Pharmacological manipulation of cGMP and NO/cGMP in CNS drug discovery

Michael A. Hollas,[a] Manel Ben Aissa,[a] Sue H. Lee, [a] Jesse M. Gordon-Blake,[a] and Gregory R.J. Thatcher,[a*]

[a]*Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, USA*

Abstract The development of small molecule modulators of NO/cGMP signaling for use in the CNS has lagged far behind the use of such clinical agents in the periphery, despite the central role played by NO/cGMP in learning and memory, and the substantial evidence that this signaling pathway is perturbed in neurodegenerative disorders, including Alzheimer's disease. The NO-chimeras, NMZ and Nitrosynapsin, have yielded beneficial and disease-modifying responses in multiple preclinical animal models, acting on $GABA_A$ and NMDA receptors, respectively, providing additional mechanisms of action relevant to synaptic and neuronal dysfunction. Several inhibitors of cGMP-specific phosphodiesterases (PDE) have replicated some of the actions of these NO-chimeras in the CNS. There is no evidence that nitrate tolerance is a phenomenon relevant to the CNS actions of NO-chimeras, and studies on nitroglycerin in the periphery continue to challenge the dogma of nitrate tolerance mechanisms. Hybrid nitrates have shown much promise in the periphery and CNS, but ~~d~~oto date only one treatment has received FDA approval, for glaucoma. The potential for allosteric modulation of soluble guanylate cyclase (sGC) in brain disorders has not yet been fully explored nor exploited; whereas multiple applications of PDE inhibitors have been explored and many have stalled in clinical trials.

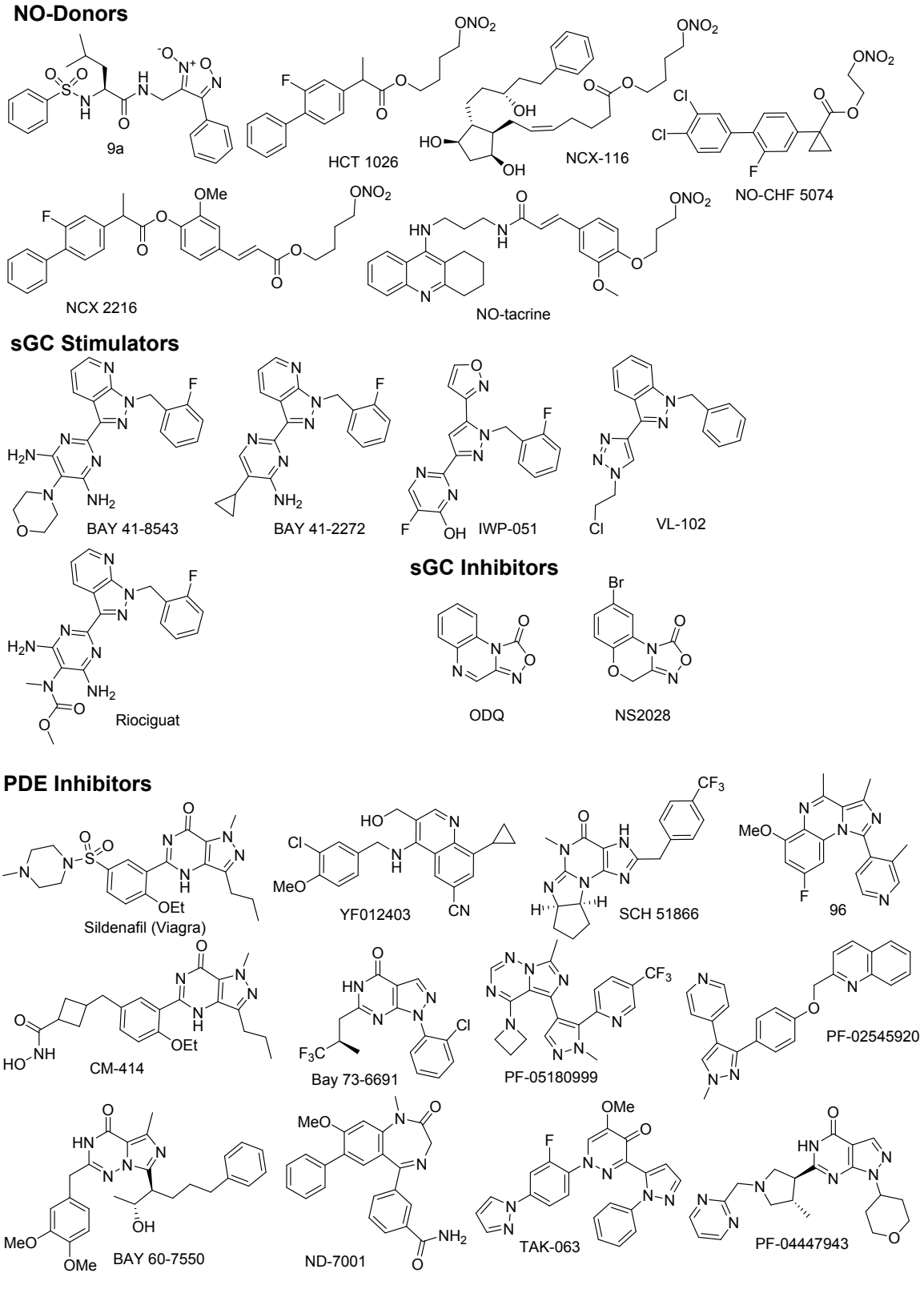
Neurodegeneration; cGMP; nitric oxide; NMDA receptor; GABA receptor; migraine; Alzheimer's disease

* Corresponding author. Tel.: +1-312-355-5282; e-mail: thatcher@uic.edu.

	Drug	Pharmaceutical Mechanism	Disease Target	Observed Effect	Model	Clinical	Refs
NO-Donors	Nitrosynapsin	NO-Hybrid drug	AD/Autism	↓Aβ-induced synapse damage	3xTg	-	[106]
	NMZ (GT-1061)	NO-Hybrid drug	AD	LTP restoration in hippocampal slices, ↑ memory, and ↓ Aβ	APP/PS1, 3xTg, and 5xFAD/hAPOE4	-	[97, 104]
	NCX-116	NO-NSAID	AD	-		FDA approved for Glaucoma	
	HCT-1026	NO-NSAID	AD	Reversed cognitive deficits induced by scopolamine, ↓ the $A\beta_{1-42}$-induced glia reaction, iNOS ↑ and p38MAPK activation	APP/PS1	-	[102, 151] [152]
	NCX-2216	NO-NSAID	AD	↓$A\beta_{1-42}$-induced glia reaction, ↑ iNOS and ↑ p38MAPK		-	[151]
	CHF-5074	NO-NSAID	AD	Reversal of contextual memory deficit	Tg2576	Phase II [176, 177]	[171] [172, 173]
	9a	Furoxan	AD	↑ LTP in hippocampal slices treated with oligomeric Aβ		-	[205]
	Sin-1	NO-Donor	AD	↓ 7-nitroindazole induced learning deficit, scopolamine-induced amnesia and hypermotility in rats		-	[228-233]
HNO-Donors	Angeli's salt	HNO-Donor	AD	↑ cerebral ischemia-reperfusion injury	Experimental stroke model - C57BL6/J	-	[239, 242]
sGC Stimulators	YC-1	sGC Stimulator	AD	LTP restoration in hippocampal slices, attenuated scopolamine-induced amnesia	adult Wistar rats	-	[255, 256]
	VL-102	sGC Stimulator	Migraine	Acute and chronic mechanical cephalic and hind-paw allodynia	C57BL/6	-	[120]
sGC Inhibitors	ODQ	sGC Inhibitor	PD, Migraine	Improved deficits in forelimb akinesia induced by 6-OHDA and MPTP. ↓ acute and chronic hyperalgesia induced by nitroglycerin	6-OHDA and MPTP treated rats	-	[266]
NOS Inhibitors	L-NMMA	NOS inhibitor	Migraine	-		Phase II [127]	
PDE Inhibitors	Sildenafil	PDE5 Inhibitor	AD	↑ synaptic function, CREB phosphorylation, and memory. Reversed cognitive impairment of Tg2576 mice	APP/PS1, aging mouse model, J20, Tg2576	-	[282] [283]
	Tadalafil	PDE5 Inhibitor	AD	↑ performance of J20 mice in the Morris water maze test	J20	-	[284-286]

UK-343664	PDE5 Inhibitor	AD	Ineffective at preventing MK-801-induced memory disruption, however, ↓ the memory impairment of scopolamine	MK-801	-	[287]
YF012403	PDE5 Inhibitor	AD	Rescued the defects in LTP, synaptic, plasticity and memory	APP/PS1	-	[288] [289]
CM-414	PDE5 Inhibitor	AD	LTP restoration in hippocampal slices. ↓ brain Aβ and tau phosphorylation, reversed a decrease in dendritic spine density on hippocampal neurons, and reversed cognitive deficits	APP/PS1, Tg2576	-	[291]
BAY 73-6691	PDE9 Inhibitor	AD	↑ acquisition, consolidation, and retention of long-term memory (LTM) in a social recognition task ↓ a scoplamine-induced retention deficit in a passive avoidance task, and MK-801-induced short-term memory deficits.	FBNF1 rats	-	[295]
PF-04447943	PDE9 Inhibitor	AD	LTP restoration in hippocampal slices, ↑ indicators of hippocampal synaptic plasticity and improved cognitive function	Tg2576	Phase II [298]	[296, 297]
BI-409306	PDE9 Inhibitor	AD, Schizophrenia	-		Phase II [299]	
SCH-51866	PDE1/5 Inhibitor	HD	No effect in the R6/2 mouse model of HD	R6/2 HD		[301]
BAY 60-7550	PDE2 Inhibitor	AD	↑ performance of rats in social and object recognition memory tasks, and reversed MK801-induced deficits	MK-801	-	[23, 302-304]
PF-05180999	PDE2 Inhibitor	Schizophrenia, Migraine	-		Phase I [306]	[305]
ND7001	PDE2 Inhibitor	Various CNS	-			[307]
Papaverine	PDE10A Inhibitor	Psychosis	↓ conditioned avoidance responding in rats and mice and ↓PCP induced hyperlocomotion	Male CD rats	-	[308] [309]
PF-02545920	PDE10A Inhibitor	HD	-		Phase II [310]	
TAK-063	PDE10A Inhibitor	Schizophrenia	↓ PCP induced hyperlocomotion	C57BL/6	-	[311]
“compound 96”	PDE10A Inhibitor	Psychosis	Reversal of MK-801 induced hyperactivity and conditioned avoidance responding	MK-801	-	[313]

Table 1: Pharmacological modulators of NO/cGMP signaling in the literature that have been utilized in disorders of the CNS, including their pharmacological targets and mode of action.



Scheme 1: Structures of pharmacological modulators of NO/cGMP signaling.