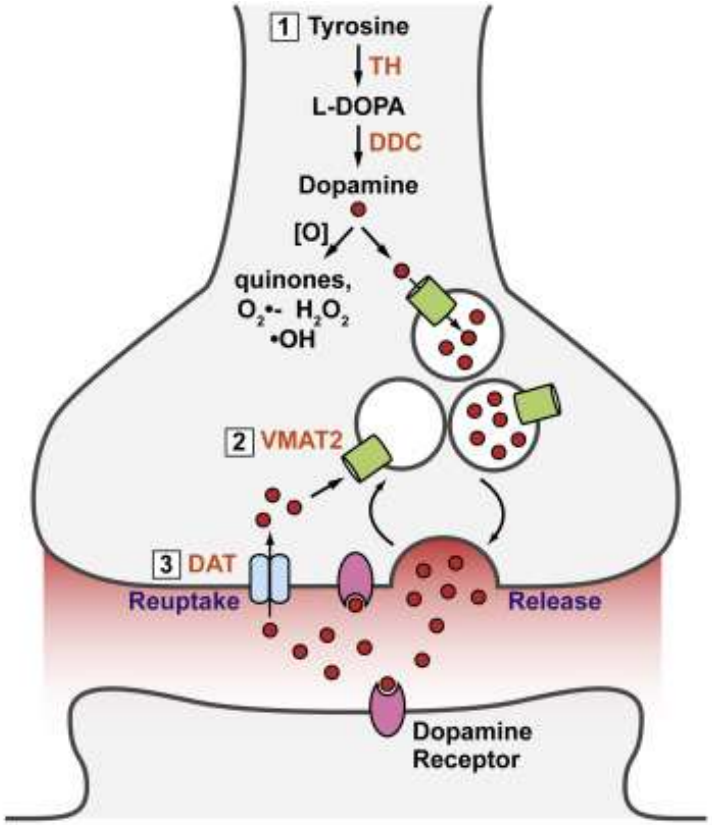
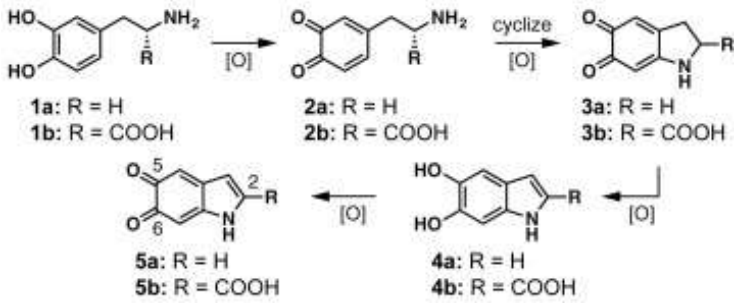
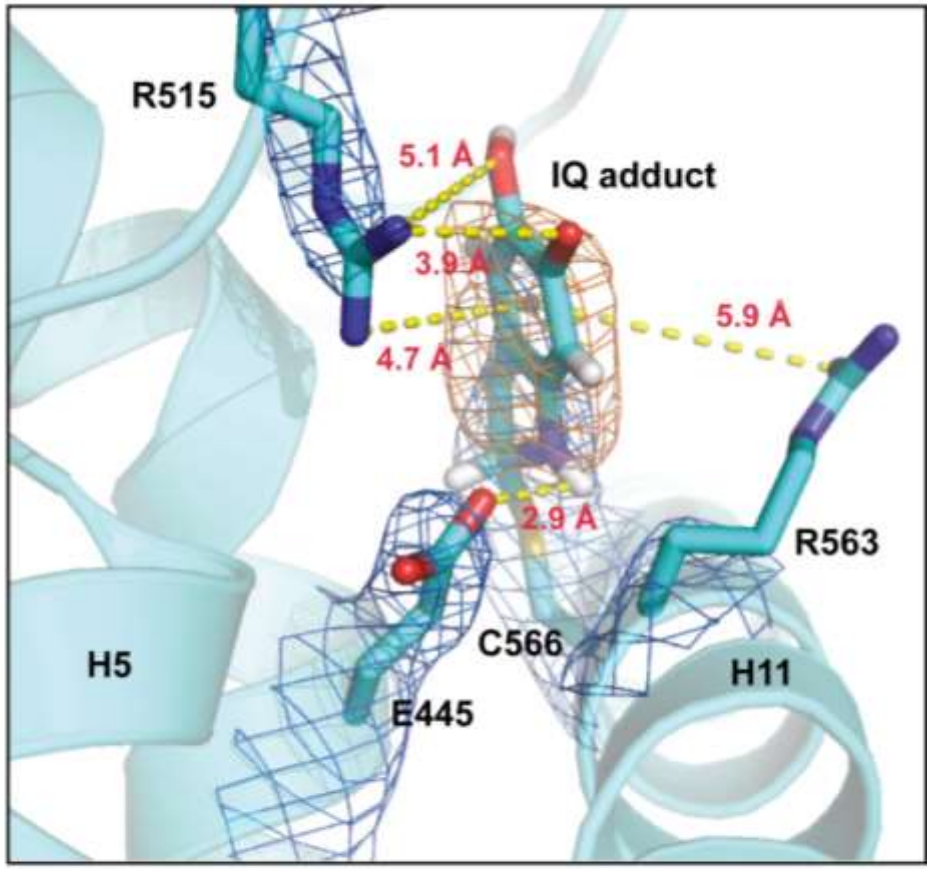
Structur-Guided Design of Nurr1 Agonists Derived from the Natural Ligand Dihydroxyindole

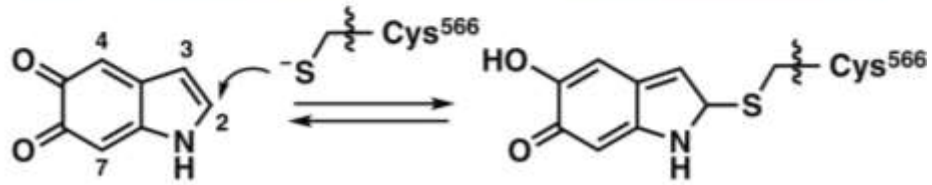
*J. Med.Chem.*2023,66,13556-13567

INTRODUCTION



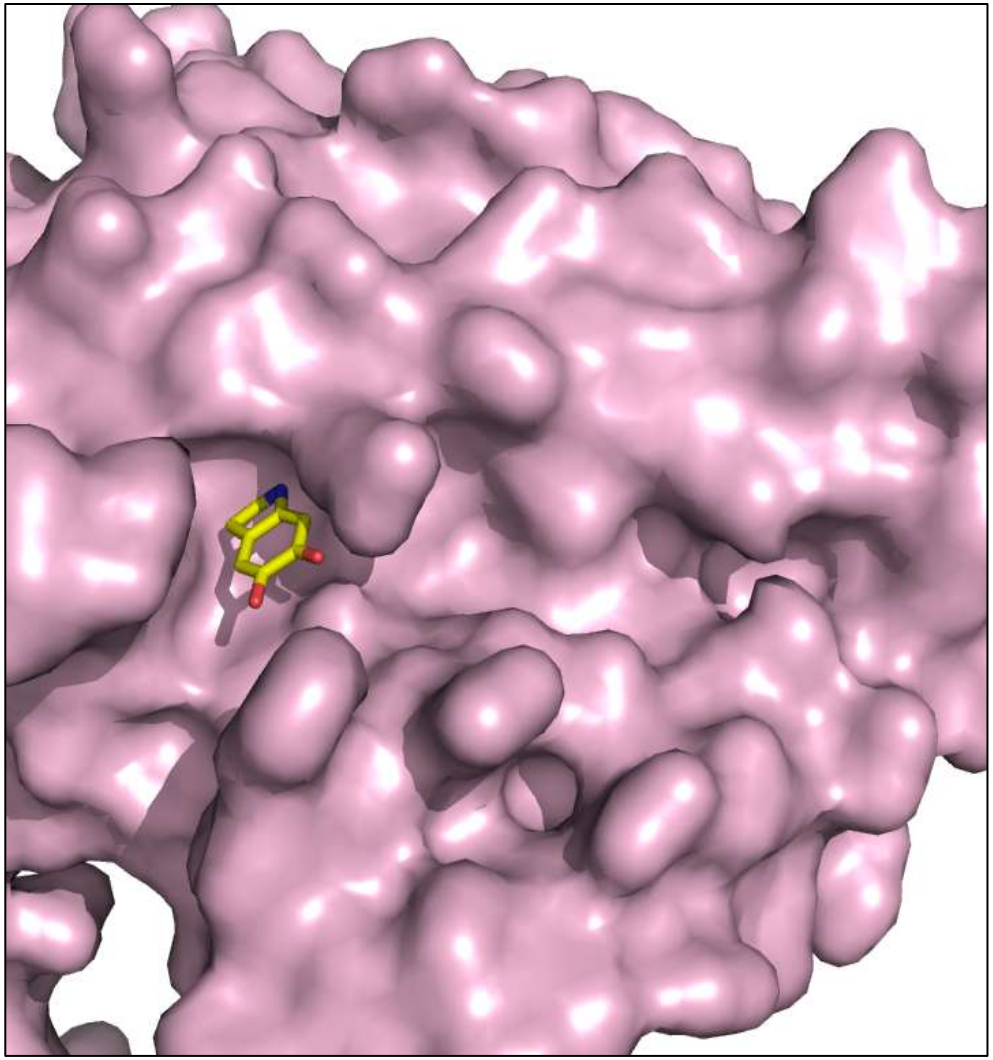






Bruning JM.et al.*Cell Chem Biol*. 2019 May 16;26(5):674-685.e6.

INTRODUCTION



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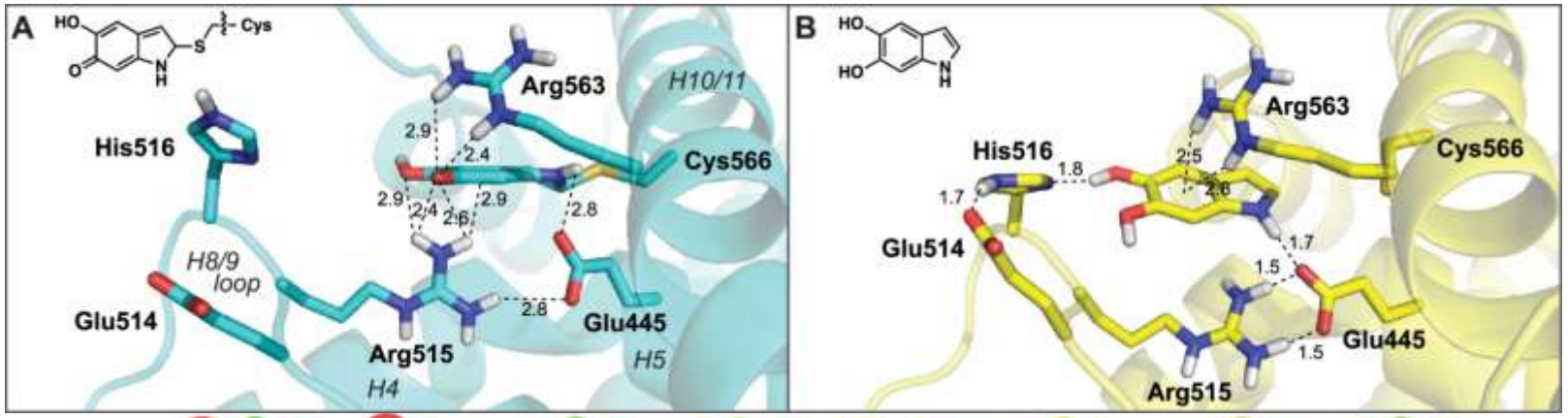
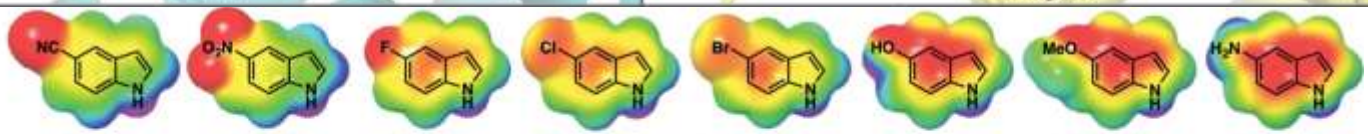
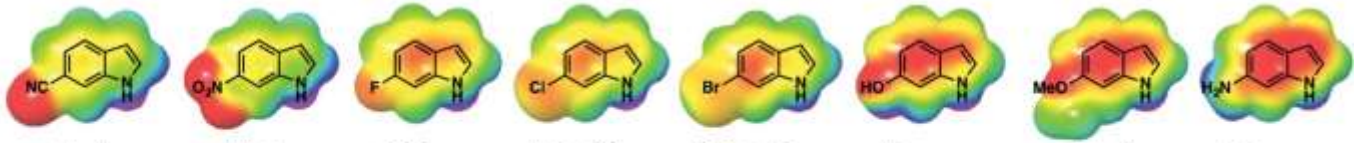
Bruning JM.et al.*Cell Chem Biol*. 2019 May 16;26(5):674-685.e6.

INTRODUCTION

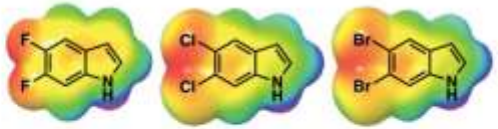




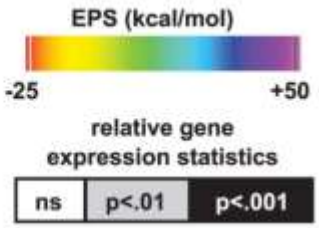
K_D (μM)	no binding	no binding	152 ± 80	15.0 ± 1.0	5.0 ± 1.0	n/a*	4.0 ± 1.0	n/a*
Th	1.16 ± 0.09	1.26 ± 0.24	**1.50 ± 0.10**	**1.78 ± 0.16**	**2.15 ± 0.12**	0.81 ± 0.05	**1.52 ± 0.17**	1.28 ± 0.09
Vmat2	1.15 ± 0.12	1.13 ± 0.18	**1.57 ± 0.08**	**2.38 ± 0.08**	**2.48 ± 0.12**	0.89 ± 0.12	**1.32 ± 0.08**	1.03 ± 0.10



K_D (μM)	no binding	no binding	>1000	172 ± 36	205 ± 76	n/a*	no binding	n/a*
Th	1.05 ± 0.06	1.02 ± 0.07	1.24 ± 0.04	1.37 ± 0.05	1.16 ± 0.33	0.69 ± 0.36	0.97 ± 0.13	0.67 ± 0.14
Vmat2	1.08 ± 0.18	1.11 ± 0.09	**1.32 ± 0.02**	**1.71 ± 0.02**	1.16 ± 0.33	1.21 ± 0.12	1.13 ± 0.13	0.83 ± 0.07



K_D (μM)	no binding	4.5 ± 0.9	2.2 ± 0.2
Th	0.96 ± 0.07	1.09 ± 0.08	0.99 ± 0.03
Vmat2	1.09 ± 0.09	1.11 ± 0.06	1.06 ± 0.10



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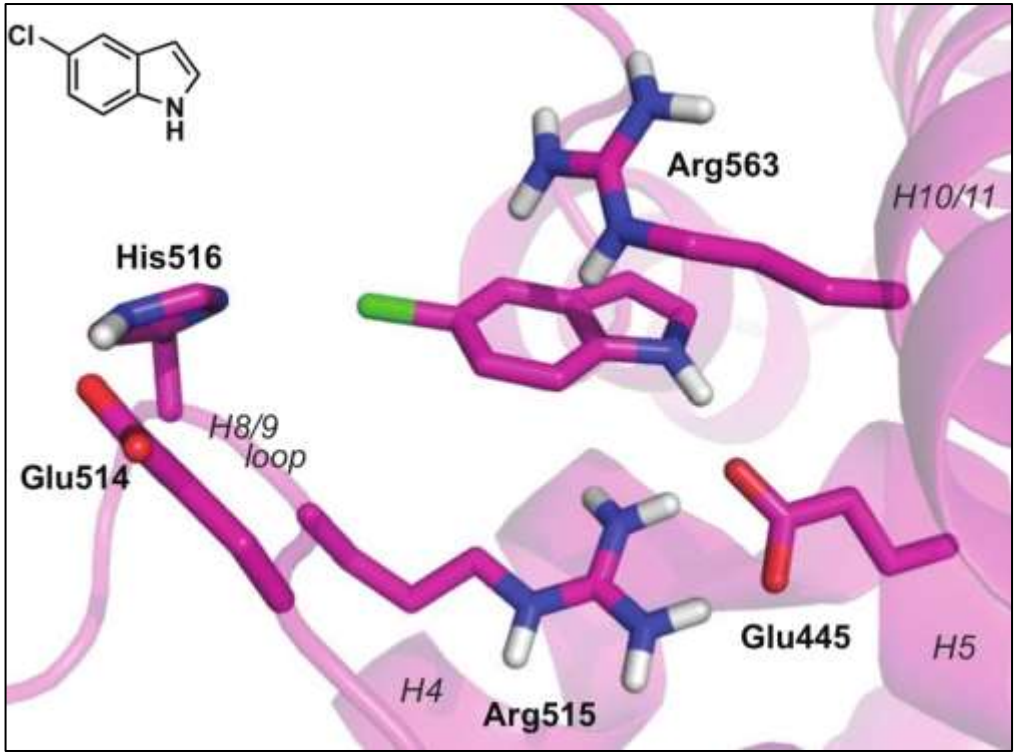
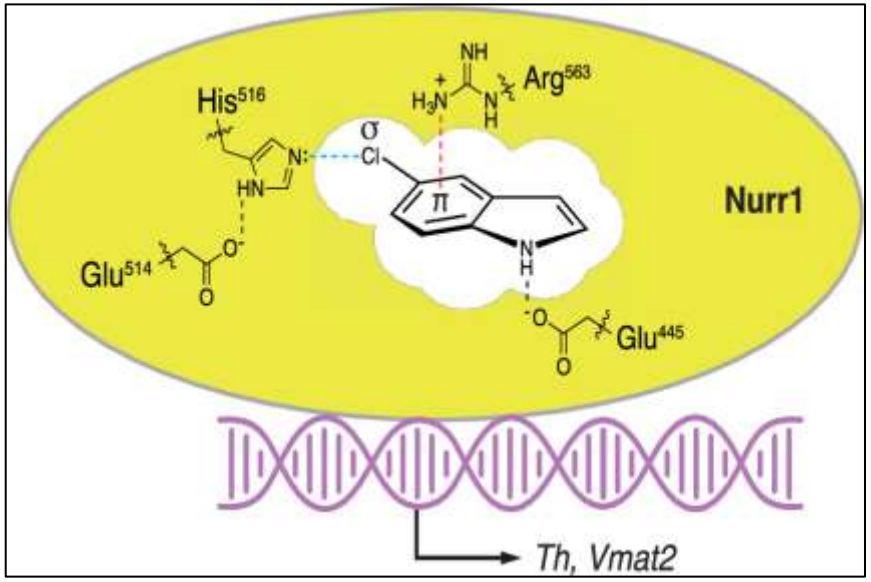
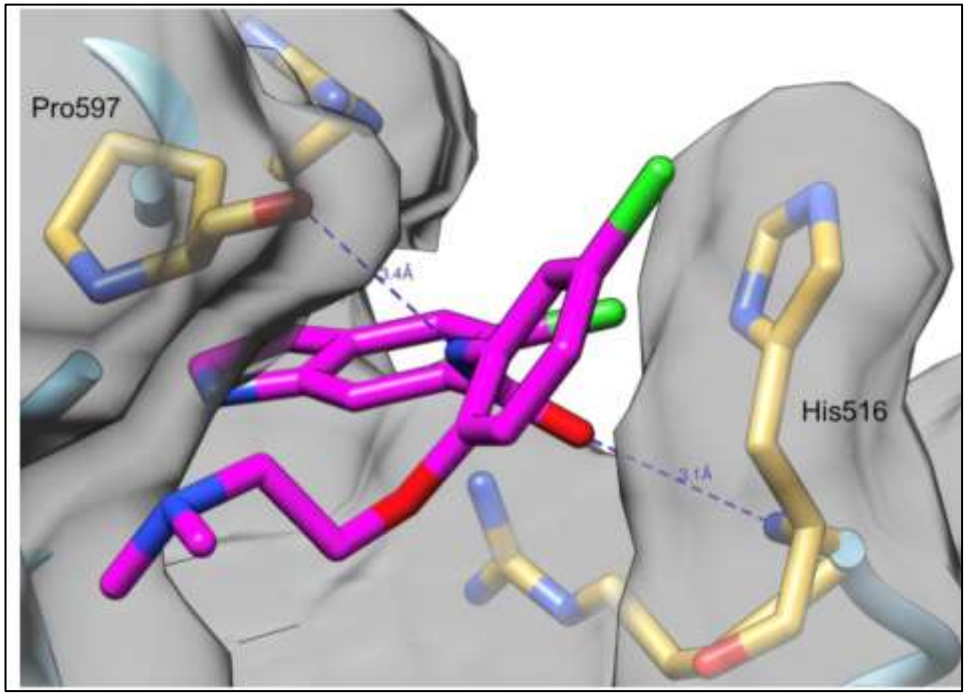
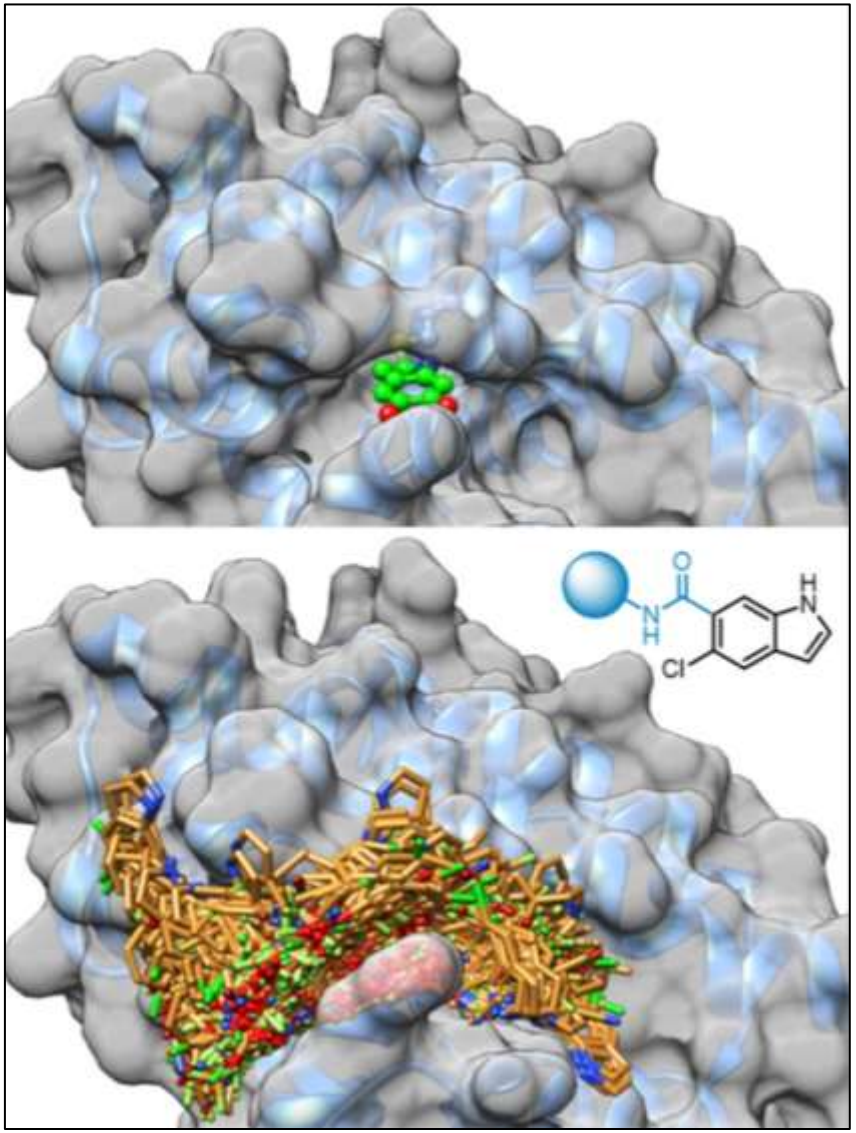
Structure-Guided Design





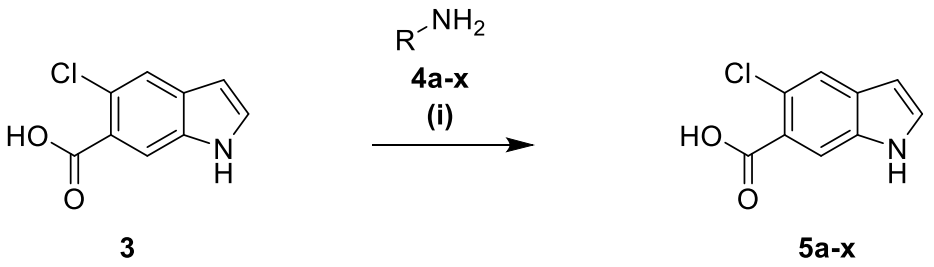
Structure-Guided Design





Compound Library Preparation and Screening

a



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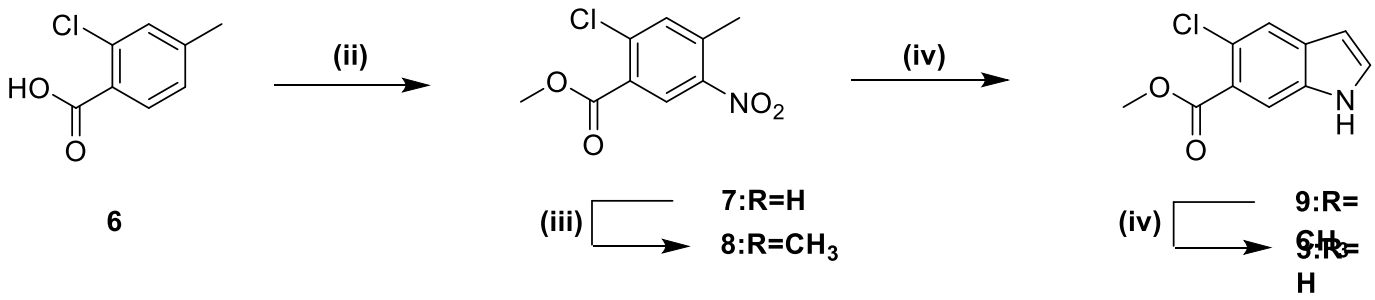
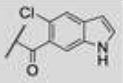
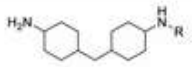
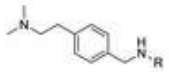
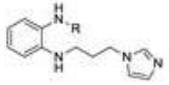
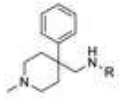
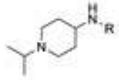
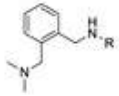
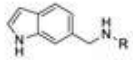
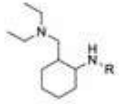
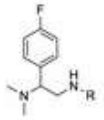
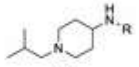
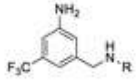
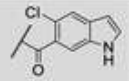
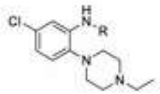
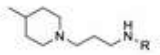
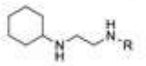
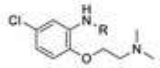
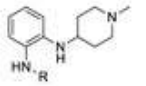
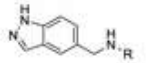
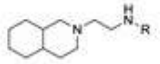
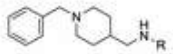
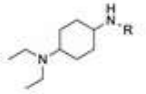
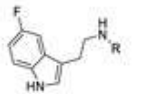
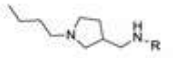
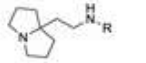
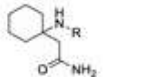


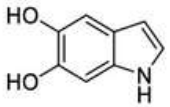
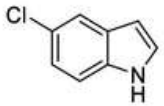
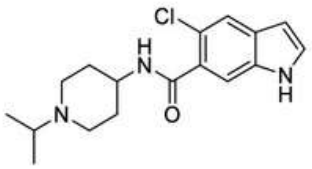
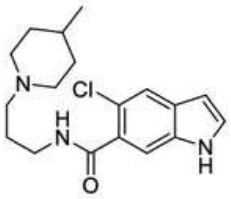
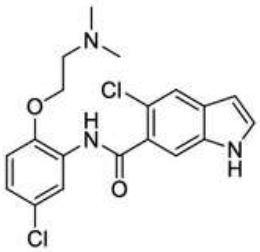
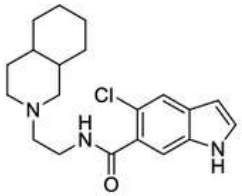
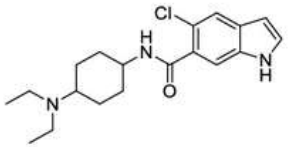
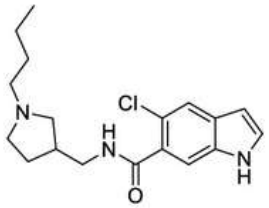
Reagents and conditions:
(i) EDC·HCl, EtOAc, rt, 36 h;
(ii) HNO3/H2SO4, 5 °C, 0.5 h, 59%;
(iii) acetyl chloride, MeOH, 50 °C, 4 h,96%;
(iv) DMF-DMA, DMF, 120 °C, 2 h; then Zn, AcOH/H2O, 80°C, 2 h, 40%;
(v) LiOH·H2O, EtOH/H2O, rt, 18 h, 94%

Compound Library Preparation and Screening

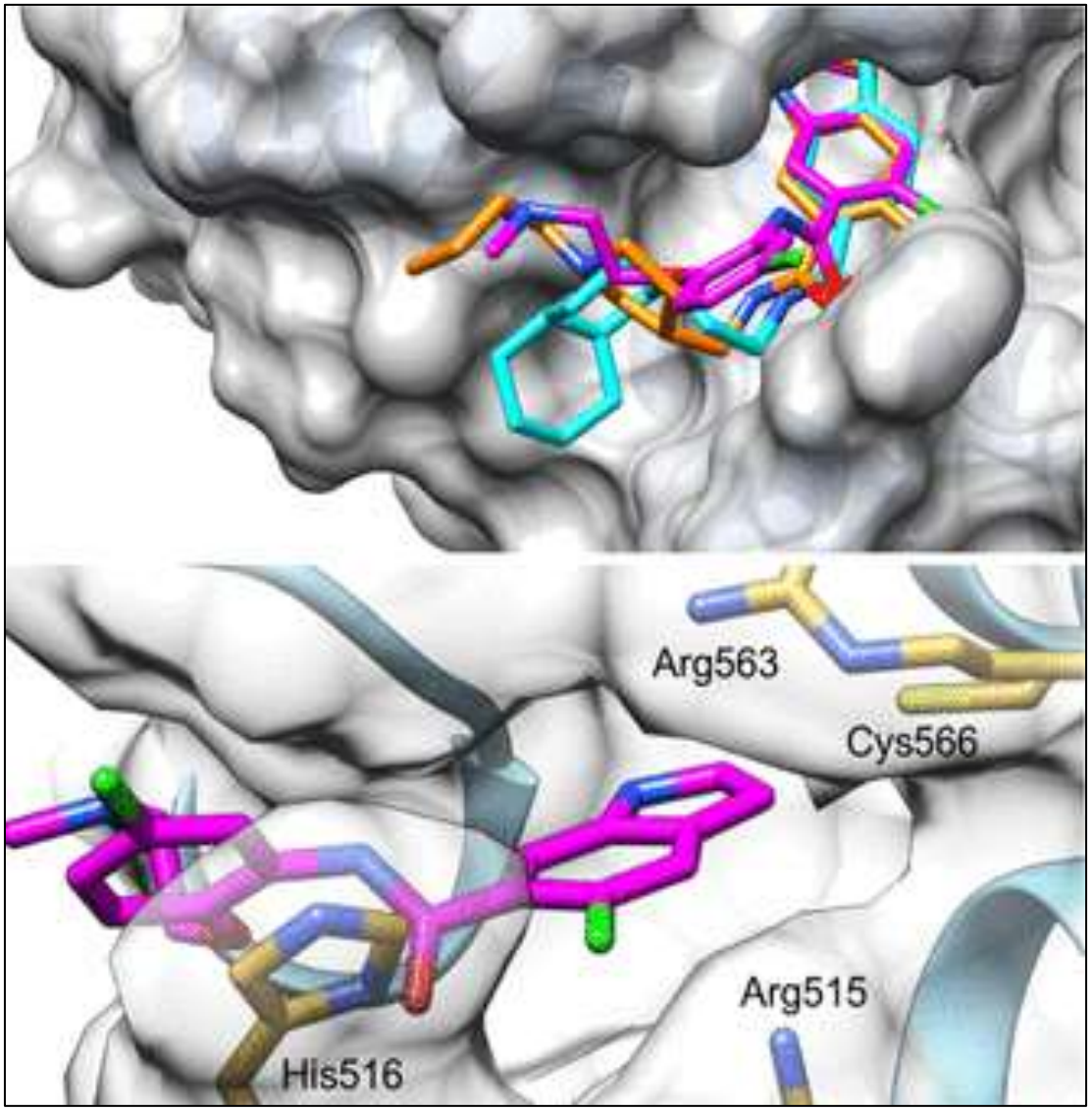
	R= H		R= 	
	ID	fold Nurr1 act.	ID	fold Nurr1 act.
	**4a**	1.10±0.08	**5a**	1.58±0.09 (toxic)
	**4b**	1.62±0.15	**5b**	1.26±0.04
	**4c**	1.29±0.09	**5c**	0.90±0.08
	**4d**	1.60±0.14	**5d**	1.36±0.09
	**4e**	1.10±0.12	**5e**	1.59±0.08
	**4f**	0.97±0.10	**5f**	0.91±0.07
	**4g**	1.24±0.05	**5g**	0.76±0.09
	**4h**	1.6±0.4 (toxic)	**5h**	1.53±0.05
	**4i**	1.02±0.14	**5i**	1.22±0.14
	**4j**	1.60±0.27	**5j**	1.29±0.08
	**4k**	1.09±0.05	**5k**	0.71±0.02 (toxic)

	R= H		R= 	
	ID	fold Nurr1 act.	ID	fold Nurr1 act.
	**4l**	0.89±0.07	**5l**	0.96±0.01
	**4m**	1.08±0.04	**5m**	1.49±0.07
	**4n**	0.96±0.12	**5n**	1.12±0.01
	**4o**	1.19±0.05	**5o**	1.60±0.01
	**4p**	1.51±0.19 (toxic)	**5p**	1.82±0.07
	**4q**	1.20±0.18	**5q**	0.72±0.08 (toxic)
	**4r**	1.05±0.13	**5r**	1.46±0.10
	**4s**	1.72±0.28	**5s**	1.36±0.01
	**4t**	0.83±0.13	**5t**	1.46±0.04
	**4u**	1.34±0.04	**5u**	0.57±0.04 (toxic)
	**4v**	1.39±0.30	**5v**	1.47±0.12
	**4w**	0.70±0.15	**5w**	1.26±0.04
	**4x**	0.86±0.08	**5x**	0.89±0.06

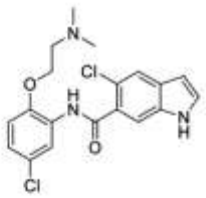
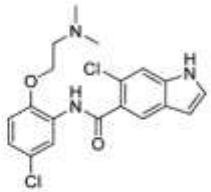
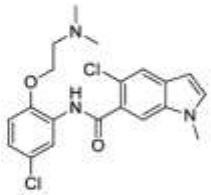
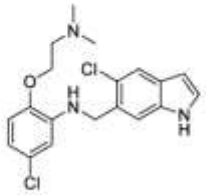
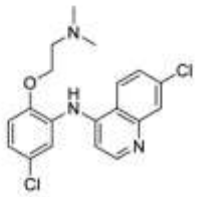
Compound Library Preparation and Screening

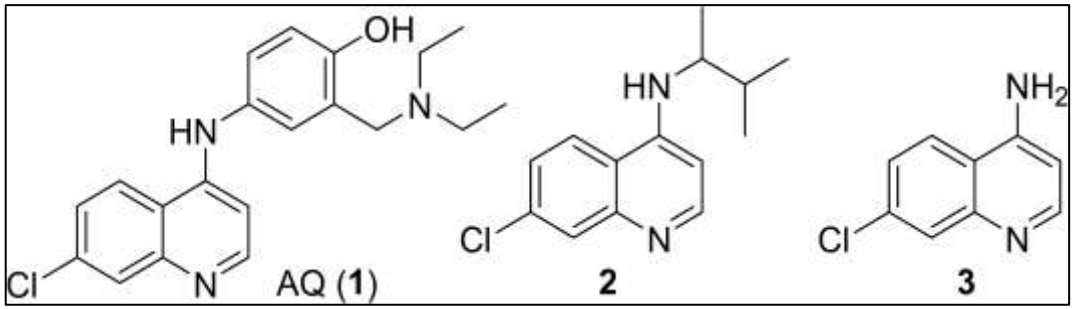
ID	structure	K_d	EC_{50} (eff.)
DHI (**2a**)		- [b]	> 100 μM[21]
2b		15 μM[22]	40±4 μM (2.4±0.1-fold act.)
5e		no binding[c]	inactive at 100 μM
5m		no binding[c]	inactive at 100 μM
5o		0.5 μM	3±1 μM (1.3±0.1-fold act.)
5r		3.2 μM	12±2 μM (1.4±0.1-fold act.)
5t		no binding[c]	inactive at 100 μM
5v		16 μM	28±6 μM (1.3±0.1-fold act.)

Binding Site Evaluation

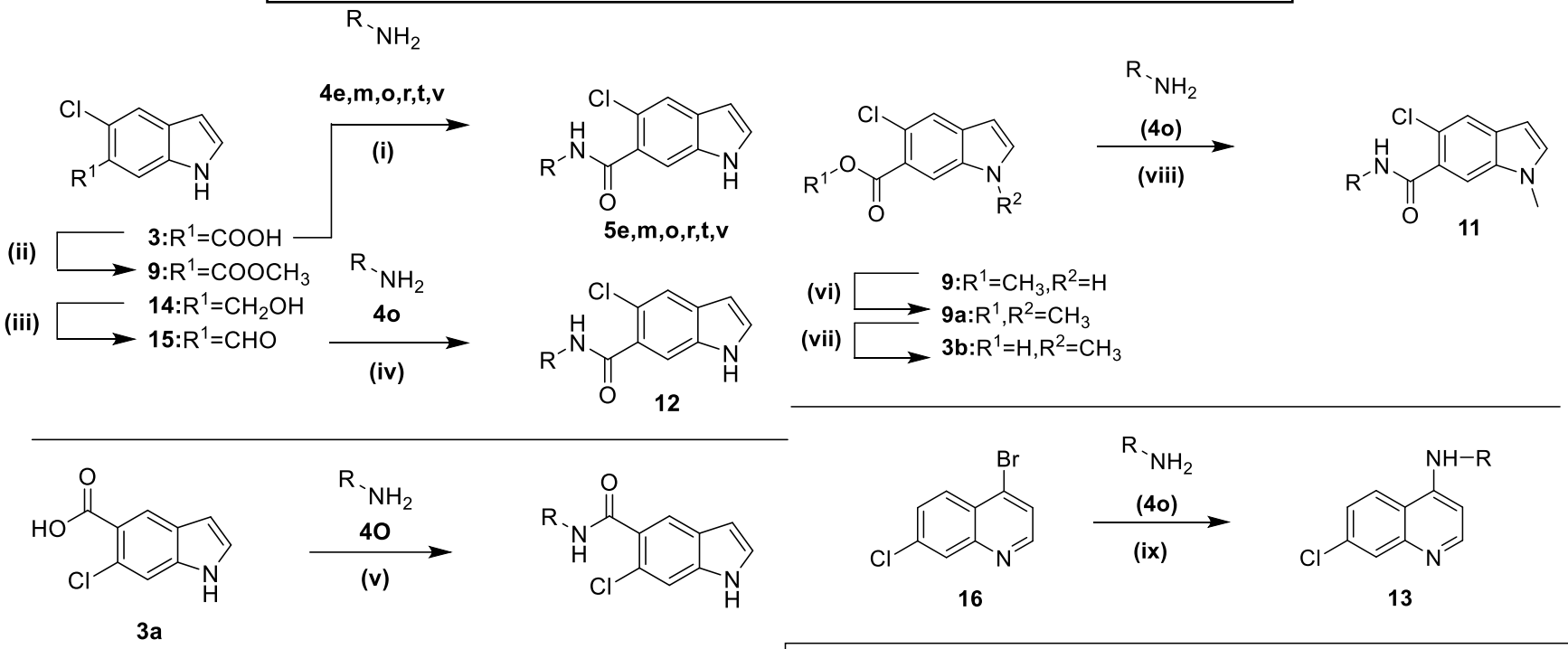


Structure-activity relationship

ID	structure	K_d	EC_{50} (eff.)
5o		0.5 μM	3±1 μM (1.3±0.1-fold act.)
10		1.6 μM	6±3 μM (1.4±0.1-fold act.)
11		1 μM	16±6 μM (1.4±0.1-fold act.)
12		1.8 μM	5±2 μM (1.4±0.1-fold act.)
13		1.5 μM	3±1 μM (1.5±0.1-fold act.)

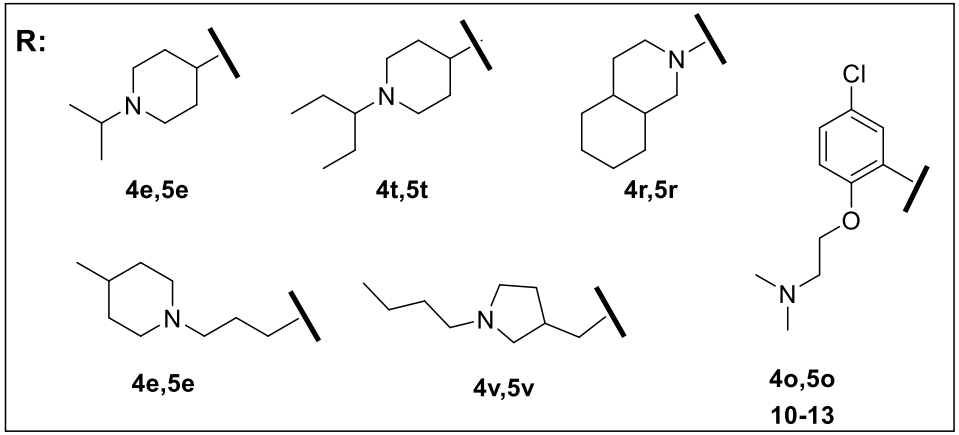


Structure-activity relationship

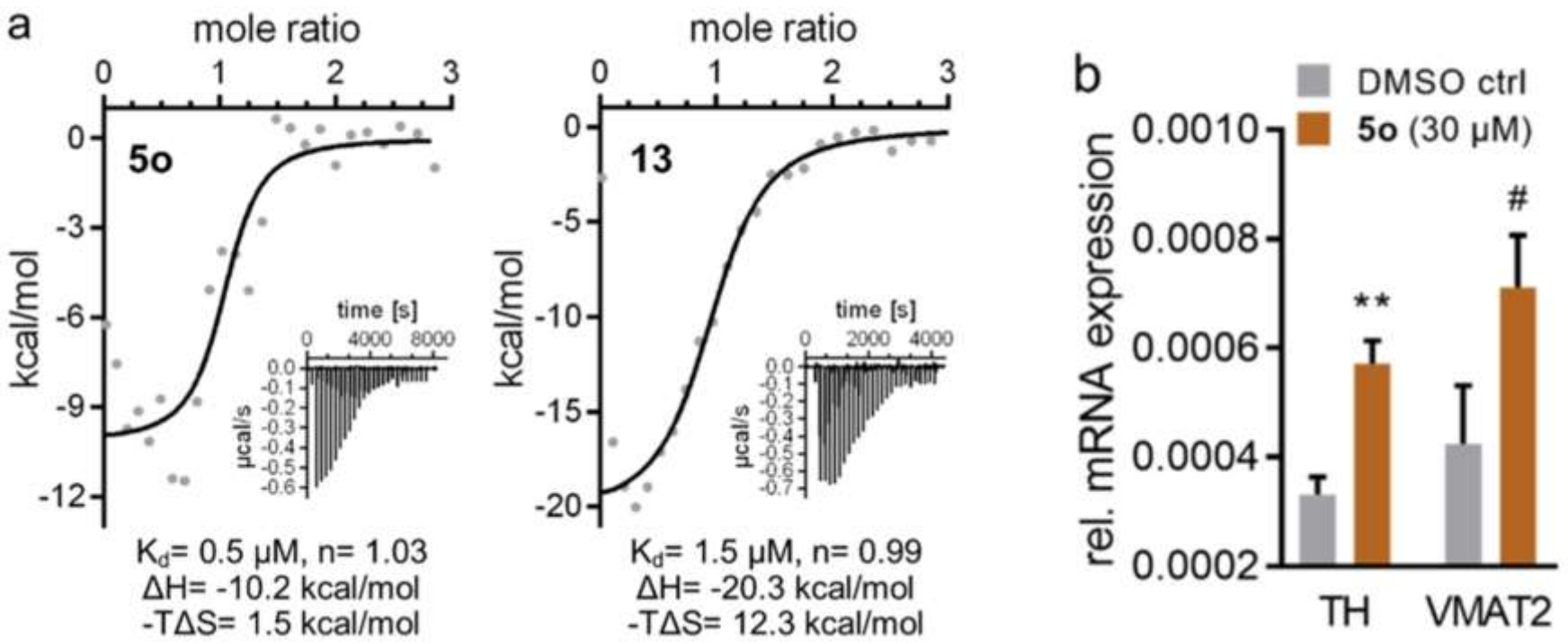


Reagents and conditions:

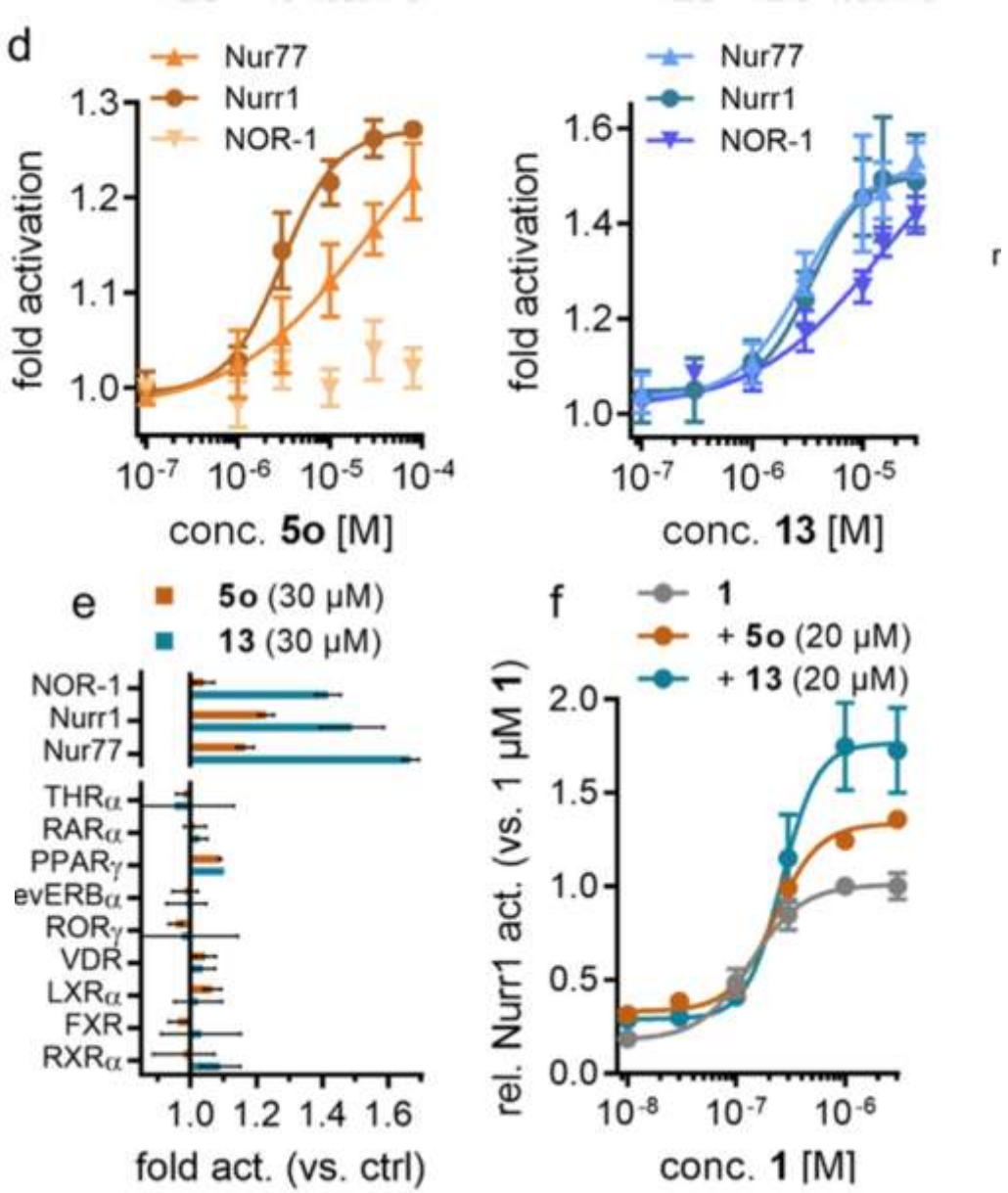
(i) EDC·HCl, TEA, $CHCl_3$, rt, 18 h, 8−32%;
(ii) LiAlH4, THF, 0 °C, 1 h, 71%;
(iii) Dess−Martinperiodinane, DCM, DMF, 0 °C−rt, 1 h, 100%;
(iv) $NaBH(OAc)_3$,AcOH, DCM, DCE, rt, 2 h, 36%;
(v) EDC·HCl, TEA, $CHCl_3$, rt, 18h, 5%;
(vi) NaH, CH_3I, DMF, 0 °C, 10 min, rt, 2 h, 33%;
(vii) $LiOH·H_2O$, EtOH, H_2O, rt, 18 h, 99%;
(viii) NMI, TCFH, DMF, 80 °C, 18h, 26%;
(ix) $Pd(OAc)_2$, BINAP, K_3PO_4, dioxane, 90 °C, 24 h, 29%.



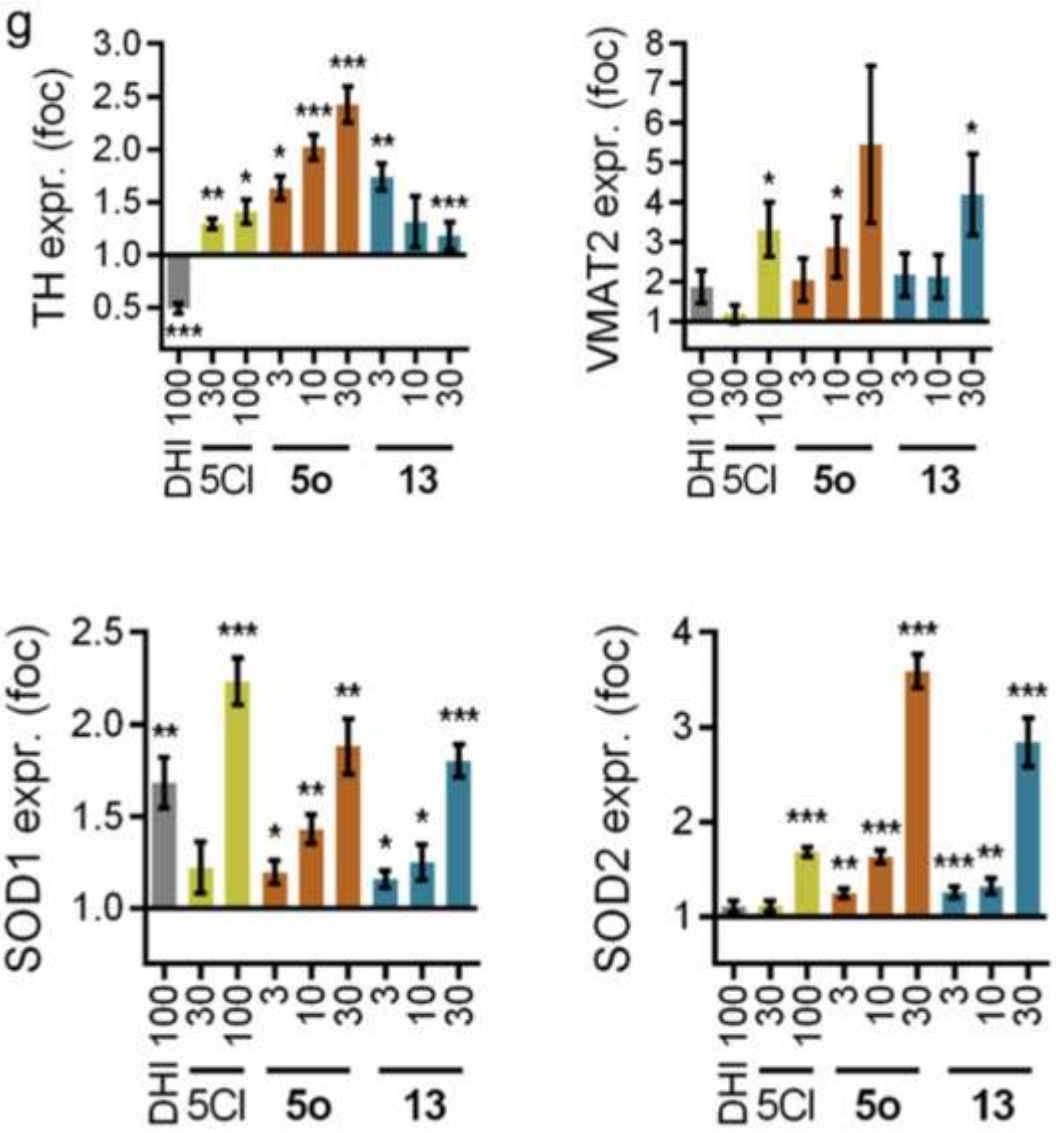
In vitro profiling of Nurr1 agonists



In vitro profiling of Nurr1 agonists



In vitro profiling of Nurr1 agonists



CONCLUSIONS

- Drug discovery based on natural ligands of nuclear receptors has been very fruitful in the past as exemplified.
- The results demonstrate that the binding site of the natural (covalent) Nurr1 ligand DHI is druggable and can be addressed by non-covalent binders with markedly enhanced potency compared to the natural template, opening a new avenue to Nurr1 agonist development.
- 5o emerged from these DHI analogues with sub-micromolar affinity to Nurr1, preference over Nur77 and selectivity over NOR-1.
- Suggests that the binding site for Nurr1 is at the H12 helix, and despite some advances in the study of Nurr1 ligands, the understanding of this receptor is still very limited.

谢 谢 观 看

汇报人：戴琪