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ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · OCTOBER 2010

Impact Factor: 3.45 · DOI: 10.1002/chin.201040130

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Original article

Synthesis and hypolipidemic activity of novel 2-(4-(2-substituted aminothiazole-4-yl) phenoxy) acetic acid derivatives

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ARTICLE INFO

Article history:
Received 10 February 2010
Received in revised form
27 March 2010
Accepted 29 March 2010
Available online 3 April 2010

Keywords:
Hypolipidemic
Aminothiazole
Phenoxy acetic acid

ABSTRACT

A novel series of aminotihazole compounds possessing phenoxy acetic acid moiety were synthesized. The synthesized compounds were evaluated for their hypolipidemic activity by using high fat diet induced hyperlipidemia in Sprague-Dawley rats.

1. Introduction

Hyperlipidemia is an elevation of lipids in the bloodstream and these lipids include fats, fatty acids, cholesterol, cholesterol esters, phospholipids, and triglycerides [1]. Fibrates in dyslipidemic patients, improve the plasma lipid profile by lowering TG, and to lesser extent, LDL cholesterol levels and by increasing HDL cholesterol level [2].

Phenoxy acetic acid pharmacophore has been used in many compounds which exhibit anti-hyperlipidemic activity, which was attached with various types of heterocycles such as thiazole [3–6], oxazole [7–9], oxadiazole [10], indole [11], benzisoxazole [12], piperidine [13] etc.

Many synthetic drugs are available to treat hyperlipidemia but are associated with multiple side effects. So, there is need to develop newer synthetic hypolipidemic agents with fewer or no side effects. From the literature survey, it was found that large number of compounds was synthesized using phenoxy acetic acid as pharmacophore which shows good hypolipidemic activity [14].

2. Chemistry

The compound 3 i.e. 2-(4-(2-aminothiazol-4-yl) phenoxy) acetic acid was synthesized by using 1-(4-hydroxyphenyl) ethanone (1) as starting material as outlined in Scheme 1.

2-(4-acetylphenoxy) acetic acid (2, Table 1) was synthesized by using 2-chloroacetic acid condensed with 1-(4-hydroxyphenyl) ethanone (1). It was undergo as cyclization with thiourea using iodine in DMF resulting in the formation of 2-(4-(2-aminothiazol-4-yl) phenoxy) acetic acid (3, Table 1). The compounds 4a-4h was prepared by treating compound 3 with different substituted halide (Table 1).

3. Hypolipidemic activity

The hypolipidemic activity of the synthesized compounds was studied in the high fat diet induced hyperlipidemic rats for 30 days by oral administration of the drug and compounds [15]. The results were compared with that obtained by the Group II (positive control). The obtained results revealed that feeding rats with high fat diet for 30 days significantly elevated the serum level of total cholesterol, triglycerides, LDL when compared with normal control rats. Moreover, induction of hyperlipidemia significantly decreased serum HDL level that of normal control rats. The obtained data revealed that the tested compounds produced variable effects on the serum levels of Cholesterol, TG, and LDL, as compared with Group II (positive control).

4. Results and discussion

4.1. Chemistry

Melting points were determined on scientific melting point apparatus in open capillaries and were uncorrected. ^{1}H NMR

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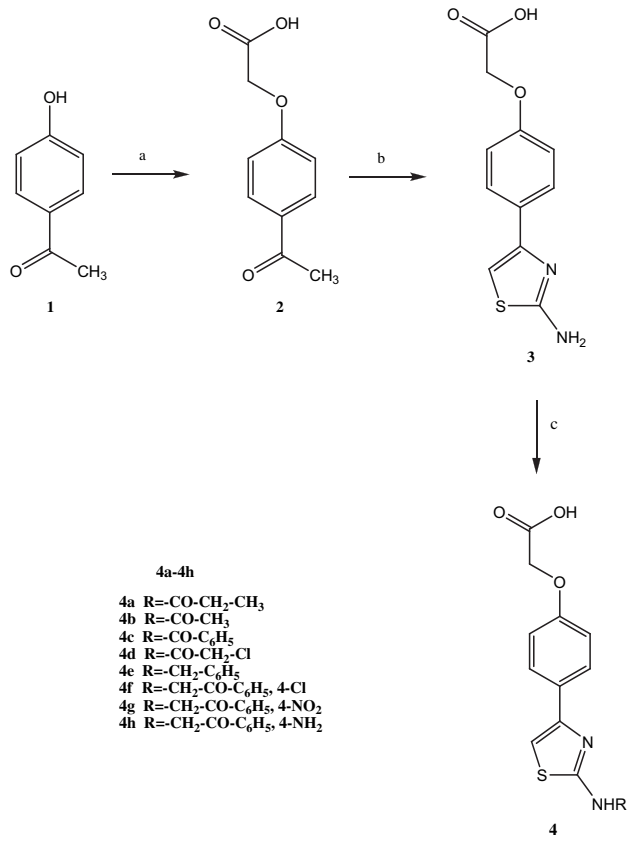
doi:10.1016/j.ejmech.2010.03.043



(a) 2-Chloro acetic acid, NaOH, H_2O; (b) Thiourea, Iodine, DMF; (c) R-X, DMF

Scheme 1. 2-(4-(2-substituted aminothiazole-4-yl) phenoxy) acetic acid derivatives.

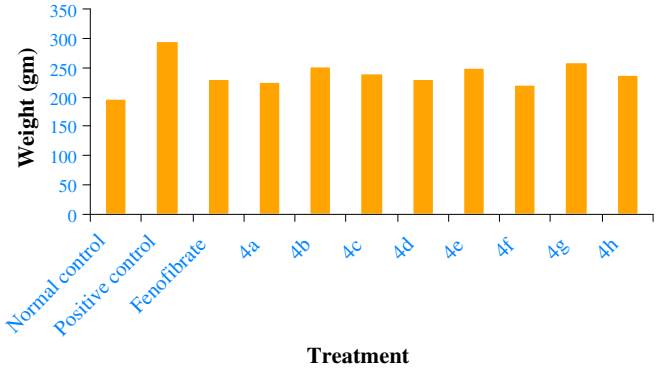


Fig. 1. Effect of the test compounds and Fenofibrate on change in body weight.

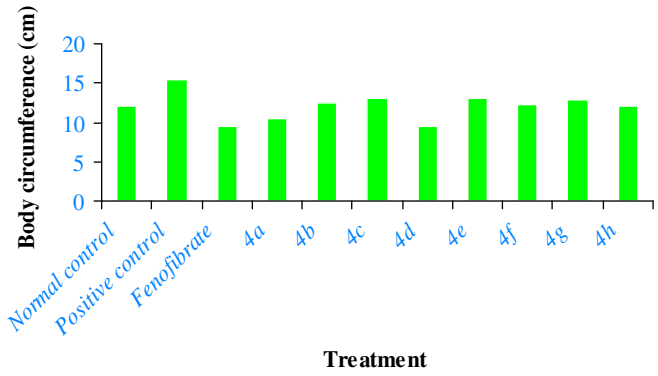


Fig. 2. Effect of the test compounds and Fenofibrate on body circumference.

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. FT-IR spectra were recorded on JASCO FT-IR 4000 using KBr powder.

4.2. Hypolipidemic activity

Sprague-Dawley rats (120–150 g) of either sex were used for the activity. Fenofibrate (250 mg/kg) was used as standard for the comparison hypolipidemic activity. Normal diet was made available for 30 days to Group I (normal control) and vehicle (10 ml/kg) was administered for last 7 days. High fat diet was made available for 30 days to Group II (positive control) and from Group III to Group XI (test group – standard group) and respective vehicle (10 ml/kg), test compounds (50 mg/kg) and standard drug (250 mg/kg) was administered for last 7 days. The various parameters like body weight, body circumference and locomotor activity were recorded every 5th day.

On 31st day, 2 ml blood was withdrawn by retro-orbital method and total lipid profile Cholesterol, triglycerides, LDL, HDL, and VLDL was determined. The group II (positive control) results were compared with group I (normal control) using student 't' test while group III to group XI were compared with group II using ANOVA followed by Dunnett's test. The change in body weight (Fig. 1), body circumference (Fig. 2), and locomotor activity (Fig. 3) for the compounds and that of standard were shown in Table 2. The total lipid i.e. HDL (Fig. 4), Cholesterol (Fig. 5), Triglycerides (Fig. 6), LDL (Fig. 7), VLDL (Fig. 8) for the compounds and that of standard were shown in Table 3.

Table 1
Experimental data of synthesized compounds 2–4h.

Compound	Molecular formula	Molecular Weight	Melting Point	% Yield
2	$C_{10}H_{10}O_4$	194	184	49.48
3	$C_{11}H_{10}N_2O_3S$	250	251	61.2
4a	$C_{14}H_{14}N_2O_4S$	306	155	58.76
4b	$C_{13}H_{12}N_2O_4S$	292	162	61.58
4c	$C_{18}H_{14}N_2O_4S$	354	180	56.44
4d	$C_{13}H_{11}ClN_2O_4S$	326	149	59.06
4e	$C_{18}H_{16}N_2O_3S$	340	110	52.29
4f	$C_{19}H_{15}ClN_2O_4S$	402	105	55.85
4g	$C_{19}H_{15}N_3O_6S$	413	121	52.05
4h	$C_{19}H_{17}N_3O_4S$	383	140	51.69

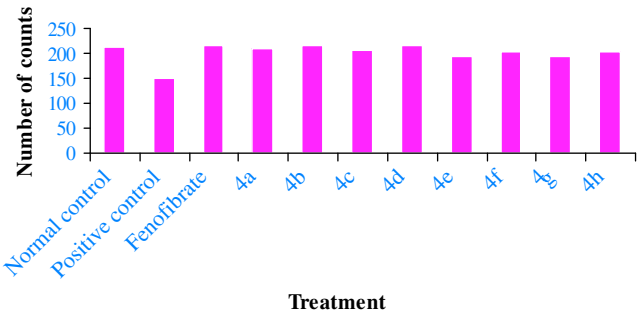


Fig. 3. Effect of the test compounds and Fenofibrate on locomotor activity.

Table 2
Data of body weight, body circumference & locomotor activity.

Compound	Parameter		
	Body weight (gm)	Body circumference (cm)	Locomotor activity (5 minutes)
Normal control	196.666 ± 3.323	12.033 ± 0.3442	213.166 ± 8.946
Positive control	295.333 ± 12.582***	15.483 ± 0.4909**	148.5 ± 8.85***
Fenofibrate	229.666 ± 9.475***	9.5 ± 0.3194***	216.666 ± 9.017***
4a	224.166 ± 3.754**	10.483 ± 0.453***	210.5 ± 9.323**
4b	250.833 ± 3.683*	12.516 ± 0.600*	217 ± 10.86 ns
4c	239.666 ± 4.566**	13.1 ± 0.658ns	206.833 ± 9.659***
4d	230.666 ± 3.783***	9.5 ± 0.319***	215 ± 13.269**
4e	248.500 ± 4.537ns	13.066 ± 0.814ns	194.833 ± 8.811*
4f	220.500 ± 1.688*	12.35 ± 0.699*	201.833 ± 10.543*
4g	258.166 ± 3.825ns	12.85 ± 0.793ns	193.666 ± 10.39ns
4h	237.333 ± 6.443**	12 ± 0.617**	204.166 ± 9.81*

The results were expressed as Mean ± SEM. The data were analyzed using One-way Analysis of Variance (ANOVA) followed by Tukey test. ($n = 5$ rats per group; $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, ns – non significant) Values are average of 5 readings.

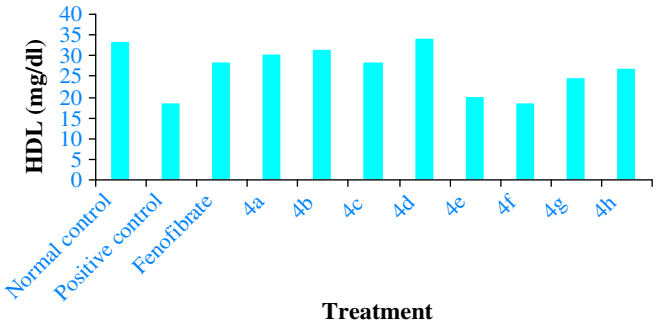


Fig. 4. Effect of the tested compounds and Fenofibrate on HDL level.

4.3. Structure activity relationship

The synthesized compounds show good hypolipidemic activity by increasing the HDL levels that of normal and positive control. Aliphatic substitution on amino group with one or two carbon chain show significant increase in HDL level and locomotor activity, reduced in body weight and significant reduction in body circumference. The presence of terminal chlorine (4d) increases antihyperlipedemic activity more effectively. Compound with aromatic substitution (4e, 4f, 4g) generally having less HDL and locomotorincreasing capacity and no reduction in body weight and

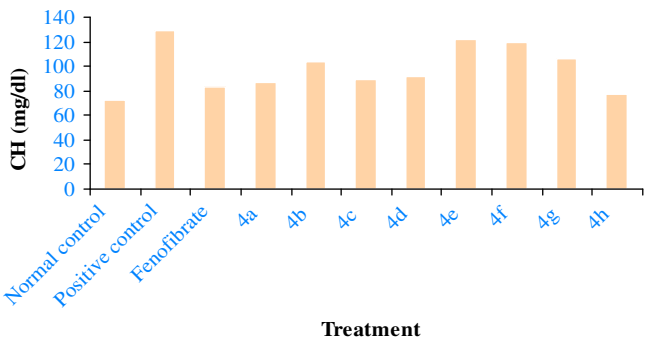


Fig. 5. Effect of the tested compounds and Fenofibrate on Cholesterol level.

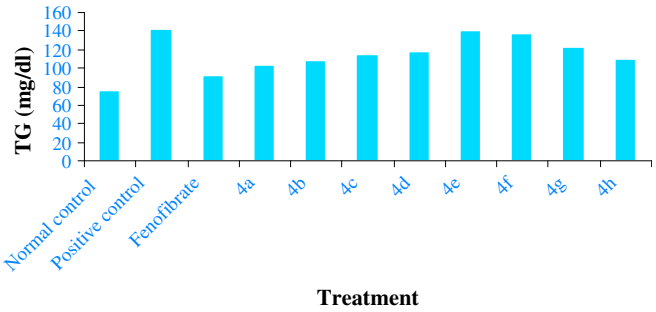


Fig. 6. Effect of the tested compounds and Fenofibrate on Triglycerides level.

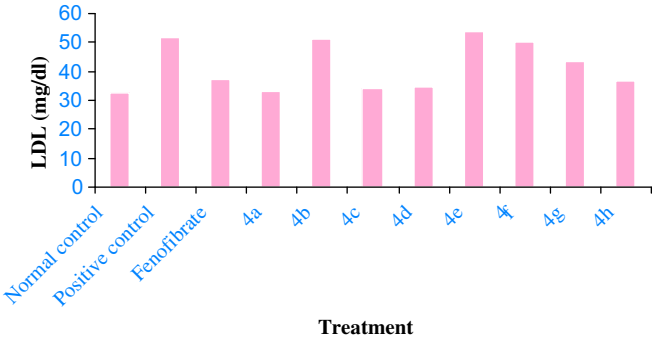


Fig. 7. Effect of the tested compounds and Fenofibrate on LDL level.

body circumference as compared to aliphatic substituent (4a, 4b, 4d). The presence of C=O spacer (4a, 4b, 4c) was more effective than -CH_2-C=O (4h) between amino group and aliphatic or aromatic substituent.

5. Conclusion

In this investigation the high fat diet fed for 30 days significantly increased the body weight in positive control as compared to normal diet group where as last 07 days treatment of given compound has shown reduced body weight by compound 4d followed by compounds 4a, 4c and 4h. In case of body circumference, compounds 4a and 4d were most effective followed by 4h. The locomotor activity measured has shown significant increase with compound 4c, followed by 4a and 4d.

From pathological investigation, the SAR data has revealed that compounds 4a, 4b, 4c, 4d, and 4h have higher antihyperlipidmeic

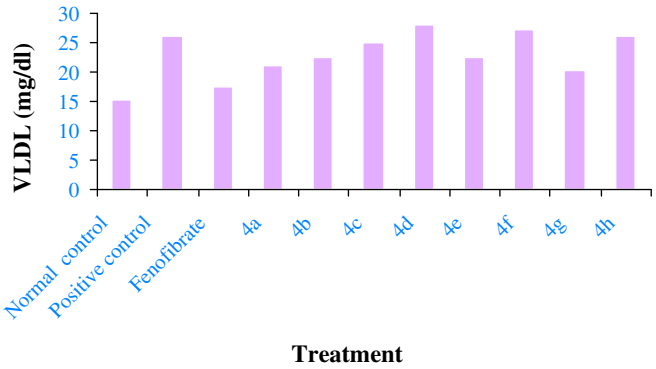


Fig. 8. Effect of the tested compounds and Fenofibrate on VLDL level.

Table 3
Data of total lipid profile (CH, TG, LDL, HDL & VLDL).

Compound	Parameter in mg/dl				
	CH	TG	LDL	HDL	VLDL
Normal control	72.6 ± 0.86	75.6 ± 2.06	32.6 ± 1.28	33.6 ± 1.50	15.2 ± ± 0.86
Positive control	128.8 ± 1.20***	142.4 ± 1.53***	51.8 ± 2.03**	18.6 ± 1.36**	26.2 ± 1.20**
Fenofibrate	83.2 ± 1.03**	91.6 ± 2.31**	37.2 ± 1.15*	28.4 ± 1.43*	17.4 ± 1.03**
4a	86.6 ± 2.13**	103.6 ± 2.65**	33.0 ± 1.64**	30.4 ± 1.63**	21 ± 1.14*
4b	104.0 ± 2.51*	107.6 ± 2.37*	51.4 ± 1.80ns	31.8 ± 1.71**	22.6 ± 1.36ns
4c	89.2 ± 2.20**	114.6 ± 2.24*	34.2 ± 1.35**	28.4 ± 1.36*	25 ± 1.64ns
4d	92.0 ± 2.21*	118.4 ± 1.03*	34.8 ± 1.93**	34.4 ± 1.20**	28 ± 1.14ns
4e	122.2 ± 2.47ns	140.2 ± 1.46ns	53.8 ± 2.41ns	20.2 ± 1.24ns	22.4 ± 0.92ns
4f	119.2 ± 2.41ns	136.6 ± 2.01ns	50.0 ± 1.41ns	18.6 ± 1.20ns	27.2 ± 1.42ns
4g	106.8 ± 1.68*	122.8 ± 1.98*	43.2 ± 1.56*	24.6 ± 1.50*	20.2 ± 1.28*
4h	77.6 ± 1.63**	110.4 ± 1.43*	36.8 ± 1.28*	27.0 ± 1.14*	26.2 ± 1.35ns

Standard dose 250 mg/kg, Test compound 50mg/kg. PC (Positive control) was compared with control. Drug treated compared with PC. The data were analyzed using One-way Analysis of Variance (ANOVA) followed by Dunnett's Test. ($n = 5$ rats per group; $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$, ns − non significant.) Values are average of 5 readings.

effect and caused appropriate modulation in HDL levels. Overall, compounds 4d and 4h were potential compounds for obesity associated hyperlipidemia.

6. Experimental

6.1. Synthesis 2-(4-acetylphenoxy) acetic acid (2) [16]

A solution of sodium hydroxide (8.8 g, 0.22 moles) and chloroacetic acid (11.35 g, 0.24 moles, 20% excess) in 110 ml distilled water was added to (13.6 g, 0.2 moles) 4-hydroxy acetophenone and the resultant solution was refluxed on an oil bath for 8.5 hrs. At regular intervals, the pH was measured and kept in the 8–9 range by the further addition of aqueous sodium hydroxide solution as necessary. The hot reaction mixture was acidified with an excess of concentrated hydrochloric acid and the white solid filtered off, washed with water and dried. This product was dissolved in 5% aqueous sodium carbonate solution and washed several times with ethyl acetate. The aqueous layer was then acidified with hydrochloric acid and the solid filtered off, washed with water and dried. This material was crystallized from ethyl acetate to get compound 2. Melting Point: −184 °C (Ref. 183–185° C.).

6.2. 2-(4-(2-aminothiazol-4-yl) phenoxy) acetic acid (3) [17]

Thiourea (30.4 g, 0.4 mole) and I_2 (50.8 g, 0.2 mole) were triturated and mixed with 2-(4-acetylphenoxy) acetic acid (38.8 g, 0.2 mole) in DMF. The mixture was heated on water bath with occasional stirring for 18 hrs. The heated solution was poured in water; the precipitate was filtered off. Crystallization was carried out by using ethanol. Melting Point: −251 °C.

IR (KBr): 3512, 3430, 3045, 1722, 1629, 1525, 1510, 1224, 1195, 932 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): $\delta = 12.3$ (s, 1H), 7.4 (s, 2H), 6–8.5 (m, 5H), 4.6 (s, 2H).

6.3. General procedure for synthesis of 2-(4-(2-substitutedaminothiazol-4-yl) phenoxy) acetic acid (4a-4h)

To a solution of 2-(4-(2-aminothiazol-4-yl) phenoxy) acetic acid (5 g, 0.02 mole) in DMF, substituted halide (0.04 mole) was added and reaction mixture was heated for 3 hrs. The completion of reaction was monitored by TLC. The resultant solution was poured into the water. The solid obtained was filtered and recrystallized from ethanol to obtained desired compounds 4a-4h.

6.3.1. 2-(4-(2-propionamidothiazol-4-yl) phenoxy) acetic acid (4a)

IR (KBr): 3500, 3219, 3000, 2916,1716,1679, 1561, 1510, 1456, 1362, 1138, 1025, 918, 850, 828 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): $\delta = 11.8$ (s, 1H), 8.4 (s, 1H), 6–8.5 (m, 5H), 3.4 (s, 2H),, 2.53 (q, 2H), 1.20 (t, 3H); MS (TOF, 1.99 e4): $m/z = 306$.

6.3.2. 2-(4-(2-acetamidothiazol-4-yl) phenoxy) acetic acid (4b)

IR (KBr): 3500, 3228, 3000, 2927, 1705, 1682, 1535, 1516, 1509, 1422, 1324, 1165, 938, 819 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): $\delta = 11.9$ (s, 1H), 8.1 (s, 1H),6–8.5 (m, 5H), 3.1(s, 2H),, 2.1 (s, 3H); MS (TOF, 1.99 e4): $m/z = 292$.

6.3.3. 2-(4-(2-benzamidothiazol-4-yl) phenoxy) acetic acid (4c)

IR (KBr): 3542, 3214, 3010,1709,1653,1546, 1512, 1476, 1219, 1108, 935, 822 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): $\delta = 12.3$ (s, 1H), 7.12 (s, 1H), 6–8.5 (m, 10H), 3.3 (s, 2H); MS (TOF, 1.99 e4): $m/z = 354$.

6.3.4. 2-(4-(2-(2-chloroacetamido) thiazol-4-yl) phenoxy) acetic acid (4d)

^{1}H NMR (400 MHz, DMSO): $\delta = 11.9$ (s, 1H), 8.1 (s, 1H), 6–8.5 (m, 5H), 4.2 (s, 2H), 3.1(s, 2H); MS (TOF, 1.99 e4): $m/z = 326$.

6.3.5. 2-(4-(2-(benzyl amino) thiazol-4-yl) phenoxy) acetic acid (4e)

^{1}H NMR (400 MHz, DMSO): $\delta = 12.2$ (s, 1H), 6–8.5 (m, 10H), 4.62 (s, 1H), 3.3 (s, 2H), 2.6 (d, 2H); MS (TOF, 1.99 e4): $m/z = 340$.

6.3.6. 2-(4-(2-(2-(4-chlorophenyl)-2-oxoethylamino) thiazol-4-yl) phenoxy) acetic acid (4f)

^{1}H NMR (400 MHz, DMSO): $\delta = 12.24$ (s, 1H), 6–8.5 (m, 9H), 4.6 (s, 1H), 3.07 (s, 2H), 2.5 (d, 2H); MS (TOF, 1.99 e4): $m/z = 402$.

6.3.7. 2-(4-(2-(2-(4-nitrophenyl)-2-oxoethylamino) thiazol-4-yl) phenoxy) acetic acid (4g)

^{1}H NMR (400 MHz, DMSO): $\delta = 12.2$ (s, 1H), 6–8.5 (m, 9H), 4.7 (s, 1H), 3.03 (s, 2H), 2.5 (d, 2H); MS (TOF, 1.99 e4): $m/z = 413$.

6.3.8. 2-(4-(2-(2-(4-aminophenyl)-2-oxoethylamino) thiazol-4-yl) phenoxy) acetic acid (4h)

^{1}H NMR (400 MHz, DMSO): $\delta = 12.24$ (s, 1H), 6–8.5 (m, 11H), 4.6 (s, 1H), 3.07 (s, 2H), 2.5 (d, 2H), MS (TOF, 1.99 e4): $m/z = 383$.

Acknowledgement

The authors thankful to the Head, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004 (MS), India for providing the laboratory facility.

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