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MACROCYCLIC COMPOUNDS: SYNTHESIS OF VARIOUS 6,15-DITHIA-2,3,8,11,12,17,19,20-OCTAAZATRICYCLO[14.2.-1.1^{7,16}]EICOSA-1,7(20),10,16(19)TETRAENE-4,13-DIONE DERIVATIVES HAVING POTENTIAL ANTITUMOR ACTIVITY

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Abstract - Acylation, carbonylation, and oxalylation of the 4-hydrazono-2-thioxoimidazolidine (**1a**) with various acyl chlorides, *N*,*N*`-carbonyldiimidazole and oxalyl chloride, gave the corresponding 4-acylhydrazono derivatives (**2a-c**), ***N*$^2$,*N*$^2$`**-bis(imidazolidine-4-ylidine)carbazide (**3**) and oxalic acid *N*^{2},*N*^{2}`-bis[(imidazolidine-4-ylidine)hydrazide] (**4**), respectively. Alkylation of **2a** produced the 2-alkylthio derivatives (**5a-f**). Reactions of **1a-b** with chloroacetyl chloride in DMAP and pyridine gave the titled macrocycles (**7a-b**). Reaction of **1a** with chloroacetyl chloride in K_2CO_3 gave a mixture of **7a** and 4-chloroacetylhydrazono derivative (**6**). Acylation of **7a-b** with acyl chlorides generated the tetraacyl-hetrophanes (**8a-d**). Compounds (**5c**) and (**7a**) displayed superior cytotoxic activity against *Ehrlich ascites* than Doxorubicin® medicament.

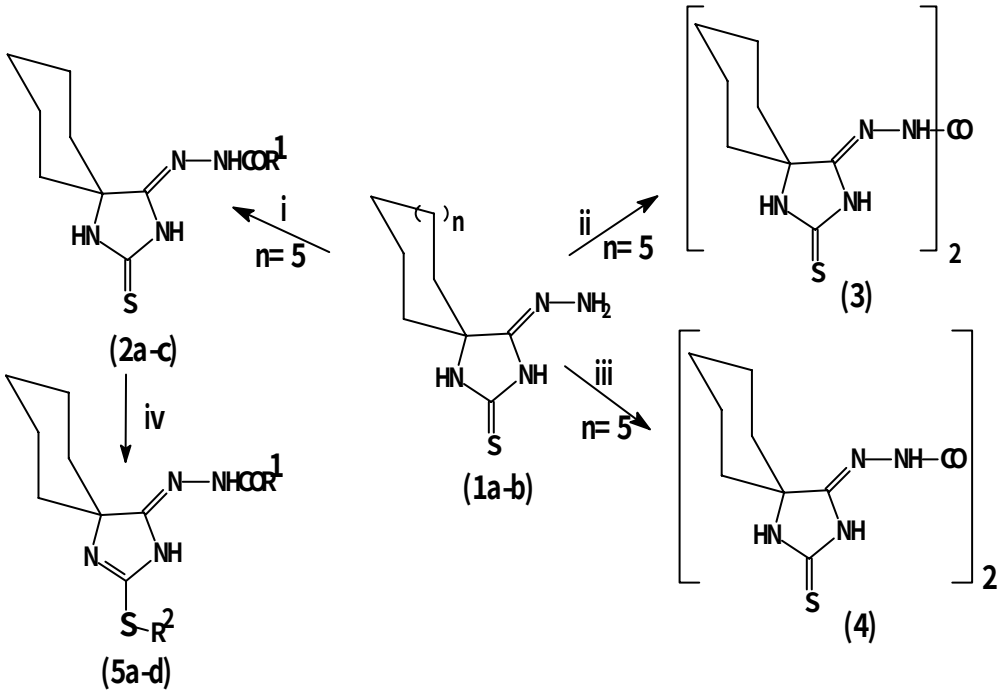
INTRODUCTION:

The recent few decades showed many attentions about the synthesis of heterocyclic macrocycles due to their interesting physical and biological properties.[1-4] Many papers have been issued for the use of many porphorines and heterophanes as complexing agents for heavy metals.[5-7] The macrocyclic structurally complex substance, halichondrin-B [8] which was isolated from a pacific sponge and showed potent cytotoxicity *in vivo* against leukemias and solid tumors in mice, combines with extreme scarcity encourage laboratory development of clinical anticancer agents.[9] Quite recently, the macrocyclic medicament, [CCI-779®],[10] was introduced clinically as potent anticancer agent. On the other hand, it was reported that certain sulfur containing aminoimidazoline derivatives exhibit potent antitumor and cytotoxic activity.[11] Accordingly, this research involves the synthesis of novel imidazoline macrocyclic compounds and evaluating their cytotoxic activity. The synthetic route for the titled macrocycles and other intermediates is outlined in Schemes **1** and **2**:

DISCUSSION

It was proved in this investigation that acylation of 4-hydrazono-2-thioxo-1,3-diazaspiro[4.5]decanes **(1a)**,[12] with various acid chlorides would result in a regioselective monoacylation reaction at the terminal hydrazono nitrogen. The FTIR and ^{1}H-NMR

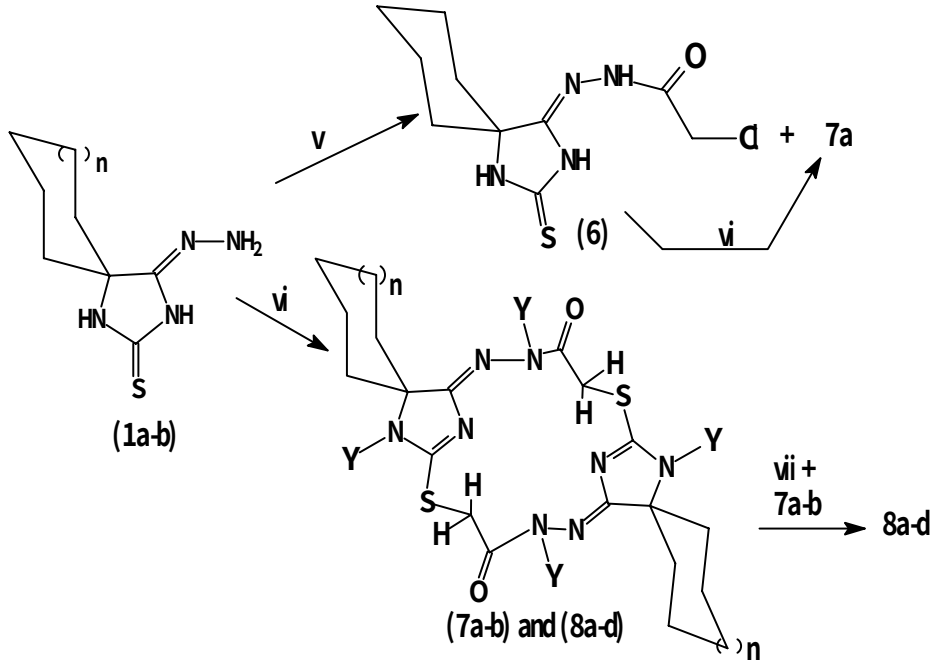
spectra of the produced 4-acylhydrazono-2-thioxo-1,3-diazaspiro[4.5]decanes **(2a-d)** showed three kinds of NH groups (Tables 2, 3), while the EIMS spectrum of **2a** showed the fragment (C_6H_5CONH) at m/z 120 (16.2%), indicating the attack at the hydrazono NH_2. Analogously, carbonylation and oxalylation of **1a** with the bifunctional reagents: *N,N`*-carbonyldiimidazole and oxalyl chloride generated the $N^2$,$N^2$`-bis(2-thioxo-1,3-diazaspiro[4.5]dec-4-ylidine)carbazide **(3)** and oxalic acid N^2,N^2`-bis[(2-thioxo-1,3-diazaspiro[4.5]dec-4-ylidine)hydrazide] **(4)**, respectively. The EIMS spectra of **3** and **4** showed molecular ion peaks matched with the bimolecular attack of the substrate (**1a)** with one mole of these reagents, while their FTIR and ^{1}H-NMR spectra showed three kinds of NH groups (Tables 2, 3). These results are further proved the preferential acylation at the terminal NH_2 group. Meanwhile, alkylation of **2a-b** with various alkyl halides in basic medium was found to be regioselective at the thione function producing the corresponding 4-acylhydrazono-2-alkylthio-1,3-diazaspiro[4.5]dec-1-ene derivatives **(5a-d)**. The ^{1}H-NMR spectra of **5a, c** showed the singlets of their CH_3 hydrogens at δ 2.51 and 2.52, while the spectra of **5b, d** showed the singlets of the benzylic hydrogens at δ 4.30 and 4.31. These data indicated *S* rather than *N* alkylation of the 2-thioxoimidazolidines **(2a-b)** which is matched with previous reported findings.[12]



1: n; a=5 , b=4 2: R^1 ; a= C_6H_5 , b=*p*-ClC_6H_4 c=C_2H_5 5: (R^1 ; R^2): a=(C_6H_5 ; CH_3) b=(C_6H_5 ; C_6H_5 CH_2) c= (*p*-ClC_6H_4 ; CH_3) d= (*p*-ClC_6H_4 ; C_6H_5 CH_2)

Scheme **1:** i-R^1COCl/THF. , ii-*N,N*-Carbonyldiimidazole/DMF. iii-Oxalyl chloride/Py/DMF. , iv-R^2 X/NaH/THF.

The above observations directed the attention to use chloroacetyl chloride as an acylating-alkylating agent for the substrates (**1a-b**) in order to get dimeric macrocyclic molecules. Accordingly, the reaction of chloroacetyl chloride with the substrate (**1a**) under different conditions was studied (Table 1). Rendering the reaction in THF at 0°C for 5 h gave 4-chloroacetylhydrazono-2-thioxo-1,3-diazaspiro[4.5]decane (**6**) in low yield together with a high amount of the unchanged substrate (**1a**) (Entry 1).



7: (n ; Y): a=(5 ; H) , b=(4 ; H) 8: (n ; Y): a=(5 ; CH_3CO) , b=(5 ; C_2H_5CO) c=(5 ; C_6H_5CO) , d=(4 ; CH_3CO)

Scheme **2:** v-$ClCH_2COCl$ / K_2CO_3 / THF. , vi- $ClCH_2COCl$ / DMAP/ Py/THF. vii- DMAP/ Py/THF. , viii-RCOCl / Py / DMF.

Allowing the above reaction to occur at room temperature would separate a mixture of **1a**, **6**, and the heterophane: 9,9,18,18-bis(cyclopentamethylene)-6,15-dithia-2,3,8,11,12-,17,19,20-octaazatricyclo[14.2.1.1^{7,16}]eicosa-1,7(20),10,16(19)-tetraene-4,13-dione **(7a)** (Entry 2). When the last reaction was conducted in the presence of K_2CO_3 a mixture of **6** and **7a** was obtained with little increase in the yield of **7a** (Entries 3, 4). Refluxing the reaction mixture in the presence of more efficient basic mixture comprising of pyridine and 4-*N*,*N*-dimethylaminopyridine (DMAP) would only produce the heterophane (**7a**) (Entry 5). Similarly, the substrate (**1b**) under the last condition gave the macrocycle (**7b**). Moreover, it was found that treatment of the isolated intermediate (**6**) with the pyridine/DMAP produced **7a**. These results indicated that the formation of the macrocycles (**7a-b**) is a typical intermolecular dimeric *S*-alkylation of two moles of the initially formed 4-chloroacetylhydrazono-2-thioxoimidazolidine intermediates. Increasing the strength of the basic catalyst increases the yield of the resulting macrocycles. The

small amount of **7a** obtained in absence of any basic catalyst (Entry 2) may be attributed to the basic character of the terminal NH_2 of the unreacted substrate **(1a)**. The components of the reactions in each case were separated on silica gel column.

Table 1: Reaction conditions to obtain **7a**:

Entry	Temp,°C	Time, h	Base	Recovered **(1a)**%	**6** %	**7a** %
1	0	5	-	63	22	-
2	Rt	5	-	11	39	18
3	rt	5	K_2CO_3	-	31	24
4	reflux	12	K_2CO_3	-	22	34
5	**reflux**	**12**	**DMAP/Py**	**-**	**-**	**66**

The EIMS spectra of the macrocycles **(7a-b)** proved their dimeric structures, while their ^{1}H-NMR spectra showed two D_2O exchangeable signals at δ 9.94-9.91 and 10.47-10.54 corresponding to the two types of NH hydrogens. Also, the same spectra displayed two duplets at δ 3.33-3.34 and 4.14-4.20 with J=13.50-14.80 Hz which could be due to the geminal coupling of axial and equatorial hydrogens of the SC$\underline{H_2}$CO moieties of the macrocyclic molecules. Such case is common in fused and bridged cyclic systems containing CH_2 groups, where they would acquire a frozen conformation at room temperature and the axial and the equatorial hydrogens of each CH_2 groups would not be chemical shift equivalents.[13] These speculations are confirmed by the OMB model for the bridged macrocycle (**7a**), where it indicates that the two hydrogens of each SC$\underline{H_2}$CO group are diastereotopic pairs. Also, the same model revealed that the two pairs of the CO, HNC=N, C=NNH, SCH_2, and the cyclohexylidene groups are seemed to be geometrically equivalents and the molecule has a center of symmetry. The above conclusions are also supported by the fact that the ^{13}C-NMR spectra of **7a-b** revealed that these pairs of groups were identical and each pair gave one signal. Thus, compound **(7a)** recorded only eight signals while compound **(7b)** showed seven signals (Table 3). These data indicated that the structures of **7a-b** should be present in symmetric forms, which may be structure A, B, or C (Figure 1).

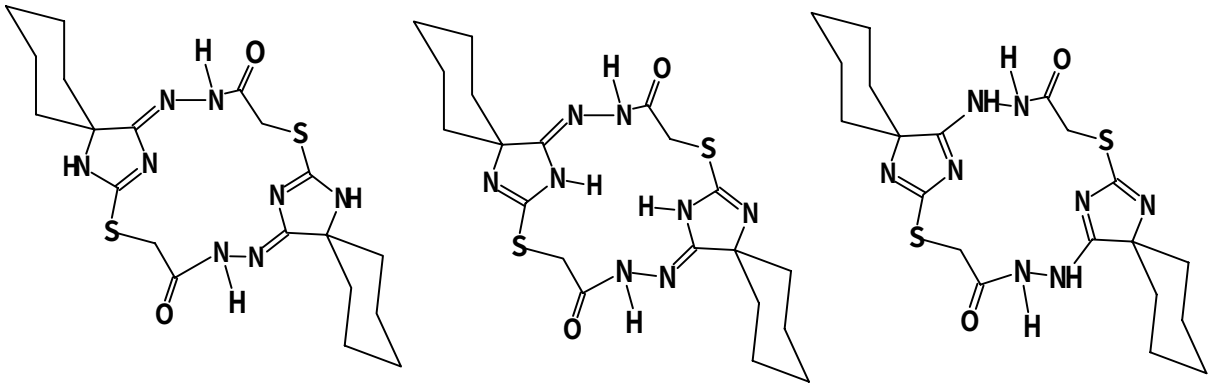


Figure 1: A=7a B C

The computational molecular orbital calculation of the heat of formation of these forms (using MNDO and CNDO/S methods), as previously reported, [15] showed that A, B, and C have heat of formations equal –94.20, -36.25 and +26.15, respectively. The relatively higher negative value of the heat of formation of structure A as compared to the other forms indicated that the formula A is the real structure of the macrocycle **(7a)**.

This research involved, also, the acylation of the macrocycles **(7a-b)** with acyl chlorides: (viz.; acetyl chloride, propanoyl chloride, and benzoyl chloride), where the corresponding 3,6,12,17-tetraacyl derivatives **(8a-d)** were isolated. The FTIR of these compounds showed the disappearance of the two NH bands of the reactants **(7a-b)** accompanied with the appearance of additional overlapped absorption bands of the tertraacyl CO groups. However, the molecular ion of **8b** at m/z 700 was not recorded in its EIMS spectrum, but the [M - $CH_3CH=C=O$] ion at 644 was detected as a result of the expected McLafferty rearrangement. The same rearrangement was also detected in the EIMS spectrum of **8a**, where both the M^+ ion at m/z 644 (4.46%) and [M - $CH_2=C=O$] ion at 602 (3.1%) were recorded.

EXPERIMENTAL

All melting points were obtained using recrystallized products are uncorrected. FTIR spectra were recorded as cm^{-1} on a Perkin-Elmar spectrophotometer. ^{1}H-NMR spectra were measured in δ scale on JEOL 90 MHz and 270 MHz spectrometers. ^{13}C-NMR spectral data were recorded in δ scale on a JEOL 270 MHz spectrometer. EIMS spectra were fulfilled on Vinnigan Mat SSQ 7000, (70 ev) mass spectrometer. Elemental analysis were performed at the *Central Laboratory, Faculty of Sciences, Ain-Shams University and the Microanalytical unite, Cairo University*. TLC monitored progress of the reaction till completion. Column chromatography was performed using 60N (Merk, 100-210 mesh, 60 Å) and flash column was performed on silica gel 60 (Merk, 40-100 mesh 60 Å). Physical and analytical data are given in Tables 2 and 3.

General Experimental Procedures for Scheme 1:

4-Hydrazono-2-thioxo-1,3-diazaspiro[4.4]nonane (**1b**): To a solution of 5,5-cyclo-tetramethylene-2,4-dithiohydantoin[12,15] (9.3 g, 0.05 mol) in ethanol (50 mL), hydrazine hydrate (98%, 8 mL, 0.15 mol) was added and the mixture was warmed at 60 °C for 30 min and evaporated under reduced pressure and the obtained solid **(1b)** was recrystallized from ethanol.

4-Acylhydrazono-2-thioxo-1,3-diazaspiro[4.5]decanes (2a-c): *General Procedure:* To a solution of 4-hydrazono-2-thioxo-1,3-diazaspiro[4.5]decane **(1a)**[12,15] (1.98 g. 0.01 mol) in THF (20 mL) and pyridine (0.79 g, 0.01 mol) was added the appropriate acid chloride (viz.: benzoyl chloride, 4-chlorobenzoyl chloride, propanoyl chloride) (0.01 mol). The reaction mixture was refluxed for 2 h and the solvent was evaporated under vacum and the obtained solid of **2a-c** was recrystallized from the appropriate solvent.

4-Acylhydrazono-2-alkylthio-1,3-diazaspiro[4.5]dec-1-enes (5a-d): *General Procedure: S*odium hydride (0.4 g, 0.01 mol, 60% in liquid paraffin) was washed with n-hexane (3 x 5 mL), suspended in THF (25 mL), and mixed with a solution of **2a-c** (0.01 mol) in THF (25 mL). The appropriate alkyl halide [viz.: methyl iodide and benzyl chloride (0.01 mol)] was then added and the reaction mixture was stirred under reflux for 12 h, the solvent was evaporated under vacum, and the residue of **5a-d** was recrystallized from the appropriate solvents.

***N*^{2},*N*^{2}`-Bis(2-thioxo-1,3-diazaspiro[4.5]dec-4-ylidine)carbazide (3):** *N,N`*-Carbonyldiimidazole (0.97 g, 0.006 mol) was added to a solution of **1a** (0.99 g, 0.005 mol) in DMF or THF (15 mL). The reaction mixture was stirred at rt for 2 h. Ice cold water (50 mL) was added and the formed precipitate of **3** was recrystallized from acetone.

Ethanedioic acid *N*^{2},*N*^{2}`-bis[(2-thioxo-1,3-diazaspiro[4.5]dec-4-ylidine)hydrazide] (4): Oxalyl chloride (0.64 g, 0.005 mol) was added to a solution of **1a** (0.99 g, 0.005 mol) and DMAP (0.61 g, 0.005 mol) in THF (50 mL). The reaction mixture was stirred at rt for 1 h. The solvent was then evaporated under vacum and the residue of **4** was recrystallized from methanol.

4-Chloroacetylhydrazono-2-thioxo-1,3-diazaspiro[4.5]decane (6): To a mixture of chloroacetyl chloride (0.68 g, 0.006 mol) in THF (30 mL) and K_2CO_3 (0.82 g, 0.006 mol) was added a solution of the substrate **(1a)** (1 g, 0.005 mol) in THF (10 mL) and the mixture was stirred at rt for 2 h and refluxed for 3 h. The solvent was then evaporated under vacum and the residue was triturated with ice-cooled water (50 mL). The separated solid was filtered, dissolved in methanol, and eluted over silica gel column with ethyl acetate-acetone-DMF mixture (6:3:1). The eluent was collected in fractions (50 mL for each one), where compound (**6**) was eluted in fractions 3 and 4 and recrystallized from the methanol. Compound (**7a**) was eluted in fractions 11-13 and recrystallized from DMF/ methanol (Table 1).

9,9,18,18-Bis(cyclopolymethylene)-6,15-dithia-2,3,8,11,12,17,19,20-octaazatricyclo-[14.2.1.1^{7,16}]eicosa-1,7(20),10,16(19)-tetraene-4,13-diones (7a-b): ***Method a:*** *General Procedure:* To a solution of chloroacetyl chloride (0.68 g, 0.006 mol) in THF (40 mL) was added a solution of the respective substrate **(1a-b)** (0.005 mol) and the mixture was stirred at rt for 2 h. A solution of DMAP (0.49 g, 0.005 mol) and pyridine (1.58 g, 0.02 mol) in THF (10 mL) was then added and the resulting mixture was refluxed for 12 h. The solvent was evaporated under vacum and the residue was triturated with ice cooled water (50 mL). The formed precipitate of **7a-b** was filtered and the obtained solid was recrystallized from the appropriate solvents.

Method b: A solution of 4-chloroacetylhydrazono-2-thioxo-1,3-diazaspiro[4.5]decane **(6)** (0.1 g, 0.0004 mol), pyridine (0.155 g, 0.0016 mol), and DMAP (0.025 g, 0.0002 mol) in THF (10 mL) was refluxed for 12 h. The mixture was filtered and the solvent was

evaporated under vacum. The residue was treated with water (10 mL), filtered, and the collected solid of **7a** was recrystallized from DMF/ methanol. Yield 0.06 g, 60 %.

3,8,12,17-Tetraacyl-9,9,18,18-bis(cyclopolymethylene)-6,15-dithia-2,3,8,11,12,17,19,20-octaazatricyclo[14.2.1.1^{7,16}]eicosa-1,7(20),10,16(19)-tetraene-4,13-diones (8a-b): *General Procedure:* To a solution of the macrocyles (**7a-b**) (0.001 mol) in DMF (1.5 mL) and pyridine (0.63 g, 0.008 mol), the respective acyl chloride (viz.; acetyl chloride, propanoyl chloride, and benzoyl chloride) (0.0012 mol) was added while stirring and the mixture was heated at 55-60 °C for 5-6 h. The reaction mixture was poured onto ice-cooled water (20 mL) and the separated product was filtered, washed with water, dried, flash chromatographed with benzene and the eluent was evaporated under vacum and the residue was recrystallized from benzene-pet. ether.

CYTOTOXIC ACTIVITY:

The effect of a varieties of the prepared compounds on the cell viability of mammary carcinoma cells (*Ehrlich ascites cells*) was examined. These tumor cells were obtained from seven days old tumor-bearing mice and prepared in cultures with 10000 cells/mL. The IC_{50} (μg/mL) of the cytotoxic activities of the tested compounds were performed using trypan blue dye exclusion test according to the method of Mcliman and further applied reprints.[16] Serial dilutions (100~1 μg/mL) of the tested compounds and the reference cancer chemotherapeutical compound, Doxorubicin®[17] were added to the cancer cell lines to determine the IC_{50}. A control culture cells was treated with the vehicle. Values are mean of three tubes of a single experiment. The results are listed in Table 4.

CONCLUSION

The IC_{50} evaluation of the cytotoxic activities of the indicated compounds (in Table 4) versus Doxorubicin® revealed that compounds (**3**, **4, 7b**, **8a**, **8b**, **8c**, and **8d**) have more or less the same cytotoxic activity like the reference drug. However the macromolecule **(7a)** and the 4-(*p*-chlorobenzoylhydrazino)-2-methylthioimidazoline **(5c)** displayed superior activity than the reference compound.

Table 2: Physical and analytical data of **1 ~ 8:**

compd	Formula	mp°C (solvent)	Yield (%)	Found(%) (required) C	H	N	ν max (cm^{-1})
1b	$C_7H_{12}N_4S$	182(decomp) (E)	85	45.65 45.72	6.52 6.78	30.43 30.52	3435,3289,3100.
***2a**	$C_{15}H_{18}N_4OS$	279-280 (E)	92	59.60 59.71	5.96 5.84	18.54 18.22	3410,3277,3085, 1680.
2b	$C_{15}H_{17}N_4OClS$	298-299 (decomp) (E)	95	53.49 53.51	5.05 5.44	16.64 16.92	3403,3278,3092, 1676.

2c	$C_{11}H_{18}N_4OS$	250-251 (decomp) (E)	85	51.96 51.62	7.08 7.21	22.04 22.23	3463,3261,3211, 1641.
***3**	$C_{17}H_{26}N_8OS_2$	205-206 (A)	92	48.34 48.41	6.16 6.43	26.54 26.31	3412,3273,3100, 1703.
***4**	$C_{18}H_{26}N_8O_2S_2$	252-253 (M)	87	48.00 48.23	5.77 6.11	24.88 25.11	3431,3275,3178, 1657.
***5a**	$C_{16}H_{20}N_4OS$	100-101 (B-pet. E)	55	60.75 61.06	6.32 6.38	17.72 17.84	3440, 3171, 1667.
5b	$C_{22}H_{24}N_4OS$	228-229 (E)	48	67.34 67.42	6.12 6.21	14.28 14.52	3346,3184,1674.
5c	$C_{16}H_{19}N_4OClS$	139-140 (E)	65	54.77 54.54	5.42 5.47	15.97 15.81	3352,3161,1662.
5d	$C_{22}H_{23}N_4OClS$	195-196 (E)	60	61.89 62.14	5.39 5.48	13.13 13.27	3422,3115,1661.
***6**	$C_{10}H_{15}N_4OClS$	247-248 (decomp) (M)	15	43.71 44.10	5.46 5.12	20.40 20.79	3383,3262,3072, 1676.
***7a**	$C_{20}H_{28}N_8O_2S_2$	305-307 (decomp) (M/DMF)	66	50.42 50.57	5.88 5.56	23.52 23.43	3433,3221,1705.
***7b**	$C_{18}H_{24}N_8O_2S_2$	301-302 (decomp) (M)	46	48.21 48.16	5.35 5.17	25.00 25.32	3451,3294,1699.
***8a**	$C_{28}H_{36}N_8O_6S_2$	140-141 (decomp) (B-pet. E)	42	52.17 52.21	5.59 5.63	17.39 17.56	1730,1700,1690, 1683,1672,1665.
***8b**	$C_{32}H_{44}N_8O_6S_2$	169-170 (decomp) (B-pet. E)	37	54.85 55.11	6.28 6.44	16.00 15.68	1745,1720,1699, 1688,1682,1671.
***8c**	$C_{48}H_{44}N_8O_6S_2$	130-131 (decomp) (B-pet. E)	17	64.57 64.81	4.93 5.21	12.55 12.74	1752,1723,1694, 1693,1659,1677.
8d	$C_{26}H_{32}N_8O_6S_2$	155-156 (decomp) (B- pet. E)	31	50.64 50.71	5.19 5.21	18.18 18.42	1732,1699,1690, 1677,1673,1666.

E=ethanol, M=methanol, DMF=dimethylformamide, B=benzene, pet. E=petrolium ether.

*EIMS, m/z of M^+ (%) and other important peaks of the following compounds:

2a: M^+: 302 (5.99), 120 (16.2), 105 (100).
3: M+2H: 424 (4.32), M+1H: 423 (1.27), M^+: 422 (1.22), 53 (100).
4: M^+: 450 (5.99), 198 (100).
5a: M^+: 316 (6.64), 77(100).
6: M^+: 336 (100), M+2: 338 (33).
7a: M^+: 476 (45.6), 164 (100).
7b: M^+: 448 (100).
8a: M^+: 644 (4.46), [M - CH_2=C=O]: 602 (3.1), [M - 2CH_2=C=O]: 560 (4.7), 280(100).
8b: [M-CH_3CH=C=O]: 644 (1.01), [M-2CH_3CH=C=O]: 588 (11.32), 177 (100).
8c: [M + H]: 893 (1.43), 105 (100).

Table 3: ^{1}H-NMR data of **2 ~ 8**:

1b 90 MHz	1.53-2.05 [m, 8H, $(CH_2)_4$], 10.20, 10.60, 11.09 (3 br s, 4H, N_1H, N_3H, and NH_2).
2a 90 MHz	1.30-1.70 [m, 10H, $(CH_2)_5$], 7.30-7.80 (m, 5H, C_6H_5), 9.90 (br s, 1H, N_1H), 9.95 (br s, 1H, N_3H), and 11.00 (br s, 1H, NHCO).
2b 90 MHz	1.30-1.86 [m, 10H, $(CH_2)_5$], 7.28 (d, J=9.6 Hz, 2H, aromatic hydrogens), 7.65 (d, J=9.6 Hz, 2H, aromatic hydrogens), 9.84 (br s, 1H, N_1H), 9.90 (br s, 1H, N_3H), and 11.00 (br s, 1H, NHCO).
2c 90 MHz	1.05 (t, J=9.0 Hz, $C\underline{H_3}CH_2$), 1.30-1.80 [m, 10H, $(CH_2)_5$], 2.05 (q, J=9.0 Hz, $CH_3C\underline{H_2}$), 9.40 (br s, 1H, N_1H), 9.90 (br s, 1H, N_3H), and 11.00 (br s, 1H, NHCO).
3	1.40-2.10 [m. 20H, $2(CH_2)_5$], 8.90 (br s, 2H, 2 N_1H)., 10.20 (br s, 2H, $2N_3H$), and 11.20 [br s, 2H, $CO(NH)_2$.
4	1.23-1.75 [m, 20H, $2(CH_2)_5$], 10.28 (br s, 2H, 2 N_1H). 10.82 (br s, 2H, $2N_3H$), and 11.68 [br s, 2H, $(CONH)_2$].
5a	1.40-1.70 [m, 10H, $(CH_2)_5$], 2.51 (s, 3H, SCH_3), 7.40-7.90 (m, 5H, C_6H_5), 9.70 (br s, 1H, N_3H), 10,05 (br s, 1H, NHCO).
5b	1.10-1.80 [m, 10H, $(CH_2)_5$], 4.30 (s, 2H, SCH_2), 7.10-7.90 (m, 10H, $2C_6H_5$), 9.60 (br s, 1H, N_3H), 9.99 (br s, 1H, NHCO).
5c	1.30-1.80 [m, 10H, $(CH_2)_5$], 2.52 (s, 3H, SCH_3), 7.31 (d, J=10.5 Hz, 2H, aromatic hydrogens), 7.62 (d, J=10.5 Hz, 2H, aromatic hydrogens), 9.45 (br s, 1H, N_3H), 9.80 (br s, 1H, NHCO).
5d	1.20-1.80 [m, 10H, $(CH_2)_5$], 4.30 (s, 2H, SCH_2),), 7.05 (d, J=10.5 Hz, 2H, aromatic hydrogens), 7.10-7.40 (m, 5H, C_6H_5), 7.60 (d, J=10.5 Hz, 2H, aromatic hydrogens), 9.50 (br s, 1H, N_3H), 9.79 (br s, 1H, NHCO).
***6**	1.20-1.90 [m, 10H, $(CH_2)_5$], 4.20 (s, 2H, SCH_2Cl), 9.89 (br s, 1H, N_1H), 10.00 (br s, 1H, N_3H), 11.65 (br s, 1H, NHCO).
***7a**	1.00-1.90 [m, 20H, $2(CH_2)_5$], 3.34 [d, J=13.5 Hz, 2H, axial hydrogens of $2(SCH_2)$], 4.13 [d, J=13.5 Hz, 2H, equatorial hydrogens of $2(SCH_2)$], 9.94 (br s, 2H, 2NH), 10.40 (br s, 2H, 2NHCO).
***7b**	1.60-1.90 [m, 16H, $2(CH_2)_4$], 3.33 [d, J=14.8 Hz, 2H, axial hydrogens of $2(SCH_2)$], 4.20 [d, J=14.8 Hz, 2H, equatorial hydrogens of $2(SCH_2)$], 9.91 (br s, 2H, 2NH), 10.54 (br s, 2H, 2NHCO).
8a	1.20-2.60 [m, 32H, $4(CH_3CO)$ and $2(CH_2)_5$], 4.20 [d, J=14.2 Hz, 2H, axial hydrogens of $2(SCH_2)$], 4.70 [d, J=14.2 Hz, 2H, equatorial hydrogens of $2(SCH_2)$].
8b	1.05-1.30 (m, 12H, $4C\underline{H_3}CH_2$), 1.39-1.95 [m, 20H, $2(CH_2)_5$], 2.20-2.70 (m, 8H, $4CH_3C\underline{H_2}$), 4.15 [d, J=14.0 Hz, 2H, axial hydrogens of $2(SCH_2)$], 4.55 [d, J=14.0 Hz, 2H, equatorial hydrogens of $2(SCH_2)$].
8d	1.60-2.65 [m, 28H, $4(CH_3CO)$ and $2(CH_2)_4$], 4.50 [d, J=14.0 Hz, 2H, axial hydrogens of $2(SCH_2)$], 4.90 [d, J=14.0 Hz, 2H, equatorial hydrogens of $2(SCH_2)$].

All the NH hydrogens are D_2O exchangeable in their ^{1}H-NMR spectra.

*^{13}C-NMR spectral data of the following compounds;

6 : 21.65, 24.00, 36.00, 42.50, 65.55, 148.00, 156.00, and 178.00.

7a: 21.61, 24.50, 32.50, 35.11, 66.50, 163.00, 166.10, 173.00

7b: 24.11, 32.52, 35.42, 72.09, 162.05, 165.12, 173.12.

Table 4: Effect of compounds (**2~ 8**) on the cell viability of mammary carcinoma cells:

Compd. No.	Cytotoxic activities IC_{50} (μg/mL)
3	60
4	55
5c	**5**
7a	**2.5**
7b	45
8a	40
8b	35
8c	50
8d	35
Doxorubicin®	**40**

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