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Synthesis, hypolipidemic and hypoglycemic activity of some novel 2-(4-(2-substituted aminothiazole-4-yl) phenoxy)-2-methyl propanoic acid derivatives

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ABSTRACT

An improved synthetic protocol for a novel series of 2-(4-(2-substituted aminothiazole-4-yl) phenoxy)-2-methyl propanoic acid derivatives has been developed using different methods of synthesis. The synthesized compounds are evaluated for their hypolipidemic and hypoglycemic activity by high fat diet induced hyperlipidemia and hyperglycemia in Sprague–Dawley rats.

Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions such as coronary heart disease, ischemic cerebrovascular disease, and peripheral vascular disease. Atherosclerosis is degenerative disorder in intima of medium and large arteries. The degeneration includes accumulation of lipids, complex carbohydrates, blood and blood products, cellular waste products. Fibrates (Fig. 1) affect lipid metabolism by lowering TG and to lesser extent LDL cholesterol levels and by increasing HDL cholesterol level.[1]

It was observed that phenoxy isobutyric acid pharmacophore has been frequently used in the synthesis of hypolipidemic agent.[2–7] Phenoxy isobutyric acid moiety was frequently coupled with heterocyclic nucleus such as benzoxazole,[2] pyrimidine,[8] thiazole,[9] trifluoromethane sulfonamide,[10] thiadiazole,[11] morpholine,[12] to have more potent antihyperlipidemic agent.

Initially, we have reported phenoxy acetic acid containing aminothiazole derivatives (Fig. 2) as antihyperlipidemic agent,[13] but it is observed that these compounds show moderate antihyperlipidemic activity. In view of this, we have attempted the synthesis of phenoxy isobutyric acid pharmacophore containing aminothiazole derivatives (Fig. 3) with improved antihyperlipidemic activity.

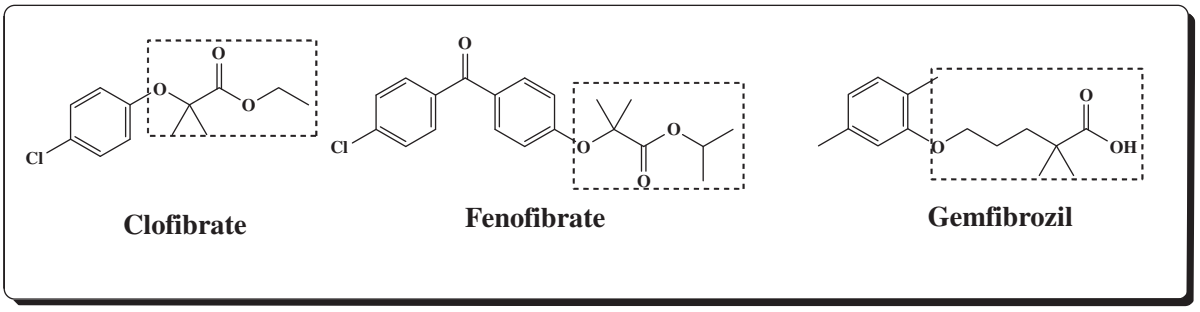

Figure 1.

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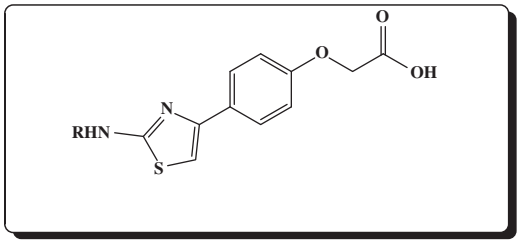


Figure 2.

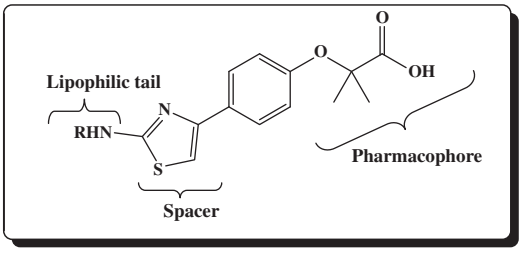
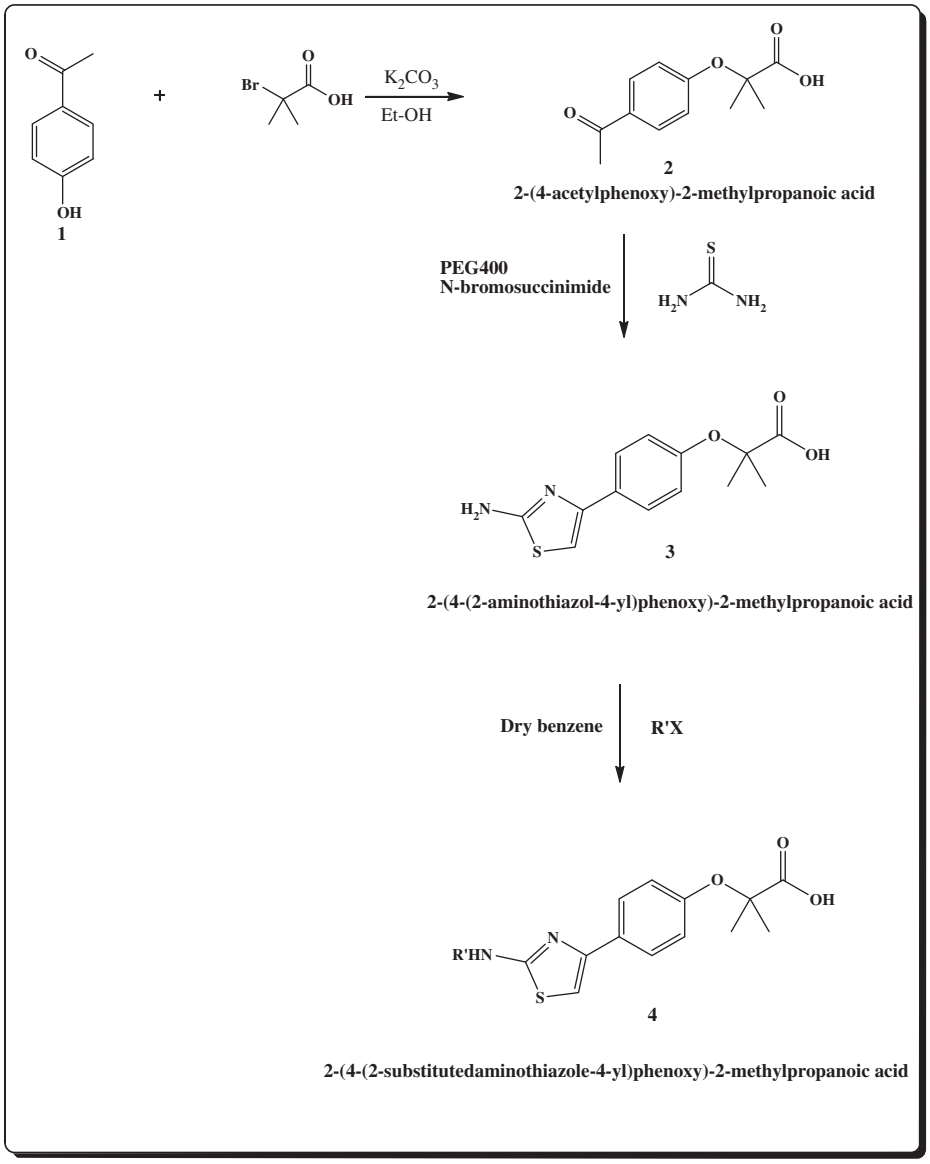


Figure 3.

In this work, we present the synthesis of phenoxy isobutyric acid pharmacophore containing aminothiazole derivatives. The 1-(4-hydroxyphenyl) ethanone (**1**) is used as starting material for the synthesis of final derivatives as outlined in Scheme 1. The 2-(4-acetyl phenoxy)-2-methyl propanoic acid (**2**) was synthesized by using 2-bromo-2-methyl propanoic acid condensed with 1-(4-hydroxyphenyl) ethanone (**1**). The 2-(4-acetyl phenoxy)-2-methyl propanoic acid (**2**) underwent cyclization with thiourea using iodine in DMF resulting in the formation of 2-(4-(2-aminothiazol-4-yl) phenoxy)-2-methylpropanoic acid (**3**). But this method were time consuming as 18 h are required to complete the reaction and only 45% yield was obtains.

So, in search of new method for synthesis of 2-aminothiazoles, we have been use reactions of 2-(4-acetyl phenoxy)-2-methyl propanoic acid, *N*-bromosuccinimide, and thiourea in PEG-400 at room temperature. The corresponding 2-aminothiazole derivatives obtained in 90% yield which was excellent and reaction required only 7 h.[14]



Scheme 1.

Table 1
Characterization data for 2-(4-(2-substituted amino thiazol-4-yl) phenoxy)-2-methyl propanoic acid

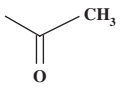
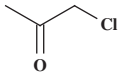
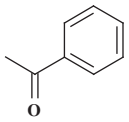
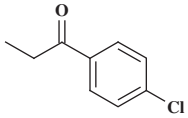
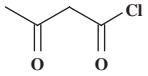
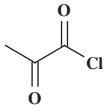
Compd	R	Molecular formula	Molecular weight	% Yield	Melting point (°C)
4a		$C_{15}H_{16}N_2O_4S$	320.34	77	140
4b		$C_{15}H_{15}ClN_2O_4S$	354.31	67	142
4c		$C_{20}H_{18}N_2O_4S$	382.38	71	130
4d		$C_{21}H_{19}ClN_2O_4S$	430.76	75	170
4e		$C_{16}H_{15}ClN_2O_5S$	382.81	66	120
4f		$C_{15}H_{13}ClN_2O_5S$	368.85	73	125

Table 2
Data of total lipid profile (CH, TG, LDL, VLDL and HDL)

Compound	Parameter in mg/dl				
	CH	TG	VLDL	LDL	HDL
Normal control	72.17 ± 0.601	75.17 ± 0.601	15.03 ± 0.120	23.13 ± 1.179	34.5 ± 0.7638
Positive control	121.5 ± 1.335[a]	135 ± 1.592[a]	27 ± 0.3183[a]	75.5 ± 1.24[a]	19 ± 0.5774[a]
Fenofibrate	105.2 ± 1.939[a]	73.17 ± 0.945[a]	14.67 ± 0.261[a]	55.33 ± 2.90[a]	33.5 ± 0.7638[a]
4a	108.3 ± 1.054[a]	80.5 ± 2.825[a]	16.1 ± 0.565[a]	60.63 ± 1.47[a]	32.67 ± 0.6667[a]
4b	111.5 ± 1.727[a]	85.5 ± 2.825[a]	17.1 ± 0.152[a]	59.53 ± 2.59[a]	34.33 ± 0.8819[a]
4c	96.5 ± 0.7638[a]	85.5 ± 0.7638[a]	15.47 ± 0.29[a]	43.67 ± 0.91[a]	37 ± 0.5774[a]
4d	108.3 ± 0.881[a]	77.33 ± 1.476[a]	16.23 ± 0.45[a]	61.18 ± 1.89[a]	32.5 ± 0.7638[a]
4e	116.5 ± 0.763[b]	81.17 ± 2.272[a]	16.53 ± 0.21[a]	67.75 ± 1.11[d]	35.83 ± 0.9458[a]
4f	96.5 ± 0.7638[a]	82.67 ± 1.085[a]	15.47 ± 0.16[a]	49.35 ± 1.00[a]	32.5 ± 0.7638[a]

Test compound = 250 mg/kg.
Reference standard, Fenofibrate = 250 mg/kg.
The results are expressed as mean ± SEM. The data is analyzed using One-way Analysis of Variance (ANOVA) followed by Tukey's test.
(n = 6).
[a] P <0.001.
[b] P <0.01.
[c] P < 0.05.
[d] Non significant.

The final compounds 2-(4-(2-substituted aminothiazole-4-yl) phenoxy)-2-methyl propanoic acid derivatives **4a–4f** was prepared by treating compound **3** with different substituted halide (Table 1).

The hypolipidemic and hypoglycemic activity of the synthesized compounds was studied in the high fat diet induced hyperlipidemic Sprague–Dawley rats for 30 days by oral administration of the drug and compounds.[15]

The results of hypolipidemic activity indicate that test compounds exhibited antihyperlipidemic and antihyperglycemic activity at a dose of 250 mg/kg. As all fibrates are analogs of phenoxy isobutyric acid which is very important for antihyperlipidemic activity. We have used phenoxy isobutyric acid pharmacophore and aminothiazole heterocycle as spacer which shows promising activity. Substitution on aminothiazole with aromatic and aliphatic groups (lipophilic tail) influences on hypolipidemic activity. Substitution on aminothiazole with aromatic and aliphatic groups using C═O spacer (**4c**) has shown increase in activity as compared to $-CH_2$ spacer (**4d**). Aromatic substitution with C═O spacer increases hypolipidemic activity as compared to aliphatic substitution. Aliphatic substitution with C═O spacer and terminal chloro group has shown highest hypolipidemic activity (**4b**, **4e**, and **4f**).

In conclusion, an improved synthetic protocol for the synthesis of a novel series of 2-(4-(2-substituted aminothiazole-4-yl) phenoxy)-2-methyl propanoic acid derivatives containing phenoxy isobutyric acid moiety as a pharmacophore has been developed using different methods of synthesis with excellent yield.[16] The present investigation showed significant antihyperlipidemic and antihyperglycemic activity to all compound of the series when compared with standard drug. The pathological investigation has revealed that compounds **4c**, **4e**, and **4b** have higher antihyperlipidemic effect and caused appropriate modulation in HDL and LDL levels. On the other hand compounds from the series also showing capacity to lower the glucose level associated with hyperlipidemia.

Hence the present series could be developed as a novel class of antihyperlipidemic and antihypoglycemic agents. However,

Table 3
Data of blood sugar level

Compound	Blood sugar (mg/dl)
Normal control	57.83 ± 0.6009
Positive control	106.3 ± 0.6666[a]
Fenofibrate	70.5 ± 0.7638[a]
4a	81.5 ± 0.7638[a]
4b	72.33 ± 1.706[a]
4c	74.5 ± 0.7638[a]
4d	74.33 ± 0.9888[a]
4e	66.67 ± 1.282[a]
4f	75.17 ± 0 .601[a]

Test compound = 250 mg/kg.
Reference standard, Fenofibrate = 250 mg/kg.
The results are expressed as mean ± SEM. The data is analyzed using One-way Analysis of Variance (ANOVA) followed by Tukey's test.
(n = 6).
[a] P <0.001.
[b] P <0.01.
[c] P <0.05.
[d] Non significant.

further structural modification is planned to increase the antihyperlipidemic and antihyperglycemic activities.

Acknowledgments

The authors thankful to the Mrs. Fatima Rafiq Zakaria Chairman Maulana Azad Educational Trust and Dr. M. H. G. Dehghan, Principal, Y. B. Chavan college of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad 431001(MS), India for providing the laboratory facility.

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16. *General*: melting points were determined on scientific melting point apparatus in open capillaries and were uncorrected. ^{1}H NMR spectra were recorded on a BRUKER AVANCE II 400 spectrometer (400 MHz) with TMS as internal standard and DMSO as a solvent. Mass spectra were recorded on Time of flight mass spectrometer.

6.1. Synthesis of 2-(4-acetyl-2-substituted phenoxy)-2-methyl propanoic acid (**2**): In 500 ml of RBF, provide with reflux condenser placed 4-hydroxy acetophenone (0.01 mol), 2-bromo-2-methyl propanoic acid (0.01 mol) and K_2CO_3 (0.03 mol) in 25 ml of distilled ethanol. Then resultant solution was refluxed in water bath. After 1 h, pH of the solution had dropped to 7, and further 1 g of K_2CO_3 was added. Refluxing was continued for a 12 h. The hot solution was acidified with concd HCl. The product was extracted with diethyl ether. Ether layer was washed with 50 ml of saturated solution of Sodium Bicarbonate. The aqueous layer was acidified with dil HCl acid. White colored solid was filtered off, washed with water dried and recrystallized by hot water to get the desired compounds (**2**). Mp 102 °C, % yield 65%.
6.2. Synthesis of 2-(4-(2-aminothiazol-4-yl) phenoxy)-2-methyl propanoic acid (**3**). Method A: Thiourea (0.4 mol) and I_2 (0.2 mol) were triturated and mixed with 2-(4-acetylphenoxy)-2-methyl propanoic acid (0.2 mol) in DMF. The mixture was heated on water bath with occasional stirring for 18 h. The heated solution was poured in water and the precipitate was filtered off. Crystallization was carried out by using ethanol. Mp 182 °C, % yield 45%.
Method B [14]: A mixture of 2-(4-acetylphenoxy)-2-methyl propanoic acid (5 mmol), *N*-bromosuccinimide (5.5 mmol) in PEG-400 (15 ml) was stirred for 6 h at rt. The formation of α-bromoketone was monitored by TLC. After completion of the bromination, thiourea (5 mmol) was added and the reaction mass further stirred for 1 h and the progress of the reaction was monitored by TLC. After the completion of the reaction mixture was added in 20 ml of distilled water. The solid obtained was filtered and recrystallized from ethanol. Mp 182 °C, % yield 90%.
6.3. Synthesis of2-(4-(2-substituted aminothiazole-4-yl) phenoxy)-2-methyl propanoic acid (**4a**–**4f**): To a solution of 2-(4-(2-aminothiazol-4-yl) phenoxy)-2-methyl propanoic acid (0.02 mol) in dry benzene a cooled solution of substituted halides (0.04 mol) in dry benzene was added drop wise. The reaction mixture was refluxed in a water bath at 80 °C for 3 h. Benzene and excess substituted halides were removed by distillation. The crude product was dried and crystallized.
6.3.1. 2-(4-(2-Acetamidothiazol-4-yl) phenoxy)-2-methylpropanoic acid (**4a**): ^{1}H NMR (400 MHz, DMSO): δ = 11.9 (s, 1H), 9.1 (s, 1H), 6–8.5 (m, 5H), 2.2 (s, 3H), 1.5 (s, 6H); MS (TOF, 1.99 e4): m/z = 320; $C_{15}H_{16}N_2O_4S$ (320.364); requires (Found): C, 56.24 (56.12); H, 5.03 (4.9); N, 8.74 (8.64).
6.3.2. 2-(4-(2-(2-Chloroacetamido) thiazol-4-yl) phenoxy)-2-methylpropanoic acid (**4b**): ^{1}H NMR (400 MHz, DMSO): δ = 12.1 (s, 1H), 9.3 (s, 1H), 6–8.8 (m, 5H), 4.2 (s, 2H), 1.5 (s, 6H); MS (TOF, 1.99 e4): m/z = 354; $C_{15}H_{15}ClN_2O_4S$ (354.8); requires (Found): C, 50.78 (50.68); H, 4.26 (4.2); N, 7.90 (7.64).
6.3.3. 2-(4-(2-Benzamidothiazol-4-yl) phenoxy)-2-methylpropanoic acid (**4c**): ^{1}H NMR (400 MHz, DMSO): δ = 11.5 (s, 1H), 9.1 (s, 1H), 6.8–8.8 (m, 10H), 1.49 (s, 6H); MS (TOF, 1.99 e4): m/z = 382; $C_{20}H_{18}N_2O_4S$ (382.43); requires (Found): C, 62.81 (62.78); H, 4.74 (4.6); N, 7.33 (7.24).
6.3.4.2-(4-(2-(2-(4-Chlorophenyl)-2-oxoethylamino) thiazol-4-yl) phenoxy)-2-methyl propanoic acid (**4d**): ^{1}H NMR (400 MHz, DMSO): δ = 11.0 (s, 1H), 6.9–7.88 (m, 9H), 4.55 (s, 1H), 4.01(s, 1H); 1.58 (s, 6H); MS (TOF, 1.99 e4): m/z = 430; $C_{21}H_{19}ClN_2O_4S$ (430.90); requires (Found): C, 58.53 (58.48); H, 4.44 (4.41); N, 6.50 (6.44).
6.3.5. 2-(4-(2-(3-Chloro-3-oxopropanamido) thiazol-4-yl) phenoxy)-2-methylpropanoic acid (**4e**): ^{1}H NMR (400 MHz, DMSO): δ = 11.0 (s, 1H), 6.9–7.88 (m, 9H), 4.55 (s, 1H), 4.01 (s, 1H), 1.58 (s, 6H); MS (TOF, 1.99 e4): m/z = 382; $C_{16}H_{15}ClN_2O_5S$ (382.81); requires (Found): C, 50.20 (50.18); H, 3.95 (3.91); N, 7.32 (7.28).
6.3.6. 2-(4-(2-(2-Chloro-2-oxoacetamido) thiazol-4-yl) phenoxy)-2-methylpropanoic acid (**4f**): ^{1}H NMR (400 MHz, DMSO): δ = 11.2 (s, 1H), 9.15 (s, IH), 6.9–7.88 (m, 5H), 1.55 (s, 6H); MS (TOF, 1.99 e4): m/z = 368; $C_{15}H_{13}ClN_2O_5S$ (368.79); requires (Found): C, 48.85 (48.78); H, 3.55 (3.50); N, 7.60 (7.58).
Pharmacological activity: Sprague–Dawley rats (120–150 g) of either sex were divided into nine groups of six animals and they were numbered individually. Normal diet was made available for 30 days to Group I. High fat diet was made available for 23 days to Group II and vehicle was administered for last 7 days. Also high fat diet was made available for 23 days to Group III–IX and test compounds **4a**–**f** (250 mg/kg) and standard drug, Fenofibrate (250 mg/kg) was administered for last 7 days respectively. On 31st day, 2 ml blood was withdrawn by retro orbital method and total lipid profile was determined by standard method (Table 2). Along with lipid profile blood sugar level was also determined (Table 3).