CASE STUDY BASED PUZZLE

BP 807 ET:COMPUER AIDED DRUG DESIGN

UNIT 2: COMFA AND COMSIA

Case Study Puzzle: 3D-QSAR in Drug Design

Topic: CoMFA and CoMSIA Approaches

Case Scenario:

A pharmaceutical research team is working on a new series of benzimidazole derivatives as potential anti-inflammatory agents.
 Ten compounds (A–J) were synthesized with different substitutions at R_1, R_2, and R_3 positions. Biological activity was measured as IC_{50} (μM) against a target enzyme.
 The researchers decided to apply 3D-QSAR techniques to understand the structure–activity relationship (SAR) and guide further optimization.
They used:

- CoMFA to analyze steric and electrostatic fields
- CoMSIA to analyze steric, electrostatic, hydrophobic, H-bond donor, and H-bond acceptor fields

Puzzle 1: Method Selection Challenge

🔍 Clue:
 One compound (Compound F) showed excellent activity despite having a bulky hydrophobic group at R_2.

Puzzle Question:

Which 3D-QSAR method is more suitable to explain the contribution of hydrophobic interactions in this case?
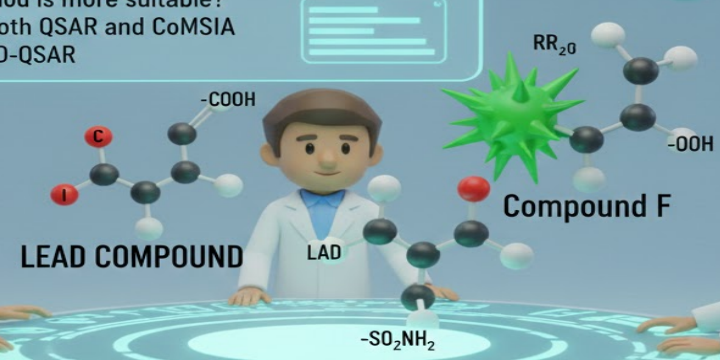Options:
 A. CoMFA only
 B. CoMSIA only
 C. Both CoMFA and CoMSIA
 D. 2D-QSAR

☞ Hint: Think about which method includes hydrophobic field descriptors.

Puzzle 2: Grid & Alignment Mystery

🔍 Clue:
During model development, the prediction accuracy dropped significantly when compound alignment was changed.

Puzzle Question:

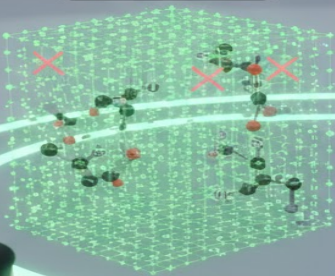Which factor is most critical in CoMFA and CoMSIA for obtaining a reliable model?
Options:
A. Molecular weight
B. Grid spacing
C. Molecular alignment
D. Number of compounds

☞ Hint: 3D-QSAR models depend heavily on spatial consistency.

Puzzle 3: Contour Map Decoder

🔍 Clue:

The CoMFA steric contour map shows:

- Green contours near R_1
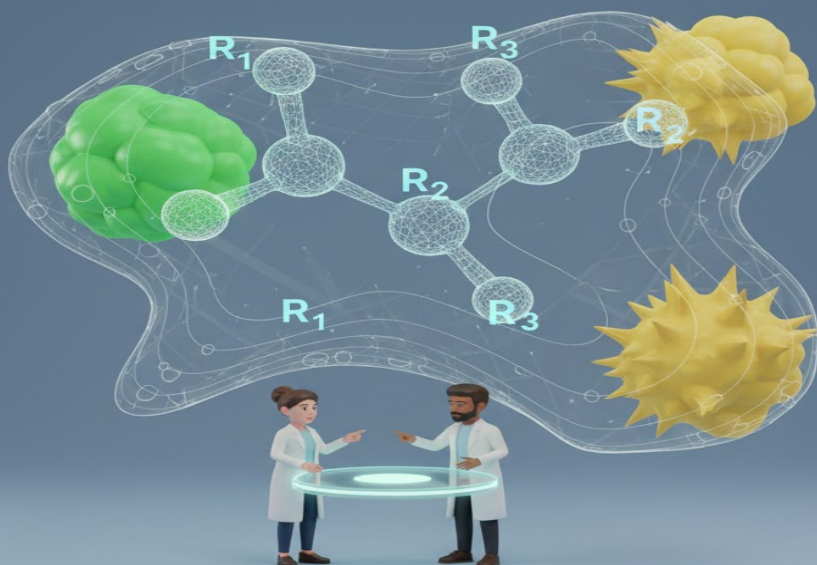- Yellow contours near R_3

Puzzle Question:

What modification is most likely to increase activity?

Options:

A. Add bulky group at R_3

B. Remove substituent at R_1

C. Add bulky group at R_1

D. Add electronegative group at R_3

☞ Hint: Green = favorable steric bulk, Yellow = unfavorable steric bulk.

Puzzle 3: Contour Map Decoder

🔍 **Puzzle Quedifation is most likely to increase activity?**

A. Add bulky group at R_3 ☐
B. Remove substiment at R_1 ☐
C. Add bulky group at R_1 ☐
D. Add elecktrangative group at R_3 ☐

💡
Hint
Green = favorable steric bulk,
Yellow, unvorarable steric bulk