Synthesis and Evaluation of the Cytotoxicities of Neoflavenes

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The synthesis of neoflavene and neoflavenes with methoxy substituents at different positions are described. As starting materials, various salicylaldehydes were run through sequential reactions such as *O*-allylation, Grignard reaction, oxidation, Wittig reaction, and ring-closing metathesis to yield the target neoflavenes in good yield. Among the prepared neoflavenes, 7-methoxy-4′-methoxyneoflavene (**6e**) and 8-methoxy-4′-methoxyneoflavene (**6f**) exhibiting potential cell toxicities against various cells were disclosed. In particular, **6f** which exhibited an IC_{50} value of 6.5 ± 2.0 and 5.1 ± 1.1 μM against gastric carcinoma and lung carcinoma cells *in vitro* was found, respectively. Meanwhile, the structure and activity relationship of our synthesized neoflavenes is further discussed briefly.

Keywords: Neoflavenes; Ring-closing metathesis; Cytotoxicities.

INTRODUCTION

Neoflavenes, which chemically belong to 4-phenyl-2*H*-chromenes or 4-phenyl-2*H*-1-benzopyrans, were originally isolated from natural sources[1] and were only paid little attention about their biological activities in current research.[2] Moreover, even some strategies for the syntheses of neoflavenes have been developed,[3-7] but their drawbacks include tedious reaction conditions, low yield, and commercially unavailable starting materials. Since the Grubbs' catalyst was discovered in 1995, the ring-closing metathesis (RCM) has been widely employed in various aspects in organic synthesis.[8] In particular, some heterocyclic compounds which were difficult to prepare, can be synthesized by RCM.

Furthermore, before our previous study,[9] the synthesis of neoflavenes which utilized RCM, has never been reported in current literature reports. In this our extended study, we would like to report a brief, efficient, and straightforward synthetic approach to the neoflavene skeleton and neoflavenes with methoxy substituents at various positions from commercially available salicylaldehydes. Our synthetic strategy is depicted in Scheme I. In addition, the cytotoxic activities of the prepared neoflavenes against various cells such as human esophageal carcinoma cells, cervical carcinoma cells, etc., are also investigated (Table 1).

RESULTS AND DISCUSSION

As in the general procedure, a mixture of salicylaldehydes (**1**) and allyl bromide in acetonitrile in the presence of K_2CO_3 was heated to reflux to give 1-allyloxybenzaldehydes (**2a-g**) in 95-98% yields. Subsequently, **2a-g** were respectively reacted with arylmagnesium chloride to give (2-allyloxyphenyl)arylmethanol **3a-g** in 91-96% yields. Compound **3a** was used as a model for the oxidation under various conditions, such as Dess-Martin oxidation,[10] Swern oxidation,[11] and MnO_2 to give **4a** in 89%, 92% and 90% yield, respectively. For the reason of easy handling and economic concerns, MnO_2 was chosen for oxidizing **3a-g** to give compounds **4a-g** in 90-96% yields. Then, compounds **4** were reacted with methylenetriphenylphosphane which had been generated from methyltriphenylphosphonium bromide and potassium *tert*-butoxide *in situ*, to undergo the Wittig reaction to give dienes **5a-g** in 92-98%

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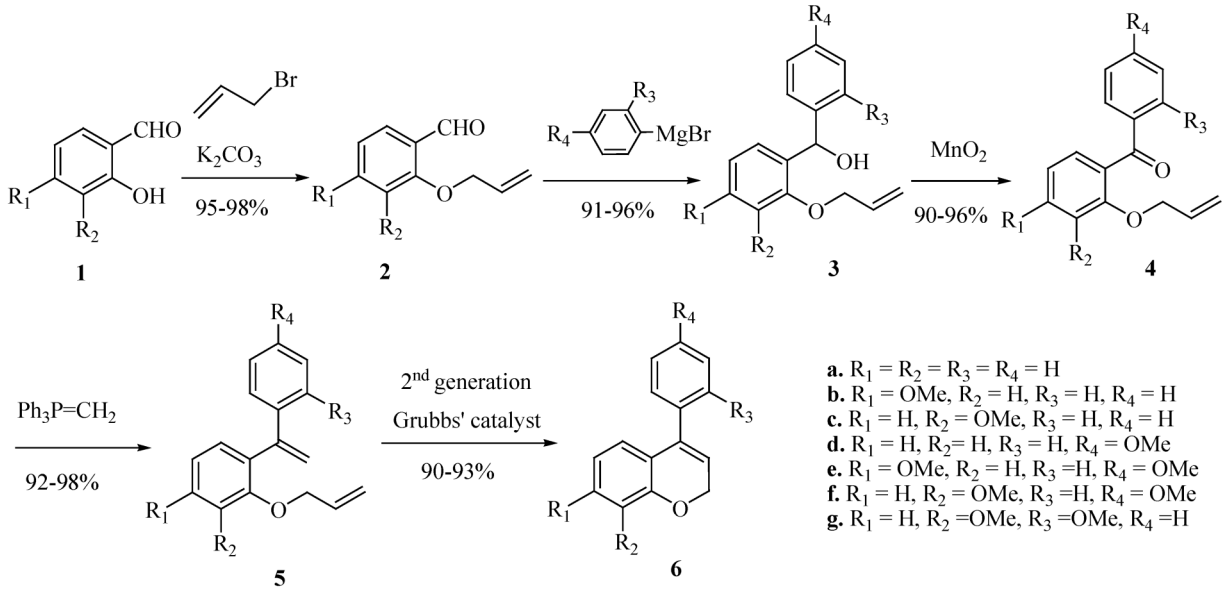
Scheme I Synthetic strategy of neoflavenes from salicylaldehydes



yields. Subsequently, the dienes which were obtained were respectively subjected to RCM using Grubbs' catalyst (II) to produce the desired neoflavenes (**6a-g**) in 90-93% yields. The structure elucidation of neoflavenes (**6a-g**) was confirmed by spectral data such as ^{1}H-NMR, ^{13}C-NMR, EI-MS, and HRMS. Furthermore, the cytotoxicity studies of the prepared neoflavenes were investigated and depicted as follows. Eight cell lines including human esophageal carcinoma (CE81T), cervical carcinoma (Hela), oral squamous carcinoma (SAS), gastric carcinoma (AGS), lung carcinoma (A549), renal cell carcinoma (786-O), hepatocellular carcinoma (SKHep) and prostate cancer (PC3) were used for cytotoxicity screening *in vitro*. The IC_{50} results are summarized in Table 1.

As shown in Table 1, two of the prepared compounds **6e** and **6f** exhibited inhibitory effects on various cells and had significant activity in human esophageal carcinoma (CE81T), cervical carcinoma (Hela), oral squamous carcinoma (SAS), gastric carcinoma (AGS), lung carcinoma (A549), hepatocellular carcinoma (SKHep) and prostate cancer (PC3). Conversely, compound **6a-d**, and **6g** did not have conspicuous signals in this test. In the present studies, regarding the activity against individual cell lines, compound **6f** exhibited the highest cytotoxic activity among our synthesized neoflavenes. The IC_{50} (μM) of **6f** toward CE81T, Hela, SAS, AGS, A549, RCC 786-O SKHep and PC3 are 10.8 ± 1.6, 10.7 ± 4.2, 13.2 ± 4.3, 6.5 ± 2.0, 5.1 ± 1.1, 10.6 ± 2.2, 9.9 ± 2.0, and 15.4 ± 5.4, respectively. Compared to **6f**, the second potent compound was compound **6e** which showed similar cytotoxicities in seven examined

Table 1. The cytotoxicities of neoflavene analogues

Cell lines / Compds	CE 81T IC_{50} (μM)	Hela IC_{50} (μM)	SAS IC_{50} (μM)	AGS IC_{50} (μM)	A549 IC_{50} (μM)	RCC 786-O IC_{50} (μM)	SKHep IC_{50} (μM)	PC-3 IC_{50} (μM)
6a	ND	ND	ND	ND	ND	ND	ND	ND
6b	ND	ND	ND	15.9 ± 4.2	ND	ND	ND	ND
6c	ND	ND	ND	ND	ND	ND	ND	ND
6d	ND	ND	ND	ND	12.4 ± 0.7	ND	ND	ND
6e	9.8 ± 1.8	11.0 ± 3.6	13.2 ± 1.6	9.1 ± 2.7	8.9 ± 0.8	ND	9.6 ± 1.7	15.8 ± 3.9
6f	10.8 ± 1.6	10.7 ± 4.2	13.2 ± 4.3	6.5 ± 2.0	5.1 ± 1.1	10.6 ± 2.2	9.9 ± 2.0	15.4 ± 5.4
6g	ND	ND	ND	ND	25.5 ± 3.8	ND	ND	ND

* ND: Not Detected

cancer cell lines, but no cytotoxicity to the renal carcinoma RCC786-O cells.

CONCLUSION

Mainly based on RCM, neoflavene and neoflavenes with methoxy substituents at different positions were synthesized. The prepared neoflavenes **6a**, **6b**, **6c**, and **6g**, which all have no methoxy group at the 4′-position in the structure, exhibited almost no cytotoxicity to the examined cancer cell lines. The neoflavene derivative **6d**, which has a 4′-methoxy group but no methoxy group at the 7-position, or 8-position, showed cytotoxicity to A549 but no cytotoxicity to the other cancer cell lines examined. Thus, the basic requirement for common cyctoxic activities must have a methoxy group at the 4′-position on the structure of neoflavenes (**6e-f**). In addition, the methoxy group presented at 8- and 7-positions (compound **6f**, **6e**) enhanced the cytotoxic activities, respectively.

EXPERIMENTAL

Melting points (Yanaco micro melting-point apparatus) were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Gemini-200 or Varian Unity plus 400 Spectrometer. Chemical shifts are indicated in parts per million with respect to TMS. Elemental analyses were recorded on a Heraeus CHN-O rapid analyzer. Mass spectra were recorded on a Chem/hp/middle spectrometer connected to a Hewlett Packard series II model gas-liquid chromatograph. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230-400 mesh) for column chromatography and precoated silica gel plates (60 F-254) for TLC were purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

General procedure for the preparation of 2-allyloxybenzaldehydes (2a-c)

As a general procedure, the solution of 2-hydroxybenzaldehyde (**1a-c**) (100 mmol) in dry acetonitrile (80 mL) was stirred and anhydrous K_2CO_3 (16.59 g, 120 mmol), allyl bromide (14.52 g, 120 mmol) in sequence were added, under dry nitrogen. The reaction mixture which was obtained was heated to reflux for 4 hr. Work-up as in the usual procedure, and purified by silica-gel column chromatography with ethyl acetate/*n*-hexane (1/15) as eluent, to yield pure **2a-c**, respectively.

2-Allyloxybenzaldehyde (2a)[12]

(15.40 g, 95%) was obtained as colorless liquid, R_f = 0.16 (ethyl acetate: *n*-hexane = 1: 15), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.65 (dt, *J* = 5.2 Hz, 1.2 Hz, 2H, $OC\underline{H}_2CH{=}CH_2$), 5.34 (ddt, *J* = 10.4 Hz, 1.2 Hz, 1.2 Hz, 1H, $OCH_2CH{=}C\underline{H}_aH_b$), 5.45 (ddt, *J* = 17.2 Hz, 1.2 Hz, 1.2 Hz, 1H, $OCH_2CH{=}CH_a\underline{H}_b$), 6.01 (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.2 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 6.97 (dd, *J* = 8.8 Hz, 0.8 Hz, 1H, ArH), 7.02 (td, *J* = 8.8 Hz, 0.8 Hz, 1H, ArH), 7.52 (td, *J* = 7.6 Hz, 1.6 Hz, 1H, ArH), 7.83 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H, ArH), 10.53 (s, 1H, CHO); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 69.04, 112.76, 117.93, 120.73, 124.96, 128.27, 132.28, 135.75, 160.83, 189.62; EI-MS (70 eV) *m/z* (rel. intensity, %) 163 ($[M+1]^+$, 100), 162 (M^+, 24), 161 (54), 133 (24), 121 (76), 120 (19), 105 (18), 92 (26); HRMS calcd for $C_{10}H_{10}O_2$: 162.0681. Found: 162.0680.

2-Allyloxy-4-methoxybenzaldehyde (2b)[13]

(18.24 g, 95%) was obtained as colorless crystal, mp 37-38 °C, R_f = 0.33 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H, OCH_3), 4.62 (dt, *J* = 5.2, 1.4 Hz, 2H, $OC\underline{H}_2CH{=}CH_2$), 5.33 (dd, *J* = 10.6, 1.4 Hz, 1H, $OCH_2CH{=}C\underline{H}_2$), 5.45 (dd, *J* = 17.4, 1.2 Hz, 1H, $OCH_2CH{=}C\underline{H}_2$), 6.04 (ddt, *J* = 17.4, 10.6, 5.2 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 6.43 (d, *J* = 2.0 Hz, 1H, ArH), 6.54 (dd, *J* = 8.8, 2.0 Hz, 1H, ArH), 7.81 (d, *J* = 8.8 Hz, 1H, ArH), 10.35 (s, 1H, $C\underline{H}O$); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.56, 69.11, 98.97, 106.00, 118.06, 119.20, 130.44, 132.23, 162.62, 165.99, 188.24; EI-MS (70 eV) *m/z* (rel. intensity, %) 193 ($[M+1]^+$, 30), 192 (M^+, 35), 164 (28), 163 (54), 151 (100), 150 (91), 135 (45), 122 (27) , 95 (28); HRMS calcd for $C_{11}H_{12}O_3$: 192.0786. Found: 192.0784.

2-Allyloxy-3-methoxybenzaldehyde (2c)[14]

(18.82 g, 98%) was obtained as colorless liquid, R_f = 0.26 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.86 (s, 3H, OCH_3), 4.62 (dt, *J* = 6, 1.2 Hz, 2H, $OC\underline{H}_2CH{=}CH_2$), 5.33 (dd, *J* = 10.2, 1.2 Hz, 1H, $OCH_2CH{=}C\underline{H}_2$), 5.45 (dd, *J* = 17.4, 1.2 Hz, 1H, $OCH_2CH{=}C\underline{H}_2$), 6.04 (ddt, *J* = 17.4, 10.2, 6 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 7.10 (m, 2H, ArH), 7.37 (dd, *J* = 6.2 ,3.2 Hz, 1H, ArH), 10.41 (s, 1H, CHO); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.89, 75.03, 113.34, 117.87, 118.86, 123.99, 129.97, 133.01, 151.05, 152.85, 190.18; EI-MS (70 eV) *m/z* (rel. intensity, %) 193 ($[M+1]^+$, 100), 192 (M^+, 54), 175 (17), 166 (20), 164 (29), 163 (55), 151 (83), 136 (17), 131 (20), 122 (20); HRMS calcd for $C_{11}H_{12}O_3$: 192.0781. Found: 192.0783.

General procedure for the preparation of (2-allyloxyphenyl)aryl methanol (3a-g)

To a stirred solution of 1-allyloxybenzaldehyde (**2**) (30 mmol) in THF (100 mL) was added phenyl-magnesium

chloride (2.0 M in THF) (36 mmol) in drops. And then the reaction mixture was continually stirred for 2 hr at room temperature. The resulting solution was concentrated *in vacuo*, and the residue which was obtained was purified by column chromatography on silica gel (ethyl acetate: *n*-hexane = 1: 15) to give pure **3a-g**.

(2-Allyloxyphenyl)phenylmethanol (3a)

(6.62 g, 92%) was obtained as colorless crystals, mp 50-51 °C, R_f = 0.10 (ethyl acetate: *n*-hexane = 1: 15), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.30 (br d, *J* = 5.6 Hz, 1H, O<u>H</u>), 4.49 (dt, *J* = 5.2 Hz, 1.2 Hz, 2H, OC<u>H</u>$_2$CH=CH$_2$), 5.12 (ddt, *J* = 10.4 Hz, 1.2 Hz, 1.2 Hz, 1H, OCH$_2$CH=C<u>H</u>$_a$H$_b$), 5.28 (ddt, *J* = 17.2 Hz, 1.2 Hz, 1.2 Hz, 1H, OCH$_2$CH=CH$_a$<u>H</u>$_b$), 5.92 (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.2 Hz, 1H, OCH$_2$C<u>H</u>=CH$_2$), 6.07 (d, *J* = 5.6 Hz, 1H, ArC<u>H</u>(OH)Ph), 6.84 (d, *J* = 8.4 Hz, 1H, Ar<u>H</u>), 6.93 (d, *J* = 7.4 Hz, 1H, ArH), 7.18-7.48 (m, 7H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 69.00, 72.28, 112.11, 117.54, 120.99, 126.50, 127.07, 127.86, 128.07, 128.55, 132.44, 132.91, 143.44, 155.68; EI-MS (70 eV) *m/z* (rel. intensity, %) 240 (M^+, 12), 200 (13), 199 (100), 197 (10), 194 (10), 182 (13), 181 (83), 153 (13), 152 (27), 121 (90), 107 (11), 105 (30), 77 (37); HRMS calcd for $C_{16}H_{16}O_2$: 240.1145. Found: 240.1147.

(2-Allyloxy-4-methoxyphenyl)phenylmethanol (3b)

(7.73 g, 95%) was obtained as colorless liquids, R_f = 0.08 (ethyl acetate: *n*-hexane = 1: 19), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.10 (br d, *J* = 3.6 Hz, 1H, O<u>H</u>), 3.73 (s, 3H, OCH_3), 4.44 (dt, *J* = 5.2, 1.4 Hz, 2H, OC<u>H</u>$_2$CH=CH$_2$), 5.21 (ddt, *J* = 10.2, 1.4, 1.4 Hz, 1H, OCH$_2$CH=C<u>H</u>$_a$H$_b$), 5.29 (ddt, *J* = 17.2, 1.4, 1.4 Hz, 1H, OCH$_2$CH=CH$_a$<u>H</u>$_b$), 5.91 (ddt, *J* = 17.2, 10.2, 5.2 Hz, 1H, OCH$_2$C<u>H</u>=CCH$_a$H$_b$), 5.99 (d, *J* = 5.6 Hz, 1H, ArC<u>H</u>(OH)Ph), 6.41 (s, 1H, ArH), 6.42 (m, 1H, ArH), 7.22 (m, 6H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 55.21, 68.79, 71.54, 99.80, 104.38, 117.47, 125.03, 126.32, 126.83, 127.93, 128.38, 132.66, 143.59, 156.47, 160.01; EI-MS (70 eV) *m/z* (rel. intensity, %) 271 ([M+1]$^+$, 3), 270 (M^+, 12), 229 (35), 227 (12), 211 (43), 168 (15), 165 (53), 164 (100), 152 (25), 151 (56), 137 (22), 106 (37), 77 (15); HRMS calcd for $C_{17}H_{18}O_3$: 270.1250. Found: 270.1253.

2-Allyloxy-3-methoxy-phenyl)phenylmethanol (3c)

(7.81 g, 96%) was obtained as colorless liquids, R_f = 0.27 (ethy lacetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.16 (br d, *J* = 4.6 Hz, 1H, O<u>H</u>), 3.80 (s, 3H, OCH_3), 4.21 (ddt, *J* = 11.8, 5.8, 1.2 Hz, 1H, OC<u>H</u>$_a$H$_b$CH=CH$_2$), 4.35 (ddt, *J* = 11.8, 5.8, 1.2 Hz, 1H, OCH$_a$<u>H</u>$_b$CH=CH$_2$), 5.15 (dd, *J* = 10.2, 1.2 Hz, 1H, OCH$_2$CH=C<u>H</u>$_{cis\text{-}gem}$H), 5.22 (dd, *J* = 17.2, 1.2 Hz, 1H, OCH$_2$CH=CH<u>H</u>$_{trans\text{-}gem}$), 5.89 (ddt, *J* = 17.2, 10.2, 5.8 Hz, 1H, OCH$_2$C<u>H</u>=CH$_2$), 6.03 (d, *J* = 4.6 Hz, 1H, ArC<u>H</u>(OH)Ph), 6.83 (dd, *J* = 7.8, 1.8 Hz, 1Hz, ArH), 6.99 (m, 2H, ArH), 7.28 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 55.63, 71.99, 73.46, 111.75, 117.50, 119.67, 123.91, 126.31, 127.01, 128.02, 133.89, 137.62, 143.74, 144.99, 152.45; EI-MS (70 eV) *m/z* (rel. intensity, %) 271 ([M+1]$^+$, 3), 270 (M^+, 14), 251 (18), 229 (52), 212 (39), 211 (100), 170 (23), 196 (83), 152 (18), 151 (21), 141 (49), 115 (17), 105 (30), 77 (25); HRMS calcd for $C_{17}H_{18}O_3$: 270.1250. Found: 270.1253.

(2′-Allyloxyphenyl)-(4″-methoxyphenyl)methanol (3d)

(7.77 g, 96%) was obtained as colorless liquids, R_f = 0.30 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.19 (br d, *J* = 5.2 Hz, 1H, OH), 3.71 (s, 3H, OCH_3), 4.44 (dt, *J* = 5.2 Hz, 1.6 Hz, 2H, OC<u>H</u>$_2$CH=CH$_a$H$_b$), 5.18 (ddt, *J* = 10.4 Hz, 1.6 Hz, 1.6 Hz, 1H, OCH$_2$CH=CC<u>H</u>$_a$H$_b$), 5.28 (ddt, *J* = 17.2 Hz, 1.6 Hz, 1.6 Hz, 1H, OCH$_2$CH=CH$_a$<u>H</u>$_b$), 5.91 (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.2 Hz, 1H, OCH$_2$C<u>H</u>=CH$_2$), 6.00 (d, *J* = 5.2 Hz, 1H, ArC<u>H</u>(OH)Ph), 6.80 (d, *J* = 8.8 Hz, 2H, ArH), 6.80 (dd, *J* = 7.6, 1.2 Hz, 1H, ArH), 6.92 (td, *J* = 7.2, 1.2 Hz, 1H, ArH), 7.18 (ddd, *J* = 7.6, 7.2, 1.6 Hz, 1H, ArH), 7.26 (d, *J* = 8.8 Hz, 2H, ArH), 7.30 (dd, *J* = 7.2, 1.6 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.01, 68.66, 71.36, 111.74, 113.33, 117.31, 120.76, 127.32, 127.69, 128.24, 132.46, 132.84, 135.55, 155.31, 158.50; EI-MS (70 eV) *m/z* (rel. intensity, %) 270 (M^+, 1), 230 (16), 229 ([M-41]$^+$, 100), 224 (18), 211 (19), 168 (13), 135 (26), 122 (24), 121 (79); ESI-HRMS calcd for $C_{17}H_{18}O_3Na$ [M+Na]$^+$: 293.1154. Found: 293.1155.

(2′-Allyloxy-4′-methoxyphenyl)-(4″-methoxyphenyl)-methanol (3e)

(8.54 g, 95%) was obtained as colorless crystal, mp 46-47 °C, R_f = 0.14 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.95 (br d, *J* = 4.0 Hz, 1H, OH), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.48 (dt, *J* = 5.2, 1.6 Hz, 2H, OC<u>H</u>$_2$CH=CH$_2$), 5.24 (ddt, *J* = 10.4, 1.6, 1.6 Hz, 1H, OCH$_2$CH=CC<u>H</u>$_a$H$_b$), 5.31 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H, OCH$_2$CH=CH$_a$<u>H</u>$_b$), 5.94 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H, OCH$_2$-C<u>H</u>=CH$_2$), 5.86 (br d, *J* = 4.0 Hz, 1H, ArC<u>H</u>(OH)Ph), 6.43 (d, *J* = 2.4 Hz, 1H, ArH), 6.45 (dd, *J* = 8.0, 2.4 Hz, 1H, ArH), 6.84 (d, *J* = 8.8 Hz, 2H, ArH), 7.13 (d, *J* = 8.0 Hz, 1H, ArH), 7.28 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.16, 55.28, 68.83, 71.32, 99.82, 104.32, 113.41, 117.58, 125.23, 127.66, 128.27, 132.73, 135.77, 156.53, 158.56, 160.03; EI-MS (70 eV) *m/z* (rel. intensity, %) 300 (M^+, 25), 259 (94), 241 (23), 198

(16), 191 (23), 164 (22), 152 (30), 151 (100), 137 (26), 135 (55); ESI-HRMS calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$: 323.1259. Found: 323.1256.

(2′-Allyloxy-3′-methoxyphenyl)-(4″-methoxyphenyl)-methanol (3f)

(8.36 g, 93%) was obtained as colorless liquid, R_f = 0.17 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.02 (br s, 1H, OH), 3.76 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.27 (ddt, *J* = 12.0, 5.6, 1.6 Hz, 1H, $OC\underline{H}_aH_bCH{=}CH_2$), 4.33 (ddt, *J* = 12.0, 5.6, 1.6 Hz, 1H, $OCH_a\underline{H}_bCH{=}CH_2$), 5.16 (ddt, *J* = 10.4, 1.6, 1.6 Hz, 1H, $OCH_2CH{=}C\underline{H}_aH_b$), 5.25 (ddt, *J* = 17.2, 1.6, 1.6 Hz, 1H, $OCH_2CH{=}CH_a\underline{H}_b$), 5.92 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 6.00 (br s, 1H, $ArC\underline{H}(OH)Ph$), 6.83 (d, *J* = 8.4 Hz, 2H, ArH), 6.84 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 6.96 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH) 7.04 (t, *J* = 8.0 Hz, 1H, ArH), 7.27 (d, *J* = 8.4 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.15, 55.64, 71.61, 73.46, 111.60, 113.46, 117.53, 119.44, 123.97, 127.67, 133.97, 135.97, 137.83, 144.91, 152.50, 158.66; EI-MS (70 eV) *m/z* (rel. intensity, %) 300 (M^+, 1), 284 (14), 283 ($[M-17]^+$, 100), 282 (8), 260 (6), 242 (6), 151 (7); ESI-HRMS calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$: 323.1259. Found: 323.1261.

(2′-Allyloxy-3′-methoxyphenyl)-(2″-methoxyphenyl)-methanol (3g)

(8.17 g, 91%) was obtained as colorless crystal, mp 121-122 °C, R_f = 0.20 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.22 (d, *J* = 4.8 Hz, 1H, OH), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.07 (ddt, *J* = 12.4, 5.6, 1.2 Hz, 1H, $OC\underline{H}_aH_bCH{=}CH_2$), 4.50 (ddt, *J* = 12.4, 5.6, 1.2 Hz, 1H, $OCH_a\underline{H}_bCH{=}CH_2$), 5.16 (ddt, *J* = 10.4, 1.6, 1.2 Hz, 1H, $OCH_2CH{=}C\underline{H}_{cis\text{-}gem}H$), 5.27 (ddt, *J* = 17.2, 1.6, 1.2 Hz, 1H, $OCH_2CH{=}CH\underline{H}_{trans\text{-}gem}$), 5.99 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 6.42 (d, *J* = 4.8 Hz, 1H, $ArC\underline{H}(OH)Ph$), 6.83-6.93 (m, 4H, ArH), 7.02 (t, *J* = 7.6 Hz, 1H, ArH), 7.21-7.25 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.27, 55.67, 66.79, 73.59, 110.36, 111.49, 117.17, 119.64, 120.47, 123.71, 127.74, 128.42, 131.32, 134.25, 136.88, 145.24, 152.38, 156.65; EI-MS (70 eV) *m/z* (rel. intensity, %) 301 ($[M+1]^+$, 3), 300 (M^+, 21), 284 (17), 283 (100), 251 (5), 241 (6), 211 (9), 147 (6); ESI-HRMS calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$: 323.1259. Found: 323.1256.

General procedure for the preparation of 2-allyloxybenzophenones (4a-g)

To (2-allyloxyphenyl)phenylmethanol (**3a-g**) (20 mmol) dissolved in anhydrous dichloromethane (85 mL) was added MnO_2 (17.39 g, 200 mmol) and stirred at room temperature for 5 hr. After the end of reaction, the mixture was filtered, and the filtration was concentrated *in vacuo*. The residue which was obtained was purified from silica-gel column chromatography to give pure **4a-g**.

2-Allyloxybenzophenone (4a)[15]

(4.31 g, 90%) was obtained as colorless liquid, R_f = 0.15 (ethyl acetate: *n*-hexane = 1: 15), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 4.44 (dt, *J* = 5.2 Hz, 1.2 Hz, 2H, $OC\underline{H}_2CH{=}CH_2$), 4.98 (ddt, *J* = 10.4 Hz, 1.2 Hz, 1.2 Hz, 1H, $OCH_2CH{=}C\underline{H}_aH_b$), 5.04 (ddt, *J* = 17.2 Hz, 1.2 Hz, 1.2 Hz, 1H, $OCH_2CH{=}CH_a\underline{H}_b$), 5.70 (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.2 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 6.96 (d, *J* = 8.0 Hz, 1H, ArH), 7.05 (td, *J* = 7.6 Hz, 0.8 Hz, 1H, ArH), 7.36-7.57 (m, 5H, ArH), 7.78-7.83 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 68.92, 112.76, 116.81, 120.79, 128.10, 129.22, 129.57, 129.74, 131.86, 132.32, 132.68, 138.11, 156.34, 196.50; EI-MS (70 eV) *m/z* (rel. intensity, %) 239 ($[M+1]^+$, 54), 238 (M^+, 21), 223 (35), 209 (45), 197 (67), 195 (35), 194 (71), 181 (76), 121 (66), 115 (45), 106 (40), 105 (100), 77 (95); HRMS calcd for $C_{16}H_{14}O_2$: 238.0988. Found: 238.0990.

(2-Allyloxy-4-methoxyphenyl)phenylmethanone (4b)[16]

(4.86 g, 91%) was obtained as colorless liquid, R_f = 0.17 (ethyl acetate: *n*-hexane = 1: 19), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H, OCH_3), 4.12 (dt, *J* = 5.6, 1.8 Hz, 2H, $OC\underline{H}_2CH{=}CH_2$), 4.97 (ddt, *J* = 17.2, 1.8, 1.8 Hz, 1H, $OCH_2CH{=}C\underline{H}_aH_b$), 5.03 (ddt, *J* = 10.8, 1.8, 1.8 Hz, 1H, $OCH_2CH{=}CH_a\underline{H}_b$), 5.69 (ddt, *J* = 17.2, 10.8, 5 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 6.48 (d, *J* = 2.2 Hz, 1H, ArH), 6.57 (dd, *J* = 8.4, 2.2 Hz, 1H, ArH), 7.46 (m, 4H, ArH), 7.71 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 55.45, 68.88, 99.81, 105.09, 116.85, 121.84, 127.94, 129.44, 132.08, 132.16, 132.23, 139.14, 158.48, 163.31, 195.73; EI-MS (70 eV) *m/z* (rel. intensity, %) 269 ($[M+1]^+$, 56), 268 (M^+, 98), 267 (28), 254 (12), 253 (60), 211 (19), 191 (15), 175 (16), 163 (23), 105 (100), 77 (22); HRMS calcd for $C_{17}H_{16}O_3$: 268.1094. Found: 268.1096.

(2-Allyloxy-3-methoxyphenyl)phenylmethanone (4c)

(4.81 g, 90%) was obtained as colorless liquid, R_f = 0.21 (ethyl acetate: *n*-hexane = 1: 19), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.86 (s, 3H, OCH_3), 4.41 (d, *J* = 5.8 Hz, 2H, $OC\underline{H}_2CH{=}CH_2$), 4.98 (dd, *J* = 10.2, 1.0 Hz, 1H, $OCH_2CH{=}C\underline{H}_aH_b$), 5.03 (dd, *J* = 17.2, 1.0 Hz, 1H, $OCH_2CH{=}CH_a\underline{H}_b$), 5.72 (ddt, *J* = 17.2, 10.2, 5.8 Hz, 1H, $OCH_2C\underline{H}{=}CH_2$), 6.93 (dd, *J* = 2.2, 1.8 Hz, 1H, ArH), 7.03 (dd, *J* = 7.8, 1.8 Hz, 1H, ArH), 7.11 (t, *J* = 7.8 Hz, 1H, ArH), 7.46 (m, 3H, ArH),

7.81 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 55.68, 74.41, 114.18, 117.06, 120.25, 123.87, 127.99, 129.58, 132.78, 133.38, 134.26, 137.51, 145.40, 152.59, 195.99; EI-MS (70 eV) *m/z* (rel. intensity, %) 269 ($[M+1]^+$, 38), 268 (M^+, 69), 267 (22), 253 (33), 240 (21), 239 (30), 227 (69), 225 (40), 222 (20), 213 (32), 212 (100), 184 (57), 151 (34), 105 (34), 77 (36); HRMS calcd for $C_{17}H_{16}O_3$: 268.1094. Found: 268.1096.

(2′-Allyloxyphenyl)-(4″-methoxyphenyl)methanone (4d)

(5.09 g, 95%) was obtained as colorless liquid, R_f = 0.32 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H, CH_3), 4.47 (dt, *J* = 4.8 Hz, 1.6 Hz, 2H, $OC\underline{H}_2CH=CH_2$), 5.07 (ddt, *J* = 10.8 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.08 (ddt, *J* = 17.2 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.79 (ddt, *J* = 17.2 Hz, 10.8 Hz, 4.8 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.89 (d, *J* = 8.8 Hz, 2H, ArH), 6.95 (d, *J* = 8.0 Hz, 1H, ArH), 7.02 (t, *J* = 7.6 Hz, 1H, ArH), 7.35 (dd, *J* = 7.6, 1.6 Hz, 1H, ArH), 7.41 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H, Ar$\underline{H}$), 7.80 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.32, 68.84, 112.65, 113.30, 116.78, 120.66, 129.27, 129.55, 130.74, 131.30, 132.04, 132.42, 155.86, 163.36, 195.01; EI-MS (70 eV) *m/z* (rel. intensity, %) 269 ($[M+1]^+$, 100), 268 (M^+, 8), 238 (8), 224 (16), 161 (8), 148 (19), 147 (7), 135 (31), 77 (8); ESI-HRMS calcd for $C_{17}H_{17}O_3$ $[M+H]^+$: 269.1178. Found: 269.1177.

(2′-Allyloxy-4′-methoxyphenyl)-(4″-methoxyphenyl)-methanone (4e)[17]

(5.66 g, 95%) was obtained as colorless liquid, R_f = 0.22 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 6H, 2 × $OC\underline{H}_3$), 4.42 (dt, *J* = 4.8, 1.6, 2H, $OC\underline{H}_2CH=CH_2$), 5.03 (ddt, *J* = 16.8, 1.6, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.04 (ddt, *J* = 10.8, 1.6, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.74 (ddt, *J* = 16.8, 10.8, 4.8 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.47 (d, *J* = 2.4 Hz, 1H, ArH), 6.53 (dd, *J* = 8.4, 2.4 Hz, 1H, ArH), 6.87 (d, *J* = 8.8 Hz, 2H, ArH), 7.36 (d, *J* = 8.4 Hz, 1H, ArH), 7.75 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.27, 55.31, 68.82, 99.76, 104.87, 113.09, 116.78, 122.17, 131.51, 131.62, 131.86, 132.19, 157.86, 162.70, 162.97, 194.26; EI-MS (70 eV) *m/z* (rel. intensity, %) 299 ($[M+1]^+$, 38), 298 (M^+, 19), 268 (64), 254 (100), 253 (51), 241 (53), 214 (54), 211 (75), 148 (79), 135 (79); ESI-HRMS calcd for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.1283. Found: 299.1285.

(2′-Allyloxy-3′-methoxyphenyl)-(4″-methoxyphenyl)-methanone (4f)

(5.67 g, 95%) was obtained as colorless liquid, R_f = 0.26 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.43 (dt, *J* = 6.0 Hz, 1.6 Hz, 2H, $OC\underline{H}_2CH=CH_2$), 5.02 (ddt, *J* = 10.4 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.08 (ddt, *J* = 17.2 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.78 (ddt, *J* = 17.2 Hz, 10.4 Hz, 6.0 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.90 (d, *J* = 8.8 Hz, 2H, ArH), 6.90 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, ArH), 7.02 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, ArH), 7.12 (t, *J* = 8.0 Hz, 1H, ArH), 7.81 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.29, 55.72, 74.60, 113.35, 113.73, 117.21, 120.16, 123.98, 130.38, 132.20, 133.59, 134.79, 145.14, 152.66, 163.51, 194.68; EI-MS (70 eV) *m/z* (rel. intensity, %) 299 ($[M+1]^+$, 100), 298 (M^+, 14), 257 (29), 242 (46), 239 (26), 214 (61), 151 (63), 135 (94), 122 (39), 77 (57); ESI-HRMS calcd for $C_{18}H_{18}O_4Na$ $[M+Na]^+$: 321.1103. Found: 321.1101.

(2′-Allyloxy-3′-methoxyphenyl)-(2″-methoxyphenyl)-methanone (4g)

(5.73 g, 96%) was obtained as colorless liquid, R_f = 0.25 (ethyl acetate: *n*-hexane = 1: 6), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.30 (dt, *J* = 6, 1.6 Hz, 2H, $OC\underline{H}_2CH=CH_2$), 5.00 (ddt, *J* = 10.4 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.04 (ddt, *J* = 17.2 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.66 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.91 (d, *J* = 8.4 Hz, 1H, ArH), 6.97 (t, *J* = 7.6 Hz, 1H, ArH), 7.01-7.10 (m, 3H, ArH), 7.43 (td, *J* = 8.4, 2, Hz, 1H, ArH), 7.50 (dd, *J* = 7.6, 2 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.67, 55.89, 74.54, 111.57, 114.85, 117.08, 120.10, 121.13, 123.89, 129.75, 130.55, 132.84, 133.62, 135.90, 146.34, 152.67, 158.49, 195.49; EI-MS (70 eV) *m/z* (rel. intensity, %) 299 ($[M+1]^+$, 42), 298 (M^+, 19), 267 (38), 257 (38), 242 (56), 151 (96), 135 (100), 122 (30), 92 (34), 77 (59); ESI-HRMS calcd for $C_{18}H_{19}O_4$ $[M+H]^+$: 299.1283. Found: 299.1285.

General procedure for the preparation of 1-allyloxy-2-(phenylvinyl)benzene (5a-g)

Under the protection of dried nitrogen, to methyltriphenylphosphonium bromide (7.15 g, 20 mmol) dissolved in anhydrous THF (50 mL) and cooled at 0 °C was added potassium *tert*-butoxide (2.25 g, 20 mmol) in portion. The resulting mixture was stirred at 0 °C for 15 min. Then, the reaction solution turned yellow and was added in drops to the solution of 2-allylbenzophenones (**4a-g**) (15 mmol) in THF (5 mL). The resulting solution was stirred for 3 hr at 0 °C. Finally, the solution was quenched with saturated NH_4Cl aq. solution. After concentration *in vacuo* to remove

THF, the mixture which was obtained was extracted with EtOAc (20 mL × 5). The organic layer was combined and washed with brine and then dried with anhydrous $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo*. The obtained residue was purified by silica-gel column chromatography (ethyl acetate: *n*-hexane = 1: 15) to give pure **5a-g**.

1-Allyloxy-2-(phenylvinyl)benzene (5a)

(3.25 g, 92%) was obtained as colorless liquid, R_f = 0.65 (ethyl acetate: *n*-hexane = 1: 15), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.33 (dt, *J* = 5.2 Hz, 1.6 Hz, 2H, $OC\underline{H}_2CH=CH_2$), 4.97-5.03 (m, 2H, $OCH_2CH=C\underline{H}_2$), 5.33, 5.68 (each d, *J* = 1.6 Hz, 1H, $Ar(Ph)C=C\underline{H}_2$), 5.62 (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.2 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.86 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H, ArH), 6.99 (td, *J* = 8.0 Hz, 0.8 Hz, 1H, ArH), 7.20-7.31 (m, 7H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 68.96, 112.79, 115.47, 116.44, 120.85, 126.43, 127.18, 127.94, 128.90, 131.30, 131.55, 132.97, 141.45, 147.33, 156.04; EI-MS (70 eV) *m/z* (rel. intensity, %) 237 ($[M+1]^+$, 7), 236 (M^+, 3), 221 (25), 208 (20), 207 (20), 195 (67), 168 (25), 167 (93), 166 (31), 165 (74), 152 (33), 145 (100), 115 (17); HRMS calcd for $C_{17}H_{16}O$: 236.1196. Found: 236.1198.

2-Allyloxy-4-methoxy-1-(1-phenylvinyl)benzene (5b)

(3.80 g, 95%) was obtained as colorless liquid, R_f = 0.60 (ethyl acetate: *n*-hexane = 1: 19), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H, OCH_3), 4.30 (dt, *J* = 4.8, 1.6 Hz, 1H, $OC\underline{H}_2CH=CH_2$), 4.98 (ddt, *J* = 18.0 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 4.99 (ddt, *J* = 11.2 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.30, 5.60 (each d, *J* = 1.6 Hz, 1H, $Ar(Ph)C=C\underline{H}_2$), 5.60 (ddt, *J* = 18.0 Hz, 11.2 Hz, 4.8 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.45 (d, *J* = 2.4 Hz, 1H, ArH), 6.51 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H, ArH), 7.25 (m, 6H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 55.26, 68.83, 100.27, 104.57, 115.05, 116.45, 124.16, 126.47, 127.07, 127.86, 131.68, 132.73, 141.81, 146.97, 156.96, 160.48; EI-MS (70 eV) *m/z* (rel. intensity, %) 267 ($[M+1]^+$, 33), 266 (M^+, 99), 265 (100), 252 (12), 251 (46), 238 (14), 237 (27), 236 (71), 235 (16), 225 (12), 223 (10), 197 (20), 165 (11); HRMS calcd for $C_{18}H_{18}O_2$: 266.1307. Found: 266.1305.

2-Allyloxy-1-methoxy-3-(1-phenylvinyl)benzene (5c)

(3.84 g, 96%) was obtained as colorless liquid, R_f = 0.44 (ethyl acetate: *n*-hexane = 1: 19), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H, OCH_3), 4.21 (dt, *J* = 5.6, 1.6 Hz, 1H, $OC\underline{H}_2CH=CH_2$), 4.97 (ddt, *J* = 10.4 Hz, 1.2 Hz, 1.2 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.02 (ddt, *J* = 17.2 Hz, 1.2 Hz, 1.2 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.32, 5.67 (each d, *J* = 1.6 Hz, 1H, $Ar(Ph)C=C\underline{H}_2$), 5.66 (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.6 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.86 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H, ArH), 6.90 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H, ArH), 7.04 (dd, *J* = 8.4 Hz, 7.6 Hz, 1H, ArH), 7.27 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.68, 73.54, 111.83, 115.69, 116.77, 122.99, 123.65, 126.60, 127.29, 127.96, 134.15, 136.51, 141.33, 145.46, 146.81, 152.91; EI-MS (70 eV) *m/z* (rel. intensity, %) 267 ($[M+1]^+$, 1), 266 (M^+, 4), 265 (4), 251 (10), 248 (12), 238 (12), 235 (12), 226 (17), 225 (100), 219 (21), 198 (13), 197 (43), 183 (13), 182 (34), 181 (18), 169 (13), 166 (25), 165 (44), 154 (21), 153 (26), 152 (20), 145 (22); HRMS calcd for $C_{18}H_{18}O_2$: 266.1301. Found: 266.1304.

1-(Allyloxy)-2-[1-(4-methoxyphenyl)vinyl]benzene (5d)

(3.83 g, 96%) was obtained as colorless crystal, mp 41-42 °C, R_f = 0.59 (ethyl acetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H, OCH_3), 4.35 (dt, *J* = 4.8 Hz, 1.6 Hz, 2H, $OC\underline{H}_2CH=CH_2$), 5.02 (ddt, *J* = 10.4 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.05 (ddt, *J* = 17.2 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.22, 5.60 (each d, *J* = 1.6 Hz, 1H, $Ar(Ph)C=C\underline{H}_2$), 5.67 (ddt, *J* = 17.2 Hz, 10.4 Hz, 4.8 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.79 (d, *J* = 8.8 Hz, 2H, ArH), 6.87 (d, *J* = 7.6 Hz, 1H, ArH), 6.97 (t, *J* = 7.6 Hz Hz, 1H, ArH), 7.23 (d, *J* = 8.8 Hz, 2H, ArH), 7.20-7.30 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.18, 68.93, 112.78, 113.29, 113.74, 116.43, 120.81, 127.54, 128.77, 131.24, 131.74, 133.04, 133.97, 146.55, 155.99, 158.96; EI-MS (70 eV) *m/z* (rel. intensity, %) 267 ($[M+1]^+$, 31), 266 (M^+, 26), 251 (14), 238 (15), 237 (21), 225 (15), 197 (29), 176 (19), 175 (100), 147 (37). HRMS calcd for $C_{18}H_{18}O_2$: 266.1307. Found: 266.1306.

2-Allyloxy-4-methoxy-1-[1-(4-methoxyphenyl)vinyl]-benzene (5e)

(4.36 g, 98%) was obtained as colorless liquid, R_f = 0.57 (ethylacetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.35 (dt, *J* = 4.8 Hz, 2.0 Hz, 1H, $OC\underline{H}_2CH=CH_2$), 5.04 (ddt, *J* =10.4 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.04 (ddt, *J* = 17.6 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.20, 5.54 (each d, *J* = 1.6 Hz, 1H, $Ar(Ph)C=C\underline{H}_2$), 5.63 (ddt, *J* = 17.6, 10.4, 4.8 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.46 (d, *J* = 2.4 Hz, 1H, ArH), 6.52 (dd, *J* = 8.0, 2.4 Hz, 1H, ArH), 6.80 (d, *J* = 8.8 Hz, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 1H, ArH), 7.24 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.24, 55.32, 68.95, 100.38, 104.59, 113.26, 113.46, 116.54,

124.45, 127.63, 131.67, 132.89, 134.41, 146.23, 156.99, 158.92, 160.39; EI-MS (70 eV) *m/z* (rel. intensity, %) 297 ($[M+1]^+$, 22), 296 (M^+, 45), 281 (47), 267 (38), 266 (100), 253 (21), 227 (55), 212 (24), 175 (28), 169 (23); ESI-HRMS calcd for $C_{19}H_{21}O_3$ $[M+H]^+$: 297.1491. Found: 297.1489.

2-Allyloxy-3-methoxy-1-[1-(4-methoxyphenyl)vinyl]-benzene (5f)

(4.27 g, 96%) was obtained as colorless liquid, R_f = 0.46 (ethyl acetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.24 (dt, *J* = 5.6 Hz, 1.6 Hz, 1H, $OC\underline{H}_2CH=CH_2$), 4.99 (ddt, *J* = 10.4 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.06 (ddt, *J* = 17.2 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.21, 5.60 (each d, *J* = 1.6 Hz, 1H, Ar(Ph)C=C$\underline{H}_2$), 5.72 (ddt, *J* = 17.2 Hz, 10.4 Hz, 6.0 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.80 (d, *J* = 8.8 Hz, 2H, ArH), 6.85 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, ArH), 6.89 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H, ArH), 7.04 (dd, *J* = 8.0 Hz, 1H, ArH), 7.24 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.14, 55.71, 73.63, 111.73, 113.33, 113.90, 116.72, 122.97, 123.62, 127.74, 133.88, 134.27, 136.76, 145.52, 146.10, 152.92, 159.04; EI-MS (70 eV) *m/z* (rel. intensity, %) 297 ($[M+1]^+$, 44), 296 (M^+, 100), 295 (52), 282 (17), 281 (49), 267 (17), 266 (38), 265 (54), 255 (18), 175 (21); ESI-HRMS calcd for $C_{19}H_{20}O_3Na$ $[M+Na]^+$: 319.1310. Found: 319.1307.

2-Allyloxy-1-methoxy-3-[1-(2-methoxy-phenyl)vinyl]-benzene (5g)

(4.31 g, 97%) was obtained as colorless liquid, R_f = 0.52 (ethyl acetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.62 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.22 (dt, *J* = 5.6 Hz, 1.6 Hz, 1H, $OC\underline{H}_2CH=CH_2$), 5.04 (ddt, *J* = 10.4 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=C\underline{H}_aH_b$), 5.12 (ddt, *J* = 17.2 Hz, 1.6 Hz, 1.6 Hz, 1H, $OCH_2CH=CH_a\underline{H}_b$), 5.59, 5.62 (each d, *J* = 2.0 Hz, 1H, Ar(Ph)C=C$\underline{H}_2$), 5.80 (ddt, *J* = 17.2 Hz, 10.4 Hz, 6.0 Hz, 1H, $OCH_2C\underline{H}=CH_2$), 6.80-6.84 (m, 2H, ArH), 6.81 (d, *J* = 7.2 Hz, 1H, ArH), 6.89 (td, *J* = 7.2 Hz, 0.8 Hz, 1H, ArH), 6.96 (dd, *J* = 8.4 Hz, 7.2 Hz, 1H, ArH), 7.21 (d, *J* = 7.2 Hz, 1H, ArH), 7.22 (td, *J* = 7.2 Hz, 1.6 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.37, 55.73, 73.14, 111.21, 111.22, 116.47, 119.31, 120.33, 122.23, 123.31, 128.33, 130.39, 131.74, 134.58, 137.31, 143.82, 145.14, 152.79, 156.81; EI-MS (70 eV) *m/z* (rel. intensity, %) 297 ($[M+1]^+$, 1), 296 (M^+, 3), 265 (21), 256 (18), 255 (100), 225 (14), 175 (27), 152 (12), 122 (24), 121 (70); ESI-HRMS calcd for $C_{19}H_{20}O_3Na$ $[M+Na]^+$: 319.1310. Found: 319.1307.

General procedure for the preparation of neoflavenes (6a-g)

To 1-allyloxy-2-(arylvinyl)benzenes (**5a-g**) (5 mmol) dissolved in dichloromethane (100 mL) was added Grubbs' catalyst (5% mol), and the reaction mixture was stirred at room temperature for 4 hr. Then, the mixture was concentrated *in vacuo* to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate: *n*-hexane = 1: 15) to give pure **6a-g**.

Neoflavene (4-Phenyl-2*H*-chromene) (6a)[18]

(0.95 g, 91%) was obtained as colorless liquid, R_f = 0.62 (ethyl acetate: *n*-hexane = 1: 15), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.86 (d, *J* = 4.0 Hz, 2H, H-2), 5.80 (t, *J* = 4.0 Hz, 1H, H-3), 6.84 (td, *J* = 8.0 Hz, 1.2 Hz, 1H, ArH), 6.90 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H, ArH), 7.00 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, ArH), 7.15 (td, *J* = 8.0 Hz, 1.6 Hz, 1H, ArH), 7.37 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 65.24, 116.16, 119.89, 121.12, 125.80, 127.74, 128.33, 128.58, 129.19, 130.03, 137.11, 154.68, 186.22; EI-MS (70 eV) *m/z* (rel. intensity, %) 208 (M^+, 75), 207 (100), 179 (21), 178 (32), 152 (15), 132 (11), 131 (33); HRMS calcd for $C_{15}H_{12}O_1$: 208.0888. Found: 208.0886.

7-Methoxyneoflavene (7-Methoxy-4-phenyl-2*H*-chromene) (6b)[19]

(1.07 g, 90%) was obtained as colorless liquid, R_f = 0.61 (ethyl acetate: *n*-hexane = 1: 19), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 3H, OCH_3), 4.81 (d, *J* = 4.0 Hz, 2H, H-2), 5.63 (t, *J* = 4.0 Hz, 1H, H-3), 6.40 (dd, *J* = 8.4 Hz, 2.4, 1H, ArH), 6.48 (d, *J* = 2.4 Hz, 1H, ArH), 6.92 (d, *J* = 8.4 Hz, 1H, ArH), 7.34 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.26, 65.46, 101.88, 106.81, 116.81, 116.90, 126.63, 127.65, 128.28, 128.50, 136.93, 138.43, 156.01, 160.52; EI-MS (70 eV) *m/z* (rel. intensity, %) 239 ($[M+1]^+$, 16), 238 (M^+, 96), 237 (100), 223 (32), 194 (22), 165 (17), 161 (26); HRMS calcd for $C_{16}H_{14}O_2$: 238.0994. Found: 238.0991.

8-Methoxyneoflavene (8-Methoxy-4-phenyl-2*H*-chromene) (6c)

(1.10 g, 92%) was obtained as colorless crystal, mp 66-68 °C (*n*-hexane + ethyl acetate) [lit.[20] 70-71 °C], R_f = 0.24 (ethyl acetate: *n*-hexane = 1: 19), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.92 (s, 3H, OCH_3), 4.92 (d, *J* = 4.0 Hz, 2H, H-2), 5.83 (t, *J* = 4.0 Hz, 1H, H-3), 6.66 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H, ArH), 6.83 (m, 2H, ArH), 7.35-7.42 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.97, 65.36, 111.97,

118.20, 119.89, 120.45, 124.35, 127.66, 128.21, 128.52, 137.08, 138.28, 143.53, 148.00; EI-MS (70 eV) *m/z* (rel. intensity, %) 239 ($[M+1]^+$, 17), 238 (M^+, 100), 237 (57), 223 (20), 207 (17), 195 (17), 167 (16), 165 (28), 161 (20); HRMS calcd for $C_{16}H_{14}O_2$: 238.0988. Found: 238.0991.

4′-Methoxyneoflavene (4-(4-Methoxyphenyl)-2*H*-chromene) (6d)

(1.09 g, 92%) was obtained as colorless crystal, mp 93-94 °C (*n*-hexane + ethyl acetate) [lit.[3] 89-92 °C], R_f = 0.58 (ethyl acetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.84 (s, 3H, OCH_3), 4.82 (d, *J* = 4.0 Hz, 2H, H-2), 5.75 (t, *J* = 4.0 Hz, 1H, H-3), 6.85 (td, *J* = 7.6 Hz, 1.2 Hz, 1H, ArH), 6.89 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H, ArH), 6.93 (d, *J* = 8.8 Hz, 2H, ArH), 7.02 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H, ArH), 7.15 (ddd, *J* = 8.0 Hz, 7.6 Hz, 1.6 Hz, 1H, ArH), 7.27 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.28, 65.21, 113.73, 116.15, 119.17, 121.10, 123.90, 125.82, 129.11, 129.72, 130.59, 136.61, 154.78, 159.25; EI-MS (70 eV) *m/z* (rel. intensity, %) 239 ($[M+1]^+$, 16), 238 (100), 237 (66), 223 (31), 207 (39), 195 (20), 194 (18), 167 (16), 165 (35), 152 (14). HRMS calcd for $C_{16}H_{14}O_2$: 238.0994. Found: 238.0996.

7-Methoxyneoflavene (7-Methoxy-4-(4-methoxyphenyl)-2*H*-chromene) (6e)

(1.25 g, 93%) was obtained as colorless crystal, mp 102-104 °C (*n*-hexane + ethyl acetate) [lit.[3] 101-103 °C], R_f = 0.58 (ethyl acetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.82 (d, *J* = 4.0 Hz, 2H, H-2), 5.62 (t, *J* = 4.0 Hz, 1H, H-3), 6.42 (dd, *J* = 8.4 Hz, 2.6 Hz, 1H, ArH), 6.49 (d, *J* = 2.6 Hz, 1H, ArH), 6.92 (d, *J* = 8.8 Hz, 2H, ArH), 6.96 (d, *J* = 8.4 Hz, 1H, ArH), 7.27 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 55.27, 55.33, 65.53, 101.92, 106.85, 113.74, 116.19, 117.13, 126.69, 129.68, 130.88, 136.53, 156.15, 159.26, 160.53; EI-MS (70 eV) *m/z* (rel. intensity, %) 269 ($[M+1]^+$, 18), 268 (M^+, 100), 267 (74), 253 (32), 237 (17), 225 (15), 165 (22), 161 (16), 153 (19), 152 (19). HRMS calcd for $C_{17}H_{16}O_3$: 268.1099. Found: 268.1099.

8-Methoxy-4′-methoxyneoflavene (8-Methoxy-4-(2-methoxy-phenyl)-2*H*-chromene) (6f)

(1.21 g, 90%) was obtained as colorless crystal, mp 68-69 °C (*n*-hexane + ethyl acetate), R_f = 0.26 (ethyl acetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.85 (d, *J* = 4.0 Hz, 2H, H-2), 5.75 (t, *J* = 4.0 Hz, 1H, H-3), 6.65 (dd, *J* = 6.8 Hz, 2.4 Hz, 1H, ArH), 6.76-6.82 (m, 2H, ArH), 6.89 (d, *J* = 8.8 Hz, 1H, ArH), 7.24 (d, *J* = 8.8 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.03, 55.85, 65.24, 111.82, 113.51, 118.12, 119.02, 120.32, 124.51, 129.55, 130.53, 136.50, 143.55, 147.91, 159.09; EI-MS (70 eV) *m/z* (rel. intensity, %) 269 ($[M+1]^+$, 19), 268 (M^+, 100), 267 (33), 253 (45), 238 (12), 237 (17), 235 (12), 225 (14), 210 (13) , 165 (16); ESI-HRMS calcd for $C_{17}H_{17}O_3$ $[M+H]^+$: 269.1178. Found: 269.1177.

8-Methoxy-2′-methoxyneoflavene (8-Methoxy-4-(2-methoxyphenyl)-2*H*-chromene) (6g)

(1.21 g, 90%) was obtained as colorless crystal, mp 123-124 °C (*n*-hexane + ethyl acetate), R_f = 0.30 (ethyl acetate: *n*-hexane = 1: 9), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.70 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.96 (d, *J* = 4.0 Hz, 2H, H-2), 5.75 (t, *J* = 4.0 Hz, 1H, H-3), 6.34 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H, ArH), 6.71 (t, *J* = 7.6 Hz, 1H, ArH), 6.77 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, ArH), 6.93 (d, *J* = 8.0 Hz, 1H, ArH), 6.97 (t, *J* = 7.6 Hz, 1H, ArH), 7.17 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H, ArH), 7.33 (td, *J* = 8.0 Hz, 1.6 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.38, 55.93, 65.61, 110.81, 111.62, 117.97, 120.19, 120.52, 121.00, 124.35, 127.28, 129.13, 130.84, 134.07, 142.71, 147.74, 157.08; EI-MS (70 eV) *m/z* (rel. intensity, %) 269 ($[M+1]^+$, 18), 268 (M^+, 100), 267 (11), 254 (11), 253 (43), 238 (18), 237 (48), 221 (9), 206 (9), 165 (13); ESI-HRMS calcd for $C_{17}H_{16}O_3Na$ $[M+Na]^+$: 291.0997. Found: 291.1000.

Cytotoxic assays

The cytotoxic potential of all synthesized neoflavenes was evaluated against a panel of human cancer cell lines using an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay.[21] Cancer cells were treated as indicated for 48 hr in medium containing 10% FBS. Then, 20 μl MTT (2 mg/mL) was added to the cultures and incubated during the final 1.5 hr. The resultant tetrazolium salt was then dissolved by the addition of dimethyl sulfoxide. Color was measured spectrophotometrically in a microtitter plate reader at 570 nm and used as a relative measure of viable cell number. The number of viable cells following treatment was compared to solvent and untreated control cells and used to determine the percent of control growth as $(Ab_{treaded}/Ab_{control}) \times 100$, where Ab represents the mean absorbance (n = 6). The concentration that killed 50% of cells (IC_{50}) was determined from the linear portion of the curve by calculating the concentration of agent that reduced absorbance in treated cells, compared to control cells, by 50%.

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REFERENCES

1. (a) Mukerjee, S. K.; Saroja, T.; Seshadri, T. R. *Tetrahedron* **1971**, *27*, 799-803. (b) Dhingra, V. K.; Mukerjee, S. K.; Saroja, T.; Seshadri, T. R. *Phytochemistry* **1971**, *10*, 2551-2551.
2. Ravise, A.; Kirkiacharian, B. S. *Phytopath. Z.* **1980**, *97*, 219-223.
3. Donnelly, D. M. X.; Finet, J. P.; Guiry, P. J.; Nesbitt, K. *Tetrahedron* **2001**, *57*, 413-423.
4. Eguchi, T.; Hoshino, Y.; Ayame, A. *Bull. Chem. Soc. Jpn*. **2002**, *75*, 581-585.
5. Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc*. **1984**, *106*, 4218-4227.
6. Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859-8868.
7. Balasubramanian, T.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun*. **1992**, *24*, 1760-1761.
8. (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 100-110. (b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc*. **1996**, *118*, 9606-9614. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18-29. (d) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 1751-1753. (e) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953-956. (f) Saito, N.; Sato, Y.; Mori, M. *Org. Lett*. **2002**, *4*, 803-805. (g) Huang, K. S.; Wang, E. C. *Tetrahedron Lett*. **2001**, *42*, 6155-6157.
9. Li, S. R.; Chen, L. Y.; Tsai, J. C.; Tzeng, J. Y.; Tsai, I. L.; Wang, E. C. *Tetrahedron Lett*. **2007**, *48*, 2139-2141.
10. Caddick, S.; Khan, S.; Frost, L. M.; Smith, N. J.; Cheung, S.; Pairaudeau, G. *Tetrahedron* **2000**, *56*, 8953-8958.
11. Ohsugi, S. I.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S. *Tetrahedron* **2003**, *59*, 8393-8398.
12. Pradhan, P. K.; Jaisankar, P.; Pal, B.; Dey, S.; Giri, V. S. *Synth. Communs*. **2004**, *34*, 2863-2872.
13. Lee, J. I.; Lee, H. S.; Kim, B. H. *Synth. Commun*. **1996**, *26*, 3201-3216.
14. Fuerstner, A.; Aissa, C. *J. Am. Chem. Soc*. **2006**, *128*, 6306-6307.
15. Black, M.; Cadogan, J. I. G.; Leardini, R.; McNab, H.; McDougald, G. *J. Chem. Soc. Perkin Trans.1* **1998**, *11*, 1825-1832.
16. Motoki, S.; Watanabe, T.; Saito, T. *Tetrahedron Lett*. **1989**, *30*, 189-172.
17. Prashad, M.; Seth, M.; Bhaduri, A. P.; Srimal, R. C. *Indian J. Chem. Sect. B* **1979**, *17*B, 496-498.
18. (a) Eguchi, T.; Hoshino, Y.; Ayame, A. *Bull. Chem. Soc. Jpn*. **2002**, *75*, 581-586. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett*. **2003**, *5*, 1055-1058.
19. Anastasiou, D.; Jackson, W. R. *Aust. J. Chem*. **1992**, *45*, 21-37.
20. Iwai, I.; Ide, J. *Chem. Pharm. Bull*. **1963**, *11*, 1042-1049.
21. Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55-63.