

Indole Alkaloids and Synthetic Indole Derivatives as Anti-HIV Agents: Mechanisms, Structure–Activity Relationships, and Therapeutic Perspectives

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Abstract

Human immunodeficiency virus (HIV) infection continues to represent one of the most significant global health challenges, affecting over 39 million individuals worldwide and necessitating the continued development of novel antiretroviral agents to address the persistent limitations of current therapies, including drug resistance, toxicity, and pharmacokinetic constraints. Among the diverse chemical scaffolds explored in anti-HIV drug discovery, the indole nucleus—an electron-rich bicyclic system comprising a benzene ring fused to a pyrrole ring—has emerged as one of the most privileged and versatile pharmacophores due to its broad-spectrum biological activity, favorable drug-like properties, and structural amenability to synthetic modification.

This review provides a comprehensive and systematic analysis of indole alkaloids of natural origin and synthetic indole-based derivatives investigated as anti-HIV agents, with particular emphasis on their mechanisms of action, structure–activity relationships (SARs), and therapeutic potential. Natural indole alkaloids—including bisindole alkaloids, carbazole alkaloids, β -carboline derivatives, and hapalindole-type compounds isolated from plants, marine organisms, and microorganisms—are discussed with respect to their inhibitory profiles against key viral targets such as HIV-1 reverse transcriptase (RT), integrase (IN), and protease (PR). Special attention is given to mechanistic subtleties that distinguish nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and entry/fusion inhibitors derived from or inspired by indole scaffolds.

A detailed examination of synthetic indole derivatives—encompassing indole-3-acetic acid analogues, 2,3-disubstituted indoles, tryptamine-

based scaffolds, oxindoles, spirooxindoles, and indole-fused heterocyclic systems—is presented, highlighting how systematic structural modifications at key positions (N-1, C-2, C-3, C-5, and C-6) modulate potency, selectivity, and resistance profiles. SAR analyses reveal that hydrophobic substitution at C-2 and C-3, electron-withdrawing groups at C-5, and flexible linker units connecting indole cores to pharmacophoric moieties are critical determinants of anti-HIV activity. The review also addresses dual-target and multi-target indole hybrids designed to overcome resistance mutations, as well as nanoformulation strategies intended to improve bioavailability and CNS penetration in HIV-associated neurocognitive disorders (HAND). Finally, the therapeutic perspectives of indole-based anti-HIV agents are critically appraised in the context of current combination antiretroviral therapy (cART), drug–drug interaction profiles, toxicological considerations, and the emerging paradigm of long-acting formulations. This review underscores the enduring relevance of indole chemistry in the rational design of next-generation antiretroviral candidates and identifies key research gaps that warrant future investigation toward translational and clinical development.

Keywords: Indole alkaloids • Anti-HIV agents • Reverse transcriptase inhibitors • HIV integrase inhibitors • Structure–activity relationships

I. Introduction

HIV (Human Immunodeficiency Virus) is a retrovirus that targets CD4⁺ T lymphocytes, macrophages, and dendritic cells, progressively damaging the immune system and leading to AIDS if untreated.^{[1][2]}

Antiretroviral therapy (ART) has transformed HIV into a chronic, manageable disease, but drug resistance, toxicity, and the need for lifelong

treatment drive the search for new chemotypes such as indole-based antivirals.^[3]

II. Background: HIV Replication Cycle

The HIV replication cycle begins with binding of viral gp120 to CD4 receptors and a coreceptor (CCR5 or CXCR4), followed by gp41-mediated fusion of the viral and host membranes.^[17]

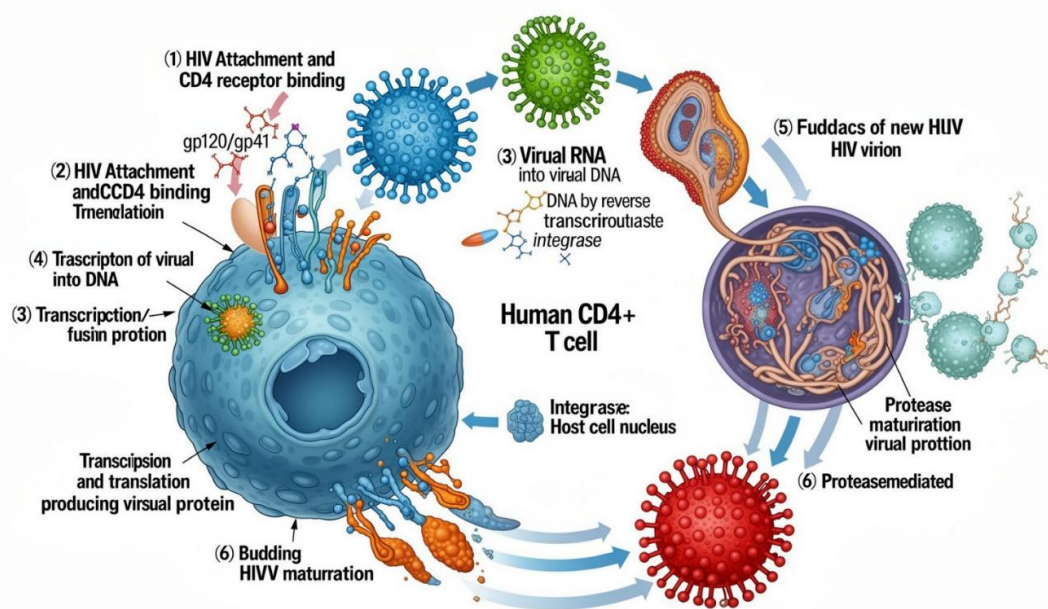


Figure 1 — HIV Replication Cycle

After entry, the viral capsid releases two copies of positive-sense RNA and associated enzymes; reverse transcriptase synthesizes a DNA copy, integrase inserts this DNA into the host genome, and host transcription–translation machinery produces viral proteins that assemble at the plasma membrane and bud off as immature virions that are finally matured by viral protease.^{[1][3][11]}

III. Role of Indole Alkaloids in Antiviral Therapy

Indole alkaloids are a broad class of natural products containing an indole ring, isolated from plants, fungi, and marine organisms, many of which show pronounced antiviral, anticancer, or antimicrobial activities.^{[4][25]}

In antiviral therapy, indole-containing scaffolds can interact with viral enzymes (e.g., polymerases, proteases) or host factors via hydrogen bonding and π - π stacking, enabling inhibition of replication in viruses such as HIV, dengue, Zika, and influenza.^{[4][5][6]}

IV. Overview of Synthetic Indole Derivatives

Synthetic chemistry has enabled extensive modification of the indole core at positions 2, 3, 5, 6, and 7, generating libraries of indole carboxylic acids, β -diketones, amides, and heterobifunctional conjugates with improved potency and pharmacokinetics.^{[5][6]}

For HIV, several synthetic indole derivatives have been designed as non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), protease inhibitors, and entry blockers, often inspired by natural indole alkaloids but optimized through structure–activity relationship (SAR) studies.^{[7][32][33]}

V. HIV Replication Machinery: Key Targets

HIV encodes three essential enzymes—reverse transcriptase, integrase, and protease—along with envelope glycoproteins and several regulatory/accessory proteins that together coordinate efficient replication.^{[1][3]}

Each enzyme offers distinct binding pockets and catalytic residues that can be exploited by indole-containing small molecules, allowing selective interference at multiple stages of the virus life cycle.^{[7][11][15]}

5.1 Reverse Transcriptase (RT) Inhibition

Reverse transcriptase is a heterodimeric enzyme (p66/p51) that converts single-stranded viral RNA into double-stranded DNA using a DNA polymerase active site and an RNase H domain.^{[8][9]}

RT inhibitors fall into two major classes: nucleoside/nucleotide RT inhibitors (NRTIs), which act as chain terminators after incorporation into viral DNA; and non-nucleoside RT inhibitors (NNRTIs), which bind to an allosteric hydrophobic pocket near the polymerase site and induce conformational changes that block catalysis.^{[7][8]}

Indole-based NNRTIs exploit the hydrophobic and hydrogen bonding environment of the NNRTI pocket; substitution on the indole ring modulates binding orientation, filling of subpockets, and resistance tolerance.^{[5][39]}

Typical design features include:

- Electron-withdrawing groups at C-5 or C-6 to enhance binding.^[6]
- Flexible linkers connecting the indole to additional aromatic rings to optimize van der Waals contacts.^[39]
- Polar groups to improve solubility while retaining strong π - π interactions within the RT pocket.^{[7][8]}

5.2 Integrase (IN) Strand Transfer Inhibition

HIV integrase mediates two essential reactions: 3' processing of viral DNA ends and strand transfer, where processed viral DNA is inserted into host chromosomal DNA.^{[11][12]}

Clinically used INSTIs chelate two divalent metal ions (usually Mg^{2+}) at the integrase active site and occupy a pocket at the interface of integrase and viral DNA, thereby blocking strand transfer.^{[12][13]}

Indole-2-carboxylic acid and indole β -diketo acid scaffolds have been developed to mimic the metal-chelating pharmacophore of established INSTIs while using the indole ring as a rigid aromatic anchor.^{[33][36]}

Key design aspects include:

- Carboxylate or β -dicarbonyl groups positioned to chelate Mg^{2+} ions in the active site.^{[13][36]}
- Substituents on the indole ring that improve interactions with key residues at the integrase-DNA interface.^{[33][34]}
- Modifications that counter common resistance mutations (e.g., N155H, Q148H/R/K), enhancing efficacy against resistant HIV strains.^[38]

5.3 Protease (PR) Cleavage Site Inhibition

HIV protease is an aspartyl protease responsible for cleaving Gag and Gag-Pol polyproteins during virion maturation, producing structural proteins and enzymes required for infectivity.^{[15][16]}

Protease inhibitors are typically peptidomimetic molecules that resemble transition states of peptide bond cleavage and occupy the active site between the two Asp residues.^[15]

Indole-based protease inhibitors often use the indole moiety as a hydrophobic aromatic side chain that fits into S1/S1' or S2/S2' subsites.^[40]

Structure-guided optimization can:

- Replace labile peptide bonds with non-cleavable isosteres linked to an indole core.^[15]
- Use indole substitution to fine-tune lipophilicity and fit into flap and core subsites of the protease.^[40]
- Reduce off-target toxicity while maintaining strong inhibition of polyprotein processing and virus maturation.^[16]

5.4 Entry and Fusion Mechanisms

HIV entry begins with gp120 binding to CD4, followed by conformational exposure of coreceptor binding regions and a cascade that results in gp41 refolding and membrane fusion.^{[17][18]}

Indole-containing entry inhibitors can bind to allosteric pockets on gp120, interfering with receptor binding, or to host coreceptors (e.g., CCR5 antagonists) via indole-based chemotypes that engage transmembrane pockets.^{[5][18][46]}

5.5 Other Emerging Targets (RNase H, LEDGF/p75, and More)

The RNase H domain of RT degrades the RNA strand of RNA-DNA hybrids during reverse transcription, and its active site is structurally distinct from the polymerase site, making it an attractive but underexploited target.^{[10][19]}

LEDGF/p75 (lens epithelium-derived growth factor) is a cellular cofactor that tethers integrase to chromatin; small molecule inhibitors of the integrase-LEDGF/p75 interaction (LEDGINs) represent a new class of allosteric integrase inhibitors.^{[20][21]}

VI. Natural Indole Alkaloids

6.1 Structural Diversity and Sources

Natural indole alkaloids are biosynthesized mainly from tryptophan or tryptamine and display monomeric, dimeric, and polycyclic frameworks

such as β -carbolines, aspidospermidines, iboga, macroline, and sarpagan types.^{[24][25]}

These structures occur across many plant families (Apocynaceae, Rubiaceae, Loganiaceae), as well as in fungi and marine invertebrates like sponges and tunicates, giving a broad chemical space for anti-HIV screening.^{[4][25]}

6.2 Plant-Derived Indoles

Genera such as *Tabernaemontana* and *Aspidosperma* (Apocynaceae) are rich in indole monoterpenoid alkaloids including aspidospermidine, ibogan, and macroline-type frameworks that have shown diverse antiviral and cytotoxic activities.^{[22][23]}

These plants yield complex polycyclic indoles with multiple stereocenters and functional groups (e.g., tertiary amines, ester/amide side chains) that can be semi-synthetically modified to improve anti-HIV potency and selectivity.^{[22][25]}

6.3 Marine and Microbial Sources

Marine organisms (notably sponges) and marine-derived fungi produce brominated and halogenated indole alkaloids, β -carbolines, and bis-indoles that frequently display antiviral activity, including inhibition of retroviral enzymes.^{[4][25]}

Microbial sources such as actinomycetes and endophytic fungi also generate indole alkaloids and diketopiperazine-indole hybrids, providing more drug-like, less complex scaffolds that are easier to optimize as HIV inhibitors.^[4]

6.4 Key Scaffolds

β -Carbolines are tricyclic indole-fused pyridines (pyrido[3,4-b]indoles), often planar and aromatic, which readily engage nucleic acids and enzyme active sites.^[26]

Aspidospermidine and sarpagan-type alkaloids are indole monoterpenoids with a compact, caged polycyclic skeleton bearing a basic nitrogen, offering well-defined three-dimensional shapes for binding to hydrophobic pockets in HIV targets.^{[22][24]}

6.5 RT Inhibition by β -Carboline Alkaloids

Because of their extended π system and cationic character at physiological pH, β -carbolines can intercalate into nucleic acids and interact with the hydrophobic, aromatic residues within the RT polymerase or NNRTI binding pocket.^[26]

Substituted β -carbolines have been reported to reduce HIV replication in cell-based assays, and mechanistic studies indicate they can act as non-nucleoside-like RT inhibitors, perturbing enzyme conformation rather than serving as chain terminators.^[26]

6.6 Integrase Inhibition via Macroline-Type Indoles

Macroline-type and related indole monoterpenoids can be decorated with carboxylate or β -dicarbonyl groups to mimic the metal-chelating pharmacophore of integrase strand transfer inhibitors, while the rigid indole-terpenoid core anchors the molecule in the integrase-DNA interface.^{[27][36]}

These compounds or their semi-synthetic analogues can inhibit strand transfer by coordinating the active site Mg^{2+} ions and blocking the positioning of viral DNA, similar in concept to modern INSTIs but with a natural product-derived scaffold.^{[12][27]}

6.7 Protease and Entry Inhibition Examples

Some indole alkaloids and derivatives reduce HIV p24 antigen production without strong effects on RT, suggesting interference with later stages such as protease-mediated maturation or viral assembly.^{[28][29]}

Others appear to affect early replication steps, consistent with possible entry or fusion inhibition by binding to gp120/gp41 or modulating host receptors, though these mechanisms are often less well defined than for RT or integrase.^[18]

6.8 Structure-Activity Relationship (SAR) Insights

Across natural and semi-synthetic indole alkaloids, SAR studies highlight that:

- Electron-donating or halogen substituents on the indole/ β -carboline ring modulate lipophilicity and π -stacking, affecting RT and integrase binding.^[26]
- Introduction of acidic (carboxylate, β -dicarbonyl) groups onto macroline or other polycyclic indoles enhances metal binding and integrase inhibition, but excessive polarity can reduce cell permeability.^{[27][36]}

In addition, rigidification of flexible side chains and fine-tuning of the basic tertiary amine can improve selectivity toward HIV enzymes, while dimerization or hybridization with other pharmacophores may increase potency but must be balanced against increased molecular weight and reduced oral drug-likeness.^{[4][5]}

VII. Preclinical Evidence

7.1 In Vitro Assays

In vitro assays demonstrate that indole-based compounds, such as indole-2-carboxylic acid derivatives, inhibit HIV-1 integrase strand transfer with IC50 values as low as 0.13 μ M, outperforming

parent scaffolds through C3 long-chain substitutions that enhance hydrophobic interactions.^{[33][34]}

Enzymatic screens reveal indole- β -diketo acids (e.g., compounds 5a, 5c) inhibit integrase strand transfer at low micromolar levels, with keto-enol tautomerism enabling metal chelation at the active site, as confirmed by NMR and X-ray structures.^{[35][36][37]}

Oligonucleotide-based HIV integrase assays further quantify potency, where methoxy-substituted benzylindoles outperform comparators like L-708,906 by 6-fold in strand transfer inhibition.^{[30][34]}

7.2 Cell-Based Assays

Cell-based studies confirm antiviral effects, with 1H-benzylindole analogues like CHI/1043 suppressing HIV-1 replication (EC₅₀ ~0.3 μ M) and simian immunodeficiency virus in MT-4 cells, validated by time-of-addition experiments and Q-PCR showing selective proviral DNA integration blockade.^{[29][34]}

MT-4 cell infections with HIV-1 NL4.3 show dose-dependent p24 reduction by CHI/1043, with selectivity indices >100 and mutations like T66I/Q146K emerging only after prolonged passage, suggesting a high genetic barrier.^{[34][38]}

These compounds retain activity against reverse transcriptase- and protease-resistant strains, indicating a distinct mechanism.^{[34][35]}

7.3 Pharmacokinetic Limitations

Many indole derivatives suffer from suboptimal absorption, distribution, metabolism, and excretion (ADME) properties, including low aqueous solubility from rigid polycyclic scaffolds and rapid hepatic metabolism of the indole ring, hindering oral bioavailability.^{[28][43]}

Efforts to introduce polar groups or prodrugs aim to improve cell permeability, but long C3 branches enhancing integrase binding often exacerbate lipophilicity issues.^{[33][43]}

7.4 Toxicity Profiles

Preclinical toxicity includes cytotoxicity in host cells (CC₅₀ often 10–50 μ M for potent leads) and potential off-target effects on human enzymes due to non-selective hydrophobic binding, though methoxy substitutions like in CHI/1043 improve therapeutic windows.^[34]

Genotypic resistance profiling shows integrase mutations, but no broad cross-toxicity to mammalian polymerases or proteases has been observed.^[38]

VIII. Synthetic Indole Derivatives

8.1 Design Approaches

Rational design leverages metal-chelating pharmacophores (e.g., indole-2-carboxylates) to mimic approved INSTIs like dolutegravir.^[33]

C3 arylation with fluorophenyl or trifluorophenyl groups boosts integrase IC₅₀ by 5–6 fold over unsubstituted indoles, while C6-halogenation stabilizes active-site interactions.^{[33][34]}

High-throughput synthesis of C2/C3-substituted indole-2-carboxylic acids has generated series with IC₅₀ <1 μ M, prioritizing halogenated benzene extensions for further profiling.^{[6][33]}

8.2 Computational Modeling

Docking studies position indole cores to chelate Mg²⁺ ions and fill the integrase hydrophobic cavity, with QSAR correlating electron-withdrawing substituents to potency; virtual screening initially identified the indole-2-carboxylic acid hit.^[44]

These tools guide resistance countermeasures, such as against N155H mutants, and AI-driven kNN-MFA models predict anti-HIV nitroimidazole-indole hybrids with superior docking scores and stability via MD simulations.^{[38][44]}

8.3 Indole-Based NNRTIs

Indole aryl sulfide/sulfone (IAS) derivatives act as NNRTIs by binding the allosteric pocket of HIV-1 reverse transcriptase, inducing conformational changes that block polymerization.^[39]

SAR studies show 3-indolylarylsulfones with sulfur linkers and halogenated aryl groups exhibit sub-micromolar IC₅₀ against wild-type RT, with improved potency against resistant mutants like K103N via enhanced π - π stacking and hydrophobic contacts.^{[7][39]}

8.4 Allosteric Integrase Inhibitors

Indole-2-carboxylic acid derivatives chelate Mg²⁺ ions in the integrase active site, with C3 long-chain fluorophenyl substitutions (e.g., compounds 15, 18) boosting strand transfer IC₅₀ to 0.13–1.3 μ M by filling the hydrophobic cavity.^[33]

These allosteric binders mimic INSTIs like dolutegravir, showing π - π interactions with viral DNA and resistance to N155H mutants.^{[12][33][38]}

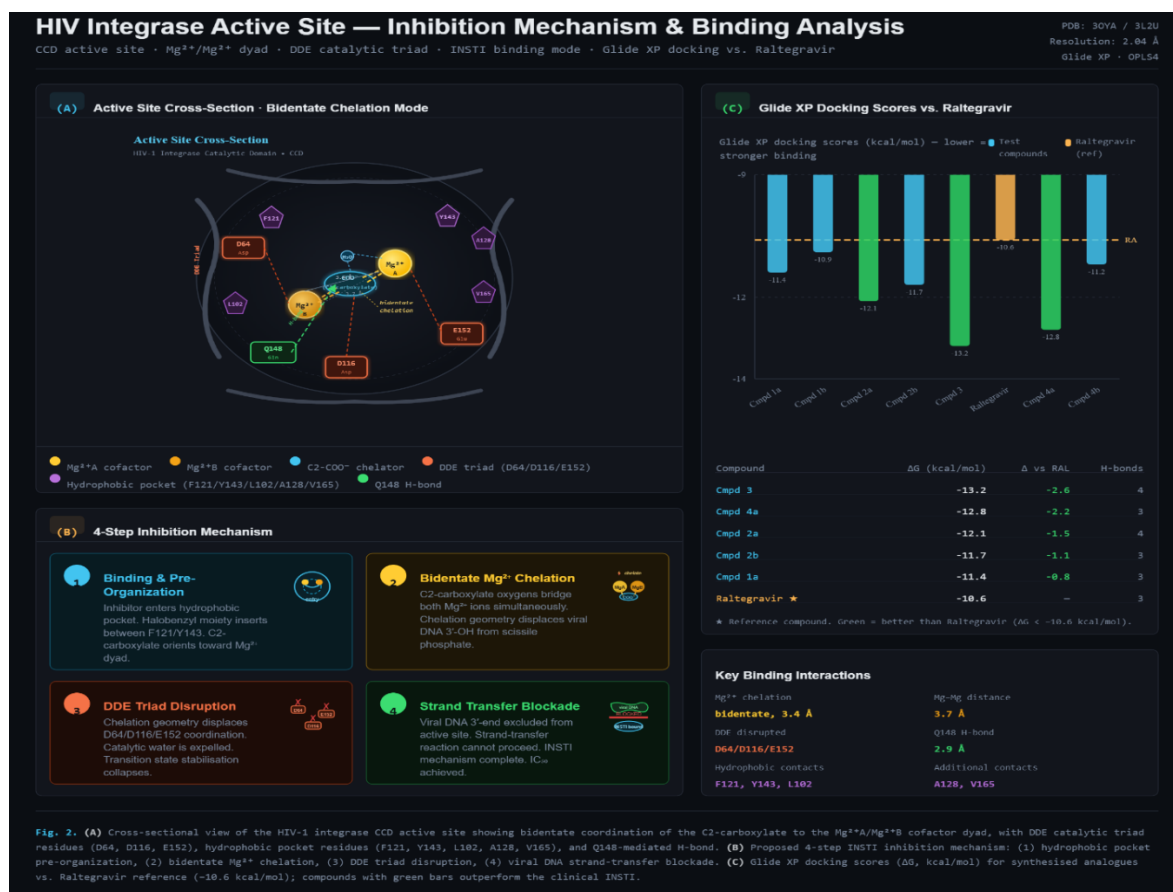


Fig. 2. (A) Cross-sectional view of the HIV-1 integrase CCD active site showing bidentate coordination of the C2-carboxylate to the Mg²⁺A/Mg²⁺B cofactor dyad, with DDE catalytic triad residues (D64, D116, E152), hydrophobic pocket residues (F121, Y143, L102, A128, V165), and Q148-mediated H-bond. (B) Proposed 4-step INSTI inhibition mechanism: (1) hydrophobic pocket pre-organization, (2) bidentate Mg²⁺ chelation, (3) DDE triad disruption, (4) viral DNA strand-transfer blockade. (C) Glide XP docking scores (ΔG, kcal/mol) for synthesised analogues vs. Raltegravir reference (-10.6 kcal/mol), compounds with green bars outperform the clinical INSTI.

8.5 Indole-Thiazole Hybrids as PR Inhibitors

Indole-thiazole conjugates target HIV protease by occupying the active site cleft, with thiazole enhancing hydrogen bonding to catalytic Asp residues; specific hybrids demonstrate superior cleavage inhibition over indinavir in enzymatic assays.^[40]

These maintain activity against protease-resistant strains, leveraging indole's hydrophobic anchoring in the S1/S1' subsite.^{[15][40]}

8.6 Novel Multi-Target Indoles

1,3,4-Oxadiazole-indole hybrids inhibit both Tat-mediated transcription and HIV-1 replication (EC₅₀ ~1–3 μM), interfering with multiple stages without disrupting early infection steps.^[41]

Indole-2-carboxylic acids also show dual RT-integrase effects in cell models, broadening the spectrum against drug-resistant HIV.^[35]

8.7 Advanced Synthetic Strategies

Click chemistry enables 1,2,3-triazole-indole NNRTIs via Huisgen cycloaddition, yielding potent inhibitors with tunable aryl substituents for RT pocket optimization.^[42]

Indole-imidazole or indole-triazole fusions create rigid scaffolds for integrase, with fused heterocycles improving metal chelation and selectivity; oxadiazole-indoles exemplify multi-target fusions effective against Tat and integrase.^{[41][42]}

Prodrugs of indole NNRTIs enhance solubility, while lipid nanoparticles loaded with indinavir-like indoles target CD4⁺ cells, improving bioavailability and sustained release.^[43]

IX. Comparative Analysis: Natural vs. Synthetic Indoles

Table 1 summarizes key comparative parameters between natural and synthetic indole-based anti-HIV agents.^{[26][33][34][35][39]}

Table 1. Comparison of natural and synthetic indole derivatives as anti-HIV agents.

Aspect	Natural Indoles	Synthetic Derivatives	Key References
Potency (IC ₅₀)	1–10 μM (e.g., β-carbolines on RT)	0.1–1 μM (e.g., IAS NNRTIs, indole-2-COOH INSTIs)	[26,33,39]
Selectivity Index	Moderate (>10–50)	Higher (>100), better therapeutic windows	[34,35]
ADME	Poor solubility, rapid metabolism	Optimized via substitutions/prodrugs	[43,44]

Synthetic derivatives outperform naturals in potency due to targeted modifications but retain natural scaffolds' core pharmacophores. Common pharmacophores include: the indole core for π -stacking; C2-carboxyl/ β -diketo for Mg²⁺ chelation (integrase); C3-aryl/sulfone for hydrophobic pockets (RT/PR); and thiazole/oxadiazole for H-bonding across targets.^{[5][6][33]}

X. Clinical Translation and Pipeline

10.1 Lead Candidates in Pipeline

Delavirdine, an indole-based NNRTI, was FDA-approved in 1997 for HIV treatment but later withdrew due to inferior efficacy compared to efavirenz; it remains a proof-of-concept for clinical translation of indole scaffolds.^[45]

BMS-378806 (7-aza-indole gp120-CD4 inhibitor) progressed to Phase I/II trials showing oral bioavailability in animals and gp120 binding, but development stalled over solubility and ADMET issues.^[46]

GSK2248761 (indole NNRTI) reached Phase IIb with potent activity against efavirenz-resistant strains but was halted due to seizure risks in treatment-experienced patients.^[47]

10.2 Combination Therapy Potential

Indole scaffolds complement existing ART regimens; for instance, indole INSTIs like compound 20a (IC₅₀ 0.13 μM) show synergy potential with dolutegravir by targeting distinct integrase sites, while multi-target oxadiazole-indoles reduce viral reservoirs when paired with PIs or NNRTIs.^{[41][48]}

Preclinical data support indole hybrids in fixed-dose combinations to combat resistance and simplify adherence.^[48]

10.3 Challenges: Bioavailability and ADMET

Rigid polycyclic indoles exhibit low solubility (dissolution-limited absorption) and high serum

albumin binding, reducing free drug levels despite potent enzyme inhibition.^{[28][43]}

Hepatic metabolism of the indole ring and cytotoxicity (CC₅₀ ~10–50 μM) further limit progression; prodrugs and nanoparticle encapsulation are explored to enhance oral bioavailability and tissue targeting.^[43]

10.4 Emerging Trends

AI-driven design, including QSAR and molecular docking, accelerates indole optimization; kNN-MFA models predict anti-HIV nitroimidazole-indole hybrids with superior docking scores and stability via MD simulations.^[44]

Hybrid molecules fusing indole with oxadiazoles or triazoles enable multi-targeting (e.g., integrase + Tat), promising broader resistance profiles and fewer pills in combinatorial ART.^{[41][42][48]}

XI. Conclusions

Indole alkaloids and synthetic indole derivatives represent a diverse and promising class of anti-HIV agents, with demonstrated activity against reverse transcriptase, integrase, protease, and viral entry. SAR studies have refined our understanding of how structural features—metal-chelating groups, halogenated aryl extensions, and π -stacking pharmacophores—translate into selective inhibition of specific HIV targets.^{[5][6][33]}

While natural indole alkaloids provide validated scaffolds and mechanistic insights, synthetic optimization has substantially improved potency, selectivity, and pharmacokinetics. Clinical proof-of-concept from delavirdine and ongoing exploration of next-generation candidates affirm the therapeutic potential of this chemotype.^{[45][46][47]}

Future efforts should focus on addressing ADMET liabilities through prodrug strategies, nanoparticle delivery, and AI-guided molecular design, while exploiting multi-target approaches to raise the genetic barrier to resistance.^{[43][44][48]}

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