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SYNTHESIS AND CHARACTERIZATION OF NOVEL ADAMANTANE BASED THIAZOLE DERIVATIVES AS POTENTIAL ANTIBACTERIAL AGENTS

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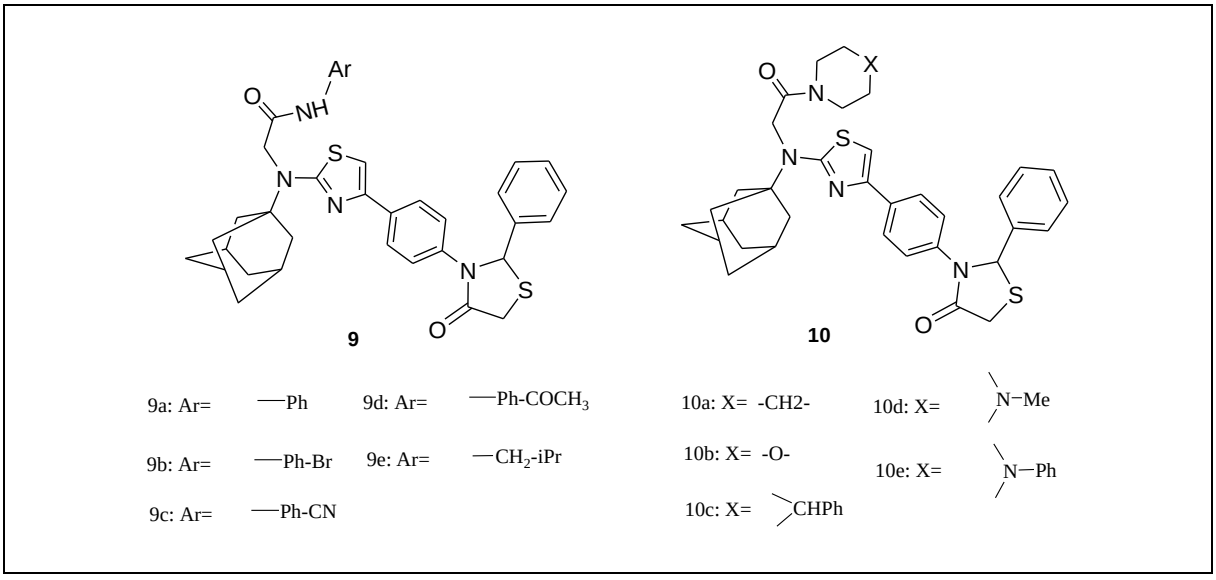


ABSCTRACT

Adamantane based thaizole derivatives is universal used in pharmaceuticals industries. A novel series of Adamantane containing thiazole derivatives (with different amides) are described, The method of chemical synthesis of these derivatives to gives excellent isolated yield and the structures of original compounds were confirmed by IR, NMR, Mass spectroscopy, and elemental analysis. All compounds were tested for antibacterial activity against S. Aureus, S. Pyogenes, E.Ccoli, P. Aeruginosa, S. Typhi and V.Parahaemolyticus.

Key words: Thiazole, Adanantane, Antibactrial activity, MIC

Introduction

Several Adamantane derivatives have long been diverse biological properties,mainaly as antiviral,anti bacterial,anti fungal,anti inflammatory agents.Admantyl derivatives were recently reported to possess 11ß HSD1 inhibitory activaties.In addition,1,2,3-triazole and 1,2,4-thiadiazole were reported constitute the pharmalogically active moiety of several compounds. On theses basis, new series of 1-Admantyl derivatives in which the adamantyl derivatives was attached to 1,2,4-triazole,1,2,4-triazolo[3,4-b][1,3,4]-thiadiazole or 1,3,4-thiadiazole nucleus have been synthesized as potential bio active agents.

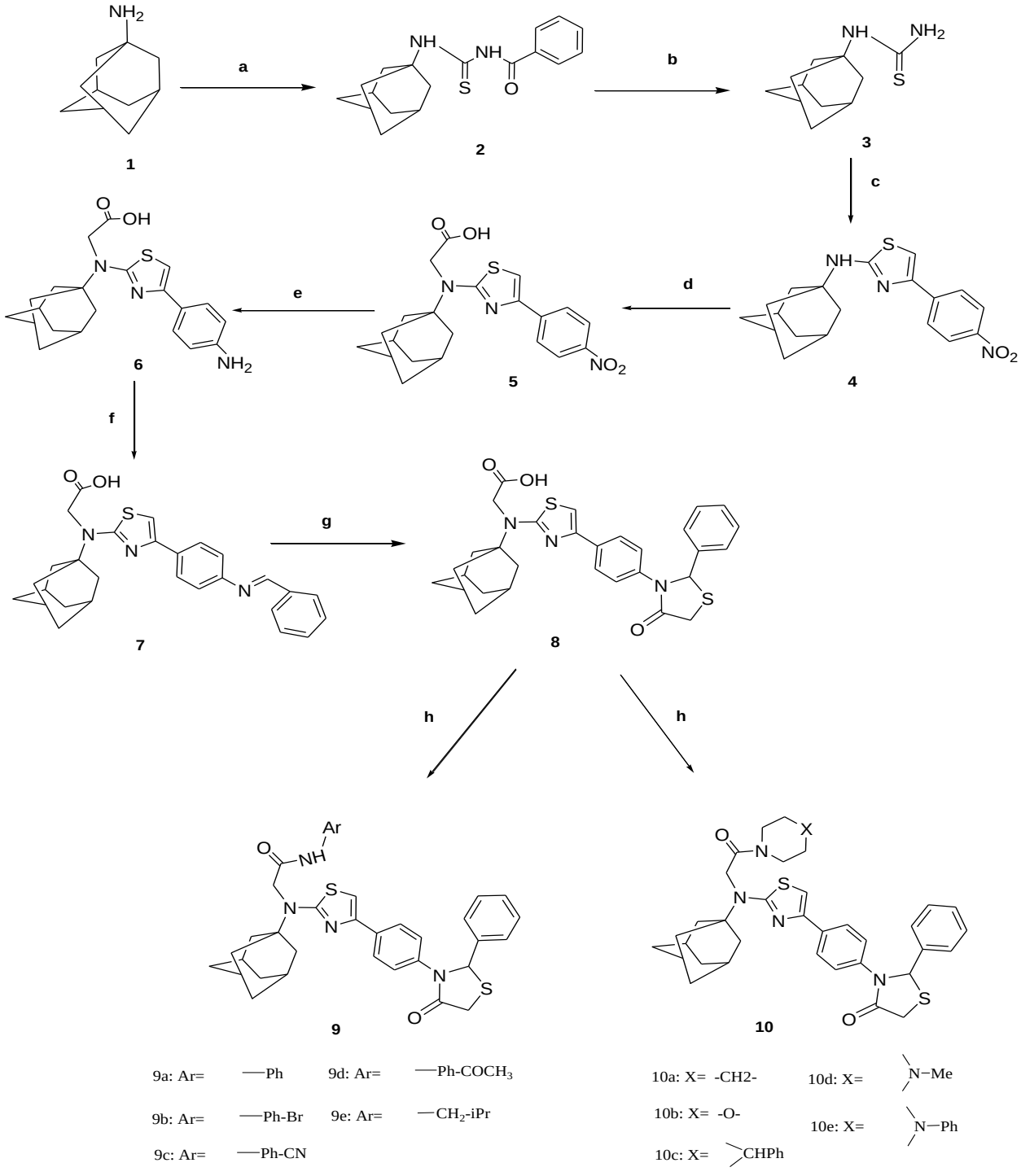
Adamantane based thiazole derivatives and its derivatives are very well known in medicinal and agricultural chemistry [1]. Among the various classes of heterocyclic compounds, thiazoles are particularly attractive since they are known to be the core structural unit of compounds with antibacterial, antifungal and anti-inflammatory activities [2-4]. They are also widely applicable for the treatment of hypertension [5] and HIV infections [6]. Numerous biologically active compounds have thiazoles as their common substructures. Compounds having 2-aminothiazole framework have been reported to show a variety of biological activities, including antibacterial activity [7]. In addition, molecules with this framework are known as adenosine receptor antagonists [8], Src family kinase inhibitors [9] and a novel class of ligands of estrogen receptors [10]. Fanetizole and sulfathiazole are well known examples of 2-aminothiazole class having anti-inflammatory and antibiotic activities respectively.

Recent studies have shown the synthesis of some new thiazole candidates as antimicrobial, antiviral and anticancer agents [11-14]. In recent literature, Feng-Chao Jiang at al [15] reported 2-aminothiazole analogues as potential neuroprotective agents for the treatment of neurological diseases. In addition Dorotea Rigamonti et al [16] reported 2-aminothiazole derivatives as modulators of transcriptional repression for treatment of huntington's disease [17].

Prompted by the observed biological activities of the above mentioned derivatives and in continuation of our ongoing studies on novel biologically active molecules, we have designed and synthesized some novel 2-aminothiazoles following Hantzsch's synthesis [18] as potential antibacterial agents.

Results and Discussion

Chemistry. The synthetic routs of compounds 9a-e and 10a-e are outlined in Scheme **1**. Adamantan-1-yl amine **1** was converted to 1-Adamantan-1-yl-3-benzoyl-thiourea **2** by treatment with benzoyl chloride and ammonium thiocyanate and then was, hydrolyzed by sodium methoxide in methanol in good yield to give Adamantan-1-yl-thiourea **3**.Compound **3** underwent Hantzsch thioazole synthesis with Bromo-1-(4-nitro-phenyl)-ethanone to give Adamantan-1-yl-[4-(4-nitro-phenyl)-thiazol-2-yl]-amine Compound **4** in good yield, Compound **4** was alkylated



Scheme-I. Reagent and condition**: (a)** NH_4SCN, Benzoyl chloride, Acetone, 30 min, Reflux., yield 78%.; **(b)** NaOMe, Methanol, RT,1 hr., yield 85%. **(c)** 2-Bromo-1-(4-nitro-phenyl)-ethanone, $NaHCO_3$ Sodium bicarbonate, reflux,2h,acetonitrile, yield 79%.; **(d) 1)** Ethyl

bromoacetate, NaH, DMF rt, 3 h. 2) Methanol,water,rt,5h,yield 78%.; **(e)** Iron Powder, Iron(III) chloride hexahydrate,Ethanol yield 86%.; **(f)** Benzaldehyde (Aromatic aldehyde),Ethanol yield 81%; **(g)** Mercapto-acetic , yield 78%.; **(h)** Ar-NH_2 or Cyclic amine ,EDCI,DIPEA,THF,rt,4-7 h., yield 69-82%.

using ethyl bromoacetate in presence of NaH in DMF to give ester derivative which was in-situ hydrolyzed to give acetic acid derivative **5** and further reduced by using Iron powder, Iron(III) chloride hexahydrate in Ethanol to obtained compound **6**.In next stage benzaldehyde attached on amino group to obtained (shift base) give (Adamantan-1-yl-{4-[4-(benzylidene-amino)-phenyl]-thiazol-2-yl}-amino)-acetic acid compound **7**.Cyclization of Compound **7** using mercapto acetic acid to give (Adamantan-1-yl-{4-[4-(2-oxo-5-phenyl-pyrrolidin-1-yl)-phenyl]-thiazol-2-yl}-amino)-acetic acid compound **8**.Amide coupling of compound **8** with various aromatic amines, as well as, secondary aliphatic amines was carried out in presence of EDCI and DIPEA to give the final compounds **9a-f** and **10a-e**.

Table 1

Physical characterization data of compounds **9a-e** and **10a-e**

Compound	Physical state	Time hours	Mp ^{0}C	Yield %	Molecular Formula/M.W
9a	White crystal	4	143-146	82	$C_{36}H_{36}N_4O_2S_2$ 620
9b	Off-white crystal	5	113-116	78	$C_{36}H_{35}BrN_4O_2S_2$ 699
9c	White crystal	5	110-112	73	$C_{37}H_{35}N_4O_2S_2$ 645
9d	White crystal	4	104-110	69	$C_{38}H_{38}N_4O_2S_2$ 662
9e	Off-White crystal	5	118-120	72	$C_{39}H_{42}N_4O_2S_2$ 662
10a	Off-White crystal	4	102-104	79	$C_{35}H_{40}N_4O_2S_2$ 612
10b	White crystal	4	98-101	76	$C_{34}H_{38}N_4O_2S_2$ 614
10c	White crystal	5	109-111	70	$C_{41}H_{44}N_4O_2S_2$ 688
10d	Off-white crystal	5	104-109	69	$C_{35}H_{41}N_4O_2S_2$

10e	White crystal	4	108-112	78	$C_{40}H_{43}N_4O_2S_2$ 627 689

The structures of all compounds 9a-f and 10a-e were determined using IR, 1H-NMR and EI-MS spectral data together with elemental analysis. IR spectra of compounds **9a-f** and **10a-e** showed absorption bands around 1637 - 1705 cm-1 regions resulting from C=O function of amide, while compound 8a-f showed one additional absorption bands around 3431 - 3451 cm-1 regions resulting from N-H function of -CONH. ^{1}H NMR spectra of compound 8a-f showed singlet proton at chemical shift around 10.38 - 10.64 ppm for PhNHCO- proton, while this proton was disappeared in compounds **9a-e**. In addition, the EI-MS spectra of **9a-f** and **10a-e** showed molecular ion peak (M+, 90%).

Biological Activities. The newly synthesized derivatives were evaluated for their *in vitro* antibacterial activity against E. Coli, P. Aeruginosa, S. Aureus, S. Pyogenes, S. typhi and V. parahaemolyticus by micro broth dilution methods[18]. The standard strains used for screening of antibacterial and antifungal activities were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. The MIC values are given in Table 1. The standard drug used for antibacterial activity was ciprofloxacin. Mueller Hinton Broth was used as nutrient medium for bacteria and sabouraud dextrose broth for fungal to grow. Inoculums size for test strain was adjusted to 108 CFU/ mL by comparing the turbidity. The serial dilutions were prepared in primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO-water (1:1 v/v) at a concentration of 2.0 mg/mL. In primary screening, 500 µg/mL, 250 µg/mL and 125 µg/mL concentrations of the synthesized drugs were taken. Data were not taken for the initial solution because of the high DMSO concentration (10%). The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100 µg/mL, 50 µg/ mL, 25 µg/mL, 12.5 µg/mL and 6.25 µg/mL concentrations. The inoculated wells were incubated overnight at 37°C in a humid atmosphere. The highest dilution showing at least 99% inhibition zone is taken as MIC.

Table 2

Antimicrobial activity data of newly synthesized compounds **9a-e** and **10a-e**

Compounds	Antibacterial MIC in µg/ml					
	E.coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*S. typhi* TCC98	*V.parahaemolyticus* MTCC 82
9a	62.5	100	200	250	100	500
9b	62.5	62.5	100	62.5	500	125
9c	100	50	62.5	250	250	500
9d	125	125	100	500	500	200
9e	500	1000	1000	125	50	200
10a	1000	500	500	1000	250	125
10b	50	125	50	125	1000	1000
10c	100	500	125	500	500	1000
10d	125	100	500	125	200	500
10e	500	125	50	250	500	500
Ciprofloxacin	25	25	50	50	-	-

The investigation of antibacterial screening revealed that all the newly synthesized compounds showed moderate to excellent inhibition. Compound **9a** shows very good activity against *E. coli* and *P. aeruginosa* while moderate activity against *S. typhi*. Compounds **9b** exhibit very good activity against all tested microorganism except *S. typhi*, while compound **9c** shows very good activity against *S. aureus* only. Compound **9d** and **9e** exhibit excellent activity against *P. aeruginosa* and *S. typhi* respectively only. Compound **10a** shows excellent activity against *E. coli* and *S. aureus*, while compound **10d** exhibits excellent activity against *P. aeruginosa* and *S. aureus*. Compound **10e** exhibits excellent activity against *S. aureus* only, while compounds **10b** and **10c** show moderate activity against one bacteria strain only.

Conclusions

Present study reports synthesis of novel (Adamantan-1-yl-{4-[4-(2-oxo-5-phenyl-pyrrolidin-1-yl)-phenyl]-thiazol-2-yl}-amino)-acetic acid and successively amide coupling with

different amines. The antibacterial screening of newly synthesize compounds was carried out against six different organism, and some of compounds exhibits moderate to excellent activity. Many known drugs posses 2-amino thiazole nucleus as active core and it well known to shows the potential pharmacological activities. The presence of diphenyl ether moiety is also instrumental in contributing to the net biological activity of a system. The antibacterial screening suggests that the newly synthesized compound **9b** having bromo substitution on phenyl ring exhibited good to excellent activity against all the tested microorganisms except S. typhi. Compound **9a** having phenyl ring only also exhibit very good activity against some organism.

Experimental Section

Melting points were determine with Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer PE-1600 FTIR spectrometer in KBr disc. 1H NMR spectra were recorded on a Varian spectrometer using TMS as an internal standard. EI-MS spectra were measured on a Waters mass spectrometer. Progress of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminum sheets (silica gel 60 F254) using a mixture of ethyl acetate and hexane (5:5 v/v). All of the solvents and materials were reagent grade and purified as required.

Synthesis of 1-Adamantan-1-yl-3-benzoyl-thiourea (2). To a suspension of NH_4SCN (3.14 g, 0.041 mol) in acetone (80 mL) was added slowly benzoylchloride (5.34 gm, 0.038 mol) under dry condition within 10 min. After completion of addition, reaction mixture was refluxed for 15 min. A solution of compound **1** (5.0 g, 0.033 mol) in acetone (30 mL) was added to above stirred suspension at such a rate that refluxes gently. After completion of addition reaction mixture was refluxed for 60 min. Reaction mixture was cooled and poured in water, resulting solid was filtered and washed with water. Solid was recrystalized in ethanol to give pure compound **2** as off-white solid, (8.1 gm) Yield 78%, mp 166 -168^{o}C. Anal. Calcd. for $C_{18}H_{22}N_2OS$: C, 68.75; H, 7.05; N, 8.91. Found: C, 68.78; H, 7.02; N, 8.89. 1H-NMR (400 MHz, DMSO-*d*6) δ 1.12-1.68 (m, 15H, , 3CH,6CH_2), 7.25-7.37 (m, 3H, ArH), 7.41-7.61 (m, 2H, ArH) 10.23 (s, 1H, NHCS), 11.59 (s, 1H, CONHCS). Mass spectrum (ES) *m*/*z* 315.4 (M+1).

Synthesis of Adamantan-1-yl-thiourea (3). To a suspension of compound 2 (8.0 g, 0.025 mol) in methanol (75 mL) was added sodium methoxide (2.02 g, 0.0375 mol), and stirred at room temperature for 1 h. Reaction mixture was poured in 5% aq. HCl and stirred for 10 min.Resulting solid was filtered, washed with water and suck dried. Solid was recrystallized from ethanol giving pure compound **3** as white solid,(4.55 g) Yield 85%, mp 177 - 180 ^{o}C. Anal. Calcd.for $C_{11}H_{18}N_2S$: C, 62.81; H, 8.63; N, 13.32. Found: C, 62.82; H, 8.64; N,13.34. 1H-NMR (400 MHz, DMSO-*d*6) δ 1.15-1.61 (m, 15H, 3CH, 6CH_2), 8.32 (s, 2H, NH_2), 10.21 (s, 1H, NHCS).Mass spectrum (ES) *m*/*z* 211.20 (M+1).

Synthesis of Adamantan-1-yl-[4-(4-nitro-phenyl)-thiazol-2-yl]-amine (4). A mixture of compound **3** (4.5 g,0.021 mol) 2-Bromo-1-(4-nitro-phenyl)-ethanone, (4.86 g, 0.022 mole) and sodium bicarbonate (3.77 g, 0.045 mol) in acetonitrile (60mL) was heated at 60 - 62 ^{o}C with stirring for 2 h. Reaction mixture was carefully poured in ice water (200 mL) and stirred for 15 min. Resulting solid was filtered and washed with water (100 mL) and hexane (40 mL). Solid was dried to give compound **4** as off-white solid,(5.85 g) Yield 79%, mp 198 - 201 ^{o}C. Anal. Calcd. for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.22; H, 5.98; N, 11.78.^{1}H-NMR (400 MHz, DMSO-*d*6) δ 1.18-1.59 (m, 15H, , 3CH,6CH_2), 4.85(s, 1H, CH), 7.38-7.48 (d, 2H, ArH), 7.51-7.73 (d, 2H, ArH), 10.15 (s, 1H, NH). Mass spectrum (ES) *m*/*z* 356.37 (M+1).

Synthesis of {Adamantan-1-yl-[4-(4-nitro-phenyl)-thiazol-2-yl]-amino}-acetic acid(5): A mixture of compound **4** (5.80g, 0.016 mol), anhydrous potassium carbonate (0.024 mol) and ethyl bromoacetate (2.94 g 0.018 mol) in Dimethyl formamide (30 ml) was stirred at 60 ^{0} C. for 3 h. Reaction mixture was cooled at 25-30^{0}C and add Methanol (30 ml) and 2N NaOH (20 ml) was added and stirred at 25-30^{0}C for 10 h. Reaction mixture was poured in ice water, washed with ethyl acetate (100 ml) and aqueous layer was acidified to pH-3 by addition of dil HCl. Solid product separated by filtration, washed with water and suck dried to give compound **5** with (5.32 g) 78 % yield. mp 223-229^{o}C. Anal. Calcd. for $C_{21}H_{23}N_2O_4S$: C, 61.00; H, 5.61; N, 10.16. Found: C, 60.98; H, 5.59; N, 10.18,^{1}H-NMR (400 MHz, DMSO-*d*6) δ 1.21-1.62 (m, 15H, 3CH,6CH_2), 4.78 (s, 1H, CH), 4.31 (s, 2H, CH_2), 7.41-7.49 (d, 2H, ArH), 7.52-7.69 (d, 2H, ArH), 12.52 (s, 1H, COOH). Mass spectrum (ES) *m*/*z* 412.32 (M-1).

Synthesis of {Adamantan-1-yl-[4-(4-amino-phenyl)-thiazol-2-yl]-amino}-acetic acid (6) A mixture of Compound **5** (5.3g ,0.012 mol) was dissolved in a mixture of ethanol (30 mL) and acetic acid (4.0 mL) in a RB flask (at least 100 mL) equipped with an efficient condenser, and the stirred mixture brought to a gentle reflux. Iron powder (5.24 g 0.093 mol) was added, followed immediately by Iron(III) chloride hexahydrate (0.57 g 0.002 mol). The mixture was refluxed for a further 3 hours, Reaction mixture was filtered through cellite bed and washed with methanol. To the filtrate was added ethyl acetate (100mL) and Water (100 mL), and the aqueous layer was repeatedly extracted with Ethyl acetate. The combined organic layers were dried and concentrated, Solid was recrystalized from rectified Ethanol to give compound **6** in (4.22g) 86 % yield. mp 205-209^{o}C. Anal. Calcd. for $C_{21}H_{25}N_3O_2S$: C, 65.77; H, 6.57; N, 10.96. Found: C, 65.75; H, 6.58; N, 10.99,^{1}H-NMR (400 MHz, DMSO-*d6*) δ 1.23-1.65 (m, 15H, 3CH,6CH_2), 4.77(s, 1H, CH), 4.28 (s, 2H, CH_2), 6.78 (s, 2H, Ar-NH). 7.38-7.45 (d, 2H, ArH), 7.51-7.67 (d, 2H, ArH), 12.55 (s, 1H, COOH). Mass spectrum (ES) *m*/*z* 384.33 (M+1).

Synthesis of (Adamantan-1-yl-{4-[4-(benzylidene-amino)-phenyl]-thiazol-2-yl}-amino)-acetic acid (7) A mixture of compound **6** (4.2 g 0.011 mol), add 50 ml ethanol, add benzaldehyde (0.011 mol) and rinse with 10 ml ethanol. The solution was reflux for 9 hours after completion of reaction cool to 25-30^{0} C and filter the solid and wash with ethanol giving product. Solid was recrystalized from ethanol diving compound **7** with (4.07g) 78% yield. mp 197-202^{o}C. Anal. Calcd. for $C_{28}H_{29}N_3O_2S$: C, 71.31; H, 6.20; N, 8.91. Found: C, 71.33; H, 6.25; N, 8.89,^{1}H-NMR (400 MHz, DMSO-*d6*) δ 1.17-1.57 (m, 15H, , 3CH,6CH_2), 4.68(s, 1H, CH), 4.22 (s, 2H, CH_2), 8.15 (s, 1H, =CH),7.38-7.41 (d, 4H, ArH), 7.55-7.69 (d, 4H, ArH), 12.52 (s, 1H, COOH). Mass spectrum (ES) *m*/*z* 472.55 (M+1).

(Adamantan-1-yl-{4-[4-(4-oxo-2-phenyl-thiazolidin-3-yl)-phenyl]-thiazol-2-yl}-amino)-acetic acid (8) A mixture Compound **7** (4.0 g 0.0084 mol), Mercapto-acetic acid (iii) (0.7 g, 0.0076 mol), in Toluene (100 ml) was stirred at 111 ^{0}C. for 8 h. Solvent was removed completely and water was added to residue, stirred for 25 min. Solid product was separated by filtration and washed with water and suck dry to give compound **8** with(3.70g) 80 % yield. mp 183-188^{o}C. Anal. Calcd. for $C_{30}H_{31}N_3O_3S_2$: C, 71.31; H, 6.20; N, 8.91. Found: C, 71.33; H, 6.21; N, 8.93,^{1}H-NMR (400 MHz, DMSO-*d6*) δ 1.22-1.55 (m, 15H, , 3CH,6CH_2), 4.71(s, 1H, CH), 4.13 (s, 2H,

CH_2), 3.75(t, 1H, CH,J=8.2 MHz) 2.11(t, 2H, CH,J=8.2 MHz), 7.05-7.11(m, 3H, ArH),7.21-7.29 (d, 4H, ArH), 7.53-7.71 (d, 2H, ArH), 12.51 (s, 1H, COOH). Mass spectrum (ES) *m*/*z* 546.66 (M+1).

General procedure for synthesis of compound 9a-e and 10a-e. A mixture of compound **8** (0.0068 mol), corresponding amine derivative (0.0068 mol), N,N-Diisopropyl ethyl amine (DIPEA) (0.0136 mol) and N, N-dimethyl amino pyridine 122.17(0.0007 mol) in THF (100ml) was stirred at 10^0 C. 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide **191.70** (EDCI) (0.0082 mmol) was added to above stirred solution portion wise. Reaction mixture was stirred at room temperature for 4-7 h. Solvent was evaporated under vacuum, water was added to residue and acidified to pH-6 by addition of dil. HCl. Solid separated was filtered, washed with water (100 ml) and suck dried. Solid was recrystallized from 95 % ethanol giving pure compound **9a-e** and **10a-e**.

2-(Adamantan-1-yl-{4-[4-(4-oxo-2-phenyl-thiazolidin-3-yl)-phenyl]-thiazol-2-yl}-amino)-N-phenyl-acetamide (9a) Obtained as white crystals, 82 % yield. mp 143-146^{o}C. Anal. Calcd. for $C_{36}H_{36}N_4O_2S_2$: C, 69.65; H, 5.84; N, 9.02. Found: C, 69.64; H, 5.86; N, 9.01, IR υ (cm^{-1}): 3433 (CON-H), 1672 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ 1.19-1.48 (m, 15H, , 3CH,6CH_2), 4.73(s, 1H, CH), 4.19 (s, 2H, CH_2), 4.13(t, 1H, CH,J=8.2 MHz),2.04 (t, 2H, CH,J=8.2 MHz), 6.92-6.94 (t,2H,ArH) 7.11-7.16 (d, 2H, ArH), 7.20-7.32 (m, 6H, ArH), 7.61-7.73 (dd, 4H, ArH), 10.40 (s, 1H, CONH). Mass spectrum (ES): m/z 621.05 (M+1).

2-(Adamantan-1-yl-{4-[4-(4-oxo-2-phenyl-thiazolidin-3-yl)-phenyl]-thiazol-2-yl}-amino)-N-(4-bromo-phenyl)-acetamide (9b) Obtained as off white crystals, 78 % yield. mp 113-118^{o}C. Anal. Calcd. for $C_{36}H_{35}$ Br $N_4O_2S_2$: C, 61.79; H, 5.04; N, 8.01. Found: C, 61.80; H, 5.05; N, 8.03, , IR υ (cm^{-1}): 3411 (CON-H), 1677 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ 1.11-1.38 (m, 15H, , 3CH,6CH_2), 4.63(s, 1H, CH), 4.17 (s, 2H, CH_2), 4.18(t, 1H, CH,J=8.2 MHz) ,2.02 (t, 2H, CH,J=8.2 MHz), 7.13-7.21 (m, 3H, ArH), 7.29-7.38 (m, 6H, ArH), 7.55-7.68 (dd, 4H, ArH), 10.35 (s, 1H, CONH). Mass spectrum (ES): m/z 700.44 (M+1).

2-(Adamantan-1-yl-{4-[4-(4-oxo-2-phenyl-thiazolidin-3-yl)-phenyl]-thiazol-2-yl}-amino)-N-(4-cyano-phenyl)-acetamide (9c) Obtained as white crystals, 73 % yield. mp 110-112^{o}C. Anal. Calcd. for $C_{37}H_{35}$ $N_5O_2S_2$: C, 68.81; H, 5.46; N, 10.84. Found: C, 68.80; H, 5.47; N, 10.85, IR υ

(cm^{-1}): 3429 (CON-H), 1681 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ 1.21-1.47 (m, 15H, , 3CH,6CH_2), 4.57(s, 1H, CH), 4.12 (s, 2H, CH_2), 4.09(t, 1H, CH,J=8.2 MHz) ,2.06 (t, 2H, CH,J=8.2 MHz), 7.11-7.17 (m, 3H, ArH), 7.22-7.31 (m, 6H, ArH), 7.49-7.57 (dd, 4H, ArH), 10.21 (s, 1H, CONH). Mass spectrum (ES): m/z 646.77 (M+1).

N-(4-Acetyl-phenyl)-2-(adamantan-1-yl-{4-[4-(4-oxo-2-phenyl-thiazolidin-3-yl)-phenyl]-thiazol-2-yl}-amino)-acetamide (9d) Obtained as white crystals, 69 % yield. mp 104-110^{o}C. Anal. Calcd. for $C_{38}H_{38}$ $N_4O_3S_2$: C, 68.85; H, 5.78; N, 8.45. Found: C, 68.86; H, 5.77; N, 8.44, IR υ (cm^{-1}): 3410 (CON-H), 1670(C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ 1.24-1.56 (m, 15H, , 3CH,6CH_2), 2.11 (s, 3H, CH_3) ,4.51(s, 1H, CH), 4.25 (s, 2H, CH_2), 4.11 (t, 1H, CH, J=8.2 MHz) 1.89(t, 2H, CH,J=8.2 MHz), 7.08-7.13 (m, 3H, ArH), 7.18-7.30 (m, 6H, ArH), 7.45-7.50 (dd, 4H, ArH), 10.11 (s, 1H, CONH). Mass spectrum (ES): m/z 663.66 (M+1).

2-(Adamantan-1-yl-{4-[4-(4-oxo-2-phenyl-thiazolidin-3-yl)-phenyl]-thiazol-2-yl}-amino)-N-(4-isopropyl-phenyl)-acetamide (9e) Obtained as off white crystals, 72 % yield. mp 118-120^{o}C. Anal. Calcd. for $C_{39}H_{42}N_4O_2S_2$: C, 70.66; H, 6.39; N, 8.45. Found: C, 70.61; H, 6.40; N, 8.44, IR υ (cm^{-1}): 3423 (CON-H), 1679(C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ 1.11-1.13 (s, 6H, ,2CH_3),1.24-1.56 (m, 15H, , 3CH, 6CH_2), 4.51(s, 1H, CH), 4.22 (s, 2H, CH_2), 4.11 (t, 1H, CH, J=8.2 MHz) 1.97 (t, 2H, CH,J=8.2 MHz), 1.75 (m, 1H, CH) 7.10-7.15 (m, 3H, ArH), 7.22-7.28 (m, 6H, ArH), 7.47-7.51 (dd, 4H, ArH), 10.18 (s, 1H, CONH). Mass spectrum (ES): m/z 663.88 (M+1).

3-(4-{2-[Adamantan-1-yl-(2-oxo-2-piperidin-1-yl-ethyl)-amino]-thiazol-4-yl}-phenyl)-2-phenyl-thiazolidin-4-one (10a) Obtained as off white crystals, 79 % yield. mp 102-104^{o}C. Anal. Calcd. For $C_{35}H_{40}N_4O_2S_2$: C, 68.59; H, 6.58; N, 9.14. Found: C, 68.58; H, 6.56; N, 9.16, IR υ (cm^{-1}): 1644 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ,1.21-1.42(m, 15H, , 3CH, 6CH_2), 1.76-1.81 (m, 6H, 3CH_2) 4.31(s, 1H, CH), 4.15 (s, 2H, CH_2), 3.97 (t, 1H, CH, J=7.2 MHz) ,3.25-3.27 (t, 4H, CH,) ,1.96 (t, 2H, CH,J=8.2 MHz), 7.12-7.14 (m, 3H, ArH), 7.23-7.26 (m, 2H, ArH),7.39-7.42 (dd, 4H, ArH),. Mass spectrum (ES): m/z 614.66 (M+1).

3-(4-{2-[Adamantan-1-yl-(2-morpholin-4-yl-2-oxo-ethyl)-amino]-thiazol-4-yl}-phenyl)-2-phenyl-thiazolidin-4-one (10b) Obtained as white crystals, 76 % yield. mp 98-101^{o}C. Anal. Calcd. for $C_{34}H_{38}N_4O_3S_2$: C, 66.42; H, 6.23; N, 9.11. Found: C, 66.40; H, 6.22; N, 9.10, IR υ

(cm^{-1}): 1641 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ,1.24-1.43(m, 15H, , 3CH, $6CH_2$), 4.39 (s, 1H, CH), 4.26 (s, 2H, CH_2), 4.10 (t, 1H, CH, J=7.2 MHz), 3.76-3.81 (m, 4H, $2CH_2$) ,3.29-3.31 (t, 4H, $2CH_2$) ,1.95(t, 2H, CH),2.02 (t, 2H, CH,J=8.2 MHz), 7.13-7.15 (m, 3H, ArH), 7.41-7.45 (dd, 4H, ArH),. Mass spectrum (ES): m/z 615.75 (M+1).

3-[4-(2-{Adamantan-1-yl-[2-oxo-2-(4-phenyl-piperidin-1-yl)-ethyl]-amino}-thiazol-4-yl)-phenyl]-2-phenyl-thiazolidin-4-one (10c) Obtained as white crystals, 70 % yield. mp 109-111^{o}C. Anal. Calcd. for $C_{41}H_{44}N_4O_2S_2$: C, 71.48; H, 6.44; N, 8.13. Found: C, 71.49; H, 6.45; N, 8.15, IR υ (cm^{-1}): 1639 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ,1.21-1.44(m, 15H, , 3CH, $6CH_2$), 4.88 (s, 1H, CH), 4.34 (s, 2H, CH_2), 4.21 (t, 1H, CH, J=7.2 MHz), 3.65-3.71 (m, 4H, $2CH_2$) ,1.90-1.93 (m, 4H, $2CH_2$,) 2.95 (m, 1H, CH), 2.05 (t, 2H, CH), 7.13-7.15 (m, 6H, ArH), 7.17-7.21 (m, 4H, ArH) 7.39-7.41 (dd, 4H, ArH),. Mass spectrum (ES): m/z 689.88 (M+1).

3-[4-(2-{Adamantan-1-yl-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amino}-thiazol-4-yl)-phenyl]-2-phenyl-thiazolidin-4-one (10d) Obtained as off-white crystals, 69 % yield. mp 104-109^{o}C. Anal. Calcd. for $C_{35}H_{41}N_5O_2S_2$: C, 66.95; H, 6.58; N, 11.15, Found: C, 66.96; H, 6.59; N, 11.16, IR υ (cm^{-1}): 1643 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ,1.26-1.39(m, 15H, , 3CH, $6CH_2$), 4.79 (s, 1H, CH), 4.44 (s, 2H, CH_2), 4.19 (t, 1H, CH, J=7.2 MHz), 3.62-3.66 (m, 4H, $2CH_2$) 2.85-2.89 (m, 4H, $2CH_2$), 2.12-2.14 (s, 3H, CH_3), 2.10 (t, 2H, CH,) 7.11-7.14 (m, 3H, ArH), 7.16-7.20 (m, 4H, ArH),7.42-7.44 (dd, 2H, ArH),. Mass spectrum (ES): m/z 628.44 (M+1).

3-[4-(2-{Adamantan-1-yl-[2-oxo-2-(4-phenyl-piperazin-1-yl)-ethyl]-amino}-thiazol-4-yl)-phenyl]-2-phenyl-thiazolidin-4-one (10e) Obtained as white crystals, 78 % yield. mp 108-112^{o}C. Anal. Calcd. for $C_{40}H_{43}N_5O_2S_2$: C, 69.63; H, 6.28; N, 10.15. Found: C, 69.65; H, 6.27; N, 10.17, IR υ (cm^{-1}): 1644 (C=O). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ,1.28-1.51(m, 15H, , 3CH, $6CH_2$), 4.81 (s, 1H, CH), 4.40 (s, 2H, CH_2), 4.22 (t, 1H, CH, J=7.2 MHz), 3.58-3.61 (m, 4H, $2CH_2$) ,3.90-3.93 (m, 4H, $2CH_2$,) 2.05 (t, 2H, CH), 7.14-7.16 (m, 6H, ArH), 7.19-7.23 (m, 4H, ArH) 7.43-7.46 (dd, 4H, ArH),. Mass spectrum (ES): m/z 690.87 (M+1).

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References

1. T.M. Potewar, S.A. Ingale, K.V. Srinivasan, Tetrahedron 63 (2007) 11066.
2. N. Hans, Swiss Patent 592103, 1977, Chem. Abstr. 1978, 88, 22886.
3. K.J. Wilson, C.R. Utig, N. Subhasinghe, J.B. Hoffman, N.J. Rudolph, R. Soll, C.J. Molloy, R. Bone, D. Green, J. Randall, Bioorg. Med. Chem. Lett. 11 (2001) 915.
4. K.D. Berlin, M.D. Herd, Proc. Okla. Acad. Sci. 71 (1991) 29.
5. W.C. Patt, H.W. Hamilton, M.D. Taylor, M.J. Ryan, D.G. Taylor, Jr., C.J.C. Connolly, A.M. Doherty, S.R. Klutchko, I. Sircar, B.A. Steinbaugh, B.L. Batley, C.A. Painchaud, S.T. Rapundalo, B.M. Michniewicz, S.C.J. Olson, J. Med. Chem. 35 (1992) 2562.
6. F.W. Bell, A.S. Cantrell, M. Hoegberg, S.R. Jaskunas, N.G. Johansson, C.L. Jordon, M.D. Kinnick, P. Lind, J.M. Morin, Jr., R. Noreen, B. Oberg, J.A. Palkowitz, C.A. Parrish, P. Pranc, C. Sahlberg, R.J. Ternansky, R.T. Vasileff, L. Vrang, S.J. West, H. Zhang, X.X. Zhou, J. Med. Chem. 38 (1995) 4929.
7. J.L. Kane, Jr., B.H. Hirth, B. Liang, B.B. Gourlie, S. Nahill, G. Barsomian, Bioorg. Med. Chem. Lett. 13 (2003) 4463.
8. J.E. Van Muijlwijk-Koezen, H. Timmerman, R.C. Vollinga, J.F. Von Drabbe Kunzel, M. De Groote, S. Visser, A.P. Ijzerman, J. Med. Chem. 44 (2001) 749.
9. J. Das, P. Chen, D. Norris, R. Padmanabha, J. Lin, R.V. Moquin, Z. Shen, L.S. Cook, A.M. Doweyko, S. Pitt, S. Pang, D.R. Shen, Q. Fang, H.F. de Fex, K.W. McIntyre, D.J. Shuster, K.M. Gillooly, K. Behnia, G.L. Schieven, J. Wityak, J.C. Barrish, J. Med. Chem. 49 (2006) 6819.
10. B.A. Fink, D.S. Mortensen, S.R. Stauffer, Z.D. Aron, J.A. Katzenellenbogen, Chem. Biol. 6 (1999) 205.
11. C.G. Bonde, N.J. Gaikwad, Bioorg. Med. Chem. 12 (2004) 2151-2161
12. G. Kucukguzel, A. Kocatepe, E. De-Clercq, F. Sahin, M. Gulluce, Eur. J. Med. Chem. 41 (2006) 353-359.

13. P. Vicini, A. Geroniki, K. Anastasia, M. Incerti, F. Zani, Bioorg. Med. Chem. 14 (2006) 3859-3864.
14. X. Zhou, L. Shao, Z. Jin, J.B. Liu, H. Dai, J.X. Fang, Heteroat. Chem. 18 (2007) 55-59.
15. W.T. Zhang, J.L. Ruan, P.F. Wu, F.C. Jiang, L.N. Zhang, W. Fang, X.L. Chen, J. Med. Chem. 52 (2009) 718–725.
16. Leone, S.; Mutti, C.; Kazantsev, A.; Sturlese, M.; Moro, S.; Cattaneo, E.; Rigamonti, D.; Contini, A. *Bioorg. Med. Chem. 2008,16,5695*
17. Hantzsch, A.; Weber, J. H. *Ber.* 1984, *20*, 3118.
18. Consiglio, G. A.; Failla, S.; Finocchiaro, P.; Giuffrida, C.; Recca, A. Phosphorus, Sulfure, and Silicon and the Related Element.2000,*165*, 7.