# ****De Novo Drug Design: Combining Pharmacophore Modeling, 3D Shape Matching, and Generative AI****

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Recent work shows that shape‑based generative reinforcement‑learning models enable scaffold hopping and diverse lead discovery [1], while voxel‑based shape autoencoders can uncover novel scaffolds from 3‑D inputs [2]. Pharmacophore modeling that exploits shape‑and‑colour Tanimoto scores (e.g., ROCS) reliably detects compounds sharing key 3‑D features beyond close analogues [3]. Building on this, we introduce an open‑source pipeline that (i) aligns ligands by shape and pharmacophoric “colour,” (ii) filters for high Tanimoto shape/colour similarity and synthetic accessibility, and (iii) uses DrugEx to propose new chemotypes meeting both criteria [4]. Using the chemokine receptor CCR2, an allosteric target involved in inflammation and metastasis, as a case study [5], we benchmark ROCS/OMEGA against RDKit/CDPKit [6, 7] and find speed‑versus‑optimisation trade‑offs on large libraries, yet comparable overlay accuracy. This integrated workflow therefore provides a practical open‑source alternative for next‑generation lead discovery.

References
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