SYNTHESIS AND ANTI-PROLIFERATIVE SCREENING OF NEW THIAZOLE COMPOUNDS

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A new series of thiazole compounds are synthesized and theirs anticancer activity was tested against breast cancer cells MCF7. The starting ethyl 2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylate was alkylated by alkyl bromides in DMF. The resulted ethyl 4-methyl-2-(4-(alkyloxy)phenyl)thiazole-5-carboxylate compounds were refluxed with hydrazine hydrate in ethanol to afford 4-methyl-2-(4-(alkyloxy)phenyl)thiazole-5-carbohydrazide compounds. These hydrazides were reacted with various cyclizing reagents to give various 1,3,4-oxadiazole and pyrazole-ring containing thiazole compounds. The antiproliferative activity was calculated on the basis of IC_{50} values. The (5-amino-3-phenyl-1H-pyrazol-1-yl)(4-methyl-2-(4-(ethoxy)phenyl)thiazol-5-yl)methanone has comparable activity with standard Paclitaxel.

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INTRODUCTION

Heterocycles including 1,3,4-oxadiazoles and pyrazoles have always attracted the attention of researchers as they showed various biological activities. The 1,3,4-oxadiazole is a key core used against various fungi[1] and bacteria-caused diseases.[2] It also reported to possess anti-viral,[3] anti-inflammatory,[4,5] anti-cancer[6,7] and central nervous system depressant[8] activities. Some important drugs like Raltegravir and Furamizole contain 1,3,4- oxadiazole cores[9] (Fig. 1).

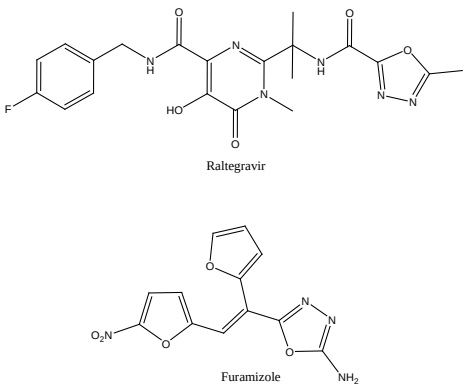


Figure 1. Important drugs containing 1,3,4-oxadiazole

Pyrazoles are the important core of organic synthesis abundantly found in the naturally occurring compounds.[10] It is found in agrochemical products as herbicides, insecticides, fungicides, etc. In medicines was found to have a variety of activities; such as antiinflammatory, anti-cancer, anti-convulsant, antifungal, antidiabetic, antiviral and anti-bacterial activities.[11-14] Some of them are depicted as bellow[12] (Fig. 2).

On observing these various biological properties associated with five-membered heterocycles, inspired us for the synthesis of 5-substituted 4-methyl-2-(4-(alkyloxy) phenyl)thiazole.

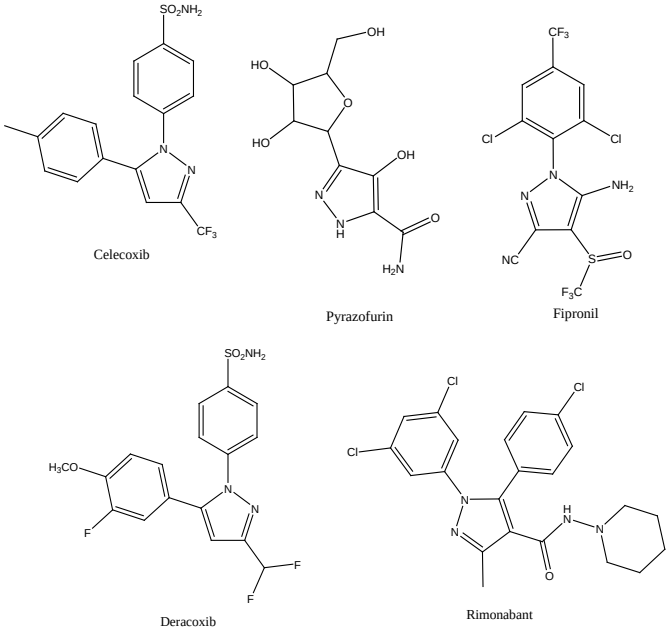
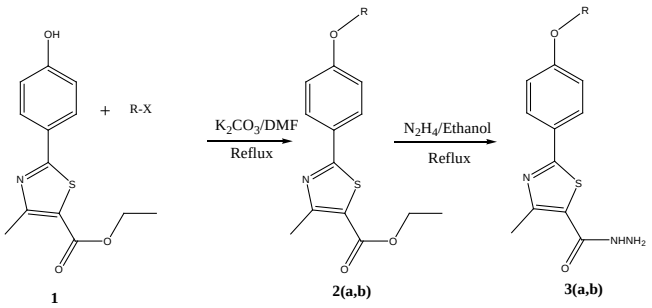


Figure 2. Important drugs containing pyrazole

RESULTS AND DISCUSSION

The parent ethyl 2-(4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (**1**) was synthesized by the reaction of 4-hydroxy benzothioamide with ethyl-2-chloroacetoacetate in ethanol. Then, the obtained compound **1** was purified by flash chromatography with n-hexane: ethyl acetate (1:1)

system. The compound **1** was then treated with n-pentyl bromide or ethyl iodide in presence of tetrabutyl ammonium iodide (TBAI), catalytic amount of KI, potassium carbonate and DMF as solvent at reflux condition to give compound ethyl 4-methyl-2-(4-(alkyloxy)phenyl)thiazole-5-carboxylates (**2a**, **2b**). Compound **2a** and **2b** were treated with hydrazine hydrate to give 4-methyl-2-(4-(alkyloxy)phenyl)thiazole-5-carbohydrazides (**3a**, **3b**). Compound **3a** and **3b** were reacted with difference cyclizing reagents to give different azole scaffolds.

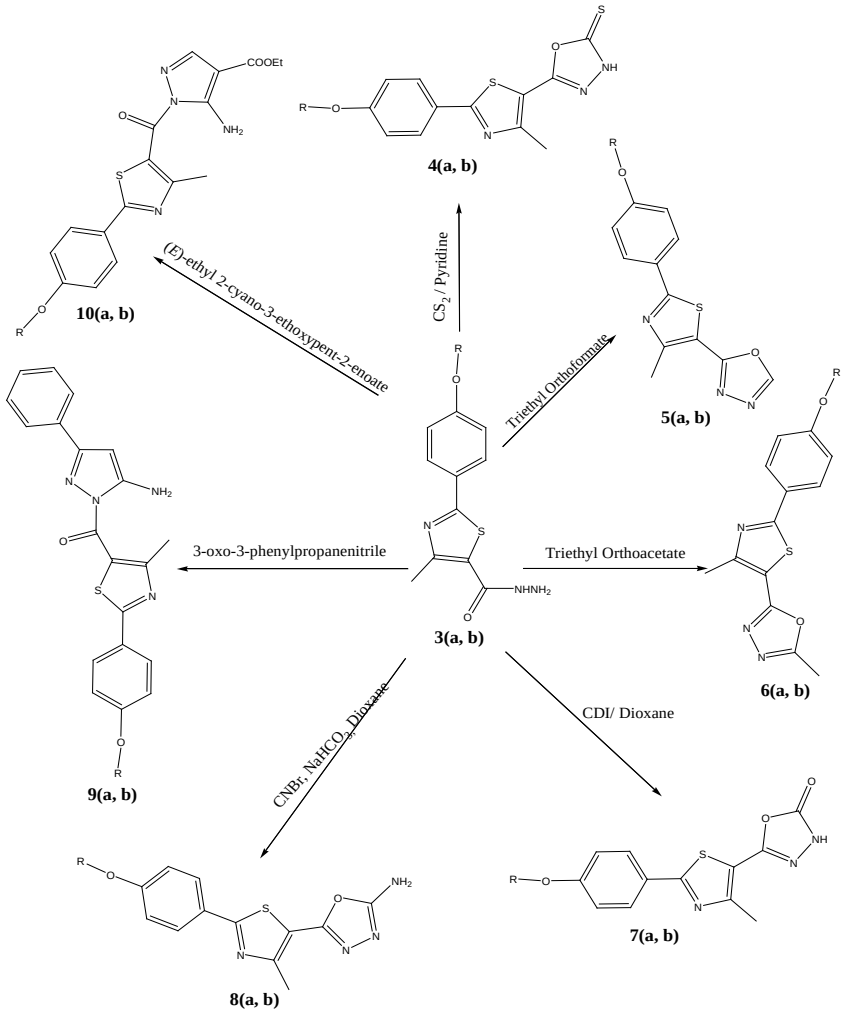


Scheme 1. Synthesis of hydrazide derivatives 3(a,b)

The key intermediate **3a** was treated with carbon disulphide and pyridine to afford 5-(4-methyl-2-(4-(pentyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadiazole-2(3H)-thione (**4a**).

The hydrazide **3a** was treated with triethyl orthoformate and triethylorthoacetate to give 2-(4-methyl-2-(4-(pentyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadiazole (**5a**) and 2-methyl-5-(4-methyl-2-(4-(pentyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadiazole (**6a**) respectively. The hydrazide **3a** on treatment with CDI in dioxane gave 5-(4-methyl-2-(4-(pentyloxy)phenyl)thiazol-5-yl)-1,3,4-oxa-diazol-2(3H)-one (**7a**).

The intermediate **3a** on treatment with cyanogen bromide and sodium hydrogen carbonate gave 5-(4-methyl-2-(4-(pentyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadiazol-2-amine (**8a**). The same compound was reacted with 3-oxo-3-phenylpropanenitrile and yielded (5-amino-3-phenyl-1H-pyrazol-1-yl)(4-methyl-2-(4-(pentyloxy)phenyl)thiazol-5-yl)methanone (**9a**). The compound **3a** was treated with (E)-ethyl 2-cyano-3-ethoxypent-2-enoate and gave (ethyl-5-amino-1H-pyrazol-1-yl-4-carboxylate)(4-methyl-2-(4-(pentyloxy)phenyl)thiazol-5-yl)methanone 10(a).



Scheme 2. Synthesis of various heterocycles **4(a,b)** to **10(a,b)** from hydrazide **3(a,b)**

In a similar way, hydrazide **3b** was treated with various cyclizing agents to obtained compounds **4b-10b** and screened for anti-proliferative activity against breast cancer cells MCF7.

Table 1. Evaluation of IC_{50} values of 4-methyl-2-(4-(alkyloxy)phenyl)thiazole derivatives

Sr. No.	Compound	IC_{50} Value (µM)
1	**4a**	26.21
2	**5a**	15.16
3	**6a**	12.65
4	**7a**	15.82
5	**8a**	59.12
6	**9a**	NA
7	**10a**	NA
8	**4b**	NA
9	**5b**	NA
10	**6b**	NA
11	**7b**	14.81
12	**8b**	93.94
13	**9b**	5.87
14	**10b**	NA
15	Paclitaxel (standard drug)	4.8

The breast cancer cells MCF7 were treated with compounds and the anti-proliferative effect was evaluated by MTT assay.

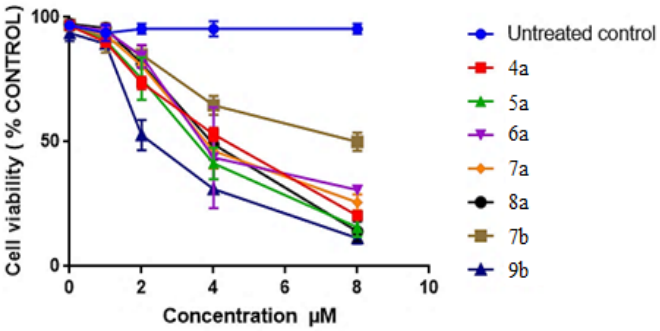


Figure 3. Dose-dependent study of cell viability

As shown in (Fig. 3), a dose-dependent decrease in the growth of cancer cells was observed with increasing concentration of the compounds. Compounds **4a**, **5a**, **6a**, **7a**, **8a** and **7b** showed less to moderate anti-proliferative activity while compound **9b** was found to show comparable activity (IC_{50}) to standard anticancer drug Paclitaxel. Among the cells, the IC_{50} value of **6a** and **9b** in MCF7 were found to be low i.e. 12.65 ± 0.5 and 5.87± 1 µM, respectively. This suggested that treatment with compounds inhibited the growth and induced apoptosis in these cells.

Significantly decreased cell viability was found in compounds treated T-47D cells (p<0.0001 compared to untreated control).

EXPERIMENTALS

All the melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1 spectrophotometer in KBr disc. ^{1}H NMR were recorded on a BRUKER AVANCE II 400MHz spectrometer in $CDCl_3$/ DMSO d_6, chemical shifts are in ppm relative to TMS. Mass spectra were taken on a Macro mass spectrometer by electron spray method (Es). The structures of various synthesized compounds were assigned on the basis of spectral studies and it has been reported in experimental protocols. The progress of reaction was monitored on Alumina coated TLC plates in ethyl acetate and n- hexane system.

The anti-cancer effect of compounds on the breast cancer cells MCF7 was evaluated by MTT Assay Kit (Thermo Inc. USA). The cells were plated at ~ 1×103 cells in 96 well plates containing 100 µL of DMEM and 0,1,2,4,8 µM compounds were added to each well. In three different wells same concentration was used . Cell death was analysed after 24 hours at 37°C. [15] MTT reagent (5 mg/mL) was added and kept for four hours incubation. The procedure was followed according to the manufacturer's instructions. The absorbance was recorded at 490 nm using a 96 well Multiscan Ascent (Thermo Inc. USA). The inhibitory effect of compounds on cell growth was assessed as percent cell viability, where cells without treatment were considered 100% viable. The statistical differences were evaluated by Students two-tailed t-test.

Synthesis of ethyl 4-methyl-2-(4-(alkyloxy)phenyl)thiazole-5-carboxylates (13a and 13b)

Compound **1** (2.63 g, 0.01 mol) was mixed with powdered potassium carbonate (2.07 gm, 0.015 mol) and DMF (25 mL). To this reaction mixture n-pentyl bromide or ethyl iodide (0.011 mol) with catalytic amount of TBAI and KI were added. The mixture was allowed to reflux for 8 h. The resulting mixture was cooled and poured ointo 100 g of ice. The precipitate obtained was filtered, dried at room temperature and purified by column chromatography using hexane: ethyl acetate system (9:1).

2a: Yield: 2.1 g (63 %); mp: 47-48 ºC; IR: (KBr, cm^{-1}): 2950, 1700, 1608, 1516, 1441, 1370, 1253, 1174, 1091;^{1}H NMR (DMSO-d_6): 0.96 (t, 3H, -CH_3), 1.33 (t, 3H, CH_3), 1.36-1.45 (m, 4H, 2CH_2), 1.75 (quintate, 2H, CH_2), 2.67 (s, 3H, Ar-CH_3), 4.02 (t, 2H, O-CH_2), 4.29 (t, 2H, O-CH_2), 7.87 (d, 2H, *J= 8 Hz*, 2Ar-H), 7.89 (d, 2H, *J=8 Hz*, 2Ar-H); M.W.= 333; Mass: (M+1) = 334.

2b: Yield: 1.8 gm (61 %); mp: 98-99 ºC; IR (KBr, cm^{-1}): 2984, 1695, 1602, 1522, 1446, 1394, 1370, 1322, 1253, 1181, 1121, 1045 ;^{1}H NMR (DMSO-d_6): 1.32 (t, 3H, -CH_3), 1.37 (t, 3H, CH_3), 2.66 (s, 3H, Ar-CH_3), 4.10 (q, 2H, O-CH_2), 4.28 (q, 2H, O-CH_2), 7.01 (d, 2H, *J= 8 Hz*, 2Ar-H), 7.87 (d, 2H, *J=8 Hz*, 2Ar-H); M.W.= 291; (M+1) = 292.

Synthesis of 4-methyl-2-(4-(alkyloxy)phenyl)thiazole-5-carbo-hydrazide (3a and 3b)

Compound **3a** or **3b** (0.006 mol) was dissolved in 15 mL of ethanol. To this mixture hydrazine hydrate (99 %) (0.5 mL, 0.009 mol) was added and refluxed for 3 hours. After the completion of reaction, the reaction mixture was cooled and poured over 50 gms of crushed ice and filtered off. The crude product was recrystallized using ethanol to afford fine yellow colored needle shaped crystals.

3a: Yield: 1.8 g (94 %); mp: 144-145 ^{o}C;IR: (KBr, cm^{-1}): 3300, 3200, 2941, 1620, 1524, 14741258, 1178 ; ^{1}H NMR (DMSO-d_6): 0.91 (t, 3H, -CH_3), 1.33-1.44 (m, 4H, 2CH_2), 1.75 (quintate, 2H, CH_2), 2.58 (s, 3H, Ar-CH_3), 4.02 (t, 2H, O-CH_2), 4.49 (s, 2H, NH_2), 7.01 (d, 2H, *J=8 Hz*, 2Ar-H), 7.83 (d, 2H, *J= 8 Hz*, 2Ar-H), 9.48 (s, 1H, NH); M.W.= 319; (M+1) = 320.

3b: Yield: 1.6 g (96 %); mp: 161-162 ^{o}C; IR (KBr, cm^{-1}): 3304, 2984, 1630, 1610, 1522, 1450, 1370, 1322, 1265, 1173, 1117, 1049;^{1}H NMR (DMSO-d_6): 1.38 (t, 3H, -CH_3), 2.59 (s, 3H, Ar-CH_3), 4.08 (q, 2H, O-CH_2), 4.46 (s, 2H, NH_2), 7.00 (d, 2H, *J=8 Hz*, 2Ar-H), 7.83 (d, 2H, *J= 8 Hz*, 2Ar-H), 9.46 (s, 1H, NH); M.W.= 277; (M+1) = 278.

5-(4-Methyl-2-(4-(alkyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadi-azole-2(3H)-thione (4a and 4b)

A mixture of **3a** or **3b** (0.002 mole) and carbon disulfide (3 mL) in pyridine (10 mL) was refluxed for 6 h. After completion of the reaction, the solvent was removed using rotary evaporator and the residue obtained was triturated with ice-water mixture and neutralized using dilute HCl. The separated solid was filtered, washed and dried and recrystallized using ethanol to give **4a** as pale yellow crystals.

4a*:* Yield: 0.580 g (80 %); mp: 186-187 ^{o}C; IR: (KBr, cm^{-1}): 3075, 2925, 1603, 1516, 1441, 1383, 1303, 1262, 1178;^{1}H NMR (DMSO-d_6): 0.89 (t, 3H, -CH_3), 1.31-1.42 (m, 4H, 2CH_2), 1.71 (quintate, 2H, CH_2), 2.65 (s, 3H, Ar-CH_3), 4.00 (t, 2H, O-CH_2), 7.02 (d, 2H, *J=8 Hz*, 2Ar-H), 7.88 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 361, (M+1) = 362.

4b*:* Yield: 0.560 g (87 %); mp: 231-232 ^{o}C; IR (KBr, cm^{-1}): 3088, 2935, 2752, 1602, 1510, 1442, 1382, 1305, 1261, 1173, 1081, 1045; ^{1}H NMR (DMSO-d_6): 1.36 (t, 3H, -CH_3), 2.66 (s, 3H, Ar-CH_3), 4.12 (q, 2H, O-CH_2), 7.07 (d, 2H, *J=8 Hz*, 2Ar-H), 7.94 (d, 2H, *J= 8 Hz*, 2Ar-H), 9.29 (s, 1H, Ar-H); M.W.= 319; (M+1) = 320.

2-(4-Methyl-2-(4-(alkyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadi-azole (5a, 5b)

Compound **3a** or **3b** (0.002 mol) was refluxed in triethyl orthoformate (10 mL) for 14 h. The extra solvent was removed under vacuum. Thus, the solid obtained was recrystallized by ethanol to afford yellowish crystals.

5a*:* Yield: 0.473 gm (72 %); mp: 81 ^{o}C; IR: (KBr, cm^{-1}): 3133, 2958, 1603, 1516, 1449, 1379, 1316, 1258, 1174, 1091;^{1}H NMR (DMSO-d_6): 0.91 (t, 3H, -CH_3), 1.35-1.39 (m, 4H, 2CH_2), 1.73-1.76 (quintate, 2H, CH_2), 2.75 (s, 3H, Ar-CH_3), 4.06 (t, 2H, O-CH_2), 7.08 (d, 2H, *J=8 Hz*, 2Ar-H), 7.96 (d, 2H, *J= 8 Hz*, 2Ar-H), 9.37 (s, 1H, Ar-H); M.W.= 329;(M+1) = 330.

5b*:* Yield: 0.43 g (75 %); mp: 145-146 ^{o}C; IR (KBr, cm^{-1}): 3119, 2984, 1606, 1519, 1437, 1378, 1270, 1305, 1265, 1177, 1045; ^{1}H NMR (DMSO-d_6): 1.38 (t, 3H, -CH_3), 2.75 (s, 3H, Ar-CH_3), 4.11 (q, 2H, O-CH_2), 7.02 (d, 2H, *J=8 Hz*, 2Ar-H), 7.92 (d, 2H, *J= 8 Hz*, 2Ar-H), 9.29 (s, 1H, Ar-H); M.W.= 287; (M+1) = 288.

2-Methyl-5-(4-methyl-2-(4-(alkyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadiazole (6a, 6b):

Compound **6a** and **6b** were prepared by refluxing **3a** or **3b**) (0.002 mol) in triethyl orthoacetate (10 mL) for 16 h. After the completion of reaction the extra solvent was removed under reduced pressure. The solid obtained was recrystallized by using ethanol to give yellow coloured crystals.

6a: Yield: 0.510 g (74 %); mp: 83-84 ^{o}C; IR: (KBr, cm^{-1}): 2958, 1603, 1574, 1445, 1420, 1399, 1303, 1258, 1178, 1020; ^{1}H NMR (DMSO-d_6, δ ppm): 0.92 (t, 3H, -CH_3), 1.40 (m, 4H, 2CH_2), 1.75 (quintate, 2H, CH_2), 2.54 (s, 3H, Ar-CH_3), 2.73 (s, 3H, Ar-CH_3), 4.02 (t, 2H, O-CH_2), 6.98 (d, 2H, *J=8 Hz*, 2Ar-H), 7.86 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 343, (M+1) = 344.

6b: Yield: 0.457 gm (76 %); mp: 147-148 ^{o}C; IR (KBr, cm^{-1}): 2991, 1596, 1571, 1474, 1441, 1375, 1312, 1258, 1170, 1120, 1041; ^{1}H NMR (DMSO-d_6, δ ppm):1.38 (t, 3H, -CH_3), 2.52 (s, 3H, Ar-CH_3), 2.73 (s, 3H, Ar-CH_3), 4.11 (q, 2H, O-CH_2), 7.04 (d, 2H, *J=8 Hz*, 2Ar-H), 7.91 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 301; (M+1) = 302.

5-(4-Methyl-2-(4-(alkyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadi-azol-2(3H)-one (7a, 7b)

The mixture of **3a** or **3b** (0.002 mol) and N,N'- carbonyl diimidazole (CDI) (0.486 gm, 0.003 mol) in dioxane (20 mL) was refluxed for 6 hours. After completion of reaction the mixture was allowed to cool and solvent was removed under reduced pressure. The solid obtained was recrystallized from ethanol to give colorless crystals.

7a*:* Yield: 0.552 g (80 %); mp: 175-176 ^{o}C; IR: (KBr, cm^{-1}): 3264, 2944, 2752, 1820, 1758, 1603, 1520, 1445, 1386, 1316, 1270, 1174, 1054; ^{1}H NMR (DMSO-d_6, δ ppm): 0.91 (t, 3H, -CH_3), 1.34-1.43 (m, 4H, 2CH_2), 1.73 (quintate, 2H, CH_2), 2.62 (s, 3H, Ar-CH_3), 4.01 (t, 2H, O-CH_2), 7.00 (d, 2H, *J=8 Hz*, 2Ar-H), 7.86 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 345; (M+1) = 346.

7b*:* Yield: 0.51 g (84 %); mp: 229-230^{o}C (Decomp.); IR: (KBr, cm^{-1}): 3292, 2978, 1635, 1523, 1445, 1389, 1322, 1260, 1171, 1115, 1078, 818;^{1}H NMR (DMSO-d_6, δ ppm): 1.38 (t, 3H, -CH_3), 2.59 (s, 3H, Ar-CH_3), 4.10 (q, 2H, O-CH_2), 4.49 (s, 1H, NH), 7.01 (d, 2H, *J=8 Hz*, 2Ar-H), 7.84 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 303; (M+1) = 304.

5-(4-Methyl-2-(4-(alkyloxy)phenyl)thiazol-5-yl)-1,3,4-oxadiazol-2-amine (8a and 8b)

The solution of sodium bicarbonate (1.92 g, 0.0114 mol) in 10 mL of water was added to a solution of **3a** or **3b** (0.002 mol) in 20 mL dioxane at room temperature. After 10 minutes of stirring cyanogens bromide (0.266 g, 0.0025 mol) was added with stirring. After 3 h of stirring, the solid precipitates out filtered, dried and recrystallized from isopropyl alcohol to afford brown-colored product.

8a*:* Yield: 0.62 g (90 %); mp: 176-177 ºC; IR: (KBr, cm^{-1}): 3417, 3334, 3108, 3050, 2950, 1679, 1603, 1571, 1516, 1449, 1375, 1325, 1241, 1178, 1012 ;^{1}H NMR (DMSO-d_6, δ ppm): 0.91 (t, 3H, -CH_3), 1.39 (m, 4H, 2CH_2), 1.75 (quintate, 2H, CH_2), 2.67 (s, 3H, Ar-CH_3), 4.02 (t, 2H, O-CH_2), 7.01 (d, 2H, *J=8 Hz*, 2Ar-H), 7.29 (s, 2H, NH_2), 7.87 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 344; (M+1) = 345

8b*:* Yield: 0.58 g (96 %); mp: 230-231 ºC;IR: 3416, 3336, 3101, 1686, 1602, 1569, 1518, 1445, 1389, 1322, 1255, 1176, 1115, 1036 (KBr, cm^{-1});^{1}H NMR (DMSO-d_6, δ ppm): 1.38 (t, 3H, -CH_3), 2.67 (s, 3H, Ar-CH_3), 4.10 (q, 2H, O-CH_2), 4.46 (s, 2H, NH_2), 7.01 (d, 2H, *J=8 Hz*, 2Ar-H), 7.28 (s, 2H, NH_2), 7.87 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 302; (M+1) = 303.

(5-Amino-3-phenyl-1H-pyrazol-1-yl)(4-methyl-2-(4-(alkyloxy)-phenyl) thiazol-5-yl)methanone (9a, 9b)

A mixture of **3a** or **3b** (0.001 mol) and 3-oxo-3-phenylpropanenitrile (0.145 g, 0.001 mol) in ethanol was refluxed for 6 h. After completion of reaction, the reaction mixture was allowed to cooled and solvent was removed under reduced pressure. Resulting solid was purified by column chromatography using n-hexane and ethyl acetate (9:1).

9a*:* Yield: 0.360 g (80 %); mp: 144-145 ºC; IR: (KBr, cm^{-1}): 3492, 3383, 2933, 1654, 1603, 1483, 1366, 1329, 1262, 1170, 945 ; ^{1}H NMR (DMSO-d_6, δ ppm): 0.92 (t, 3H, -CH_3), 1.34-1.49 (m, 4H, 2CH_2), 1.79 (quintate, 2H, CH_2), 2.84 (s, 3H, Ar-CH_3), 4.05 (t, 2H, O-CH_2), 5.87 (s, 1H, Ar-H), 6.84 (s, 2H, NH_2), 7.01 (d, 2H, *J=8 Hz*, 2Ar-H), 7.41-7.50 (m, 3H, 3Ar-H), 7.88 (d, 2H, *J= 8 Hz*, 2Ar-H), 8.00 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 446;(M+1) = 447.

9b*:* Yield: 0.327 g (81 %); mp: 204-205ºC; IR: (KBr, cm^{-1}): 3416, 3225, 2988, 1663, 1602, 1479, 1367, 1328, 1255, 1171, 1042 , 892; ^{1}H NMR (DMSO-d_6, δ ppm): 1.41 (t, 3H, -CH_3), 2.84 (s, 3H, Ar-CH_3), 4.12 (q, 2H, O-CH_2), 5.88 (s, 1H, Ar-H), 6.88 (s, 2H, NH_2), 7.04 (d, 2H, *J=8 Hz*, 2Ar-H), 7.41-7.50 (m, 3H, 3Ar-H), 7.9 (d, 2H, *J= 8 Hz*, 2Ar-H), 8.00 (d, 2H, J= 8 Hz, 2Ar-H); M.W.= 404; (M+1) = 405.

(Ethyl 5-amino-1H-pyrazol-1-yl-4-carboxylate)(4-methyl-2-(4-(alkyloxy)phenyl)thiazol-5-yl)methanone (10a, 10b)

A mixture of **3a** or **3b** (0.001 mol) and ethyl (ethoxymethylene)cyanoacetate (0.169 g, 0.001 mol) in ethanol (10 mL) was heated under reflux for 10 hours. After completion of reaction the reaction mixture was allowed to cool and the solvent was reduced under reduced pressure. The resulting solid was purified by column chromatography using n-hexane and ethyl acetate (9:1).

10a: Yield: 0.360 g (81 %); mp: 173-174 ºC; IR: (KBr, cm^{-1}) 3458, 3334, 2975, 1687, 1670, 1612, 1553, 1479, 1362, 1329, 1287, 1253, 1174, 1108, 1049, 887; ^{1}H NMR ($CDCl_3$, δ ppm): 0.94 (t, 3H, -CH_3), 1.36 (t, 3H, -CH_3), 1.40-1.48 (m, 4H, 2CH_2), 1.81 (quintate, 2H, CH_2), 2.89 (s, 3H, Ar-CH_3), 4.02 (t, 2H, O-CH_2), 4.31 (t, 2H, O-CH_2), 6.91 (d, 2H, *J=8 Hz*, 2Ar-H), 7.24 (S, 2H, NH_2,), 7.75 (s, 1H, Ar-H), 8.00 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 442; (M+1) = 443.

10b: Yield: 0.345 g (86 %); mp: 205-206 ºC; IR: (KBr, cm^{-1}): 3449, 3336, 2978, 1691, 1669, 1602, 1557, 1361, 1328, 1288, 1249, 1171, 1104, 886; ^{1}H NMR ($CDCl_3$, δ ppm):1.36 (t, 3H, -CH_3), 1.44 (t, 3H, -CH_3), 2.89 (s, 3H, Ar-CH_3), 4.10 (q, 2H, O-CH_2), 4.31 (q, 2H, O-CH_2), 6.95 (d, 2H, *J=8 Hz*, 2Ar-H), 7.24 (s, 2H, NH_2), 7.75 (s, 1H, Ar-H), 8.00 (d, 2H, *J= 8 Hz*, 2Ar-H); M.W.= 400; (M+1) = 401.

CONCLUSION

A series of new thiazole derivatives was synthesized and screened for antiproliferative activity. Compounds **4a**, **5a**, **6a**, **7a**, **8a**, **7b** showed less activity while compound **9b** was found to show moderate activity (IC_{50}) as compare to standard anticancer drug Paclitaxel.

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