Synthesis and Biological Evaluation of 3-Styrylchromone Derivatives as Free Radical Scavengers and α-Glucosidase Inhibitors

Koichi Takao, Ryo Ishikawa, and Yoshiaki Sugita*

Laboratory of Bioorganic Chemistry, Department of Pharmaceutical and Health Sciences, Faculty of Pharmaceutical Sciences, Josai University; 1–1 Keyaki-dai, Sakado, Saitama 350–0295, Japan.
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A series of 3-styrylchromone derivatives (4–20) were synthesized and the structure–activity relationships for α-glucosidase inhibition and antioxidant activities were analyzed. Among the synthesized compounds, compounds 15 and 20, which contain a catechol moiety, showed both potent 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity (15: EC_{50}=17 μM; 20: EC_{50}=23 μM) and α-glucosidase inhibitory activity (15: IC_{50}=16 μM; 20: IC_{50}=10 μM). Our data suggest that 3-styrylchromone derivatives are novel α-glucosidase inhibitors that have the potential to counteract diet-induced hyperglycemia in diabetes.

Key words 3-styrylchromone; α-glucosidase inhibitor; antioxidant; structure–activity relationship

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from insufficiency of secretion or action of endogenous insulin. α-Glucosidase has been recognized as a therapeutic target for modulation of postprandial hyperglycemia. α-Glycosidase inhibitors act to delay glucose absorption, making them potent drugs to control blood glucose levels.[1] On the other hand, antioxidants function as free radical scavengers, chelating agents for pro-oxidant metals, quenchers of singlet oxygen formation, and reducing agents.[2,3] Because of their antioxidant characteristics, antioxidants are important in the prevention of human diseases. The accumulated evidence suggests that diabetic patients are under oxidative stress and that oxidative stress plays a major role in the pathogenesis of diabetes mellitus.[4] Recently, several researchers have evaluated α-glucosidase inhibitors possessing free-radical scavenging activity.[5–11]

4*H*-1-Benzopyran-4-ones (chromones) are an important class of oxygenated heterocyclic compounds, and have attracted the attention of organic chemists and biochemists due to their biological activities and occurrence in natural products. This chromone core structure is found in flavones, isoflavones, and 2-styrylchromones. Flavones and isoflavones are distributed in several species of plants. In contrast, 2-styrylchromones constitute a small group of naturally occurring chromones. Synthetic 2-styrylchromones possess a number of biological activities, including antioxidant,[12,13] anti-allergic,[14] anti-inflammatory,[15] antitumor,[16–18] and antiviral[19–21] effects. The synthesis and evaluation of biological activities of 2-styrylchromones has been extensively investigated, while studies dealing with 3-styrylchromones are few. Moreover, although there are some examples of the synthesis of 3-styrylchromones,[22–27] only a few studies have evaluated the biological activity of 3-styrylchromones.[22,28] In order to further explore novel biological activities, a series of 3-styrylchromone derivatives were synthesized, containing newly prepared compounds, and structure–activity relationships in regards to antioxidant activity and α-glycosidase inhibition were investigated.

Results and Discussion

Chemistry 3-Styrylchromone derivatives presented in this study were synthesized by Knoevenagel condensation of the appropriate 3-formylchromone with selected phenylacetic acid derivatives, by means of a modified previous procedure[22] (Chart 1). This required the preparation of 3-formylchromone derivatives (**2a**, **2b** and **2c**) necessary for the synthesis of 3-styrylchromone derivatives (R^1=H, OMe and OH). Synthesis of **2a** and **2b** was prepared by Vilsmeier–Haack treatment of 2′-hydroxyacetophenones **1a** and **1b**, respectively, according to published procedures,[29,30] and **2c** was also synthesized from **1c** according to the same procedure. Having **2a**, **2b** and **2c** in hand, the final step was condensation with phenylacetic acid derivatives (**3a**–**g**) in the presence of *tert*-BuOK in dry pyridine to provide the 3-styrylchromone derivatives (**4**–**13**) and allyl-protected products of 3-styrylchromones (**14**–**20**), respectively. 3-Styrylchromones having the allyloxy group were submitted to a deprotection step, using $Pd(PPh_3)_4$ in the presence of morpholine in degassed anhydrated THF, for removing the allyl group and affording 3-styrylchromones bearing the hydroxyl group (**14**–**20**).

Biological Activity All synthesized compounds were evaluated for their 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and α-glucosidase inhibitory activities.

As shown in Table 1, modifications of 3-styrylchromones on the chromone ring (A-ring) and the phenyl group (B-ring) of the styryl moiety revealed some interesting structure–activity relationships. As a result, the introduction of the methoxy group or halogen atom (F or Cl) substituent (**4**–**13**) on the B-ring did not show DPPH radical scavenging activity, while the introduction of the hydroxyl group did. It was evident that the 3′,4′-dihydroxy derivatives (**15** and **17**) were more potent than the 4′-hydroxy derivatives (**14** and **16**). These compounds (**15** and **17**) have in common a catechol group in the B-ring, which is known to be an important structural feature of the antioxidant activity.[31,32] In contrast, it was noted that the introduction of a hydroxyl group at the 6-position on the chromone ring did not increase the DPPH radical scavenging activity of 3-styrylchromones (**4**, **14** and **15** *versus* **18**, **19** and **20**, respectively). These results indicate that hydroxyl groups on the B-ring play a more vital role than those on the A-ring.

It was also found that the number of hydroxyl groups pref-

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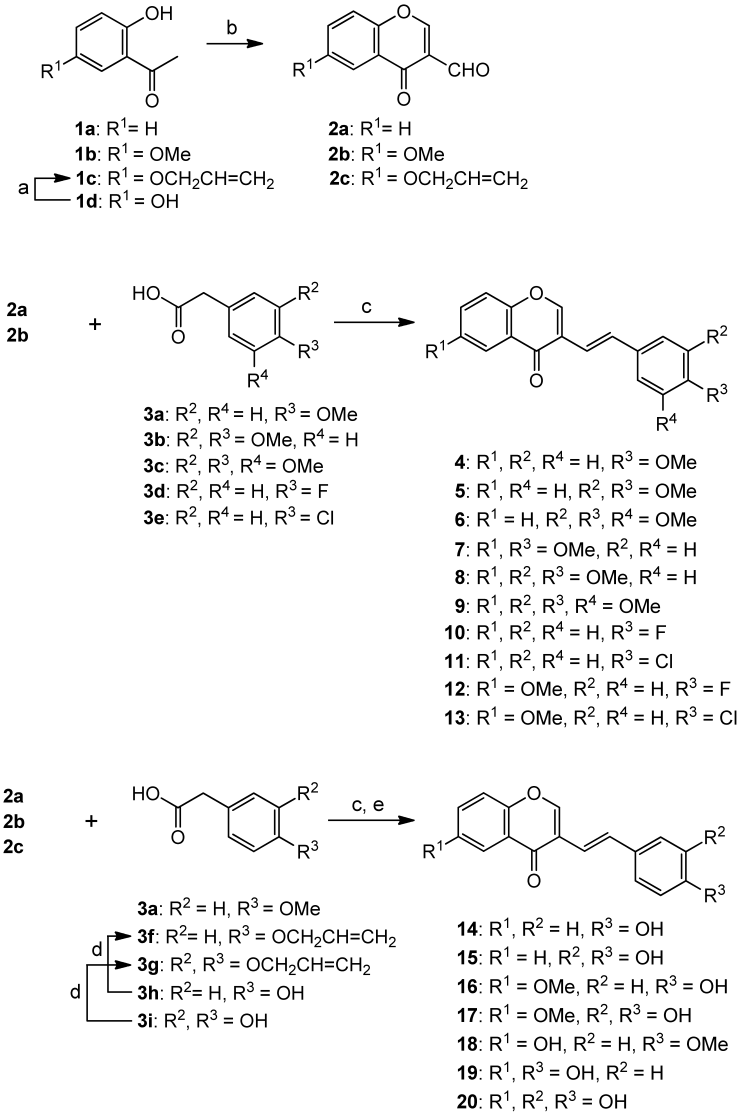
* To whom correspondence should be addressed. e-mail: sugita@josai.ac.jp



Reagents and conditions: (a) allylbromide, K_2CO_3, acetone, reflux; (b) DMF/$POCl_3$; (c) *tert*-BuOK, dry pyridine, reflux; (d) allylbromide, K_2CO_3, EtOH and then KOH; (e) $Pd(PPh_3)_4$, morpholine, THF, 60°C.

Chart 1. Protocol for the Synthesis 3-Styrylchromone Derivatives **4**–**20**

erably attached to the B-ring might play an important role in the α-glucosidase inhibitory activity (**14** and **16** *versus* **15** and **17**, respectively). Interestingly, the introduction of a halogen at the 4′-position also increased the activity (**10** and **11**). It is known that halogens can impose molecular conformation or influence the potency of a product due to their steric and/or electronic effects. Conti and Desideri also reported on the inhibition of anti-picornavirus activity with halogen-substituted 3-styrylchromone.[22] It was also noted that the introduction of a methoxy group at the 6-position on the chromone ring decreased the activity (**10** and **11** *versus* **12** and **13**, **14** and **15** *versus* **16** and **17**, respectively), while the introduction of a hydroxyl group on the chromone ring increased the activity (**4**, **14** and **15** *versus* **18**, **19** and **20**, respectively). These results indicate that the hydroxylation at the 6-position of the chromone ring is important for the α-glucosidase inhibitory activity. It has been reported that some flavonoids and polyphenols, as well as sugar derivatives, were found to have an effect on α-glucosidase inhibitory activity.[6,7,33] It appears that this effect is associated with the polyphenols present in 3-styrylchromones. Of the synthesized compounds, compounds **15**, **19** and **20** showed potent activity, and exhibited superior antihyperglycemic activity to the commercial antihyperglycemic drug, acarbose, which has the structural features of a tetrasaccharide.

The potency of α-glucosidase inhibition and the antioxidant activity of the synthesized 3-styrylchromones shared similar chemical features and functional groups, such as the presence of hydroxyl and methoxy groups, as shown in Table 1. Introduction of the hydroxyl group on the phenyl group of the styryl moiety increased both α-glucosidase inhibition and antioxidant activity, and 3′,4′-dihydroxy derivatives were more potent than the 4′-hydroxy derivatives (**14** and **19** *versus* **15** and **20**, respectively). In addition, the introduction of a hydroxyl group at the 6-position on the chromone ring resulted in even greater increase in α-glucosidase inhibition (**14** and **15** *versus* **19** and **20**, respectively), but a slight decrease in antioxidant activity. In contrast, a methoxy substitution at the 6-position on the chromone ring resulted in a reduction of both activities (**14** and **15** *versus* **16** and **17**, respectively).

Table 1. DPPH Scavenging and α-Glucosidase Inhibitory Activities of 3-Styrylchromone Derivatives

Compound	R^1	R^2	R^3	R^4	DPPH scavenging activity EC_{50} (μM)	α-Glucosidase inhibitory activity IC_{50} (μM)
4	H	H	OMe	H	>200	>100
5	H	OMe	OMe	H	>200	>100
6	H	OMe	OMe	OMe	>200	>100
7	OMe	H	OMe	H	>200	>100
8	OMe	OMe	OMe	H	>200	>100
9	OMe	OMe	OMe	OMe	>200	>100
10	H	H	F	H	>200	23
11	H	H	Cl	H	>200	16
12	OMe	H	F	H	>200	>100
13	OMe	H	Cl	H	>200	57
14	H	H	OH	H	60	39
15	H	OH	OH	H	17	16
16	OMe	H	OH	H	78	>100
17	OMe	OH	OH	H	22	68
18	OH	H	OMe	H	>200	33
19	OH	H	OH	H	125	9
20	OH	OH	OH	H	23	10
Ascorbic acid					23	
Acarbose						>100

Conclusion

A series of 3-styrylchromone derivatives (**4**–**20**) were synthesized and evaluated for DPPH free radical scavenging and α-glucosidase inhibitory activities. As a result, compounds **15** and **20**, possessing a catechol moiety in the B-ring, showed potent activity in both assays. This indicates that the introduction of a hydroxyl group on the phenyl group of the styryl moiety is important for the α-glucosidase inhibition and antioxidant activities. This is the first report identifying the DPPH free radical scavenging and α-glucosidase inhibitory activities of 3-styrylchromone derivatives. These results suggest that 3-styrylchromone derivatives are novel α-glucosidase inhibitors that may counteract diet-induced hyperglycemia.

Experimental

Chemistry All reagents and solvents were purchased from commercial sources. Analytical thin-layer chromatography was performed on silica-coated plates (silica gel 60 F-254, Merck) and visualized under UV light. Column chromatography was carried out using silica gel (Wakogel C-200, Wako). All melting points were determined using a Yanagimoto micro-hot stage and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 400-MR spectrometer using tetramethylsilane as the internal standard. MS spectra were measured using a JEOL JMS-700 spectrometer. Elemental analyses were carried out on a Yanaco CHN MT-6 elemental analyzer.

Synthesis of 3-Formylchromones 3-Formylchromones **2a**–**c** were synthesized according to previous methods.[29,30] The products (**2a**, **2b**) were identified by their melting points and ^{1}H-NMR spectra.

3-Formyl-6-(2-propenyloxy)-4*H*-1-benzopyran-4-one (**2c**): Yield 53%. Yellow needles. mp 118–119°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 10.40 (1H, s, CHO), 8.54 (1H, s, H-2), 7.66 (1H, d, J=3.1 Hz, H-5), 7.48 (1H, d, J=9.2 Hz, H-8), 7.36 (1H, dd, J=9.2, 3.1 Hz, H-7), 6.07 (1H, ddt, J=17.3, 10.5, 5.3 Hz, –C*H*=CH_2), 5.47 (1H, dq, J=17.3, 1.5 Hz, –CH=C*H*$_2$), 5.35 (1H, dq, J=10.5, 1.5 Hz, –CH=C*H*$_2$), 4.66 (2H, dt, J=5.3, 1.5 Hz, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 188.8, 175.8, 160.2, 156.8, 150.9, 132.2, 126.1, 124.8, 120.0, 119.6, 118.5, 106.5, 69.5. High resolution mass spectrum (HR-MS) *m/z*: Calcd for $C_{13}H_{10}O_4$ (M^+): 230.0579; Found: 230.0571.

Synthesis of 4-(2-Propenyloxy)benzeneacetic Acid (3f) The compound (**3f**) was synthesized by a modified previous procedure.[34] Solid K_2CO_3 (16.6 g, 120 mol) was added to a solution of 4-hydroxyphenylacetic acid (**3h**, 4.6 g, 30 mmol) and allylbromide (9.4 g, 75 mmol) in EtOH (150 mL) at room temperature, and the mixture was refluxed for 5 h. To the cooled slurry was added KOH (6.7 g, 120 mmol) and stirring was continued for 12 h. The solvent was removed, the residue taken up in H_2O (500 mL), washed with Et_2O (100 mL), acidified with conc. HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt=1 : 1) to give the title compound (**3f**) in 92% yield. Colorless solid. mp 76–77°C (lit.[34] mp 69.5–71.9°C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.19 (2H, d, J=8.6 Hz, H-2′ and H-6′), 6.88 (2H, d, J=8.6 Hz, H-3′ and H-5′), 6.05 (1H, ddt, J=17.2, 10.5, 5.3 Hz, –C*H*=CH_2), 5.41 (1H, dq, J=17.2, 1.5 Hz, –CH=C*H*$_2$), 5.28 (1H, dq, J=10.5, 1.5 Hz, –CH=C*H*$_2$), 4.52 (2H, dt, J=5.3, 1.5 Hz, CH_2), 3.58 (2H, s, CH_2). MS (electron ionization (EI)) *m/z*: 192 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[34]

3,4-Bis(2-propenyloxy)benzeneacetic Acid (**3g**): According to the procedure for the preparation of compound (**3f**), 3,4-dihydroxyphenylacetic acid (**3i**, 6.8 g, 50 mmol) and allylbromide (24.2 g, 200 mmol) were treated with K_2CO_3 (41 g, 300 mol) followed by KOH (11.2 g, 200 mmol) to give the title compound (**3g**) in 92% yield. Colorless semisolid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.86–6.75 (3H, m, aromatic), 6.06 (2H, m, –C*H*=CH_2), 5.40 (2H, m, –CH=C*H*$_2$), 5.27 (2H, m, –CH=C*H*$_2$), 4.59 (4H, m, CH_2), 3.56 (2H, s, CH_2). HR-MS *m/z*: Calcd for $C_{14}H_{16}O_4$ (M^+): 248.1049; Found: 248.1028.

General Procedure for Preparation of (*E*)-3-Styryl-4*H*-1-

benzopyran-4-one Derivative (4–13) To a solution of the corresponding 3-formylchromone (**2**, 2 mmol) and phenylacetic acid (**3**, 10 mmol) in dry pyridine (20 mL), *tert*-BuOK (3 mmol) was added. The mixture was refluxed until complete disappearance of 3-formylchromone (6–22 h). After the reaction mixture was diluted with ice-water and acidified to pH 2 with 5 N HCl, the sample was extracted with AcOEt. The combined organic layer was washed with saturated $NaHCO_3$ solution and then with brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt=5 : 1) to give the corresponding 3-styryl-4*H*-1-benzopyran-4-one derivative.

3-[(1*E*)-2-(4-Methoxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**4**): Yield 40%. Pale yellow amorphous. mp 133–134°C (lit.[24] 123–124°C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.30 (1H, dd, *J*=8.0, 1.7 Hz, H-5), 8.10 (1H, d, *J*=0.8 Hz, H-2), 7.67 (1H, ddd, *J*=8.5, 7.1, 1.7 Hz, H-7), 7.56 (1H, d, *J*=16.4 Hz, H-β), 7.47 (1H, m, H-8), 7.47 (2H, d, *J*=8.9 Hz, H-2′ and H-6′), 7.42 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-6), 6.90 (2H, d, *J*=8.9 Hz, H-3′ and H-5′), 6.87 (1H, dd, *J*=16.4, 0.8 Hz, H-α), 3.83 (3H, s, OMe). MS-EI *m/z*: 278 $[M]^+$. The ^{1}H-NMR spectrum was similar to that previously reported.[24]

3-[(1*E*)-2-(3,4-Dimethoxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**5**): Yield 63%. Pale yellow needles. mp 128–129°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.31 (1H, dd, *J*=8.0, 1.7 Hz, H-5), 8.12 (1H, d, *J*=0.7 Hz, H-2), 7.68 (1H, ddd, *J*=8.5, 7.1, 1.7 Hz, H-7), 7.54 (1H, d, *J*=16.3 Hz, H-β), 7.48 (1H, dd, *J*=8.5, 1.1 Hz, H-8), 7.43 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-6), 7.10 (1H, d, *J*=2.0 Hz, H-2′), 7.07 (1H, dd, *J*=8.2, 2.0 Hz, H-6′), 6.88 (1H, dd, *J*=16.3, 0.7 Hz, H-α), 6.86 (1H, d, *J*=8.2 Hz, H-5′), 3.95 (3H, s, OMe), 3.91 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.7, 155.8, 152.5, 149.1, 133.5, 131.3, 130.4, 126.2, 125.2, 124.0, 122.0, 120.0, 118.0, 116.9, 111.1, 108.7, 55.9, 55.8. MS (EI) *m/z*: 308 $[M]^+$. *Anal*. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.26; H, 5.26.

3-[(1*E*)-2-(3,4,5-Trimethoxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**6**): Yield 62%. Yellow solid. mp 156–157°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.30 (1H, dd, *J*=8.0, 1.7 Hz, H-5), 8.13 (1H, d, *J*=0.8 Hz, H-2), 7.69 (1H, ddd, *J*=8.5, 7.1, 1.7 Hz, H-7), 7.58 (1H, d, *J*=16.2 Hz, H-β), 7.48 (1H, dd, *J*=8.5, 1.1 Hz, H-8), 7.43 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-6), 6.90 (1H, dd, *J*=16.2, 0.8 Hz, H-α), 6.76 (2H, s, H-2′ and H-6′), 3.92 (6H, s, OMe), 3.87 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.6, 155.8, 153.3, 153.0, 138.0, 133.6, 133.1, 131.6, 126.2, 125.3, 124.0, 121.6, 118.4, 118.0, 103.6, 61.0, 56.1. HR-MS *m/z*: Calcd for $C_{20}H_{18}O_5$ (M^+): 338.1154; Found: 338.1127.

6-Methoxy-3-[(1*E*)-2-(4-methoxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**7**): Yield 69%. Yellow needles. mp 137–138°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.09 (1H, d, *J*=0.8 Hz, H-2), 7.65 (1H, d, *J*=3.1 Hz, H-5), 7.55 (1H, d, *J*=16.3 Hz, H-β), 7.47 (2H, d, *J*=8.7 Hz, H-2′ and H-6′), 7.41 (1H, d, *J*=9.1 Hz, H-8), 7.26 (1H, dd, *J*=9.1, 3.1 Hz, H-7), 6.90 (2H, d, *J*=8.7 Hz, H-3′ and H-5′), 6.88 (1H, dd, *J*=16.3, 0.8 Hz, H-α), 3.92 (3H, s, OMe), 3.83 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.4, 159.4, 156.9, 152.4, 150.7, 130.9, 130.2, 127.8, 124.6, 123.6, 121.2, 119.4, 116.9, 114.1, 105.1, 55.9, 55.3. MS-EI *m/z*: 308 $[M]^+$. *Anal*. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.12; H, 5.28.

6-Methoxy-3-[(1*E*)-2-(3,4-dimethoxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**8**): Yield 63%. Light brown solid. mp 135–136°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.11 (1H, d, *J*=0.8 Hz, H-2), 7.66 (1H, d, *J*=3.1 Hz, H-5), 7.53 (1H, d, *J*=16.3 Hz, H-β), 7.41 (1H, d, *J*=9.1 Hz, H-8), 7.27 (1H, dd, *J*=9.1, 3.1 Hz, H-7), 7.10 (1H, d, *J*=1.9 Hz, H-2′), 7.07 (1H, dd, *J*=8.2, 1.9 Hz, H-6′), 6.89 (1H, dd, *J*=16.3, 0.8 Hz, H-α), 6.86 (1H, dd, *J*=8.2 Hz, H-5′), 3.95 (3H, s, OMe), 3.92 (3H, s, OMe), 3.91 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.4, 156.9, 152.4, 150.7, 149.04 149.01, 131.1, 130.5, 124.6, 123.6, 121.1, 120.0, 119.4, 117.1, 111.1, 108.7, 105.1, 55.9 (2C), 55.8. MS-EI *m/z*: 338 $[M]^+$. *Anal*. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 71.04; H, 6.39.

6-Methoxy-3-[(1*E*)-2-(3,4,5-trimethoxyphenyl)-ethenyl]-4*H*-1-benzopyran-4-one (**9**): Yield 83%. Pale yellow amorphous. mp 128–129°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.12 (1H, d, *J*=0.8 Hz, H-2), 7.66 (1H, d, *J*=3.1 Hz, H-5), 7.57 (1H, d, *J*=16.3 Hz, H-β), 7.42 (1H, d, *J*=9.0 Hz, H-8), 7.27 (1H, dd, *J*=9.0, 3.1 Hz, H-7), 6.91 (1H, dd, *J*=16.3, 0.8 Hz, H-α), 6.76 (2H, s, H-2′ and H-6′), 3.93 (3H, s, OMe), 3.92 (6H, s, OMe), 3.87 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.4, 157.0, 153.3, 152.8, 150.6, 138.0, 133.1, 131.4, 124.6, 123.7, 120.8, 119.5, 118.6, 105.1, 103.6, 61.0, 56.1, 55.9. MS-EI *m/z*: 368 $[M]^+$. *Anal*. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.67; H, 5.51.

3-[(1*E*)-2-(4-Fluorophenyl)ethenyl]-4*H*-1-benzopyran-4-one (**10**): Yield 80%. Colorless amorphous. mp 142–143°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.31 (1H, dd, *J*=8.0, 1.7 Hz, H-5), 8.11 (1H, d, *J*=0.7 Hz, H-2), 7.68 (1H, ddd, *J*=8.5, 7.1, 1.7 Hz, H-7), 7.62 (1H, d, *J*=16.3 Hz, H-β), 7.48 (1H, dd, *J*=8.5, 1.1 Hz, H-8), 7.48 (2H, m, H-2′ and H-6′), 7.43 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz, H-6), 7.05 (2H, m, H-3′ and H-5′), 6.88 (1H, dd, *J*=16.3, 0.7 Hz, H-α). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.6, 162.4 (d, $^1J_{C\text{-}F}$=248 Hz), 155.8, 153.1, 133.6, 133.5, 130.5, 128.1 (d, $^3J_{C\text{-}F}$=8 Hz), 126.2, 125.3, 124.1, 121.6, 118.8, 118.0, 115.5 (d, $^2J_{C\text{-}F}$=22 Hz). MS-EI *m/z*: 266 $[M]^+$. *Anal*. Calcd for $C_{17}H_{11}FO_2$: C, 76.68; H, 4.16. Found: C, 76.64; H, 4.21.

3-[(1*E*)-2-(4-Chlorophenyl)ethenyl]-4*H*-1-benzopyran-4-one (**11**): Yield 82%. Colorless amorphous. mp 157–158°C (lit.[25] 159–160°C). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.30 (1H, dd, *J*=8.0, 1.7 Hz, H-5), 8.11 (1H, d, *J*=0.8 Hz, H-2), 7.68 (1H, ddd, *J*=8.5, 7.1, 1.7 Hz, H-7), 7.64 (1H, d, *J*=16.3 Hz, H-β), 7.48 (1H, dd, *J*=8.5, 1.1 Hz, H-8), 7.46–7.41 (1H, m, H-6), 7.45 (2H, d, *J*=8.5 Hz, H-2′ and H-6′), 7.32 (2H, d, *J*=8.5 Hz, H-3′ and H-5′), 6.93 (1H, dd, *J*=16.3, 0.8 Hz, H-α). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.5, 155.7, 153.4, 135.9, 133.6, 133.4, 130.4, 128.8, 127.7, 126.2, 125.3, 124.0, 121.4, 119.7, 118.1. MS-EI *m/z*: 282 $[M]^+$. The ^{1}H and ^{13}C-NMR spectra were similar to that previously reported.[25]

3-[(1*E*)-2-(4-Fluorophenyl)ethenyl]-6-methoxy-4*H*-1-benzopyran-4-one (**12**): Yield 86%. Pale yellow amorphous. mp 154–155°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.09 (1H, d, *J*=0.8 Hz, H-2), 7.65 (1H, d, *J*=3.1 Hz, H-5), 7.61 (1H, d, *J*=16.3 Hz, H-β), 7.49 (2H, m, H-2′ and H-6′), 7.41 (1H, d, *J*=9.1 Hz, H-8), 7.27 (1H, dd, *J*=9.1, 3.1 Hz, H-7), 7.05 (2H, m, H-3′ and H-5′), 6.90 (1H, dd, *J*=16.3, 0.8 Hz, H-α), 3.92 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.4, 162.4 (d, $^1J_{C\text{-}F}$=247 Hz), 157.0, 152.9, 150.6, 133.6, 130.3, 128.1 (d, $^3J_{C\text{-}F}$=8 Hz), 124.6, 123.7, 120.8, 119.5, 119.0, 115.5 (d, $^2J_{C\text{-}F}$=22 Hz), 105.1, 55.9. MS-EI *m/z*: 296 $[M]^+$. *Anal*. Calcd for $C_{18}H_{13}FO_3$: C, 72.97; H, 4.42. Found: C, 73.20; H, 4.47.

3-[(1*E*)-2-(4-Chlorophenyl)ethenyl]-6-methoxy-4*H*-1-benzopyran-4-one (**13**): Yield 80%. Pale yellow needles. mp 134–135°C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.10 (1H, d, J=0.8 Hz, H-2), 7.65 (1H, d, J=3.1 Hz, H-5), 7.63 (1H, d, J=16.3 Hz, H-β), 7.45 (2H, d, J=8.5 Hz, H-2′ and H-6′), 7.42 (1H, d, J=9.1 Hz, H-8), 7.33 (2H, d, J=8.5 Hz, H-3′ and H-5′), 7.27 (1H, dd, J=9.1, 3.1 Hz, H-7), 6.95 (1H, dd, J=16.3, 0.8 Hz, H-α), 3.92 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 176.3, 157.1, 153.2, 150.6, 135.9, 133.3, 130.2, 128.8, 127.7, 124.6, 123.7, 120.6, 119.9, 119.5, 105.1, 55.9. MS-EI *m*/*z*: 312 $[M]^+$. *Anal*. Calcd for $C_{18}H_{13}ClO_3$: C, 69.13; H, 4.19. Found: C, 69.31; H, 4.19.

General Procedure for Preparation of 3-Styrylchromones Having the Hydroxyl Group (14–20) According to the general procedure for preparation of (*E*)-3-styryl-4*H*-1-benzopyran-4-one derivative, the corresponding 3-formylchromone (**2**, 2 mmol) and phenylacetic acid (**3a**, **3f** or **3g**, 10 mmol) were treated with *tert*-BuOK (3 mmol) and then the residue was passed once through a short silica gel column (hexane : AcOEt=5 : 1) and the solvent was evaporated. The obtained allyl protected compound (1.0 mmol) was dissolved in degassed anhydrated tetrahydrofuran (THF) (50 mL) and morpholine (10 equiv. per allyl group to be cleaved) was added $Pd(PPh_3)_4$ (5 mol%). The green mixture was stirred at 60°C (monitored by TLC) and concentrated under reduced pressure. The residue was treated with saturated NH_4Cl solution and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt=2 : 1) to give the title compound.

3-[(1*E*)-2-(4-Hydroxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**14**)**:** Yield 30% (2 steps). Ocher amorphous. mp 209–211°C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.63 (1H, br s, OH), 8.64 (1H, d, J=0.7 Hz, H-2), 8.15 (1H, dd, J=8.0, 1.7 Hz, H-5), 7.81 (1H, ddd, J=8.5, 7.1, 1.7 Hz, H-7), 7.68 (1H, dd, J=8.5, 1.0 Hz, H-8), 7.61 (1H, d, J=16.4 Hz, H-β), 7.52 (1H, ddd, J=8.0, 7.1, 1.1 Hz, H-6), 7.37 (2H, d, J=8.6 Hz, H-2′ and H-6′), 6.84 (1H, dd, J=16.4, 0.7 Hz, H-α), 6.78 (2H, d, J=8.6 Hz, H-3′ and H-5′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 176.2, 157.9, 155.7, 154.9, 134.4, 131.2, 128.7, 128.1, 125.9, 125.8, 123.8, 121.4, 118.9, 116.5, 116.1. HR-MS *m*/*z*: Calcd for $C_{17}H_{12}O_3$ (M^+): 264.0786; Found: 264.0774.

3-[(1*E*)-2-(3,4-Dihydroxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**15**): Yield 49% (2 steps). Ocher amorphous. mp 186–188°C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.11 (2H, br s, OH), 8.66 (1H, s, H-2), 8.14 (1H, dd, J=8.0, 1.7 Hz, H-5), 7.82 (1H, ddd, J=8.5, 7.1, 1.7 Hz, H-7), 7.68 (1H, dd, J=8.5, 1.0 Hz, H-8), 7.52 (1H, d, J=16.4 Hz, H-β), 7.52 (1H, m, H-6), 6.95 (1H, d, J=2.0 Hz, H-2′), 6.81 (1H, dd, J=8.1, 2.0 Hz, H-6′), 6.76 (1H, d, J=16.4 Hz, H-α), 6.73 (1H, d, J=8.1 Hz, H-5′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 176.0, 155.7, 154.7, 146.2, 145.9, 134.4, 131.4, 129.2, 125.9, 125.8, 123.8, 121.4, 118.9, 118.8, 116.22, 116.20, 113.4. MS-EI *m*/*z*: 280 $[M]^+$. *Anal*. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.75; H, 4.39.

3-[(1*E*)-2-(4-Hydroxyphenyl)ethenyl]-6-methoxy-4*H*-1-benzopyran-4-one (**16**): Yield 64% (2 steps). Ocher needles. mp 209–211°C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.61 (1H, br s, OH), 8.62 (1H, d, J=0.7 Hz, H-2), 7.65 (1H, d, J=9.1 Hz, H-8), 7.58 (1H, d, J=16.4 Hz, H-β), 7.50 (1H, d, J=3.1 Hz, H-5), 7.41 (1H, dd, J=9.2, 3.1 Hz, H-7), 7.37 (2H, d, J=8.6 Hz, H-2′ and H-6′), 6.84 (1H, dd, J=16.4, 0.7 Hz, H-α), 6.78 (2H, d, J=8.6 Hz, H-3′ and H-5′), 3.88 (3H, s, OMe). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 175.7, 157.8, 157.0, 154.6, 150.5, 131.0, 128.7, 128.1, 124.5, 123.6, 120.6, 120.5, 116.6, 116.1, 105.4, 56.2. MS (EI) *m*/*z*: 294 $[M]^+$. *Anal*. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.27; H, 4.81.

3-[(1*E*)-2-(3,4-Dihydroxyphenyl)ethenyl]-6-methoxy-4*H*-1-benzopyran-4-one (**17**): Yield 55% (2 steps). Ocher amorphous. mp 219–221°C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.10 (2H, br s, OH), 8.64 (1H, s, H-2), 7.65 (1H, d, J=9.1 Hz, H-8), 7.51 (1H, d, J=3.1 Hz, H-5), 7.50 (1H, d, J=16.4 Hz, H-β), 7.41 (1H, dd, J=9.1, 3.1 Hz, H-7), 6.95 (1H, d, J=2.0 Hz, H-2′), 6.80 (1H, m, H-6′), 6.77 (1H, d, J=16.4 Hz, H-α), 6.74 (1H, m, H-5′), 3.88 (3H, s, OMe). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 175.7, 157.0, 154.5, 150.5, 146.2, 145.9, 131.2, 129.3, 124.4, 123.6, 120.6, 120.5, 118.9, 116.3, 116.2, 113.3, 105.4, 56.2. MS-EI *m*/*z*: 310 $[M]^+$. *Anal*. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.60; H, 4.65.

6-Hydroxy-3-[(1*E*)-2-(4-methoxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**18**): Yield 53% (2 steps). Colorless amorphous. mp 236–237°C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.06 (1H, br s, OH), 8.59 (1H, d, J=0.7 Hz, H-2), 7.65 (1H, d, J=16.4 Hz, H-β), 7.55 (1H, d, J=9.0 Hz, H-8), 7.41 (1H, d, J=3.0 Hz, H-5), 7.48 (2H, d, J=8.7 Hz, H-2′ and H-6′), 7.24 (1H, dd, J=9.0, 3.0 Hz, H-7), 6.90 (1H, dd, J=16.4, 0.7 Hz, H-α), 6.96 (2H, d, J=8.7 Hz, H-3′ and H-5′), 3.78 (3H, s, OMe). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 175.8, 159.4, 155.3, 155.0, 149.5, 130.40, 130.37, 127.9, 124.7, 123.5, 120.2, 120.1, 118.0, 114.7, 108.2, 55.6. MS (EI) *m*/*z*: 294 $[M]^+$. *Anal*. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.22; H, 4.83.

6-Hydroxy-3-[(1*E*)-2-(4-hydroxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**19**): Yield 41% (2 steps). Ocher amorphous. mp 293–295°C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 10.00 (1H, br s, OH), 9.63 (1H, br s, OH), 8.57 (1H, d, J=0.7 Hz, H-2), 7.58 (1H, d, J=16.4 Hz, H-β), 7.54 (1H, d, J=9.0 Hz, H-8), 7.40 (1H, d, J=3.0 Hz, H-5), 7.36 (2H, d, J=8.6 Hz, H-2′ and H-6′), 7.23 (1H, dd, J=9.0, 3.0 Hz, H-7), 6.82 (1H, dd, J=16.4, 0.7 Hz, H-α), 6.77 (2H, d, J=8.6 Hz, H-3′ and H-5′). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 175.8, 157.8, 155.3, 154.7, 149.5, 130.8, 128.8, 128.0, 124.7, 123.4, 120.3, 120.2, 116.8, 116.1, 108.2. MS (EI) *m*/*z*: 280 $[M]^+$. *Anal*. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.66; H, 4.45.

6-Hydroxy-3-[(1*E*)-2-(3,4-dihydroxyphenyl)ethenyl]-4*H*-1-benzopyran-4-one (**20**): Yield 36% (2 steps). Brown solid. mp 258–260°C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 9.90 (1H, br s, OH), 9.18 (2H, br s, OH), 8.59 (1H, d, J=0.8 Hz, H-2), 7.54 (1H, d, J=9.0 Hz, H-8), 7.49 (1H, d, J=16.4 Hz, H-β), 7.40 (1H, d, J=3.0 Hz, H-5), 7.23 (1H, dd, J=9.0, 3.0 Hz, H-7), 6.94 (1H, d, J=2.0 Hz, H-2′), 6.79 (1H, dd, J=8.1, 2.0 Hz, H-6′), 6.74 (1H, dd, J=16.4, 0.8 Hz, H-α), 6.73 (1H, d, J=8.1, H-5′), 3.88 (3H, s, OMe). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 175.8, 155.3, 154.6, 149.5, 146.1, 145.9, 131.0, 129.4, 124.7, 123.4, 120.3, 120.2, 118.8, 116.6, 116.2, 113.3, 108.2. HR-MS *m*/*z*: Calcd for $C_{17}H_{12}O_5$ (M^+): 296.0685. Found: 296.0672.

Biological Assay α-Glucosidase from *Saccharomyces cerevisiae* and 4-nitrophenyl α-D-glucopyranoside (PNP-G) were purchased from Sigma Chemical Co., St. Louis, MO, U.S.A. DPPH radical was purchased from Tokyo Chemical Industry Co., Tokyo, Japan.

DPPH Radical Scavenging Assay DPPH radical scavenging activity was measured according to the method of Nile

et al.[35] with minor modifications. Briefly, 180 μL of 100 μM DPPH solution in MeOH was mixed with 20 μL of various concentrations of the sample solution in MeOH. The absorbance of the mixture was measured at 517 nm using a micro-plate reader (Molecular Devices SPECTRA MAX 190). The sample solution was replaced by MeOH as a control. Ascorbic acid was used as a positive control.

α-Glucosidase Inhibitory Assay α-Glucosidase inhibitory activity was assayed using the method of Mabkhot *et al.*[36] with minor modifications. Briefly, 210 μL of 50 mM phosphate buffer (pH 7.0) containing 100 mM NaCl, 30 μL of 0.25 U/mL α-glucosidase dissolved in the buffer, 30 μL of 7 mM PNP-G as a substrate dissolved in the buffer, and 30 μL of various concentrations of samples dissolved in dimethyl sulfoxide (DMSO) were mixed and the increment in absorption at 400 nm, due to the hydrolysis of PNP-G by α-glucosidase, was monitored continuously with a micro-plate reader (Molecular Devices SPECTRA MAX 190). The sample solution was replaced by DMSO as a control. Acarbose was used as a positive control.

References

1) Puls W., Keup U., Krause H. P., Thomas G., Hoffmeister F., *Naturwissenschaften*, **64**, 536–537 (1977).
2) Rice-Evans C. A., Miller N. J., Bolwell P. G., Bramley P. M., Pridham J. B., *Free Radic. Res.*, **22**, 375–383 (1995).
3) Luiz M., Biasutti A., Garcia N. A., *Redox Rep.*, **7**, 23–28 (2002).
4) Baynes J. W., Thorpe S. R., *Diabetes*, **48**, 1–9 (1999).
5) Nimal Christhudas I. V. S., Praveen Kumar P., Agastian P., *Curr. Microbiol.*, **67**, 69–76 (2013).
6) Kim J.-S., Kwon Y.-S., Sa Y.-J., Kim M.-J., *J. Agric. Food Chem.*, **59**, 138–144 (2011).
7) Kumar G. S., Tiwari A. K., Rao V. R., Prasad K. R., Ali A. Z., Babu K. S., *J. Asian Nat. Prod. Res.*, **12**, 978–984 (2010).
8) Raju B. C., Tiwari A. K., Kumar J. A., Ali A. Z., Agawane S. B., Saidachary G., Madhusudana K., *Bioorg. Med. Chem.*, **18**, 358–365 (2010).
9) Ranga Rao R., Tiwari A. K., Prabhakar Reddy P., Suresh Babu K., Ali A. Z., Madhusudana K., Madhusudana Rao J., *Bioorg. Med. Chem.*, **17**, 5170–5175 (2009).
10) Yao Y., Sang W., Zhou M., Ren G., *J. Agric. Food Chem.*, **58**, 770–774 (2010).
11) Ansari F. L., Umbreen S., Hussain L., Makhmoor T., Nawaz S. A., Lodhi M. A., Khan S. N., Shaheen F., Choudhary M. I., Atta-ur-Rahman, *Chem. Biodivers.*, **2**, 487–496 (2005).
12) Filipe P., Silva A. M. S., Morliere P., Brito C. M., Patterson L. K., Hug G. L., Silva J. N., Cavaleiro J. A. S., Maziere J. C., Freitas J. P., Santus R., *Biochem. Pharmacol.*, **67**, 2207–2218 (2004).
13) Gomes A., Fernandes E., Silva A. M. S., Santos C. M. M., Pinto D. C. G. A., Cavaleiro J. A. S., Lima J. L. F. C., *Bioorg. Med. Chem.*, **15**, 6027–6036 (2007).
14) Doria G., Romeo C., Forgione A., Sberze P., Tibolla N., Corno M. L., Cruzzola G., Cadelli G., *Eur. J. Med. Chem.*, **14**, 347–351 (1979).
15) Gomes A., Fernandes E., Silva A. M. S., Pinto D. C. G. A., Santos C. M. M., Cavaleiro J. A. S., Lima J. L. F. C., *Biochem. Pharmacol.*, **78**, 171–177 (2009).
16) Momoi K., Sugita Y., Ishihara M., Satoh K., Kikuchi H., Hashimoto K., Yokoe I., Nishikawa H., Fujisawa S., Sakagami H., *In Vivo*, **19**, 157–163 (2005).
17) Marinho J., Pedro M., Pinto D. C. G. A., Silva A. M. S., Cavaleiro J. A. S., Sunkel C. E., Nascimento M. S. J., *Biochem. Pharmacol.*, **75**, 826–835 (2008).
18) Shaw A. Y., Chang C. Y., Liau H. H., Lu P. J., Chen H. L., Yang C. N., Li H. Y., *Eur. J. Med. Chem.*, **44**, 2552–2562 (2009).
19) Desideri N., Conti C., Mastromarino P., Mastropaolo F., *Antivir. Chem. Chemother.*, **11**, 373–381 (2000).
20) Desideri N., Mastromarino P., Conti C., *Antivir. Chem. Chemother.*, **14**, 195–203 (2003).
21) Conti C., Mastromarino P., Goldoni P., Portalone G., Desideri N., *Antivir. Chem. Chemother.*, **16**, 267–276 (2005).
22) Conti C., Desideri N., *Bioorg. Med. Chem.*, **18**, 6480–6488 (2010).
23) Silva V. L. M., Silva A. M. S., Pinto D. C. G. A., Cavaleiro J. A. S., Vasas A., Patonay T., *Monatsh. Chem.*, **139**, 1307–1315 (2008).
24) Dang A.-T., Miller D. O., Dawe L. N., Bodwell G. J., *Org. Lett.*, **10**, 233–236 (2008).
25) Sandulache A., Silva A. M. S., Pinto D. C. G. A., Almeida L. M. P. M., Cavaleiro J. A. S., *New J. Chem.*, **27**, 1592–1598 (2003).
26) Silva V. L. M., Silva A. M. S., Pinto D. C. G. A., Cavaleiro J. A. S., Patonay T., *Synlett*, **2004**, 2717–2720 (2004).
27) Silva A. M. S., Pinto D. C. G. A., Cavaleiro J. A. S., Levai A., Patonay T., *ARKIVOC*, **2004**, 106–123 (2004).
28) Sonawane S. A., Chavan V. P., Shingare M. S., Karale B. K., *Indian J. Heterocycl. Chem.*, **12**, 65–66 (2002).
29) Harnisch H., *Justus Liebigs Ann. Chem.*, **765**, 8–14 (1973).
30) Nohara A., Umetani T., Sanno Y., *Tetrahedron*, **30**, 3553–3561 (1974).
31) Pietta P.-G., *J. Nat. Prod.*, **63**, 1035–1042 (2000).
32) Gomes A., Fernandes E., Garcia M. B. Q., Silva A. M. S., Pinto D. C. G. A., Santos C. M. M., Cavaleiro J. A. S., Lima J. L. F. C., *Bioorg. Med. Chem.*, **16**, 7939–7943 (2008).
33) Yoshikawa M., Shimada H., Nishida N., Li Y., Toguchida I., Yamahara J., Matsuda H., *Chem. Pharm. Bull.*, **46**, 113–119 (1998).
34) Wu H.-P., Lu T.-N., Hsu N.-Y., Chang C.-C., *Eur. J. Org. Chem.*, **2013**, 2898–2905 (2013).
35) Nile S. H., Kim S. H., Ko E. Y., Park S.W., *Biomed. Res. Int.*, **2013**, ID 718065 (2013).
36) Mabkhot Y. N., Barakat A., Al-Majid A. M., Alshahrani S., Yousuf S., Choudhary M. I., *Chem. Cent. J.*, **7**, 112 (2013).