

Review Article

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Advances in synthesis and anticancer applications of organo-tellurium compounds

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Abstract: The present review deeply delves the major methods for the synthesis of organotellurium compounds along with their biological significance. Elaboration of various precursors (ligands) including Schiff bases, naphthoquinones, amino acids, β -hydroxy alkylated compounds, β -phenyltelluro alcohols, β -aryltelluro amines, β -aryl-chalcogenium azides, chalcogenobiotin, benzene-sulfonamide, carbonic anhydrase, and Sulpha compounds has been briefly described. Furthermore, the article investigates their possible biological uses, specifically as antioxidant and anticancer agents while comparing their effectiveness with their respective ligands and with the standard medications in terms IC_{50} values. All types of details are haunted to make the information a priceless resource for researchers who wish to probe deeper into and examine the diverse roles that organotellurium complexes play in biological settings.

Keywords: Te complexes; synthesis of tellurium complexes; anticancer activity; antioxidant activity; Te complexes antioxidant activity

1 Introduction

The aging process and age-related diseases such as cancer, Parkinson's disease, and Alzheimer's are associated with oxidative stress, which is marked by increased levels of reactive oxygen species (ROS) and decreased antioxidant defenses. As a result, the development of novel antioxidants is urgently needed to protect cells from oxidative damage. Although antioxidant mimetics have been developed, their effectiveness in biological systems has been inconsistent, indicating ongoing challenges in this field.¹ Cancer is a formidable disease that threatens world health.^{2,3} According to the World Health Organization (WHO), Cancer is the second most common cause of death worldwide, taking around 9.6 million lives annually. This is a concerning figure, since it represents nearly one in six fatalities globally. The aging of the population, genetic predispositions, unhealthy lifestyles, and the influence of environmental variables are some of the causes contributing to the growth in cancer incidence.^{4,5} The absence of disease-modifying medications, limited variety, and unfavorable combinations with current treatments are causing widespread pandemics and serious harm to economies and public health. Therefore, a great deal of research efforts are concentrated on developing new pharmacological compounds from metals in an effort to overcome these constraints and provide useful remedies that have significant biological benefit for humans.^{6–8}

Metal-coordinated complexes are the focus of increasing biological research because of their unique properties, which enable precise interactions with biomolecules including DNA and proteins for a range of beneficial bio-functions. These substances are helpful indicators of intricate biological processes and may prove to be helpful in the creation of novel therapeutics.^{9–13} Better biological performance of these complexes than ligands alone is a crucial feature for therapeutic applications.¹⁴ The important advancement of cisplatin's discovery as an anticancer medication spurred further investigation and development of other metal complexes for a variety of biological applications.^{15,16} This trend emphasizes how important metal complexes are to the advancement of biological science's therapeutic approaches. Coordination

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chemistry with tellurium (Te) ligands has advanced significantly in the last three decades. Although it was originally closely related to selenium chemistry, it has subsequently grown into its own independent field.^{13,16–19} Tellurium (Te), a metalloid found in the periodic table alongside sulfur and selenium (Se), has chemical and biological properties that are remarkably comparable to Se.^{20–22} While Se was once deemed hazardous, it has since become an essential element, playing important roles in a variety of therapies.²³ Te, on the other hand, is considered a rare, non-essential trace element.²⁴ Despite this, investigations have shown that the average human body contains Te level upto 0.5 g, surpassing that of all trace elements except iron, zinc, and rubidium.^{25,26} Selenium is critical in therapy for cancer, HIV/AIDS, and age-related disorders, providing promising treatment options.^{27–29} Te's toxicity varies based on the chemical form and quantity eaten, with symptoms including nausea, somnolence, and garlic odor caused by dimethyl telluride.³⁰ Additionally, Te can impair cholesterol synthesis and promote peripheral neuropathy, as evidenced by changes in myelin protein transcription and cognitive abnormalities in rats.^{31–33} Te also has hemolytic and genotoxic effects on human blood cells and causes cytotoxicity in rat hippocampus astrocytes.³⁴ Te's toxicity, on the other hand, has gotten less attention than Se's, presumably because humans have less regular interaction with Te compounds.³⁵ Overall, while Te's toxicity and biological impacts are significant, they are comparatively underexplored in comparison to Se, emphasizing the need for additional research to explain Te's modes of action and potential health implications.^{30,36} Te has become increasingly important and useful in coordination chemistry due to its distinct amphoteric characteristics to react with both acid and bases and its capacity to adopt a wide range of oxidation states, 0 (native tellurium), –2 (tellurides), +4 (tellurites), and +6 (tellurates) both fractional and integral.^{37–39} Te's adaptability has been highlighted by this groundbreaking study, which has made it a notable component in the field.^{40,41} Organotellurium compounds are strong antioxidants that provide defense against damage caused by reactive oxygen species (ROS). They resemble the enzyme glutathione peroxidase (GPx). Their potency in counteracting oxidative stress in the body is increased by their capacity to oxidize from Te(II) to Te(IV). This is the reason for their antioxidant action.^{42,43} Tellurium complexes for medicines have been the subject of extensive investigation in recent decades.^{44,45} Both inorganic and organic Te derivatives have antibacterial, anticancer, and antiepileptogenic effects. Promising discoveries indicate that Te could follow selenium's trajectory from toxicity to essentiality in medicine.^{46–48} This comprehensive review examines synthesis methods for producing organotellurium compounds using various types of ligands, focusing on

their emerging biological uses. Comparative investigation, including IC₅₀ values, demonstrates their antioxidant and anticancer properties. Valuable insights are provided, assisting researchers in understanding and investigating their several biological activities.

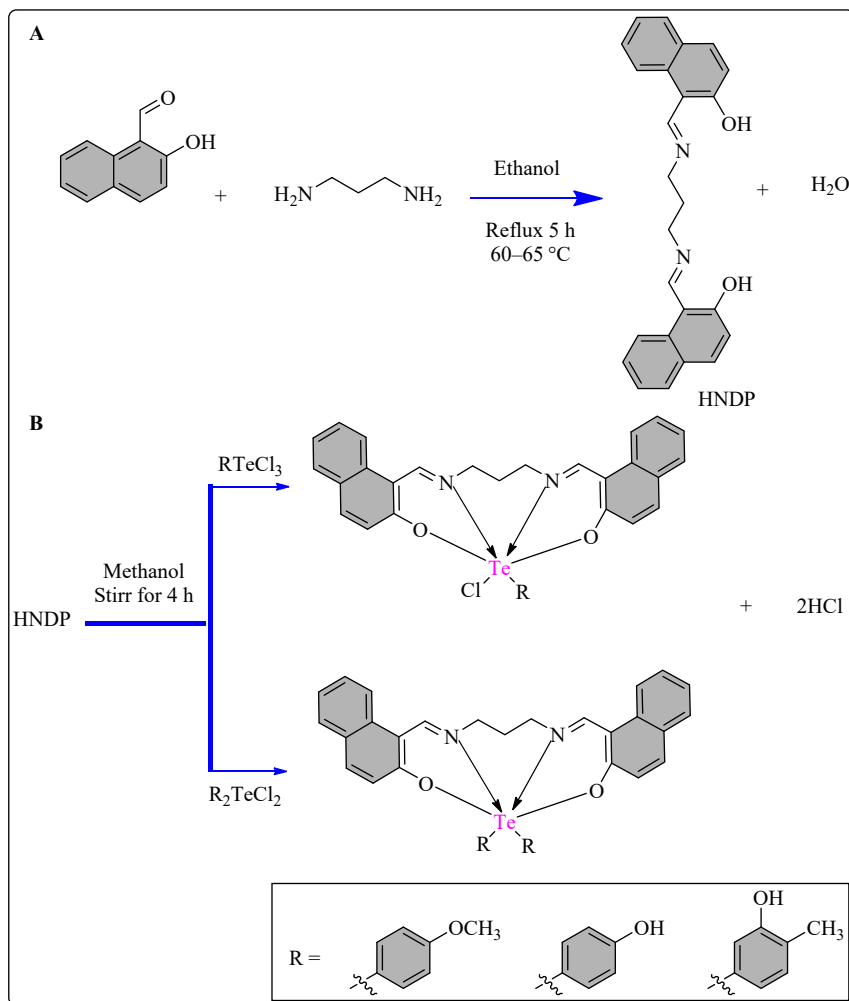
2 Synthesis of Te complexes and anticancer potential

2.1 Schiff base based Te complexes (1–6)

A tetradentate Schiff base ligand, L1 (HNDP), was prepared by refluxing a mixture of 2-Hydroxy-1-naphthaldehyde and 1,3-diaminopropane in absolute ethanol for 5 h at 60–65 °C. The yellow precipitates formed upon condensation were filtered, purified with ethanol, dried, and stored under vacuum (Scheme 1A). Subsequently, various hexa-coordinated Te (IV) complexes (1–6) were synthesized using the HNDP ligand. The method involved refluxing and stirring a 1 mM solution of HNDP with 1 mM of different Te (IV) chlorides (R₁TeCl₃/R₂TeCl₂) in methanol for 4 h (Scheme 1B).⁴⁹ Instant complexation occurred, resulting in the formation of precipitated solids. These solids were filtered, washed with petroleum ether, dried, and then stored under vacuum for further use. The synthesized compounds (1–6) (Figure 1) were evaluated for their cytotoxicity against L929, PC3, and Saos-2 cell lines using the MTT assay (Table 1). The IC₅₀ values were determined, representing the concentration causing 50 % cell death compared to controls. Schiff base HNDP showed no activity against L929 cells but limited activity against PC3 and Saos-2 cells. Most complexes demonstrated enhanced activity compared to HNDP. Complex 1 exhibited the best activity against L929 cells, comparable to doxorubicin.⁵⁰ Complex 3 showed promising activity against PC3 cells,⁵¹ and complexes 1, 3, and 5 were most effective against Saos-2 cells, surpassing the performance of doxorubicin used as the standard drug.⁵²

2.2 Naphthoquinone based Te complexes (7–9)

The synthetic process was started with conversion of 2-hydroxynaphthalene-1,4-dione, a commercially available starting material, into propargyl alkylated lawsone (L2) (Scheme 2). Rocha et al. reported a 60 % yield utilizing propargyl bromide, potassium carbonate, and dimethylformamide (DMF) as solvents for 24 h at 60 °C.^{53,54} Additionally, a well-known method that has been documented in the literature



Scheme 1: Methodology for the synthesis of A) Schiff base ligand HNNDP and B) HNNDP based Te complexes.

might be used to create diorganoyl dichalcogenides (A–C).⁵⁵ Using this process, the Grignard reagent was formed by reacting bromobenzene (which may be substituted), which subsequently facilitates the production of the target product. The target molecules were then produced using L2, diphenyl ditelluride (A–C), copper iodide (CuI), and 2.0 mL of DMSO in a traditional process.⁵⁶ In order to produce Csp-chalcogen bonds, CuI was used in a chemical reaction. The reaction proceeded effectively, indicating the suitability of the selected materials and circumstances for attaining the desired chemical conversion.⁵⁷ Three diorganoyl ditellurides (A–C) were employed in the procedure for evaluating the biological impact of different chalcogens on the target structure as well as the adaptability of the developed technique. In this approach, the compound library was enlarged by synthesizing these chalcogen derivatives. In this case, compounds 7–9 had moderate to good yields, with 9 (chlorine-substituted) having the greatest yield of 60 %. Compound 8 (containing a methyl group) was collected with a yield of 55 %, but the unsubstituted aromatic ring in 7 yielded 49 %, indicating a

consistent effect independent of substituents. The cytotoxic activity of the three synthesized samples (7–9) was tested in SCC-9 cells, a type of human tongue cancer cell renowned for its sensitivity to cytotoxic chemicals.^{58–60} The normal cell control was made out of NIH3T3 murine fibroblasts. Carboplatin, a conventional chemotherapy agent for oral cancer treatment, and doxorubicin, which is routinely used to treat a variety of cancers, acted as positive controls.^{61,62} Notably, all drugs showed dose-dependent cytotoxicity in SCC9 cells, outperforming carboplatin in anticancer activity. Their IC_{50} values are shown in Table 2. Surprisingly, these complexes (7–9) also showed more cytotoxicity in SCC-9 cells than standard drugs as well as derivatives of diorganoyl diselenides or thiophenol. Complexes 7–9 were also tested against carboplatin on the NIH3T3 cell line to establish their selectivity index (S.I.). A high S.I. value (≥ 2) implies selective toxicity against cancer cells, whereas a S.I. < 2 indicates potential general toxicity.⁶³ Complexes 7–9 showed stronger cytotoxicity in NIH3T3 cells than other diorganoyl diselenide derivatives, with 7 having the highest selectivity index (S.I. = 3.53) of all examined

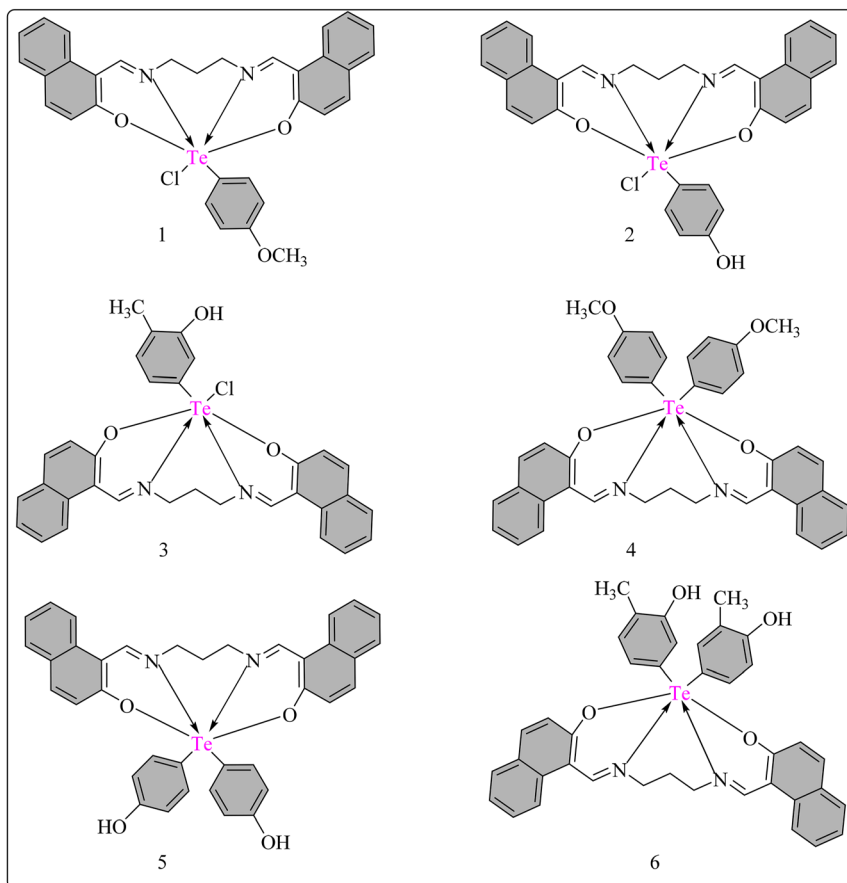


Figure 1: Structural representation of HNBP based hexa-coordinated Te(IV) complexes.

Table 1: Visualize the comparison of IC_{50} values of ligand L1 and its associated complexes.

Compound	IC_{50} (μM)		
	L929	PC3	Saos-2
Doxorubicin	1.08 ± 0.55	3.76 ± 1.1	37 ± 16
L1	Nil	48.26 ± 0.10	57.06 ± 0.09
1	3.06 ± 0.02	16.19 ± 0.04	14.77 ± 0.04
2	6.74 ± 0.01	14.86 ± 0.05	161.56 ± 0.11
3	8.36 ± 0.04	3.14 ± 0.02	30.77 ± 0.02
4	10.36 ± 0.08	15.01 ± 0.05	140.50 ± 0.14
5	7.34 ± 0.07	42.48 ± 0.18	21.02 ± 0.07
6	9.82 ± 0.03	17.58 ± 0.09	78.80 ± 0.06

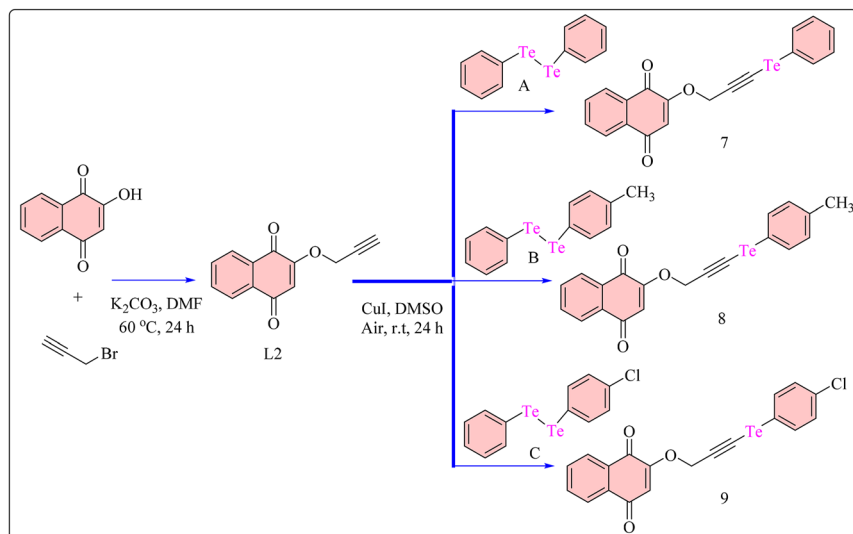
chalcogen-naphthoquinones. All novel compounds demonstrated better selectivity than carboplatin (S.I. = 0.27) and the majority compared to doxorubicin (S.I. = 0.61).⁶⁴

2.3 Amino acid-based Te complexes (10–12)

The synthesis of complex 10 followed conventional protocols,⁴⁷ beginning with L-Tellurocysteine in a round bottom

flask filled with degassed distilled water and N_2 . After 15 min of stirring with H_2O_2 and concentrated HCl at $0^\circ C$, the solution became transparent (Scheme 3). The colorless solid complex 10, a zwitterionic Te(IV), was obtained after 16 h of freeze-drying. To avoid breakdown, storage at temperatures below $10^\circ C$ was recommended. Complex 10, showed substantial dose-dependent anticancer activity against MCF-7 cells. The maximum efficacy was reported at doses ranging from 2.5 to 20 $\mu g/mL$, leading to a considerable reduction in cell viability. Although cell viability decreased less at higher dosages, anticancer activity was consistent throughout the analysis, with good to moderate efficacy observed up to 60 $\mu g/mL$. Complex 10 demonstrated effective anticancer action against MFC-7 breast cancer cells, with an IC_{50} value of $2.86 \pm 0.02 \mu g/mL$.⁶⁵ The mechanism of action could be attributed to its similarity to AS101, redox-modulating properties, and interaction with cysteine thiol residues, which could inhibit integrin activity and IL-10 secretion, sensitizing tumors to chemotherapeutic treatments and specifically targeting cancerous cells.^{30,47}

Complex 11 was produced through the addition of tellurocysteine⁶⁶ to a mixture of degassed EtOH and water in a round-bottom flask under a N_2 environment at temperatures



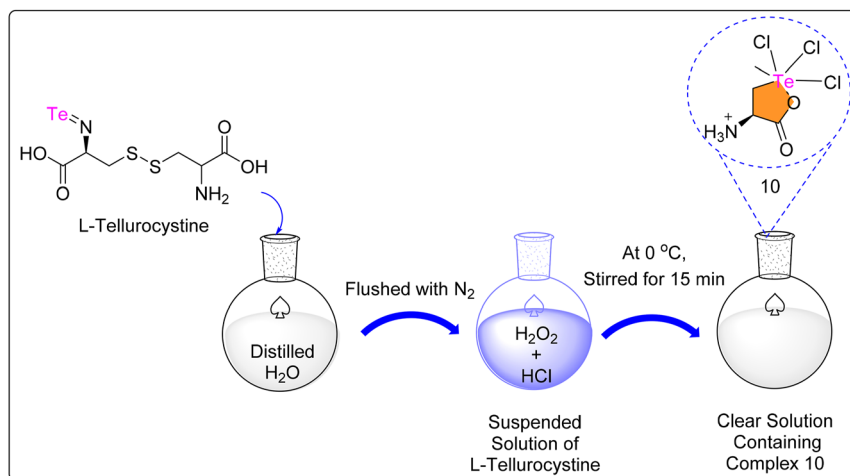
Scheme 2: Methodology for the synthesis of naphthoquinone based Te(IV) complexes.

Table 2: Visualize the comparison of IC_{50} values and S.I. of L2 complexes with standard drugs.

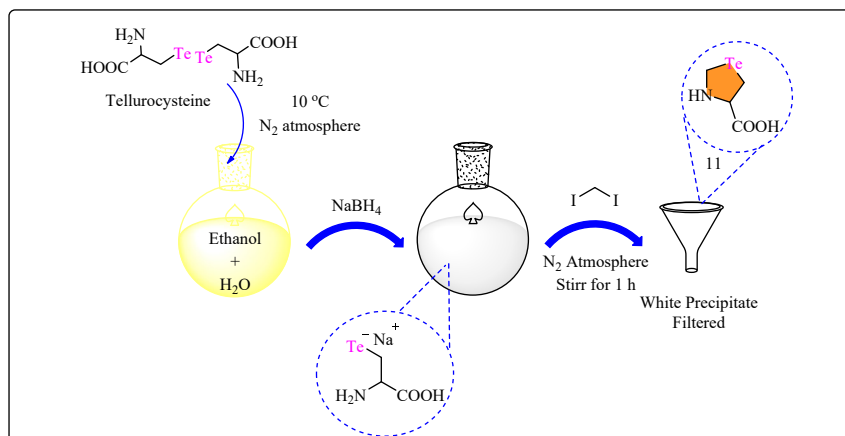
Compound	SSC9	NIH3T3	
		IC_{50} (μM)	S.I.
Carboplatin	571.9	155.70	0.27
Doxorubicin	2.705	1.66	0.61
7	1.648	5.83	3.53
8	4.001	2.27	0.57
9	2.885	4.90	1.70

below 10 °C (Scheme 4A). Sodium borohydride was progressively introduced, yielding a clear solution. Diiodomethane was then gradually added, resulting in the production of a white precipitate. The precipitate was filtered, washed, and dried before being stored. Complex 12

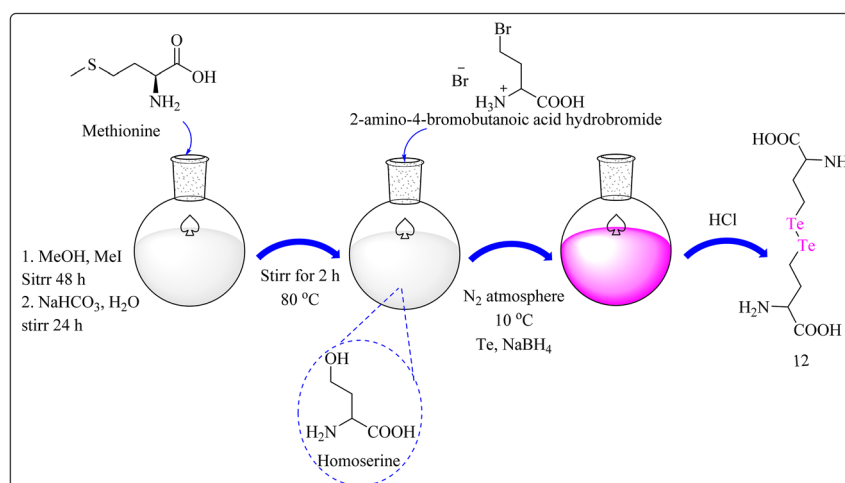
was synthesized from L-methionine using a technique described in the literature for selenohomocystine.⁶⁷ First, L-methionine was converted into homoserine using a two-step procedure using iodomethane in methanol and hydrobromic acid (Scheme 4B). Te powder was then suspended in ethanol under N_2 and reduced by $NaBH_4$ to get Na_2Te_2 . The solution was then heated for 24 h at 80 °C with 2-amino-4-bromobutanoic acid hydrobromide. Following evaporation and HCl treatment, the resultant mixture was washed with diethyl ether and dried, producing tellurohomocystine 12. Compound 11 and 12 were tested for cytotoxicity on MCF-7 cells at doses of up to 125 $\mu g/mL$. Both compounds showed a concentration-dependent decrease in cell viability, which was identical to the trend seen with the positive control, doxorubicine. Notably, amino acid compound 11 was more toxic to MCF-7 cells than telluro compound 12 at various doses. The IC_{50} value for complex 11



Scheme 3: Methodology for the synthesis of zwitterionic Te complex.¹⁰



Scheme 4 (A): Methodology for the synthesis of telluro amino acid complex 11.



Scheme 4 (B): Methodology for the synthesis of ditelluride amino acid complex 12.

and 12 was $7.29 \pm 0.27 \mu\text{g/mL}$ and $25.36 \pm 0.12 \mu\text{g/mL}$, respectively.⁶⁸

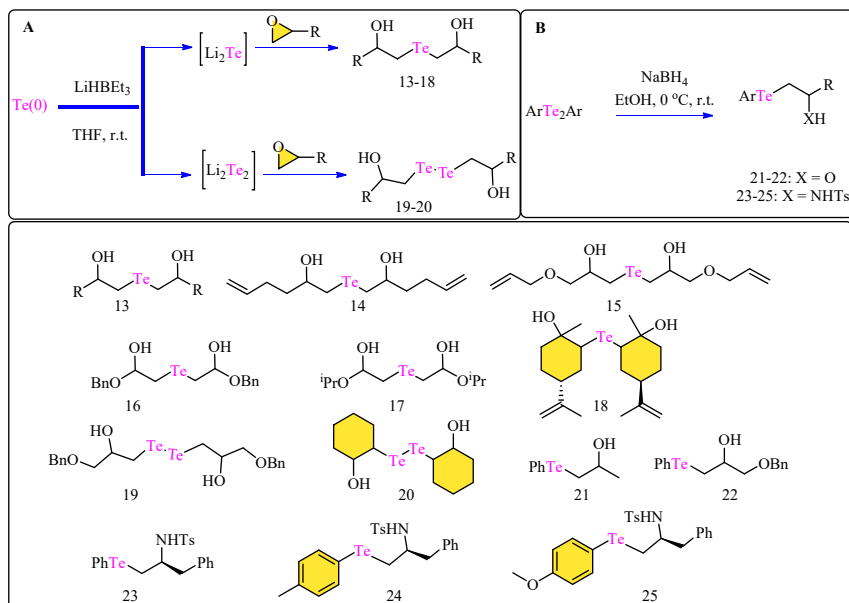
2.4 β -hydroxy alkylated Te complexes (13–20)

Li_2Te was produced by reacting LiEt_3BH with elemental tellurium powder in THF solution, as described in the literature.⁶⁹ The resultant Li_2Te suspension in THF was treated with an epoxide and stirred at room temperature for 12 h (Scheme 5A). The mixture was then diluted with Et_2O , filtered, and washed with saturated NH_4Cl and H_2O . The organic phase was dried over Na_2SO_4 , filtered, and evaporated at low pressure. The crude product was purified by flash column chromatography, resulting in β -hydroxy tellurides 13–20. Additionally, ditellurides 13 and 14 were produced utilizing a similar technique that took advantage of Li_2Te_2 's reactivity.^{70–72}

2.5 β -phenyltelluro alcohols (21–22) and β -aryltelluro amines (23–25) Te complexes

Unsymmetrical aryl-alkyl tellurides 23–25 with hydroxy and amino functionalities were produced by ring-opening reactions between epoxides or aziridines and aryl tellurolates.^{73,74} These tellurolates were produced *in situ* by reducing diaryl ditellurides with NaBH_4 in EtOH at 0°C in an inert environment (Scheme 5B). The following addition of epoxides or aziridines started the reaction, which continued until completion, as measured by TLC. The intended β -phenyltelluro-alcohols 21–22 or β -aryltelluro-amines 23–25 were obtained after quenching with saturated aqueous NH_4Cl , extraction, and purification with flash chromatography.⁷⁵

Following the DTT oxidation test results, researchers investigated the cell-protective properties of their manufactured compounds. Prior to undertaking these tests, they



Scheme 5: Methodology for the synthesis of (A) β -hydroxy alkylated Te complexes (13–20) and (B) telluride based β -phenyltelluro alcohols 21–22 and β -aryltelluro amines 23–25 complexes.

assessed the cytotoxicity of the organochalcogen derivatives, taking into account the shortage and inconsistent nature of the available data. The majority of compounds showed negligible cytotoxicity, with certain tellurated derivatives exhibiting no deleterious effects on cell viability at dosages up to 100 μM . However, complexes 23–25 were insoluble during testing. Notably, among the examined series, GPx-like tellurated complexes 13 and 15 had the lowest toxicity. As Table 3 shows the IC_{50} values of synthesized complexes (13–25), complex 21 and 22 proved to be the most efficient of all the telluride complexes.⁷¹

2.6 β -aryl-chalcogenium azides based Te complexes (26–27)

Complex 26 and 27 β -aryl-chalcogenium azides with tellurium (Figure 2), were synthesized using recognized techniques, as previously published.⁷⁶ Phenylalaninol, valinol, and leucinol, which are commercially available α -amino alcohols, were the starting materials for the chiral β -chalcogenium amine compounds 26–27. Using di-tert-butyl dicarbonate, they were transformed into N-Boc-protected amino alcohols. Alcohol mesylates were produced through further mesylation in THF and Et_3N using mesyl chloride. Then, utilizing aryl dichalcogenides and NaBH_4 in THF-ethanol, the β -aminomesylates were transformed with organochalcogenium moieties via organochalcogenolate synthesis.⁷⁷ In the initial study, researchers evaluated the potential anticancer effects of complexes 26 and 27 on bladder cancerous cells *in vitro*. The MTT assay demonstrated a dose-dependent reduction in the survival of the human bladder cancer cell line (5,637) after 48 h of

Table 3: Illustrate the IC_{50} values of complexes 13–25.

Compound	IC_{50} (μM)
13	>100
14	100 *
15	> 100
16	20.7
17	80.7
18	22.9
19	31.9
20	49.3
21	8.5
22	19.8
23	ND
24	ND
25	ND

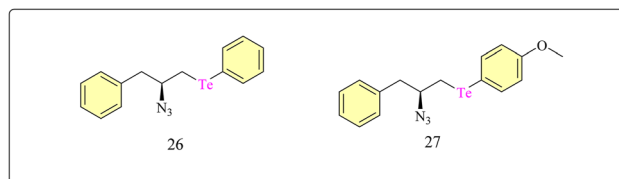


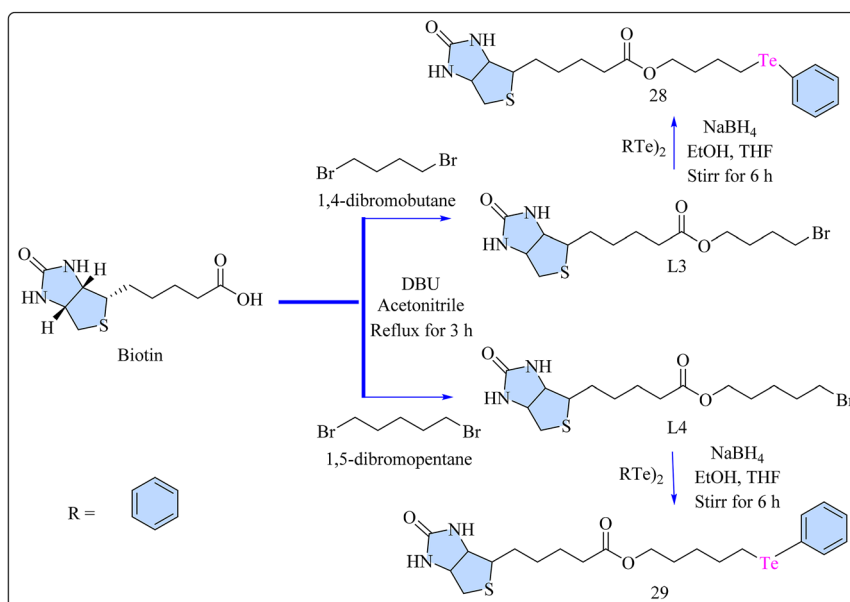
Figure 2: Structural representation of Te complex 26 and 27.

incubation with both drugs. This suggests a dose-dependent link between drug concentration and cellular response, since higher doses lead to a greater loss in cell survival. It also showed that the action of the drugs on the cancer cells is directly correlated with the concentration of given dosage. Surprisingly, at concentrations as low as 1 μM , these organochalcogen compounds displayed an average suppression of more than 50 % of cancer cell viability. After 48 h of exposure, the IC_{50} values for 26 and 27 were $1.57 \pm 0.70 \mu\text{M}$ and $0.48 \pm 0.13 \mu\text{M}$, respectively. Compound 27 showed slightly higher cytotoxicity, inhibiting 50 % of cellular viability at lower doses. The IC_{50} concentration values of 1.6 μM for complex 26 and 0.5 μM for complex 27 were chosen for further investigations.⁷⁸

2.7 Chalcogenobiotin Te complexes (28–29)

Ligands L3 and L4 were synthesized, by mixing 1,4-dibromobutane and 1,5-dibromopentane separately with biotin in a two-necked rounded bottom flask under an argon environment. In order to preserve the integrity of reactive chemicals and ensure the success of complex reactions, an argon atmosphere is necessary during the organic synthesis process. Researchers may more effectively control the reaction conditions and produce higher yields of the intended products with fewer side reactions or contaminants by keeping oxygen and moisture out of the reaction⁷⁹ Se. The flask had a reflux condenser and magnetic stirring. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was dissolved in acetonitrile, and the reaction mixture was

allowed to reflux for 3 h with stirring (Scheme 6). The solvent was then evaporated and obtained solid material was purified using silica gel column chromatography, resulting in the desired product. A rotary evaporator was used to evaporate the solvent, yielding a vacuum-dried product. The synthesized ligands L3 and L4 were used in the development of biotin-based Te(IV) complexes, 28 and 29.⁸⁰ Chalcogenolate generation was started by combining diorganoyl ditelluride, NaBH_4 , and EtOH in an argon environment. Biotinyl bromoalkyl ester L3 and L4 were added to THF and stirred for 6 h. The mixture was then washed with NH_4Cl and ethyl acetate, before being dried, filtered, and evaporated to remove the organic phase. The complexes 28 and 29 were purified using silica gel chromatography. Tumor cells, due to their increased metabolic activity, have a higher demand for important vitamins like biotin, which is required for cellular function.^{81,82} Cytotoxicity of biotin, 28 and 29 complexes were evaluated on 5,637 cell lines at various concentrations. Biotin and its Selenium complexes exhibited no cytotoxicity against tumor cells.^{80,83} However, tellurium complexes 28 and 29 displayed potent antiproliferative activity against 5,637 cells at lower concentrations. Like biotin, heptyl(phenyl)tellane had minimal cytotoxicity, which decreased over time, emphasizing the necessity of phenyl tellurium-biotin conjugation for improved antitumoral activity. Tellurium biotin derivatives 28 and 29 significantly reduced 5,637 cell viability in a time-dose dependent manner, but selenium derivatives did not cause



Scheme 6: Methodology for the synthesis of biotin ligand L3 and L4 and their Te(IV) complexes 28 as well as 29.

Table 4: The obtained IC_{50} values for the Te complex 28 and 29.

Compound	IC_{50} 24 h	IC_{50} 48 h
L3-L4	–	–
28	5.8 ± 3.11	4.73 ± 2.13
29	7.63 ± 3.17	6.71 ± 1.87
Heptyl(phenyl)tellane	–	–

cytotoxicity. The IC_{50} values for complex 28 and 29 shown in Table 4, that were measured using the MTT reduction assay, showed that they had cytotoxic effects on 5,637 cells at low concentrations, indicating that chalcogenobiotin derivatives are attractive anticancer possibilities for bladder cancer.⁸⁰

2.8 Benzenesulfonamide based Te complexes (30a–36g)

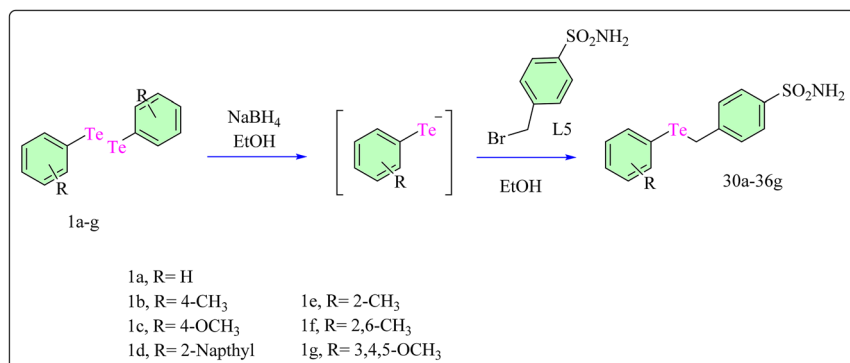
Diphenylditellurides 1a–g were reduced with $NaBH_4$ before being treated with 4-(bromomethyl)benzenesulfonamide (L5) to get complexes 30a–36g. This two-step procedure produces telluride complexes 30a–36g in high yield. The reduction step with $NaBH_4$ promotes the synthesis of telluride intermediates, which combine with 4-(bromomethyl) benzenesulfonamide to yield the desired molecules (Scheme 7). This synthetic approach has been previously reported and shows efficiency in synthesizing the target chemicals.^{84,85}

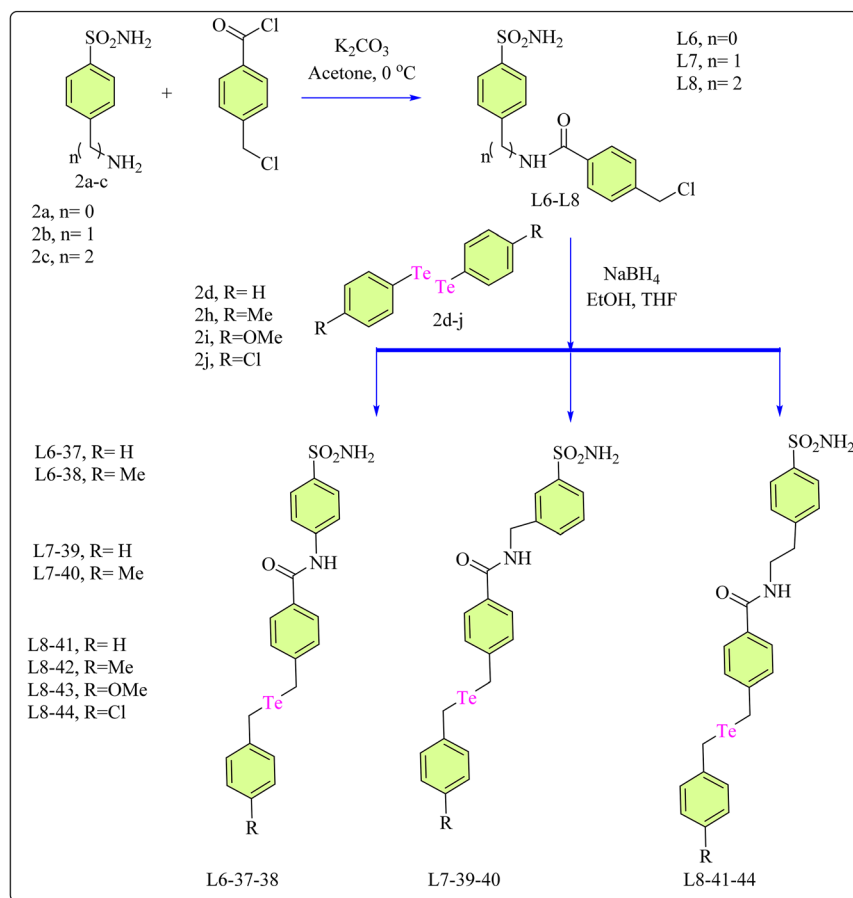
Several tellurides containing sulfonamide (30a–36g) and acetazolamide (AAZ) were tested for inhibitory activity against several human carbonic anhydrase (CA) isoforms (I, II, IV, VII, and IX) using a stopped-flow carbon dioxide hydration assay.⁸⁶ Telluride complexes 30a–36g with benzenesulfonamide had variable inhibitory efficacy among CA isoforms, which was modulated by aromatic ring alterations. Compounds containing para and ortho substituents (31b, 32c, 34e, and 35f) showed higher inhibition than 30a. CA IX, one of

the 15 human isoforms, is significantly overexpressed in several hypoxic malignancies, making it a recognized pharmacological target.⁸⁷ hCA IX is typically found in tumor cells and has restricted diffusion in cells that are normal. Its presence makes a major contribution to exogenous acidification along with cytosolic alkalization.⁸⁸ Complex 30a and 36g, which contain sulfonamide, were tested against MDA-MB-231 cells because they increased hCA IX expression in hypoxic circumstances.⁸⁹ At 1 μ M, 30a demonstrated significant activity, killing over 90 % of cells in normoxia, while 36g had slightly lower efficacy with 18 % viability. At 10 μ M, both drugs reduced viability to less than 5 %. In hypoxia, 30a had a viability of 16 % at 1 μ M and 13 % at 10 μ M, while 36g had high activity, killing 65 % and over 85 % of cells. Despite a decrease in efficacy in hypoxia, both drugs maintained significant potency. Their redox characteristics are thought to contribute to this action by changing the amounts of oxidative agents. Notably, their success in normoxia shows a larger therapeutic potential than hCA IX inhibition, warranting further investigation against various tumor types.⁸⁵

2.9 Carbonic anhydrase based Te complexes (37–44)

To target the tumor-associated hCA IX and hCA XII isoforms, a main sulfonamide moiety was combined with an organotellurium tail to control selectivity against these carbonic anhydrase (CAs).^{90–92} Recent study on chalcogen CA inhibitors has led to the development of organotellurides for this particular purpose.⁷⁵ A simple, modular, and fast two-step synthesis produced a variety of functionalized tellurides with a benzenesulfonamide moiety. Ligands L6–L8 were synthesized, by dissolving amino sulfonamide 2a–c and K_2CO_3 in acetone at 0 °C, which was then added to 4-(chloromethyl)benzoyl chloride (Scheme 8). After 1 h of stirring, the solvent was withdrawn and water was added to precipitate the result, which was then filtered and washed with

**Scheme 7:** Methodology for the synthesis of benzenesulfonamide based Te complexes.



Scheme 8: Methodology for the synthesis of CA based ligands (L6-L8) and their Telluride complexes.

diethyl ether. Complexes 37–44 were synthesized by treating ditelluride 2d–j in ethanol/THF with NaBH_4 until reduced. The mixture was then agitated for 2 h with a THF solution containing the appropriate amide derivative L6–L8. The reaction was then saturated with NH_4Cl , extracted with ethyl acetate, and rinsed with water and brine. The organic phase was dried with Na_2SO_4 , while the solvent was evaporated under vacuum. The crude product was purified using flash column chromatography.⁹³

The synthesized complexes were tested for cytotoxicity, compound 38 proved cytotoxic to NHDF and cancer cell lines LN-229, SaOS-2, and HepG2 at a concentration of roughly 100 μM (Table 5). It was likewise cytotoxic to MeWo cells at

lesser dosages. Compound 42 caused cytotoxicity in NHDF, LN-229, and HepG2 cells at 100 μM , whereas MeWo and SaOS-2 cells were cytotoxic at 70 μM and 30 μM , respectively. Compound 43 exhibited cytotoxicity against NHDF cells at 30 μM and had significant effects on cancer cells at lower doses. These findings were verified by the IC_{50} values for each cancer cell line. The selective index (SI) is an important statistic for determining chemical activity against cancer, with larger values suggesting stronger selectivity. Complexes 38 and 42 did not meet the SI threshold (≥ 10) for the cancer cell lines examined.⁹⁴ Similarly, compound 43 does not meet this threshold in LN-229 and SaOS-2 cells. Nonetheless, compound 43 has promisingly high SIs for HepG2 (SI = 26.5) and MeWo (SI = 87.8) cells, indicating prospective applicability for targeted therapy in hepatocellular carcinoma and melanoma, respectively.⁹³

Table 5: IC_{50} values obtained for CA based complexes against different tumor cell lines.

Compound		NHDF	MeWo	LN-229	SaOS-2	HepG2
38	IC_{50} (μM)	300.9	81.76	357.7	305.4	544.9
	SI	–	3.7	0.8	1.0	0.6
42	IC_{50} (μM)	409.3	97.75	184.7	85.49	321.2
	SI	–	4.2	2.2	4.8	1.3
43	IC_{50} (μM)	62.5	0.7121	12.11	7.834	2.356
	SI	–	87.8	5.2	8.0	26.5

2.10 Sulpha based Te complexes (45–48)

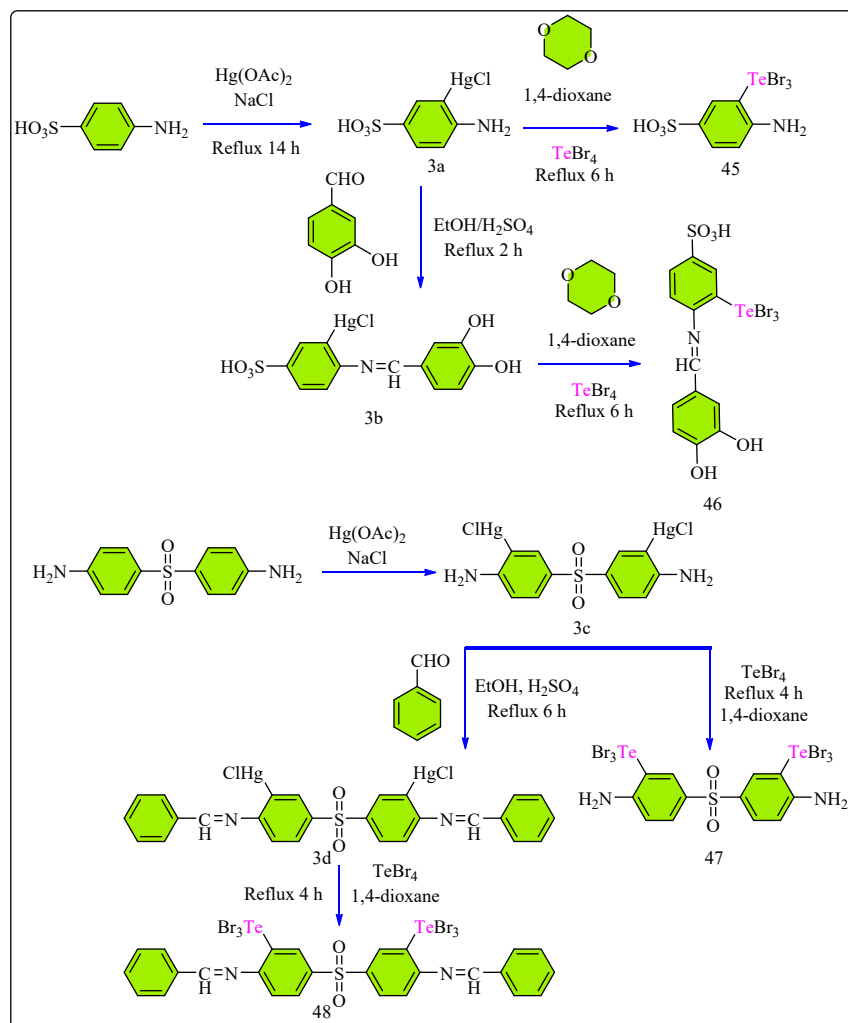
Complex 3a was prepared by heating mercuric acetate and 4-aminobenzenesulfonic acid in ethanol for 14 h, then adding NaCl to boiling methanol and filtering, washing, and

drying (Scheme 9). This complex was subsequently utilized to create Te complex 45 by refluxing tellurium tetrabromide with complex 3a in 1,4-dioxane under an argon environment, followed by recrystallization from dichloromethane and methanol to obtain brown crystals.⁹⁵ Complex 3a was also used to create Hg complex 3b, which serves as a precursor for Te complex 46. Complex 3b was synthesized by refluxing a mixture of 3,4-dihydroxybenzaldehyde and complex 3a in ethanol with the addition of sulfuric acid, providing a yellowish solid after filtration, washing, and recrystallization. Similarly, complex 3c was created by combining 4,4'-sulfonyldianiline and mercuric acetate with NaCl, using the same steps as complex 3a. Complex 3c was then used to synthesize Te complex 47 and Hg complex 3d, following procedures similar to those employed for complexes 45 and 3b. Finally, complex 3d was used to generate Te complex 48. *In vitro*, several complexes were tested for their anticarcinogenic properties against T24 bladder cells and PC-3 human prostate cells. Complexes 45, 46, 47, and 48

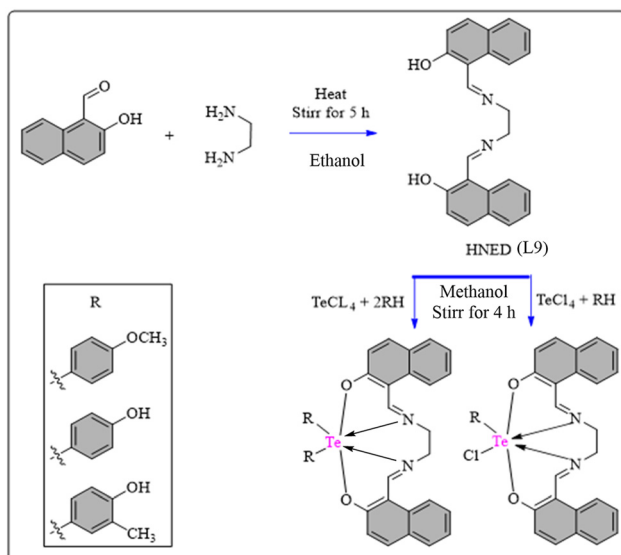
showed significant anticarcinogenic efficacy. Complex 46 and 47 performed particularly well towards both types of tumor cells, outperforming complex 46 and 48, as seen in Table 6. This observed activity is most likely attributable to the presence of chemically active elements such as sulfur, oxygen, nitrogen, and tellurium.^{96–98} Tellurium, in specific, has shown potential in blocking enzymes involved in tumor proliferation.^{46,99} Notably, complex 46 had a lower IC₅₀ value than complex 47 against cancer cells, indicating greater efficacy. Table 6 shows that complex 46 has a higher

Table 6: Obtained IC₅₀ values for Sulpha based Te complex 46 and 47, showed their anticancer potential.

Compound	IC ₅₀ (μM)	
	PC-3	T24
46	22.26 ± 3.21	24.12 ± 4.44
47	27.53 ± 4.72	48.82 ± 4.84



Scheme 9: Representation of reaction pathways for the synthesis of Sulpha based Te complexes.



Scheme 10: Methodology for the synthesis of HNED Schiff base ligand and Te complexes.

activity than complex 47. This difference could be ascribed to the presence of both phenolic and azomethine groups, as well as intermolecular chalcogen bonding aided by tellurium atoms. These interactions allow the chemicals to effectively engage cancer cell proteins, resulting in powerful inhibitory effects.⁹⁵

3 Synthesis of Te complexes and antioxidant activity

3.1 Schiff base Te(IV) complexes

The synthesis of the HNED (L9) Schiff base ligand involved slowly mixing 2-Hydroxy-1-naphthaldehyde with ethylenediamine in warm ethanol under reflux for 5 h (Scheme 10). The resulting crude precipitate was purified through petroleum ether and $\text{CH}_3\text{CH}_2\text{OH}$, then dried. Complexes were prepared

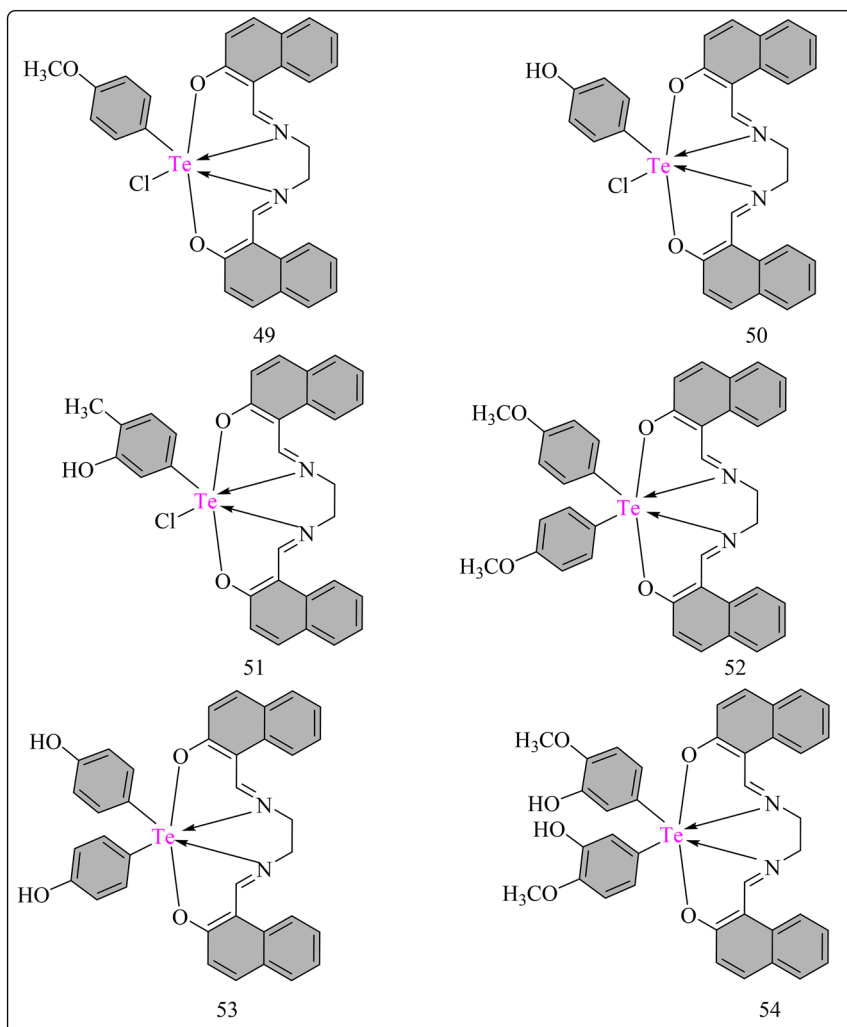


Figure 3: Structural representation of L9 based hexa-coordinated Te(IV) complexes.

by mixing equivalent amounts of L9 (1 mmol) with various aryl Te(IV) chlorides ($\text{RTeCl}_3/\text{R}_2\text{TeCl}_2$) dissolved in warm CH_3OH , followed by continuous stirring for 4 h. The obtained complexes, acquired through solvent evaporation, underwent further purification, recrystallization using a mixture of petroleum ether and CH_3OH , and drying. Both the ligand and complexes were then stored in a desiccator over CaCl_2 . L9 Schiff base coordinates to tellurium in octahedral geometry (Figure 3). The synthesized compounds were evaluated for antioxidant capabilities using the DPPH scavenging method, with ascorbic acid as standard. The results, reported in Table 7, show the IC_{50} values. The L9 ligand exhibited low scavenging ability ($\text{IC}_{50} = 227.05 \pm 0.63 \mu\text{g/mL}$). However, coordination with tellurium ion significantly enhanced

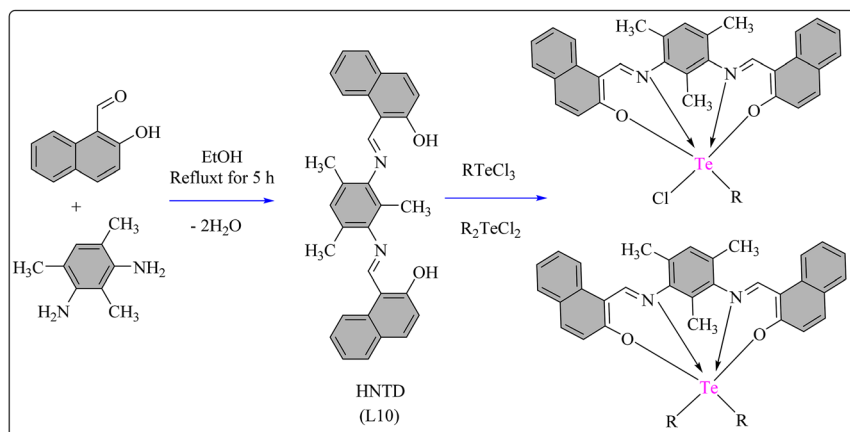
scavenging ability in complexes 49–54 ($\text{IC}_{50} = 81.90 \pm 0.31$ to $191.84 \pm 0.50 \mu\text{g/mL}$). Complex 51 and 54 showed the highest scavenging ability ($\text{IC}_{50} = 91.48 \pm 0.38$ and $81.90 \pm 0.31 \mu\text{g/mL}$), in comparison to ascorbic acid.¹⁰⁰

The HNTD (L10) Schiff base ligand was developed through a condensation reaction between 2-Hydroxy-1-naphthaldehyde and 2,4,6-trimethyl-1,3-phenylenediamine dissolved in ethanol (Scheme 11). After refluxing the colored mixture at 60°C for a duration of 5 h, yellow solid precipitates were produced and recrystallized using an ethanol and petroleum ether solution. The resultant L10 ligand was dried under CaCl_2 and then used to synthesize Te(IV) complexes via reactions with different organotellurium chlorides (Figure 4). The synthesized complexes^{55–60} showed higher reactivity against free radicals, with IC_{50} values ranging from 96.32 ± 0.40 to $283.90 \pm 0.69 \mu\text{g/mL}$, compared to L10's IC_{50} of $379.46 \pm 0.91 \mu\text{g/mL}$ (Table 7). This improvement shows a significant increase in radical quenching capabilities by chelation with tellurium ion. Complexes 55 and 58 showed IC_{50} values (100.96 ± 0.32 and $96.32 \pm 0.40 \mu\text{g/mL}$) similar to ascorbic acid, indicating high antioxidant activity.¹⁰¹ These findings emphasize the potential utility of the produced complexes as efficient antioxidants, underlining the relevance of chelation with tellurium ions in boosting their radical quenching.

H2NA (L11) Schiff base was synthesized using a known method.¹⁰² 2-Hydroxy-1-naphthaldehyde was dissolved in 20 mL of $\text{CH}_3\text{CH}_2\text{OH}$ and combined separately with ethanolic solutions of 2-nitroaniline and 4-nitroaniline to synthesize the L11 and L12 ligands, respectively (Scheme 12). The resulting mixtures were refluxed over a water bath for 4 h, yielding precipitates. These precipitates were subsequently filtered, purified using absolute ethanol, and dried under vacuum. The synthesis of L11 and L12 Schiff base Te(IV) complexes followed a method analogous to that described for the L9 Te(IV) complexes, resulting in

Table 7: Analysis of minimal inhibitory concentrations of ligand L9, L10 and corresponding Te complexes for their antioxidant potential.

Compound	% Scavenging activity at various concentration (in $\mu\text{g/mL}$)					IC_{50} (μM)
	20	40	60	80	100	
L9	7.23	13.54	15.56	19.00	24.81	227.05 ± 0.63
49	22.56	31.04	35.56	40.02	51.00	102.38 ± 0.40
50	5.01	14.03	18.99	24.98	28.01	171.55 ± 0.30
51	30.00	38.41	42.98	47.00	51.30	91.48 ± 0.38
52	26.20	34.22	39.45	43.32	48.13	104.38 ± 0.38
53	9.00	14.05	19.31	25.07	27.09	191.84 ± 0.50
54	29.99	39.10	44.50	50.10	54.00	81.90 ± 0.31
Ascorbic acid	37.01	42.06	48.03	51.33	55.66	73.71 ± 0.37
L10	10.49	12.01	14.04	17.20	19.07	379.46 ± 0.91
55	22.35	31.40	36.08	40.89	51.02	100.96 ± 0.32
56	5.42	12.88	17.29	25.12	37.06	141.02 ± 0.35
57	5.03	10.75	17.72	22.03	34.14	152.21 ± 0.38
58	23.14	31.53	38.03	44.04	51.14	96.32 ± 0.40
59	12.74	15.76	17.48	22.46	26.64	239.66 ± 0.91
60	9.48	10.38	15.11	18.22	21.24	283.90 ± 0.69
Ascorbic acid	37.01	42.06	48.03	51.33	55.66	418.52 ± 0.02



Scheme 11: Methodology for the synthesis of L10 ligand based Te hexa-coordinated complexes.

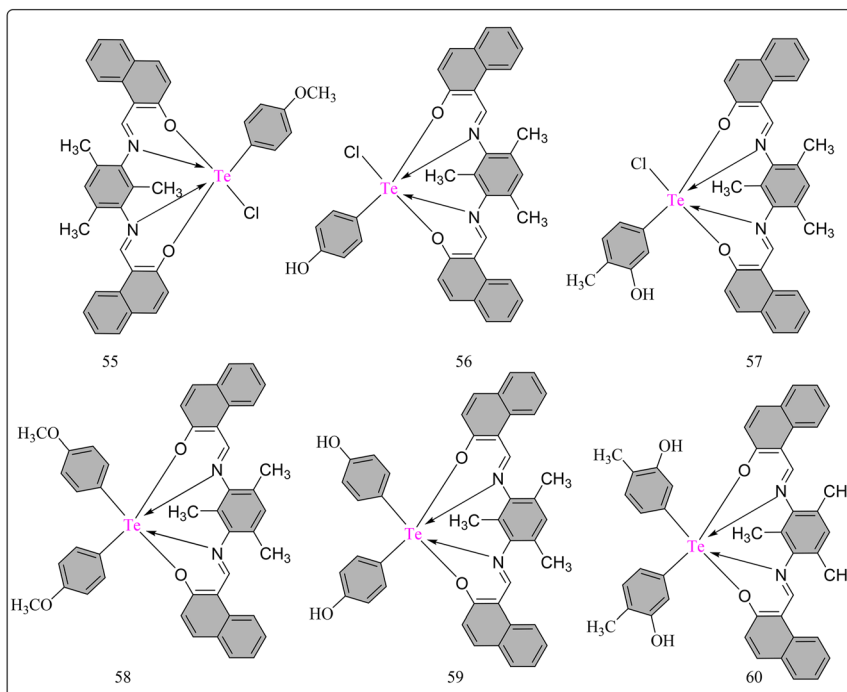
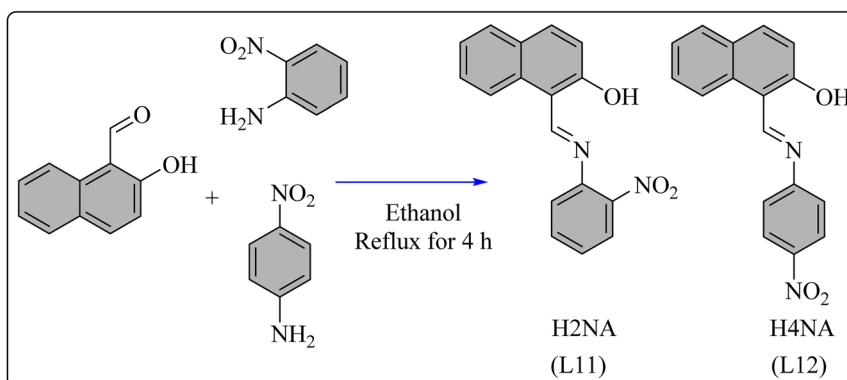


Figure 4: Structural representation of L10 ligand based hexa-coordinated Te(IV) complexes.



Scheme 12: Methodology for the synthesis of L11 and L12 ligand and their Te complexes.

complexes exhibiting a distorted square bipyramidal geometry. The antioxidant potential of ligand L11 and its Te(IV) complexes (61–66) shown in Figure 5 was evaluated using the DPPH assay,¹⁰³ with results compiled in Table 8. The percentage radical scavenging power increased with increasing sample concentration. L11 exhibited low radical scavenging activity ($IC_{50} = 2,487.77 \pm 0.05 \mu M$) compared to the standard ascorbic acid ($IC_{50} = 418.52 \pm 0.02 \mu M$). Chelation with tellurium atom enhanced scavenging activity. Complexes 61, 62, and 64 showed higher scavenging activity ($IC_{50} = 109.22 \pm 0.08 \mu M$, $106.23 \pm 0.03 \mu M$, and $106.34 \pm 0.09 \mu M$, respectively) compared to the standard antioxidant. Complexes 61, 62, and 64 demonstrate potential as effective free radical scavengers, while complex 65 displayed moderate scavenging activity ($IC_{50} = 123.90 \pm 0.07 \mu M$) comparable to the standard antioxidant.¹⁰⁴ The complexes 67, 68, and 69,

originating from the L12 schiff base ligand, displayed notable scavenging efficacy against free radicals, as evidenced by their low IC_{50} values of 80.32 ± 0.45 , 83.60 ± 0.43 , and $79.80 \pm 0.29 \mu g/mL$, respectively. These values are comparable to the IC_{50} value of the well-established antioxidant, ascorbic acid ($IC_{50} = 73.71 \pm 0.37 \mu g/mL$), highlighting the substantial antioxidant potential of these complexes.¹⁰⁵ This enhancement in activity can be attributed to the presence of either a *p*-hydroxy or *p*-methoxy substituent on the aryl group of the complexes. Previous research has indicated that such substituents tend to augment the antioxidant activity of compounds derived from pyrazolones. The inclusion of these specific substituents is likely altering the electronic and steric properties of the complexes, thereby enhancing their ability to effectively scavenge free radicals.¹⁰⁶

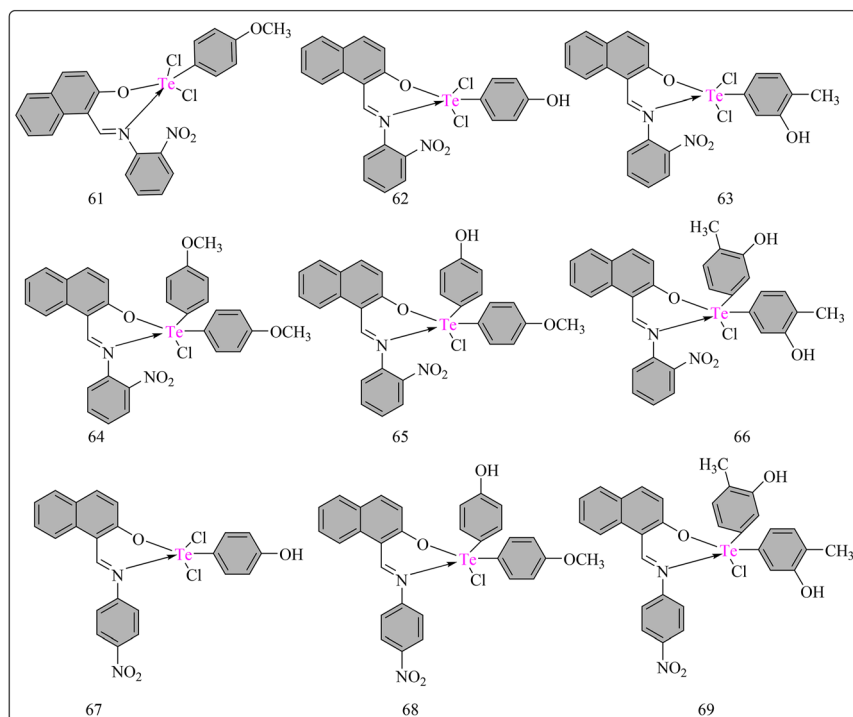
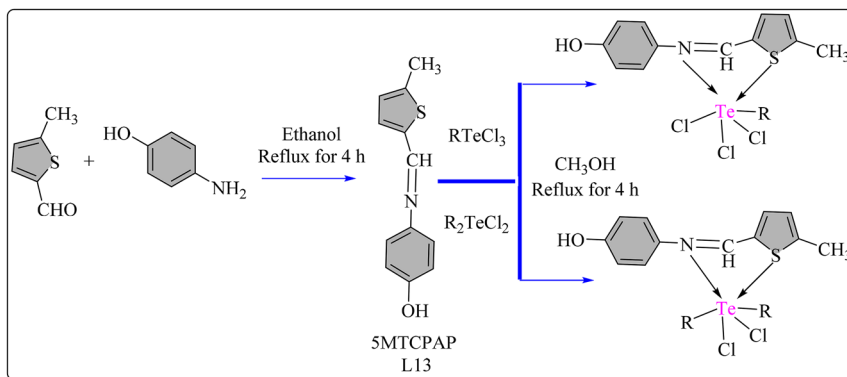


Figure 5: Structural representation of H₂NA and H₄NA based penta-coordinated Te(IV) complexes.

Table 8: Comparison of IC₅₀ values of ligands L11, L12, L13, and L14 with their Te complexes.

Compound	% Scavenging activity at various concentration (in µg/mL)					IC ₅₀ (µM)
	20	40	60	80	100	
L11	3.70	4.60	5.76	7.01	9.18	2,487.77 ± 0.05
61	26.05	38.21	49.14	59.03	64.98	109.22 ± 0.08
62	29.00	40.02	51.50	58.54	65.64	106.23 ± 0.03
63	26.04	27.79	28.95	30.70	32.18	560.44 ± 0.04
64	31.55	40.33	48.55	53.25	58.17	106.34 ± 0.09
65	28.64	35.62	43.52	52.14	55.90	123.90 ± 0.07
66	25.09	27.71	29.01	31.96	33.18	391.32 ± 0.05
Ascorbic acid	37.01	42.06	48.03	51.33	55.66	418.52 ± 0.02
L12	–	–	–	–	–	313.25 ± 0.94
67	–	–	–	–	–	80.32 ± 0.45
68	–	–	–	–	–	83.60 ± 0.43
69	–	–	–	–	–	79.80 ± 0.29
Ascorbic acid	–	–	–	–	–	73.71 ± 0.37
L13	14.98	20.79	28.61	34.14	42.32	124.16
70	16.41	23.98	33.51	39.12	45.21	110.46
71	29.14	39.54	48.40	58.91	65.31	63.78
72	30.57	38.14	44.17	52.36	59.24	74.26
73	15.63	24.39	31.14	39.35	44.40	112.46
74	18.92	25.41	33.54	42.70	47.22	104.48
75	30.14	36.75	47.61	52.23	58.11	74.09
Ascorbic acid	26.60	39.34	47.72	56.18	63.90	67.13
L14	–	–	–	–	–	124.01
76	–	–	–	–	–	110.55
77	–	–	–	–	–	59.20
78	–	–	–	–	–	141.09
79	–	–	–	–	–	90.01
80	–	–	–	–	–	155.91
81	–	–	–	–	–	86.37

5MTCAP (L13) schiff base ligand was synthesized by refluxing 5-methyl-2-thiophene carboxaldehyde and *p*-aminophenol in ethanol for 4 h, yielding brown filtrates, which were subsequently recrystallized using absolute ethanol. Complexes were synthesized by combining 2 mmol of Te(IV) chlorides with 2 mmol of L13 in methanol and refluxing for 4 h at 80 °C (Scheme 13). The reaction mixture was then concentrated and filtered, followed by purification with petroleum ether and methanol. Both the ligand and complexes were dried using anhydrous CaCl₂. The radical scavenging activity of Schiff base L13 ligand and its Te(IV) complexes (70–75) shown in Figure 6 was investigated using the standard DPPH assay,¹⁰⁷ with Table 8 presenting antioxidant behavior data for the complexes. UV–Vis spectroscopy was employed to obtain results, correlated with Ascorbic acid as the standard. The antioxidant activity increased with the % radical scavenging ability and sample complex concentration. At 100 µg/mL concentration, L13 exhibited 14.98 % radical scavenging activity, which increased upon chelation with Te(IV) complexes. The scavenging activity of ligand L13 was enhanced upon chelation with Te atom, with complex 71 exhibiting higher radical scavenging ability 65.3 % than ascorbic acid. However, the L13 displayed lower antioxidant ability (IC₅₀ = 124.16 ± 0.03 µM) compared to the standard ascorbic acid (IC₅₀ = 67.12 ± 0.05 µM). Complexes 71 (IC₅₀ = 63.78 µM) and 72 (IC₅₀ = 74.26 µM) displayed moderate antioxidant activity compared to ascorbic acid, indicating their potential as antioxidant agents.¹⁰⁸ NMeIATP (L14) schiff base ligand was synthesized by refluxing N-methylisatin with



Scheme 13: Methodology for the synthesis of L13 ligand and its Te complexes.

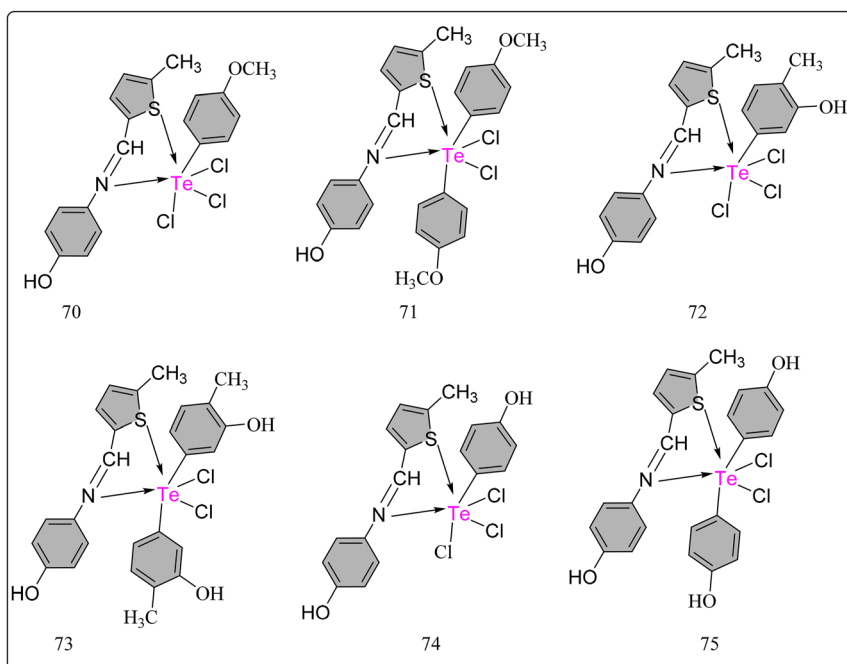
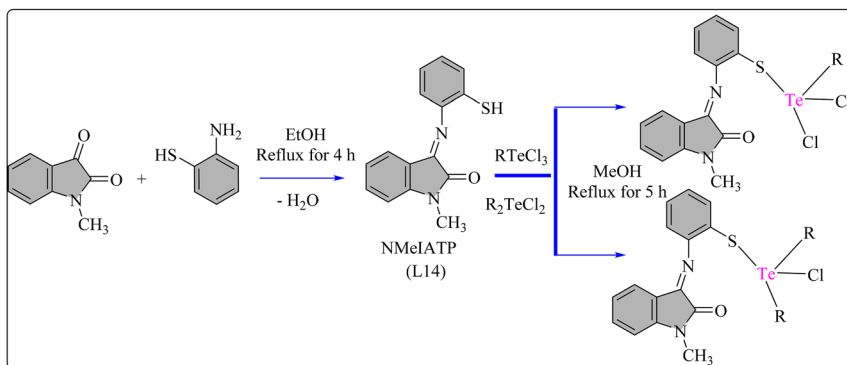


Figure 6: Structural representation of L13 ligand based hexa-coordinated Te complexes.



Scheme 14: Methodology for the synthesis of L14 ligand and its Te complexes.

2-aminothiophenol in 50 mL EtOH for 4 h, yielding an orange solid upon cooling and recrystallization with methanol (Scheme 14). Schiff base ligand (15 mmol) was then combined with solutions of $\text{RTeCl}_3/\text{R}_2\text{TeCl}_2$ in 50 mL methanol and refluxed for 5 h. The resulting products were filtered,

adjusted to a pH of around seven with CH_3ONa , recrystallized from methanol, and dried over anhydrous CaCl_2 . L14 ligand and all Te(IV) complexes shown in Figure 7 were assessed for antioxidant activity using DPPH free radical assay in DMSO/methanol with UV–Visible spectroscopy, compared to

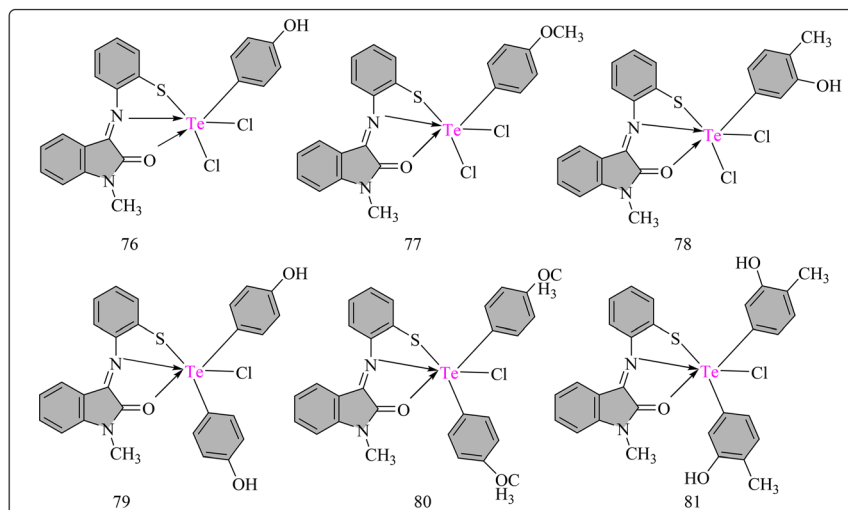
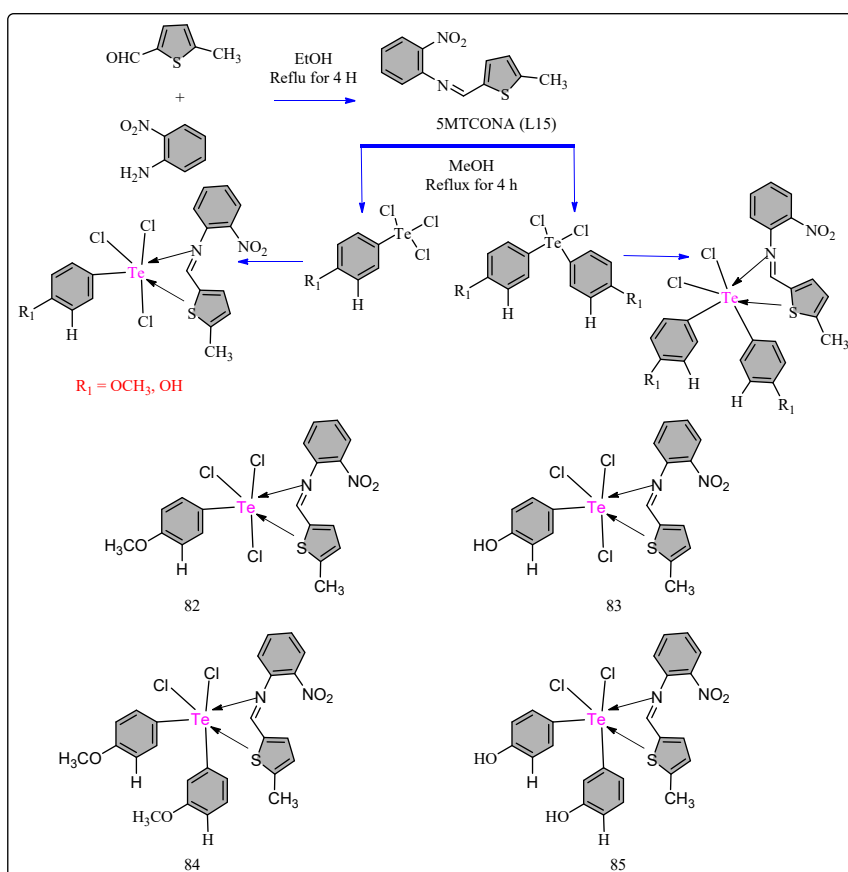


Figure 7: Structural representation of L14 ligand based hexa-coordinated Te complexes.

Ascorbic acid. All complexes (76–81) exhibited good antioxidant activity (IC_{50}). Complexes 77, 79, and 81 displayed stronger activity (Table 8), with complex 77 showing the highest activity ($IC_{50} = 59.20 \mu\text{g/mL}$), surpassing Ascorbic acid ($IC_{50} = 71.03 \mu\text{g/mL}$). Except for complexes 78 and 80, other complexes demonstrated higher activity than L14.¹⁰⁹

5-methyl-2-thiophene carboxaldehyde and 2-nitroaniline were refluxed in ethanol to produce the 5MTCONA (L15) schiff base ligand, which was subsequently used to create L15-containing Te complexes. The process required combining L15 with arylated Te chlorides in the presence of methyl alcohol and refluxing for 4 h (Scheme 15). To obtain



Scheme 15: Methodology for the synthesis of L15 ligand and its Te hexa-coordinated complexes.

Table 9: Illustration of IC_{50} values of ligand L15 and its Te complexes at various concentrations.

Compound	% Scavenging activity at various concentration (in $\mu\text{g/mL}$)					IC_{50} (μM)
	20	40	60	80	100	
L15	10.98	13.65	20.79	24.56	29.20	187.36
82	30.62	37.89	45.12	52.41	59.11	73.90
83	27.70	37.25	46.52	53.21	64.40	68.87
84	20.89	28.14	36.21	45.65	53.32	91.94
85	26.12	33.54	40.61	49.55	58.74	80.39
Ascorbic acid	29.81	36.15	48.21	54.64	60.31	70.49

the final products, the chemicals were filtered and purified using petroleum ether and methanol, and then dried over an anhydrous solution of calcium chloride. The antioxidant activity results show that as the percentage radical scavenging ability increases, correspondingly increases the concentration of experimental complexes (82–85). The Schiff base L15 had the lowest radical scavenging activity among the investigated complexes ($IC_{50} = 187.36 \pm 0.45 \mu\text{g/mL}$) compared to ascorbic acid as a reference ($IC_{50} = 70.49 \pm 0.28 \mu\text{g/mL}$) (Table 9). The complexes 82, 83, and 85, with IC_{50} values of $73.91 \pm 0.50 \mu\text{g/mL}$, $68.870 \pm 0.43 \mu\text{g/mL}$, and $80.39 \pm 0.37 \mu\text{g/mL}$, respectively, exhibit the strongest radical scavenging activity equivalent to ascorbic acid. The complex 84 ($IC_{50} = 91.94 \pm 0.50 \mu\text{g/mL}$) has modest antioxidant activity.¹¹⁰

4 Summary and outlook

This in-depth review covers important synthetic techniques and navigates the rapidly expanding field of organotellurium compounds, illuminating its numerous applications in the biological and material science fields. It emphasizes how crucial it is to synthesis these compounds with a variety of ligands, such as Schiff bases, amino acids, naphthoquinones, and β -hydroxy alkylated compounds all of which are well-known for their stability and adaptability in assisting the synthesis of organotellurium complexes. This study demonstrates the proven efficacy of organotellurium complexes as antioxidants and anticancer agents, emphasizing their future outlook. By means of comparisons to standard drugs, the research highlights their capacity for addressing significant health issues. Furthermore, the study shows that although organic ligands by themselves have some anticancer and antioxidant potential, when they are complexed with tellurium, they become much more effective, highlighting the amazing improvement in their therapeutic potency.

Although organotellurium compounds have a lot of potential, there are also a lot of challenges and disadvantages.

One major drawback compared to other compounds derived from metals is the very limited knowledge of their mechanisms of action. Further study is required to fully understand their potential in solving complex biological and material science problems. Moreover, the complex and resource-intensive nature of the synthesis of organotellurium compounds may pose challenges to scalability and cost-effectiveness for large-scale applications. Additionally, concerns about their potential toxicity and environmental impacts necessitate the design of mitigation measures and the use of extreme caution in their development and implementation. In conclusion, all of the potential that organotellurium compounds hold for solving significant problems in biology and materials science remains untapped. This review offers valuable insights on synthetic methods, potential applications, and future directions for advancing our understanding and exploration of organotellurium compounds in several scientific domains.

Research ethics: Not applicable.

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