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Synthesis and properties of N-substituted amides and their isosteric analogs containing polycyclic fragments: I. N-((1S,2S,3S,5R)-(+)-isopinocampheyl) amides and thioamides

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Preparation has been carried out of a focused library of N-((1S,2S,3S,5R)-(+)-isopinocampheyl)aryl amides and the matching thioamide derivatives, all with simple H, F, or Cl groups on the aryl part. The synthesis has turned out straightforward: enantiopure (1S,2S,3S,5R)-(+)-isopinocampheylamine has been coupled directly with the relevant aromatic acid chlorides or thioacyl chlorides. After work-up and purification, the products have been obtained in solid yields of 71–81%. Full confirmation has relied on melting point checks, full ^{1}H and ^{13}C NMR spectra, plus elemental analysis. SwissADME and SILICOS-IT predictions reveal low micromolar aqueous solubility (4.3–27.0 μM), which decrease markedly with aryl halogenation. Molinspiration LogP values range from 4.03 to 5.69, and of particular interest, C=O to C=S replacement further lowers solubility in matched pairs. PASSOnline screening highlights prostaglandin E_1 antagonism as the dominant predicted activity (Pa 0.763–0.838, Pi 0.001–0.002), alongside strong profiles for autoimmune disorders (Pa 0.630–0.759) and rheumatoid arthritis (Pa 0.559–0.739) treatment. The thioamide subset additionally shows anti-obesity potential (Pa 0.724–0.783). SwissTargetPrediction repeatedly suggests interactions with P2X purinoceptor 7, soluble epoxide hydrolase, acetylcholinesterase, muscarinic M_2 receptor, and histamine H_2 receptor.

Keywords: Isopinocampheylamine, N-Substituted amide, Thioamide, Computer screening, SwissADME, PASSOnline