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Designing an Ivermectin-Based Patentable Analogy for Cancer Therapy. Strategies in Drug Development and Targeted Delivery

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Abstract: ***Cancer globally continues to be one of the leading causes of death and ranks as the second leading cause of mortality in the United States. Nevertheless, early detection and innovative treatment options can significantly enhance cancer care, improving patients' quality of life and longevity. Current cancer therapies, which include surgery, radiation, chemotherapy, and immunotherapy, often encounter challenges related to selectivity for specific tumors and ineffective drug delivery mechanisms. These hurdles can result in low therapeutic efficacy and increased costs for patients. The development of innovative cancer therapies is increasingly focused on targeted, cost-effective solutions that address the limitations of traditional treatments. This study explores the potential of designing a patentable analog of Ivermectin, a known antiparasitic agent, for application in oncology. Drawing from structural pharmacology, the research emphasizes techniques such as pharmacophore modeling, scaffold design, hybridization with benzimidazole derivatives, and biosostric replacements to enhance drug efficacy and selectivity. It also outlines delivery mechanisms involving nanocarriers and prodrugs for improved therapeutic outcomes. By evaluating Ivermectin structural attributes and precedents in hormone analogs, the paper advocates pharmaceutical innovation through analog development.***

Keywords: Ivermectin analog, cancer therapy, nanocarriers, drug repurposing, targeted delivery.

1. Introduction

There is a growing body of evidence that anti-parasitic medications such as Ivermectin, Fenbendazole, and Mebendazole could hold the key to curing cancer [1-6]. This hypothesis is supported by nearly two decades of medical literature suggesting a potential link between parasitic infections and cancer, providing a compelling rationale for the use of anti-parasitic drugs in cancer therapy [7-15].

If these anti-parasitic drugs are repurposed for cancer treatment, as some have suggested [3], they could offer a cost-effective solution. Although it may not lead to substantial profits for pharmaceutical companies, it could significantly reduce the financial burden on patients. However, the negative perceptions surrounding Ivermectin, particularly in the wake of its controversial use in treating COVID-19, could discourage a pharmaceutical company from pursuing its development as a cancer treatment. Instead, the company might develop a patentable Ivermectin analog with similar efficacy. This approach is significant because it presents an opportunity to transform low-cost, repurposed antiparasitic drugs into viable, patentable cancer therapies, offering both economic and therapeutic benefits.

There are successful precedents for this strategic approach. For example, Isotretinoin, a derivative of Vitamin A, was marketed as 'Accutane' for acne treatment and commanded a high price. Despite the equal effectiveness of Vitamin A, the pharmaceutical company effectively positioned the new drug as superior [16-17]. Another notable example is the development of various hormone analogs as patentable molecules for Hormone Replacement Therapy (HRT). Natural hormones were modified in these cases to create new, patentable products.

The purpose of this report is to review and suggest ways and approaches a pharmaceutical company might explore in order to create efficacious and patentable derivatives and analogs of Ivermectin for anti-cancer therapy.

2. Materials and Methods

The data sources used for this paper include materials published within four years before the publication date. The sources comprise Google Scholar, Google, Yandex.com, Zotero, and ScienceDirect. The search keywords focused on how analogies are created; Ivermectin's anticancer efficacy; scaffold design for Ivermectin; identification of Ivermectin pharmacophores; effective delivery systems for Ivermectin; possible cancer properties of Ivermectin, Fenbendazole, and Mebendazole. This comprehensive search strategy was designed to ensure that no relevant literature was overlooked.

To address gaps identified in the existing literature, non-traditional research platforms for PhD research were also utilized, including ResearchGate, CORE, and Zenodo. These platforms offer alternatives to conventional databases, providing access to a diverse range of academic outputs. Any additional publications relevant to this review were also retrieved, and all selected articles underwent qualitative assessment.
The chosen databases were selected for their relevance and significance, providing insights that directly address the research question. This selection followed a clear and systematic approach, ensuring valid, reliable, and reproducible results. Consequently, this approach enables a thorough evaluation of the study's findings, reinforcing the robustness of the research process.

3. Result and Discussion

Ivermectin Therapeutic Benefits

Ivermectin, a synthetic derivative of avermectin from the bacterium Streptomyces avermectinius, is a macrocyclic lactone drug. It exhibits a potent antiparasitic effect and an exceptionally favorable safety profile (1). The U.S. Food and Drug Administration has approved this treatment for both oral and parenteral use in humans and animals. It targets specific intestinal infections caused by threadworms (strongyloidiasis) and river blindness (onchocerciasis), as well as other worm infections (2). Moreover, Ivermectin, recognized for its effectiveness and impressive safety profile, has surfaced as a promising candidate for cancer therapy. Research has indicated its potential therapeutic benefits in vitro and in murine cancer models. It has shown significant efficacy in addressing Stage IV cancer (5). In mouse studies, Ivermectin has been observed to reduce tumor volume by over 50%, even at doses below the maximum safety limits established for humans (6).

However, it is essential to recognize that these findings may not necessarily translate into clinical efficacy. The challenge lies in determining whether the antitumor effects observed in preclinical studies can be safely and effectively replicated in patients with cancer (5). It is essential to recognize that many existing cancer therapies, primarily those based on chemotherapy or immunotherapy, often exhibit limited effectiveness. This underscores the need to explore new treatment alternatives by developing an analogy of Ivermectin.

To develop an analog, a thorough understanding of the pharmacophore is crucial. This understanding is vital for pharmaceutical companies aiming to develop a potentially patentable analog of Ivermectin, as it underpins the compound. The potential for patentable analogs presents a unique opportunity for pharmaceutical companies, making the understanding of pharmacophores even more crucial (7-8).

Understanding the structural characteristics of ivermectin, including its chemical and biological properties (8), is crucial for its remarkable ability to interact with and target biological receptor proteins, as well as for the potential to modify and transform the macrocycle into an effective targeted delivery system. This enhancement improves its pharmacokinetic properties, enabling precise targeting to achieve therapeutic effects. This knowledge guides the selection of molecular components for modification, substitution, or retention, as well as those that should remain unchanged (11).

Structural Characteristics of Ivermectin

Ivermectin is a stereochemical compound distinguished by its unique three-dimensional arrangement of atoms. It features a 16-membered macrocyclic lactone, a significant ring-like structure that serves as the compound's core (9). It has a molecular formula C48H74O14. Ivermectin consists of two closely related homologs, B1a and B1b. While structurally similar, they differ by a single side chain and a specific chemical group attached to carbon-25 within their molecular frameworks. The “a “variants possess a sec-butyl group at C25, whereas the “b” variants contain an isopropyl group. These homolog mixtures typically range from 80% to 90% for B1a and 10% to 20% for B1b (16). The two chemical variants, 22,23-dihydroavermectin B1a and 22,23-dihydroavermectin B1b, are produced by modifying or hydrogenating the double bond between positions 22 and 23 of the parent compound, avermectin B1. This modification involves adding a hydrogen atom at C22 or a hydroxyl group at C23. This difference in chemical structure leads to significant functional consequences for ivermectin (17-18)

Ivermectin also possesses distinct structural features that are crucial to its ability to target protein receptors. Key components include spiroketal, benzofuran, and disaccharide moieties. Notably, the spiroketal element serves as a rigid pharmacophore, interacting with biological targets and providing a strong scaffold. This scaffold ensures the precise three-dimensional orientation of the side chains, a feature of utmost importance for effective binding (21). This precise orientation allows Ivermectin to bind to its protein receptors effectively. These side chains, linked by a single carbon atom with an oxygen atom adjacent to the spirocarbon, are a structural characteristic fundamental to the architecture and functionality of Ivermectin (19). The spiroketal motif is essential for the compound's binding capabilities and interactions with biological protein receptors, maintaining a rigid structure that supports various biological activities (17).

Meanwhile, the benzofuran moiety interacts with the protein receptor binding site through deep insertion, forming crucial hydrogen bonds and hydrophobic interactions that enhance its efficacy (22). This characteristic makes it a promising candidate for the design and development of new therapeutic agents (21). A notable feature of the benzofuran structure is the hydroxyl group located at the 5th carbon atom of the ring. This C5-hydroxyl group is vital for facilitating specific interactions and biological activity. However, its overall impact may vary depending on the compound's structure. Modifications or substitutions at this C5 position can significantly influence the molecule's biological activity, particularly its anticancer properties and other pharmacological effects. The disaccharide portion, while not essential for high activity at specific receptors, is positioned on the exterior of the binding pocket and interacts with the surrounding environment, contributing to the overall stability of Ivermectin (23).

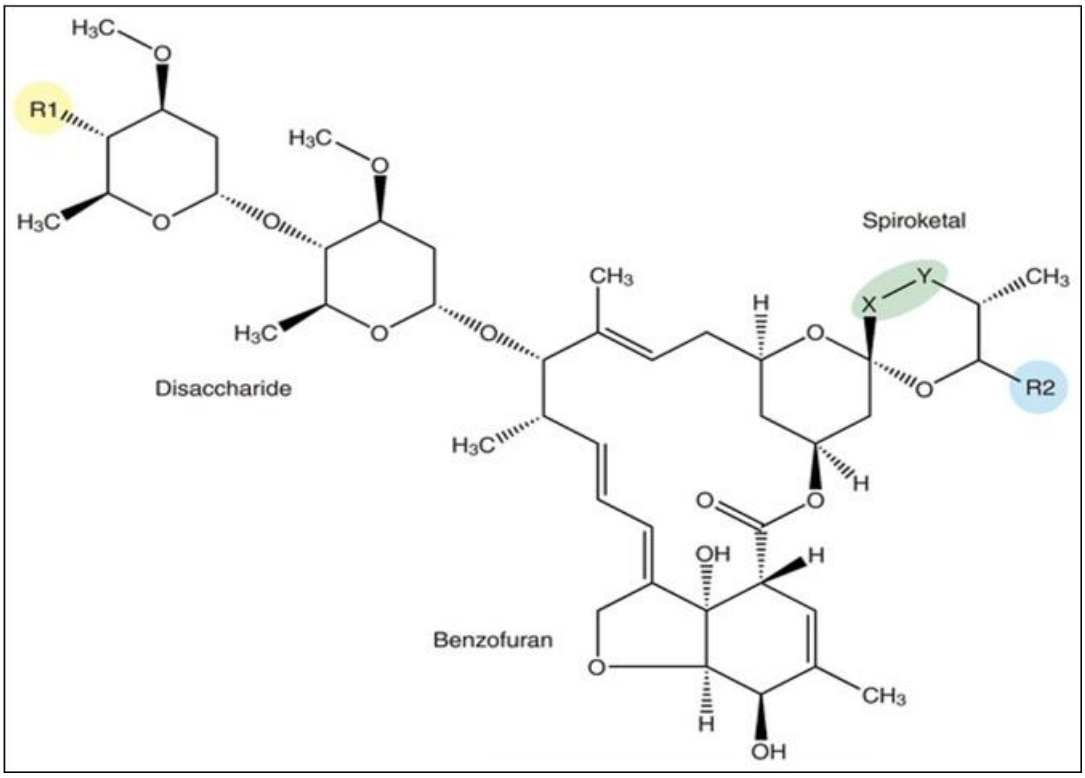

Figure 1: Physical Structure of Ivermectin

Techniques in Designing Analogy

Designing an analog involves several stages, beginning with a comprehensive understanding of the compound's or molecule's pharmacophore. This essential component interacts with biological target protein receptors to produce the desired effect. The core structure is crucial to developing a successful analog and serves as the foundation for the design process (11). The next phase involves identifying molecular components that can be modified, altered, or substituted. This will require a detailed series of targeted modifications to change the compound's properties. Once these modifications are made, candidate analogs are designed using software that predicts their properties and biological activities before synthesis (12). This approach streamlines the screening and prioritization of the most promising molecules for further testing.

Furthermore, implementing planned modifications to create new analog compounds in the laboratory or employing a diverted total synthesis strategy for more complex molecules represents additional techniques for predicting potential analogs. This allows the synthetic pathway to diverge at an intermediate stage, generating various analogs. Careful analysis of how structural modifications influence their behavior is integral to this process. Computational techniques are utilized, especially quantitative structure-activity relationship (QSAR) studies (13). These techniques, which employ linear or non-linear models, are particularly effective at predicting the potency of new analogs (12).

Another method involves biological assays, in which each new analog is evaluated for its activity, such as its efficacy against specific enzymes or effects on cell cultures. These assessments constitute the final phase of the testing process. The results are analyzed to provide insights into the structure-activity relationship, thereby identifying modifications that enhance desirable properties while recognizing those that may hinder them. This knowledge is then applied in the design of the next generation of more refined analogs. The iterative design, synthesis, and testing cycle, a crucial part of the process, continues until the compound satisfies the necessary potency, selectivity, and safety standards (14).

Analogy of Ivermectin derived from the avermectin family of compounds.

Table 1

Name	Compound Modifications/Structure	Chemical Formula
Abamectin	Adding a double bond at the C22–23 position enhances the compound's efficacy compared to Ivermectin.	$C_{48}H_{72}O_{14}$
Doramectin	Replacing the sec-butyl moiety with a cyclohexyl group increases hydrophobicity and extends the biological half-life.	$C_{50}H_{74}O_{14}$
Eprinomectin	Eprinomectin consists of two closely related compounds, B1a and B1b, in a 9:1 ratio, while Ivermectin has an 8:1 ratio.	$C_{50}H_{75}NO_{14}$
Emamectin	Emamectin is a mixture, typically consisting of 10% B1b and 90% B1a	$C_{49}H$ 75NO_{13} for B1a and $C_{48}H$ 73NO_{13} for B1b
Selamectin	Lacks a second carbohydrate unit and has a cyclohexyl ring with a ketoxime substituent instead of an isopropyl/isobutyl group and a hydroxyl group.	$C_{43}H_{63}NO_{11}$
Moxidectin	Substituted olefinic side chain at carbon 25 and methoxime group at carbon 23.	$C_{37}H_{53}NO_8$

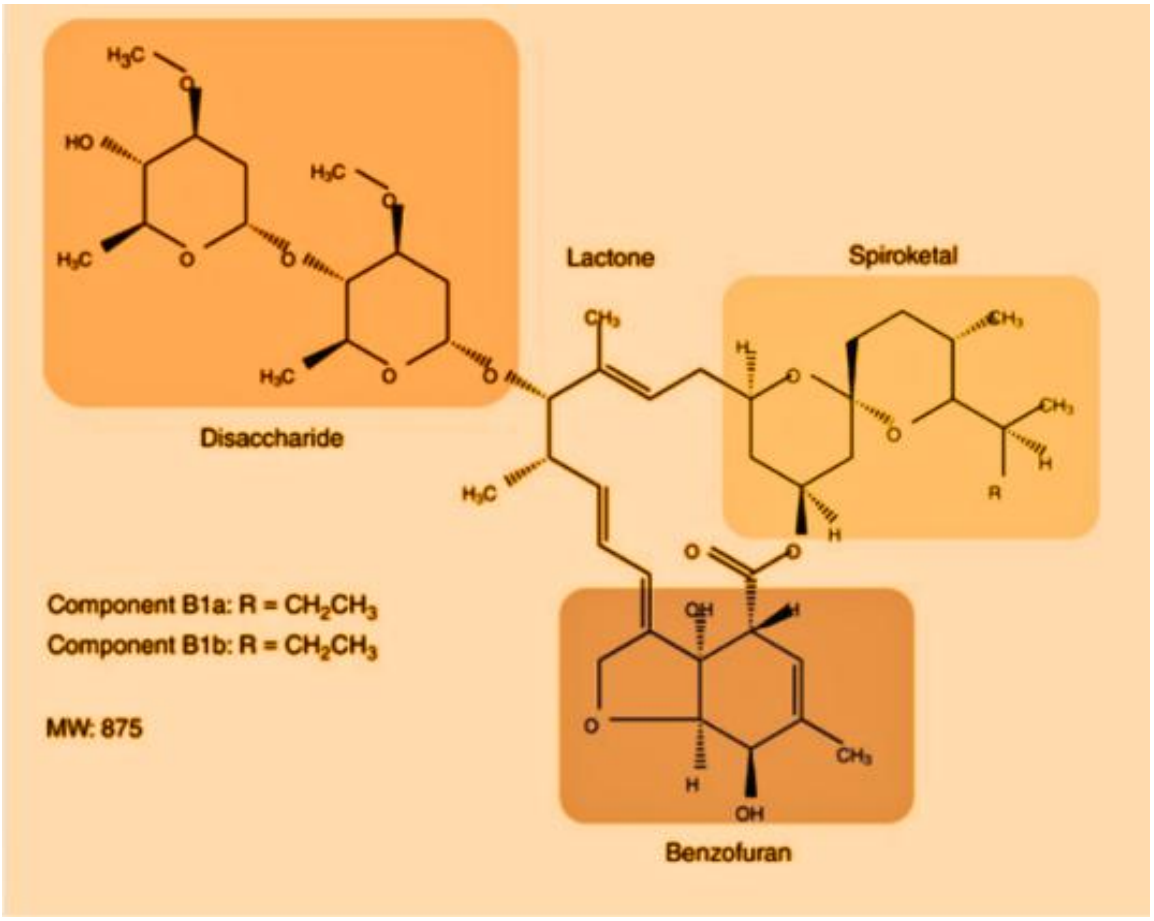

Figure 2 (a): Structural features of ivermectin

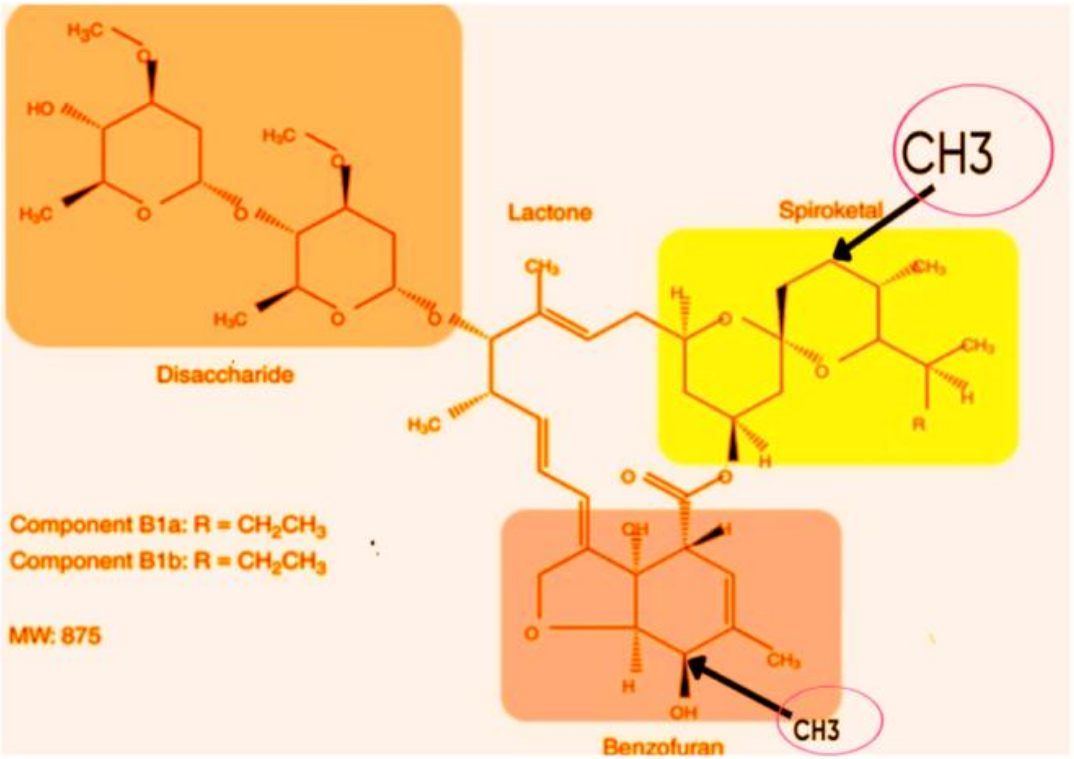

Figure 2 (b): Possible Modification Points to create an Analogy of Ivermectin
Note: Modifications of Ivermectin can enhance its pharmacological properties, increase bioavailability, and extend its half-life.

Progesterone Modified to Progestins

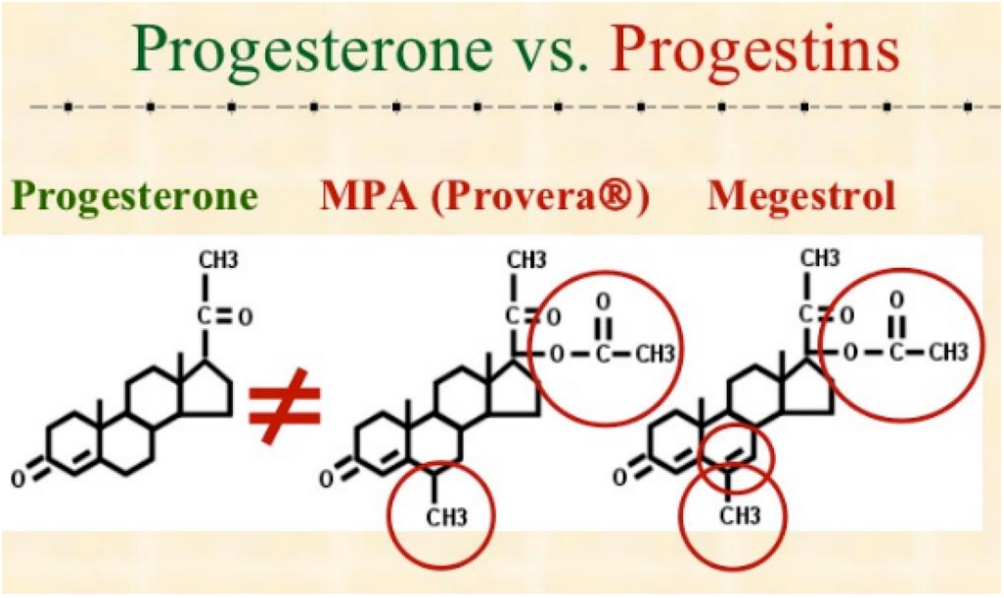

Figure 3 (a): Patentable analogy: Hormone Replacement Therapy (HRT)

Note: Modifications of progesterone into progestins, achieved by adding an ethynyl group at C-17, enhance their pharmacological properties, improving oral bioavailability and extending their half-life.

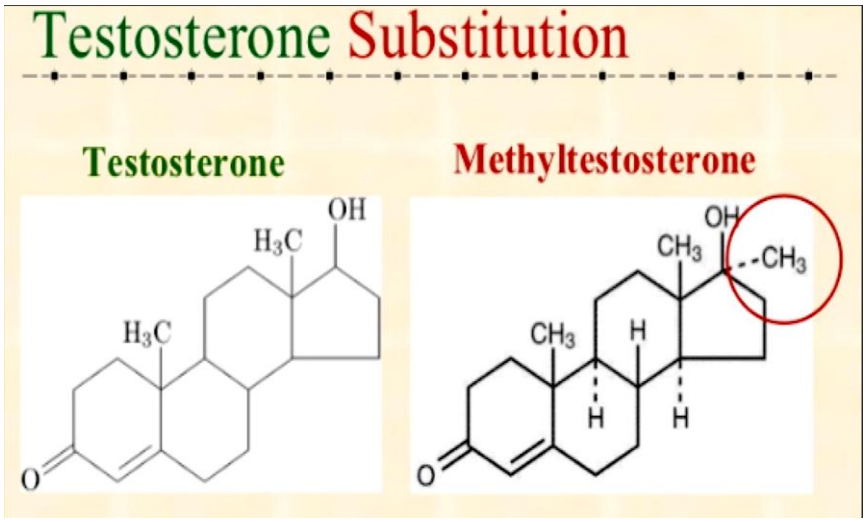

Figure 3 (b)

Note: Modification of Testosterone to methyltestosterone by adding a methyl group at C17 of testosterone, enhancing its oral bioavailability.

4. Discussion

Research conducted over the past two decades has established a connection between parasitic infections and cancer (7-15). As additional evidence surfaces regarding the effectiveness of antiparasitic medications such as Ivermectin, Fenbendazole, and Mebendazole as potential cancer therapies, the development of a patentable analog of Ivermectin that mirrors its efficacy could represent a significant advancement in cancer treatment, potentially revolutionizing the future landscape of cancer therapy (1-6). These suggested approaches to developing such an analog as a potential anti-cancer drug offer a compelling opportunity and an exciting prospect for pharmaceutical companies.

One effective strategy a pharmaceutical company can utilize in designing such an analog is the Hybrid technique, which targets biological tissues by combining two drugs (22). This approach involves a meticulous process of linking drugs that share the exact mechanism of action or connecting those that operate through different mechanisms. In this case, Ivermectin and the antiparasitic medications Fenbendazole and Mebendazole, which are benzimidazoles, interact with receptor proteins in distinct ways to elicit a therapeutic response (24).

Ivermectin binds to glutamate-gated chloride channels, which are the receptor proteins that facilitate the influx of chloride ions. This influx causes hyperpolarization of nerve and muscle cells, leading to paralysis and ultimately the death of

the parasite (23). In contrast, Fenbendazole and Mebendazole target the β-tubulin protein, preventing microtubule formation, which is critical for cell division and glucose uptake, thereby leading to the parasite's demise (25). Interestingly, these mechanisms of action can also be applied in cancer therapy.

Combining these antiparasitic medications, pharmacophoric moieties, and cleavable hybrids can create new entities with synergistic effects or a broader therapeutic profile via an ester linkage (26), thereby merging components from distinct molecules. The pharmacophoric moieties, crucial in drug design, analog creation, and the discovery process, play a significant role. Their biological activity and interactions depend on a molecule's specific three-dimensional structural features, including hydrophobic regions, hydrogen bond donors and acceptors, charged groups, and aromatic rings. These characteristics ensure their biological activity and target interaction (27).

The success of combining these moieties relies heavily on the pharmacophoric moieties themselves, their mechanisms of action (how they interact with their biological targets), high selectivity for their respective targets, and the careful selection of a linker to connect the pharmacophores (22-27). This strategy is particularly vital in designing new anti-cancer hybrids and offers a promising approach for developing anti-cancer drugs based on Ivermectin.

The emphasis is on harnessing the combination of pharmacophoric moieties within a novel molecular structure to preserve their affinity and activity towards biological targets. Under physiological or enzymatic conditions, these hybrids release two medications with independent actions at the site of activity. The primary goal of cleavable hybrid drugs is to significantly improve poor pharmacokinetic properties and enable a gradual delivery of the two therapeutic entities within the body, while enhancing selectivity and antineoplastic activity by directly releasing the drugs into targeted tissues (25-27).

Designing new analogs using established anticancer warheads, such as tubulin-binding motifs or kinase inhibitors (26), can also be an option for pharmaceutical companies. Dual-action hybrids can be developed by fusing the ivermectin pharmacophore with these recognized anticancer agents. This strategic combination results in bifunctional molecules that simultaneously engage cancer via both ivermectin-related pathways and traditional anticancer mechanisms. The potential for patent protection is significant, underscoring the uniqueness and marketability of this approach despite the considerable complexity introduced during development.

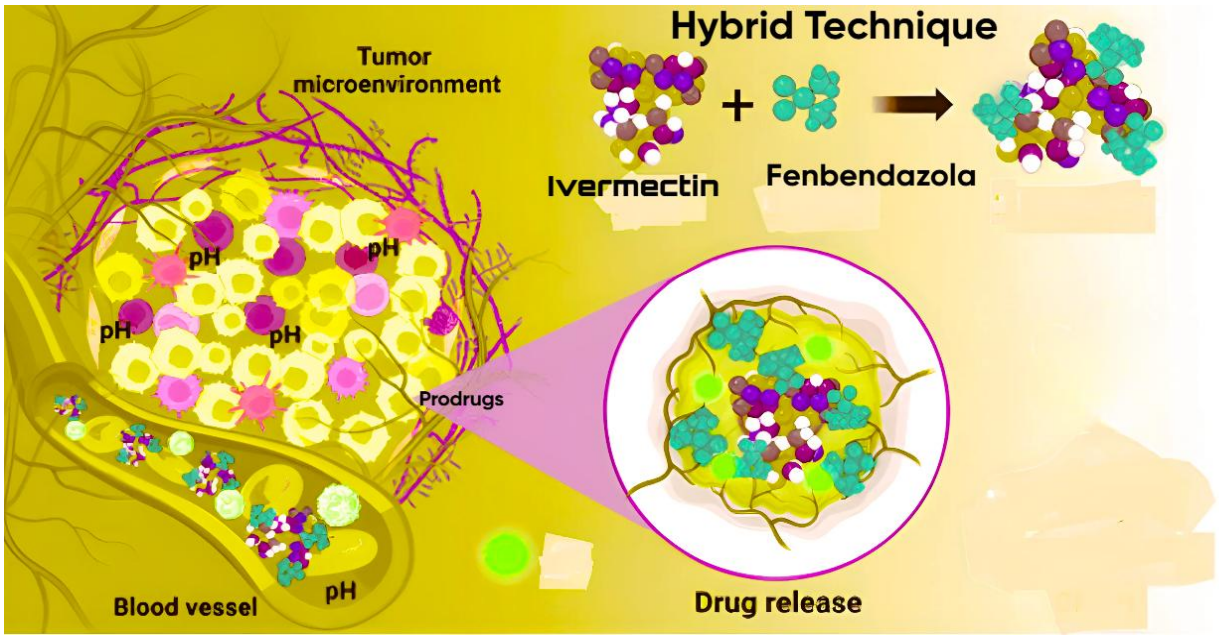

Figure 4: Hybrid technique

In addition to the hybrid approach, pharmaceutical companies can utilize isosterism techniques to develop new molecules that are analogs of Ivermectin (28). These methods involve substituting or modifying specific atoms or groups of atoms with others that possess similar electronic and steric properties. Such substitutions facilitate changes in the molecular properties without significantly altering their overall structure, function, or target potency (29). The isosteric replacement approach primarily aims to optimize lead compounds by rational molecular modifications. It enhances pharmacokinetics during advanced drug design and improves pharmacodynamic behaviors at receptors, enzymes, or channels. However, this approach has little to no effect on the compounds' potency (30). This method, often considered a practical and superior alternative to modern lead optimization techniques (31), is a valuable tool in drug development.

Pharmaceutical companies can also employ bioisosteric replacement techniques to design Ivermectin analogues (Figure 2b). This approach involves modifying various compound characteristics, such as size, shape, electronic distribution, lipophilicity, polarizability, dipole moment, polarity, and pKa (32), while ensuring strong interactions

with the target. When developing an analogue of Ivermectin, the three-dimensional arrangement of atoms within the molecule must be considered (31). This method involves isolating or designing individual stereoisomers or epimers. After isolating these forms, functional groups are substituted with alternatives that possess similar biological, chemical, and physical properties. Such methodology optimizes drug candidates by minimizing rapid metabolic cleavage, thereby extending their half-life and reducing the formation of toxic metabolites (30-32), while preserving therapeutic efficacy. The primary aim of these modifications is to address pharmacokinetic and metabolic challenges, rather than simply enhancing potency (29), which often significantly contributes to the failure of many drug candidates.

Bioisosteres compounds or structures with similar biological activities and comparable traits, such as topology, volume, electronic configurations, or physicochemical properties, are a central focus in drug design. Extensive research on their impact on drug target selectivity, bioactivity, efficacy, potency, membrane permeability, biotransformation pathways, and toxicity profiles highlights their crucial role in modern drug development (32).

The Final Approach the pharmaceutical industry can utilize is a series-based scaffold technique to create analogs of anti-cancer drugs based on ivermectin. This method involves examining a series of related active compounds with diverse core structures through a computational process known as scaffold hopping (33). The aim is to identify conserved structural features and design new scaffolds incorporating synthetic information and substitution sites to develop additional analogs while maintaining biological activity (34).

5. Conclusion

Chemotherapy, radiation, immunotherapy, and surgery are well-established treatments for various types of cancer. However, these methods can be costly for patients and often do not provide targeted solutions for specific tumors. Given these challenges, there is a pressing need for alternative therapeutic approaches. Pharmaceutical companies should explore the potential of developing an Ivermectin analog as a nontraditional avenue for cancer treatment.

Ivermectin and other anti-parasitic therapies, such as Fenbendazole and Mebendazole, have shown promising efficacy in treating cancer based on mechanisms observed in vitro and in murine models. Translating these findings into clinical applications for human patients is certainly a worthwhile pursuit. This research is driven not only by the potential therapeutic advantages of Ivermectin compared to existing treatments but also by the profits pharmaceutical companies may reap from effectively marketing such therapies, as in the case of Accutane, which is derived from vitamin A for acne, which can be mutually beneficial.
However, these findings warrant caution. Future research should prioritize preclinical trials and structure-activity relationship mapping to validate these analogs for clinical use.

It is important to note that the investigation into these therapies has sparked considerable interest in non-traditional research platforms and has also drawn attention within conventional frameworks, backed by patient evidence. The suggested approach of creating anti-cancer drugs based on Ivermectin, which can be patented, has the potential to revolutionize the global fight against cancer.

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