New Serotonergics with High Intracellular Bioavailability as Potentially Neuroplastic and Geroprotective Agents

Yaroslav G. Zaitsev ORCID: 0000-0002-0069-2997 https://doi.org/10.5281/zenodo.18216431

January 2026 · Scientific Preprint

Data Availability & Methodology: Targets: 5-HT1A, 2A/B; MAPK/NF-κB; Neurogenics. In Silico: SAR Library (80+ scaffolds); pKi; ADME/Tox. Status: Preprint (2026). License: CC BY 4.0. Contact: nabrosovnabrosov@gmail.com. Author: Ya. G. Zaitsev.

Abstract

Erinacine A (*Hericium erinaceus)* and psilocybin exhibit partially overlapping pharmacological profiles(pKi 5-HT ≈ 6.3 and 7.2 in silico respectively), but differ significantly in lipophilicity and the type of neuroplasticity induced. Carvacrol(Sisti et al., 2021), α-bisabolol(Kim et al., 2025), and β-asarone(Dong et al., 2014), which share serotonergic properties(Figure**)**, also show potential as neurotrophic agents.

Furthermore, activation of 5-HT receptors leads to the upregulation of CREB and NF-κB/MAPK signaling pathways, thereby inducing neurogenesis, also serotonergic structures are aimed at targeted induction of BDNF in learning and memory areas CA1 and CA3 of the hippocampus (Jiang et al., 2016). This mechanism has been demonstrated by several lipophilic agents, including antidepressants like captodiamine(Ring & Regan, 2013) and neuroprotective terpenes such as carvacrol, α-bisabolol (Arunachalam et al., 2022), and β-asarone. The neurogenic potential of these compounds correlates with their affinity for 5-HT receptors (Figure). Similarly, schisandrins(Li et al., 2019) (in silico pKi ≈ 6.58) from Schisandra chinensis and ginsenosides(Han et al., 2024) (in silico pKi ≈ 6.4) from Panax ginseng have been extensively documented as potent neuroprotective and neurotrophic agents.

Fast neuroplasticity (e.g., psilocybin(Golden et al., 2022), ketamine(Kopelman et al., 2023)) promotes synaptogenesis but can duplicate pathological connections and increase neural noise. In contrast, slow neuroplasticity—true neurogenesis and myelinogenesis—appears to be more beneficial for organic brain damage, depression, Alzheimer's disease, and related conditions. The lipophilic and amphiphilic synthetic terpenes and tryptophols presented in this study are designed for deep (intracellular) neurotrophic activity, targeting 5-HT1A receptors and potential allosteric sites. This is achieved through both deep regional penetration averaged mimetics and the selectivity of some candidates with high 5-HT1A affinity, as confirmed by in silico analysis (https://serotoninai.streamlit.app).

Study structures exhibit varying levels of affinity (from moderate to high- pKi ≈ 7.8), different gradations of selectivity, high lipophilicity, and excellent bioavailability. Their deep penetration hypothetically ensures sustained "slow neuroplasticity" and more comprehensive 5-HT modulation. Furthermore, this study presents potential pharmacological analogs of hericenones: ultra-lipophilic lipophilic serotonin mimetics with potential activity within myelin sheaths and axons. Finally, psilocybin has also been shown to extend replicative lifespan by up to 50% through telomerase modulation and reduction of oxidative stress (Kato et al., 2025).

Keywords: Erinacine A, hericenones, Hericium erinaceus, neurotrophic agents, rational drug design, non-psychedelic neuroplasticity, slow neuroplasticity, lipophilic 5-HT1A mimetics, NGF/BDNF induction, telomerase modulation, geroprotectors, MAPK/NF-κB signaling, in silico screening, SAR library.

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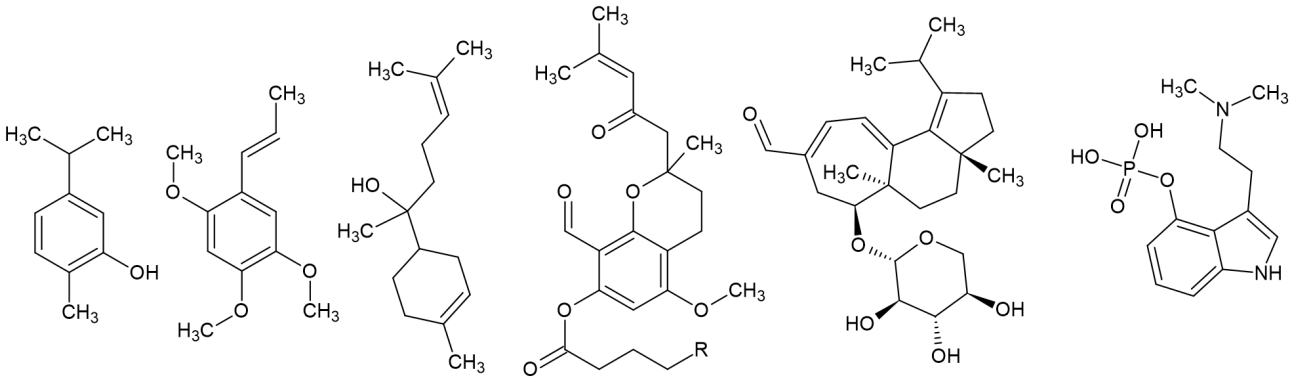
1. Introduction

Figure



Reference compounds: Carvacrol – β-Asarone – α-Bisabolol – Hericenones – Erinacine A – Psilocybin

pKi 5-HT$_{1A}$; α-Bisabolol – 5.15, Carvacrol – 5.4, β-Asarone – 5.4, Hericenones – 5.753, Erinacine A – 6.052, Psilocin – 7.0
pKi 5-HT$_{2A}$; β-Asarone – 5.2, Carvacrol – 5.236, Hericenones – 5.889, α-Bisabolol – 6.11, Erinacine A – 6.207, Psilocin – 7.2
pKi 5-HT$_{2B}$; α-Bisabolol – 5.57, β-Asarone – 5.78, Carvacrol – 5.794, Hericenones – 5.921, Erinacine A – 6.264, Psilocin – 6.34

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2. Rationale and Proposed Structures

Natural neurotrophic terpenes and terpenoids often exhibit their activity due to their ultra-high lipophilicity, despite the spatial noise of random radicals and suboptimal pharmacophoric positions. Low receptor affinity, low mimetic capacity, suboptimal bioavailability, limited physicochemical diversity, as well as inherent difficulties in purification and production, are insurmountable obstacles to full-fledged pharmacological practice. In this context, the search for and development of pharmacologically sound, bioavailable, and amphiphilic agents with pronounced neurotrophic activity is a standard solution.

The development of dozens of original core compounds—characterized by specific pharmacokinetic properties, in silico determined activity, strictly graded affinity within a bioavailable amphiphilic profile—represents the path to realizing a full therapeutic spectrum. This spectrum ranges from averaged, pro-native allosteric modulators (Nguyen et al., 2024), (Brunetti et al., 2025) based on short pharmacological serotonin analogs to specialized, highly selective, and high-affinity 5-HT1A agents(Casarotto et al., 2021), (Jiang et al., 2016), (Kato et al., 2025).

Table

ID	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A°2)	Lipinski Rule	CNS-MPO	SMILES
E01		6.1	5.5	5.95	203.24	1.92	-2.33	2.12	-2.53	2	2	45.25	Yes (0 violations)	4.5	COC1=CC=CC2=C1C(\C=C\CO)=CN2
E02		6.14	5.21	5.58	220.26	2.78	-3.98	3.05	-4.41	3	0	27.69	Yes (0 violations)	4.9	COC1=CC=C(OC2CC2)C=C1OCC=C
E03		6.2	5.1	5.7	358.39	2.8	-5.02	3.18	-4.32	6	0	71.06	Yes (0 violations)	5.4	CCOC1=CC(C=O)=CC=C1OCCOC1=C(OCC)C=C(C=O)C=C1
E04		6.2	5.2	5.63	310.39	1.65	-2.77	2.26	-3.62	5	0	46.15	Yes (0 violations)	5.9	COCCOCCOCCOC1=C(OC)C=C(CC=C)C=C1
E05		6.2	5.7	5.42	302.36	2.88	-4.21	2.89	-3.77	4	0	36.92	Yes (0 violations)	5.4	C(COCCOC1=CC=CC=C1)OCCOC1=CC=CC=C1
E06		6.2	5.3	6	185.23	2.88	-4.68	2.74	-7.65	1	1	32.86	Yes (0 violations)	5.1	O=C(C1CC1)C1=CNC2=C1C=CC=C2

ID	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A^2)	Lipinski Rule	CNS-MPO	SMILES
E07		6.2	5.5	5.6	372.42	3.03	-5.14	3.32	-4.31	6	0	71.06	Yes (0 violations)	5.2	CCOC1=CC=C(C=O)C=C1OCCCOC1=C(OCC)C=C(C=O)C=C1
E08		6.2	6	5.7	238.33	1.57	-2.71	2.67	-3.7	3	0	27.69	Yes (0 violations)	5	C1CC1OC1CC(OC2CC2)C(C1)OC1CC1
E09		6.23	5.5	5.6	232.28	2.29	-3.93	2.68	-4.39	3	0	35.53	Yes (0 violations)	5.4	COC1=CC(\C=C\C(C)=O)=CC=C1OC1CC1
E010		6.23	5.6	5.53	190.24	3.29	-4.34	3.17	-4.57	2	0	18.46	Yes (0 violations)	4.3	C1CC1OC1=CC(OC2CC2)=CC=C1
E011		6.24	5.42	5.7	294.35	1.68	-3.88	2.09	-3.77	5	0	53.99	Yes (0 violations)	6	COCCOCCOC1=CC(=CC=C1OC)C(=O)C1CC1
E012		6.25	5.13	5.7	178.23	2.24	-2.6	2.23	-2.75	2	1	29.46	Yes (0 violations)	5.2	OCCOC1=CC=CC=C1CC=C
E013		6.27	5.4	6.14	187.24	2.3	-2.82	2.39	-3.1	1	2	36.02	Yes (0 violations)	5.1	OC(C1CC1)C1=CNC2=C1C=CC=C2

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A˚2)	Lipinski Rule	CNS-MPO	SMILES
E014		6.28	5.6	5.7	190.24	2.65	-2.72	2.69	-3.01	2	1	29.46	Yes (0 violations)	5	OC1CC1OC1=CC=CC=C1CC=C
E015		6.3	5.8	5.4	254.33	4.41	-5	3.88	-4.56	2	0	18.46	Yes (0 violations)	3.4	C=CCC1=C(OCCOC2=CC=CC=C2)C=CC=C1
E016		6.3	5.3	5.8	308.42	3.27	-4.21	3.06	-3.64	4	0	36.92	Yes (0 violations)	5.2	CCC1=C(OCCOCCOC)C=C(COCC2CC2)C=C1
E017		6.3	5.7	5.5	246.35	4	-5.01	3.67	-4.07	2	0	32.64	Yes (0 violations)	4.3	C(CC1=CC=C(OC2CCCC2)C=C1)OC1CC1
E018		6.32	5.7	5.6	246.31	3.89	-5.5	3.57	-4.4	3	0	27.69	Yes (0 violations)	4.2	C1CC1OC1=CC(OC2CC2)=CC(OC2CC2)=C1
E019		6.33	5.7	6	173.22	2.97	-3.43	3.12	-4.89	1	1	25.02	Yes (0 violations)	4.5	C1CC1OC1=CC=CC2=C1C=CN2
E020		6.4	5.3	5.9	296.36	1.59	-2.53	2.44	-3.62	5	0	46.15	Yes (0 violations)	5.8	COCCOCCOCC1=CC(OC)=C(OC2CC2)C=C1
E021		6.4	5.4	6	289.38	3.86	-3.45	3.41	-4.19	3	1	51.32	Yes (0 violations)	4.7	CCCCCC(OC)C(=O)OCC1=CNC2=C1C=CC=C2
E022		6.4	6	5.9	448.51	4.12	-6.06	3.58	-4.17	6	0	71.06	Yes (0 violations)	4	COC1=C(OC2CC2)C=CC(\C=C\C(=O)CC(=O)\C=C\C2=CC(OC)=C(OC3CC3)C=C2)=C1

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A°2)	Lipinski Rule	CNS-MPO	SMILES
E023		6.4	5.4	6.1	291.35	1.47	-2.57	1.94	-2.53	4	2	63.71	Yes (0 violations)	5.5	COCCOCCOC1=CC=CC2=C1C(\C=C\CO)=CN2
E024		6.4	5.5	5.8	174.24	3.68	-4.12	3.44	-4.87	1	0	9.23	Yes (0 violations)	3.9	C=CCC1=CC=CC=C1OC1CC1
E025		6.5	5.5	5.8	216.32	4.36	-4.91	4.08	-3.36	1	1	20.23	Yes (0 violations)	3.2	CCC1=CC=C(C=C1)C(O)(C1CC1)C1CC1
E026		6.5	5.7	5.8	400.56	6.4	-6.51	4.77	-6.4	4	0	36.92	Yes 1 violation: MLOGP>4.15	3.4	CCOC1=CC=CC=C1OCCCCCCCCOC1=CC=CC=C1OCC
E027		6.5	5.2	6	191.23	1.97	-2.82	2.19	-4.05	2	1	34.25	Yes (0 violations)	5.5	COCCOC1=CC=CC2=C1C=CN2
E028		6.5	5.4	5.7	204.27	3.27	-4.04	3.18	-4.61	2	0	18.46	Yes (0 violations)	4.3	COC1=C(OC2CC2)C=CC(CC=C)=C1
E029		6.5	5.2	5.8	277.32	1.58	-2.46	1.34	-3.83	4	1	60.55	Yes (0 violations)	5.8	COCCOCCOC(=O)CC1=CNC2=C1C=CC=C2

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A°2)	Lipinski Rule	CNS-MPO	SMILES
E030		6.5	5.7	5.9	259.31	2.1	-3.04	1.7	-3.24	3	3	65.48	Yes (0 violations)	5.2	OC1(CC1)C(OC1=CC=CC2=C1C=CN2)C1(O)CC1
E031		6.5	6	6	294.39	5.35	-5.76	4.27	-4.56	2	0	18.46	Yes 1 violation: MLOGP>4.15	3	C=CCC1=CC=CC=C1OCCOC1=C(CC=C)C=CC=C1
E032		6.5	5.3	5.7	312.37	3.66	-5.2	3.49	-4.42	4	0	44.76	Yes (0 violations)	4.9	COC1=C(OCCOC2=CC=CC=C2CC=C)C=CC(C=O)=C1
E033		6.5	5.3	5.7	236.31	2.97	-2.58	3.14	-4.02	3	0	27.69	Yes (0 violations)	4.8	CCOCC1=CC(OCC)=C(OC2CC2)C=C1
E034		6.5	5.4	5.7	368.47	1.84	-3.39	2.59	-3.5	6	0	55.38	Yes (0 violations)	5.6	COCCOCCOC1=CC=C(CC2CC2)C=C1OCCOCCOC
E035		6.52	5.2	5.8	402.44	2.46	-3.93	2.95	-3.93	7	0	80.29	Yes (0 violations)	5.2	CCOC1=CC(C=O)=CC=C1OCCOCCOC1=CC=C(C=O)C=C1OCC

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A°2)	Lipinski Rule	CNS-MPO	SMILES
E036		6.5	6.2	6	474.6	6.11	-6.57	4.94	-4.2	5	0	53.99	Yes (0 violations)	3.2	CCOC1=CC(\C=C2\CCC\C(=C\C3=CC(OCC)=C(OC4CC4)C=C3)C2=O)=CC=C1OC1CC1
E037		6.53	5.9	6	324.42	4.58	-5.63	4.09	-4.41	3	0	27.69	Yes (0 violations)	3.6	CCOC1=CC=C(\C=C\COC2=C(OC)C=C(CC=C)C=C2)C=C1
E038		6.6	5	6	263.34	1.63	-1.94	2.02	-2.23	3	1	43.48	Yes (0 violations)	5.8	COCCOCCOCCC1=CNC2=C1C=CC=C2
E039		6.6	5	5.5	208.26	2.05	-2.12	2.46	-4	3	0	27.69	Yes (0 violations)	5.2	COCCOC1=C(OC2CC2)C=CC=C1
E040		6.6	5.3	5.8	404.5	3.03	-4.33	3.38	-3.72	6	0	55.38	Yes (0 violations)	5	CCOC1=CC=CC=C1OCCCOCCOCCOC1=CC=CC=C1OCC
E041		6.6	6	5.9	338.45	5.11	-5.49	4.03	-4.01	3	0	27.69	Yes (0 violations)	3.4	C=CCC1=CC=CC=C1OCCOCCOC1=C(CC=C)C=CC=C1
E042		6.6	5	5.8	235.28	1.67	-2.48	2.06	-3.8	3	1	43.48	Yes (0 violations)	5.8	COCCOCCOC1=CC=CC2=C1C=CN2

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A^2)	Lipinski Rule	CNS-MPO	SMILES
E043		6.6	6	6	460.57	5.88	-6.59	4.82	-4.22	5	0	53.99	Yes (0 violations)	5	CCOC1=CC(\C=C2\CC\C(=C\C3=CC(OCC)=C(OC4CC4)C=C3)C2=O)=CC=C1OC1CC1
E044		6.6	6.2	5.7	476.57	4.8	-6.57	4.07	-4.18	5	0	71.06	Yes (0 violations)	3.3	CCOC1=CC(\C=C\C(=O)CC(=O)\C=C\C2=CC(OCC)=C(OC3CC3)C=C2)=CC=C1OC1CC1
E045		6.6	5.8	5.8	310.3	4.25	-5.28	4.01	-4.41	3	0	27.69	Yes (0 violations)	3.8	CCOC1=CC=C(\C=C\C2=CC=C(OC3CC3)C=C2)C=C1OC
E046		6.6	5.4	5.8	280.36	2.31	-3.42	2.7	-3.77	4	0	36.92	Yes (0 violations)	5.5	COCCOCCOC1=CC(CC2CC2)=CC=C1OC
E047		6.62	5.4	6	204.27	2.85	-3.5	3.09	-4.61	2	0	18.46	Yes (0 violations)	4.5	COC1=C(OC2CC2)C=CC(\C=C\C)=C1
E048		6.7	5.4	6	381.47	1.17	-2.18	1.88	-3.42	6	1	71.17	Yes (0 violations)	5.7	COCCOCCOCCC1=CNC2=C1C=C(OCCOCCOC)C=C2
E049		6.7	6	5.9	382.5	4.95	-5.45	3.8	-3.78	4	0	36.92	Yes (0 violations)	3.8	C=CCC1=CC=CC=C1OCCOCCOCCOC1=C(CC=C)C=CC=C1
E050		6.7	5.8	5.9	322.4	4.67	-5.51	4.11	-4.41	3	0	27.69	Yes (0 violations)	3.6	COC1=C(OC2CC2)C=CC(\C=C\C2=CC=C(OC3CC3)C=C2)=C1

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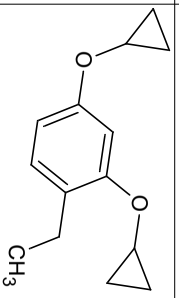
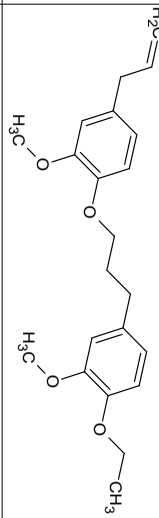
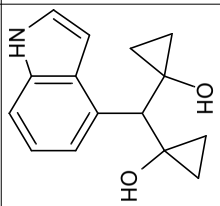
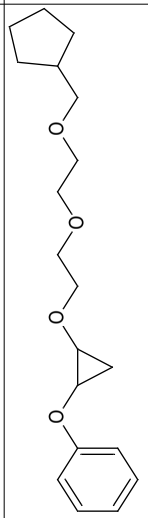
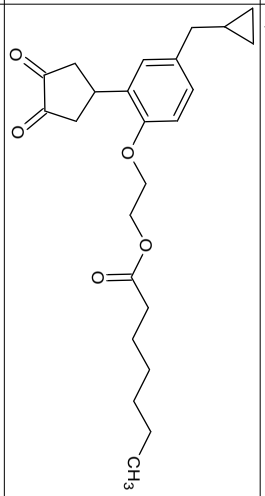
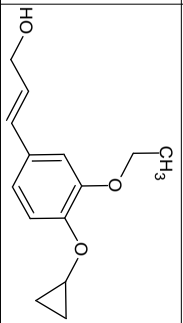
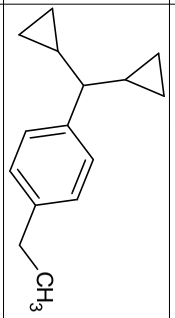
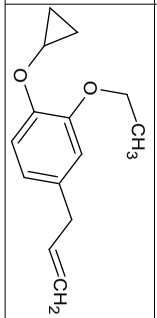
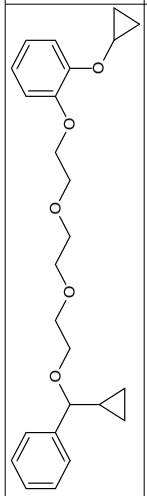
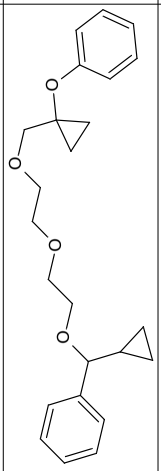
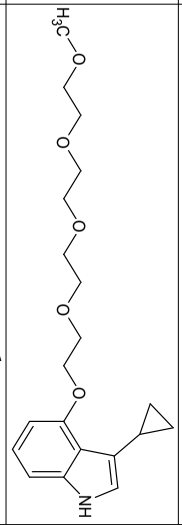
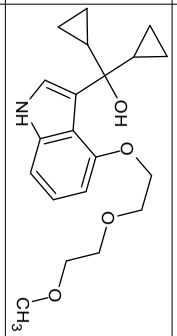
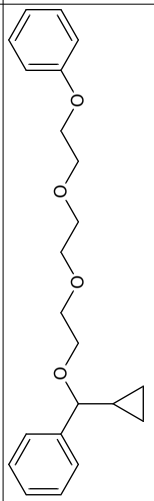
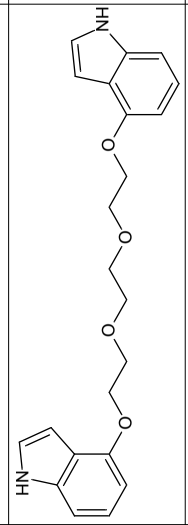
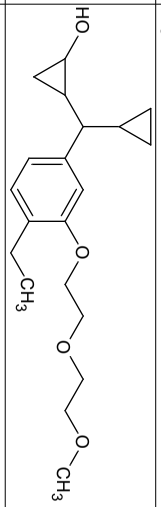
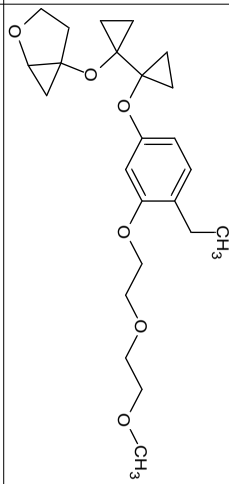
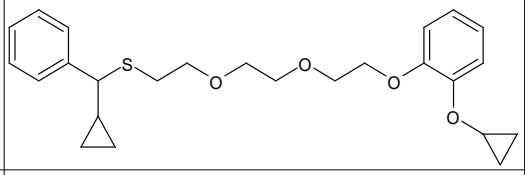
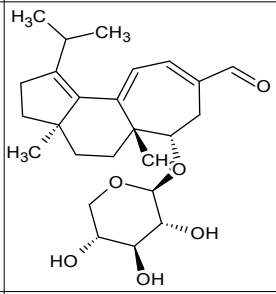
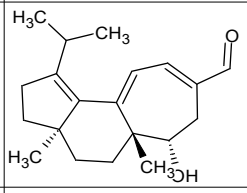
Chemical Structure								
pKi (5-HT$_{1A}$)	6.7	6.7	6.7	6.73	6.73	6.74	6.75	6.78
pKi (5-HT$_{2A}$)	5.8	6.2	5.9	5.6	5.8	5.3	5.6	5.5
pKi (5-HT$_{2B}$)	5.8	6	6	5.4	5.8	5.8	6.1	5.7
MW(Da)	218.3	356.46	243.31	320.43	400.51	234.25	200.32	218.3
ClogP	4.25	4.67	1.75	3.17	5.53	2.33	4.99	3.65
ClogS	-3.45	-5.12	-2.82	-4.2	-6.34	-2.74	-5.6	-3.64
ClogD	3.87	3.99	1.49	3.28	4.33	2.92	4.42	3.5
pKa (basic)	-4.56	-4.3	-2.69	-3.65	-4.58	-2.53	n/a	-4.62
HBA	2	4	2	4	5	3	0	2
HBD	0	0	3	0	0	1	0	0
TPSA (A˚2)	18.46	36.92	56.25	36.92	69.67	38.69	0	18.46
Lipinski Rule	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes 1 violation: MLOGP>4.15	Yes (0 violations)
CNS-MPO	3.4	4	5.2	5.1	3.7	5.5	3	3.9
SMILES	CCC1=CC=C(OC2CC2)C=C1OC1CC1	CCOC1=C(OC)C=C(CCCOC2=C(OC)C=C(CC=C)C=C2)C=C1	OC1(CC1)C(C1=CC=CC2=C1C=CN2)C1(O)CC1	C(COCC1CCCC1OCCOC1CC1=CC=C1)C1CC1	CCCCCCC(=O)OCCOC1=C(C=C(CC2CC2)C=C1)C1CC(=O)C1	CCOC1=C(OC2CC2)C=C(\C=C\CO)C=C1	CCC1=CC=C(C=C1)C(C1CC1)C1CC1	CCOC1=CC(C=C)=CC=C1OC1CC1

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A°2)	Lipinski Rule	CNS-MPO	SMILES
E059		6.78	5.54	5.8	278.39	3.99	-4.21	3.37	-3.79	3	0	27.69	Yes (0 violations)	4.2	CCC1=CC=C(CC2CC2)C=C1OCCOCCOC
E060		6.79	5.64	5.56	362.47	2.9	-4.49	3.16	-3.68	5	0	53.99	Yes (0 violations)	5.4	CC(=O)C(OCCOCCOC1CC1OC1=CC=CC=C1)C1CCCC1
E061		6.8	5.8	5.67	328.41	2.95	-3.92	3.15	-3.66	4	0	36.92	Yes (0 violations)	5.3	C(COCC1=CC=CC=C1)OCCOC1CC1OC1=CC=CC=C1
E062		6.81	5.5	5.9	218.3	3.22	-3.84	3.42	-4.61	2	0	18.46	Yes (0 violations)	4.2	CCOC1=C(OC2CC2)C=CC(\C=C\C)=C1
E063		6.82	5	5.6	323.39	1.22	-2.51	1.88	-3.52	5	1	61.94	Yes (0 violations)	5.8	COCCOCCOCCOCCOC1=CC=CC2=C1C=CN2
E064		6.86	5.57	5.7	364.48	3.98	-4.1	3.48	-3.62	5	0	46.15	Yes (0 violations)	4.7	CCC1=C(OCCOCCOC)C=C(OC2CC2OC2CCCC2)C=C1
E065		6.87	5.55	5.7	259.31	1.18	-2.77	1.1	-3.38	3	4	76.48	Yes (0 violations)	5	OC(C1=CC=CC2=C1C=CN2)(C1(O)CC1)C1(O)CC1
E066		6.87	6.1	5.8	396.53	5.13	-5.64	3.85	-3.76	4	0	36.92	Yes (0 violations)	3.7	C=CCC1=CC=CC=C1OCCOCCCOCCOC1=CC=CC=C1CC=C
E067		6.9	5.6	5.8	290.4	4.22	-4.5	3.41	-3.79	3	0	27.69	Yes (0 violations)	4.1	COCCOCCOC1=CC(CC2CC2)=CC=C1C1CC1

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A°2)	Lipinski Rule	CNS-MPO	SMILES
E068		6.9	6.1	6	306.4	5.73	-6.06	4.4	-4.58	2	0	18.46	Yes (0 violations)	3	C=CCC1=CC=CC=C1OC1CC1OC1=CC=CC=C1CC=C
E069		6.91	6.2	6	338.45	5.32	-5.97	4.52	-4.41	3	0	27.69	Yes (0 violations)	3.4	CCCOC1=CC=C(\C=C\C2=CC=C(OC3CC3)C(OCC)=C2)C=C1
E070		6.93	6.17	5.95	338.19	4.4	-6.1	4.4	-4.41	3	0	27.69	Yes (0 violations)	3.7	CCCOC1=CC=C(\C=C\COC2=CC=C(C=C2)C2CC2)C=C1OC
E071		6.94	5.7	5.7	376.54	4.98	-4.92	3.75	-3.63	4	0	36.92	Yes (0 violations)	3.9	COCCOCCOC1=CC(CCOCC2CCCC2C2CC2)=CC=C1C
E072		7.03	5.6	6.08	380.48	5.13	-6.1	4.48	-4.31	4	0	36.92	Yes (0 violations)	3.7	CCOC1=C(OC2CC2)C=CC(\C=C\C2=CC(OCC)=C(OC3CC3)C=C2)=C1
E073		7.04	5.76	5.78	404.5	2.59	-4.74	3.03	-3.68	6	0	71.06	Yes (0 violations)	5.2	CC(=O)C(OCCOCCOC1CC1OC1=CC=CC=C1C(C)=O)C1CCCC1
E074		7.17	5.7	5.83	404.26	4.66	-4.64	3.57	-3.53	5	0	46.15	Yes (0 violations)	4.1	CCC1=C(OCCOCCOC)C=C(OC2(CC2)C2(CC2)OC2CCCC2)C=C1
E075		7.2	5.7	5.9	318.46	4.85	-5.44	3.84	-3.79	3	0	27.69	Yes (0 violations)	3.5	CCC1=CC=C(C=C1OCCOCCOC)C(C1CC1)C1CC1

	E084	E083	E082	E081	E080	E079	E078	E077	E076
Chemical Structure									
pKi (5-HT$_{1A}$)	7.7	7.6	7.57	7.4	7.4	7.36	7.36	7.34	7.32
pKi (5-HT$_{2A}$)	5.9	5.7	6	5.3	5.7	5.8	5.8	5.8	5.8
pKi (5-HT$_{2B}$)	6	6	5.9	6	6.1	5.6	5.9	5.9	5.9
MW(Da)	412.35	400.51	382.5	363.45	345.44	356.46	380.44	334.46	418.53
ClogP	4.26	3.63	4.48	1.88	2.8	3.72	3.41	3.26	2.97
ClogS	-4.67	-4.46	-4.79	-3.46	-3.77	-4.2	-5.27	-3.98	-4.73
ClogD	3.59	3.52	3.5	2.53	3	3.32	3.37	3.21	3.13
pKa (basic)	-3.64	-3.64	-3.66	-3.52	-3.35	-3.66	-3.78	-2.63	-3.53
HBA	5	5	4	5	4	4	4	4	6
HBD	0	0	0	1	2	0	2	1	0
TPSA (A˚2)	46.15	46.15	36.92	61.94	63.71	36.92	68.5	47.92	55.38
Lipinski Rule	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)	Yes (0 violations)
CNS-MPO	4.2	4.6	4.3	5.5	5	4.8	4.5	5.1	5
SMILES	C(COCCOC1=CC=CC=C1OCCOC1CC1)OCCOC1=CC=CC=C1	CCOC1=CC=CC=C1OCCOCCOC(C1)C1=CC=CC=C1	C(COCC1(CC1)OC1=CC=CC=C1)OCCOCC1=CC=CC=C1	COCCOCCOCCOCC2(NC=C2C2)CC2)=CC=C1	COCCOCCOC1=CC=CC2=C1C(=CN2)C(O)(C1CC1)C1CC1	C(COCCOC1=CC=CC=C1)OCCOC1CC1	C(COCCOC1=C2C=CNC2=CC=C1)OCCOCC1=CC=CC2=C1C=CN2	CCC1=CC=C(C=C1OCCOCCO2)C(C1CC1)C1CC1O	CCC1=CC=C(OC2(CC2)C2(CC2)OC23CC2OCC3)C=C1OCCOCCOC

	Chemical Structure	pKi (5-HT$_{1A}$)	pKi (5-HT$_{2A}$)	pKi (5-HT$_{2B}$)	MW(Da)	ClogP	ClogS	ClogD	pKa (basic)	HBA	HBD	TPSA (A°2)	Lipinski Rule	CNS-MPO	SMILES
E085		7.85	6.2	5.9	428.59	4.74	-5.48	3.92	-3.78	4	0	36.92	Yes (0 violations)	3.5	C(COCCSC(C1CC1)C1=CC=CC=C1)OCCOC1=CC=CC=C1OC1CC1
EA		6	6.2	6.26	432.56	2.9	-4.59	2.1	-3.53	6	3	96.22	Yes (0 violations)	4.4	CC(C)C1=C2C3=CC=C(C[C@@H]([C@@]3(CC[C@]2(CC1)C)C)O[C@H]4[C@@H]([C@H]([C@@H](CO4)O)O)O)C=O
	Erinacine A (Positive Control)														
EAA		5.4	6.3	6.4	300.44	3.85	-4.62	2.87	-3	2	1	37.3	Yes (0 violations)	4.8	CC(C)C1=C2C3=CC=C(C[C@H](O)[C@]3(C)CC[C@@]2(C)CC1)C=O
	Erinacine A Aglycone (Positive Control)														

3. Predicted Advantages

- Synthesis 1–4 steps from commercial precursors
- Superior blood-brain and intracellular barrier penetration (logP 1-5.)
- Elimination of 5-HT$_2$B agonism → no valvulopathy risk
- Activity of MAPK and NF-κB, reduces inflammation and activates neurogenesis
- Sustained NGF/BDNF induction without hallucinogenic effects
- Adjustable elimination half-life via lipophilicity tuning
- Potential telomerase activation and geroprotective properties
- High expected metabolic stability and low toxicity

4. Conclusion

The structures presented in this study demonstrate a broad spectrum of affinity for serotonin receptors, often possess increased potential for penetration across the blood-brain barrier and biomembranes, are free of molecular ballast, and provide a good starting point for precisely determining optimal toxicological and pharmacokinetic properties in subsequent stages of research. The structures are synthesized in 1-4 steps using clean, simple, and accessible pharmacological synthesis methods from readily available starting materials, which is often crucial for lipophilic candidates, terpenes, and terpenoids.

The structures contain fine amphiphilic amine-mimeticity ligands, such as dienes and cyclopropane radicals, polyether chains, and alcohol groups. Thus, not only the allosteric and modulatory properties of the candidates but also their full mimetic properties can be realized. Given their high affinity for serotonin receptors, some of the candidates may exhibit the full spectrum of effects characteristic of potent serotonergic agents, ultralipophilic and amphiphilic, deeply penetrating, potent 5-HT mimetics, hypothetically involved in all of the above-mentioned neuroplastic and geroprotective scenarios.

The in silico analysis summarized in the table demonstrates high affinity values for 5-HT and CNS-MPO for the most common pharmacological nuclei, such as indoles and polyether linkages. In contrast, underrepresented diene radicals, cyclopropyl radicals, substituted allylbenzene-based nuclei, and alkylated cinnamic alcohols have low CNS-MPO values. Given that the history of pharmacology is poor in lipophilic, nitrogen-free, centrally active substances (e.g., fenpentadiol), the in silico data are based on heterochemical compounds, and there are no reference standards for non-nitrogenous lipophilic substances other than natural terpenes, terpenoids, and saponins, there is likely significant variability in the assessment of LogP, CNS-MPO, active permeability, and some other parameters. Dynamic calculations of polyethyleneglycol behavior, the high amphiphilicity of cyclopropane and the allyl radical, and the exotic nuclei and radicals of these compounds are extremely challenging for in silico evaluation using existing databases and algorithms. Furthermore, the ultra lipophilicity of candidates like hericenones can be interpreted as excessive lipophilicity, but this may be a guarantee of accumulation in the myelin sheath, indicating that existing algorithms are not designed for structures deep regional delivery. Thus, researched structures represent a case of working in a pharmacological blind spot, which introduces some inaccuracies, but also potentially offers great potential for new classes of pharmacological agents and therapeutic approaches.

A wide range of pharmacological properties of structures can also be provided by a large number of fundamentally different new nuclei, which facilitates the development of drugs of various therapeutic classes and is an integral part of the development of drugs for complex pathologies.

Acknowledgments

Manuscript edited and formatted with assistance from AI. No funding was received.

Digital Resources

Affinity calculation SerotoninAI: https://serotoninai.streamlit.app/
Definitions of physicochemical characteristics and pharmacokinetic descriptors:
SwissTargetPrediction (https://www.swissadme.ch/index.php)
ADMETlab 2.0 (https://admetmesh.scbdd.com/service/evaluation/cal)
Chemaxon (https://chemaxon.com/)

References

Arunachalam, S., Meeran, M. F. N., Azimullah, S., Jha, N. K., Saraswathiamma, D., Albawardi, A., Beiram, R., & Ojha, S. (2022). *α-Bisabolol attenuates NF-κB/MAPK signaling activation and ER-stress-mediated apoptosis by invoking Nrf2-mediated antioxidant defense systems against doxorubicin-induced testicular toxicity in rats. Nutrients, 14*(21), 4648. https://doi.org/10.3390/nu14214648

Brezun, J. M., & Daszuta, A. (1999). *Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neuroscience, 89*(4), 999-1002. https://doi.org/10.1016/s0306-4522(98)00693-9

Brunetti, L., Francavilla, F., Leopoldo, M., and Lacivita, E. (2024). *Allosteric modulators of serotonin receptors: A review from medicinal chemistry. Pharmaceutics (Basel), 17*(6), 695. https://pmc.ncbi.nlm.nih.gov/articles/PMC11206742/

Casarotto, P. C., Girych, M., Fred, S. M., Kovaleva, V., Enkavi, G., Biojone, C., ... & Castrén, E. (2021). *Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. Cell, 184*(5), 1299-1313. https://doi.org/10.1016/j.cell.2021.01.034

Chiu, C. H., Chyau, C. C., Chen, C. C., Lee, L. Y., Chen, W. P., Liu, J. L., Lin, W. H., & Mong, M. C. (2018). *Erinacine A-enriched Hericium erinaceus mycelium produces antidepressant-like effects through modulating BDNF/PI3K/Akt/GSK-3β signaling in mice. International Journal of Molecular Sciences, 19*(2), 341. https://doi.org/10.3390/ijms19020341

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: *A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, 7*, 42717. https://doi.org/10.1038/srep42717

National Center for Biotechnology Information. (2024). PubChem Compound Summary. https://pubchem.ncbi.nlm.nih.gov/

Dong, H., Gao, Z., Rong, H., Jin, M., & Zhang, X. (2014). *β-asarone reverses chronic unpredictable mild stress-induced depression-like behavior and promotes hippocampal neurogenesis in rats. Molecules, 19*(5), 5634–5649. https://doi.org/10.3390/molecules19055634

Golden, C. T., & Chadderton, P. (2022). *Psilocybin reduces low frequency oscillatory power and neuronal phase-locking in the anterior cingulate cortex of awake rodents. Scientific Reports, 12*(1), 12702. https://doi.org/10.1038/s41598-022-16325-w

Han, D., Zhao, Z., Mao, T., Gao, M., Yang, X., & Gao, Y. (2024). *Ginsenoside Rg1: A neuroprotective natural dammarane-type triterpenoid saponin with anti-depressive properties. CNS Neuroscience & Therapeutics, 30*(12), e70150. https://onlinelibrary.wiley.com/doi/10.1111/cns.70150

Jiang, D. G., Jin, S. L., Li, G. Y., Li, Q. Q., Li, Z. R., Ma, H. X., Zhuo, C. J., Jiang, R. H., & Ye, M. J. (2016). *Serotonin regulates brain-derived neurotrophic factor expression in select brain regions during acute psychological stress. Neural Regeneration Research, 11*(9), 1471–1479. https://doi.org/10.4103/1673-5374.191222

Kopelman, J., Keller, T. A., Panny, B., Griffo, A., Degutis, M., Spotts, C., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M. L., Mathew, S. J., Howland, R. H., & Price, R. B. (2023). *Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression. Molecular Psychiatry, 28*(10), 4233–4242. https://www.nature.com/articles/s41398-023-02451-0

Kato, K., Kleinhenz, J. M., Shin, Y. J., Coarfa, C., Zarrabi, A. J., & Hecker, L. (2025). *Psilocybin treatment extends cellular lifespan and improves survival of aged mice. npj Aging, 11*(1), 55. https://doi.org/10.1038/s41514-025-00244-x

Kim, S., Seong, S. B., Seong, K. J., Mun, B. R., Choi, W. S., Jung, J. Y., & Kim, W. J. (2025). *Alpha-Bisabolol alleviates LPS-reduced hippocampal neurogenesis and cognitive function by anti-inflammatory action via downregulating MAPK and NF-κB signaling in mice. Brain Research Bulletin*, 111690. https://pubmed.ncbi.nlm.nih.gov/41412265/

Li, C.-L., Tsuang, Y.-H., & Tsai, T.-H. (2019). *Neuroprotective effect of Schisandra chinensis on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonian syndrome in C57BL/6 mice. Nutrients, 11*(7), 1671; https://doi.org/10.3390/nu11071671

Massart, R., Mongeau, R., & Lanfumey, L. (2012). *Beyond the monoaminergic hypothesis: neuroplasticity and epigenetic changes in a transgenic mouse model of depression. Philosophical Transactions of the Royal Society B: Biological Sciences, 367*(1601), 2485–2494. https://doi.org/10.1098/rstb.2012.0212

National Center for Biotechnology Information. (2024). PubChem compound summary. https://pubchem.ncbi.nlm.nih.gov/

Nguyen, H., Cheng, M. H., Lee, J. Y., Aggarwal, S., Mortensen, O. V., & Bahar, I. (2024). *Allosteric modulation of serotonin and dopamine transporters: New insights from computations and experiments. Current Research in Physiology, 7,* 100125. https://doi.org/10.1016/j.crphys.2024.100125

Qin, Y., Mahdavi, A., Bertschy, M., Anderson, P. M., Kulikova, S., & Pinault, D. (2022). *The psychotomimetic ketamine disrupts the transfer of late sensory information in the corticothalamic network. European Journal of Neuroscience, 56*(8), 5219–5240. https://doi.org/10.1111/ejn.15845

Ring, R. M., & Regan, C. M. (2013). *Captodiamine, a putative antidepressant, enhances hypothalamic BDNF expression in vivo by synergistic 5-HT2c receptor antagonism and sigma-1 receptor agonism. Journal of Psychopharmacology, 27*(10), 930–939. https://pubmed.ncbi.nlm.nih.gov/23863923/

Zamanian, M. Y., Kujawska, M., Nikbakhtzadeh, M., Hassanshahi, A., Ramezanpour, S., Kamiab, Z., & Bazmandegan, G. (2021). Carvacrol as a potential neuroprotective agent for neurological diseases: A systematic review article. *CNS & Neurological Disorders - Drug Targets*, *20*(10), 942–953. https://pubmed.ncbi.nlm.nih.gov/33970850/