Drug-Likeness Beyond Lipinski: Rethinking Natural Product Developability Through Bioavailability, Structural Complexity, Formulation Feasibility, and Safety Logic

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ABSTRACT

Natural products continue to challenge conventional drug-discovery screening because many structurally rich candidates do not fit comfortably within simplified small-molecule drug-likeness rules, yet rule violation alone does not determine whether a candidate can be developed. This article proposes a conceptual developability framework for natural product candidates that distinguishes heuristic drug-likeness from development-facing decision logic. The framework is constructed through four interacting domains: bioavailability, structural complexity, formulation feasibility, and safety logic. Rather than reducing bioavailability to oral absorption, complexity to molecular burden, formulation to universal rescue, or safety to natural origin, the proposed architecture evaluates whether evidence patterns support progression, conditional optimization, formulation- or route-dependent rescue, evidence-insufficient hold, or deprioritization. The framework emphasizes route-sensitive exposure, interpretable structural behavior, realistic formulation pathways, exposure-dependent safety, and visible uncertainty. Its principal contribution is a structured decision logic that connects heterogeneous evidence to candidate progression without inventing numerical thresholds or collapsing decisions into a single score. The framework is proposed as a conceptual architecture for natural product developability assessment and has not been prospectively validated.

Key Words: *Natural products, Drug-likeness, Developability, Bioavailability, Structural complexity, Formulation feasibility*

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INTRODUCTION

Drug-likeness rules have become deeply embedded in early discovery because they offer rapid, interpretable filters for large collections of candidate molecules. Their appeal lies in screening efficiency: they help identify compounds whose physicochemical profiles may be compatible with common development expectations, particularly oral small-molecule delivery. Natural products, however, often occupy chemically diverse regions that are not easily captured by simplified property filters. Their scaffold diversity and biological relevance remain important for drug discovery, but those same features make them difficult test cases for rigid screening logic [1].

The central difficulty is not that drug-likeness rules are irrelevant, but that they are often asked to answer the wrong question. A rule can flag a property pattern that may deserve attention, but it cannot independently establish whether a candidate can be formulated, exposed, tolerated,

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manufactured, or optimized. Developability is therefore broader than compliance with an early screening heuristic. It requires attention to progression-relevant properties, including DMPK behavior, physicochemical tractability, and development context [2].

This distinction matters especially for natural products because structural complexity may be simultaneously informative, problematic, and incompletely understood. A stereochemically rich or conformationally adaptive scaffold may create challenges in characterization, permeability prediction, metabolism, or formulation, yet it may also provide interaction patterns not well represented in flatter screening libraries. Similarly, a low-solubility compound may fail a conventional expectation while remaining plausible under a specific delivery strategy. The relevant question is not whether the molecule resembles an idealized oral small molecule, but whether its liabilities are interpretable, manageable, and compatible with the intended development context.

The evidence used in discovery decisions is also fragmented. Bioavailability is often considered through solubility or permeability surrogates; structural complexity is handled through property cutoffs; formulation is evaluated after exposure limitations appear; and safety is frequently treated as a later-stage screen. Computational ADMET models can help prioritize candidates, but their outputs remain predictions and should not be treated as final proof of developability [3]. A natural product candidate can therefore be falsely rejected when one dimension is overemphasized or falsely reassured when a favorable prediction hides unresolved risks.

This article develops an original conceptual framework for evaluating natural product developability beyond conventional Lipinski-style reasoning. The framework does not argue that all natural products deserve exemption from property rules. Instead, it proposes a structured decision architecture in which bioavailability, structural complexity, formulation feasibility, and safety logic interact to produce transparent candidate states. The objective is to move from isolated descriptors toward contextual evidence interpretation, while preserving uncertainty and avoiding unvalidated scoring claims.

Limits of conventional drug-likeness rules

Conventional property rules remain useful because they summarize recurring relationships between molecular properties and common development challenges. They can improve screening discipline, reduce obvious liabilities, and encourage attention to solubility, permeability, and molecular size before expensive development work begins. Their limitation emerges when they are converted from heuristics into absolute verdicts. Evidence from beyond-rule-of-five analyses, approved oral drug property trends, and measured physicochemical appraisals supports the view that rule-based filters should inform rather than dominate candidate decisions [4-6].

The problem is amplified when a rule originally designed for practical screening becomes a proxy for developability itself. A compound may satisfy conventional expectations and still fail because of unstable formulation behavior, extensive first-pass metabolism, reactive metabolites, or exposure-dependent toxicity. Conversely, a compound outside conventional property space may remain developable if its exposure barrier is route-specific, formulation-rescuable, or mechanistically understood. The Rule of Five therefore casts its longest shadow when it prevents decision-makers from asking which liability is actually development-limiting [7].

A balanced interpretation also requires recognizing that not every exception is acceptable. Beyond-rule-of-five space is not automatically superior, and structural size or polarity cannot be justified merely by invoking natural-product origin. The more useful position is conditional: rule violations should trigger explanation, evidence generation, and contextual interpretation. When a candidate exceeds conventional property expectations, the decision should ask whether exposure, formulation, and safety remain compatible with the intended use rather than whether the candidate deserves exemption by category [1].

False reassurance is as important as false rejection. A compound that appears conventionally drug-like may still have poor developability if permeability is offset by rapid metabolism, solubility is insufficient at the intended dose, or a predicted safety profile lacks experimental support. Large-scale in silico ADMET approaches can help identify patterns, but they cannot replace integrated judgment about the candidate, route, evidence quality, and development objective [8]. Drug-likeness compliance is therefore neither a guarantee of progression nor a substitute for evidence-linked developability reasoning.

For natural products, the key mismatch is that conventional filters often compress heterogeneous questions into a binary pass/fail label. Structural complexity, solubility, permeability, formulation dependence, and safety cannot be interpreted responsibly through a single property rule. The proposed framework therefore treats conventional drug-likeness as an input that may reveal a concern, not as the final decision. The principal mismatches between conventional drug-likeness heuristics and natural product developability are summarized in **Table 1**.

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Table 1. Conceptual Limitations of Conventional Drug-Likeness Rules When Applied to Natural Products

Conventional heuristic	Intended screening logic	Potential natural product mismatch	Developability information omitted	Risk of false rejection or false reassurance	Required contextual reinterpretation
Molecular size or weight cutoff	Reduce risk of poor permeability and exposure	Complex scaffolds may exceed preferred ranges while retaining adaptive behavior	Conformation, intramolecular interactions, route, formulation options	False rejection of candidates with interpretable exposure behavior	Ask whether size creates a demonstrated exposure, formulation, or safety barrier
Hydrogen-bond donor/acceptor limits	Flag polarity-related absorption concerns	Functional-group density may be partly shielded or context-dependent	Chameleonicity, solvent-dependent polarity, tissue exposure	False rejection when polarity is dynamically managed	Interpret polarity as exposed, shielded, or uncertain rather than simply excessive
Lipophilicity window	Balance solubility, permeability, and safety risk	Natural products may combine lipophilic domains with polar functional groups	Solubility mechanism, transporter effects, metabolic liability	False reassurance when lipophilicity appears acceptable but metabolism or toxicity is unresolved	Link lipophilicity to exposure, formulation, and safety evidence
Solubility expectation	Avoid dissolution-limited exposure	Poor aqueous solubility may be formulation-sensitive	Solid state, stability, dose burden, enabling formulations	False rejection of formulation-rescuable compounds or false rescue assumption	Classify as manageable, conditional, uncertain, or incompatible
Rule compliance	Identify candidates likely to progress	Rule-compliant compounds can still fail for DMPK, formulation, or safety reasons	First-pass loss, metabolite risk, manufacturability, route-specific safety	False reassurance from apparent drug-likeness	Require integrated developability assessment before progression

Bioavailability and structural complexity

Bioavailability is not a single number and should not be equated only with oral absorption. For an orally intended natural product, relevant exposure may depend on dissolution, solubility, intestinal permeability, physiological conditions, and pharmacokinetic processes that unfold together rather than independently. Physiologically based absorption models illustrate why oral exposure interpretation must integrate compound properties with gastrointestinal and systemic processes [8]. For other routes, the central question shifts from oral absorption to whether the intended tissue or systemic exposure is feasible and controllable.

Oral exposure is also sensitive to local gastrointestinal conditions that can be especially relevant for chemically complex candidates. Food effects and gastrointestinal pH can alter dissolution, solubilization, and absorption behavior, making apparent exposure feasibility context-dependent [9]. Even when absorption occurs, metabolism and first-pass processes can reduce parent systemic exposure or generate metabolites that change efficacy and safety interpretation [10]. A candidate with favorable permeability but extensive presystemic loss therefore presents a different developability problem from a candidate that cannot dissolve or cross membranes.

Transporters further complicate the relationship between molecular structure and exposure. Transporter interactions can affect absorption, distribution, elimination, and drug–drug interaction risk, so they belong in both bioavailability and safety logic [11]. Industrial property analyses also show that permeability and bioavailability expectations are related to molecular properties but should not be reduced to any single descriptor [12]. The decision implication is that natural product exposure must be decomposed into mechanisms rather than summarized as simply "bioavailable" or "not bioavailable."

Structural complexity enters this exposure logic as both a possible liability and an interpretive requirement. Natural products can contain stereochemical richness, dense functionalization, three-dimensional scaffolds, macrocyclic features, and flexible or conformationally constrained regions. These features may increase uncertainty in permeability prediction, metabolism, solid-state behavior, and analytical characterization. Bioavailability reviews emphasize that exposure limitations can arise from interacting solubility, permeability, metabolism, and delivery constraints rather than one isolated property [13].

A more refined view is needed for complex beyond-rule-of-five candidates. Chameleonic behavior and conformational adaptation can influence the exposure of polarity, thereby affecting permeability and solubility in some compounds [1, 14–17]. Macrocycles illustrate why structural complexity cannot be interpreted as automatically favorable or unfavorable; they can provide useful chemical-space features, but their conformational behavior, permeability, and optimization constraints require careful assessment [16]. The developability

question is therefore whether the observed complexity is mechanistically interpretable and compatible with the intended route.

This reasoning avoids romanticizing complexity. Structural richness is not proof of target selectivity, oral exposure, or safety, and beyond-rule-of-five behavior is not automatically advantageous. Chameleonicity-related properties may support oral bRo5 design decisions, but they do not establish full developability because formulation feasibility, metabolism, and safety remain separate requirements [18]. In the proposed framework, structural complexity is classified as manageable behavior, conditional opportunity, unresolved uncertainty, or true development liability only after interaction with exposure, formulation, and safety evidence.

Formulation feasibility and safety logic

Formulation feasibility is a development variable, not a universal rescue mechanism. Lipid-based systems, amorphous solid dispersions, and manufacturing-aware dispersion strategies show that exposure can sometimes be improved for poorly soluble candidates when the formulation mechanism is plausible and technically workable [19-21]. However, improved apparent solubility or dissolution does not by itself prove that a natural product is developable. The formulation question must include dose, stability, route, excipient compatibility, manufacturability, and whether the exposure gained is therapeutically and safely useful.

Different enabling technologies also carry different assumptions. Electrospun amorphous solid dispersions illustrate one route by which poorly water-soluble drugs may be handled through specialized formulation approaches [22]. Yet such technologies should be interpreted as options within a feasibility assessment rather than as general proof of rescue. A compound that requires a complex formulation at an impractical dose or with unstable physical behavior remains conditionally limited or incompatible, even if the underlying technology is scientifically credible.

Nanocarrier systems make this caution especially clear. They may address delivery barriers, but they also require careful characterization and have limitations that affect translation [23]. Delivery dependence can change the exposure profile, biodistribution, and route-specific risk of a candidate. Thus, formulation cannot be isolated from safety logic because the formulation that improves exposure may also change the magnitude, duration, tissue distribution, or variability of exposure.

Safety reasoning must begin before late-stage development because natural origin does not establish safety. Metabolite safety testing is relevant when circulating or reactive metabolites may contribute to risk during development [24]. A natural product candidate may have acceptable parent-compound properties yet generate metabolites that alter exposure margins or create organ-specific liabilities. The framework therefore treats metabolism as a bridge between bioavailability and safety rather than as a purely pharmacokinetic annotation.

Reactive functionalities and bioactivation risks deserve particular attention. Chemically reactive metabolites may create safety concerns that cannot be neutralized by potency, historical use, or improved formulation [25]. If formulation increases systemic exposure, a previously minor safety signal can become more important. This is why safety compatibility must be evaluated relative to expected exposure, route, dose duration, and accumulation potential rather than as an isolated yes/no attribute.

Computational toxicity prediction can assist safety assessment, but it cannot independently confirm clinical safety [26]. Preclinical models, including those used for drug-induced liver injury, also have known limitations in predicting human risk [27]. These uncertainties do not make safety assessment impossible; they make explicit uncertainty handling necessary. The interacting evidence domains that connect exposure, molecular complexity, formulation feasibility, and safety are organized in **Table 2**.

Table 2. Integrated Evidence Domains Linking Bioavailability, Structural Complexity, Formulation Feasibility, and Safety Logic

Evidence domain	Key question	Relevant candidate attributes	Major uncertainty	Cross-domain interaction	Potential development implication	Inappropriate inference to avoid
Bioavailability	Is relevant exposure feasible for the intended use?	Solubility, dissolution, permeability, metabolism, transport, route, variability	Whether measured or predicted exposure reflects intended route and dose	Exposure modifies safety and may depend on formulation	Advance, optimize, rescue, or hold depending on exposure pattern	Treating one predicted bioavailability value as a final verdict
Structural complexity	Is complexity interpretable as	Stereochemistry, 3D shape, macrocyclic	Whether complexity	Complexity modifies	Interpret, optimize,	Assuming complexity is

	behavior, uncertainty, or liability?	character, flexibility, intramolecular interactions	creates manageable behavior or unresolved liabilities	permeability, metabolism, formulation, and safety	characterize, or deprioritize	automatically beneficial or harmful
Formulation feasibility	Can the limitation be realistically managed?	Solid state, stability, excipient compatibility, dose burden, delivery dependence, scalability	Whether rescue is practical beyond theoretical solubility enhancement	Formulation changes exposure and may change safety	Conditional optimization or formulation-/route-dependent rescue	Assuming formulation can rescue every physicochemical limitation
Safety logic	Is risk compatible with intended exposure?	Reactive groups, metabolites, off-target effects, organ toxicity, interactions, accumulation	Whether predictive or preclinical signals translate to intended use	Exposure and formulation can increase or reduce safety relevance	Advance, hold, optimize, or deprioritize	Treating natural origin or favorable prediction as safety proof
Cross-domain coherence	Do the domains support the same decision?	Alignment among exposure, complexity, formulation, and safety evidence	Whether one unresolved domain dominates the decision	Trade-offs may convert opportunity into liability or limitation into rescue	Transparent state assignment	Collapsing all evidence into an unexplained score

Natural product developability criteria

Natural product developability criteria must begin with context rather than cutoffs. A compound cannot be classified responsibly until the intended indication, route, exposure objective, dose context, and evidence maturity are defined. The same solubility or permeability problem may be decisive for an oral chronic therapy but less decisive for a local, short-duration, or non-oral strategy. The first criterion is therefore context-defined exposure relevance, because only context determines which limitation matters.

The second criterion is bioavailability feasibility across mechanisms. Dissolution, permeability, metabolism, and physiological exposure conditions should be interpreted together rather than as independent pass/fail boxes [8]. Poor exposure may indicate a solubility problem, a permeability problem, metabolic loss, transporter involvement, or a formulation-route mismatch. Each explanation leads to a different next decision: optimization, formulation rescue, route reconsideration, evidence generation, or deprioritization.

The third criterion is route and interaction compatibility. Transporter effects can influence both exposure and interaction risk, making them relevant to candidate progression rather than peripheral annotation [11]. A natural product candidate with uncertain transporter involvement may not require immediate rejection, but it does require uncertainty labeling and targeted evidence generation. Route-sensitive evaluation prevents the framework from equating poor oral feasibility with universal development failure.

The fourth criterion is interpretable structural complexity. Structural richness should be examined for conformational behavior, polarity exposure, macrocyclic or beyond-rule-of-five features, and complexity-related uncertainty rather than treated as a scalar penalty. Molecular properties and chameleonicity can guide oral bRo5 design, but they must be interpreted as tools rather than proof of development readiness [18]. A candidate is more favorable when complexity explains manageable behavior; it is more concerning when complexity hides unresolved metabolism, formulation, or safety liabilities.

The fifth criterion is formulation realism. Amorphous solid dispersion mechanisms may support exposure improvement in suitable cases, but the candidate must still satisfy stability, dose, and route logic [20]. Manufacturing strategy is also part of feasibility because a formulation that works conceptually may still be difficult to produce, scale, or control [21]. The proposed criteria therefore distinguish formulation challenge, formulation-rescuable limitation, and formulation incompatibility.

The sixth criterion is safety compatibility under intended exposure. Reactive metabolite or bioactivation concerns should move a candidate toward optimization, hold, or deprioritization unless evidence supports compatibility with the intended use [25]. Computational toxicity evidence can help prioritize investigation, but it should not erase uncertainty or establish safety by itself [26]. Together, these criteria transform developability from a property checklist into a conditional decision system. The proposed criteria and their corresponding decision consequences are presented in **Table 3**.

Table 3. Proposed Natural Product Developability Criteria and Their Decision Consequences

Developability criterion	Evidence question	Favorable pattern	Conditional pattern	Concerning pattern	Decision consequence	Uncertainty note
Context-defined exposure feasibility	Is the exposure objective clear for the intended route and use?	Route, dose context, and exposure objective are defined	Exposure objective is plausible but incompletely specified	Candidate judged without route or exposure context	Proceed to domain assessment or hold for context definition	Missing context can make all later decisions unreliable
Mechanistic bioavailability interpretation	Which mechanism limits exposure?	Limitation is absent or mechanistically manageable	Solubility, permeability, metabolism, or transport issue may be addressable	Exposure barrier conflicts with intended use and lacks plausible rescue	Advance, optimize, rescue, hold, or deprioritize	One bioavailability descriptor is insufficient
Interpretable structural complexity	What does complexity do to behavior?	Complexity is characterized and compatible with exposure and safety	Complexity may be adaptive but needs evidence	Complexity creates unmanageable uncertainty or liability	Advance, optimize, hold, or deprioritize	Complexity is neither automatic value nor automatic failure
Formulation realism	Is rescue feasible in development terms?	Formulation route is stable, dose-compatible, and manufacturable	Rescue depends on enabling technology or route adaptation	Required formulation is unstable, impractical, unsafe, or unscalable	Conditional optimization, rescue, hold, or deprioritize	Theoretical solubility enhancement is not enough
Safety compatibility	Is risk compatible with intended exposure?	No dominant intrinsic or exposure-dependent concern	Risk may be manageable with exposure control or further testing	Intrinsic or exposure-dependent safety concern conflicts with use	Advance, optimize, hold, or deprioritize	Favorable prediction is not clinical safety proof
Cross-domain coherence	Do the domains support the same decision?	Evidence aligns across exposure, complexity, formulation, and safety	One or more domains require bounded optimization	Multiple domains conflict or one concern dominates	Assign final conceptual state	Conflicts should remain visible, not hidden in a score

Proposed developability framework

The proposed framework begins by separating candidate context from molecular description. A natural product candidate is not evaluated only as a structure but as a candidate for a particular indication, route, dose context, exposure objective, and development stage. This framing aligns with developability molecule assessment, where progression decisions depend on properties relevant to development rather than potency or structural appeal alone [2]. Context definition is therefore Gate 1: without it, the same property profile can be misclassified.

Formulation feasibility and safety logic are assessed as interacting gates rather than separate late-stage topics. A solubility or dissolution limitation may be formulation-rescuable only when the rescue path is plausible for stability, dose burden, route, manufacturability, and scalability. Similarly, a safety signal is interpreted relative to intended exposure, route, metabolite profile, and chronic-use implications. Predictive models can support this process, but their outputs remain inputs to judgment rather than validation of the framework [3].

After context definition, the framework evaluates bioavailability logic as a route-sensitive exposure question. DMPK reasoning is central because absorption, distribution, metabolism, and pharmacokinetics determine whether a molecule can achieve relevant exposure under development conditions [28]. The framework distinguishes oral exposure, systemic exposure, tissue exposure, and route-specific exposure feasibility. It also separates exposure limitation from exposure variability and from metabolite-driven changes in activity or risk.

Structural complexity is then interpreted rather than penalized. The framework asks whether stereochemical richness, three-dimensionality, macrocyclic character, flexibility, intramolecular interactions, or chameleonic behavior creates manageable exposure behavior, useful uncertainty requiring characterization, or a development liability. This domain does not function as a reward for natural products or as a penalty for noncompliance. Instead, it forces the candidate decision to state what complexity is doing to exposure, formulation, metabolism, and safety.

Cross-domain integration is the central step. The framework does not average domain outputs or assign an invented score; it asks whether the evidence pattern is coherent, whether trade-offs are explicit, whether rescue is

credible, and whether residual uncertainty blocks progression. A candidate with poor oral exposure may move toward route-dependent rescue if non-oral exposure is compatible with the intended use, while a candidate with improved formulation exposure may require renewed safety scrutiny. The integrated decision architecture and its alternative developability outcomes are shown in **Figure 1**.

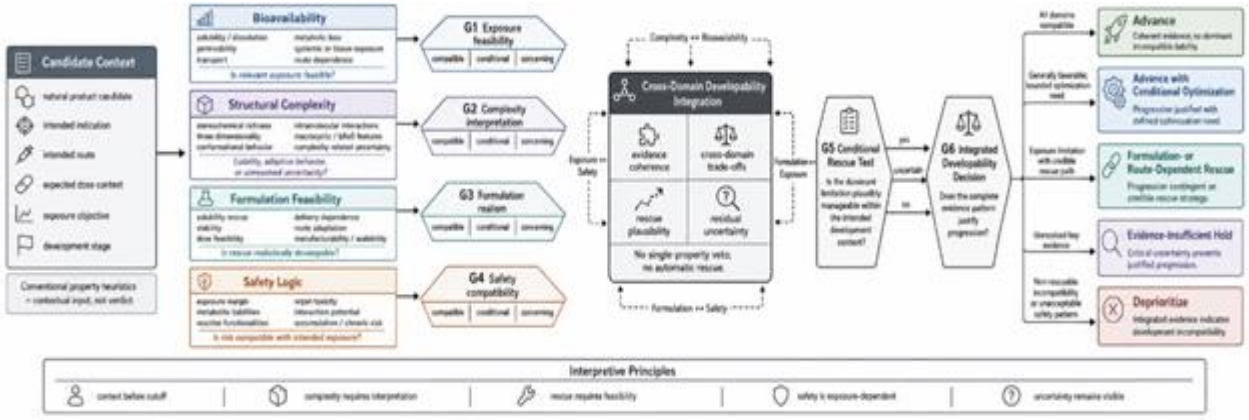

Figure 1. Integrated Developability Framework for Natural Products Beyond Conventional Drug-Likeness Rules

Alt-text

A wide left-to-right developability decision framework begins with a natural product candidate and intended-use context. Four aligned evidence domains evaluate bioavailability, structural complexity, formulation feasibility, and safety logic. Domain-specific findings enter an integration layer that tests cross-domain compatibility, rescue plausibility, route dependence, and uncertainty. Explicit decision gates then direct the candidate toward one of five outcomes: Advance, Advance with Conditional Optimization, Formulation- or Route-Dependent Rescue, Evidence-Insufficient Hold, or Deprioritize.

The framework assigns five states: Advance, Advance with Conditional Optimization, Formulation- or Route-Dependent Rescue, Evidence-Insufficient Hold, and Deprioritize. Advance is reserved for coherent evidence with no dominant incompatible liability. Advance with Conditional Optimization applies when progression is reasonable but requires a defined optimization task. Formulation- or Route-Dependent Rescue applies when a candidate is not viable under the initial assumption but remains plausible under a credible delivery or route strategy.

Evidence-Insufficient Hold is an important state because it prevents uncertainty from being misread as success or failure. It applies when critical information about exposure, structural behavior, formulation feasibility, metabolism, or safety is missing or conflicting. Deprioritize applies when the integrated pattern indicates development incompatibility under the current context. These states are conceptual decision categories rather than empirically validated outcome predictors.

CONCLUSION

Conventional drug-likeness rules are valuable screening tools, but they are insufficient as final developability logic for natural products. Their main limitation is not that they are wrong, but that they are incomplete when used to judge structurally complex candidates whose exposure, formulation, and safety profiles depend on context. A natural product candidate should therefore not be advanced or rejected solely because it fits or violates a conventional rule.

The framework proposed here reframes developability as an interaction among bioavailability, structural complexity, formulation feasibility, and safety logic. It distinguishes oral exposure from route-specific exposure feasibility, structural complexity from structural liability, formulation challenge from formulation-rescuable limitation, and intrinsic safety concern from exposure-dependent safety concern. This structure supports more transparent progression decisions because it shows how evidence changes candidate interpretation rather than hiding trade-offs behind a single score.

The principal conceptual contribution is a qualitative, evidence-linked architecture for assigning natural product candidates to five development states without inventing thresholds, datasets, or predictive performance claims. The framework is intended to guide reasoning, evidence generation, and communication across discovery and early development. Prospective validation, case-based testing, and refinement against real candidate outcomes remain necessary before the architecture can be treated as a validated decision system.

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