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Original article

Discovery of amide based fibrates as possible antidyslipidemic and antioxidant agents☆

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ABSTRACT

A novel series of amide based fibrates were synthesized and evaluated for antidyslipidemic activity in triton induced hyperlipidemic rats. Interestingly, the compound **13** produced striking reduction in serum levels of total cholesterol (TC), phospholipids (PL) and triglycerides (TG). In addition, it exhibited improved lipoprotein lipase activity and found to possess moderate radical scavenging potential. The results of the above studies shows that the compounds synthesized on fibrate based pharmacophores might result in identification of new lead for dyslipidemia.

1. Introduction

Elevated plasma triglycerides and low high density lipoprotein cholesterol (HDL-C) are diagnostic markers for metabolic syndrome, these abnormalities are among the key risk factors for cardiovascular diseases [1,2]. Current therapies include both increasing high density lipoprotein cholesterol (HDL-C) levels and lowering LDL-C. HDL-C based approaches are much more complex and sometimes disappointing. These negative results stimulated interest on drugs that focus on lowering LDL-cholesterol, of these therapeutics statins (HMG-CoA reductase inhibitors) are pretty effective. However, statins can hardly normalize the high density lipoprotein abnormality and most patients still experience adverse coronary events despite statin therapy. In addition, recent reports of undesirable side effects (myopathy) of some 'super statins' indicate that the scope of improving the potency of this class of drugs may be modest [3]. The fibrate class of drugs (1–3, Fig. 1) have been widely used for the clinical treatment of dyslipidemia by lowering serum triglycerides and raising HDL-cholesterol (HDL-C) and remain the current treatment of choice for patients with severe hypertriglyceridemia [4,5]. Mechanistic studies reveals that the hypolipidemic effect of the fibrate drugs is attributed to the activation of peroxisome proliferator-activated receptors (PPARα) [6–8] which is one of the three isoforms (α, γ and δ) of PPARs [9]. The elevation of HDL-cholesterol levels observed with fibrates arises in part from the transcriptional induction of the major HDL apolipoproteins, apoA-I and apoA-II [10]. Unfortunately a combination of fibrates and statins has met with serious safety concerns as exemplified by the withdrawal of cerivastatin in 2001. Therefore, there is a constant need for a different class of potent compounds to treat dyslipidemia without severe side effects.

Additionally, oxidative stress is an important factor for the development and progression of coronary heart diseases (CHD). The involvement of hydroxyl free radicals has been found to be a major causative factor for the peroxidative damage to lipoproteins present in the blood, which are responsible for the initiation and progression of atherosclerosis [11]. Furthermore, in hyperglycemic patients, several non-enzymatic glycosylations occurs accompanied by glucose oxidation catalyzed by Cu_2^{+} and Fe_2^{+} resulting in the formation of $O_2^{\bullet}$ and $^{\bullet}OH$ radicals which further accelerates the risk of cardiac diseases in dyslipidemic subjects. As multiple mechanisms are involved in the development of atherosclerosis

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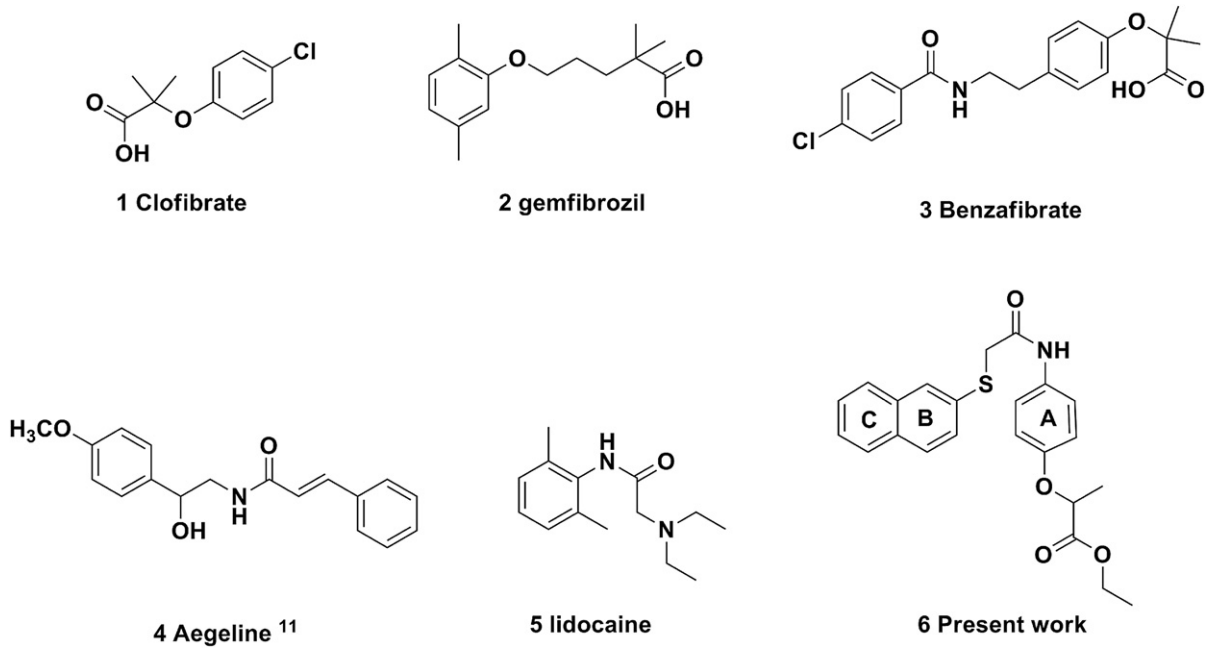


Fig. 1. Chemical structures of some biologically important fibrates and our prototype.

(hyperlipidemia, oxidative stress, and inflammation), agents with at least two mechanisms of action may offer a therapeutic benefit compared to those only targeting a single mechanism [12].

Carboxamides represent an important class of compounds found in versatile building blocks for the preparation of pharmaceuticals [13]. Moreover, this class of compounds has been clinically used as therapeutic options [14] such as, lidoderm (5, Fig. 1) and benzafibrate (3, Fig. 1) [15]. Furthermore, the natural product amide, aegeline (4, Fig. 1) was reported to exhibit antidyslipidemic activity [16]. In continuation of our drug discovery programme on new antidyslipidemic agents [17–21], and our laboratory experiences on molecular hybridization approach [22–25], we herein report the synthesis and biological evaluation of amide based fibrate hybrids as possible antidyslipidemic agents. In this context a series of novel amide based fibrates were synthesized (our prototype **6** in Fig. 1) and evaluated for their lipid lowering and anti-oxidant potential. Fig. 1 showed chemical structures of some important fibrates and our synthesized prototype. The frequently prescribed hypolipidemic agent, gemfibrozil (2, Fig. 1) having a 5-phenoxypentanoic moiety instead of the fibric acid moiety is also considered a fibrate because of having almost similar pharmacological properties as the other classical fibrates like clofibrate (1, Fig. 1).

2. Chemistry

The detailed synthetic route of the target compounds (**8**–**14** & **18**–**28**) is outlined in Scheme 1. Following reported procedures, treating phenol/thiophenol (**6**–**7** & **15**–**17**) with ethyl bromoacetate in the presence of K_2CO_3 afforded the corresponding esters derivatives (**6a**–**7a** & **15a**–**17a**) which were then subjected to basic hydrolysis with potassium hydroxide furnished their respective acids (**6b**–**7b** & **15b**–**17b**), further these were transformed to the corresponding acid chlorides by using thionyl chloride. Condensation of the acid chlorides with 4-hydroxy aniline furnished their corresponding amide derivatives (**6c**–**7c** & **15c**–**17c**). The desired amide based fibrate hybrids (**8**–**14** & **18**–**28**), were obtained in excellent yield by treating the amides with appropriate substituted 2-bromoesters in the presence of K_2CO_3. General synthetic scheme is shown in Scheme 1. All the synthesized compounds were characterized using ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry (Supporting information).

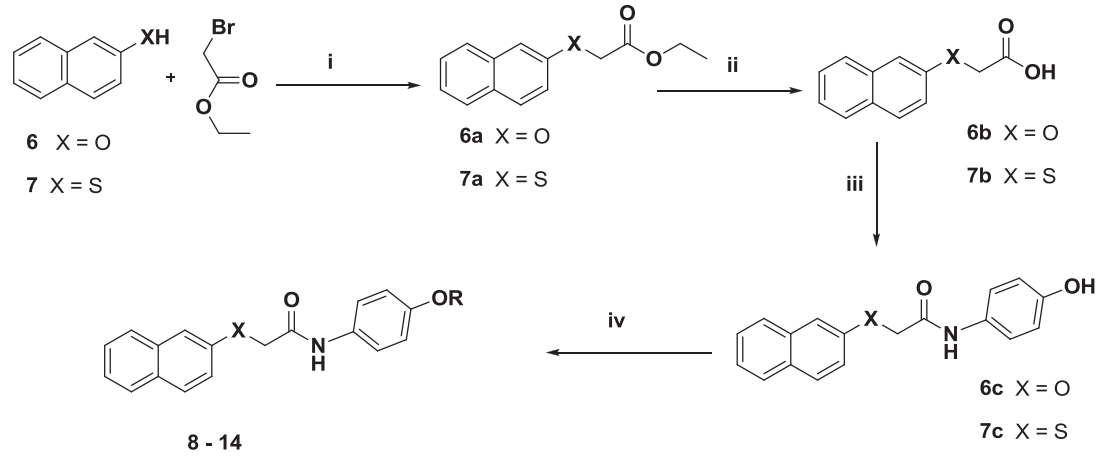
3. Pharmacology

3.1. Animals used

Rats (Charles Foster strain, male, adult, body weight 200–225 g) were kept in a room with controlled temperature (25–26 °C), humidity (60–80%) and12/12 h light/dark cycle (light on from 8.00 A.M. to 8.00 P.M.) under hygienic conditions. Animals, which were acclimatized for one week before starting the experiment, had free access to the normal diet and water.

3.2. Lipid lowering and post heparin lipolytic activity

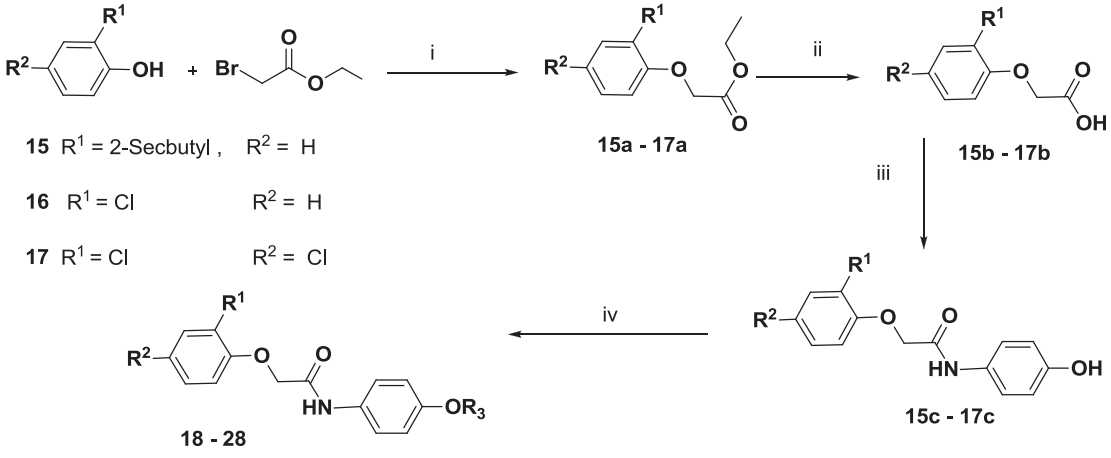
Rats were divided into twelve groups, control, triton induced, triton plus **8**–**14** & **18**–**28**, and gemfibrozil (100 mg/kg) treated groups, containing six rats in each group. In this experiment of 18 h, hyperlipidemia was developed by administration of triton WR-1339 (Sigma chemical company, St. Louis, MO, USA) at a dose of 400 mg/kg body weight intraperitoneally to animals of all the groups except the control. These derivatives were macerated with gum acacia (0.2% w/v), suspended in water and fed simultaneously with triton with a dose of 100 mg/kg p.o. to the animals of treated group and the diet being withdrawn. Animals of control and triton group without treatment with amide based fibrate compounds were given same amount of gum acacia suspension (vehicle). After 18 h of treatment the animals were anaesthetized with thiopentone solution (50 mg/kg b.w.) prepared in normal saline and then 1.0 ml blood was withdrawn from retro-orbital sinus using glass capillary in EDTA coated eppendorf tube (3.0 mg/ml blood). The blood was centrifuged (at 2500 g) at 4 °C for 10 min and plasma was separated. Plasma was diluted with normal saline (ratio of 1:3) and used for analysis of total cholesterol (TC), triglycerides (TG) and phospholipids (PL) by standard enzymatic methods [26] and post heparin lipolytic activity (PHLA)



8 X = O, R = -CH(CH$_3$)COOC$_2$H$_5$; **11** X = O, R = -CH$_2$COOC$_2$H$_5$; **14** X = S, R = -CH(C$_2$H$_5$)COOC$_2$H$_5$

9 X = O, R = -CH(C$_2$H$_5$)COOC$_2$H$_5$; **12** X = O, R = -CH(CH$_2$)$_2$COOC$_2$H$_5$

10 X = O, R = -C(CH$_3$)$_2$COOC$_2$H$_5$; **13** X = S, R = -CH(CH$_3$)COOC$_2$H$_5$



15 R^1 = 2-Secbutyl , R^2 = H

16 R^1 = Cl R^2 = H

17 R^1 = Cl R^2 = Cl

18 R^1 = 2-Secbutyl, R^2 = H, R^3 = -CH(CH$_3$)COOC$_2$H$_5$; **24** R^1 = Cl R^2 = H, R^3 = -CH(CH$_2$)$_2$COOC$_2$H$_5$

19 R^1 = 2-Secbutyl, R^2 = H, R^3 = -CH(C$_2$H$_5$)COOC$_2$H$_5$; **25** R^1 = Cl R^2 = Cl, R^3 = -CH(CH$_3$)COOC$_2$H$_5$

20 R^1 = 2-Secbutyl, R^2 = H, R^3 = -C(CH$_3$)$_2$COOC$_2$H$_5$; **26** R^1 = Cl R^2 = Cl, R^3 = -C(CH$_3$)$_2$COOC$_2$H$_5$

21 R^1 = 2-Secbutyl, R^2 = H, R^3 = -CH(CH$_2$)$_2$COOC$_2$H$_5$; **27** R^1 = Cl R^2 = Cl, R^3 = -CH(C$_2$H$_5$)COOC$_2$H$_5$

22 R^1 = Cl R^2 = H, R^3 = -CH(CH$_3$)COOC$_2$H$_5$; **28** R^1 = Cl R^2 = Cl, R^3 = -CH(CH$_2$)$_2$COOC$_2$H$_5$

23 R^1 = Cl R^2 = H, R^3 = -CH$_2$COOC$_2$H$_5$

Scheme 1. Synthesis of novel amide based fibrates. Reagents and conditions: (i) K_2CO_3, CH_3CN, 100 °C, 4 h (ii) 20% aq. KOH, MeOH, rt, 30 min. (iii) (a) Benzene, $SOCl_2$, reflux, 2 h, (b) Benzene, 4-Hydroxy aniline, reflux, 2 h (iv) Different bromoesters, K_2CO_3, CH_3CN, 100 °C, 4 h.

were assayed (wing and Robinson, 1968) using spectrophotometer, Beckmann auto-analyzer and standard kits purchased from Beckmann Coulter International, USA.

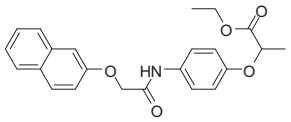
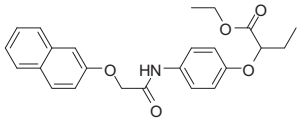
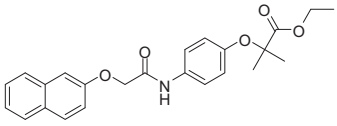
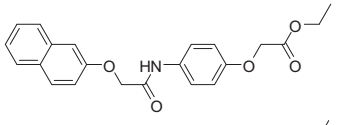
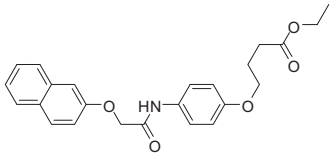
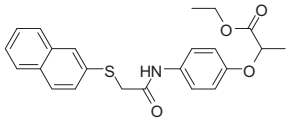
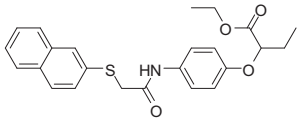
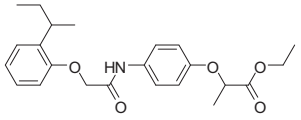
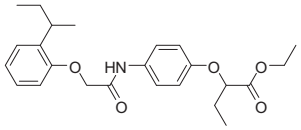
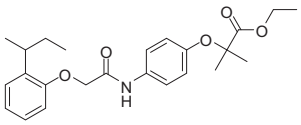
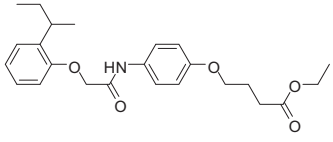
3.3. Lipoprotein lipase activity

The incubation mixture containing 0.2 ml plasma, 0.01 ml intralipid emulsion, 0.1 ml heparin (0.1% w/v, in normal saline), 0.5 ml BSA (2.5% in Tris–HCl buffer), and 0.3 ml Tris–HCl buffer was incubated at 37 °C for 90 min in metabolic shaker (parallel to the reference containing incubation mixture without enzyme source) [27].

3.4. Antioxidant activity (generation of free radicals)

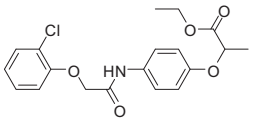
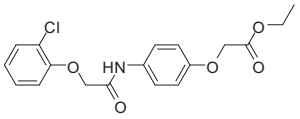
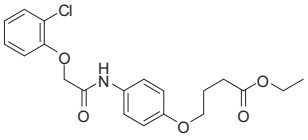
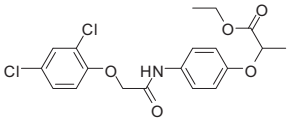
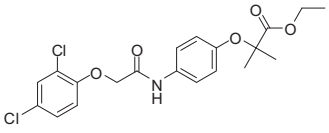
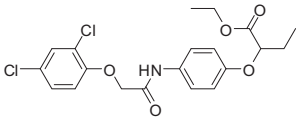
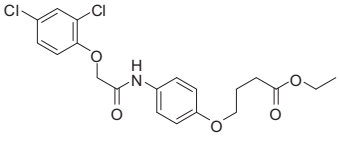
Superoxide anions (O^{-2}) were generated enzymatically [28] by xanthine (160 mM), xanthine oxidase (0.04 U) and nitroblue tetrazolium (320 μM) in absence or presence of compounds (100 μg/ml) in 100 mM phosphate buffer (pH 8.2). Fractions were

Table 1
The lipid lowering activity of amide based fibrates (100 mg/kg) in triton treated hyperlipidemic rats. Triton treated group is compared with control and drug treated group is compared with triton group.

Compound no.	Structure	Total cholesterol (TC)[a]	Phospholipids (PL)[a]	Triglyceride (TG)[a]	PHLA[b]
8		−23***	−25***	−26***	+26***
9		−12*	−9^{NS}	−13*	+12*
10		−25***	−24***	−27***	+23***
11		−14*	−14*	−11*	+15*
12		−21**	−19*	−22**	+17*
13		−26***	−24***	−28***	+24***
14		−6^{NS}	−4^{NS}	−5^{NS}	+7^{NS}
18		−24***	−23***	−24***	+15*
19		−10*	−9^{NS}	−9^{NS}	+5^{NS}
20		−7^{NS}	−10^{NS}	−6^{NS}	+14*
21		−9^{NS}	−10^{NS}	−11*	+13*

(*continued on next page*)

Table 1 (*continued*)

Compound no.	Structure	Total cholesterol (TC)[a]	Phospholipids (PL)[a]	Triglyceride (TG)[a]	PHLA[b]
22		−25***	−26***	−25***	+23***
23		-6^{NS}	-9^{NS}	-6^{NS}	$+9^{NS}$
24		-9^{NS}	-6^{NS}	-8^{NS}	+12*
25		-8^{NS}	-7^{NS}	−10*	+10*
26		-8^{NS}	-4^{NS}	−13*	$+9^{NS}$
27		-2^{NS}	-3^{NS}	-5^{NS}	$+4^{NS}$
28		-9^{NS}	-8^{NS}	-7^{NS}	+12*
	Gemfibrozil	−31***	−33***	−33***	+31***

Values are mean ± SD of six rats, ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; ^{NS} = Non significant.
[a] mg/dl.
[b] *n* mol. of free fatty acids formed/h/ml of plasma.

sonicated well in phosphate buffer before use. The reaction mixtures were incubated at 37 °C and after 30 min the reaction was stopped by adding 0.5 ml glacial acetic acid. The amount of formazone formed was measured at 560 nm on a spectrophotometer. Percentage inhibition was calculated taking absorption coefficient of formazone as $7.2 \times 10^3\ M^{-1}\ cm^{-1}$. In another set of experiment, an effect of compounds on generation of hydroxyl radicals (OH^-) was also studied by non-enzymic reactants [29]. Briefly OH^- were generated in a non-enzymic system comprised of deoxy ribose (2.8 mM), $FeSO_4{\cdot}7H_2O$ (2 mM), sodium ascorbate (2.0 mM) and H_2O_2 (2.8 mM) in 50 mM KH_2PO_4 buffer, pH 7.4 to a final volume of 2.5 ml. The above reaction mixtures in the absence or presence of compounds (100 μg/ml) were incubated at 37 °C for 90 min. Reference samples and reagent blanks were also run simultaneously. Malondialdehyde (MDA) content in both experimental and reference samples were estimated spectrophotometrically by thiobarbituric acid method as mentioned above [30].

3.5. Statistical evaluation

Data were analyzed using Student's *t*-test. The hyperlipidemic groups were compared with control drug treated groups. Similarly the generations of oxygen free radicals with different amide based fibrates were compared with that of their formation without compounds. $P < 0.05$ was considered to be significant.

4. Results and discussion

4.1. The lipid lowering activity of amide based fibrates

The present study has been undertaken to evaluate the antidyslipidemic activity of amide based fibrates (**8**–**14** & **18**–**28**) in an acute triton induced hyperlipidemic model [26,31,32]. Administration of triton WR–1339 in rats induced marked hyperlipidemia as evidenced by increase in the plasma level of total cholesterol TC

(4.05 fold), phospholipids PL (3.31 fold) and triglyceride TG (2.67 fold) as compared to control. Triton treated rats caused inhibition of plasma PHLA (post heparin lipolytic activity) (28%) as compared to control. Treatment of hyperlipidemic rats with amide based fibrates (**8**–**14** & **18**–**28**) at the dose of 100 mg/kg p.o. reversed the plasma levels of lipid with varying extents. The synthesized derivatives inhibited cholesterol biosynthesis and potentiated the activity of lipolytic enzymes to early clearance of lipids from circulation in triton induced hyperlipidemia. Compound **13** was found to be the most potent in the series as it showed 26%, 24% and 28%, lowering in TC, PL and TG respectively, while compounds **8**, **10**, and **22** showed good activity and compounds **12** and **18** showed moderate activity. These data were comparable with standard hypolipidemic drug gemfibrozil which at the dose of 100 mg/kg decreased levels of TC, PL and TG in plasma by 31%, 33% and 33%, respectively. Compounds **8** and **13** showed significant reversal of PHLA in plasma of hyperlipidemic rats by 26% and 24%, respectively, comparable to gemfibrozil, which caused 31% reversal of activity of this enzyme as compared to control group and the results are summarized in Table 1.

4.2. Lipoprotein lipase activity of active compounds

Further these active compounds (**8**, **10**, **13**, **18**, and **22**) were screened for their lipoprotein lipase activity (LPLA). During triton WR-1339 induction in rat lipase activity of LPL were partially deactivated which was responsible for the breakdown of higher lipids into smaller one. As a result lipids level were increased in blood plasma, our active compounds re-activated the LPL activity and improved the lipid profile. Out of the five compounds tested, compounds **8** and **13** showed 24% and 26% increase in compared to standard drug gemfibrozil which showed 30% increase, while remaining compounds exhibited moderate activity. The results are summarized in Table 2.

4.3. Antioxidant activities of amide based fibrates

In another experiment, antioxidant activities of amide based fibrates **8**–**14** & **18**–**28** were evaluated by generating free radicals *in vitro* in the absence and presence of these compounds. The scavenging potential of amide based fibrates **8**–**14** & **18**–**28** at 200 μg/ml against formation of $O_2^{\bullet}$ and $^{\bullet}OH$ in non-enzymic system was studied. Further, their effect on lipid peroxidation in microsomes was also studied and the results are shown in Fig. 2. Among the **18** compounds evaluated, compounds **8**, **10**, **12**, **13**, **18**, and **22** showed significant decrease in superoxide anions inhibition by 25%, 30%, 27%, 31%, 25%, and 33%, hydroxyl radicals inhibition by 25%, 22%, 25%, 28%, 25%, and 26%, and microsomal lipid peroxidation inhibition by 22%, 22%, 29%, 35%, 25%, and 26%, respectively. The standard drug alloperinol at 200 μg/ml showed 41% inhibition in superoxide anions. Manitol and α-tocopherol at the dose of 200 μg/ml showed 41% inhibition of hydroxyl ions and 49% inhibition of microsomal lipid peroxidation respectively. The scavenging potential of other derivatives was modest. The wide variation in the free radical scavenging potential may be due to the variation in the proton-electron transfer by the derivatives due to difference in their structures and stability.

5. Conclusion

In conclusion, inspired by the molecular hybridization approach, a series of novel amide based fibrates were synthesized and evaluated for their anti-hyperlipidemic and *in vitro* anti-oxidant activities. Among the synthesized compounds, the compound **13** was found to be the most promising, owing to the ability as hypolipidemic, together with the reduction of intracellular reactive oxygen species content and improved lipoprotein lipase activity. This finding encourages us to continue the efforts towards the optimization of this structural moiety as an important scaffold for the potential treatment of dyslipidemia.

6. Experimental

All reagents were commercial and were used without further purification. Chromatography was carried on silica gel (100–120 mesh). All reactions were monitored by TLC (silica gel plates with fluorescence F_{254} were used). Melting points were recorded on an electrically heated melting point apparatus and are uncorrected. The ^1H NMR and ^{13}C NMR spectra were determined on Bruker Advance DRX-300 MHz spectrometer using TMS as an internal reference. All shifts are given in ppm and multiplicity (s = singlet, d = doublet, m = multiplet). The electrospray mass spectra were recorded on a Thermo Finnigan LCQ Advantage max ion trap mass spectrometer. IR spectra were recorded on Perkin Elmer AC-1 spectrophotometer in the range of 400–4000 cm^{-1}.

6.1. General procedure for synthesis of compounds *6a–7a & 15a–17a*

A round-bottomed flask was charged with phenol or thiophenol compound (1.0 eq.), ethyl bromoacetate (1.2 eq.) and K_2CO_3 (3.0 eq.) followed by acetone (15 ml). The resulting mixture was refluxed in a pre-heated oil bath for 4 h under magnetic stirring. After cooling to room temperature, acetone was filtered over a pad of celite and rinsed with acetone (50 ml). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with ethyl acetate/hexane (1:9) as eluent to afford corresponding esters (**6a**–**7a** & **15a**–**17a**) in high purity with good yields.

6.1.1. Ethyl 2-(naphthalen-2-yloxy) acetate (*6a*)

From 2-naphthalol and ethyl bromoacetate; white crystal solid, yield: 95%; mp 165–167 °C; IR(KBr, cm^{-1}): 3020, 2925, 1718, 1645, 1566, 1504, 1217, 1073; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.81–7.73 (m, 3H)7.49–7.45 (m, 1H) 7.41–7.38 (m, 1H) 7.28–7.25 (m, 1H) 7.10 (d, J = 1.9 Hz, 1H) 4.76 (s, 2H) 4.32 (q, J = 7.1 Hz, 2H)1.33 (t, J = 7.1 Hz, 3H); ESI–MS: (m/z): 231 $(M + H)^+$.

6.1.2. Ethyl 2-(2, 4-dichlorophenoxy) acetate (*17a*)

From 2,4 dichlorophenol and ethyl bromoacetate; white crystal solid, yield: 92%; mp 175–177 °C; IR(KBr, cm^{-1}): 3010, 2915, 1715,

Table 2
Lipoprotein lipase activity of active compounds (**8**, **10**, **13**, **18**, and **22**).

	Control	Triton	Triton + comp. **8**	Triton + comp.**10**	Triton + comp.**13**	Triton + comp.**18**	Triton + comp.**22**	Triton + gemfibrozil
LPL activity[a]	125.77 ± 10.18	70.33 ± 5.16*** (−44) Over control	92.80 ± 8.16*** (+24) Over triton	90.23 ± 7.92** (+22) Over triton	95.62 ± 8.93*** (+26) Over triton	84.16 ± 6.00** (+16) Over triton	88.63 ± 5.17** (+21) Over triton	100.18 ± 9.10*** (+30) Over triton

Values are mean ± SD of six rats ***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.
[a] n mole fatty acid formed/h/mg protein.

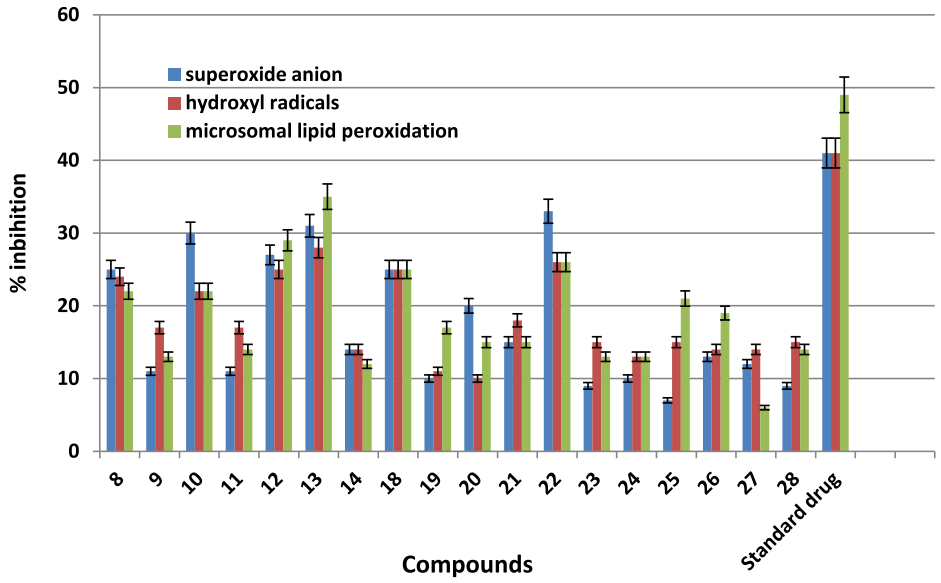


Fig. 2. The effect of amide based fibrate derivatives (200 μg/ml) on superoxide ion (*n* mol. formazone formed/min), hydroxyl ion (*n* mol. MDA formed/h) and lipid peroxidation in microsomes (*n* mol. MDA formed/mg protein) was shown (standard drugs for superoxide anions-alloperinol (200 μg/ml), hydroxyl ions-manitol and for microsomal lipid peroxidation-a-tocopherol (200 μg/ml) were used). Values are mean ± SD of six animals.

1635, 1560, 1514, 1210, 1073; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.40 (d, J = 2.4 Hz, 1H) 7.40 (dd, J = 2.4 Hz, 1H) 6.79 (d, J = 8.7 Hz, 1H) 4.69 (s, 2H) 4.28 (q, J = 7.1 Hz, 2H)1.30 (t, J = 7.1 Hz, 3H); ESI–MS: (m/z): 249 $(M + H)^+$.

6.2. General procedure for synthesis of compounds **6b**–**7b** & **15b**–**17b**

The ester compound (**6a**–**7a** & **15a**–**17a**) was dissolved in methanol (30 ml) then subjected to basic hydrolysis with 30% aq. KOH (15 ml) in a round-bottomed flask, the resulting mixture was stirred at room temperature for 1 h. After completion of reaction, methanol was removed under reduced pressure subsequently neutralized with dil.HCl. The resulted white solid was filtered and dried in vacuum produced the respective acid (**6b**–**7b** & **15b**–**17b**) in good yields.

6.2.1. 2-(Naphthalen-2-yloxy) acetic acid (**6b**)

From **6a**; white solid, yield: 90%; mp 265–267 °C; IR(KBr, cm^{-1}): 3452, 3020, 2925, 1718, 1645, 1566, 1504, 1217, 1073; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.84–7.76 (m, 3H)7.46–7.41 (m, 1H) 7.36–7.31 (m, 1H) 7.24–7.17 (m, 2H) 4.75 (s, 2H); ESI–MS: (m/z): 203 $(M + H)^+$.

6.2.2. 2-(2, 4-Dichlorophenoxy) acetic acid (**17b**)

From **17a**; white crystal solid, yield: 87%; mp 205–207 °C; IR(KBr, cm^{-1}): 3412, 3010, 2915, 1715, 1635, 1560, 1514, 1210, 1073; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.56 (d, J = 2.4 Hz, 1H) 7.33 (dd, J = 2.4 Hz, 1H) 7.05 (d, J = 8.9 Hz, 1H) 4.81 (s, 2H); ESI–MS: (m/z): 222 $(M + H)^+$.

6.3. General procedure for synthesis of compounds **6c**–**7c** & **15c**–**17c**

A 50 ml round-bottomed flask was charged with a magnetic stirrer, dry benzene (10 ml), acid compound (**6b**–**7b** & **15b**–**17b**) and thionyl chloride (1.0 ml). The reaction mixture was refluxed for 2 h, after completion of required time remove the solvent and excess $SOCl_2$ under reduced pressure. This acid chloride was again dissolved in dry benzene (10 ml) followed by addition of 4-hydroxy aniline in excess, the resulted mixture was refluxed until the acid chloride had been completely consumed as judged by TLC. After completion of reaction the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with MeOH/CH_3Cl (0.5:9.5) to afford 4-hydroxy amides (**6c**–**7c** & **15c**–**17c**) in good yields.

6.3.1. N-(4-hydroxyphenyl)-2-(naphthalen-2-yloxy) acetamide (**6c**)

From **6b** and 4-hydroxy aniline; brown colour solid, yield: 85%; mp 265–267 °C; IR(KBr, cm^{-1}): 3452, 3010, 2915, 1728, 1645, 1556, 1514, 1217, 1073; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.89 (s, NH) 9.26 (s, OH) 7.88–7.78 (m, 3H)7.46–7.29 (m, 6H) 6.72 (d, J = 8.79 Hz, 2H) 4.76 (s, 2H); ESI–MS: (m/z): 294 $(M + H)^+$.

6.3.2. 2-(2, 4-Dichlorophenoxy)-N-(4-hydroxyphenyl) acetamide (**17c**)

From **17b** and 4-hydroxy aniline; brown color solid, yield: 85%; mp 215–217 °C; IR(KBr, cm^{-1}): 3450, 3010, 2915, 1735, 1635, 1550, 1514, 1210, 1173; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.88 (s, NH) 9.25 (s, OH) 7.59 (d, J = 2.4 Hz, 1H) 7.38–7.35 (m, 3H) 7.09 (d, J = 8.9 Hz, 1H) 6.70 (d, J = 8.7 Hz, 2H) 4.79 (s, 2H); ESI–MS: (m/z): 313 $(M + H)^+$.

6.4. General procedure for synthesis of novel amide based fibrates (**8**–**14** & **18**–**28**)

A round-bottomed flask was charged with 4-hydroxy amide compounds (**6c**–**7c** & **15c**–**17c**) (1.0 eq.), different substituted bromoesters (1.2 eq.) and K_2CO_3 (3.0 eq.) followed by acetone (15 ml). The resulting mixture was refluxed under magnetic stirring in a pre-heated oil bath until the 4-hydroxy amide had been completely consumed as judged by TLC. After cooling to room temperature, acetone was filtered over a pad of celite and rinsed with acetone (50 ml). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with ethyl acetate/hexane (4:6) as eluent to afford target amide based fibrates (**8**–**14** & **18**–**28**) in good yields.

6.4.1. Ethyl2-(4-(2-(naphthalen-2-yloxy)acetamido)phenoxy) propanoate (**8**)

From **6c** and ethyl 2-bromopropionate; white solid, yield: 80%; mp: 265–267 °C; IR(KBr, cm^{-1}): 3401, 2940, 2285, 1718, 1645, 1566, 1504, 1217, 1059; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, NH) 7.83–7.74 (m, 3H) 7.50–7.37 (m, 4H) 7.26–7.21 (m, 2H) 6.87 (d,

J = 9.0 Hz, 2H) 4.75–4.68 (m, 3H) 4.21 (q, J = 7.1 Hz, 2H) 1.61 (d, J = 6.7 Hz, 3H) 1.25 (t, J = 7.1 Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.2, 166.0, 154.9, 154.8, 134.3, 130.8, 129.6, 127.8, 127.1, 126.9, 124.6, 121.9, 118.1, 115.7, 107.9, 73.0, 67.6, 61.4, 18.6, 14.2; ESI–MS: (m/z): 394 $(M + H)^+$.

*6.4.2. Ethyl 2-(4-(2-(naphthalen-2-yloxy)acetamido)phenoxy) butanoate (**9**)*

From **6c** and ethyl 2-bromobutyrate; white solid, yield: 75%; mp: 285–287 °C; IR(KBr, cm^{-1}): 3502, 2940, 2282, 1727, 1680, 1528, 1417, 1219, 1059, 762; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, NH) 7.83–7.74 (m, 3H) 7.50–7.39 (m, 4H) 7.37–7.21 (m, 2H) 6.88 (d, J = 8.9 Hz, 2H) 4.72 (s, 2H) 4.52 (t, J = 6.2 Hz, 1H) 4.21 (q, J = 7.1 Hz, 2H) 2.03–1.93 (m, 2H) 1.24 (t, J = 7.1 Hz, 3H) 1.07 (t, J = 7.3 Hz, 3H); ESI–MS: (m/z): 408 $(M + H)^+$.

*6.4.3. Ethyl2-methyl-2-(4-(2-(naphthalen-2-yloxy)acetamido) phenoxy)propanoate (**10**)*

From **6c** and ethyl 2-bromo -2-methylpropionate; white solid, yield: 80%; mp: 275–277 °C; IR(KBr, cm^{-1}): 3401, 2940, 2285, 1718, 1645, 1566, 1504, 1217, 1059; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, NH) 7.83–7.74 (m, 3H) 7.50–7.37 (m, 4H) 7.26–7.21 (m, 2H) 6.86 (d, J = 8.8 Hz, 2H) 4.72 (s, 2H) 4.23 (q, J = 7.1 Hz, 2H) 1.57 (s, 6H) 1.26 (t, J = 7.0 Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.1, 165.9, 154.8, 152.4, 134.2, 131.4, 130.0, 129.6, 127.7, 127.0, 126.8, 124.5, 121.3, 120.1, 118.0, 107.9, 79.5, 67.6, 61.4, 25.3, 14.1; ESI–MS: (m/z): 408 $(M + H)^+$.

*6.4.4. Ethyl 2-(4-(2-(naphthalen-2-yloxy)acetamido)phenoxy) acetate (**11**)*

From **6c** and ethyl bromoacetate; white solid, yield: 82%; mp: 255–257 °C; IR(KBr, cm^{-1}): 3501, 2930, 2285, 1718, 1645, 1556, 1504, 1227, 1019; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.23 (s, NH) 7.83–7.74 (m, 3H) 7.53–7.37 (m, 3H) 7.26–7.21 (m, 3H) 6.90 (d, J = 8.9 Hz, 2H) 4.72 (s, 2H) 4.60 (s, 2H) 4.26 (q, J = 7.0 Hz, 2H) 1.29 (t, J = 7.1 Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.9, 166.0, 155.0, 154.9, 134.3, 130.9, 130.1, 129.6, 127.7, 127.1, 126.9, 124.6, 122.0, 118.1, 115.2, 107.9, 67.6, 65.8, 61.5, 14.2; ESI–MS: (m/z): 380 $(M + H)^+$.

*6.4.5. Ethyl 4-(4-(2-(naphthalen-2-yloxy)acetamido)phenoxy) butanoate(**12**)*

From **6c** and ethyl 4-bromobutyrate; white solid, yield: 78%; mp: 272–274 °C; IR(KBr, cm^{-1}): 3502, 2940, 2272, 1727, 1680, 1518, 1417, 1219, 1059, 762; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, NH) 7.83–7.74 (m, 3H) 7.50–7.37 (m, 4H) 7.27–7.21 (m, 2H) 6.87 (d, J = 8.9 Hz, 2H) 4.72 (s, 2H) 4.14 (q, J = 7.0 Hz, 2H) 3.99 (t, J = 6.0 Hz, 2H) 2.50 (t, J = 7.2 Hz, 2H) 2.14–2.05 (m, 2H) 1.26 (t, J = 7.1 Hz, 3H); ESI–MS: (m/z): 408 $(M + H)^+$.

*6.4.6. Ethyl 2-(4-(2-(naphthalen-2-ylthio)acetamido)phenoxy) propanoate (**13**)*

From **7c** and ethyl 2-bromopropionate; white solid, yield: 80%; mp: 292–294 °C; IR(KBr, cm^{-1}): 3511, 2910, 2285, 1718, 1556, 1504, 1227, 1019; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.52 (s, NH) 7.79–7.72 (m, 4H) 7.48–7.39 (m, 3H) 7.34 (d, J = 9.0 Hz, 2H) 6.80 (d, J = 8.9 Hz, 2H) 4.67 (q, J = 6.8 Hz, 1H) 4.18 (q, J = 8.9 Hz, 2H) 3.84 (s, 2H) 1.58 (d, J = 6.7 Hz, 3H) 1.22 (t, J = 7.1 Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.1, 165.9, 154.8, 133.8, 132.1, 131.7, 131.3, 129.2, 127.8, 127.3, 127.0, 126.6, 126.3, 126.2, 121.8, 115.7, 73.1, 61.4, 38.2, 18.6, 14.2; ESI–MS: (m/z): 410 $(M + H)^+$.

*6.4.7. Ethyl 2-(4-(2-(naphthalen-2-ylthio)acetamido)phenoxy) butanoate (**14**)*

From **7c** and ethyl 2-bromo -2-methylpropionate; white solid, yield: 82%; mp: 295–297 °C; IR(KBr, cm^{-1}): 3305, 3013, 2275, 1718, 1556, 1504, 1327, 1019; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.52 (s, NH) 7.79–7.72 (m, 4H) 7.48–7.39 (m, 3H) 7.33 (d, J = 8.9 Hz, 2H) 6.81 (d, J = 9.0 Hz, 2H) 4.47 (t, J = 6.2 Hz, 1H) 4.18 (q, J = 7.1 Hz, 2H) 3.84 (s, 2H) 1.99–1.90 (m, 2H) 1.22 (t, J = 7.1 Hz, 3H) 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.7, 165.9, 155.1, 133.8, 132.1, 131.7, 131.2, 129.2, 127.8, 127.3, 127.0, 126.6, 126.3, 126.1, 121.8, 115.7, 78.2, 61.2, 38.2, 26.2, 14.2, 9.7; ESI–MS: (m/z): 423 $(M + H)^+$.

*6.4.8. Ethyl 2-(4-(2-(2-sec-butylphenoxy)acetamido)phenoxy) propanoate (**18**)*

From **15c** and ethyl 2-bromopropionate; yellow liquid, yield: 82%; IR(KBr, cm^{-1}): 3405, 2275, 1678, 1556, 1217, 1049; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.21 (s, NH) 7.47 (d, J = 8.9 Hz, 2H) 7.26–7.16 (m, 2H) 7.06–7.01 (m, 1H) 6.89–6.84 (m, 3H) 4.72 (q, J = 6.6 Hz, 1H) 4.59 (s, 1H) 4.25–4.18 (m, 2H) 3.19–3.08 (m, 1H) 1.61 (d, J = 6.7 Hz, 3H) 1.30–1.23 (m, 6H) 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ:172.0, 166.2, 154.7, 154.5, 135.7, 130.9, 127.3, 127.0, 122.5, 121.4, 115.7, 112.3, 73.0, 68.0, 61.2, 34.2, 30.0, 20.5, 18.5, 14.1, 12.4; ESI–MS: (m/z): 400 $(M + H)^+$.

*6.4.9. Ethyl 2-(4-(2-(2-sec-butylphenoxy)acetamido)phenoxy) butanoate (**19**)*

From **15c** and ethyl 2-bromobutyrate; yellow liquid, yield: 80%; IR(KBr, cm^{-1}): 3415, 2275, 1688, 1556, 1217, 1039; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.21 (s, NH) 7.46 (d, J = 8.9 Hz, 2H) 7.26–7.16 (m, 2H) 7.06–7.01 (m, 1H) 6.90–6.84 (m, 3H) 4.60 (s, 2H) 4.52 (t, J = 6.2 Hz, 1H) 4.21 (q, J = 7.1 Hz, 2H) 3.17–3.10 (m, 1H) 2.03–1.93 (m, 2H) 1.71–1.63 (m, 2H) 1.30–1.23 (m, 6H) 1.08 (t, J = 7.3 Hz, 3H) 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.6, 166.3, 155.2, 154.6, 135.9, 130.9, 127.4, 127.1, 122.6, 121.6, 115.9, 112.4, 78.3, 68.1, 61.2, 34.3, 30.1, 26.2, 20.6, 14.3, 12.5, 9.7; ESI–MS: (m/z): 414 $(M + H)^+$.

*6.4.10. Ethyl2-(4-(2-(2-sec-butylphenoxy)acetamido)phenoxy)-2-methylpropanoate (**20**)*

From **15c** and ethyl 2-bromo -2-methylpropionate; yellow liquid, yield: 86%; IR(KBr, cm^{-1}): 3405, 2272, 1678, 1556, 1217, 1039; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, NH) 7.44 (d, J = 8.9 Hz, 2H) 7.26–7.16 (m, 2H) 7.06–7.01 (m, 1H) 6.88–6.84 (m, 3H) 4.59 (s, 2H) 4.23 (q, J = 7.1 Hz, 2H) 3.19–3.07 (m, 1H) 1.71–1.64 (m, 2H) 1.57 (s, 6H) 1.30–1.24 (m, 6H) 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.2, 166.3, 154.6, 152.4, 135.8, 131.6, 127.4, 127.1, 122.6, 121.0, 120.3, 112.4, 79.6, 68.1, 61.5, 34.3, 30.1, 25.4, 20.6, 14.2, 12.5; ESI–MS: (m/z): 414 $(M + H)^+$.

*6.4.11. Ethyl 4-(4-(2-(2-sec-butylphenoxy)acetamido)phenoxy) butanoate (**21**)*

From **15c** and ethyl 4-bromobutyrate; yellow liquid, yield: 86%; mp: 215–217 °C; IR(KBr, cm^{-1}): 3409, 2283, 1689, 1524, 1219, 1049, 726; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, NH) 7.49–7.46 (m, 2H) 7.28–7.18 (m, 2H) 7.08–7.03 (m, 1H) 6.91–6.87 (m, 3H) 4.62 (s, 2H) 4.17 (q, J = 7.1 Hz, 2H) 4.02 (t, J = 6.1 Hz, 2H) 3.20–3.10 (m, 1H) 2.53 (t, J = 6.3 Hz, 2H) 2.17–2.08 (m, 2H) 1.74–1.66 (m, 2H) 1.33–1.25 (m, 6H) 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.2, 166.3, 156.1, 154.7, 135.9, 130.2, 127.4, 127.1, 122.6, 121.7, 115.0, 112.4, 68.1, 67.1, 60.5, 34.3, 30.9, 30.1, 24.7, 20.6, 14.3, 12.5; ESI–MS: (m/z): 414 $(M + H)^+$.

*6.4.12. Ethyl 2-(4-(2-(2-chlorophenoxy)acetamido)phenoxy) propanoate (**22**)*

From **16c** and ethyl 2-bromopropionate; white solid, yield: 85%; mp: 215–217 °C; IR(KBr, cm^{-1}): 3315, 3013, 2275, 1678, 1556, 1504, 1327, 1019; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.58 (s, NH) 7.55–7.52 (m, 2H) 7.46–7.43 (m, 1H) 7.32–7.26 (m, 1H) 7.06–6.96 (m, 2H) 6.90 (d, J = 9.0 Hz, 2H) 4.74 (q, J = 6.8 Hz, 1H) 4.66 (s, 2H) 4.23 (q, J = 7.1 Hz, 2H) 1.62 (d, J = 6.7 Hz, 2H) 1.27 (t, J = 7.3 Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.2, 165.5, 154.8, 152.7, 130.9, 130.5, 128.3, 123.2, 123.0, 121.6, 115.8, 114.3, 73.1, 68.3, 61.4, 18.6, 14.2; ESI–MS: (m/z): 378 $(M + H)^+$.

*6.4.13. Ethyl 2-(4-(2-(2-chlorophenoxy)acetamido)phenoxy) acetate (**23**)*

From **16c** and ethyl bromoacetate; white solid, yield: 84%; mp: 205–207 °C; IR(KBr, cm^{-1}): 3325, 3023, 2265, 1678, 1556, 1514, 1327, 1020; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.59 (s, NH) 7.55 (d, $J = 8.9$ Hz, 2H) 7.46–7.44 (m, 1H) 7.32–7.27 (m, 1H) 7.06–6.92 (m, 4H) 4.66 (s, 2H) 4.63 (s, 2H) 4.29 (q, $J = 7.1$ Hz, 2H) 1.32 (t, $J = 7.1$ Hz, 3H); ESI–MS: (m/z): 364 $(M + H)^+$.

*6.4.14. Ethyl 4-(4-(2-(2-chlorophenoxy)acetamido)phenoxy) butanoate (**24**)*

From **16c** and ethyl 2-bromo -2-methylpropionate; white solid, yield: 80%; mp: 235–237 °C; IR(KBr, cm^{-1}): 3466, 3020, 2374, 1690, 1598, 1527, 1377, 1222, 1051, 765; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.56 (s, NH) 7.52 (d, $J = 8.9$ Hz, 2H) 7.46–7.44 (m, 1H) 7.32–7.27 (m, 1H) 7.06–6.97 (m, 2H) 6.90 (d, $J = 8.9$ Hz, 2H) 4.67 (s, 2H) 4.16 (q, $J = 7.1$ Hz, 2H) 4.02 (t, $J = 8.0$ Hz, 2H) 2.53 (t, $J = 7.1$ Hz, 2H) 2.17–2.10 (m, 2H) 1.28 (t, $J = 7.1$ Hz, 3H); ESI–MS: (m/z): 392 $(M + H)^+$.

*6.4.15. Ethyl 2-(4-(2-(2, 4-dichlorophenoxy)acetamido)phenoxy) propanoate (**25**)*

From **17c** and ethyl 2-bromopropionate; white solid, yield: 85%; mp: 265–267 °C; IR(KBr, cm^{-1}): 3415, 3013, 2275, 1678, 1556, 1327, 1019; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.46 (s, NH) 7.53–7.50 (m, 2H) 7.46 (d, $J = 2.4$ Hz, 1H) 7.28–7.24 (m, 1H) 6.92–6.88 (m, 3H) 4.74 (q, $J = 6.7$ Hz, 1H) 4.63 (s, 2H) 4.23 (q, $J = 7.1$ Hz, 2H) 1.63 (d, $J = 6.7$ Hz, 3H) 1.27 (t, $J = 7.1$ Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.1, 164.9, 154.9, 151.5, 130.8, 130.3, 128.3, 127.8, 123.9, 121.7, 115.8, 115.0 73.1, 68.5, 61.4, 18.6, 14.2; ESI–MS: (m/z): 412 $(M + H)^+$.

*6.4.16. Ethyl2-(4-(2-(2, 4-dichlorophenoxy) acetamido) phenoxy)-2-methylpropanoate (**26**)*

From **17c** and ethyl 2-bromo -2-methylpropionate; white solid, yield: 82%; mp: 275–277 °C; IR(KBr, cm^{-1}): 3435, 3023, 2275, 1678, 1556, 1327, 1019; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.45 (s, NH) 7.48–7.44 (m, 3H) 7.26–7.23 (m, 1H) 6.90–6.85 (m, 3H) 4.61 (s, 2H) 4.23 (q, $J = 7.1$ Hz, 2H) 1.56 (s, 6H) 1.26 (t, $J = 7.1$ Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.2, 164.9, 152.5, 151.5, 131.5, 130.3, 128.2, 127.8, 123.8, 121.1, 120.2, 115.0, 79.6, 68.5, 61.5, 25.4, 14.2; ESI–MS: (m/z): 426 $(M + H)^+$.

*6.4.17. Ethyl 2-(4-(2-(2, 4-dichlorophenoxy)acetamido)phenoxy) butanoate (**27**)*

From **17c** and ethyl 2-bromobutyrate white solid, yield: 85%; mp: 270–272 °C; IR(KBr, cm^{-1}): 3425, 3013, 2275, 1678, 1556, 1327, 1029; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.44 (s, NH) 7.50–7.43 (m, 3H) 7.26–7.23 (m, 1H) 6.90–6.87 (m, 3H) 4.61 (s, 2H) 4.52 (t, $J = 6.2$ Hz, 1H) 4.21 (q, $J = 7.1$ Hz, 2H) 2.03–1.93(m, 2H) 1.25 (t, $J = 7.1$ Hz, 3H) 1.08 (t, $J = 7.1$ Hz, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.6, 164.9, 155.2, 151.5, 130.7, 130.3, 128.2, 127.8, 123.8, 121.6, 115.8, 115.0, 78.2, 68.5, 61.2, 26.2, 14.2, 9.7; ESI–MS: (m/z): 426 $(M + H)^+$.

*6.4.18. Ethyl 4-(4-(2-(2, 4-dichlorophenoxy)acetamido)phenoxy) butanoate (**28**)*

From **17c** and ethyl 4-bromobutyrate; white solid, yield: 78%; mp: 278–280 °C; IR(KBr, cm^{-1}): 3541, 3013, 2289, 1686, 1533, 1218, 1102, 769; ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.43 (s, NH) 7.50–7.43 (m, 3H) 7.26–7.23 (m, 1H) 6.90–6.86 (m, 3H) 4.61 (s, 2H) 4.14 (q, $J = 7.1$ Hz, 2H) 3.99 (t, $J = 6.1$ Hz, 2H) 2.51 (t, $J = 7.2$ Hz, 2H) 2.14–2.05(m, 2H) 1.25 (t, $J = 7.1$ Hz, 3H); ESI–MS: (m/z): 426 $(M + H)^+$.

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Appendix A. Supporting information

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.09.040.

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