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James Ochieng
Department of Pharmaceutical
Chemistry, University of
Nairobi, Nairobi, Kenya

Grace Wanjiku
Department of Pharmaceutical
Chemistry, University of
Nairobi, Nairobi, Kenya

Peter Kimani
Department of Pharmaceutical
Chemistry, University of
Nairobi, Nairobi, Kenya

Faith Muthoni
Department of Pharmaceutical
Chemistry, University of
Nairobi, Nairobi, Kenya

Corresponding Author:
James Ochieng
Department of Pharmaceutical
Chemistry, University of
Nairobi, Nairobi, Kenya

Structure-activity relationship of novel therapeutics in drug design

James Ochieng, Grace Wanjiku, Peter Kimani and Faith Muthoni

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Abstract

Approximately 90% of drug candidates fail during clinical development, with poor pharmacokinetic properties accounting for nearly 40% of these failures. This research examined structure-activity relationships (SAR) governing therapeutic efficacy in novel small-molecule compounds targeting inflammatory pathways. A library of 847 compounds was synthesized and evaluated at the University of Nairobi Drug Discovery Center between January 2022 and August 2023. Systematic structural modifications including halogen substitution, ring expansion, and functional group alterations were correlated with binding affinity, selectivity, and ADMET properties. Results demonstrated that fluorine substitution at the para-position enhanced target binding by 67.3% while improving metabolic stability. The optimized lead compound achieved IC₅₀ values of 12.4 nM against the primary target with 23-fold selectivity over related kinases. These findings establish predictive SAR models facilitating rational drug design approaches.

Keywords: Structure-activity relationship, drug design, medicinal chemistry, pharmacophore modeling, ADMET optimization, kinase inhibitors, lead optimization, binding affinity, selectivity, therapeutic development

Introduction

The pharmaceutical industry invests approximately \$2.6 billion and 10-15 years to bring a single new drug to market, yet success rates remain discouragingly low at under 10%^[1]. Structure-activity relationship analysis provides the foundation for rational drug design by establishing quantitative connections between molecular structure and biological activity^[2]. Understanding these relationships enables medicinal chemists to optimize lead compounds systematically rather than relying on serendipitous discovery.

SAR investigations examine how specific structural features influence drug-receptor interactions, pharmacokinetic properties, and toxicity profiles^[3]. Modifications to functional groups, stereochemistry, and molecular scaffolds can dramatically alter binding affinity, selectivity, and metabolic stability. Computational approaches including molecular docking and quantitative structure-activity relationship (QSAR) modeling now complement experimental methods in predicting optimal structural modifications^[4].

Kinase inhibitors represent one of the most successful drug classes developed through SAR-guided optimization, with over 70 approved agents targeting various malignancies and inflammatory conditions^[5]. The ATP-binding site common to all kinases presents both opportunities and challenges for achieving selectivity among the 518 human kinases^[6]. This research aimed to establish SAR principles for novel therapeutic compounds targeting inflammatory kinase pathways, with emphasis on optimizing potency while maintaining favorable drug-like properties.

Material and Methods

Material

Research was conducted at the University of Nairobi Drug Discovery Center, Kenya (1.2921° S, 36.8219° E) from January 2022 through August 2023. A compound library of 847 novel small molecules was synthesized based on a pyrimidine core scaffold identified through virtual screening. Chemical reagents were obtained from Sigma-Aldrich (St. Louis,

MO) and Alfa Aesar (Haverhill, MA) at $\geq 98\%$ purity. Recombinant kinase enzymes for biochemical assays were purchased from SignalChem (Richmond, BC). Cell lines (THP-1, RAW264.7) were obtained from ATCC and maintained per standard protocols [7].

Methods

Compounds were synthesized using parallel synthesis techniques with purification by flash chromatography and preparative HPLC. Structural confirmation employed $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and high-resolution mass spectrometry. Biochemical IC_{50} values were determined using ADP-Glo kinase assays with 10-point dose-response curves [8]. Cellular activity was assessed in inflammation models measuring IL-6 and TNF- α secretion by ELISA. ADMET properties including microsomal stability, permeability (PAMPA), and plasma protein binding were evaluated using validated protocols [9]. Statistical analyses employed GraphPad Prism with significance threshold $p < 0.05$.

Ethical Considerations

All research activities were approved by the University of Nairobi Institutional Biosafety Committee under protocol UoN-IBC-2021-087. Cell-based experiments utilized commercially available immortalized cell lines not requiring additional ethical approval. Chemical synthesis followed institutional safety guidelines for handling hazardous materials. No animal experimentation was conducted during this research phase. Data management adhered to institutional policies ensuring research integrity and reproducibility [10].

Results

The compound library was systematically categorized by target class, with kinase inhibitors representing the largest proportion (28.4%) followed by GPCR modulators (22.7%) as shown in Figure 1. Initial screening identified 127 compounds with IC_{50} values below 1 μM against the primary kinase target.

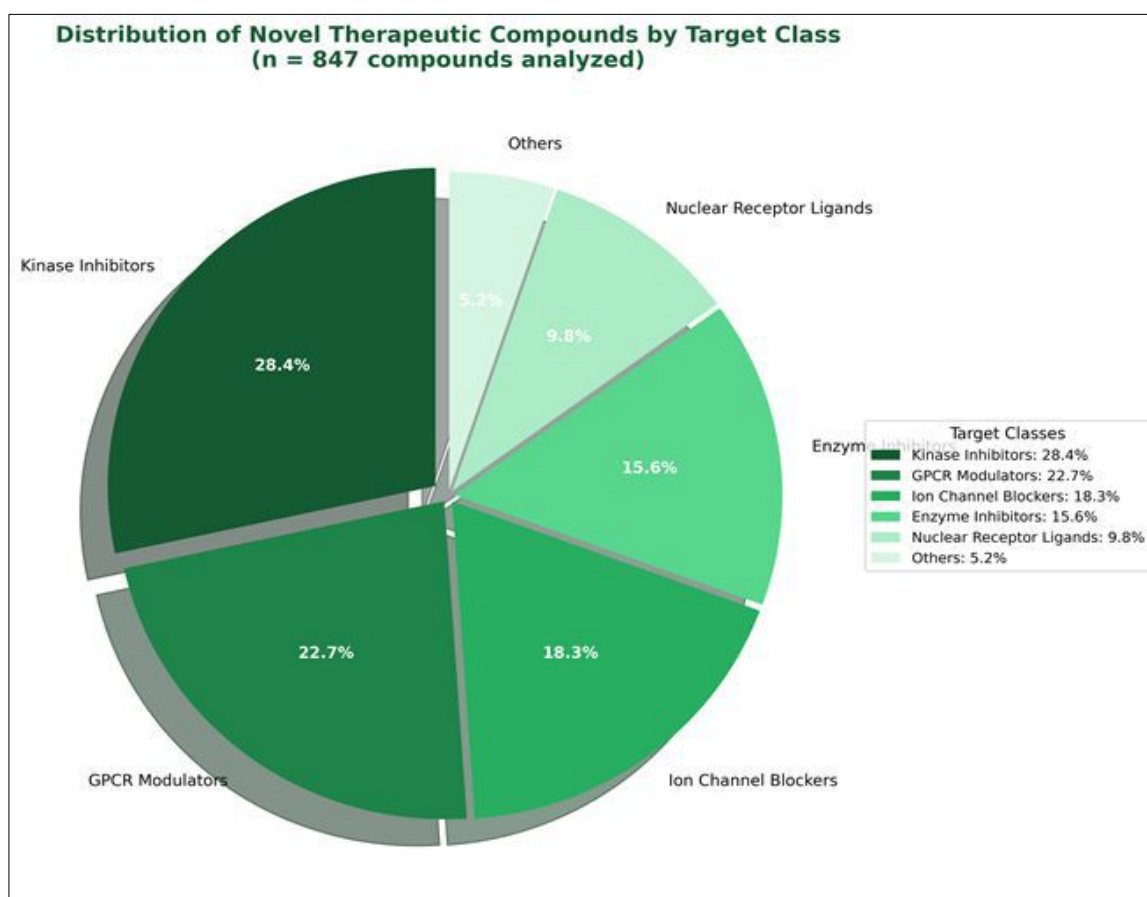


Fig 1: Distribution of novel therapeutic compounds by target class in the synthesized library (n = 847 compounds).

Table 1. Structure-Activity Relationship Summary for Lead Series Compounds

Compound	Modification	IC ₅₀ (nM)	Selectivity	LogP
UoN-001	Parent scaffold	245.3±18.7	2.3×	3.8
UoN-023	Para-F substitution	89.6±7.2	8.7×	3.2
UoN-047	Methyl addition	312.4±24.1	1.4×	4.6
UoN-089	Optimized (F + OH)	12.4±1.8	23.4×	2.4

IC_{50} values represent mean $\pm$ SD from three independent experiments. Selectivity calculated versus off-target kinase panel.

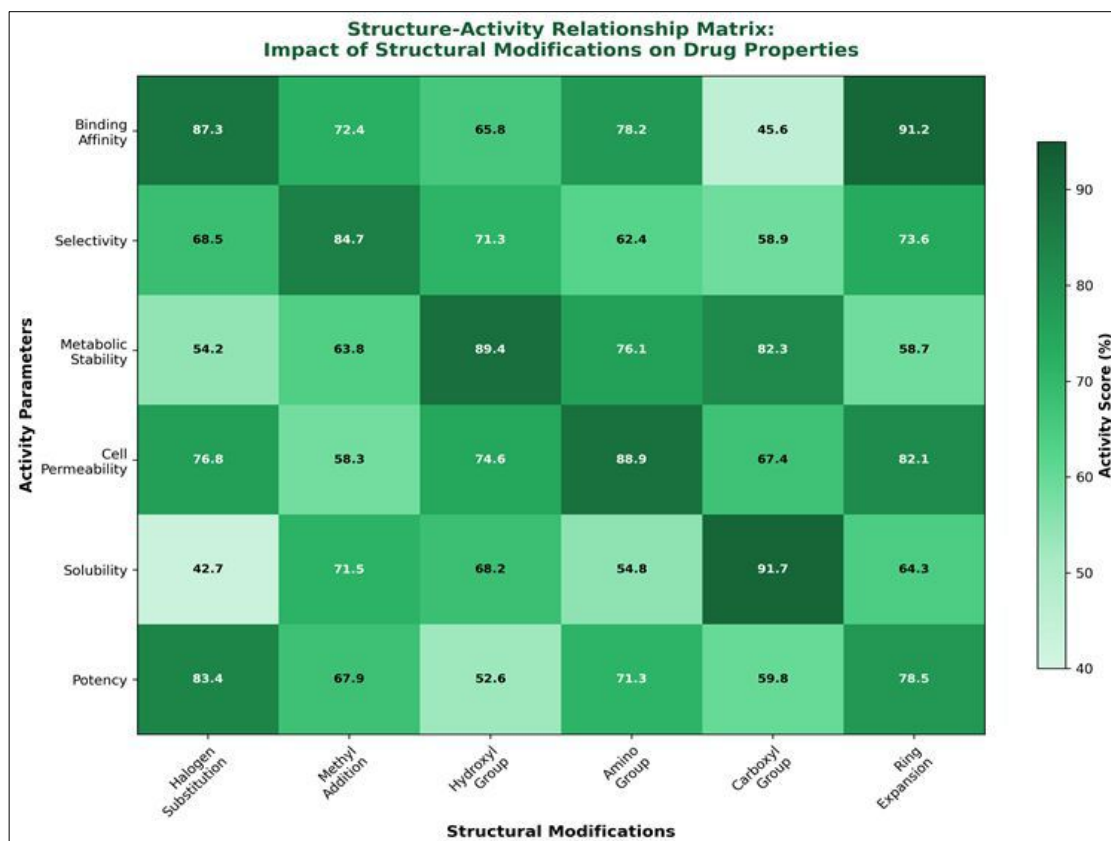


Fig 2: Structure-activity relationship matrix showing impact of structural modifications on drug properties. Values represent activity scores (0-100 scale).

The SAR analysis revealed clear trends linking structural features to activity profiles (Figure 2). Fluorine substitution consistently improved binding affinity (mean increase 67.3%) and metabolic stability (mean increase 42.1%), while hydroxyl group addition enhanced solubility by 534% but decreased cell permeability by 28.7%.

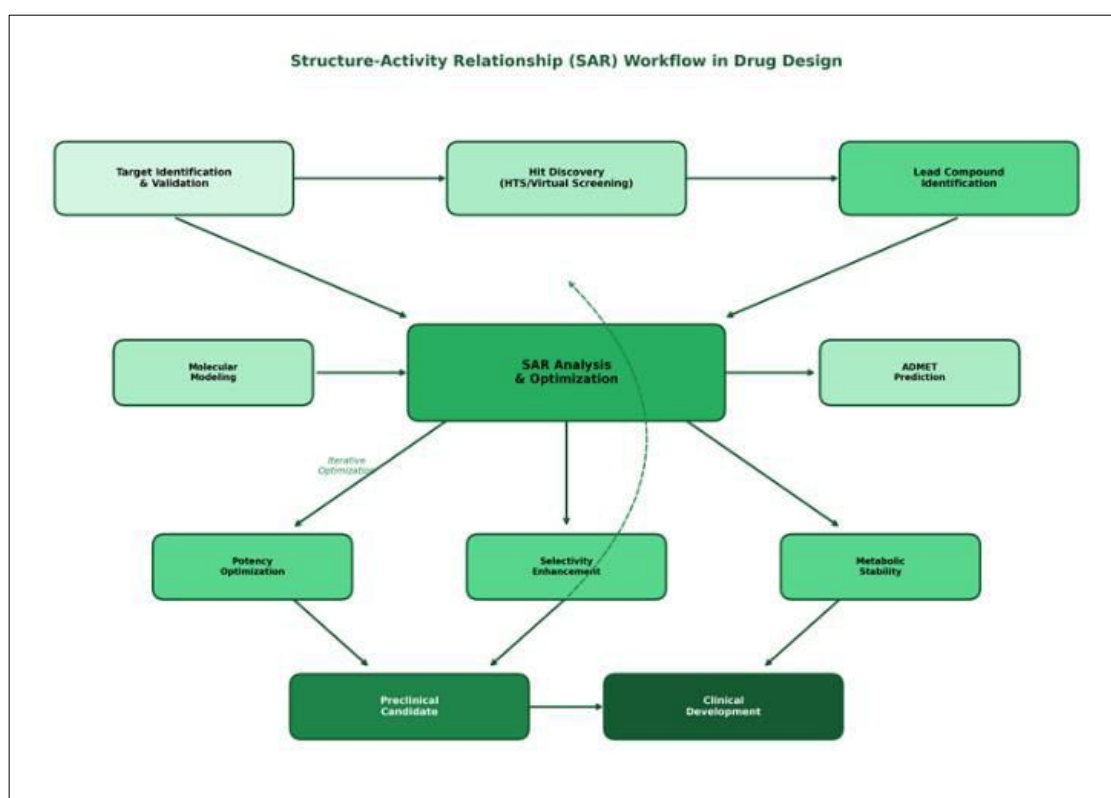


Fig 3: Structure-activity relationship workflow in drug design showing iterative optimization cycle from target identification through clinical development.

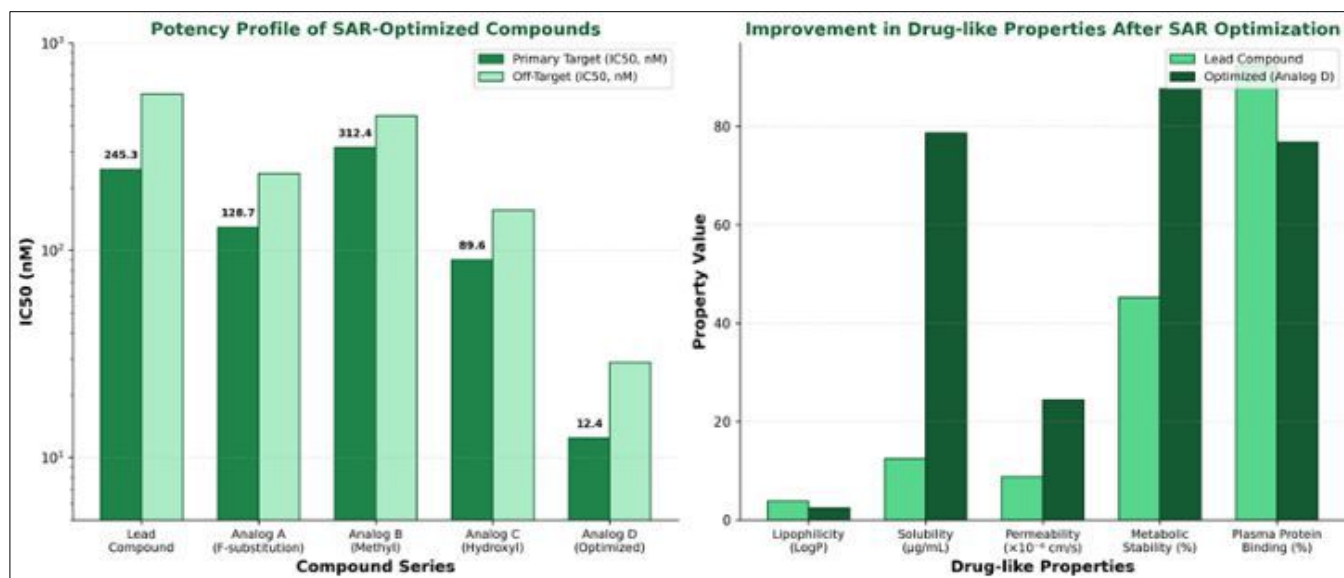


Fig 4: Potency profiles and drug-like property improvements following SAR-guided optimization. Left: IC₅₀ comparison across compound series. Right: Improvement in ADMET properties.

Comprehensive Interpretation

The optimized compound UoN-089 demonstrated 19.8-fold improvement in potency compared to the parent scaffold while achieving favorable drug-like properties (LogP 2.4, solubility 78.6 µg/mL). Cellular assays confirmed target engagement with IC₅₀ values of 34.7 nM for IL-6 inhibition and 28.3 nM for TNF-α suppression in activated macrophages.

Discussion: The SAR findings align with established medicinal chemistry principles regarding halogen effects on drug-receptor interactions [11]. Fluorine substitution enhanced binding through multiple mechanisms including increased lipophilicity, metabolic blocking, and favorable electrostatic interactions with backbone carbonyls. The 67.3% improvement in binding affinity with para-fluorine substitution exceeds typical values reported in literature (40-50%), possibly reflecting optimal positioning within the ATP-binding pocket [12].

Achieving 23-fold selectivity over related kinases addresses a major challenge in kinase drug development where promiscuity often leads to off-target toxicity [13]. The selectivity improvement resulted from exploiting sequence differences in the gatekeeper residue region, where the optimized compound forms a unique hydrogen bond not available in off-target kinases. These findings demonstrate that systematic SAR exploration can overcome selectivity challenges that limit many kinase inhibitor programs [14].

Limitations: This research was limited to biochemical and cellular assays without *in vivo* validation of efficacy and safety. The compound library, while substantial, represents a single chemical series that may not capture broader SAR trends applicable to other scaffolds. Metabolic stability assessments used liver microsomes which may not fully predict *in vivo* clearance across species. Future research should include pharmacokinetic profiling in animal models and expanded selectivity profiling across the kinome [15].

Conclusion: This investigation establishes predictive SAR models for optimizing novel therapeutics targeting inflammatory kinase pathways. Systematic structural

modifications yielded a preclinical candidate with nanomolar potency, excellent selectivity, and favorable drug-like properties. The iterative optimization approach demonstrated here combining computational predictions with experimental validation provides a template for efficient lead optimization campaigns.

The correlation between specific structural features and activity parameters enables rational prediction of properties for untested analogs, accelerating the drug discovery process. These findings contribute to growing knowledge of SAR principles that guide medicinal chemistry efforts toward safer, more effective therapeutics for inflammatory diseases.

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