Synthesis and antidyslipidemic activity of chalcone fibrates

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ity of Chalcone Fibrates

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Abstract:

A series of chalcone based PPAR-Ŭ agonists were synthesized and evaluated for their antidyslipidemic activity in high fructose high fat fed dyslipidemic Syrian golden hamsters. Most of the compounds exhibited antidyslipidemic activity. The compounds 4c & 4f have been identified as most potent antidyslipidemics. A definite structure-activity relationship was observed while varying the nature as well as the position of the substituent.

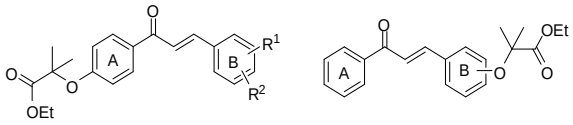
Keywords:

Chalcones, Fibrate, Antidyslipidaemic activity, High fructose high fat diet (HFD), Syrian Golden Hamsters

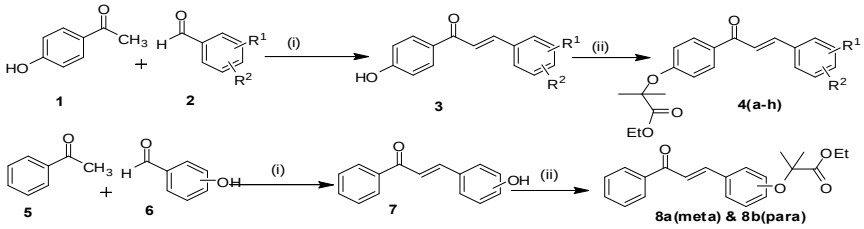
Dyslipidemia, a common lipid abnormality is characterized by elevated low density lipoprotein cholesterol (LDL-ç), triglycerides (TGs), or low level of high density lipoprotein cholesterol (HDL-c) in serum.[1] The high level of LDL-c, low HDL-c and TG are recognized as independent risk factors for coronary heart disease (CHD)[2] as well as of initiation of diabetes and the leading cause of cardiovascular morbidity and death in industrialized countries.[3] Triglycerides are important source of energy from food while cholesterol is an essential component of the human cell membrane and a precursor for steroid hormones and bile acids. However, the presence of the continuously increased level of lipids cause a health problem under oxidative stress conditions which arise due to the lack of physical activities. Oxidative stress plays an imperative role in diabetic and hyperlipidemic patients leading to macrovascular and microvascular complications.[4] The currently available lipid lowering drugs like statins lower cholesterol by interfering with the cholesterol biosynthetic pathway[5] while fibrates decrease triglyceride levels by stimulating the *β*-oxidation pathway.[6] However, their chronic use manifests myalgia and rhabdomyolysis which are associated with muscular pain and increased level of creatinine kinases[7] which therefore necessitates search for safer drugs.

The chalcones (1, 3-diaryl-2-propene-1-ones) belong to the flavonoid family and consists of open chain flavonoids in which the two aromatic rings are joined by a three-carbon Ŭ, ß-unsaturated carbonyl system. This natural product is being consumed daily through fruits and vegetables, has attracted our attention to explore hybrid structures with them for anti-dyslipidemic activity as chalcones also exhibits antioxidant activity.[8] In continuation of our program of utilizing antioxidant potential of chalcones for design of agents for diseases associated with metabolic syndrome,[9] we report here the synthesis of fibrate class of compounds

A and B (fig. 1) and their lipid lowering and antidiabetic after a patent publication by Zhong et al.[10]



The general synthetic plan employed to prepare the different chalcones is condensation.



Scheme 1. Reagents: (i) aq. NaOH, Methanol, r.t.; (ii) $EtOOCC(CH_3)_2Br$, K_2CO_3, Methyl isobutyl ketone.

Hydroxy chalcones 3 & 7 prepared by Claisenï Schmidt[11] from corresponding acetophenones andbenzaldehydes were reacted with $EtOOCC(CH_3)_2Br$ in presence of potassium carbonate to yield derivatives of compounds 4 & 8. The compounds were then tested for their antidyslipidemic and antidiabetic activities.

Table 1. Compounds synthesized via Scheme 1

Compounds	R^1	R^2	Position	%Yield	m. p.
4a	Cl	Cl	3, 5	63.64	94-96^{0}C
4b	H	Cl	4	76.92	112-114^{0}C
4c	H	NO_2	4	91.54	126-128^{0}C
4d	H	CH_3	4	81.08	83-85^{0}C
4e	H	Cl	2	55.56	viscous oil
4f		H	3, 4	77.46	98-100^{0}C
4g	H	OCH_3	4	70.22	viscous oil
4h	H	F	4	72.92	110-112^{0}C
8a	H	H	3	76.56	viscous oil
8b	H	H	4	45.23	viscous oil

Antidyslipidemic activity evaluation of compounds in Syrian golden hamsters male (body weight 100-120g, age 6-8 weeks old) was fed with high fructose high fat diet (55% fructose, 13% fats) for one month for the development of dyslipidemia.[12] Dyslipidemic hamsters were selected and grouped for the evaluation of antidyslipidemic activity. Group 1st was treated as sham treated control group and was given 1% gum acacia. Other groups were treated as treatment group and were dosed at 30 mg/kg body weight of test compounds. The standard drug treated group was given fenofibrate at the 30 mg/kg dose. Dose dependant antidyslipidemic activities were also studied in these hamsters and the desired compound was dosed at 10 mg/kg and 30 mg/kg dose to their respective groups. Treatments were done for 7 days. Body weight was measured daily to

ty of compounds. At the end of experiment blood was
s of eye for the estimations of serum triglyceride, total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, lipoprotein lipase and fasting serum glucose by using Roche diagnostic kits. Glycerol and non-esterified free fatty acid (NEFA) were estimated using Randox kits. Serum insulin level was estimated by ELISA method using Mercodia kits

Table 2. Antidyslipidemic activity evaluation in Syrian golden hamsters

Groups	FBG	Insulin	TG	CHOL	HDL-c	LDL-c
4a[AA]	-8.40	-12.1	-17.4	-16.9	+10.1	-16.8
4b[AA]	+5.40	-22.2	-22.7*	-23.7*	-2.52	-20.5*
4c[AA]	-7.49	-24.3	-30.4*	-25.0*	+5.88	-28.5**
4d[AA]	-12.9	-10.8	-22.7	-23.4*	+2.52	-19.8
4e[AA]	+4.65	+2.39	-21.3	-0.48	+15.6	-16.4
4f[AA]	-14.8	-19.4	-41.6**	-26.8*	+9.80	-41.7**
4g[AA]	-16.9	-5.87	-31.2*	-9.30	-9.90	-27.4*
4h[AA]	-18.4	-4.90	-22.2	-16.8	+4.80	-23.2*
8a[AA]	-10.5	-5.89	-18.5	-11.5	+2.10	-15.3
8b[AA]	+8.80	+6.78	-25.1*	-17.8	+10.8	-16.8
Fenofibrate ÀÀ	-5.40	-11.5	-28.9**	-16.9	+9.80	-30.1**

% Change in fasting blood glucose (FBG), insulin and serum lipid profile as compare to control.[AA]on day 7[th]; [AA]30 mg/kg dose; Statistical significance: *p <0.05, **p<0.01.

In the present study, experiments were carried out to investigate the antidyslipidemic effects of chalcone derivatives in the HFD fed dyslipidemic hamster model.

Feeding of high fructose diet (fructose 55 and fat 13% etc.) resulted in the alteration of serum lipid profile (Table 3 and 4). It is evident from the table 2 that continuous post feeding of chalcone compounds at the 30 mg/kg dose for 7 days resulted in the significant improvement of dyslipidemia in HFD fed hamsters. The treatment of compounds showed marked decrease in the serum triglyceride concentration, some of them showing significant lowering are compounds 4b, 4c, 4f, 4g and 8b. These compounds in general lower the serum cholesterol as well as low density lipoprotein cholesterol (LDL-c). However, the compounds 4b, 4c, 4d, and 4f showed significant reduction in serum cholesterol. The compounds 4b, 4c, 4f, and 4g also significantly lowered the low density lipoprotein. These compounds also elevate the level of good cholesterol i.e. high density lipoprotein (HDL-c) except 4b, and 4g. Compounds 4a, 4e and 4f resulted in the marked increase in the serum HDL-c concentration while compounds 4b, 4c & 4f decreased insulin levels.

Thus few of the synthesized compounds have shown moderate to good antidyslipidemic as well as antidiabetic activities. The compounds with PPAR-Ü pharmacophore on ring A have shown better activities than on ring B. In ring A substituted compounds, the electron withdrawing groups on ring B enhance the activities in comparison to other groups. No definite conclusion could be drawn regarding the type of substitution responsible for the activity. However, the compounds 4c & 4f with nitro and methylenedioxy groups respectively have shown good activities.

n HFD fed hamsters

Groups	(mg/dl)	(mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	l Glycero (µmol/l)	NEFA (mmol/l)	LPL (U/l)
ND control	132.4±7.8	175.4±5.9	48.6±5.1	60.0±8.5	210.0±22.2	1.98±0.15	52.4±5.5
HFD control (1% vehicle)	334.6±37.8	747.1±64.9#	142.8±6.80#	265.5±26.6#	1353.0±75.5#	6,50±0.40#	30.4±3.70#
HFD+ 4c (10 mg/kg)	282.2±37.7* (-15.6)	597.4±35.7* (-20.0)	138.0±13.7 (-3.36)	220.0±21.3 (-16.9)	1245.7±61.8 (-7.93)	6.40±0.50 (-2.45)	33.7±3.80 (+10.8)
HFD+ 4c (30 mg/kg)	250.8±22.1* (-25.0)	520.2±57.7* (-30.4)	151.2±7.59 (+5.88)	189.5±10.6* (-28.5)	1119.9±50.5 (-17.2)	5.50±0.35 (-15.9)	37.8±4.20 (+21.7)
HFD+ Feno (30 mg/kg)	277.8±22.3 (-16.9)	529.8±30.7* (-28.9)	156.8±12.8 (+9.80)	185.1±11.2** (-30.1)	1050.2±45.5* (-22.4)	5.40±0.30 (-17.4)	36.8±3.60 (+21.1)*

Data are mean ± SE values of six hamsters per group. Statistical significance: # p<0.01 as compared to normal diet (ND) control, *** p<0.001, ** p<0.01, * p<0.05 as compared to HFD control.

These two compounds (4c & 4f) showing promising antidyslipidemic activity were followed for the dose dependent study in HFD fed dyslipidemic Syrian golden hamsters. The dose dependent (at 10 and 30 mg/kg) antidyslipidemic effects of these compounds in HFD fed hamsters are summarized in Table 3. In the experiment with compound 4c at 10 mg/kg dose however, all the animals did not respond as compare to HFD control but lowered the TG, Chol, LDL-c, glycerol and NEFA by 20.0, 15.6, 16.9, 7.93 and 2.45% respectively. Little decrease in HDL-c Concentration and mild increase in lipoprotein lipase activity were also observed. After 7 days post treatment at 30 mg/kg resulted in the significant decrease in the TG (30.4%, p<0.05), Chol (25.0%, p<0.05) and LDL-c (28.5%, p<0.05) and also caused mild decrease in glycerol (17.2%) and NEFA (15.9%) levels. Little increase in HDL-c level (5.88%) and marked elevation in lipoprotein lipase activity were observed as compare to HFD control (21.7%).

Table 4. Dose dependent effect of 4f on HFD fed hamsters.

Groups	Chol (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	l Glycero (µmol/l)	NEFA (mmol/l)	LPL (U/l)
ND control	132.4±7.8	175.4±5.9	48.6±5.1	60.0±8.5	210.0±22.2	1.98±0.15	52.4±5.5
HFD control (1% vehicle)	334.6±37.8#	747.1±64.9#	142.8±6.80#	265.5±26.6#	1353.0±75.5#	6,50±0.40#	30.4±3.70#
HFD+ 4f (10 mg/kg)	272.2±18.6 (-18.6)	597.4±35.7* (-20.0)	148.2±8.90 (+3.78)	198.2±10.8* (-25.2)	1150.5±43.3 (-14.9)	6.10±0.30 (-6.73)	34.8±3.60 (+14.5)
HFD+ 4f (30 mg/kg)	244.8±13.1** (-26.8)	436.1±27.7** (-41.6)	156.8±7.60 (+9.80)	154.4±6.60** (-41.7)	1015.2±27.9 (-24.9)	5.20±0.20 (-20.5)	39.6±4.10* (+30.2)

156.8±12.8 (+9.80)	185.1±11.2** (-30.1)	1050.2±45.5* (-22.4)	5.40±0.30 (-17.4)	36.8±3.60* (+21.1)

Data are mean ± SE values of six hamsters per group. Statistical significance: #p<0.01 as compared to normal diet (ND) control, *** p<0.001, ** p<0.01, * p<0.05 as compared to HFD control.

Table 4 presents the dose dependent antidyslipidemic effect of 4f in HFD fed Syrian golden hamsters. The compound 4f at 10 mg/kg dose results in the significant reduction in the serum TG (20.0%, p<0.05) and LDL-c (25.2%, p<0.05) and showed mild decrease in the serum Chol (18.6%), glycerol (14.9%), and NEFA (6.73%). Mild increase in lipoprotein lipase (14.5%) was observed after post treatment of compound 4f at 10 mg/kg dose. Post treatment of compound 4f at 30 mg/kg dose, lowered the levels of TG (41.6%, p<0.01), Chol (26.8%, p<0.01), LDL-c (41.7%, p<.01), glycerol (24.9%) and NEFA (20.5%). Marked increase in HDL-c (9.80%) and lipoprotein lipase activity (30.2%, p<0.05) was also observed.

The interesting feature of these compounds is to increase in the level of good cholesterol i.e. HDL-c, but the marked effect was shown at 30 mg/kg dose. High fructose and high fat fed Syrian golden hamsters showed increased level of glycerol and non-esterified free fatty acid as compared to normal diet fed hamsters, because of feeding of HFD diet, these animals resulted in the decrease of lipoprotein lipase activity. Treatment with these compounds lowered the elevated level of glycerol as well as non-esterified free fatty acid by activating the lipoprotein lipase activity. The 10 mg/kg repeated dose for 7 days of 4c showed comparatively less effect as compared to 4f. The standard drug fenofibrate treatment at the same dose showed marked reduction in TG (28.9%, p<0.05), Chol (16.9), LDL-c (30.1%, p<0.01), glycerol (22.4%, p<0.05), NEFA (17.4%). Marked increase in HDL-c (9.80%) and lipoprotein lipase activity (21.1% p<0.05) was also observed. Among all the compounds, 4f showed better antidyslipidemic activity as compared to the compound 4c and fenofibrate at the same dose level. These compounds exhibited similar antidyslipidemic profile as fenofibrate. It is also clear from fig 1 that at the day 0 all the groups have nearly same value of insulin level but after 7 days post treatment with compounds 4c, 4f and fenofibrate at 30 mg/kg dose caused reduction in serum insulin level and were found to be 13.8, 22.2 and 11.2% respectively. Compounds 4c and 4f also exhibited a mild reduction of ~6.85 and 6.25% respectively in body weight after 7 days post treatment. It is evident from the fig 2 that the pattern of lowering in body weight after post treatment with the both compounds is nearly same.

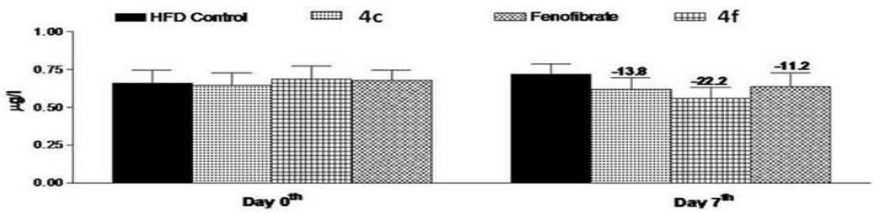


Fig. 1. Effect of 4c & 4f on serum insulin level (mean±SE) in HFD fed Syrian golden hamsters

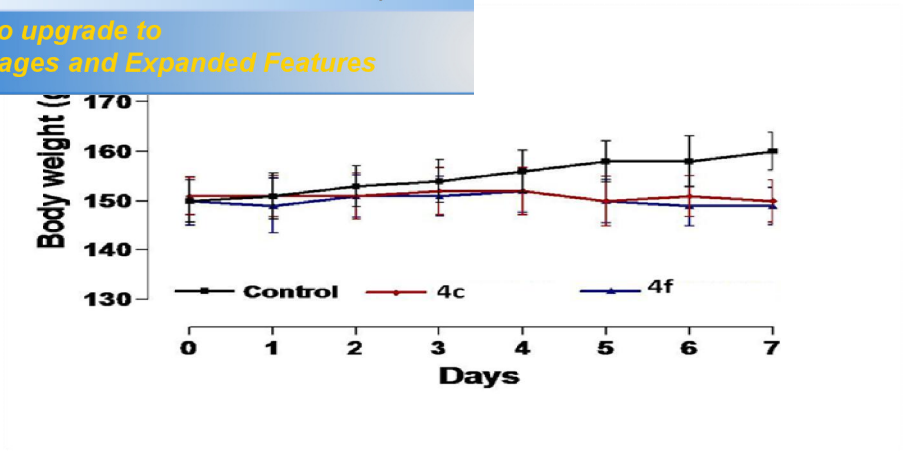


Fig. 2. Represents the body weight reducing activity of compounds

Thus the compounds with PPAR-Ŭpharmacophore at 4-position in ring A of chalcone exhibits antidyslipidemic activity comparable to fenofibrate. The compounds with nitro and methelenedioxy group in the ring B are specifically more active as compared to other compounds.

General procedure for the synthesis of chalcone fibrates: To a stirred solution of acetophenone (14.7 mM) in methanol (50 mL) was added 20 ml NaOH (20% aq.) and benzaldehyde (17.6 mM) at room temperature and stirring was continued for another 5-6 hr. After completion the reaction mixture is extracted with chloroform and solvent removed from organic layer to yield crude product 3 which was purified on silica-gel column. The compound 3 (1.71 mM) was further treated with $EtOOCC(CH_3)_2Br$ (2.05 mM) in methylisobutyl ketone in presence of K_2CO_3(qs) at 110^oC for 4-6 h. After completion of the reaction and filtration of the solid, the solvent was removed from filtrate and the products 4 & 8 were purified by column chromatography.[14]

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References and notes

1. Mohiuddin, S. M.; Pepine, C. J.; Kelly, M. T.; Buttler, S. M.; Setze, C. M.; Sleep, D. J.; Stolzenbach, J. C. *Am. Heart J.* **2009**, *157*, 195.
2. (a) Sharrett, A. R.; Ballantyne, C. M.; Coady, S. A.; Heiss, G.; Sorlie, P. D.; Catellier, D.; Patsch, W. *Circulation* **2001**, *104*, 1108; (b) Sarwar, N.; Danesh, J.; Eiriksdottir, G.; Sigurdsson, G.; Wareham, N.; Bingham, S.; Boekholdt, S. M.; Khaw, K. T.; Gudnason, V. *Circulation* **2007**, *115*, 450.
3. Abello, F.; Baracco, V.; Guardamagna, O. *Nutr. Metab.Cardiovas. Dis.* **2008**, *18*, 35.
4. Leiter, L. A. *Diabetes Res. Clin. Pract.* **2005**, *68(Suppl.2),* S3.
5. (a) Krukemyer, J. J.; Talbert, R. L. *Pharmacotherapy* **1987**, *7*, 198; (b) Hebert, P. R.; Gaziano, J. M.; Chan, K. S.; Hennekens, C. H. *J. Am. Med. Assoc. (JAMA)* **1997**, *278*, 313.

B. *Curr. Opin. Lipidol*. **1999**, *10*, 561; (b) Ozasa, H.; i, T.; Hashimoto, T. *J. Biochem.***1985**, *97*, 1273.
7. (a) Jacob, S. S.; Jacob, S.; Williams. C.; Deeg, M. A. *Diabetes Care* **2005**, *28(5),* 1258; (b) Rallidis, L. S.; Apostolou, T. S. *Hellenic J. Cardiol*. **2002**, *43*, 219.
8. Vaya, J.; Belinky, P. A.; Aviram, M. *Free Radical Biol. Med*. **1997**, *23*, 302.
9. (a) Satyanarayana, M; Tiwari, P; Tripathi, B. K.; Srivastava, A. K.; Pratap, R. *Bioorg. Med. Chem*. **2004**, *12*, 883; (b) Shukla, P.; Singh, A. B.; Srivastava, A. K.; Pratap, R. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 799; (c) Pratap, R.; Satyanarayana, M.; Nath, C.; Raghubir, R.; Puri, A.; Chander, R.; Tiwari, P.; Tripathi, B. K.; Srivastava, A. K. *US Patent* 7,807,712 B2, **2010**.
10. Zhong, B.; Li, W.; He, X.; Li, M.; Liu, H.; Chen, L. *Chinese Patent, Publication no* 1,016,133,34, **2009**.
11. Sogawa, S.; Nihro, Y.; Ueda, H.; Izumi, A.; Miki, T.; Matsumoto, H.; Satoh, T. *J. Med. Chem.* **1993**, *36*, 3904.
12. (a) Maurya, S. K.; Raj, K.; Srivastava, A. K. *Indian J. Clin. Biochem.* **2009**, *24(4),* 404; (b) Kumar, A.; Sharma, S.; Tripathi, V. D.; Maurya, R. A.; Srivastava, S. P.; Bhatia, G.; Tamarkar, A. K.; Srivastava, A. K. *Bioorg. Med. Chem.* **2010**, *18(11),* 4138.
13. (a) Olsson, R.; Carlsson, P. O. *Diabetologia*, **2005**, *48*, 469; (b) Rydtren, T.; Sandler, S. *Eur. J. Endocrinol*. **2002**, *147,* 543.
14. Spectral data of the compounds:

2-[4-{3-(3, 5-Dichloro-phenyl)-acryloyl}-phenoxy]-2- methyl-propionic acid ethyl ester (**4a**): Yield: 64%; m.p.: 94-96^{0}C; MS (ESI): 407, 409(M^+, M^{+2}), IR(KBr): 3021, 2359, 1606; ^{1}HNMR (200MHz,$CDCl_3$): ŭ 7.97 (d, *J* = 8.84Hz, 2H, 2ô,6ô-H), 7.72 (s, 1H, 4H), 7.68 (d, *J* = 15.74Hz, 1H, ƀ-H), 7.49 (d, *J* = 15.72Hz, 1H, Ŭ-H), 7.47 (d, *J* = 2.68Hz, 2H, 2,6-H), 6.89 (d, *J* = 8.86Hz, 2H, 3ô,5ô-H), 4.24 (q, 2H, OCH_2), 1.67 (s, 6H, C-CH_3), 1.23 (t, 3H, CH_3).

2-[4-{3-(4-Chloro-phenyl)-acryloyl}-phenoxy]-2-methyl- propionic acid ethyl ester (**4b**): Yield: 77%; m.p.: 112-114^{0}C; MS(ESI): 373(M+1), IR (KBr): 3424, 3021, 2359, 1604; ^{1}HNMR (300MHz, $CDCl_3$): ŭ 7.97 (d, *J* = 8.85Hz, 2H, 2ô,6ô-H), 7.74 (d, *J* = 15.63Hz, 1H, ƀ-H), 7.56 (d, *J* = 8.49Hz, 2H, 2,6-H), 7.49 (d, *J* = 15.63Hz, 1H, Ŭ-H), 7.38 (d, *J* = 8.46Hz, 2H, 3,5-H), 6.88 (d, *J* = 8.85Hz, 2H, 3ô,5ô-H), 4.23 (q, 2H, OCH_2), 1.67 (s, 6H, C-CH_3), 1.23 (t, 3H, CH_3).

2-[4-{3-(4-Nitro-phenyl)-acryloyl}-phenoxy]-2-methyl-propionic acid ethyl ester (**4c**): Yield: 92%; m.p.: 126-128^{0}C; MS(ESI): 384 M+1); IR (KBr): 3020, 2358, 1732, 1601; ^{1}HNMR (300MHz, $CDCl_3$): ŭ 8.28 (d, *J* = 8.82Hz, 2H, 3,5-H), 7.99 (d, *J* = 8.91Hz, 2H, 2ô,6ô-H), 7.80 (d, *J* = 15.66Hz, 1H, ƀ-H), 7.78 (d, *J* = 8.7Hz, 2H, 2,6-H), 7.63 (d, *J* = 15.69Hz, 1H, Ŭ-H), 6.90 (d, *J* = 8.85Hz, 2H, 3ô,5ô-H), 4.25 (q, 2H, OCH_2), 1.68 (s, 6H, C-CH_3), 1.23 (t, 3H, CH_3).

2-[4-{3-(4-methyl-phenyl)-acryloyl}-phenoxy]-2-methyl- propionic acid ethyl ester (**4d**): Yield: 81%; m.p.: 83-85^{0}C; MS(ESI): 353(M+1); IR(KBr): 3021, 2360, 1600; ^{1}HNMR(300MHz, $CDCl_3$): ŭ 7.90 (d, *J* = 8.85Hz, 2H, 2ô,6ô-H), 7.71 (d, *J* = 15.63Hz, 1H, ƀ-H), 7.47 (d, *J* = 7.10Hz, 2H, 2,6-H), 7.42 (d, *J* = 15.69Hz, 1H, Ŭ-H), 7.14 (d, *J* = 7.98Hz, 2H, 3,5-H), 6.81 (d, *J* = 8.85Hz, 2H, 3ô,5ô-H), 4.17 (q, 2H, OCH_2), 2.32 (s, 3H, CH_3), 1.60 (s, 6H, C-CH_3), 1.15 (t, 3H, CH_3).

2-[4-{3-(2-Chloro-phenyl)-acryloyl}-phenoxy]-2-methyl-propionic acid ethyl ester (**4e**): Yield: 56%; MS(ESI): 373(M+1); IR(Neat): 3021, 2361, 1653; ^{1}HNMR(300MHz,

1H, ß-H), 7.90 (d, *J* = 8.82Hz, 2H 2ô,6ô-H), 7.65 (d, *J* = 15.66Hz, 1H, Ŭ-H), 7.36 (m, 1H, 4-H), 7.34-7-28 (m, 2H, 3, 5ï H), 6.81 (d, *J* = 8.85, 2H, 3ô,5ô-H), 4.15 (q, 2H, OCH_2), 1.58 (s, 6H, C-CH_3), 1.15 (t, 3H, CH_3).

2-[4-{3-Benzo(1,3)dioxol-5-yl-acryloyl}-phenoxy]-2-methyl-propionic acid ethyl ester (**4f**): Yield: 78%; m. p.: 98-100^{0}C; MS(ESI): 383(M+1); IR(KBr): 3021, 2360, 1598; ^{1}HNMR (300MHz, $CDCl_3$): ŭ 7.89 (d, *J* = 8.79Hz, 2H, 2ô,6ô-H), 7.65 (d, *J* = 15.36Hz, 1H, ß-H), 7.29 (d, *J* = 15.51Hz, 1H, Ŭ-H), 7.20 (s, 1H, 2-H), 7.09 (m, 2H, 3ô, 5ô-H), 6.82-6.76 (m, 2H, 5,6-H), 5.96 (s, 2H, OCH_2O), 4.17 (q, 2H, OCH_2), 1.60 (s, 6H, C-CH_3), 1.18 (t, 3H, CH_3).

2-[4-{3-(2-Methoxy-phenyl)-acryloyl}-phenoxy]-2- methyl-propionic acid ethyl ester (**4g**): Yield: 70%; MS(ESI): 369(M+1); IR(Neat): 3022, 2362, 1600; ^{1}HNMR(300MHz, $CDCl_3$): ŭ 7.75 (d, *J* = 15.66Hz, 1H, ß-H), 7.63-7.57 (m, 3H, 6, 2ô,6ô-H), 7.46 (d, *J* = 14.88Hz, 1H, Ŭ-H), 7.06-7.03 (m, 1H, 4-H), 7.37-7-30 (m, 2H, 3, 5ï H), 6.92 (d, *J* = 8.67, 2H, 3ô,5ô-H), 4.24 (q, 2H, OCH_2), 3.84 (s, 3H, OCH_3), 1.58 (s, 6H, C-CH_3), 1.22 (t, 3H, CH_3).

2-[4-{3-(4-Fluoro-phenyl)-acryloyl}-phenoxy]-2-methyl-propionic acid ethyl ester (**4h**): Yield: 73%; m.p.: 110-112^{0}C; MS(ESI): 357(M+1), IR(KBr): 3422, 3020, 2360, 1600; ^{1}HNMR(300MHz, $CDCl_3$): ŭ 7.98 (d, *J* = 8.82Hz, 2H, 2ô,6ô-H), 7.77 (d, *J* = 15.66Hz, 1H, ß-H), 7.64 (d, *J* = 8.49Hz, 2H, 2,6-H), 7.46 (d, *J* = 15.60Hz, 1H, Ŭ-H), 7.09 (d, *J* = 9.00Hz, 2H, 3,5-H), 6.90 (d, *J* = 8.82Hz, 2H, 3ô,5ô-H), 4.23 (q, 2H, OCH_2), 1.68 (s, 6H, C-CH_3), 1.26 (t, 3H, CH_3).

2-Methyl-2-[3-(3-oxo-3-phenyl-propenyl)-phenoxy]-propionic acid ethyl ester (**8a**): Yield: 77%; MS(ESI): 339(M+1); IR(KBr): 3420, 3021, 2362, 1602; ^{1}HNMR (300MHz, $CDCl_3$): ŭ 8.03 (d, *J* = 7.35Hz, 2H, 2ô,6ô-H), 7.76 (d, *J* = 15.69Hz, 1H, ß-H), 7.50 (d, *J* = 15.99Hz, 1H, Ŭ-H), 7.61-7.50 (m, 3H, 3ô, 4ô, 5ô-H), 7.31-7.20 (m, 2H, 5, 6-H), 7.17 (s, 1H, 2-H), 6.90 (m, 1H, 4-H), 4.27 (q, 2H, -OCH_2), 1.65 (s, 6H, C-CH_3), 1.25 (t, 3H, CH_3).

2-Methyl-2-[4-(3-oxo-3-phenyl-propenyl)-phenoxy]-propionic acid ethyl ester (**8b**): Yield: 45%; MS(ESI): 339(M+1); IR(KBr): 3418, 3025, 2363, 1601; ^{1}HNMR (300MHz, $CDCl_3$): ŭ 7.94 (d, *J* = 7.20Hz, 2H, 2ô,6ô-H), 7.71 (d, *J* = 15.60Hz, 1H, ß-H), 7.53-7.31 (m, 6H, 3ô,4ô,5ô, 2, 6, Ŭ-H), 6.87 (d, *J* = 8.70Hz, 2H, 3, 5-H), 4.25 (q, 2H, OCH_2), 1.68 (s, 6H, C-CH_3), 1.23 (t, 3H, CH_3).