



Chemical Novelty Is Not Pharmacological Novelty When Natural Product Discovery Prioritizes Unusual Structures Without Demonstrating New Mechanisms or Therapeutic Functions

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ABSTRACT

Natural product discovery often treats unusual molecular architecture as an intrinsically high-value signal, because rare scaffolds can expand explored chemical space and expose medicinal chemists to combinations of shape, stereochemistry, functionality, and biosynthetic logic that are uncommon in conventional libraries. The difficulty is not that chemical novelty lacks value, but that it is frequently allowed to stand in for stronger claims about target, mechanism, pathway, phenotype, or therapeutic function. This theoretical perspective argues that such claims belong to different evidentiary levels. Chemical novelty concerns how a molecule differs from reference chemistry, whereas pharmacological novelty concerns whether it produces a meaningfully different biological interaction, mechanism, network consequence, or therapeutically relevant function. A multidimensional novelty framework is therefore proposed in which structural difference is treated as one discovery attribute rather than as a surrogate for downstream biological difference. The analysis distinguishes scaffold and substructure novelty from target novelty, target engagement from causal mechanism, multi-target activity from network-level novelty, and phenotypic difference from therapeutic functional difference. It also emphasizes asymmetric cases in which new chemistry reaches familiar pharmacology and familiar chemistry remains pharmacologically valuable. The framework is intended to improve claim discipline and portfolio prioritization, not to supply a validated scoring system or universal threshold. Its applicability depends on representation choices, assay context, target evidence, biological model relevance, exposure, and the predictive validity of evidence used for downstream decisions.

Key Words: *Natural products, Chemical novelty, Pharmacological novelty, Target validation, Phenotypic discovery, Drug prioritization*

eIJPPR 2025; 15(6):125-133

HOW TO CITE THIS ARTICLE: Schneider N, Frank T, Müller A, Meier C. Chemical Novelty Is Not Pharmacological Novelty When Natural Product Discovery Prioritizes Unusual Structures Without Demonstrating New Mechanisms or Therapeutic Functions. Int J Pharm Phytopharmacol Res. 2025;15(6):125-33. <https://doi.org/10.51847/ZFX6egujTG>

INTRODUCTION

Natural products remain major sources of drug-discovery inspiration because they provide complex, evolutionarily generated chemistry, privileged motifs, and routes into molecular property space that is not always well

represented in conventional screening collections. Contemporary reviews continue to place natural products and their derivatives within discovery strategies that span isolation, synthesis, target identification, mechanistic characterization, optimization, and translation, while historical analyses show persistent contributions of

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Received: 27 August 2025; **Revised:** 29 November 2025; **Accepted:** 05 December 2025

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natural-product-related chemistry to approved therapeutics [1–3]. None of this requires chemical novelty to be dismissed. It requires chemical novelty to be located correctly within the chain of claims that moves from structure to pharmacology.

The central problem is evidentiary substitution. A molecule can be unprecedented relative to a database, distant from known scaffolds, or assembled through an unusual natural-product-inspired design strategy and still bind an established target, perturb a familiar pathway, or reproduce a known cellular phenotype. Conversely, a chemically familiar scaffold can acquire important pharmacology through a different binding mode, selectivity pattern, exposure profile, tissue context, or functional consequence. Structure and pharmacology can therefore covary, but one does not logically certify the other.

This perspective proposes that “novelty” should be treated as a family of claim types rather than as a single prestige label. Chemical novelty describes difference in molecular representation. Target novelty concerns whether the relevant biological target relationship is genuinely new. Mechanistic novelty concerns whether causal molecular events differ in a consequential way. Network novelty concerns whether downstream pathway organization differs rather than merely receiving a different proximal input. Functional novelty concerns whether the compound produces a therapeutically meaningful biological effect not captured by existing interventions or known response classes. These distinctions are proposed as an interpretive framework, not as validated categories with fixed quantitative boundaries. Their value is to make the evidentiary burden proportional to the claim being made.

Why chemical novelty became a dominant natural product value proposition

Chemical novelty is attractive partly because it is observable early. Retrospective analyses of natural-product discovery can map structures, descriptors, scaffold relationships, and historical coverage of chemical space before a complete pharmacological account exists [4]. Recent analysis of microbial natural products similarly treats diversity and redundancy as measurable structural properties, demonstrating that unusualness can be studied explicitly as a chemical-space problem [5]. This operational convenience matters: discovery teams can rank a structure as rare or distant long before they can establish causal mechanism, network behavior, or therapeutic differentiation.

A second reason is that natural-product character can be genuinely useful. Comparative chemoinformatics indicates that natural-product-related structural features occur non-randomly among successful small-molecule discovery compounds [6]. The appropriate inference, however, is that natural-product-derived chemistry can enrich medicinal chemistry with useful structural information and design opportunities. It is not that natural-product character, rarity, or scaffold distance automatically supplies a new mechanism. Chemical novelty is therefore best treated as an exploration signal: it can justify attention, synthesis, assay investment, or protection of underexplored chemical space without predetermining what kind of biological novelty will follow.

The distinction is summarized in **Table 1**, which separates what early structure-level evidence can legitimately establish from what remains pharmacologically unearned.

Table 1. Structural novelty as a discovery construct: claims supported at the chemical level and claims that remain unearned

Construct	Manuscript-derived meaning	Evidence it can support	Claim it cannot establish by itself
Chemical novelty	Difference from reference chemistry under a stated representation	Unusualness, distance, rarity, or underexplored chemical space [4]	New target, mechanism, pathway, or therapeutic function
Chemical diversity	Breadth or redundancy within a defined structure collection	Comparative coverage of structural space [5]	Biological diversity across assays or disease contexts
Natural-product structural character	Presence of NP-related features or fragments within a compound set	Structural association with drug-discovery-relevant chemistry [6]	Causal explanation of development success or pharmacological novelty
Pharmacological novelty	Proposed downstream claim about differentiated biological interaction or function	Requires evidence beyond structure	Cannot be inferred from scaffold rarity alone

Note: The final row is a proposed conceptual distinction developed in this perspective; it is not a validated classification threshold.

Figure 1 makes the same asymmetry visible: unusual structure can legitimately increase discovery interest, but it

encounters an evidentiary boundary before it can support downstream pharmacological claims.

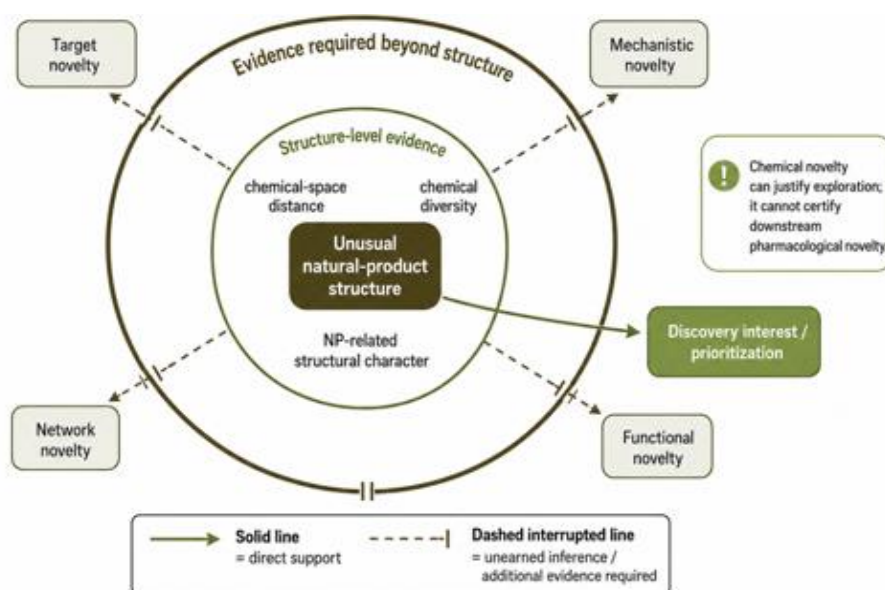


Figure 1. The novelty firewall between unusual natural-product chemistry and downstream pharmacological claims

Structural novelty at the scaffold and substructure levels

Once chemical novelty is treated as a distinct claim, the next question is how it is represented. Modern natural-product databases make structure comparison reproducible enough to support analyses of scaffolds, substructures, descriptors, stereochemical content, and related molecular properties, but every novelty estimate remains conditional on database scope and standardization [7]. A structure can be unique because the comparison set is narrow, because tautomeric or stereochemical normalization differs, or because the chosen representation emphasizes one level of molecular organization over another. Structural novelty is therefore not a property that exists independently of a reference frame.

Bioactivity resources reinforce this separation because they maintain chemical structures, targets, assays, and measured activities as distinct data layers [8]. A compound may be structurally distant while its biological annotations cluster with a familiar pharmacological class, or structurally close while producing materially different activities under a different assay or context. The database architecture does not prove biological independence, but it makes clear that structural and pharmacological claims require different evidence objects.

Contemporary natural-product-like and pseudo-natural-product strategies sharpen the point. Targeted sampling of natural-product space can deliberately generate molecules from underexplored regions and then subject them to experimental biological screening; pseudo-natural-product synthesis can likewise create unprecedented fragment combinations whose biological behavior must still be profiled rather than inferred from construction alone [9–11]. The experimental sequence matters. Structural design

generates hypotheses about biology. It does not complete the biological argument. For this perspective, scaffold novelty and substructure novelty are therefore treated as legitimate, representation-dependent discovery descriptors whose pharmacological significance remains an empirical question.

Target novelty is a different scientific claim

Target novelty begins where structural comparison ends. A molecular target is a biological object with its own evidence history, disease relevance, tractability, and pharmacological context. Comprehensive mapping of drug targets shows that target identity can be catalogued independently of the chemical novelty of the ligands acting on it [12]. An unusual natural-product scaffold can therefore engage a well-established target without making that target new; likewise, a familiar chemotype could become important if it establishes a credible relationship with a previously unexploited target.

Target novelty also should not be confused with target confidence. Human genetics can strengthen the rationale for selecting or validating a target in drug development, and recent analyses indicate that genetically supported target hypotheses can be informative for clinical-development outcomes [13, 14]. That evidence concerns the plausibility and translational support of the target relationship. It does not prove that a particular compound engages the target as proposed, nor does it make the ligand chemically novel.

The distinction proposed here is deliberately conservative. A target-level novelty claim should specify whether the novelty lies in the biological target itself, in the ligand–target relationship, in the binding site or mode, or only in

the chemotype used to reach an already established target. These are different scientific achievements. Treating them as interchangeable inflates the meaning of a new scaffold and obscures cases in which the real contribution is improved tractability, selectivity, or experimental access to familiar target biology.

Mechanistic novelty requires more than binding a different protein

Mechanism is a stronger claim than target contact. Cellular thermal-shift approaches such as CETSA and thermal proteome profiling can support target engagement or help identify proteins whose stability changes in the presence of a natural product, but the resulting signal is one evidentiary layer rather than a complete causal mechanism [15]. Chemical proteomics similarly expands the ability to nominate or identify candidate natural-product targets, while remaining vulnerable to probe effects, nonspecific interactions, abundance biases, and context dependence [16].

Recent natural-product target-identification strategies increasingly combine computational, proteomic, biochemical, and cellular approaches rather than treating any single method as definitive [17]. This convergence is important because mechanistic novelty should concern a causal sequence: the compound engages a relevant molecular entity, that engagement changes a biological process in a distinguishable way, and the change plausibly accounts for the observed phenotype. A new protein hit without that chain may reflect collateral binding, assay context, or an intermediate event rather than a new therapeutic mechanism.

Structured target-assessment recommendations likewise emphasize convergent evidence, relevance, and transparent validation rather than isolated affinity or binding observations [18]. Building on that logic, this perspective proposes that a pharmacological mechanism should be called novel only when the evidence distinguishes it from known explanations at the level appropriate to the claim. That may involve orthogonal engagement evidence, perturbation or rescue, temporal concordance, pathway readouts, or other context-appropriate tests. No single package is universally mandatory, but the burden must rise as the claim moves from “binds a different protein” to “operates through a new mechanism.”

Pathway novelty and network-level redundancy

Even a credible new target relationship does not guarantee a new pathway consequence. Polypharmacology makes the distinction unavoidable because one molecule can produce multiple target activities, and structure–multiple activity relationships can span several pharmacological

annotations at once [19]. In that setting, novelty at the proximal target level can coexist with redundancy downstream: different targets may converge on the same signaling node, stress response, transcriptional program, or physiological endpoint.

Recent analyses of drug polypharmacology likewise illustrate that clinically relevant compounds can act through more than one target and that the importance of each interaction depends on exposure, tissue context, and the concentration range reached in practice [20]. Counting targets therefore cannot serve as a network-novelty metric. Nor should a pathway be called novel simply because a different upstream protein was perturbed.

The proposed distinction in this perspective is that network novelty requires evidence of differentiated downstream organization or consequence, not merely a different point of entry. Such evidence might include pathway-resolved perturbation, time-dependent signaling behavior, multi-omic response patterns, or functional interactions that cannot be explained by the established network response. The exact tests will vary by system, and network evidence can remain ambiguous because convergent biology is common. That ambiguity is not a defect in the framework; it is the reason target, mechanism, and network novelty should remain separate claims.

Functional novelty as a therapeutic criterion

Phenotypic drug discovery provides a useful counterweight to structure-first and target-first reasoning because it begins with an integrated biological response rather than with a prespecified molecular target. Phenotypic screening can identify compounds that alter cellular or organismal states in ways that would not have been predicted from known target annotations, but the approach also makes target deconvolution and mechanistic interpretation more demanding [21]. For novelty claims, this means that a differentiated phenotype is informative precisely because it measures something other than structural distance.

Yet phenotypic difference is not automatically therapeutic functional difference. Recent assessments of phenotypic discovery emphasize both its successes and its dependence on model relevance, assay design, mechanistic follow-up, and translation across biological scales [22]. A compound that produces a distinct cellular response may still converge on a familiar disease-relevant endpoint, or the response may disappear under more physiologically relevant exposure conditions. The proposed criterion here therefore places therapeutic functional novelty above assay-level difference: the relevant question is whether the compound produces a differentiated biological consequence that matters to the intended therapeutic problem.

Image-based profiling makes this distinction especially visible. Deep-learning approaches can encode complex cellular morphology and identify phenotypic similarities or differences that are difficult to capture with manually selected features [23]. Those embeddings are useful comparative measurements, but distance in a learned representation is not intrinsically a new mechanism. Morphological profiling can likewise support mode-of-

action hypothesis generation and comparison with reference compounds, while remaining sensitive to cell type, imaging protocol, batch effects, and the composition of the reference set [24]. Functional novelty should therefore be claimed at the level actually measured.

Table 2 distinguishes the evidence states that are often compressed into a single claim of “new biology.”

Table 2. From observed activity to therapeutic functional novelty: distinctions in what each evidence layer can establish

Evidence layer	What is demonstrated	What remains unresolved	Appropriate novelty claim
Target engagement	Interaction with a candidate target in the tested context [15]	Causal contribution to phenotype	Target-engagement evidence
Target assessment	Convergent support for target relevance and tractability [18]	Whether the compound produces a differentiated function	Target-level confidence
Phenotypic response	Integrated biological change in the chosen model [21]	Mechanism and therapeutic relevance	Phenotypic difference
Morphological profile	Similarity or difference in high-content cellular state [24]	Causality, organismal translation, clinical meaning	Profile-level novelty
Therapeutic functional novelty	Proposed category: differentiated function relevant to the therapeutic problem	Prospective validation and context dependence	Pharmacological novelty only when supported beyond assay-level difference

Note: The final row is a proposed conceptual synthesis. No quantitative threshold is implied.

When new chemistry reaches an old biological endpoint

Direct counterexamples make the non-equivalence of chemical and pharmacological novelty more than a semantic concern. Scaffold hopping from natural products to synthetic mimetics has shown that substantial structural change can preserve intended biological activity [25]. The resulting chemistry may be novel in scaffold terms while the core pharmacological function remains recognizably related to that of the source compound. Structural distance therefore can coexist with functional continuity.

A more recent pseudo-natural-product example sharpens the point. Morphological profiling identified a novel chemotype that was subsequently associated with Aurora kinase inhibition, an established target class [26]. The achievement is chemically and methodologically meaningful, but its novelty resides in the chemotype and discovery route rather than in the existence of Aurora kinase pharmacology itself.

These cases should not be interpreted as arguments against scaffold innovation. Scaffold hopping can create new opportunities for medicinal chemistry even when biological function is retained [25]. Likewise, a new chemotype directed toward known pharmacology may prove valuable if it ultimately offers differentiated selectivity, physicochemical properties, exposure, resistance behavior, or developability, although such advantages must be demonstrated rather than presumed [26]. The appropriate conclusion is therefore asymmetric:

new chemistry can reach old biology, and old biology does not erase the potential value of new chemistry.

A chemical–mechanistic–functional novelty matrix

The distinctions developed above can be organized as a proposed multidimensional novelty matrix. The first dimension is chemical: how far the molecule lies from a defined structural reference under an explicit representation. Chemical-space analyses provide the necessary basis for this dimension [4]. The second is pharmacological, but it must be decomposed into target, mechanism, network, and function rather than treated as one binary variable. Drug-target mapping demonstrates why target identity is independently classifiable [12]. Phenotypic discovery demonstrates why functional response is another independent evidentiary object [21]. The matrix is not intended to produce a universal novelty score. Its purpose is to preserve discordance. A candidate can occupy a high-chemical/low-pharmacological-novelty region when an unprecedented scaffold produces an established mechanism. It can occupy a lower-chemical/high-pharmacological-novelty region when a familiar chemotype produces a differentiated, well-supported biological function. Intermediate cases include new target relationships that converge on familiar networks, altered binding modes at known targets, and novel cellular phenotypes whose therapeutic meaning remains unresolved.

A useful property of the matrix is that it permits novelty to decrease as evidence improves. Early in discovery, a candidate may appear highly differentiated because only its structure and a sparse phenotype are known. Target identification or comparison with reference perturbations may later reveal familiar pharmacology. That revision should be treated as successful scientific resolution rather than as loss of value. Conversely, mechanistic follow-up can increase pharmacological novelty even when chemical novelty is modest. The proposed framework therefore treats novelty classifications as evidence-dependent states that may be revised without forcing the underlying compound into a single permanent label.

That separation changes the question asked during prioritization. Instead of asking whether a compound is “novel,” the proposed matrix asks: novel in which dimension, relative to what reference, supported by what evidence, and relevant to which decision? The framework is deliberately non-numeric because the available evidence does not establish transferable weights or thresholds across discovery programs.

Evidence needed to claim pharmacological novelty

Novelty becomes decision-relevant only when the supporting evidence is predictive for the decision being made. Predictive-validity analyses in drug discovery emphasize that attractive surrogate measurements are useful only to the extent that they inform downstream outcomes in the intended context [27]. A structural novelty score may therefore be highly valid for selecting compounds that expand chemical space while being weak evidence for selecting compounds expected to deliver differentiated therapeutic biology.

The evidentiary burden should rise with claim strength. Target engagement can support the statement that a compound interacts with a protein in a cellular context [15]. Structured target assessment can strengthen the case that the target is biologically relevant and that the evidence is internally coherent [18]. Phenotypic discovery can demonstrate integrated functional response in an experimental model [21]. None of these evidence types alone necessarily establishes therapeutic functional novelty.

This perspective therefore proposes claim-proportional evidence. A target-novelty claim needs credible target identity and relevance. A mechanistic-novelty claim needs causal discrimination from competing explanations. A network-novelty claim needs evidence that downstream organization or consequence differs, not merely that a different proximal target was engaged. A therapeutic-function claim needs disease-relevant functional evidence and, where appropriate, exposure and translational support.

The exact experimental package must remain context dependent.

Reporting should mirror that claim structure. A study describing a “novel” natural product should identify the reference set and representation used for the structural claim, then separately state whether target engagement, causal mechanism, network consequence, phenotype, or therapeutic function was actually tested. Bioactivity resources illustrate why structure, assay, target, and activity annotations should not be collapsed into one field [8]. Target-assessment guidance similarly favors transparent evidentiary qualification over categorical certainty [18]. Where novelty is being used to justify portfolio advancement, the downstream decision and its validation endpoint should also be stated because predictive validity is decision specific [27]. This reporting discipline would make negative or familiar pharmacology interpretable rather than rhetorically inconvenient.

Re-ranking discovery portfolios using multiple forms of novelty

Natural-product portfolios could use these distinctions without abandoning chemical exploration. Natural-product-related structural features can carry discovery value [6], and targeted sampling of underexplored natural-product-like space can generate experimentally useful candidates [9]. The proposed change is to prevent those features from receiving automatic credit for mechanistic or therapeutic novelty.

Portfolio ranking could instead update several evidence dimensions independently. Human-genetic evidence can strengthen confidence in a target without changing the novelty of the ligand scaffold [13]. Polypharmacological evidence can alter how a candidate is interpreted at the network level without implying that every additional target constitutes a new mechanism [19]. Structural rarity, target confidence, causal mechanism, phenotypic differentiation, and therapeutic relevance would therefore enter the decision as separate evidence states.

The practical advantage is not a guaranteed improvement in portfolio performance; that would require prospective testing. Rather, the framework makes disagreements diagnosable. A chemically spectacular compound may remain high priority because it expands accessible space, while its pharmacological novelty remains unproven. Another compound may be structurally familiar but rise because its biological evidence differentiates it from existing options. A third may be deprioritized because its apparent novelty collapses after target or phenotypic comparison.

Any re-ranking system built from these distinctions should be evaluated against decision-relevant downstream outcomes rather than assumed to be superior because it is

more multidimensional [27]. Until such validation exists, the framework is best used as a claim-discipline and portfolio-reasoning tool.

Why chemically familiar compounds can still be pharmacologically important

A novelty framework can generate the opposite error if it rewards difference so aggressively that familiar chemistry is undervalued. Historical drug-source analyses show that natural products, derivatives, and related chemistries have contributed repeatedly to therapeutics [3]. Comparative analyses of successful small molecules also indicate that natural-product-related structural features can remain useful within contemporary medicinal chemistry [6]. Neither observation requires unprecedented scaffolds.

Familiar chemistry can be valuable because medicinal chemistry is not a competition for structural surprise. Scaffold hopping demonstrates that biological function can sometimes be retained while chemistry changes substantially [25], which implies the converse caution: structural familiarity does not determine pharmacological triviality. The pseudo-natural-product Aurora kinase example likewise shows that a new chemotype can be valuable even when its proximal pharmacology belongs to a known target class [26].

The relevant decision is therefore not whether a compound is chemically familiar, but whether it solves an important discovery problem. Improved selectivity, exposure, tissue distribution, safety, synthetic accessibility, resistance profile, or functional performance could justify prioritization, but none should be credited without direct evidence. Novelty and value overlap only partially.

Conceptual boundaries

The proposed framework is bounded first by measurement. Chemical novelty changes with the reference database, standardization procedure, descriptor set, fingerprint, scaffold definition, and similarity metric. Bioactivity databases also contain heterogeneous assays and annotation confidence, so proximity or distance across their chemical and pharmacological layers must be interpreted cautiously [8]. Phenotypic novelty is equally conditional on model system, endpoint, assay timing, concentration, and the biological state represented; phenotypic discovery literature repeatedly emphasizes these translational constraints [22].

Second, target and mechanism classifications remain evidence dependent. Convergent target assessment can reduce uncertainty but does not convert an early discovery claim into universal mechanistic certainty [18]. Predictive validity is likewise context specific: evidence useful for one decision stage may perform poorly for another [27].

Third, the framework is primarily intended for small-molecule natural-product and natural-product-inspired discovery. Mixtures, biologics, covalent modalities, formulation-dependent systems, and interventions whose function emerges from multicomponent composition may require additional novelty dimensions. The framework also does not establish that pharmacological novelty should always be preferred. Familiar mechanisms can be therapeutically important, and structurally unusual molecules can be valuable for reasons unrelated to new biology.

Finally, novelty is time dependent. A target, pathway, or phenotype described as unprecedented at discovery may become familiar as databases, reference compounds, and mechanistic knowledge expand. Conversely, reannotation can reveal differences that were previously invisible. Claims should therefore specify the comparator landscape available at the time of analysis and remain open to revision. This is particularly important for computational similarity measures and phenotypic reference atlases, where database growth can change the apparent distance of the same compound without changing the molecule itself.

CONCLUSION

Chemical novelty is a legitimate discovery achievement, but it answers a structural question. Pharmacological novelty answers a biological one. Treating the two as interchangeable risks promoting unusual scaffolds before target identity, causal mechanism, network consequence, or therapeutic function has been distinguished from what is already known.

This perspective proposes that novelty claims be decomposed into chemical, target, mechanistic, network, and functional dimensions, with evidence matched to the level of claim. The framework preserves productive asymmetry: chemically unprecedented compounds may reproduce familiar pharmacology, while chemically familiar compounds may remain highly valuable when they deliver a meaningful biological or developability advantage.

The proposal is not a validated scoring system and does not prescribe universal thresholds or portfolio weights. Its purpose is narrower: to make novelty claims auditable, to prevent structural rarity from acting as a surrogate for therapeutic differentiation, and to clarify what evidence is still missing. Natural-product discovery gains more, not less, from unusual chemistry when the significance of that chemistry is tested rather than assumed.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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