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Abstract *N*-formyl peptide receptor (FPR1) and *N*-formyl peptide receptor-like 1 (FPRL1, now known as FPR2) are G protein-coupled receptors involved in host defense and sensing cellular dysfunction. Because of the potential for FPR1/FPR2 as a therapeutic target, our recent high-throughput screening efforts have focused on the identification of unique nonpeptide agonists of FPR1/FPR2. In the present studies, we screened a chemolibrary of drug-like molecules for their ability to induce intracellular calcium mobilization in RBL-2H3 cells transfected with human FPR1 or FPR2. Screening of these compounds resulted in the identification of novel and potent agonists that activated both FPR1 and FPR2, as well as compounds that were specific for either FPR1 or FPR2 with EC

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values in the low micromolar range. Specificity of the compounds was supported by analysis of calcium mobilization in HL-60 cells transfected with human FPR1 and FPR2. In addition, all but one agonist activated intracellular calcium flux and chemotaxis in human neutrophils, irrespective of agonist specificity for FPR1 or FPR2. Molecular modeling of the group of FPR1 and FPR2 agonists using field point methodology allowed us to create pharmacophore models for ligand binding sites and formulate requirements for these specific

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-formyl peptide receptor agonists. These studies further demonstrate that agonists of FPR1/FPR2 include compounds with wide chemical diversity and that analysis of such compounds can enhance our understanding of their ligand/receptor interaction.