GREENPHARMA – PRESTWICK CHEMICAL : CATALYSTS OF YOUR DRUG DISCOVERY

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Drug discovery is a time-consuming, high-cost and high-risk process associated with a low success rate. Several angles and a range of valuable tools have been developed to achieve this strategy and accelerate lead discovery. Among these tools, highly relevant and smart chemical screening libraries have been designed to ensure screening performance. The libraries are focused on approved drugs, drugs fragments and more recently drugs combinations. Those combinations have proven to be a valuable method in different therapeutic areas, *.e.g.* promising results were obtained in alcohol addiction recently[1].

Furthermore, once a hit is found, post-HTS analysis can offer deeper investigation, from ligand and structure-based analogue search to custom synthesis of relevant compounds. Medicinal Chemistry allows to support drug discovery projects in multiple ways, coupled with both chemoinformatic and organic synthesis development[2].

PRESTWICK CHEMICAL LIBRARIES:

Library screening is the shortest and fastest route to obtain a drug candidate. Valuable and focused libraries were designed to ensure maximal chemical and therapeutic diversity and **high-quality hits, the main ones are:**

PRESTWICK CHEMICAL DRUG LIBRARY®
A collection of 1520 structurally diverse & relevant approved drugs

PRESTWICK ORIGINAL MOLECULES LIBRARY
Innovative compounds with drug-like properties

PRESTWICK DRUG-FRAGMENT LIBRARY
1456 molecules arising from smart fragmentation of approved drugs

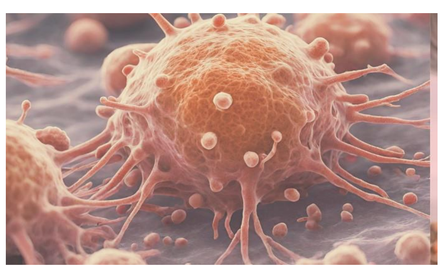
PRESTWICK-GREENPHARMA PHYTOCHEMICAL LIBRARY
A well-chosen set of bioactive natural compounds

PRESTWICK PEPTIDIC MACROCYLE LIBRARY
Exclusive compounds to cast a wider net of protein interactions

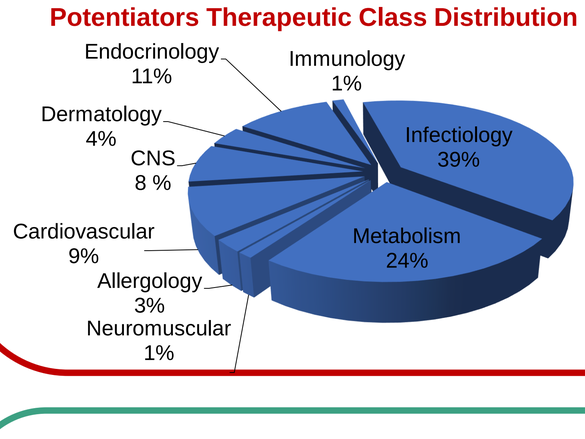
PRESTWICK ONCOMBO LIBRARY: DRUG COMBINATIONS DEDICATED FOR ONCOLOGY RESEARCH

Key features:

- Combining known anticancer drugs with potentiating drugs
- Simultaneously targeting different mechanisms



Potentiators Therapeutic Class Distribution

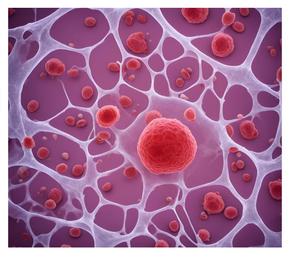


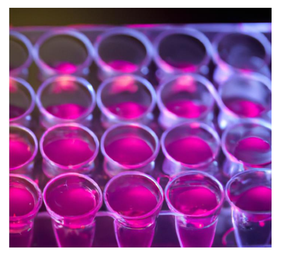
Goals:

- Destabilization of tumor survival process
- Sensitization of tumor cells
- Enhancement of anticancer activity
- Toxicity reduction

Step 2: Hit Expansion

- Molecules were tested for their cytotoxic activity against **Liposarcoma**
- **2 hits** with different structures were identified





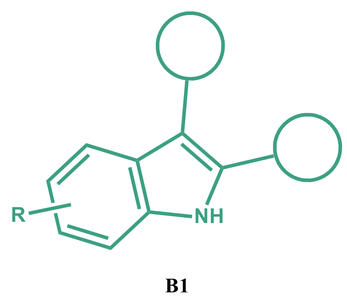
IC50= 350nM (B1) et 650nM (Z1)
Compared to 200nM for reference X

- Compound **B1** was retained, and further analogs were provided for QSAR studies

Step 3: Lead Optimization

Upon the QSAR studies, 30 compounds were synthesized according to several criteria:

- Incorporation of nitrogenated indole core
- Modification of substituents
- Bioisosters replacements



B1

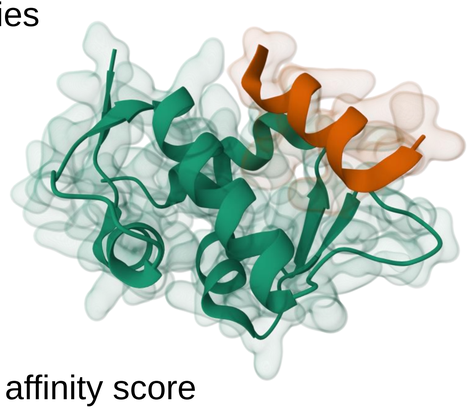
New Chemical Entities with enhanced affinity and drug-like properties:

- **IC50= 350nM (B1) → 25nM (B15)**
- Limited Solubility → Excellent Solubility
- Higher Metabolic Stability (Human liver S9 fraction)

FROM SCREENING TO DRUG CANDIDATE: NCE DESIGN TO TARGET LIPOSARCOMA

Step 1: Tackling the Biological Target

- Molecule database from Ambinter with 36M+ molecules including the Prestwick Chemical Libraries
- Virtual screening conducted on the 3D structure of target protein
- Molecules selected according to higher affinity score and lower logP value than the reference X.
  20 of them were chosen for in vitro testing.



Conclusion

In the drug discovery process, starting with **relevant screening compounds** increases hit quality and the probability of obtaining safe, soluble and oral bioavailable leads. In addition, the know-how in **design**, chemo-informatics and **medicinal chemistry** paved the way to discover a **NCE with higher potency and stability** and enhanced physicochemical properties.

References:

1. Aubin H-J, Berlin I, Guiraud J, Bruhwyler J, Batel P, Perney P, et al. Prazosin and cyproheptadine in combination in the treatment of alcohol use disorder: A randomized, double-blind, placebo-controlled trial. Addiction. 2024.

2. Bettayeb K, Sallam H, Ferandin Y, et al. N-&-N, a new class of cell death-inducing kinase inhibitors derived from the purine roscovitine. Mol Cancer Ther. 2008;7(9):2713-2724