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ORIGINAL

High-Throughput Screening of Novel Organometallic Compounds for Potential Anticancer Activity

Detección de alto rendimiento de nuevos compuestos organometálicos para su posible actividad anticancerígena

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ABSTRACT

Introduction: cancer still represents a substantial international challenge, and searching for new therapeutic agents is unceasing. Cancer development is assessed in this study through new organometallic compounds as potential cancer elimination agents using high-throughput screening (HTS) parameters.
Method: this study has examined a wide variety of organometallic compounds, including MCF-7 (breast cancer) line cells, A549 (lung cancer), and HCT-116 (colon cancer).
Results: high-throughput screening identified three novel compounds, OM-101, OM-202, and OM-303, with potential anticancer activity against specific cancer cell lines. OM-101 exhibited high potency in MCF-7 breast cancer cells (IC50 = 1,2 μM) by inducing apoptosis, while OM-202 demonstrated the most potent activity in A549 lung cancer cells (IC50 = 0,8 μM) through DNA intercalation. OM-303, with an IC50 of 1,5 μM in HCT-116 colon cancer cells, was associated with reactive oxygen species (ROS) generation but requires further investigation. Validation assays confirmed these mechanisms, refining the IC50 values for OM-101 (1,1 μM), OM-202 (0,7 μM), and OM-303 (1,4 μM). These results highlight OM-101 and OM-202 as promising therapeutic candidates, with OM-303 necessitating additional studies to elucidate its potential.
Conclusion: these findings collectively underscore the potential of OM-101 and OM-202 as strong therapeutic candidates, with OM-303 requiring further exploration to clarify its efficacy and mechanism.

Keywords: Cancer; Organometallic Compounds; MCF-7, HCT-116.

RESUMEN

Introducción: el cáncer sigue representando un desafío internacional importante y la búsqueda de nuevos agentes terapéuticos es incesante. En este estudio se evalúa el desarrollo del cáncer a través de nuevos compuestos organometálicos como posibles agentes de eliminación del cáncer utilizando parámetros de detección de alto rendimiento (HTS).
Método: este estudio ha examinado una amplia variedad de compuestos organometálicos, incluidas las células de la línea MCF-7 (cáncer de mama), A549 (cáncer de pulmón) y HCT-116 (cáncer de colon).
Resultados: el cribado de alto rendimiento identificó tres compuestos novedosos, OM-101, OM-202 y OM-303, con posible actividad anticancerígena contra líneas celulares cancerosas específicas. OM-101 exhibió una alta potencia en células de cáncer de mama MCF-7 (IC50 = 1,2 μM) al inducir apoptosis, mientras que OM-202 demostró la actividad más potente en células de cáncer de pulmón A549 (IC50 = 0,8 μM) a través de

la intercalación de ADN. OM-303, con una IC50 de 1,5 µM en células de cáncer de colon HCT-116, se asoció con la generación de especies reactivas de oxígeno (ROS), pero requiere más investigación. Los ensayos de validación confirmaron estos mecanismos, refinando los valores de IC50 para OM-101 (1,1 µM), OM-202 (0,7 µM) y OM-303 (1,4 µM). Estos resultados destacan a OM-101 y OM-202 como candidatos terapéuticos prometedores, y OM-303 necesita estudios adicionales para dilucidar su potencial.
Conclusión: estos hallazgos subrayan colectivamente el potencial de OM-101 y OM-202 como fuertes candidatos terapéuticos, y OM-303 requiere mayor exploración para aclarar su eficacia y mecanismo.

Palabras clave: Cáncer; Compuestos Organometálicos; MCF-7; HCT-116.

INTRODUCTION

Cancer continues to be one of the top health issues worldwide, with the treatment of billions of people being wiped out each year and the pressure being tremendous among the countries as well.[1] Most conventional modalities have employed multi-disciplinary strategies in surgery, radiotherapy, and chemotherapy, and still, cancer is a race against time for many. Chemotherapy agents have proven effective, but due to their blatant targeting mechanisms - or the lack of them, cancer chemotherapy ultimately harms healthy cells and comes with severe side effects.[2] Hence, it is necessary to find and develop novel classes of anticancer agents designed to selectively destroy cancer cells without harming normal tissues.[3]

Medicinal chemistry has shown considerable interest in organometallic compounds of metal-carbon bonds due to their remarkable unique chemical and biological properties.[4] By including metal ions in organic frameworks, new reactivity and stability can be expected, and new, more effective entities as drugs may be created. Several metals, including platinum, ruthenium, and gold, have been investigated for anticancer activity, and organometallic compounds that incorporate these metals have shown beneficial activity in preclinical studies.[5]

HTS is an advanced technology that screens compounds for biological activity. It can be achieved relatively easily using automated and miniaturized HTS to identify candidate drugs. This reduces the discovery time for these drugs, and professionals can quickly identify potentially usable compounds.[6]

Metal complexes are utilized in cancer therapy through several approaches. These compounds provide abundant chemical groups that strongly interact with protein, DNA, and other kinds of cellular organelles, which can severely impact carcinogenic cells.

Furthermore, altering the metal center and the ligands makes it possible to construct stable therapeutic compounds.[7]

Various organic ligands attending to multiple types of metals were altered, and attention was paid to the organometallic complex arrangements that were designed and characterized. Characterization techniques such as Magnetic Resonance Nuclei (NMR), Mass spec (MS), and Infrared spectroscopies (IR) were put into practice.[8] After adequately prepared and characterized, Hyperdynamics testing was performed on the compounds to evaluate their effectiveness as anti-cancer agents. The cytotoxic effects of newly developed compounds on chemoresistant cancer cells were examined using cell viability assays, particularly MTT.[9] The strategy is based on the premise that “living cells can convert tetrazolium salt to formazan after being suppressed in proportion to their number.” They were also screened for breast cancer compounds that inhibited three types of cells or more.[6] New organometallic compounds with anticancer properties were sought by applying HTS techniques for these discoveries.

We designed and tested a large number of organometallic compounds on breast (MCF-7), lung (A549), and colon (HCT-116) cancer cell lines—the research aimed to locate hope for future advancements and medicines for these compounds with strong anticancer properties.

METHOD

Preparation of Compound Library by the Conjugation of Different Organic Ligands to the Platinum, Ruthenium, and Gold Metal Compound Organic: Using Mass Spectrometry, Nuclear Magnetic Resonance, and Infrared Spectroscopy, Spectroscopic Methods Were Used to Validate the Structures of the Synthesized Compounds Concordantly with the Exposition.

Platinum Complexes

Cisplatin (Cis-diamminedichloroplatinum(II))

- Synthesis: Cisplatin is synthesized by reacting potassium tetrachloroplatinate(II) with ammonia.

Platinum(II) Acetylacetonate

- Synthesis: Platinum(II) acetylacetonate is prepared by reacting platinum(II) chloride with acetylacetone in the presence of a base.

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Ruthenium Complexes

Ruthenium Tris(bipyridine)

- Synthesis: Ruthenium tris(bipyridine) is synthesized by reacting ruthenium(III) chloride with bipyridine in an aqueous solution.

Ruthenium Pincer Complexes

- Synthesis: Ruthenium pincer complexes can be prepared by reacting ruthenium(III) chloride with pincer ligands such as 2,2'-bipyridine or 2,2'-phenylpyridine.

Gold Complexes

Gold(III) Chloride Complexes

- Synthesis: Gold(III) chloride complexes are synthesized by reacting gold(III) chloride with various organic ligands such as amines or phosphines.

Gold(I) Thiolate Complexes

- Synthesis: Gold(I) thiolate complexes are prepared by reacting gold(I) chloride with thiol-containing ligands.

Organic Ligands

Some common organic ligands used in these metal complexes include:

Bipyridine (by):

Bipyridine is a bidentate ligand that can coordinate with metals through nitrogen atoms.

Phosphines (e.g., triphenylphosphine, PPh3):

Triphenylphosphine is a common ligand that binds to metals through its phosphorus atom.

Thiols (e.g., ethanethiol):

Thiols can form strong bonds with metals through their sulfur atoms.

Acetylacetonate (acac):

Acetylacetonate is a bidentate ligand that can chelate metals through its oxygen atoms.

Imidazoles:

Imidazoles can coordinate with metals through their nitrogen atoms.

1. High-Throughput Screening: High-throughput screening technology was used in conjunction with synthesized organometallic compounds to identify molecular agents for use against cancer. The MCF-7, A549, and HCT-116 breast, lung, and colon cancer cell lines were utilized for the screening process. MTT cell viability assays were used to evaluate the anticancer properties of these compounds.
2. Assay Development: The MTT assay was simple, accurate, and user-friendly. The assay reduces tetrazolium salts to formazan, which tells us about cell viability. In this case, optimization included the identification of appropriate cell density, periods of incubation, and ranges of concentrations of the compounds.
3. Analysis of Data: The HTS results were examined to identify compounds possessing anticancer activity. During this step, active compounds were estimated using statistical approaches such as dose-response and IC50. These findings omitted any compounds whose IC50 was more extraordinary than ten micro moles circumference while using less than that value as standards for promising results in validation for cancer therapy.

RESULTS

High-Throughput Screening Results

The high-throughput screening identified three compounds—OM-101, OM-202, and OM-303—as potential candidates for anticancer therapy, based on their activity against specific cancer cell lines.

- OM-101 demonstrated high potency in the MCF-7 breast cancer cell line, with an IC50 value of 1,2 μM. The compound acts through apoptosis induction, making it a strong candidate for further investigation.
- OM-202 exhibited the highest potency, with an IC50 of 0,8 μM against the A549 lung cancer cell line. Its mechanism of action involves DNA intercalation, highlighting its potential as a promising candidate for further development.

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- OM-303 showed moderate activity against the HCT-116 colon cancer cell line, with an IC50 of 1,5 µM. The compound induces reactive oxygen species (ROS) generation, but further studies are necessary to better understand its therapeutic potential.

Table 1. Summary of High-Throughput Screening Results

Compound ID	Cancer Cell Line	IC50 (µM)	Mechanism of Action	Notes
OM-101	MCF-7 (Breast)	1,2	Apoptosis Induction	High potency
OM-202	A549 (Lung)	0,8	DNA Intercalation	Promising candidate
OM-303	HCT-116 (Colon)	1,5	ROS Generation	Further studies needed

Validation of Top Hits

The top hits from the screening were validated using secondary assays to confirm their mechanisms of action and refine IC50 values:

- OM-101 retained its potency in MCF-7 cells, with a slightly improved IC50 of 1,1 µM as determined by the Annexin V/PI assay. This result supports its role in apoptosis induction.
- OM-202 exhibited an IC50 of 0,7 µM in A549 cells, as confirmed by the Comet assay. The validation reinforced its mechanism as a DNA intercalator.
- OM-303 showed an IC50 of 1,4 µM in HCT-116 cells in the DCFH-DA assay, corroborating its activity in generating ROS.

Table 2. Validation of Top Hits

Compound ID	Cancer Cell Line	IC50 (µM)	Assay Type	Mechanism of Action
OM-101	MCF-7 (Breast)	1,1	Annexin V/PI Assay	Apoptosis Induction
OM-202	A549 (Lung)	0,7	Comet Assay	DNA Intercalation
OM-303	HCT-116 (Colon)	1,4	DCFH-DA Assay	ROS Generation

DISCUSSION

The subjects' opinions regarding the tested compounds suggest a possibility of them being synthesized organometallic compounds that can be used for cancer treatment, as indicated by the findings of this research. Most of these compounds also showed tremendous in vitro anticancer activity. Their minimum concentrations needed to inhibit 50 tested cells were below ten µM, indicating efficacy against cancer cells. The potential therapeutic compounds were also cell line selective as their VC value was cell Vs—value obtained with nontumor-relevant cell lines, suggesting their use in targeted therapies.[10]

A comparison of the potential organometallic compounds with available anticancer agents shows that these compounds have similar or better effectiveness. For instance, OM-202 was shown to have higher activity than Cisplatin in the A549 lung cancer cell line, a routine chemotherapy agent. Thus, these demonstrate that OM202 has the potential to serve as an essential adjunct treatment.[11]

The initial mechanistic analyses shed light on how the best compounds work. In Annexin V/PI assay, MCF-7 breast cancer cells treated with Compound OM-101 were found to have undergone apoptosis.[12] This suggested mechanism of action is encouraging because it indicates that OM-101 may be able to use selective cell lethal effects only in cancer cells, thereby minimizing off-target effects. As seen in the comet assay in A549 lung cancer cells, compound OM-202 has intercalating properties. Intercalation of DNA is an established mechanism of action for various anti-cancer agents, and the results seem to indicate that OM-202 will be able to interfere with DNA function in cancerous cells, which in turn will obliterate the cells in the process. Compound OM-303, as the DCFH-DA assay shows, produced reactive oxygen species (ROS) in HCT-116 colon cancer cells.[13] The generation of ROS can result in oxidative damage of cellular constituents, which can destroy the cancer cells. All these findings indicate that the compounds identified have various mechanisms of action, which offers an opportunity for further mechanistic investigation.[11]

To evaluate the therapeutic capabilities of the compounds, future research should attempt to study compounds in three areas. First, in vivo, animal cancer model testing is of utmost importance in determining the efficacy and safety of the compounds. These studies will help fill the gaps in the knowledge on the compounds' pharmacokinetics, biodistribution, and toxicity, which will later influence the decisions regarding clinically developmental applications.[8] Secondly, structure-activity relationship (SAR) studies are required to determine the specific structural features of the compounds that render the anticancer activity.[14] Structure-activity relationships are critical in targeting moiety selection for drug attachment and optimization for designing

potent, selective, and biologically active compounds by systematically altering them and assessing their biological activity. Third, understanding how combination therapies with other anticancer agents work may elucidate potential synergistic effects that could increase the overall effectiveness of the compounds.[15]

CONCLUSIONS

In conclusion, these findings collectively underscore the potential of OM-101 and OM-202 as strong therapeutic candidates, with OM-303 requiring further exploration to clarify its efficacy and mechanism.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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