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Anti microbial study of newly formed complexes of transition and inner transition metals with antiulcer drug and RNA bases

Sarika Verma*, Sarita shrivastva and Poonam Rani

** Dep. of Engineering Chemistry SAM college of Eng. and Tech, Bhopal*
Chemical laboratory, Govt. Motilal Vigyan Mahavidhalaya, Bhopal

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ABSTRACT

Binary and Ternary complexes of Transition metals (Co, Cu, Cr, Cd, Mn) and Inner transition metals (Th, Ce, Gd) have been synthesized by reacting their metal salts with antiulcer drug, namely Omeparazole (OME) and RNA bases namely Uracil(URA)/Adenine(ADE). The complexes are colored solids which are insoluble in cold water and freely soluble in DMF, DMSO and Ethanol. In this study, these metal complexes have been screened for their antibacterial activity towards Pseudomonas aeruginosa, Pseudomonas diminuta, Escherichia Coli , Streptococus Faecali Bacterias and antifungal activity towards Aspergillus Nidulans Fungi respectively .The results obtained were compared with that of the parent drug .The study reveals that the metal chelates (complexes) shows a remarkable resistance as compared with the parent drug.

Keywords: Omeparazole (OME), Uracil (URA) ,Adenine (ADE), Antibacterial and Antifungal activity.

INTRODUCTION

The Transition and Inner transition metal ions are known to have the Small radii and variable coordination number ranging from 3 to 12, which make them excellent spacers in assembling fascinating metal organic frameworks. These metal complexes are of continuing interest mainly due to their structural and catalytical properties and their application in diagnostic pharmaceutical and laser technology [1 -6].They have been found to exhibit anticancer and fungicidal properties also [7]. In the lanthanide complexes with various types of multidentate ligand , the metal can achieve high coordination number giving structural difference responsible for their important properties.

Antiulcer drugs act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H^+/K^+ ATPase, or, more common, gastric *proton pump*) of the gastric parietal cell.In the present study the Omeparazole (OME) ,anti ulcer drug with

the molecular structure shown in figure 1 is used as one of the ligand for the formation of ternary complex. Its chemical name is - (5-methoxy- 2- {{(4-Methoxy-3, 5-dimethy- 1-pyridiny) methyl} sulfinyI}-IH-benzimidazole) [8].It is a substituted Benzimidazole with the capacity to inhibit gastric H+, K+, ATPase , the proton transporting enzyme in the parietal cells that secrete HCL in stomach (wolmark et al 1983).

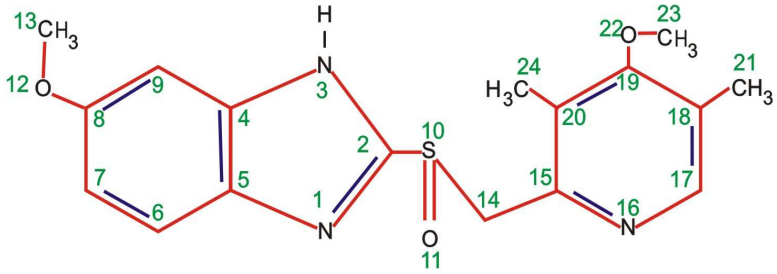

Fig 1: OMEPARAZOLE

As the interaction of metal ions with nucleobases is of great interest because of their relevance to the essential, medical or toxic bioactivity of metal, where nucleobase molecule can coordinate as exogenous ligands in metalloproteins, function as cofactors in the enzymatic systems and construct important cell structures e.g. RNA. [9]

Thus, the RNA bases namely Uracil and Adenine is selected as the secondary ligand for the formation of ternary complexes. Uracil is 2 Oxy - 4-Oxy pyrimidine or 2, 4 Pyrimidinedione or 2, 4 - dihydroxy prymidine or 2, 4 pyrimidine diol. It is naturally occurring pyramidine derivative [10]. The base posses the N- and O- donor ligands and their molecular structure is shown in fig. 2

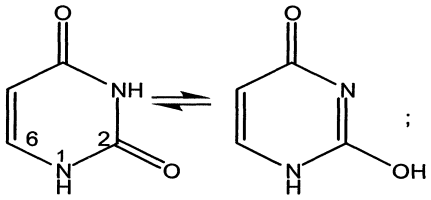

Fig 2: URACIL

Adenine is a 9*H*-Purin-6-amine with a variety of roles in biochemistry including cellular respiration, in the form of both the energy-rich adenosine triphosphate (ATP) and the cofactor nicotinamide adenine binucleatide (NAD) and protein synthesis, as a chemical component of DNA and RNA [11] and shown in figure 3.

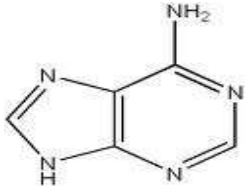

Fig 3: ADENINE

Bactericidal study, a part of a biological science, is just over a century old. Bacteriology has a close link with curative medicine in regard to the precise diagnosis and the rational treatment

of microbial disease. It is closely concerned with the epidemiology and the control of infection in any community where the transmission and disease producing capacity of the infecting micro organisms may by facilitated by environmental or host factors.

In recent years it has been shown that, in many cases, certain metal complexes of a drug are proved more potent that pure drug The increase in potency is due to binding of a drug with metal ions dressed it up with some special physico-chemical properties helpful in its biological activities; such as low dissociation constant, special redox potential, electron distribution and lipid solubility [12-16]. Taking in consideration the above in present study some Metal complexes of Omeparazole with Uracil/Adenine (synthesized in the study) have been screened for their activity towards Bacteria Viz *Pseudomonas aeruginosa*, *Pseudomonas diminuta*, *Escherichia Coli*, *Streptococcus Faecalis* and Fungi *Aspergillus Nidulans.* The metal ions used for the present study and for the preparation of chelates includes the essential elements required by the body[17-18] .They are involved in wide variety of biochemical functions in the body but most acts as primarily in enzyme system.[19-21]

MATERIALS AND METHODS

All the chemicals used throughout the course of experimental were either BDH or E merck quality. Pure sample of Omeparazole is obtained from Nosch lab, Hyderabad, India. The ligand as well as metal complexes were analyzed by standard methods. Material used are Petri plates 90mm, synthesized metal complexes of OME/URA/ADE ,Agar Base, Autoclave ,Incubator, Balance, pH meter Microscope ,Water bath, Petri dishes.

Preparation of the complexes

Binary and mixed ligand complexes of OME/URA/ADE were prepared by refluxing aqueous solution of metal salt with aqueous solution of pure salt of OME/URA/ADE in 1:1:1 molar ratio for 3 or 4 hours over water bath [22-24]. The solution on refluxing gave insoluble complex; [25-26].The complexes were stored in airtight bottles.

The Antimicrobial activity of the ligand (OME, URA, and ADE) and metal Complexes was checked by disc diffusion technique.

The antibacterial activity of the metal salts, ligand and the corresponding complexes were assayed simultaneously against *Pseudomonas aeruginosa*, *Escherichia Coli*, *Pseudomonas diminuta*, *Streptococcus Faecalis* bacteria and the antifungal activity of the ligand, metal salts and the corresponding metal complexes were tested against the pathogenic fungi *Aspergillus Nidulans* by paper disk method at room temperature .

The solvent used for making test samples and standard was alcohol and DMSO and were evaluated at a concentration of 10 μg. The disk formed by what man filter paper no.1 having diameter 6 mm were soaked in the solution of compound. The zones of inhibition against all the microorganisms were measured after 48 hours of incubation in centimeters.

The composition of metal complexes was ascertained by conducting conduct metric methods; potentiometric methods; melting points were recorded on a labotech apparatus and are uncorrected .Spectra of isolate complex for NMR spectra were recorded on bruker DRX-300 ;chemical shifts are given in units relative to the internal standard tetramethylsilane and refer to chloroform-d($CDCl_3$).Infrared spectra were recorded on Varian 1000 FTIR

spectrophotometer using KBr Pallets in the range of 4000 cm^{-1} to 400 cm^{-1} .Elemental analysis of C,H,N was performed on a carlo erba mode 1108 elemental analyzer.The Mass spectra were done on a jeol SX-102 spectrophotometer using argon as the FAB gas. Elico, SL191 double beam uv-vis spectrophotometer is used for recording u.v-vis spectra.

The antimicrobial agents are used for therapy of disease depend upon for effectiveness upon their capacity to inhibit the multiplication of or to kill the invading microorganism under the condition which exist in vivo. The antiulcer drug and its complexes were screened in vivo for the sensitivity test.

RESULTS AND DISCUSSION

Antimicrobial Study of Binary and Mixed ligand complexes of Inner transition metal with OME and URA

The result of antimicrobial screening of the OME, URA and its metal complexes and synthesized complex with evaluated against *P. aerugenosa, Escherichia Coli* are given in table 1-2 and figure 4 .

The binary complexes of OME with Th metal show more activity as compared to parent drug OME, where as binary complex of Ce and Gd show almost similar effect as OME with E.Coli. Ome inhibits the 0.7 cm inhibition zone with Pseudomonas species. The complexes of Th, Ce ,Gd with OME shows moderate inhibition activity as compared to Ome for Pseudomonas species.

In case of uracil the antibacterial activity in E.Coli is much lowered as compared to free metal ions, but its binary complexes showed more inhibitory activity .for ex. Complex of Th & uracil shows 1.2 cm inhibitory zone.

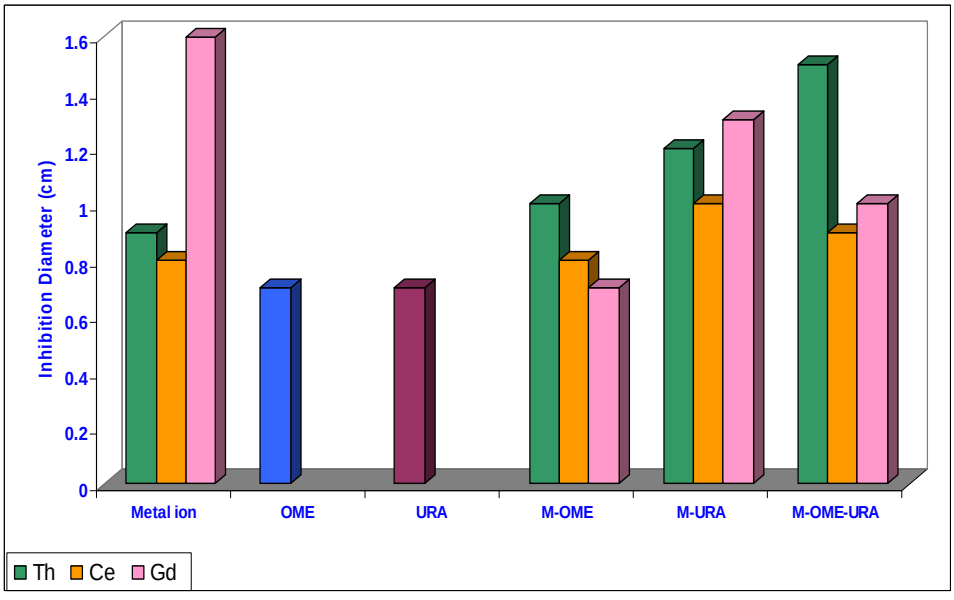

Fig 4. Comparison of Sensitivity Test ofOmeparazole, Uracil & Their Complexes against E.Coli Culture

The binary complexes of Th &Gd with uracil shows higher acivity with pseudomonas as compared to pure uracil and cytosine, but the complexes of Ce has shown the similar inhibition zone of .7 cm.

In case of ternary complexes of metals with OME & uracil, Th complex shows higher inhibition area of 1.5 cm .The moderate activity was shown by ternary complexes Ce and Gd.

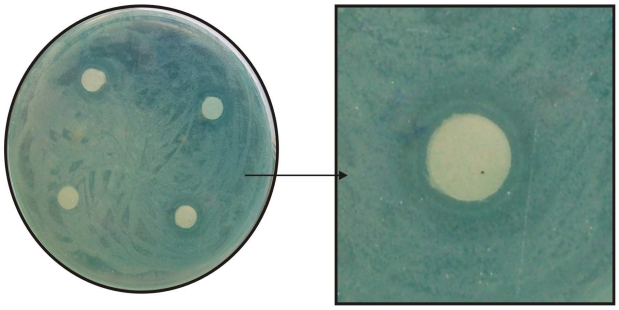

Fig. 3.1 Effect of Th on P. arugenosa

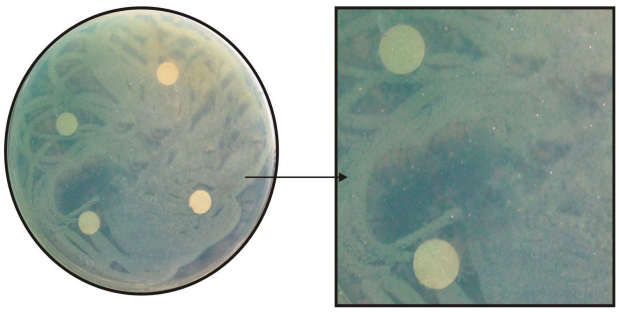

Fig 3.2 Effect of OME on P. arugenosa

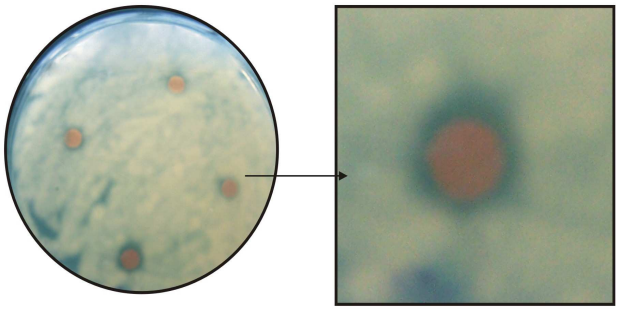

Fig. 3.3 Effect of Th-OME on P. arugenosa

Table : 1 Sensitivity Test of Omeparazole, Uracil & Their Complexes against E.Coli Culture

Sr.No.		Inhibition Diameter(cm)					
		Metal ion	OME	URA	M-OME	M-URA	M-OME-URA
1	Th	0.9	0.7	0.7	1	1.2	1.5
2	Ce	0.8	0.7	0.7	0.8	1	0.9
3	Gd	1.6	0.7	0.7	0.7	1.3	1

Table: 2 Sensitivity Test of Omeparazole, Uracil & Their Complexes against P.arugenosa Culture

Sr.No.		Inhibition Diameter(cm)					
		Metal ion	OME	URA	M-OME	M-URA	M-OME-URA
1	Th	0.9	0.7	1.2	0.6	1.1	0.6
2	Ce	0.8	0.7	1.2	0.7	0.7	0.7
3	Gd	0.6	0.7	1.2	0.6	1.2	0.7

Antimicrobial Study of Binary and Mixed ligand complexes of Transition metal with OME and ADE.

The result of antimicrobial screening of the OME, ADE and its metal complexes and synthesized complex with *Streptococcus Faecalis, Pseudomonas diminuta bacteria and Aspergillus nidulans fungus shown in table 3-5 and figure 5.*

In Streptococus Faecalis culture The binary complexes of Ome with Cd(ll) metal ion show no inhibitory activity Where as binary complex of Cr(ll) metal ion show less inhibitory activity as compared to parent drug Ome. But Mn(ll), Co(ll), Cu(ll) shows higher antibacterial activity. In Pseudomonas diminuta culture the binary complexes of ome with Mn(ll), Co(ll) metal ion show on inhibitory activity where as binary complexes of Cr(ll),Cd(ll),Cu shows higher Antibacterial activity.

In of Streptococcus faecalis culture the ternary complex of ome with cd(ll) show less inhibitory activity as compared to parent drug ome .Where as Cu(ll) show similar effect as ome with Streptococus Faecalis culture. But Mn(ll), Cr(ll), Co(ll) show higher antibacterial activity. In Pseudomonas diminuta culture the ternary complexes of ome with Co(ll) metal ion show on inhibitory activity where as in binary complexes of Mn(ll),Cr(ll),Cd(ll),Cu shows higher Antibacterial activity.

The Order of Inhibition zone are-

Co(ll)<Cd(ll)<Mn(ll)<Cu(ll)<Cr(ll).

Table: 3 Sensitivity Test of Omeparazole, Adenine & Their Complexes against Streptococus Faecalis Culture

Sr.No.		Inhibition Diameter (cm)			
		Metal ion	OME	M-OME	M-OME-ADE
1	Cu	1.5	0.8	1.6	1.4
2	Co	1.6	0.8	2.3	1.5
3	Cr	1.2	0.8	1.0	1.8
4	Mn	1.2	0.8	1.6	1.6
5	Cd	2.0	0.8	-	1.3

Table: 4 Sensitivity Test of Omeparazole, Adenine & Their Complexes against Pseudomonas diminuta Culture

Sr.No.		Inhibition Diameter (cm)			
		Metal ion	OME	M-OME	M-OME-ADE
1	Cu	1.1	0.8	1.1	1.8
2	Co	1.6	0.8	-	-
3	Cr	1.2	0.8	1.6	1.9
4	Mn	1.2	0.8	-	1.2
5	Cd	2.0	0.8	1.7	1.5

In Aspergillus nidulans culture the binary complex of ome with Co (ll) show similar effect as parent drug ome with Aspergillus nidulans culture. Where as Mn (ll), Cr (ll), Co(ll), Cu shows higher Antifungal activity.

Higher anti microbial activity of certain metal complexes than the original drug is due to the fact that complexation with metals imparts some important characteristics to the drug which are helpful in its biological activity e.g such as low dissociation constant(strong metal ligand bond), special redox potential, electron distribution and lipid solubility. It also helps in the natural process of bond formation and bond cleavage and the group transfer reaction.

Table: 5 Sensitivity test of Omeparazole, Adenine & Their Complexes against Aspergillus nidulans Culture

Sr.No.		Inhibition Diameter (cm)			
		Metal ion	OME	M-OME	M-OME-ADE
1	Cu	1.6	0.5	1.9	2.0
2	Co	2.0	0.5	1.8	2.1
3	Cr	1.8	0.5	2.0	1.9
4	Mn	1.4	0.5	1.9	2.3
5	Cd	1.0	0.5	2.0	2.2

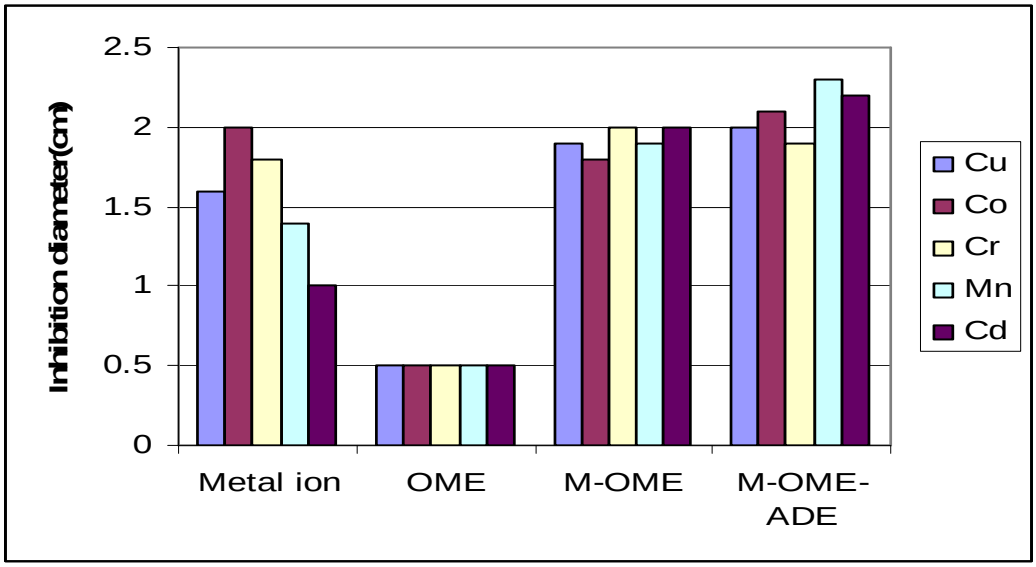

Fig 5. Comparison of Sensitivity Test of Omeparazole, Uracil & Their Complexes against E.Coli Culture

As a result, the metal complexes has increased duration of action and possess enhanced blood concentration, which may probably be due to a comparatively faster diffusion of the metal chelate and through the organism due to its more liposoluble (more covalent metal to ligand bond) on being coordinated with the metal ion forming stable chelates.The higher biocidal activity of the metal chelate may also due to the combined bioactive effect of the metal and the ligand and the higher concentration of the ligand in the chelate.

The antigrowth (inhibition) of the bacteria may be due to the exchange of trace metal of the metalo-enzyme with the metal ions of the chelate under test and/or due to steric control of the encumbered and bulky chelate molecule. The result of the present study clearly indicate formation of chelates with involvement of N and O atom in metal to ligand bond resulting in a sufficient high covalent nature of chelate molecules and hence lipid solubility. The activity of adrug depends on its bioavailability, which in turn depends, apart from other factors, upon its particle size. It has been shown that the reduction in particle size increases the activity, it increases the solubility of the drug and hence its bioavailability. It is evident to note that the complexes having particle size leads to note that the complexes having micro particle size leads to higher solubility and activity.

CONCLUSION

The results of biological screening indicate that complexes are more active than free ligand. Increased activity of the complex can be explained on the basis of chelation theory .If the orbital of each metal ion overlaps the ligand orbital increases which enhances the

lipophilicity of complexes due to delocalization of π electron in the chelate ring. This may be due to higher stability of the metal complex than the drug.

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REFERENCES

[1] J. Nis., M. Kam., H. Mat. And K. Mik., *Tetrahedron*, **2002**,58, 8345.
[2] A. Louie Etal, *Nat. Biotechno.* , **2000**, 18,321.
[3] R. Reisfeld etal. , laser and excited states of rare earths, springer **1977**.
[4] F. cotton etal. Advance inorganic chemistry, cp.11, j.willey,6 edition,1999.
[5] C. Picard etal., *Bioorganic & Medicinal Chemistry Letters*, ,**2006**, 16, 5309-5312.
[6] S. Aime, etal, *Coordination Chemistry Reviews*, **2006**, 250, 1562-1579.
[7] S. J. Franklin, *Current Opinion in Chemical Biology*, **2001**,5, 201-208.
[8] Carlsson,E. Lindberg, P, Vanunge, S.*chem. Brit.*, **2002**, 38, 42.
[9] Xiong etal. , *Russian J. Of Coordination Chem.*, **2007**, 33, 306-311.
[10] Garrett, Reginald H.; Grisham, Diaries M. Principals of biochemistry with a human focus. United States: Brooks/Cole Thomson Learning, **1997**.
[11] Shapiro, Robent "The Prebiotic Role of Adenine: A Critical analysis, June, **1995**.
[12] H. Sigel, "Metal ion in Biological System",ed;Marcel Dekkar,New York, 1982-1984, 10-14.
[13] G.L. Eichhorn,"Co-ordination Compound in Natural Products",in J.C. Bailar, Reinhold, New York.
[14] P.B.Chakrawarti. and A.Shinde ,*J. India Chem.Soc*, **1993**,70,240;
[15] G. L. Eichhorn, "Metal Ions in Biological System",eds;H.Sigel and A. Sigel, Marcel Dekkar, New York. , **1989**, 25.
[16] A.T. Florence and D.Atwood, "Physico Chemical Principal of Pharmacy", Mac.Millan, London, **1986**.
[17] H. Sigel, In Metal Ions in Biological Systems, Vol. 3, marcel dekker, new york, **1974**.
[18] Y. Marcus,I. Elierzer, *Coord. Chem. Rev* **1969**, 4,273.
[19] Good man and gilman "the pharmacological basis of therapeutics "M.c. Millan N.Y., 1985,79(5),466.
[20] L. Halleman, C.C Stock, *J. Bio. Chem*., **1938**. 125, 77
[21] B.L. Valle, J.E. Coleman, *Compr. Biochem*., **1968**,8, 1458.
[22] Chakrawarti P .B. , *J. Indian Chem. Soc* **2001** ,78, 273
[23] Martell A.E. and Calvin M, "Chemistry Of The Metal Chelate Compound", Printice hall, **1959**.
[24] Jacques A, "Complex ion in Aqueous solution." Longmans, Green and Co. Ltd., London, **1960**.
[25] Lewis J. and Nilkins R.G. , " Modern coordination chemistry Inter science publishers "Inc. N.Y.**1960**
[26] Bailar J.C., The Chemistry of the Co-ordination Compounds, Reinhold Publishing Corporation N.Y. **1956**.