Scientia Pharmaceutica (Sci. Pharm.) **71**, 195–209 (2003)

Adamantane Derivatives, Part III* : Synthesis of Some Aminoadamantanes as Novel Antitumor Agents

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Abstract

New series of 1-(1-adamantyl)semicarbazide **3a**, 1-(1-adamantyl)-4-(4-substituted phenyl)semicarbazides **3b-e**, 1-(1-adamantyl)-3-(substituted amino-sulfonyl)ureas **5a-g**, 1-(1-adamantyl)-4-(1-adamantylamino-methylene)-semi-carbazide **7**, 1-(1-adamantyl)-4-(1-adamantylcarbonylmethyl)semicarbazide **8**, 1-(1-adamantyl)-4-acylsemicarbazides **9a-d** and 1-(1-adamantyl)-4-(1-adamantylamino-carbonyl)thiosemicarbazide **10** have been synthesized and tested for their antitumor activity. Among them, compounds **3a**, **5a**, **9a**, and **9d** exhibited a broad spectrum antitumor activity with full panel (MG-MID) median growth inhibition (GI_{50}) of 10.5, 12.0, 6.8 and 5.5 μM respectively. In addition, compounds **3a**, **3c**, and **5d** proved to be of moderate selectivity toward leukemia cell lines with ratios of 3.0, 3.9 and 4.0 respectively. Moreover, compounds **5a** and **5g** showed moderate selectivity toward melanoma cell lines with ratios of 3.6 and 4.4 respectively. The detailed synthesis, specroscopic and biological data are reported.

Keywords

Adamantyl Semicarbazides, Adamantyl Sulfonylureas and, Adamantyl Thiosemicarbazide, Synthesis, Antitumor Evaluation.

Introduction

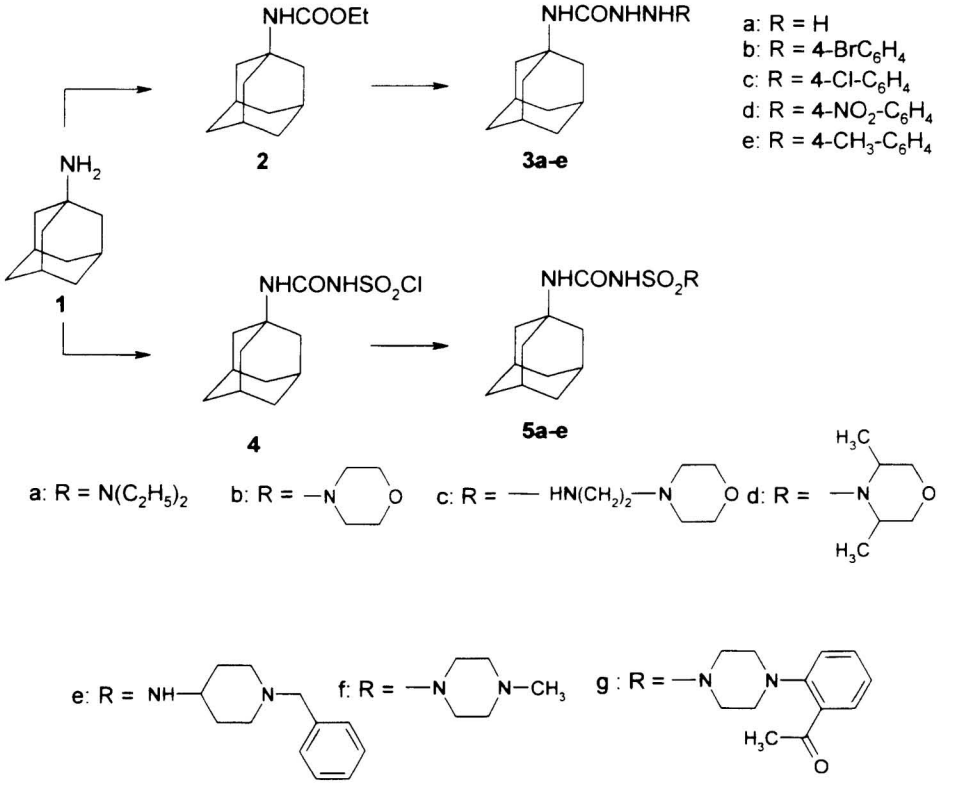
Adamantane nucleus has received considerable attention of medicinal chemists where many of its substituted derivatives have pronounced anticancer[1-8] and antiviral activities[1,9-12]. Recently, we reported on the antitumor and antiviral activity of a new series of adamantanes[12,13]. As a continuation to our previous efforts aiming to locate new active adamantane containing antitumor agent(s) with enhanced potency, a new series of 1- (1- adamantyl)semicarbazide **3a**, 1-(1-adamantyl)-4-(4-substituted phenyl)semicarbazides **3b-e**, 1-(1-adamantyl)-3-(substituted aminosulfonyl)ureas **5a-g**, 1-(1-adamantyl)-4-(1-adamantylaminomethylene)-semicarbazide **7**, 1-(1- adamantyl)-4-(1-adamantylcarbonylmethyl) semicarbazide **8**, 1-(1-adamantyl)-4-acylsemicarbazides **9a-d** and 1-(1-adamantyl)-4-(1-adamantylaminocarbonyl)thiosemicarbazide **10** have been synthesized where some functional groups which are believed to contribute to the antitumor activity such as, sulfonylurea, semicarbazides and thiosemicarbazides moieties[8,14-18]were incorporated in order to detect their effect with regard to activity.

Result and Discussion

Scheme 1 outline the synthetic pathway used to obtain compounds **3a-e** and **5a-g**, 1-(Ethoxycarbonylamino)adamantane **2** was obtained via the reaction of 1-aminoadamantane **1** with ethyl chloroformate in dry toulene and in the presence of triethylamine. Upon treatment of compound **2** with either hydrazine hydrate or the appropriate phenylhydrazine, this afforded the corresponding 1-(1-adamantyl)semicarbazide **3a** and 1-(1-adamantyl)-4-(4-substituted phenyl) semicarbazides **3b-e** respectively. The reaction of chlorosulfonyl isocyanate with 1-aminoadamantane **1** in dry toluene yielded 1-(1-adamantyl)-3- chlorosulfonyl urea **4** in a good yield. Moreover, 1-(1-adamantyl)-3-(substituted aminosulfonyl)ureas **5a-g** were obtained through heating **4** with the appropriate amine in the same solvent, dry toluene. (Scheme 1, Table 1). Treatment of **3a** with triethyl orthoformate afforded 1-(1-adamantyl)-4- (ethoxymethylene)semicarbazide **6** which was then reacted with 1- aminoadamantane to yield the corresponding 1-(1-adamantyl)-4-(1-

adamantylaminomethylene)semicarbazide **7**. Upon reacting compound **3a** with 1-adamantyl bromomethyl ketone in dry acetone, 1- (1-adamantyl) -4-(1-adamantylcarbonylmethyl)semicarbazide **8** was obtained, while 1- (1- adamantyl)-4-acylsemicarbazides **9a-d** were obtained through heating the same compound **3a** with the appropriate acid chloride in dichloromethane. On the other hand, treatment of **3a** with 1-adamantyl isothiocyanate in ethanol, furnished 1-(1-adamantyl)-4-(1-adamantylaminocarbonyl)thiosemicarbazide **10**. (Scheme 2, Table 1).

Scheme 1



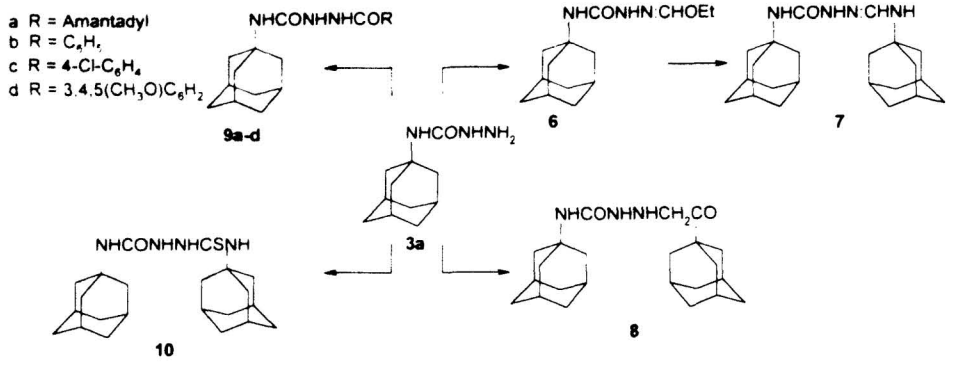


Table 1: Characterization data of the synthesized compounds:

Comp	R	Solvent	M.P. °C	Yield %	Formulae
3a	H	$CHCl_3$	113-15	62	$C_{11}H_{19}N_3O$
3b	4-Br C_6H_4	EtOH	125-7	57	$C_{17}H_{22}BrN_3O$
3c	4-Cl C_6H_4	EtOH	118-19	59	$C_{17}H_{22}ClN_3O$
3d	4-NO_2 C_6H_4	EtOH	105-7	53	$C_{17}H_{22}N_4O_3$
3e	4-CH_3 C_6H_4	$CHCl_3$	115-17	50	$C_{18}H_{25}N_3O$
5a	$N(C_2H_5)_2$	EtOAC	221-3	78	$C_{15}H_{27}N_3O_3S$
5b	4- morpholino	$CHCl_3$-EtOH	211-13	73	$C_{15}H_{25}N_3O_4S$
5c	4-(2-Aminoethyl)morpholino	$CHCl_3$-EtOH	215-17	78	$C_{17}H_{30}N_4O_4S$
5d	2,6-dimethylpiperidino	$CHCl_3$-EtOH	251-3	62	$C_{18}H_{31}N_3O_3S$
5e	1-benzyl-4-aminopiperidine	EtOH	213-15	65	$C_{23}H_{34}N_4O_3S$
5f	4-methyl-1-piperazinyl	EtOH	237-9	58	$C_{16}H_{28}N_4O_3S$
5g	4-(2-methoxyphenyl)-1-piperazinyl	$CHCl_3$	232-5	63	$C_{22}H_{32}N_4O_4S$
9a	adamantyl	EtOH	118-19	62	$C_{22}H_{33}N_3O_2$
9b	C_6H_5	Pet. ether -Benz	151-3	68	$C_{18}H_{23}N_3O_2$
9c	4-ClC_6H_4	Acetone	172-3	57	$C_{18}H_{22}N_3O_2$
9d	3,4,5-$(OCH_3)_3C_6H_2$	EtOH	163-5	52	$C_{21}H_{29}N_3O_5$

Antitumor Evaluation

All the synthesized compounds were subjected to the NCI *in vitro* disease oriented human cells screening panel assay[19-21]. About 60 cell lines of nine tumor subpanels were incubated with five concentrations (0.01 – 100 μM) for each compound and were used to create log concentration versus % growth inhibition curves. Three response parameters (GI_{50} , TGI and LC_{50}) were calculated for each cell line. The GI_{50} value corresponds to compound's concentration causing 50% decrease in net cell growth. The TGI value is the compound's concentration resulting in total growth inhibition and the LC_{50} value is the compound's concentration causing a net 50% loss of initial cells at the end of the incubation period (48 h). Subpanel and full panel mean graph midpoint values (MG – MID) for certain agents are the average of individual real and default GI_{50}, TGI or LC_{50} values of all cells lines in the subpanel or the fullpanel, respectively[21]. The NCI antitumor drug discovery screen has been designed to distinguish between broad – spectrum antitumor compounds and tumor as subpanel – selective agents[20].

In this study, the preliminary screening data of NCI , using a 3-cell line panel indicated that, only compounds **3a-c, 5a-g** and **9a-d** showed cytotoxic activity. With regard to sensitivity against individual cell lines, compounds **3a** , **5b**, **5d** and **9a** proved to be effective against MOLT -4 leukemia cell line with GI_{50} values of 7.3 , 5.2 , 9.8 and 6.8 μM respectively. Moreover compounds **5a**, **5c** and **9d** proved to be effective against the same cell line with GI_{50} values of 17.5, 15.9 and 13.5 μM respectively. Non small cell lung cancer EKVX proved to be sensitive toward compounds **9a-d** with GI_{50} values of 0.79 , 8.3 , 7.5 and 0.53 μM respectively. On the other hand, compounds **5a, b**, **f**, **g** , **9a** and **9d** are particularly effective against melanoma LOXIMVI with GI_{50} values of 1.5, 9.3, 7.5 , 5.8, 11.9, and 3.9 μM respectively, while compounds **3a** and **3b, 9a**, **9d**, showed effectiveness toward ovarian cancer OVCAR-3 with GI_{50} values of 0.93, 1.4, 9.8 and 9.5 μM respectively. Regarding breast cancer T-47D higher sensitivity was observed with only compound

9a, d with GI_{50} value of 0.93 and 5.5 μM (table 2). With regard to broad spectrum antitumor activity, the active compounds showed GI_{50}< 100 μM against leukemia, non – small cell lung, colon, melanoma, ovarian, renal, prostate and breast cancer subpanel cell lines (Table 3). Compounds **3a** , **5a** , **9a** and **9d** showed effective growth inhibition GI_{50} (MG – MID) values of 10.5 , 12.0 , 6.8 and 5.5 μM respectively, while compounds **3b**, **3c, 5b** , **5c** and **5f** showed GI_{50} (MG – MID) concentration range of 22.0 – 35.5 μM. On the other hand, compounds **5d**, **5g**, **9b** and **9c** are the least effective members of this series with GI_{50} (MG – MID) concentration range of 40.5 – 57.3 μM. The ratio obtained by dividing the compounds full panel MG-MID (μM) by its individual subpanel MG – MID concentration (μM) is considered as a measure for the compounds selectivity[21]. Ratios between 3 and 6 refer to moderate selectivity, while ratios greater than 6 indicate selectivity toward the corresponding cell line – subpanel. Most of the tested compounds proved to be non selective with broad spectrum antitumor activity against the nine tumor subpanels used, except compounds **3a, 3c** and **5d** that showed moderate selectivity at the GI_{50} level toward leukemia cell lines with ratios of 3.0, 3.9 and 4.0 respectively, while compounds **5a** and **5g** showed moderate selectivity at the GI_{50} level toward melanoma cell lines with ratios of 3.6 and 4.4 respectively (Table 3).

The activity of the tested compounds, could be correlated to structure variations and modifications. The obtained screening results showed that, among the tested compounds, 1-(1-adamantyl)semicarbazide **3a,** 1-(1-adamantyl)-3-(N,N-dimethyl-aminosulfonyl)urea **5a,** 1-(1-adamantyl)-4-(1-adamantoyl)semicarbazide **9a** and 1-(1-adamantyl)-4-(3,4,5-trimethoxybenzoyl)semicarbazide **9d** are the most active members with GI_{50} (MG-MID) values of 10.5,12.0, 6.8 and 5.5 μM respectively. Regarding compounds **3a-e,** the 4-unsubstituted semicarbazide derivative **3a** is the most active member of this series GI_{50} (MG-MID) 10.5 μM, introduction of substituted aryl moieties at position **4** of the semicarbazide function afforded compounds **3b** and **3c** with a remarkable decrease in the magnitude of the antitumor activity, GI_{50} (MG-MID) values of 35.5 and 29.5 μM respectively. Upon reacting **3a**

with different acyl moieties, this yielded the corresponding 1-(1-adamantyl)-4-acyl-semicarbazides **9a-d**, in these compounds, the presence of either adamantoyl or trimethoxybenzoyl function, gave compounds **9a,d** with a remarkable increase in the antitumor potency, GI_{50} (MG-MID) values of 6.8 and 5.5 μM respectively. On the other hand, the presence of either benzoyl **9b** or p-chlorobenzoyl moiety **9c** led to a dramatic decrease in the antitumor potency, GI_{50} (MG-MID) values of 40.5and 57.3 μM respectively. In case of compounds **5a-d,** the presence of diethylamino group in the sulfonylurea moiety **5a**, favored the antitumor activity rather than the presence of mopholino **5b**, substituted morpholino **5c**, substituted piperidino **5d, e** and substituted piperazino **5f, g,** as shown by **5a** > **5b, c, d, f, g,** with GI_{50} (MG-MID) values of 12.0 > 22.0, 26.9, 51.5, 33.5 and 53.6 μM respectively.

Table 2. Growth inhibitory concentration (GI_{50}) of some selected in vivo cell lines (μM)[a]

Comp. No.	Leukemia MOLT-4	Non small cell lung cancer EKVX	Melanoma LOXIMVI	Ovarian OVCAR-3	Breast cancer T-47D
3a	7.3	29.3	26.5	0.93	28.6
3b	20.3	19.8	40.3	1.4	32.4
3c	28.3	21.5	23.5	30.6	-[b]
5a	17.5	53.1	1.5	26.8	40.5
5b	5.2	-	9.3	42.5	28.7
5c	15.9	-	23.4	25.3	66.5
5d	9.8	-	32.5	34.3	70.4
5f	44.5	-	7.5	62.2	-
5g	23.5	-	8.5	18.9	-
9a	6.8	0.79	11.9	9.8	0.93

9b	52.8	8.3	52.5	30.5	50.7
9c	60.0	7.5	38.3	54.9	42.3
9d	13.5	0.53	3.9	9.5	5.5

a- Data obtained from NCI's *in vitro* disease – oriented human tumor cell screen (sea references 19 – 21 for more details)

b- GI_{50} value > 100 μmol / L

Experimental

Synthesis

Elemental analyses (C,H,N) were performed on Perkin-Elmer 2400 analyzer (Perkin–Elmer. Norwalk, CT. USA) at the Central Laboratory of the College of Pharmacy, King Saud University. All the compounds were within ± 0.4 % of the theoretical values. Melting points were determined in open capillaries on an electrothermal melting-point apparatus (Electrothermal Engineering Ltd., Essex, UK) and are uncorrected. ^{1}HNMR spectra were recorded in DMSO-d_6 on a Varian EM 360 (90 MHz) instrument using tetramethylsilan (TMS) as an internal standard (chemical shift in δ ppm).

1-(Ethoxycarbonylamino)adamantane (2) . Ethyl chloroformate (1.63 ml, 0.01 5mol) was added dropwise to a stirred solution of 1-aminoadamantane (1.51g, 0.01 mol) and triethylamine (1.01 ml, .01 mol) in dry toulene (50 ml). The reaction mixture was then heated under reflux for 6h, then evaporated *in vacuo* and the obtained residue was triturated with ice water, filtered, dried and crystallized from pet. ether – benzene to afford 72%, **2**, m.p 136-8 °C, Analysis ($C_{13}H_{21}NO_2$) C,H,N . ^{1}HNMR (DMSO – d_6), **2** : δ 0.98 (t, 3H, J= 7.0 Hz , CH_3) , 1.75 – 2.12 (m, 15H, adamantyl – H). 2.95 – 3.12 (q, 2H. J = 7.0 Hz. CH_2), 9.50 (brs. 1H. NH).

1-(1-Adamantyl)semicarbazide (3a). Hydrazine hydrate 98% (2.5 ml, 0.05 mol) was added dropwise to **2** (0.01 mol) over a period of 15 min. The reaction mixture was then heated under reflux for 4 h., evaporated *in vacuo* and the obtained residue

was triturated with ice – water (50 ml), filtered, dried and crystallized (Table 1). ^{1}HNMR(DMSO – d_6), **3a** : δ 1.93-2.12 (m, 15H, adamantyl), 4.23 (brs , 2H, NH_2), 8.32 (brs , 1H, NH), 9.59 (brs, 1H, NH).

1-(1-Adamantyl)–4-(4-substituted phenyl)semicarbazides (3b-e) . Compound **2** (2.23 g, 0.01 mol) was added portionwise to a stirred solution of the appropriate phenyl hydrazine (0.01 mol) and triethylamine (5.06 ml, 0.05 mol) in ethanol (50 ml). The reaction mixture was heated under reflux for 6h. . On cooling, the separated solid was filtered, washed with ice – water, dried and crystallized (Table 1). ^{1}HNMR (DMSO – d_6), **3b**: δ 1.79 - 1.95 (m, 15H, adamantyl-H) , 7.03 (brs , 1H, NH), 7.23 – 7.93 (dd, 4H, Ar-H), 9.50 (brs, 1H, NH), 10.03 (brs , 1H NH), **3d :** δ 1.83 - 2.12(m, 15H, adamantyl-H) , 6.7 (brs , 1H, NH), 7.1 – 7.7 (dd , 4H, Ar-H), 8.5, 8.7 (brm, 2H, NH), **3e** : δ 1.68-1.89 (m, 15H, adamantyl-H), 2.21 (s, 3H, CH_3), 6.99 (brs, 1H, NH) , 7.31-7.93 (dd, 4H, Ar-H), 9.31 (brs, 1H, NH), 10.55 (brs, 1H, NH).

1-(1-Adamantyl)–3-chlorosulfonylurea (4). Chlorosulfonyl isocyanate (1.42 ml, 0.01 mol) was added dropwise to an ice – cooled solution of 1-aminoadamantane(1.51 g, 0.01 mol) in dry toluene (50 ml), The reaction mixture was stirred at room temperature for 2h, and then at 100 °C for 3h., evaporated *in vacuo* and the obtained residue was crystallized from Pet. ether -benzene to afford 80% **4** , m.p175-7°C , Analysis ($C_{11}H_{17}Cl\ N_2O_3S$) C, H ,N. ^{1}HNMR (DMSO-d_6), **4** : δ 1.79-1.99 (m, 15H, adamantyl-H) , 7.53 (brs , 1H, NH), 9.53 (brs , 1H, NH).

1-(1-Adamantyl)-3-(substituted aminosulfonyl)ureas (5a-g). To a stirred solution of **4** (2.93 g, 0.01 mol) and triethylamine (1.01 ml, 0.01 mol) in dry toluene (50 ml), the appropriate amine (0.02 mol) was added over a period of 15 min. The reaction mixture was heated under reflux for 3-6 h. Solvent was then evaporated *in vacuo*, the obtained residue was triturated with ice-water, filtered, dried and crystallized (Table. 1). ^{1}HNMR (DMSO-d_6), **5a** : δ 1.03-1.09 (t, 6H, J = 7.2 Hz, CH_3), 1.69-2.01 (m , 15H, adamantyl-H), 4.23-4.40 (q , 4H, CH_2), 9.53 (brs, 1H, NH), 10.63 (brs , 1H NH), **5b** : δ 1.73-1.99 (m, 15H, adamantyl-H) , 2.54-2.58 (m , 4H, morpholine-H), 3.71-3.80 (m, 4H, morpholine-H), 8.99, (brs, 1H, NH). 9.54 (brs, 1H, NH), **5d** : δ 1.27

(d, 6H, CH_3), 1.49-1.58 (m, 6H, piperidine-H) , 1.79-1.99 (m, 15H, adamantyl-H), 2.55-2.69 (m , 2H, piperidine -H) , 10.66 (brs , 1H, NH), 11.55 (brs , 1H, NH), **5f** : δ 1.85-2.01 (m, 15H, adamantyl-H), 2.32 (s , 3H, N-CH_3) . 2.45-2.65 (m, 8H, piperazine-H) , 7.96 (brs , 1H, NH), 9.53 (brs , 1H, NH), **5g** : δ 1.79-1.98, (m, 15H, adamantyl - H), 2.40-2.63 (m, 8H, piperazine-H), 3.95 (s, 3H, OCH_3), 6.98-7.83 (m, 5H, Ar-H , NH) , 10.5 (brs, 1H, NH).

1-(1-Adamantyl)-4-(ethoxymethylene)semicasrbazide (6) . A mixture of **3a** (2.09 g, 0.01 mol) and triethyl orthoformate (20 ml) was stirred for 1 h. at 80 °C. the reaction mixture was evaporated *in vacuo* and the obtained residue was triturated with diethyl ether, collected by filtration, washed with diethyl ether, dried and crystallized from petroleum ether-benzene to afford 65% **6**, m.p 97-9 °C. analysis ($C_{14}H_{23}N_3O_2$) C, H, N. ^{1}HNMR ($CDCl_3$), **6** : δ 1.09-1.15 (t , 3H , J=7.0 Hz CH_3), 1.69-1.99 (m , 15H , adamantyl-H), 3.99-4.02 (q , 2H , J = 7.0 Hz , CH_2), 6.85 (s , 1H, = CH), 9.59 (brs , 1H , NH), 10.55 (brs , 1H , NH).

1-(1-Adamantyl)-4-(1-adamantylaminomethylene)semicarbazide (7). A mixture of **6** (2.65 g, 0.01 mol) and 1- aminoadamantane (1.51 g , 0.01 mol) in n-butanol (20 ml) was heated under reflux for 4h. The reaction mixtures was evaporated *in vacuo* and the obtained residue was crystallized from chloroform – ethanol to yield 52% **7**, m.p. 145-7 °C. Anal ($C_{22}H_{34}N_4O$) C, H, N. ^{1}HNMR (DMSO-d_6), **7** : δ 1.59-1.73 (m , 15H , adamantyl-H), 1.81-2.12 (m , 15H , adamantyl-H), 6.86 (s, 1H = CH), 9.34 (brs , 1H , NH) 10.53 (brs , 1H , NH), 11.56 (brs , 1H , NH).

1-(1-Adamantyl)-4-(1-adamantylcarbonylmethyl)semicarbazide (8) . A mixture of **3a** (2.09 g, 0.01 mol) , 1- adamantyl bromomethyl ketone (2.57 g , 0.01 mol) and sodium bicarbonate (1.68 g , 0.02 mol) in dry acetone (50 ml) was heated under reflux for 5h. After cooling, the resulting precipitate was collected, washed with acetone and water and crystallized from acetone to yield 48% g **8** , m.p. 105-7 °C. Anal. ($C_{23}H_{35}N_3O_2$) C, H, N. ^{1}HNMR (DMSO-d_6), **8** : δ 1.66-1.79 (m , 15H , adamantyl-H), 1.81-2.22 (m , 15H , adamantyl-H), 4.45 (d , 2H , CH_2), 6.79 (brs , 1H, NH) 7.96 (brs , 1H , NH), 11.63 (brs , 1H , NH).

1-(1-Adamantyl)-4-acyl-semicarbazides (9a-d). The appropriate acid chloride (0.1 mol) was added to a stirred solution of **3a** (10.45 g, 0.05 mol) and triethylamine (5.06 ml, 0.05 mol) in dichloromethene (60 ml), the reaction mixture was then heated under reflux at 70 °C for 3h. On cooling, the separated solid was filtered, washed with ice – water, dried and crystallized (Table 1) . ^{1}HNMR ($CDCl_3$), **9a** : δ 1.66-1.78 (m , 15H , adamantyl-H), 1.81-2.13 (m, 15H, adamantyl-H), 6.49-6.53 (brm, 2H, NH), 7.77 (brs, 1H , NH), **9b** : δ 1.72-1.99 (m, 15H, adamantyl-H), 6.83 (brs, 1H, NH), 7.12-7.59 (m, 6H, Ar-H, NH) , 10.59 (brs, 1H, NH), **9d** : δ 1.68-1.98 (m, 15H, adamantyl-H) 3.92 (s, 3H, OCH_3), 3.97 (s, 3H , OCH_3), 4.01 (s, 3H, OCH_3) , 6.55 (brs, 1H, NH) , 7.48 (s, 2H, Ar-H), 9.53-9.60 (brm , 2H , NH).

1-(1-Adamantyl)-4-(1-adamantylaminocarbonyl)thiosemicarbazide (10). 1-Adamantyl isothiocyanate (1.93 g, 0.01 mol) was added portion wise to a stirred solution of **3a** (2.09 g, 0.01 mol) in ethanol (50 ml). The reaction mixture was heated under reflux for 6h. , evaporated *in vacuo* and the obtained solid was triturated with cold petroleum ether, filtered, dried and crystallized from ethanol to yield 68% **8**, m.p. 122-5 °C. Anal ($C_{22}H_{34}N_4$ OS) C, H, N. ^{1}HNMR (DMSO-d_6), **10** : δ 1.68-1.77 (m , 15H , adamantyl-H), 1.79-2.03 (m , 15H , adamantyl-H), 6.77 (brs , 1H, NH), 8.26-8.33 (brm , 2H , NH) 9.34 (brs , 1H , NH).

Antitumor activity

Under a sterile condition, cell lines were grown in RPMI 1640 media (Gibco, NY, USA) supplemented with 10% fetal bovine serum (biocell, CA, USA), $5x10^5$ cell/ml was used to test the growth inhibition activity of the synthesized compounds. The concentrations of the compounds ranging from 0.01 – 100 μM were prepared in phosphate buffer saline. Each compound was initially solubilized in dimethyl sulfoxide (DMSO), however, each final dilution contained less than 1% DMSO. Solutions of different concentrations (0.2 ml) were pipetted into separate well of a microtiter tray in duplicate. Cell culture (1.8 ml) containing a cell population of $6x10^4$ cells/ml was pipetted into each well. Controls, Containing only phosphate buffer saline and DMSO at identical dilutions, were also prepared in the same manner.

These cultures were incubated in a humidified incubator at 37°C. The incubator was supplied with 5% CO_2 atmosphere. After 48 hrs, cells in each well were diluted 10 Times with saline and counted by using a coulter counter. The counts were corrected for the dilution[19-21].

Acknowledgment.

The author would like to express her gratitude and thanks to the National Cancer Institute (NCI), Bethesda Maryland, USA for doing the antitumor testing of the new compounds.

References

[1] Settimo A, Marini A M, Primofiore G, Settiom F.
Synthesis and evaluation of aminoadamantane derivatives for in vitro anti HIV and antitumor activities
Farmaco. 1995, 50, 321-323.

[2] Chimirri A, Grasso S, Monforte A M, Rao A, Zappala M.
Synthesis and antitumor activity evaluation of -1,2,3,- oxadiazoline derivatives.
Formaco. 1995, 50, 125

[3] Chimirri A, Gitto R, Grasso S, Monforte A M, Zappala M.
Synthesis and antitumor activity evaluation of 1-[(arylidene)amino]-adamantanes.
Farmaco. 1994; 49: 649-510.

[4] Wang J J, Chern Y T, Liu T Y, Chi C W.
In *vitro* and in *vivo* growth inhibition of cancer cells by adamantylmaleimide derivatives.
Anticancer Drug Res. 1998;13 : 779-796.

[5] Wang J J, Liu T Y, Yin P H, Wu C W, Chern Y T, Chi C W.
Adamantylmaleimide induced change in adhesion molecules and ROS are involved in apoptosis of human gastric cancer cells.

Anticancer Res. 2000; 20 : 3067-3073.

[6] Wang J J, Chern Y T.
Biological activities of new poly(N-1-adamantylmaleimide) and poly(N-1-diadamantylmaleimide).
J. Biomater. Sci. Polym. Ed. 1996; 7 : 905-915.

[7] Wang J J, Wang S S, Lee C F, Chung M A, Chern YT.
In vitro antitumor and antimicrobial activities of N-substituents of maleimide by adamantane and diamantane.
Chemotherapy. 1997; 43 : 182-189.

[8] Andreani A, Rambaldi M, Locatelli A, Bossa R, Fraccari A, Galatulas I.
Potential antitumor agents XXII [1] synthesis and cytotoxic activity of imidazo[2,1-b]thiazole adamantylthioureas.
J. Pharm. Belg. 1993; 48 : 378-382.

[9] Iwahashi J, Tsuji K, Ishibashi T, Kajiwara J, Mori I R, Hara K, Kashiwagi T, Ohtsu Y, Hamada Y, Maoda H, Toyoda T.
Isolation of amantadine-resistant influenza A viruses (H3N2) from patients following administration of amantadine in Japan.
J. Chin. Microbiol. 2001; 39: 1652-1653.

[10] Martino V D, Boudjema H, Delacour T, Cazier A, Caron C, Coutarel P, Dumouchel P, Cadranel J F.
Treatment of chronic hepatitis C with amantadine hydrochloride in patients who had not responded to previous treatment with interferon-alpha and/or ribavirin.
Clin. Infect. Dis. 2001; 32 : 830-831.

[11] Fytas G, Marakos P, Kolocouris N, Foscolos G B, Pouli N, Vamvakides A.
3-cyclopentyl-1-adamantanamines and adamantane methylamines, antiviral activity evaluation and convulsions studies.
Farmaco. 1994; 49 : 641-647.

[12] El-Sherbeny M A.

Synthesis, antitumor and anti HIV-1 testing of certain heterocyclic systems containing adamantane nucleus .
Arch. Pharm. 2000; 333 : 323-328 .

[13] El-Sherbeny M A.
Adamantane derivatives part II : synthesis, DNA binding and antitumor evaluation .
Med. Chem. Res. 2002;11 : 74-86.

[14] Mohamad F, Spees M M, Grindey G B.
Sulfonylureas: A new class of cancer chemotherapeutic agents.
J. Med. Chem. 1992; 35 : 3012-3016.

[15] Houghton P J, Houghton J A.
Antitumor diarylsulfonylureas: novel agents with unfulfilled promise.
Investigational New Drugs. 1996; 14 : 271-280.

[16] Howbert J J, Grossman C S, Crowell A, Rieder B J, Harper R W, Kramer K E, Vtao E, Aikins J A, poore G A, Rinzel S M, Grindey G B, Shaw W N, Todd G C.
Novel agents effective against solid tumors : The diarylsulfonylureas . synthesis, activities, and analysis of quantitative structure-activity relationships.
J. Med. Chem. 1990; 33 : 2394.

[17] El-Sherbeny M A, Youssef K M, Al-Shafeih F S, Al-Obaid A M.
Novel pyridothienopyrimidine and pyidothienothiazine derivatives as potential antiviral and antitumor agents.
J. Med. Chem. Res. 2000; 10 : 122-135.

[18] El-Subbagh H I.
Antitumor Screening of new cyclopenteno[b]thiophene, benzo[b]thiophene, thieno[2,3-c]pyridine and pyrido[4-, 3-, 4,5]thieno[2,3-d]pyrimidine analogs.
Saudi Pharm. J. 1999; 7 : 34-38 .

[19] Grever M, Sehepartz S, Chabners B.

The national cancer institute cancer drug discovery and development program.
Semin Oncol 1992; 19 : 622.

[20] Monks A, Schudiero D, Skehan P.
Feasibility of a higher flux anticancer drug screen utilizing a derive panel of human tumor cell lines in culture.
J. Natl. Cancer Inst. 1991; 83 : 757.

[21] Boyd M, Paull K.
Some practical considerations and applications of the national cancer institute in vitro anticancer drug discovery screen.
Drug Dev. Res. 1995; 43 : 91-109.

Received January 8th, 2003
Accepted April 23rd, 2003