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Review Article

Unlocking Synergistic Action: Harnessing Hybrid Drugs for Better Therapeutic Outcomes

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In the face of mounting global health challenges, the simultaneous burden of malaria, cancer and cardiovascular disease presents an urgent call for therapeutic innovation. The growing complexity of these diseases poses significant challenge to conventional therapeutic approaches. Monotherapy often falls short due to issues like drug resistance, patient non-compliance and multifactorial disease mechanism. In this context, hybrid drug technology has emerged as a promising alternative offering a synergistic strategy by integrating multiple pharmacophores into a single molecular framework giving a compiling solution to multifaceted challenges by targeting heterogeneous pathophysiology an emerging drug resistance. In this present review article we will explore what hybrid drug technology is, its importance, mechanistic versatility and therapeutic promise of hybrid molecules that integrate anti-malarial scaffold, cytotoxic agents and cardio protective moieties. We will look into what is a linker, its types, selection criteria and advantages will be mentioned that are rarely covered in any article. Additionally, overview on various hybrid drug molecules in different disease condition has been encompassed to the parent moiety.

Keywords: pharmacophore, antibody-drug conjugant, therapeutic innovation, multifactorial disease mechanisms, dual action agents, drug resistance, molecular engineering.

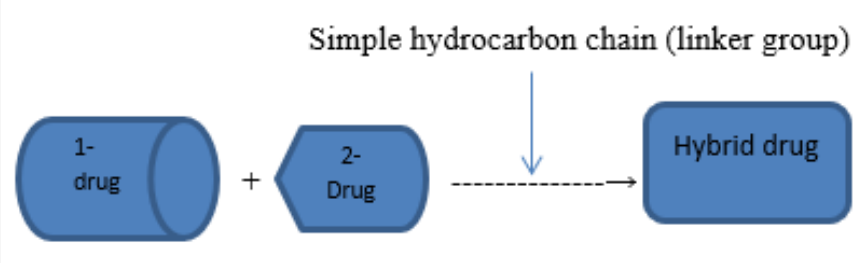
INTRODUCTION

In the ever-evolving landscape of pharmaceutical innovation and an era where complex diseases from cancer to many infections demands multidimensional therapeutic strategies, hybrid drug technology has emerged as a transformative approach that blurs the boundary between traditional pharmacology and molecular engineering.[1,2] This development shows a paradigmatic shift by joining the gap between chemistry and clinical need. Rather than combining dose in fixed concentrations, using polypharmacy approach or conventional therapies, hybrid drugs are rationally designed molecules that integrates two or more pharmacophores(either identical or distinct) into a single chemical entity which offers a unified mechanism to tackle multifunctional pathologies.[1] These hybrid molecules are often referred to as multifunctional drugs or dual action agents, which are engineered to simultaneously target multiple biological pathways.[3] This paradigm not only enhances therapeutic efficacy but also addresses challenges such as drug resistance, poor bioavailability, and patient compliance. These hybrid drugs are mainly of 3 types, i.e.

1. Linked hybrids: two pharmacophores are connected through linker.
2. Fused hybrids: two pharmacophores are chemically fused into a single framework.
3. Merged hybrids: overlapping pharmacophores share common structural elements.

To design and discover newer drugs was the toughest target to achieve as hit and lead stages becomes more crucial, hence the need for hybrid drugs aroused.

Hybrid drugs are also known as multi-target directed compound, multifunctional ligands, chimeras and etc.



For emerging a hybrid drug, linker plays a vital role. Linkers are chemical structure that connects two or more different therapeutic agents, creating a single molecule with potentially enhanced properties.[4] Notably, Telisotuzumab Vedotin (Emrelis) has successfully transitioned from trials to become a marketed anticancer hybrid, proving its efficacy in clinical practice. Simultaneously, cutting-edge research is advancing at the University of California, where our Astimezole-Chloroquine hybrid and an innovative zatebradine and Aryloxypropanolamine hybrid are showing exceptional promise in preclinical trials for treating resistant malignancies. Furthermore, our ongoing Clinical Research in the antifungal sector is bridging the gap between design and delivery, aiming to provide highly potent, single-entity solutions for complex fungal infections.[8,9,12,14]

Linkers: the unsung architects of bioactivity.

Linkers serves as the molecular bridges used to bind distinct pharmacologically active units into one concise hybrid drug. Though overlooked due to its small size, the linker is far more than just glue. It hold the power to contract, influence and even activate the behaviour of the hybrid drug. The objective is to preserve or enhance the individual activities of the pharmacophores, while also imparting synergistic therapeutic effects, improved targets or optimised pharmacokinetic property. With respect to the manner of attachment of the individual components, particular consideration should be given to the (i) mechanism of action of the individual ligands, (ii) nature of the linker unit employed[10], (iii) distance between the individual components and,(iv) molecular geometry, if known, of the individual ligand binding sites.[4,5] Although hybrid drugs are inherently difficult to synthesize and characterize due to their high molecular weight and complex architecture, recent innovations in linker technology have successfully surpassed these traditional disadvantages. Modern linkers are no longer just passive spacers but have evolved into sophisticated, stimuli-responsive bridges—such as pH-sensitive, redox-active, or enzyme-cleavable motifs—that ensure the simultaneous and stable delivery of diverse pharmacophores specifically to the tumor microenvironment. This review article highlights several groundbreaking hybrid drugs that have redefined the 2024–2025 clinical landscape[5,7,8]

Types of linkers:

There are basically 2 class of linkers <i.e.

1. Directly linked hybrid drug: connect via functional group
2. Spacer linked hybrid drugs: this is sub classified as:

2.1: cleavable linkers:

Ester linked linker which bound through plasma esterase and release 2 different drugs.

Example: No-Aspirin, 5-Flurouracil Cytarabine, VNLG/114

It includes:

- Enzyme labile linkers
- pH sensitive linkers
- Redox sensitive linkers

2.2: Non- cleavable linkers:

Non hydrolysed bonds make them connected and shows chemically as well as enzyme stability. Example: PHENYLINDOLE-ANILINE

MUSTARD, ESTRADIOAL-ANILINE MUSTARD. It includes:

- Thio-ester linker
- Amide linker
- Ether linker

Linker should possess properties like stability, cleavage specificity, non-immunogenic, biocompatible, and non- toxic. As these entities have architectural complexity, it requires guided synthesis and robust analytical validation. Over the past decades, advancements in medicinal chemistry, molecular modelling and high throughput screening have accelerated the rational design of hybrid compounds tailored for specific therapeutic outcomes.

Design considerations for choosing linker:

1. Stability in systemic circulation.
2. Trigger to release in tumour environment.
3. hydrophilicity/lipophilicity balance.
4. Length and flexibility to prevent steric hindrance.
5. Biocompatibility and non-toxicity of the linker and its by-product.

Role of linkers:

Far from being passive connectors, linkers play active role in:

1. **Molecular spacer:** Linker ensures that the active parts of the hybrid drug maintain their structural independence and don't interfere with each other.

2. **Optimising spatial arrangement and pharmacodynamics:** to maintain the ideal distance and orientation between units for precise molecular interaction. It also [prevents stearic hindrance between the two pharmacophores moieties. They also influence the binding site, selectivity and overall biological activity of hybrid compound by fine turning the distance and orientation between active sites.

3. **Improved solubility and stability:** hydrophilic and flexible linkers can improve aqueous solubility and chemical stability of poorly soluble hybrid molecules.

4. **Pharmacokinetic modulation:** the chemical nature of the linker can modulate key pharmacokinetic parameter such as absorption, distribution, metabolism and excretion, optimising in-vivo drug performance.

5. **Targeted delivery agent:** some linkers are cleavable designed to break under certain conditions (like acidic environment in cancer cells) releasing the active drugs only at the diseased site. The precision reduces side effects and increases therapeutic impact.

The incorporation of linker in hybrid rug technology holds strategic importance and humorous advantages:

- Simplified dosage form
- Reduced resistance
- Therapeutic precision
- Versatility
- Stability and safety

Hybrid drug techniques are now actively explored across a range of therapeutic areas including oncology, infectious disease, and cardiovascular disorder and central nervous system conditions. Here, in this article we will discuss few hybrid drug molecules used in various diseases like:

- Cancer
- Malarial
- Cardiovascular
- Fungal

There are numerous hybrid drugs and hybrid drug molecules present and continuously gets researched for this type of broad spectrum diseases, the predicted ratio for hybrid drugs for above mentioned diseases is shown below:

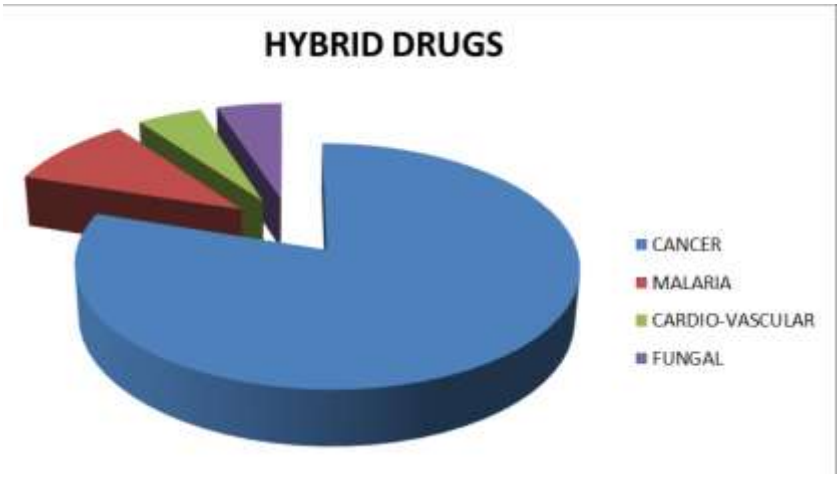


Fig (A): Hybrid Drug ratio for various diseases[5].

Experimenital

Hybrid Drugs for Cancer

Introduction

"CANCER", it is one of the most lethal diseases in the world known till. In 2024, nearly 9.7 million cancer-related deaths have occurred. It has become a burden leading to deaths globally. About 1 in 5 people develop cancer in their lifetime and 1 in 12 women die from this disease. There are various treatment types which fully cure in some cases and may fail prominently. There are 2 types of treatment i.e. LOCAL treatment and SYSTEMIC treatment.

For local treatment we have:

- Surgery
- Radiation therapy
- Interventional radiology

For systemic treatment we have:

- Chemotherapy
- Immunotherapy
- Targeted therapy
- Hormone therapy
- Stem cell transplant

There are various classes of drugs used in cancer treatment for different forms of cancer; it could be localised cancer like breast cancer, hepatic cancer, colon cancer, systemic cancer etc. Though there's a very broad classification of drugs for anti-cancer, it lack efficacy at some level. Hence a need for hybrid drug in cancer therapy is required which properly attacks the targeted cell and shows greater potency. It includes two different pharmacophores which one combination get us the best results. Human anatomy and physiology is very wide and hence is gets easier to target specific cell, tissue, organ with the help of only "required drug". In this specific portion various hybrid molecules of different classes are mentioned where the pharmacophores are joined together with a linker to get a desired effect in reducing cancer cells or inhibiting cancer.

Hybrid Drug Targeting HDAC And DNA Alkylation:

The recent development of hybrid drug which specifically target histone deacetylase (HDACs) and DNA through alkylation represent a novel approach in anti-cancer treatment. The dual function includes epigenetic modulation with cytotoxic DNA damage with shows synergistic mechanism and enhanced therapeutic efficacy.

- HDAC, these are the enzyme primarily responsible for removing acetyl group from lysine residue which is present in histone and non-histone proteins, this eventually shows chromatin condensation and transcriptional repression.[6] FDA has approved HDAC inhibitor (e.g.: vorinostat- romidepsin) has validated the clinical relevance in haematological malignances. In cancer, HDAC activity silences tumour suppressor genes, resistance to apoptosis and

uncontrolled proliferation. HDAC inhibition results in:

1. Relaxation of chromatin architecture facilitates transcriptional reactivation of silenced gene.
2. Apoptosis and induction of cell cycle
3. Differentiation related gene expression
4. Enhanced DNA damage response signalling pathway

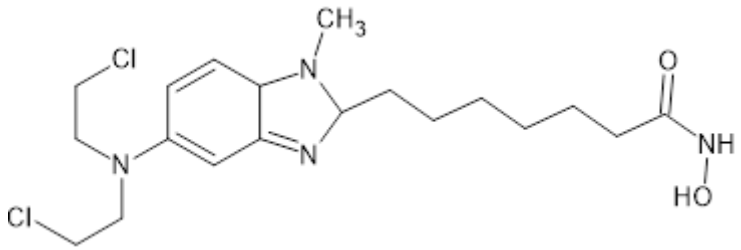
- DNA alkylation:

Genotoxic stress and DNA alkylating agents covalently modify DNA bases primarily at N7 position of guanine leading to various steps:

1. Strand breaks and DNA cross-linking
2. Inhibition of DNA replication and transcription
3. Triggers apoptotic pathways

Epigenetic reprogrammed cellular environment is observed by adjoining these alkylating moieties with HDAC inhibitors as it provides targeted genotoxic stress.

1. Vorinostat- Bendamustine Hybrid Drug:



Fig(B): Structure Of Vorinostat-Bendamustine Hybrid Drug.

In this hybrid (NL-101) Two moieties which are fused are Vorinostat (HDAC inhibitor)and bendamustine (DNA alkylators).NL-101 is engineered by directly substituting the side chain of bendamustine with hydroxamic acid moiety of vorinostat(SAHA) effectively merging both functional groups without an additional spacer or traditional linker.[7] Thus it avoids potential issues with metabolic breakdown or linker instability and supports coordinated delivery of HDAC inhibition and DNA damaging actions. When administered, this hybrid enters in blood stream and reaches tumor cells as an intact molecule. Once it reaches inside cancer cell the alkylating part causes DNA crosslinks leading to strand breakage.[8] The HDAC-inhibiting part causes accumulation of acetalylated histone and proteins which eventually affect gene expression and trigger programmed apoptosis.

These actions are coordinated, not sequential or independent on breakdown.

IC50 value for HDAC receptor (1-6) is 10nm – 107nm while that of NCI 60 which is a 60-unit long chain has IC50 value 2.2µm. This hybrid shows greater inhibitory constant as compared to bendamustine with IC50=7.7 µM.[9]

Table-1: Comparative Features of Hybrid Drugs with Bendamustine and Vorinostat.

Sr	Feature	Nl-101 Hybrid	Bendamustine Alone	Vorinostat (Saha) Alone
1	DNA -Alkylation	Yes, Inherited	Yes	No
2	HDAC -Inhibition	Yes, Inherited	No	Yes
3	Cell-Cycle Arrest/ Apoptosis	Yes, Dual Mechanism	Yes, DNA Damage	Yes, History Changes+ DNA Damage
4	In-Vivo Efficacy	Yes, Superior In AML Mouse Models	Yes, But Less Effective	-, Not Tested In This Combination.

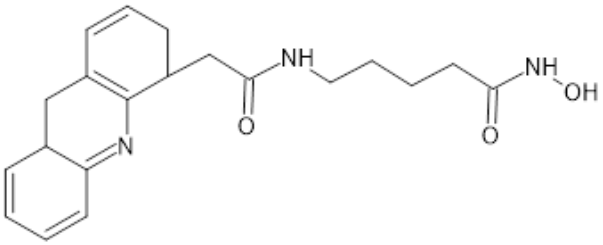
Merits of HDAC inhibitor hybrids:

- Synergistic toxicity: HDAC inhibitors relax chromatin structure and increases DNA accessibility to alkylators.
- Resistance circumvention: effective targeting may reduce the resistance of drug through compensatory pathway.
- Improved pharmacokinetics: drug may get superior bioavailability and tumour accumulation compared to combination therapy.
- Simplified administration: single agent improves patient compliance.

Hybrid Drug Targeting HDAC Inhibitors and Topoisomerase:

This hybrid molecule comprise the fusion of two pharmacophpres i.e. HDAC inhibitor and a TOPOISOMERASE which are fundamentally distinct yet they are interdependent for neoplastic proliferation. As referred before, HDAC are epigenetic modulators as they catalyse deacetylation of histone and non-histone proteins which results in silencing of tumour suppressor genes and maintenance of an undifferentiated cellular phenotype. On the other hand, TOPOISOMERASE are the enzymes that modulate topological state of DNA with on-going vital processes like replication, transcription, and chromosomal segregation.[10] Inhibiters of both topoisomerase- 1 and topoisomerase- 2 are the agents which breaks the DNA strand and stalling the replication fork which results in cytotoxic activity. Within this hybrid molecule we will study the drug prepared from hydroxamic acid pharmacophpres (vorinostat, a HDAC inhibitor) and a camptothecin analogue (topoisomerase -1 inhibitor) which showed potent anti-cancer activity, reduced drug resistance, and improved pharmacokinetic profile in pre-clinical model.

2. DACA-Vorinostat Hybrid Drug:



Fig(C): Structure Of Daca-Vorinostat Hybrid Drug.

This hybrid involves two moieties i.e. a DACA (N-[2-(dimethyl amino) ethyl] acridine-4-carboxomide) which a DNA intercalating cytotoxic agent and vorinostat which is a histone deacetylase inhibitor gets us a new drug molecule which has genotoxic and epigenetic variability in cancer cells.[11] DACA is a topoisomerase-2 inhibitor which when bind to DNA disrupts replication and transcription of DNA. And thereby breaking the double strand of DNA leading to apoptotic cell death.It allows to target on hypoxic tumour cells that overcome few form of drug resistance linked with classical chemotherapeutics. When vorinostat and DACA is administered through hybrid mode, increment in therapeutic action and potency is observed. It offers a prolonged effect on cancer cell.

Table -2: IC50 values for different receptors.

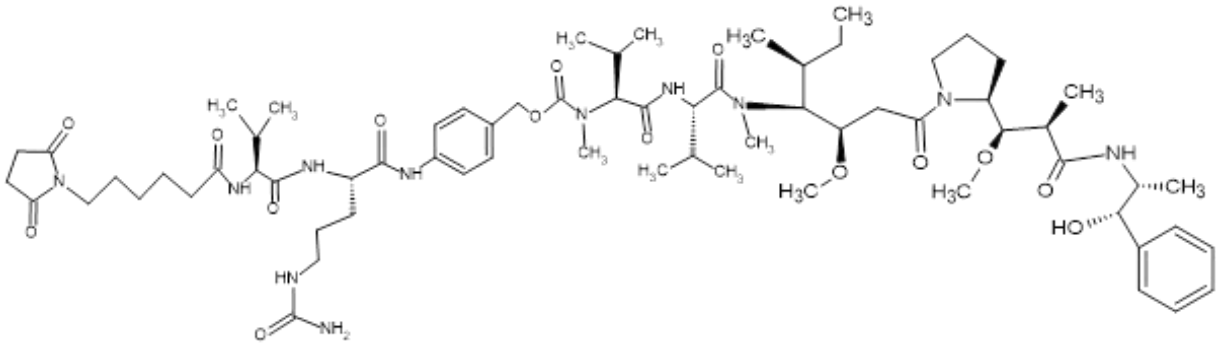
Receptor	IC50 Values
HDAC-1	16.6nm
HDAC-6	2.2nm
DU-145	0.16µm
PC-3	0.31µm

Some features of this hybrid molecule:

- Enhanced DNA damage: vorinostat facilitates the intercalation of DACA into DNA as it relaxes the chromatin structure that increases the damage on tumour cells.
- Epigenetic sensitization: vorinostat sensitises tumour cells to DACA induced DNA damage by down-regulating and promoting repair mechanisms and proapoptotic pathways respectively.
- Overcoming resistance: Carcinogenic cells with DNA repair pathways and epigenetically silenced apoptosis are more vulnerable to this assault.

3. Telisotuzumab Vedotin Hybrid

Brand name – Emrelis, Teliso-V



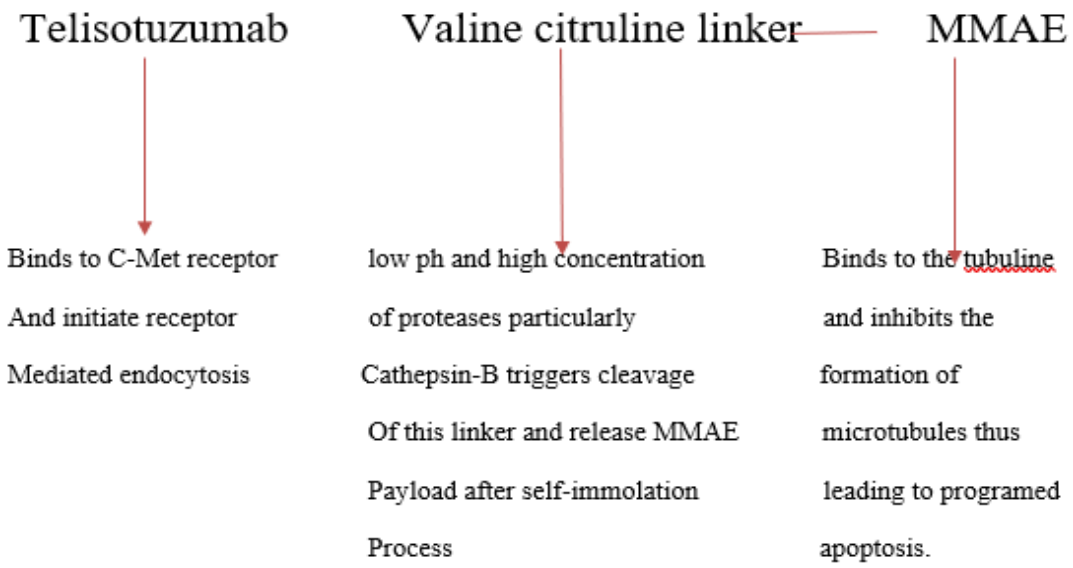
Fig(D): Structure of Telisotuzumab-Vedotin Hybrid Drug.

This drug belongs to the class of antibody – drug conjugate (ADC) [ADC is a specialized cancer therapeutic strategy that combines a highly targeted monoclonal antibody with a potent cytotoxic payload (chemotherapy drug) via a stable linker and eventually acts as "smart bombs"].[11]

Three core pharmacophores which are fused to form this hybrid drug are as follows:

- Targeting Pharmacophores: Telisotuzumab is a humanized monoclonal antibody designed to recognize and bind to the C-Met receptor protein, which is often over expressed on the surface of various cancer cells [C-Met receptors are cell surface protein when bound to its ligand "hepatocyte growth factor "(HGF) normally promotes cell growth, migration and wound healing. [13] Where as during cancer, aberrant HGF / C-Met signaling contributes to tumor development allowing cancer cell to proliferate, invade surrounding tissue and spread to distant organs].
- Cytotoxic pharmacophore: Mono-methyl auristatin E (MMAE) is a potent synthetic anti-microtubule agent that disrupts cell division and induces apoptosis.
- Linker pharmacophore:_Valine-citrulline (VC) peptide linker is protease -cleavable linker connects the MMAE-payload to the Telisotuzumab antibody.[14] The linker is designed to be stable in blood stream (to avoid premature release of MMAE) but is selectively cleaved by enzymes inside the cancer cell after the ADC is internalized releasing the cytotoxic MMAE payload.

Here's a stepwise breakdown of what happens to the hybrid drug once it is administer in the body:



- The entire intact antibody-drug conjugate first binds to the C-Met receptor on surface of cancer cell triggering receptor mediated endocytosis, entire complex (antibody, linker and MMAE payload) is brought inside the cell and it is enveloped in an endosome.

- Endosome then matures and transports the ADC to the lysosomes

(Cell recycling center). In lysosomes, the antibody part of the ADC is degraded by powerful hydrolytic enzyme [This enzymatic degradation marks the end of telisotuzumab as a therapeutic agent].

- Along with this process, simultaneously at low ph in lysosome and high concentration of protease particularly cathepsin B triggers cleavage of linker by recognizing dipeptide segment.

- This enzymatic cut triggers the spontaneous intramolecular reaction in para-amino carbamate (PABC) space. This "self-immolation" or '1-6 eliminators' causes PABC part of the linker to fragment. This fragmentation of PABC spacer releases the active MMAE drug molecule in its unmodified highly potent form.

- Thereafter PABC itself breaks down releasing CO2 and a non-toxic Quinone methide. Remaining fragments including valine, citruline, and PABC derivatives are small and simple molecules which get cleared like other cellular waste easily from the body.

- Once the linker is cleaved, it releases the active MMAE drug directly into the cell's cytoplasm.[15] MMAE (anti-mitotic agent) diffuse through the cytoplasm and binds to tubulin [protein that forms microtubule] leading to blockage of polymeriasation[assembling tubulin proteins into microtubule] which eventually leads to disruption of existing microtubule network and inhibition of formation of new microtubules. (Microtubules are essential for forming mitotic spindle, structure that separates chromosomes during cell division).

- Disruption of mitotic spindle activates a "spindle assembly checkpoint" which triggers a cell cycle arrest at G2/M phase. This prolonged arrest ultimately leads to the prolonged death of the cancer cells.

- Thereafter this MMAE released into surrounding fluid, a portion of it may diffuse into adjacent cell contributing to "Bystander effect". Due to small and lipophilic structure it diffuses into extracellular fluid and blood which is taken up by live and broken down into various metabolites mediated by CYP3A4/5n enzyme pathway. The processed metabolites are secreted from the lover to the bile. The bile containing drug and its by-products travels to intestine and is ultimately excreted from the body in form of faeces.

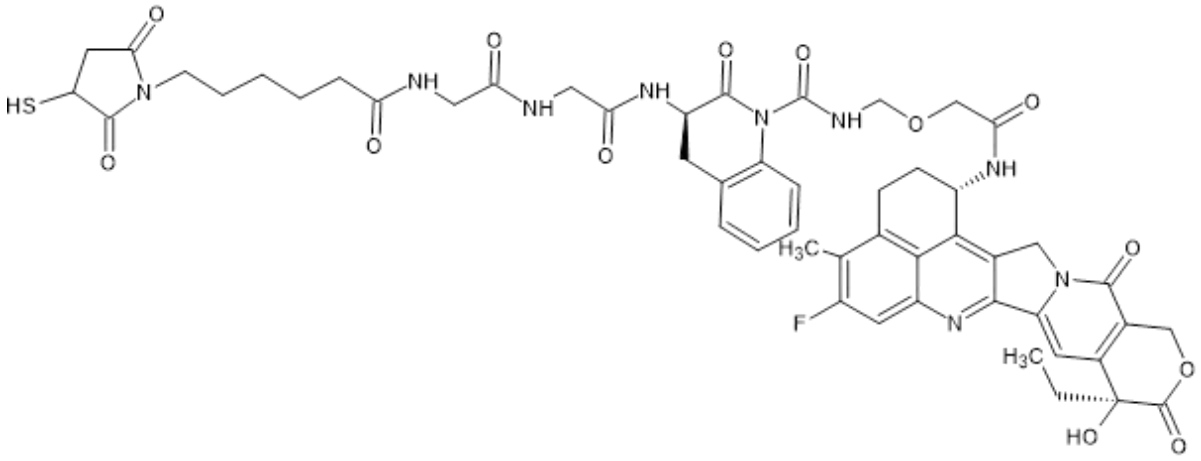
Merits:

1. **Highly specific targeting.**
2. **Potent payload.**
3. **High c-met overexpression:** the drug is approved for patients with NSCLC that has high c-met protein overexpression. (more than or 50% of tumor cells with strong stain)
4. **Reduced systemic toxicity:** specific valine-citruline linker is used which is stable in blood stream to avoid premature release of MMAE and reduce the risk of systemic toxicity.

Addresses resistance: it is a promising option for patients with EGFR mutated NSCLC who has developed resistance to targeted therapies, especially when used in combination with other drugs like osimertinin. This drug is given through IV infusion over a short period and repeated over 14 days. It has shorter half-life (4-5 days) hence it is given once in 2 weeks. It was approved on 14th may 2025 by FD.

4. Transtuzumab Deruxtecan Hybrid

Brand name: Enhertu



Fig(E): Structure of Transtuzumab-Deruxtecan Hybrid Drug.

This advanced hybrid drug got approval by U.S. in January 2025 for HR positive/ HER2-negative type of breast cancer. It operates through its unique antibody-drug conjugate (ADC) mechanism, which allows it to deliver a potent chemotherapy payload directly into cancer cells that have even minimal HER2 expression.

[HR positive: A hormone-receptor-positive tumor is a tumor which consists of cells that express receptors for certain hormones. The term most commonly refers to estrogen receptor positive tumors, but can also include progesterone receptor positive tumors.]

[HER2- receptor: Human epidermal growth factor receptor 2 ia a protein that plays a key role in regulating cell growth and survival.when a cancer cell is HER2- positive, it means that cancer cell produce high levels of this Protein. Overexpression of HER2 can drive aggressive tumor growth and proliferation] Historically, tumours with very low HER2 expression were classified as HER2-negative and were not candidates for HER2 targeted therapies. This changed when research revealed that even small amounts of HER2 on the cell surface could be used as a Target for Antibody-drug conjugate's (ADCs). Enhertu's design is specifically suited for this task. Its step-wise process in the body is precisely engineered to maximize tumor cell death while minimizing harm to healthy tissue. The process occurs in a sequence of steps: drug administration, systemic circulation, targeted binding, intracellular uptake, linker cleavage, payload release, and cell death.

1. Administration:

Trastuzumab deruxtecan is administered into the bloodstream via intravenous (IV) infusion, typically over a period of 30 to 90 minutes.

2. Systematic circulation: Once in the bloodstream, the ADC remains largely intact, thanks to its stable, cleavable tetrapeptide-based linker. The linker ensures the potent chemotherapy payload, deruxtecan, stays attached to the trastuzumab antibody, preventing it from damaging healthy cells in the systemic circulation.

3. Target binding:

The trastuzumab antibody component acts as a "homing device," traveling through the bloodstream to seek out cancer cells with HER2 receptors on their surface. The antibody binds specifically to these receptors, distinguishing them from most healthy cells, which express significantly lower levels of HER2.

4. Intracellular uptake:

After binding to the HER2 receptor, the cancer cell internalizes the entire ADC complex through a process called endocytosis, pulling the drug inside the cell.

5. Linker cleavage and payload release:

Once inside the cancer cell's lysosomes, the tetrapeptide linker is broken down by specific enzymes known as cathepsins. These enzymes are overexpressed within the tumour environment and trigger the cleavage of the linker, releasing the active chemotherapy payload, deruxtecan (DXd).

6. Payload action and cell death:

Direct cytotoxic effect: The released deruxtecan payload inhibits DNA topoisomerase I, an enzyme essential for DNA replication. By blocking this enzyme, deruxtecan causes DNA damage, leading to cell cycle arrest and programmed cell death (apoptosis) in the targeted cancer cell.

Bystander effect: A unique feature of deruxtecan is its high membrane permeability. After it is released, it can diffuse out of the HER2-positive cancer cell and enter neighboring cancer cells, even those with low or no HER2 expression. This bystander effect kills adjacent cancer cells, addressing tumor heterogeneity and potentially increasing the overall effectiveness of the treatment.

7. Metabolism and Excretion

Antibody metabolism: The trastuzumab antibody component is catabolized into small peptides and amino acids within the cells, similar to the metabolism of natural immunoglobulin G (IgG).

Payload excretion: The deruxtecan payload is cleared from the systemic circulation, mainly through the bile and ultimately eliminated from the body via fecal excretion. Preclinical studies show the payload is rapidly cleared from the circulation, minimizing off-target toxicity.

Other information:

Standard dose: 5.4 mg/kg IV q3W (breast, HER2-low, NSCLC, other solid tumors)
1st infusion: ~90 min
Subsequent (if well tolerated): ~30 min
Dose reductions (avoid further escalation): 5.4 mg/kg (first week) → 4.4 mg/kg (second week) → 3.2 mg/kg (third week).

Hybrid Drugs for Malaria

Introduction

Malaria is a widespread disease that increases day by day due to poor hygiene conditions. It is caused by female anopheles mosquito and undergoes into 2 distinct phases, i.e.

1. In human
2. In mosquito

There is a wide pathology for malaria which shows how recurrent fevers come and cold, shiver, body pain happens. Many antibiotics are prescribed for malaria and various therapies are applied to eradicate it but the main problem arise is the drug resistance, malarial parasite becomes resistant to antibiotics and we need newer antibiotic every time. Hence hybrid drugs are used here to overcome this problem of resistance. Till now we were using chloroquine as a prominent drug for malaria but due to resistance we had to shift on artemisinin therapies which include two or more drugs to be used in combination in order to overcome

resistance problem. To produce or to make a new drugs costs more as compare to costing require to produce a new hybrid drug as it have many advantages over single entity like low drug-drug interaction, good bioavailability, targeted delivery, and many more.[16,17]

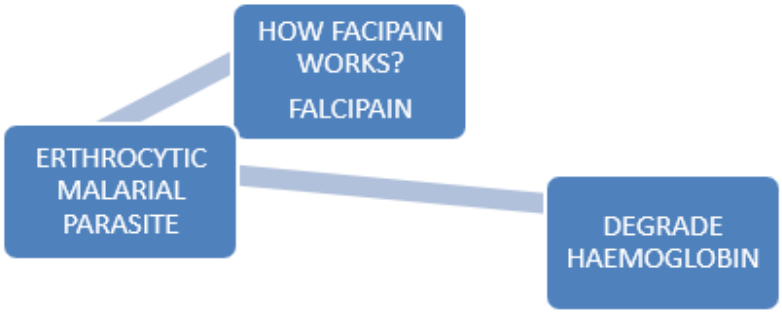
As every coin has two sides, hybrid drug too follow this, it also have some limitations like:

- Complexity for design and synthesis
- Pharmacokinetic profiles
- Pharmacodynamics profiles
- Costs associated for more complex drugs

Though hybrid drugs are prepared from natural, semisynthetic, and synthetic ways, the most prominent is the synthetic pathway. It is because natural and semisynthetic pathways require active medicinal compound which is totally of natural origin and excessive usage of natural products could consume any individual specie of plant.[17,18] There were many scientists who contributed in this field to get newer and potent hybrid medicines with the help of Artemisinins, chloroquine and other compounds.[16] We shall be discussing about the parent moieties, their hybrid drugs and related factors.

Hybrid Drugs:

1. Olson ET. Al. 1999, in his studies showed and proved that falcipains are required by p.falciparum. This falcipain is a compound of papain family which has cysteine proteases helpful for parasite development.[18]



In order to block this degradation process, compounds like fluoromethyl ketones or vinyl sulfones are added with artemisinins to make a hybrid drug molecule which stops this process. So the compound formed is called Artemesinin-Dipeptidyl Vinyl Sulfone Hybrid. This compound eventually inhibits chloroquine resistant p. falciparum in range of Ic50 value2-5nm active more than artimisinin and equally potent with artelinic acid.[18] Fig (F).

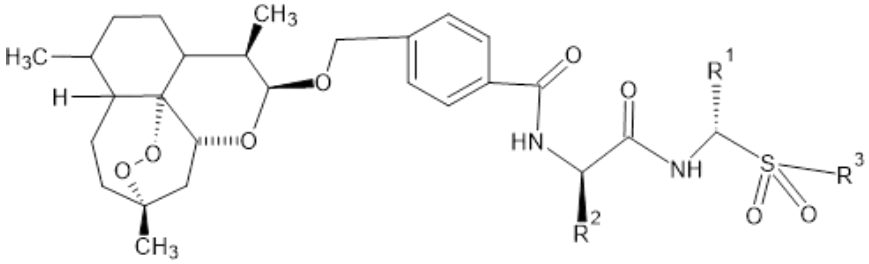
Mechanism of artemisinin: The growth of malarial parasite depends upon amino acids which are obtained from haemoglobin; they consume haemoglobin which releases heme (iron containing molecule), a toxic by-product that gets neutralise into hemozoin by parasite itself. The drug artemisinin has a unique endoperoxide bridge crucial for its action. Interaction of iron from heme with the endoperoxide bridge breaks down and produce highly reactive free radicals like carbon centred or reactive oxygen species.[18] These carbon centred free radicals effectively target essential parasite components like proteins and lipids. It disrupts the normal functioning and life cycle of malarial parasite leading to death.

Mechanism of vinyl sulfones: The drug has carbon-carbon double bond which is electron deficient due to strong electron withdrawing effect of sulfones group. This makes it a potent electrophile readily reacts with nucleophiles with thiol group of cysteine residues found in active site of enzyme. This forms conjugate addition or binds vinyl sulfones with target proteins cysteine residue and this binding permanently modifies the enzyme leading to inactivation. When combine with artemisinin, they inhibit falcipains (responsible to break haemoglobin) vinyl sulfones prevent haemoglobin degradation that leads to build up of undigested haemoglobin and kills the parasite.[18,19]

Linker used: Dipeptidyl. It is a 4-hydroxymethyl benzoic acid moiety. It adjoins vinyl sulfones with Endoperoxide Bridge.

Table-3: Attachment of different alkyl groups on different hybrid molecules.

Compound	R1	R2	R3
4a	CH_2Ph	H	Ph
4e	$CH2CH_2PH$	CH_2PH	Me
4f	$CH2CH_2PH$	CH_2CHMe_2	Me



Fig(F): Structure of Artemesinin Dipeptidyl Vinyl Sulfone Hybrid Drug.

2. Artemisinin- Quinazoline Hybrid Drug:

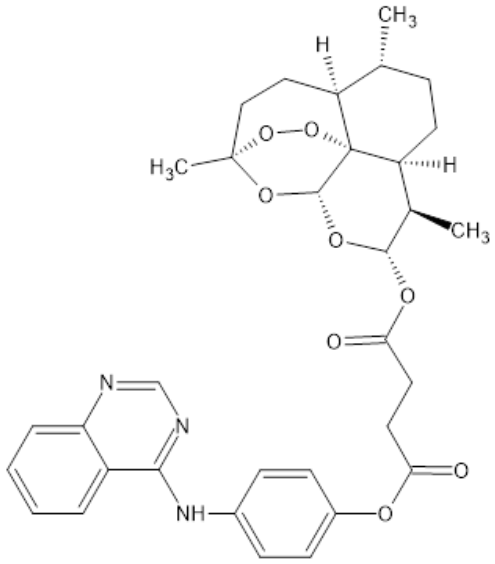
There are many different strains of p. falciparum which is evaluated in laboratory, one of which is 3D7 (CQs). Hence the need for this hybrid become necessity, thereby Tsogoeva et.al. In 2017 evaluated this hybrid molecules to use against 3D7 strain.[21] He used 2 parent moiety i.e., quinazoline derivative and artesunic acid which got him six different hybrid molecules. After evaluating this hybrid drugs, in experiments he concluded that the EC50 value for hybrid (G) was 3.8nm while EC50 value of hybrid (H) was 1.4nm. While the EC50 value of Dihydroartemisinin (DHA) is 2.4nm. Hence, he proved that this hybrid molecule showed more efficient antimalarial activity compared to DHA.[21]

Mechanism of artemisinin: The growth of malarial parasite depends upon amino acids which are obtained from haemoglobin; they consume haemoglobin which releases heme (iron containing molecule), a toxic by-product that gets neutralise into hemozoin by parasite itself. The drug artemisinin has a unique endoperoxide bridge crucial for its action.[18] Interaction of iron from heme with the endoperoxide bridge breaks down and produce highly reactive free radicals like carbon centred or reactive oxygen species. These carbon centred free radicals effectively target essential parasite components like proteins and lipids. It disrupts the normal functioning and life cycle of malarial parasite leading to death.[22]

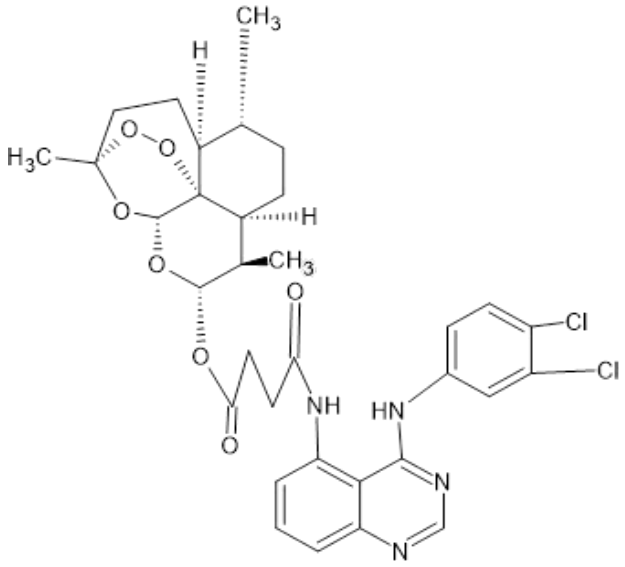
Mechanism of quinazoline: Quinazoline drugs (geftinib, erlotinib) are referred to as ATP mimetic. Their structure basically their quinazoline core and its substitutions are deigned to mimic chemical properties and shape of ATP allowing drugs to bind on ATP binding sites of protein kinases. Hence they block the attachment of actual ATP from binding to receptor and thereby preventing the enzymes function.[21] When combined with artemisinin, they inhibit the parasites life cycle enzyme which is protein kinases (PfPK7) and even eukaryotic translation initiation factor hence it affect the maturation and metabolism of parasite.

Linker used: 4 different types of linker can be used totally depending on type of synthesis it follows. The linkers can be:

a. Ester
b. Ether
c. Amide
d. Chiral



Fig(G): Structure Of Artemesinin Quinazoline Hybrid-1



Fig(H): Structure Of Artemesinin Quinazoline Hybrid Drug-2

2. Chloroquine- astemizole hybrid drug:

Whitlock in 2009 synthesised this molecule by adjoining chloroquine and astemizole with a core linker which showed beneficial anti-plasmodial activity.[24,25] Three different hybrid molecules were prepared by joining both parent moieties.[24,25] Showed more potency as compare to chloroquine but when tested in-vivo for p.berghei strain of malaria was, we observed the activity was lower compared to chloroquine. They had IC50 values like:

Fig (I)-23nm
Fig (J)-64nm
Fig (K)-37nm

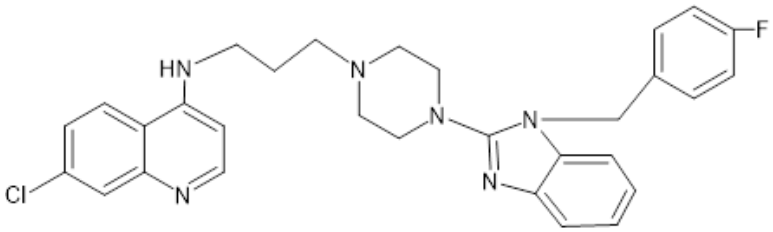
When both (J) and (K) given through i.p route at a dose of 4 × 50mg/kg and 4 ×20 mg/kg, he observed reduction in parasitaemia. Moreover, at high doses, reduction in parasitaemia was observed in 13 animals compared to chloroquine upto 99%, whereas 3 animals showed 80% reduction in 8 days.[23]

Mechanism of chloroquine (CQ): Parasite gets its nutrition by digesting haemoglobin in their acidic food vacuole. The breakdown of haemoglobin releases toxic by-product heme or ferriprotoporphyrin IX. This free heme is so toxic to parasite as it can damage the cell membranes.[23,25] To overcome it, parasite has a unique detoxification pathway which

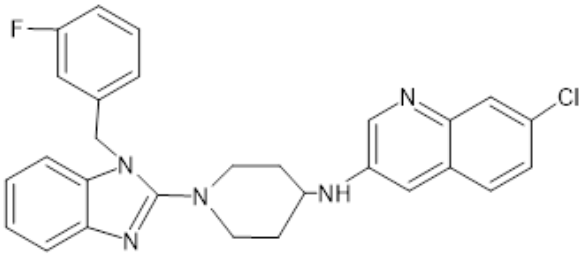
polymerises heme monomers into an inert, insoluble crystalline pigment hemozoin important for parasites survival. CQ enters the RBC then diffuses into acidic ph of food vacuole, it gets protonated there with positive charge that is unable to diffuse back out of vacuole causing to accumulate at high concentrations hence exploits ph gradient. It acts as powerful inhibitor of heme polymerisation as it forms a toxic complex with free heme preventing heme from being polymerised to hemozoin.[24] As a result, unpolymerised heme accumulates inside food vacuole and shows lethal effects like disruption of cell membrane, oxidative stresses, inhibition of parasite enzymes and parasite gets killed.[23]

Mechanism of astemizole: When body encounters an allergen, histamine, a chemical messenger is released from immune system. It binds and activates H1 receptor in various tissues throughout the body. This causes symptoms like sneezing, itching, swelling, redness. Astemizole reversibly and competitively binds to same H1 receptor that histamine would have binded. As no histamine has bind, it supresses allergic response.[23]

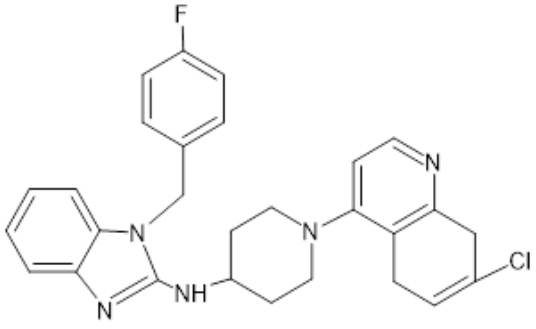
Linker used: a piperazine or an aminopiperidine linker.



Fig(I): Structure Of Chloroquine Astemizole Hybrid Drug-1



Fig(J): Structure of Chloroquine Astemizole Hybrid Drug-2



Fig(K): Structure of Chloroquine Astemizole Hybrid Drug-3

4. Chloroquine- thiazolidinone hybrid drug:

Kouznetsov et.al. in 2011 combined two different moiety which are thiazolidinone with benzylamine at c4 position. Six different hybrid molecules were obtained that were:

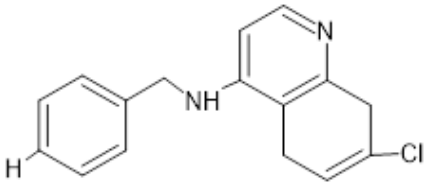
Fig (L), (M), (N), (O), (P), (Q)

They were effective against chloroquine (IC50= 0.5 µm) and IC50 values of molecules (L, M, N, P) ranging from 0.30µm-0.44µm.[27] Compound (O) have IC50 of 0.38µm were that of (Q) was 0.54µm. Both block the β-haematin by FPIX (ferriprotoporphyrin) biocrystallization inhibition. They showed low toxicity in 3774 murine macrophages and HepG2 cells (hepatocellular carcinoma cells). When in-vivo studies were performed, it was found that at 10 mg/kg/day (P), (Q) showed reduce parasitaemia by 80% and 100% while (L) showed only 25%. And (Q) showed better lipophilicity, absorption, distribution.[26]

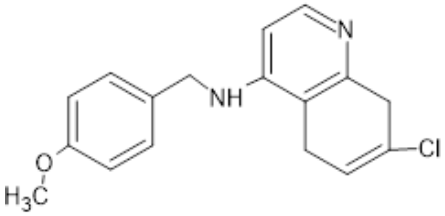
Mechanism of chloroquine: Parasite gets its nutrition by digesting haemoglobin in their acidic food vacuole. The breakdown of haemoglobin releases toxic by-product heme or ferriprotoporphyrin IX. This free heme is so toxic to parasite as it can damage the cell membranes.[23,25] To overcome it, parasite has a unique detoxification pathway which polymerises heme monomers into an inert, insoluble crystalline pigment hemozoin important for parasites survival. CQ enters the RBC then diffuses into acidic ph of food vacuole, it gets protonated there with positive charge that is unable to diffuse back out of vacuole causing to accumulate at high concentrations hence exploits ph gradient. It acts as powerful inhibitor of heme polymerisation as it forms a toxic complex with free heme preventing heme from being polymerised to hemozoin.[24] As a result, unpolymerised heme accumulates inside food vacuole and shows lethal effects like disruption of cell membrane, oxidative stresses, inhibition of parasite enzymes and parasite gets killed.[23]

Mechanism of Thiazolidinone: PPARγ is peroxisome proliferator activated receptor gamma is used for gene expression responsible for various functions like energy metabolism, cell differentiation. Thiazolidinone acts as agonist of PPARγ, when it gets activated with retinoid X receptor (RXR) gets binds to DNA that controls transcription of genes. This increases insulin sensitivity by promoting adipocyte differentiation into smaller, more insulin-sensitive cells.it also affects glucose and lipid metabolism, reduces fatty acid and improve insulin action. When combined with chloroquine, they inhibit the key metabolic pathway that is isoprenoid biosynthesis within apicoplast, here parasite is not killed instead it completes current life cycle and replicate but new daughter cells emerge from infected RBC are viable.[27]

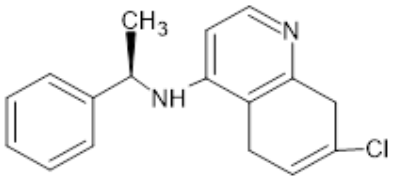
Linker used: aminoalkyl chains or amide bonds.



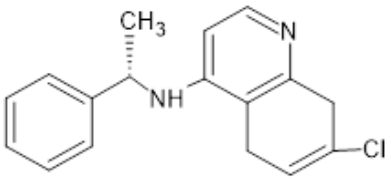
Fig(L): Structure Of Chloroquine Thiazolidinone Hybrid Drug-1



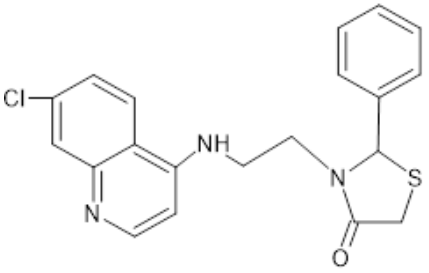
Fig(M): Structure of Chloroquine Thiazolidinone Hybrid Drug-2



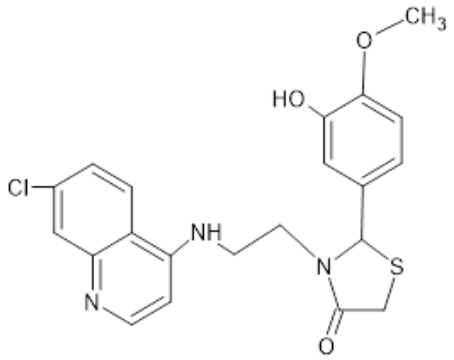
Fig(N): Structure Of Chloroquine Thiazolidinone Hybrid Drug-3



Fig(O): Structure Of Chloroquine Thiazolidinone Hybrid Drug-4



Fig(P): Structure Of Chloroquine Thiazolidinone Hybrid Drug-5



Fig(Q): Structure of Chloroquine Thiazolidinone Hybrid Drug-6

5. Ciprofloxacin Based Molecule:

Mukhopadhyay et.al. In 2020 synthesised a new hybrid molecule by parent moiety, ciprofloxacin. He prepared hybrids of acridine, quinolone, sulfonamaide, and cinnamoyl moieties. He used ciprofloxacin and chloroquine in-vitro against strains:

1. $CQ^{S}Pf3D7$
2. $CQ^{R}PfW2$

Out of all molecules, two molecules showed prominent activity against Pf strains that were Fig (R) AND Fig (S) and showed 2×10^{-2} and 7×10^{-2} fold more antimalarial activity when compared to ciprofloxacin.[29] Both drugs have greater potency in different life cycle of malaria as shown below in table:

Table-4: IC50 values of different strains of 2 different hybrid compounds.

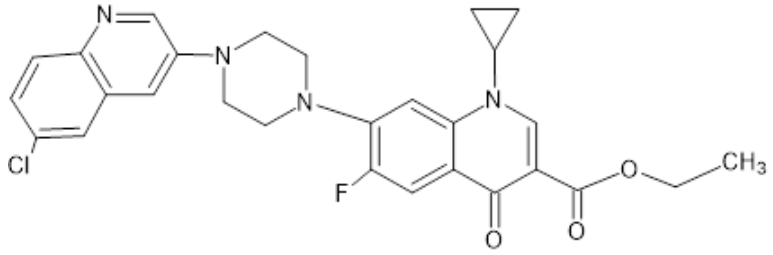
Life-Cycle	Compound	Strain	IC50
First Life-Cycle	R	3D7	25.52nm
		W2	63.17nm
		3D7	37.63nm
		W2	146.2nm
Second life-cycle	S	3D7	13.52nm
		W2	30.64nm
		3D7	14.83nm
		W2	37.63nm

Later cytotoxity of chloroquine-ciprofloxacin is performed against mammalian fibroblast NIH3T3 by MIT assay using concentration range from 0.31230-20µm. And the results proved that this hybrid molecule in not cytotoxic upto range of 10µm and showed no haemolysis of RBC at highest concentration, i.e. 10µm-45µm which is more effective in schizont stage of malarial life cycle.

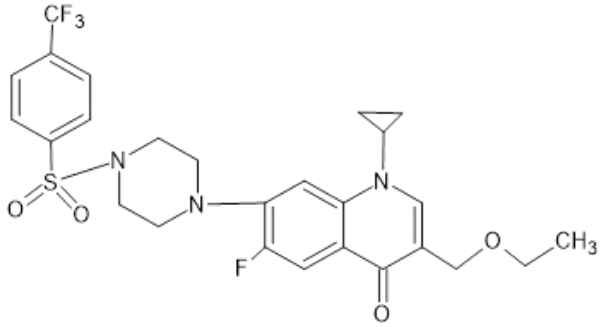
Mechanism of chloroquine: Parasite gets its nutrition by digesting haemoglobin in their acidic food vacuole. The breakdown of haemoglobin releases toxic by-product heme or ferriprotoporphyrin IX. This free heme is so toxic to parasite as it can damage the cell membranes[23,25]. To overcome it, parasite has a unique detoxification pathway which polymerises heme monomers into an inert, insoluble crystalline pigment hemozoin important for parasites survival. CQ enters the RBC then diffuses into acidic ph of food vacuole, it gets protonated there with positive charge that is unable to diffuse back out of vacuole causing to accumulate at high concentrations hence exploits ph gradient. It acts as powerful inhibitor of heme polymerisation as it forms a toxic complex with free heme preventing heme from being polymerised to hemozoin.[27] As a result, unpolymerised heme accumulates inside food vacuole and shows lethal effects like disruption of cell membrane, oxidative stresses, inhibition of parasite enzymes and parasite gets killed.[23]

Mechanism of ciprofloxacin: The drug directly targets bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Both are required for managing supercoiled DNA structure and separates replicated DNA strands during bacterial cell division. Ciprofloxacin inhibits these enzymes disrupting normal DNA synthesised repair leading to cell death. It binds with higher affinity with DNA gyrase than to mammalian cell which makes it selective antibacterial agent.[28]

Linker used: secondary amine of piperazine moiety at c-7 position of ciprofloxacin corresponding to chloroquine.



Fig(R): Structure Of Chloroquine Ciprofloxacin Hybrid Drug-1



Fig(S): Structure Of Chloroquine Ciprofloxacin Hybrid Drug-2.

Table-5: The side-effects of moiety along with the reduced effects which are observed in hybrid molecule.

Sr No.	Feature	Con-Ventional Drug	Hybrid Drug
1	GI ISSUE: Vomiting, nausea, stomach upset.	Yes	Reduced
2	Toxicity of: Neurology, renal, blood, cardiology.	Long term	Reduce to short term for cardiology and retinology.
3	Haematological: Neutropenia, thrombocytopenia, anaemia	Causes anaemia and blood toxicity.	Reduced the side effects
4	Hepatic: Liver stress.	Increased	Reduced
5	Allergic conditions: Skin allergy and rashes, corrosive and irritant effects.	It is positively seen.	Reduced rashes and irritancy
6	Cardiovascular: Prolongation of QT interval (increases irregular heartbeats)	Positively observed	Reduced
7	Ocular: Retinopathy, Keratopathy, Blurred vision, Diplopia.	Observed	Reduce all symptoms of ocular
8	Targeted toxicity	Yes	Mitigate targeted toxicity
9	Body changes: Fluid retention, Weight gain, bone fracture.	Obvious symptoms of thiazolidinone.	Reduced all drug symptoms

Hybrid Drugs for Cardiovascular Diseases

Cardiovascular Diseases is one of the primary causes of deaths globally accountable for over 17.9 million deaths per annum. CVS diseases have broad spectrum of disorders that includes cardiac heart failure (CHF), coronary artery disease, cerebrovascular disease (e.g. stroke), peripheral arterial disease, vasodilation, deep vein thrombosis and pulmonary embolism. Cardiovascular disease drug therapy falls under broad spectrum of drug classes inclusive of antihypertensives, antiaginal agents, antiarrhythmics, anticoagulant agents, antiplatelet agents, diuretics, vasodilators, lipid-lowering agents (e.g. statins), inotropic agents. Even having wide drug therapy drugs, it faces many hurdles in treatment and eventually death rate due to CVS diseases growing vigorously. Many classes of drugs can't be administered due drug interactions and adverse drug reactions. CVS disease drugs work on multiple mechanism of action depending upon the condition. There are many receptors involve in pathophysiology of disease and therefore require drug which can act upon all the sites simultaneously while producing minimal side effects or adverse effects. Tackling this problem of drug therapy 'hybrid drug molecules' are introduced and taking over the interest of many researchers and pharmaceutical companies to develop hybrid drug molecules. Hybrized drug molecules work on two or more site simultaneously increasing efficacy of the drug and minimizing adverse drug reactions or side effects. Two pharmacophores are attached with linker/spacer and give synergic effect.

Hybrid Drug Molecules

Around the globe, various pharmaceutical companies and scientists are researching over numerous hybrid drug molecules working on multiple diseases. There are many drugs already existing in the market are combined with each other resulting in new entity of hybridized drug molecules. As to overcome hurdles in disease having complex pathway for treatment multiple target drug comes to in picture.

Here a short list of hybrid drug classes:

1. Anti-oxidants hybrids
2. Adrenergic Receptor Blockers
3. Calcium Channel Blockers
4. Anti- Adipogenic hybrids

There are various drugs falls under above mention classes.

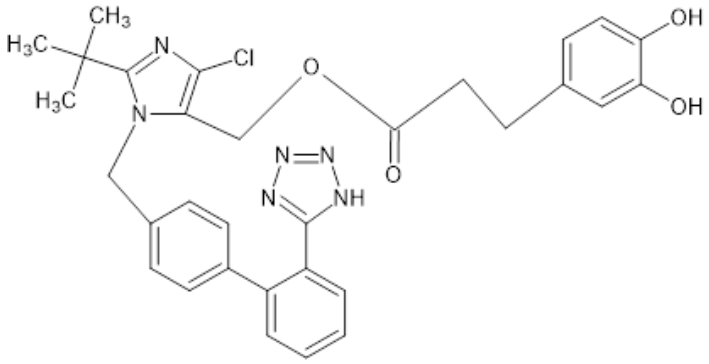
1. Anti-oxidants Hybrids

Losartan is infamous inhibitor of AT1 angiotensin II receptor used in hypertension. Garcia *et al.*[38] discovered a series of antioxidant-sartan hybrids by adding polyphenolic compounds to the hydroxymethyl side chain of the Losartan. Fig(T). Drugs designed to simultaneously targeting oxidative stress and angiotensin II to prevent possible damage to CVS. The studies of this hybrid showed the results that the administration of an antioxidant moiety to sartan had caused increase in antioxidative property while not affecting its basic potency. Antioxidant property to hypertensive drug showed good results as the potency of the hypertensive drug remains the same to control the hypertension but the antioxidant moiety assures the minimal damage to structural damage caused by hypertension preventing the possible damage. The positive results piqued the interest of scientists to improve the properties of these hybrids by incorporating different linkers between losartan and antioxidant moiety like ester, amide and amine linkers with their biological evaluation. The new hybrid drugs showed effective activity against angiotensin II receptor but not as potence as the losartan.

Mechanism of Losartan: It selectively blocks the Angiotensin II Type 1 (AT_1) receptor-a potent vasoconstrictor.

Mechanism of polyphenolic compounds: Polyphenols donate hydrogen atoms from their hydroxyl groups to neutralize reactive oxygen species (ROS) like •OH, $•O_2^-$, and H_2O_2.

Linkers: The commonly used linkers for this category of drugs are ester, amine and amide groups.



Fig(T): Structure of Polyphenolic-Losartan Hybrid Drug.

2. Hybrids acting as adrenergic receptor blockers

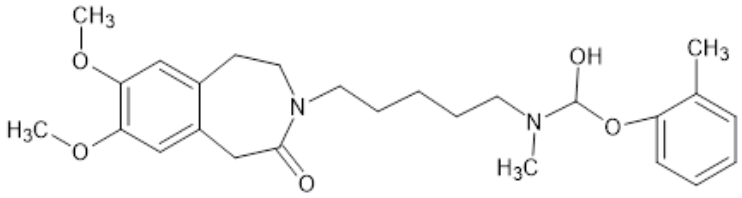
To lower heart rate without weakening the heart's contraction or causing low blood pressure, Zatebradine is used[39]. Zatebradine consists of benzazepinone ring, three carbon chains and its basic nitrogen atom who works as main feature of the drug and its terminal arylalkyl moiety allows the substitution that can affects its biological activity. Inspired from this structure, Bisi *et al.*[40] designed the hybrid molecules combining benzazepinone ring, three carbon chain, and basic nitrogen atom of Zatebradine with β-blocker aryloxy propanolamine group (Fig-U).

Mechanism of Zatebradine: Zatebradine inhibits the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which mediate the funny current (I_f) in the sinoatrial (SA) node. The I_f current is crucial for initiating spontaneous depolarization and regulating heart rate. By blocking this current, zatebradine slows the rate of diastolic depolarization, reducing heart rate without affecting myocardial contractility or conduction velocity.

Mechanism of aryloxy propanolamine: These compounds competitively inhibit β_1 and/or β_2 adrenergic receptors, preventing catecholamines (like epinephrine and norepinephrine) from binding. This leads to

(a)Reduced heart rate and contractility (β_1 blockade).
(b)Bronchoconstriction and vasodilation modulation (β_2 blockade)

Linkers: Alkyl chains are used to link this hybrid class.



Fig(U): Structure Of Zatebradine-Aryloxypropanolamine.

3. Hybrid Acting As Calcium Ion Channel Blockers

Christiaans *et al.*[44] Developed a series of hybrid molecules designed to maintain calcium channel blocking activity while introducing cardiotonic effects, aiming to address the negative inotropic action commonly linked with dihydropyridine (DHP) calcium-channel blockers. Their strategy involved combining a 1, 4-dihydropyridine moiety, known for its vasodilatory and negative inotropic effects, with cardio-tonic moiety. The in vitro assays measured calcium channel blocking activity and radioligand binding to dihydropyridine receptors. Among the synthesized compounds, those incorporating alkythiomethyl chains demonstrated superior performance, with the hexyl-linked hybrid molecule standing out(Fig-V). It showed strong calcium channel blocking activity (pIC_{50} = 6.54 μM) and moderate histamine H_2 agonism (pEC_{50} = 6.28 μM).

Additionally, it exhibited excellent receptor binding affinities, with KD values of 8.07 μM for calcium channel receptors and 5.93 μM for histamine H_2 receptors.

Mechanism of Dihydropyridine (DHP) derivatives: it binds to the α_1-subunit of the L-type calcium channel. They stabilize the inactivated state, reducing calcium influx during depolarization. This leads to:

- Vasodilation (↓ peripheral resistance)
- Reduced cardiac workload (↓ afterload)
- Anti-anginal and antihypertensive effects

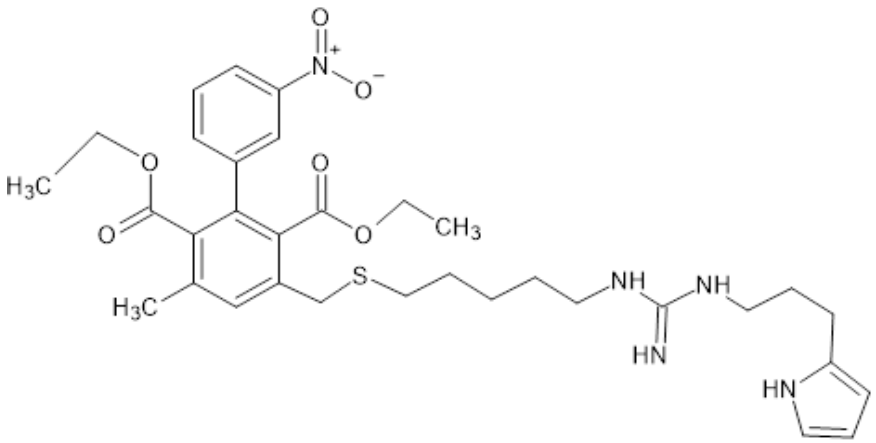
DHPs interact with the dihydropyridine receptor domain within the channel pore, often via hydrophobic and π–π interactions.

Mechanism of Cardiotonic moiety (Histamine H_2 Agonist): Agonism at H_2 receptors activates adenylyl cyclase via Gs protein which increases cAMP results in activation of protein kinase A (PKA). PKA phosphorylates L-type calcium channels and contractile proteins which leads to increase in intracellular Ca^{2+}, enhancing inotropy (contractile force).

Table-6: Mechanism and benefit of pharmacophores.

Component	Action	Synergy Benefit
CCB (DHP core)	↓ Ca^{2+} influx → vasodilation	Reduces afterload, lowers BP
H_2 agonist	↑ cAMP → ↑ Ca^{2+} → ↑ inotropy	Supports cardiac output
Alkythiomethyl	Enhances binding & permeability	Improves dual-target delivery

Linkers: DHP is linked to cardiotonic moiety by alkyl chains, alkythiomethyl, ether, amide, urea/carbamate, aromatic spacers or triazole ring.



Fig(V): Stucture Of Dihydropyridine derivative and Cardiotonic moiety Hybrid Drug.

4. Anti-Adipogenic Hybrids

Anti-adipogenic hybrid molecules represent a promising class of compounds designed to inhibit fat cell formation by combining two or more bioactive pharmacophores into a single chemical entity. These hybrids often exhibit enhanced potency, selectivity, and multi-target activity compared to their parent molecules (Fig-W).

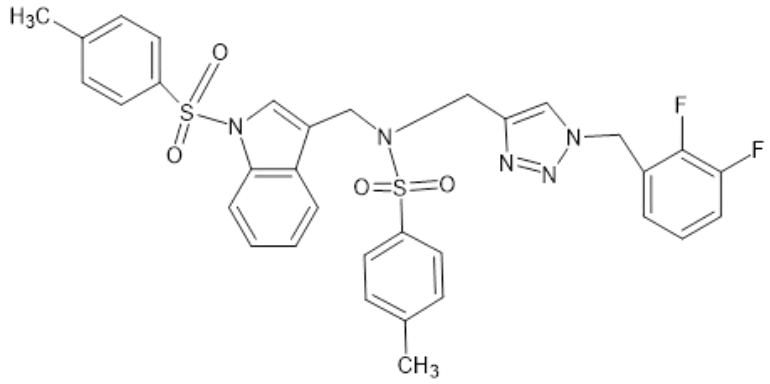
Recent advances in medicinal chemistry have enabled the rational design of hybrids such as indole–triazole, flavonoid–phenol, and azole–benzyl derivatives, which interfere with key adipogenic pathways including PPARγ, C/EBPα, and Wnt/β-catenin signalling. By targeting early stages of adipocyte differentiation and modulating lipid metabolism, these compounds not only suppress adipogenesis but also show potential in managing dyslipidaemia and insulin resistance. Rajang *et al.*[43] developed a novel

series of triazole clubbed indole hybrid molecules using click chemistry approach and evaluated them for anti-adipogenic activity in 3T3-L1 preadipocytes. Among the compounds evaluated, compound 37 demonstrated strong anti-adipogenic activity, with an IC_{50} of 1.67 μM, and was identified as the lead candidate. Compounds featuring a 3-substituted indole and a triazole ring bearing a 2, 3-difluorobenzyl group showed greater potency than those with other substitutions.

Mechanism of triazole: Triazole compounds can suppress the conversion of preadipocytes into mature adipocytes. This is often achieved by downregulating key transcription factors that are PPARγ (Peroxisome proliferator-activated receptor gamma) and C/EBPα (CCAAT/enhancer-binding protein alpha). These factors are master regulators of adipogenesis; their inhibition halts lipid accumulation and adipocyte maturation.

Mechanism of Insole: Some indole metabolites, like indole-3-acrylic acid (IA), stimulate STAT1 phosphorylation, which interferes with adipogenic gene expression. This leads to reduced lipid accumulation and adipocyte formation.

Linker: commonly used linkers are alkyl/alkylene, amide, ether, amino acid spacer or self-immolative linkers.



Fig(W): Structure Of Insole Triazole Hybrid Drug.

Anti-Fungal:

Fungal infections are life-threating diseases occurred now which could be either superficial or immunocompromised that kills nearly 1.5 billion individuals a year.[46] Azole class of drugs are the optimum selectivity of drugs as they have more safety profiles giving fungi static effect by inhibiting cytochromep450.[47] Fluconazole is the representative of the class which has various properties like:

- Broad anti-fungal spectra
- Low hepatotoxicity
- Good oral absorption
- High bioavailability
- Extensive tissue distribution

However the current widespread of fungus have led to resistance and newer drug discovery become essential. Candida is foremost and well known concerning specie of fungi as it causes systemic infection with 50% mortality rate. Hence, implementation of hybrid drug concept becomes necessary here.[47]

1. Coumarin-Thiazole Hybrids

Coumarin is a natural benzopyrone compound found in many plants such as Tonka beans, cinnamon, sweet clover and lavender.[48,50] Natural derivatives like umbelliferone exhibits mild to moderate antifungal activity whereas synthetic derivatives like halogenated or hybrid forms show enhanced potency and tailored selectivity (Fig-X).

It works by following mechanism:

1. Cell wall disruption
2. Membrane integrity interference
3. Induction of apoptosis via DNA fragmentation, mitochondrial membrane depolarization, cytochrome C release and activation of fungal metacaspases.

Table-7: Spectrum of activity.

Candida Albicans	Growth Inhibition and Apoptosis
Aspergillus Niger	Mic~16µg/Ml
Botrytis Cinerea	Potent Ec_{50} Values [< 15µg/Ml]

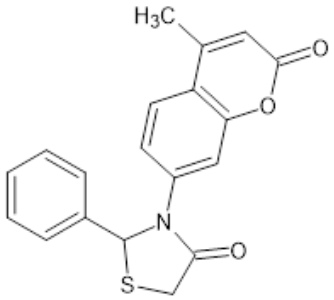
Limitations:

1. Some Coumarin [especially natural ones] may have low water solubility or bioavailability.
2. It may cause hepatotoxicity when high doses are taken.
3. Structural optimization is often necessary to improve pharmacological profiles.

Simultaneously triazole heterocyclic ring containing one sulphur and one nitrogen also possesses broad spectrum of antifungal activity against various pathogenic fungus including Candida species and Cryptococcus.

Mechanism Of Action: Thiazole compounds can disrupt fungal cell membranes and inhibit essential enzymes like lanosterol 14α- demthylase [CYP51] which is crucial for fungal growth. This multifunctional property often outperforms it from existing agents like fluconazole and ketoconazole.[49]

Limitations: Thiazole- based antifungal agents, while giving promising results, faces limitations such as drug efflux leading to reduced efficacy, risk of drug resistance development with prolonged use.



Fig(X): Hybrid Structure of Coumarin-Thiazole

Coumarin-thiazole hybrid shows activity against P.roquefortii and A. Niger. This hybrid exhibits activity against antifungal resistant strains.

Table-7: Effectiveness of hybrid strains over 2 different fungus.

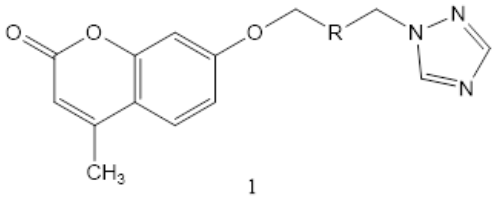
Compound	R	P. roquefortii	A. niger
Griseofluvin	-	2	17
1	3- OCH_3	20	13
2	4- OCH_3	17	11
3	4-F	9	13

Table-8: Comparison of hybrid drug on 2 different fungus.

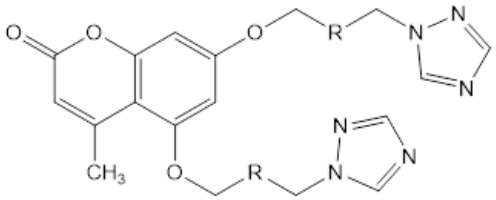
Property	P. roquefortii	A. niger
Synergistic mechanism of action	Combined action of multiple fungal targets -e, g. disrupting cell wall integrity and inducing oxidative stress.	Usually act via single mechanisms (e.g., apoptosis induction by Coumarin, CYP51 inhibition by thiazole)
Enhanced potency (lower MICs)	Hybrids often show greater antifungal potency at lower concentrations. E.g., some coumarin-thiazole compounds show >90% inhibition at 0.5 mg/mL	Moderate potency, often requiring higher doses or structural optimization.
Broader spectrum of Activity	Effective against a wider range of fungal species, including resistant strains (e.g., Candida, Fusarium, Rhizoctonia)	Narrower spectrum or strain-specific activity in some cases

Reduced Resistance Development	Multi-target action makes it harder for fungi to develop resistance, as multiple pathways are attacked simultaneously	Single-target agents are more susceptible to drug resistance mechanisms
Improved Pharmacokinetics (in some cases)	Hybrids can be designed to balance hydrophobicity and solubility, aiding in better absorption, distribution, or formulation	Natural coumarins and thiazoles often suffer from poor solubility or stability
Synergy with Existing Antifungals	Some hybrids show synergistic effects with standard drugs like amphotericin B or fluconazole, potentially lowering required doses	Synergy not always observed with individual agents, or not as strong

2. Coumarin- Triazole Hybrid Drug:



1



2

Compound	R	MIC (μ/ml)
Fluconazole	-	128
1	$-(CH_2)_2-$	8
1	$-(CH_2)_3-$	16
2	$-(CH_2)_2-$	2
2	$-(CH_2)_3-$	16

compound 1- Fig Y1
Compound 2- Fig Y2

Coumarin is poorly water-soluble drug but shows solubility in organic solvents. It can be prepared by Perkin reaction, pechmann condensation, and knoevenagel condensation. Moreover it is used as anti-coagulant, anti-cancer, anti-microbial. In silico docking and ADMET studies revealed favourable pharmacokinetics to these molecules to be better drug candidate.[48] Triazole is amphoteric in nature and hydrophilic. It is used as anti-fungal, anti-cancer, anti-viral, anti-hypertensive, and anti-parasitic.[49]

Mechanism of Coumarin: drug causes fungal cell to self-destruct through programmed cell death which involves harmful reactive oxygen species that damage the cell, disrupt mitochondria that kills the fungus. Some Coumarin also inhibits formation of ergostrol important for fungal cell membrane.[48]

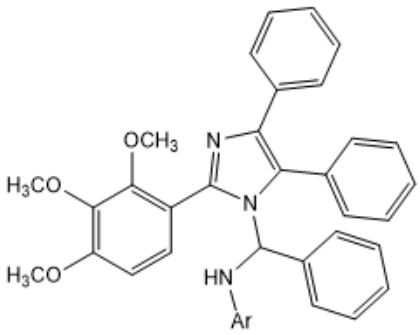
Mechanism of triazole: drug inhibits the enzyme lanosterol 14-α-demthylase essential for ergostrol synthesis leading to accumulation of toxic sterol precursors and deficiency of ergostrol, required for fungal cell membrane and fungal cell death occurs.[49]

Linker Used: Oxymethylene linker, alkyl linker, 1,2,3 triazole ring itself.

Table-9: The side-effects of moiety along with the reduced effects which are observed in hybrid molecule.

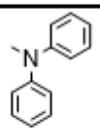
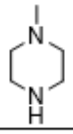
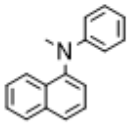
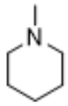
Sr no	Side effects	Parent moiety	Hybrid drug
1.	G.I. issue: Nausea, diarrhea,stomach-pain	Observed	Reduced
2.	Neurological: Headache, dizziness	Observed	Reduced
3.	Dermatologcal: Skin rash	Observed	Reduced
4.	Hepatotoxicity	Observed	Cured
5.	Cardiac: QT prolongation, CHF	Observed	Cured
6.	Skin necrosis	Observed	Reduced
7.	Steven-Johnson syndrome	Observed	Cured
8.	Blurred vision	Observed	Reduced
9.	Bleeding and haemorrhage	Observed	Reduced
10.	Purple toe syndrome	Observed	Cured

3. Triphenyl-Imidazole Hybrid



Fig(Z): Structure Of Triphenyl-Imidazole Hybrid Drug.

Table-10: Zone of inhibition for 2 different fungus.

Compound	Ar	A.niger	C.albicans
		Zone of inhibition (mm)	
1		27	28
2		27	28
3		24	20
4		26	29
Griseofulvin	-	36	39

Triphenyl-imidazole is broad spectrum of drugs acting as anti-fungal, anti-bacterial, and anti-inflammatory. Its basic mechanism of action is to act as anti-fungal by penetrating/ disrupting bacterial cell membrane giving bacteriocidal effect.[E] Triphenyl-imidazole is efficient against A. niger and C. albicans strains.[50] A. niger causes aspergillus, otomycosis (ear infection), cutaneous and wound infections, Black-mold contamination. C.albicans causes most common bacterial infections like oral thrush, Candidiasis (like cutaneous candidiasis, vaginal candidiasis, Esophageal candidiasis), Diaperrash.[People usually left the infection untreated infection]. And let it cure itself which may worsen usually left the infection untreated infection]. And let it cure itself which may worsen the infection.

Mechanism of action of this class of hybrid drugs has similar action as of the other imidazole derivatives. Triphenyl-imidazole disrupts cell membrane interfering with ergosterol biosynthesis causing leakage of cellular contents eventually leads to cell death of bacteria.[51]

Linkers used: Amide, triazole, ether, thio-ether, alkyl chain, urea.

Table-11: The side-effects of moiety along with the reduced effects which are observed in hybrid molecule.

Sr.no	Side effect	Conventional drugs	Hybrid drugs
1.	Drowsiness	Observed	Reduced
2.	Dry mouth	Observed	Reduced
3.	Blurred vision	Observed	Reduced
4.	Urinary retention	Observed	Reduced
5.	Hallucinations	Observed	Reduced
5.	Local skin irritation	Observed	Reduced
6.	Itching	Observed	Reduced
7.	Flushing	Observed	Reduced
8.	Contact dermitis	Observed	Reduced
9.	Rashes	Observed	Reduced

RESULTS AND DISCUSSION

Who Are Making Hybrid Drugs?

Hybrid drugs are prepared by many institutions as they are given foremost concern in therapies for the mitigation of diseases. Many of which are still in development and clinical trial phases like piperaquine, it has two 4-aminoquinoline moieties as parent moieties. Ferroquine which is in clinical trial phase -2.

A. Hybrid drugs are prepared by non-governmental organisations.

B. Public- private partnership:

B-1: Medicines for malaria venture (MMV): not for profit product development partnership.
B-2: Global health innovative technology fund: public private sector that funds research.

C. Pharmaceutical companies: like Novartis and Sanofi.

D. Academic and research institutes:

D-1: University of Cape Town
D-2: Multiple universities and research institutes in Europe and u.s.

E. In India:

E-1: Zydus Cadila
E-2: Cipla
E-3: Ranbaxy Lab
E-4: Csir

CHALLENGES:

Hybrid drug is one of the greatest achievement human has unlocked for whole world. It has been a remarkable progress in the medical field which treats numerous diseases and cure many disorders, but as there are two sides of every story, there comes some challenges for hybrid molecules/ drugs which are broadly classified in 3 types that are namely synthesising, formulating, and usage.

1. **While synthesising:** The main challenge in synthesis of hybrid molecule is to create a simple, stable molecule which could give action more compared to their individual moieties.

Synthetic Complexity: Synthetic pathway of hybrid molecule is a multi-step process that can be long above that one must require a very good knowledge of organic chemistry. The reaction chosen to perform must contain preserved conditions to react finely with each other. Sensitivity to heat, Ph and other environmental factors are also taken into considerations.

Selection Of Linker: A liner is not just a group but an important factor which can alter or influence drug properties to avoid that one must have thorough knowledge of linkers. The length and rigidity of linker could can the binding affinity to receptor site. The linker should be optimum; if it is too much stable then drug will be unable to release pharmacophores at respective site. If the linker is too much labile then it may degrade quickly to their parent moiety.

Purification and Characterisation: Every reaction produces some side products to some intermediates; hence purification becomes a crucial step to be done.

2. **While formulating:** it is a process of changing drug molecule into suitable formulations it has some unique challenges, let's discuss it.

Solubility and Bioavavilbilty: Combining two parent moieties could drastically lead to change the physical and chemical property of the hybrid drug. A hybrid drug might be hydrophobic then it cannot be dissolved in water so the bioavailability will be less and hence no or less effect is seen in an individual;

Chemical And Ophysicak Stability: A hybrid drug should be stable from manufacturing to the time when patient administer it simple it should have a good shelf life. Combination of 2 different molecules is more susceptible to degrade from light, heat, moisture which results in loss of potency and hence thereafter it will require some special storage conditions.

FUTURE PROSPECT

The future of hybrid drugs is immense. They show a paradigm shift in drug design which is more sophisticated and easy way to treat any disorder. With the help of these drugs, we could overcome resistance which is the main obstacle for any anti-bacterial drug.

Linking of 2 pharmacophores offers enhanced efficacy as a synergistic effect. We could see wide range of broad-spectrum bacteria for which conventional; drugs are narrow spectrum as a result hybrid drugs are used having broad therapeutic spectrum. Challenges for synthesising hybrid drug is complex process which sometimes gives us newer drug (accidental discovery), and can be overcome by continuous research and development of hybrid drug. Advanced computational tools are beneficial for the ease of work like computational modelling that concise complex information to simpler form. Another is computational molecular docking that predicts the binding orientation of proteins, molecules and other is computational molecular editor that allows creating, managing, and presenting chemical structure, reactions and related data in visually appealing form. This type of advancement makes it easy for scientist to formulate any hybrid drug which has a great growing future in accordance with the diseases.

CONCLUSION

The advancement of hybrid drugs marks a significant milestone in the fight against complex diseases like cancer, malaria, and cardiovascular ailments. By integrating two or more therapeutic agents into a single molecule, these innovative drugs offer a multi-pronged attack on diseases, which is particularly effective in overcoming drug resistance. This integrated approach makes it much harder for pathogens or cancerous cells to adapt and neutralize the treatment, as they are simultaneously targeted from multiple angles. Beyond their ability to bypass resistance, hybrid drugs are designed to address several critical challenges in traditional medicine. By consolidating multiple treatments into one, they lead to less drug-drug interaction, simplifying medication regimens and reducing the potential for adverse effects. This streamlined approach also lessens the strain on the body's organs, contributing to less organ failure and improved safety. The reduced complexity of the treatment plan, along with a decrease in side effects, directly enhances patient compliance. When a treatment is easier to manage and has a better safety profile, patients are more likely to stick with it, ultimately leading to better health outcomes. This holistic strategy heralds a new era of more effective, safer, and more user-friendly therapies for some of the world's most challenging diseases.

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