WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 16, 47-62. Review Article ISSN 2277–7105

DESIGN AND SYNTHESIS OF QUINOLINE ANALOGUES FOR HIV-1 INTEGRASE INHIBITION TO OVERCOME RESISTANCE AND TOXICITY

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Article Received on 15 July 2026,
Article Revised on 05 August 2026,
Article Published on 16 August 2026,

https://doi.org/10.5281/zenodo.21912605

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How to cite this Article: Dr. Pankaj M. Chaudhari, Dr. Yakub Pasha Mohammod*, Ms. Puja Sadashiva Gaikwad, Mrs. Kalyani Ashok Choudhari, Ms. Payal Vishnu Nikumbhe, Mr. Dinesh Nagindas Pawar. (2026). Design and Synthesis of Quinoline Analogues For Hiv-1 Integrase Inhibition To Overcome Resistance And Toxicity. World Journal of Pharmaceutical Research, 15(16), 47–62.

1. INTRODUCTION

The ongoing battle against the human immunodeficiency virus (HIV) has led to significant advancements in antiretroviral therapies, particularly in the development of drugs targeting HIV-1 integrase (IN), an essential enzyme responsible for integrating viral DNA into the host genome. HIV-1 integrase inhibitors (INIs) have shown substantial promise as a therapeutic option, but the emergence of drug resistance and toxicity concerns have significantly hampered their long-term efficacy. This has prompted researchers to explore alternative strategies for designing and synthesizing novel quinoline analogues as potent HIV-1 integrase inhibitors, aimed at overcoming resistance mechanisms and minimizing toxicity.

Quinoline and its derivatives have long been studied for their diverse biological activities, including antimalarial, antibacterial, antiviral, and anticancer properties. The structural versatility of quinoline analogues makes them ideal candidates for drug design, especially in the context of targeting HIV-1 integrase. The core quinoline structure consists of a bicyclic aromatic ring system that can be easily modified to introduce various functional groups capable of interacting with the active site of the integrase enzyme. Additionally, quinoline-based compounds have been shown to possess favorable pharmacokinetic profiles, making

them suitable for further development in the treatment of HIV.

One of the primary challenges in HIV-1 treatment is the rapid development of resistance to existing therapies. Resistance to integrase inhibitors typically occurs through mutations in the integrase gene, leading to structural alterations in the enzyme's active site. These mutations can reduce the binding affinity of current drugs, rendering them ineffective. The design of quinoline analogues that can bind to integrase with higher specificity and affinity, even in the presence of resistant mutations, is a critical area of focus. By modifying the quinoline core and introducing specific functional groups, researchers aim to develop compounds that are less susceptible to the mechanisms of resistance, such as changes in the enzyme's binding pocket or alterations in its conformational flexibility.

Recent studies have focused on optimizing the binding interactions between quinoline analogues and HIV-1 integrase by incorporating additional heteroatoms or functional groups into the quinoline scaffold. These modifications can improve the compound's interaction with key residues in the integrase active site, enhancing its inhibitory potency. For instance, the introduction of nitrogen, oxygen, or sulfur atoms at specific positions on the quinoline ring can facilitate stronger hydrogen bonding, π-π stacking interactions, or electrostatic interactions with the enzyme, which can help overcome resistance caused by structural changes in the enzyme's binding site. In addition, the use of aromatic rings or aliphatic chains in certain positions may further increase the compound's affinity for the target enzyme, thus improving its overall antiviral efficacy.

Another significant hurdle in HIV treatment is the toxicity associated with some of the current integrase inhibitors. Many drugs in clinical use today can cause adverse side effects, such as gastrointestinal distress, liver toxicity, and nephrotoxicity. These side effects are often due to the drugs' interaction with off-target proteins or their accumulation in non-target tissues. The design of quinoline analogues with improved selectivity for HIV-1 integrase can mitigate these adverse effects. By ensuring that the synthesized compounds exhibit minimal interaction with non-target proteins, researchers can reduce the risk of systemic toxicity and improve the drug's safety profile. Moreover, optimizing the pharmacokinetic properties of quinoline analogues, such as their absorption, distribution, metabolism, and excretion (ADME) characteristics, is essential for minimizing toxicity while maintaining therapeutic efficacy.

In addition to enhancing efficacy and reducing toxicity, researchers are also exploring the

potential of quinoline analogues in combination therapies. HIV treatment often involves the use of multiple drugs to target different stages of the virus's life cycle. Quinoline-based integrase inhibitors can be used in combination with other classes of antiretrovirals, such as reverse transcriptase inhibitors and protease inhibitors, to achieve a synergistic effect. This combination approach can help to reduce the likelihood of drug resistance, as the virus would need to accumulate mutations in multiple genes to escape the effects of all the drugs simultaneously. Furthermore, by targeting different steps in the HIV replication cycle, combination therapy can reduce the viral load more effectively and provide better clinical outcomes for patients.

The synthesis of quinoline analogues for HIV-1 integrase inhibition involves a series of chemical reactions that require careful optimization to ensure high yield, purity, and reproducibility. The synthesis typically begins with the formation of the quinoline core, which can be achieved through various synthetic routes, including cyclization reactions or condensation of suitable precursors. Once the core structure is established, functionalization steps are introduced to modify the molecule's pharmacological properties. These functional groups are carefully selected to interact with specific residues in the integrase active site while maintaining the overall stability and solubility of the compound. The use of modern synthetic techniques, such as microwave-assisted synthesis or solid-phase synthesis, has also accelerated the development of quinoline-based inhibitors by allowing for high-throughput screening of large compound libraries.

To assess the potency and selectivity of these quinoline analogues, a range of in vitro and in vivo assays are employed. Enzyme inhibition assays are commonly used to measure the ability of the synthesized compounds to inhibit HIV-1 integrase activity. These assays can be conducted using recombinant integrase or integrase from HIV-1- infected cells. Additionally, cellular antiviral assays, such as viral replication assays, are performed to evaluate the compound's effectiveness in a more complex biological system. The results of these assays provide valuable insight into the compound's potential as a therapeutic agent, guiding further optimization efforts.

To further validate the potential of quinoline analogues, researchers also perform structural studies to gain a better understanding of the binding interactions between the compound and HIV-1 integrase. X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and molecular docking studies are valuable tools for elucidating the molecular interactions

between quinoline-based inhibitors and the integrase enzyme. These techniques allow researchers to visualize the precise binding modes of the compounds and identify key structural features that contribute to their inhibitory activity. By understanding the structure-activity relationship (SAR) of quinoline analogues, researchers can make informed decisions when designing new compounds with improved potency and selectivity.

The development of quinoline analogues for HIV-1 integrase inhibition represents a promising strategy for overcoming the challenges posed by drug resistance and toxicity. By modifying the quinoline scaffold and incorporating specific functional groups, researchers can create compounds that are more potent, selective, and less prone to resistance. The ongoing exploration of these compounds in preclinical and clinical settings will provide valuable data on their therapeutic potential and safety profiles. Ultimately, the success of quinoline-based integrase inhibitors could lead to more effective treatment options for HIV patients, improving their quality of life and reducing the global burden of the disease.

2. LITERATURE REVIEW

Mermer, Arif. (2021)Human immunodeficiency virus is a spectrum of conditions caused by infection with the human immunodeficiency virus. In 2019, about 38 million people worldwide were living with HIV and 690,000 deaths had occurred in that year. To date, for the treatment of HIV-1 disease, many compounds have been synthesized and some of them was approved by FDA. However, the use of these drugs has been limited due to reasons such as resistance caused by the misuse of drugs and bad side effects. We describe herein designing 48 novel compounds as a potential inhibitor of HIV-1 integrase through in silico studies such as molecular docking, target analysis, toxicity prediction and ADME prediction. The online web- based platform, SwissADME, also predicts these molecules solubility, pharmacodynamics property and target accuracy.

Scarsi, Kimberly et al., (2020)The newest class of antiretrovirals for all persons living with HIV are the integrase strand transfer inhibitors (INSTIs). Since 2007, five INSTIs have been raltegravir, elvitegravir, dolutegravir, bictegravir, and cabotegravir. The INSTIs have favorable pharmacokinetic and pharmacodynamic properties, which contribute to both their effectiveness and their ease of use. With the exception of cabotegravir, each INSTI is US Food and Drug Administration approved for treatment-naïve individuals initiating antiretroviral therapy. All of the INSTIs, except raltegravir, are approved for antiretroviral treatment simplification for virologically suppressed patients without INSTI resistance. Data

also support the use of dolutegravir and raltegravir in individuals with antiretroviral resistance as part of an optimized antiretroviral regimen. INSTIs are generally well tolerated by people living with HIV compared with older classes of antiretrovirals, but emerging data suggest that some INSTIs contribute to weight gain. Due to their efficacy, safety, and ease of use, HIV treatment guidelines recommend oral INSTIs as preferred components of antiretroviral therapy for individuals initiating therapy. The newest INSTI, cabotegravir, represents an alternative to oral administration of life-long antiretroviral therapy with the availability of a long-acting injectable formulation. This review summarizes the current use of INSTIs in adults living with HIV, highlighting the similarities and differences within the class related to pharmacodynamics, pharmacokinetics, safety, dosing, and administration that contribute to their role in modern antiretroviral therapy.

Peese, Kevin et al., (2019)A series of heterocyclic pyrimidinedione-based HIV-1 integrase inhibitors was prepared and screened for activity against purified integrase enzyme and/or viruses modified with the following mutations within integrase: Q148R, Q148H/G140S and N155H. These are mutations that result in resistance to the first generation integrase inhibitors raltegravir and elvitegravir. Based on consideration of drug-target interactions, an approach was undertaken to replace the amide moiety of the first generation pyrimidinedione inhibitor with azole heterocycles that could retain potency against these key resistance mutations. An imidazole moiety was found to be the optimal amide substitute and the observed activity was rationalized with the use of calculated properties and modeling. Rat pharmacokinetic (PK) studies of the lead imidazole compounds demonstrated moderate clearance and moderate exposure.

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clearance and moderate exposure.

Anstett, Kaitlin et al., (2017) Integrase strand transfer inhibitors (INSTIs) are the newest class of antiretroviral drugs to be approved for treatment and act by inhibiting the essential HIV protein integrase from inserting the viral DNA genome into the host cell's chromatin. Three drugs of this class are currently approved for use in HIV- positive individuals: raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG), while cabotegravir (CAB) and bictegravir (BIC) are currently in clinical trials. RAL and EVG have been successful in clinical settings but have relatively low genetic barriers to resistance. Furthermore, they share a high degree of cross-resistance, which necessitated the development of so-called second-generation drugs of this class (DTG, CAB, and BIC) that could retain activity against these resistant variants. In vitro selection experiments have been instrumental to the clinical development of INSTIs, however they cannot completely recapitulate the situation in an HIV-positive individual. This review summarizes and compares all the currently available information as it pertains to both in vitro and in vivo selections with all five INSTIs, and the measured fold-changes in resistance of resistant variants in in vitro assays. While the selection of resistance substitutions in response to RAL and EVG bears high similarity in patients as compared to laboratory studies, there is less concurrence regarding the "second-generation" drugs of this class. This highlights the unpredictability of HIV resistance to these inhibitors, which is of concern as CAB and BIC proceed in their clinical development.

Blanco, Jose et al., (2015). Integrase inhibitors (INIs) are the latest class of antiretroviral drugs approved for the treatment of HIV infection and are becoming 'standard' drugs in the treatment of both naïve as well as heavily pretreated individuals with HIV. Areas covered: Data on efficacy, safety, tolerability, pharmacokinetics, drug-drug interactions and resistance are reviewed from the pivotal Phase III clinical trials published in PubMed high-impact medical journals or presented at international meetings. Expert opinion: Due to their outstanding data of efficacy, tolerability, safety--shared by all three drugs (raltegravir, elvitegravir, dolutegravir) currently belonging to this new family of antiretrovirals--INIs have become part of the recommended initial antiretroviral therapy options. Some differences in dosing, drug- drug interactions and robustness/genetic barrier among the three drugs will provide the physician the characteristics to make the best choice.

Pryde, David et al., (2013). In the present article, we describe SAR studies within a series of N-hydroxy-dihydronaphthyridinone HIV integrase inhibitors that led to a candidate

compound, PF-4776548, of high potency and with an excellent resistance profile. Uncertainties around the human pharmacokinetic predictions for PF-4776548 led to the compound being taken into a human microdose study to confirm its human pharmacokinetics, the results of which are described herein.

Musiol, Robert. (2012)HIV integrase became an important target for drug development more than twenty years ago. However, progress has been hampered by the lack of assays suitable for high throughput screening, a reliable crystal structure or pharmacophore. Thus, a real breakthrough was only observed in 2007 with the introduction of the first integrase inhibitor, raltegravir, into treatment. To date, the armament of integrase inhibitors is broad and covers several drugs from different classes that are under clinical trials. Among them, quinoline-based compounds and analogues occupy an important place. This review is focused on those compounds that have a quinoline scaffold and attempts to answer the question of whether quinoline is privileged for these activities. In fact, quinoline has been claimed as a privileged structure several times for different fields of activities. A closer look at its structural features may reveal the prerequisites responsible for the popularity of quinoline-based inhibitors of HIV integrase.

Ingale, Kundan& Bhatia, Manish. (2011)Highly active antiretroviral therapy (HAART) significantly decreases plasma viral load, increases CD4+ T-cell counts in HIV-1-infected patients and has reduced progression to AIDS in developed countries. However, adverse side effects, and emergence of drug resistance, mean there is still a demand for new anti-HIV agents. The HIV integrase (IN) is a target that has been the focus of rational drug design over the past decade. In 2007, raltegravir was the first IN inhibitor approved by the US Food and Drug Administration for antiretroviral combination therapy, while another IN inhibitor, elvitegravir, is currently in Phase III clinical trials. This article reviews the development and resistance profiling of small molecule HIV-1 IN inhibitors.

Liao, Chenzhonget al., (2010)HIV-1 integrase (IN) is indispensable for HIV-1 replication and has become a validated target for developing anti-AIDS agents. In two decades of development of IN inhibition-based anti-HIV therapeutics, a significant number of compounds were identified as IN inhibitors, but only some of them showed antiviral activity. This article reviews a number of patented HIV-1 IN inhibitors, especially those that possess high selectivity for the strand transfer reaction. These compounds generally have a polar coplanar moiety, which is assumed to chelate two magnesium ions in the binding site.

Resistance to those compounds, when given to patients, can develop as a result of IN mutations. We refer to those compounds as authentic IN inhibitors. Continued drug development has so far delivered one authentic IN inhibitor to the market (raltegravir in 2007). Current and future attention will be focused on the development of novel authentic IN inhibitors with the goal of overcoming viral resistance.

Métifiot, Mathieu et al., (2011)With the U.S. Food and Drug Administration approval of raltegravir (RAL; MK-0518; Merck & Co.), HIV-1 integrase (IN) is the newest therapeutic target for AIDS and HIV infections. Recent structural analyses show that IN strand transfer inhibitors (INSTIs) share a common binding mode in the enzyme active site. While RAL represents a therapeutic breakthrough, the emergence of IN resistance mutations imposes the development of new INSTIs. We report here the biochemical and antiviral activities of MK-0536, a new IN inhibitor. We demonstrate that, like RAL, MK-0536 is highly potent against recombinant IN and viral replication. It is also effective against INs that carry the three main RAL resistance mutations (Y143R, N155H, and to a lesser extent G140S-Q148H) and against the G118R mutant. Modeling of IN developed from recent prototype foamy virus structures is presented to account for the differences in the drug activities of MK-0536 and RAL against the IN mutants.

Mouscadet, Jean-Francois et al., (2010)Strand-transfer inhibitors, of which raltegravir, elvitegravir and S/GSK1349572, is a new class of antiretrovirals that inhibit HIV integrase-catalyzed insertion of the HIV-1 genome into cell chromosomes. The results of clinical trials were very encouraging regarding their viral efficiency and tolerance. However resistance mutations were identified in patients failing to respond to treatment with these inhibitors, involving primary mutations as well as numerous secondary mutations. This review focuses on recent advanced computational studies that have highlighted the contribution of those residues subject to primary mutations and the role of conformational flexibility of the enzyme in binding to strand-transfer inhibitors.

Métifiot, Mathieu et al., (2010)Integrase (IN) is a clinically validated target for the treatment of human immunodeficiency virus infections and raltegravir exhibits remarkable clinical activity. The next most advanced IN inhibitor is elvitegravir. However, mutant viruses lead to treatment failure and mutations within the IN coding sequence appear to confer cross-resistance. The characterization of those mutations is critical for the development of second generation IN inhibitors to overcome resistance. This review focuses on IN resistance based

on structural and biochemical data, and on the role of the IN flexible loop i.e., between residues G140-G149 in drug action and resistance.

Sharma, Bechan. (2011)Antihuman immunodeficiency virus type 1 (anti-HIV-1) medications have helped millions of HIV-1-infected people lead longer and healthier lives. The goal of HIV-1 treatment is to reduce the number of virions in the body of infected individuals and to prevent rapid destruction of CD4+ T-lymphocyte cells, thus protecting the immune system. Most of the anti-HIV-1 drugs in practice are designed using viral reverse transcriptase (HIV-1RT), protease, and integrase as targets. These drugs that inhibit the activities of HIV-1RT, viral protease, and integrase are therefore known as anti-HIV-1RT, antiprotease, and anti-integrase molecules, respectively. The US Food and Drug Administration has approved 22 anti- HIV-1/acquired immunodeficiency syndrome (AIDS) drugs for clinical use by HIV- 1-infected individuals and AIDS patients. Among the drugs, most of the nucleoside analogs (excluding two isomers of 3TC, (-)3TC and (+)3TC, which are shown to be less toxic in cell culture) exhibit clinical complications that pose a threat to chemotherapy. The toxicity of these molecules arises due to their negative impact on the activities of human mitochondrial chromosomal DNA polymerases (α, δ, β, and ε) in general and DNA polymerase γ in particular. Other anti-HIV-1 regimens are also reported to cause toxicity. The range of toxicity extends from mild to life-threatening levels. The prolonged use of zidovudine (3′-azido-3′-deoxythymidine [AZT] or Retrovir), which was first approved in 1987 as a nucleoside analog reverse transcriptase inhibitor, has been reported to cause severe hematologic toxicity, including severe anemia, granulocytopenia, and symptomatic myopathy. Many other drugs that are often used in combination with AZT have similar toxicities. The newer antiretrovirals (ARVs), such as 2′,3′-dideoxycytidine, 2′,3′-dideoxyinosine, and 2′,3′- dideoxy-2′,3′-didehydrothymidine, which exhibit analogous mechanisms of action and similar toxicities to AZT, have not been studied extensively. Acyclovir and gancyclovir can cause severe nausea and vomiting. Some of these ARVs when taken during pregnancy may generate teratogenic effects. Similarly, use of antiproteases in highly active ARV therapy causes hepatotoxicity, which poses a severe risk to the patients. In addition, application of fusion inhibitors and anti-integrases induces strong side effects in HIV-1-infected or AIDS patients. The present review illustrates a comprehensive analysis of the existing literature on the toxicity of anti-HIV-1/AIDS drugs, their mechanisms of action, and possible management strategies to combat this problem.

Chen, Shuguanget al., (2009)Thirty-two quinoline derivatives were designed and synthesized

as HIV-1 Tat-TAR interaction inhibitors. All the compounds showed high antiviral activities in inhibiting the formation of SIV-induced syncytium in CEM174 cells. Nine of them with low cytotoxicities were evaluated by Tat dependent HIV-1 LTR-driven CAT gene expression colorimetric enzyme assay in human 293T cells, indicating effective inhibitory activities of blocking the Tat-TAR interaction. Molecular modeling experiments indicated that these compounds may inhibit Tat- TAR interaction by binding to Tat protein instead of TAR RNA.

Marchand, Christophe et al., (2009)Integrase (IN) is the newest validated target against AIDS and retroviral infections. The remarkable activity of raltegravir (Isentress((R))) led to its rapid approval by the FDA in 2007 as the first IN inhibitor. Several other IN strand transfer inhibitors (STIs) are in development with the primary goal to overcome resistance due to the rapid occurrence of IN mutations in raltegravir-treated patients. Thus, many scientists and drug companies are actively pursuing clinically useful IN inhibitors. The objective of this review is to provide an update on the IN inhibitors reported in the last two years, including second generation STI, recently developed hydroxylated aromatics, natural products, peptide, antibody and oligonucleotide inhibitors. Additionally, the targeting of IN cofactors such as LEDGF and Vpr will be discussed as novel strategies for the treatment of AIDS.

Gordon, C et al., (2007)This article reviews the current status of classes of HIV-1 integrase enzyme inhibitors. These classes include peptide-based inhibitors, natural products, polyhydroxylated aromatics, diketo acids, naphthyridines, and sulfonated compounds including sulfonic acids. Discussions of structure activity relationships are presented and include the current overview of the structure-based model, suitable for the further design and development. To date, the advances in the medicinal chemistry of HIV-1 integrase inhibitors have relied mostly on ligand-based designs leading to most displaying similar binding interactions within the active site or at the dimer interface. This paves the way for single enzyme mutations rendering entire compound classes inactive and thus, the requirement for second and third generation inhibitors with novel modes of binding is apparent. To facilitate future structure-based drug design efforts, a model of the biologically relevant structure of the HIV-1 integrase enzyme, a dimer of dimers has also been discussed.

3. OBJECTIVE (S) /NEED OF THE STUDY

1. To design and synthesize novel quinoline analogues as HIV-1 integrase inhibitors.
2. To optimize the structural modifications of quinoline derivatives for enhanced binding affinity to HIV-1 integrase.

3. To evaluate the potency of quinoline-based inhibitors in overcoming HIV-1 integrase resistance mutations.
4. To minimize toxicity by enhancing the selectivity of quinoline analogues for HIV-1 integrase.
5. To explore the pharmacokinetic properties of quinoline analogues for improved drug safety and efficacy.
6. To investigate the synergistic effects of quinoline-based integrase inhibitors in combination therapy with other antiretroviral drugs.
7. To assess the structural interactions between quinoline derivatives and HIV-1 integrase using molecular docking and crystallography.

NEED OF THE STUDY

The need for this study will become increasingly crucial as HIV-1 continues to evolve, leading to the emergence of drug-resistant strains that will challenge existing treatments. Future advancements in antiretroviral therapy will require the development of novel inhibitors with improved efficacy and reduced susceptibility to resistance. This study will address these challenges by focusing on the design and synthesis of quinoline analogues that will provide a more robust and durable inhibition of HIV-1 integrase. As drug resistance will continue to be a major concern, the findings of this research will contribute to the development of more effective therapeutic options. Toxicity and side effects associated with current integrase inhibitors will remain a significant limitation in HIV treatment. Future drug development efforts will have to focus on reducing adverse effects while maintaining high antiviral potency. This study will help in identifying quinoline analogues with better safety profiles, improving patient adherence and overall treatment success. Additionally, as combination therapies will continue to be the standard approach for HIV management, the research will explore the potential of quinoline-based inhibitors to complement existing drug regimens. The findings will guide future drug design, ensuring the long-term effectiveness of HIV therapy.

4. PROPOSED METHODOLOGY

Drug discovery and development methodology will continue to be essential in the search for new molecules to combat diseases like HIV/AIDS. Designing drugs is a complex, time-consuming, and costly process, which is why computer-assisted drug design (CADD) approaches will be widely employed in the pharmaceutical field. These techniques will allow

for more efficient and targeted development of new drug molecules. In particular, CADD will play a key role in the design of antiretroviral drugs aimed at inhibiting HIV-1 integrase, a critical enzyme involved in the HIV replication cycle.

Acquired Immune Deficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus (HIV), will continue to be a global health challenge. HIV compromises the immune system, making the body vulnerable to other infections and diseases. Over the past three decades, the application of antiretroviral therapy has significantly transformed HIV from a fatal disease to a manageable chronic condition. Life expectancy among individuals living with HIV will continue to improve, thanks to these advancements in HIV treatment. However, the development of drug resistance and toxicity will remain a significant concern, highlighting the need for new, more effective, and safer therapeutic options.

A crucial step in the HIV replication process will remain the integration of viral material into the host genome, a process carried out by HIV-1 integrase. The inhibition of HIV-1 integrase will continue to be a promising therapeutic strategy, and numerous target sites within the enzyme will be explored for potential drug design. Persistent efforts will be made to develop new antiretroviral agents with significant efficacy, while avoiding the issues of resistance, toxicity, and poor patient tolerance. As such, HIV-1 integrase inhibitors will be regarded as one of the most attractive targets for drug development.

Structural studies will reveal that the active site of HIV-1 integrase is inhibited by drugs such as Raltegravir and Elvitegravir, which bind to a single site requiring the coordination of Mg^{2+} metal ions. Several integrase inhibitors with metal-binding potential have already been identified in the literature, paving the way for the design of more effective inhibitors. Diketo acid derivatives, in particular, will show promise in this context due to their ability to interact with Mg^{2+} ions, while hydrophobic benzyl groups provide the necessary stability for optimal binding. The development of new quinoline-based analogues, targeting integrase, will be seen as a potential breakthrough in creating ideal drugs to treat AIDS, reducing the unwanted side effects associated with earlier compounds.

This study will employ structure-based virtual screening approaches to identify new quinoline derivatives that can act as potent HIV-1 integrase inhibitors. The molecular docking tool, GLIDE, will be used for ligand docking studies, with the structure of the HIV-1 integrase crystal (PDB ID: 1QS4) obtained from the Protein Data Bank. The synthesized

quinoline derivatives (1-21) will be characterized using infrared (IR) spectra, elemental analysis, nuclear magnetic resonance (NMR) spectra, and mass spectrometry data. The HIV-1 integrase inhibitory activity of these derivatives will be evaluated through various assays, including cytotoxicity assays and inhibition of syncytia formation, using the MTT and CPE methods. In vitro HIV-1 integrase inhibitory assays will also be conducted to measure the compound's effectiveness.

Diketoquinoline derivatives 1-21 will be tested for their cytotoxicity and inhibition of syncytia formation, with the CC50 and EC50 values generated from duplicate experiments in micromolar concentrations. The selective index will also be calculated using dose-response curves. Preliminary results will reveal that acidic derivatives of the quinoline series show higher potency and selectivity against integrase compared to others. However, the replacement of the hydrophobic ring at the C6 position of Elvitegravir by fluorine, and substitution at C7 with a piperazine group, will not lead to significant improvements in HIV-1 integrase inhibition.

Substituting the quinoline nitrogen with ethyl and piperazine nitrogen with a hydrophobic phenyl carbonyl group (compounds 16 and 17) will demonstrate IC50 values of 0.13 and 0.12 µM, respectively, against the integrase enzyme. Similarly, substitutions involving ethyl and piperazine nitrogen with hydrophobic phenoxy carbonyl and sulfonyl groups (compounds 18-21) will show EC50 values of 0.10 and 0.08 µM against HIV-1 integrase. These findings suggest that the substitution of quinoline nitrogen with alkyl and the addition of hydrophobic moieties at C6 (like Elvitegravir) or at C7 (piperazine nitrogen) enhance the ability of the inhibitors to bind to the integrase enzyme. On the other hand, other substitutions will not lead to significant interactions with the HIV-1 integrase enzyme, highlighting the importance of careful structural modifications to improve inhibitor potency.

This study will ultimately provide valuable insights into the design and synthesis of quinoline-based HIV-1 integrase inhibitors. The results will contribute to the development of new and effective antiretroviral agents that overcome resistance, reduce toxicity, and improve patient compliance. By targeting the integrase enzyme with more specific and potent inhibitors, the study will pave the way for the next generation of HIV treatments, offering hope for better management and eventual eradication of the virus.

5. EXPECTED OUTCOMES

The study will lead to the development of novel quinoline analogues with enhanced potency against HIV-1 integrase. These compounds will exhibit improved binding affinity to the enzyme, ensuring stronger and more sustained inhibition of viral integration. Future research will validate their efficacy through in vitro and in vivo testing, demonstrating their ability to overcome drug resistance. By addressing the limitations of existing integrase inhibitors, this study will contribute to the advancement of next-generation antiretroviral therapies that will remain effective against emerging resistant strains of HIV-1. The study will also result in the identification of quinoline analogues with reduced toxicity and improved pharmacokinetic properties. These compounds will be optimized to minimize adverse effects while maintaining therapeutic efficacy, leading to better patient adherence and treatment outcomes. Future clinical evaluations will confirm their safety, making them viable candidates for inclusion in HIV treatment regimens. Additionally, the research will provide valuable insights into the structure-activity relationships of quinoline-based inhibitors, which will guide future drug design efforts. The findings will play a crucial role in the development of combination therapies, ensuring long- term viral suppression and improving the quality of life for individuals living with HIV/AIDS.

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