
# FACULTY OF ENGINEERING AND TECHNOLOGY

## Department of Biotechnology

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# INDIRECTDRUG DESIGN

The indirect drug design approach involves comparative analysis of structural features of known active and inactive molecules that are complementary with a hypothetical receptor site.

If the site geometry is not known, as is often the case, the designer must base the design on other ligand molecules that design on the other ligand molecules that bind well to the site.

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# Ligand

- **A ligand is an ion or molecule (functional group) that binds to a central metal atom to form a coordination complex.**

- **Ligand selection is a critical consideration in many practical areas, including bioinorganic and medicinal chemistry, homogeneous catalysis, and environmental chemistry.**

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# Stratergies in IdDd

**•The Appropriate strategy to use in the design of drugs depends on available knowledge about the structure of the macromolecular target.**

***Indirect drug designing aka Ligand based drug designing:***

**•It relies on knowledge of other molecules that bind to the biological target of interest**

**•These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must posses in order to bind to the target.**

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# PHARMACOPHORE

- **Pharmacophore model:**

**–Set of points in space defining the binding of ligands with target.**

**–Key factors in developing such a model are the determination of functional groups essential for binding, their correspondence from one ligand to another, and the common spatial arrangement of these groups when bound to the receptor.**

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# PHARMACOPHORE

- **"A molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon) biological activity" Paul Erlich, early 1990.**
- **"a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's activity" Peter Gund, 1977.**

# Other techniques

## Quantitative Structure-Activity Relationships (QSAR)

- **A QSAR relates a numerical description of molecular structure or properties to known biological activity:**
  - **Activity = *f* (molecular descriptors)**
  - **Success of QSAR: right descriptors + right method (form of *f* )**

# Other techniques

## Quantitative Structure-Activity Relationships (QSAR)

- **A QSAR should be:**
  - **explanatory (for structures with activity data)**
  - **predictive (for structures without activity data)**
- **A QSAR can be used to explain or optimise:**
  - **localised properties of molecules such as binding properties**
  - **whole molecule properties such as uptake and distribution**

**•Correlate general properties of molecules with their biological activities**

# Other techniques

## Quantitative Structure-Activity Relationships (QSAR)

- **The earliest examples of QSAR were *Hansch analysis* and *Free-Wilson Analysis*,**

- **Free-Wilson defined a function that equates activity (defined as log of 1 / the concentration) with weighted descriptors, the weightings, or coefficients, being determined by linear regression. That is, we have the equation:**

$$\text{Log } (1/C) = a1x1 + a2x2 + a3x3 \ldots$$

**where C is the concentration required for activity, x1, x2, x3, etc are the descriptor values (usually 1 or 0 to represent absence or presence of features), and a1, a2, a3, etc are the coefficients derived from linear regression.**

# XYZ

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# XYZ

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# XYZ

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# XYZ

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# XYZ

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# XYZ

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# MCQs

1. A
2. A
3. A
4. A
5. A
6. A
7. A
8. A
9. A
10. A