar to those of abyssinin

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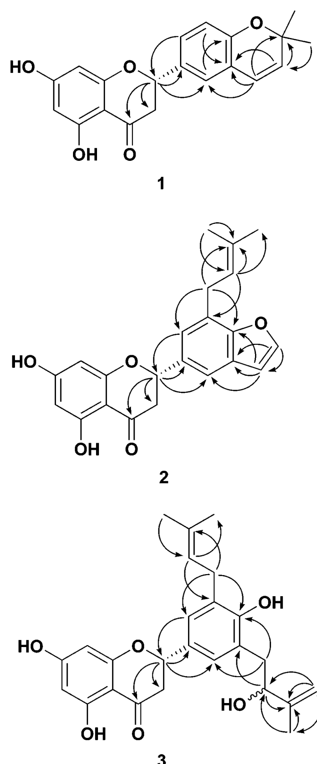

Figure 1. Key HMBC correlations of compounds **1**–**3**.

I,[14] with the exception of a methoxy group. The location of the 2,2-dimethylpyran unit on the B ring was determined on the basis of the HMBC correlations observed (Figure 1). The 2*S* absolute configuration of compound **1** was confirmed by its circular dichroism (CD) spectrum, which had a positive Cotton effect near 223 nm and negative Cotton effect near 288 nm.[14,19] Thus, the structure of compound **1**, named abyssinoflavanone V, was determined as 2*S*-5,7-dihydroxy-2″,2″-dimethylpyrano[5″,6″:3′,4′]-flavanone.

Compound **2** was isolated as a white powder, $[\alpha]_D^{25}$ −32.5 (*c* 0.1, MeOH). The molecular formula $C_{22}H_{20}O_5$ was assigned for **2** by the molecular ion peak at *m/z* 364.1311 $[M]^+$ (calcd for $C_{22}H_{20}O_5$, 364.1311) in HREIMS. Similar to **1**, the UV, CD, and ^{1}H and ^{13}C NMR data of **2** resembled those of a flavanone. A pair of olefinic protons at δ_H 6.94 (1H, d, *J* = 2.4 Hz, H-3‴) and 7.89 (1H, d, *J* = 2.4 Hz, H-2‴) in the ^{1}H NMR spectrum and olefinic carbons (δ_C 108.0 (C-3‴) and 147.0 (C-2‴) in the ^{13}C NMR spectrum were suggestive of a benzofuran moiety, in agreement with the data of abyssinoflavanone IV.[20] Furthermore, the ^{1}H NMR spectrum of **2** also displayed resonances assignable as a prenyl group [(δ 1.72 (3H, br s), 1.78 (3H, br s), 3.65 (2H, br d, *J* = 7.2 Hz), and 5.43 (1H, m)], which was located at C-5′ by HMBC (Figure 1). The C-2 configuration of **2**, abyssinoflavanone VI, was determined as *S* by the negative specific rotation and CD data.[20]

Compound **3** was obtained as a white powder, and its molecular formula was determined as $C_{25}H_{28}O_6$ from the molecular ion peak at *m/z* 424.1878 $[M]^+$ (calcd for $C_{25}H_{28}O_6$, 424.1886) in the HREIMS. The $[\alpha]_D$, UV, CD, and ^{1}H and ^{13}C NMR (Table 1) data of **3** were characteristic of a flavanone skeleton. Similar to **2**, ^{1}H and ^{13}C NMR spectra of **3** also showed the presence of a prenyl group [δ_H 1.71 (6H, br s), 3.45 (2H, br d, *J* = 7.2 Hz), and 5.34 (1H, m); δ_C 17.9, 25.9, 29.2, 123.9, and 132.2]. However, these additionally showed doublet of doublets protons at δ_H 2.82 (1H, *J* = 6.4, 14.4 Hz) and 2.98 (1H, *J* = 8.8, 14.4 Hz), a methine proton at δ_H 4.41, two singlets at δ_H 4.82 (1H, s) and 5.03 (1H, s), and a methyl resonance at δ 1.81 (3H, s), together with carbon resonances of a benzylic carbon at δ_C 39.6 (C-1″), an oxygenated carbon at δ 78.1 (C-2″), a quaternary carbon at δ 148.2 (C-3″), an olefinic methylene carbon at δ 110.9, and a methyl carbon at δ 18.4 (C-5″). These observations suggest the existence of a 2-hydroxy-3-methylbut-3-enyl group. Furthermore, a pair of *meta*-coupled protons at δ_H 7.14 and 7.17, due to the unsymmetrical substitution pattern of the B ring, implied that the prenyl and a 2-hydroxy-3-methylbut-3-enyl group should be located at C-3′ or C-5′ of **3**, respectively. The relative positions of these groups were confirmed by long-range correlations in the HMBC (Figure 1). The configuration at C-2 was inferred to be 2*S*, as indicated by CD data.[20,21] Hence, compound **3** was identified as a new flavanone, abyssinoflavanone VII.

The isolates **1**–**13** were assayed for their inhibitory activity against PTP1B, and the results are presented in Table 2. The known PTP1B inhibitors, RK-682 (IC_{50} = 4.5 ± 0.5 μM) and ursolic acid (IC_{50} = 3.6 ± 0.2 μM),[22a,b] were used as the positive controls. Compounds **1**–**13**, except for **1** and **8**, inhibited dose-dependently PTP1B activity, yielding IC_{50} values ranging from 14.2 ± 1.7 to 26.7 ± 1.2 μM. Most of the isolates from *E. abyssinica* have the 5,7-dihydroxyflavanone skeleton or its chalcone analogues and differ as to the substitution patterns in the B ring. Compounds **1** and **8**, which were fused as the 2,2-dimethylpyran moiety on the B ring, exhibited a significantly lower PTP1B inhibitory activity than compounds **5**, **6**, and **9**, on which similar positions were attached as prenyl and hydroxy groups. Furthermore, compound **11** showed a higher activity than that of **8**, indicating that the addition of a prenyl group or methoxy substituent into the B ring may be responsible for increasing PTP1B activity. Although structure–activity relationships of flavanones bearing prenyl groups were not thoroughly investigated, our results indicate that substitution of prenyl groups on flavonoids may be important for *in vitro* PTP1B inhibitory activity, and cyclization between a hydroxy group and the prenyl group in the B ring without prenyl or methoxy groups may decrease the activity. Therefore, further investigation and optimization of prenylated flavanone derivatives might enable the discovery of new PTP1B inhibitors that are potentially useful in the treatment of type-2 diabetes as well as obesity.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO P-1020 polarimeter using a 100 mm glass microcell. UV spectra were measured with a Shimadzu spectrophotometer. The CD spectra were recorded in MeOH on a JASCO J-715 spectrometer. NMR spectra were obtained on a Varian Inova 400 MHz spectrometer with TMS as the internal standard. EIMS and HREIMS data were recorded on a Micromass QTOF2 (Micromass, Wythenshawe, UK) mass spectrometer. Column chromatography was conducted on silica gel (63–200 μm particle size) and RP-18 (40–63 μm particle size) from Merck. TLC was carried out with silica gel 60 F_{254} plates from Merck. HPLC was carried out using a Shimadzu System LC-10AD pump equipped with a model SPD-10Avp UV detector and an Optima Pak C_{18} column (10 × 250 mm, 10 μm particle size, RS Tech Korea).

Plant Material. The stem bark of *E. abyssinica* was collected in June 2005 in Mukono, Uganda. The sample was botanically authenticated by Prof. John Silike-Muruumu, and its voucher specimen (No. 0001) has been deposited at the Department of Botany, Makerere University, Uganda.

Extraction and Isolation. The dried stem bark (5 kg) was extracted with MeOH at room temperature for 3 days. After the solvent was removed under reduced pressure, the residue was suspended in H_2O and then partitioned with EtOAc and *n*-BuOH successively. The EtOAc fraction was concentrated to dryness (105 g). Part of this fraction (3 g) was chromatographed on a silica gel column (6.5 × 35 cm; 63–200 μm particle size) using a gradient of $CHCl_3$–MeOH (20:1 → 5:1) to yield 10 subfractions (Fr.1–Fr.10) according to their TLC profiles. The PTP1B inhibitory activity was concentrated in Fr.3, which eluted with $CHCl_3$–MeOH, 10:1 → 5:1 (1.5 g, IC_{50} = 16.7 μg/mL). This fraction was further chromatographed over a silica gel column (4 × 27 cm) using a stepwise gradient of hexane–EtOAc (20:1 → 0:1) to give 10 subfractions (Fr.3-1–Fr.3-10). Further purification of Fr.3-2 (600 mg) by semipreparative HPLC (UV detector at 320 nm, flow rate 2 mL/

Table 1. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data of Compounds **1**−**3** in Me_2CO-d_6

	1		**2**		**3**[a]	
position	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
2	79.9	5.45 dd (12.8, 2.8)	80.5	5.63 dd (12.8, 2.8)	80.3	5.39 dd (12.8, 3.2)
3_{ax}	43.5	3.06 dd (16.8, 12.8)	44.1	3.05 dd (17.2, 12.8)	43.6	3.18 dd (17.2, 12.8)
3_{eq}		2.80 dd (16.8, 2.8)		2.81 dd (17.2, 2.8)		2.70 dd (17.2, 3.2)
4	197.2		197.1		197.4	
5	165.4		165.4		165.4	
6	97.0	5.95 d (2.0)	97.0	5.96 d (2.0)	96.8	5.94 s
7	167.7		167.5		164.5	
8	96.0	5.98 d (2.0)	96.0	5.99 d (2.0)	95.9	5.94 s
9	164.4		164.5		164.5	
10	103.2		103.3		103.3	
1′	132.3		135.1		130.7	
2′	125.8	7.24 d (2.0)	123.6	7.68 d (1.6)	127.1	7.17 d (2.0)
3′	128.5		128.5		128.5	
4′	154.3		154.4		155.4	
5′	117.1	6.78 d (8.0)	126.4		127.6	
6′	122.3	7.31 dd (8.0, 2.0)	118.2	7.35 d (1.6)	123.9	7.14 d (2.0)
1″			29.0	3.65 br d (7.2)	39.6	2.98 dd (14.4, 8.8) 2.82 dd (14.4, 6.4)
2″	77.3		122.5	5.43 m	78.1	4.41 d (8.8)
3″	132.3	5.78 d (10.0)	133.8		148.2	
4″	122.8	6.44 d (10.0)	25.9	1.78 br s	110.9	4.82 s 5.03 s
5″	28.3	1.42 br s	18.0	1.72 br s	18.4	1.81 s
6″	28.3	1.42 br s				
1‴					29.2	3.45 br d (7.2)
2‴			147.0	7.89 d (2.4)	123.9	5.34 m
3‴			108.0	6.94 d (2.4)	132.2	
4‴					17.9	1.71 s
5‴					25.9	1.71 s

[a] Resonances that partially overlapped are distinguished when measured in CD_3OD (see Experimental Section).

Table 2. Inhibitory Activity of Compounds **1**−**13** against PTP1B

compound	inhibitory activity[a]
abyssinoflavone V (**1**)	>60
abyssinoflavone VI (**2**)	18.9 ± 1.9
abyssinoflavone VII (**3**)	15.7 ± 0.4
sigmoidin F (**4**)	14.2 ± 1.7
sigmoidin B (**5**)	19.4 ± 2.3
abyssinin II (**6**)	17.3 ± 1.4
sigmoidin A (**7**)	14.4 ± 0.8
sigmoidin C (**8**)	>60
5-deoxyabyssinin II (**9**)	19.2 ± 1.1
3′-prenylnaringenin (**10**)	26.7 ± 1.2
abyssinin I (**11**)	18.2 ± 1.4
abyssinone-VI (**12**)	20.6 ± 2.1
licoagrochalcone A (**13**)	16.9 ± 0.7
RK-682[b]	4.5 ± 0.5
ursolic acid[b]	3.6 ± 0.2

[a] Results are expressed as IC_{50} values (μM), determined by regression analyses and expressed as the mean ± SD of three replicates. [b] Positive control.[22a,b]

min) eluting with a gradient of 80% → 95% MeCN in H_2O over 50 min gave compounds **4** (56.0 mg, t_R = 11.4 min), **1** (4.7 mg, t_R = 15.2 min), **12** (5.9 mg, t_R = 16.2 min), and **5** (24.3 mg, t_R = 17.1 min). Fr.3-3 (357 mg) was further purified by preparative HPLC (UV detector at 320 nm, flow rate 2 mL/min) using a gradient of 60% → 80% MeCN in H_2O as mobile phase over 50 min to give compounds **6** (38.9 mg, t_R = 18.3 min), **7** (42.8 mg, t_R = 20.6 min), and **2** (9.8 mg, t_R = 22.3 min). Finally, Fr.3-6 (400 mg) was separated by HPLC (UV detector at 320 nm, flow rate 2 mL/min) using an isocratic solvent system of 56% MeCN in H_2O over 30 min, whereafter 65% MeCN in H_2O over 20 min gave compounds **8** (28.6 mg, t_R = 19.2 min), **9** (6.7 mg, t_R = 22.2 min), **10** (12.9 mg, t_R = 24.3 min), **11** (2.5 mg, t_R = 26.4 min), **13** (8.8 mg, t_R = 32.3 min), and **3** (1.9 mg, t_R = 42.8 min).

Abyssinoflavanone V (1): white, amorphous powder; $[\alpha]_D^{25}$ −21.5 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 233 (4.64), 296 (4.22), 326 (3.45) nm; CD (c 0.55, MeOH) $[\theta]_{325}$ +8.5, $[\theta]_{288}$ −31.9, $[\theta]_{223}$ +40.9; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS m/z 338.1157 $[M]^+$ (calcd for $C_{20}H_{18}O_5$, 338.1154).

Abyssinoflavanone VI (2): white, amorphous powder; $[\alpha]_D^{25}$ −32.5 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 213 (−4.80), 296 (−4.22), 328 (3.47) nm; CD (c 0.59, MeOH) $[\theta]_{330}$ +6.3, $[\theta]_{285}$ −28.8, $[\theta]_{211}$ +47.5; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS m/z 364.1311 $[M]^+$ (calcd for $C_{22}H_{20}O_5$, 364.1311).

Abyssinoflavanone VII (3): white powder; $[\alpha]_D^{25}$−4.7 (c 0.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 228 (4.23), 288 (4.05), 329 (−3.39) nm; CD (c 0.47, MeOH) $[\theta]_{326}$ +3.4, $[\theta]_{289}$ −10.5, $[\theta]_{224}$ +7.9, $[\theta]_{200}$ +24.7; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.17 (1H, d, J = 2.0 Hz, H-2′), 7.14 (1H, d, J = 2.0 Hz, H-6′), 5.94 (2H, s, H-6 and 8), 5.39 (2H, dd, J = 12.8, 3.2 Hz, H-2), 5.34 (1H, m, H-2‴), 5.03 (1H, s, H-4″), 4.81 (1H, s, H-4″), 4.41 (1H, d, J = 8.8 Hz, H-2″), 3.45 (2H, br d, J = 7.2 Hz, H-1‴), 3.18 (1H, dd, J = 17.2, 12.8 Hz, H-2_{ax}), 2.70 (1H, dd, J = 17.2, 3.2 Hz, H-2_{eq}), 2.98 (1H, dd, J = 14.4, 8.8 Hz, H-1″), 2.82 (1H, dd, J = 14.4, 6.4 Hz, H-1″), 1.78 (6H, br s, H-4‴ and 5‴), 1.81 (3H, s, H-5″); ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS m/z 424.1878 $[M]^+$ (calcd for $C_{25}H_{28}O_6$, 424.1886).

PTP1B Assay. PTP1B (human, recombinant) was purchased from BIOMOL International LP (Plymouth Meeting, PA). The inhibitory effect of test compounds on enzyme activity was measured by a method described previously.[22] To each 96 well (final volume: 100 μL) was added 2 mM pNPP and PTP1B (0.05−0.1 μg) in a buffer containing 50 mM citrate (pH 6.0), 0.1 M NaCl, 1 mM EDTA, and 1 mM dithiothreitol (DTT), with or without test compounds. Following incubation at 37 °C for 30 min, the reaction was terminated with 10 M NaOH. The amount of produced p-nitrophenol was estimated by measuring the absorbance at 405 nm. The nonenzymatic hydrolysis of 2 mM pNPP was corrected by measuring the increase in absorbance at 405 nm obtained in the absence of PTP1B enzyme.

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