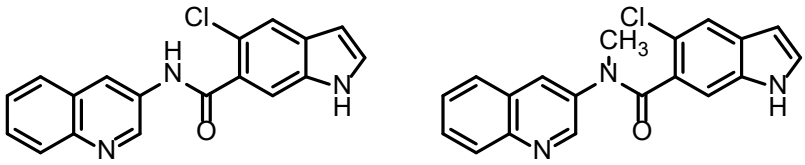
Overview



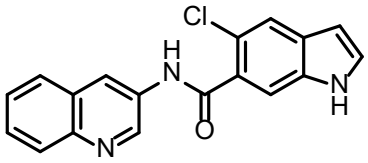
Chemical structures of ME43 and the negative control ME113.

Based on the Nurr1-DHI complex structure, we have identified high-affinity ligands (Kd 0.08–0.12 μM) targeting the DHI binding site of Nurr1. Optimization of this ligand scaffold yielded a potent NR4A agonist **ME43,** characterized by favorable physicochemical properties, high selectivity, and low toxicity, making it a valuable chemical probe for studying Nurr1 activation via the DHI site. Treatment of neuronal cells with ME43 led to increased expression of Nurr1-regulated neuroprotective genes, including brain-derived neurotrophic factor (BDNF), supporting therapeutic potential of Nurr1 activation in combating neurodegenerative diseases.

Biological activity summary:

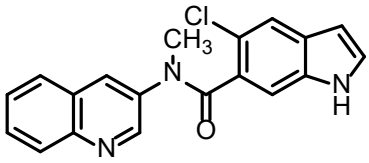
- Binding affinity (ITC): Kd 0.12 μM to recombinant Nurr1
- Cellular potency was determined in Gal4-NR4A hybrid reporter assays yielding the following data: EC50 (Nur77) = 0.04±0.01 μM (eff. 2.0 ± 0.1-fold); EC50 (Nurr1) = 0.06 ± 0.02 μM (eff. 1.9 ± 0.1-fold); EC50 (NOR1) = 0.07±0.03 μM (eff. 2.0 ± 0.2-fold).
- ME43 activated full-length human Nurr1 on the response elements for the monomer (NBRE, EC50 = 0.07 ± 0.02 μM), homodimer (NurRE, EC50 = 0.027 ± 0.008 μM) and RXR heterodimer (DR5, EC50 = 0.014 ± 0.006 μM) with consistently low nanomolar potency.
- ME43 induced neuroprotective gene expression (mRNA) in N27 cells at 1 μM.
- ME43 is selective over nuclear receptors outside the NR4A family with moderate PXR activation at 3 μM (EC_{50} = 1.5 ± 0.6 μM)

Properties



ME43

Physical and chemical properties for ME43	
Molecular weight	321,76
Molecular formula	$C_{18}H_{12}ClN_3O$
IUPAC name	5-Chloro-*N*-(quinolin-3-yl)-1*H*-indole-6-carboxamide
AlogP	4.15
PSA	57.78
No. of chiral centers	0
No. of rotatable bonds	3
No. of hydrogen bond acceptors	3
No. of hydrogen bond donors	2
Storage	Stable as a solid at room temperature. Store DMSO stock solutions (10 mM) at -20 °C. Use only 1 freeze/thaw cycle per aliquot. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution	Soluble in DMSO up to 10 mM



ME113

Physical and chemical properties for ME113	
Molecular weight	335.79
Molecular formula	$C_{19}H_{14}ClN_3O$
IUPAC name	5-Chloro-*N*-methyl-*N*-(quinolin-3-yl)-1*H*-indole-6-carboxamide
AlogP	4.18
PSA	48.99
No. of chiral centers	0
No. of rotatable bonds	4
No. of hydrogen bond acceptors	3
No. of hydrogen bond donors	1
Storage	Stable as a solid at room temperature.

	Store DMSO stock solutions (10 mM) at -20 °C. Use only 1 freeze/thaw cycle per aliquot. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution	Soluble in DMSO up to 10 mM

SMILES:
ME43: ClC1=C(C(NC2=CC(C=CC=C3)=C3N=C2)=O)C=C(NC=C4)C4=C1
ME113: ClC1=C(C(N(C)C2=CC(C=CC=C3)=C3N=C2)=O)C=C(NC=C4)C4=C1

InChI:
ME43: InChI=1S/C18H12ClN3O/c19-15-8-12-5-6-20-17(12)9-14(15)18(23)22-13-7-11-3-1-2-4-16(11)21-10-13/h1-10,20H,(H,22,23)
ME113: InChI=1S/C19H14ClN3O/c1-23(14-8-12-4-2-3-5-17(12)22-11-14)19(24)15-10-18-13(6-7-21-18)9-16(15)20/h2-11,21H,1H3

InChIKey:
ME43: ZJPUSKBFLQMYJU-UHFFFAOYSA-N
ME113: AUSKEAIAMTVFBX-UHFFFAOYSA-N

References

Markus Egner, Romy Busch, Úrsula López-García, Max Lewandowski, Georg Höfner, Thomas Wein, Julian A. Marschner, and Daniel Merk. A Nurr1 Agonist Derived from the Natural Ligand DHI Induces Neuroprotective Gene Expression. *J. Med. Chem.*, **2025**, *68*, 4829–4847.

https://doi.org/10.1021/acs.jmedchem.4c03104