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STRUCTURAL ALERTS FOR PROMISCUITY AND TOXICITY: THE GOOD, THE BAD, OR THE UGLY?

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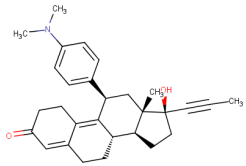
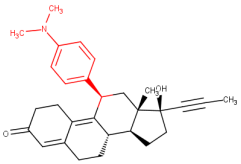
Structural alerts are widely accepted in chemical toxicology, regulatory decision support, and medicinal chemistry as simple and transparent means to flag potential chemical hazards, group compounds into categories for read-across, or eliminate as false hits from screening campaigns (so called PAINS, or Pan Assay Interference compoundS. However, there has been a growing concern that alerts disproportionally flag too many chemicals as toxic, or active, which questions their reliability as toxicity (or activity) markers. Conversely, the rigorously developed and properly validated statistical QSAR models can accurately and reliably predict the chemical bioactivity; however, their use in regulatory decision support has been hampered by the lack of transparency and interpretability. We demonstrate that contrary to the common perception of QSAR models as "black boxes" they can be used to identify statistically significant chemical substructures (QSAR-based alerts) that influence toxicity. We show through several case studies, especially, skin sensitization and bioactivit profiling, that the mere presence of structural alerts in a chemical, irrespective of the derivation method (expert-based or QSAR-based), should be perceived at best as hypotheses of possible biological effects but cannot be blindly relied on for reaching conclusions about chemical safety or lack thereof. We will discuss a new approach that synergistically integrates structural alerts and rigorously validated QSAR models for both more transparent and accurate bioactivity or toxiicty assesment of new chemicals.



Mifepristone

- FDA-approved Abortifacient



Mifepristone

- PAINS Alert: anil_di_alk_E

1. Alves V.M. et al. *Green Chem*., 2016, **18**: 4348-4360.
2. Capuzzi S.J. et al. *J Chem Inf Model*., 2017, **57(3)**: 417-427.

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