Understanding solubility of small molecules:

Features Identified by XAI Analysis

- Presence of an atom at an aromatic/non-aromatic boundary

- Presence of two heteroatoms bonded to each other

- Presence of an atom with three heteroatom neighbors

Presence of an atom at an aromatic/non-aromatic boundary:

Explanation: This feature is negatively correlated with solubility, as indicated by its strong negative correlation with SHAP values. The presence of such boundaries may affect the molecular planarity and symmetry, which are known to influence solubility.

Scientific Evidence: The SHAP analysis shows a strong negative correlation (correlation coefficient: -0.9531) with an average impact of 0.4801 (XpertAI, 2023). Additionally, disrupting molecular planarity and symmetry by eliminating aromaticity can enhance solubility (Ishikawa & Hashimoto, 2011).

Hypothesis: The presence of an atom at an aromatic/non-aromatic boundary reduces solubility by maintaining molecular planarity and symmetry, which are less favorable for solubility.

Presence of two heteroatoms bonded to each other:

Explanation: This feature also shows a strong negative correlation with solubility. The bonding of heteroatoms can influence the electronic distribution and hydrogen bonding potential, which are critical for solubility.

Scientific Evidence: The SHAP analysis indicates a strong negative correlation (correlation coefficient: -0.9688) with an average impact of 0.3475 (XpertAI, 2023). The presence of polar atoms like nitrogen or oxygen can alter solubility by affecting hydrogen bonding (Walker, 2017).

Hypothesis: The bonding of two heteroatoms may reduce solubility by altering the electronic distribution and reducing favorable hydrogen bonding interactions.

Presence of an atom with three heteroatom neighbors:

Explanation: This feature is negatively correlated with solubility, likely due to the complex electronic environment created by multiple heteroatom neighbors, which can affect solubility.

Scientific Evidence: The SHAP analysis shows a strong negative correlation (correlation coefficient: -0.9601) with an average impact of 0.2489 (XpertAI, 2023). The presence of multiple heteroatoms can influence solubility by affecting the molecule's electronic properties (Walker, 2017).

Hypothesis: An atom with three heteroatom neighbors may reduce solubility by creating an electronic environment that is less conducive to solubility.

Summary

The features identified by the XAI analysis, such as the presence of an atom at an aromatic/non-aromatic boundary, two heteroatoms bonded to each other, and an atom with three heteroatom neighbors, all show strong negative correlations with solubility. These features likely influence solubility by affecting molecular planarity, symmetry, electronic distribution, and hydrogen bonding potential. The presence of aromatic boundaries and heteroatom interactions can maintain

molecular structures that are less favorable for solubility, as supported by the SHAP analysis and literature on molecular modifications for solubility enhancement (XpertAI, 2023; Ishikawa & Hashimoto, 2011; Walker, 2017).

References

1. XpertAI. (2024). XAI Summary.

2. Ishikawa, M., & Hashimoto, Y. (2011). Improvement in Aqueous Solubility in Small Molecule Drug Discovery Programs by Disruption of Molecular Planarity and Symmetry.

3. Walker, M. A. (2017). Improvement in aqueous solubility achieved via small molecular changes.

Explanation generated with XpertAI (2024)