SYNTHESIS, CHARACTERIZATION AND ANTIFERTILITY ACTIVITY OF NEW UNSYMMENTRICAL MACROCYCLIC COMPLEXES OF TIN(II)

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ABSTRACT

A new series of unsymmetrical macrocyclic complexes of tin(II) has been prepared by the template process using bis(3-oxo-2-butylidene)propane-1,3-diamine as precursor. This affords a method to synthesize these complexes with various ring sizes. The tetradentate macrocyclic precursor [N₄mL] reacts with SnCl₂ and different diamines in a 1:1:1 molar ratio in refluxing methanol to give complexes of the type [Sn(N₄mL)Cl₂]. The ring expansion has been achieved by varying the diamine between the two diacetyl amino nitrogen atoms. The macrocyclic precursor and its metal complexes have been characterized on the basis of elemental analysis, molar conductance, molecular weight determinations, IR, ¹H NMR, ¹³C NMR, ¹¹⁹Sn NMR and electronic spectral studies. An octahedral geometry around the metal ion is suggested for these complexes. On the basis of molecular weights and conductivity measurements, their monomeric and non-electrolytic nature has been confirmed. The precursor and complexes have been screened in vitro against a number of pathogenic fungi and bacteria to assess their growth inhibiting potential. The testicular sperm density and testicular sperm morphology, sperm motility, density of cauda epididymal spermatozoa and fertility in mating trials and biochemical parameters of reproductive organs have been examined and discussed.

INTRODUCTION

The coordination chemistry of macrocyclic precursors is a fascinating area which has attracted the attention of inorganic chemists. Macrocyclic polyaamines complexes of bivalent transition metals have been of great interest due to their importance as an essential metalloenzyme active site¹ and this will help in furthering our understanding of biological systems². These precursors are also of theoretical interest as they are capable of furnishing an environment of controlled geometry and precursor filed strength³. The successful application of several 1, 4, 7, 10-tetraazaacyclododecane (cyclen) precursors to the synthesis of macrocyclic complexes stems mainly from their use as models for protein-metal binding sites in biological systems⁴ and as selective complexing agents for metal ion⁵, such as therapeutic reagents for the treatment of metal toxicity⁶,⁷. Nowadays interest is focussed on the synthesis of macrocyclic complexes with potential medicinal applications, as contrast-enhancing agents in magnetic resonance imaging (MRI)⁸,⁹ as n.m.r. shift and relaxation reagents¹⁰,¹¹ and as RNA cleavage catalyst¹²,¹³,¹⁴.

Organotin compounds exhibits a broad spectrum of biological activity which includes bactericidal, fungicidal¹⁵ antitumor¹⁶ and caridical derivatives¹⁷. Our ongoing work of tin(II) derivatives involving such systems led us to describe the synthstic and stereochemical features of some diorganotin complexes. The biochemistry of synthetic organometallic has generated active research relating to their biochemical significance¹⁸. The importance of metal-nitrogen bonding and their prominence in agricultural, medicinal and industrial chemistry led us to synthesize and screen the precursors and their macrocyclic compounds for their antifungal, antibacterial and antifertility activities.

MATERIALS AND METHODS

All reagents were obtained commercially and by standard procedures. All solvents were of reagent grade. SnCl₂ was from Sarabhai and Glaxo make. The reactions were carried out under strictly anhydrous conditions.

Preparation of bis(3-oxo-2-butylidene)propane-1,3-diamine

In a 100 ml short necked round bottomed flask, diacetyl was taken in ethanol and to this was added 1,3-diaminopropane in ethanol. The reaction was carried out in 2:1 molar ratio heated under reflux for 12 hours. The reaction mixture was cooled and the reddish brown compound obtained was recrystallised from ethanol (Yield 78%).

Preparation of complexes

The reaction mixture containing bis(3-oxo-2-butylidene)propane-1,3-diamine, diamine and tin chloride in 1:1:1 ratio in methanol was heated under reflux for 36 hours. The reaction mixture was cooled, transferred to an evaporating dish and set aside for a few hours, whereupon a dark coloured compound separated out. The product formed was washed and dried under reduced pressure, which was recrystallised from a 1:1 mixture of toluene and n-hexane in 78% yield. The physical properties and analytical data are summarized in Table I.
Table I: Physical Properties and Analytical Data of Precursor and its Compounds

| Compound                  | Colour    | M.P. (°C) | M   | N   | Cl  | C   | H   | Mol.Wt. Found (Calcd) |
|---------------------------|-----------|-----------|-----|-----|-----|-----|-----|------------------------|
| C_11H_18N_2O_2            | Reddish   | 167-169   | -   | 13.11 | - | 62.88 | 8.61 | 186.23 (210.28) |
| [Sn(C_7H_22N_4)Cl_2]      | Brown     | 210-213   | 25.33 | 11.95 | 14.99 | 43.35 | 4.67 | 459.05 (471.98) |
| [Sn(C_16H_23N_5)Cl_2]     | Orange    | 198-200   | 25.12 | 14.63 | 14.79 | 40.83 | 4.84 | 443.92 (474.98) |
| [Sn(C_8H_27N_5)Cl_2]      | Red       | 260-262   | 25.60 | 14.88 | 15.05 | 38.56 | 5.80 | 438.98 (466.99) |
| [Sn(CH_2_4N_4)Cl_2]       | Dark Brown| Above 300 | 22.80 | 10.82 | 13.43 | 48.29 | 4.60 | 494.59 (522.13) |

Analytical Methods and Physical Measurements

Conductivity measurements in dry DMF were performed with a Systronics conductivity bridge type 305 and molecular weights were determined by the Rast Camphor method. IR spectra were recorded on Perkin - Elmer 577 Grating Spectrophotometer. HNMR spectra were recorded on a Jeol FX-90Q Spectrometer in methanol and DMSO-d_6 using TMS as internal standard. Electronic spectra were recorded on a Hitachi U-2000 Spectrophotometer. ^13C NMR spectra were recorded in methanol, using TMS as the standard and ^119Sn NMR spectra were recorded on a Jeol FX-90Q Spectrometer at 33.35 MHz. The chemical shifts were determined relative to the external reference tetramethyltin. Nitrogen and chlorine were estimated by Kjeldahl's and Volhard's method, respectively. Tin was estimated gravimetrically as SnO_2. Carbon and hydrogen analyses were performed at CDRI, Lucknow.

BIOLOGICAL STUDIES

Bactericidal and fungicidal activities data of precursor and its respective complexes against pathogenic bacteria and fungi are given in Tables II and III. A culture of the test organisms was grown on PDA media (Starch, glucose, agar-agar and water) for fungi and agar media (Peptone, beef extract, agar-agar, NaCl and water) for bacteria for several days at the optimum temperature for growth. All the glassware used were sterilized in an autoclave before use. The radial growth method^19 and paper disc-plate method^20 were employed to evaluate the fungicidal (at 25 ± 1°C) and bactericidal (at 30 ± 1°C) activities, respectively.

Table II: Fungicidal Screening Data of Precursor and its Compounds (percentage inhibition after 96 h)

| Compound                  | Fusarium oxysporum | Macrophomina phaseolina |
|---------------------------|---------------------|------------------------|
| Conc.                     | 50                  | 100 200 50 100 200     |
| C_11H_18N_2O_2            | 33                  | 46 56 30 42 47         |
| [Sn(C_7H_22N_4)Cl_2]      | 47                  | 65 74 42 53 60         |
| [Sn(C_16H_23N_5)Cl_2]     | 66                  | 70 78 52 66 71         |
| [Sn(C_8H_27N_5)Cl_2]      | 34                  | 41 69 39 47 58         |
| [Sn(CH_2_4N_4)Cl_2]       | 71                  | 77 84 59 69 81         |
| Standard (Bavistin)       | 86                  | 100 100 82 100 100     |

Table III: Antibacterial Activity of Precursor and its Compounds (percentage inhibition (mm) after 24 h) (Conc. in ppm)

| Compound                  | Escherichia coli (-) | Staphylococcus aureus (+) |
|---------------------------|----------------------|--------------------------|
| Conc.                     | 500 1000             | 500 1000                 |
| C_11H_18N_2O_2            | 3 5                  | 4 6                      |
| [Sn(C_7H_22N_4)Cl_2]      | 6 7                  | 8 9                      |
| [Sn(C_16H_23N_5)Cl_2]     | 9 10                 | 11 12                    |
| [Sn(C_8H_27N_5)Cl_2]      | 4 6                  | 5 7                      |
| [Sn(CH_2_4N_4)Cl_2]       | 11 12                | 13 15                    |
| Standard (Streptomycin)   | 17 18                | 15 17                    |

Antifertility Activity

Male Wistar strains rats obtained from ICMR, New Delhi were used. Animals were housed in steel cages and maintained under standard conditions (12 h light/12 h dark cycle; 25 ± 3°C; 35-60% humidity). They were maintained on standard diet (Hindustan Lever Ltd., Mumbai) and water was provided ad libitum. Prove fertile male rats were taken and provided into six groups of six each. The group A served as vehicle (olive oil) treated control. Animals of group B and C received starting
Material and precursor (50 mg/kg b. wt. orally) suspended in olive oil for a period of 60 days. The animals of groups D, E and F received same dose of its [Sn(C_{12}H_{22}N_{4})Cl_{2}], [Sn(C_{17}H_{23}N_{5})Cl_{2}] and [Sn(C_{25}H_{27}N_{5})Cl_{2}] complexes, respectively for the same period. On day 61, testes, epididymis, seminal vesicle and ventral prostate were removed, fat and connective tissue cleared off and kept at 20°C until assayed for total protein, sialic acid, total cholesterol, glycogen and fructose by using standard laboratory techniques.

**Fertility Test**

The mating exposure tests of all animals were performed from day 55 to day 60. They were cohabited with proestrous females in ratio 1:3. The vaginal plug and the presence of sperm in the vaginal smear were checked for positive mating. The mated females were separated to note the implantation sites on day 16 of pregnancy through leprotomy.

**RESULTS AND DISCUSSION**

The elemental analyses and analytical data of the prepared complexes are given in Table I. All the complexes are stable at room temperature and non-hygroscopic. The products so obtained are soluble in common organic solvents, DMF and DMSO. Complexes have been found to be monomeric as evidenced by their molecular weight determinations. The low values of their molar conductivities (14-26 Ω^{-1} cm^{2} mol^{-1}) in anhydrous dimethylformamide show them to be non-electrolytes.

**Spectral Studies**

**IR Spectra**

The infrared spectra of the precursor and its tin complexes were recorded and important features may be summarized as follows. In the IR spectra of the complexes, the stretching and deformation vibrations of any NH2 signal are absent, indicating the formation of complexes. Strong bands appearing in the range 1615-1600 cm^{-1} are assigned to the coordinated vC=N stretching vibrations in all the complexes. Two distinct bands of the methyl moiety occurring at 2962 cm^{-1} (vCH_{3}) and 2865 cm^{-1} (vsCH_{3}) are present in all the complexes. Strong and sharp bands in the spectra of the metal complexes for C-H stretching and bending vibrations appear at ca 2820 and 1430 cm^{-1}, respectively.

**{1}H NMR Spectra**

The {1}H NMR spectrum of the precursor does not show any NH_{2} signal any more indicating that the proposed macrocyclic skeleton has been formed. A singlet observed at δ 3.14 - 3.56 ppm in the complexes may be assigned to methylene protons adjacent to nitrogen. A complex pattern in the region 2.15 – 2.25 ppm was assigned as middle methylene protons of 1,3-diaminopropane moiety. The shift of the signals towards lower field is an identification of the coordination of the precursor. A singlet observed at δ1.23-1.68 ppm in complexes and precursor is attributable to methyl protons. The complex patterns of aromatic protons were observed at 8.730-8.30 ppm in the spectra of the precursor as well as complexes. Chemical shift values are given in Table IV.

| Table IV: {1}H NMR Data (δ, ppm) of Precursor and its Compounds (in DMSO-d_{6}) |
|---------------------------------------------|----------------|----------------|----------------|
| Compound                                     | R              | -CH_{3}(s)     | >NH             | -CH_{2}-         |
| C_{11}H_{13}N_{4}O_{2}                        | 3.14 (4H)      | -              | 1.23 (12H)      | -               |
| [SnC_{12}H_{22}N_{4}Cl_{2}]                  | 3.45 (4H)      | 8.15 (H_{3,4}d)| 7.30 (H_{1,6}d)| 1.57 (12H)      |
| [SnC_{17}H_{23}N_{5}Cl_{2}]                  | 3.36 (4H)      | 8.00 (H_{3,4}s)| 7.38 (H_{d})    | 1.68 (12H)      |
| [SnC_{25}H_{27}N_{5}Cl_{2}]                  | 3.40 (12H)     | -              | 1.28 (12H)      | 4.33            |
| [SnC_{36}H_{27}N_{5}Cl_{2}]                  | 3.56 (4H)      | 8.3 (H_{3,4})  | 7.30 (H_{1,6}d)| 1.46 (12H)      |
| [SnC_{35}H_{24}N_{4}Cl_{2}]                  | 3.05 (4H)      | 7.76 (H_{1,2},b)| 6.72 (H_{2,3})  | 1.20 (12H)      |
| [SnC_{36}H_{24}N_{4}Cl_{2}]                  | 3.05 (4H)      | 7.76 (H_{1,2},b)| 6.70 (H_{1,6}d)| -               |

| Table IV: {1}H NMR Data (δ, ppm) of Precursor and its Compounds (in methanol) |
|---------------------------------------------|----------------|----------------|----------------|
| Compound                                     | R              | -CH_{3}(s)     | >NH             | -CH_{2}-         |
| C_{11}H_{13}N_{4}O_{2}                        | 2.61 (4H)      | -              | 1.02 (12H)      | -               |
| [SnC_{12}H_{22}N_{4}Cl_{2}]                  | 2.94 (4H)      | 7.63 (H_{3,4}d)| 6.78 (H_{1,6}d)| 1.05 (12H)      |
| [SnC_{17}H_{23}N_{5}Cl_{2}]                  | 2.79 (4H)      | 7.42 (H_{3,4}s)| 6.88 (H_{d})    | 1.10 (12H)      |
| [SnC_{25}H_{27}N_{5}Cl_{2}]                  | 2.84 (12H)     | -              | 6.74 (H_{1,6}d)| 1.01 (12H)      |
| [SnC_{36}H_{27}N_{5}Cl_{2}]                  | 3.05 (4H)      | 7.76 (H_{3,4}) | 6.72 (H_{2,3})  | 1.20 (12H)      |
| [SnC_{35}H_{24}N_{4}Cl_{2}]                  | 3.05 (4H)      | 7.76 (H_{1,2},b)| 6.70 (H_{1,6}d)| -               |

**{119}Sn NMR Spectra**

The {119}Sn NMR spectrum of the complex [Sn(C_{15}H_{27}N_{5})Cl_{2}] shows the signal at δ-568.96 ppm which gives good agreement with a hexacoordinated tin.

**{13}C NMR Spectra**

The {13}C NMR spectra of the unsymmetrical complexes are comparable to those of their precursor and the assigned peaks position are listed in Table V. The shift of carbons attached to nitrogen indicate the
involvement of these atoms in coordination and support the formation of macrocyclic framework, as reported earlier also\textsuperscript{24,25}.

Table V: \textsuperscript{13}C NMR Spectral Data (\(\delta, \text{ ppm}\)) of Precursor and its Compounds

| Compound | >C=O | >N-CH\(_2\) | >C=N | -CH\(_3\) | R       | -CH\(_2\)- |
|----------|------|-----------|------|--------|---------|-----------|
| C\(_{11}\)H\(_{20}\)N\(_2\)O\(_2\) | 168.34 | 40.89 | 151.98 | 12.30 | - | 28.52 |
| [Sn(C\(_{17}\)H\(_{22}\)N\(_4\))Cl\(_2\)] | - | 43.54 | 162.04 | 16.82 | C\(_{16}\), 129.74; C\(_{25}\), 127.21; C\(_{36}\), 125.82 | 31.78 |
| [Sn(C\(_{6}\)H\(_{13}\)N\(_3\))Cl\(_2\)] | - | 45.28 | 158.45 | 11.26 | C\(_{16}\), 136.60; C\(_{25}\), 125.09; C\(_{36}\), 124.38 | 26.01 |
| [Sn(C\(_{9}\)H\(_{27}\)N\(_3\))Cl\(_2\)] | - | 40.96 | 165.73 | 19.02 | - | 33.05 |
| [Sn(C\(_{2}\)H\(_{4}\)N\(_4\))Cl\(_2\)] | - | 44.48 | 160.82 | 12.40 | C\(_{25}\), 128.63; C\(_{36}\), 127.83; C\(_{45}\), 126.71 | 35.92 |

Electronic Spectra

The electronic spectra of the complexes were recorded in distilled DMSO. The absorption maximum appear at 423 nm in the case of precursor can be assigned to the n-\(\pi^*\) transitions of the azomethine group. This band is shifted by 10-15 nm, which is consistent with the nitrogen coordination of macrocyclic precursor\textsuperscript{26}. In addition to this band, the spectra of the metal complexes exhibit bands around 295 nm and 339 nm due to \(\pi-\pi^*\) electronic transitions. However, the position of these remains almost same as that of the precursor.

On the basis of above evidences, structure (I) may be proposed.

![Chemical Structure](image)

Biochemical Aspects

From Tables II and III, it is clear that the toxicity increases as the concentration and complexation increased. The mechanism of the toxicity of these complexes to microorganisms may be due to the inhibition of energy or ATP production\textsuperscript{21}, for instance by inhibition of respiration or by uncoupling of oxidative phosphorylation. The energy producing processes are located partly in the cytoplasm and partly in the mitochondria. It is apparent from the bactericidal activity towards \textit{Staphylococcus aureus} as compared to \textit{Escherichia coli}. The reason is the difference in the structure of the cell walls of organisms with (+) and (-) strains, respectively. The walls of Gram(-) cells are more complex than those of Gram (+) cells. The lipopolysaccharide forms an outer lipid membrane and contributes to the complex antigenic specificity of Gram(-) cells.

Starting material, precursors and their complexes treatment did not alter the body weights of rats. However, the weights of testes, epididymis, seminal vesicle and ventral prostate were reduced significantly. (Table VI)
### Table VI: Changes in the Body Weight of Reproductive Organs after Treatment with Various Compounds

| Group | Treatment     | Body Weight (g) | Testes | Epididymis | Ventral Prostate | Seminal Vesicle |
|-------|---------------|-----------------|--------|------------|-----------------|----------------|
|       |               | Initial         | Final  | Mg/100 g b. wt. |                 |                |
| A     | Control       | 240±15          | 260±10* | 1350±45  | 600±10          | 320±10         | 650±15         |
| B     | C₄H₆O₂       | 235±8           | 245±10* | 1120±20  | 510±20          | 280±15         | 550±10         |
| C     | C₃H₄N₂O₂     | 220±9           | 230±12* | 1050±30  | 450±10          | 200±15         | 525±12         |
| D     | [Sn(C₇H₂₂N₄)CI₂] | 245±11         | 250±14* | 1020±20  | 430±15          | 190±10         | 503±8          |
| E     | [Sn(C₆H₃N₂)CI₂] | 238±10         | 246±8*  | 905±30   | 410±10          | 170±5          | 500±15         |
| F     | [Sn(CsH₇N)CI₂]  | 210±15         | 225±13* | 900±20   | 405±15          | 155±10         | 450±9          |

* a = p < 0.05, b = p < 0.001, c = p = NS. Group B compared with A, Groups C, D, E and F compared with B.

### Sperm Concentration / Motility / Fertility

Oral administration of various complexes to rats significantly reduced sperm concentration of testes and epididymis. The motility of cauda epididymal sperms was also reduced significantly. Various compounds reduced the fertility of male rats (Table VII).

### Table VII: Sperm Motility, Concentration and Fertility after Treatment with Precursor and Compounds

| Group | Treatment     | Sperm Motility (%) | Sperm Density (Million/ml) | Fertility (%) |
|-------|---------------|---------------------|----------------------------|---------------|
|       |               | Cauda Epididymis    | Testes                    | Cauda epididymis |
| A     | Control       | 74.5±2.4           | 4.30±0.25                 | 55.2±3.0      | 100% (+ve)     |
| B     | C₄H₆O₂       | 60.5±7.0*          | 2.9±0.3*                  | 45±2.0*       | 85% (+ve)      |
| C     | C₃H₄N₂O₂     | 45±5.0*            | 2.0±0.02*                 | 30±1.0*       | 90% (+ve)      |
| D     | [Sn(C₇H₂₂N₄)CI₂] | 40±5.3*          | 1.9±0.01*                 | 25±2.0*       | 92% (+ve)      |
| E     | [Sn(C₆H₃N₂)CI₂] | 38±3.5*            | 1.1±0.2*                  | 20±3.0*       | 95% (+ve)      |
| F     | [Sn(CsH₇N)CI₂]  | 35±3.2*            | 0.8±0.3*                  | 15±2.0*       | 90% (+ve)      |

*Cf Table VI

### BIOCHEMICAL PARAMETERS

Protein contents of testes, epididymis, auxiliary glands (seminal vesicle and ventral prostate) were reduced significantly after treatments with various compounds as compared to controls. Sialic acid contents of the testes, epididymis, seminal vesicle and ventral prostate were depleted (Table VIII). Testicular glycogen, cholesterol and seminal vesicular fructose were decreased significantly (Table IX).

### Table VIII: Effects of Various Compounds on Total Protein and Sialic acid Contents of Various Reproductive Organs of Male Rats

| Group | Treatment     | Total Protein (mg/gm) | Sialic Acid (mg/gm) |
|-------|---------------|-----------------------|---------------------|
|       |               | Testes                | Epididymis          | Ventral Prostate | Seminal Vesicle |
| A     | Control       | 180±5                 | 275±10              | 170±8           | 190±10         | 4.5±0.3         | 6.0±0.1         | 5.3±0.2         | 4.3±0.1         |
| B     | C₄H₆O₂       | 159±2*                | 215±15*             | 140±5*          | 150±5*         | 3.7±0.1*        | 5.0±0.2*        | 4.5±0.2*        | 3.9±0.2*        |
| C     | C₃H₄N₂O₂     | 125±10b               | 180±5*              | 112±3*          | 125±2b         | 2.9±0.2b        | 4.0±0.02b       | 4.3±0.1b        | 3.1±0.1b        |
| D     | [Sn(C₇H₂₂N₄)CI₂] | 120±7b              | 150±8*              | 100±3b          | 115±4b         | 2.5±0.1b        | 3.8±0.01b       | 4.2±0.2b        | 3.0±0.2b        |
| E     | [Sn(C₆H₃N₂)CI₂] | 105±10b              | 130±10b             | 98±0.7b         | 108±7b         | 2.4±0.2b        | 3.9±0.02b       | 4.0±0.1b        | 2.9±0.3b        |
| F     | [Sn(CsH₇N)CI₂]  | 100±15b              | 110±7b              | 100±5b          | 105±8b         | 2.5±0.08b       | 3.5±0.01b       | 3.5±0.2b        | 2.8±0.2b        |

*Cf Table VI

The present study indicates that oral administration of various compounds brought about a significant reduction in weight of testes, epididymis, ventral prostate and seminal vesicles. The reduced testicular and sex accessories weight reflect wide spread cellular alteration and androgen depletion in the sex organs. Significant reduction in the sperm motility of cauda epididymis was observed in all experimental groups. This may be due to an interference with enzyme reactions including the oxidation phosphorylation uncoupling. Our biochemical studies revealed reduction in testicular glycerogen probably due to a decrease of the number of post meiotic germ cells, which are sites of the glucose metabolism. Decreased protein contents of testes and sex accessories after administration of these complexes could be correlated with loss of total membrane protein and fall in circulating androgen. Reduced sialic acid contents of seminal vesicle caused degenerative changes on the structural integrity sperm cells. Addition of the tin moiety and diamines enhance the activity.
Table IX: Changes in Tissue Cholesterol, Glycogen and Fructose Contents after Treatment with Various Compounds in Male Rats

| Group | Treatment          | Testicular Cholesterol (mg/gm) | Testicular Glycogen (mg/gm) | Seminal Vesicular Fructose (mg/gm) |
|-------|--------------------|-------------------------------|-----------------------------|-----------------------------------|
| A     | Control            | 7.9±0.5                       | 4.83±0.5                    | 480±18                            |
| B     | C6H6O2             | 6.9±0.03                      | 4.0±0.3                     | 390±10                            |
| C     | C1H2N4O2           | 6.2±0.07                      | 3.9±0.05                    | 300±15                            |
| D     | [Sn(C7H2N4)Cl2]    | 6.0±0.03                      | 3.8±0.03                    | 250±20                            |
| E     | [Sn(C16H23N5)Cl2]  | 5.0±0.07                      | 3.0±0.03                    | 230±15                            |
| F     | [Sn(CsH27Ns)Cl2]   | 4.4±0.09                      | 3.1±0.03                    | 150±10                            |

Cf Table VI

Nevertheless, the present results amply demonstrate the effects of these compounds on the male reproductive system of rats and the important endocrine function of biosynthesis and secretion of androgen 35. Further, the current study strongly demonstrate that compound E and F are more effective in inhibiting fertility.

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