第四章 實驗部分

第一節 試藥與溶媒

(一)購自德國 E. Merck**公司者：**

Acetic anhydride (98.5%)
Chloroform-*d* for NMR spectroscopy (99.8%)
Dimethyl sulfoxide-d_6 for NMR spectroscopy (99.8%)
Dimethyl sulfoxide GR dry (max.0.05% H_2O) (99.8%)
Ethyl 2-furancarboxylate
Ethanol absolute
Molecular sieve 0.4 nm
Methyl iodide
N,*N*-Dimethylformamide (99.5%)
Nitric acid fuming GR (100%)
Pyridine
Phosphorus pentoxide (P_2O_5)
Silica gel 60 (70-230 mesh，ASTM)
Sodium hydride suspension (80% in paraffin oil)
Sodium hydrogen carbonate GR (99.5%)
Sulfuric acid GR (95-97%)
Toluene

(二)購自瑞士 Fluka**公司者：**

2-Hydroxy-3-methylbenzoic acid

(三)購自英國 Lancaster**公司者：**

Cesium fluoride
2-Hydroxy-4-methylbenzoic acid
2-Hydroxy-3-methoxybenzoic acid
2-Hydroxy-5-iodobenzoic acid
Methyl salicylate
Malonic acid
5-Nitrofurfural
Sodium hydride (60% w/w dispersion in mineral oil)

(四)購自美國 Aldrich**公司者：**

2-Hydroxy-5-methylbenzoic acid
2-Hydroxy-4-methoxybenzoic acid
2-Hydroxy-5-methoxybenzoic acid
2-Hydroxy-6-methoxybenzoic acid

(五)購自日本東京化成工業株式會社者：

2-Hydroxy-6-methylbenzoic acid ethyl ester

2-Hydroxy-4-chlorobenzoic acid
2-Hydroxy-5-chlorobenzoic acid
2-Hydroxy-5-bromobenzoic acid

(六)購自日本和光工業株式會社者：

Magnesium sulfate anhydrous (95%)
Potassium hydroxide (85%)
Sodium hydroxide (>96%)

(七)購自景明化工股份有限公司者：

Acetone
Benzene
Chloroform
Diethyl ether
Ethyl acetate
Methanol
n-Hexane

(八)購自台灣省菸酒公賣局者：

Ethanol (95%)

(九)購自中華民國聯工化學廠者：

Hydrochloric acid

(十)購自美國 Tedia **公司者：**

Ammonium hydroxide (Ammonia solution)

第二節 重要儀器與實驗材料

(一)融點測定器 (Melting Point Apparatus)：

採用Yanaco MP-500D Micro Melting Point Apparatus**測定，測定範圍在**40~500 **℃之間，其測定溫度數據為未經校正者。**

(二)紫外-可見光波譜儀 (UV-visible Spectrophotometer)：

採用Shimadzu UV-160A UV-visible Recording Spectrophotometer **測定。使用甲醇為溶劑，最大吸收波長** (λmax)**單位為**nm**，而以**log ε **表示**Molar absorptivity**。**

(三)紅外線波譜儀 (Infrared Spectrophotometer**，簡稱**IR)：

使用Nicolet Impact 400 FT-IR Spectrophotometer**測定，以溴化鉀**(KBr)**粉末為打錠稀釋劑，利用聚苯乙烯** (polystyrene)**薄膜校正，波譜單位為波數** (cm^{-1})**。**

(四)質譜儀 (Mass Spectrophotometer)：

EIMS**使用**VG PLATFORM II FISONS instrument**測定，離子化電壓為** (ionization voltage)**為**70 ev**，單位為***m/z***。**

(五)霍式轉換核磁共振波譜儀 (Fourier-Transform Nuclear Magnetic Resonance Spectrometer,**簡稱為**FT-NMR)：

採用Bruker ADVANCE DPX-200 FT-NMR Spectrometer**測定。**Internal standard**為**Tetramethylsilane (TMS)**，化學位移** (chemical shift)**以**δ**表示，單位**ppm**，以***J***表示偶合常數** (coupling constant)**，單位**Hz**；峰線訊號以**"*s*"**表示單峰** (singlet)**，**"*d*"**表示二重峰** (doublet)**，**"*t*"**表示三重峰** (triplet)**，**"*q*"**表示四重峰** (quartet)**，**"*m* "**表示多重峰** (multiplet)**，**"*br*"**表示寬峰** (broad)**，**"*d d*"**表示雙二重峰** (double doublet)**，**"*ddd*"**表示參二重峰** (double double doublet)**。**

(六)元素分析儀 (Elemental Analyzer)：

採用Heraeus CHN-OS RAPID**元素分析儀測定，元素分析值皆在理論值**±4**%以內。**

(七)管柱層析 (Column Chromatography)：

以德國E. Merck**公司出品之**silica gel 60 (Kieselgel 60**，**70-230 mesh**，**ASTM)**當充填劑。**

(八)薄層層析 (Thin-layer Chromatography)：

採用德國E. Merck**公司出品之**TLC aluminium sheets silica gel 60 F_{254} pre-coated 25 sheets 20×20 cm**，**layer thickness 0.2 mm (Art. 5554)**。**

(九)紫外光燈 (UV lamp)：

使用CAMAG UV-Cabinet II**，短波長**254 nm**，長波長**366 nm**。**

第三節 化學合成方法

壹、Substituted salicylic acid methyl esters (2-4及6-13)之合成

2-Hydroxy-3-methylbenzoic acid methyl ester (2)之合成[55]

秤取2-hydroxy-3-methylbenzoic acid 24.34 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)；(1:1.5:1.5)；**於室溫下**250 mL DMF**中攪拌**24**小時，反應液過濾後將濾液倒入乙酸乙酯中，再以**5%**碳酸氫鈉溶液清洗，取乙酸乙酯層，以無水硫酸鎂脫水過濾後，減壓濃縮蒸除溶媒，所得之粗產物以矽膠管柱層析法(正己烷)分離純化，得到**2-hydroxy-3-methylbenzoic acid methyl ester (**2**)之無色液體**23.46 g (**產率**88.3%)。EIMS *m/z* (rel. int) 166 $[M]^+$ (67.3), 134 (100); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.27 (3H, *s*, CH_3), 3.93 (3H, *s*, COO$\underline{C}H_3$), 6.78 (1H, *dd*, *J*=8.0 Hz, H-5), 7.30 (1H, *d*, *J*=8.0 Hz, H-4), 7.68 (1H, *d*, *J*=8.0 Hz, H-6), 11.02 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.6 (CH_3), 52.2 (COO$\underline{C}H_3$), 111.6 (C-1), 118.4 (C-5), 126.5 (C-3), 127.3 (C-6), 136.4 (C-4), 160.0 (C-2), 171.0 ($\underline{C}$O)。

2-Hydroxy-4-methylbenzoic acid methyl ester (3)之合成[55]

秤取 2-hydroxy-4-methylbenzoic acid 24.34 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物 2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:4**)分離純化，得到** 2-hydroxy-4-methylbenzoic acid methyl ester (**3**)**之淡黃色液體** 24.34 g (**產率** 96.4%)。EIMS *m/z* (rel. int): 166 $[M]^+$ (85.1), 134 (100); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39 (3H, *s*, CH_3), 3.89 (3H, *s*, COO$\underline{C}H_3$), 6.66 (1H, *dd*, *J*=8.0 Hz, H-5), 6.72 (1H, *s*, H-3), 7.67 (1H, *d*, *J*=8.1 Hz, H-6), 10.73 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4 (CH_3), 52.0 (COO$\underline{C}H_3$), 109.7 (C-1), 117.6 (C-3), 120.4 (C-5), 129.6 (C-6), 146.9 (C-4), 161.5 (C-2), 170.5 ($\underline{C}$O)。

2-Hydroxy-5-methylbenzoic acid methyl ester (4)之合成[55]

秤取 2-hydroxy-5-methylbenzoic acid 24.34 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物 2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:4**)分離純化，得到** 2-hydroxy-5-methylbenzoic acid methyl ester (**4**)**之無色液體** 23.40 g (**產率** 88.1%)。EIMS *m/z* (rel. int): 166 $[M]^+$ (58.0), 134 (100); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.27 (3H, *s*, CH_3), 3.93 (3H, *s*, COO$\underline{C}H_3$), 6.87 (1H, *d*, *J*=8.4 Hz, H-3), 7.24 (1H, *dd*, *J*=8.4 Hz, H-4), 7.62 (1H, *d*, *J*=8.4 Hz, H-6), 10.64 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.3 (CH_3), 52.1 (COO$\underline{C}H_3$), 111.8 (C-1), 117.3 (C-3), 128.3

(C-5), 129.5 (C-6), 136.6 (C-4), 159.4 (C-2), 170.5 (CO)。

2-Hydroxy-3-methoxybenzoic acid methyl ester (6)之合成

秤取 2-hydroxy-3-methoxybenzoic acid 26.90 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物 2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:5)**分離純化，得到** 2-hydroxy-3-methoxybenzoic acid methyl ester (**6**)**之白色粉末狀結晶** 21.58 g (**產率** 74.0%)。mp: 67-67.5 **℃**; EIMS *m/z* (rel. int): 182 $[M]^+$ (55.5), 122 (100); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 3.86 (3H, *s*, COO$\underline{C}H_3$), 3.90 (3H, *s*, OCH_3-3), 6.77 (1H, *t*, *J*= 8.0 Hz, H-5), 7.00 (1H, *d*, *J*=8.0 Hz, H-4), 7.38 (1H, *d*, *J*=8.1 Hz, H-6), 10.96 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 52.3 (COO$\underline{C}H_3$), 56.1 (OCH_3-3), 112.5 (C-1), 116.4 (C-4), 118.4 (C-5), 120.9 (C-6), 148.4 (C-2), 151.9 (C-3), 170.8 (CO)。

2-Hydroxy-4-methoxybenzoic acid methyl ester (7)之合成

秤取2-hydroxy-4-methoxybenzoic acid 26.90 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:3)**分離純化，得到**2-hydroxy-4-methoxybenzoic acid methyl ester (**7**)**之白色粉末狀結晶**25.02 g (**產率**85.8%)。mp: 51-51.5 **℃**; EIMS *m/z* (rel. int): 182 $[M]^+$ (22.2), 150 (100); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 3.80 (3H, *s*, COO$\underline{C}H_3$), 3.89 (3H , *s*, OCH_3-4), 6.38-6.43 (2H, *m*, H-3,5), 7.71 (1H, *d*, *J*=7.2 Hz, H-6), 10.96 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 51.9 (COO$\underline{C}H_3$), 55.4 (O CH_3-4), 100.7 (C-3), 105.4 (C-5), 107.5 (C-1), 131.2 (C-6), 163.8 (C-2), 165.6 (C-4), 170.4 (CO)。

2-Hydroxy-5-methoxybenzoic acid methyl ester (8)之合成

秤取2-hydroxy-5-methoxybenzoic acid 26.90 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:3)**分離純化，得到**2-hydroxy-5-methoxybenzoic acid methyl ester (**8**)**之無色液體**20.00 g (**產率**68.6%)。EIMS *m/z* (rel. int): 182 $[M]^+$ (23.4), 79 (100); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 3.75 (3H, *s*, COO$\underline{C}H_3$), 3.92 (3H, *s*, OCH_3-5), 6.89 (1H, *d*, *J*=9.1 Hz, H-3), 7.06 (1H, *dd*, *J*=9.1, 3.1 Hz, H-4), 7.26 (1H, *d*, *J*=3.1 Hz, H-6), 10.35 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 52.3 (COO$\underline{C}H_3$), 55.8 (OCH_3-5), 111.8 (C-1), 111.8 (C-6), 118.5 (C-3), 124.0 (C-4), 152.0 (C-2), 156.0 (C-5), 170.3 (CO)。

2-Hydroxy-6-methoxybenzoic acid methyl ester (9)之合成

秤取2-hydroxy-6-methoxybenzoic acid 26.90 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方**

法同化合物2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷=1:8)**分離純化，得到**2-hydroxy-6-methoxybenzoic acid methyl ester (**9**)**之白色粉末狀結晶**24.50 g (**產率**84.1%)。mp: 46.5-47.5 **℃**; EIMS *m/z* (rel. int): 182 $[M]^+$ (29.9), 107 (100); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 3.84 (3H, *s*, COO$\underline{C}H_3$), 3.93 (3H, *s*, OCH_3-6), 6.39 (1H, *d*, *J*= 8.3 Hz, H-3), 6.57 (1H, *d*, *J*=8.3 Hz, H-5), 7.31 (1H, *t*, *J*=8.3 Hz, H-4), 11.48 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 52.4 (COO$\underline{C}H_3$), 56.1 (OCH_3-6), 102.2 (C-1), 103.0 (C-5), 110.1 (C-3), 135.1 (C-4), 160.8 (C-2), 163.5 (C-6), 171.6 ($\underline{C}$O)。

2-Hydroxy-4-chlorobenzoic acid methyl ester (10)之合成

秤取2-hydroxy-4-chlorobenzoic acid 27.60 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:5)**分離純化，得到**2-hydroxy-4-chlorobenzoic acid methyl ester (**10**)**之無色液體**23.52 g (**產率**79.0%)。EIMS *m/z* (rel. int): 188 $[M]^+$+2 (6.0), 186 $[M]^+$ (18.0), 63 (100); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 3.92 (3H, *s*, COO$\underline{C}H_3$), 6.83 (1H, *dd*, *J*=8.6, 2.0 Hz, H-5), 6.97 (1H, *d*, *J*=2.0 Hz, H-3), 7.72 (1H, *d*, *J*=8.6 Hz, H-6), 10.82 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 52.4 (COO$\underline{C}H_3$), 111.0 (C-1), 117.7 (C-3), 119.8 (C-5), 130.9 (C-6), 141.4 (C-4), 162.1 (C-2), 169.9 ($\underline{C}$O)。

2-Hydroxy-5-chlorobenzoic acid methyl ester (11)之合成

秤取2-hydroxy-5-chlorobenzoic acid 27.60 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:3)**分離純化，得到**2-hydroxy-5-chlorobenzoic acid methyl ester (**11**)**之白色粉末狀結晶**26.17 g (**產率**87.9%)。mp: 46.5-47 **℃**; EIMS *m/z* (rel. int): 188 $[M]^+$+2 (16.6), 186 $[M]^+$ (49.8), 154 (100); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 3.94 (3H, *s*, COO$\underline{C}H_3$), 6.91 (1H, *d*, *J*=8.9 Hz, H-3), 7.37 (1H, *dd*, *J*=8.9, 2.7 Hz, H-4), 7.78 (1H, *d*, *J*=2.7 Hz, H-6), 10.65 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 52.6(COO$\underline{C}H_3$), 113.3 (C-1), 119.2 (C-3), 123.9 (C-5), 129.2 (C-6), 135.6 (C-4), 160.1 (C-2), 169.6 ($\underline{C}$O)。

2-Hydroxy-5-bromobenzoic acid methyl ester (12)之合成

秤取 2-hydroxy-5-bromobenzoic acid 34.72 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物 2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:6)**分離純化，得到** 2-hydroxy-5-bromobenzoic acid methyl ester (**12**)**之白色粉末狀結晶** 22.82 g (**產率** 62.0%)。mp: 62.5-63 **℃**; EIMS *m/z* (rel. int): 232 $[M]^+$+2 (23.3), 230 $[M]^+$ (23.3), 63 (100); ^{1}H NMR (200 MHz,

$CDCl_3$): δ 3.94 (3H, *s*, COO$\underline{CH_3}$), 6.86 (1H, *d*, *J*=8.9 Hz, H-3), 7.50 (1H, *dd*, *J*=8.9, 2.5 Hz, H-4), 7.92 (1H, *d*, *J*=2.5 Hz, H-6), 10.67 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.6 (COO$\underline{CH_3}$), 110.8 (C-5), 113.8 (C-1), 119.6 (C-3), 132.2 (C-6), 138.4 (C-4), 160.6 (C-2), 169.5 ($\underline{C}$O)。

2-Hydroxy-5-iodobenzoic acid methyl ester (13)之合成

秤取 2-hydroxy-5-iodobenzoic acid 42.24 g (0.16 mol)，cesium fluoride 34.46 g (0.24 mol)，methyl iodide 34.06 g (0.24 mol)，**其合成方法同化合物 2，所得之粗產物以矽膠管柱層析法(乙酸乙酯:正己烷**=1:6) **分離純化，得到** 2-hydroxy-5-iodobenzoic acid methyl ester (**13**)**之白色粉末狀結晶** 30.87 g (**產率** 69.4%)。mp: 55.5-56 **℃**; EIMS *m/z* (rel. int): 278 $[M]^+$ (3.1), 63 (100); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.93 (3H, *s*, COO$\underline{CH_3}$), 6.75 (1H, *d*, *J*=8.8 Hz, H-3), 7.67 (1H, *dd*, *J*=8.8, 2.3 Hz, H-4), 8.10 (1H, *d*, *J*=2.3 Hz, H-6), 10.69 (1H, *s*, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.6 (COO$\underline{CH_3}$), 80.0 (C-5), 114.5 (C-1), 120.0 (C-3), 138.3 (C-6), 144.0 (C-4), 161.2 (C-2), 169.3 ($\underline{C}$O)。

貳、Ethyl 5-nitro-2-furoate (14)之合成[55]

取200 mL的醋酸酐加入三頸瓶中，降低溫度至-10 ℃，取60 mL的發煙硝酸，緩慢滴加入醋酸酐中，保持溫度於-10 ℃下，將ethyl furoate 43.0 g (0.307 mol)溶於60 mL醋酸酐中，而後將此溶液緩慢滴加入反應液中，整個滴加過程維持反應溫度於-10 ℃下，加完後保持於-10 ℃—5 ℃下攪拌2小時，然後將其倒入碎冰水溶液中攪拌，而後以10% NaOH溶液中和，接著以乙醚萃取，取乙醚層，而後加入60 mL pyridine於室溫下攪拌1小時，減壓濃縮去除多餘的乙醚，將pyridine溶液倒入冰水中，攪拌後，過濾，固體部份直接溶於乙醚中，而水溶液以乙醚萃取，混和乙醚層以無水硫酸鎂脫水，減壓濃縮至乾，以醇水混合溶媒做再結晶，得到ethyl 5-nitro-2-furoate (**14**)之亮黃棕色結晶26.81 g (產率47.1%)。mp: 102-102.5 ℃; EIMS *m/z* (rel. int): 185 $[M]^+$ (10.8), 99 (100); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 4.42 (2H, *q*, *J*= 7.1 Hz, $COO\underline{CH_2}CH_3$), 7.28 (1H, *d*, *J*=3.8 Hz, H-4), 7.34 (1H, *d*, *J*=3.8 Hz, H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 ($COOCH_2\underline{CH_3}$), 62.3 ($COO\underline{CH_2}CH_3$), 111.5 (C-3), 118.6 (C-4), 145.0 (C-2), 152.3 (C-5), 156.9 (<u>C</u>O)。

參、Ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)furan-2-

carboxylates (21-33)之合成

Ethyl 5-(2'-methoxycarbonylphenoxy)furan-2-carboxylate (21)之合成[55]

取 DMSO 50 mL **於三頸瓶，加入** methyl salicylate 7.61 g (0.05 mol)**，將其攪拌，取** 80% NaH 1.5 g (0.05 mol)**分次加入，繼而取** ethyl 5-nitro-2-furoate 7.59 g (0.041 mol)**溶於** 50 mL DMSO **中，慢慢滴加此溶液至上述白色懸浮液中，保持溫度於** 84 –86 **℃攪拌** 24 **小時後，倒入冰水中攪拌，以氯仿抽取，再以** 5% KOH **溶液清洗，再以水洗掉** KOH**，氯仿層以無水硫酸鎂脫水，減壓濃縮為深棕色液體，經矽膠管柱層析法(苯)分離純化，得到** ethyl 5-(2'-methoxycarbonyl-phenoxy)furan-2-carboxylate (**21**)**之淡黃色液體** 5.36 g (**產率** 45.0%)。EIMS *m/z* (rel. int): 290 $[M]^+$ (21.6), 170 (100); UV λ_{max}nm (MeOH) (logε): 276 (4.21); IR (KBr) cm^{-1}: 1721 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (3H, *t*, *J*= 7.1 Hz, $COOCH_2\underline{CH_3}$), 3.82 (3H, *s*, $COO\underline{CH_3}$), 4.29 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.37 (1H, *d*, *J*=3.5 Hz, H-4), 7.09 (1H, *d*, *J*=3.5 Hz, H-3), 7.10 (1H, *d*, *J*=7.8 Hz, H-6'), 7.28 (1H, *dd*, *J*=7.8 Hz, H-4'), 7.50 (1H, *ddd*, *J*=7.8 Hz, H-5'), 7.90 (1H, *d*, *J*=7.8 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 ($COOCH_2\underline{CH_3}$), 52.3 ($COO\underline{CH_3}$), 60.6 ($COO\underline{CH_2}CH_3$), 88.9 (C-4), 120.3 (C-6'), 120.5 (C-3), 122.4 (C-2'), 125.4 (C-4'), 132.1 (C-3'), 133.9 (C-5'), 136.2 (C-2), 153.5 (C-1'), 158.2 ($\underline{C}OOCH_2CH_3$), 160.0 (C-5), 165.1 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 61.99; H, 4.85。

Ethyl 5-(2'-methoxycarbonyl-6'-methylphenoxy)furan-2-carboxylate (22)之合成[55]

取 DMSO 50 mL **於三頸瓶，加入** 2-hydroxy-3-methylbenzoic acid methyl ester (**2**) 8.30 g (0.05 mol)**，其合成方法同化合物 21，經矽膠管柱層析法(苯)分離純化，得到** ethyl 5-(2'-methoxycarbonyl-6'-methyl-phenoxy)furan-2-carboxylate (**22**)**之淡黃色液體** 4.86 g (**產率** 39.0%)。EIMS *m/z* (rel. int): 304 $[M]^+$ (24.9), 170 (100); UV λ_{max}nm (MeOH) (logε): 279 (4.49), 207 (4.56); IR (KBr) cm^{-1}: 1721 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 2.26 (3H, *s*, CH_3-6'), 3.77 (3H, *s*, $COO\underline{CH_3}$), 4.32 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.01 (1H, *d*, *J*=3.6 Hz, H-4), 7.07 (1H, *d*, *J*=3.6 Hz, H-3), 7.25 (1H, *dd*, *J*=7.6 Hz, H-4'), 7.43 (1H, *d*, *J*=7.6 Hz, H-5'), 7.79 (1H, *d*, *J*=7.6 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($COOCH_2\underline{CH_3}$), 15.8 (CH_3-6'), 52.3 ($COO\underline{CH_3}$), 60.5 ($COO\underline{CH_2}CH_3$), 85.2 (C-4), 120.9 (C-3), 123.9 (C-2'), 126.1 (C-4'), 129.8 (C-3'), 132.2 (C-6'), 135.4 (C-2), 135.8

(C-5'), 150.1 (C-1'), 158.3 (<u>C</u>OOCH$_2$CH$_3$), 161.3 (C-5), 165.2 (<u>C</u>OOCH$_3$); Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.08; H, 5.32。

Ethyl 5-(2'-methoxycarbonyl-5'-methylphenoxy)furan-2-carboxylate (23)之合成[55]

取 DMSO 50 mL **於三頸瓶，加入** 2-hydroxy-4-methylbenzoic acid methyl ester (**3**) 8.30 g (0.05 mol)**，其合成方法同化合物 21，經矽膠管柱層析法(苯)分離純化，得到** ethyl 5-(2'-methoxycarbonyl-5'-methyl-phenoxy)furan-2-carboxylate (**23**)**之淡黃色液體** 5.24 g (**產率** 42.0%)。EIMS *m/z* (rel. int): 304 $[M]^+$ (27.2), 170 (100); UV λ_{max}nm (MeOH) (logε): 274 (4.33), 236 (4.22); IR (KBr) cm^{-1}: 1716 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (3H, *t*, *J*=7.0 Hz, COOCH$_2$<u>CH$_3$</u>), 2.27 (3H, *s*, CH$_3$-5'), 3.73 (3H, *s*, COO<u>CH$_3$</u>), 4.24 (2H, *q*, *J*=7.0 Hz, COO<u>CH$_2$</u>CH$_3$), 5.30 (1H, *d*, *J*=3.5 Hz, H-4), 6.87 (1H, *s*, H-6'), 7.00 (1H, *d*, *J*=3.5 Hz, H-3), 7.05 (1H, *d*, *J*=8.0 Hz, H-4'), 7.82 (1H, *d*, *J*=8.0 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 (COOCH$_2$<u>CH$_3$</u>), 21.3 (CH$_3$-5'), 52.1 (COO<u>CH$_3$</u>), 60.5 (COO<u>CH$_2$</u>CH$_3$), 88.7 (C-4), 119.5 (C-2'), 120.5 (C-3), 121.0 (C-6'), 126.3 (C-4'), 132.1 (C-3'), 136.1 (C-2), 145.3 (C-5'), 153.6 (C-1'), 158.2 (<u>C</u>OOCH$_2$CH$_3$), 160.3 (C-5), 165.0 (<u>C</u>OOCH$_3$); Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.95; H, 5.29。

Ethyl 5-(2'-methoxycarbonyl-4'-methylphenoxy)furan-2-carboxylate (24)之合成[55]

取 DMSO 50 mL **於三頸瓶，加入** 2-hydroxy-5-methylbenzoic acid methyl ester (**4**) 8.30 g (0.05 mol)**，其合成方法同化合物 21，經矽膠管柱層析法(苯)分離純化，得到** ethyl 5-(2'-methoxycarbonyl-4'-methyl-phenoxy)furan-2-carboxylate (**24**)**之淡黃色液體** 5.49 g (**產率** 44.0%)。EIMS *m/z* (rel. int): 304 $[M]^+$ (32.3), 170 (100); UV λ_{max}nm (MeOH) (logε): 276 (4.48); IR (KBr) cm^{-1}: 1732 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (3H, *t*, *J*=7.1 Hz, COOCH$_2$<u>CH$_3$</u>), 2.33 (3H, *s*, CH$_3$-4'), 3.79 (3H, *s*, COO<u>CH$_3$</u>), 4.28 (2H, *q*, *J*=7.1 Hz, COO<u>CH$_2$</u>CH$_3$), 5.29 (1H, *d*, *J*=3.6 Hz, H-4), 7.02 (1H, *d*, *J*=8.4 Hz, H-6'), 7.07 (1H, *d*, *J*=3.6 Hz, H-3), 7.29 (1H, *dd*, *J*=8.4, 2.3 Hz, H-5'), 7.71(1H, *d*, *J*=2.3 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 (COOCH$_2$<u>CH$_3$</u>), 20.5 (CH$_3$-4'), 52.2 (COO<u>CH$_3$</u>), 60.5 (COO<u>CH$_2$</u>CH$_3$), 88.1 (C-4), 120.5 (C-3), 120.6 (C-6'), 122.2 (C-2'), 132.3 (C-3'), 134.4 (C-5'), 135.5 (C-4'), 136.0 (C-2), 151.2 (C-1'), 158.2 (<u>C</u>OOCH$_2$CH$_3$), 160.7 (C-5), 165.2 (<u>C</u>OOCH$_3$); Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.99; H, 5.28。

Ethyl 5-(2'-ethoxycarbonyl-3'-methylphenoxy)furan-2-carboxylate (25)之合成

取DMSO 50 mL**於三頸瓶，加入**2-hydroxy-6-methylbenzoic acid ethyl ester 9.01 g (0.05 mol)**，其合成方法同化合物21，經矽膠管柱層析法(苯)分離純化，得到**ethyl 5-(2'-ethoxycarbonyl-3'-methylphenoxy)-furan-2-carboxylate (**25**)**之淡黃色液體**5.41 g (**產率**41.5%)。EIMS *m/z* (rel. int): 318 $[M]^+$ (17.3), 156 (100); UV λ_{max}nm (MeOH) (logε): 274 (4.72), 208 (4.64); IR (KBr) cm^{-1}: 1725 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$-C-2), 1.32 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$-C-2'), 2.36 (3H, *s*, CH_3-3'), 4.28 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$-C-2), 4.35 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$-C-2'), 5.45 (1H, *d*, *J*=3.6 Hz, H-4), 6.92 (1H, *d*, *J*=8.0 Hz, H-6'), 7.04 (1H, *d*, *J*=7.6 Hz, H-4'), 7.10 (1H, *d*, *J*=3.6 Hz, H-3), 7.26 (1H, *t*, *J*=8.0 Hz, H-5'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 ($COOCH_2\underline{CH_3}$-C-2), 14.3 ($COOCH_2\underline{CH_3}$-C-2'), 19.4 (CH_3-3'), 60.7 ($COO\underline{CH_2}CH_3$-C-2), 61.5 ($COO\underline{CH_2}CH_3$-C-2'), 89.6 (C-4), 116.1 (C-6'), 120.4 (C-3), 125.9 (C-2'), 127.1 (C-4'), 130.6 (C-5'), 136.4 (C-3'), 138.0 (C-2), 151.9 (C-1'), 158.2 ($\underline{C}O$-C-2), 159.9 (C-5), 166.3 ($\underline{C}O$-C-2'); Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.02; H, 5.68。

Ethyl 5-(2'-methoxycarbonyl-6'-methoxyphenoxy)furan-2-carboxylate (26)之合成

取DMSO 50 mL**於三頸瓶，加入**2-hydroxy-3-methoxybenzoic acid methyl ester (**6**) 9.11 g (0.05 mol)**，其合成方法同化合物21，經矽膠管柱層分法(乙酸乙酯:正己烷**=1:3)**分離純化，得到**ethyl 5-(2'-methoxy-carbonyl-6'-methoxyphenoxy)furan-2-carboxylate (**26**)之淡黃色液體** 4.12 g (**產率**31.4%)。EIMS *m/z* (rel. int): 320 $[M]^+$ (29.9), 122 (100); UV λ_{max}nm (MeOH) (logε): 279 (4.78), 207 (4.60); IR (KBr) cm^{-1}: 1725 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 3.78 (3H, *s*, $COO\underline{CH_3}$), 3.79 (3H, *s*, OCH_3-6'), 4.28 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.10 (1H, *d*, *J*=3.6 Hz, H-4), 7.06 (1H, *d*, *J*= 3.6 Hz, H-3), 7.15 (1H, *dd*, *J*=8.1, 1.7 Hz, H-5'), 7.26 (1H, *t*, *J*=8.1 Hz, H-4'), 7.47 (1H, *dd*, *J*=8.1, 1.7 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 ($COOCH_2\underline{CH_3}$), 52.4 ($COO\underline{CH_3}$), 56.4 (OCH_3-6'), 60.4 ($COO\underline{CH_2}CH_3$), 85.5 (C-4), 116.8 (C-5'), 121.0 (C-3), 122.8 (C-3'), 125.2 (C-2'), 126.6 (C-4'), 135.2 (C-2), 141.6 (C-1'), 152.3 (C-6'), 158.4 ($\underline{C}OOCH_2CH_3$), 161.5 (C-5), 165.1 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{16}H_{16}O_7$: C, 59.99; H, 5.04. Found: C, 59.81; H, 5.02。

Ethyl 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furan-2-carboxylate (27)之合成

取DMSO 50 mL**於三頸瓶，加入**2-hydroxy-4-methoxybenzoic acid

methyl ester (**7**) 9.11 g (0.05 mol)，其合成方法同化合物**21**，經矽膠管柱層析法(乙酸乙酯:正己烷=1:4)分離純化，得到ethyl 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furan-2-carboxylate (**27**)之淡黃色液體 5.13 g (產率39.0%)。EIMS *m/z* (rel. int): 320 $[M]^+$ (19.1), 170 (100); UV λ_{max}nm (MeOH) (logε): 258 (4.36), 207 (4.52); IR (KBr) cm^{-1}: 1725 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 3.70 (3H, *s*, $COO\underline{CH_3}$), 3.72 (3H, *s*, OCH_3-5'), 4.21 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.32 (1H, *d*, *J*=3.6 Hz, H-4), 6.56 (1H, *d*, *J*= 2.5 Hz, H-6'), 6.70 (1H, *dd*, *J*=8.8, 2.5 Hz, H-4'), 7.03 (1H, *d*, *J*=3.6 Hz, H-3), 7.84 (1H, *d*, *J*=8.8 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 ($COOCH_2\underline{CH_3}$), 51.7 ($COO\underline{CH_3}$), 55.5 (OCH_3-5'), 60.4 ($COO\underline{CH_2}CH_3$), 88.6 (C-4), 106.2 (C-6'), 110.8 (C-4'), 114.3 (C-2'), 120.3(C-3), 133.7 (C-3'), 136.1 (C-2), 155.1 ($\underline{C}OOCH_2CH_3$), 158.0 (C-1'), 159.9 (C-5), 163.9 (C-5'), 164.5 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{16}H_{16}O_7$: C, 59.99; H, 5.04. Found: C, 59.91; H, 5.03。

Ethyl 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furan-2-carboxylate (28)之合成

取DMSO 50 mL於三頸瓶，加入2-hydroxy-5-methoxybenzoic acid methyl ester (**8**) 9.11 g (0.05 mol)，其合成方法同化合物**21**，經矽膠管柱層析法(乙酸乙酯:正己烷=1:6)分離純化，得到ethyl 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furan-2-carboxylate (**28**)之淡黃色液體 4.46 g (產率35.3%)。EIMS *m/z* (rel. int): 320 $[M]^+$ (16.1), 150 (100); UV λ_{max}nm (MeOH) (logε): 276 (4.23), 211 (4.24); IR (KBr) cm^{-1}: 1728 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 3.80 (3H, *s*, $COO\underline{CH_3}$), 3.82 (3H, *s*, OCH_3-4'), 4.30 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.21 (1H, *d*, *J*=3.6 Hz, H-4), 7.00-7.14 (3H, *m*, H-3, 5', 6'), 7.42 (1H, *d*, *J*=2.9 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($COOCH_2\underline{CH_3}$), 52.5 ($COO\underline{CH_3}$), 55.8 (OCH_3-4'), 60.6 ($COO\underline{CH_2}CH_3$), 87.2 (C-4), 115.9 (C-3'), 120.0 (C-6'), 120.7 (C-3), 122.7 (C-5'), 123.6 (C-2'), 135.8 (C-2), 146.8 (C-1'), 156.9 (C-4'), 158.4 ($\underline{C}OOCH_2CH_3$), 161.5 (C-5), 165.0 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{16}H_{16}O_7$: C, 59.99; H, 5.04. Found: C, 59.78; H, 5.06。

Ethyl 5-(2'-methoxycarbonyl-3'-methoxyphenoxy)furan-2-carboxylate (29)之合成

取DMSO 50 mL於三頸瓶，加入2-hydroxy-6-methoxybenzoic acid methyl ester (**9**) 9.11 g (0.05 mol)，其合成方法同化合物**21**，經矽膠管柱層析法(乙酸乙酯:正己烷=1:4)分離純化，得到ethyl 5-(2'-methoxycarbonyl-3'-methoxyphenoxy)furan-2-carboxylate (**29**)之淡黃色液體

4.10 g (產率25.6%)。EIMS *m/z* (rel. int): 320 $[M]^+$ (67.2), 150 (100); UV λ_{max}nm (MeOH) (logε): 273 (4.36), 206 (4.34); IR (KBr) cm^{-1}: 1721 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 3.83 (3H, *s*, $COO\underline{CH_3}$), 3.85 (3H, *s*, OCH_3-3'), 4.30 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.56 (1H, *d*, *J*=3.6 Hz, H-4), 6.64 (1H, *d*, *J*=8.4 Hz, H-6'), 6.74 (1H, *d*, *J*=8.4 Hz, H-4'), 7.10 (1H, *d*, *J*=3.6 Hz, H-3), 7.30 (1H, *t*, *J*=8.4 Hz, H-5'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($COOCH_2\underline{CH_3}$), 52.6 ($COO\underline{CH_3}$), 56.2 (OCH_3-3'), 60.8 ($COO\underline{CH_2}CH_3$), 90.8 (C-4), 107.7 (C-4'), 110.0 (C-6'), 115.2 (C-2'), 120.3 (C-3), 131.4 (C-5'), 136.6 (C-2), 152.8 ($\underline{C}OOCH_2CH_3$), 157.7 (C-1'), 158.2 (C-3'), 158.9 (C-5), 165.1 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{16}H_{16}O_7$: C, 59.99; H, 5.04. Found: C, 59.88; H, 5.05。

Ethyl 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furan-2-carboxylate (30)之合成

取DMSO 50 mL**於三頸瓶，加入**2-hydroxy-4-chlorobenzoic acid methyl ester (**10**) 9.31 g (0.05 mol)**，其合成方法同化合物21，經矽膠管柱層析法(苯)分離純化，得到**ethyl 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furan-2-carboxylate (**30**)**之淡黃色液體**3.54 g (**產率**26.6%)。EIMS *m/z* (rel. int): 326 $[M]^+$+2 (5.0), 324 $[M]^+$ (15.0), 170 (100); UV λ_{max}nm (MeOH) (logε): 271 (4.85), 239 (4.90); IR (KBr) cm^{-1}: 1728 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 3.83 (3H, *s*, $COO\underline{CH_3}$), 4.32 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.53 (1H, *d*, *J*=3.6 Hz, H-4), 7.09 (1H, *d*, *J*=2.0 Hz, H-6'), 7.13 (1H, *d*, *J*=3.6 Hz, H-3), 7.24 (1H, *dd*, *J*=8.4, 2.0 Hz, H-4'), 7.89 (1H, *d*, *J*=8.4 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($COOCH_2\underline{CH_3}$), 52.5 ($COO\underline{CH_3}$), 60.9 ($COO\underline{CH_2}CH_3$), 90.4 (C-4), 120.3 (C-3), 120.3 (C-6'), 120.8 (C-2'), 125.6 (C-4'), 133.3 (C-3'), 137.0 (C-2), 139.6 (C-5'), 154.5 ($\underline{C}OOCH_2CH_3$), 158.2 (C-1'), 158.7 (C-5), 164.5 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{15}H_{13}ClO_6$: C, 55.48; H, 4.04. Found: C, 55.36; H, 4.03。

Ethyl 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furan-2-carboxylate (31)之合成

取DMSO 50 mL**於三頸瓶，加入**2-hydroxy-5-chlorobenzoic acid methyl ester (**11**) 9.31 g (0.05 mol)**，其合成方法同化合物21，經矽膠管柱層析法(苯)分離純化，得到**ethyl 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furan-2-carboxylate (**31**)**之淡黃色液體**3.68 g (**產率**27.6%)。EIMS *m/z* (rel. int): 326 $[M]^+$+2 (7.0), 324 $[M]^+$ (21.0), 170 (100); UV λ_{max}nm (MeOH) (logε): 272 (4.15), 207 (4.39); IR (KBr) cm^{-1}: 1728 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$),

3.83 (3H, *s*, COO$\underline{CH_3}$), 4.30 (2H, *q*, *J*=7.1 Hz, COO$\underline{CH_2}CH_3$), 5.44 (1H, *d*, *J*=3.6 Hz, H-4), 7.05-7.11 (2H, *m*, H-3, 6'), 7.46 (1H, *dd*, *J*=8.8, 2.7 Hz, H-5'), 7.90 (1H, *d*, *J*=2.7 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($COOCH_2\underline{CH_3}$), 52.7 (COO$\underline{CH_3}$), 60.8 (COO$\underline{CH_2}CH_3$), 89.5 (C-4), 120.4 (C-6'), 121.7 (C-3), 123.8 (C-2'), 130.8 (C-4'), 131.9 (C-3'), 133.7 (C-5'), 136.7 (C-2), 152.3 (C-1'), 158.2 ($\underline{C}OOCH_2CH_3$), 159.4 (C-5), 164.0 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{15}H_{13}ClO_6$: C, 55.48; H, 4.04. Found: C, 55.28; H, 4.05。

Ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (32)之合成

取DMSO 50 mL**於三頸瓶，加入**2-hydroxy-5-bromobenzoic acid methyl ester (**12**) 11.51 g (0.05 mol)**，其合成方法同化合物21，經矽膠管柱層析法(苯)分離純化，得到**ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**)**之淡黃色液體**4.73 g (**產率**31.2%)。EIMS *m/z* (rel. int): 370 $[M]^+$+2 (9.2), 368 $[M]^+$ (9.2), 170 (100); UV λ$_{max}$nm (MeOH) (logε): 272 (5.01), 206 (4.81); IR (KBr) cm^{-1}: 1740 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 3.83 (3H, *s*, COO$\underline{CH_3}$), 4.29 (2H, *q*, *J*=7.1 Hz, COO$\underline{CH_2}CH_3$), 5.45 (1H, *d*, *J*=3.6 Hz, H-4), 7.00 (1H, *d*, *J*=8.7 Hz, H-6'), 7.10 (1H, *d*, *J*=3.6 Hz, H-3), 7.59 (1H, *dd*, *J*=8.7, 2.5 Hz, H-5'), 8.04 (1H, *d*, *J*=2.5 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($COOCH_2\underline{CH_3}$), 52.7 (COO$\underline{CH_3}$), 60.8 (COO$\underline{CH_2}CH_3$), 89.7 (C-4), 118.1 (C-4'), 120.3 (C-3), 120.6 (C-2'), 121.9 (C-6'), 124.1 (C-2), 134.8 (C-3'), 136.6 (C-5'), 152.9 (C-1'), 158.1 ($\underline{C}OOCH_2CH_3$), 159.2 (C-5), 163.9 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{15}H_{13}BrO_6$: C, 48.80; H, 3.55. Found: C, 48.68; H, 3.54。

Ethyl 5-(2'-methoxycarbonyl-4'-iodophenoxy)furan-2-carboxylate (33)之合成

取 DMSO 50 mL **於三頸瓶，加入** 2-hydroxy-5-iodobenzoic acid methyl ester (**13**) 13.90 g (0.05 mol)**，其合成方法同化合物 21，經矽膠管柱層析法(苯)分離純化，得到** ethyl 5-(2'-methoxycarbonyl-4'-iodophenoxy)furan-2-carboxylate (**33**)**之淡黃色液體** 4.56 g (**產率** 26.7%)。EIMS *m/z* (rel. int): 416 $[M]^+$ (25.2), 170 (100); UV λ$_{max}$nm (MeOH) (logε): 273 (4.46), 216 (4.45); IR (KBr) cm^{-1}: 1729 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 3.83 (3H, *s*, COO$\underline{CH_3}$), 4.30 (2H, *q*, *J*=7.1 Hz, COO$\underline{CH_2}CH_3$), 5.47 (1H, *d*, *J*=3.6 Hz, H-4), 6.87 (1H, *d*, *J*=8.7 Hz, H-6'), 7.11 (1H, *d*, *J*=3.6 Hz, H-3), 7.79 (1H, *dd*, *J*=8.7, 2.3 Hz, H-5'), 8.22 (1H, *d*, *J*=2.3 Hz, H-3'); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($COOCH_2\underline{CH_3}$), 52.7 (COO$\underline{CH_3}$), 60.8 (COO$\underline{CH_2}CH_3$),

88.4 (C-4'), 89.9 (C-4), 120.4 (C-3), 122.0 (C-6'), 124.3 (C-2'), 136.8 (C-2), 140.7 (C-3'), 142.6 (C-5'), 153.8 (C-1'), 158.2 ($\underline{C}OOCH_2CH_3$), 159.1 (C-5), 163.8 ($\underline{C}OOCH_3$); Anal. Calcd for $C_{15}H_{13}IO_6$: C, 43.29; H, 3.15. Found: C, 43.17; H, 3.16。

肆、5-(2'-Carboxyl substituted phenoxy)furan-2-carboxylic acids (41-

48 及 50-53)之合成

5-(2'-Carboxylphenoxy)furan-2-carboxylic acid (41)之合成[55]

秤取ethyl 5-(2'-methoxycarbonylphenoxy)furan-2-carboxylate (**21**) 2.90 g (0.01 mol)**加入**20% NaOH**溶液**10 mL，**在水浴中迴流**8**小時，以**TLC**追蹤至完全水解，放冷，以乙醚清洗，水層加熱蒸去乙醚後，以**20% H_2SO_4**溶液酸化至**Congo Red Paper**變色，產生白色沈澱物，以乙醚萃取，取乙醚層以無水硫酸鎂脫水，減壓濃縮得到白色粉末，以乙醇-水做再結晶，得到**5-(2'-carboxylphenoxy)furan-2-carboxylic acid (**41**)之白色粉末狀結晶**1.74 g (**產率**70.0%)。mp: 161.5-162 ℃; EIMS *m/z* (rel. int): 248 $[M]^+$ (4.7), 120 (100); UV λ_{max}nm (MeOH) (logε): 273 (4.45); IR (KBr) cm^{-1}: 1686 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.50 (1H, *d*, *J*=3.5 Hz, H-4), 7.00 (1H, *d*, *J*=3.5 Hz, H-3), 7.10 (1H, *d*, *J*=7.8 Hz, H-6'), 7.30 (1H, *dd*, *J*=7.8 Hz, H-4'), 7.60 (1H, *dd*, *J*=7.8 Hz, H-5'), 7.90 (1H, *d*, *J*= 7.8 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 89.0 (C-4), 120.8 (C-3), 120.9 (C-6'), 124.1 (C-2'), 126.3 (C-4'), 132.1 (C-3'), 134.3 (C-5'), 136.9 (C-2), 153.0 (C-1'), 159.3 (CO-C-2), 159.9 (C-5), 166.1 (CO-C-2'); Anal. Calcd for $C_{12}H_8O_6$: C, 58.07; H, 3.25. Found: C, 57.99; H, 3.26。

5-(2'-Carboxyl-6'-methylphenoxy)furan-2-carboxylic acid (42)之合成[55]

秤取ethyl 5-(2'-methoxycarbonyl-6'-methylphenoxy)furan-2-carboxylate (**22**) 3.04 g (0.01 mol)，**其合成方法同化合物 41，得到**5-(2'-carboxyl-6'-methylphenoxy)furan-2-carboxylic acid (**42**)**之白色粉末狀結晶** 1.59 g (**產率** 60.5%)。mp: 181.5-182 ℃; EIMS *m/z* (rel. int): 262 $[M]^+$ (5.7), 134 (100); UV λ_{max}nm (MeOH) (logε): 274 (4.72), 208 (4.58); IR (KBr) cm^{-1}: 1686 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.18 (3H, *s*, CH_3-6'), 5.10 (1H, *d*, *J*=3.6 Hz, H-4), 7.06 (1H, *d*, *J*=3.6 Hz, H-3), 7.33 (1H, *dd*, *J*=7.6 Hz, H-4'), 7.58 (1H, *d*, *J*=7.6 Hz, H-5'), 7.72 (1H, *d*, *J*=7.6 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 15.7 (CH_3-6'), 85.6 (C-4), 121.4 (C-3), 125.2 (C-2'), 126.9 (C-4'), 130.0 (C-3'), 131.9 (C-6'), 135.7 (C-2), 136.0 (C-5'), 150.2 (C-1'), 159.2 (CO-C-2), 161.0 (C-5), 166.0 (CO-C-2'); Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.47; H, 3.83。

5-(2'-Carboxyl-5'-methylphenoxy)furan-2-carboxylic acid (43)之合成[55]

秤取ethyl

5-(2'-methoxycarbonyl-5'-methylphenoxy)furan-2-carboxylate (**23**) 3.04 g (0.01 mol)，其合成方法同化合物 41，得到 5-(2'-carboxyl-5'-methylphenoxy)furan-2-carboxylic acid (**43**)之白色粉末狀結晶 1.70 g (產率 65.0%)。mp: 181.5-182 ℃; EIMS *m/z* (rel. int): 262 $[M]^+$ (8.6), 134 (100); UV λ_{max}nm (MeOH) (logε): 270 (4.10), 235 (4.03); IR (KBr) cm^{-1}: 1694 (C=O), 1651 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.33 (3H, *s*, CH_3-5'), 5.48 (1H, *d*, *J*=3.6 Hz, H-4), 7.10 (1H, *s*, H-6'), 7.17 (1H, *d*, *J*=3.6 Hz, H-3), 7.19 (1H, *d*, *J*=8.0 Hz, H-4'), 7.80 (1H, *d*, *J*=8.0 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 21.2 (CH_3-5'), 88.7 (C-4), 120.8 (C-3), 121.1 (C-2'), 121.5 (C-6'), 127.1 (C-4'), 132.2 (C-3'), 136.4 (C-2), 145.4 (C-5'), 153.1 (C-1'), 159.2 (CO-C-2), 160.2 (C-5), 165.8 (CO-C-2'); Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.41; H, 3.85。

5-(2'-Carboxyl-4'-methylphenoxy)furan-2-carboxylic acid (44)之合成[55]

秤取 ethyl 5-(2'-methoxycarbonyl-4'-methylphenoxy)furan-2-carboxylate (**24**) 3.04 g (0.01 mol)，其合成方法同化合物 41，得到 5-(2'-carboxyl-4'-methylphenoxy)furan-2-carboxylic acid (**44**)之白色粉末狀結晶 1.86 g (產率 71.0%)。mp: 183.5-184 ℃; EIMS *m/z* (rel. int): 262 $[M]^+$ (8.9), 134 (100); UV λ_{max}nm (MeOH) (logε): 273 (4.38); IR (KBr) cm^{-1}: 1690 (C=O), 1663 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.34 (3H, *s*, CH_3-4'), 5.43 (1H, *d*, *J*=3.6 Hz, H-4), 7.15 (1H, *d*, *J*=3.6 Hz, H-3), 7.18 (1H, *d*, *J*=8.3 Hz, H-6'), 7.44 (1H, *d*, *J*=8.3, 1.9 Hz, H-5'), 7.69 (1H, *d*, *J*= 1.9 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 20.5 (CH_3-4'), 88.2 (C-4), 121.2 (C-3), 121.3 (C-6'), 123.7 (C-2'), 132.3 (C-3'), 134.8 (C-5'), 135.9 (C-4'), 136.3 (C-2), 150.8 (C-1'), 159.2 (CO-C-2), 160.6 (C-5), 166.0 (CO-C-2'); Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.83; H, 3.83。

5-(2'-Carboxyl-3'-methylphenoxy)furan-2-carboxylic acid (45)之合成

秤取 ethyl 5-(2'-ethoxycarbonyl-3'-methylphenoxy)furan-2-carboxylate (**25**) 3.18 g (0.01 mol)，其合成方法同化合物 41，得到 5-(2'-carboxyl-3'-methylphenoxy)furan-2-carboxylic acid (**45**)之白色粉末狀結晶1.61 g (產率61.3%)。mp: 169.5-170 ℃; EIMS *m/z* (rel. int): 262 $[M]^+$ (4.6), 135 (100); UV λ_{max}nm (MeOH) (logε): 268 (4.70), 208 (4.56); IR (KBr) cm^{-1}: 1701 (C=O), 1663 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.32 (3H, *s*, CH_3-3'), 5.73 (1H, *d*, *J*=3.8 Hz, H-4), 7.01

(1H, *d*, *J*=8.1 Hz, H-4'), 7.17 (1H, *d*, *J*=7.7 Hz, H-6'), 7.20 (1H, *d*, *J*=3.8 Hz, H-3), 7.37 (1H, *t*, *J*= 8.1, 7.7 Hz, H-5'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 19.1 (CH_3-3'), 90.6 (C-4), 115.9 (C-4'), 120.7 (C-3), 127.0 (C-2'), 127.3 (C-6'), 130.7 (C-5'), 136.8 (C-2), 136.8 (C-3'), 150.9 (C-1'), 158.8 (CO-C-2), 158.9 (C-5), 167.5 (CO-C-2'); Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.37; H, 3.85。

5-(2'-Carboxyl-6'-methoxyphenoxy)furan-2-carboxylic acid (46)之合成

秤取 ethyl 5-(2'-methoxycarbonyl-6'-methoxyphenoxy)furan-2-carboxylate (**26**) 3.20 g (0.01 mol)，**其合成方法同化合物41，得到** 5-(2'-carboxyl-6'-methoxyphenoxy)furan-2-carboxylic acid (**46**)**之白色粉末狀結晶**1.72 g (**產率**61.8%)。mp: 195.5-196 ℃; EIMS *m/z* (rel. int): 278 $[M]^+$ (23.5), 151 (100); UV λ_{max}nm (MeOH) (logε): 278 (4.71), 206 (4.53); IR (KBr) cm^{-1}: 1682 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.79 (3H, *s*, OCH_3-6'), 5.20 (1H, *d*, *J*=3.6 Hz, H-4), 7.11 (1H, *d*, *J*=3.6 Hz, H-3), 7.34-7.47 (3H, *m*, H-3', 4', and 5'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 56.6 (OCH_3-6'), 85.4 (C-4), 117.5 (C-5'), 121.3 (C-3), 122.5 (C-3'), 126.1 (C-2'), 127.3 (C-4'), 135.2 (C-2), 140.5 (C-1'), 152.0 (C-6'), 159.0 (CO-C-2), 161.1 (C-5), 165.7 (CO-C-2'); Anal. Calcd for $C_{13}H_{10}O_7$: C, 56.12; H, 3.62. Found: C, 56.04; H, 3.61。

5-(2'-Carboxyl-5'-methoxyphenoxy)furan-2-carboxylic acid (47)之合成

秤取 ethyl 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furan-2-carboxylate (**27**) 3.20 g (0.01 mol)，**其合成方法同化合物41，得到** 5-(2'-carboxyl-5'-methoxyphenoxy)furan-2-carboxylic acid (**47**)**之白色粉末狀結晶**1.98 g (**產率**71.0%)。mp: 206-206.5 ℃; EIMS *m/z* (rel. int): 278 $[M]^+$ (13.9), 151 (100); UV λ_{max}nm (MeOH) (logε): 256 (4.27), 208 (4.41); IR (KBr) cm^{-1}: 1694 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.81 (3H, *s*, OCH_3-5'), 5.48 (1H, *d*, *J*=3.6 Hz, H-4), 6.85 (1H, *d*, *J*=2.5 Hz, H-6'), 6.96 (1H, *dd*, *J*=8.8, 2.5 Hz, H-4'), 7.16 (1H, *d*, *J*=3.6 Hz, H-3), 7.90 (1H, *d*, *J*=8.8 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 56.2 (OCH_3-5'), 88.1 (C-4), 107.0 (C-6'), 112.0 (C-4'), 115.4 (C-2'), 121.0 (C-3), 134.0 (C-3'), 136.1 (C-2), 154.6 (C-1'), 159.0 (CO-C-2), 160.1 (C-5'), 163.9 (C-5), 165.2 (CO-C-2'); Anal. Calcd for $C_{13}H_{10}O_7$: C, 56.12; H, 3.62. Found: C, 55.98; H, 3.63。

5-(2'-Carboxyl-4'-methoxyphenoxy)furan-2-carboxylic acid (48)之合

成

秤取 ethyl 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furan-2-carboxylate (**28**) 3.20 g (0.01 mol)，**其合成方法同化合物41，得到** 5-(2'-carboxyl-4'-methoxyphenoxy)furan-2-carboxylic acid (**48**)**之白色粉末狀結晶**1.80 g (**產率**64.9%)。mp: 209.5-210 ℃; EIMS *m/z* (rel. int): 278 $[M]^+$ (9.2), 150 (100); UV λ_{max}nm (MeOH) (logε): 275 (4.35), 209 (4.30); IR (KBr) cm^{-1}: 1701 (C=O), 1655 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.80 (3H, *s*, OCH_3-4'), 5.33 (1H, *d*, *J*=3.6 Hz, H-4), 7.14 (1H, *d*, *J*=3.6 Hz, H-3), 7.20 (1H, *dd*, *J*=8.9, 2.9 Hz, H-5'), 7.30 (1H, *d*, *J*=8.9 Hz, H-6'), 7.36 (1H, *d*, *J*=2.9 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 56.0 (OCH_3-4'), 87.2 (C-4), 116.0 (C-3'), 119.7 (C-5'), 121.1 (C-3), 123.2 (C-6'), 124.9 (C-2'), 135.9 (C-2), 146.0 (C-1'), 156.9 (C-4'), 159.0 (CO-C-2), 161.2 (C-5), 165.5 (CO-C-2'); Anal. Calcd for $C_{13}H_{10}O_7$: C, 56.12; H, 3.62. Found: C, 55.91; H, 3.61。

5-(2'-Carboxyl-5'-chlorophenoxy)furan-2-carboxylic acid (50)之合成

秤取 ethyl 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furan-2-carboxylate (**30**) 3.25 g (0.01 mol)，**其合成方法同化合物41，得到** 5-(2'-carboxyl-5'-chlorophenoxy)furan-2-carboxylic acid (**50**)**之白色粉末狀結晶**1.53 g (**產率**63.4%)。mp: 191-191.5 ℃; EIMS *m/z* (rel. int): 284 $[M]^+$+2 (1.0), 282 $[M]^+$ (3.0), 155 (100); UV λ_{max}nm (MeOH) (logε): 268 (4.55), 238 (4.54), 206 (4.43); IR (KBr) cm^{-1}: 1701 (C=O), 1678 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.64 (1H, *d*, *J*=3.6 Hz, H-4), 7.18 (1H, *d*, *J*= 3.6 Hz, H-3), 7.45-7.50 (2H, *m*, H-4', 6'), 7.91 (1H, *d*, *J*=7.7 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 89.3 (C-4), 120.8 (C-3), 121.2 (C-6'), 122.7 (C-2'), 126.4 (C-4'), 133.6 (C-3'), 136.7 (C-2), 138.0 (C-5'), 153.5 (C-1'), 159.0 (CO-C-2), 159.1 (C-5), 165.0 (CO-C-2'); Anal. Calcd for $C_{12}H_7ClO_6$: C, 51.00; H, 2.50. Found: C, 51.12; H, 2.49。

5-(2'-Carboxyl-4'-chlorophenoxy)furan-2-carboxylic acid (51)之合成

秤取 ethyl 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furan-2-carboxylate (**31**) 3.25 g (0.01 mol)，**其合成方法同化合物41，得到** 5-(2'-carboxyl-4'-chlorophenoxy)furan-2-carboxylic acid (**51**)**之白色粉末狀結晶**1.63 g (**產率**67.8%)。mp: 200.5-201 ℃; EIMS *m/z* (rel. int): 284 $[M]^+$+2 (4.0), 282 $[M]^+$ (12.0), 155 (100); UV λ_{max}nm (MeOH) (logε): 272 (4.61); IR (KBr) cm^{-1}: 1694 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.63 (1H, *d*, *J*=3.6 Hz, H-4), 7.19 (1H, *d*, *J*=3.6 Hz, H-3),

7.34 (1H, *d*, *J*=8.8 Hz, H-6'), 7.71 (1H, *dd*, *J*=8.8, 2.7 Hz, H-5'), 7.87 (1H, *d*, *J*=2.7 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 89.2 (C-4), 120.8 (C-3), 122.9 (C-6'), 125.5 (C-2'), 130.0 (C-4'), 131.2 (C-3'), 133.8 (C-5'), 136.6 (C-2), 151.6 (C-1'), 158.9 (CO-C-2), 159.3 (C-5), 164.6 (CO-C-2'); Anal. Calcd for $C_{12}H_7ClO_6$: C, 51.00; H, 2.50. Found: C, 50.81; H, 2.51。

5-(2'-Carboxyl-4'-bromophenoxy)furan-2-carboxylic acid (52)之合成

秤取 ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**) 3.69 g (0.01 mol)，**其合成方法同化合物41，得到** 5-(2'-carboxyl-4'-bromophenoxy)furan-2-carboxylic acid (**52**)**之白色粉末狀結晶**1.96 g (**產率**68.9%)。mp: 211.5-212 ℃; EIMS *m/z* (rel. int): 330 $[M]^+$+2 (4.1), 328 $[M]^+$ (4.1), 198 (100); UV λ_{max}nm (MeOH) (logε): 270 (4.32), 209 (4.29); IR (KBr) cm^{-1}: 1694 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.64 (1H, *d*, *J*=3.6 Hz, H-4), 7.19 (1H, *d*, *J*=3.6 Hz, H-3), 7.27 (1H, *d*, *J*= 8.8 Hz, H-6'), 7.82 (1H, *dd*, *J*=8.8, 2.6 Hz, H-5'), 7.99 (1H, *d*, *J*=2.6 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 89.3 (C-4), 117.9 (C-4'), 120.8 (C-3), 123.2 (C-6'), 125.8 (C-2'), 134.2 (C-3'), 136.7 (C-2), 136.8 (C-5'), 152.1 (C-1'), 158.9 (CO-C-2), 159.2 (C-5), 164.5 (CO-C-2'); Anal. Calcd for $C_{12}H_7BrO_6$: C, 44.06; H, 2.16. Found: C, 44.15; H, 2.15。

5-(2'-Carboxyl-4'-iodophenoxy)furan-2-carboxylic acid (53)之合成

秤取 ethyl 5-(2'-methoxycarbonyl-4'-iodophenoxy)furan-2-carboxylate (**33**) 4.16 g (0.01 mol)，**其合成方法同化合物41，得到** 5-(2'-carboxyl-4'-iodophenoxy)furan-2-carboxylic acid (**53**)**之白色粉末狀結晶**2.49 g (**產率**66.6%)。mp: 231.5-232 ℃; EIMS *m/z* (rel. int): 374 $[M]^+$ (12.8), 247 (100); UV λ_{max}nm (MeOH) (logε): 267 (4.22), 215 (4.22); IR (KBr) cm^{-1}: 1690 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.64 (1H, *d*, *J*=3.6 Hz, H-4), 7.10 (1H, *d*, *J*=8.6 Hz, H-6'), 7.19 (1H, *d*, *J*=3.6 Hz, H-3), 7.96 (1H, *dd*, *J*=8.6, 2.3 Hz, H-5'), 8.14 (1H, *d*, *J*=2.3 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 89.4 (C-4), 90.2 (C-4'), 120.8 (C-3), 123.1 (C-6'), 125.8 (C-2'), 136.6 (C-2), 140.0 (C-3'), 142.6 (C-5'), 152.8 (C-1'), 158.9 (CO-C-2), 159.1 (C-5), 164.5 (CO-C-2'); Anal. Calcd for $C_{12}H_7IO_6$: C, 38.53; H, 1.89. Found: C, 38.68; H, 1.88。

伍、Substituted furo[2,3-*b*]chromone-2-carboxylic acid ethyl esters (61-68 及 70-73)之合成

Ethyl furo[2,3-*b*]chromone-2-carboxylate (61)之合成[55]

量取甲苯 20 mL 及 phosphorus pentoxide 3.5 g (0.025 mol)加入三頸瓶中，慢慢滴加 absolute alcohol 2 mL (0.034 mol)，置於 100 ℃下加熱攪拌迴流 1 小時，使其形成 polyphosphoric acid ethyl ester (PPE)，將 5-(2'-carboxylphenoxy)furan-2-carboxylic acid (**41**) 1.0 g (0.0038 mol) 慢慢加入攪拌迴流 6 小時，以 TLC 檢查後放冷攪拌，而後加入 10 mL 水破壞 PPE，甲苯層以 5% NaOH 溶液 15 mL 清洗，再以水洗掉 NaOH，取甲苯層以無水硫酸鎂脫水，減壓濃縮為棕色固體，經矽膠管柱層析法(氯仿)分離純化，再經減壓濃縮至乾得到棕色固體，粗產物以正己烷-氯仿做再結晶，得到 ethyl furo[2,3-*b*]chromone-2-carboxylate (**61**)之淡黃色針狀結晶 0.290 g (產率 27.8%)。mp: 145-147 ℃; EIMS *m/z* (rel. int): 258 $[M]^+$ (89.7), 186 (100); UV λ_{max}nm (MeOH) (logε): 305 (4.45), 261 (4.55), 244 (4.59), 215 (4.45); IR (KBr) cm^{-1}: 1725 (COO), 1671 (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 4.39 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.47 (1H, *ddd*, *J*=8.0, 1.2 Hz, H-6), 7.55 (1H, *dd*, *J*=8.0, 1.2 Hz, H-8), 7.63 (1H, *s*, H-3), 7.72 (1H, *ddd*, *J*=8.0, 1.7 Hz, H-7), 8.29 (1H, *dd*, *J*=8.0, 1.7 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 ($OCH_2\underline{CH_3}$), 61.7 ($O\underline{CH_2}CH_3$), 104.6 (C-3a), 114.1 (C-3), 117.9 (C-6), 123.1 (C-4a), 125.9 (C-8), 126.8 (C-5), 134.1 (C-7), 138.4 (C-2), 153.3 (C-8a), 157.7 (COO), 162.8 (C-9a), 173.4 (CO); Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.11; H, 3.90. Found: C, 65.19; H, 3.91。

Ethyl 8-methylfuro[2,3-*b*]chromone-2-carboxylate (62)之合成[55]

其合成方法同化合物61，量取5-(2'-carboxyl-6'-methylphenoxy)-furan-2-carboxylic acid (**42**) 1.0 g (0.0036 mol)慢慢加入攪拌迴流6小時，得到ethyl 8-methylfuro[2,3-*b*]chromone-2-carboxylate (**62**)之淡黃色

針狀結晶0.320 g (**產率**30.8%)。mp: 157-159 **℃**; EIMS *m/z* (rel. int): 272 $[M]^+$ (100); UV λ_{max}nm (MeOH) (logε): 305 (4.82), 269 (4.83); IR (KBr) cm^{-1}: 1725 (COO), 1667 (CO); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 1.41 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 2.55 (3H, *s*, CH_3), 4.42 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.38 (1H, *dd*, *J*=7.8 Hz, H-6), 7.57 (1H, *d*, *J*=7.8 Hz, H-7), 7.66 (1H, *s*, H-3), 8.16 (1H, *d*, *J*=7.8 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 14.2 ($OCH_2\underline{CH_3}$), 15.6 (CH_3), 61.7 ($O\underline{CH_2}CH_3$), 104.3 (C-3a), 114.1 (C-3), 123.0 (C-4a), 124.5 (C-5), 125.4 (C-6), 127.5 (C-8), 135.4 (C-7), 138.3 (C-2), 151.9 (C-8a), 157.8 (<u>C</u>OO), 162.9 (C-9a), 173.8 (<u>C</u>O); Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.25; H, 4.45。

Ethyl 7-methylfuro[2,3-*b*]chromone-2-carboxylate (63)之合成[55]

其合成方法同化合物61，量取5-(2'-carboxyl-5'-methylphenoxy)-furan-2-carboxylic acid (**43**) 1.0 g (0.0036 mol)**慢慢加入攪拌迴流**6**小時, 得到**ethyl 7-methylfuro[2,3-*b*]chromone-2-carboxylate (**63**)**之淡黃色針狀結晶**0.280 g (**產率**26.9%)。mp: 160.5-161 **℃**; EIMS *m/z* (rel. int): 272 $[M]^+$ (93.2), 200 (100); UV λ_{max}nm (MeOH) (logε): 306 (4.22), 274 (4.35), 248 (4.41), 215 (4.17); IR (KBr) cm^{-1}: 1721 (COO), 1655 (CO); ^{1}H-NMR (200 MHz, $CDCl_3$): **δ** 1.40 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 2.52 (3H, *s*, CH_3), 4.41 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.29 (1H, *d*, *J*=8.1 Hz, H-6), 7.37 (1H, *s*, H-8), 7.65 (1H, *s*, H-3), 8.19 (1H, *d*, *J*=8.1 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 14.2 ($OCH_2\underline{CH_3}$), 21.7(CH_3), 61.6 ($O\underline{CH_2}CH_3$), 104.5 (C-3a), 114.2 (C-3), 117.8 (C-8), 120.7 (C-4a), 126.5 (C-5), 127.2 (C-6), 138.2 (C-2), 145.7 (C-7), 153.4 (C-8a), 157.8 (<u>C</u>OO), 162.8 (C-9a), 173.5 (<u>C</u>O); Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.31; H, 4.43。

Ethyl 6-methylfuro[2,3-*b*]chromone-2-carboxylate (64)之合成[55]

其合成方法同化合物61，量取5-(2'-carboxyl-4'-methylphenoxy)-furan-2-carboxylic acid (**44**) 1.0 g (0.0036 mol)**慢慢加入攪拌迴流**6**小時, 得到**ethyl 6-methylfuro[2,3-*b*]chromone-2-carboxylate (**64**)**之淡黃色針狀結晶**0.290 g (**產率**27.9%)。mp: 160-162 **℃**; EIMS *m/z* (rel. int): 272 $[M]^+$ (100); UV λ_{max}nm (MeOH) (logε): 309 (4.52), 266 (4.68), 243 (4.74), 220 (4.66); IR (KBr) cm^{-1}: 1721 (COO), 1659 (CO); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 1.40 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 2.48 (3H, *s*, CH_3), 4.41 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.49 (1H, *d*, *J*=8.0 Hz, H-8), 7.52 (1H, *dd*, *J*=8.0, 1.4 Hz, H-7), 7.65 (1H, *s*, H-3), 8.09 (1H, *d*, *J*=1.4 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 14.2 ($OCH_2\underline{CH_3}$), 20.8 (CH_3), 61.6 ($O\underline{CH_2}CH_3$), 104.5 (C-3a), 114.2 (C-3), 117.6 (C-8), 122.7 (C-4a), 126.3 (C-5), 135.2 (C-7), 136.0 (C-6), 138.3 (C-2), 151.6 (C-8a), 157.8

(COO), 162.9 (C-9a), 173.6 (CO); Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.05; H, 4.45。

Ethyl 5-methylfuro[2,3-*b*]chromone-2-carboxylate (65)之合成

其合成方法同化合物61，量取5-(2'-carboxyl-3'-methylphenoxy)-furan-2-carboxylic acid (**45**) 1.0 g (0.0036 mol)**慢慢加入攪拌迴流**6**小時，得到**ethyl 5-methylfuro[2,3-*b*]chromone-2-carboxylate (**65**)**之淡黃色針狀結晶**0.208 g (**產率**20.0%)。mp: 169-170 ℃; EIMS *m/z* (rel. int): 272 $[M]^+$ (100); UV λ_{max}nm (MeOH) (logε): 313 (4.59), 245 (4.74), 223 (4.66); IR (KBr) cm^{-1}: 1736 (COO), 1670 (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 2.91 (3H, *s*, CH_3), 4.39 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.22 (1H, *d*, *J*=8.1 Hz, H-6), 7.39 (1H, *d*, *J*=8.0 Hz, H-8), 7.54 (1H, *t*, *J*=8.1, 8.0 Hz, H-7), 7.60 (1H, *s*, H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 ($OCH_2\underline{CH_3}$), 23.0 (CH_3), 61.7 ($O\underline{CH_2}CH_3$), 105.3 (C-3a), 114.5 (C-3), 116.2 (C-8), 121.4 (C-4a), 129.1 (C-6), 132.8 (C-7), 138.2 (C-2), 142.5 (C-5), 155.1 (C-8a), 157.9 (COO), 162.0 (C-9a), 175.8 (CO); Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.41; H, 4.43。

Ethyl 8-methoxyfuro[2,3-*b*]chromone-2-carboxylate (66)之合成

其合成方法同化合物61，量取5-(2'-carboxyl-6'-methoxyphenoxy)-furan-2-carboxylic acid (**46**) 1.0 g (0.0035 mol)**慢慢加入攪拌迴流**6**小時，得到**ethyl 8-methoxyfuro[2,3-*b*]chromone-2-carboxylate (**66**)**之白色粉末狀結晶**0.246 g (**產率**23.7%)，mp: >300 ℃; EIMS *m/z* (rel. int): 288 $[M]^+$ (100); UV λ_{max}nm (MeOH) (logε): 316 (4.48), 250 (4.73), 227 (4.79); IR (KBr) cm^{-1}: 1736 (COO), 1677 (CO); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.31 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 3.98 (3H, *s*, OCH_3), 4.33 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.43-7.55 (2H, *m*, H-5, 7), 7.67 (1H, *dd*, *J*=7.3, 2.0 Hz, H-6), 7.75 (1H, *s*, H-3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.3 ($OCH_2\underline{CH_3}$), 56.8 (OCH_3), 61.7 ($O\underline{CH_2}CH_3$), 104.4 (C-3a), 114.4 (C-3), 116.7 (C-6), 116.7 (C-7), 123.8 (C-4a), 126.2 (C-5), 138.0 (C-2), 143.1 (C-8a), 148.5 (C-8), 157.5 (COO), 162.9 (C-9a), 173.0 (CO); Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.19. Found: C, 62.58; H, 4.20。

Ethyl 7-methoxyfuro[2,3-*b*]chromone-2-carboxylate (67)之合成

其合成方法同化合物61，量取5-(2'-carboxyl-5'-methoxyphenoxy)-furan-2-carboxylic acid (**47**) 1.0 g (0.0035 mol)**慢慢加入攪拌迴流**6**小時，得到**ethyl 7-methoxyfuro[2,3-*b*]chromone-2-carboxylate (**67**)**之黃色粉末狀結晶**0.298 g (**產率**28.7%)。mp: 171-172 ℃; EIMS *m/z* (rel. int): 288 $[M]^+$ (100); UV λ_{max}nm (MeOH) (logε): 291 (4.79), 248 (4.79); IR

(KBr) cm^{-1}: 1723 (COO), 1657 (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 3.91 (3H, *s*, OCH_3), 4.38 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 6.94 (1H, *d*, *J*=2.4 Hz, H-8), 7.01 (1H, *dd*, *J*=8.8, 2.4 Hz, H-6), 7.61 (1H, *s*, H-3), 8.19 (1H, *d*, *J*=8.8 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 ($OCH_2\underline{CH_3}$), 56.0 (OCH_3), 61.6 ($O\underline{CH_2}CH_3$), 101.1 (C-8), 104.4 (C-3a), 114.2 (C-3), 114.2 (C-6), 116.7 (C-4a), 128.1 (C-5), 138.2 (C-2), 155.1 (C-7), 157.9 (<u>C</u>OO), 162.8 (C-9a), 164.4 (C-8a), 173.0 (<u>C</u>O); Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.19. Found: C, 62.31; H, 4.18。

Ethyl 6-methoxyfuro[2,3-*b*]chromone-2-carboxylate (68)之合成

其合成方法同化合物61，量取5-(2'-carboxyl-4'-methoxyphenoxy)-furan-2-carboxylic acid (**48**) 1.0 g (0.0035 mol)**慢慢加入攪拌迴流**6**小時，得到**ethyl 6-methoxyfuro[2,3-*b*]chromone-2-carboxylate (**68**)**之黃色粉末狀結晶**0.216 g (**產率**20.8**%**)。mp: 147-148 **℃**; EIMS *m/z* (rel. int): 288 $[M]^+$ (100); UV λ_{max}nm (MeOH) (logε): 321 (4.06), 246 (4.43), 218 (4.46); IR (KBr) cm^{-1}: 1723 (COO), 1677 (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 3.89 (3H, *s*, OCH_3), 4.39 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.27 (1H, *dd*, *J*=9.4, 3.2 Hz, H-7), 7.48 (1H, *d*, *J*=9.4 Hz, H-8), 7.64 (1H, *s*, H-3), 7.67 (1H, *d*, *J*=3.2 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 ($OCH_2\underline{CH_3}$), 56.0 (OCH_3), 61.7 ($O\underline{CH_2}CH_3$), 104.2 (C-3a), 106.8 (C-5), 114.1 (C-3), 119.2 (C-8), 123.4 (C-7), 123.8 (C-4a), 138.4 (C-2), 147.9 (C-8a), 157.4 (C-6), 157.9 (<u>C</u>OO), 163.0 (C-9a), 173.4 (<u>C</u>O); Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.19. Found: C, 62.38; H, 4.20。

Ethyl 7-chlorofuro[2,3-*b*]chromone-2-carboxylate (70)之合成

其合成方法同化合物61，量取5-(2'-carboxyl-5'-chlorophenoxy)-furan-2-carboxylic acid (**50**) 1.0 g (0.0035 mol)**慢慢加入攪拌迴流**50**分鐘，得到**ethyl 7-chlorofuro[2,3-*b*]chromone-2-carboxylate (**70**)**之淡黃色粉末狀結晶**0.240 g (**產率**23.1**%**)。mp: 203.5-204 **℃**; EIMS *m/z* (rel. int): 294 $[M]^+$ +2 (13.9), 292 $[M]^+$ (41.7), 220 (100); UV λ_{max}nm (MeOH) (logε): 302 (4.82), 275 (4.86); IR (KBr) cm^{-1}: 1723 (COO), 1664 (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 1.39 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{CH_3}$), 4.40 (2H, *q*, *J*=7.1 Hz, $O\underline{CH_2}CH_3$), 7.46 (1H, *dd*, *J*=8.6, 1.9 Hz, H-6), 7.60 (1H, *d*, *J*=1.9 Hz, H-8), 7.63 (1H, *s*, H-3), 8.25 (1H, *d*, *J*=8.6 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 ($OCH_2\underline{CH_3}$) , 61.9 ($O\underline{CH_2}CH_3$), 104.9 (C-3a), 114.0 (C-3), 118.2 (C-8), 121.8 (C-4a), 126.8 (C-6), 128.1 (C-5), 138.8 (C-2), 140.2 (C-7), 153.4 (<u>C</u>OO), 157.7 (C-8a), 162.6 (C-9a), 172.6 (<u>C</u>O); Anal. Calcd for $C_{14}H_9ClO_5$: C, 7.45; H, 3.10. Found: C, 57.56; H, 3.11。

Ethyl 6-chlorofuro[2,3-*b*]chromone-2-carboxylate (71)之合成

其合成方法同化合物61，量取5-(2'-carboxyl-4'-chlorophenoxy)-furan-2-carboxylic acid (**51**) 1.0 g (0.0035 mol)**慢慢加入攪拌迴流**70**分鐘，得到**ethyl 6-chlorofuro[2,3-*b*]chromone-2-carboxylate (**71**)**之淡黃色針狀結晶**0.209 g (**產率**20.1**%**)。mp: 201.5-202 **℃**; EIMS *m/z* (rel. int): 294 $[M]^+$ +2 (23.9), 292 $[M]^+$ (71.7), 53 (100); UV λ_{max}nm (MeOH) (logε): 311 (4.54), 260 (4.77), 241 (4.76), 221 (4.70); IR (KBr) cm^{-1}: 1730 (COO), 1663 (CO); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 1.39 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{C}H_3$), 4.40 (2H, *q*, *J*=7.1 Hz, $O\underline{C}H_2CH_3$), 7.53 (1H, *d*, *J*=8.9 Hz, H-8), 7.62 (1H, *s*, H-3), 7.67 (1H, *dd*, *J*=8.9, 2.6 Hz, H-7), 8.26 (1H, *d*, *J*= 2.6 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 14.2 ($OCH_2\underline{C}H_3$), 61.8 ($O\underline{C}H_2CH_3$), 104.6 (C-3a), 113.9 (C-3), 119.6 (C-8), 124.3 (C-4a), 126.4 (C-5), 132.0 (C-6), 134.2 (C-7), 138.8 (C-2), 151.6 (C-8a), 157.6 (<u>C</u>OO), 162.8 (C-9a), 172.2 (<u>C</u>O); Anal. Calcd for $C_{14}H_9ClO_5$: C, 57.45; H, 3.10. Found: C, 57.23; H, 3.09。

Ethyl 6-bromofuro[2,3-*b*]chromone-2-carboxylate (72)之合成

其合成方法同化合物61，量取5-(2'-carboxyl-4'-bromophenoxy)-furan-2-carboxylic acid (**52**) 1.0 g (0.0030 mol)**慢慢加入攪拌迴流**6**小時，得到**ethyl 6-bromofuro[2,3-*b*]chromone-2-carboxylate (**72**)**之黃色粉末狀結晶**0.236 g (**產率**22.9**%**)。mp: 204.5-205 **℃**; EIMS *m/z* (rel. int): 338 $[M]^+$+2 (79.2), 336 $[M]^+$ (79.2), , 53 (100); UV λ_{max}nm (MeOH) (logε): 312 (4.76), 270 (4.92); IR (KBr) cm^{-1}: 1736 (COO), 1670 (CO); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 1.39 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{C}H_3$), 4.40 (2H, *q*, *J*=7.1 Hz, $O\underline{C}H_2CH_3$), 7.46 (1H, *d*, *J*=8.9 Hz, H-8), 7.62 (1H, *s*, H-3), 7.81 (1H, *dd*, *J*=8.9, 2.5 Hz, H-7), 8.43 (1H, *d*, *J*=2.5 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): **δ** 14.2 ($OCH_2\underline{C}H_3$), 61.9 ($O\underline{C}H_2CH_3$), 104.7 (C-3a), 114.0 (C-3), 119.5 (C-6), 119.8 (C-8), 124.6 (C-4a), 129.6 (C-5), 137.0 (C-7), 138.9 (C-2), 152.2 (C-8a), 157.6 (<u>C</u>OO), 162.8 (C-9a), 172.1 (<u>C</u>O); Anal. Calcd for $C_{14}H_9BrO_5$: C, 49.87; H, 2.69. Found: C, 49.75; H, 2.68。

Ethyl 6-iodofuro[2,3-*b*]chromone-2-carboxylate (73)之合成

其合成方法同化合物 61，**量取** 5-(2'-carboxyl-4'-iodophenoxy)-furan-2-carboxylic acid (**53**)1.0 g (0.0026 mol)**慢慢加入攪拌迴流** 6 **小時，得到** ethyl 6-iodofuro[2,3-*b*]chromone-2-carboxylate (**73**)**之黃色粉末狀結晶** 0.212 g (**產率** 20.6**%**)。mp: 218.5-219 **℃**; EIMS *m/z* (rel. int): 384 $[M]^+$ (100); UV λ_{max}nm (MeOH) (logε): 315 (4.62), 245 (4.98); IR (KBr) cm^{-1}: 1725 (COO), 1663 (CO); ^{1}H NMR (200 MHz, $CDCl_3$): **δ** 1.39 (3H, *t*, *J*=7.1 Hz, $OCH_2\underline{C}H_3$), 4.40 (2H, *q*, *J*=7.1 Hz, $O\underline{C}H_2CH_3$),

7.34 (1H, *d*, *J*=8.8 Hz, H-8), 7.64 (1H, *s*, H-3), 8.00 (1H, *dd*, *J*=8.8, 2.2 Hz, H-7), 8.63 (1H, *d*, *J*= 2.2 Hz, H-5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 ($OCH_2\underline{C}H_3$), 61.9 ($O\underline{C}H_2CH_3$), 89.9 (C-6), 104.8 (C-3a), 114.0 (C-3), 120.0 (C-8), 124.8 (C-4a), 135.8 (C-5), 138.8 (C-2), 142.7 (C-7), 153.0 (C-8a), 157.7 (COO), 162.7 (C-9a), 172.0 (CO); Anal. Calcd for $C_{14}H_9IO_5$: C, 43.77; H, 2.36. Found: C, 43.61; H, 2.37。

陸、5-(2'-Alkoxycarbonyl substituted phenoxy)furfurals (81-93)之合成

5-(2'-Methoxycarbonylphenoxy)furfural (81)之合成

取 DMSO 150 mL 於三頸瓶，加入 methyl salicylate 18.258 g (0.12 mol)，使其攪拌，取 60% NaH 4.8 g (0.12 mol)分次加入，繼而取 5-nitrofurfural 14.109 g (0.1 mol)溶於 90 mL DMSO 中，慢慢滴加此溶液至上述白色懸浮液中，於室溫下攪拌 23 小時後，倒入冰水中攪拌，以氯仿抽取，再以 5% KOH 溶液清洗，再以水洗掉 KOH，氯仿層以無水硫酸鎂脫水，減壓濃縮為深棕色液體，經矽膠管柱層析法(氯仿)分離純化，得到 5-(2'-methoxycarbonylphenoxy)furfural (**81**)之棕色液體 3.838 g (產率 13.0%)。EIMS *m/z* (rel. int): 246 $[M]^+$ (19.0), 126 (100); UV λ_{max}nm (MeOH) (log ε): 302 (4.60), 209 (4.36); IR (KBr) cm^{-1}: 1729 (C=O), 1675 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.82 (3H, *s*, $COO\underline{C}H_3$), 5.44 (1H, *d*, *J*= 3.7 Hz, H-4), 7.20 (1H, *d*, *J*=3.7 Hz, H-3), 7.25 (1H, *d*, *J*=1.1 Hz, H-6'), 7.35 (1H, *ddd*, *J*=7.7, 1.1 Hz, H-4'), 7.58 (1H, *ddd*, *J*=7.7, 1.8 Hz, H-5'), 7.99 (1H, *dd*, *J*=7.7, 1.8 Hz, H-3'), 9.37 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.4 ($COO\underline{C}H_3$), 89.0 (C-4), 121.6 (C-3), 123.0 (C-2'), 125.3 (C-6'), 126.3 (C-4'), 132.3 (C-3'), 134.1 (C-5'), 144.8 (C-2), 152.7 (C-1'), 163.1 (C-5), 164.8 ($\underline{C}OOCH_3$), 175.6 ($\underline{C}HO$)。

5-(2'-Methoxycarbonyl-6'-methylphenoxy)furfural (82)之合成

取 DMSO 150 mL 於三頸瓶，加入 2-hydroxy-3-methylbenzoic acid methyl ester (**2**) 19.938 g (0.12 mol)，其合成方法同化合物 **81**，經矽膠管柱層析法(氯仿)分離純化，得到 5-(2'-methoxycarbonyl-6'-methyl-phenoxy)furfural (**82**)之棕色液體 3.707 g (產率 11.9%)。EIMS *m/z* (rel. int): 260 $[M]^+$ (39.2), 134 (100); UV λ_{max}nm (MeOH) (log ε): 302 (4.58); IR (KBr) cm^{-1}: 1736 (C=O), 1670 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$):

δ 2.27 (3H, *s*, CH_3-6'), 3.77 (3H, *s*, COO$\underline{CH_3}$), 5.23 (1H, *d*, *J*=3.8 Hz, H-4), 7.18 (1H, *d*, *J*=3.8 Hz, H-3), 7.29 (1H, *t*, *J*=7.6 Hz, H-4'), 7.48 (1H, *dd*, *J*=7.6, 1.7 Hz, H-5'), 7.83 (1H, *dd*, *J*=7.6, 1.7 Hz, H-3'), 9.34 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.9 (CH_3-6'), 52.4 (COO$\underline{CH_3}$), 87.0 (C-4), 123.7 (C-3), 126.5 (C-4'), 126.5 (C-6'), 130.0 (C-3'), 132.1 (C-2'), 136.0 (C-5'), 144.5 (C-2), 150.3 (C-1'), 163.6 (C-5), 165.0 ($\underline{C}OOCH_3$), 175.3 ($\underline{C}HO$)。

5-(2'-Methoxycarbonyl-5'-methylphenoxy)furfural (83)之合成

取 DMSO 150 mL **於三頸瓶, 加入** 2-hydroxy-4-methylbenzoic acid methyl ester (**3**) 19.938 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱層析法(氯仿)分離純化，得到** 5-(2'-methoxycarbonyl-5'-methyl-phenoxy)furfural (**83**)**之棕色粉末狀結晶** 3.162 g (**產率** 10.1%)。mp: 60.5-61.5 **℃**; EIMS *m/z* (rel. int): 260 $[M]^+$ (41.0), 134 (100); UV λ $_{max}$nm (MeOH) (log ε): 301 (4.79), 231 (4.55), 208 (4.55); IR (KBr) cm^{-1}: 1723 (C=O), 1670 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.38 (3H, *s*, CH_3-5'), 3.77 (3H, *s*, COO$\underline{CH_3}$), 5.40 (1H, *d*, *J*=3.8 Hz, H-4), 7.00 (1H, *s*, H-6'), 7.13 (1H, *d*, *J*= 8.0 Hz, H-4'), 7.18 (1H, *d*, *J*=3.8 Hz, H-3), 7.87 (1H, *d*, *J*=8.0 Hz, H-3'), 9.34 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4 (CH_3-5'), 52.2 (COO$\underline{CH_3}$), 88.9 (C-4), 119.9 (C-2'), 122.2 (C-6'), 125.4 (C-3), 127.2 (C-4'), 132.3 (C-3'), 144.7 (C-2), 145.6 (C-5'), 152.7 (C-1'), 163.3 (C-5), 164.8 ($\underline{C}OOCH_3$), 175.5 ($\underline{C}HO$)。

5-(2'-Methoxycarbonyl-4'-methylphenoxy)furfural (84)之合成

取 DMSO 150 mL **於三頸瓶, 加入** 2-hydroxy-5-methylbenzoic acid methyl ester (**4**) 19.938 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱層析法(氯仿)分離純化，得到** 5-(2'-methoxycarbonyl-4'-methyl-phenoxy)furfural (**84**)**之棕色液體** 4.361 g (**產率** 14.0%)。EIMS *m/z* (rel. int): 260 $[M]^+$ (27.5), 134 (100); UV λ $_{max}$nm (MeOH) (log ε): 311 (3.99), 238 (4.16), 211 (4.60); IR (KBr) cm^{-1}: 1729 (C=O), 1677 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (3H, *s*, CH_3-4'), 3.78 (3H, *s*, COO$\underline{CH_3}$), 5.36 (1H, *d*, *J*=3.7 Hz, H-4), 7.10 (1H, *d*, *J*=8.3 Hz, H-6'), 7.16 (1H, *d*, *J*=3.7 Hz, H-3), 7.35 (1H, *dd*, *J*=8.3, 2.3 Hz, H-5'), 7.76 (1H, *d*, *J*=2.3 Hz, H-3'), 9.33 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.6 (CH_3-4'), 52.3 (COO$\underline{CH_3}$), 88.5 (C-4), 121.6 (C-6'), 122.6 (C-2'), 125.4 (C-3), 132.6 (C-3'), 134.7 (C-5'), 136.4 (C-4'), 144.7 (C-2), 150.4 (C-1'), 163.6 (C-5), 165.0 ($\underline{C}OOCH_3$), 175.5 ($\underline{C}HO$)。

5-(2'-Ethoxycarbonyl-3'-methylphenoxy)furfural (85)之合成

取 DMSO 150 mL **於三頸瓶, 加入** 2-hydroxy-6-methylbenzoic acid ethyl ester 21.624 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱**

層析法(氯仿)分離純化，得到 5-(2'-ethoxycarbonyl-3'-methylphenoxy)-furfural (**85**)之黃色液體 6.225 g (產率 18.9%)。EIMS *m/z* (rel. int): 274 $[M]^+$ (30.6), 112 (100); UV λ_{max}nm (MeOH) (log ε): 301 (4.39), 210 (4.58); IR (KBr) cm^{-1}: 1736 (C=O), 1677 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 2.36 (3H, *s*, CH_3-3'), 4.29 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.48 (1H, *d*, *J*=3.7 Hz, H-4), 6.99 (1H, *d*, *J*=7.9 Hz, H-6'), 7.10 (1H, *d*, *J*=7.9 Hz, H-4'), 7.17 (1H, *d*, *J*=3.7 Hz, H-3), 7.30 (1H, *t*, *J*=7.9 Hz, H-5'), 9.35 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 ($COOCH_2\underline{CH_3}$), 19.5 (CH_3-3'), 61.5 ($COO\underline{CH_2}CH_3$), 89.6 (C-4), 117.1 (C-6'), 125.0 (C-3), 126.2 (C-2'), 128.0 (C-4'), 130.8 (C-5'), 138.4 (C-3'), 144.8 (C-2), 150.9 (C-1'), 162.8 (C-5), 166.0 ($\underline{C}OOCH_2CH_3$), 175.6 ($\underline{C}HO$)。

5-(2'-Methoxycarbonyl-6'-methoxyphenoxy)furfural (86)之合成

取 DMSO 150 mL 於三頸瓶，加入 2-hydroxy-3-methoxybenzoic acid methyl ester (**6**) 21.864 g (0.12 mol)，其合成方法同化合物 **81**，經矽膠管柱層析法(正己烷:乙酸乙酯=2:1)分離純化，得到 5-(2'-methoxycarbonyl-6'-methoxyphenoxy)furfural (**86**)之綠色粉末狀結晶 1.027 g (產率 3.1%)。mp: 79-80 ℃; EIMS *m/z* (rel. int): 276 $[M]^+$ (14.2), 150 (100); UV λ_{max}nm (MeOH) (log ε): 305 (4.65), 209 (4.60); IR (KBr) cm^{-1}: 1736 (C=O), 1670 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (3H, *s*, $COO\underline{CH_3}$), 3.83 (3H, *s*, OCH_3-6'), 5.35 (1H, *d*, *J*=3.8 Hz, H-4), 7.19 (1H, *d*, *J*=3.8 Hz, H-3), 7.20 (1H, *dd*, *J*=8.0, 1.7 Hz, H-5'), 7.32 (1H, *t*, *J*=8.0 Hz, H-4'), 7.53 (1H, *dd*, *J*=8.0, 1.7 Hz, H-3'), 9.33 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.5 ($COO\underline{CH_3}$), 56.4 (OCH_3-6'), 87.3 (C-4), 116.9 (C-5'), 122.9 (C-3'), 125.0 (C-2'), 127.0 (C-3), 127.0 (C-4'), 141.1 (C-1'), 144.3 (C-2), 152.1 (C-6'), 163.7 (C-5), 164.8 ($\underline{C}OOCH_3$), 175.3 ($\underline{C}HO$)。

5-(2'-Methoxycarbonyl-5'-methoxyphenoxy)furfural (87)之合成

取 DMSO 150 mL 於三頸瓶，加入 2-hydroxy-4-methoxybenzoic acid methyl ester (**7**) 21.864 g (0.12 mol)，其合成方法同化合物 **81**，經矽膠管柱層析法(氯仿)分離純化，得到 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furfural (**87**)之綠色粉末狀結晶 1.370 g (產率 4.1%)。mp: 99-100 ℃; EIMS *m/z* (rel. int): 276 $[M]^+$ (41.6), 63 (100); UV λ_{max}nm (MeOH) (log ε): 301 (4.64), 254 (4.50), 209 (4.51); IR (KBr) cm^{-1}: 1723 (C=O), 1670 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.75 (3H, *s*, $COO\underline{CH_3}$), 3.83 (3H, *s*, OCH_3-5'), 5.42 (1H, *d*, *J*=3.7 Hz, H-4), 6.70 (1H, *d*, *J*=2.5 Hz, H-6'), 6.83 (1H, *dd*, *J*=8.8, 2.5 Hz, H-4'), 7.18 (1H, *d*, *J*=3.7 Hz, H-3), 7.97 (1H, *d*, *J*=8.8 Hz, H-3'),

9.34 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.1 (COO<u>C</u>H_3), 55.8 (OCH_3-5'), 88.9 (C-4), 107.5 (C-6'), 111.8 (C-4'), 114.9 (C-2'), 125.2 (C-3), 134.0 (C-3'), 144.7 (C-2), 154.3 (C-1'), 163.1 (C-5'), 164.2 (C-5), 164.4 (<u>C</u>OOCH$_3$), 175.6 (<u>C</u>HO)。

5-(2'-Methoxycarbonyl-4'-methoxyphenoxy)furfural (88)之合成

取 DMSO 150 mL **於三頸瓶，加入** 2-hydroxy-5-methoxybenzoic acid methyl ester (**8**) 21.864 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱層析法**(**氯仿**)**分離純化，得到** 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furfural (**88**)**之棕色粉末狀結晶** 6.481 g (**產率** 19.5%)。mp: 50.5-51.5 **℃**; EIMS *m/z* (rel. int): 276 $[M]^+$ (21.1), 150 (100); UV **λ**$_{max}$nm (MeOH) (log **ε**): 306 (4.16), 209 (4.18); IR (KBr) cm^{-1}: 1729 (C=O), 1664 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.78 (3H, *s*, COO<u>C</u>H_3), 3.83 (3H, *s*, OCH_3-4'), 5.31 (1H, *d*, *J*=3.8 Hz, H-4), 7.07 (1H, *dd*, *J*=9.0, 3.0 Hz, H-5'), 7.14-7.18 (2H, *m*, H-3 and 6'), 7.45 (1H, *d*, *J*= 3.0 Hz, H-3'), 9.32 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.5 (COO<u>C</u>H_3), 55.9 (OCH_3-4'), 88.0 (C-4), 116.1 (C-3'), 120.1 (C-5'), 123.3 (C-6'), 123.7 (C-2'), 125.8 (C-3), 144.5 (C-2), 146.0 (C-1'), 157.4 (C-4'), 164.1 (C-5), 164.7 (<u>C</u>OOCH$_3$), 175.4 (<u>C</u>HO)。

5-(2'-Methoxycarbonyl-3'-methoxyphenoxy)furfural (89)之合成

取 DMSO 150 mL **於三頸瓶，加入** 2-hydroxy-6-methoxybenzoic acid methyl ester (**9**) 21.864 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱層析法**(**正己烷**:**乙酸乙酯**=2:1)**分離純化，得到** 5-(2'-methoxycarbonyl-3'-methoxyphenoxy)furfural (**89**)**之黃色液體** 7.820 g (**產率** 23.6%)。EIMS *m/z* (rel. int): 276 $[M]^+$ (6.7), 55 (100); UV **λ**$_{max}$nm (MeOH) (log **ε**): 298 (4.79), 209 (4.61); IR (KBr) cm^{-1}: 1737 (C=O), 1675 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.83 (3H, *s*, COO<u>C</u>H_3), 3.84 (3H, *s*, OCH_3-3'), 5.59 (1H, *d*, *J*=3.8 Hz, H-4), 6.73 (1H, *d*, *J*=8.4 Hz, H-6'), 6.80 (1H, *d*, *J*=8.4 Hz, H-4'), 7.18 (1H, *d*, *J*=3.8 Hz, H-3), 7.35 (1H, *t*, *J*=8.4 Hz, H-5'), 9.37 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.7 (COO<u>C</u>H_3), 56.3 (OCH_3-3'), 90.7 (C-4), 108.6 (C-4'), 111.1 (C-6'), 115.9 (C-2'), 124.8 (C-3), 131.7 (C-5'), 145.0 (C-2), 151.8 (C-1'), 157.9 (C-3'), 161.9 (C-5), 164.8 (<u>C</u>OOCH$_3$), 175.9 (<u>C</u>HO)。

5-(2'-Methoxycarbonyl-5'-chlorophenoxy)furfural (90)之合成

取 DMSO 150 mL **於三頸瓶，加入** 2-hydroxy-4-chlorobenzoic acid methyl ester (**10**) 22.391 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱層析法**(**氯仿**:**苯**=1:1)**分離純化，得到** 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furfural (**90**)**之綠色粉末狀結晶** 1.069 g (**產率** 3.2%)。mp: 79.5-80.5 **℃**; EIMS *m/z* (rel. int): 282

$[M]^+$+2 (3.5), 280 $[M]^+$ (10.5), 126 (100); UV λ_{max}nm (MeOH) (log ε): 302 (4.53), 235 (4.37), 206 (4.44); IR (KBr) cm^{-1}: 1721 (C=O), 1667 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 (3H, *s*, COO<u>C</u>H$_3$), 5.54 (1H, *d*, *J*= 3.8 Hz, H-4), 7.19 (1H, *s*, H-6'), 7.21 (1H, *d*, *J*=3.8 Hz, H-3), 7.31 (1H, *dd*, *J*=8.5, 2.0 Hz, H-4'), 7.93 (1H, *d*, *J*=8.5 Hz, H-3'), 9.38 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.6 (COO<u>C</u>H$_3$), 89.9 (C-4), 121.3 (C-2'), 121.8 (C-6'), 125.0 (C-3), 126.6 (C-4'), 133.4 (C-3'), 139.8 (C-5'), 145.1 (C-2), 153.3 (C-1'), 161.9 (C-5), 164.0 (<u>C</u>OOCH$_3$), 175.7 (<u>C</u>HO)。

5-(2'-Methoxycarbonyl-4'-chlorophenoxy)furfural (91)之合成

取 DMSO 150 mL **於三頸瓶，加入** 2-hydroxy-5-chlorobenzoic acid methyl ester (**11**) 22.391 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱層析法(氯仿)分離純化，得到** 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furfural (**91**)**之棕色液體** 1.875 g (**產率** 5.6%)。EIMS *m/z* (rel. int): 282 $[M]^+$+2 (2.9), 280 $[M]^+$ (8.7), 126 (100); UV λ_{max}nm (MeOH) (log ε): 301 (4.71), 208 (4.61); IR (KBr) cm^{-1}: 1729 (C=O), 1675 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (3H, *s*, COO<u>C</u>H$_3$), 5.48 (1H, *d*, *J*=3.7 Hz, H-4), 7.15-7.20 (2H, *m*, H-3 and 6'), 7.52 (1H, *dd*, *J*=8.7, 2.7 Hz, H-5'), 7.95 (1H, *d*, *J*=2.7 Hz, H-3'), 9.36 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.7 (COO<u>C</u>H$_3$), 89.3 (C-4), 123.0 (C-6'), 124.3 (C-2'), 125.2 (C-3), 131.8 (C-4'), 132.1 (C-3'), 134.0 (C-5'), 144.9 (C-2), 151.2 (C-1'), 162.4 (C-5), 163.6 (<u>C</u>OOCH$_3$), 175.6 (<u>C</u>HO)。

5-(2'-Methoxycarbonyl-4'-bromophenoxy)furfural (92)之合成

取 DMSO 150 mL **於三頸瓶，加入** 2-hydroxy-5-bromobenzoic acid methyl ester (**12**) 27.725 g (0.12 mol)**，其合成方法同化合物 81，經矽膠管柱層析法(氯仿：苯** =1:1) **分離純化，得到** 5-(2'-methoxycarbonyl-4'-bromophenoxy)furfural (**92**)**之黃色液體** 4.716 g (**產率** 12.1%)。EIMS *m/z* (rel. int): 326 $[M]^+$+2 (10.5), 324 $[M]^+$ (10.5), 126 (100); UV λ_{max}nm (MeOH) (log ε): 300 (4.89), 212 (4.78); IR (KBr) cm^{-1}: 1737 (C=O), 1667 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (3H, *s*, COO<u>C</u>H$_3$), 5.48 (1H, *d*, *J*= 3.7 Hz, H-4), 7.10 (1H, *d*, *J*=8.7 Hz, H-6'), 7.19 (1H, *d*, *J*=3.7 Hz, H-3), 7.66 (1H, *dd*, *J*=8.7, 2.6 Hz, H-5'), 8.09 (1H, *d*, *J*=2.6 Hz, H-3'), 9.36 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.7 (COO<u>C</u>H$_3$), 89.4 (C-4), 119.2 (C-4'), 123.2 (C-6'), 124.5 (C-2'), 125.2 (C-3), 135.1 (C-3'), 137.0 (C-5'), 145.0 (C-2), 151.8 (C-1'), 162.3 (C-5), 163.5 (<u>C</u>OOCH$_3$), 175.6 (<u>C</u>HO)。

5-(2'-Methoxycarbonyl-4'-iodophenoxy)furfural (93)之合成

取 DMSO 150 mL **於三頸瓶，加入** 2-hydroxy-5-iodobenzoic acid

methyl ester (**13**) 33.365 g (0.12 mol)，其合成方法同化合物 **81**，經矽膠管柱層析法（氯仿：苯 =1:1) 分離純化，得到 5-(2'-methoxycarbonyl-4'-iodophenoxy)furfural (**93**)之棕色粉末狀結晶 5.447 g (產率 12.2%)。mp: 59.5-60.5 ℃; EIMS *m/z* (rel. int): 372 $[M]^+$ (15.3), 126 (100); UV λ_{max}nm (MeOH) (log ε): 305 (4.44), 218 (4.41); IR (KBr) cm^{-1}: 1729 (C=O), 1659 (CHO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (3H, *s*, COO$\underline{CH_3}$), 5.52 (1H, *d*, *J*= 3.7 Hz, H-4), 6.96 (1H, *d*, *J*=8.6 Hz, H-6'), 7.19 (1H, *d*, *J*=3.7 Hz, H-3), 7.84 (1H, *dd*, *J*=8.6, 2.3 Hz, H-5'), 8.27 (1H, *d*, *J*=2.3 Hz, H-3'), 9.38 (1H, *s*, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.7 (COO$\underline{CH_3}$), 89.5 (C-4), 89.5 (C-4'), 123.3 (C-6'), 124.7 (C-2'), 125.1 (C-3), 141.0 (C-3'), 142.9 (C-5'), 145.0 (C-2), 152.6 (C-1'), 162.1 (C-5), 163.4 ($\underline{C}OOCH_3$), 175.6 ($\underline{C}$HO)。

柒、5-(2'-Alkoxycarbonyl substituted phenoxy)-2-furanacrylic acids (101-109)及 5-(2'-Carboxyl substituted phenoxy)-2-furanacrylic acids (111-114, 116-118 及 120-123)之合成

5-(2'-Methoxycarbonylphenoxy)-2-furanacrylic acid (101) 及 5-(2'-carboxylphenoxy)-2-furanacrylic acid (111)之合成

取化合物 5-(2'-methoxycarbonylphenoxy)furfural (**81**) 3.838 g (0.016 mol)**於茄形瓶，加入** malonic acid 1.665 g (0.016 mol)**及** pyridine 0.775 mL (0.0096 mol)**混合攪拌，並於** boiling water bath **中加熱反應** 2 **小時後，冷卻加水稀釋，加濃氨水** (ammonia water)**把酸溶解，過濾、水洗，合併濾液，再用** dil. HCl (1:1) **溶液酸化，酸化過程中需攪拌及冷卻，一直到** Congo Red Paper **變色，濾取沉澱物，得到棕色粉末，以乙醇-水做再結晶，得到** 5-(2'-carboxylphenoxy)-2-furanacrylic acid (**111**)**之棕色粉末狀結晶** 1.320 g (**產率** 30.9%)。mp: 218.5-219.5 ℃; EIMS *m/z* (rel. int): 274 $[M]^+$ (0.8), 136 (100); UV λ_{max}nm (MeOH) (log ε): 315 (4.74), 208 (4.51); IR (KBr) cm^{-1}: 1690 (C=O), 1644 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.66 (1H, *d*, *J*=3.5 Hz, H-4), 5.94 (1H, *d*, *J*=15.7 Hz, CH=$\underline{CH}$-COOH), 6.90 (1H, *d*, *J*=3.5 Hz, H-3), 7.18 (1H, *dd*, *J*=8.0, 1.1 Hz, H-6'), 7.28 (1H, *d*, *J*=15.7 Hz, $\underline{CH}$=CH-COOH), 7.30 (1H, *ddd*, *J*=7.5, 1.1 Hz, H-4'), 7.50 (1H, *ddd*, *J*=8.0, 1.8 Hz, H-5'), 7.61 (1H, *dd*, *J*=7.5, 1.8 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 90.9 (C-4), 113.9 (CH=$\underline{CH}$-COOH), 118.6 (C-3), 119.0 (C-6'), 125.6 (C-4'), 128.3 (C-2'), 130.1 (C-3'), 130.8 ($\underline{CH}$=CH-COOH), 132.0 (C-5'), 143.0 (C-2), 151.8 (C-1'), 158.7 (C-5), 166.9 ($\underline{C}$OOH), 167.7 (CH=CH-$\underline{C}$OOH)。**再結晶後的濾液，經矽膠管柱層析法(氯仿)分離純化，得到橘色粉末，以乙醇-水做再結晶，得到** 5-(2'-methoxycarbonylphenoxy)-2-

furanacrylic acid (**101**)之棕色片狀結晶 0.508 g (產率 11.3%)。mp: 151.5-152.5 ℃; EIMS *m/z* (rel. int): 288 $[M]^+$ (58.6), 136 (100); UV λ_{max}nm (MeOH) (log ε): 315 (4.15); IR (KBr) cm^{-1}: 1698 (C=O), 1667 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.76 (3H, *s*, COO<u>CH</u>$_3$), 5.59 (1H, *d*, *J*=3.5 Hz, H-4), 5.92 (1H, *d*, *J*=15.7 Hz, CH=<u>CH</u>-COOH), 6.89 (1H, *d*, *J*=3.5 Hz, H-3), 7.27 (1H, *d*, *J*=15.7 Hz, <u>CH</u>=CH-COOH), 7.32 (1H, *dd*, *J*=8.1, 1.1 Hz, H-6'), 7.40 (1H, *ddd*, *J*=7.7, 1.1 Hz, H-4'), 7.68 (1H, *ddd*, *J*=8.1, 1.8 Hz, H-5'), 7.89 (1H, *dd*, *J*=7.7, 1.8 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 52.6 (COO<u>CH</u>$_3$), 89.9 (C-4), 113.7 (CH=<u>CH</u>-COOH), 118.6 (C-3), 120.7 (C-6'), 122.4 (C-2'), 126.1 (C-4'), 130.7 (<u>CH</u>=CH-COOH), 131.8 (C-3'), 134.7 (C-5'), 142.8 (C-2), 153.2 (C-1'), 159.2 (C-5), 164.9 (<u>C</u>OOCH$_3$), 167.7 (CH=CH-<u>C</u>OOH)。

5-(2'-Methoxycarbonyl-6'-methylphenoxy)-2-furanacrylic acid (102)之合成

取化合物 5-(2'-methoxycarbonyl-6'-methylphenoxy)furfural (**82**) 3.567 g (0.014 mol)於茄形瓶，加入 malonic acid 1.457 g (0.014 mol)及 pyridine 0.678 mL (0.0084 mol)混合攪拌，並於 boiling water bath 中加熱反應 2 小時後，冷卻加水稀釋，加濃氨水 (ammonia water)把酸溶解，過濾、水洗，合併濾液，再用 dil. HCl (1:1) 溶液酸化，酸化過程中需攪拌及冷卻，一直到 Congo Red Paper 變色，以乙醚萃取，取乙醚層以無水硫酸鎂脫水，減壓濃縮得到棕色液體，然後於冰浴內靜置 1 小時，濾取沉澱物，得到橘色粉末，以乙醇-水做再結晶，得到 5-(2'-methoxycarbonyl-6'-methylphenoxy)-2-furanacrylic acid (**102**)之橘色針狀結晶 1.542 g (產率 37.2%)。mp: 141.5-142.5 ℃; EIMS *m/z* (rel. int): 302 $[M]^+$ (30.8), 136 (100); UV λ_{max}nm (MeOH) (log ε): 326 (4.76), 207 (4.54); IR (KBr) cm^{-1}: 1729 (C=O), 1670 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.22 (3H, *s*, CH$_3$-6'), 3.69 (3H, *s*, COO<u>CH</u>$_3$), 5.17 (1H, *d*, *J*=3.5 Hz, H-4), 5.87 (1H, *d*, *J*=15.6 Hz, CH=<u>CH</u>-COOH), 6.80 (1H, *d*, *J*=3.5 Hz, H-3), 7.24 (1H, *d*, *J*=15.6 Hz, <u>CH</u>=CH-COOH), 7.36 (1H, *t*, *J*= 7.7 Hz, H-4'), 7.62 (1H, *dd*, *J*=7.7, 1.4 Hz, H-5'), 7.73 (1H, *dd*, *J*=7.7, 1.4 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 15.7 (CH$_3$-6'), 52.5 (COO<u>CH</u>$_3$), 86.4 (C-4), 112.8 (CH=<u>CH</u>-COOH), 119.2 (C-3), 123.9 (C-2'), 126.9 (C-4'), 129.7 (C-3'), 130.8 (<u>CH</u>=CH-COOH), 132.1 (C-6'), 136.4 (C-5'), 142.0 (C-2), 150.2 (C-1'), 160.5 (C-5), 164.9 (<u>C</u>OOCH$_3$), 167.8 (CH=CH-<u>C</u>OOH)。

5-(2'-Methoxycarbonyl-5'-methylphenoxy)-2-furanacrylic acid (103)及 5-(2'-carboxyl-5'-methylphenoxy)-2-furanacrylic acid (113)之合成

取化合物 5-(2'-methoxycarbonyl-5'-methylphenoxy)furfural (**83**)

3.037 g (0.012 mol)於茄形瓶，加入 malonic acid 1.249 g (0.012 mol)及 pyridine 0.581 mL (0.0072 mol)混合攪拌，並於 boiling water bath 中加熱反應 7 小時後，冷卻加水稀釋，加濃氨水 (ammonia water)把酸溶解，過濾、水洗，合併濾液，再用 dil. HCl (1:1) 溶液酸化，酸化過程中需攪拌及冷卻，一直到 Congo Red Paper 變色，以乙醚萃取，取乙醚層以無水硫酸鎂脫水，減壓濃縮得到棕色液體，然後於冰浴內靜置 1 小時，濾取沉澱物，得到橘色粉末，以乙醇-水做再結晶，得到 5-(2'-carboxyl-5'-methylphenoxy)-2-furanacrylic acid (**113**)之白色粉末狀結晶 0.8 g (產率 23.8%)。mp: 227-228 ℃; EIMS *m/z* (rel. int): 288 $[M]^+$ (3.2), 136 (100); UV λ_{max}nm (MeOH) (log ε): 317 (4.59), 231 (4.39), 206 (4.51); IR (KBr) cm^{-1}: 1670 (C=O), 1624 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.30 (3H, *s*, CH_3-5'), 5.64 (1H, *d*, *J*= 3.5 Hz, H-4), 5.93 (1H, *d*, *J*= 15.6 Hz, CH=<u>CH</u>-COOH), 6.89 (1H, *d*, *J*=3.5 Hz, H-3), 6.99 (1H, *s*, H-6'), 7.12 (1H, *d*, *J*=7.8 Hz, H-4'), 7.27 (1H, *d*, *J*=15.6 Hz, <u>CH</u>=CH-COOH), 7.54 (1H, *d*, *J*=7.8 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 21.1 (CH_3-5'), 90.9 (C-4), 113.9 (CH=<u>CH</u>-COOH), 118.7 (C-3), 119.3 (C-6'), 125.0 (C-2'), 126.3 (C-4'), 130.2 (C-3'), 130.9 (<u>CH</u>=CH-COOH), 142.7 (C-5'), 142.9 (C-2), 151.9 (C-1'), 158.8 (C-5), 166.7 (<u>C</u>OOH), 167.8 (CH=CH-<u>C</u>OOH)。再結晶後的濾液，經矽膠管柱層析法(氯仿:乙酸乙酯=2:1)分離純化，得到橘色粉末，以乙醇-水做再結晶，得到 5-(2'-methoxycarbonyl-5'-methylphenoxy)-2-furanacrylic acid (**103**)之橘色針狀結晶 0.320 g (產率 9.1%)。mp: 155.5-156.5 ℃; EIMS *m/z* (rel. int): 302 $[M]^+$ (30.4), 136 (100); UV λ_{max}nm (MeOH) (log ε): 318 (4.35), 232 (4.17); IR (KBr) cm^{-1}: 1729 (C=O), 1670 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.34 (3H, *s*, CH_3-5'), 3.72 (3H, *s*, COO<u>CH_3</u>), 5.52 (1H, *d*, *J*=3.6 Hz, H-4), 5.91 (1H, *d*, *J*=15.7 Hz, CH=<u>CH</u>-COOH), 6.87 (1H, *d*, *J*=3.6 Hz, H-3), 7.13 (1H, *s*, H-6'), 7.21 (1H, *d*, *J*=7.9 Hz, H-4'), 7.26 (1H, *d*, *J*=15.7 Hz, <u>CH</u>=CH-COOH), 7.79 (1H, *d*, *J*=7.9 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 21.2 (CH_3-5'), 52.5 (COO<u>CH_3</u>), 89.6 (C-4), 113.6 (CH=<u>CH</u>-COOH), 118.8 (C-3), 119.5 (C-2'), 121.3 (C-6'), 127.0 (C-4'), 130.9 (<u>CH</u>=CH-COOH), 131.9 (C-3'), 142.7 (C-5'), 145.9 (C-2), 153.3 (C-1'), 159.5 (C-5), 164.8 (<u>C</u>OOCH$_3$), 167.8 (CH=CH-<u>C</u>OOH)。

5-(2'-Methoxycarbonyl-4'-methylphenoxy)-2-furanacrylic acid (104)之合成

取化合物 5-(2'-methoxycarbonyl-4'-methylphenoxy)furfural (**84**) 4.158 g (0.016 mol)於茄形瓶，加入 malonic acid 1.665 g (0.016 mol)及 pyridine 0.775 mL (0.0096 mol)混合攪拌，並於 boiling water bath 中加

熱反應 7 **小時後，冷卻加水稀釋，加濃氨水** (ammonia water)**把酸溶解，過濾、水洗，合併濾液，再用** dil. HCl (1:1) **溶液酸化，酸化過程中需攪拌及冷卻，一直到** Congo Red Paper **變色，以乙醚萃取，取乙醚層以無水硫酸鎂脫水，減壓濃縮得到棕色粉末，以乙醇-水做再結晶, 得到** 5-(2'-methoxycarbonyl-4'-methylphenoxy)-2-furanacrylic acid (**104**)**之棕色粉末狀結晶** 1.2 g (**產率** 24.8%)。mp: 187-188 **℃**; EIMS *m/z* (rel. int): 302 $[M]^+$ (23.6), 136 (100); UV λ_{max}nm (MeOH) (log ε): 322 (4.48), 206 (4.43); IR (KBr) cm^{-1}: 1723 (C=O), 1670 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.33 (3H, *s*, CH_3-4'), 3.74 (3H, *s*, $COO\underline{CH_3}$), 5.48 (1H, *d*, *J*=3.5 Hz, H-4), 5.89 (1H, *d*, *J*=15.6 Hz, CH=$\underline{CH}$-COOH), 6.85 (1H, *d*, *J*=3.5 Hz, H-3), 7.21 (1H, *d*, *J*=8.4 Hz, H-6'), 7.25 (1H, *d*, *J*=15.6 Hz, $\underline{CH}$=CH-COOH), 7.47 (1H, *dd*, *J*=8.4, 2.1 Hz, H-5'), 7.68 (1H, *d*, *J*=2.1 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 20.4 (CH_3-4'), 52.6 ($COO\underline{CH_3}$), 89.2 (C-4), 113.5 (CH=$\underline{CH}$-COOH), 118.8 (C-3), 121.0 (C-6'), 122.3 (C-2'), 130.9 ($\underline{CH}$=CH-COOH), 132.0 (C-3'), 135.2 (C-5'), 135.9 (C-4'), 142.6 (C-2), 151.0 (C-1'), 159.9 (C-5), 165.0 ($\underline{C}OOCH_3$), 167.8 (CH=CH-$\underline{C}$OOH)。

5-(2'-Ethoxycarbonyl-3'-methylphenoxy)-2-furanacrylic acid (105)之合成

取化合物 5-(2'-ethoxycarbonyl-3'-methylphenoxy)furfural (**85**) 5.992 g (0.022 mol)**於茄形瓶，加入** malonic acid 2.289 g (0.022 mol)**及** pyridine 1.065 mL (0.0132 mol)**混合攪拌，其合成方法同化合物 104，減壓濃縮得到棕色液體，經矽膠管柱層析法(氯仿)分離純化，得到橘色粉末，以乙醇-水做再結晶，得到** 5-(2'-ethoxycarbonyl-3'-methyl-phenoxy)-2-furanacrylic acid (**105**)**之橘色針狀結晶** 1.867 g (**產率** 27.0 %)。mp: 113.5-114.5 **℃**; EIMS *m/z* (rel. int): 316 $[M]^+$ (13.8), 136 (100); UV λ_{max}nm (MeOH) (log ε): 317 (4.48), 206 (4.33); IR (KBr) cm^{-1}: 1736 (C=O), 1670 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.19 (3H, *t*, *J*=7.1 Hz, $COOCH_2\underline{CH_3}$), 2.29 (3H, *s*, CH_3-3'), 4.26 (2H, *q*, *J*=7.1 Hz, $COO\underline{CH_2}CH_3$), 5.68 (1H, *d*, *J*=3.5 Hz, H-4), 5.92 (1H, *d*, *J*=15.7 Hz, CH=$\underline{CH}$-COOH), 6.88 (1H, *d*, *J*=3.5 Hz, H-3), 7.08 (1H, *d*, *J*=8.0 Hz, H-6'), 7.18 (1H, *d*, *J*=8.0 Hz, H-4'), 7.26 (1H, *d*, *J*=15.7 Hz, $\underline{CH}$=CH-COOH), 7.41 (1H, *t*, *J*=8.0 Hz, H-5'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.2 ($COOCH_2\underline{CH_3}$), 19.1 (CH_3-3'), 61.6 ($COO\underline{CH_2}CH_3$), 90.9 (C-4), 114.1 (CH=$\underline{CH}$-COOH), 116.4 (C-6'), 118.5 (C-3), 125.7 (C-2'), 127.6 (C-4'), 130.8 ($\underline{CH}$=CH-COOH), 131.6 (C-5'), 137.6 (C-3'), 143.0 (C-2), 151.6 (C-1'), 158.7 (C-5), 166.1 ($\underline{C}OOCH_3$), 167.8 (CH=CH-$\underline{C}$OOH)。

5-(2'-Methoxycarbonyl-6'-methoxyphenoxy)-2-furanacrylic acid (106)之合成

取化合物 5-(2'-methoxycarbonyl-6'-methoxyphenoxy)furfural (**86**) 2.053 g (0.0074 mol)**於茄形瓶，加入** malonic acid 0.77 g (0.0074 mol) **及** pyridine 0.358 mL (0.00444 mol)**混合攪拌，其合成方法同化合物104，減壓濃縮得到棕色液體，經矽膠管柱層析法(氯仿)分離純化，得到深橘色粉末，以乙醇-水做再結晶，得到** 5-(2'-methoxycarbonyl-6'-methoxyphenoxy)-2-furanacrylic acid (**106**)**之橘色粉末狀結晶** 0.21 g (**產率** 8.9%)。mp: 158.5-159.5 **℃**; EIMS *m/z* (rel. int): 318 $[M]^+$ (45.4), 136 (100); UV λ_{max}nm (MeOH) (log **ε**): 327 (4.60), 208 (4.62); IR (KBr) cm^{-1}: 1729 (C=O), 1682 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): **δ** 3.72 (3H, *s*, COO$\underline{CH_3}$), 3.80 (3H, *s*, OCH_3-6'), 5.20 (1H, *d*, *J*=3.5 Hz, H-4), 5.85 (1H, *d*, *J*=15.6 Hz, CH=$\underline{CH}$-COOH), 6.80 (1H, *d*, *J*=3.5 Hz, H-3), 7.24 (1H, *d*, *J*=15.6 Hz, $\underline{CH}$=CH-COOH), 7.40-7.51 (3H, *m*, H-3', 4', and 5'); ^{13}C NMR (50 MHz, DMSO-d_6): **δ** 52.6 (COO$\underline{CH_3}$), 56.6 (OCH_3-6'), 86.1 (C-4), 112.5 (CH=$\underline{CH}$-COOH), 118.0 (C-5'), 119.2 (C-3), 122.3 (C-2'), 124.8 (C-3'), 127.5 (C-4'), 130.8 ($\underline{CH}$=CH-COOH), 140.7 (C-1'), 141.6 (C-2), 152.1 (C-6'), 160.8 (C-5), 164.6 ($\underline{C}OOCH_3$), 167.8 (CH=CH-$\underline{C}$OOH)。

5-(2'-Methoxycarbonyl-5'-methoxyphenoxy)-2-furanacrylic acid (107)及 5-(2'-carboxyl-5'-methoxyphenoxy)-2-furanacrylic acid (117)之合成

取化合物 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)furfural (**87**) 2.0 g (0.0073 mol)**於茄形瓶，加入** malonic acid 0.760 g (0.0073 mol)**及** pyridine 0.355 mL (0.0044 mol)**混合攪拌，並於** boiling water bath **中加熱反應** 2 **小時後，冷卻加水稀釋，加濃氨水** (ammonia water)**把酸溶解，過濾、水洗，合併濾液，再用** dil. HCl (1:1) **溶液酸化，酸化過程中需攪拌及冷卻，一直到** Congo Red Paper **變色，濾取沉澱物，得到橘色粉末，以乙醇-水做再結晶，分別得到** 5-(2'-methoxycarbonyl-5'-methoxyphenoxy)-2-furanacrylic acid (**107**)**之橘色粉末狀結晶** 0.191 g (**產率** 8.3%)。mp: 129.5-130.5 **℃**; EIMS *m/z* (rel. int): 318 $[M]^+$ (7.4), 136 (100); UV λ_{max}nm (MeOH) (log **ε**): 322 (4.58), 251 (4.45), 209 (4.56); IR (KBr) cm^{-1}: 1706 (C=O), 1636 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): **δ** 3.71 (3H, *s*, COO$\underline{CH_3}$), 3.81 (3H, *s*, OCH_3-5'), 5.53 (1H, *d*, *J*=3.5 Hz, H-4), 5.92 (1H, *d*, *J*=15.6 Hz, CH=$\underline{CH}$-COOH), 6.86-6.89 (2H, *m*, H-3 and 6'), 6.97 (1H, *dd*, *J*=8.8, 2.5 Hz, H-4'), 7.27 (1H, *d*, *J*= 15.6 Hz, $\underline{CH}$=CH-COOH), 7.90 (1H, *d*, *J*=8.8 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): **δ** 52.2 (COO$\underline{CH_3}$), 56.2

(OCH_3-5'), 89.1 (C-4), 106.9 (C-6'), 112.0 (C-4'), 113.4 (CH=CH-COOH), 114.2 (C-2'), 118.7 (C-3), 130.8 (CH=CH-COOH), 133.8 (C-3'), 142.6 (C-2), 154.9 (C-1'), 159.5 (C-5), 164.1 (C-5'), 164.2 ($COOCH_3$), 167.7(CH=CH-COOH) **和** 5-(2'-carboxyl-5'-methoxyphenoxy)-2-furanacrylic acid (**117**)**之棕色粉末狀結晶** 0.286 g (**產率** 13.0%)。mp: 254-255 **℃**; EIMS *m/z* (rel. int): 304 $[M]^+$ (2.2), 151 (100); UV λ_{max}nm (MeOH) (log **ε**): 315 (4.47), 251 (4.30), 207 (4.50); IR (KBr) cm^{-1}: 1697 (C=O), 1651 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): **δ** 3.76 (3H, *s*, OCH_3-5'), 5.68 (1H, *d*, *J*=3.5 Hz, H-4), 5.94 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 6.71 (1H, *d*, *J*=2.4 Hz, H-6'), 6.87-6.92 (2H, *m*, H-3 and 4'), 7.28 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 7.67 (1H, *d*, *J*=8.6 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): **δ** 56.0 (OCH_3-5'), 90.9 (C-4), 104.9 (C-6'), 111.1 (C-4'), 113.9 (CH=CH-COOH), 118.6 (C-3), 119.7 (C-2'), 130.8 (CH=CH-COOH), 132.0 (C-3'), 142.9 (C-2), 153.3 (C-1'), 158.5 (C-5), 162.2 (C-5'), 166.1 (COOH), 167.7 (CH=CH-COOH)。

5-(2'-Methoxycarbonyl-4'-methoxyphenoxy)-2-furanacrylic acid (108) 之合成

取化合物 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)furfural (**88**) 6.381 g (0.0231 mol)**於茄形瓶，加入** malonic acid 2.404 g (0.0231 mol) **及** pyridine 1.122 mL (0.0139 mol)**混合攪拌，其合成方法同化合物 104，減壓濃縮得到橘色粉末，經矽膠管柱層析法(正己烷:乙酸乙酯** =2:1)**分離純化，得到橘色粉末，以乙醇-水做再結晶，得到** 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)-2-furanacrylic acid (**108**)**之橘色針狀結晶** 0.79 g (**產率** 10.7%)。mp: 133-134 **℃**; EIMS *m/z* (rel. int): 318 $[M]^+$ (5.2), 63 (100); UV λ_{max}nm (MeOH) (log **ε**): 324 (4.69), 209 (4.66); IR (KBr) cm^{-1}: 1729 (C=O), 1675 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): **δ** 3.74 (3H, *s*, $COOCH_3$), 3.80 (3H, *s*, OCH_3-4'), 5.38 (1H, *d*, *J*=3.5 Hz, H-4), 5.89 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 6.84 (1H, *d*, *J*=3.5 Hz, H-3), 7.20-7.36 (4H, *m*, H-3', 5', 6' and CH=CH-COOH); ^{13}C NMR (50 MHz, DMSO-d_6): **δ** 52.7 ($COOCH_3$), 56.1 (OCH_3-4'), 88.2 (C-4), 113.2 (CH=CH-COOH), 115.8 (C-3'), 119.0 (C-3), 120.2 (C-6'), 123.2 (C-5'), 123.6 (C-2'), 130.8 (CH=CH-COOH), 142.3 (C-2), 146.2 (C-1'), 156.8 (C-4'), 160.7 (C-5), 164.6 ($COOCH_3$), 167.8 (CH=CH-COOH)。

5-(2'-Methoxycarbonyl-3'-methoxyphenoxy)-2-furanacrylic acid (109) 之合成

取化合物 5-(2'-methoxycarbonyl-3'-methoxyphenoxy)furfural (**89**)

7.320 g (0.0265 mol)於茄形瓶，加入 malonic acid 2.758 g (0.0265 mol) 及 pyridine 1.283 mL (0.0159 mol)混合攪拌，其合成方法同化合物 **104**, 減壓濃縮得到橘色粉末, 以乙醇-水做再結晶, 得到 5-(2'-methoxy-carbonyl-3'-methoxyphenoxy)-2-furanacrylic acid (**109**)之橘色粉末狀結晶 4.501 g (產率 53.4%)。mp: 175.5-176.5 ℃; EIMS *m/z* (rel. int): 318 $[M]^+$ (12.8), 107 (100); UV λ_{max}nm (MeOH) (log ε): 313 (4.48), 206 (4.42); IR (KBr) cm^{-1}: 1737 (C=O), 1682 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.77 (3H, *s*, COO$\underline{CH_3}$), 3.81 (3H, *s*, OCH_3-3'), 5.83 (1H, *d*, *J*=3.5 Hz, H-4), 5.95 (1H, *d*, *J*=15.6 Hz, CH=$\underline{CH}$-COOH), 6.77 (1H, *d*, *J*=8.4 Hz, H-6'), 7.91 (1H, *d*, *J*=3.5 Hz, H-3), 7.00 (1H, *d*, *J*=8.4 Hz, H-4'), 7.27 (1H, *d*, *J*=15.7 Hz, $\underline{CH}$=CH-COOH), 7.46 (1H, *t*, *J*=8.4 Hz, H-5'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 52.8 (COO$\underline{CH_3}$), 56.6 (OCH_3-3'), 92.2 (C-4), 108.8 (C-4'), 109.9 (C-6'), 114.5 (CH=$\underline{CH}$-COOH), 114.8 (C-2'), 118.3 (C-3), 130.8 ($\underline{CH}$=CH-COOH), 132.4 (C-5'), 143.4 (C-2), 152.3 (C-1'), 157.4 (C-3'), 157.6 (C-5), 164.9 ($\underline{C}OOCH_3$), 167.7 (CH=CH-$\underline{C}$OOH)。

5-(2'-Carboxyl-6'-methylphenoxy)-2-furanacrylic acid (112)之合成

取 5-(2'-methoxycarbonyl-6'-methylphenoxy)-2-furanacrylic acid (**102**) 0.605 g (0.002 mol)加入10 mL的10% NaOH 1.0 g (0.025 mol)，在水浴中加熱迴流6小時，以TLC追蹤至完全水解，放冷，以乙醚清洗，水層加熱蒸去乙醚後，再用dil. HCl (1:1) 溶液酸化中和，酸化過程中需攪拌及冷卻，一直到Congo Red Paper變色，得到白色沈澱物，以乙醚萃取，取乙醚層以無水硫酸鎂脫水，減壓濃縮得到黃色粉末，以乙醇-水做再結晶，得到 5-(2'-carboxyl-6'-methylphenoxy)-2-furanacrylic acid (**112**)之黃色粉末狀結晶0.334 g (產率58.0%)。mp: 198-199 ℃; EIMS *m/z* (rel. int): 288 $[M]^+$ (1.3), 135 (100); UV λ_{max}nm (MeOH) (log ε): 329 (4.74), 206 (4.47); IR (KBr) cm^{-1}: 1690 (C=O), 1667 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.21 (3H, *s*, CH_3-6'), 5.11 (1H, *d*, *J*=3.6 Hz, H-4), 5.86 (1H, *d*, *J*=15.6 Hz, CH=$\underline{CH}$-COOH), 6.81 (1H, *d*, *J*=3.6 Hz, H-3), 7.24 (1H, *d*, *J*=15.6 Hz, $\underline{CH}$=CH-COOH), 7.34 (1H, *t*, *J*=7.7 Hz, H-4'), 7.58 (1H, *dd*, *J*=7.7, 1.8 Hz, H-5'), 7.73 (1H, *dd*, *J*=7.7, 1.8 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 15.7 (CH_3-6'), 86.0 (C-4), 112.6 (CH=$\underline{CH}$-COOH), 119.3 (C-3), 125.2 (C-2'), 126.7 (C-6'), 129.8 (C-4'), 130.8 (C-3'), 131.8 ($\underline{CH}$=CH-COOH), 135.9 (C-5'), 141.8 (C-2), 150.1 (C-1'), 160.8 (C-5), 166.0 ($\underline{C}$OOH), 167.8 (CH=CH-$\underline{C}$OOH)。

5-(2'-Carboxyl-4'-methylphenoxy)-2-furanacrylic acid (114)之合成

取 5-(2'-methoxycarbonyl-4'-methylphenoxy)-2-furanacrylic acid

(**104**) 0.605 g (0.002 mol)，其合成方法同化合物**112**，得到 5-(2'-carboxyl-4'-methylphenoxy)-2-furanacrylic acid (**114**)之黃色粉末狀結晶0.207 g (產率35.9%)。mp: 181.5-182.5 ℃; EIMS *m/z* (rel. int): 288 $[M]^+$ (1.3), 77 (100); UV λ_{max}nm (MeOH) (log ε): 327 (4.67), 207 (4.51); IR (KBr) cm^{-1}: 1716 (C=O), 1618 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.34 (3H, *s*, CH_3-4'), 5.40 (1H, *d*, *J*= 3.5 Hz, H-4), 5.89 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 6.85 (1H, *d*, *J*=3.5 Hz, H-3), 7.20 (1H, *d*, *J*=8.5 Hz, H-6'), 7.25 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 7.44 (1H, *dd*, *J*= 8.5, 2.1 Hz, H-5'), 7.69 (1H, *d*, *J*=2.1 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 20.4 (CH_3-4'), 88.5 (C-4), 113.2 (CH=CH-COOH), 119.0 (C-3), 121.1 (C-6'), 123.6 (C-2'), 130.8 (CH=CH-COOH), 132.1 (C-3'), 134.6 (C-5'), 135.7 (C-4'), 142.3 (C-2), 150.8 (C-1'), 160.4 (C-5), 166.0 (COOH), 167.8 (CH=CH-COOH)。

5-(2'-Carboxyl-6'-methoxyphenoxy)-2-furanacrylic acid (116)之合成

取 5-(2'-methoxycarbonyl-6'-methoxyphenoxy)-2-furanacrylic acid (**106**) 0.150 g (0.0005 mol)，其合成方法同化合物**112**，得到 5-(2'-carboxyl-6'-methoxyphenoxy)-2-furanacrylic acid (**116**)之黃色粉末狀結晶0.099 g (產率69.2%)。mp: 189.5-190.5 ℃; EIMS *m/z* (rel. int): 304 $[M]^+$ (14.0), 151 (100); UV λ_{max}nm (MeOH) (log ε): 331 (4.78), 210 (4.68); IR (KBr) cm^{-1}: 1682 (C=O), 1636 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.79 (3H, *s*, OCH_3-6'), 5.15 (1H, *d*, *J*=3.5 Hz, H-4), 5.84 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 6.80 (1H, *d*, *J*=3.5 Hz, H-3), 7.23 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 7.39-7.44 (3H, *m*, H-3', 4', and 5'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 56.6 (OCH_3-6'), 85.9 (C-4), 112.3 (CH=CH-COOH), 117.4 (C-5'), 119.4 (C-3), 122.5 (C-3'), 126.2 (C-2'), 127.4 (C-4'), 130.8 (CH=CH-COOH), 140.5 (C-1'), 141.4 (C-2), 152.0 (C-6'), 161.1 (C-5), 165.8 (COOH), 167.8 (CH=CH-COOH)。

5-(2'-Carboxyl-4'-methoxyphenoxy)-2-furanacrylic acid (118)之合成

取 5-(2'-methoxycarbonyl-4'-methoxyphenoxy)-2-furanacrylic acid (**108**) 0.637 g (0.002 mol)，其合成方法同化合物**112**，得到 5-(2'-carboxyl-4'-methoxyphenoxy)-2-furanacrylic acid (**118**)之黃色粉末狀結晶0.458 g (產率75.3%)。mp: 193.5-194.5 ℃; EIMS *m/z* (rel. int): 304 $[M]^+$ (21.2), 63 (100); UV λ_{max}nm (MeOH) (log ε): 330 (4.31), 206 (4.32); IR (KBr) cm^{-1}: 1698 (C=O), 1637 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.80 (3H, *s*, OCH_3-4'), 5.31 (1H, *d*, *J*=3.5 Hz, H-4), 5.88 (1H, *d*, *J*=15.6 Hz, CH=CH-COOH), 6.83 (1H, *d*, *J*=3.5 Hz, H-3), 7.16-7.33 (3H, *m*, H-5', 6' and CH=CH-COOH), 7.35 (1H, *d*, *J*=3.0 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 56.0 (OCH_3-4'), 87.6 (C-4),

112.9 (CH=CH-COOH), 115.9 (C-3'), 119.1 (C-3), 119.7 (C-6'), 123.2 (C-5'), 125.1 (C-2'), 130.8 (CH=CH-COOH), 142.1 (C-2), 146.1 (C-1'), 156.8 (C-4'), 161.2 (C-5), 165.7 (COOH), 167.8 (CH=CH-COOH)。

5-(2'-Carboxyl-5'-chlorophenoxy)-2-furanacrylic acid (120)之合成

取化合物 5-(2'-methoxycarbonyl-5'-chlorophenoxy)furfural (**90**) 0.839 g (0.003 mol)**於茄形瓶，加入**malonic acid 0.31218 g (0.003 mol) **及**pyridine 0.15 mL (0.0018 mol)**混合攪拌，並於**boiling water bath**中加熱反應**7**小時後，冷卻加水稀釋，加濃氨水** (ammonia water)**把酸溶解，過濾、水洗，合併濾液，再用**dil. HCl (1:1) **溶液酸化，酸化過程中需攪拌及冷卻，一直到**Congo Red Paper**變色，濾取沉澱物，得到棕色粉末，以乙醇-水做再結晶，得到** 5-(2'-carboxyl-5'-chlorophenoxy)-2-furanacrylic acid (**120**)**之棕色粉末狀結晶**0.225 g (**產率**24.4%)。mp: >300 **℃**; EIMS *m/z* (rel. int): 310 $[M]^+$+2 (0.2), 308 $[M]^+$ (0.6), 136 (100) ; UV λ_{max}nm (MeOH) (log ε): 306 (4.28), 206 (4.33); IR (KBr) cm^{-1}: 1690 (C=O), 1644 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.76 (1H, *d*, *J*= 3.5 Hz, H-4), 5.96 (1H, *d*, *J*=15.7 Hz, CH=CH-COOH), 6.92 (1H, *d*, *J*= 3.5 Hz, H-3), 7.28 (1H, *d*, *J*=15.7 Hz, CH=CH-COOH), 7.31 (1H, *d*, *J*= 2.0 Hz, H-6'), 7.40 (1H, *dd*, *J*=8.3, 2.0 Hz, H-4'), 7.64 (1H, *d*, *J*=8.3 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 91.5 (C-4), 114.3 (CH=CH-COOH), 118.4 (C-3), 119.0 (C-6'), 125.7 (C-4'), 127.2 (C-2'), 130.7 (CH=CH-COOH), 131.6 (C-3'), 135.6 (C-5'), 143.2 (C-2), 152.4 (C-1'), 157.8 (C-5), 165.8 (COOH), 167.6 (CH=CH-COOH)。

5-(2'-Carboxyl-4'-chlorophenoxy)-2-furanacrylic acid (121)之合成

取化合物 5-(2'-methoxycarbonyl-4'-chlorophenoxy)furfural (**91**) 1.804 g (0.0064 mol)**於茄形瓶，加入**malonic acid 0.666 g (0.0064 mol) **及**pyridine 0.31 mL (0.00384 mol)**混合攪拌，其合成方法同化合物120，得到淡黃棕色粉末，以乙醇-水做再結晶，得到** 5-(2'-carboxyl-4'-chlorophenoxy)-2-furanacrylic acid (**121**)**之棕色粉末狀結晶**0.425 g (**產率**21.4%)。mp: 211-212 **℃**; EIMS *m/z* (rel. int): 310 $[M]^+$+2 (0.3), 308 $[M]^+$ (0.9), 136 (100); UV λ_{max}nm (MeOH) (log ε): 311 (4.35), 206 (4.40); IR (KBr) cm^{-1}: 1690 (C=O), 1644 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.72 (1H, *d*, *J*=3.5 Hz, H-4), 5.95 (1H, *d*, *J*=15.7 Hz, CH=CH-COOH), 6.91 (1H, *d*, *J*=3.5 Hz, H-3), 7.24 (1H, *d*, *J*=8.8 Hz, H-6'), 7.28 (1H, *d*, *J*=15.7 Hz, CH=CH-COOH), 7.56 (1H, *dd*, *J*=8.8, 2.7 Hz, H-5'), 7.63 (1H, *d*, *J*=2.7 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 91.1 (C-4), 114.2 (CH=CH-COOH), 118.4 (C-3), 121.0 (C-6'), 129.4 (C-3'), 129.4 (C-4'), 130.1 (C-2'), 130.7 (CH=CH-COOH),

131.6 (C-5'), 143.1 (C-2), 150.5 (C-1'), 158.2 (C-5), 165.4 (COOH), 167.6 (CH=CH-COOH)。

5-(2'-Carboxyl-4'-bromophenoxy)-2-furanacrylic acid (122)之合成

取化合物 5-(2'-methoxycarbonyl-4'-bromophenoxy)furfural (**92**) 4.276 g (0.0132 mol)**於茄形瓶，加入**malonic acid 1.374 g (0.0132 mol) **及**pyridine 0.64 mL (0.00792 mol)**混合攪拌，其合成方法同化合物120，得到黃橘色粉末，以乙醇-水做再結晶，得到** 5-(2'-carboxyl-4'-bromophenoxy)-2-furanacrylic acid (**122**)**之棕色片狀結晶**2.002 g (**產率**43.1%)。mp: 231-232 ℃; EIS *m/z* (rel. int): 353 $[M]^+$+2 (3.8), 351 $[M]^+$ (3.8), 136 (100); UV λ_{max}nm (MeOH) (log ε): 312 (4.78), 209 (4.73); IR (KBr) cm^{-1}: 1690 (C=O), 1644 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.73 (1H, *d*, *J*=3.5 Hz, H-4), 5.95 (1H, *d*, *J*=15.7 Hz, CH=CH-COOH), 6.91 (1H, *d*, *J*=3.5 Hz, H-3), 7.17 (1H, *d*, *J*=8.7 Hz, H-6'), 7.27 (1H, *d*, *J*= 15.7 Hz, CH=CH-COOH), 7.68 (1H, *dd*, *J*=8.7, 2.5 Hz, H-5'), 7.74 (1H, *d*, *J*=2.5 Hz, H-3'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 91.3 (C-4), 114.2 (CH=CH-COOH), 117.3 (C-4'), 118.4 (C-3), 121.3 (C-6'), 130.3 (C-2'), 130.7 (CH=CH-COOH), 132.3 (C-3'), 134.5 (C-5'), 143.1 (C-2), 151.0 (C-1'), 158.1 (C-5), 165.3 (COOH), 167.6 (CH=CH-COOH)。

5-(2'-Carboxyl-4'-iodophenoxy)-2-furanacrylic acid (123)之合成

取化合物5-(2'-methoxycarbonyl-4'-iodophenoxy)furfural (**93**) 5.226 g (0.0140 mol)**於茄形瓶，加入**malonic acid 1.45684 g (0.0140 mol)**及** pyridine 0.678 mL (0.0084 mol)**混合攪拌，其合成方法同化合物120，得到黃橘色粉末，以乙醇-水做再結晶，得到**5-(2'-carboxyl-4'-iodo-phenoxy)-2-furanacrylic acid (**123**)**之棕色粉末狀結晶**0.946 g (**產率**16.8 %)。mp: 243.5-244.5 ℃; EIMS *m/z* (rel. int): 400 $[M]^+$ (0.4), 136 (100); UV λ_{max}nm (MeOH) (log ε): 311 (4.54), 209 (4.57); IR (KBr) cm^{-1}: 1690 (C=O), 1644 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.73 (1H, *d*, *J*=3.5 Hz, H-4), 5.95 (1H, *d*, *J*=15.7 Hz, CH=CH-COOH), 6.91 (1H, *d*, *J*=3.5 Hz, H-3), 7.01 (1H, *d*, *J*=8.5 Hz, H-6'), 7.27 (1H, *d*, *J*=15.7 Hz, CH=CH-COOH), 7.79-7.88 (2H, *m*, H-3' and 5'); ^{13}C NMR (50 MHz, DMSO-d_6): δ 89.6 (C-4'), 91.3 (C-4), 114.2 (CH=CH-COOH), 118.4 (C-3), 121.2 (C-6'), 130.4 (C-2'), 130.7 (CH=CH-COOH), 138.0 (C-3'), 140.3 (C-5'), 143.1 (C-2), 151.7 (C-1'), 158.0 (C-5), 165.3 (COOH), 167.6 (CH=CH-COOH)。

第四節 藥理試驗方法與材料

壹、抗血小板凝集活性試驗方法：

1.**血小板凝集引發劑的製備：**

(1)Thrombin：**購自** Park Davis Co. USA；**以** 50% (v/v) glycerol **溶解製備成** 100 NIH units/mL **的** stock solution。

(2)Arachidonic acid (AA)：**購自** Sigma Chem. Co. USA；**以去離子水溶解成** 100 μM **或** 200 μM **的濃度。**

(3)Collagen (type 1，bovine Achilles tendon)：**購自** Sigma Chem. Co. USA；**溶解在** 25 mM **醋酸水溶液中，在** 4 **℃中研磨成均勻的懸浮液後，以** l mg/mL **的濃度分裝；貯存於**-70 **℃中，使用前再解凍研磨均勻，使濃度成為** 10 μg/mL。

(4)Platelet-activating factor (PAF)：**購自** Sigma Chem. Co. USA；**溶於** chloroform **中，貯存於**-20 **℃中，使用前以** 0.9 % NaCl **稀釋，使濃度成為** 2 ng/mL。

2.**血小板懸浮液的製備**[95,96]：

(1)**從兔子耳靜脈抽出血液與** 100 mM EDTA **以** 1：14 (v/v)**的比例混合，使** EDTA **的最終濃度為** 6 mM，**在室溫下立即以** 90×g **離心** 10 **分鐘，取出上層富含血小板的血漿** (platelet- rich plasma)，**再將其以** 500×g **離心** 10 **分鐘，除去血漿後，將下層的血小板** (platelet pellets)**以含有** EDTA (2 mM)**及** Bovin serum albumin (3.5

mg/mL)的 Tyrode's solution (calcium free)清洗之，在相同轉速(500×g)下離心 10 分鐘，所得的血小板以不含有 EDTA 的 Tyrode's solution 清洗之，再於相同的條件下離心後，取血小板層，將其懸浮於 Tyrode's solution 中，其組成如下 (mM)：NaCl (136.8), KCl (2.8), $NaHCO_3$ (11.9), $MgCl_2$ (l.1), NaH_2PO_4 (0.33), $CaCl_2$ (1.0) and glucose (11.2)；並以 Coulter counter (Model ZM)計數，調整血小板數約為 4.5×10^8 platelets/mL，最後放置 30 分鐘進行實驗。

(2)從人類肱靜脈抽出血液與 Anticoagulant citrate dextrose solution (ACD，含 citric acid, sodium citrate, glucose)以 1：9 的比例混合，在室溫下立即以 600×g 離心 9 分鐘，取出上層富含血小板的血漿(PRP)，在 PRP 中加入 heparin 和 PGE_1 ，以 2800 rpm 離心 6 分鐘，除去血漿後，將下層的血小板 (platelet pellets)以 Tyrode's solution (calcium free)清洗之，得到的懸浮液加入 PGE_1，以轉速 2300 rpm 離心 6 分鐘，所得的血小板再以 Tyrode's solution 清洗之，在加入 PGE_1 後於相同的條件下離心，取出血小板層，將其懸浮於 Tyrode's solution 中，其組成除 BSA (3.5 mg/mL)外，其他如下 (mM)：NaCl (136.9), KCl (2.7), $NaHCO_3$ (11.9), $MgCl_2$ (1), NaH_2PO_4 (0.4), $CaCl_2$ (2) and glucose (11.1)；並以 Coulter counter (Model ZM)計數，調整血小板數約為 3.75×10^8 platelets/mL，如此就可以進行實驗。

3.血小板凝集的試驗[97,98]：

利用混濁度法 (turbidimetric method)的原理來測定凝集程度，並以 dual-Channel Lumiaggregometer (Model 1020, PayTon, Canada) 測定之。將血小板懸浮液 0.4 毫升加入經 Silicone 包衣的小玻璃管中，並以小磁棒做每分鐘 900 轉 (900 rpm)的攪拌，若未特別說明，均在加入測試的化合物 3 分鐘後，再加入凝集引發劑，經 6 分鐘後觀察結果。為了排除溶媒 (DMSO)的影響，在血小板溶液的濃度為 0.5%。全部反應過程皆在 37 ℃中進行，凝集程度的表示方法如下。

凝集 % = $[(A_1-A_2) / (A_1-A_b)] \times 100\%$

A_1：加入凝集引發劑前的吸光度

A_2：加入凝集引發劑後的吸光度

A_b：Tyrode's solution 的吸光度

貳、抗過敏活性試驗方法：

1.肥滿細胞懸浮液的製備[99]：

大鼠經頸部放血後 (exsanguinated rats; Sprague-Dawley, 250-300 g)，取 10 mL 含肝素的 Tyrode's solution (Tyrode's sol'n A)注入鼠腹腔內，按摩 1-2 分鐘並取出腹腔溶液，經 38% bovine serum albumin (BSA，牛血清蛋白)溶液離心，沉澱細胞經清洗後，並懸浮於 Tyrode's solution B，其組成如下 (mM)：NaCl (137), KCl (2.7), $NaHCO_3$ (12), $MgCl_2$ (1.0), NaH_2PO_4 (0.3), $CaCl_2$ (1.0), glucose (5.6) and BSA 0.1%。肥滿細胞數目調整成每毫升 1- l.5×10^6 個細胞，並測定細胞存活率。

2.實驗方法：

Mast cell degranulation method：

(1)組織胺 (histamine)釋放反應的測定[100]：

將此肥滿細胞懸浮液分別與 0.5% DMSO 或檢品溶液於 37 ℃培養 3 分鐘，個別加入 compound 48/80 (10 μg/mL)與之作用，經 15 分鐘後，加入冰浴過的 Tyrode's solution 來中止反應，混合液經離心 (1000×g)10 分鐘後取出上清液，在 pH 12.5 的條件下，利用上清液中所含的 histamine 與 0.2% *o*-phthaldialdehyde 聚合後，以螢光分光光度計在 350/450 nm 下測量組織胺含量。

(2) β - glucuronidase 釋放反應的測定[101]：

同 histamine 釋放反應，將所得含 β - glucuronidase 的上清液，

利用 phenolphthalein-β-D-glucuronide 作為受質，以分光光度計在 550 nm 下測量所含的β-glucuronidase。

Histamine 及β-glucuronidase 的釋放表示如下：

Release % = [(releases elicited by secretagogue - spontaneous release) / total content]×100

(total content 是將細胞懸浮於 Triton X-l00 所測量的值)

參、抗發炎活性試驗方法：

1.嗜中性白血球懸浮液的製備[102]：

大白鼠 (Sprague Dawley, 250-300 g)以 pentobarbital (60 mg/kg) 腹腔注射麻醉後，從腹腔大動脈抽取血液 (以 100 mM EDTA 當抗凝劑)，與 dextran 混合後在試管中靜置使紅血球沈澱。取上清液離心 (400×g)10 分鐘，丟棄大部份上清液，將沈澱細胞懸浮液輕輕加至含有 Ficoll-Hypaque 的試管中，離心 (500×g)30 分鐘。將沈澱的細胞懸浮在 Hanks' balanced salt solution (HBSS) (含有 10 mM *N*-(2-hydroxyethyl)piperazine-*N*'-(2-ethanesulfonic acid) (HEPES)，pH 7.4 及 4 mM $NaHCO_3$)，離心 (700×g)10 分鐘，並以低張的 NaCl solution (0.05%)使沈澱細胞中剩餘的紅血球破裂，以去除紅血球；再用含有 0.25% bovine serum albumin (BSA)的高張 NaCl solution (1.75%)清洗並調整至等張，使細胞懸浮在 HBSS 中 (l×10^7 cells/mL)，即可製備純度及存活率均大於 95%的嗜中性白血球懸浮液。

2.實驗方法：

(A)Neutrophil degranulation method：

(1)β-glucuronidase 釋放反應的測定[103]：

將嗜中性白血球細胞懸浮液分別與 0.5% DMSO 或檢品溶液在 37 ℃培養 3 分鐘後，個別加入 fMLP (lμM)與之作用，經 45 分鐘後，加入冰浴過之 Tyrode's solution 來中止反應，混

合液經離心 (1000×g)10 分鐘後取出上清液，利用上清液中的 β-glucuronidase 與 phenolphthalein-β-D-glucuronide 反應後，經由分光光度計在 550 nm 下測量其中所含的 β-glucuronidase。

(2)Lysozyme 釋放反應的測定[101]：

同β- glucuronidase 釋放反應之處理後，將所得含 lysozyme 的上清液，利用 *Micrococcus lysodeikticus* 細胞作為受質，在分光光度計 450 nm 下測量 。

β-glucuronidase 及 lysozyme 的釋放表示如下：

release % = [(release elicited by secretagogue – spontaneous release)/total content]×100

(total content 是將細胞懸浮於 Triton X-l00 後所測量的值)

(B)Superoxide formation method：

Superoxide anion 釋放反應的測定[104]：

將含嗜中性白血球的細胞懸浮液 (2×10^6 cells/mL) 及 ferricytochrome *c* (0.5 mg/mL)的比色槽，置於 37 ℃恆溫的雙光束分光光譜儀中熱 3 分鐘，再將 fMLP (0.3 μM)或 PMA (3 nM)分別加入檢品及參考溶液中 30 分鐘，對照組比色槽另含有 6.6 μg/mL 的 superoxide dismutase (SOD)。加測試的化合物後，在 550 nm 下測定 SOD 可抑制 ferricytochrome *c* 吸光值的變化。

$O_2^{\cdot -}$ (superoxide anion)的量是以下式計算[105]：

$O_2^{\cdot -}$ (nmol)=19.08×absorbance

肆、NO (nitric oxide)**及** TNF-**α實驗方法：**

1.**材料：**

(1)Iscove's modified Dulbecco's medium (IMDM)**與牛胚胎血清** (fetal bovine serum, FBS)**：購自** Gibco BRL (Gaithersburg)。

(2)TNF-**α酵素免疫分析** (enzyme immunoassay, EIA) kit**：購自** Genzyme Co. (MA)。

(3)**老鼠干擾素-γ** (mouse interferon-**γ**, IFN-**γ**)**：購自** R&D Systems (MN)。

(4)RAW 264.7 mouse macrophage-like cell line**：購自** American Type Culture Collection, MD.。

(5)Dulbecco's modified Eagle's medium (DMEM)**與犢牛胚胎血清** (fetal calf serum)**：購自** Gibco BRL (Gaithersburg)。

(6)**其餘試藥皆購自** Sigma (St. Louis, MO.)。

2.**細胞培養與前處理**[106]**：**

RAW 264.7 mouse macrophage-like cell line **則以含有** 5% heat-inactivated fetal calf serum、100 units/mL penicillin **與** 100 **μ**g/mL streptomycin **的** DMEM **培養；在前處理時，將細胞與待測藥物在** 37 **℃混合** 1 **小時，然後以** 1 μg/mL **的** LPS (*Escherichia coli*, serotype 0111:B4)**刺激** 24 **小時，最後保存於**-70 **℃中，需要時才取出。**

Murine microglial cell lines N9 **係以含有** 2% heat-inactivated FBS **與抗生素的** IMDM **培養；在前處理時，將細胞與待測藥物在** 37 **℃**

混合 1 小時，然後以 10 ng/mL 的 LPS (*Escherichia coli*, serotype 0111:B4)加 10 U/mL IFN-γ 刺激 24 小時，最後保存於-70 ℃中，需要時才取出。

3.NO 的測定[37]：

在細胞培養基中，NO 的生成可以根據 Griess reaction 所得到的 nitrite 含量測定出來。依序將 40 μL 的 5 mM sulfanilamide、10 μL 的 2M HCl 及 20 μL 的 40 mM naphthylethylenediamine 加入 150 μL 培養基中，培養基在室溫下放置 10 分鐘後，利用 microplate 計數器在 550 nm 下測其吸光度。一氧化氮標準曲線則以 $NaNO_2$ 於相同條件下所求得。

4.TNF-α 的測定：

培養基中的 TNF-α 測定是使用 TNF-α enzyme immunoassay (EIA) kit，依照廠商提供的操作步驟進行測定。