

Preparation, Characterization and Biological Studies on Pyridoxylidene-Cephalexin Schiff Base Complexes of Aryltellurium (IV)

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Abstract

A novel Schiff base pyridoxylidene-cephalexin (HPL-CPX) synthesized from pyridoxal and cephalexin, form complexes with aryltellurium (IV) trichlorides and diaryltellurium (IV) dichlorides of the type $PL-CPX.ArTeCl_2$ and $PL-CPH.Ar_2TeCl$ (where $Ar=p$ -methoxyphenyl, p -ethoxyphenyl, p -hydroxyphenyl and 3-methyl-4-hydroxyphenyl). They have been characterized by elemental analyses, molar conductance, IR and 1H NMR spectroscopy. The spectral studies predict that the coordination of Schiff base to tellurium in a uninegative bidentate manner with $-N$, $-O$ donor sites of the azomethine-N and deprotonated phenolic-O to give six membered chelate rings with penta coordinated tellurium centre having Ψ -trigonal bipyramidal geometry. The synthesized ligand, and its aryltellurium complexes was screened for its antimicrobial activity against various bacterial and fungal strains.

Keywords: Pyridoxal; Cephalexin; Aryltellurium (IV); Diaryltellurium (IV); Antibacterial; Antifungal activities

Introduction

Cephalexin is a beta-lactam antibiotic within a class of first generation cephalosporin [1,2]. It was first reported by Brotzu in 1948 and appeared to inhibit the synthesis of bacterial cell wall and act against both gram positive and gram-negative bacteria.

Pyridoxal is a close analog of pyridoxine (also known as vitamin B6) [3] and this makes the Schiff bases with cephalexin and their aryltellurium complexes attractive candidates for their biological activity [4]. Due to their structural varieties and very unique characteristics and because of their excellent donor abilities and chelating agents [5-9], the Schiff bases are the most versatile studied ligands in coordination chemistry [10,11]. Intramolecular hydrogen bonding between OH hydrogen and C=N nitrogen atom of Schiff base determines the biological properties [12] like antiviral [13-15], antifungal [16-18], antibacterial [19-21] and anticancer [22-26].

Also, the aryltellurium (IV) chlorides act as Lewis acids [27-43] and form complexes with several N-, O- and S- donor bases. In view of this we herein report some new complexes of aryltellurium (IV) trichlorides, ArTeCl_3 and diaryltellurium (IV) dichlorides, Ar_2TeCl_2 with pyridoxylidene-cephalexin Schiff base (HPL-CPX).

Experimental

Materials and methods

All the chemicals used were of analytical reagent grade. All preparations were carried out under an atmosphere of dry nitrogen and the solvents used were purified and dried by standard method [44,45]. p-Methoxyphenyltellurium (IV) trichloride [46,47], bis (p-methoxyphenyl) tellurium (IV) dichloride [47,48], p-ethoxyphenyltellurium (IV) trichloride [49], bis (p-ethoxyphenyl) tellurium dichloride [49] p-hydroxyphenyltellurium (IV) trichloride [50], bis (p-hydroxyphenyl) tellurium (IV) dichloride [50], 3-methyl-4-hydroxyphenyltellurium (IV) trichloride [51] and bis (3-methyl-4-hydroxyphenyl) tellurium (IV) dichloride [51] were prepared by the reactions of TeCl_4 with anisole, phenetole, phenol, o-cresol respectively, by the methods reported in the literature [46-51].

Preparation of pyridoxylidene-cephalexin Schiff base (HPL-CPX) [52]

Equimolar quantity of saturated methanolic solution of cephalixin drug and pyridoxal 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 1 h. A clear dark yellow colored solution was obtained. The Schiff base ligand was isolated by crystallization after volume reduction by evaporation. The crystalline product was dried under vacuum and kept in desiccator over P_4O_{10} until further use. Yield=75%, M.pt.(decomp.)=184°C-186°C. Analyses (Calculated) $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$: C(57.82), H(5.26) and N(11.24); Found: C(57.71), H(5.19) and N(11.09).

Preparation of pyridoxylidene-cephalexin 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 monosodium salt of HPL-CPX i.e., NaPL-CPX in equimolar ratio, yield PL-CPX. ArTeCl_2 and PL-CPX. 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 isolate the sodium salt. 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 h-4 h, 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 colored product. This was filtered, washed with benzene+methanol (1:1) and dried in vacuum desiccator over P_4O_{10} .

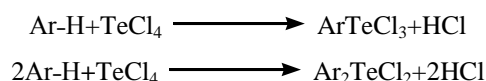
Physical studies

Conductance studies were performed under dry condition at $25 \pm 2^\circ\text{C}$ in DMSO with a dip type conductivity cell on microprocessor based conductivity bridge type MICROSIL.

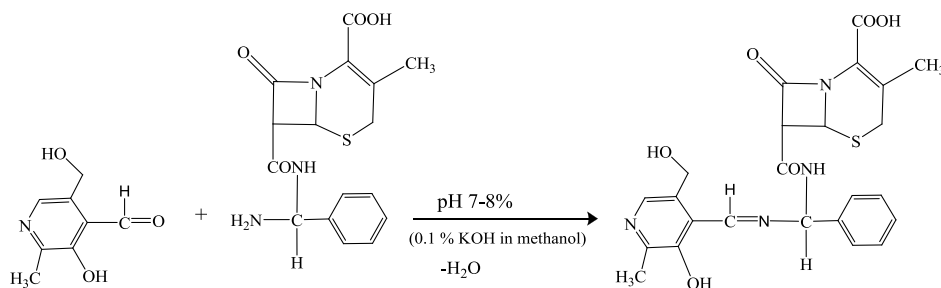
Infrared spectra (4000 cm^{-1} to 400 cm^{-1}) were recorded in KBr pellets on Alpha Bruker FT-IR spectrometer and far IR (400 cm^{-1} to 50 cm^{-1}) was obtained in polyethylene pellets on a F.T. Infra-Red Spectrophotometer Model RZX (Perkin Elmer) at SAIF, Panjab University Chandigarh. Proton magnetic resonance spectra were recorded in DMSO- d_6 using TMS as an internal reference on BRUKER AVANCE II 400 NMR spectrometer at Sophisticated Analytical Instrumentation Facility, Punjab University Chandigarh. The antimicrobial screening was carried out by tube dilution method.

Results and Discussion

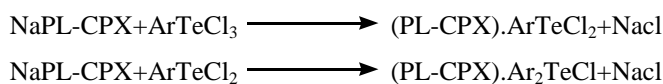
TeCl_4 when heated with anisole [46-48], phenetole [49], phenol [50], o-cresol [51] (Ar-H) appears to undergo Friedel-Crafts type condensation reaction whereby TeCl_4^{3+} unit attacks a position para to the methoxy/ethoxy/hydroxy groups in the aromatic rings, thus resulting in the formation of aryltellurium (IV) trichlorides and diaryltellurium (IV) dichlorides.



Preparation of pyridoxylidene-cephalexin Schiff base (HPL-CPX) by the reaction of cephalixin drug and pyridoxal can be represented by following equations.



Sodium salt of pyridoxylidene-cephalexin Schiff base (NaPL-CPX) reacts with aryltellurium (IV) trichlorides and diaryltellurium (IV) dichlorides in 1:1 molar ratio to yield the corresponding aryltellurium (IV) complexes.



All the tellurium (IV) complexes are colored, crystalline solids, stable at room temperature and non-hygroscopic in nature. The complexes have been analyzed 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 (Λ_M) data for the complexes in DMSO are compiled in TABLE 1. The Λ_M value at ca. 10^{-3} M for aryltellurium (IV) complexes in DMSO lie in the range $34.68\text{ S cm}^2\text{ mol}^{-1}$ to $65.80\text{ S cm}^2\text{ mol}^{-1}$ which predict the weak electrolyte to 1:1 electrolyte [53,54] type behavior of these complexes in DMSO, probably due to ionization into $\text{ArTeCl}\cdot\text{PL-CPX}^+/\text{Ar}_2\text{Te}\cdot\text{PL-CPX}^+$ and Cl^- in DMSO. The higher Λ_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 PL-CPX^- along with Cl^- in DMSO.

TABLE 1. Analytical data, molar conductance and physical properties of pyridoxylidene-cephalexin Schiff base complexes of tellurium (IV).

Compound No.	Complex (Ar)	Empirical formula (Formula Wt.)	Colour (yield, %)	M. Pt. (°C) dec.	Analyses % found (calculated)					Λ_M at ca. 10^{-3} M S $\text{cm}^2 \text{mol}^{-1}$ in DMSO
					C	H	N	Te	Cl	
Schiff base	HPL-CPX	$\text{C}_{24}\text{H}_{24}\text{N}_4\text{O}_6\text{S}$ (496.54)	Dark yellow (75)	184-186	57.32 (58.05)	5.15 (4.87)	11.03 (11.28)	-	-	-
1	(PL-CPX). ArTeCl_2 (<i>p</i> -methoxyphenyl)	$\text{C}_{31}\text{H}_{30}\text{Cl}_2\text{N}_4\text{O}_7\text{S}$ Te (801.16)	Green (90)	134-136	46.25 (46.47)	3.99 (3.77)	6.87 (6.99)	15.77 (15.93)	8.73 (8.85)	34.68
2	(PL-CPX). ArTeCl_2 (<i>p</i> -ethoxyphenyl)	$\text{C}_{32}\text{H}_{32}\text{Cl}_2\text{N}_4\text{O}_7\text{S}$ Te (815.19)	Light brown (87)	150-152	46.98 (47.15)	4.11 (3.96)	6.77 (6.87)	15.50 (15.65)	8.57 (8.70)	35.80
3	(PL-CPX). ArTeCl_2 (<i>p</i> -hydroxyphenyl)	$\text{C}_{30}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_7\text{S}$ Te (787.14)	Light green (85)	120-122	45.51 (45.78)	3.76 (3.59)	7.01 (7.12)	16.03 (16.21)	8.87 (9.01)	56.14
4	(PL-CPX). ArTeCl_2 (3-methyl-4-hydroxyphenyl)	$\text{C}_{31}\text{H}_{30}\text{Cl}_2\text{N}_4\text{O}_7\text{S}$ Te (801.16)	Brown (80)	116-118	46.18 (46.47)	3.92 (3.77)	6.85 (6.99)	15.83 (15.93)	8.69 (8.85)	52.58
5	(PL-CPX). Ar_2TeCl (<i>p</i> -methoxyphenyl)	$\text{C}_{38}\text{H}_{37}\text{ClN}_4\text{O}_8\text{STe}$ (872.84)	Light yellow (85)	130-132	52.05 (52.29)	4.35 (4.27)	6.27 (6.42)	14.51 (14.62)	3.95 (4.06)	42.25
6	(PL-CPX). Ar_2TeCl (<i>p</i> -ethoxyphenyl)	$\text{C}_{40}\text{H}_{41}\text{ClN}_4\text{O}_8\text{STe}$ (900.89)	Light brown (82)	128-130	53.11 (53.33)	4.73 (4.59)	6.17 (6.22)	14.07 (14.16)	3.85 (3.94)	65.80
7	(PL-CPX). Ar_2TeCl (<i>p</i> -hydroxyphenyl)	$\text{C}_{36}\text{H}_{33}\text{ClN}_4\text{O}_8\text{STe}$ (844.79)	Dark yellow (84)	124-126	50.89 (51.18)	4.15 (3.94)	6.55 (6.63)	14.94 (15.10)	4.07 (4.20)	45.38
8	(PL-CPX). Ar_2TeCl (3-methyl-4-hydroxyphenyl)	$\text{C}_{38}\text{H}_{37}\text{ClN}_4\text{O}_8\text{STe}$ (872.84)	Brown (75)	122-124	52.08 (52.29)	4.39 (4.27)	6.23 (6.42)	14.49 (14.62)	3.90 (4.06)	39.76
Values of Λ_M reported [53,54] for 1:1 electrolytes in DMSO=50-70 $\text{S cm}^2 \text{mol}^{-1}$										

Infrared spectra

The IR data of Schiff base and its tellurium (IV) complexes are listed in TABLE 2. The spectra of 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 $\text{ArTeCl}_3/\text{Ar}_2\text{TeCl}_2$.

TABLE 2. Important infrared absorption bands (cm^{-1}) of Schiff base and complexes.

Compound	Methanolic ($-\text{CH}_2\text{OH}$) $\nu_{(\text{O-H})}$	Phenolic $\nu_{(\text{O-H})}$	Azomethine $\nu_{(\text{C=N})}$	$\nu_{(\text{C-O})}$	$\nu_{(\text{Te-N})}$	$\nu_{(\text{Te-O})}$
HPL-CPX	3205 mb	2878 b	1672 m	1221 s	-	-
1	2934 mb	-	1675 mb	1296 s	416 m	272 w
2	3100 mb	-	1680 mb	1290 s	420 m	277 w
3	3058 mb	-	1675 mb	1329 s	426 s	280 w
4	3124 mb	-	1674 mb	1305 s	417 s	290 w
5	3172 mb	-	1677 s	1298 s	419 s	298 w
6	3224 mb	-	1675 s	1281 s	412 m	275 w
7	3159 mb	-	1671 mb	1274 s	416 m	280 w
8	1285 mb	-	1669 s	1371 s	424 m	287 w
s=sharp, b=broad, mb=medium broad, sh=shoulder, w=weak						

In IR spectra of ligand shows a broad band around 3200 cm^{-1} indicates the presence of methanolic OH. This band is also observed in the Schiff base tellurium complexes, as methanolic group ($-\text{CH}_2\text{OH}$) attached to pyridoxal ring does not participate in coordination [4,55,56]. A broad weak band in Schiff base in the range of 2800 cm^{-1} to 2900 cm^{-1} is assigned to an intramolecular hydrogen bond [57,58] between OH hydrogen of phenolic group and nitrogen of azomethine group. This band disappear on complexation with tellurium atom and shows that the phenolic group of pyridoxal moiety is involved in bonding [59]. Also, an intense ligand band at 1221 cm^{-1} (phenolic $-\text{C-O}$) in free ligand has shifted to higher frequency side in complexes, further proved that the phenolic group coordinates to tellurium atom [60,61] after deprotonation.

The vibration of the azomethine group of Schiff base observed 61-63 at 1672 cm^{-1} , shift to lower or higher side [62-65] by $\pm 10 \text{ cm}^{-1}$ in the Schiff base tellurium complexes, indicating coordination through azomethine nitrogen. The two new bands appear in range 272 cm^{-1} to 298 cm^{-1} and 412 cm^{-1} to 426 cm^{-1} assigned due to $\nu(\text{Te-O})$ 66-69 and $\nu(\text{Te-N})$ mode 70 of vibration [65-70].

Thus, IR data predict the monobasic bidentate nature of the Schiff base (HPL-CPX) involving azomethine nitrogen atom and phenolic oxygen after deprotonation giving rise to six membered chelate rings with the penta coordinated tellurium centre.

^1H NMR spectra

In order to identify the solution structure of Schiff base (HPL-CPX) and its complexes, ^1H NMR spectra were recorded in DMSO-d_6 and are given in TABLE 3. The ^1H resonance of the phenolic group at 8.65δ ppm in Schiff base due to presence of intramolecular hydrogen bonding [71-73] disappear on complexation indicating the involvement of phenolic oxygen in the coordination after deprotonation [64]. The signal due to the methanolic proton is observed at around 5.37δ ppm which remains intact in the complexes, this confirm that it does not take part in bonding [73]. The azomethine protons [51,63,72] which

resonate as a singlet at 8.12 δ ppm in parent Schiff base is shifted towards downfield side in the complexes. This clearly demonstrate [61,72] the coordination of azomethine nitrogen to tellurium.

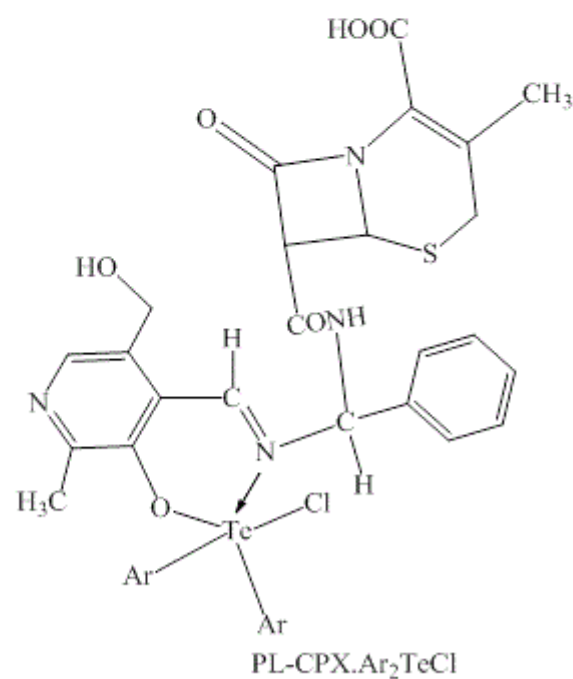
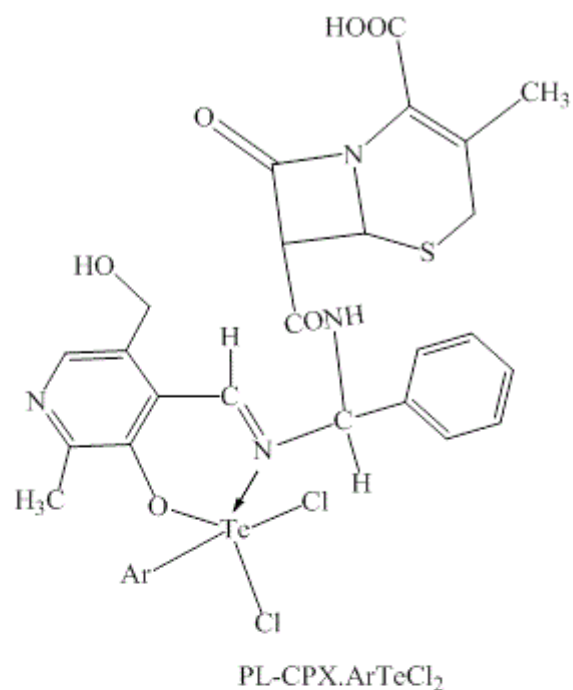
TABLE 3. ^1H NMR spectral data of Schiff base and complexes in DMSO-d_6 .

Compound	Phenolic-OH	Methanolic-OH	Azomethine-H	N-substituted methine proton
HPL-CPX	8.655 m	5.669 s	8.123 d	8.482 d
1	-	5.166 s	8.160 d	8.396 s
2	-	5.225 s	8.123 d	8.301 s
3	8.132 s*	5.331 s	8.226 d	8.321 s
4	8.495 s*	5.724 s	8.131 d	8.011 s
5	-	5.337 s	8.163 d	8.189 s
6	-	5.330 s	8.145 d	8.160 s
7	9.891 s*	5.333 s	8.147 d	8.201 s
8	9.911 s*	5.235 s	8.144d	8.159 s
s=singlet, d=doublet, m=multiplet. * Due to phenolic OH of ArTe and Ar_2Te moieties.				

Thus pyridoxylidene-cephalexin act as a monobasic bidentate $-\text{N}$, $-\text{O}$ chelating ligand in PL-CPX.ArTeCl_2 and $\text{PL-CPX.Ar}_2\text{TeCl}$ complexes giving five coordinate tellurium having Ψ -trigonal bipyramidal geometry in these complexes as predicated from IR studies as well. The proposed structures are as below (FIG. 1).

Biological activities

The pyridoxylidene-cephalexin Schiff base (HPL-CPX) 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 [74]. Dilution of test and standard compounds were prepared double strength nutrient broth-I.P (Antibacterial) and Sabouraud dextrose broth-I.P (Antifungal) [75]. The samples were incubated at $37 \pm 1^\circ\text{C}$ for 24 h (bacteria), $25 \pm 1^\circ\text{C}$ for 7 days (*A. niger*), $30 \pm 1^\circ\text{C}$ for 15 days (*A. flavus*), $35 \pm 1^\circ\text{C}$ for 72 h (*A. fumigates*) respectively and results were recorded in terms of MIC values and are presented in the TABLE 4.



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

FIG. 1. Proposed structures of complexes.

The data show that the complexes of aryltellurium (IV) exhibit moderate antibacterial and antifungal activity. The antimicrobial activity shows following trend:



PL-CPX.Ar₂TeCl (Ar=p-hydroxyphenyl) shows substantial activity against *P. aeruginosa*, whereas PL-CPX.Ar₂TeCl (Ar=4-methoxy-4-hydroxyphenyl) exhibit appreciable activity against *E. coli*. Aryltellurium Schiff base complexes are moderately more effective against fungal strain than Schiff base itself.

TABLE 4. Minimum inhibitory concentration, MIC ($\mu\text{g/mL}$); (-) resistant.

Compound	Bacteria strains						Fungal strains		
	<i>S. aureus</i> (ATCC 11632)	<i>S. typhi</i> (ATCC 15499)	<i>P. aeruginosa</i> (ATCC 23564)	<i>E. coli</i> (ATCC 35218)	<i>B. cereus</i> (MTCC 7350)	<i>P. rettgeri</i> (DRDE strain)	<i>A. niger</i>	<i>A. fumigates</i>	<i>A. flavus</i>
HPL-CPX	5.0	-	-	-	1.25	2.5	20	5.0	1.25
1	5.0	-	-	-	1.25	2.5	-	1.25	5.0
2	-	-	-	-	-	-	-	-	-
3	1.25	2.5	1.25	5.0	-	-	5.0	-	-
4	-	-	5.0	1.25	0.625	-	20	5.0	1.25
5	10	10	20	-	5.0	5.0	-	-	2.5
6	1.25	2.5	1.25	5.0	-	-	20	5.0	1.25
7	5.0	10	5.0	20	-	0.625	5.0	2.5	-
8	20	-	20	-	10	20	5.0	1.25	5.0

Conclusion

Aryltellurium (IV) and diaryltellurium (IV) dichlorides upon reaction with sodium salt of Schiff base (NaPL-CPX) derived from pyridoxal and cephalixin yield new complexes of tellurium (IV). The synthesized complexes were characterized by elemental analyses, conductance measurement, IR and ¹H NMR spectral studies. The analytical data suggest that the Schiff base complexes have 1:1 stoichiometry. The Schiff base (HPL-CPX) in these complexes acts as a monobasic bidentate ligand through azomethine nitrogen and phenolic oxygen after deprotonation. Based on these studies, distorted trigonal bipyramidal geometry with six membered chelate ring with tellurium centre has been suggested. The complexes have been observed to possess moderate antimicrobial activity against bacterial and fungal strains.

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