A Study of Hydroxamic Acids and their Complexes and their Biological Activity and Therapeutic Values Especially as Anticancer Medicine.

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Abstract

Hydroxamic acids are versatile ligands that can coordinate to metal ions, forming stable complexes. They have been extensively studied for their potential as **Anticancer** agents, particularly as histone deacetylase (HDAC) inhibitors and many more as **Antibacterial, Antiviral and Antifungal.**

Current paper is on various aspects of synthesis, structure and property of Ni and Pt metals complexes vs biological property. Hydroxamic acid has better attachment with Platinum metals group than others ligands on cancer therapy. We have used and demonstrated mechanism on biological activity and IR based stability of the complexes and mechanism of hydroxamic acid complexes on HDAC enzyme, binding to DNA and induce crosslinking of the complex by various justification. Further more research is indeed needed to overcome the shortcomings on hydroxamic acid Pt. metal complexes vs biological activity.

Hydroxamic acid derivatives and their complexes shows various therapeutic values against all of them which has well tolerable **Efficacy.** Efficacy of o/m/p-NBHA and other hydroxamic acids and their complexes have following characteristics which has high affinity for metal ions, strong chelating ability, selective inhibition of enzymes, antimicrobial activity against various pathogens, environmental compatibility and subsequently **Safety in human**.

Ongoing research on NBHA for more biological activities are needed to fully understand their potentiality. In this paper we have emphasised and enhances the hydroxamic acid with Pt. group transition metal complexes as biological activity and therapeutic values on antibacterial, antifungal, antiviral and anticancer. We have gone through the previous references.

Key words: Hydroxamic Acids, Hydroxamic Acids Complexes with Transition Metals like NBHA, HDAC etc.

Introduction

Hydroxamic acids and complexes exhibit a number of biological activities.

1. **Antibacterial:** Inhibits bacterial growth specially against gram positive bacteria.
   Interfering with cell wall synthesis. It inhibits enzymes which involved in peptidoglycan synthesis (essential for bacterial cell wall formation). Ref: Theodor Curtius (1857-1928). A German Chemist, Ernst-Boris Chain (1906-1979). A German British Biochemist, James Gowains (1924-2020) and Edward Abraham (1913-1999). A British Biochemist.
2. **Antifungal:** Show activity against various fungal species including Candida and Aspergillus. As antifungal agents, hydroxamic acids exhibit activity against a range of fungal species. Mechanism of hydroxamic acids acts as antifungals.
   a) Inhibition of fungal enzymes.
   b) Description of fungal cell membrane.
   c) Interference with fungal iron mechanism.
   d) Induction of fungal oxidative stress.

As antifungal discovery done by Albert Neuberger (1908-1996). A German British Biochemist in 1940. Hans Peter Rast (1923-2007). A Swiss chemist in 1950 and 1960. Rajinder Singh Bedi (1955-present). An Indian chemist.

3. **Antiviral:** Exhibit activity against certain viruses, such as HIV and influenza even in the case of Hepatitis B and Covid-19. Researchers who have studied hydroxamic acids as antiviral properties. Dr. Philip Furman, Dr. Raymond Schinaz and Dr. Kazno Nagai.

   Ongoing research on NBHA as an antiviral, antifungal, antibacterial and anticancer agents and their studies are needed to fully understand its potentiality against viruses in the context of O-NBHA'S mechanism. O - nitrobenzohydroxamic acid (O-NBHA) exhibited potent antiviral activity against SARS – COV - 2. Suberoyl amide hydroxamic acid (SAHA) showed antiviral activity against SARS – COV - 2 and inhibited viral replication. SAHA - Exhibited antiviral activity against HBV and reduce viral DNA levels.

4. **Anticancer:**

Hydroxamic acids and their complexes as anticancer therapy

Platinum-based coordination compounds with hydroxamic acid ligands can interact with tumours cells. Researchers are focusing on these compounds. Efficacy of o/m/p-NBHA and other hydroxamic acids and their complexes have following characteristics: high affinity for metal ions, strong chelating ability, selective inhibition of enzymes, antimicrobial activity against various pathogens, environmental compatibility etc.

There is no FDA approved hydroxamic acids drugs for treating corona virus infected individual. However, some hydroxamic acid derivatives have shown potential antiviral activity against corona viruses in Preclinical studies such as SAHA (Vorinostat) exhibited antiviral activity against SARS – COV – 2. Panobinostat showed antiviral activity against SARS – COV – 2 and Belinostat exhibited antiviral activity against SARS – COV – 2. o/m/p- NBHA may also show antiviral activity against SARS – COV – 2. o/m/p - NBHA complexes are based on preclinical studies and more research is needed to confirm efficacy and safety and to get approval from FDA.

Potential of Pt (II) and Nickel (II) Complexes with Hydroxamic Acid Ligands in Cancer Therapy

Platinum (II) complexes have a well-established history in cancer chemotherapy with Cisplatin being a prime example. These complexes often exhibit significant cytotoxicity towards cancer cells due to their ability to bind to DNA and disrupt its replication process.

Hydroxamic acids are versatile ligands that can coordinate to metal ions, forming stable complexes. They have been extensively studied for their potential as anticancer agents, particularly as histone deacetylase (HDAC) inhibitors, and their ability to bind to DNA and disrupt its replication process.

Synergistic Effects :

1. The combination of hydroxamic acid ligands with Platinum (II) and Nickel (II) complexes introduces dual function agents that target both HDAC enzymes and DNA.
2. Platinum (II) complexes and Nickel (II) bind to DNA and induce crosslinking, thereby disrupting replication and transcription in cancer cells.
3. Hydroxamic acids enhance the therapeutic potential by inhibiting HDACs, leading to hyperacetylation of histones and reactivation of tumor - suppressor genes.
4. This dual mechanism amplifies DNA damage responses, making cancer cells more susceptible to apoptosis.
5. Hydroxamic acid Platinum (II) and Nickel (II) complexes demonstrate improved selectivity for cancer cells, minimizing off-target effects in healthy tissues.

6. The incorporation of hydroxamic acids into Platinum (II) and Nickel (II) frameworks optimizes their pharmacokinetic properties, enhancing cellular uptake and bioavailability.
7. Synergy between these components results in reduced drug resistance, a common challenge in cancer chemotherapy.
8. Preclinical studies highlight the potential of these complexes to overcome limitations of stand alone HDAC inhibitors or platinum-based drugs.
9. The molecular design of these conjugates enables customization for targeting specific cancer types or HDAC isoforms.
10. Clinical investigations are underway to validate the efficacy and safety of hydroxamic acid Platinum (II) and Nickel (II) hybrids in treating advanced malignancies.

We have gone through the study of Vorinostat which is hydroxamic acid derivative. It is being used for the treatment of tumor used as oral drug by the oncologist on prescription basis in USA.
Vorinostat was the first histone deacetylase inhibitor approved by the U.S. Food and Drug Administration (FDA) for the treatment of cutaneous T- cell lymphoma (CTCL) on October 6, 2006. We have synthesized Platinum and Nickel metal complexes with hydroxamic acid as ligands.

Hydroxamic acid complexes: We have synthesized and studied the characteristics properties of Sodium $Na[Ni(C_7H_5O_4N_3)_2(NO)Cl]$ and bis – (m – nitrobenzohydroxamato) Platinum (II) monohydrate having the monochlorobis (O – nitrobenzohydroxamato) Nitrosyl Nickelate (II) having the formula $Pt(C_6H_4CON_2HO_3)_2.H_2O$.

Therapeutic values:

Hydroxamic acid derivatives as anticancer therapy-

- SAHA (Vorinostat) by Ronald Breslow and its team in 1990 and approved in VSA_FDA in 2006: Prescription medicine approved for cutaneous T-cell lymphoma.
- Panobinostat invented by Novartis Pharmaceuticals in 2001 and approved in VSA_FDA in 2015: Approved for multiple myeloma.
- Belinostat invented by Prof. Stephen M. Turner in 2000 got approval from UK FDA in 2014: Approved for peripheral T-cell lymphoma pixantrone – Investigated for breast cancer and lymphoma.
- Tucidinostat invented by Prof. Xiang-Ju Wang in 2005. Still clinical trial is going on from 2015: Investigated for solid tumors and hematological malignancies.

To see the better biological properties, we have studied and synthesized few more hydroxamic acids with Pt. group transition metal complexes which are as follows:

Experimental:-

Synthesis and Structure of Hydroxamic acids and their Platinum group transition metals complexes.

Hydroxamic acids were first discovered by the German chemist named Theodor Curtius in 1880. He synthesized benzohydroxamic acid while studying the reaction of hydroxylamine with acid chloride. The general formula for an acid chloride is R-CO-Cl where R is an organic group. Apart from the synthesis, first naturally occurring hydroxamic acid, fusariniac was isolated from the fungus fusarium in 1963 by Japanese chemist Y. Shimojo. Example of acid chlorides are as follows.

CH_3COCl, acetyl chloride

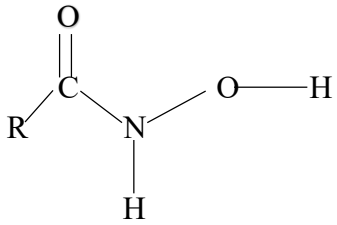
C_6H_5COCl, benzoyl chloride

Acid chlorides to react with hydroxyl amine leading to the formation of hydroxamic acids.

NH_2OH – Hydroxylamine is a derivative of ammonia with one of the hydrogen atom replaced by a hydroxyl group.

The reaction is as follows-

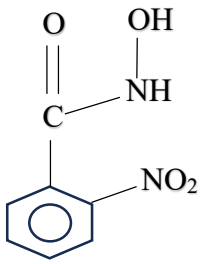
$$R\text{-}CO\text{-}Cl + NH_2OH \longrightarrow R\text{-}CO\text{-}NHOH + HCl$$



Therefore, R-CO-NHOH (Hydroxamic acid) is a functional group where R may be alkyl and aryl group. This reaction involves the nucleophilic attack of hydroxylamine on the electrophilic carbonyl carbon of the acid chloride leading to the formation of hydroxamic acid and hydrogen chloride.

Preparation of O – nitro benzohydroxamic acid:

Anhydrous hydroxylamine hydrochloride (8gm) was dissolved in anhydrous methanol (40gm) by refluxing on a steam bath. Potassium hydroxide (9gm) was also dissolved in methanol (25gm). The two solutions were cooled in ice and mixed well in stoppered flask whereby KCl was precipitated which was filtered off. Ethyl O – nitro benzoate (8gm) was then added to the mixture and the brownish liquid was kept overnight at room temperature. It was then concentrated by evaporation, cooled in freezing mixture followed by the addition of dilute HCl until distinctly acid where by ortho – nitro – benzohydroxamic acid was precipitated. It was filtered, washed with cold water and recrystallized from 0.5N hot acetic acid. The final product was a white crystalline solid having a faint brownish tint.



Structure of Ortho – nitro benzohydroxamic acid
Molecular Formula – $C_7H_6N_2O_4$

HYDROXAMIC ACID COMPLEX:

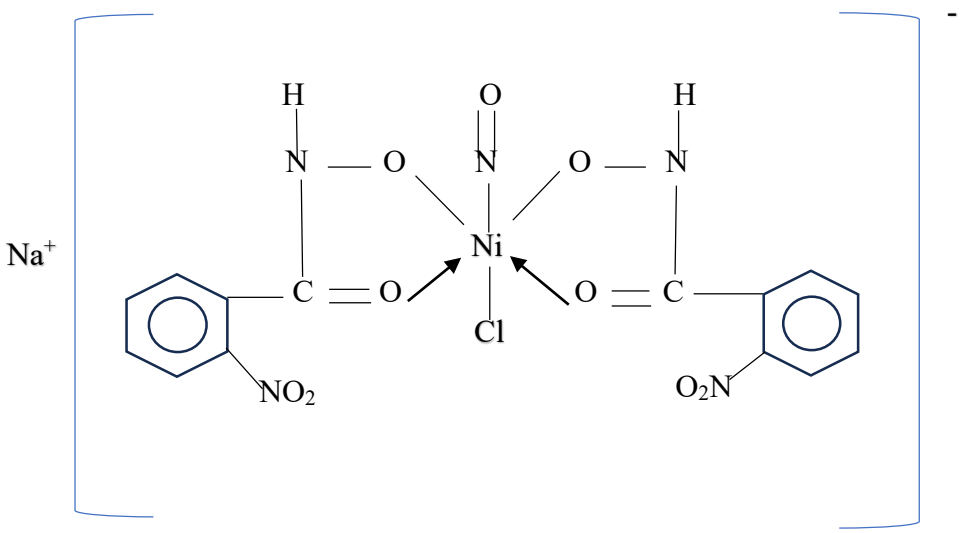
1. Synthesis of Na – monochlorobis (O - nitrobenzohydroxamato) Nitrosyl Nickelate (II):

Reagents used – Sodium Hexachloronickelate (IV); O – nitrobenzohydroxamic acid (Prepared in the laboratory), alcohol, benzene etc. All chemicals used were of extra pure quality.

Procedure:

As aqueous solution of sodium nitrohexachloronickelate (IV) was prepared by dissolving 2 gms. of sodium hexachloronickelate in 100ml. of distilled water. Another aqueous solution of O – nitrobenzohydroxamic acid was prepared by dissolving 6 gms. of O – nitrobenzohydroxamic acid in 100ml. of distilled water. The two aqueous

solutions were mixed and the mixture was heated slowly for one hour and strongly for further three hours when brown black precipitate appeared which after cooling was filtered, washed with water, alcohol and benzene. It was dried in air. The product was Sodium monochlorobis (O – nitrobenzohydroxamato) Nitrosyl Nickelate (II) having the formula $Na[Ni(C_7H_5O_4N_3)_2(NO)Cl]$.



Na – monochlorobis (O - nitrobenzohydroxamato) Nitrosyl Nickelate (II)

Structure may be possible on meta and para position

Coordination Complex Structure Prediction on the basis of Crystal Field Theory:

Atomic number of Ni – 28
Atomic mass – 58.7
Electronic Configuration – $[Ar]4s^2 3d^8$
Ligands behave as strong field ligands
Coordination Number – 6
Hybridisation – sp^3d^2
Outer Orbital Complex
Structure – Octahedral
Order of energy of orbitals = $dx^2–y^2 = dz^2 > dxy = dxz = dyz$

- The $dx^2–y^2 = dz^2$ orbital contains one – one electrons and the orbitals are high in energy.
- The dxy, dxz, dyz orbitals accommodate all 6 electrons in paired states.
- The complex is paramagnetic in nature.

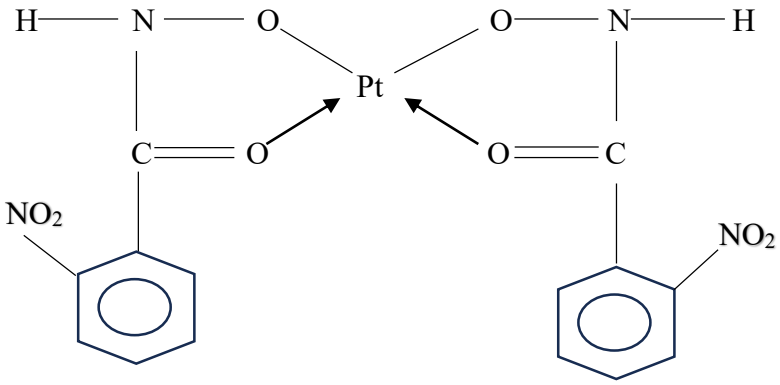
2. Synthesis of bis – (O – nitro – benzohydroxamato) Platinum (II):

Reagents used: Platinum (II) chloride, P^H Paper, Sodium acetate, O – nitro – benzohydroxamic acid (Prepared in the laboratory), Ethanol, Benzene.

Procedure:

An aqueous solution of Platinum (II) chloride was prepared by dissolving 2gm. of Platinum (II) chloride in 60 ml. of distilled water. The aqueous solution of $PtCl_2$ was buffered to 5 – 6 P^H by concentrated aqueous sodium acetate solution. Aqueous solution of O – nitrobenzohydroxamic acid was prepared by dissolving 6gm. of O – nitrobenzohydroxamic acid in 60 ml. of water. The two solution were mixed, thoroughly stirred, the pale – yellow wish green precipitate formed was filtered, washed with water, ethanol and benzene repeatedly. It has then dried in

air. The product was bis – (m – nitrobenzohydroxamato) Platinum (II) monohydrate having the formula $Pt(C_6H_4CON_2HO_3)_2.H_2O$.



bis – (O – nitro – benzohydroxamato) Platinum (II)

Structure may be possible on meta and para position

Coordination Complex Structure Prediction on the basis of Crystal Field Theory:

Atomic Number of Pt – 78

Atomic Mass – 195.08

Electronic Configuration – $[Xe]4f^{14}5d^{9}6s^{1}$

Coordination Number – 4

Hybridisation – dsp^2

Structure – Square Planar

Inner orbital complex

Extended Case of Jahn teller Distortion (Z_{out}).

ligands behave as Strong Field Ligands

Order of energy of orbitals = $dx^2–y^2 > dz^2 > dxy > dxz \approx dyz$

- The $dx^2–y^2$ orbital remains unoccupied because of its high energy.
- The dz^2, dxy, dxz, dyz orbitals accommodate all 8 electrons in paired states, resulting in a diamagnetic complex.

IR Spectroscopic technique used for the study of Platinum group transition metal complexes with hydroxamic acids:

Observed Infra - red frequency (cm^{-1}) and band assignment of hydroxamic acid complexes of transition metal:

(Solid in Nujol)

	A	B	Predominant modes band assignments
	X	X	
	1585	1670 1659 1640	- ט (CO) (nu)
			- NO_2
	1570 1530	1590 1560 1540	- δ (CNH)
	1520	1520	- δ (NH)
	1470		- ט (CN)
	1150		
	1025	1020	- ט (NO)
	925	885	

where ,

A = Bis - (O – nitro benzohydroxamato) Platinum(II) Monohydrate $Pt(C_6H_4CON_2HO_3)_2.H_2O$

B = Sodium Monochloro bis – (O-nitro-benzohydroxamato) Nitrosyl Nickelate(II) $Na[Ni(C_7H_5O_4N_3)_2.(NO)Cl]$

Infra – red spectroscopic studies were necessitated to investigate the structures of hydroxamic acid complexes of Pt. and Ni metals in the present investigation.

Hydroxamic acids are characterized in solid states by 3 bands between 3300 – 2800 cm^{-1} (ט *OH, טNH and טCH), a band near 1640 cm^{-1} (ט C = 0), a band near 1550 cm^{-1} (π = CNH), a variable intensity band at 1440 – 1360 cm^{-1} and a strong band near 900 cm^{-1}. Accordingly we shall be concerned in examining these bands in our hydroxamic acid complexes of Ni and Pt metals.

***The symbol used are ט- stretching; σ- deformation and π- out of plane bending.**

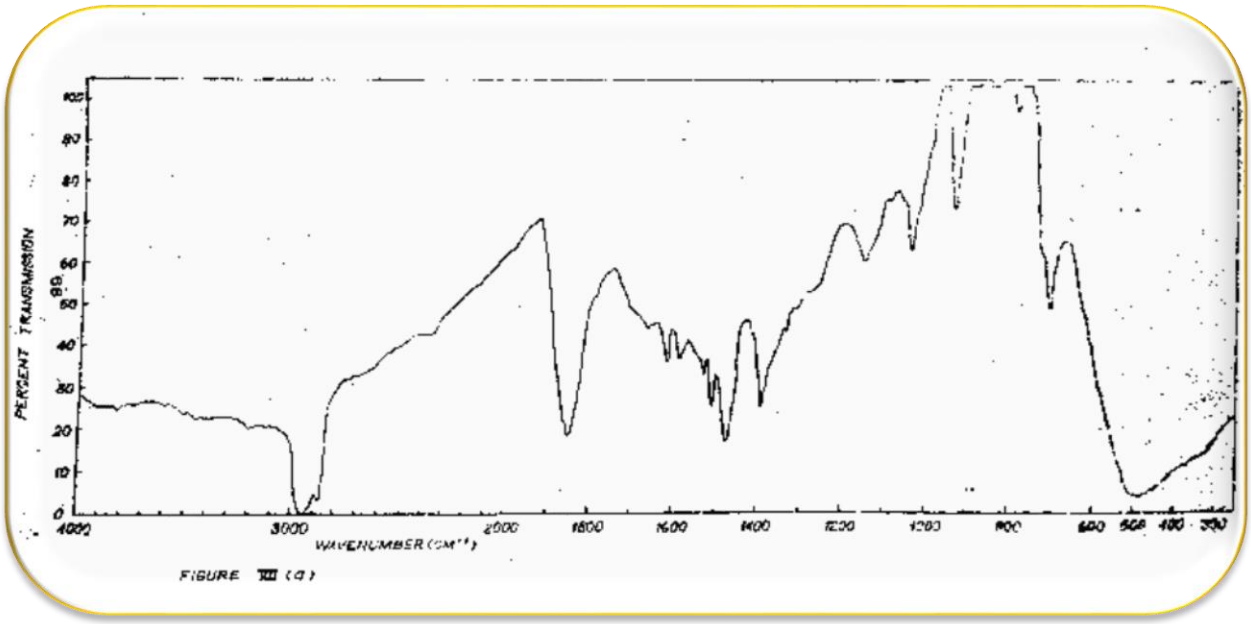


FIGURE III (a)

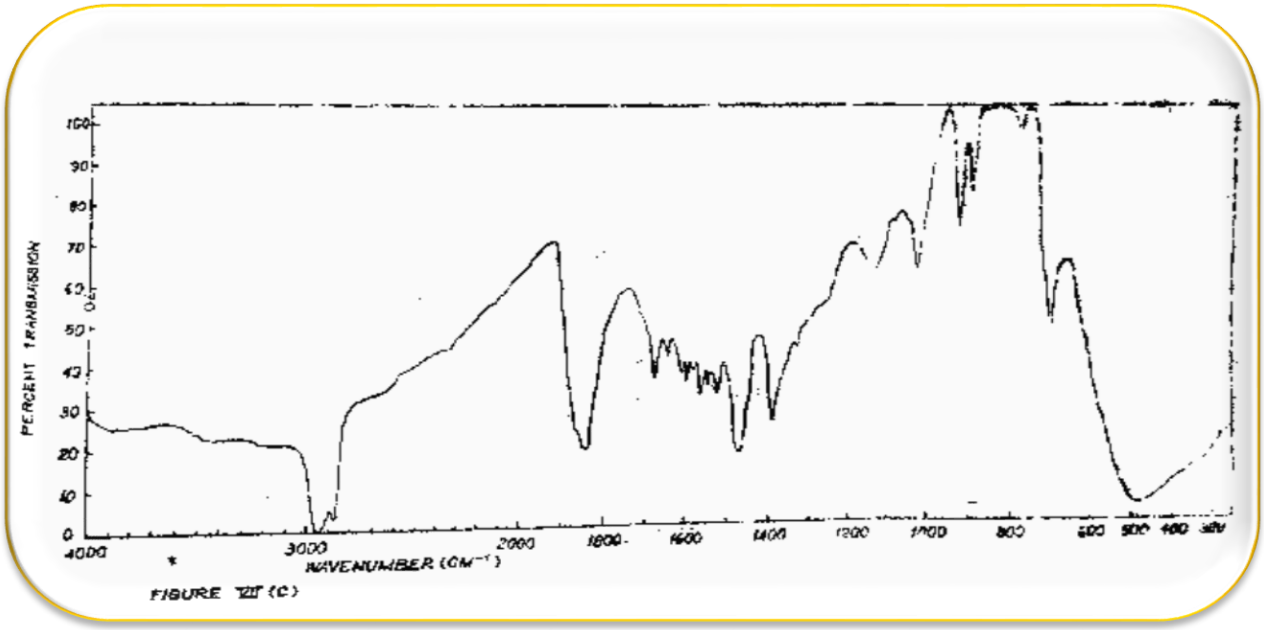


FIGURE VII (C)

Results and Discussions:-

Justification of the compound on the basis of the Crystal field theory, hybridization and IR data shows the stability of the compound**.**

Hydroxamic acid complexes with Pt. group transition metals are preferred to inhibit cancer cells for following factors:-

Stability: Hydroxamic acids form stable complexes with transition metals, which ensures that the complex remains intact in the biological process.

Selectivity: Transition metals like Rhodium, Platinum, Osmium, etc. have a high affinity for hydroxamic acids, allowing for selective targeting of cancer cells.

Redox Properties: Transition metals can undergo redox reactions, generating reactive oxygen species that damage cancer cells.

Enzyme inhibition: Hydroxamic acid metal complexes can inhibit enzymes crucial for cancer cell survival, such as histone deacetylases (HDACs).

DNA binding: some hydroxamic acid metal complexes can bind to DNA, disrupting cancer cells.

Lower toxicity: Hydroxamic acid metal complexes often exhibit lower toxicity towards normal cells compared to traditional chemotherapy medicine.

Hydroxamic acid has better attachment with Platinum group transition metals than others ligands on cancer therapy:-

In the context of cancer therapy, hydroxamic acids exhibit several advantages that make them promising ligands for **Platinum metals group.**

1. Enhanced Cellular Uptake: Hydroxamic acids can facilitate the uptake of **Platinum metals group** based drugs into cancer cells. This is crucial because many Platinum drugs have limited cellular permeability, hindering their effectiveness.
2. Improved Drug Stability: The coordination of hydroxamic acids to Platinum can enhance the stability of the resulting complexes. This can prevent premature drug degradation, leading to better therapeutic outcomes.
3. Targeted Drug Delivery: Hydroxamic acids can be conjugated to carrier molecules or targeting ligands, enabling the selective delivery of **Platinum metals group** drugs to cancer cells. This targeted approach can minimize side effects and improve therapeutic efficacy.

4. Overcoming Drug Resistance: **Platinum metals group** drugs often encounter resistance mechanisms in cancer cells. Hydroxamic acids can help to overcome these resistance mechanisms, making them more effective in treating resistant tumors.
5. Synergistic Effects: Hydroxamic acids can exhibit synergistic effects with **Platinum metals group**, enhancing their anti-cancer activity. This can be achieved through various mechanisms, such as inhibiting DNA repair pathways or modulating cellular signaling.

Mechanism of Action of hydroxamic acid with Pt. group metal complexes on cancer cells mainly focus on HDAC enzyme, binding to DNA and induce crosslinking:

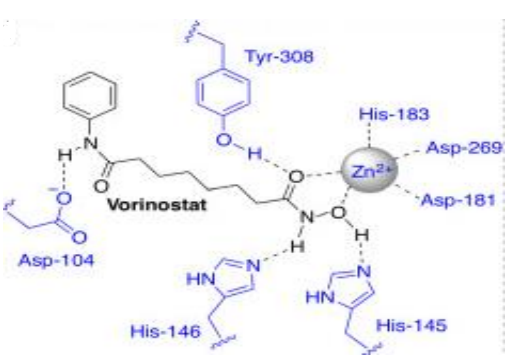
HDACs (Histone Deacetylases):

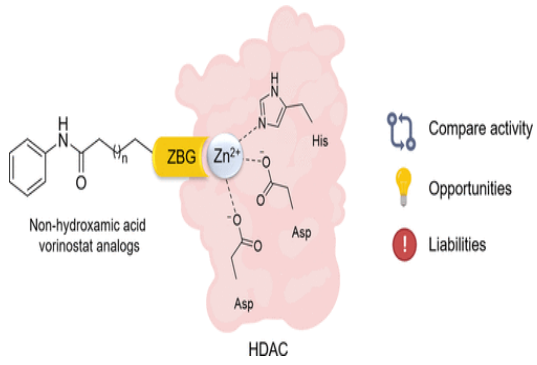
- Enzymes that remove acetyl groups from histone proteins.
- This process, known as deacetylation, leads to chromatin condensation, making genes less accessible for transcription.
- Dysregulation of HDACs is linked to various diseases, including cancer.
- Molecules that block the activity of HDACs.
- By inhibiting HDACs, they prevent deacetylation, leading to increased gene expression.

Hydroxamic acid complexes inhibit HDAC enzymes by directly targeting their active site, which contains a zinc ion essential for enzymatic activity. Here is a simplified explanation of the process:

1. HDACs require the zinc ion in their active site to catalyze the removal of acetyl groups from histone proteins.
2. Hydroxamic acid molecules have a functional group (-CONHOH) that binds strongly to this zinc ion.
3. By attaching to the zinc, hydroxamic acid blocks the enzyme's ability to function, effectively "turning it off."
4. This inhibition causes histone proteins to retain their acetyl groups, resulting in a more open and relaxed chromatin structure.
5. The relaxed chromatin allows genes that were previously repressed to become active again, leading to the production of proteins that can slow cancer growth or trigger cell death.
6. This mechanism not only targets cancer cells but can also influence other cellular processes, such as inflammation and immune response.

By stopping HDACs from removing acetyl groups, hydroxamic acid complexes play a crucial role in restoring normal cellular function and have significant therapeutic potential in various diseases.





Where,
His - Histidine, Asp – Aspartic acid, Tyr - Tyrosine
Histone acetylation by HA and HA with Pt. group transition metal complexes relax chromatin allowing for gene transcription. HDACs remove acetyl groups which results in condensed chromatin and suppression of gene transcription. In tumour cells, suppression of gene transcription of tumour suppressor and DNA repair genes can

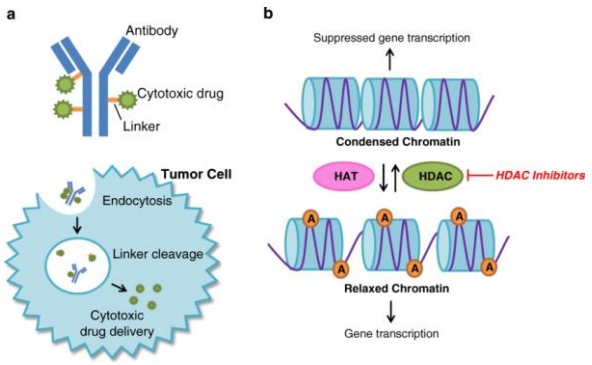
allow for tumour growth. HDAC inhibitors prevent the removal of acetyl groups by HDACs leaving chromatin in its relaxed state allowing for gene transcription.

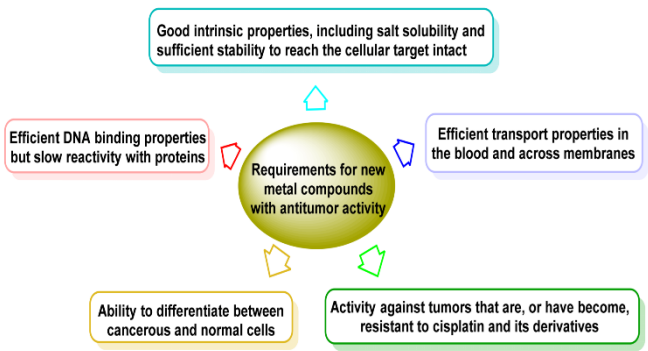
Mechanism of Binding to DNA and induce crosslinking with hydroxamic acid Pt. group metal complexes:

DNA crosslinking occurs when two strands of DNA are chemically linked, which can disrupt their normal function. This process can be induced (caused) by certain chemicals, such as hydroxamic complexes. Let's break this down in simple terms:

1. DNA Structure: DNA is made up of two strands twisted together in a double helix. These strands need to separate temporarily for the cell to copy DNA or make proteins.
2. Crosslinking: Crosslinking happens when a chemical creates a bond between the two strands of DNA, preventing them from separating. This can stop important cellular processes like replication or repair, which can kill harmful cells, such as cancer cells.
3. Hydroxamic Complexes: These are chemical compounds that contain a hydroxamic acid group. They can interact with DNA, sometimes forming strong bonds with it or other molecules around it.
4. Crosslinking Works: Hydroxamic complexes can chemically react with DNA, attaching to it in specific ways. If they bind to both strands of DNA at the same time, they create a "crosslink," which locks the strands together.
5. Scope: Induced crosslinking with hydroxamic complexes is studied in medicine and biochemistry because it can:
    - Help in cancer treatments by damaging the DNA of cancer cells.
    - Be used to study DNA structure and function in labs.

Consequently, Hydroxamic acid Pt. metal complexes are chemicals that can attach to DNA and make the two strands stick together. This process is useful for understanding DNA behaviour and developing treatments for diseases like cancer.





Chemotherapeutic Effects: Hydroxamic acids Pt. group transition metal complex based drugs provides a number of health benefits :- ***Resistance development in human -***

Increasing interferon production- Hydroxamic acids can stimulate the production of interferon, which are essential for antiviral defense.

Activating immune cells – Hydroxamic acids can activate immune cells, such as macrophages and dendritic cells to reorganise and eliminate infected cells.
Combination therapy- may enhance efficacy against coronavirus. Some potential combination as- Remdesivir, Chloroquine/Hydroxychloroquine. Combination therapies to achieve optimal antiviral activity.
Metal chelation Therapy- Hydroxamic acid complexes can be used to treat metal poisoning such as iron.
Cancer treatment – HDAC inhibitors like vorinostat and cis-platin overload are used to treat cutaneous T-cell lymphoma at (SAHA).
Neurodegenerative disease - HA complexes are used to treat Alzheimer's, Parkinson disease and so many diseases.

Mathematical Expression of Hydroxamic acid and Hydroxamic acid complex action on tumor cells.

These equations helps to explain the interactions and dynamics of the system.
Binding of hydroxamic acid and hydroxamic acid complex to tumor cells:
It means how much it is capable to bind (interact).
We know according to rate law expression:

$$B + C \underset{K_2}{\overset{K_1}{\rightleftharpoons}} BC \text{ (fast reaction with equilibrium)}$$

$K_{eq.}$ = Equilibrium constant

K_1/K_2 = Rate constant

K_1 = Association rate constant

K_2 = Dissociation rate constant

K = Rate constant (speed), describe the how much speed the rate of reaction occurs.

[B] = Hydroxamic acid complex/Hydroxamic acid

[C] = tumor cell

[BC] = Bound complex

1. Inhibition of tumor cell growth can be represented by the rate law expression.

$$B + C \underset{K_4}{\overset{K_3}{\rightleftharpoons}} BC,\ K_{eq} = K_3/K_4$$

$$-d[B]/dt = -d[C]/dt = -d[BC]/dt = K_3[B][C]$$

$$d[C]/dt = -K_3[B][C]$$

$d[C]/dt$ — Tumor cell growth change over time

K_3 — (Inhibition rate constant of tumor cell)

2. Degradation of Hydroxamic acid complex/Hydroxamic acid over time.

$$B + C \underset{K_4}{\overset{K_3}{\rightleftharpoons}} BC$$

$$-d[B]/dt = K_4[BC]$$
$$d[B]/dt = -K_4[BC]$$

↓

Degradation of hydroxamic acid/hydroxamic acid complex over time

3. Tumor cell death: It means decaying of tumor cell over time.

$$B + C \underset{K_5}{\overset{K_4}{\rightleftharpoons}} BC,\ K_{eq.} = K_4/K_5$$

$$-d[C]/dt = K_5[BC]$$
$$d[C]/dt = -K_5[BC]$$

↓

death rate constant of tumor cell

Pt Metal - Transition metal with hydroxamic acid complexes have shown potential in cancer treatment due to their ability to inhibit histone deacetylases (HDACs) and DNA binding and induce cross linking leading to apoptosis (cell death).

General Mathematical Expression:

Let's consider a transition metal hydroxamic acid complex, [M(L)] (M = metal, L = hydroxamic acid ligand):

$[M] + [L] \rightleftharpoons [M(L)]$

Kinetic Parameters:

1. Association rate constant (k_1): $[M] + [L] \rightarrow [M(L)]$

2. Dissociation rate constant (k_{-1}): $[M(L)] \rightarrow [M] + [L]$

Mathematical Expression:

$d[M(L)]/dt = k_1*[M]*[L] - k_{-1}*[M(L)]$

On Applying Steady - State Approximation:

At Equilibrium, $d[M(L)]/dt = 0$

$K_d = k_{-1}/k_1 = [M] * [L] / [M(L)]$

where k_d is the Dissociation constant.

HDAC Inhibition:

The complex [M(L)] inhibits HDAC activity:

$HDAC + [M(L)] \rightleftharpoons HDAC\text{-}[M(L)]$

Mathematical Expression:

$r = R\ max * [HDAC\text{-}[M(L)]) / (K_m + [HDAC\text{-}[M(L)]))$

where:

- r: HDAC activity

- R max: maximum velocity

- K_m: Michaelis Menten constant

- [HDAC-[M(L)]]: concentration of HDAC-[M(L)] complex

Apoptosis Induction:

The inhibited HDAC activity leads to apoptosis:

$d[Cell]/dt = -k_{apop} * [Cell] * [HDAC\text{-}[M(L)]]$

where:

- [Cell]: cancer cell concentration

- k_{apop}: apoptosis rate constant

Long-Lasting Medicine:

The transition metal hydroxamic acid complex's stability and slow dissociation rate (k_{-1}) contribute to its long-lasting effect:

$t_{1/2} = 0.693/k_{-1}$

where $t_{1/2}$ is the half-life of the complex.

Example Complexes:

1. Ni (II)-hydroxamic acid complex: [Ni(HA)] (HA = hydroxamic acid)

2. Pt (II)-hydroxamic acid complex: [Pt(HA)]

Conclusion:

In this paper we have emphasised and enhances the hydroxamic acid with Pt. group transition metal complexes as biological activity and therapeutic values on antibacterial, antifungal, antiviral and anticancer. We have gone through the previous references. Current paper is on various aspects of synthesis, structure and property of Ni and Pt metals complexes vs biological property. Hydroxamic acid has better attachment with platinum metals group than others ligands on cancer therapy. We have used and demonstrated mechanism on biological activity and IR based stability of the complexes and mechanism of hydroxamic acid complexes on HDAC enzyme, binding to DNA and induce crosslinking of the complex by various justification. Further more research is indeed needed to overcome the shortcomings on hydroxamic acid Pt. metal complexes vs biological activity.

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