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Review

Novel Hybrid Molecules for Anticancer Therapy: A Comprehensive Review

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Abstract:

The investigation of novel hybrid molecules has been prompted by the search for effective anticancer medicines. These molecules offer intriguing pathways for battling cancer through creative processes, and they have been the subject of this investigation. This extensive study provides a synthesis of the existing literature on hybrid compounds that have been created for anticancer therapy. It sheds light on the various structural compositions of these molecules as well as the many mechanisms of action that they possess. The review begins with an overview of traditional anticancer techniques and the limits of those approaches. It then goes on to outline the logic for harnessing hybrid molecules, highlighting the potential of hybrid molecules to overcome resistance and boost therapeutic efficacy. The advantages of hybrid molecules over conventional medicines are highlighted, along with the many methodologies for building hybrid molecules, such as conjugation, combination, and hybridization of pharmacophores. In addition, molecular targets that are essential for the progression of cancer and treatment are investigated, which offers insights into the rational design of hybrid compounds. In this study, the significance of hybrid molecules in preclinical and clinical settings is highlighted by the presentation of sample case studies. These case studies provide light on the chemical structures, mechanisms of action, and therapeutic results of hybrid molecules. Techniques for synthesis and characterisation are investigated, with a particular focus on the significance of structure-activity relationship studies in the process of developing hybrid compounds for inhibitory efficacy against cancer. Additionally, the obstacles that are currently being faced in the field as well as the future approaches that are being pursued are discussed, which paves the way for further developments in the creation and translation of novel hybrid molecules for the treatment of cancer.

Keywords: *Molecular, Hybridization, Anticancer, Agents, Cell Lines, In Vitro, Pharmacophore Novel, Hybrid, Molecules, Anticancer Therapy, Hybrid molecules, Anticancer therapy, Drug design, Combination therapy, Cancer treatment, and Cancer treatment.*

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Introduction:

The journey toward the development of effective anticancer medicines continues to be a challenging endeavor, which is underscored by the complex and wide-ranging character of cancer. Despite the fact that conventional methods such as chemotherapy, radiation therapy, and medical procedure have made significant advancements in the treatment of cancer, their viability is sometimes hampered by inherent obstacles. These obstacles include basic harmfulness, medication obstruction, and off-target impacts. As a result of these challenges, there has been a growing interest in the development of novel hybrid molecules as a potentially effective method for the treatment of cancer. Hybrid compounds, which combine diverse pharmacophores or beneficial modalities into a single

element, present an outstanding opportunity to overcome the flaws of conventional treatments and address the various molecular instruments that are responsible for the progression of cancer [1].

The anticancer medicines that are currently available each have a few limitations that make it difficult for them to effectively battle the complexities of cancer. Despite the fact that chemotherapy is widely used, it frequently has limited beneficial windows and indiscriminate cytotoxicity, which leads to severe adverse effects and a reduction in patient dignity. In addition, the development of multidrug resistance is a significant obstacle to the long-term viability of chemotherapy, which renders a great number of conventional anticancer medicines useless throughout the course of the treatment process. In spite of the fact that they are intended to specifically block certain molecular targets that are involved in the genesis and progression of cancer, designated treatments are frequently rendered ineffective due to the development of obstruction systems and the limited target specificity. Despite the fact that immunotherapy is a progressive method that utilizes the body's immune system to target cancer cells, it is only effective in a subset of individuals and can lead to resistant related adverse events. As a consequence of this, there is an urgent need for alternative helpful techniques that are capable of addressing these challenges and working on quiet results [2].

The purpose of this survey is to provide a comprehensive overview of the role that innovative hybrid molecules play in the treatment of cancer. We plan to explain the thinking behind the development of hybrid molecules, as well as their various fundamental sytheses and multi-layered methods of activity, by synthesizing the ongoing collection of writing that has been accumulated. In addition, we will investigate the systems that are utilized in the process of building hybrid molecules, which includes the synthesis, combination, and hybridization of pharmacophores, and we will highlight the potential advantages that these systems have over conventional treatments. Through the assessment of preclinical and clinical examinations, as well as commendable contextual studies, we will demonstrate the restorative capacity of hybrid molecules in resolving the limitations of the anticancer treatments that are now available. Additionally, we will study the challenges that are currently being faced in the field as well as the potential future implications of these challenges. Our ultimate goal is to stimulate further advancements in the interpretation of novel hybrid molecules for the treatment of cancer [3].

An Overview of the Hybrid Drug Concept in the Field of Anticancer Agent Development:

A change in context in medicine design that is pointed toward improving supportive practicality and overcoming the constraints of customary anticancer treatments is tended to by the idea of hybrid drugs in the field of anticancer specialty improvement. There exist hybrid prescriptions, otherwise called hybrid molecules or multi-designated agents, which are intensifies that combine no less than two pharmacophores with various instruments of action into a single molecular component. Hybrid drugs are otherwise called hybrid molecules. This system exploits the synergistic interactions that happen between various pharmacophores in request to accomplish upgraded helpful impacts, like increased power, further created selectivity, and lower drug opposition [4].

The capability of hybrid medications to simultaneously target multiple molecular targets or pathways that are involved in the progression and improvement of cancer is one of the most significant advantages of these type of drugs. The disease known as cancer is a heterogeneous infection that is characterized by abnormal signaling pathways, genetic alterations, and cellular cycles that exhibit dysregulation. Additionally, hybrid medications have the ability to exert a more significant command over cancer cell multiplication, endurance, and metastasis, which ultimately leads to improved treatment outcomes. This is accomplished by targeting a variety of biological targets or pathways. In addition, addressing different pathways reduces the likelihood of blockage improvement. This is because cancer cells are less likely to evade treatment by acquiring changes in multiple targets simultaneously when they are targeted by multiple pathways [5].

The development of hybrid pharmaceuticals requires careful selection and improvement of pharmacophores in order to ensure optimal synergistic interactions and beneficial outcomes resulting from the drug's implementation. When selecting pharmacophores, it is possible to take into consideration the components of activity that are associated with them. For instance, one might target certain signaling pathways or cellular cycles that are involved in the progression of cancer. Furthermore, the architecture of the compound as well as the features of the pharmacophores should be improved in order to ensure perfect drug-like properties such as dissolvability, soundness, and bioavailability [6].

The design of hybrid pharmaceuticals can be accomplished by the utilization of a few different processes, such as the production, combination, and hybridization of pharmacophores. In order to create a single molecular element

that possesses integrated beneficial qualities, formation requires the introduction of a substance linker that connects at least two pharmacophores to one another. For the purpose of achieving synergistic effects, combination therapy involves the simultaneous administration of at least two different medications, each of which has a unique mechanism of action. Creating a unique synthetic element with increased beneficial qualities can be accomplished through the process of hybridization, which entails fusing at least two pharmacophores into a single particle [7].
It has been demonstrated that hybrid medications have shown promising results in both preclinical and clinical tests across a variety of cancer types. Some examples of hybrid drugs include double kinase inhibitors, which simultaneously target a number of signaling pathways that are involved in the expansion and endurance of cancer cells, and immunizer drug forms, which combine monoclonal antibodies that target specific cancer antigens with cytotoxic payloads in order to deliver chemotherapy to cancer cells in a targeted manner. The fact that these hybrid medications have demonstrated superior survivability, decreased toxicity, and improved patient outcomes in comparison to conventional treatments demonstrates the potential of hybrid drug techniques in the development of anticancer specialists [8].
The concept of hybrid medications seeks to address a promising approach in the field of anticancer specialist improvement, which is aimed at overcoming the limitations of conventional treatments. Hybrid pharmaceuticals are medications that are created by merging many pharmacophores, each of which has a unique mechanism of action, into a single molecular molecule. These drugs have the potential to improve therapeutic efficacy, reduce drug resistance, and improve results in terms of tolerance. Continued inventive work in this field has an incredible commitment to the discovery of novel hybrid pharmaceuticals with restorative profiles that have been worked on and a wider range of applicability in the treatment of cancer [9].

1. Combining drug pharmacophoric moieties:

a) **Directly linked pharmacophoric groups**: The connecting of two pharmacophores is accomplished in a straightforward manner without the use of a spacer particle in this method. When it comes to cancer treatment, this could involve connecting two pharmacophores that target biochemical pathways that are either highly similar to one another or completely different from one another during the process of cancer improvement.

b) **Linked by a spacer**: On the other hand, a spacer particle gives the pharmacophoric groupings the ability to be connected with one another. In addition to providing adaptability, the spacer modifies the distance between the pharmacophores, which in turn affects the hybrid particle's interaction with its goals.

Purpose in Anticancer Therapy:

According to this technology, the incorporation of various pharmacophores into a single particle is intended to enhance the restorative viability of the treatment against cancer. Hybrid molecules are able to focus on several pathways or molecular targets at the same time because they combine pharmacophores with comparable or synergistic instruments of activity. This allows hybrid molecules to potentially overcome drug resistance and improve treatment outcomes [10].

2. Combining two or more entire drugs:

a) Directly linked hybrid drugs: Whole medications are connected to one another through the utilization of a beneficial gathering in this manner. It is possible to hydrolyze esters, carbamates, or amides using enzymes, which results in the release of dynamic drug moieties. These are examples of models.

b) Merged or overlapped hybrid drugs: These hybrids are formed by the overlapping of underlying themes or pharmacophores from two different medications, which ultimately results in a particle that is largely unique and possesses property combinations of both of the parent drugs.

c) Spacer linked hybrid drugs:

- **Non-cleavable**: It is not necessary for these hybrids to undergo enzymatic hydrolysis because they possess stable linkers. The exercises of both parent medications are going to be kept at their disposal.
- **Cleavable**: Under conditions that are either physiological or enzymatic, cleavable linkers release the parent medicines. It is possible for them to further develop pharmacokinetics or to selectively transport medications to the tissues of interest.

Purpose in Anticancer Therapy: The process of hybridizing entire pharmaceuticals provides opportunities to combine the benefits of many therapies, such as boosting selectivity, improving pharmacokinetics, or altering the kinetics of drug discharge. Taking this method has the potential to bring about synergistic effects and has been shown to be effective in the treatment of cancer.

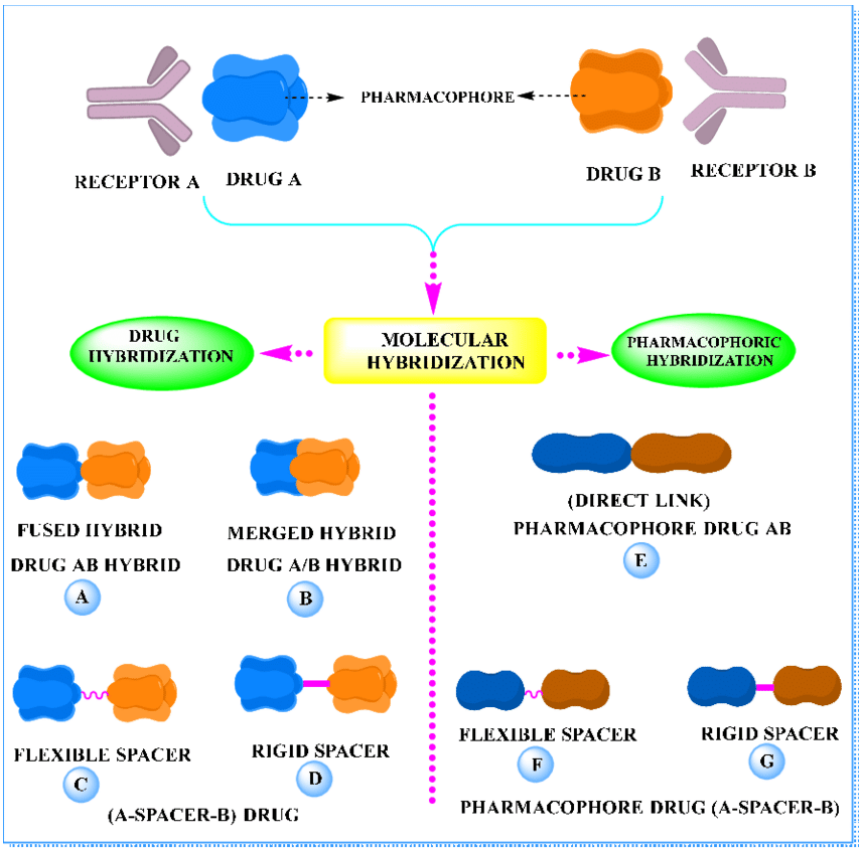

Figure 1: It is possible to hybridise molecules using a variety of techniques.

Integration of Concepts in Anticancer Therapy: When it comes to the treatment of cancer, hybrid molecules that are developed utilizing these processes are intended to solve the challenges of cancer heterogeneity, drug blockage, and off-target effects. When compared to conventional treatments, hybrids have the potential to provide superior selectivity, power, and beneficial characteristics. This is achieved through the deliberate combination of pharmacophores or entire medicines [11].

Innovative hybrid molecules are a promising approach to the treatment of cancer, since they have the potential to improve the viability of the treatment while simultaneously reducing the number of adverse effects. The incorporation of various pharmacophores or complete pharmaceuticals into these hybrids provides a guarantee that they would be able to overcome the obstacles that are now being faced by anticancer treatments and make progress in the treatment of many types of cancer [12].

Mechanisms of Action of Hybrid Molecules:

In order to exert their anticancer effects, hybrid molecules employ a variety of different systems that have an effect on the synergistic interactions that occur between the pharmacophores or molecular moieties that make up their constituents. These systems frequently target important pathways or molecular targets that are trapped in the movement of cancer, providing a multi-layered approach to dealing with the disruption of cancer formation and endurance [13].

Specifically targeting specific signaling pathways that are essential for the growth, survival, and metastasis of cancer cells is one of the ways that hybrid compounds are able to exert their anticancer effects. Hybrid compounds, for instance, have the potential to inhibit receptor tyrosine kinases (RTKs), such as the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor receptor (VEGFR), both of which play critical roles in

the promotion of growth, angiogenesis, and metastasis. These signaling pathways can be blocked by hybrid molecules, which can thus hamper the formation of growth and the spread of metastatic disease [14].

Through the use of hybrid molecules, intracellular signaling pathways that are involved in the regulation of cell cycle movement, apoptosis, and DNA repair mechanisms could be altered. For example, hybrids that target specific components of the PI3K/AKT/mTOR pathway have the potential to disrupt aberrant signaling in cancer cells, which can result in the halt of the cell cycle and the activation of death. The same is true for hybrids that interfere with DNA repair processes, such as poly (ADP-ribose) polymerase (PARP) inhibitors. These hybrids make cancer cells more susceptible to DNA damage, which ultimately leads to cytotoxicity and a recurrence of growth [15].

There is a possibility that hybrid compounds could exhibit immunomodulatory effects by either increasing antitumor insensitive responses or suppressing immunosuppressive systems inside the growth microenvironment. For instance, the combination of safe checkpoint inhibitors with cytotoxic medications or designated agents in hybrid formulations has the potential to enhance the antitumor resistance of white blood cells, which can result in a robust growth relapse and delayed endurance in cancer patients [16].

In the context of the progression of cancer, examples of hybrid compounds that target specific pathways or molecular foci include the following:

1. Dual kinase inhibitors: These hybrids target on distinct kinases implicated in aberrant signaling pathways at the same time. For instance, the mitogen-enacted protein kinase (MAPK) route or the phosphoinositide 3-kinase (PI3K) pathway are examples of these types of kinases. As a result of their ability to block several kinases, these hybrids are able to significantly disrupt oncogenic signaling and to defeat the opposition tools associated with single-target inhibitors.
2. PROTACs, also known as proteolysis-targeting figments, are hybrid molecules that recruit specific objective proteins to the proteasome of the cell in order to corrupt them. By simultaneously attaching to an objective protein and an E3 ubiquitin ligase, PROTACs cause the ubiquitination and subsequent debasement of the objective protein. This, in turn, leads to the specific suppression of oncogenic pathways or proteins that are implicated in the migration of cancer.
3. Antibody-drug forms, often known as ADCs, are a type of medication that combines the specificity of monoclonal antibodies with the lethal potency of small particle medicines. As a result of the precise delivery of cytotoxic payloads to cancer cells that display specific cell surface antigens, anti-cancer drugs (ADCs) are able to promote targeted cell death while simultaneously limiting the negative effects of asymmetrical effects. ADCs that target HER2-positive breast cancer cells with trastuzumab form cytotoxic drugs such as DM1 or MMAE. These models are used to study the effectiveness of these medicines.

Multitargeted methods, which are given by hybrid molecules, offer a number of advantages, including enhanced viability, a reduced likelihood of drug resistance, and a wider range of remedial applicability. Hybrid molecules have the ability to conquer the heterogeneity of cancer cells and limit the formation of safe aggregates. This is accomplished by simultaneously targeting a variety of pathways or molecular targets that are involved in the progression of cancer. Furthermore, multitargeted methods have the potential to synergize with preexisting treatments or immunotherapies in order to broaden the anticancer effects and help with the comprehension of the desired outcomes [17].

It is possible for hybrid compounds to exert their anticancer effects through a variety of distinct systems that target specific pathways or molecular targets that are involved in the progression of cancer. Double kinase inhibitors, PROTACs, and immune response drug forms are examples of models that demonstrate the benefits of multitargeted methods in terms of overcoming drug resistance and improving restorative adequacy. It is guaranteed that the advancement of cancer treatment and the improvement of patient outcomes will be achieved through continued exploration and innovation in hybrid atom design [18].

Hybrid drugs as a potential solution to the problem of drug resistance in anticancer treatment:

Hybrid medications have emerged as a viable option for combating beneficial impediment and further developing results in the field of cancer treatment. This is because the complexity of multifactorial diseases necessitates the utilization of a diverse methodology. Hybrid molecules, which are defined as substance elements with distinct underlying domains and exhibiting a variety of organic capabilities, give an advantage while simultaneously targeting a number of different cancer-related pathways. Hybrid medications are characterized by improved

remedial viability, lower poisonousness, and higher flexibility against the improvement of opposition. These characteristics are achieved by integrating a combination of drugs into a single particle. The technology of molecular hybridization, which is informed by developing information on carcinogenesis and cancer opposition instruments, provides a powerful means to overcome drug blockage through the use of robotic reasoning [19].
It is the intention of the professionals to circumvent the current obstruction components and to handle the ever-changing landscape of cancer therapy by means of the conventional creation of hybrid medications. By successfully attacking multiple symptoms of cancer at the same time, hybrids that have been suitably constructed hold the promise of preventing the overexpression of obstructive components and enhancing patient outcomes. The purpose of this study is to investigate the prudent design of hybrid medications in light of conventional blockage systems. The findings of this study provide insights into the potential of hybrid molecules as an exceptional strategy in the treatment of cancer [20].

Recent Developments in Hybrids Used to Fight Cancer:

a) Quinazoline Based Hybrids

In the pursuit of novel hybrid molecules for the treatment of cancer, the utilization of compounds based on quinazoline emerges as a compelling path. This is due to the fact that these compounds possess a variety of bioactive properties and are expected to have restorative benefits. Quinazoline is a heterocyclic molecule that has been linked to a variety of pharmacological activities. These activities include anticonvulsant and pain alleviating effects, as well as anticancer and mitigating effects. It is particularly noteworthy for its inhibitory activity on kinases, which are among the most important targets in the development of cancer treatment. Taking use of this versatile platform, researchers have incorporated and explored quinazoline-based imidazole hybrids with the objective of addressing the anticancer potential of these compounds against Epidermal Development Component Receptor (EGFR) and HT-29 cells, in both normoxic and hypoxic settings [21].
Compound 1(a) emerged as the champion entertainer, demonstrating excellent inhibitory impacts with IC50 upsides of 0.47 nM, 2.21 µM, and 1.61 µM against EGFR and HT-29 cells, respectively. The integrated combinations demonstrated significant anticancer action, with compound 1(a) emerging as the champion entertainer. These findings provide insight on the potentially restorative capabilities of imidazole hybrids based on quinazoline in the fight against the progression of cancer through the body. Quite simply, the design of these hybrids, which is depicted in Figure 2, includes the necessary incorporation of quinazoline and imidazole moieties. This may be done in order to take advantage of synergistic interactions and better pharmacological effects [22].
The in vitro antiproliferative movement against HT-29 cells and the EGFR inhibitory activity of combinations 1(b-e), which are enumerated in Table 1, further highlight the multifaceted nature of their anticancer efficacy. Because hybrid molecules provide a sophisticated methodology that can focus on many pathways at the same time, our findings highlight the significance of researching hybrid molecules in cancer therapy. This is because hybrid molecules have the potential to reduce the development of drug resistance and improve the likelihood of beneficial outcomes.One of the most important steps in the process of developing novel anticancer drugs is the formulation and evaluation of hybrids based on quinazoline and imidazole respectively. By capitalizing on the distinct bioactive features of quinazoline and imidazole, these hybrid compounds present a potentially fruitful avenue for the development of more effective anticancer medicines. As research in this area continues to advance, additional research into hybrid molecules presents the opportunity to rethink the standards for cancer treatment and to make progress in comprehending the outcomes [23].

1a

Figure 2: The structure of quinazoline-based imidazole hybrids, followed by the chemical that shows the most promise

Table 1: The Results of the Compound Screening

Compound	R1	R2	R3	R4	n	EGFR (IC50 nM)	HT-29 (IC50 µM) - Normoxia	HT-29 (IC50 µM) - Hypoxia
1b	Cl	F	NO2	H	5	0.33	12.88	9.82
1c	Br	H	NO2	H	2	0.65	4.49	4.02
1d	ethynyl	H	NO2	H	3	0.55	10.09	5.95
1e	ethynyl	H	NO2	H	5	0.51	2.92	3.45
Gefitinib						0.46	3.62	5.22

The plan and assessment of quinazoline-based urea hybrids, which was driven by Zhang et al. (2016), comprise a significant step in the right direction in the field of generating novel hybrid molecules for the treatment of cancer. Two of the main receptors embroiled in the movement of cancer are the Epidermal Advancement Part Receptor (EGFR) and the Vascular Endothelial Improvement Variable Receptor-2 (VEGFR-2). These hybrids were created with the express reason for targeting these receptors. More specifically, the mixed combinations exhibited solid anticancer movement, with compound 3(a) demonstrating extraordinary imperativeness with IC50 potential gains of 1.0 nM and 79 nM against EGFR and VEGFR-2, separately. The way that this ampleness is better than that of the control drug vandetanib exhibits the capacity of the quinazoline-based urea hybrids to be of helpful help. The design of these hybrids, which is portrayed in Figure 4, includes the basic integration of quinazoline and urea subjects. This integration might have the option to gain by synergistic interactions and upgraded pharmacological impacts. Also, the in vitro EGFR and VEGFR-2 inhibitory development of combinations 3(b-e), which is nitty gritty in Table 2, validates the far-reaching nature of their anticancer viability. These findings feature the meaning of investigating hybrid molecules as a possibly compelling candidate for the treatment of cancer. Hybrid molecules offer an expanded methodology that objectives numerous pathways at the same time and can possibly conquer drug opposition components. As the examination in this space continues to develop, extra examination into quinazoline-based urea hybrids might deliver exceptional insights and add to the headway of successful anticancer medicines [24].

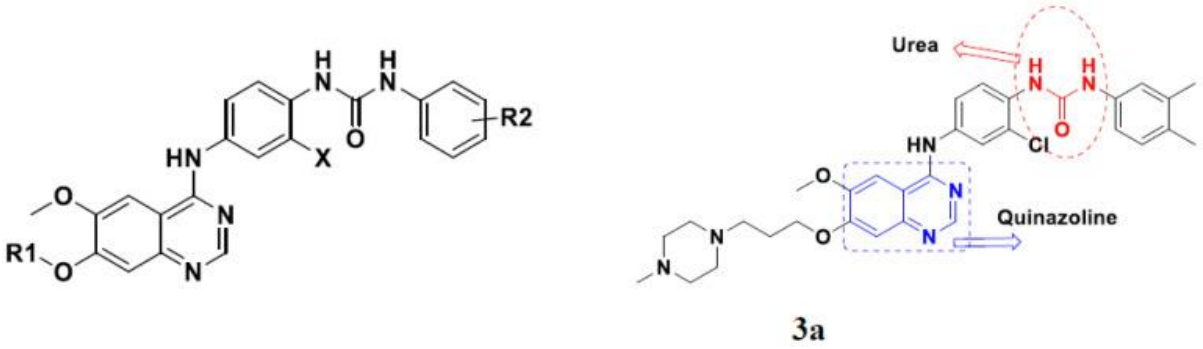

Figure 3: The structure of quinazoline-based urea hybrids, specifically the chemical that shows the most promise

Table 2: Compound Screening Results with IC50 Values for EGFR

Compound	R1	R2	X	EGFR (IC50 nM)
3b	m-Cl, p-F	Cl	15	15
3c	m-CH3, p-CH3	Cl	77	52
3d	o-CH3	Cl	14	179
3e	H	Cl	15	262
Vandetanib			12	14

Hybrids based on quinazoline that have been approved by the FDA or are active in clinical trials:

The clinical interpretation of hybrid mixtures in view of quinazoline addresses a critical achievement in the quest for innovative anticancer treatments. There have been various hybrids of quinazoline that have been assessed in clinical preliminary examinations during the beyond couple of years, and they have shown promising outcomes in the treatment of different cancers. Prominently, the Food and Drug Administration (FDA) has given its

endorsement to a couple quinazoline-based protein inhibitors for the treatment of different sorts of malignancies. This exhibits the convenience of this classification of blends from a restorative standpoint. Certain meds, for example, dacomitinib, erlotinib, gefitinib, afatinib, and lapatinib, have been supported by the Food and Drug Administration (FDA). These drugs target explicit molecular pathways that are involved in the movement of cancer (Figure 4). With regards to the treatment of different sorts of cancer, these supports feature the restorative importance and plausibility of hybrid prescriptions in light of quinazoline.In expansion, ongoing clinical preliminary examinations are continuing to concentrate on the capability of hybrid molecules in view of quinazoline for the treatment of different kinds of cancer. The hybrids in view of quinazoline that are as of now being investigated are summed up in Table 8, which likewise gives information regarding the expected pertinence of these hybrids across an assortment of cancer types. The reason for these preliminary investigations is to examine a coordinated work to foster a supportive stockpile against cancer by utilizing the interesting characteristics of hybrids in view of quinazoline. The capacity of these blends to beat drug obstruction instruments and further develop patient results is ensured by the way that they target explicit molecular targets and pathways [25].

The significant job that quinazoline-based hybrid molecules play as possibly compelling anticancer medicines is featured by the clinical assessment and FDA endorsement of these kinds of mixtures. These blends give a multi-layered way to deal with the treatment of cancer to target different molecular pathways that are involved in the improvement of growths. In the mission for successful anticancer medicines, quinazoline-based hybrids are addressing a confident indication. This is on the grounds that momentum research is continuing to disentangle the intricacies of cancer science. These combinations can possibly change cancer therapy ideal models and have an effect in the existences of patients all over the world in the event that they are exposed to additional exploration and get clinical endorsement [26].

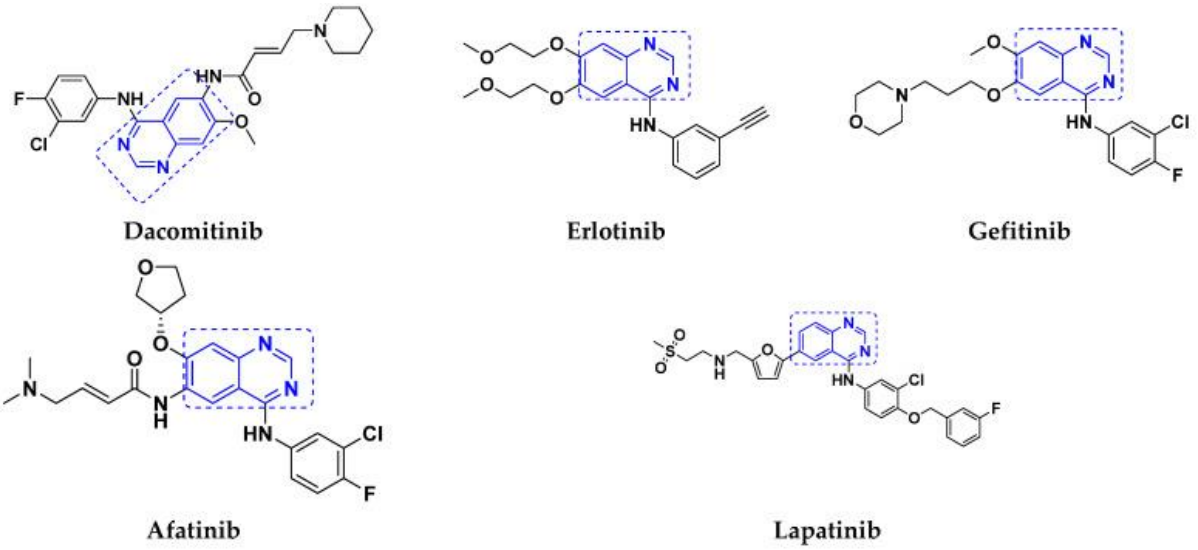

Figure4: Clinical trials and FDA-approved medications that contain quinazoline hybrids.

Table 3: Pharmaceutical Compounds and Targets in Cancer Treatment

Company Name	Compound Name	Drug Target	Type of Cancer	Status
AstraZeneca	Vandetanib	Kinase inhibitor	Medullary thyroid cancer	Approved
Boehringer Ingelheim	Afatinib	Tyrosine kinase	Non-small cell lung Carcinoma	Approved
Pfizer	Dacomitinib	EGFR inhibitor	Non-small cell lung carcinoma	Approved
AstraZeneca and Teva	Gefitinib	EGFR inhibitor	Breast and Lung cancer	Approved
Roche Pharmaceuticals	Erlotinib	EGFR inhibitor	Pancreatic cancer and non-small cell lung cancer	Approved
GlaxoSmithKline (GSK)	Lapatinib	Dual tyrosine kinase inhibitor	Solid tumors and Breast cancer	Approved
AstraZeneca	Sapitinib (AZD 8931)	Erb8 receptor tyrosine kinase	Breast cancer and metastatic cancer	Clinical trials
Array Biopharma	Tucatinib (ARRY 380)	Kinase inhibitor	Breast cancer	Approved
Selleck chemicals	Barasertib (AZD 1152)	Aurora Kinase	Tumor lymphoma, solid tumors and myeloid leukemia	Clinical trials
Spectrum Pharmaceuticals	Poziotinib	Tyrosine kinase	Breast cancer	Clinical trials
AstraZeneca	AZD 3759	EGFR antagonist	Non-small cell lung Cancer	Clinical trials
Curis Inc.	CUDC-101	Histone deacetylase, EGFR and HER2	Advanced/Liver/Neck/Gastric/Head/non-small cell lung cancer and Breast	Clinical trials
Beta-Phama	Icotinib	EGFR-TK1 inhibitor	Non-small cell lung cancer	Approved

Structural Diversity and Classification:

The innovative design systems of hybrid molecules, which mix several pharmacophores or molecular moieties with distinct substance structures, are the source of the outstanding primary variety that hybrid molecules exhibit in the field of anticancer research. As a result of this variety, professionals are able to target various molecular pathways and cellular cycles that are involved in the progression of cancer, which offers prospective avenues for remedial action.

It is possible to characterize hybrid compounds by taking into consideration a few standards, such as their synthetic architecture, pharmacophores, or mode of activity. The classification of hybrid compounds according to the concept of their constituent pharmacophores or key themes is one approach that is considered to be a regular arrangement. For instance, hybrid molecules may combine components of small natural molecules, peptides, nucleic acids, or regular things, amongst other possible components. In addition, they can be classified according to the mechanism by which they exert their effects, such as DNA-binding compounds, kinase inhibitors, protease inhibitors, or immunomodulators [27].

Examples of hybrid molecule classes include:

1. In the first place, there are small particle peptide hybrids. These hybrids combine the fundamental components of small natural molecules with the functional characteristics of peptides. Furthermore, in comparison to their separate components, they typically exhibit a more developed target specificity and an enhanced pharmacological movement. For example, peptidomimetics that incorporate small atom themes have the ability to target protein interactions that are implicated in cancer signaling pathways with a high degree of affinity and selectivity [28].
2. Antibody-drug forms, often known as ADCs, are a category of hybrid molecules that are composed of monoclonal antibodies that have evolved into lethal medicines by the intervention of linker molecules. This strategy allows for the targeted delivery of powerful anticancer drugs to cancer cells that display certain cell surface antigens, therefore reducing the level of fundamental toxicity. It has been demonstrated that ADCs are effective in treating a variety of malignancies, including lymphoma and breast cancer, by selectively delivering cytotoxic payloads to growth cells while sparing healthy tissues throughout the treatment process [29].
3. Hybrids based on nucleic acids: These hybrids mix nucleic acid frameworks, such as DNA or RNA, with other molecular elements in order to modify the quality of the articulation or to suppress certain cellular targets that are associated in the progression of cancer. Antisense oligonucleotide hybrids, for example, have the ability to hybridize with integral mRNA arrangements, which results in the blockage of protein interpretation and the disruption of oncogenic signaling cascades. Aptamer-drug combinations, in their most basic form, make use of nucleic corrosive aptamers in order to precisely target cancer cells and deliver beneficial payloads [30].
4. Hybrids of natural substances: Hybrid molecules based on natural substances combine the inherent variety and bioactivity of natural substances with modifications that are made or semi-engineered in order to improve their curative qualities. In many cases, these hybrids exhibit a variety of different components of activity, such as the prevention of cell growth, the induction of death, and the balancing of cellular signaling pathways. Among the models are hybrids derived from polyphenols, alkaloids, terpenoids, and flavonoids. These compounds have demonstrated their efficacy as anticancer agents by interacting with cancer cells in a variety of ways [31].

The vast array of hybrid compounds that are being investigated for their potential to combat cancer encompasses a wide range of substance structures, pharmacophores, and activity mechanisms. By integrating molecular elements that are complementary to one another, hybrid molecules provide unique therapeutic approaches for the treatment of cancer, with increased viability and decreased toxicity. The continued investigation and development of hybrid particle design hold a tremendous amount of potential for increasing cancer treatment and improving patient outcomes [32].

Preclinical and Clinical Studies:

The article titled "Novel Hybrid Molecules for Anticancer Therapy: A Far-reaching Survey" draws attention to the significant role that preclinical and clinical evaluations play in the progression of hybrid particle-based medicines for the treatment of cancer. In order to create the groundwork for clinical interpretation, preclinical investigations

serve as the cornerstone. These investigations involve carefully examining the pharmacological properties, components of activity, and predicted toxicity levels of novel hybrid mixes [33].

In the course of preclinical tests, researchers embark on a journey through a multitude of in vitro and in vivo models in order to assess the cytotoxicity of hybrid compounds against various cancer cell lines that are representative of various types of cancer. This preliminary analysis not only provides fundamental insights into the feasibility of the mixes across a variety of cancer kinds, but it also assists specialists in identifying viable competitors that exhibit intense anticancer action. Furthermore, preclinical investigations delve into the complex systems that are responsible for the hybrid molecules' technique of activity. These investigations provide light on the molecular pathways that the hybrid molecules concentrate on in order to either restrict the multiplication of cancer cells or induce apoptosis. By gaining an understanding of these systems, not only is it possible to validate the restorative potential of hybrid mixtures, but it also permits the design of these combinations to be refined for improved viability.

An essential component of the preclinical evaluation process is the identification of the pharmacokinetic features of hybrid molecules. These qualities include the retention, dissemination, digestion, and discharge of the hybrid molecules in living organisms. By deciphering the pharmacokinetic profiles of the mixtures, specialists are able to acquire significant insights into the bioavailability and tissue-explicit gathering of the mixtures, which are critical factors in determining the effectiveness of the mixtures [34].

As a result of the identification and depiction of prospective competitors in preclinical tests, the translation of these combinations into clinical preliminary studies becomes an extremely important effort. This remarkable cycle requires the navigation of administrative paths, the construction of rigorous clinical preliminary conventions, and the recruitment of appropriate patient associates in order to evaluate the safety and viability of hybrid atom-based medicines.

Beginning with stage I preliminaries, which are aimed at determining the health, tolerability, and pharmacokinetics of the hybrid particle in a limited patient population, clinical preliminary studies are conducted in a technique that is phased. These preliminary steps play a significant role in deciding the portion that has been suffered the most and in determining the amount that is recommended for subsequent assessments [35].

When hybrid molecules reach the stage II preliminary stage, a larger cohort of patients is chosen to evaluate their potential in the treatment of unambiguous cancer types. In the course of these preliminary investigations, objective reaction rates, movement-free endurance, and general endurance were comprehensively surveyed. The results of these investigations provided fundamental insights into the healing potential of the mixes and guided the subsequent turn of events [36].

During stage III preliminaries, which are the culmination of clinical assessment, vast scope attempts are made with the purpose of definitively assessing the viability and security of hybrid particle-based treatments in comparison to standard treatments or false treatments. By providing convincing evidence to support administrative endorsement and possible clinical use, these crucial preliminary studies are helping to shape the landscape of appropriate models for cancer therapeutic applications [37].

In spite of the fact that favorable outcomes from clinical preliminary studies could pave the way for administrative approval and clinical acceptance of hybrid molecules, it is essential to acknowledge the inherent challenges and uncertainties. It is important to note that not all mixes that demonstrate promise in preclinical tests will be successful in clinical trials. This highlights the need of conducting comprehensive evaluations and continuously refining the formulations in order to achieve the desired outcomes [38].

When it comes to the trajectory of events and the evaluation of hybrid atom-based treatments for cancer, preclinical and clinical investigations serve as crucial grounds of support [39]. In the end, these meticulously organized experiments provide fundamental insights into the anticancer efficacy, health profile, and pharmacokinetic aspects of the mixes, which ultimately guide their clinical interpretation and prospective effect on tolerant consideration[40].

Challenges and Future Perspectives:

The paper titled "Novel Hybrid Molecules for Anticancer Therapy: An Exhaustive Survey" delves into the promising field of hybrid particle-based anticancer therapy. It highlights both the genuine capacity of this therapy as well as the challenges that are preventing its clinical interpretation. This topic revolves around the complex

process of synthesizing and optimizing hybrid mixtures, which provides enormous challenges due to the demand for beneficial pharmacokinetic features and the moderation of possible toxic levels. This process is at the heart of this discussion .

The results of the study indicate the fundamental necessity of resolving these challenges in order to advance restorative viability and clinical reception. For the purpose of overcoming these challenges, analysts are investigating novel approaches that encompass both rational medication design and advanced drug delivery technology.By utilizing techniques such as construction action relationship (SAR) research and computational modeling, rational drug design is getting closer. These techniques offer avenues for refining molecular designs in order to further improve drug-like qualities while simultaneously eliminating inappropriate effects. The goal of the scientists is to develop mixes that have increased beneficial potential and decreased harmfulness profiles. This will be accomplished by merging multiple pharmacophores into a single particle.

Additionally, developments in drug delivery technologies, like as nanoparticle-based information and designated delivery systems, show promise for enhancing the bioavailability of hybrid molecules and causing them to accumulate in certain tissues. The viability of anticancer therapy is improved as a result of these developments, which also contribute to the reduction of basic poisonousness, which ultimately leads to improved patient outcomes.

One of the most significant challenges in the treatment of cancer is the growing resistance to drugs, which underscores the importance of creating methods to overcome the components that cause obstruction. In such a manner, hybrid molecules provide an outstanding benefit by targeting a variety of signaling pathways and cellular cycles that are involved in the progression of cancer. Because hybrid medications are able to avoid blockage systems, they have the potential to overcome challenges that are associated with conventional treatments. Taking a look into the future, the field of hybrid particle-based anticancer therapy offers a significant commitment for the implementation of clinical applications and future advancements. Emerging patterns, such as the incorporation of artificial intelligence and machine learning calculations in the process of drug creation, present opportunities to assist in the differentiation of evidence and the development of hybrid molecules that possess enhanced therapeutic characteristics.

Additionally, the rising understanding of growth heterogeneity and tailored medicine approaches provide avenues for adapting hybrid therapies to individual patient profiles, thereby maximizing beneficial adequacy and lowering treatment-related toxin levels. This makes it possible to design hybrid treatments to individual patient profiles. A variety of approaches are required in order to address the challenges that are associated with the occurrence of hybrid molecules and the clinical interpretation of their interpretation. The scientists are able to overcome obstacles and saddle the maximum capacity of hybrid atom-based anticancer therapy by utilizing rational drug design, innovative drug conveyance techniques, and insights from preclinical and clinical examinations. This will result in a revolution in the standards of cancer treatment and an improvement in patient outcomes.

Conclusion:

Medical chemists have begun on a mission to discover novel therapeutic approaches in order to solve the intricate problems that are posed by the formidable disease of cancer. This endeavor is taking place within the expanding field of cancer treatment. The researchers have shifted their attention to combination therapy and the development of hybrid chemotherapeutics as possible paths for better efficacy. This is because they are aware of the limits of standard single-agent techniques. In this exhaustive review, the rational design concepts that drive the generation of anticancer medicines using molecular hybridization are investigated in depth. This technique develops unique scaffolds that are endowed with greater therapeutic potential. This is accomplished by synergistically integrating two distinct molecular entities from different molecules. The diversity that is inherent in molecular hybridization makes it possible to create molecules that have many modes of action, which in turn offers the promise of fewer adverse effects and more effectiveness. Although the examples that were highlighted in this study provide a glimpse into the possibilities of hybrid molecules, it is important to note that these examples only represent a small portion of the broad terrain that is waiting to be explored. The investigation of novel hybrid molecules has enormous promise in terms of altering therapy paradigms and making substantial achievements in the fight against this complicated disease. This is because cancer treatment is continuing to advance.

References:

[1] Rana A., Alex J.M., Chauhan M., Joshi G., Kumar R. A review on pharmacophoric designs of antiproliferative agents. *Med. Chem. Res.* 2015;24:903–920. doi: 10.1007/s00044-014-1196-5. [CrossRef] [Google Scholar]

[2] Kori S. An overview: Several causes of breast cancer. *Epidemol. Int. J.* 2018;2:000107. doi: 10.23880/EIJ-16000107. [CrossRef] [Google Scholar]

[3] Hassanpour S.H., Dehghani M. Review of cancer from perspective of molecular. *J. Cancer Res. Pract.* 2017;4:127–129. doi: 10.1016/j.jcrpr.2017.07.001. [CrossRef] [Google Scholar]

[4] Sung H., Ferlay J., Siegel R.L., Laversanne M., Soerjomataram I., Jemal A., Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J. Clin.* 2021;71:209–249. doi: 10.3322/caac.21660. [PubMed] [CrossRef] [Google Scholar]

[5] Philip C.C., Mathew A., John M.J. Cancer care: Challenges in the developing world. *Cancer Res. Treat.* 2018;1:58–62. [Google Scholar]

[6] Penny L.K., Wallace H.M. The challenges for cancer chemoprevention. *Chem. Soc. Rev.* 2015;44:8836–8847. doi: 10.1039/C5CS00705D. [PubMed] [CrossRef] [Google Scholar]

[7] Zugazagoitia J., Guedes C., Ponce S., Ferrer I., Molina-Pinelo S., Paz-Ares L. Current challenges in cancer treatment. *Clin. Ther.* 2016;38:1551–1566. doi: 10.1016/j.clinthera.2016.03.026. [PubMed] [CrossRef] [Google Scholar]

[8] Zhong L., Li Y., Xiong L., Wang W., Wu M., Yuan T., Yang W., Tian C., Miao Z., Wang T. Small molecules in targeted cancer therapy: Advances, challenges, and future perspectives. *Signal Transduct. Target. Ther.* 2021;6:201. doi: 10.1038/s41392-021-00572-w. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[9] Chakraborty S., Rahman T. The difficulties in cancer treatment. *Ecancermedicalscience.* 2012;6:ed16. [PMC free article] [PubMed] [Google Scholar]

[10] Shalini, Kumar V. Have molecular hybrids delivered effective anticancer treatments and what should future drug discovery focus on? *Expert Opin. Drug Discov.* 2021;16:335–363. doi: 10.1080/17460441.2021.1850686. [PubMed] [CrossRef] [Google Scholar]

[11] Bass A.K., El-Zoghbi M.S., Nageeb E.S.M., Mohamed M.F., Badr M., Abuo-Rahma G.E.D.A. Comprehensive review for anticancer hybridized multitargeting HDAC inhibitors. *Eur. J. Med. Chem.* 2021;209:112904. doi: 10.1016/j.ejmech.2020.112904. [PubMed] [CrossRef] [Google Scholar]

[12] Gediya L.K., Njar V.C. Promise and challenges in drug discovery and development of hybrid anticancer drugs. *Expert Opin. Drug Discov.* 2009;4:1099–1111. doi: 10.1517/17460440903341705. [PubMed] [CrossRef] [Google Scholar]

[13] Moustafa A.M.Y., Bakare S.B. Synthesis of some hybrid 7-hydroxy quinolinone derivatives as anti breast cancer drugs. *Res. Chem. Intermed.* 2019;45:3895–3912. doi: 10.1007/s11164-019-03827-y. [CrossRef] [Google Scholar]

[14] Nepali K., Sharma S., Sharma M., Bedi P., Dhar K. Rational approaches, design strategies, structure activity relationship and mechanistic insights for anticancer hybrids. *Eur. J. Med. Chem.* 2014;77:422–487. doi: 10.1016/j.ejmech.2014.03.018. [PubMed] [CrossRef] [Google Scholar]

[15] Decker M. Hybrid molecules incorporating natural products: Applications in cancer therapy, neurodegenerative disorders and beyond. *Curr. Med. Chem.* 2011;18:1464–1475. doi: 10.2174/092986711795328355. [PubMed] [CrossRef] [Google Scholar]

[16] Kerru N., Singh P., Koorbanally N., Raj R., Kumar V. Recent advances (2015–2016) in anticancer hybrids. *Eur. J. Med. Chem.* 2017;142:179–212. doi: 10.1016/j.ejmech.2017.07.033. [PubMed] [CrossRef] [Google Scholar]

[17] Szumilak M., Wiktorowska-Owczarek A., Stanczak A. Hybrid drugs—A strategy for overcoming anticancer drug resistance? *Molecules.* 2021;26:2601. doi: 10.3390/molecules26092601. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[18] Abbot V., Sharma P., Dhiman S., Noolvi M.N., Patel H.M., Bhardwaj V. Small hybrid heteroaromatics: Resourceful biological tools in cancer research. *RSC Adv.* 2017;7:28313–28349. doi: 10.1039/C6RA24662A. [CrossRef] [Google Scholar]

[19] Fortin S., Bérubé G. Advances in the development of hybrid anticancer drugs. *Expert Opin. Drug Discov.* 2013;8:1029–1047. doi: 10.1517/17460441.2013.798296. [PubMed] [CrossRef] [Google Scholar]

[20] Mishra S., Singh P. Hybrid molecules: The privileged scaffolds for various pharmaceuticals. *Eur. J. Med. Chem.* 2016;124:500–536. [PubMed] [Google Scholar]

[21] Zheng W., Zhao Y., Luo Q., Zhang Y., Wu K., Wang F. Multi-targeted anticancer agents. *Curr. Top. Med. Chem.* 2017;17:3084–3098. doi: 10.2174/1568026617666170707124126. [PubMed] [CrossRef] [Google Scholar]

[22] Chamseddine I.M., Rejniak K.A. Hybrid modeling frameworks of tumor development and treatment. *Wiley Interdiscip. Rev. Syst. Biol. Med.* 2020;12:e1461. doi: 10.1002/wsbm.1461. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[23] Alagarsamy V., Chitra K., Saravanan G., Solomon V.R., Sulthana M., Narendhar B. An overview of quinazolines: Pharmacological significance and recent developments. *Eur. J. Med. Chem.* 2018;151:628–685. doi: 10.1016/j.ejmech.2018.03.076. [PubMed] [CrossRef] [Google Scholar]

[24] Das D., Hong J. Recent advancements of 4-aminoquinazoline derivatives as kinase inhibitors and their applications in medicinal chemistry. *Eur. J. Med. Chem.* 2019;170:55–72. doi: 10.1016/j.ejmech.2019.03.004. [PubMed] [CrossRef] [Google Scholar]

[25] Cheng W., Zhu S., Ma X., Qiu N., Peng P., Sheng R., Hu Y. Design, synthesis and biological evaluation of 6-(nitroimidazole-1H-alkyloxyl)-4-anilinoquinazolines as efficient EGFR inhibitors exerting cytotoxic effects both under normoxia and hypoxia. *Eur. J. Med. Chem.* 2015;89:826–834. doi: 10.1016/j.ejmech.2014.11.010. [PubMed] [CrossRef] [Google Scholar]

[26] Zhang Y., Gao H., Liu R., Liu J., Chen L., Li X., Zhao L., Wang W., Li B. Quinazoline-1-deoxynojirimycin hybrids as high active dual inhibitors of EGFR and α-glucosidase. *Bioorg. Med. Chem. Lett.* 2017;27:4309–4313. doi: 10.1016/j.bmcl.2017.08.035. [PubMed] [CrossRef] [Google Scholar]

[27] Zhang H.Q., Gong F.H., Ye J.Q., Zhang C., Yue X.H., Li C.G., Xu Y.G., Sun L.P. Design and discovery of 4-anilinoquinazoline-urea derivatives as dual TK inhibitors of EGFR and VEGFR-2. *Eur. J. Med. Chem.* 2017;125:245–254. doi: 10.1016/j.ejmech.2016.09.039. [PubMed] [CrossRef] [Google Scholar]

[28] Yadav R.R., Guru S.K., Joshi P., Mahajan G., Mintoo M.J., Kumar V., Bharate S.S., Mondhe D.M., Vishwakarma R.A., Bhushan S. 6-Aryl substituted 4-(4-cyanomethyl) phenylamino quinazolines as a new class of isoform-selective PI3K-alpha inhibitors. *Eur. J. Med. Chem.* 2016;122:731–743. doi: 10.1016/j.ejmech.2016.07.006. [PubMed] [CrossRef] [Google Scholar]

[29] Ding H.W., Deng C.L., Li D.D., Liu D.D., Chai S.M., Wang W., Zhang Y., Chen K., Li X., Wang J. Design, synthesis and biological evaluation of novel 4-aminoquinazolines as dual target inhibitors of EGFR-PI3Kα *Eur. J. Med. Chem.* 2018;146:460–470. doi: 10.1016/j.ejmech.2018.01.081. [PubMed] [CrossRef] [Google Scholar]

[30] Fan Y.H., Ding H.W., Liu D.D., Song H.R., Xu Y.N., Wang J. Novel 4-aminoquinazoline derivatives induce growth inhibition, cell cycle arrest and apoptosis via PI3Kα inhibition. *Bioorg. Med. Chem.* 2018;26:1675–1685. doi: 10.1016/j.bmc.2018.02.015. [PubMed] [CrossRef] [Google Scholar]

[31] Fröhlich T., Reiter C., Ibrahim M.M., Beutel J., Hutterer C., Zeitträger I., Bahsi H., Leidenberger M., Friedrich O., Kappes B. Synthesis of novel hybrids of quinazoline and artemisinin with high activities against Plasmodium falciparum, human cytomegalovirus, and leukemia cells. *ACS Omega.* 2017;2:2422–2431. doi: 10.1021/acsomega.7b00310. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[32] Yang S.M., Urban D.J., Yoshioka M., Strovel J.W., Fletcher S., Wang A.Q., Xu X., Shah P., Hu X., Hall M.D. Discovery and lead identification of quinazoline-based BRD4 inhibitors. *Bioorg. Med. Chem. Lett.* 2018;28:3483–3488. doi: 10.1016/j.bmcl.2018.08.039. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[33] Lee H.A., Hyun S.A., Byun B., Chae J.H., Kim K.S. Electrophysiological mechanisms of vandetanib-induced cardiotoxicity: Comparison of action potentials in rabbit Purkinje fibers and pluripotent stem cell-derived cardiomyocytes. *PLoS ONE.* 2018;13:e0195577. doi: 10.1371/journal.pone.0195577. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[34] Cheng C.C., Chang J., Huang S.C.C., Lin H.C., Ho A.S., Lim K.H., Chang C.C., Huang L., Chang Y.C., Chang Y.F. YM155 as an inhibitor of cancer stemness simultaneously inhibits autophosphorylation of epidermal growth factor receptor and G9a-mediated stemness in lung cancer cells. *PLoS ONE.* 2017;12:e0182149. doi: 10.1371/journal.pone.0182149. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[35] Han W., Pan H., Chen Y., Sun J., Wang Y., Li J., Ge W., Feng L., Lin X., Wang X. EGFR tyrosine kinase inhibitors activate autophagy as a cytoprotective response in human lung cancer cells. *PLoS ONE.* 2011;6:e18691. doi: 10.1371/journal.pone.0018691. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[36] Tabasum S., Singh R.P. Fisetin suppresses migration, invasion and stem-cell-like phenotype of human non-small cell lung carcinoma cells via attenuation of epithelial to mesenchymal transition. *Chem. Biol. Interact.* 2019;303:14–21. doi: 10.1016/j.cbi.2019.02.020. [PubMed] [CrossRef] [Google Scholar]

[37] Eno M.R., El-Gendy B.E.D.M., Cameron M.D. P450 3A-catalyzed O-dealkylation of lapatinib induces mitochondrial stress and activates Nrf2. *Chem. Res. Toxicol.* 2016;29:784–796. doi: 10.1021/acs.chemrestox.5b00524. [PubMed] [CrossRef] [Google Scholar]

[38] Pham H.T.T., Maurer B., Prchal-Murphy M., Grausenburger R., Grundschober E., Javaheri T., Nivarthi H., Boersma A., Kolbe T., Elabd M. STAT5B N642H is a driver mutation for T cell neoplasia. *J. Clin. Investig.* 2018;128:387–401. doi: 10.1172/JCI94509. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[39] Sun H., Mediwala S.N., Szafran A.T., Mancini M.A., Marcelli M. CUDC-101, a novel inhibitor of full-length androgen receptor (flAR) and androgen receptor variant 7 (AR-V7) activity: Mechanism of action and in vivo efficacy. *Horm. Cancer.* 2016;7:196–210. doi: 10.1007/s12672-016-0257-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[40] Zhou Y., Li Y., Ni H.M., Ding W.X., Zhong H. Nrf2 but not autophagy inhibition is associated with the survival of wild-type epidermal growth factor receptor non-small cell lung cancer cells. *Toxicol. Appl. Pharmacol.* 2016;310:140–149. doi: 10.1016/j.taap.2016.09.010. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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