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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

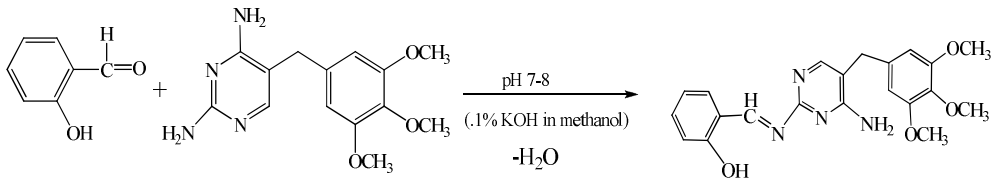
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

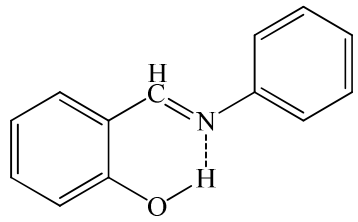



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

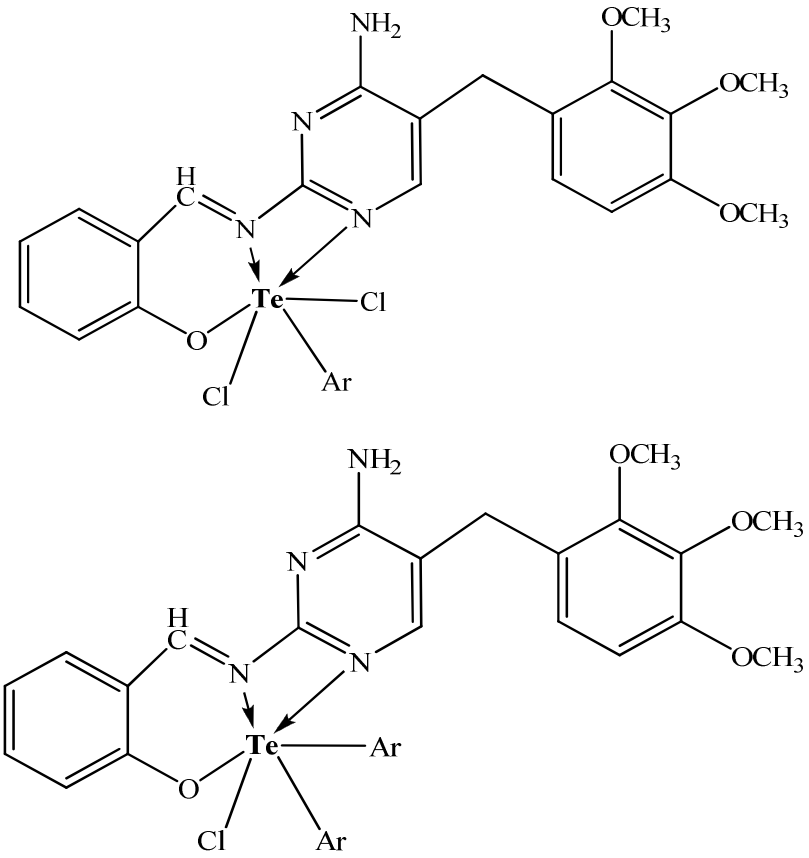
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

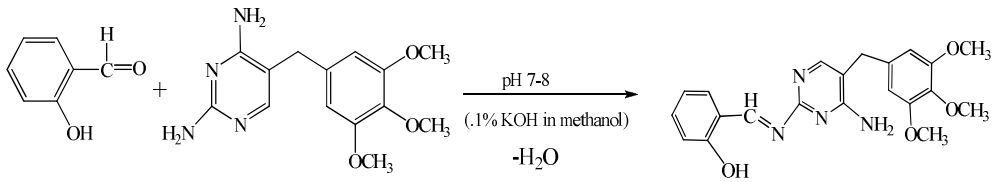
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

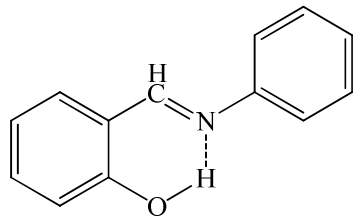



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

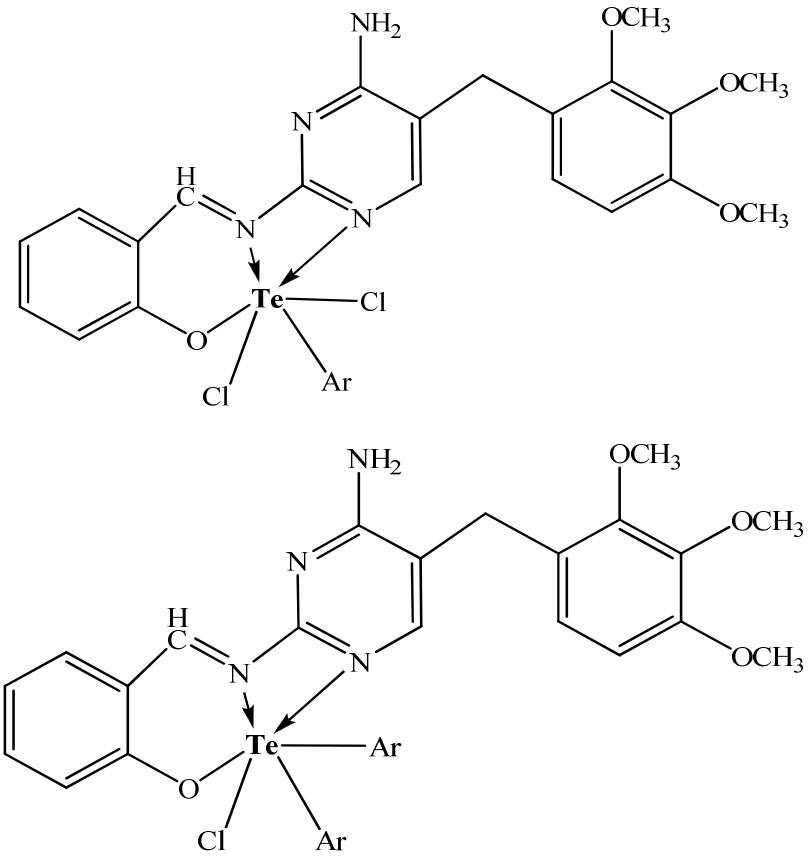
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

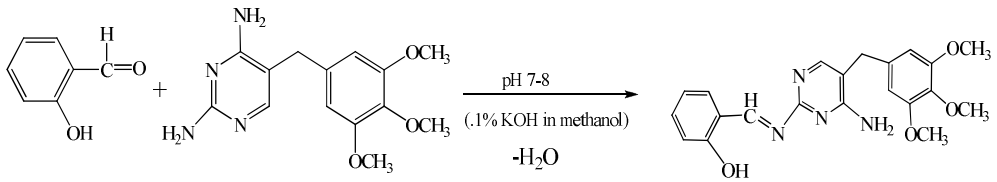
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

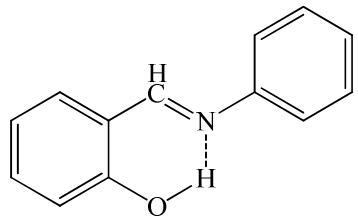



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

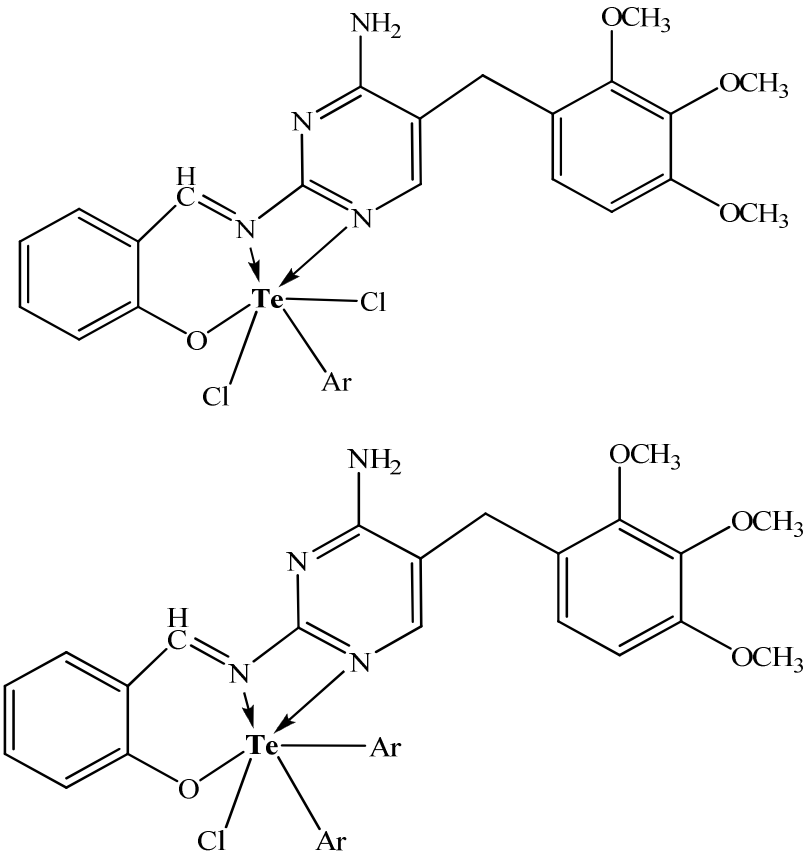
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

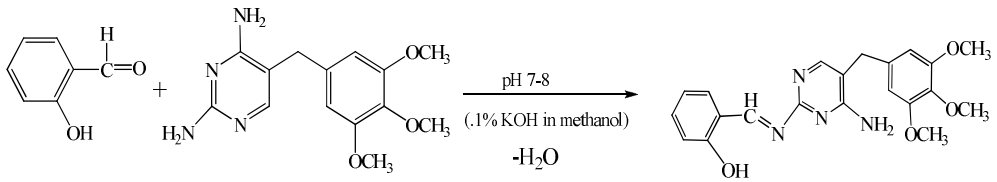
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

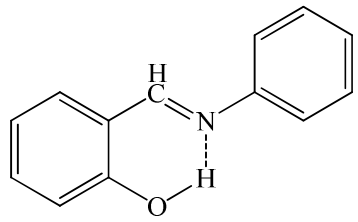



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

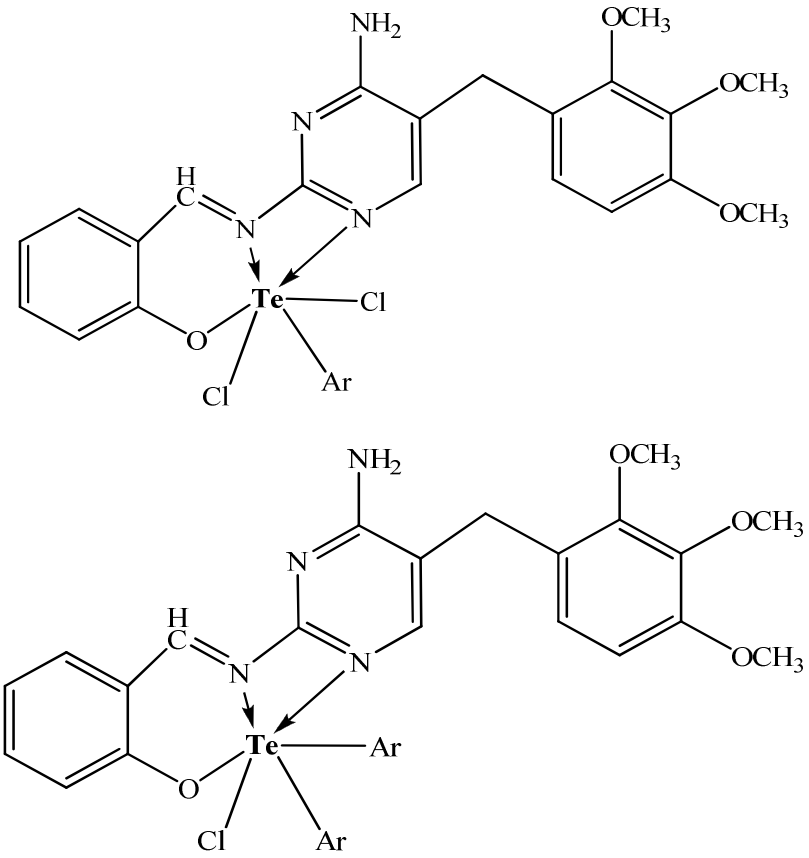
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

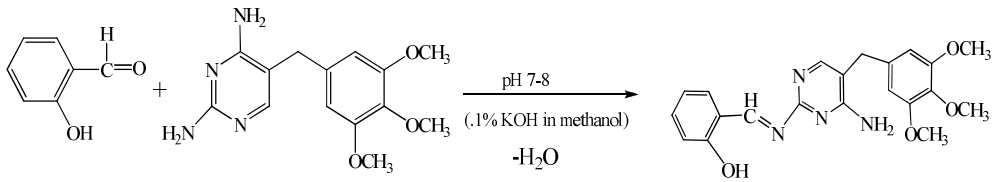
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

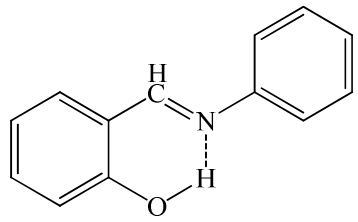



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

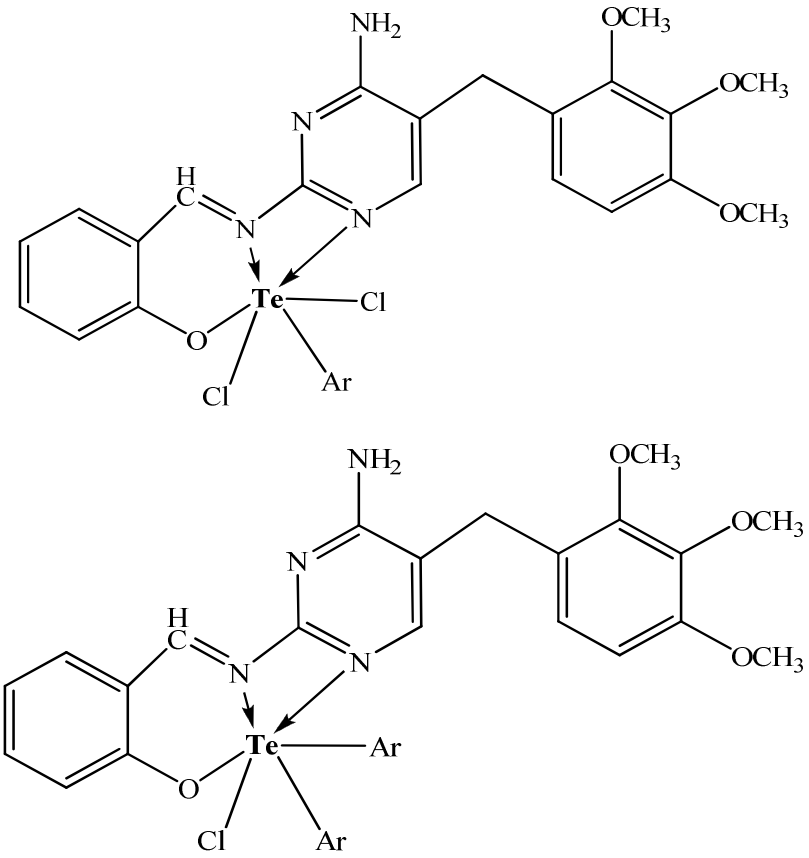
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

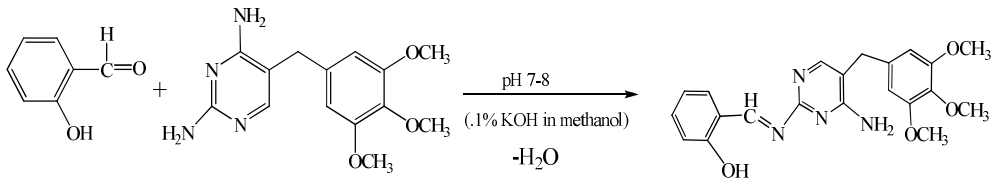
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

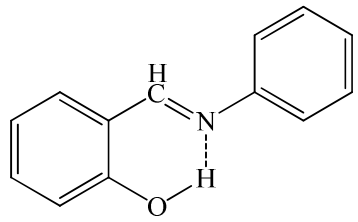



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

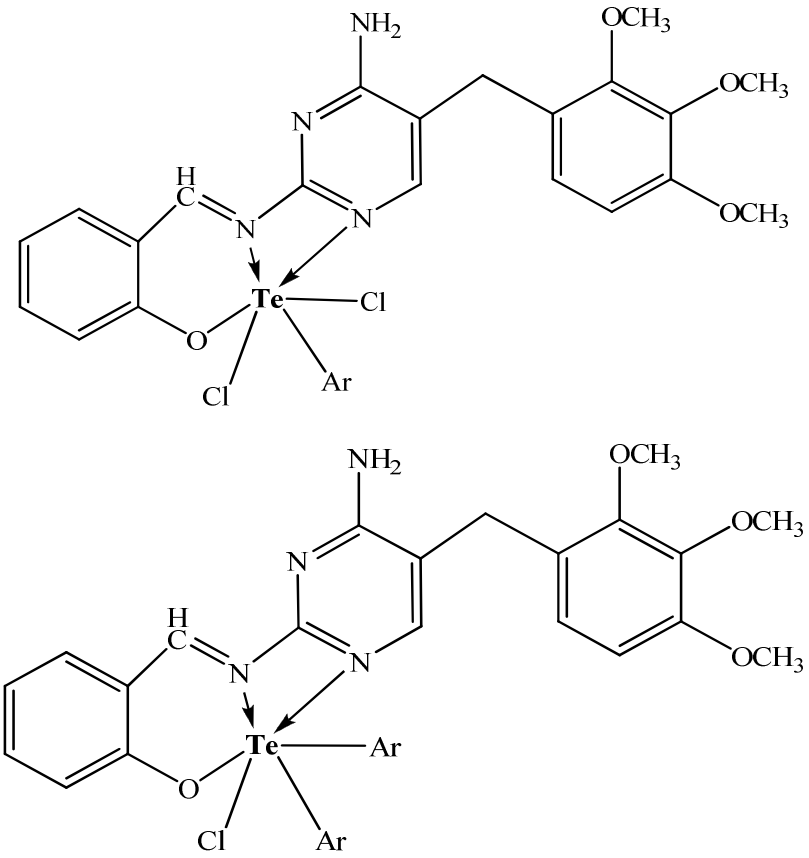
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

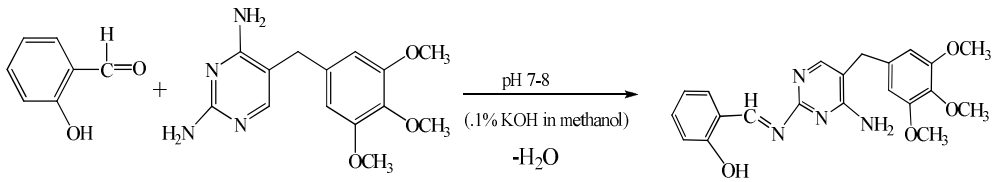
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

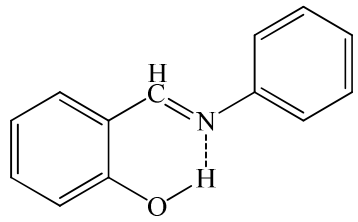



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

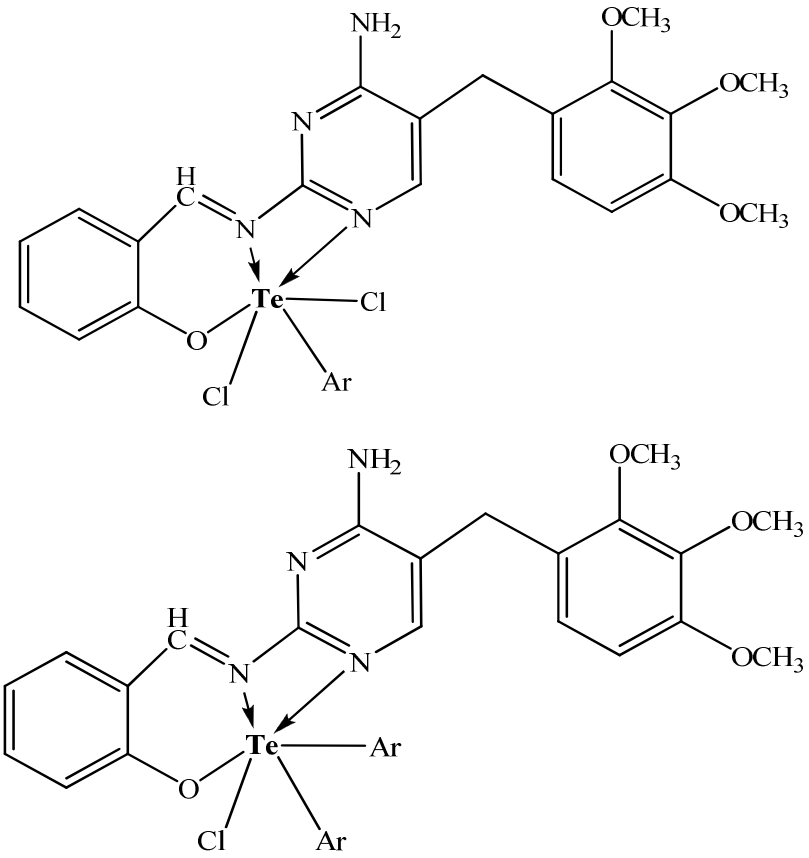
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

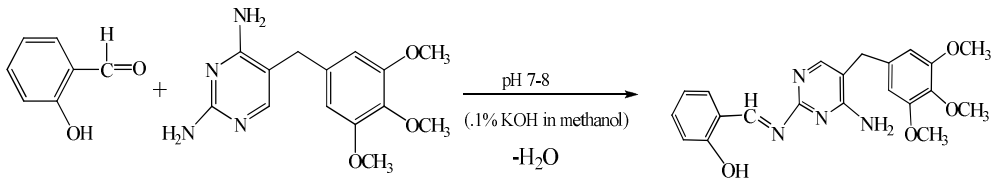
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

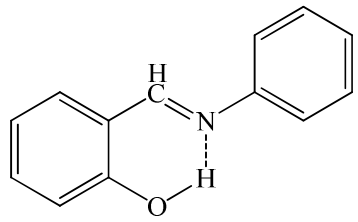



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

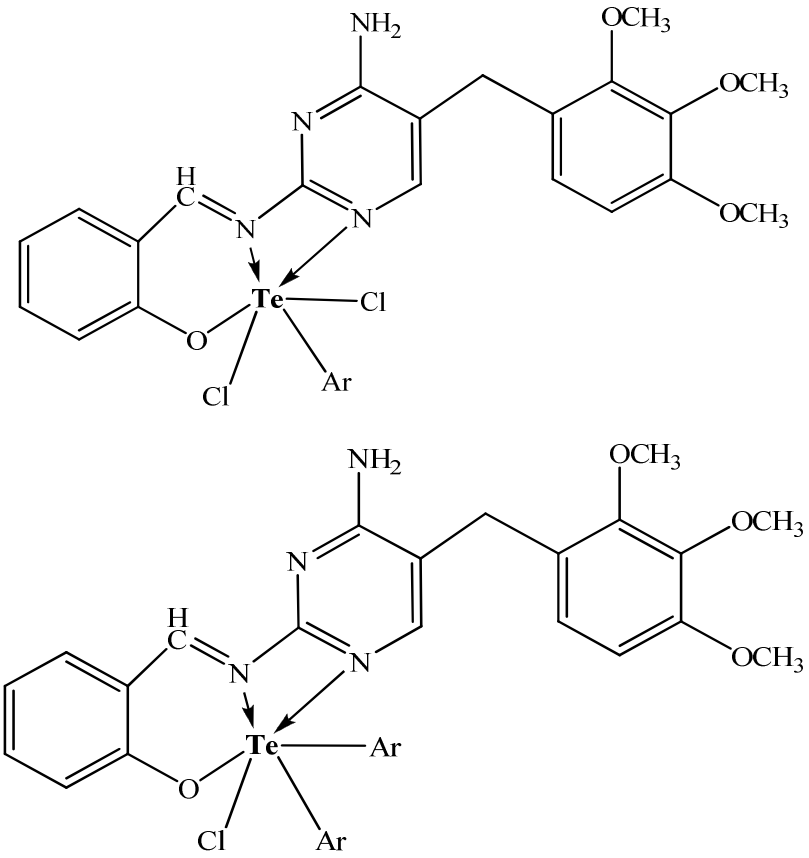
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

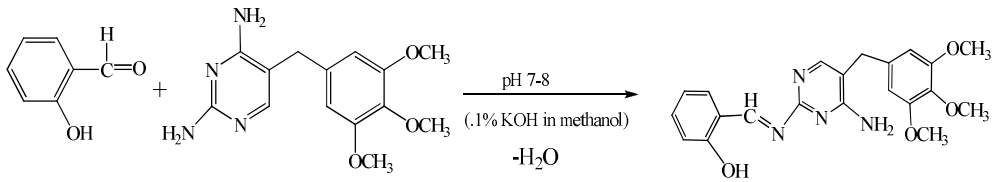
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

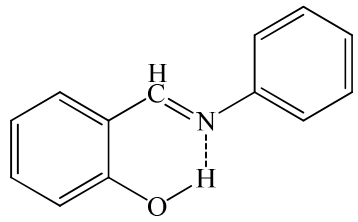



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

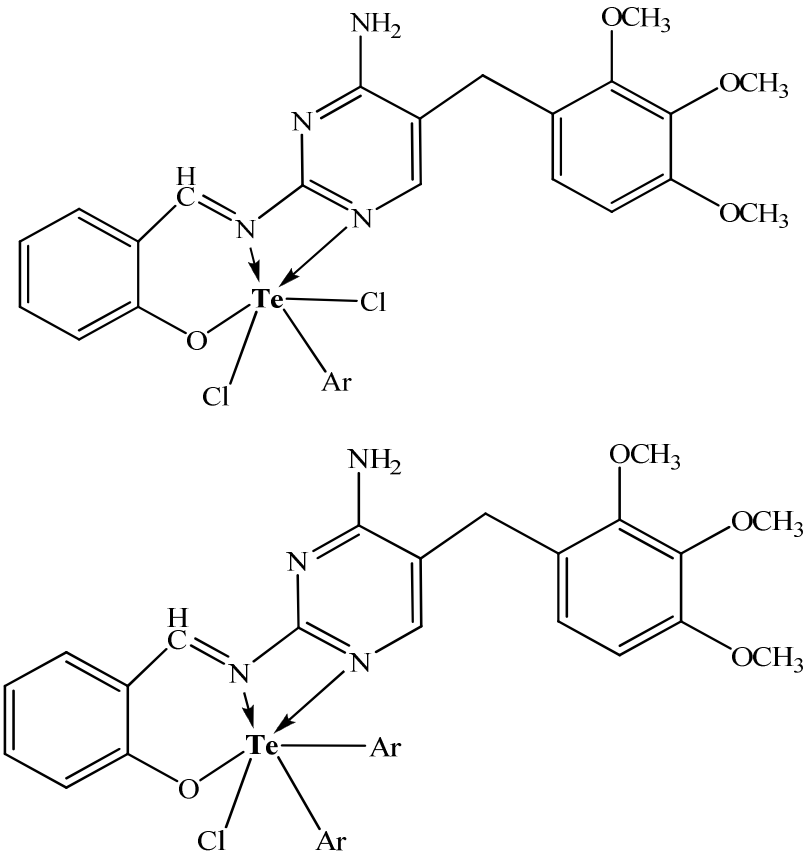
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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**RESEARCH ARTICLE**

# Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium(IV)

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**Abstract:** A novel monobasic tridentate Schiff base salicylidene-trimethoprim, Sal-TMP, synthesized from trimethoprim and salicylaldehyde, form stable complexes with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides of the type Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ (where Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl). These have been characterized by elemental analyses, molar conductance, IR and $^1H$ NMR spectroscopy. The spectral studies predict the bonding of ligand through phenolic oxygen of Schiff base after deprotonation, nitrogen of the azomethine group and pyrimidine nitrogen to give hexa-coordinated tellurium(IV) complexes. The complexes have also been screened for their antimicrobial activities against various bacteria and fungi organisms.

**Keywords:** Salicylidene-trimethoprim Schiff base, Aryltellurium(IV), Diaryltellurium(IV), Antibacterial, Antifungal activities

## Introduction

Trimethoprim and its derivatives are broad spectrum antimicrobial agents with anti-parasitic activity[1-6] and were first described by Roth and coworker[5]. Schiff bases, also known as azomethine due to presence of –C=N– group, play important role in biological system, such as anticancer[7-12], antibacterial[13-15], antiviral[16-18], antifungal[19-21] and other biological properties[22-27] and also have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as chelating agent[28-32]. Medicinal chemists have reported new derivatives of trimethoprim(TMZ)[33-35] including the Schiff base derived from salicylaldehyde[2-4,36,37].

Also, aryltellurium(IV) chlorides are known[38-54] to act as Lewis acids and form complexes with several N-, O- and S- donor bases. In view of this, we herein report some new complexes derived from aryltellurium(IV) trichlorides, $RTeCl_3$ and diaryltellurium(IV) dichlorides, $R_2TeCl_2$ with salicylidene-trimethoprim Schiff base(Sal-TMP).

## Experimental

All preparations were carried out under dry $N_2$ atmosphere and the solvents used were purified by standard method[55,56] before use. The purity of compounds was checked by thin layer chromatography using silica gel-G (Merck). Melting points were determined in open capillary tube and are uncorrected.

Carbon, hydrogen and nitrogen analyses were obtained microanalytically from SAIF, Panjab University Chandigarh on a ThermoFinnigan CHNS analyser. Conductivity was measured in DMSO at 25±2 $^oC$ with dip type conductivity cell on a microprocessor based conductivity bridge type MICROSIL.

IR (4000-400 $cm^{-1}$) and far IR (400-50 $cm^{-1}$) spectra were recorded in KBr/polyethylene pellets on a FT-Infrared spectrophotometer model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO-$d_6$ using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer. The antimicrobial screening was carried out by tube dilution method at Department of Pharmaceutical Sciences, M. D. University, Rohtak, India.

### *Preparation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

*p*-Methoxyphenyltellurium(IV) trichloride[57,58], bis(*p*-methoxyphenyl)tellurium(IV) dichloride[58,59], *p*-ethoxyphenyltellurium (IV) trichloride[60], bis(*p*-ethoxyphenyl)tellurium dichloride[60] *p*-hydroxyphenyltellurium(IV) trichloride[61], bis(*p*-hydroxyphenyl) tellurium(IV) dichloride[61], 3-methyl-4-hydroxyphenyltellurium(IV) trichloride[62] and bis(3-methyl-4-hydroxyphenyl)tellurium(IV) dichloride[62] were prepared by the reactions of $TeCl_4$ with anisole, phenetole, phenol, *o*-cresol respectively, by the methods reported in the literature[57-62].

### *Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP)*

Equimolar quantity of saturated methanolic solution of drug and salicylaldehyde were mixed thoroughly. To this mixture 0.1% methanolic KOH was added to adjust the pH of the solution between 7-8 and was refluxed for 2 hours. A clear yellowish-green coloured solution was obtained. After completion of the reaction, the Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was filtered and dried under *vacuum* and kept in desiccator over $P_4O_{10}$ until further use. Yield = 80%, M.pt.(decomp.)=188-190 $^oC$. Analysis (Calculated) $C_{21}H_{22}N_4O_4$:C(63.95), H(5.62) and N(14.20); Found: C(63.50), H(5.27) and N(13.99).

### *Preparation of salicylidene-trimethoprim complexes of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides*

Aryltellurium(IV) trichlorides, $ArTeCl_3$ and diaryltellurium(IV) dichlorides $Ar_2TeCl_2$ (Ar= *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl), when reacted with sodium salt of salicylidene-trimethoprim in equimolar ratio, yield Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ type complexes.

Sodium salt of the ligand was prepared by reacting equimolar (1:1) quantity of sodium metal and Schiff base in methanol. The solvent was distilled off to obtain sodium salt of Schiff base. Then a methanolic saturated solution of 2 mmol of aryltellurium(IV) trichloride or diaryltellurium(IV) dichloride was added dropwise to suspension of 2 mmol of sodium salt of Schiff base in about 50 mL benzene under reflux. The reaction mixture was further refluxed for 3-4 hours, cooled and precipitated sodium chloride was filtered off. The filtrate was then concentrated to about one third of original volume under reduced pressure and cooled in an ice bath to obtain coloured product. This was filtered, washed with benzene + methanol (1:1) and dried *in vacuum* desiccator over $P_4O_{10}$.

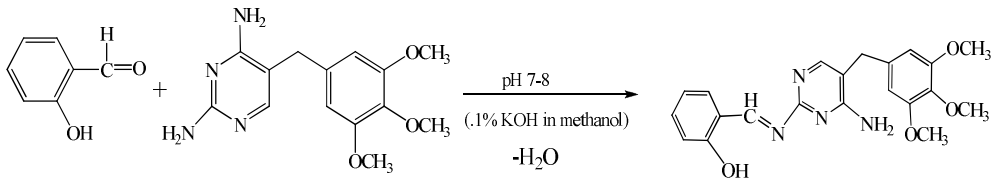
## Results and Discussion

$TeCl_4$ when heated with anisole[57-59], phenetole[60], phenol[61], *o*-cresol[62] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby $TeCl_3^+$ unit attacks a position *para* to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides.

$$Ar\text{-}H + TeCl_4 \longrightarrow ArTeCl_3 + HCl \quad (1)$$

$$2\ Ar\text{-}H + TeCl_4 \longrightarrow Ar_2TeCl_2 + 2\ HCl \quad (2)$$

Preparation of salicylidene-trimethoprim Schiff base (Sal-TMP) by the reaction of trimethoprim drug and salicylaldehyde can be represented by following equations.




Sodium salt of salicylidene-trimethoprim Schiff base (Sal-TMP) reacts with aryltellurium(IV) trichlorides and diaryltellurium(IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium(IV) complexes.

$$\text{Sal-TMP} + ArTeCl_3 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).ArTeCl_2 \quad (3)$$

$$\text{Sal-TMP} + Ar_2TeCl_2 \xrightarrow[-NaCl]{Na/CH_3OH} (\text{Sal-TMP}).Ar_2TeCl_2 \quad (4)$$

All the tellurium(IV) complexes are coloured, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analysed for their tellurium, chlorine, carbon, hydrogen and nitrogen contents and the data along with their physical properties and yields are presented in Table 1.

### *Conductance studies*

Molar conductance ($\Lambda_M$) data for the complexes in DMSO are complied in Table 1. The $\Lambda_M$ value at *ca.* $10^{-3}$ M for aryltellurium(IV) complexes in DMSO lie in the range 27.36-91.83 S $cm^2$ $mol^{-1}$ which predict the non electrolyte to 1:1 electrolyte[63,64] type behaviour of these complexes in DMSO, probably due to ionization into $ArTeCl.Sal\text{-}TMP^+/Ar_2Te.Sal\text{-}TMP^+$ and $Cl^-$ in DMSO. This conductance behavoiur of tellurium(IV) salicylidene-trimethoprim Schiff base complexes is different from those of transition metal complexes[65], which are reported to be non-electrolytes. The higher $\Lambda_M$ values for some complexes may be due to steric factors and donor behaviour of DMSO to result in probable dissociation into solvated cation and $L^-$ along with $Cl^-$ in DMSO.

### *Infrared spectra*

The IR data of Schiff base and its tellurium(IV) complexes are listed in Table 2. The spectra of Sal-TMP Schiff base complexes are quite complex and an attempt has therefore been made to identify the donor sites by comparing the spectra of complexes with parent ligand and $ArTeCl_3/Ar_2TeCl_2$.

**Table 1.** Analytical data, molar conductance and physical properties of salicylidene-trimethoprim Schiff base (Sal-TMP) complexes of tellurium(IV)

| Compound No. | Complex (Ar) | Empirical formula (Formula Wt.) | Colour (Yield, %) | M. Pt. °C dec. | Analyses % Found (Calculated) | | | | | $\Lambda_M$ at *ca.* $10^{-3}$ M S $cm^2mol^{-1}$ in DMSO |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | Te | Cl | |
| Schiff Base | Sal-TMP | $C_{21}H_{22}N_4O_4$ | Yellowish –green (80) | 188-190 | 63.50 (63.95) | 5.27 (5.62) | 13.99 (14.20) | - | - | - |
| I | (Sal-TMP).$ArTeCl_2$ (*p*-methoxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (92) | 230-232 | 47.88 (48.11) | 3.99 (4.04) | 7.75 (8.01) | 18.07 (18.24) | 9.89 (10.01) | 53.19 |
| II | (Sal-TMP).$ArTeCl_2$ (*p*-ethoxyphenyl) | $C_{29}H_{30}Cl_2N_4O_5Te$ (713.08) | Cream (85) | 258-260 | 48.12 (48.85) | 3.87 (4.24) | 7.52 (7.86) | 17.38 (17.89) | 9.52 (9.81) | 52.88 |
| III | (Sal-TMP).$ArTeCl_2$ (*p*-hydroxyphenyl) | $C_{27}H_{26}Cl_2N_4O_5Te$ (685.03) | Dark cream (94) | 208-210 | 46.78 (47.34) | 3.50 (3.83) | 7.88 (8.18) | 18.28 (18.63) | 9.98 (10.21) | 55.73 |
| IV | (Sal-TMP).$ArTeCl_2$ (3-methyl-4-hydroxyphenyl) | $C_{28}H_{28}Cl_2N_4O_5Te$ (699.05) | Light cream (80) | 198-200 | 47.58 (48.11) | 3.84 (4.04) | 7.80 (8.01) | 18.15 (18.24) | 9.85 (10.01) | 58.68 |
| V | (Sal-TMP).$Ar_2TeCl$ (*p*-methoxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Pale yellow (84) | 130-132 | 53.84 (54.54) | 4.31 (4.58) | 7.11 (7.27) | 16.43 (16.56) | 4.42 (4.60) | 91.83 |
| VI | (Sal-TMP).$Ar_2TeCl$ (*p*-ethoxyphenyl) | $C_{37}H_{39}ClN_4O_6Te$ (798.78) | Light yellow (86) | 150-152 | 54.84 (55.63) | 4.53 (4.92) | 6.84 (7.01) | 15.50 (15.97) | 4.30 (4.44) | 35.90 |
| VII | (Sal-TMP).$Ar_2TeCl$ (*p*-hydroxyphenyl) | $C_{33}H_{31}ClN_4O_6Te$ (742.68) | Red (89) | 146-148 | 52.84 (53.37) | 4.01 (4.21) | 7.27 (7.54) | 16.89 (17.18) | 4.52 (4.77) | 36.00 |
| VIII | (Sal-TMP).$Ar_2TeCl$ (3-methyl-4-hydroxyphenyl) | $C_{35}H_{35}ClN_4O_6Te$ (770.73) | Brown (78) | 140-142 | 53.80 (54.54) | 4.34 (4.58) | 7.09 (7.27) | 16.45 (16.56) | 4.32 (4.60) | 27.36 |

*Values of $\Lambda_M$ reported[63 64] for 1:1 electrolytes in DMSO=50-70 S $cm^2$ $mol^{-1}$*

**Table 2**. Important infrared absorption bands ($cm^{-1}$) of Schiff base (Sal-TMP) and complexes

| Compound | $\nu_{(O-H)}$ | $\nu_{(N-H)}$ | $\nu_{(C=N)}$ | $\nu_{(C=N)\ pyrimidine}$ | $\nu_{(C-O)}$ | $\nu_{(Te-N)}$ | $\nu_{(Te-O)}$ |
|---|---|---|---|---|---|---|---|
| Sal-TMP | 2836 w | 3317 m 3119 m | 1636 sh | 1633 w 1593 s | 1263 s | - | - |
| I | - | 3323 m 3184 m | 1674 mb | 1644 mb 1587 s | 1341 s | 415 m | 288 w |
| II | - | 3323 m 3170 m | 1647 sh | **1586 s | 1304 s | 420 m | 295w |
| III | 3405 m* | 3323 m 3150 m | 1674 mb | 1641 mb 1586 s | 1341 s | 419 s | 270 w |
| IV | 3398 m* | 3319 m 3172 m | 1652 mb | 1649 mb 1587 s | 1333 s | 450 s | 277 w |
| V | - | 3325 m 3178 m | 1645 sh | **1587 s | 1333 s | 416 s | 290 w |
| VI | - | 3320 m 3158 m | 1640 sh | **1590 s | 1331 s | 410 m | 273 w |
| VII | 3401 w* | 3324 m 3168 m | 1674 mb | 1643 mb 1584 s | 1340 s | 418 m | 285 w |
| VIII | 3463 w* | 3304 m 3106 m | 1634 sh | 1643 mb 1584 s | 1340 s | 422 m | 287 w |

*s=sharp, m=medium, mb=medium broad, sh=shoulder, w=weak, *Due to phenolic OH of Rte and $R_2Te$ moieties; **band not resolved due to overlapping of band* $\boldsymbol{\nu_{(C=N)}}$

Examination of the Schiff base (Sal-TMP) spectrum shows the presence of the hydrogen bonded conjugated- chelate ring system[66-68] with its centre at ~2832 $cm^{-1}$. Thus intramolecular H- bonding is occurring by means of the formation of a quasi six- membered ring involving the OH ----N=C bond.

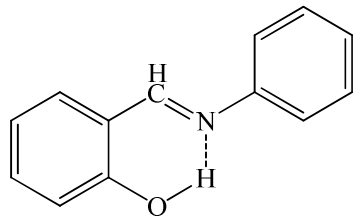



**Figure 1**. Hydrogen bonding

Thus band disappear on chelation with aryltellurium(IV) chlorides[69]. Hydrogen bond contributes to planarity of the molecule which helps in chelation[70]. Also an intense ligand band at 1263 $cm^{-1}$ (phenolic –C-O) in free ligand has shifted to higher frequency side in complexes. All these indicate that the hydroxyl group of salicylaldehyde of Schiff base is involved in coordination with tellurium[71-73].

In addition, the spectra of the Schiff base shown shoulder at 1636 $cm^{-1}$ with slightly resolved weak band at 1633 $cm^{-1}$ and sharp band at 1593 $cm^{-1}$ assigned to $\nu_{(C=N)}$ mode for vibration of azomethine group[2,4,65,74-76] and $\nu_{(C=N)pyrim.}$ For pyrimidine ring[4,77]. These shift in aryltellurium Schiff base complexes towards higher and lower value[74-79] reflecting that ligand coordinate through nitrogen atom of azomethine and pyrimidine ring.

The medium intensity band at 3317 $cm^{-1}$ and 3119 $cm^{-1}$ due to $\nu_{(N-H)}$ asymmetric and symmetric vibrations respectively indicate the non involvement of the nitrogen atom of $NH_2$ group attached to pyrimidine in coordination. The appearance of new weak bands around 270-295 $cm^{-1}$ due to $\nu_{(Te-O)}$[80-83] mode and medium to strong band in the range of 410-422 $cm^{-1}$ due to $\nu_{(Te-N)}$ mode[84] further supports the involvement of phenolic oxygen (after deprotonation), azomethine and pyrimidine nitrogen atoms of Schiff base in the coordination.

Thus, IR data predict the tridentate nature of Sal-TMP involving azomethine nitrogen atom, phenolic oxygen after deprotonation and pyrimidine ring nitrogen giving rise to two-six and four membered chelate rings with the tellurium centre.

### *$^1$H NMR spectra*

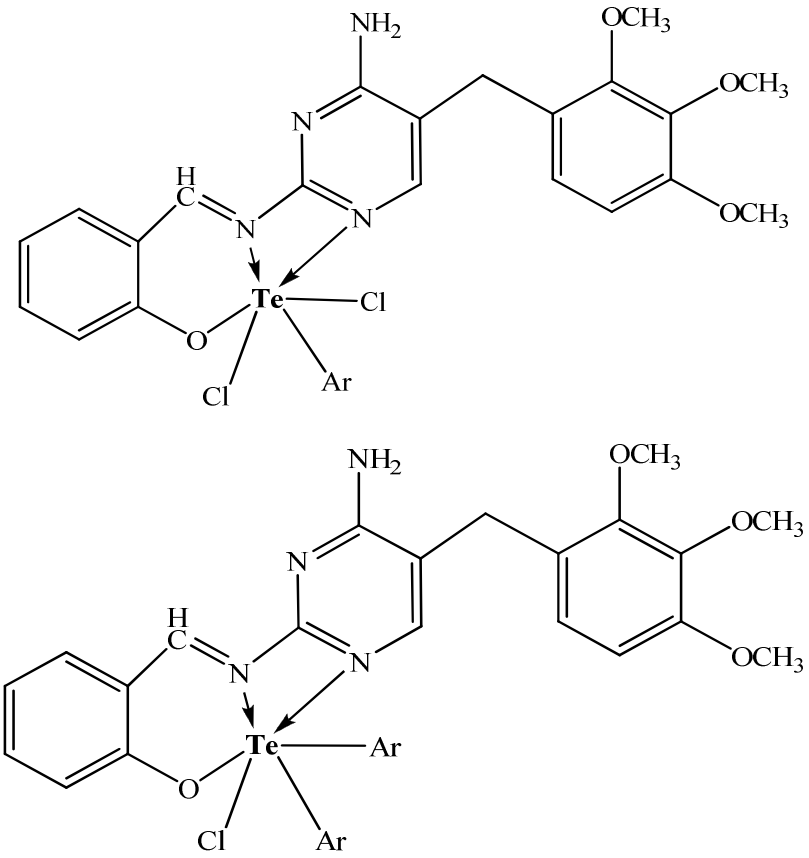
In order to identify the solution structure of Schiff base (Sal-TMP) and its complexes, $^1$H NMR spectra were recorded in DMSO-$d_6$ and given in Table 3. The proton resonance of the OH group at 10.92 δ ppm[76,85] in Schiff base due to presence of intramolecular hydrogen bonding[74] disappear on complexation indicating the involvement of phenolic oxygen in the coordination *via* deprotonation[76]. The azomethine protons which resonate as a singlet at 10.02 δ ppm, the coordination of azomethine nitrogen to tellurium in the complexes are clearly demonstrated by a downfield shift of the peak[86].

**Table 3.** $^1$H NMR spectral data of Schiff base (Sal-TMP) and complexes in DMSO-$d_6$

| Compound | Chemical Shift, δ ppm |
|---|---|
| Sal-TMP | 2.525(s, 2H, methylene), 3.551-3.745(s, 9H, -$OCH_3$), 5.672(s,1H, pyrimidine), 6.508(s, 2H, −$NH_2$), 7.526-8.169(m, 6H, aromatic proton), 10.021(s, 1H, azomethine), 10.921(s, 1H, Schiff base OH) |
| I | 2.539(s, 2H, methylene), 3.598-3.840(s, 12H, −$OCH_3$), 6.574(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.383-7.522(m, 10H, aromatic proton), 10.209(s, 1H, azomethine) |
| II | 1.335(t, 3H, -$OCH_2CH_3$), 2.546(s, 2H, methylene), 3.963(q, 2H, −$OCH_2CH_3$), 3.515-3.875(s, 9H, −$OCH_3$), 6.540(s, 1H, pyrimidine), 6.950(s, 2H, −$NH_2$), 6.993-7.809(m, 10H, aromatic proton), 10.193(s, 1H, azomethine) |
| III | 2.548(s, 2H, methylene), 3.601-3.783(s, 9H, -$OCH_3$), 6.569(s,1H, pyrimidine), 6.914(s, 2H, −$NH_2$), 7.370-7.787(m, 10H, aromatic proton), 8.155(s, 1H, phenolic OH of RTe), 10.201(s, 1H, azomethine) |
| IV | 2.536(s, 2H, methylene), 2.527(s, 3H, -$CH_3$), 3.587-3.770(s, 9H, −$OCH_3$), 6.605(s, 1H, pyrimidine), 6.918(s, 2H, −$NH_2$), 7.051-7.671(m, 9H, aromatic proton), 8.251(s, 1H, phenolic OH of RTe), 10.239(s, 1H, azomethine) |
| V | 2.528(s, 2H, methylene), 3.673-3.877(s, 15H, −$OCH_3$), 6.516(s,1H, pyrimidine), 6.882(s, 2H, -$NH_2$), 6.910-7.804(m, 14H, aromatic proton), 10.186(s, 1H, azomethine) |
| VI | 1.363(t, 6H, −$OCH_2\mathbf{CH_3}$), 2.531(s, 2H, methylene), 4.019(q, 4H, -$O\mathbf{CH_2}CH_3$), 3.555-3.765(s, 9H, −$OCH_3$), 6.510(s, 1H, pyrimidine), 6.924(s, 2H, −$NH_2$), 7.524-7.805(m, 14H, aromatic proton), 10.216(s, 1H, azomethine) |
| VII | 2.545(s, 2H, methylene), 3.568-3.926(s, 9H, -$OCH_3$), 6.554(s, 1H, pyrimidine), 6.884(s, 2H, −$NH_2$), 7.488-7.678(m, 14H, aromatic proton), 8.249(s, 2H, phenolic OH of $R_2Te$), 10.238(s, 1H, azomethine) |
| VIII | 2.538(s, 2H, methylene), 2.529(s, 6H, -$CH_3$), 3.555-3.750(s, 9H, −$OCH_3$), 6.502(s, 1H, pyrimidine), 6.926(s, 2H, −$NH_2$), 7.126-7.868(m, 12H, aromatic proton), 8.149(s, 2H, phenolic OH of $R_2Te$), 10.239(s, 1H, azomethine) |

*s=singlet, q=quartet, t=triplet, m=multiplet*

The characterstic downfield shifting of proton signal in all complexes observed in region 5.67 δ ppm is due to pyrimidine proton in Schiff base clearly indicate the coordination through pyrimidine nitrogen atom[87]. The signal due to –NH proton is observed around 6.51 δ ppm which remain intact with slight variation in complexes is due to the proton bounded to nitrogen experience quadruple effect[87]. Thus salicylidene-trimethoprim act as a tridentate –N, –N, –O chelating ligand in Sal-TMP.$ArTeCl_2$ and Sal-TMP.$Ar_2TeCl$ complexes giving six coordinate tellurium having distorted octahedral geometry in these complexes as predicated from IR studies as well. The proposed structures are as given below (Figure 2).




Sal-TMP.$Ar_2TeCl$

Ar = *p*-methoxyphenyl, *p*-ethoxyphenyl, *p*-hydroxyphenyl and 3-methyl-4-hydroxyphenyl

**Figure 2.** Proposed structures of complexes

*Biological Activity*

The salicylidene-trimethoprim Schiff base (Sal-TMP) and newly synthesized aryltellurium(IV) schiff base complexes were evaluated for their antimicrobial activity *in vitro* against Gram +ve bacteria (*S. aureus* ATCC 11632 and *B. cereus* MTCC 7350), Gram –ve bacteria (*E. coli* ATCC 35218, *P. aeruginosa* ATCC 23564, *S. typhi* ATCC 15499 and *P. rettgeri* DRDE) and fungal strains (*A. niger, A. fumigates* and *A. flavus*) by tube dilution method[88]. Dilution of test and standard compounds were prepared double strength nutrient broth- I.P (Antibacterial) and Sabouraud Dextrose Broth –I.P (Antifungal)[89]. The samples were incubated at 37±1 ºC for 24 h (bacteria), 25±1 ºC for 7 days (*A. niger*), 30 ±1 ºC for 15 days (*A. flavus*), 35±1 ºC for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC (The lowest concentration of test substances which inhibited values are presented in the Table 4.

The data show that the Sal-TMP complexes of aryltellurium(IV) exhibit more antimicrobial activity towards bacteria as compared to fungii. The antibacterial activity shows following trend.

Sal-TMP.$Ar_2TeCl$ > Sal-TMP.$ArTeCl_2$ ≈ Sal-TMP Schiff base

Sal-TMP.$Ar_2TeCl$ and Sal-TMP.$ArTeCl_2$ complexes have activity towards *S. typhi* and more effectively against *B. cereus* but Schiff base does not show activity against these bacterial strains. Schiff base and its complexes show almost similar activity against fungal strains.

**Table 4.** Minimum Inhibitory Concentration, MIC, µg/mL; (-) Resistant

| Compound | Bacteria strains | | | | | | Fungal strains | | |
|---|---|---|---|---|---|---|---|---|---|
| | *S. aureus* (ATCC 11632) | *S. typhi* (ATCC 15499) | *P. aeruginosa* (ATCC 23564) | *E. coli* (ATCC 35218) | *B. cereus* (MTCC 7350) | *P. rettgeri* (DRDE strain) | *A. niger* | *A. fumigates* | *A. flavus* |
| Sal-TMP | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |
| I | 2.5 | - | 1.25 | - | 0.625 | 5.0 | - | - | - |
| II | 5.0 | - | - | - | 1.25 | 2.5 | 20 | 5.0 | 1.25 |
| III | - | 20 | 10 | 5.0 | 1.25 | - | 5.0 | - | - |
| IV | 1.25 | 2.5 | 1.25 | 5.0 | - | - | 5.0 | 10 | 5.0 |
| V | - | 20 | 10 | 5.0 | 1.25 | - | 20 | - | - |
| VI | 1.25 | 2.5 | 1.25 | 5.0 | - | - | - | 5.0 | - |
| VII | 1.25 | - | 5.0 | 1.25 | 0.625 | 5.0 | - | 10 | - |
| VIII | 2.5 | - | 1.25 | 5.0 | - | - | 20 | 5.0 | 1.25 |

## Conclusion

Aryltellurium(IV) and diaryltellurium(IV) dichlorides upon reaction with Schiff base(Sal-TMP) derived from salicylaldehyde and trimethoprim yield new complexes of tellurium(IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and $^1$H NMR spectral studies. The analytical data suggest that the Sal-TMP Schiff base complexes have 1:1 stoichiometry. The Schiff bases (Sal-TMP) in these complexes functions as a uninegative tridentate ligand through azomethine nitrogen, phenolic oxygen after deprotonation and pyrimidine ring nitrogen atoms. Based on these studies, distorted octahedral geometry with two chelating rings has been assigned to these complexes. The complexes have been observed to possess substantial antimicrobial activity especially against bacteria.

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