

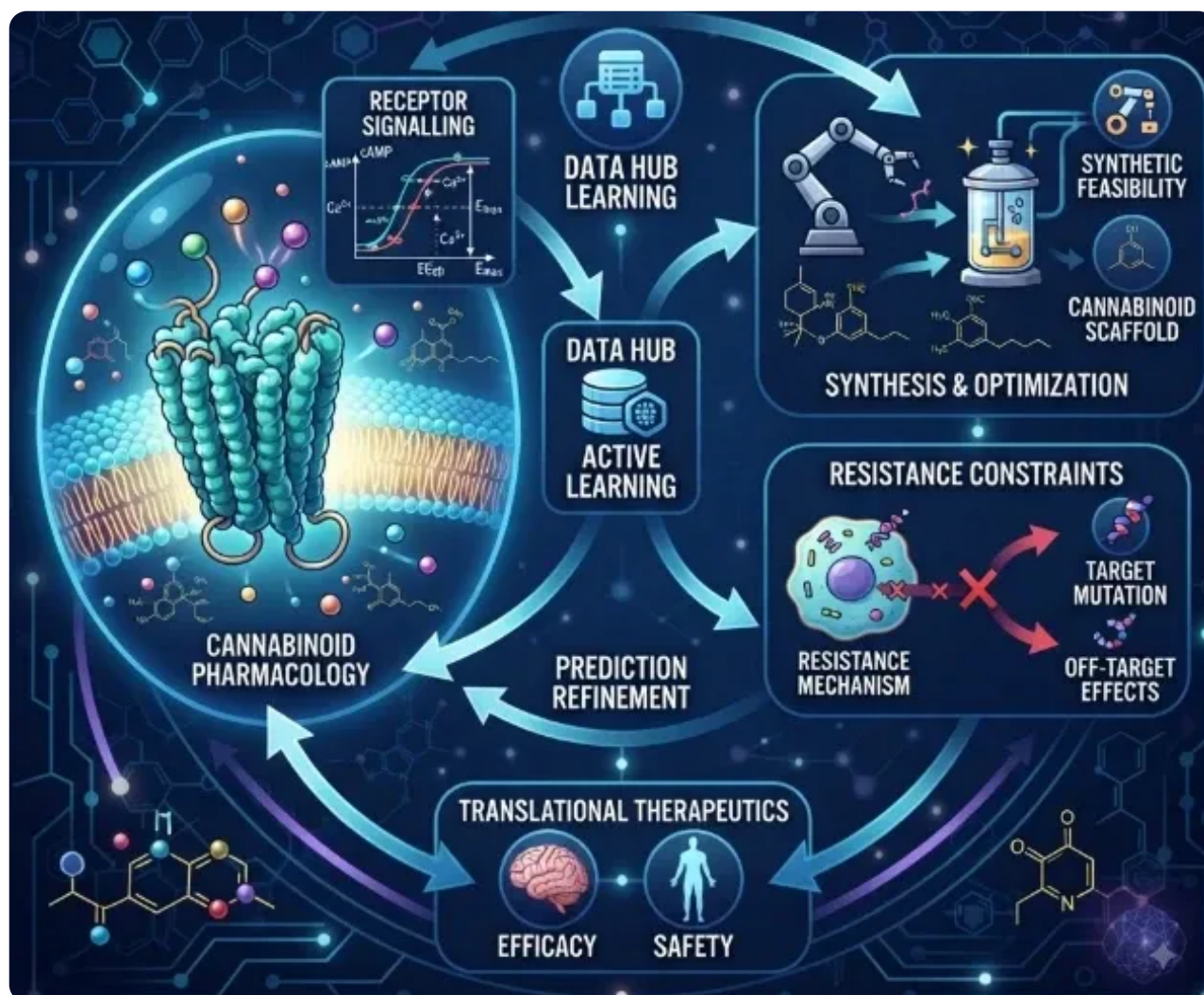
Closed-Loop Medicinal Chemistry: Active Learning with Synthesis and Resistance Constraints for Cannabinoid Pharmacology, Receptor Signalling, Drug Discovery and Translational Therapeutics Category

Md. Humayan Kabir

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Abstract

This article presents closed-loop cannabinoid medicinal chemistry as an iterative learning system that combines receptor pharmacology, synthesis, exposure, safety, and tolerance. CB1 and CB2 affinity alone are insufficient optimization targets because ligand structure can alter G-protein activity, arrestin recruitment, receptor internalization, functional selectivity, allostery, off-target effects, and pharmacokinetics. Active learning, structure-based design, parallel synthesis, multipathway signaling assays, selectivity panels, tolerance models, and iterative pharmacokinetics are proposed for selecting compounds that provide both performance and information gain. The key decision becomes which next molecule most reduces uncertainty while satisfying chemical and biological constraints. Pain mechanism, inflammatory status, central versus peripheral exposure, prior cannabinoid use, and comedication are treated as context variables. Risks include psychoactivity, receptor desensitization, off-target GPCR activity, species differences, and metabolite effects. Synthetic accessibility, stereochemical control, solubility, purity, and scalable routes are integrated as hard constraints. Overall, the article argues that cannabinoid design should operate as a prospective learning loop rather than a linear campaign focused on binding affinity or potency.



The closed-loop approach to medicinal chemistry of cannabinoids has reached a stage where it no longer just seeks to identify the potency, delivery or association of a certain result, but demands to explain why and when a result is achieved. An affinity, signaling efficacy, allostery, off-target activity, pharmacokinetics, and tolerance mechanistic network rests at the core of this change. It is important that that network matters because a ligand that looks good in one binding assay may not be successful because it has poor synthetic route, unexpected side effects on the target, species differences, or tolerance to the ligand is quick. Therefore, a better development strategy considers mechanism, context and uncertainty as intertwined design variables, not as separate tasks to be done at different points in the development process.

The case of the discovery of Cannabinoids as a drug demonstrates the limitations of receptor binding as an optimization target. CB1 and CB2 receptors are coupled to several signaling pathways and there are several aspects of ligand structure that impact on G-protein activity, arrestin recruitment, receptor internalization, efficacy and off-target pharmacology. In 2024, structure-based work also showed that there is a signaling profile

in the preclinical models that is different from classical orthosteric agonism via allosteric modulation. Each synthesis round can incorporate multipathway pharmacology, exposure, safety, and synthetic feasibility into models, instead of just affinity, an approach that is well suited to this complexity.

The outcome is a new discovery approach, an active learning, structure-based design approach, a parallel synthesis approach, multipathway signaling assays, selectivity panels, resistance or tolerance models, and iterative pharmacokinetics. None of these tools is uniquely decisive - each only measures a subset of a larger biological or clinical process. As independent measurements begin to all align with a single causal narrative, with an increasing level of confidence, across dose, time, model system and in the relevant biological context. Not all of the results are consistent, and that is important because when there are conflicting results there may be hidden mechanisms, assay artifacts, population differences, or exposure limitations that are worth exploring before expensive development efforts are undertaken.

When deciding which compound to move forward, the problem is what will give the maximum information gain which is compliant to the chemical and biological constraints. To answer that question, it's necessary to make explicit comparisons between the intended mechanism and plausible alternative mechanisms, such as off-target activity, parallel pathways, differential exposure, or measurement bias. Perturbation experiments are particularly informative because the removal, blocking or restoration of a proposed component can be done to determine whether the observed effect is dependent on this component. Successful challenging tests are therefore the necessary basis for Mechanistic confidence and not the repetition of confirmation within one favourable assay.

All of the outcomes of closed-loop cannabinoid medicinal chemistry will be different in context. Relevant variations include pain mechanism, inflammatory status, exposure to the target in the central versus peripheral nervous system, prior cannabinoid exposure, and comedications. An intervention can be effective in one set of these conditions and less effective, more toxic or have a different biological effect in another set of conditions. Stratification becomes more useful when based on variables that are related to mechanism or exposure as these variables are more likely to account for differences in treatment performance than descriptive categories.

The same importance should be given to risk assessment since psychoactivity, receptor desensitization, off-target GPCR activity, species-specific pharmacology and metabolite effects. Early safety studies are best conducted with the same mechanistic approach as

efficacy, which can uncover unwanted effects back to target biology, carrier behavior, exposure, metabolites, or analytical bias. An approach to reduce the risk of safety being a late checklist that is not tied to discovery logic. It also helps to make clearer trade-offs when efficacy is needed to be increased by increasing the amount of exposure, spreading the modulation of the pathway across more tissues, or lengthening the persistence in sensitive tissues.

The added layer is translational development, as a faster progress towards CB ligands with known signaling profiles and safe margins. Experiments with preclinical success become more informative when they replicate clinically relevant time, dose, biological barriers, history of therapy, and factors that can cause a range in experimental results. It's not very meaningful to move from a convenient model to a complicated model; it's more helpful to have a series of models that solve particular uncertainty questions. Therefore, a specific choice must be made for each step: proceed, redesign, limit the target population, change the dose, collect different kind of mechanistic data, etc.

The synthetic accessibility, stereochemical control, solubility, purity, and scalable routes are hard constraints and are part of the optimization loop, which in turn involves manufacturing and analytical control. A biological explanation is only valuable if the biological material tested is consistent between batches and the inputs to the assays are well characterised. Critical attributes must, therefore, have ranges of acceptability, measurable attributes and records linking process conditions to the biological performance. It is a particularly vital discipline for complex molecules, nanoparticles, biomaterials, and studies with lots of data where a small change in exposure, signaling, or apparent treatment response can significantly affect the study result.

A better distinction between prediction and confirmation is also an added advantage for data analysis in closed loop CBMC. Though a computational model, a machine learning algorithm, a causal estimator, a mechanistic simulation can rank hypotheses, integrate high-dimensional measurements, and highlight uncertainty, the output of the model is not biological truth. The useful models make assumptions and quantify calibration, mark areas with low information support and suggest further experiments for information that alters the decision. Retrospective validation is important, but not enough: prospective validation is still necessary, since patterns which are successful in the past may not be successful in the future under new populations, new batches, or new biological conditions.

Another big change is in time, as many processes that are key to closed-loop cannabinoid medicinal chemistry are time dependent. There are many different pathways to achieving

early response, adaptation, clearance, programming of immunity, remodeling of tissue, adherence, or resistance, even when a single endpoint appears to be favorable.

Longitudinal measures show whether an intervention will create a stable state, a temporary variation or a delayed liability. Time resolved data also help to understand the mechanism of cause, as it is revealed before, rather than after the downstream phenotype occurs.

An experimental design is more efficient if all studies are associated with a specific uncertainty budget. Questions concerning CB1 and CB2 affinity, signaling efficacy, functional selectivity, off-target activity, pharmacokinetics and tolerance can be prioritized by using their ability to shift the choice of the next compound (based on both novelty and chemical and biological considerations) that provides the best information gain, not by novelty alone. Complementary models are then replicated to determine if the conclusion is dependent on one assay, one laboratory condition or one population. This discipline can reduce wasted optimization and is useful for reporting negative results as they reduce the number of plausible mechanisms and enhance the following design iteration.

Traceability of claims to measurements is also essential for regulatory and clinical credibility. A closed loop for cannabinoid medicinal chemistry is more robust if raw observations, processing choices, model assumptions, deviations to the protocol and material properties are linked from initial experiments to translational studies. Such traceability aids the discrimination of "true" biological variation from "noise" and allows for subsequent review of safety or effectiveness. It also provides a framework for revising conclusions in the event that new information alters a previous assumption.

There is also a need to be more accurate in communicating around this field. Some phrases like targeted, selective, durable, safe, predictive, or personalized are meaningless unless combined with a measurement, comparator, population, and uncertainty range. The transparency of reporting makes negative results more useful and helps to discourage reporting of any exploratory findings as mechanisms. Precision provides a common metric for assessing the validity of a claim based on direct measurement, calibrated inference, or an untested assumption for researchers, developers, clinicians and regulators alike.

It is, therefore, not a single new technology but a more closed loop between chemical or formulation, mechanism measurement, quantitative modeling, context safety, manufacturing control and clinically relevant context, which is the strongest direction in

the development of closed loop cannabinoid medicinal chemistry. It is easier to make progress if a failed assumption is discovered early and mechanisms that work are deliberately tested by making them difficult. That logic makes design cycles experimental learning systems instead of potency campaigns that are linear. There are a few valuable innovations across the field, all of which are based on a development system that learns from each experiment, with causal understanding, real world relevance and reproducibility as core principles guiding every decision.