Lecture Notes: Session 5 - Physicochemical Properties: Bioisosterism

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Introduction

This lecture focuses on bioisosterism, a key strategy in medicinal chemistry for optimizing drug properties. Bioisosterism involves replacing a functional group or atom in a molecule with another that has similar physicochemical or biological properties, aiming to enhance potency, selectivity, or safety. The session explores classical and non-classical bioisosteres, their applications in improving potency or reducing toxicity, and uses sulfonamides as a primary example to illustrate practical applications.

1 Bioisosterism

Bioisosterism is the replacement of an atom or group in a molecule with another that maintains similar steric, electronic, or physicochemical properties, thereby preserving or enhancing biological activity. Bioisosteres are used to improve pharmacokinetic properties, receptor binding, or reduce side effects.

1.1 Classical Bioisosterism

Classical bioisosteres are atoms or groups with similar valence electron configurations, size, or electronegativity, allowing them to mimic the original group's behavior.

Key Examples:

- **F for H:** Fluorine (F) replaces hydrogen (H) due to similar size (van der Waals radii: F = 1.47 Å, H = 1.20 Å) and high electronegativity, enhancing lipophilicity or metabolic stability.
- **OH for SH:** Hydroxyl (OH) and thiol (SH) groups share similar hydrogen-bonding capabilities.
- **CH_3 for NH_2:** Methyl and amine groups can mimic steric properties in certain contexts.
- **COOH for SO_3H:** Carboxylic acid and sulfonic acid groups share acidic properties and hydrogen-bonding potential.

Example - Sulfonamides (Sulfanilamide to Sulfisoxazole):

- **Sulfanilamide Structure:** H_2N — c1ccc(S(=O)(=O)N)cc1
- **Bioisosteric Replacement:** The sulfonamide group (-SO_2NH_2) in sulfanilamide mimics the para-aminobenzoic acid (PABA) carboxyl group (-COOH) in bacterial folate synthesis, acting as a competitive inhibitor.
- **Sulfisoxazole:** Replaces the -NH_2 in the sulfonamide group with an isoxazole ring: H_2N — c1ccc(S(=O)(=O)NC2=NOC(C)=C2C)cc1 — CH_3.
- **Impact:** The isoxazole ring increases lipophilicity and potency, improving antibacterial activity while maintaining PABA mimicry.

1.2 Non-Classical Bioisosterism

Non-classical bioisosteres involve groups that do not share similar valence or electronic properties but produce comparable biological effects due to steric or electronic mimicry.
Key Examples:

- **Tetrazole for Carboxylic Acid:** The tetrazole ring mimics the acidity and planarity of a carboxyl group but has different electronic properties.
- **-**Amide for Ester: Amides (-CONH-) and esters (-COO-) share similar hydrogen-bonding capabilities but differ in metabolic stability.
- **-**Thiophene for Benzene: Thiophene mimics benzene's aromaticity but alters electronic distribution.

Example - Losartan (Angiotensin II Receptor Antagonist):

- **Structure:** c1cc(c2nc(Cl)c(CO)n2CCCC)ccc1c3ccccc3c4nnn[nH]4 — CH_2OH — $CH_2CH_2CH_3$
- **Bioisosteric Replacement:** The tetrazole ring replaces a carboxylic acid group in earlier angiotensin II antagonists.
- **Impact:** Tetrazole enhances lipophilicity, improving oral bioavailability, and maintains receptor binding due to similar acidity (pKa 4–5).

2 Applications in Improving Potency or Reducing Toxicity

Bioisosterism is a powerful tool in medicinal chemistry for optimizing drug properties. Key applications include:

- **Enhancing Potency:**
  - Replacing a group to improve receptor binding affinity (e.g., isoxazole in sulfisoxazole enhances antibacterial potency).
  - Modifying lipophilicity to improve membrane penetration (e.g., fluorine substitution in antipsychotics like haloperidol).
- **Reducing Toxicity:**

  - Replacing metabolically labile groups to increase stability (e.g., tetrazole in losartan reduces hepatic metabolism compared to carboxylic acid).
  - Minimizing off-target effects by altering electronic properties (e.g., thiophene for benzene reduces CYP450 interactions).
- **Improving Pharmacokinetics:**
  - Enhancing solubility or bioavailability (e.g., amide for ester increases hydrolytic stability).
  - Optimizing duration of action by reducing clearance (e.g., fluorine substitution in statins like atorvastatin).

Example - Sulfonamides (Continued):

- **Problem:** Sulfanilamide has moderate potency and rapid clearance.
- **Bioisosteric Solution:** Introducing an isoxazole ring (sulfisoxazole) increases lipophilicity and receptor affinity, enhancing potency and duration.
- **Outcome:** Improved antibacterial efficacy and reduced dosing frequency.

3 Clinical Implications

- **Potency Optimization:** Bioisosteric replacements, like isoxazole in sulfonamides, allow drugs to compete more effectively with endogenous substrates (e.g., PABA), improving therapeutic outcomes.
- **Toxicity Reduction:** Replacing carboxylic acid with tetrazole in losartan reduces metabolic toxicity while maintaining efficacy, suitable for long-term hypertension management.
- **Formulation and Delivery:** Bioisosteres improve solubility or stability, aiding formulation (e.g., tetrazole's lipophilicity in losartan enhances oral absorption).

4 Key Learning Points

- Bioisosterism involves replacing atoms or groups with similar physicochemical or biological properties to optimize drug performance.
- Classical bioisosteres (e.g., F for H, COOH for SO_3H) mimic size and electronic properties, while non-classical bioisosteres (e.g., tetrazole for carboxylic acid) focus on biological equivalence.
- Applications include enhancing potency (e.g., sulfisoxazole), reducing toxicity (e.g., losartan), and improving pharmacokinetics.
- Sulfonamides and losartan exemplify how bioisosterism drives drug design by balancing efficacy and safety.