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Synthesis, Characterization and Antitumor Activity of Some New Oganotellurium Compounds Containing Azomethine Group, Part One

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ABSTRACT

New tellurated schiff bases were synthesized by the reaction of the corresponding mercurated Schiff bases compounds **A1-A3** with tellurium tetrabromide in 1:1 mole ratio and that gave organyltellurium tribromides **A4-A6**. On the other hand, when mercurated schiff bases and tellurium tetrabromide brought together in 2:1 mole ratio gave diorganyltellurium dibromides compounds **A10**-**A12** followed by reduction with hydrazine hydrate gave new diorganyl tellurides **A13-A15**. Reduction of compounds **A4**-**A6** by hydrazine hydrate gave new ditellurides **A7-A9**. All compounds were characterized by elemental analysis, IR, ^{1}H , ^{13}C NMR, HSQC-NMR and mass spectra. *Invitro* anti-tumor bioactivity of some compounds were tested.

Keywords: Schiff-base; 3,4-dihydroxy benzaldehyde; Tellurium tetrabromide; HSQC- NMR; Antitumor.

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1. INTRODUCTION

There is an increasing in the synthesis of aromatic organic tellurium compounds containing electron donor nitrogen atom at position ortho to the tellurium atom [1,2] . Thus azo [3], Schiff bases [4,5], *N,N*-dimethylbenzyl amine [6] and para-substtituted anilines [2] can be ortho tellurated by various methods. McWhinnie and co-workers [7] prepared bis (*o*-aminophenyl)ditelluride by the reaction of (2-phenylazophenyl) tellurium trichloride with sodium tetrahydroborate. AL-Rubaie and co-workers [8] have reported several organotellurium compounds containing amino group in *ortho* position to tellurium atom, such as $ArTeBr_3$, Ar_2Te_2 and Ar_2Te, by the reaction of corresponding 2-amino aryl mercury chloride with tellurium tetrabromide in glacial acetic acid. These new compounds were used as precursor for the prepartion of new polymers containing tellurium *via* solution polycondensation techniques [9].

Phenols reacted with tellurium tetrachloride under relatively mild conditions in chloroform or carbon tetrachloride solution to give insoluble aryltellurium trichlorides, even when a twofold quantity of phenols was used [10,11].

Sadekov *et al* [12] made considerable contributions to the chemistry of tellurated azomethines and several tellurated Schiff bases were prepared and characterized. The ability of *β*-bromotellurenylvinyl aldehydes and monohalotellurobenzaldehydes [13] to form schiff base enable this methodology to prepare a wide range of organotellurium compounds containing -CH=N groups [14].

The aim of the present work was to synthesize some new diaryltellurium compounds containing azomethine group, and study of their biological activity as antitumor agents.

2. EXPERIMENTAL

2.1. Physical measurements

The IR spectra were recorded in the range 4000-200 cm^{-1} on a Pye-Unicam SP3-300 spectrometer using KBr discs. ^{1}H , ^{13}C and HSQC-NMR spectra were measured on a Brucker at 600, 400 and 250 MHz, with TMS as internal reference. Microanalysis for carbon, hydrogen and nitrogen were carried out by a Perkin-Elmer 240B Elemental Analyzer. Mass spectra of compounds were recorded at the analytical laboratory of Tarbiat Modares, University Tehran , Iran using Agilent Technologies-5975C spectrometer at an ionizing potential of 70 eV. Melting points of all solid compounds were determined by using a thermo.Scintific (9100), Electro thermal Engineering LTD, and uncorrected.

2.2 . Synthesis

Arylmercuric chloride containing amino group.

The compounds (2-amino-5-sulfophenyl)mercury(II)chloride , (2-amino-5- (aminooxysulfonyl) phenyl) mercury(II)chloride , (2-amino-5- carboxyphenyl) mercury(II) chloride, (5-acetyl-2-aminophenyl)mercury(II) chloride , (2-aminonaphthalen-1-yl)mercury(II) chloride, (4-hydroxyphenyl)mercury(II) chloride were prepared according to previously published procedure [15].

Synthesis of Arylmercuric chloride containing azomethine group

A mixture of 8.00 mmol of (2-amino-5-(aminooxysulfonyl)phenyl)mercury (II) chloride (3.25g) or (2-amino-5-carboxyphenyl)mercury(II) chloride (2.97g) or (5-acetyl-2-aminophenyl)mercury(II) chloride (2.95g) in 50 ml of ethanol and 3,4-dihydroxybenzaldehyde (8.00 mmole,1.104g) with 4-5 drops of sulfuric acid were refluxed with stirring for 2 h. After cooling, the precipitate was collected by filtration and washed several times with ethanol. The solid product was twice recrystallized from a mixture of ethanol and benzene (3:2) to give a yellowish solid of **A1**-**A3** compounds.

Aryltellurium tribromide (A4-A6)

The compounds were synthesized according to the literature [16] with some modifications:

A mixture of tellurium tetrabromide (4.00 mmol ,1.78 g) and arylmercuric chlorides **A1**(2.01 g) or **A2**(1.96 g) or A**3**(1.95 g) (4.00 mmol) each case in 50 ml of dry chloroform was refluxed with stirring for 4 h under argon atmosphere. The resulting solution was cooled and filtered. Recrystallization of the product from a mixture of diethyl ether and hexane (7:3) gave a redish-brown solid.

Diaryl ditullrides (Ar_2Te_2) (A7-A9)

Aryltellurium tribromide **A4**(1.97g) or **A5**(1.87g) or **A6**(1.86g) (3.00 mmol) was refluxed in ethanol (25 ml). An ethanolic solution of hydrazine hydrate was added drop wise to the refluxing solution until the evaluation of nitrogen was ceased. The resulting solution was cooled to room temperature and filtered. Recrystallization of the product by a hot ethanol gave a dark redish-brown solid of compounds **A7-A9**. Yields, color and melting points for these compounds are given in Table 1.

Diaryltellurium Dibromides (Ar_2TeBr_2) (A10-A12)

A mixture of tellurium tetrabromide (2.00 mmol ,0.89 g) and arylmercuric chloride **A1**(2.01 g) or **A2**(1.96 g) or **A3**(1.95 g) (4.00 mmol) in 35ml of dry chloroform was refluxed with stirring for 4 h under argon gas atmosphere. The resulting solution was cooled and filtered. Recrystallization of the product from a mixture of ethanol and chloroform (4:1) gave a brown to yellowish brown solid. Yields, colors and melting points for compounds **A10-A12** are given in Table1.

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Diaryl tellurides (Ar_2Te) (A13-A15)

Diaryltellurium dibromides **A10** (1.97 g) or **A11**(1.87 g) or **A12**(1.86 g)) (2.00 mmol) was dissolved in 25 ml of ethanol and refluxed . A solution of hydrazine hydrate in ethanol was added drop wisely to the refluxed solution until nitrogen evolution was ceased. The resulting solution was cooled to room temperature and filtered. The crude product was twice recrystallized from a mixture of ethanol and dichloromethane to obtain a yellow or yellowish orange solid. Yields, colors and melting points for compounds **A13-A15** are given in Table 1.

3. RESULTS and DISCUSSION

Isolated yields, melting points, colors and carbon, hydrogen, and nitrogen analytical data for all new and organotellurium compounds are given in Table 1. The present work describes the synthesis of new tellurated Schiff bases by reaction of corresponding mercurated Schiff bases (**A1**-**A3**), which in turn prepared from the reaction of aryl mercury chloride with 3,4-dihydroxy benzaldehyde, with tellurium tetrabromide in 1:1 ratio to produce the required tellurium containing materials ($ArTeBr_3$), that's compounds **(A4-A6**), (Scheme 1). When tellurated Schiff bases and tellurium tetrabromide brought together in 2:1 ratio gave the symmetrical diaryltelluride dibromides compounds (**A10-A12**).

Reduction of compounds (**A4-A6**) by ethanolic solution of hydrazine hydrate gave the corresponding ditellurides (**A7**-**A9**) in good yields. Furthermore, the diorganyl tellurides **A13**, **A14** and **A15** were prepared by the reduction of compounds **A10**, **A11** and **A12** respectively by hydrazine hydrate in boiling ethanol.

IR spectra for all compounds A**6-**A**15** displayed common features in certain regions and characteristic bands in the fingerprint and other regions. The IR spectra of all prepared compounds show one or two broad strong bands in the rang 3498-3209 cm^{-1} due to ν(O-H). The IR spectra confirm the presence of the azomethine groups (-CH=N-) stretching with a sharp region around 1633 - 1492 cm^{-1} (Table 1). The IR spectra of compounds (**A6**, **A8**, **A11**, **A12**, **A14**, **A15**) show a band at 1701- 1622 cm^{-1} range can be attributed to carbonyl group C=O**.**

The ^{1}H NMR spectra of studied compounds **A6**- **A10** and **A13**-**A15** were recorded in DMSO*d6* solution and show all the expected protons with proper intensity ratio, Table 1. It is worthy to note that the proton of azomethine resonate as a singlet between 9.70-7.88 ppm these values are in agreement with previously reported data [16.17]. The aromatic protons of all compounds appeared within the range 8.02-5.81 ppm by singlet, doublet and multiple signals. The ^{1}H NMR spectra of compounds **A6**, **A9** and **A15** showed a singlet signal at 2.42, 2.42 and 2.38 ppm respectively due to methyl protons[18], compounds **A7, A10** and **A13** showed a singlet signal at 8.12 , 7.65 and 5.86 ppm respectively can be attributed to amino protons [19], while compounds **A8** and **A14** showed singlet signal at 12.1 ppm and 11.44 ppm can be assign to hydroxyl proton for carboxyl group [18]. The signals of phenolic hydroxyl protons does not appear for all studied compounds [20,21].

The ^{1}H NMR spectra of compound **A9** appeared two singlet signals at 7.94 and 7.88 ppm in ratio 3:1 as well as tow singlet signals at 2.42 and 2.38 ppm in ratio 3:1, this confirms having of two rotational isomers: Trans rotamer 70% and Cis rotamer 30% , this case appeared clearly in ^{13}C NMR spectrum **.**

Carbon-13 NMR spectra gave further support to the formation of these new compounds (Table 1). ^{13}C NMR spectra of compound **A6** show a low field signal at 194.1 ppm can be attributed to carbon atom of carbonyl group, while compound **A9** it showed two signals at 192.93 and 192.54 ppm due to carbonyl carbon atom for trans and cis isomers [22]. ^{13}C NMR spectra of **A6** and **A9** show a low field signal at 161.05ppm and (162.66 ppm trans,161.52ppm cis) can be attributed to aromatic carbon atoms which attached with nitrogen atom (CH=N-C) [23]. The spectra revealed the presence of -CH=N- group around 160 ppm. The ^{13}C NMR spectra show a high field at 25.67ppm for **A6** and (24.63ppm trans, 23.776 ppm cis) for **A9** due to carbon atom of methyl group [15].

The HSQC NMR spectrum of compound **A6** shows the cross peak at δH/δC= 8.3/159 ppm due to azomethine group (N=CH), a set of cross peaks: δH/δC =7.9/116, 7.3/128, 7.1/130, 7.5/116 ppm and overlapping cross peak at δH/δC =7.6/131 ppm can be assigned to aromatic protons and carbon .while the cross peak at δH/δC =2.4/27 ppm can be attributed to methyl group, Table 2, Figure 1.

The mass spectra of compounds **A4**, **A7**, **A8** and **A15** was recorded at 70 eV, and gave further support for its structures. The mass spectra of compound **A4** exhibited the peak of molecular ion $[M]^+$ at *m/z* (661) with a low intensity. While compounds **A7**, **A8** and **A15** do not exhibited the peaks owing to their molecular ions $[M]^+$ [24,25]. Nonetheless exhibited the fragments which due to these compounds. All compounds show peak at *m/z* (201.9-202.0) with 43-100 % abundance due to fragment ion $[C_6H_5Te]^+$ [26] and peak at *m/z* (81.7-82) with 28-100 % abundance due to fragment ion $[C_4O_2H_2]^+$. Important fragments were also observed, confirming the proposed structures.

3.1 Invitro anti-tumor bioactivity of some studied compounds .

Synthesized compounds have been tested for their anti tumor activity towards human PC3 and T24 cancer cells. Three compounds (**A5**, **A6**, and **A18**) show activity, Table 3. As a next step the activity of compound A**18** was tested in a dose range between 3 and 100 µM towards PC3 and T24 cells. Show the effect to cell growth inhibition (I%) of PC3 and T24. The cell growth inhibition activity at 100µM is 96.02 % towards PC3 and 94.84 % towards T24. Table 3 shows that the half maximal inhibitory concentration (1C50), is a measure of the effectiveness of a compound in inhibiting biological. The range of IC50 is between 18.26 and 52.53 µM. While the range of IC50 is between 29.12 and 55.42 µM.

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In conclusion, a new series of symmetrical and unsymmetrical aryltellurium compounds were prepared by new and convenient method of these compounds exhibit some biological activity as antitumor compounds.

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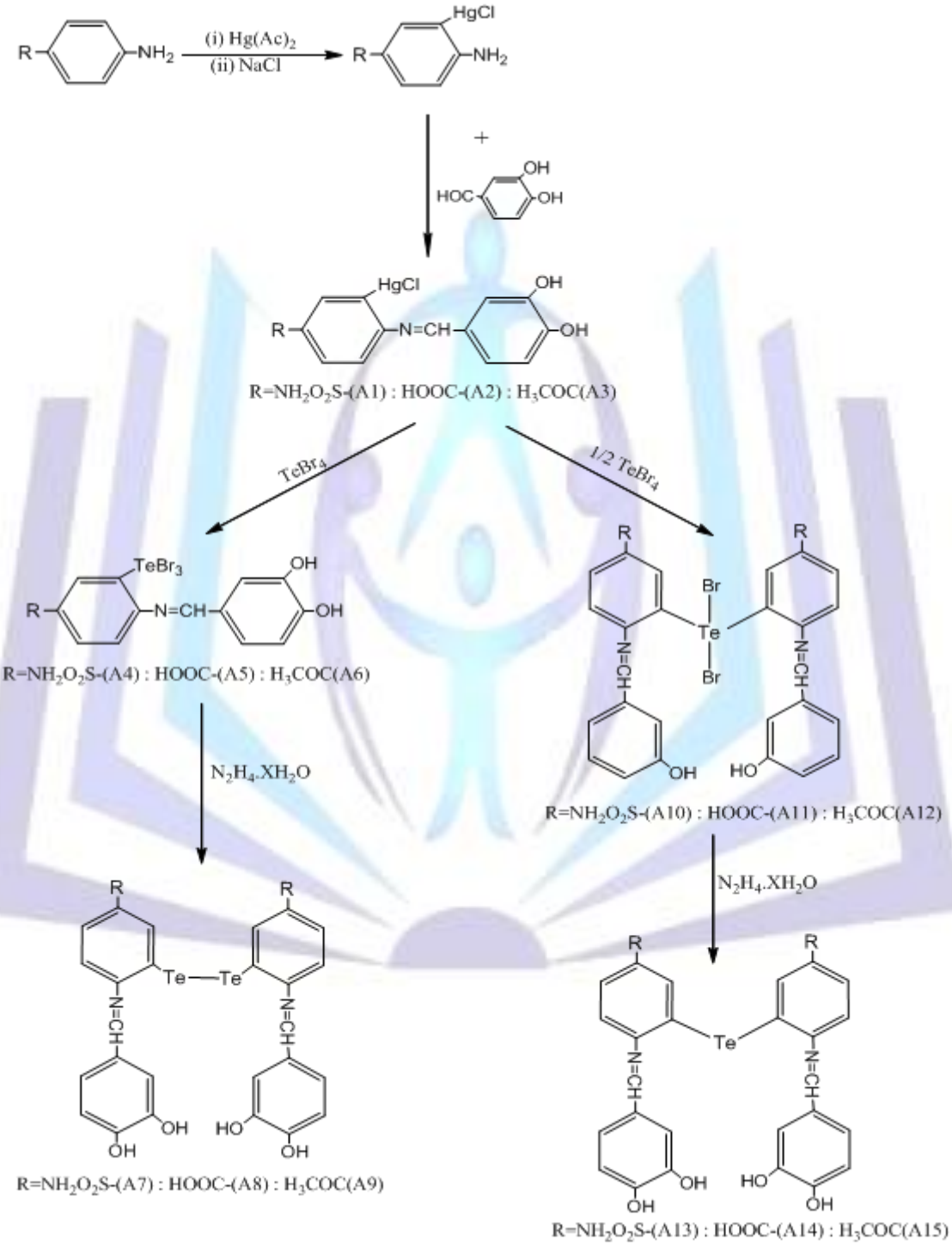

Scheme 1 : preparation methods of organotellurium compounds containing azomethaine group A1-A15

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Table 1 : Some physical properties ,elemental analysis , Infra red and 1H NMR Spectroscopy for new organotellurium compounds containing azomethine group.

Comp.	Color	Melting Point(°C)	Yield%	Analysis;Calculated (Found) C%	H%	N%	IR Cm^{-1}	^1H NMR; DMSO-d6(ppm)
A6[a]	Yellowish brown	220-222 dec.	85	28.65 (28.98)	1.87 (1.95)	1.91 (2.25)	3435*, 3024, 1685, 1615	2.42 (s , 3H , CH3), 7.05-7.89 (m,6H, Ar-H) 8.35 (s , 1H , CH=N)
A7	Reddish brown	208-210 dec.	72	36.93 (37.27)	2.55 (2.64)	6.60 (6.68)	3452*,3055, 1618	6.65 (d , 2H , Ar-H), 7.70-6.80 (m , 8H , Ar-H), 8.02 (d, 2H, Ar-H), 8.12 (s, 4H , NH_2), 8.45 (s,2H ,2CH=N)
A8	Yellowish brown	248-250 dec.	77				3394*, 3209, 1680, 1618	6.81(d,2H, Ar-H),6.96(d, 2H,Ar-H), 7.1(s,2H , Ar-H), 7.88-7.64(m,2H),8.37(s,2H, 2CH=N), 12.10 (s ,2H,2OH)
A9[b]	Dark brown	180-182 dec.	75	47.07 (47.18)	2.98 (3.17)	3.44 (3.66)	3408*, 2910, 1622	Trans: 2.42(s,6H,CH3), 7.64-6.57 (m ,12H , Ar-H) 7.94 (s , 2H , CH=N). Cis: 2.38(s,6H,CH3), 7.64-6.57(m ,12H , Ar-H), 7.88 (s , 2H , CH=N).
A10	Yellowish brown	190-192 dec.	70				3380, 3350 3229*, 3109 2900, 1622	6.55-7.53 (m,12H, Ar-H) 7.65(s, 4H , NH_2), 9.45 s ,1H ,CH=N).
A11	Yellow	183-185 dec.	69	41.72 (42.04)	2.35 (2.52)	3.42 (3.50)	3466*, 3371*, 3105, 1650, 1604	
A12	Brown	172-175 dec.	68				3435*, 3107 2908, 1624, 1595	
A13	Reddish brown	175-177 dec.	66	43.51 (43.97)	3.07 (3.12)	7.31 (7.88)	3414*, 2902 1624	5.86(s*, 4H,NH_2), 6.59(d,2H, Ar-H),6.96-6.86(m,6H,Ar-H) 7.45(d,2H,Ar-H), 7.77(s,2H, Ar-H), 8.11 (s, 2H , 2CH=N)
A14	Yellow	176-178 dec.	77				3431*, 3060, 2960, 1624 2960	6.81(d,2H,Ar-H),7.17(d,2H, Ar-H),7.57-7.23(m,6H,Ar-H) 7.65(d,2H, Ar-H),8.34(s,2H, 2CH=N), 11.33(s , 2H , 2OH)
A15	Brown	158-160 dec.	71	56.29 (56.64)	3.77 (3.80)	4.27 (4.40)	3439*, 3045 2990, 1622, 1577	2.38(s,3H,CH_3),6.58(d,Ar-H) 7.54-6.80(m,8H,Ar-H),7.68 (d,2H, Ar-H),9.63(s,2H,C=N)

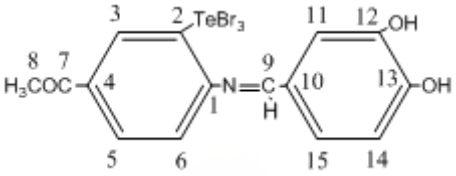
*broad singlet

[a] ^{13}C NMR in DMSO-d_6 : 194.10, 161.05,159.46,146.25,141.75,130.10,128.03,125.16,116.52(2C),25.67.

[b] **^{13}C NMR in DMSO-d_6 : Trans rotamer**, 192.93 , 162.66(2C), 160.11(2C), 146.24 (2C), 142.96 (2C), 132.37, 130.42, 126.07, 117.37(4C), 24.63(2C); **Cis rotamer**,192.54 (2C), 161.52 (2C), 159.39 (2C),

144.37 (2C), 142.41(2C), 130.02, 125.03, 116.68(4C), 23.77(2C).

Table 2: HSQC NMR data of compounds A6

Compound structure	Position	Carbon (ppm)	Proton(ppm)
	3 + 6	130	7.5
	5	128	7.1
	8	27	2.4
	9	159	8.3
	11	116	7.5
	14	116	7.9
	15	128	7.3

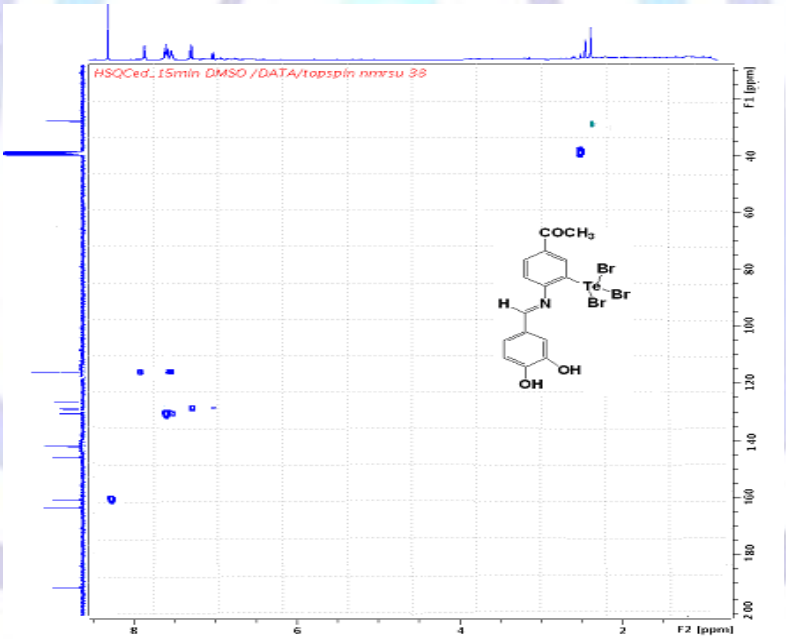


Figure 1: HSQC NMR spectrum of Compound A6 at 600 MHz

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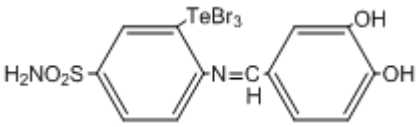
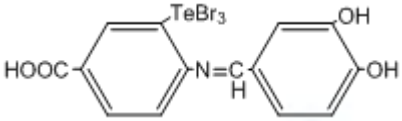
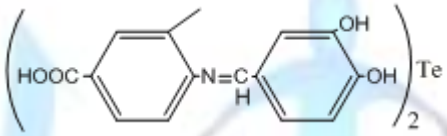
Table 3. Screening results of studied compounds against Prostate cancer cells PC24 and Bladder Cancer cells T24

Sample	Structure	PC3 cells	T24 cells
A5		++	+
A6		+	+
A18		++	++

+ = low activity , ++ = high activity

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