Supporting Information to:

In silico Target Fishing for Rationalized Ligand Discovery Exemplified on Constituents of *Ruta graveolens*

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Fig. 1S Hitting pharmacophore models from the parallel screen of compounds **1** – **16** for the targets AChE, HRV coat protein, and CB_2 receptor.

AChE inhibitor models:

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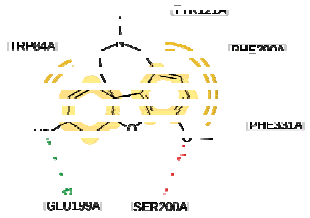
model</td>
<td> 
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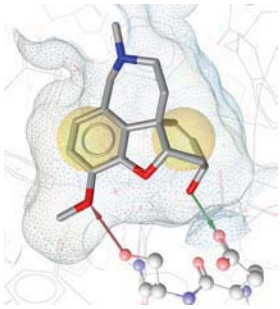
<td>  </td>
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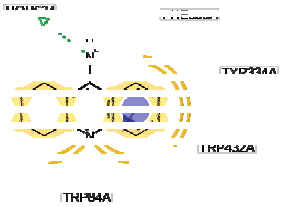
<td> 
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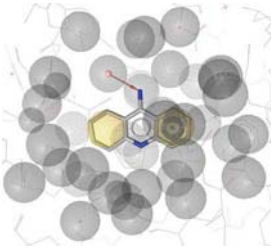
<td>  </td>
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HRV coat protein inhibitor models:

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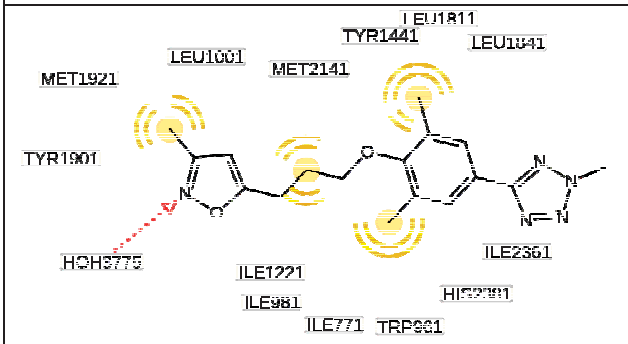
<td> 
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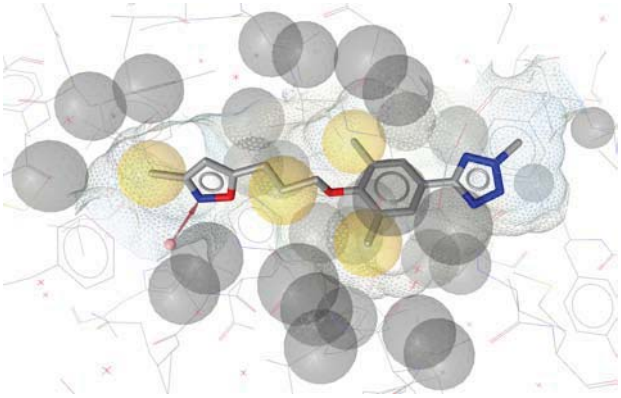
<td rowspan="2">  </td>
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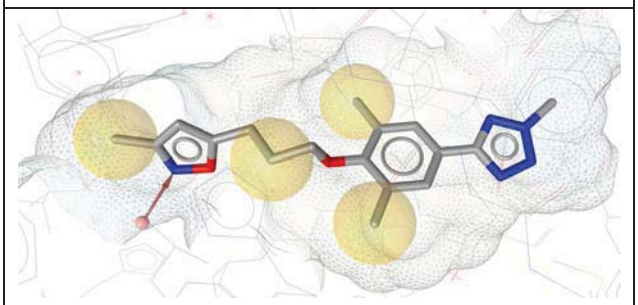
<td>  </td>
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<td colspan="2">R 61837-based model</td>
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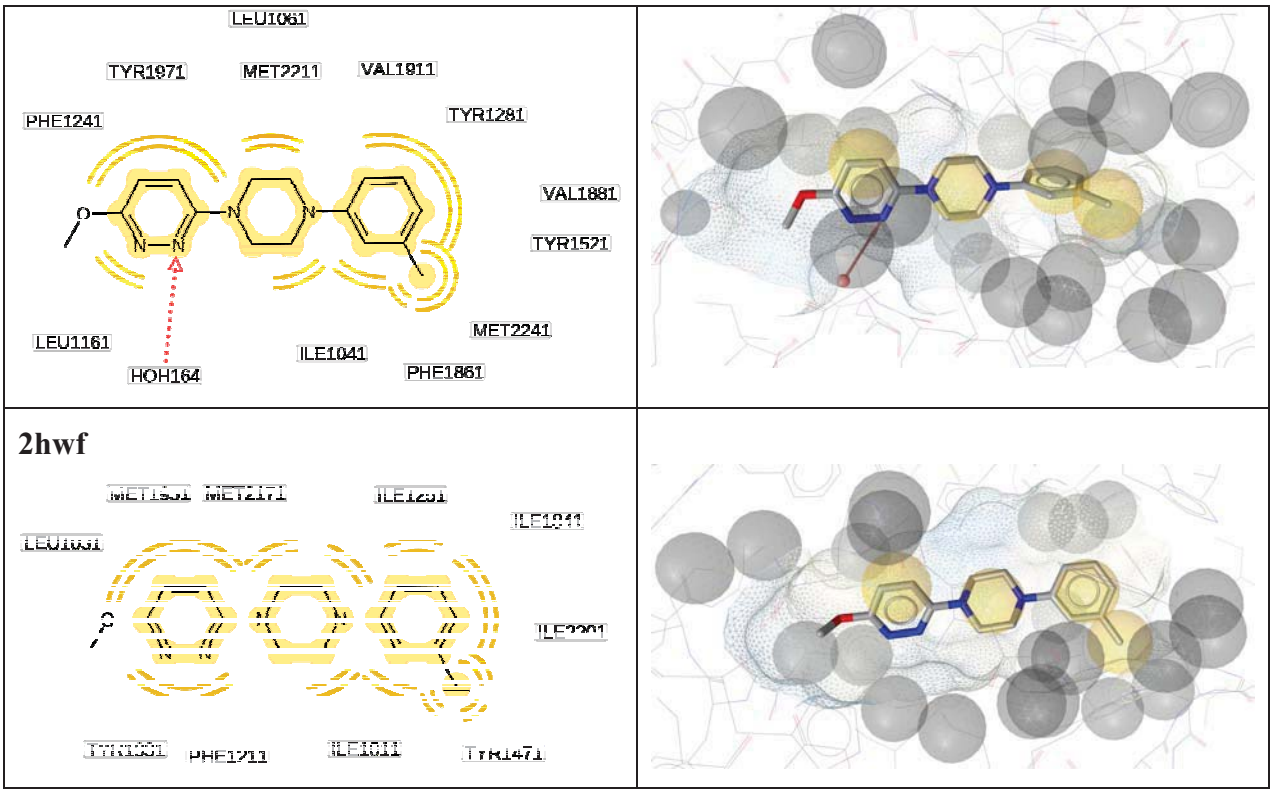


CB_2 ligands model:

The generation and experimental validation of the hitting CB_2 pharmacophore model has just been presented by Markt et al. [46]. For its generation, five highly active and selective CB_2 agonists were submitted to conformational analysis and aligned employing the HipHop algorithm implemented in Catalyst 4.11 (Accelrys Inc.). The resulting pharmacophore model consists of one hydrogen bond acceptor, one hydrophobic, two hydrophobic aliphatic, and one hydrophobic aromatic feature. The shape of the highly active agonist AM1241 was added to the model to improve its restrictiveness.

Fig. 2S Ligand-based pharmacophore model for CB_2 agonists. Chemical features of the model are colour-coded: hydrogen bond acceptor – green; hydrophobic – cyan; hydrophobic aromatic – dark blue; hydrophobic aliphatic – light blue; shape – grey.

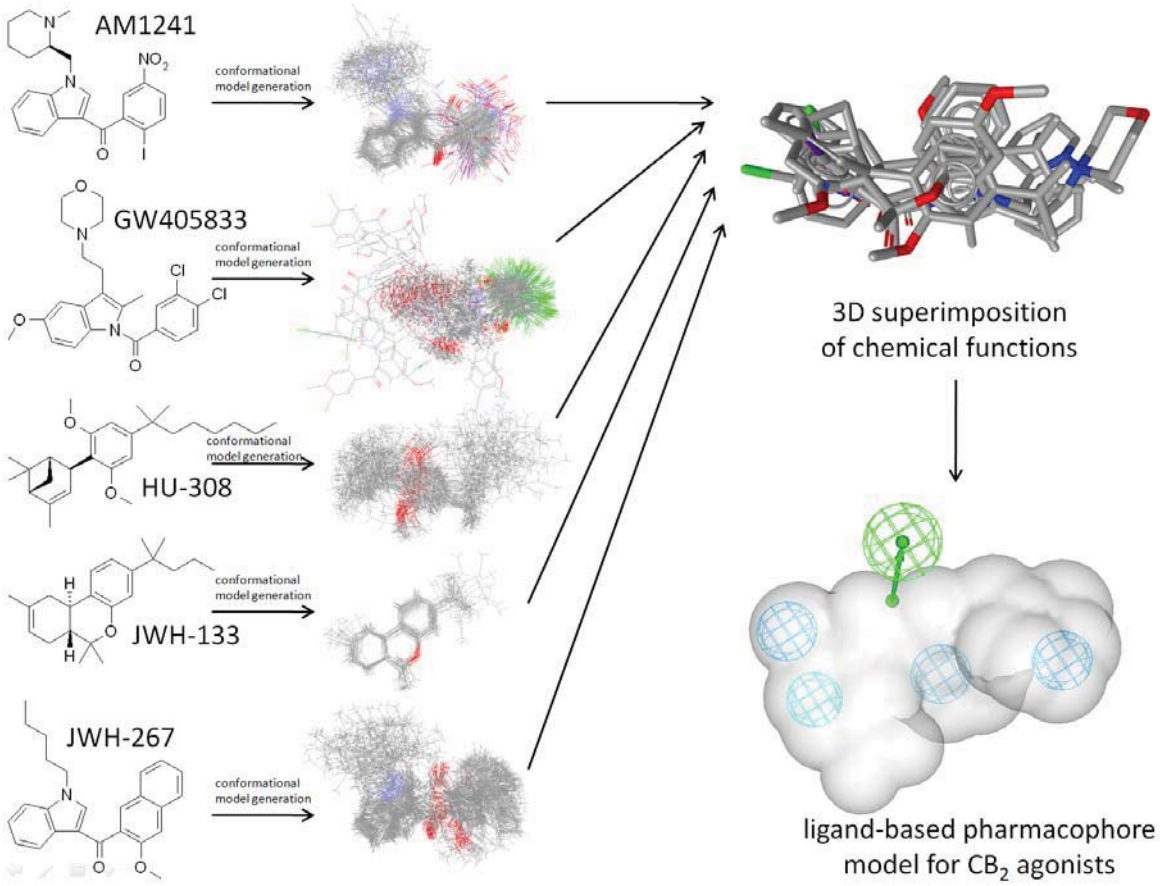
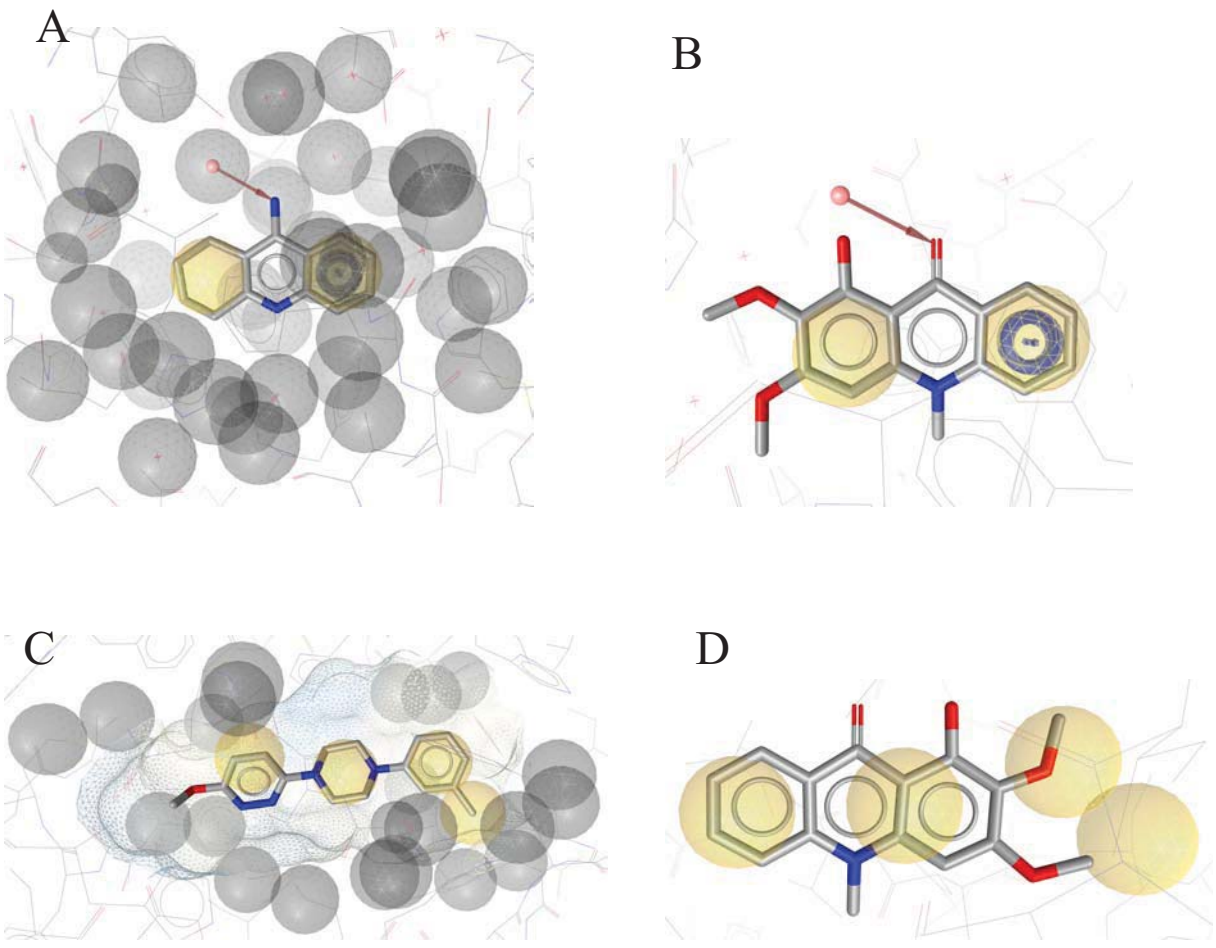


Fig. 3S Alignment of selected bioactive hits to a hitting pharmacophore model. **A**: Tacrin-based AChE inhibitor pharmacophore model. **B**: Compound **1** fitted into the tacrin-based model. **C**: R 61837-based model for HRV coat protein inhibitors. **D**: Compound **1** fitted into the R 61837-based model. **E**: The highly potent CB_2 agonist JWH-267 fitted into the ligand-based CB_2 pharmacophore model. **F**: Compound **3** fitted into the ligand-based CB_2 model. Chemical features of the models are colour-coded. Structure-based models (Fig. **3S A-D**; LigandScout): hydrogen bond acceptor: red; hydrophobic: yellow; exclusion volumes: grey. Ligand-based models (Fig. **3S E, F**; Discovery Studio): hydrogen bond acceptor: green; hydrophobic: cyan; hydrophobic aromatic: dark blue; hydrophobic aliphatic: light blue; shape: grey. For a clearer depiction of the fitting conformations, no excluded volume spheres are shown for the virtual hits.



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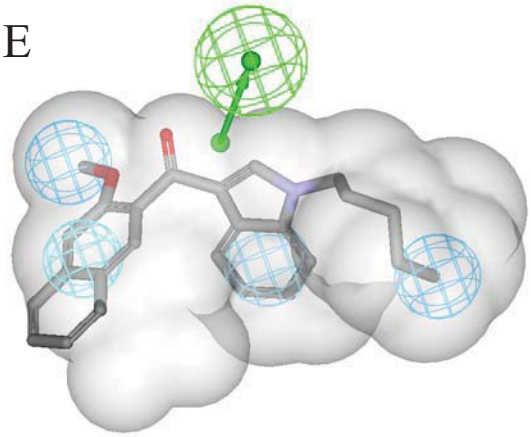

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