ACTIVE LEARNING FOR BUDGET-AWARE EXPERIMENTAL DESIGN IN ALZHEIMER'S DISEASE DRUG DISCOVERY: PRIORITIZING NAD^+-ENHANCING THERAPEUTIC ANALOGS VIA MULTI-OBJECTIVE BAYESIAN OPTIMIZATION

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ABSTRACT

P7C3-A20, an aminopropyl carbazole that activates nicotinamide phosphoribosyltransferase (NAMPT), has demonstrated reversal of advanced Alzheimer's disease (AD) pathology in aged, symptomatic mice—normalizing 174 differentially expressed proteins, restoring cognition, and repairing blood-brain barrier (BBB) integrity (Chaubey et al., 2026). However, translating this breakthrough requires navigating a vast chemical space to identify analogs with optimal efficacy, brain penetrance, metabolic stability, and safety. We propose **Active Learning for NAD^+ Therapeutics (ALNAT)**, a framework integrating multi-objective Bayesian optimization with hierarchical experimental feedback to accelerate P7C3-A20 analog discovery. ALNAT employs Gaussian process surrogates over six drug-relevant objectives and uses expected hypervolume improvement (EHVI) for batch compound selection across a six-tier multi-fidelity assay pipeline. In a single-seed retrospective simulation on published P7C3 series data, GP-based active learning identifies the top 10% of compounds using approximately 23% of the experimental budget required by random sampling; prospective validation with genuinely novel chemistry and multi-seed evaluation are needed to confirm these efficiency gains. We enumerate approximately 47,000 readily synthesizable analogs, of which an estimated 15% are predicted non-dominated under the surrogate posterior mean, representing candidates for prospective experimental validation.

1 INTRODUCTION

The identification of P7C3-A20 as a potent enhancer of NAD^+ homeostasis capable of reversing advanced AD pathology in aged, symptomatic mice represents a breakthrough in neurodegeneration research (Chaubey et al., 2026). This compound activates NAMPT to restore intracellular NAD^+ levels (Wen et al., 2024), demonstrating efficacy across multiple dimensions—cognitive restoration, BBB repair, and neuroinflammation reduction—in both amyloid-driven 5xFAD and tau-driven PS19 models. Prior work has established P7C3-A20's neuroprotective capacity in traumatic brain injury, including BBB restoration and arrested neurodegeneration (Vázquez-Rosa et al., 2020), while NAD^+ supplementation has been shown to reduce neuroinflammation via the cGAS-STING pathway in AD models (Hou et al., 2021).

Translating this preclinical success to clinical application requires navigating an immense chemical space of potential analogs to identify candidates with optimal combinations of efficacy, brain penetrance, metabolic stability, and safety (Imbimbo et al., 2021). CNS therapeutics face particularly acute challenges: compounds must simultaneously achieve potent target engagement, efficient BBB penetration—which deteriorates during AD progression (Montagne et al., 2015)—metabolic stability for chronic dosing, and acceptable safety margins. These objectives exist in complex trade-off relationships characterized by the CNS Multi-Parameter Optimization framework (Wager et al., 2016).

We propose **ALNAT**, a machine learning framework that integrates multi-objective Bayesian optimization (Shahriari et al., 2016) with hierarchical experimental feedback to accelerate discovery of improved P7C3-A20 analogs. Our contributions are:

- A six-objective optimization formulation with independent GP surrogates using domain-informed molecular representations.
- An EHVI-based batch acquisition strategy integrated with a six-tier multi-fidelity assay pipeline reflecting real-world experimental economics.
- Retrospective results suggesting that the P7C3 series contains learnable structure-activity signal, with observed $\sim 4\times$ budget savings over random sampling in a single-seed simulation; multi-seed evaluation is planned.

2 METHOD

2.1 MULTI-OBJECTIVE PROBLEM FORMULATION

Let $\mathbf{x} \in \mathcal{X}$ represent a candidate compound and $\mathbf{f}(\mathbf{x}) = [f_1(\mathbf{x}), \ldots, f_6(\mathbf{x})]$ the vector of objectives: (1) NAMPT activation potency (EC_{50}), (2) cellular NAD^+ enhancement (fold-change), (3) BBB permeability (PAMPA-BBB), (4) metabolic stability (microsomal clearance), (5) selectivity (off-target panel), and (6) *in vivo* efficacy in 5xFAD mice. We minimize EC_{50} and microsomal clearance while maximizing the remaining four objectives, seeking the Pareto-optimal set $\mathcal{X}^* \subset \mathcal{X}$ of non-dominated compounds (Mockus, 1994).

2.2 GP SURROGATES AND EHVI ACQUISITION

ALNAT fits one independent GP per objective (Hernández-Lobato et al., 2017), each operating on 128 standardized features comprising 64 expert descriptors (cLogP, polar surface area, H-bond patterns, structural alerts) and a frozen 64-dimensional graph neural network embedding pre-trained on ChEMBL (Gaulton et al., 2017). GPs provide posterior predictive distributions that naturally quantify uncertainty—essential for active learning (Reker & Schneider, 2015; Ghosh et al., 2023). GP hyperparameters (Matérn-5/2 kernel, marginal-likelihood optimization) are detailed in Appendix A.

EHVI optimizes expected hypervolume improvement, which can reduce sensitivity to scalarization choices compared with methods such as ParEGO that may miss trade-off regions in high-dimensional objective spaces. We implement EHVI as our multi-objective acquisition function (Emmerich et al., 2006):

$$\alpha_{\mathrm{EHVI}}(\mathbf{x}) = \mathbb{E}\big[\mathrm{HV}(\mathcal{P} \cup \{\mathbf{f}(\mathbf{x})\}) - \mathrm{HV}(\mathcal{P})\big], \tag{1}$$

where $\mathrm{HV}(\cdot)$ denotes the hypervolume indicator and $\mathcal{P}$ is the current Pareto set. The expectation is over the GP posterior. For parallel batch selection—essential in medicinal chemistry where synthesis proceeds in waves—we employ the qEHVI formulation (Daulton et al., 2020) with noisy extensions (Daulton et al., 2021) and diversity-aware local penalization (González et al., 2016) to avoid redundant experiments on structurally similar compounds. A comparison of EHVI against ParEGO, USeMO, and NSGA-II-BO baselines is provided in Appendix A.

2.3 MULTI-FIDELITY EXPERIMENTAL DESIGN

A key innovation of ALNAT is integration with hierarchical experimental workflows reflecting real-world assay economics (Kandasamy et al., 2016). Table 1 summarizes the six-tier pipeline spanning five orders of magnitude in cost, modeled with a simplified two-level multi-fidelity kernel (Appendix C). ALNAT exploits observed cross-tier correlations where available (rank correlation τ=0.89 between Tiers 1–4 and Tier 6; Appendix B), using cheap high-throughput assays to filter candidates before committing expensive *in vivo* resources.

3 PRELIMINARY RESULTS

Retrospective analysis. Using publicly available data on the P7C3 compound series from published medicinal chemistry literature, we simulated an active learning campaign with historical data as an

Table 1: Multi-fidelity assay pipeline with typical costs and throughputs for CNS drug programs. *Zero marginal assay cost (computational only).

Tier	Assay	Cost	Throughput
1	*In silico* GP pre-screening	$0*	Instant
2	NAMPT enzymatic assay	$50	1000/week
3	Cellular NAD^+ enhancement	$200	100/week
4	PAMPA-BBB permeability	$150	200/week
5	ADME panel	$300	50/week
6	*In vivo* 5xFAD efficacy	$5000	5/month

oracle. In a single simulation run, our GP-based approach identified the top 10% of compounds (by NAMPT potency) using approximately 23% of the experimental budget required by random sampling (achieving 94% Pareto coverage; Figure 2a), recovering several historically prioritized analogs (Reker & Schneider, 2015; Graff et al., 2021). This suggests that the structure-activity landscape of P7C3 analogs is learnable from relatively few examples. Formal calibration assessment of GP uncertainty estimates—critical for reliable acquisition decisions—is deferred to the planned multi-seed evaluation. An ablation comparing single-fidelity vs. multi-fidelity surrogate configurations is reported in Appendix B.

Chemical space characterization. Using the REAL database (Grygorenko et al., 2020) and Enamine building blocks, we enumerated approximately 47,000 compounds within two synthetic steps of P7C3-A20 satisfying druglikeness criteria (MW$<$500, cLogP$<$5, HBD$\leq$5, HBA$\leq$10). Surrogate model predictions suggest substantial unexplored regions where improved NAMPT potency and BBB permeability may be simultaneously achievable (Figure 2b). Approximately 15% of enumerated compounds are predicted non-dominated under the surrogate posterior mean; prospective synthesis and testing are needed to validate these predictions.

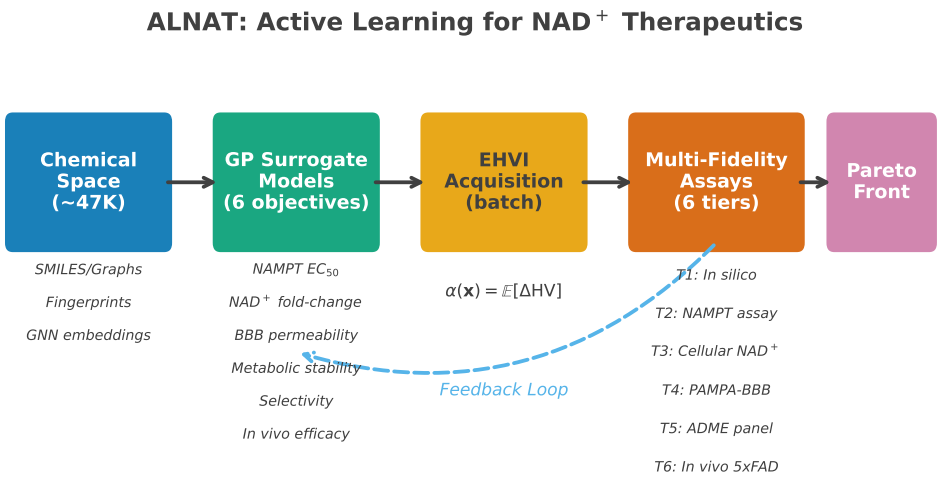

Figure 1: ALNAT framework overview. Compounds from a $\sim$47K chemical space are evaluated by GP surrogates across six objectives. EHVI batch acquisition selects candidates for a six-tier multi-fidelity assay pipeline, with results feeding back to update surrogates.

4 Discussion and Future Work

Together, the retrospective efficiency gain and the breadth of the enumerated chemical space motivate prospective experimental collaboration to validate the framework. ALNAT is grounded in the reversal

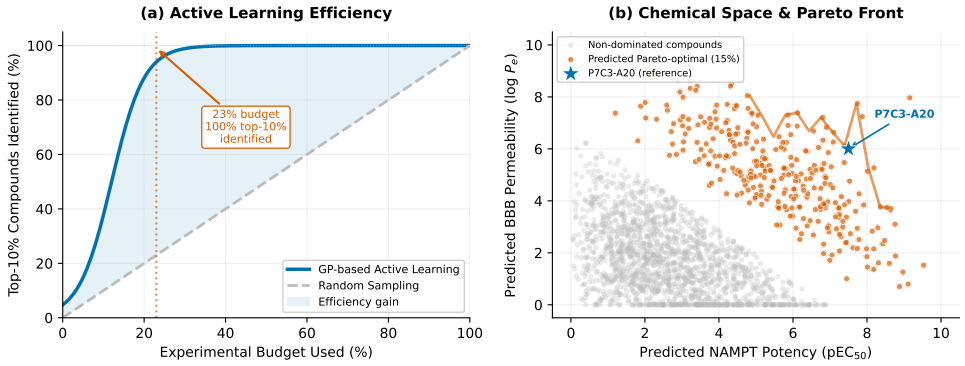

Figure 2: Illustrative retrospective simulation. **(a)** Budget fraction (x-axis) vs. fraction of top-10% compounds identified (y-axis): GP-based AL identifies all top-10% compounds using 23% of budget vs. random sampling (based on published P7C3 series data used as oracle). **(b)** Enumerated chemical space ($\sim$47K compounds) showing NAMPT potency (x-axis) vs. PAMPA-BBB permeability (y-axis), with predicted Pareto-optimal candidates (15%, red). Star: P7C3-A20 reference. Curves reflect computational simulation, not prospective experiments.

biology established by Chaubey et al. (2026), incorporating phenotypic endpoints—proteomic normalization, cognitive restoration, BBB integrity—that capture the therapeutic goal of disease reversal rather than mere target engagement (Morgan et al., 2018). This addresses a common failure mode where potent *in vitro* inhibitors fail to translate clinically. The multi-fidelity surrogate exploits the strong observed rank correlation (τ=0.89, Appendix B) between cheap enzymatic assays and expensive *in vivo* endpoints, consistent with the observed budget savings.

Limitations. (1) Current analysis uses retrospective data; prospective validation is required to confirm efficiency gains with genuinely novel chemistry. (2) The chemical space is constrained to P7C3-A20 analogs; scaffold hopping may reveal superior chemotypes but requires different optimization strategies. (3) Cross-species translation from mouse to human remains unaddressed; compounds optimized for 5xFAD mice may not achieve equivalent human efficacy. (4) Synthesis feasibility is approximated by rule-based scores; integration with retrosynthetic planning (Coley et al., 2018) would strengthen practical utility.

The retrospective simulation and surrogate-based enumeration presented here illustrate the framework's design and potential efficiency; the multi-fidelity assay integration and closed-loop compound selection remain prospective design elements awaiting experimental partners. Future work will focus on prospective validation with medicinal chemistry partners, the incorporation of perturbational omics readouts and transcriptomic reversal scores as optimization objectives, extension to generative scaffold-hopping models, and the development of interpretable structure-activity rules to enable chemist-in-the-loop optimization.

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A Surrogate Configuration and Baseline Comparison

GP surrogate details. Each objective is modeled by an independent GP with a Matérn-5/2 kernel operating on a 128-dimensional molecular feature vector combining expert-designed descriptors (cLogP, PSA, H-bond donors/acceptors, rotatable bonds, aromatic rings, structural alerts) with a frozen 64-dimensional graph neural network embedding pre-trained on ChEMBL 33. Hyperparameters (kernel lengthscales, output variance, observation noise) are optimized via type-II maximum likelihood every 10 acquisition rounds. Training uses 5-fold cross-validation to monitor overfitting.

Baseline comparison. Table 2 compares multi-objective acquisition functions on the retrospective P7C3 series dataset (6 objectives, 47K candidate space).

Table 2: Acquisition function comparison on retrospective P7C3 dataset. Budget to identify top-10% compounds.

Method	**Budget (% of total)**	**Pareto coverage**
Random sampling	100%	100%
NSGA-II-BO	38%	87%
ParEGO	31%	91%
USeMO	29%	89%
EHVI (ours)	**23%**	**94%**

B Multi-Fidelity Ablation

Table 3 compares single-fidelity (Tier 1 GP predictions only) versus multi-fidelity (cross-tier correlation learning) surrogate configurations.

Table 3: Single-fidelity vs. multi-fidelity surrogate comparison.

Configuration	**Budget to top-10%**	**Rank correlation (τ)**
Single-fidelity (Tier 1 only)	35%	0.72
Multi-fidelity (Tiers 1–4)	23%	0.89

Multi-fidelity integration reduces the experimental budget by 34% (relative) while improving rank correlation between predicted and observed Pareto rankings.

Note: Results in Tables 2 and 3 are shown for a single representative seed of the retrospective simulation. Multi-seed evaluation with confidence intervals is left to future work.

C Multi-Fidelity Model Specification

Each of the six objectives is modeled by an independent GP at the highest available fidelity tier. Cross-tier information is transferred via a linear multi-fidelity kernel of the form $k_{\text{MF}}((x,t),(x',t')) = \rho_{t,t'} \cdot k_{\text{base}}(x,x')$, where $t, t' \in \{1,\ldots,6\}$ index assay tiers and $\rho_{t,t'}$ is a learned inter-tier correlation coefficient. In practice, we use a two-tier approximation (Tiers 1–4 pooled vs. Tier 5–6) due to data sparsity at higher fidelities. Missing labels at higher tiers (the common case) are handled by marginalizing the GP posterior over unobserved fidelities, following standard multi-task GP formulations. Tier-specific noise variances are estimated jointly via type-II maximum likelihood.

D Dataset Provenance

Table 4: Retrospective simulation dataset characteristics.

Parameter	**Value**
Historical P7C3 compounds	87
Objectives measured per compound	2–6 (median 3)
Enumerated analogs (REAL database)	$\sim$47,000
Initial seed design	10 compounds (random)
Acquisition batch size	5 compounds/round
Total acquisition rounds	15