



Slow Binding Deserves More Weight in Natural Product Lead Selection When Potency, Residence Time, and Functional Duration Tell Different Stories

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ABSTRACT

Natural-product lead selection is often dominated by equilibrium potency, even when candidates differ substantially in how rapidly they associate with a target, how slowly they dissociate, and how long their pharmacological effects persist after extracellular drug concentrations decline. This creates a ranking problem: a compound that appears weaker at a conventional endpoint may sustain target engagement or function longer than a nominally more potent comparator, whereas a long residence time may also fail to translate because of exposure limitations, rapid target turnover, weak rebinding, or cellular context. This article develops an original pharmacological framework for interpreting such discordance. The analysis separates equilibrium potency, association rate, dissociation rate, residence time, functional duration, rebinding, exposure, and target turnover rather than treating them as interchangeable indicators of binding strength. It argues that slow binding deserves additional lead-selection weight only when the kinetic difference is experimentally credible, survives functional testing, and remains pharmacologically meaningful in the relevant biological system. Natural-product examples illustrate why stereochemistry, macrocyclic architecture, conformational transitions, and multistate binding can generate kinetic behavior not captured by equilibrium potency alone. The proposed framework is therefore conditional rather than score based: kinetics can upgrade, downgrade, or leave unchanged a potency-led ranking depending on mechanistic and contextual evidence. The approach does not establish a universal residence-time threshold, prospective ranking accuracy, therapeutic superiority, or implementation readiness. Its purpose is to make kinetic evidence proportionate to what has actually been measured and to identify when discordant potency and duration warrant deeper mechanistic investigation.

Key Words: Natural products, Binding kinetics, Residence time, Target engagement, Rebinding, Lead selection

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INTRODUCTION

Potency remains an efficient first-pass language for ranking leads, but an equilibrium or endpoint value does not specify how a ligand reaches that state or how long the target remains occupied after free concentration changes. Binding kinetics add this temporal dimension through

association and dissociation processes, and residence time can therefore distinguish compounds whose equilibrium measurements appear similar [1]. The implication is not that potency is uninformative. Rather, potency becomes an incomplete ranking variable when the biological question is explicitly temporal.

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A ranking error can occur in either direction. A highly potent compound may equilibrate rapidly yet lose target engagement soon after free drug declines, whereas a less impressive endpoint value may belong to a ligand whose slow approach to equilibrium masks a persistent complex. Conversely, prolonged molecular residence may add little if clinically or experimentally relevant exposure never permits adequate initial occupancy. The resulting problem is not solved by replacing one scalar descriptor with another. It requires determining which descriptor is informative for the pharmacological timescale that matters. That incompleteness is especially relevant to natural-product lead selection because natural-product chemical space includes rigid scaffolds, macrocycles, stereochemically dense structures, peptides, and other architectures whose discovery opportunities coexist with substantial developability complexity [2]. Structural complexity should not itself be treated as evidence of slow binding, however. Nor should natural origin be interpreted as a pharmacokinetic or mechanistic advantage. The narrower question is whether experimentally demonstrated kinetic behavior contributes information that would otherwise be lost when related natural-product leads are ordered principally by apparent potency.

Recent pharmacology supports treating binding kinetics as translationally relevant while resisting any simple rule that “longer residence time is better.” Ligand–receptor kinetic parameters can modify relationships among concentration, engagement, and response, while direct experimental work demonstrates that residence time can influence in-vivo target occupancy through more than one pathway [3, 4]. These observations justify a lead-selection problem, not a universal ranking formula. The framework proposed here therefore begins with an evidence hierarchy: establish whether the potency comparison is kinetically interpretable; determine whether association or dissociation genuinely differs; test whether that difference persists in function or target engagement; and then ask whether exposure, turnover, and cellular biology preserve its value. Only after those steps should kinetic evidence change the priority assigned by potency alone.

Slow association, slow dissociation, and mechanistic diversity

“Slow binding” is not a single mechanistic state. A long-lived complex can arise from structural rearrangements, conformational gating, induced-fit-like transitions, restricted exit pathways, or interaction networks that stabilize later states of the bound complex [5]. Accordingly, a small dissociation-rate constant is an observed kinetic property, not a sufficient explanation of the molecular mechanism that produced it. Two compounds with comparable residence times may

therefore reach that phenotype through different structural trajectories and need not share the same susceptibility to mutation, conformational state, solvent environment, or competing ligand.

Association also matters. Living-cell kinetic studies show that association and dissociation can be resolved in receptor systems whose conformational and allosteric states differ from simplified biochemical preparations [6]. A lead with very slow association may require an exposure magnitude or duration that is difficult to achieve before elimination, despite displaying an attractive dissociation profile once bound. Rapid association followed by slow dissociation can produce a different temporal pattern even when equilibrium affinity is similar. For lead selection, k_{on} and k_{off} should therefore remain separate descriptors until the biological context justifies combining their implications.

Slow-binding inhibitor research further shows that kinetic behavior differs across targets, isoforms, and mechanistic classes [7]. This heterogeneity is relevant to natural products, where stereochemistry and conformational constraint may reshape access pathways or bound-state rearrangements without predictably changing equilibrium affinity. The proposed framework consequently rejects “slow binding” as a binary label. It instead asks which kinetic step is slow, whether the observation is reproducible under appropriate assay conditions, whether a multistep mechanism is plausible, and whether mechanistic interpretation is supported independently rather than read directly from a fitted rate constant.

Residence time versus apparent potency

Apparent potency can be misleading when an assay terminates before a slow-binding system approaches equilibrium. Time-dependent inhibitor studies demonstrate that measured potency and subclass selectivity can change with incubation conditions, making endpoint values partly dependent on assay chronology rather than only on the final binding state [8]. A weaker-looking compound may therefore have had insufficient time to express its eventual occupancy, whereas a fast-equilibrating comparator can appear favored simply because the experiment preferentially resolves rapid binding.

This creates an important distinction between a genuine potency difference and a kinetic observation window. Extending incubation is not automatically the correct solution: biological degradation, substrate depletion, target instability, or nonequilibrium cellular processes can make indefinite equilibration unrealistic. Instead, assay duration should be interpreted in relation to the kinetic mechanism and to the timescale relevant for the intended pharmacological use.

Natural-product-derived macrocyclic Gαq inhibitors make the distinction more concrete. Within related analogues, affinity and residence-time relationships can be separated experimentally, showing that structural determinants of tight binding are not necessarily identical to those that prolong complex lifetime [9]. Such evidence prevents potency from serving as an implicit proxy for all desirable binding behavior and demonstrates why matched natural-product or semisynthetic series can be especially informative when potency and kinetics diverge.

Slow reversible acetylcholinesterase inhibitors provide another example of time-dependent pharmacology in which inhibition cannot be represented adequately by a single equilibrium-style endpoint [10]. The lesson is methodological rather than therapeutic. A kinetics-aware ranking should treat potency and residence time as distinct dimensions until evidence shows that they are concordant in the relevant system. If both favor the same lead, kinetics may strengthen confidence without changing rank. If they diverge, the divergence becomes a mechanistic signal requiring functional and contextual testing rather than an automatic reason to select the slower-dissociating candidate.

Functional duration and rebinding

Residence time describes persistence of a molecular complex under a defined kinetic model; functional duration describes persistence of a biological effect. They can coincide, but they need not. Rebinding after microscopic dissociation, local drug retention, tissue or membrane partitioning, continuing free-drug exposure, and delayed recovery of downstream signaling can all

extend apparent duration beyond the lifetime of one isolated ligand–target encounter. Conversely, poor delivery to the target or distribution-limited exposure can suppress the practical importance of a favorable dissociation rate [11, 12].

The distinction matters because prolonged function after washout is not, by itself, proof of slow dissociation. A compound retained locally may repeatedly re-engage its target; a signaling network may remain altered after occupancy has ended; or an intracellular reservoir may sustain free concentrations despite nominal extracellular washout. Functional persistence therefore becomes most informative when interpreted alongside kinetic and exposure measurements capable of discriminating among these alternatives.

Controlled alteration of ligand residence time in the vasopressin V2 receptor system has shown that changing kinetics can modify pharmacological duration under defined experimental conditions [13]. Such evidence strengthens causal plausibility for that system because kinetics itself was manipulated rather than inferred from unrelated compounds. It does not justify assuming that every prolonged response is residence-time driven.

The proposed decision rule is consequently conservative: residence time should alter lead priority only when a credible kinetic difference is accompanied by pharmacologically relevant persistence and when plausible nonkinetic explanations have been examined. **Table 1** summarizes the context–method pairings that can distinguish a genuine kinetic advantage from an apparent one before slow binding is allowed to influence lead selection.

Table 1. Context-dependent measurements for interpreting discordance between potency, residence time, and persistence

Context	Principal ambiguity	Informative approach	Lead-selection interpretation
Potency shifts with incubation	Disequilibrium versus intrinsic difference	Time-resolved inhibition or binding [8]	Delay re-ranking until kinetics are adequately resolved
Similar potency, different dissociation	Equilibrium similarity versus temporal divergence	Direct association/dissociation measurements [9]	Treat residence time as independent information
Long residence, short functional effect	Molecular persistence without system translation	Washout function plus target engagement [11]	Do not reward slow dissociation automatically
Prolonged effect beyond isolated-complex lifetime	Rebinding, continued exposure, or downstream hysteresis	Exposure-sensitive pulse-chase or occupancy analysis [12]	Identify the persistence mechanism before attributing value
Kinetics experimentally altered	Association versus kinetic contribution	Controlled kinetic perturbation with functional follow-up [13]	Give kinetics greater weight only within the demonstrated context

Note: Evidence-derived observations are distinguished from the proposed lead-selection interpretations in the final column. No universal kinetic threshold or sufficient single assay is implied.

Exposure, target turnover, and cellular context

The relevance of residence time changes when the molecular complex is placed inside a pharmacokinetic and biological system. Target turnover is particularly important because synthesis and degradation determine how long occupied target remains a meaningful fraction of the

available target pool. Quantitative pharmacology shows that turnover can alter in-vivo potency, efficacy, and clearance relationships, so a slowly dissociating ligand may lose its apparent advantage when newly synthesized target rapidly restores unoccupied capacity [14]. The converse is also possible: slow turnover can preserve the

consequences of persistent engagement. For lead selection, residence time should therefore be interpreted relative to target renewal rather than as an absolute duration.

Cellular context introduces another layer. Endogenous-receptor kinetic assays demonstrate that association and dissociation can be interrogated in living cells, where receptor abundance, membrane environment, conformational state, trafficking, and competing interactions differ from purified-protein conditions [15]. Such measurements do not automatically reproduce tissue or organismal pharmacology, but they narrow the gap between biochemical kinetics and functional context.

Exposure completes the triad. A long-lived complex cannot compensate for insufficient free concentration to establish useful occupancy, while prolonged local exposure may make rapid microscopic dissociation appear functionally persistent through repeated engagement. The proposed framework therefore treats exposure, turnover, and cellular context as modifiers of kinetic meaning rather than downstream details. A residence-time difference deserves increasing decision weight only when the lead can reach the target, occupancy can be established on the relevant timescale, and biological renewal does not erase the expected persistence.

The same molecular kinetic constants can also acquire different importance under different concentration trajectories. Slow association may be negligible when exposure is sustained, yet decisive when the exposure window is brief. Likewise, slow dissociation is most informative when free-drug concentration falls enough for dissociation to become the competing process. The framework therefore evaluates kinetics against the expected concentration–time course rather than treating rate constants as context-free lead attributes. Where these conditions remain uncertain, discordant potency and residence time should trigger measurement rather than premature ranking.

When slow binding adds therapeutic value

Slow binding becomes valuable when temporal engagement solves a pharmacological problem that

potency alone does not resolve. The strongest case is not merely a low k_{off} , but a chain of concordant observations: credible kinetic separation between leads, persistence of engagement or function after free concentration falls, and a biological context in which that persistence is desirable. The natural cyclic peptide SR-A3 illustrates this logic. Stereochemical differences were linked to binding kinetics and rebinding behavior alongside prolonged pharmacological effects in the studied eEF1A system [16]. The example shows that natural-product architecture can encode kinetic information with functional consequences, without establishing that natural products generally possess advantageous residence times.

The same logic identifies when apparent kinetic superiority should receive little additional weight. In antibacterial LpxC inhibition, translation from residence time to time-dependent activity depends on target turnover and vulnerability [17]. Thus, prolonged molecular binding is pharmacologically valuable only insofar as the biological system preserves and uses that persistence.

Here, “therapeutic value” is used narrowly as a desirable pharmacological property of a candidate, not as evidence of clinical effectiveness. Persistence may be useful when continuous target coverage is sought despite fluctuating exposure, but less useful when rapid titration, reversibility, or episodic intervention is preferred. The desired temporal profile can therefore differ by indication, route, compartment, and safety margin. The proposed weighting decision is tied to a predefined pharmacological objective: without one, a longer residence time is merely longer.

This article therefore proposes a conditional value criterion: slow binding should upgrade a lead only when it contributes a duration of target engagement or function that is relevant to the intended pharmacology and cannot be explained more parsimoniously by residual exposure, rebinding, assay disequilibrium, or downstream hysteresis. A kinetic advantage that changes no meaningful system-level outcome is descriptive rather than decisional.

Table 2 identifies the principal ways in which an apparently attractive slow-binding signal can be misread before it is translated into lead-selection value.

Table 2. Failure modes that can falsely inflate the apparent value of slow binding

Failure mode	Apparent advantage	Mitigation before re-ranking	Proposed interpretation
Incomplete equilibration	Weaker endpoint potency appears rescued by later inhibition	Repeat time-resolved measurements	Do not convert assay delay into presumed therapeutic persistence
Residual or local exposure	Washout response appears residence-driven	Couple functional washout with exposure-sensitive engagement	Separate molecular persistence from continuing drug availability
Rebinding	Repeated engagement mimics one long-lived complex	Use designs that interrogate local free ligand	Treat rebinding as a system mechanism, not intrinsic residence
Rapid target renewal	Long molecular residence appears sufficient	Measure or model turnover relative to engagement	Slow binding may add little when new target rapidly appears [17]

Context-specific persistence	One model shows prolonged response	Test an orthogonal biological context	Preserve the advantage as system-bounded [16]
Note: The first three columns summarize evidence-informed interpretive problems and measurement responses developed in the preceding sections; the final column expresses the proposed framework. No single mitigation is sufficient in every target system.			

Figure 1 translates the preceding argument into a pharmacological decision architecture in which a slow-binding observation must pass progressively more contextual tests before it is allowed to alter lead priority.

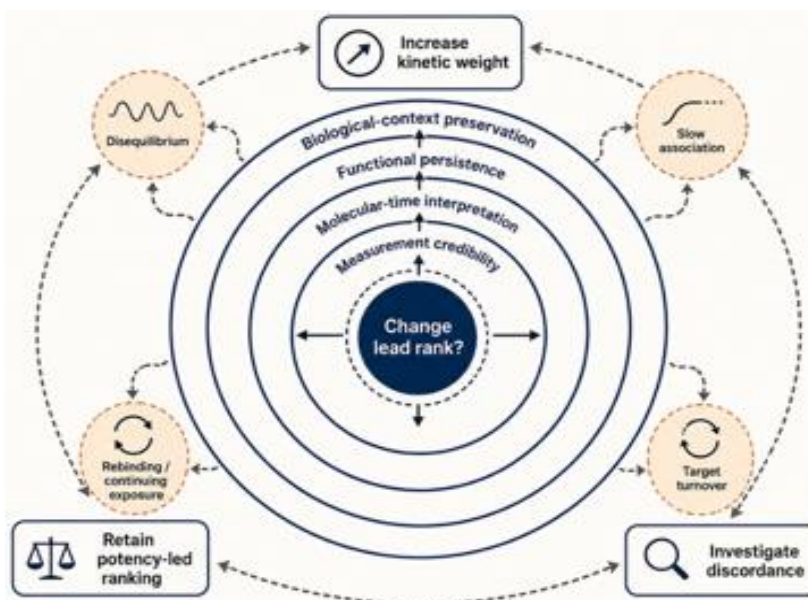


Figure 1. From slow-binding observation to kinetic priority: conditional gates across pharmacological time scales

When slow binding creates development liability

Slow binding can also create a development burden rather than a pharmacological advantage. Kinetic characterization requires assays that resolve time-dependent association and dissociation with adequate dynamic range, temporal sampling, and throughput. High-throughput kinetic technologies are increasingly available, but incorporating them into discovery still imposes platform, reagent, analysis, and quality-control demands beyond a single endpoint potency screen [18]. A kinetic phenotype that cannot be reproduced or measured robustly should therefore carry less ranking weight, regardless of its apparent attractiveness.

Pharmacological liabilities can arise when temporal persistence conflicts with the desired control of exposure or effect. Slow association may delay useful occupancy; prolonged engagement may become undesirable when rapid reversibility is needed after adverse pharmacology; and long residence can contribute little when systemic exposure or target biology is rate limiting. Mechanistic PK/PD models that incorporate drug–target binding kinetics illustrate why exposure and binding cannot be interpreted independently [19]. A lead with impressive molecular persistence may still produce limited system-level duration, whereas another with less extreme

residence time may generate adequate temporal coverage because its exposure profile is more favorable.

A further liability is interpretive lock-in. Once a slow-off phenotype is treated as a success criterion, subsequent chemistry can be optimized toward progressively longer persistence without demonstrating that the increment remains functional or useful. The framework instead requires rechecking translation as kinetics changes. This prevents residence time from becoming a surrogate endpoint inside the discovery program itself.

The proposed framework therefore treats “slow” as neither an optimization objective nor a liability by definition. Its value is directional and indication dependent. A desirable residence time is one whose temporal consequences fit the required onset, duration, reversibility, dosing context, and biological turnover. Where these requirements are unknown, selecting for slower dissociation risks optimizing a measurable property before establishing why that property matters.

The kinetics-weighted lead-selection framework

The proposed Kinetics-Weighted Lead-Selection Framework is a conditional re-ranking procedure rather than a numerical score. It begins from the potency-led order already available to a discovery program and asks whether kinetic evidence is strong enough, distinct enough,

and pharmacologically relevant enough to justify changing that order. This is practical because medicinal chemistry can deliberately modify binding kinetics through structural changes, although the effective strategy depends on target and chemotype [20]. The framework does not assume that increasing residence time is always an appropriate optimization direction.

The first decision is evidential: was potency measured under conditions that make the comparison interpretable, and are association and dissociation estimates sufficiently credible to establish real kinetic discordance? The second is mechanistic: does the kinetic phenotype have a plausible molecular explanation, or might assay chronology, probe behavior, or model choice account for it? The third is translational: does the difference survive a functional or engagement experiment after changing free-drug conditions? The fourth is contextual: do exposure, rebinding, target turnover, and cellular environment preserve the difference on the pharmacological timescale of interest?

Only then is weighting considered. Thermodynamic and kinetic profiles are separable optimization dimensions, so

a lead can be strong on one and weak on the other without either measurement being erroneous [21]. The proposed rule is therefore asymmetric: kinetics should have little power to rescue weak potency when useful occupancy cannot be achieved, but substantial power to break a potency tie or reverse a modest potency advantage when credible temporal persistence is both demonstrated and desirable. Conversely, kinetics should downgrade a nominally potent lead when slow association or unwanted persistence conflicts with the required pharmacology.

Computational estimates may help prioritize which compounds merit expensive kinetic experiments, but predicted association, dissociation, or residence time remains method dependent and should not be treated as equivalent to measurement [22]. In this framework, computation supplies hypotheses and triage evidence; experimentally anchored kinetics carries greater decision authority when lead rank materially changes.

Table 3 compares the alternative representations of a discordant lead profile and makes explicit the assumptions introduced as increasing kinetic and contextual information is added.

Table 3. Lead representations for decisions when potency and duration disagree

Representation	Information retained	Critical assumption	Appropriate decision use	Status
Potency-only	Endpoint activity or equilibrium strength	Timing does not alter rank	Efficient initial triage	Established descriptor; incomplete when discordance is suspected
Potency plus residence time	Activity plus complex persistence	Dissociation-derived persistence is meaningful	Detect temporal differentiation	Intermediate representation
Full kinetic profile	Potency, association, dissociation	Rate estimates are experimentally credible	Diagnose how divergence arises	Evidence-led representation
Context-weighted kinetic profile	Kinetics, functional persistence, exposure, turnover, cellular context	System modifiers are sufficiently characterized	Re-rank discordant leads	Proposed decision representation
Predicted kinetic profile	Computational kinetic estimates	Simulation domain and validation are adequate	Prioritize confirmatory experiments	Supportive only [22]

Note: Increasing representational complexity does not guarantee better lead selection. Additional dimensions should be retained only when measured with sufficient credibility and relevance to the decision.

Decision scenarios for discordant potency and duration

Three recurring scenarios clarify how the framework changes interpretation without imposing a universal score. First, consider two related natural-product leads with similar equilibrium potency but substantially different residence times. Macrocyclic Gαq inhibitors provide an empirical precedent for separating structure–affinity from structure–residence-time relationships [23]. If the longer-residence analogue also shows appropriate functional persistence under conditions that minimize continuing free drug, kinetic evidence can legitimately break the potency tie. If functional duration remains equivalent, the kinetic difference should be recorded but need not determine priority.

Second, consider a more potent lead whose duration is shorter than that of a modestly weaker analogue. The framework does not automatically select the longer-lasting compound. Instead, the discordance should prompt orthogonal mechanistic interrogation. NMR analysis of FR900359 demonstrates that inhibitor binding can produce detectable structural responses in the G-protein complex [24]. Structural evidence can therefore help determine whether unusual kinetics reflects a meaningful conformational mechanism rather than assay behavior, although structural change alone does not establish pharmacological superiority.

Third, the apparently simple ligand–target pair may itself be the wrong representation. Recent work on cyclic Gq/11

inhibitors indicates that these molecules can stabilize heterotrimeric protein complexes as molecular glues [25]. In such a case, a single binary residence-time value may compress a multicomponent mechanism whose persistence depends on complex state. The representation should therefore expand when the mechanism demands it rather than force a complex pharmacology into a single dissociation parameter.

A fourth practical scenario is a potent, long-residence lead with unusually slow association. Such a molecule can look ideal after long incubation yet underperform when the available exposure window is too brief to establish occupancy. Here the framework can downgrade rather than reward slow binding: the attractive off-rate does not automatically compensate for an onset problem. The relevant comparison is the whole temporal trajectory of engagement, not the most favorable individual rate constant.

Across these scenarios, kinetic information has three possible consequences: upgrade, when credible persistence adds desired pharmacological duration; downgrade, when onset or persistence conflicts with the intended profile; or hold, when kinetic differences do not survive contextual testing. The important decision is not which metric wins, but whether the evidence supporting temporal behavior is strong enough to change a lead choice that would otherwise be made from potency.

Boundary conditions and measurement requirements

A kinetics-weighted decision is only as defensible as the measurements supporting it. Lead-changing claims should ideally include direct or otherwise well-validated kinetic measurements, explicit assay timing, concentration conditions, model assumptions, and evidence that the fitted mechanism is identifiable. Pre-equilibrium approaches in living cells demonstrate that association and dissociation constants can be estimated without waiting for conventional equilibrium, although the suitability of any particular assay remains modality and system dependent [26]. Orthogonal confirmation becomes especially important when small kinetic differences would reverse a lead ranking.

Measurement design should also distinguish molecular residence from functional washout. Useful experiments may combine binding kinetics, target engagement, pulse-chase or washout pharmacology, exposure measurements, and target-turnover information at compatible timescales. The framework does not require every modality for every project; it requires enough independent evidence to exclude the most plausible competing explanation for the claimed kinetic advantage.

Computational kinetics can extend this evidence base but introduces its own boundaries. Milestoning and related

approaches can estimate rare binding or unbinding events, yet results depend on setup, sampling, state definitions, and methodological assumptions [27]. Predictions should therefore be accompanied by uncertainty, domain information, and experimental checks appropriate to the decision being made.

Temporal alignment is itself a boundary condition. A biochemical k_{off} measured over hours, a cellular washout response measured over minutes, and plasma exposure sampled at another interval cannot be combined meaningfully unless the sampling windows resolve the processes being compared. The framework therefore requires timescale compatibility before apparently concordant kinetic, functional, and exposure data are interpreted as one mechanism. A predicted long residence time can justify measurement priority; it should not, by itself, justify selecting a natural-product lead over an experimentally better-characterized comparator.

Limitations

The framework is conceptual and has not been prospectively validated as a lead-ranking algorithm. Its conditions are derived from heterogeneous pharmacological, medicinal-chemistry, structural, cellular, PK/PD, and computational evidence rather than from a standardized natural-product benchmark. Natural-product-specific kinetic studies remain much less extensive than the general residence-time literature, so transfer across scaffold classes, target families, and assay platforms requires caution.

Computational components present additional uncertainty. Force fields, sampling, learned representations, state definitions, and practical usability can materially affect ligand-binding kinetic simulations, while calculated free energies and kinetic parameters require domain-aware validation before they inform discovery decisions [28, 29]. The framework consequently assigns computational kinetics a supportive rather than determinative role.

It also intentionally supplies no universal residence-time threshold, weighting coefficient, or rule for the magnitude of potency difference that kinetics should overturn. Such quantities would require prospective matched-series studies with predefined decisions and independent outcomes. Finally, functional duration can reflect signaling hysteresis, compartmental drug retention, active metabolites, irreversible chemistry, or other mechanisms not reducible to reversible binding kinetics. The framework is intended to expose these alternatives, not to force them into a residence-time explanation.

CONCLUSION

Natural-product lead selection becomes vulnerable to misranking when potency, molecular residence, and functional duration disagree and the disagreement is collapsed into a single notion of “strong binding.” The proposed framework instead treats equilibrium activity, association, dissociation, persistence, exposure, turnover, and cellular context as distinct but interacting sources of evidence.

Slow binding deserves greater weight when the kinetic difference is measured credibly, survives a pharmacologically relevant functional or engagement test, remains meaningful after exposure and target renewal are considered, and produces a temporal profile that suits the intended use. It deserves little additional weight when persistence is explained more convincingly by continuing exposure, rebinding, assay disequilibrium, downstream memory, or an inadequately resolved mechanism.

This approach does not replace potency-led screening or prescribe a universal optimum. It specifies when a potency ranking has become pharmacologically underdetermined and when kinetic evidence is strong enough to justify reconsideration. Prospective validation across matched natural-product and semisynthetic series is required before the framework can be treated as a predictive selection instrument.

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