IJPSR (2015), Vol. 6, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 August, 2014; received in revised form, 16 February, 2015; accepted, 25 March, 2015; published 01 April, 2015

SYNTHESIS AND EVALUATION OF NOVEL THIOSEMICARBAZONE DERIVATIVES AS ANTICANCER AGENTS

Niharika Gokhale [1]* and Sanjay Jain [2]

Department of Pharmaceutical Sciences, Gyan vihar University [1], Jaipur Rajasthan, India
Smriti College of Pharmaceutical Education [2], Indore Madhya Pradesh, India

Keywords:

Adamantyl, Thiosemicarbazones Antiproliferative, Ribonucleotide Reductase.

Correspondence to Author:
Mrs. Niharika Gokhale

Research Scholar, Gyan vihar University, Jaipur, Rajasthan, India

E-mail: niharikasubhedar@gmail.com

ABSTRACT: Thiosemicarbazobes are the compounds that possess wide range of biological activities. Presently the areas in which thiosemicarbazones receiving more attention is its use against cancer. Reports from the SAR studies confirms that the thiosemicarbazones with heterocyclic moiety shows carcinogenic potency. These are potent ribonucleotide reductase inhibitor. Adamantyl derivatives is also having interesting biological properties and most promising towards anticancer activity. The value of adamantyl group in drug design is multidimensional. A novel series of compounds of thiosemicarbazones were prepared by conjugating adamantyl group and using aromatic substitution. The various substitutions on thiosemicarbazones were reported as anti cancer activity and adamantyl group also show antiproliferative activity against some cell lines, so in present work 20 compounds were prepared on the basis of best results of QSAR studies and they were screened for anticancer activity using cell line studies. The results were compared with standard drug doxorubicin, 3 compounds show more inhibitory action than standard drug.

INTRODUCTION: The cancer is one of the leading cause of deaths worldwide, in developing countries it is second leading cause of death while in developed countries it is leading cause of death. Till 2030 one among eight peoples of world will suffer from this disease[1]. The cancerous cells have property to proliferate uncontrollably and defensive apoptosis due to inactivation of tumor suppressive genes. The cells of cancer also invade easily and ability to metastasize in normal tissues [2-3]. Cancer is a complex disease with various genetic and epigenetic alterations. The all alteration also having much difference which is a challenge for synthesizing new analogues as anticancer agent [4]. Thiosemicarbazones is rapidly investigated compounds with different pharmacological actions [5]. The fused thiosemicarbazones show potential anticancer effects.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(4).1792-04

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(4).1792-04

The groups like benzopyridine, acetyl pyridine, metals like palladium, platinum and nickel when fused with thiosemicarbazone then they show cytotoxic activity against various solid cell tumors [6-9].

The substitution of adamantane and its derivative have been known for antiviral effect [10-14], anti microbial effect [15-18] and as anti inflammatory agent [17-21]. Substitution on thiopyrimidine, caboxamide and acetamide [22-24] shows potential cytotoxic effects.

So in the present work a novel series of compounds of thiosemicarbazones were prepared by conjugating Adamantyl Group and using aromatic Substitution.

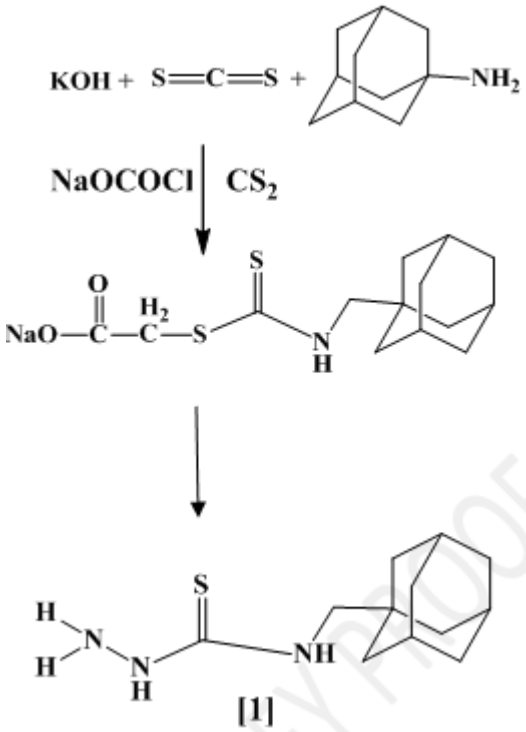
Experimental work:

Synthesis of Compounds:

For synthesis of aromatic/heterocyclic substituted thiosemicarbazone derivatives two step reaction was performed. Amantadine (0.01 mol), ethanolic solution of potassium hydroxide (1.68 gm 0.03 mol) were mixed together. The mixture was cooled below 10^{o}C and Carbon disulphide (1.8mL,

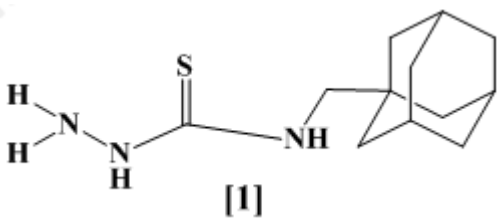
0.03mol) was added gradually with constant stirring d till CS_2 had completely dissolved. After standing for overnight, thioglycolic acid was obtained. It was shaked with a solution of sodium chloroacetate (1.0 mol) followed by hydrazine hydrate (5 ml, 100%) and was refluxed for two hours with continuous strirring. The filtrate was concentrated to half its initial volume and allowed to stand overnight, at 0^oC. Dry ether (20mL) was added and the yellow ppt. was filtered, washed with ether and dried and recrystallized from ethanol**. (Compound 1)**

Scheme:

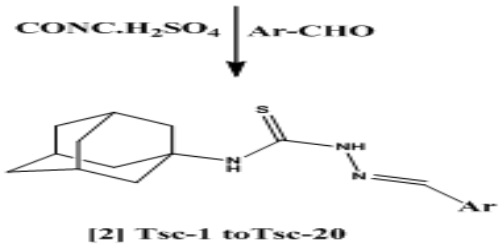


[1]

A mixture of carboxaldehyde (0.5mmol), thiosemicarbazide (0.55mmol) andconc. sulfuric acid (0.4mL) in 5mL of ethanol was heated under reflux for 4 h. The mixture was then cooled to room temperature, filtered and rinsed with cold solution of 50 % aqueous ethanol and diethyl ether respectively**.** By this scheme Compounds 2 Tsc-1 to Tsc-20 were prepared. (**Table 1**)



[1]



[2] Tsc-1 toTsc-20

AR-AROMATIC/HETEROCYCLIC SUBSTITUTIONS

Characterization of Synthesized Compounds:

General:

After synthesizing the different compounds, they were lyophilized and their % yields were calculated. The Melting points of all Compounds were determined by the capillary method using Melting Point Apparatus (Lab-Hosp, Mumbai). Triplicate observations were recorded for melting range determination.

NMR Analysis:

^1H NMR and C^{13} NMR spectra of all synthesized were recorded on Bruker (400 MHz) spectrometer. The samples were dissolved and measured in DMSO. Chemical shifts are reported as δ (ppm) relative to Tetramethylsilane [TMS] as a standard. Various shifts in the peaks were interpreted for different groups present in conjugated system.

ESI MASS Spectoroscopy:

The electrospray mass spectra were recorded on a MICROMASS QUATTRO II triple mass spectrometer. The samples (dissolved in suitable solvents such as methanol/acetonitrile/DMSO) were introduced into ESI source through a syringe pump at the rate of 5µl/min. The ESI capillary was set at 3.5 KV and the cone voltage was 40 V. The spectra were collected in 6S scans and print outs are averaged spectra of 6-8 scans. Spectra recorded at high mass units are computerized decovoluted.

Elemental Analysis:

The elemental analysis of Carbon, Hydrogen and other elements were performed by CHNS/O Elemental Analyzer (Perkin Elmer PE 2400). This analyzer was used for knowing concentration of C, H, N, S and O in newly synthesized compounds.

Cytotoxic Assay:

Cytotoxicity was evaluated by the 3-(4,5-dimethyl-2-thiazolyl)- 2,5-diphenyl-2H-tetrazolium bromide (MTT) assay which measures the cellular metabolic

viability[24]. The cells were cultured in 96-well plates and, 12 h after incubation, they were treated with different concentrations of test compounds.

Another group of cells was treated with the same concentrations of Doxorubicin as a standard drug. Compounds were previously dissolved in DMSO and the final concentrations were adjusted, through an 8-fold serial dilution, in DMEM in such manner that the final DMSO concentration was lower than 0.5%. After 48 h-treatment the cells were incubated with MTT (0.5 mg ml^{-1}), and formazan crystals were solubilised in DMSO Absorbance was measured in a microplate reader at 570 nm.

Tests using DMSO (0.5% in DMEM) as negative control were carried out in parallel. IC50 values were calculated as the concentration of compound that induced 50% of cytotoxicity. Data were presented as average ± standard deviation. All experiments were carried out in quadruplicates and repeated in at least three independent experiments with full agreement between the results. The statistical significance was assessed using Student's t-test ($p < 0.05$).

RESULTS AND DISCUSSION:

The prepared compounds were characterized for Melting point, different spectral analysis, and elemental analysis and *In- Vitro* Cell line studies.

General:

The melting point of different compounds with their molecular weight, Molecular formula and % yield was given in **Table 2**.

NMR, ESI Mass Spectroscopy and elemental analysis:

The data for ^{1}H NMR, ^{13}C NMR, ESI mass and elemental analysis were represented for different compounds as follows.

1. **(Tsc-1)** 1-(adamantan-1-yl)-3-[(E)-(1H-indol-3-ylmethylidene) amino] thiourea **^{1}H NMR (DMSO- d_6 , 400MHz): δ** 1.66-1.74(t, 6H, Adamantane-H), 2.13(s, 3H, Adamantane-H), 2.35 (s, 6H, Adamantane-H), 8.05(s, 1H, CH=N), 8.13(s,1H, NH),11.32 (s,1H, CS-NH), 9.84 (s,1H,NH-Indole),7.18 (s,1H,CH,Indole), 7.41(s,2H, Ar-CH), 7.47 (s,2H,Ar-CH) **^{13}C NMR: δ** 147.19 (C=N), 177.52(C=S), 28.5, 36.4, 39.8, 43.2 (Adamantane-C), 111.5 (Indole-C), 102.5, 119.3, 120.8, 124.7, 127.5, 135.5 (Ar-C). **ESI-MS m/z:** 353 (M^{+} +1) **Anal. Calcd for $C_{20}H_{24}N_4S$:** C, 68.14; H, 6.86; N, 15.89. S, 9.08 **Found:** C, 68.12; H, 6.56; N, 15.34; S, 9.24

2. **(Tsc-2)1-(adamantan-1-yl)-3-[(E)-(1H-1,3-benzoimidazol-2 yl methylidene) amino] thiourea ^{1}H NMR (DMSO- d_6 , 400MHz): δ** 1.66 (s, 6H, Adamantane-H), 2.08-2.21 (m, 9H, Adamantane-H), 8.02 (s, 1H, CH=N), 8.23(s,1H, NH),11.30 (s,1H, CS-NH), 9.84 (s,1H,NH-Indole),7.8 (s,1H,Imidazole), 7.5-7.98 (m,8H, Ar-CH). **^{13}C NMR: δ** 148.21 (C=N), 176.82 (C=S), 29.53, 37.41, 38.51, 40.53 (Adamantane-C), 121.12, 122.43, 123.90, 126.85, 130.56 (Ar-C). **ESI-MS m/z:** 355 (M^{+} +2). **Anal. Calcd for $C_{19}H_{23}N_5S$:** C, 64.56; H, 6.56; N, 19.81. S, 9.07 **Found:** C, 65.12; H, 6.48; N, 18.34; S, 9.04

3. **(Tsc-3) 3-(adamantan - 1-yl) – 1 - [(E)-{[3-(naphthalen-2-yl) phenyl] methylidene} amino] thiourea: ^{1}H NMR (DMSO- d_6, 400MHz): δ** 1.62-1.84 (m, 6H, Adamantane-H), 1.91 -2.06 (m, 9H, Adamantane-H), 8.04 (s, 1H, CH=N), 8.34 (s, 1H, NH), 11.53 (s, 1H, CS-NH), 6.98-8.63 (m, 11H, Ar-CH). **^{13}C NMR: δ** 150.63 (C=N), 178.65 (C=S), 27.42, 33.62, 34.91, 38.02 (Adamantane-C), 126.26, 128.13, 130.31, 131.34, 134.35, 135.32 (Ar-C). **ESI-MS m/z:** 440 (M^{+} +1) **Anal. Calcd for $C_{28}H_{29}N_3S$:** C, 76.42; H, 6.66; N, 9.55. S, 7.30 **Found:** C, 76.35; H, 6.74; N, 8.68. S, 8.98.

4. **(Tsc-4)1-(adamantan-1-yl) – 3 - [(E) - ({5-[3-(hydroxynitroso) phenyl] furan - 2 yl} methylidene) amino] thiourea**: **^{1}H NMR (DMSO- d_6 , 400MHz): δ** 1.68-1.86 (m, 6H, Adamantane-H), 2.06-2.23 (m, 9H, Adamantane-H), 8.23 (s, 1H, CH=N), 7.93 (s,1H, NH),11.63 (s,1H, CS-NH), 6.68 (s,1H, Furan-CH),7.04-7.15(m,4H, Ar-CH) **^{13}C NMR: δ** 146.53 (C=N), 174.32 (C=S), 28.58, 37.36, 38.54, 32.33 (Adamantane-C), 126.26, 128.13, 130.31, 131.14, 134.25, 135.82, 144.34 (Ar-C). **ESI-MS m/z:** 426 (M^{+} +2) **Anal. Calcd for $C_{22}H_{24}N_4O_3S$:** C, 62.34; H,

5.60; N, 13.10. S, 7.55 **Found:** C, 63.15; H, 6.04; N, 12.46. S, 7.72

5. **(Tsc-5)1-(adamantan-1-yl)-3-[(E) - {[2- (3-nitrophenyl)imidazo[1,2-a] pyridin-3-yl] methylidene} amino] thiourea**: **^{1}H NMR (DMSO- *d_6*, 400MHz): δ** 1.84-1.99 (m, 6H, Adamantane-H), 2.13-2.27 (m, 9H, Adamantane-H), 8.34 (s, 1H, CH=N), 7.52 (s, 1H, NH), 11.82 (s, 1H, CS-NH), 6.90-8.30 (m, 8H, Ar-CH) **^{13}C NMR: δ** 148.21 (C=N), 178.22 (C=S), 29.24, 36.42, 40.52, 42.34 (Adamantane-C), 112.35, 122.29, 126.64, 128.43, 141.28, 145.32, 148.28 (Ar-C). **ESI-MS m/z:** 475 (M^+ +1) **Anal. Calcd for $C_{25}H_{26}N_6O_2S$:** C, 63.24; H, 5.32; N, 17.62. S, 6.73 **Found:** C, 62.35; H, 6.18; N, 16.32. S, 6.72

6. **(Tsc-6) 3 - (adamantan-1-yl) - 1 -[(E)-[(2,4,5 trimethoxyphenyl) methylidene]amino] thiourea**: **^{1}H NMR (DMSO- *d_6* , 400MHz): δ** 1.68-1.88 (m, 6H, Adamantane-H), 1.98-2.10 (m, 9H, Adamantane-H), 8.18 (s, 1H, CH=N), 7.53 (s,1H, NH),11.38 (s,1H, CS-NH), 6.98 (s,2H, Ar-CH), 3.62 (s,3H,OCH_3), 3.72 (s,6H,OCH_3) **^{13}C NMR: δ** 146.09 (C=N), 178.60 (C=S), 27.61, 34.23, 35.24, 38, 98 (Adamantane-C), 98.47, 110.39, 112.46, 120.21, 122.26 (Ar-C), 55.32, 54.43, 56.18 (Methoxy-C) **ESI-MS m/z:** 404 (M^+ +1) **Anal. Calcd for $C_{21}H_{29}N_3O_3S$:** C, 62.51; H, 7.24; N, 10.41. S, 7.95 **Found:** C, 62.48; H, 6.39; N, 9.38. S, 7.98

7. **(Tsc-7) 3 - [(E)-{[(4S)-4- (acetylsulfanyl)-2-formylpyrazolidin-1-yl] methylidene} amino]-1-(adamantan-1-yl) thiourea: ^{1}H NMR (DMSO- *d_6* , 400MHz): δ** 1.78 (s, 6H, Adamantane-H), 2.08 (s, 9H, Adamantane-H), 8.29 (s, 1H, CH=N), 7.50 (s,1H, NH),10.82 (s,1H, CS-NH), 4.26-4.52 (m,4H, pyrazolidine-CH), 3.08 (s,3H,OCH_3), 8.82 (s,1H,CHO) **^{13}C NMR: δ** 143.60 (C=N), 179.50 (C=S), 28.60, 33.24, 35.24, 39, 98 (Adamantane-C), 60.82, 62.36, 57.43 (Pyrazolidine-C), 45.34 (Alkyl-C), 168.41 (N-C=0), 184.32(S-C=O) **ESI-MS m/z:** 410 (M^+ +1) **Anal. Calcd for $C_{18}H_{27}N_5O_2S_2$:** C, 52.79; H, 6.64; N, 17.10. S, 15.66 **Found:** C, 52.68; H, 6.75; N, 17.48. S, 14.64.

8. **(Tsc-8) 3-(adamantan-1-yl)-1-[(E)-{[3,4-bis(benzyloxy)phenyl]methylidene}amino]thiourea: ^{1}H NMR (DMSO- *d_6* , 400MHz): δ** 1.62-2.13 (m, 15H, Adamantane-H), 8.42 (s, 1H, CH=N), 7.52 (s,1H, NH),11.32 (s,1H, CS-NH), 4.23-4.26 (m,4H,O-CH_2),7.23-7.48 (m,6H, Ar-CH), 7.54-7.62 (m,7H, Ar-CH) **^{13}C NMR: δ** 144.25 (C=N), 175.69 (C=S), 28.63, 32.98, 36.18, 42.29 (Adamantane-C), 62.32 (CH_2), 111.82, 120.97,1 27.65, 128.86, 132.43, 136.57, 143.64, 146.32, 148.53 (Ar-CH) **ESI-MS m/z:** 527 (M^+ +2) **Anal. Calcd for $C_{32}H_{35}N_3O_2S$:** C, 73.10; H, 6.72; N, 7.96. S, 6.16 **Found:** C, 75.10; H, 6.85; N, 6.98. S, 6.58.

9. **(Tsc-9)3-(adamantan-1-yl)-1-[(E)-{[3-(3-hydroxyphenyl) phenyl]methylidene}amino] thiourea ^{1}H NMR (DMSO- *d_6*, 400MHz): δ** 1.72 (s, 6H, Adamantane-H), 2.16 (s, 9H, Adamantane-H), 8.34 (s, 1H, CH=N), 7.35 (s, 1H, NH), 11.33 (s, 1H, CS-NH), 7.40-7.58 (m, 8H, Ar-CH), 4.78 (s, 1H, OH) **^{13}C NMR: δ** 141.25 (C=N), 177.62 (C=S), 26.23, 31.82, 34.24, 40.30 (Adamantane-C), 126.35, 128.23, 130.37, 132.43, 148.74, 151.94 (Ar-CH) **ESI-MS m/z:** 405 (M^+), **Anal. Calcd for $C_{24}H_{27}N_3OS$:** C, 71.05; H, 6.71; N, 10.32. S, 7.92. **Found:** C, 70.14; H, 6.92; N, 10.58. S, 6.98.

10. **(Tsc-10) 3 - (adamantan-1-yl) – 1 - [(E)-({4-[(4fluorophenyl) methoxy] phenyl} methylidene) amino] thiourea: ^{1}H NMR (DMSO- *d_6*, 400MHz): δ** 1.76 (s, 6H, Adamantane-H), 2.08 (s, 9H, Adamantane-H), 9.32 (s, 1H, CH=N), 7.46 (s, 1H, NH), 11.72 (s, 1H, CS-NH), 6.23 (d, 2H, CH_2), 7.58-7.70 (m, 8H, Ar-CH). **^{13}C NMR: δ** 136.82 (C=N), 178.54 (C=S), 27.44, 32.58, 34.34, 39.45 (Adamantane-C), 64.42(O-CH_2), 114.58, 115.76, 124.28, 131.52, 133.49, 136.57, 138.49, 162.54 (Ar-CH) **ESI-MS m/z:** 438 (M^+ +1) **Anal. Calcd for $C_{25}H_{28}$ FN_3OS:** C, 68.64; H, 6.44; N, 9.62. S, 7.34. **Found:** C, 70.37; H, 6.52; N, 10.13. S, 7.18

11. **Tsc-11) 3-(adamantan-1-yl)-1-[(E)-[(2-amino-6-bromo - 4 - oxo- 4H -chromen-3-yl) methylidene] amino] thiourea ^{1}H NMR (DMSO- *d*$_6$, 400MHz): δ** 1.58-2.13 (m, 15H, Adamantane-H), 9.28 (s, 1H, CH=N), 7.28 (s, 1H, NH), 11.80 (s, 1H, CS-NH), 8.94 (s, 2H, NH_2), 7.64-7.82 (m, 3H, Ar-CH). **^{13}C NMR: δ** 134.92 (C=N), 177.98 (C=S), 24.68, 26.58, 29.82, 36.48 (Adamantane-C), 64.42(O-CH_2), 98.55, 117.28, 124.35, 126.13, 152.53, 154.65 (Chromyl-CH) **ESI-MS m/z:** 477 (M^+ +2) **Anal. Calcd for $C_{21}H_{23}BrN_4O_2S$:** C, 53.06; H, 4.86; N, 11.72. S, 6.76. **Found:** C, 55.06; H, 4.96; N, 11.76. S, 6.89.

12. **Tsc-12) 1-(adamantan – 1 - yl) -3-[(E)-{8-oxatricyclo [7.4.0.0 {2, 7}] trideca-1(13), 2, 4, 6, 9, 11-hexaen-4-ylmethylidene} amino] thiourea ^{1}H NMR (DMSO- *d*$_6$, 400MHz): δ** 1.68 (s, 6H, Adamantane-H), 2.14 (s, 9H, Adamantane-H), 9.32 (s, 1H, CH=N), 7.38 (s, 1H, NH), 11.52 (s, 1H, CS-NH), 8.94 (s, 2H, NH_2), 7.42-7.80 (m, 7H, Ar-CH). **^{13}C NMR: δ** 140.23 (C=N), 177.54 (C=S), 29.32, 32.45, 40.36, 41.42 (Adamantane-C), 98.75, 110.87, 121.57, 123.45, 132.61, 134.87, 136.93, 140.22, 143.28 (Aryl & Furan CH) **ESI-MS m/z:** 404 (M^+ +1) **Anal. Calcd for $C_{24}H_{25}N_3OS$:** C, 71.44; H, 6.28; N, 10.42. S, 7.92. **Found:** C, 70.89; H, 7.34; N, 10.58. S, 7.95.

13. **(Tsc-13) 1-(adamantan-1-yl)-3-[(E)-{[5-(dimethylamino) furan-2-yl] methylidene} amino] thiourea ^{1}H NMR (DMSO- *d*$_6$, 400MHz): δ** 1.63-2.02 (m, 15H, Adamantane-H), 8.92 (s, 1H, CH=N), 7.29 (s, 1H, NH), 11.32 (s, 1H, CS-NH), 6.82 (s, 1H, Furan-H), 7.23 (s, 1H, Furan-H), 2.54 (m, 6H, CH_3). **^{13}C NMR: δ** 138.56 (C=N), 178.24 (C=S), 30.23, 32.45, 34.36, 35.42 (Adamantane-C), 105.07, 111.31, 141.82, 145.68 (Furan CH), 38.4 (N-CH_3) **ESI-MS m/z:** 347 (M^+ +1) **Anal. Calcd for $C_{18}H_{26}N_4OS$:** C, 62.49; H, 7.56; N, 16.17. S, 9.25. **Found:** C, 61.87; H, 6.96; N, 16.87. S, 8.75.

14. **(Tsc-14) 3 - (adamantan-1-yl) – 1 - [(E)-{[3-cyano-4-(dimethylamino)-2-fluorophenyl] methylidene} amino] thiourea ^{1}H NMR (DMSO- *d*$_6$, 400MHz): δ** 1.63-1.82 (m, 6H, Adamantane-H),1.95- 2.34 (m, 9H, Adamantane-H), 9.02 (s, 1H, CH=N), 7.28 (s, 1H, NH), 11.45 (s, 1H, CS-NH), 3.52- 4.02 (m, 6H, CH_3), 7.92 (s, 2H, Ar-CH). **^{13}C NMR: δ** 148.54 (C=N), 174.25 (C=S), 28.32, 31.46, 32.32, 34.42 (Adamantane-C), 40.80 (N-CH_3) 98.75, 115.87(CN)89.43,96.28,110.26,113.48 (Aryl CH) **ESI-MS m/z:** 400 (M^+ +1) **Anal. Calcd for $C_{21}H_{26}FN_5S$:** C, 63.04; H, 6.56; N, 17.52. S, 8.03. **Found:** C, 63.18; H, 7.06; N, 17.98. S, 9.83.

15. **(Tsc-15) 3 - (adamantan-1-yl) - 1-[(E)-[(2-chloro-6-methylquinolin-3-yl) methylidene] amino] thiourea ^{1}H NMR (DMSO- *d*$_6$, 400MHz): δ** 1.56-1.78 (m, 6H, Adamantane-H),1.94- 2.32 (m, 9H, Adamantane-H), 8.43 (s, 1H, CH=N), 7.42 (s, 1H, NH), 11.23 (s, 1H, CS-NH), 2.42 (s, 3H, CH_3), 8.52-9.62 (m, 4H, Ar-CH). **^{13}C NMR: δ** 146.43 (C=N), 172.38 (C=S), 30.23, 36.59, 40.24, 41.32 (Adamantane-C), 20.48 (CH_3) 118.23, 122.12, 124.28, 126.31, 128.18, 132.57, 142.76, 151.63 (Aryl CH) **ESI-MS m/z:** 412 ($M^{+)}$ **Anal. Calcd for $C_{22}H_{25}ClN_4S$:** C, 63.94; H, 6.12; N, 13.72. S, 7.76. **Found:** C, 64.18; H, 7.01; N, 13.12. S, 7.08

16. **(Tsc-16) 3-(adamantan-1-yl)-1-[(E)-[(2-chloro-6-methylquinolin-3-yl) methylidene] amino] thiourea ^{1}H NMR (DMSO- *d*$_6$, 400MHz): δ** 1.71-2.01 (m, 6H, Adamantane-H), 2.12- 2.41 (m, 9H, Adamantane-H), 9.10 (s, 1H, CH=N), 7.49 (s, 1H, NH), 11.26 (s, 1H, CS-NH), 7.52-8.83 (m, 6H, Ar-CH). **^{13}C NMR: δ** 148.25 (C=N), 176.88 (C=S), 30.34, 32.36, 34.42, 41.08 (Adamantane-C), 119.56, 120.87, 121.52, 128.72, 130.65, 131.72, 144.81 (Aryl CH) **ESI-MS m/z:** 366 (M^+ +2) **Anal. Calcd for $C_{21}H_{24}N_4S$:** C, 69.25; H, 6.64; N, 15.37. S, 8.86. **Found:** C, 67.97; H, 6.85; N, 14.65. S, 8.64

17. **(Tsc-17) 1 - (adamantan-1-yl) – 3 - [(E)-[(1-methyl-1H-imidazol – 2 - yl) methylidene] amino] thiourea ^{1}H NMR (DMSO- *d*$_6$, 400MHz): δ** 1.72-2.03 (m, 15H, Adamantane-H), 8.83 (s, 1H, CH=N), 7.64 (s, 1H, NH), 11.53 (s, 1H, CS-NH), 3.48(s, 3H, CH_3) 6.84-7.16 (m, 2H, Ar-CH). **^{13}C NMR: δ** 143.36

(C=N), 174.25 (C=S), 30.07, 32.48, 34.36, 40.14 (Adamantane-C), 32.32(CH_3) 120.43, 130.26, 132.47 (Imidazole CH) **ESI-MS m/z:** 318 (M^+ +1) **Anal. Calcd for $C_{16}H_{23}N_5S$:** C, 60.53; H, 7.37; N, 22.05. S, 10.13. **Found** C, 60.38; H, 7.58; N, 22.87. S, 9.98

18. **(Tsc-18) 3 - (adamantan -1-yl) – 1 - [(E)-{[(2R,4R)- 2 – bromopiperidin - 4 - yl] methylidene} amino] thiourea ^{1}H NMR (DMSO- d_6, 400MHz): δ** 1.71 (s, 6H, Adamantane-H), 2.21 (s, 9H, Adamantane-H), 8.26 (s, 1H, CH=N), 7.42 (s, 1H, NH), 11.53 (s, 1H, CS-NH), 1.93(s, 1H, NH- Piperidine) 1.42-1.86 (m, 8H, Piperidine). **^{13}C NMR: δ** 144.35 (C=N), 175.23 (C=S), 28.46, 29.54, 30.88, 34.69 (Adamantane-C), 21.56, 23.56, 24.58, 26.76, 27.89 (Aryl CH) **ESI-MS m/z:** 400 (M^+ +1) **Anal. Calcd for $C_{17}H_{27}BrN_4S$:** C, 51.13; H, 6.83; N, 14.06. S, 8.04. **Found:** C, 51.26; H, 6.97; N, 15.86. S, 8.57

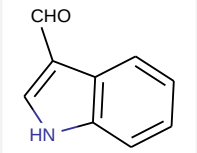
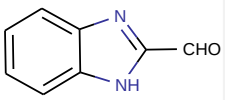
19. **(Tsc-19) 1-(adamantan-1-yl) – 3 - [(E)-[(4-bromothiophen-2-yl) methylidene] amino] thiourea ^{1}H NMR (DMSO- d_6, 400MHz): δ** 1.69-1.78 (m, 6H, Adamantane-H), 1.86- 2.02 (m, 9H, Adamantane-H), 8.43 (s, 1H, CH=N), 7.68 (s, 1H, NH), 11.62 (s, 1H, CS-NH), 6.88 (s, 2H, Thiophene). **^{13}C NMR: δ** 146.43 (C=N), 174.64 (C=S), 30.53, 32.34, 34.58, 41.08 (Adamantane-C), 113.43, 122.53, 124.63, 128.53 (Thiophene CH) **ESI-MS m/z:** 399 (M^+ +1) **Anal. Calcd for $C_{16}H_{20}BrN_3S_2$:** C, 48.24; H, 5.06; N, 10.57. S, 16.17. **Found:** C, 48.78; H, 5.76; N, 10.43; S, 15.23

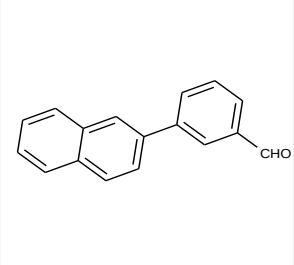
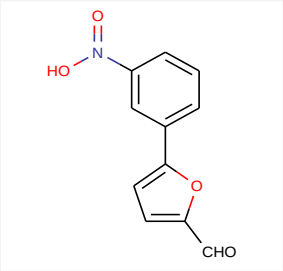
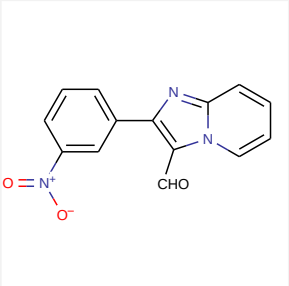
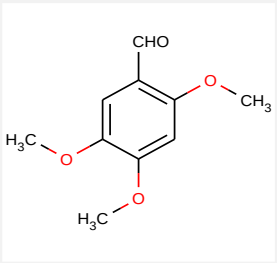
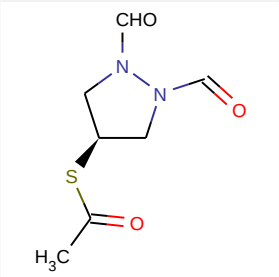
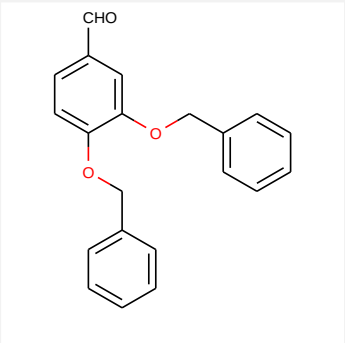
20. **(Tsc-20) 1-(adamantan-1-yl)-3-[(E)-[(3,5-dimethyl - 1,2-oxazol – 4 - yl) methylidene] amino] thiourea: ^{1}H NMR (DMSO- d_6, 400MHz): δ** 1.63-1.84 (m, 6H, Adamantane-H), 1.92 (s, 9H, Adamantane-H), 8.23 (s, 1H, CH=N), 7.32 (s, 1H, NH), 11.38 (s, 1H, CS-NH), 2.08 (s, 6H, CH_3) . **^{13}C NMR: δ** 146.25 (C=N), 172.98 (C=S), 29.43, 30.68, 31.42, 34.32 (Adamantane-C), 156.36 (CH_3), 100.46, 130.61, 146.34 (Oxazole C) **ESI-MS m/z:** 333 (M^+ +1) **Anal. Calcd for $C_{17}H_{24}N_4OS$:** C, 64.41; H, 7.28; N, 16.83; S, 9.64. **Found:** C, 63.48; H, 7.43; N, 15.88; S, 9.43.

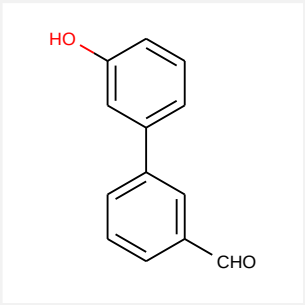
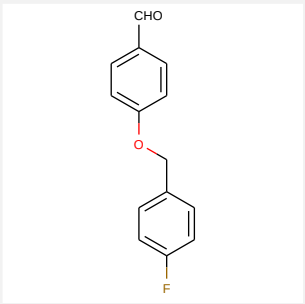
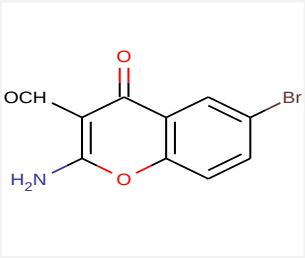
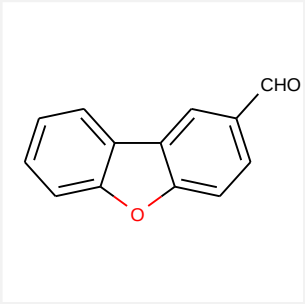
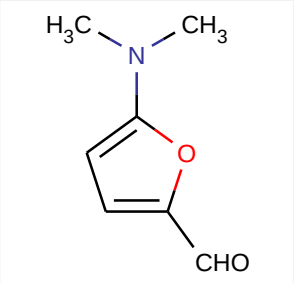
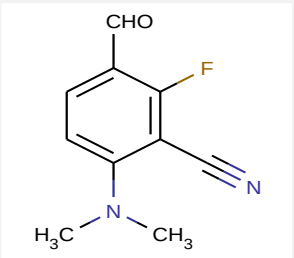
Cytotoxic Studies:

The % cell inhibitions of different compounds were estimated by MTT assay. The IC_{50} values of different batches were represented in table no 3-4. (Tsc- 1 to Tsc-10 in table 3 and Tsc- 11 to Tsc 20 in **Table 4**). The values were compared with standard drug doxorubicin and R^2 values were calculated. It was found that Amongst all the tested compounds Tsc-1, Tsc-2, Tsc-5, Tsc-7, Tsc-11, Tsc-12, Tsc-15, Tsc-16 and Tsc-18 gives highest potential effect on MCF-7 cell lines. Same ways compounds Tsc-3, Tsc-4, Tsc-13, Tsc-17 and Tsc-19 has comparable activity with Std. drug Doxorubicin as IC_{50} values were almost same. While IC_{50} values of Tsc-6, Tsc-8, Tsc-9, Tsc-10, Tsc-14 and Tsc-20 has less effective as compare to std. drug.

TABLE 1: HETEROCYCLIC SUBSTITUTION WITH THEIR CODE

Code	SUBSTITUTIONS	STRUCTURES
Tsc-1	**Ar(a)** 1H-indole-3-carbaldehyde	
Tsc-2	**Ar(b)** 1H-1,3-benzodiazole-2-carbaldehyde	

Tsc-3	**Ar(c)** 3-(naphthalene-2-yl)benzaldehyde	
Tsc-4	**Ar(d)** 5-[3-(Hydroxynitroso)phenyl]furan-2-carbaldehyde	
Tsc-5	**Ar(e)** 2-(3-nitrophenyl)imidazo[1,2]pyridine-3-carbaldehyde	
Tsc-6	**Ar(f)** 2,4,5-trimethoxybenzaldehyde	
Tsc-7	**Ar(g)** 4-(acetylsulfanyl)pyrazolidine-1,2-dicabaldehyde	
Tsc-8	**Ar(h)** 3,4-bis(benzyloxy)benzaldehyde	

Tsc-9	**Ar(i)** 3-(3-hydroxyphenyl)benzaldehyde	
Tsc-10	**Ar(j)** 4-[(4-fluorophenyl)methoxy]benzaldehyde	
Tsc-11	**Ar(k)** 2-amino-6-bromo-4-oxo-4H-chromene-3 carbaldehyde	
Tsc-12	**Ar(l)** 8-oxatricyclo{2,7}]trideca-1(13),2,4,6,9,11-hexaene-4-carbaldehyde	
Tsc-13	**Ar(m)** 5-(dimethylamino)furan-2-carbaldehyde	
Tsc-14	**Ar(n)** 6-(dimethylamino)-2-fluoro-3-formylbenzonitrile	

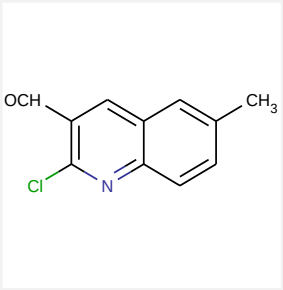
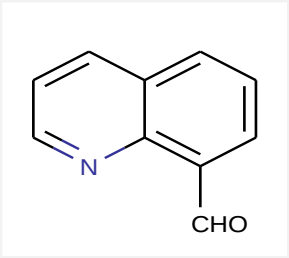
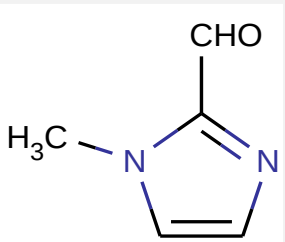
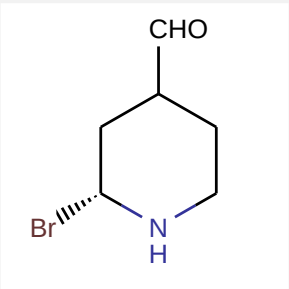
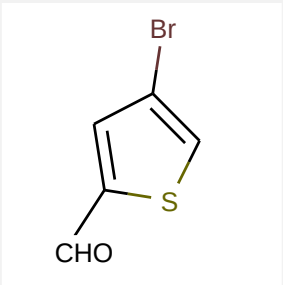
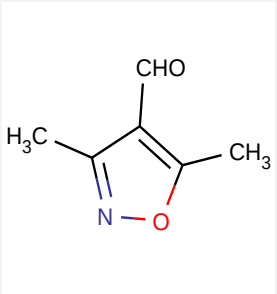
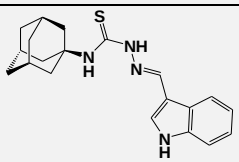
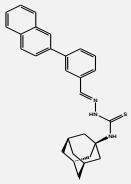
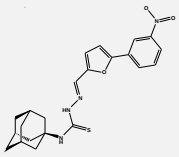
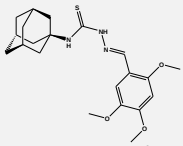
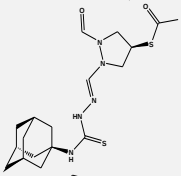
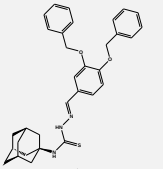
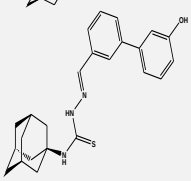
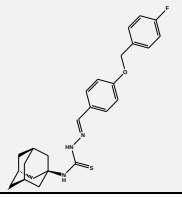
Tsc-15	**Ar(o)** 2-chloro-6-methylquinoline-3-carbaldehyde	
Tsc-16	**Ar(p)** quinoline-8-carbaldehyde	
Tsc-17	**Ar(q)** 1-methyl-1H-imidazole-2-carbaldehyde	
Tsc-18	**Ar(r)** 2-bromopiperidine-4-carbaldehyde	
Tsc-19	**Ar(s)** 4-bromothiophene-2-carbaldehyde	
Tsc-20	**Ar(t)** 3,5-dimethyl-1,2-oxazole-4-carbaldehyde	

TABLE 2: GENERAL PROPERTIES OF SYNTHESIZED COMPOUNDS

Compound Coding	Name of compound	Structure of compound	Molecular formula	Mole weight	Melting Point (℃)	Yield (%)
Tsc-1	1-(adamantan-1-yl)-3-[(E)-(1H-indol-3-ylmethylidene)amino]thiourea		$C_{20}H_{24}N_4S$	352.50	178-180	42
Tsc-2	1-(adamantan-1-yl)-3-[(E)-(1H-1,3-benzoimidazol-2-ylmethylidene)amino]thiourea		$C_{19}H_{23}N_5S$	353.17	238-240	51
Tsc-3	**1.** 3-(adamantan-1-yl)-1-[(E)-{[3-(naphthalen-2-yl)phenyl]methylidene}amino]thiourea		$C_{28}H_{29}N_3S$	439.21	110-112	69
Tsc-4	1-(adamantan-1-yl)-3-[(E)-({5-[3-(hydroxynitroso)phenyl]furan-2-yl}methylidene)amino]thiourea		$C_{22}H_{24}N_4O_3S$	424.16	162-164	54
Tsc-5	1-(adamantan-1-yl)-3-[(E)-{[2-(3-nitrophenyl)imidazo[1,2-a]pyridin-3-yl]methylidene}amino]thiourea		$C_{25}H_{26}N_6O_2S$	474.18	230-232	66
Tsc-6	3-(adamantan-1-yl)-1-[(E)-[(2,4,5-trimethoxyphenyl)methylidene]amino]thiourea		$C_{21}H_{29}N_3O_3S$	403.54	108-110	56
Tsc-7	3-[(E)-{[(4S)-4-(acetylsulfanyl)-2-formylpyrazolidin-1-yl]methylidene}amino]-1-(adamantan-1-yl)thiourea		$C_{18}H_{27}N_5O_2S_2$	409.16	186-188	62
Tsc-8	3-(adamantan-1-yl)-1-[(E)-{[3,4-bis(benzyloxy)phenyl]methylidene}amino]thiourea		$C_{32}H_{35}N_3O_2S$	525.24	190-192	53
Tsc-9	3-(adamantan-1-yl)-1-[(E)-{[3-(3-hydroxyphenyl)phenyl]methylidene}amino]thiourea		$C_{24}H_{27}N_3OS$	405.56	188-190	54
Tsc-10	3-(adamantan-1-yl)-1-[(E)-({4-[(4-fluorophenyl)methoxy]phenyl}methylidene)amino]thiourea		$C_{25}H_{28}FN_3OS$	437.57	149-151	67

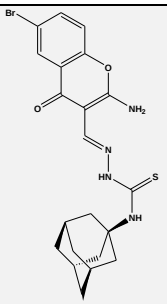
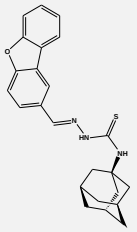
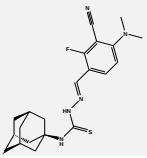
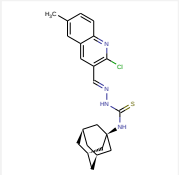
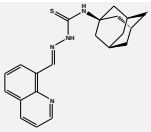
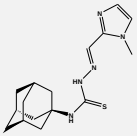
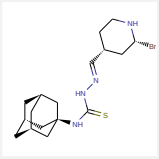
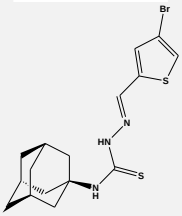
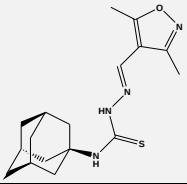
Tsc-11	3-(adamantan-1-yl)-1-[(E)-[(2-amino-6-bromo-4-oxo-4H-chromen-3-yl)methylidene]amino]thiourea		$C_{21}H_{23}BrN_4O_2S$	475.48	223-225	65
Tsc-12	1-(adamantan-1-yl)-3-[(E)-{8-oxatricyclo[7.4.0.0{2,7}]trideca-1(13),2,4,6,9,11-hexaen-4-ylmethylidene} amino] thiourea		$C_{24}H_{25}N_3OS$	403.53	217-218	66
Tsc-13	1-(adamantan-1-yl)-3-[(E)-{[5-(dimethylamino)furan-2-yl]methylidene}amino]thiourea		$C_{18}H_{26}N_4OS$	346.49	198-201	53
Tsc-14	3-(adamantan-1-yl)-1-[(E)-{[3-cyano-4-(dimethylamino)-2-fluorophenyl] methylidene} amino] thiourea		$C_{21}H_{26}FN_5S$	399.53	188-190	49
Tsc-15	3-(adamantan-1-yl)-1-[(E)-[(2-chloro-6-methylquinolin-3-yl) methylidene] amino] thiourea		$C_{22}H_{25}ClN_4S$	412.94	223-225	56
Tsc-16	3-(adamantan-1-yl)-1-[(E)-[(2-chloro-6-methylquinolin-3-yl)methylidene]amino]thiourea		$C_{21}H_{24}N_4S$	364.17	210-212	53
Tsc-17	1-(adamantan-1-yl)-3-[(E)-[(1-methyl-1H-imidazol-2-yl)methylidene]amino]thiourea		$C_{16}H_{23}N_5S$	317.49	200-202	41
Tsc-18	3-(adamantan-1-yl)-1-[(E)-{[(2R,4R)-2-bromopiperidin-4-yl]methylidene}amino]thiourea		$C_{17}H_{27}BrN_4S$	399.28	189-191	40
Tsc-19	1-(adamantan-1-yl)-3-[(E)-[(4-bromothiophen-2-yl)methylidene]amino]thiourea		$C_{16}H_{20}BrN_3S_2$	398.38	193-195	54
Tsc-20	1-(adamantan-1-yl)-3-[(E)-[(3,5-dimethyl-1,2-oxazol-4-yl) methylidene] amino] thiourea		$C_{17}H_{24}N_4OS$	332.46	210-212	62

TABLE 3: % CELL GROWTH INHIBITION OF TEST COMPOUNDS ON MCF-7 CELL LINE.

Conc. µM/ml	Log conc.	% Cell Inhibition										
		Tsc-1	Tsc -2	Tsc -3	Tsc -4	Tsc -5	Tsc -6	Tsc -7	Tsc -8	Tsc -9	Tsc -10	Std. Doxorubicin
0.01	-2.29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.03
0.02	-1.82	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-4.06	0.00	11.25
0.05	-1.34	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-9.26	-5.08	15.26
0.14	-0.86	0.00	18.00	10.10	5.23	12.82	00.00	08.09	0.00	-9.26	-3.18	20.31
0.41	-0.39	0.00	30.00	15.26	7.34	19.53	11.44	10.97	2.23	5.00	5.00	27.46
1.23	0.09	42.83	58.56	20.64	15.27	27.82	16.35	23.34	7.44	6.26	6.00	36.17
3.70	0.57	72.70	62.37	32.83	38.22	35.36	20.58	46.41	20.10	5.00	11.58	40.87
11.11	1.05	85.92	80.32	48.70	42.44	45.15	33.52	58.36	22.66	60.06	56.12	49.03
33.33	1.52	90.16	70.38	56.84	54.18	58.72	48.61	64.74	24.33	83.76	63.36	61.52
100.00	2.00	70.64	90.64	68.92	68.12	60.38	55.47	72.48	46.01	56.31	69.56	78.24
IC_{50} (µM/ml)		**1.463**	**1.317**	**3.499**	**3.203**	**1.337**	**4.532**	**2.354**	**5.629**	**5.889**	**6.673**	**3.710**
R^2		**0.949**	**0.920**	**0.984**	**0.985**	**0.980**	**0.975**	**0.995**	**0.930**	**0.836**	**0.985**	**0.919**

TABLE 4: % CELL GROWTH INHIBITION OF TEST COMPOUNDS ON MCF-7 CELL LINE

Conc. µM/ml	Log conc.	% Cell Inhibition										
		Tsc -11	Tsc -12	Tsc -13	Tsc -14	Tsc -15	Tsc -16	Tsc -17	Tsc -18	Tsc -19	Tsc -20	Std. Doxorubicin
0.01	-2.29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.03
0.02	-1.82	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	11.25
0.05	-1.34	-10.10	0.00	0.00	0.00	0.00	0.00	-7.62	-5.00	0.00	-2.62	15.26
0.14	-0.86	14.62	0.00	4.18	0.00	0.00	0.00	5.34	10.89	5.28	6.29	20.31
0.41	-0.39	29.65	15.97	6.88	0.00	0.00	18.54	5.90	18.09	5.98	7.49	27.46
1.23	0.09	34.43	29.65	13.74	18.08	29.49	23.38	12.21	28.08	13.34	15.32	36.17
3.70	0.57	48.33	35.38	28.52	36.38	39.71	38.67	25.53	48.65	27.34	34.21	40.87
11.11	1.05	58.56	42.36	47.34	67.76	45.35	46.45	48.65	55.76	49.58	46.38	49.03
33.33	1.52	65.21	64.68	55.21	90.69	56.08	66.83	52.45	58.85	54.31	58.90	61.52
100.00	2.00	72.45	70.31	69.03	62.59	68.63	70.39	58.43	65.86	70.43	69.91	78.24
IC_{50} (µM/ml)		**1.289**	**2.562**	**3.452**	**4.452**	**2.889**	**2.684**	**3.826**	**1.262**	**3.471**	**4.137**	**3.710**
R^2		**0.964**	**0.968**	**0.994**	**0.929**	**0.963**	**0.977**	**0.980**	**0.986**	**0.991**	**0.993**	**0.9197**

CONCLUSION: In present work, 20 compounds of thiosemicarbazones were synthesized by conjugating Admantyl Group and using aromatic Substitution. The synthesized compounds were characterized on basis of Melting point, ^{1}H- NMR, ^{13}C NMR, ESI- mass and elemental analysis. The results of cytotoxic assay prove that some compounds shows more effective than standard drug. So this fusion of thiosemicarbazones with adamantyl group may be used further for synthesizing new anticancer compounds.

REFERENCES:

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J. Clin 2011; 61: 69–90.
2. Hiss DC and Gabriels GA: Implications of endoplasmic reticulum stress, the unfolded protein response and apoptosis for molecular cancer therapy. Part I: targeting p53, Mdm2, GADD153/CHOP, GRP78/BiP and heat shock proteins. Expert Opin. Drug Discov 2009; 4: 799–821.
3. Hanahan D and Weinberg RA: The hallmarks of cancer. Cell 2000; 100 (1); 57–70.
4. Wang Z and Sun Y: Targeting p53 for Novel Anticancer Therapy. Translational Oncology 2010 ; 3(1) : 1-12.
5. Beraldo H and Gambino D: The wide pharmacological versatility of semicarbazones, thiosemicarba-zones and their metal complexes. Mini-Rev. Med. Chem 2004; 4: 31-39.
6. Quiroga AG, Perez JM, Montero EI, Masaguer JR, Alonso C and Navarro- Ranninger CJJ: Palladated and platinated complexes derived from phenylacetaldehyde thiosemicarbazone with cytotoxic activity in cis-DDP resistant tumor cells. Formation of DNA interstrand cross-links by these complexes. Inorg. Biochem 1998; 70: 117-123.
7. Quiroga AG and Navarro-Ranninger C: Contribution to the sar field of metallated and coordination complexes studies of the palladium and platinum derivatives with selected thiosemicarbazones as antitumoral drugs. Coord. Chem. Rev 2004; 248: 119-133.
8. Bal T, Atasever B, Solakoglu Z, Erdem-Kuruca S and Ulkuseven B: Synthesis, characterisation and cytotoxic properties of the N1, N4-diarylidene-S-methyl-thiosemicarbazone chelates with Fe (III) and Ni (II). Eur. J. Med. Chem 2007; 42: 161-167.
9. Soares MA, Lessa JA, Mendes IC, Da Silva JC, Dos Santos RG, Salum LB, Daghestani H, Andricopulo AD, Day BW, Vogt A, Pesquero JL, Rocha WR and Beraldo H:

N[4]-Phenyl-substituted 2-acetylpyridine thiosemi carbazones: Cytotoxicity against human tumor cells, structure activity relationship studies and investigation on the mechanism of action. Bioorg. Med. Chem 2012; 20: 3396–3409.

10. Vernier VG, Harmon JB, Stump JM, Lynes TE and Marvel JP: The toxicologic and pharmacologic properties of amantadine hydrochloride.Toxicol. Appl. Pharmacol 1969; 15: 642-665.
11. Rabinovich S, Baldini JT and Bannister R: The therapeutic efficacy of rimantadine HCl in a naturally occurring influenza A2 outbreak. Am. J. Med. Sci 1969; 257: 328-335.
12. Scherm A and Peteri D: Antiviral 1-(aminoethoxyacetylamino) adamantanes. Chem. Abstr 1971; 74: 99516.
13. Stylianakis I, Kolocouris A, Kolocouris N, Fytas G, Foscolos GB, Padalko E, Neyts J and De Clerq E: Spiro[pyrrolidine-2,2'-adamantanes]: synthesis, anti-influenza virus activity and conformational properties. Bioorg. Med. Chem. Lett 2003; 13: 1699-1703.
14. Kolocouris N, Foscolos GB, Kolocouris A, Marakos P, Pouli N, Fytas G, Ikeda S and DeClercq E: Synthesis and antiviral activity evaluation of some aminoadamantane derivatives. J. Med. Chem 1994; 37: 2896-2902.
15. Orzeszko A, Kamin´ska B and Starosciak BJ: Synthesis and antimicrobial activity of new adamantane derivatives III. IL Farmaco 2002; 57: 619-624.
16. Antoniadou-Vyza E, Tsitsa P, Hytiroglou E and Tsantili-Kakoulidou A: New adamantan-2-ol and adamantan-1-methanol derivatives as potent antibacterials. Synthesis, antibacterial activity andlipophilicity studies. Eur. J. Med. Chem 1996; 31:105-110.
17. El-Emam AA: Synthesis and Biological Activity of Certain 1-Adamantyl Derivatives. Chin. Pharm. J 1990; 42: 309-315.
18. El-Emam AA and Ibrahim TM: Synthesis and anti-inflammatory and analgesic activity of some 3-(1-adamantyl)-4-substituted-5-mercapto-1, 2, 4-triazoles. Arzneim. Forsch. /Drug Res 1991; 41: 1260-1264.
19. Al-Deeb AA, Al-Omar MA, El-Brollosy NR, Habib, EE, Ibrahim, TM and El-Emam AA: Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]acetic acids, 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]propionic acids and related derivatives. Arzneim.-Forsch./Drug Res 2006; 56: 40-47.
20. Georgiev VS, Bennett GA, Radov LA, Kamp, DK and Trusso LA: Synthesis and biological activity of 2-adamantanone oxime carbamate derivatives. Arch. Pharm 1987; 320: 465-470.
21. Su, X.; Halem, H.A.; Thomas, M. P.; Moutrille, C.; Culler, M. D.; Vicker, N.; Potter, V. L. B. Adamantyl carboxamides and acetamides as potent human 11β-hydroxysteroid dehydrogenase type 1 inhibitors. Bioorg. Med. Chem 2012; 20: 6394–6402.
22. Sittukul P: Synthesis and structure activity relationship of 2- thiopyrimidine-4-one analogs as antimicrobial and anticancer agents. European Journal of Medicinal Chemistry 2011; 46: 738-742.
23. Plumb JA, Miloroy R and Kaye SB: Effects of the pH dependence of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide-formazan absorption on chemosensitivity determined by a novel tetrazolium-based assay. Cancer Res 1989; 49: 4435-4440.
24. Soares MA, Lessa JA, Mendes IC, Da Silva JG, dos Santos RG, Salum LB, Daghestani H, Andricopulo AD, Day BW and Vogt A: Phenyl- substituted 2 acetyl pyridine thiosemicarbaznes: cytotoxicity against human tumor cells, structure –activity relationship studies and investigation on the mechanism of action. Bioorg. Med. Chem 2012; 20: 3396–3409.

How to cite this article:
Gokhale N and Jain S: Synthesis and Evaluation of Novel Thiosemicarbazone Derivatives as Anticancer Agents. Int J Pharm Sci Res 2015; 6(4): 1792-04.doi: 10.13040/IJPSR.0975-8232.6(4).1792-04.