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CHA UNIVERSITY

약학과 김 석 호

연구 관심 분야

- Small molecule discovery through **DTS** strategy
 - : DHPV
 - : Corniculatolide
- **염증성 장질환** 관련 화합물 발굴
 - : Xanthohumol - Flavanone계 천연물을 이용한 IBD, 대장암 치료 효능 및 기전 규명
- **분화 조절** 연구 및 **stemo-toxic** small molecule
 - : 지방세포 분화 억제 물질 개발 (Nrf2)
 - : Stemo-toxic small molecule (미분화 줄기세포 제거)
 - : 뇌질환 관련 치료제 개발 (ERRg agonist)
- 기타 연구
 - : Antimicrobial agent 개발

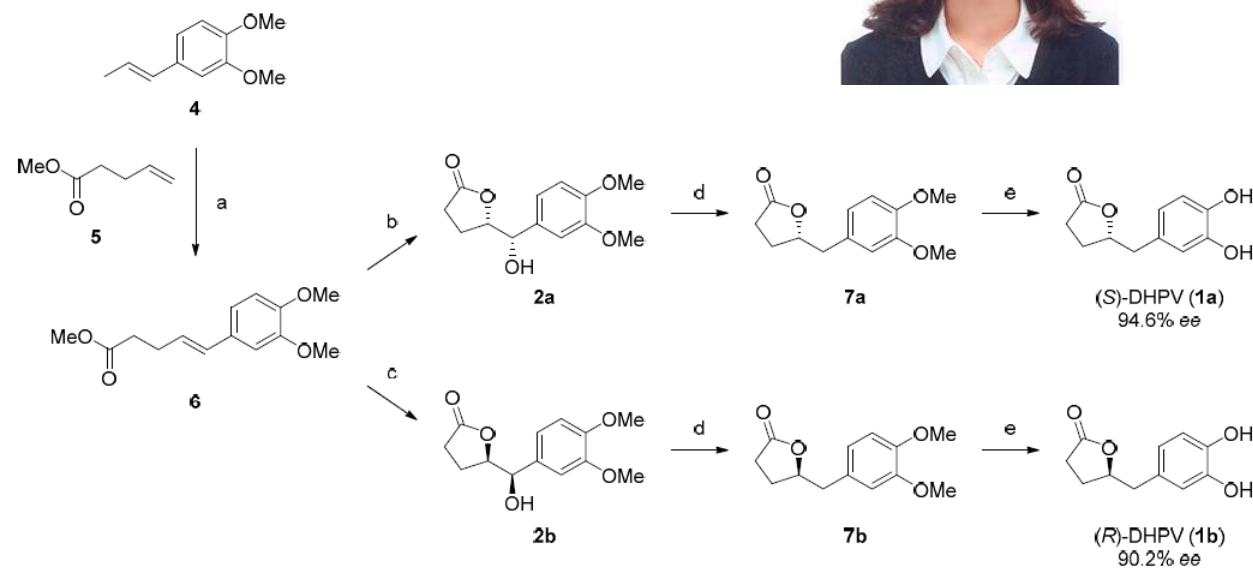
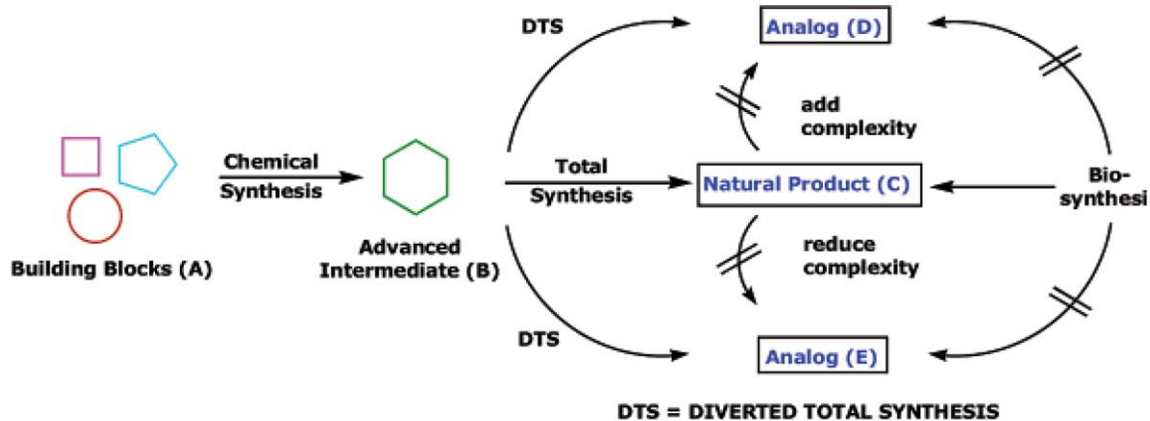
연구 관심 분야



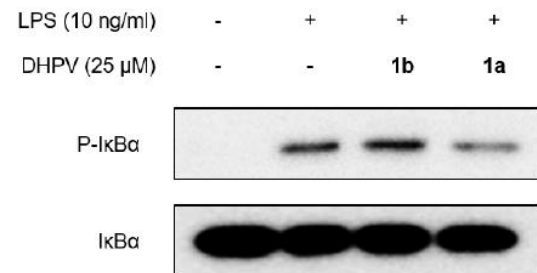
➤ Small molecule discovery through **DTS** strategy

: DHPV

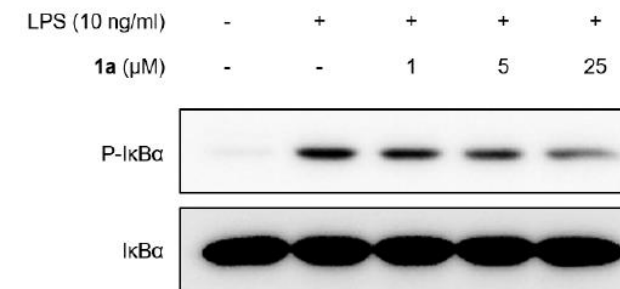
: Corniculatolide



A



B



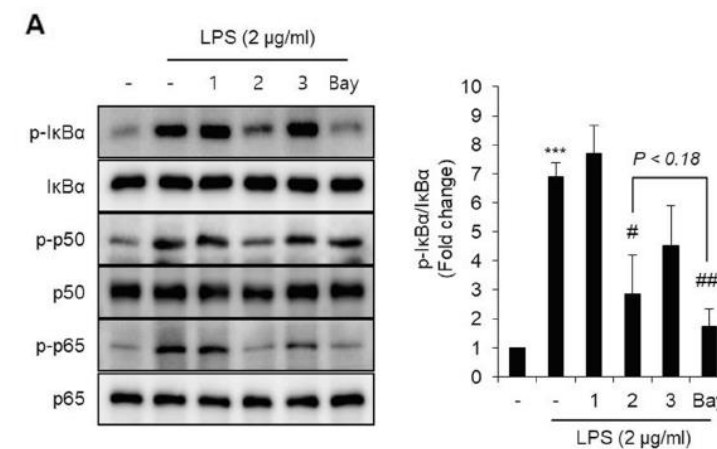
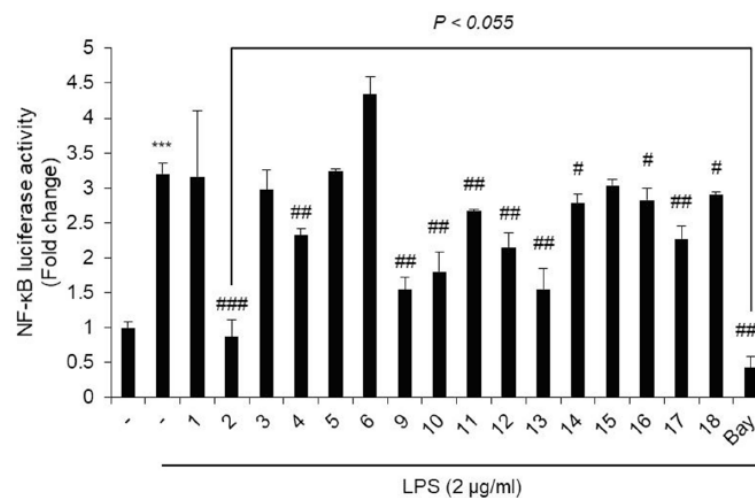
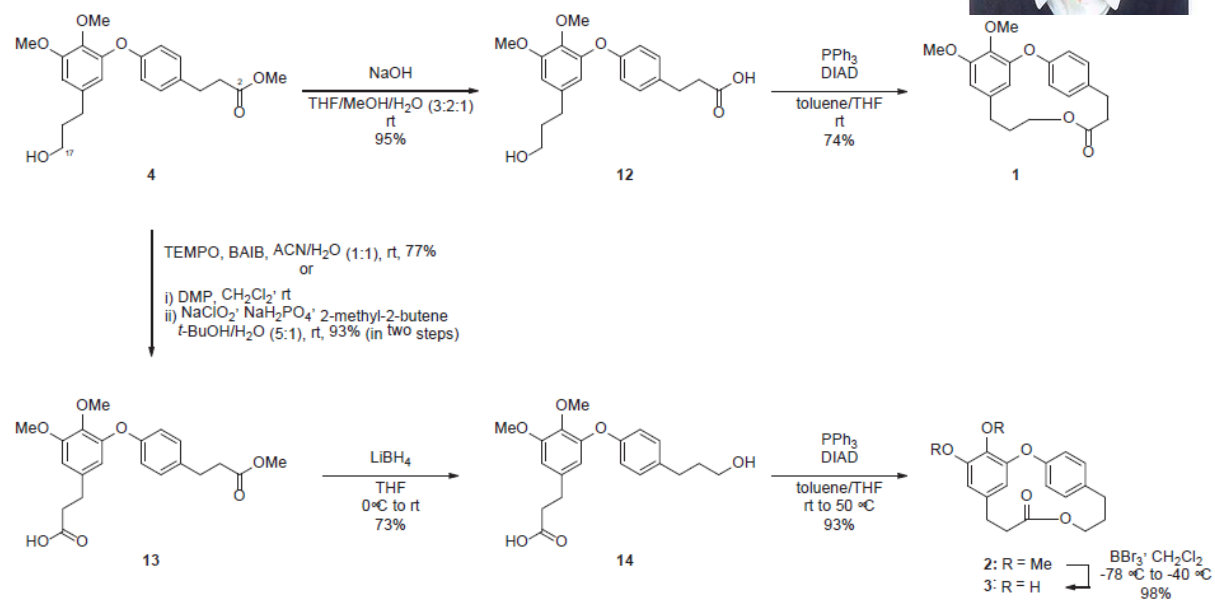
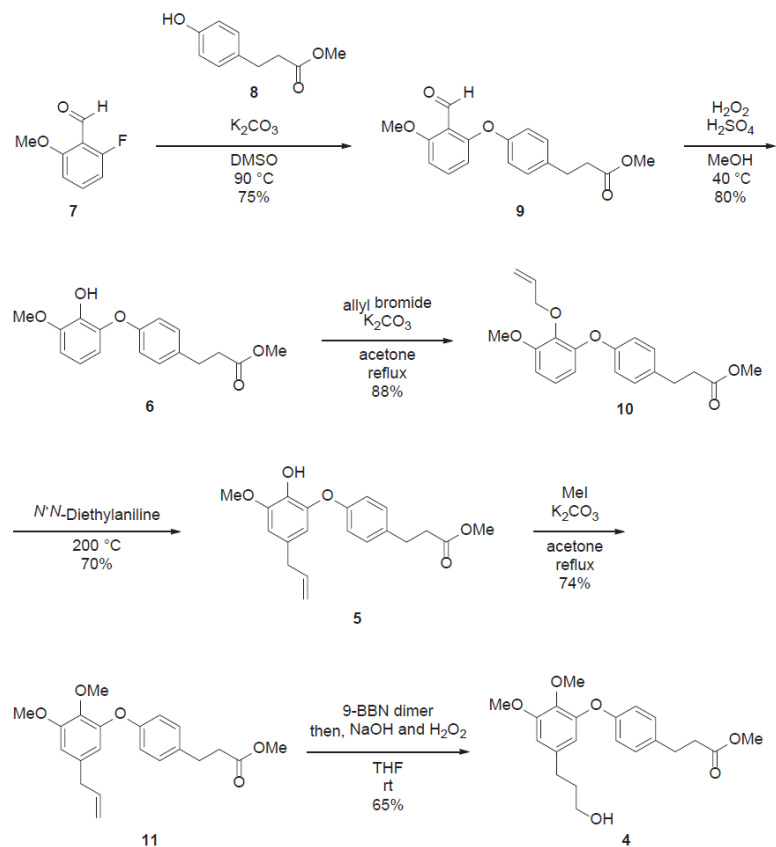
연구 관심 분야



➤ Small molecule discovery through **DTS** strategy

: DHPV

: Corniculatolide



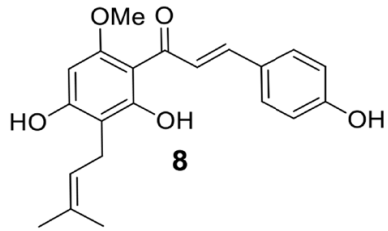
연구 관심 분야



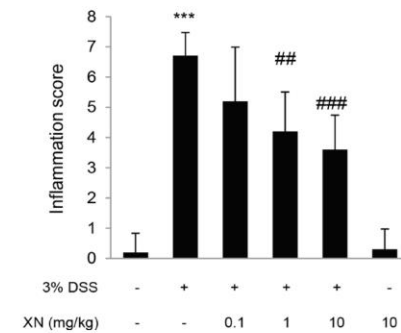
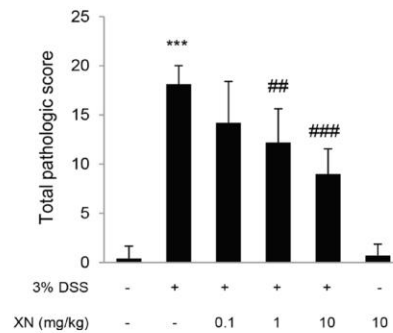
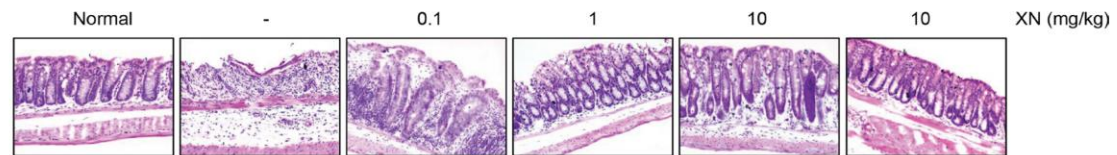
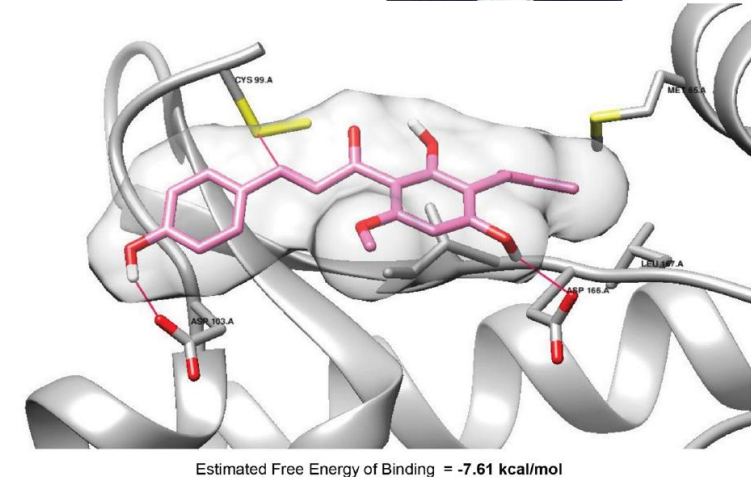
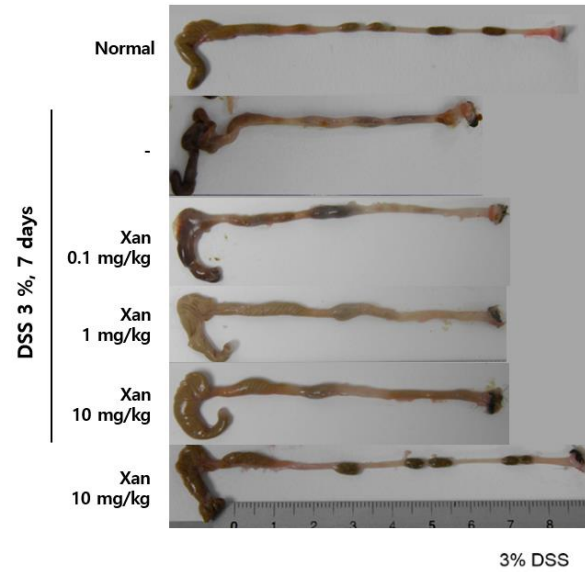
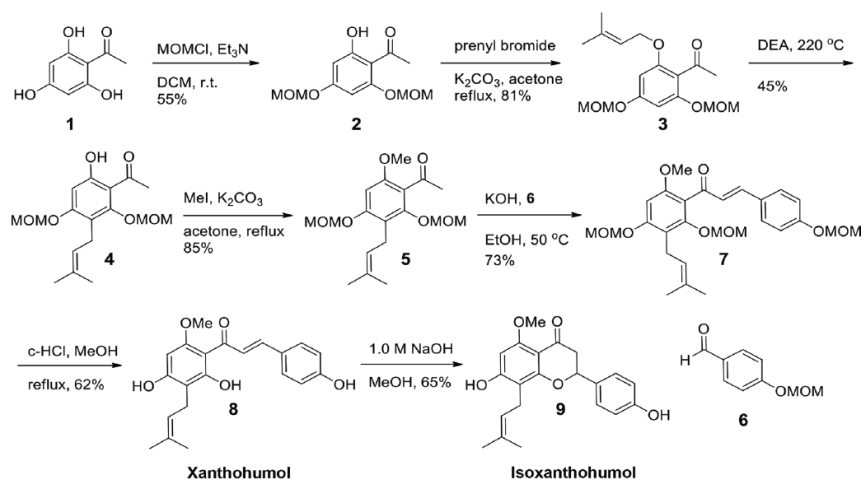
▶ 염증성 장질환 관련 화합물 발굴

: Xanthohumol - Flavanone계 천연물

: IBD, 대장암 치료 효능 및 기전 규명



Xanthohumol

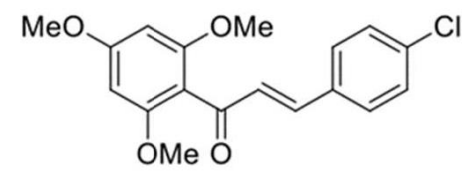
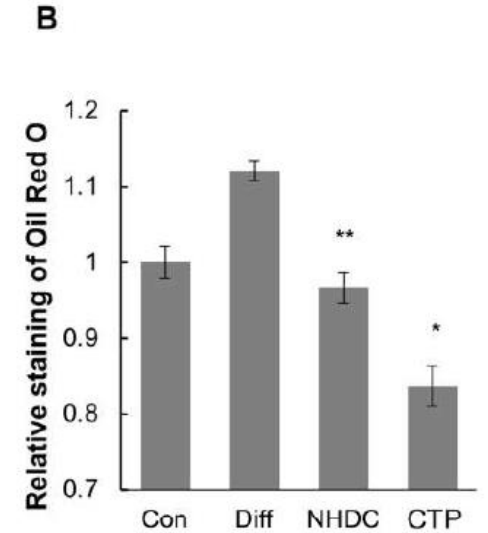
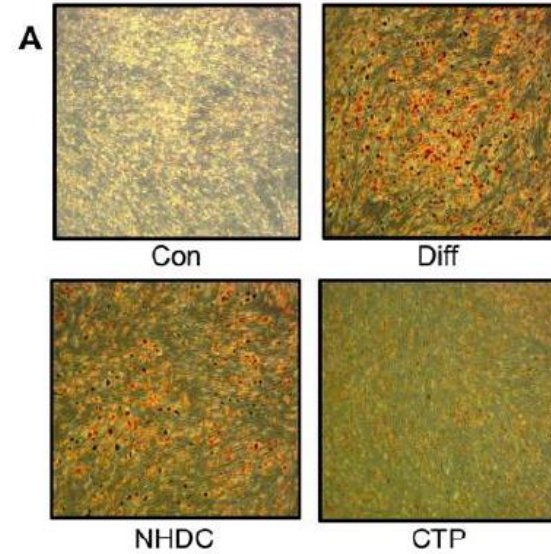
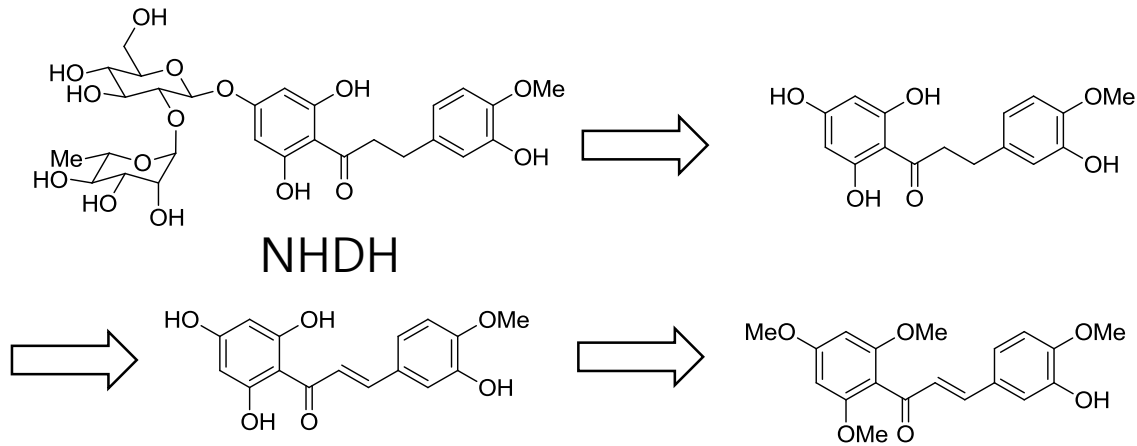


Oncotarget 2018, 9 (1), 866-880

연구 관심 분야

➤ 분화 조절 연구 및 **stemo-toxic** small molecule

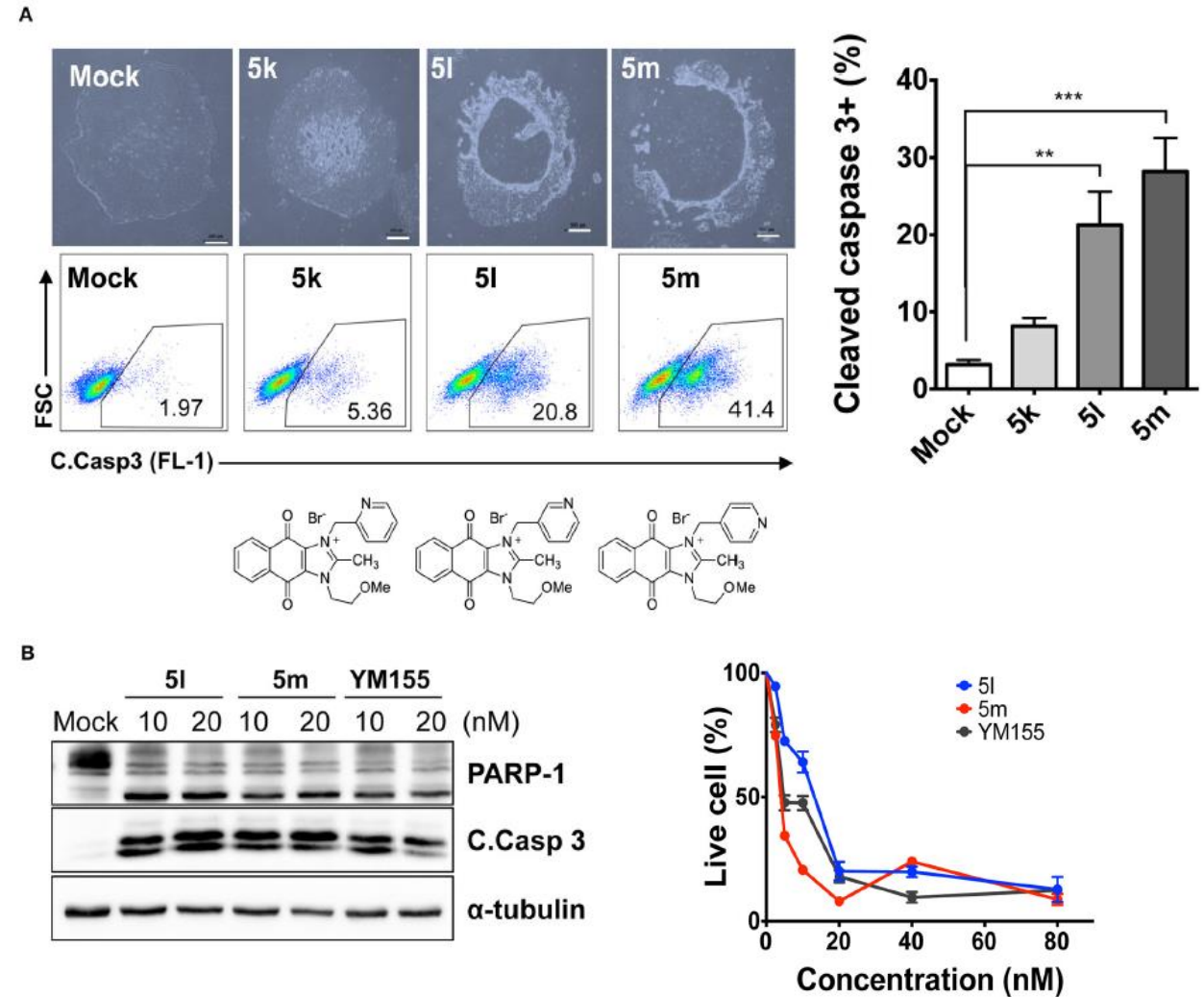
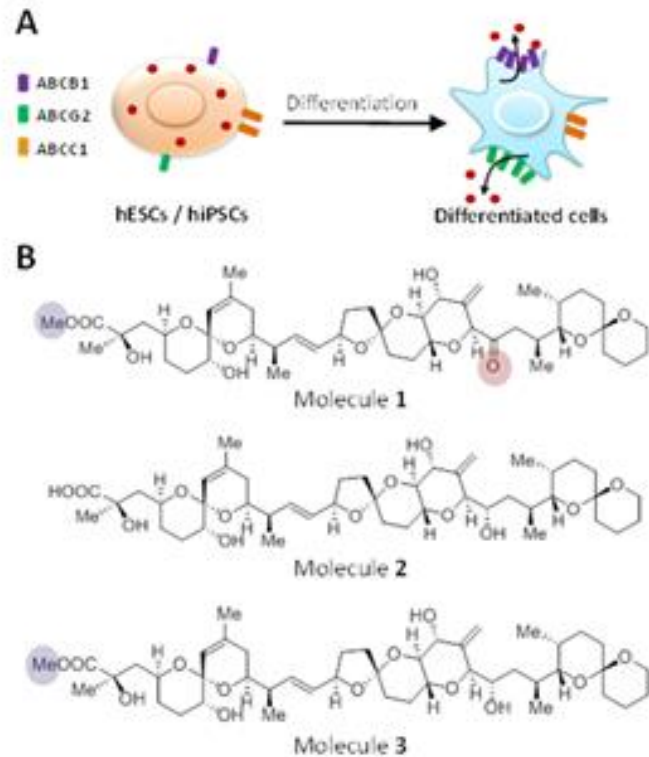
: 지방세포 분화 억제 물질 개발 (Nrf2)



연구 관심 분야

➤ 분화 조절 연구 및 **stemo-toxic** small molecule

: Stemo-toxic small molecule (미분화 줄기세포 제거)

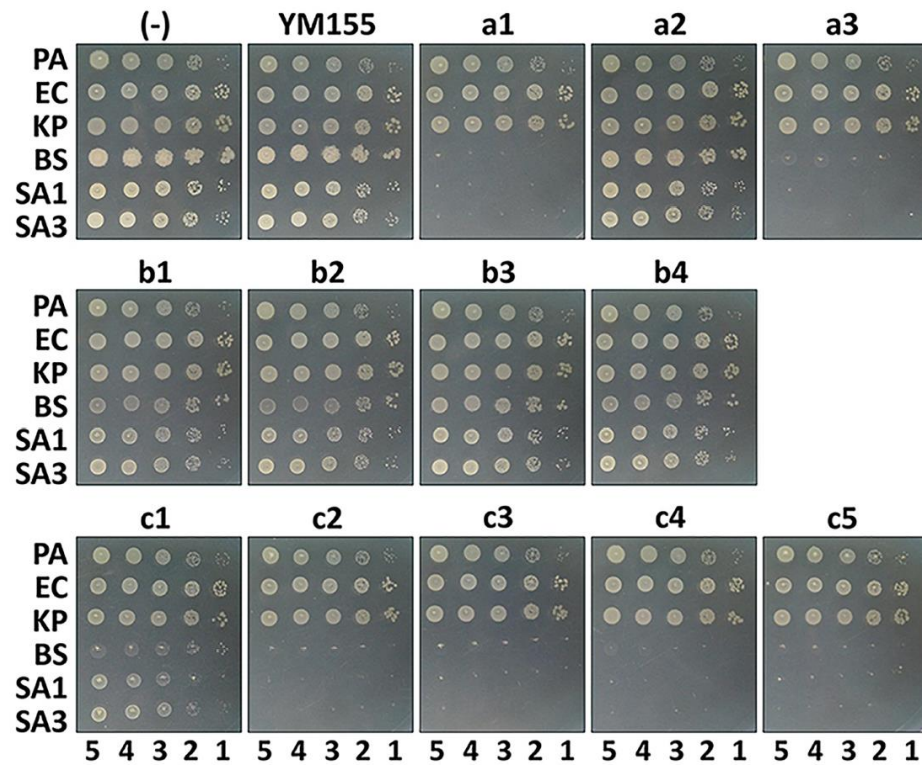


연구 관심 분야



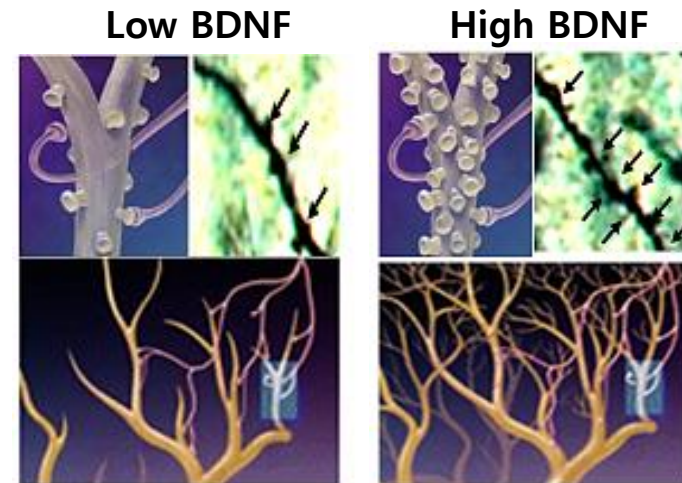
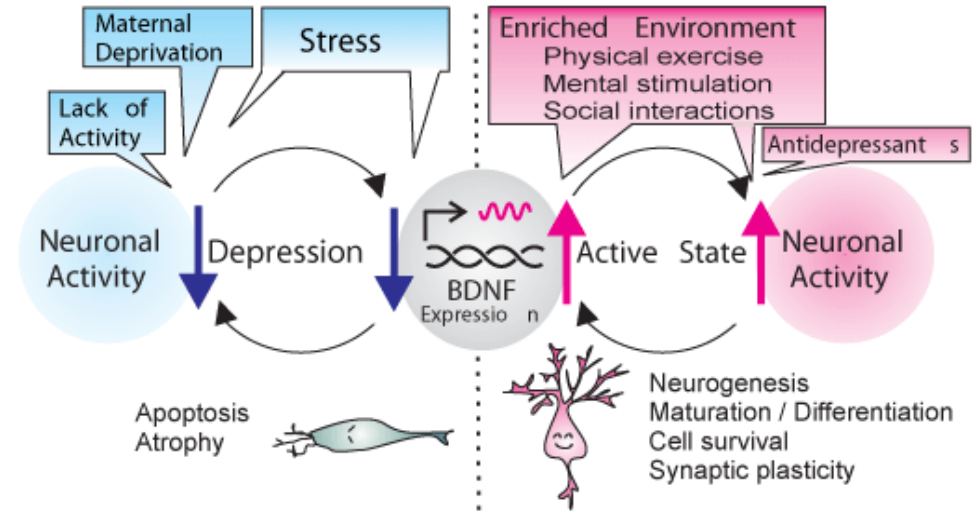
➤ 기타 연구

: Antimicrobial agent 개발 (repurposing)



뇌질환 관련 치료제 개발 (ERRg agonist)

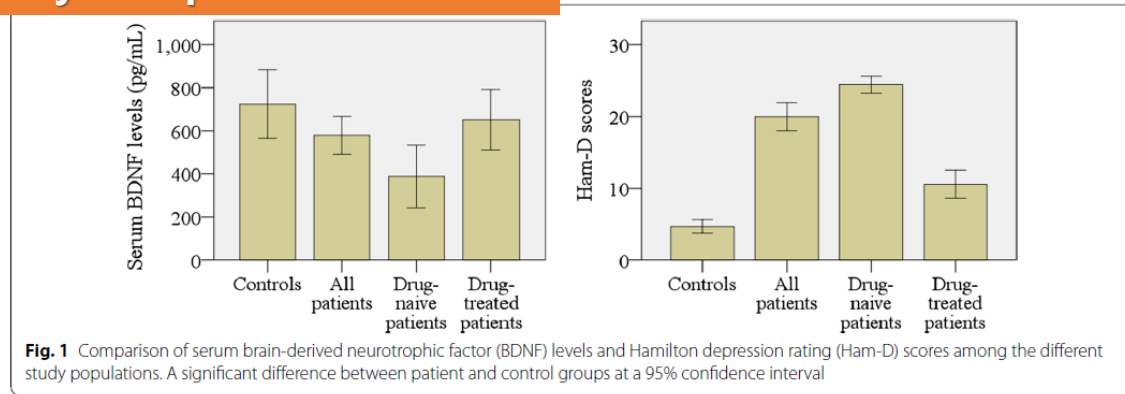
- **BDNF** (Brain-derived neurotrophic factor)
- BDNF is a member of the **neurotrophin family**, which also includes nerve growth factor, neurotrophin-3, and neurotrophin-4/5.
- BDNF protein levels are regulated during **development**, and it is highly expressed in various regions of the **adult brain**.
- In the CNS, BDNF plays a key role in the **growth** and **differentiation** of **newly produced neurons**, **neurogenesis**, formation of **synapses**, and neuronal **survival**.



뇌질환 관련 치료제 개발 (ERRg agonist)

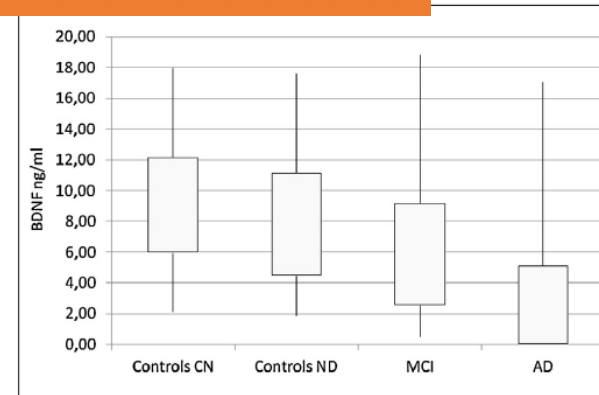
- **Low BDNF** level may be involved in the pathophysiology of **neuropsychological disorders** including major depressive disorder, Alzheimer's disease and Parkinson's disease.

Major Depressive Disorder



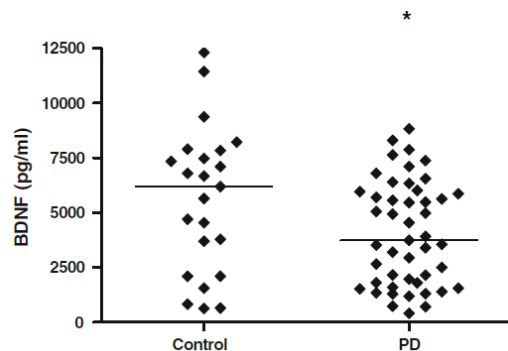
(Emon et al., BMC Res Notes, 2020)

Alzheimer's Disease



(Siuda et al., Neurol Neurochir Pol, 2016)

Parkinson's Disease



(Scalzo et al., J Neurol, 2010)

Table 1
Brain-derived neurotrophic factor (BDNF) concentrations in the brains from control and parkinsonian patients*

Brain region	BDNF concentration	
	Control patients (ng/mg protein)	Parkinsonian patients (ng/mg protein)
Caudate (17)	1.55 ± 0.43 (100)	0.37 ± 0.04 (23.9)*
Putamen (6)	1.20 ± 0.38 (100)	0.21 ± 0.03 (17.5)*
Substantia nigra (19)	0.45 ± 0.09 (100)	0.25 ± 0.02 (55.6)*
Cerebellum (5)	0.22 ± 0.04 (100)	0.15 ± 0.02 (68.2)
Frontal cortex (5)	0.21 ± 0.03 (100)	0.16 ± 0.03 (76.2)

(Mogi et al., Neurosci Lett, 1999)

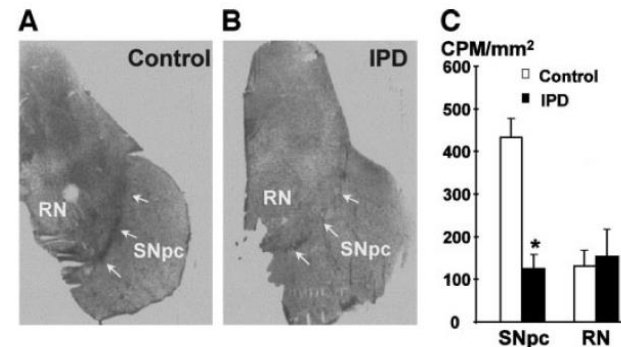


FIG. 1. BDNF mRNA expression in control ($n = 3$) and PD ($n = 4$) substantia nigra pars compacta (SNpc) and red nucleus (RN). (A)

(Howells et al., Exp Neurol, 2000)

뇌질환 관련 치료제 개발 (ERRg agonist)

- BDNF is being considered as a new **therapeutic target** for various **neurological diseases**.

Novel small-molecule regulating BDNF ?

There is certain **barriers** to clinical application of BDNF, such as **short *in vivo* half-life**, undesired **immune response** after delivery, and **poor bioavailability** associated with insufficient permeability through the BBB.

International Journal of Molecular Sciences

Journal of Depression and Anxiety

Research Article

International Journal of Molecular Sciences

International Journal of Molecular Sciences

MDPI

MDPI

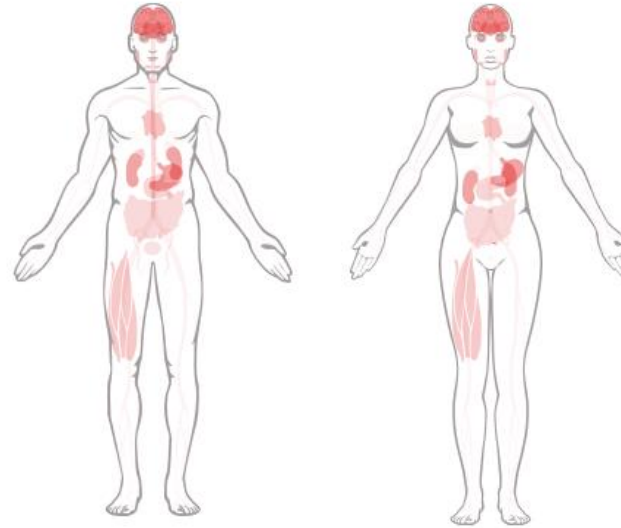
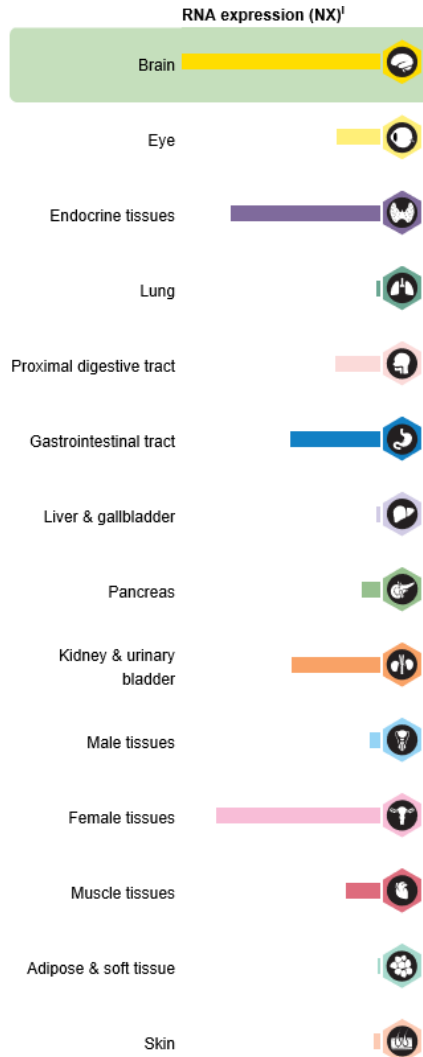
MDPI

check for updates

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뇌질환 관련 치료제 개발 (ERRγ agonist)

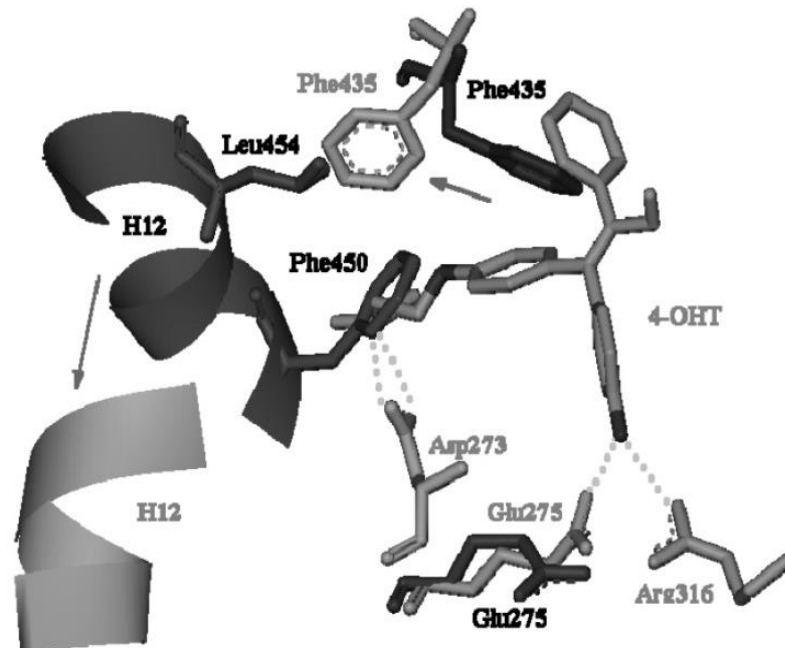
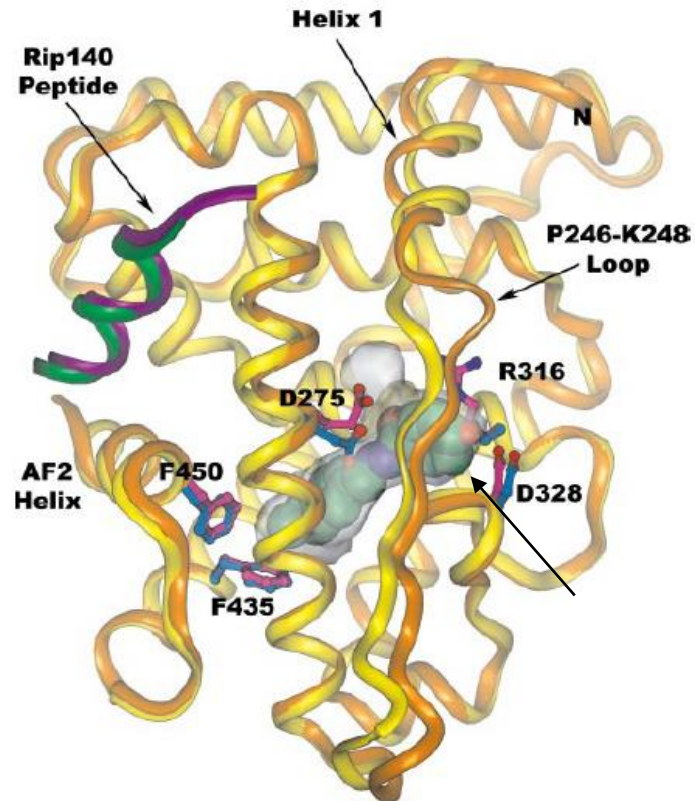
➤ ERRγ (Estrogen-related receptor gamma)



- ERRγ is expressed in the **embryo** and **adult tissues**, such as the brain, skeletal muscle, heart, and liver, where it regulates metabolic signals by acting as a **transcription factor, growth factor, and hormone**.
- In spite of the abundant expression of ERRγ in the **nervous system** during development as well as in the adult brain, its **biological role in the nervous system is largely unknown**.

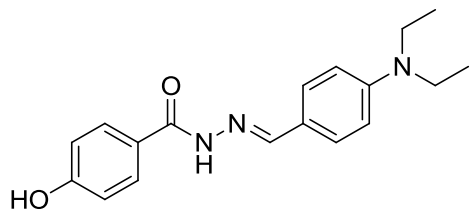
뇌질환 관련 치료제 개발 (ERRg agonist)

- Orphan nuclear receptor
- Possesses ligand-independent transcriptional activity
- Constitutively active due to the active conformation of its LBD



뇌질환 관련 치료제 개발 (ERRg agonist)

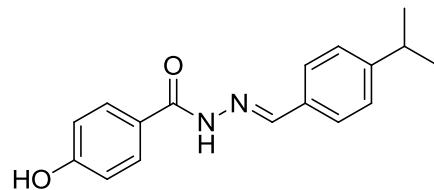
➤ ERRg agonist



DY-131

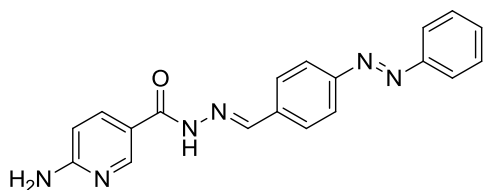
BMCL **2005**, 15,1311-1313

Mol. Hum. Reprod. **2015**, 21(2), 206



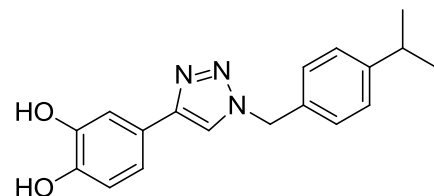
GSK-4716

JMC **2005**, 48, 3107



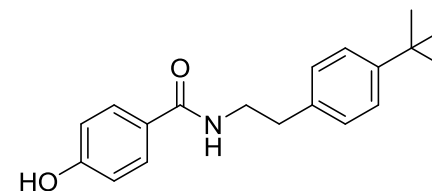
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J. Comb. Chem. **2009**, 11, 928-937



2e

BMC **2015**, 23, 3751-3760

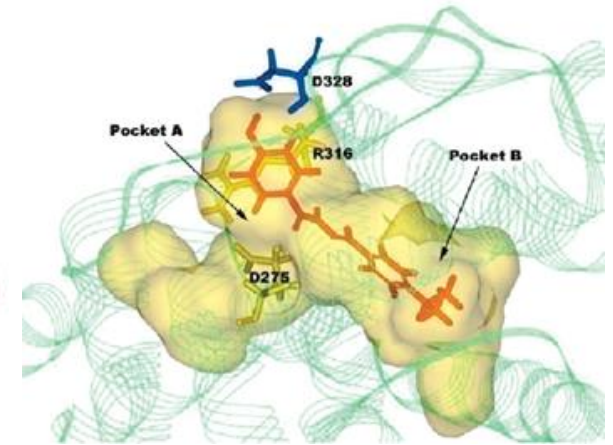
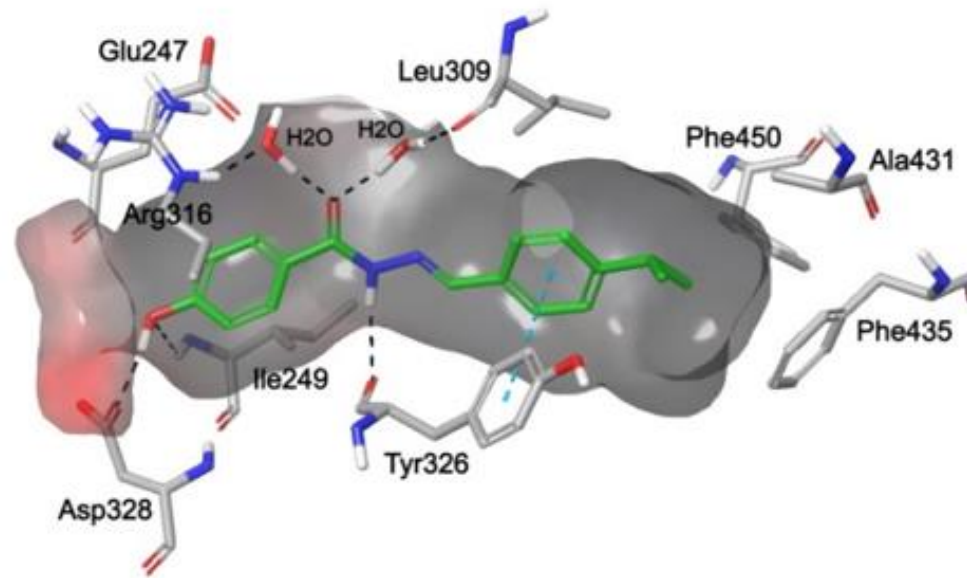
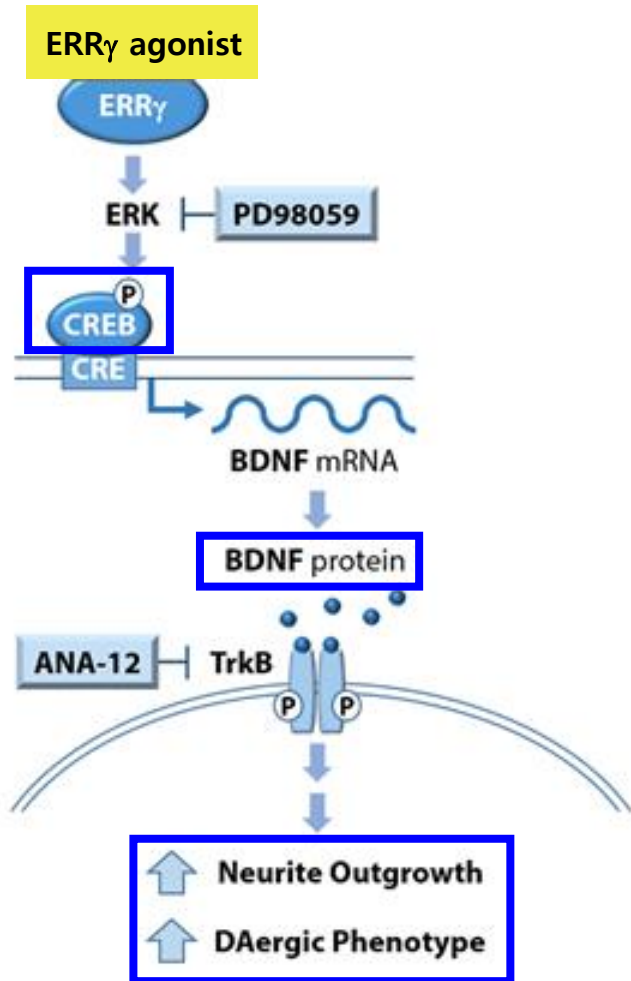


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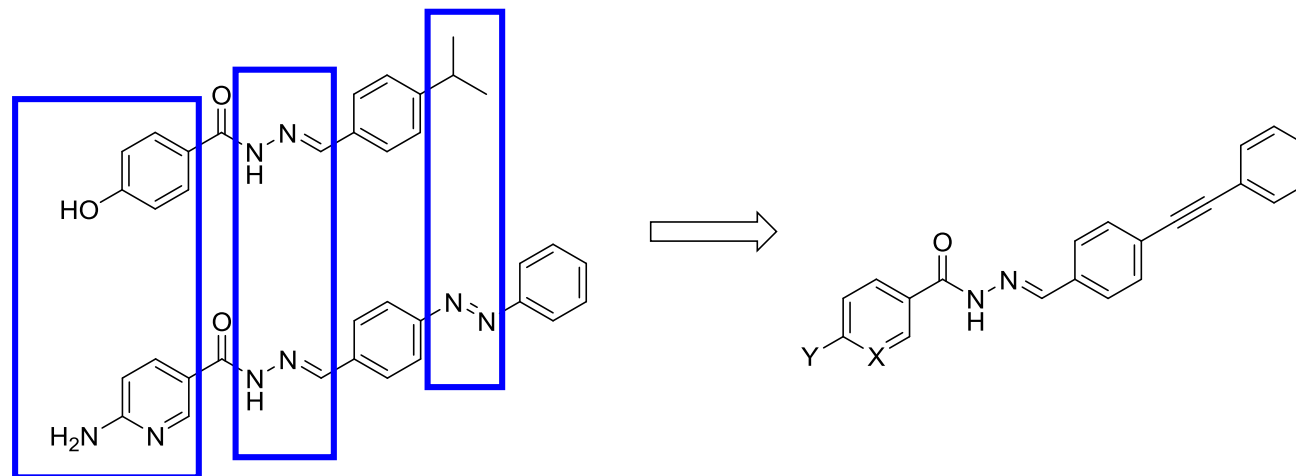
BMCL **2018**, 28,1313-1319

뇌질환 관련 치료제 개발 (ERRg agonist)

Design Strategy

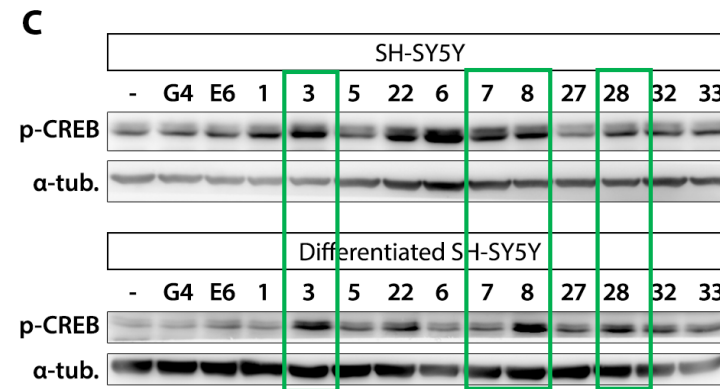
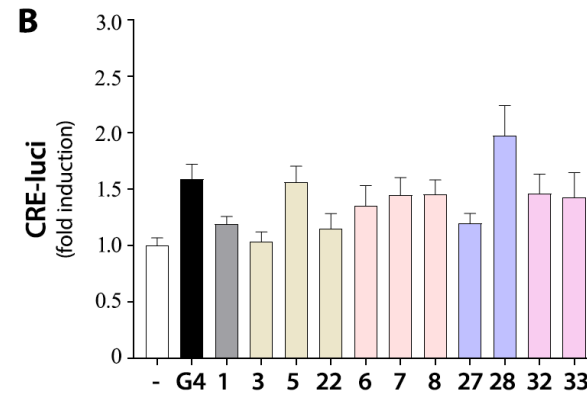
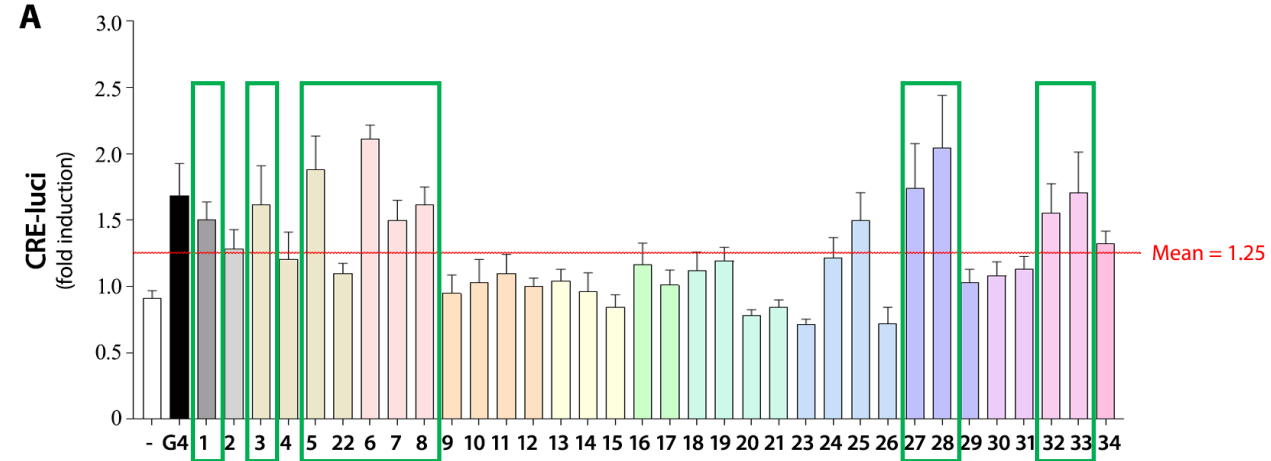


Park S.B. et al.



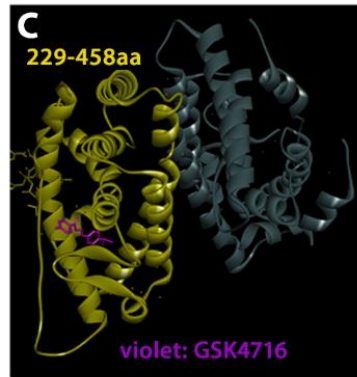
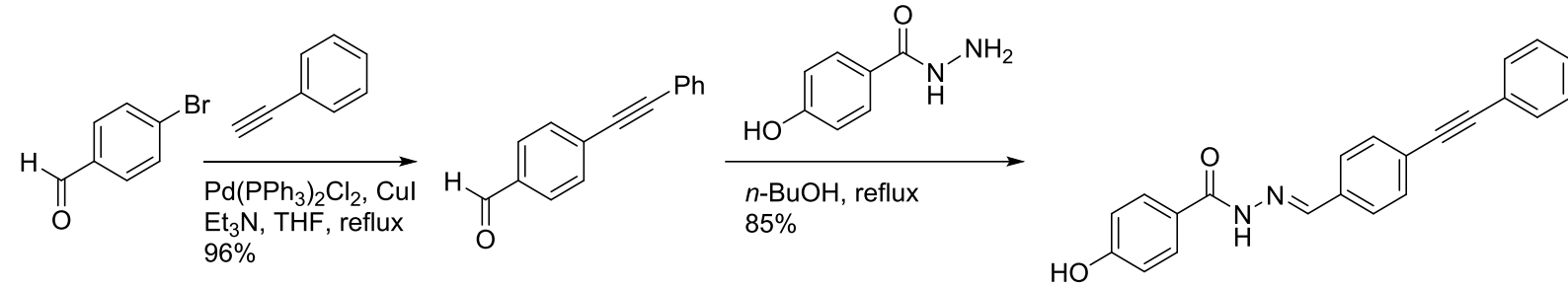
뇌질환 관련 치료제 개발 (ERRg agonist)

➤ Primary Screening

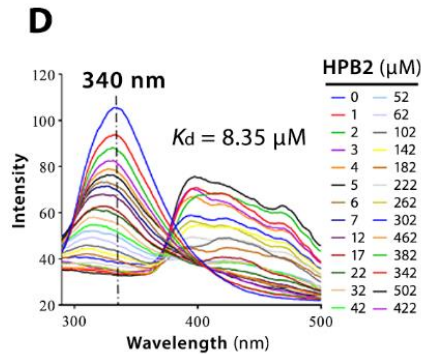


뇌질환 관련 치료제 개발 (ERRg agonist)

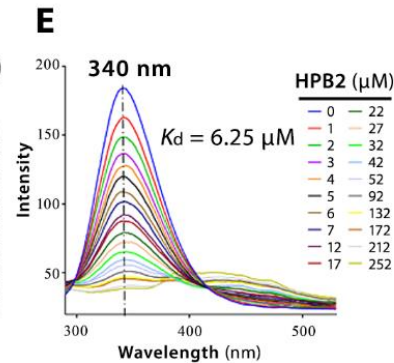
➤ HPB2 as a ERR γ agonist



Full length ERR γ



Ligand binding pocket



Rat Liver Microsomal stability

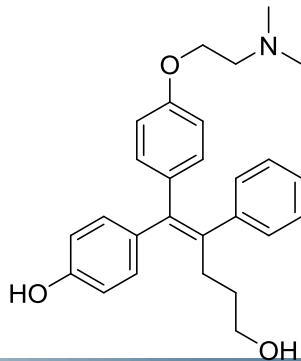
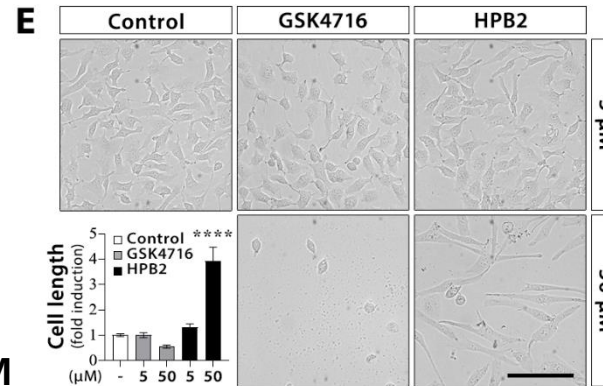
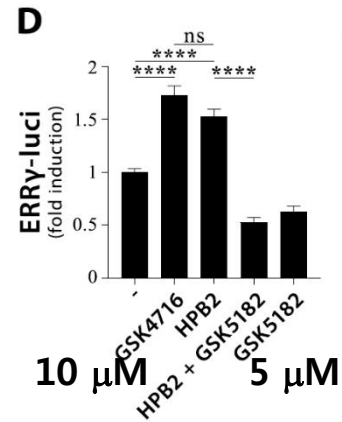
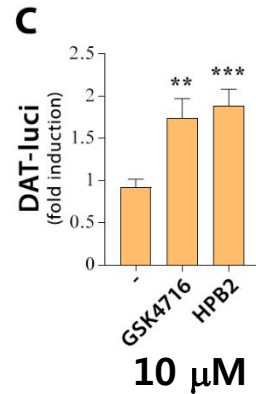
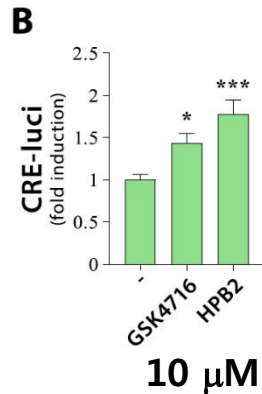
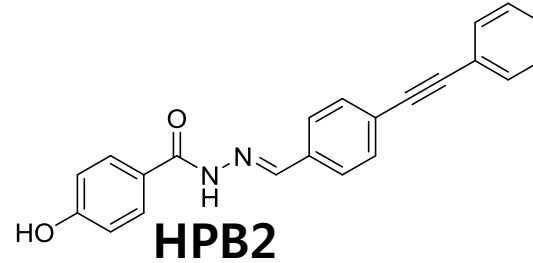
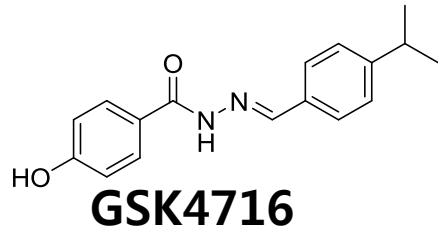
Compound	% remaining at 30 min	Half-life (min)	stability
GSK4716	45	24.45	moderate
HPB2	81.2	114.98	high

BBB penetration in Mice (1 h after intra-peritoneal injection)

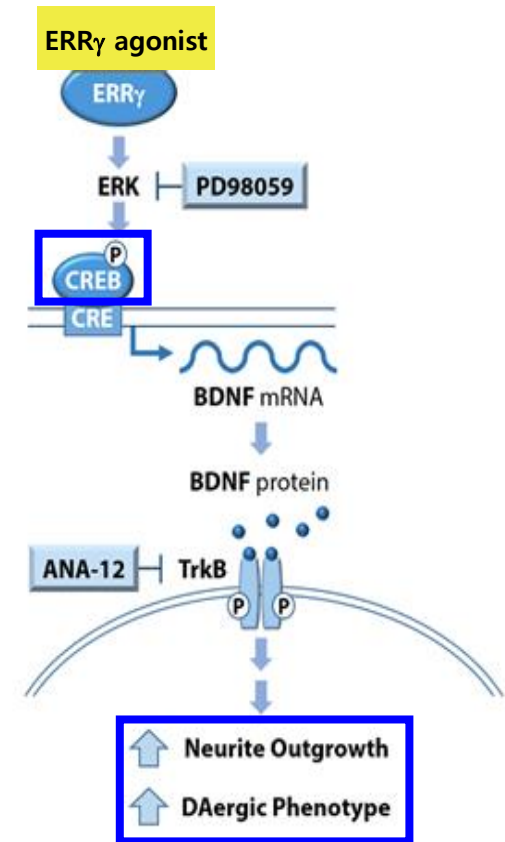
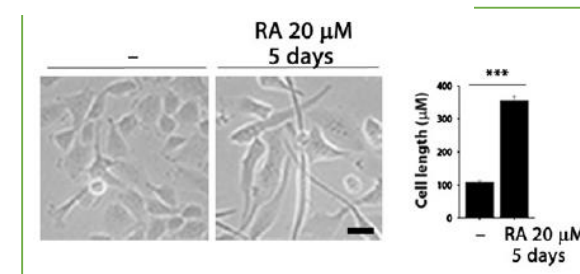
Compound	Brain Conc ($\mu\text{g}/\text{mL}$)	Plasma Conc ($\mu\text{g}/\text{mL}$)	B/P Ratio
HPB2	0.031 \pm 0.011	0.242 \pm 0.132	0.283 \pm 0.069

Moderate $0.2 \leq \text{Ratio} < 2.0$

뇌질환 관련 치료제 개발 (ERRγ agonist)



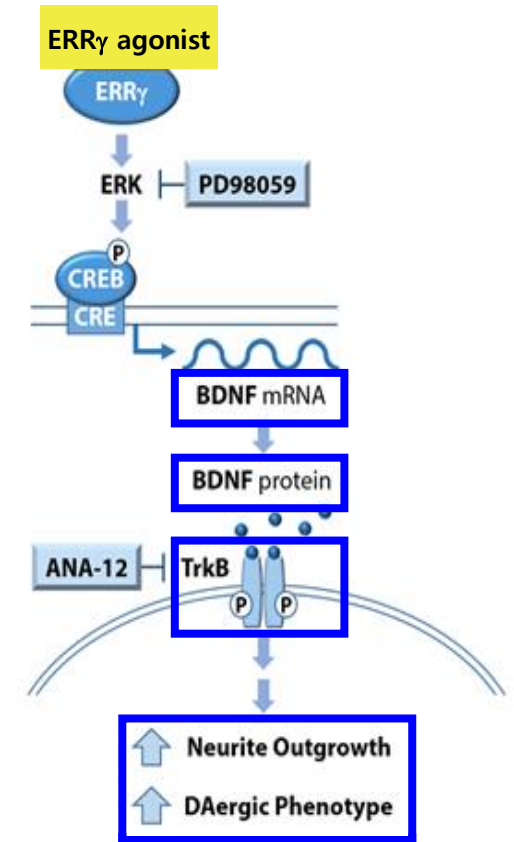
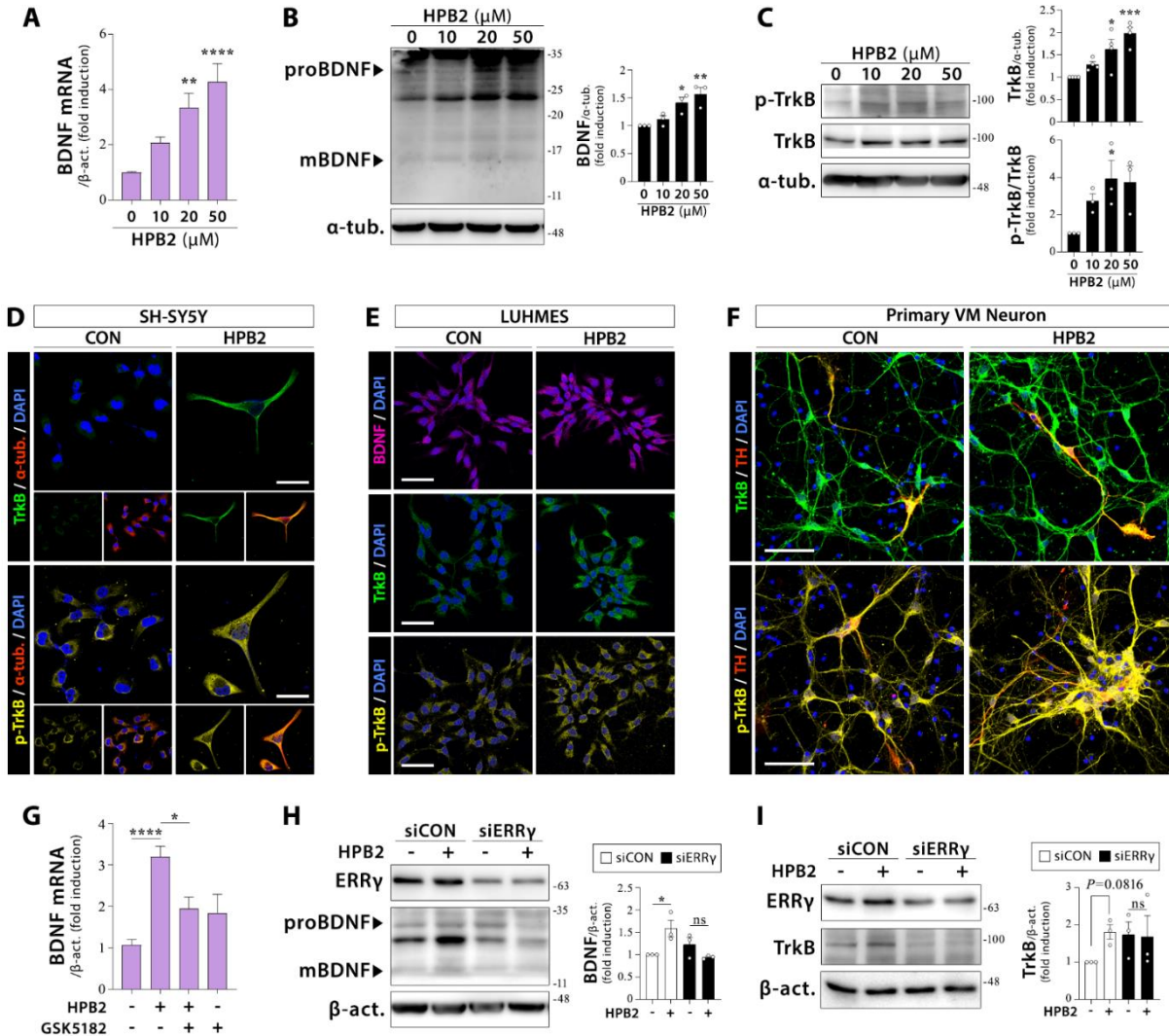
✓ **GSK5182: ERRγ**
inverse agonist



(Lim et al., J Neurochem, 2015)

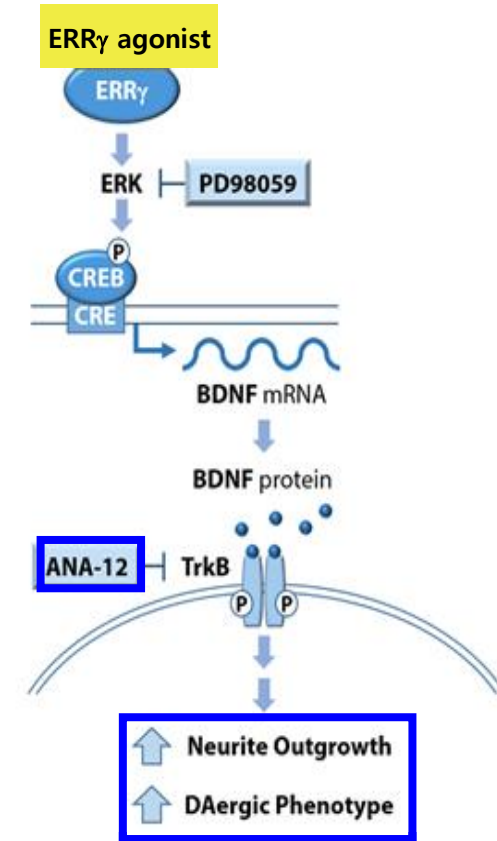
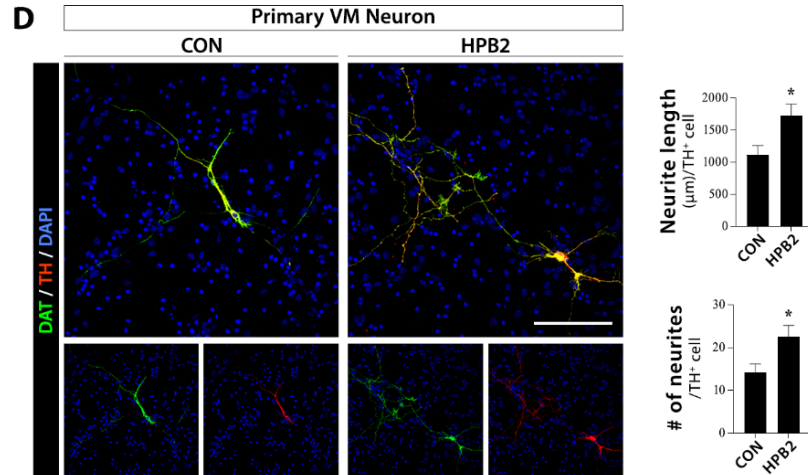
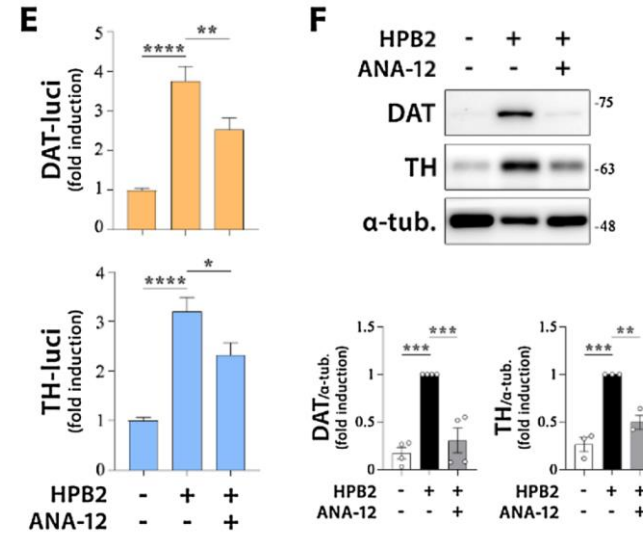
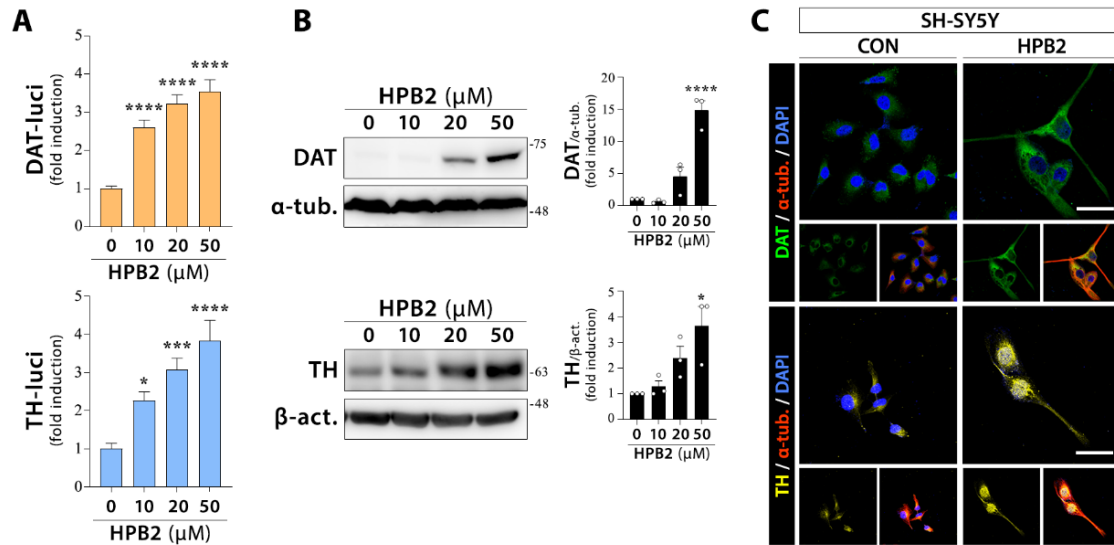
뇌질환 관련 치료제 개발 (ERRγ agonist)

➤ BDNF-TrkB signaling pathway



뇌질환 관련 치료제 개발 (ERRg agonist)

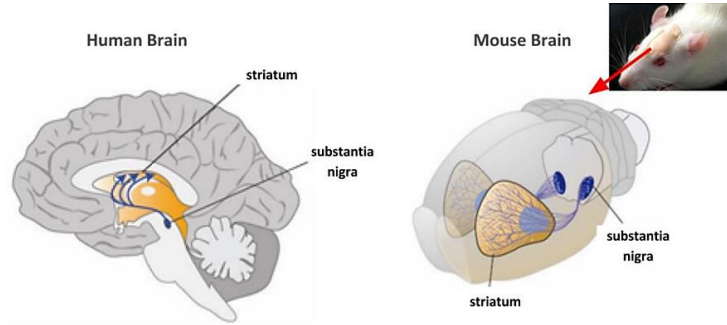
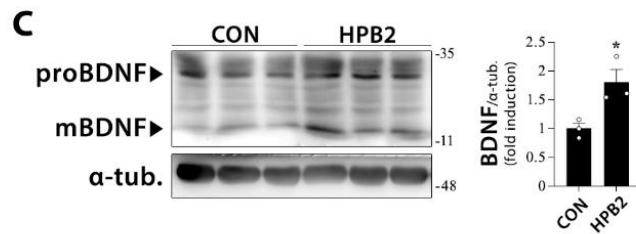
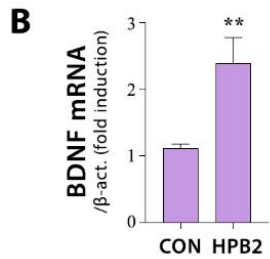
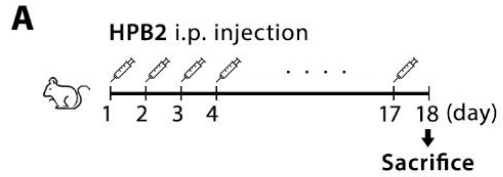
➤ Dopaminergic Phenotype



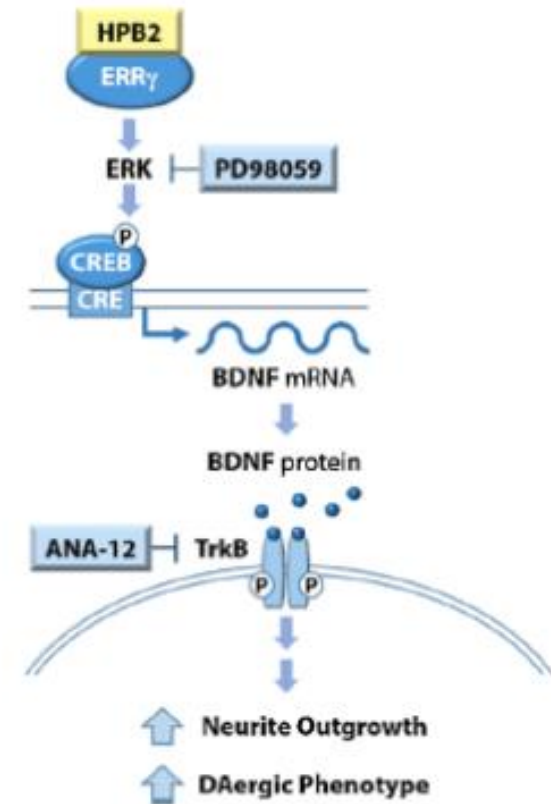
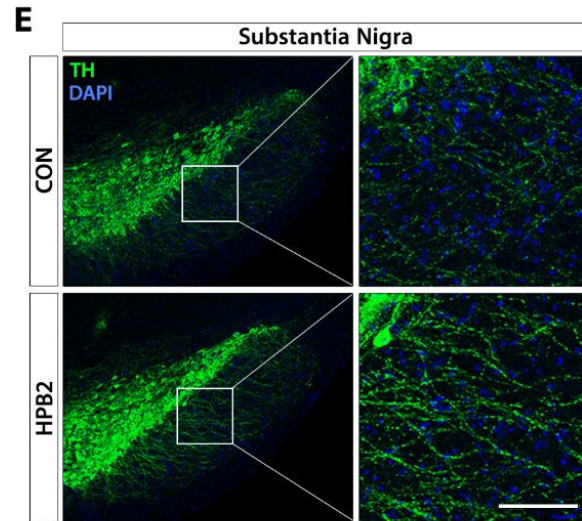
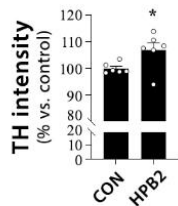
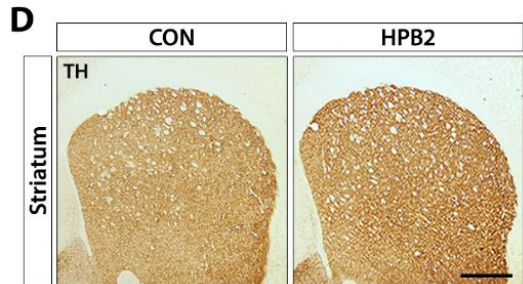
- ✓ DAT (Dopamine transporter)
- ✓ TH (Tyrosine hydroxylase)

뇌질환 관련 치료제 개발 (ERRg agonist)

➤ HPB2 upregulates BDNF and increases neurite length and number of DAergic neurons in mice brain



✓ Nigrostriatal pathway



Acetylene Group, Friend or Foe in Medicinal Chemistry

Tanaji T. Talele*



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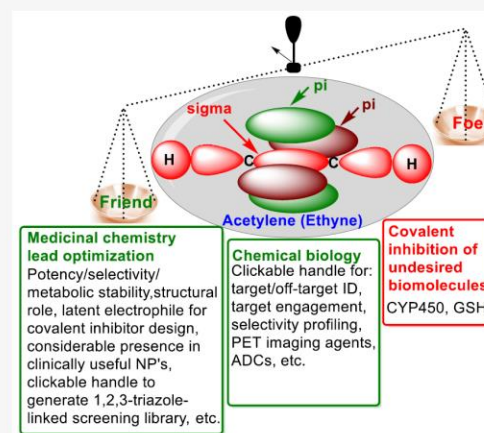
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ABSTRACT: The use of an acetylene (ethynyl) group in medicinal chemistry coincides with the launch of the *Journal of Medicinal Chemistry* in 1959. Since then, the acetylene group has been broadly exploited in drug discovery and development. As a result, it has become recognized as a privileged structural feature for targeting a wide range of therapeutic target proteins, including MAO, tyrosine kinases, BACE1, steroid receptors, mGlu5 receptors, FFA1/GPR40, and HIV-1 RT. Furthermore, a terminal alkyne functionality is frequently introduced in chemical biology probes as a click handle to identify molecular targets and to assess target engagement. This Perspective is divided into three parts encompassing: (1) the physicochemical properties of the ethynyl group, (2) the advantages and disadvantages of the ethynyl group in medicinal chemistry, and (3) the impact of the ethynyl group on chemical biology approaches.





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ERR γ ligand HPB2 upregulates BDNF-TrkB and enhances dopaminergic neuronal phenotype

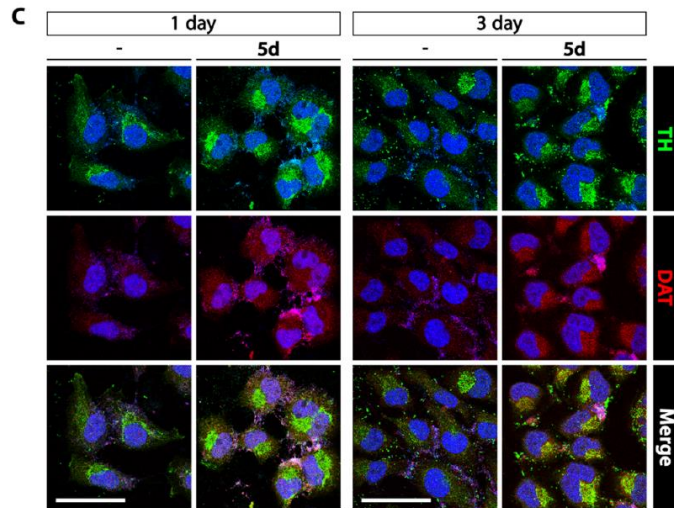
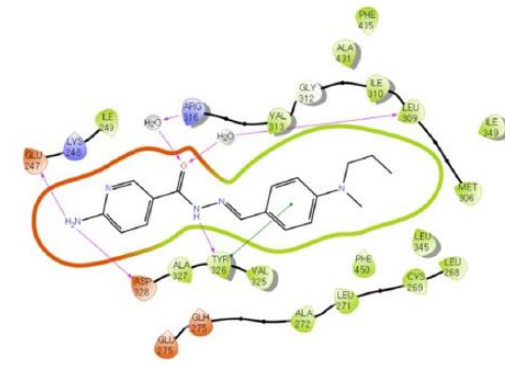
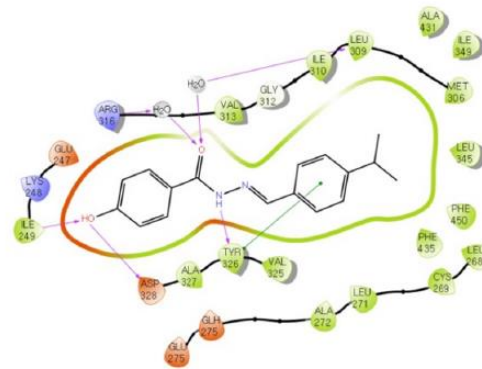
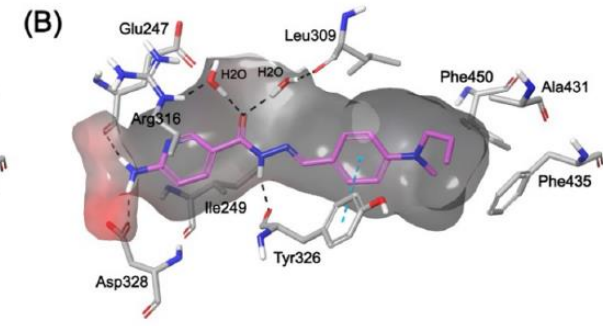
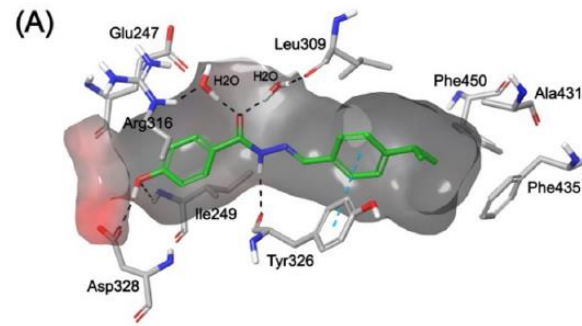
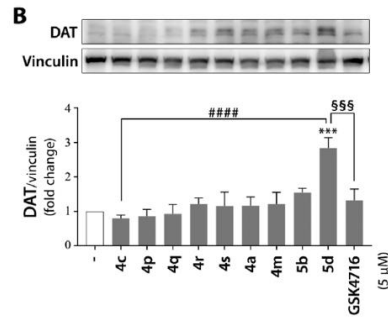
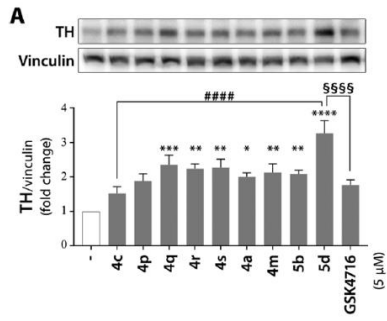
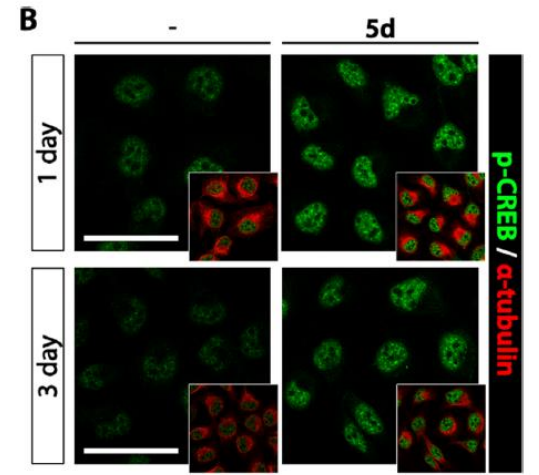
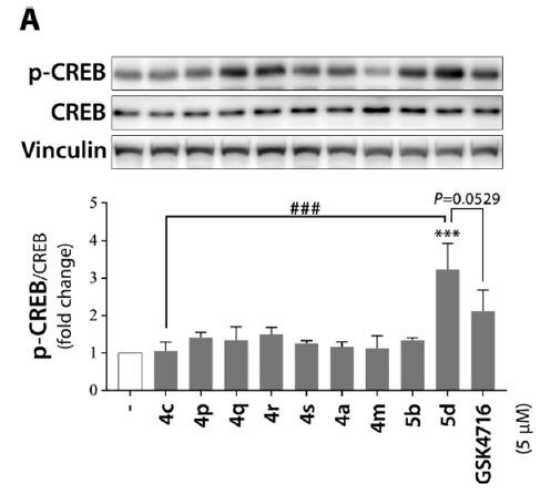
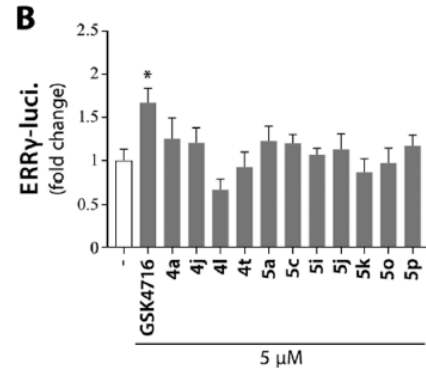
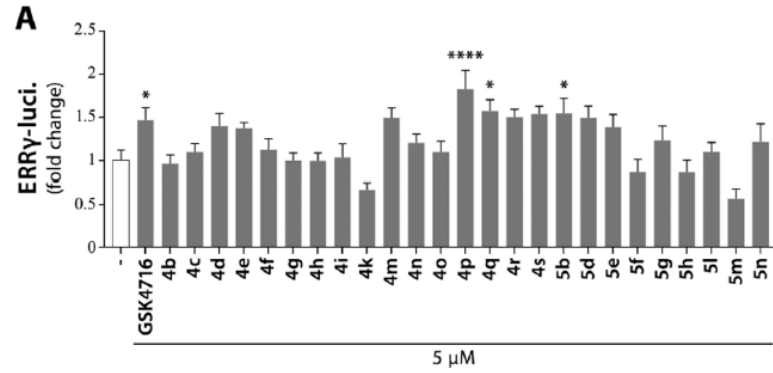
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Discovery of new ERR γ agonists regulating dopaminergic neuronal phenotype in SH-SY5Y cells

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