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Review

2-Phenethylamines in Medicinal Chemistry: A Review

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Abstract: A concise review covering updated presence and role of 2-phenethylamines in medicinal chemistry is presented. Open-chain, flexible alicyclic amine derivatives of this motif are enumerated in key therapeutic targets, listing medicinal chemistry hits and appealing screening compounds. Latest reports in discovering new bioactive 2-phenethylamines by research groups are covered too.

Keywords: 2-phenethylamine; medicinal chemistry; ligands; adrenoceptors; carbonyl anhydrase; dopamine receptor; DAT; 5-HT; MAO; PPAR; sigma receptors; TAAR1

1. Introduction

The 2-phenethylamine motif is widely present in nature, from simple, open-chain structures to more complex polycyclic molecular arrangements. The importance of this moiety is probably best exemplified by the endogenous catecholamines dopamine, norepinephrine and epinephrine (an example of open-chain 2-phenethylamines), exhibiting a central role in dopaminergic neurons, which play a critical role in voluntary movement, stress or mood [1]. Several naturally occurring alkaloids, i.e., morphine, (*S*)-reticuline or berberine, embedded in the 2-phenethylamine unit form more complex cyclic frameworks derived from its natural biosynthetic pathways (Figure 1).

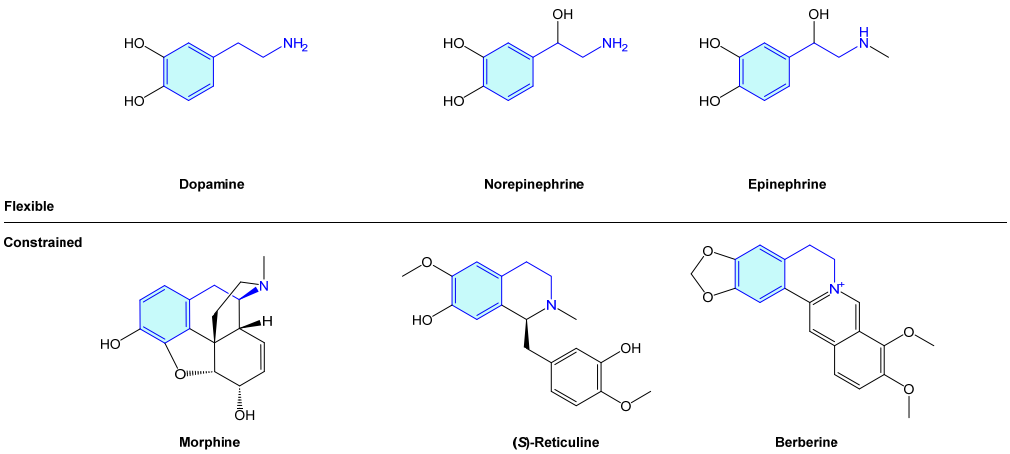

Figure 1. Examples of naturally occurring biologically active compounds displaying a 2-phenethylamine scaffold.

Additionally, in addition to their prominent therapeutic applications, it is worth mentioning the recreational use of a long list of alkaloids incorporating the aforementioned moiety ("designer drugs") [2], responsible for drug abuse-related conditions [3–8]. Surprisingly, the literature lacks a comprehensive summary that bundles up 2-phenethylamine-based structures and known therapeutic targets, including basic hits or advanced leads. Pairing these will present an appealing opportunity to both new and experienced researchers to summarize

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2-phenethylamines target binding and therapeutic scope, as well as selectivity/antitarget issues. Considering all these, a review covering the medicinal chemistry landscape is presented here as a brief, central resource linking up 2-phenethylamine hits and receptors. From the structural point of view, 2-phenethylamines present a vast therapeutic chemical space, not just as is, but considering different substitutions, functional group decorations, ring enclosures or heteroaromatic analogues. Describing such a massive quantity of scaffolds with the phenethylamine resemblance is beyond the scope of this review and more, such asly requires a dedicated book. For this reason, the present review covers only structures where there is an alicyclic amine (Figure 2, blue examples), clustering them all under the 2-phenethylamine label. The authors believe that such cases as 2-heteroaryl ethylamines or cyclic amines, despite presenting 2-phenethylamine resemblance, represent other categorized entities (i.e., tetrahydroisoquinolines or 3-phenyl-pirrolidines examples) on their own, worth independent review (Figure 2, red examples). This review also covers those 2-phenethylamines where the phenyl ring is condensed with a heteroaryl ring, as the primary motif ring is a phenyl one.

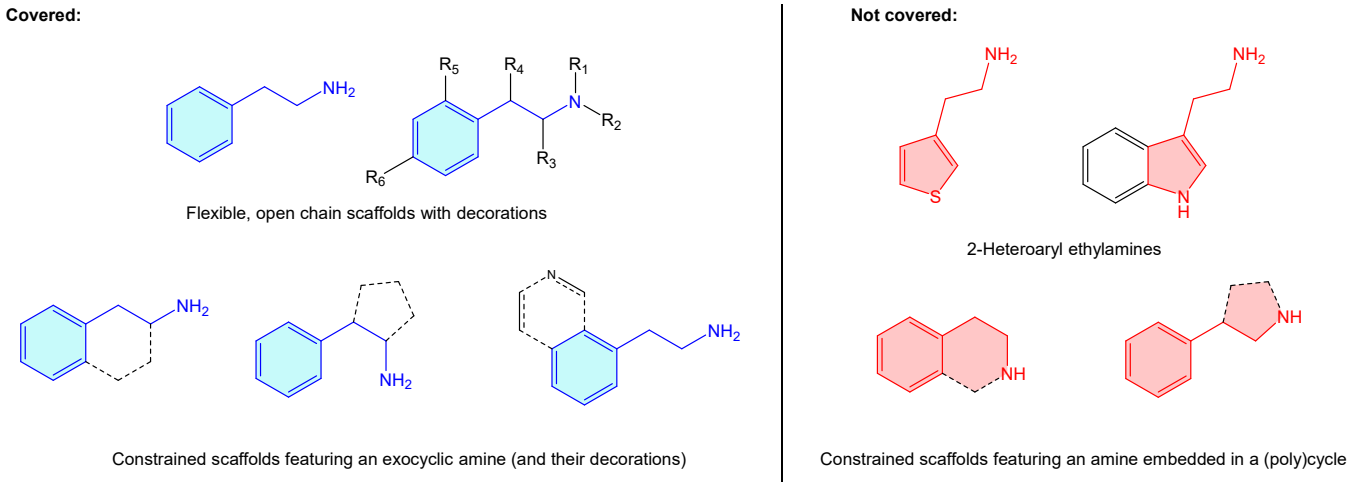


Figure 2. Description of 2-phenethylamine scope of the present review.

This review is divided in sections covering those molecular targets where 2-phenethylamines were found to be biologically relevant. Medicinal chemistry leads and state-of-the-art research on novel molecules are described here.

2. 2-Phenethylamine Targets of Biological Importance

2.1. Adenosine Receptors

Adenosine receptors family are G-protein-coupled receptors (GPCR) widely distributed in human body tissue. They have four members, named A_1, A_{2A}, A_{2B} and A_3, with well-reported activities in mediating inflammation, cardiovascular vasodilation or central and peripheral nervous system pathological responses [9–12].

The 2-phenethylamine moiety may be found in a range of AR (adenosine receptors) ligands, such as *N*6-(2-phenylethyl)adenosine (**1**) [13], APNEA (*N*6-[2-(4-ainophenyl) ethyl]adenosine) (**2**) [14,15], CGS 21680 (**3**) [16–19] or ZM241385 (**4**) [20–22]. Murai et al. synthesized photoreactive CGS 21680 derivatives comprising photophores, such as benzophenone **5** or phenylazide **6** for photoaffinity labeling (Figure 3). This allows elucidation of the functional analysis of adenosine receptor A_{2A} through competitive binding assays against [^{3}H]-NECA (*N*-ethyladenosine-5′-uronamide) [23].

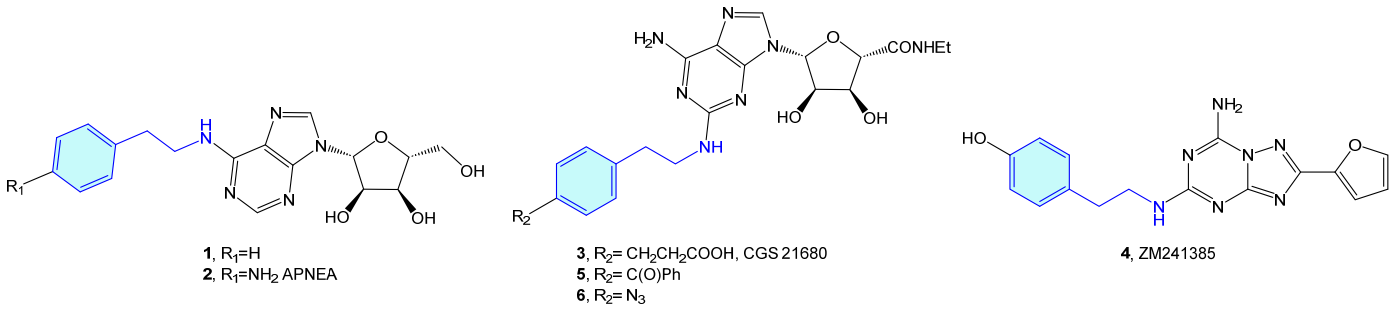


Figure 3. 2-Phenylethyl-based AR ligands.

2.2. α-Adrenergic Receptors

Another class of GPCR targeted by 2-phenethylamines are constituted by α-adrenergic receptors (or α-adrenoceptors). There are two main groups of α-adrenergic receptors, α_1 and α_2, with several subtypes within (α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}). Group α_1 is distributed in cardiovascular, intestinal, CNS and urinary systems, while group α_2 is located in pancreas, CNS, and cardiovascular regions as well [24].

Probably the best representatives of the 2-phenethylamine chemical space are the endogenous catecholamines L-DOPA (**7**), dopamine (**8**), norepinephrine (**9**) (noradrenaline) and epinephrine (**10**) (adrenaline), biosynthetically produced in cascade from phenylalanine (**11**)/tyrosine (**12**) naturally occurring amino acids (Figure 4).

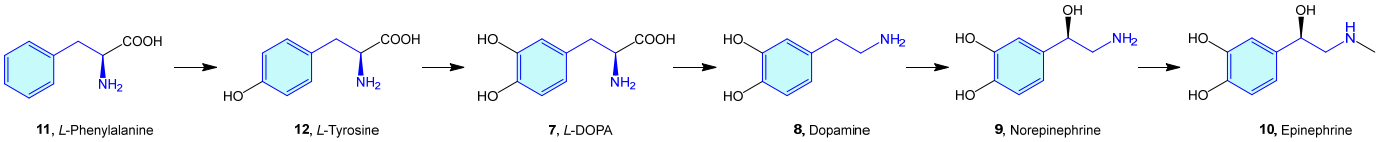


Figure 4. Catecholamine biosynthetic pathways.

Based on these catecholamines, several studies were performed to investigate the effect of chirality, further functionalization, and activity on different derivatives [25–31]. This later triggered the elaboration of many derivatives conserving the 2-phenylethyl moiety, which have been frequently used in the context of medicinal chemistry as tool compounds (Figure 5, Table 1).

Table 1. α-Adrenergic medicinal chemistry leads.

Molecule	Name	Primary Targets	Secondary Targets	References
13	D2343	α_1	β_2-adrenoceptor	[32]
14	Dobutamine	α_1	β_1, β_2-adrenoceptors	[33–35]
15	Etilefrine	α_1	AMP-activated protein kinase (AMPK)	[36]
16	HEAT (BE2254)	α_1		[37–39]
17	Labetalol	α_1	β-adrenoceptors	[40]
18	Methyldopa	α_2		[41,42]
19	OPC-28326	α_2		[43,44]
20	Phenylephrine	α_1		[45,46]
21	Silodosin	α_1		[47,48]
22	Synephrine	α_1	β-adrenoceptors	[49,50]
23	Tamsulosin	α_1		[51]
24	Ulimorelin	α_1	Ghrelin receptor (GRLN)	[52]

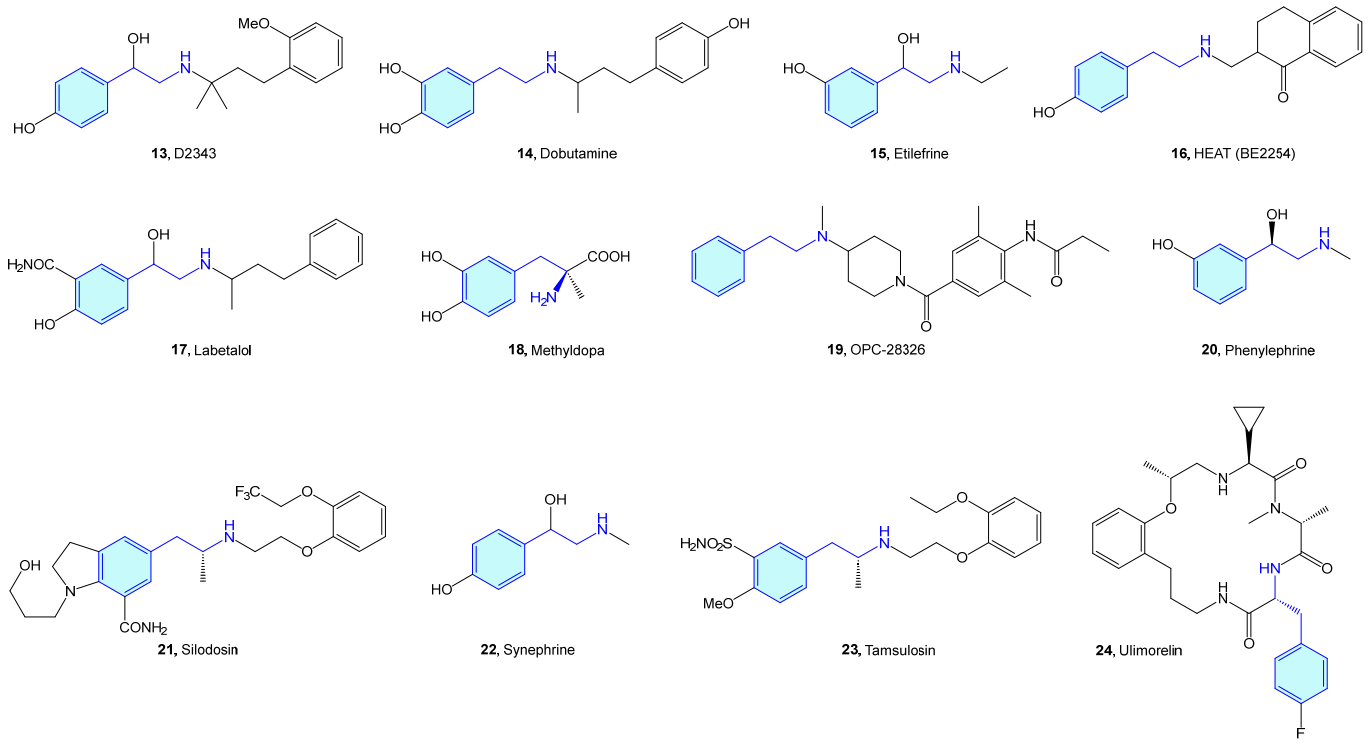


Figure 5. 2-Phenylethyl-based α-adrenergic medicinal chemistry leads.

2.3. β-Adrenergic Receptors

Close to the previously described α-type, the β-adrenergic receptors are also activated by catecholamines norepinephrine and epinephrine. There are three receptor subtypes (β_1, β_2 and β_3) that are implicated in diverse cardiovascular and pulmonary functions [53,54], leading to a vast ligand chemical space (Figure 6, Table 2) to treat cardiogenic shock, heart failure, asthma, overactive bladder (agonists), arrhythmias, hypertension (antagonists commonly known as beta blockers) [55].

Table 2. β-Adrenergic medicinal chemistry leads.

Molecule	Name	Primary Targets	Secondary Targets	References
25	Amibegron	β_3		[56,57]
26	Arbutamine	β		[58–60]
27	Bambuterol	β		[61]
28	Batefenterol	β_2	Muscarinic M2, M3	[62,63]
29	BI-167107	β_2		[64]
30	BRL 37344 sodium	β_3		[65]
31	Brombuterol	β		[66]
32	Bromchlorbuterol	β		[67]
33	CL 316243	β_3		[68,69]
34	Clenproperol	β_2		[70]
35	Clorprenaline	β_2		[71]
36	Denopamine	β_1		[72]
37	Dopexamine	β_2		[73]
38	Epanolol	β		[74]
39	Fenoterol	β_2		[75,76]
40	Guanfacine	β_1	α_2-adrenoceptors	[77]
41	HOKU-81	β_2		[78]
42	Imoxiterol	β		[79]
43	Indacaterol	β		[80]
44	Isoprenaline	β		[81–83]

Table 2. *Cont.*

Molecule	Name	Primary Targets	Secondary Targets	References
45	Isoxsuprine	β	N-methyl-D-aspartate (NMDA)	[84]
46	KUC-7322	β_3		[85]
47	KUL-7211	β		[86]
48	L748337	β_3		[87]
49	L755507	β_3		[88]
50	Levalbuterol	β_2		[89]
51	Lubabegron	β		[90]
52	LY377604	β_3		[91]
53	Mapenterol	β_2		[92]
54	Metaproterenol	β_2		[93,94]
55	Mirabegron	β_3		[95]
56	N-5984	β_3		[96]
57	Naminterol	β_2		[97]
58	Navafenterol	β_2	Muscarinic M3	[98]
59	Octopamine	β		[99,100]
60	Olodaterol	β_2		[101,102]
61	Pamatolol	β		[103]
62	PF-610355	β_2		[104,105]
63	Phenylethanolamine A	β		[106]
64	Pronethalol	β		[107]
65	Reproterol	β_2	Phosphodiesterase (PDE)	[108]
66	Ritodrine	β_2		[109]
67	Ro 363	β_1		[110]
68	Rotigotine	β	α_2-adrenoceptor, 5-HT_{1A}, Dopamine D2, D3, D4, D5	[111]
69	Salbutamol	β_2		[112]
70	Salmeterol	β_2		[113]
71	SB-206606	β_3		[114]
72	Sibenadet	β	Dopamine D2	[115]
73	Solabegron	β_3		[116]
74	Sulfinalol	β		[117]
75	Synephrine	β	α-adrenoceptor	[118]
76	Talibegron	β_3		[119]
77	TD-5471	β_2		[120]
78	Terbutaline	β_2		[121,122]
79	Tulobuterol	β_2		[123]
80	Vilanterol	β		[124,125]
81	Zinterol	β_2		[126]
82	ZK-90055	β_2		[127]
83	-	β_3		[128]
84	-	β_3		[129]

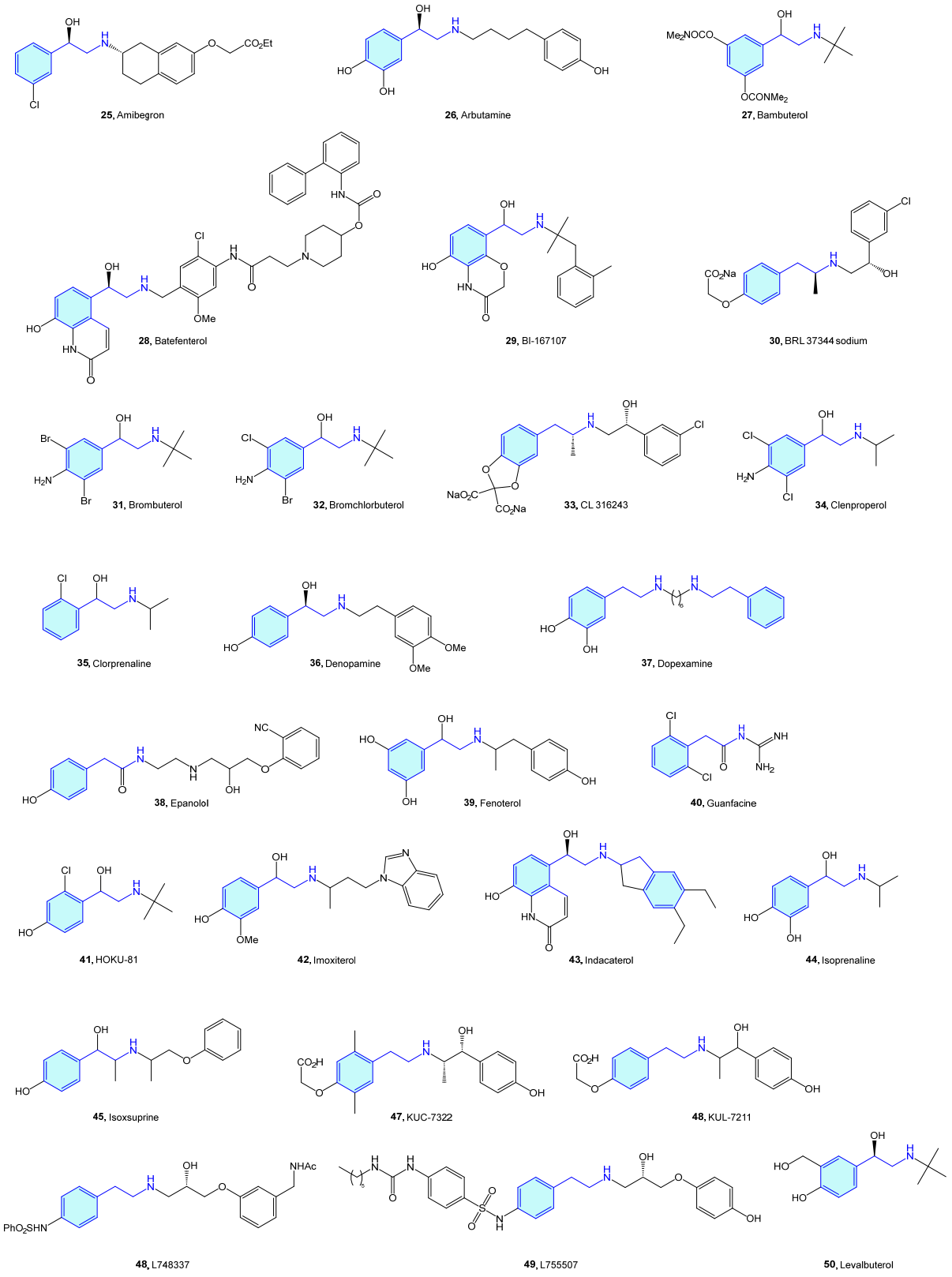


Figure 6. *Cont.*

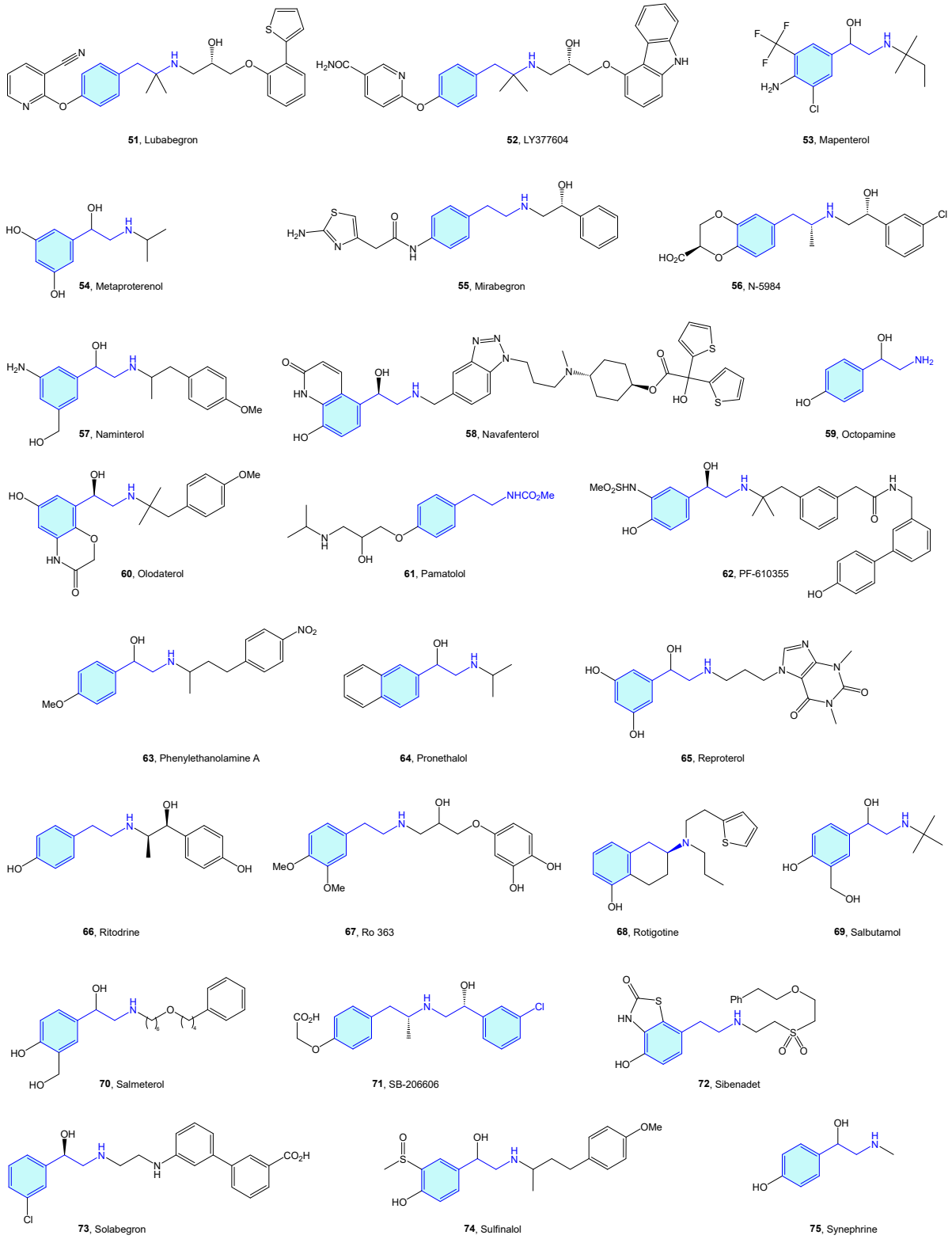


Figure 6. *Cont.*

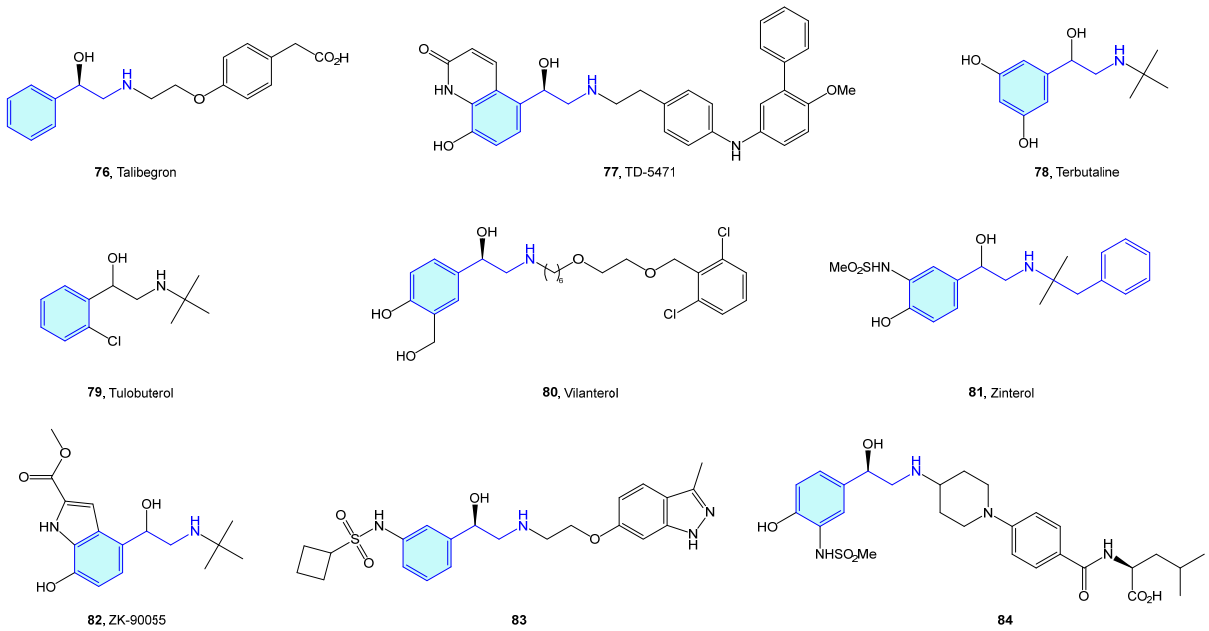


Figure 6. 2-Phenylethyl-based β-adrenergic medicinal chemistry leads.

2.4. Aldose Reductase

ALR2 aldose reductase is an enzyme of the polyol pathway responsible for the transformation of glucose into sorbitol, with relevant involvement in long-term diabetic complications. A series of modified 2-phenethylamines **85** comprising the insertion of aliphatic chains, aromatic rings or carboxylic acids were elaborated by Sun et al. [130]. This resulted in the obtention of a small library of derivatives with low inhibition effects towards in vitro pig kidney ALR2 (Figure 7).

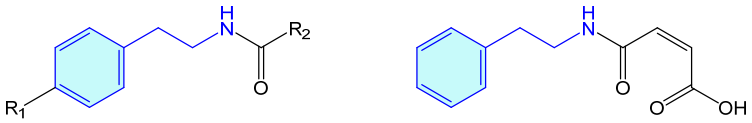


Figure 7. 2-Phenylethyl-based ALR2 ligands by Sun et al [130].

2.5. Carbonic Anhydrase

Carbonic anhydrases (CAs) are Zn-based (also Fe-based) metalloenzymes present across all living organisms of the different life kingdoms. Divided in eight different families (α, β, γ, δ, ε, ζ, η, θ, and t types), they catalyze the hydration of carbon dioxide to bicarbonate, with the purpose of transporting CO_2 to HCO_3^- between tissue types, contributing to pH homeostasis, bone calcification and electrolyte transport, and ultimately participate in biogenic routes/processes, such as lipogenesis, ureagenesis or gluconeogenesis [131–133].

Several groups have independently used 2-phenethylamine based sulfamides and monothiocarbamates (Figure 8) as CA inhibitors, as frequently targeting a specific CA is related to a certain syndrome or disease, such as glaucoma [134], obesity [135], or certain types of cancer [136].

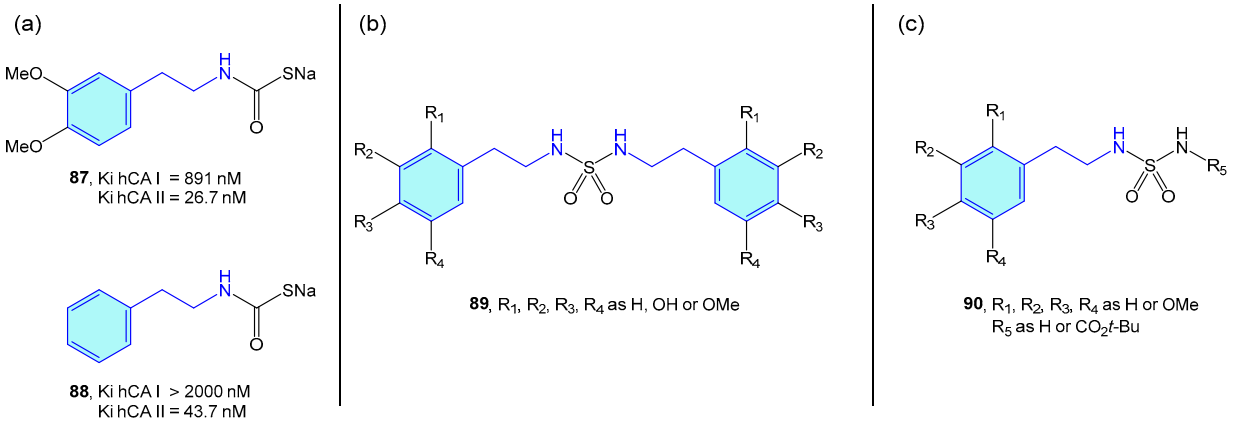


Figure 8. 2-Phenylethyl-based CA ligands.

Nocentini et al. tested phenethylamine monothiocarbamates **87** and **88** as well as other cyclic derivatives against human CA I/II (hCA), with 26–43 nM activities in type II (Figure 8a) [137]. Symmetric sulfamides were employed by Topal et al. (Figure 8b) with hCAI/II inhibition demonstrated at nanomolar level [138]. Branched sulfamides integrating the 1-phenyl-2-phenethylamine scaffold, elaborated by Akıncıoğlu et al. [139] were found to be single-digit nanomolar inhibitors of both type I/II hCA (Figure 8c).

2.6. Dopamine β-Hydroxylase

Dopamine β-hdroxylase (DBH) is a Cu-based oxidoreductase that controls dopamine transformation into norepinephrine (Figure 2) in several neuron types (like adrenergic or noradrenergic ones) [140]. Limited studies have been developed on the use of modified 2-phenethylamines to target DBH. Kruse et al. [141] developed 2-vinyl- and 2-alkynyl-based 2-phenethylamines with moderate vitro activities (Figure 9).

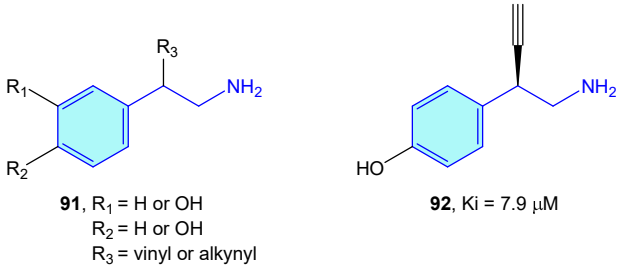


Figure 9. 2-Phenylethyl-based DBH ligands by Kruse et al [141].

More advanced DBH inhibitors are constituted by imidazolethione amines, such as etamicastat [142,143], nepicastat [144] or zamicastat [145], with low resemblance to dopaminergic amines.

2.7. Dipeptidyl Peptidases (DPP)

Dipeptidyl peptidases are exopeptidases responsible for proteolytic transformations, specifically cleaving the peptide bond after the penultimate proline residue. DPP4 is a serine protease displaying a critical role in cell adhesion, inflammation processes and immune regulation by deactivating GLP-1 and hence lowering blood glucose levels [146]. Type 2 diabetes is the main therapeutic area were DPP4 ligands have been discovered (Figures 10 and 11, Table 3).

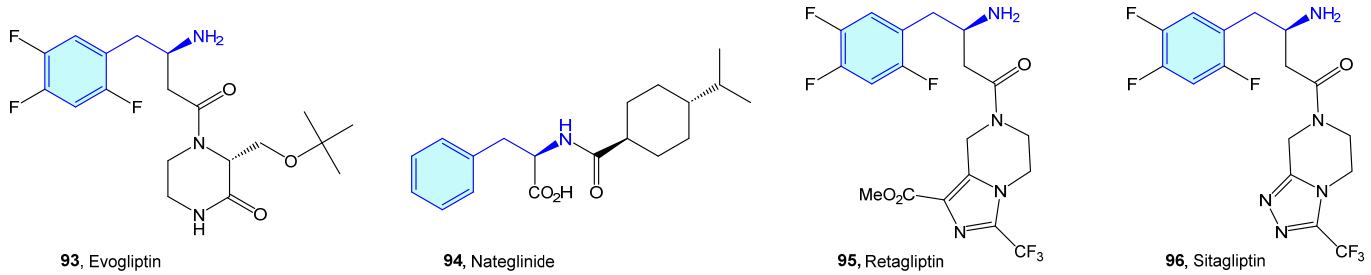


Figure 10. 2-Phenylethyl-based DPP4 medicinal chemistry leads.

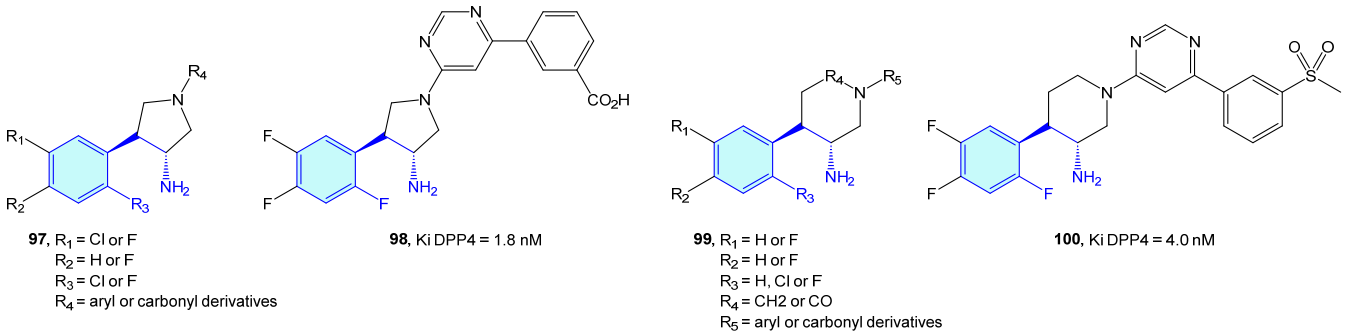


Figure 11. 2-Phenylethyl-based DPP4 receptor ligands.

Table 3. DPP4 medicinal chemistry leads.

Molecule	Name	Primary Targets	Secondary Targets	References
93	Evogliptin	DPP4		[147–149]
94	Nateglinide	DPP4		[150]
95	Retagliptin	DPP4		[151]
96	Sitagliptin	DPP4		[152,153]

Backes et al. [154] and and Pei et al. [155] developed pyrrolidine-constrained and piperidine-constrained phenethylamines selectively targeting DPP4 with interesting PK profiles (Figure 11).

2.8. Dopamine Receptors (DX)

Dopamine receptors are a class of GPCR widely distributed in the brain, with key functionalities related to cognition, motivation and muscular drive. Pharmacologically, they are grouped into two families: D1-type (D1 and D5 receptors) and D2-type (D2S, D2L, D3 and D4) [156,157]. Medicinal chemistry of D1/D2-type receptor ligands addresses mainly the treatment of schizophrenia. From the chemical point of view concerning this review, a few small molecules presenting a basic 2-phenethylamine structure are reported in the literature (Figure 12, Table 4).

Table 4. Dopamine receptor medicinal chemistry leads.

Molecule	Name	Primary Targets	Secondary Targets	References
101	A-77636	D1		[158]
102	A68930	D1		[159]
103	Ansofaxine	D		[160]
104	Oxidopamine	D		[161]
105	Ropinirole	D2, D3, D4		[162]
106	5-OH-DPAT	D		[163]

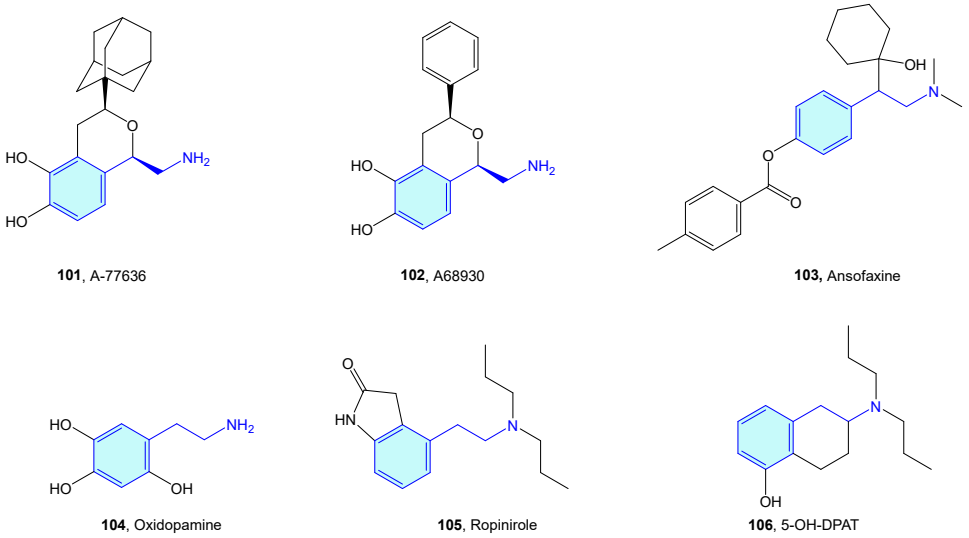


Figure 12. 2-Phenylethyl-based dopamine receptor medicinal chemistry leads.

2.9. Dopamine Transporter (DAT)

The dopamine transporter receptor modulates the availability of released dopamine in the synaptic space by relocating it back into the presynaptic cell. It serves as a main target for recreational drugs as well as psychostimulant and antidepressant drugs. Classically, DAT ligands are classified in amphetamine-type and cocaine-type structures [164]. While cocaine-type molecules exert inhibitory binding to DAT, amphetamine-type ones are substrates that are effectively transported to the presynaptic neuron, stimulating efflux of cytosolic dopamine [165].

Amphetamine-type DAT ligands can be grouped in two families: amphetamine derivatives **107** and cathinone derivatives **114**. Amphetamines are 1-alkyl-2-phenethylamine derivatives **107** summarized below (Figure 13, Table 5). SAR attributes [166] are well known in this series, with diversification of the biological response with aryl substitutions, pharmacokinetic parameter shift upon alkylation of the amino group and decrease in dopaminergic pathways influenced by elongation of the alkyl chain at position 1. Due to being controlled substances in most countries, the number of compounds is constantly increasing, trying to avoid the introduction of compounds in the corresponding prohibition lists of each state [164,167]. Major concerns of this series are neurotoxicity, myocardial infarction, aneurysms, pulmonary hypertension, and tooth decay [168].

Table 5. Dopamine transporter classical binders.

Molecule	Name	References
108	Ephedrine	[169]
109	Amphetamine	[170]
110	Methamphetamine	[170]
111	MDMA	[170]
112	MBDB	[170]
113	MDEA	[170]
115	Cathinone	[170]
116	Methcathinone	[170]
117	Mephedrone	[170]
118	Pyrovalerone	[170]
119	Methylone	[170]
120	Ethylone	[170]

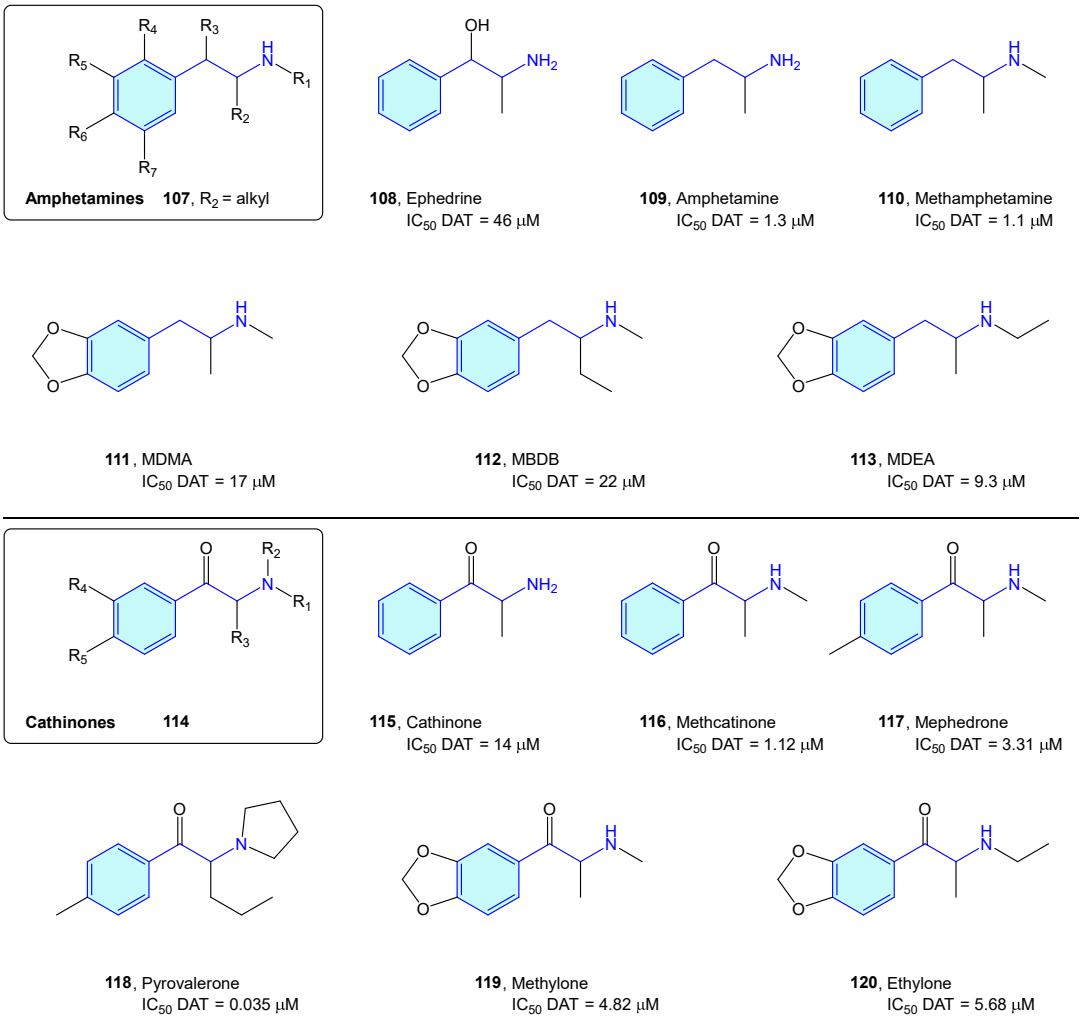


Figure 13. Amphetamine/cathinone-type families.

2.10. Galectin-1 Receptor

Galectins are a family of soluble carbohydrate binding proteins with several roles in inflammation, immune response, autophagy or signaling. Comprising 16 members, only 12 are expressed in humans [171]. Tejler et al. [172] described the synthesis of lactose derivatives, such as **121** with the phenethylamine moiety by 1,3-dipolar cycloadditions, with selective galectin-1 inhibition (Figure 14).

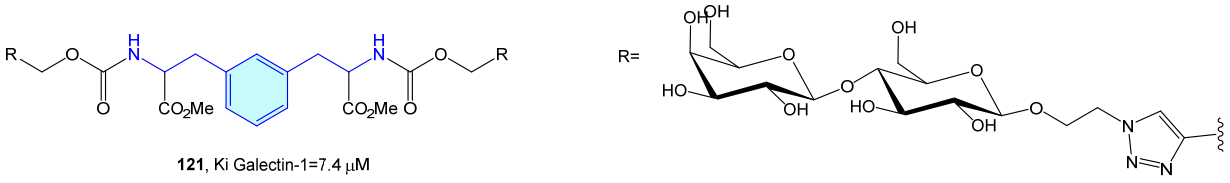
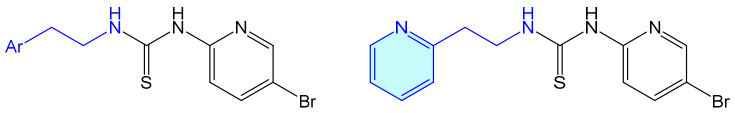


Figure 14. 2-Phenylethyl-based galectin-1 receptor ligands.

2.11. HIV-1 Reverse Transcriptase Receptor

Human immunodeficiency virus (HIV), origin of acquired immunodeficiency syndrome (AIDS), is a single-stranded (ss) RNA virus whose infection and propagation mechanisms requires reverse transcription into double-stranded (ds) DNA as a critical stage [173]. HIV-1 reverse transcriptase receptor (HIV-1 RT) is a well-explored target for antiretroviral therapies [174].

Venkatachalam et al. [175] designed a library of phenethyl thiourea compounds with good potency against HIV-1 RT inhibition without any evidence of cytotoxicity [175–177]. Eventually (Figure 15), these derivatives evolve in the phenethylthiazolylthiourea (PETT) family, with trovirdine as its prominent inhibitor [178–180].

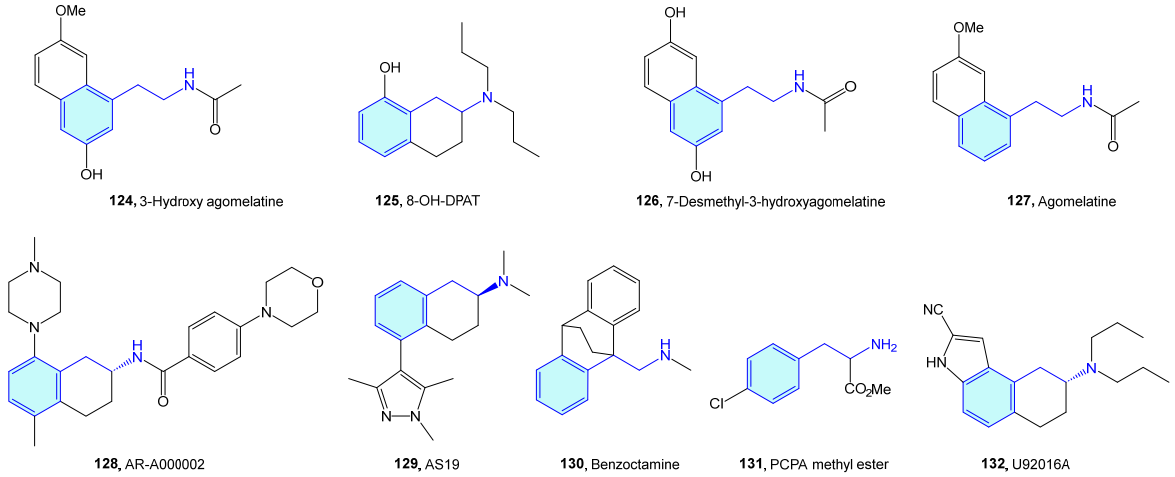


122, Ar= Ph, 2-thiophenyl, 3-indole, 2-piridyl **123**, Trovirdine, IC50 HIV-1 RT=7 nM

Figure 15. 2-Phenylethyl-based HIV-1 RT receptor ligands.

2.12. 5-Hydroxytriptamine (5-HT) Receptors

5-Hydroxytryptamine (5-HT) receptors are one of the most extensively studied receptor families, with seven subtypes (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7) identified [181]. Therapeutic indications of 5-HT ligands and advanced leads (Figure 16, Table 6) cover different conditions, such as migraine, depression, social phobia, obsessive–compulsive disorder, anxiety, schizophrenia, eating disorders, panic-disorders, hypertension, pulmonary hypertension, emesis, vomiting, and irritable bowel syndrome (IBS) [182].



124, 3-Hydroxy agomelatine **125**, 8-OH-DPAT **126**, 7-Desmethyl-3-hydroxyagomelatine **127**, Agomelatine

128, AR-A000002 **129**, AS19 **130**, Benzoctamine **131**, PCPA methyl ester **132**, U92016A

Figure 16. 2-Phenylethyl-based 5-HT medicinal chemistry leads.

Table 6. 5-HT medicinal chemistry leads.

Molecule	Name	Primary Targets	Secondary Targets	References
124	3-Hydroxy agomelatine	5-HT_{2C}		[183]
125	8-OH-DPAT	5-HT_{1A}		[184,185]
126	7-Desmethyl-3-hydroxyagomelatine	5-HT_{2C}	Melatonin MT1, MT2	[186]
127	Agomelatine	5-HT	Melatonin MT1, MT2	[187]
128	AR-A000002	5-HT_{1B}		[188]
129	AS19	5-HT_7		[189,190]
130	Benzoctamine	5-HT		[191]
131	PCPA methyl ester	5-HT		[192]
132	U92016A	5-HT_{1A}		[193,194]

A novel class of 2-phenethylamines with hallucinogenic/psychedelic effects are N-benzylphenethylamines or NBOMes (**133**, **134**) (Figure 17) [195]. These agents have a selective binding profile towards 5-HT_2 receptor subtypes (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}), making them promising therapeutic compounds. Traditionally, the assumption of converting the primary amine into a secondary one was associated with a prominent loss in 5-HT_{2A} activity. N-benzyl substitution was found to be the exception, increasing affinity and potency at the receptor [196]. SAR exploration of the NBOMes scaffold led to defining avoidable regions for SAR expansion, while mapping tolerated substitutions seeking potency/selectivity [197]. From the original 25X-NBOMe halide derivatives [198], different derivatives have evolved.

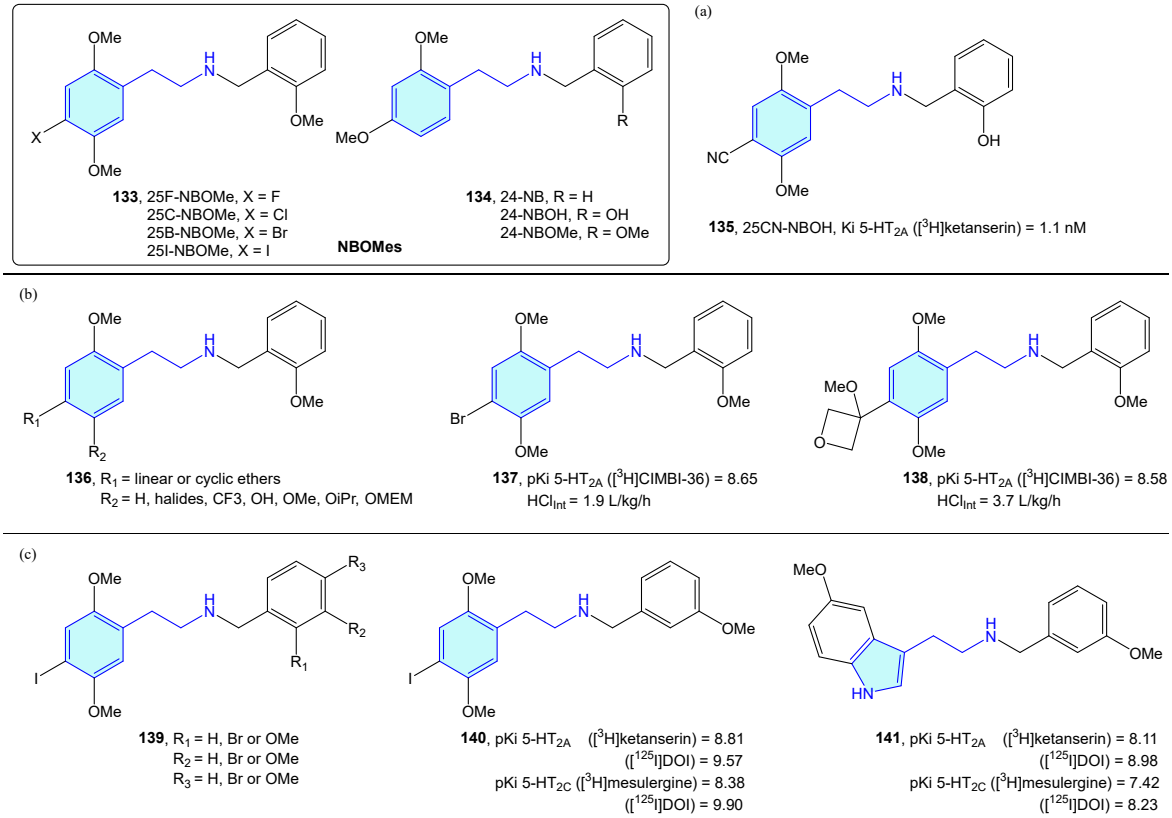


Figure 17. NBOMes with 5-HT receptor activity.

Jensen et al. developed 25CN-NBOH (**135**) (Figure 17a) as a result of halide substitution by the cyano moiety, displaying high-picomolar/low-nanomolar binding affinities (competition binding assays with [^{3}H]ketanserin) and functional potencies at 5-HT_{2A} receptor. Leth-Petersen et al. [199] designed a library of 25B-NBOMe analogues **136**, such as **137** or **138** in the search of decreasing intrinsic clearance (Figure 17b). Despite the authors' efforts to decrease intrinsic clearance by lipophilicity reduction, no correlation was found, although several 5-HT_2 potent compounds were synthesized. Nichols et al. [200] explored the impact of methoxy and bromo scanning along the benzyl ring of 25I-NBOMe (**139**). Ortho or meta positions enhanced activity, whereas the para substitution reduced it. One of the best derivatives was **140**, which was compared with its tryptamine congener **141**, less potent overall in the 5-HT_2 assays performed (Figure 17c).

NBOMes and polyalkoxylated phenethylamines could be envisaged as mescaline (Figure 16, **142**) evolving structures. In this sense, significant efforts have been made to derive rational SAR maps together with attractive bioactive chemical matter [201]. Marcher-Rørsted et al. [202] reported the insertion of 2,5-dimethoxy motif in phenethylamine-like 5-HT_{2A} agonists. They demonstrated that this motif is relevant for in vivo potency, but without observed correlations in affinity or potency in competition binding assays (Figure 18a).

Oxygen-to-sulfur exchange reduces hallucinogenic-associated activity [203], while removal of one of the 2- or 5-position methoxy groups decreased in vivo activity [166]. Porter et al. [204] have derived 3-amino-chromanes and tetrahydroquinolines as selective 5-HT_{2B}/5-HT_7 ligands (Figure 18b). 5-HT_{2B} is not considered an optimal target, due to valvular heart disease and myofibroblast proliferation by long-term consumption of selective agonists [205,206]. 5-HT_7 is implicated in sleep, mood and circadian rhythm functions [207]. Kolaczynska et al. [208] analyzed the impact in 5-HT activity of 4-alkoxy exploration of 2,5-dimethoxyphenethylamines and amphetamines (Figure 18c). Both derivatives were found to interact strongly and selectively with 5-HT_{2A}, demonstrating that size and lipophilicity increase in this region favors 5-$HT_{2A/C}$ affinity. Schultz et al. [209] and Nichols et al. [210] explored the fusion of furane/pyrane rings with the aromatic ring, as probes of the binding pocket size of 5-HT_{2A} receptor subtype and lone pair suitable orientation of the 2,5-oxy substituents, furnishing nanomolar-range receptor affinities (Figure 18d). McLean et al. [211] portrayed the conformationally restriction of 2-phenethylamines via 1-aminomethylbenzo cycloalkanes syntheses (Figure 18e). Benzocyclobutene derivative **153**'s strong potency against 5-HT_{2A} showed the hypothesis that the side chain of the phenethylamine binds in an out-of-the-plane conformation. Some of these conformationally restricted phenethylamines exhibit affinity for muscarinic receptors [212].

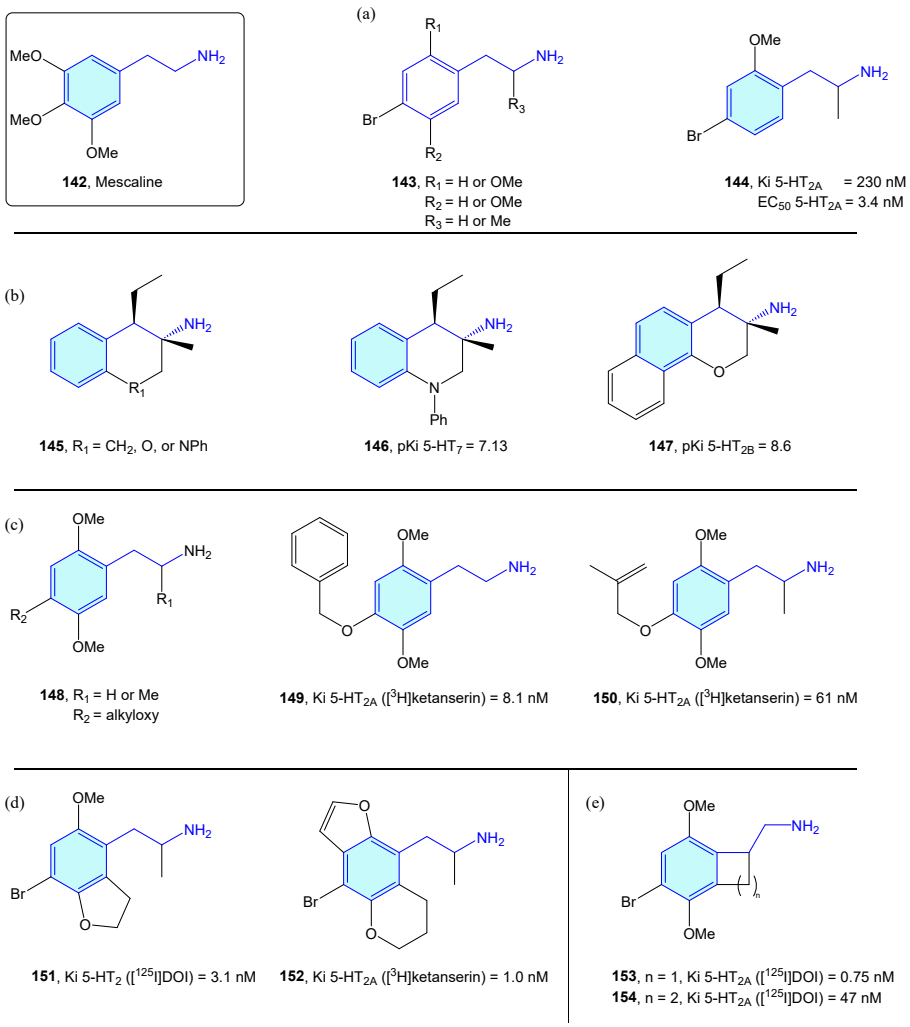


Figure 18. 2-Phenethylamines with 5-HT receptor activity.

2.13. Monoamine Oxidase (MAO) Receptors

Monoamine oxidases (MAO) are flavin-containing enzymes that catalyze the oxidative deamination of monoamines, which are bound to the outer membrane of mitochondria. Common MAO substrates are 5-hydroxy-tryptamine and catecholamines (dopamine, norepinephrine and epinephrine). MAO A and MAO B are the two enzyme isoforms, sharing a 70% sequence identity and differentiating each other in the substrate scope [213]. Theoretical approaches to rationalize isoform selection by substrates have been described [214,215]. As these two oxidases are responsible for neurotransmitter inactivation by oxidation, their dysfunction drives several neurological disorders, hence the therapeutic attractiveness (Figure 19, Table 7).

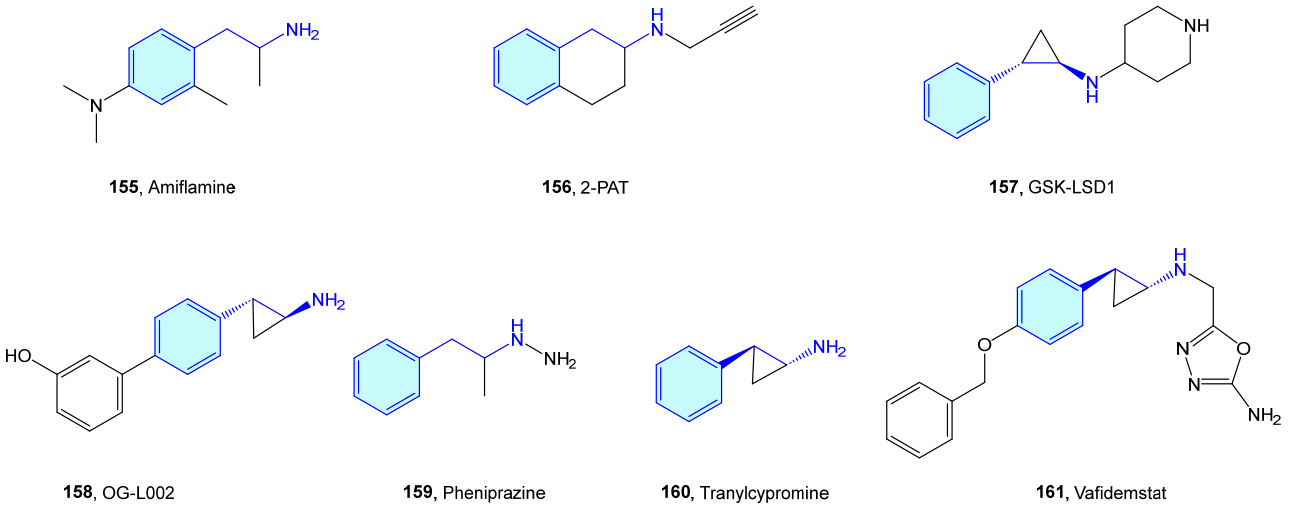


Figure 19. 2-Phenethylamine MAO medicinal chemistry leads.

Table 7. MAO medicinal chemistry leads.

Molecule	Name	Primary Targets	Secondary Targets	References
155	Amiflamine	MAO A		[216]
156	2-PAT	MAO A, B		[217]
157	GSK-LSD1	MAO	Lysine specific demethylase 1 (LSD1)	[218]
158	OG-L002	MAO A, B		[219]
159	Pheniprazine	MAO		[220]
160	Tranylcypromine	MAO		[221]
161	Vafidemstat	MAO B	Lysine specific demethylase 1 (LSD1)	[222]

2.14. Opioid Receptors

Opioid receptors are a class of GPCR proteins consisting of three receptor types, mainly μ-, δ-, and κ- types, with a variety of functional roles in the nervous system, such as pain signaling, growth, respiration, and immunological response [223,224]. Opioid ligands modulate neuronal inhibition and ultimately analgesia. Relevant side effects are well known, such as constipation or drug dependence/abuse.

Takahashi et al. [225–230] derived a small series of flexible 2-phenethylamines with analgesic activities, with moderate potency effects when compared with pentazocine or morphine (Figure 20a). Manchado et al. [231] developed quick asymmetric routes furnishing this type of derivative. Spetea et al. [232] developed selective diphenethylamine-based tertiary amines as κ-opioid receptors with 100-fold and 1000-fold selectivity difference compared with its congeners (Figure 20b).

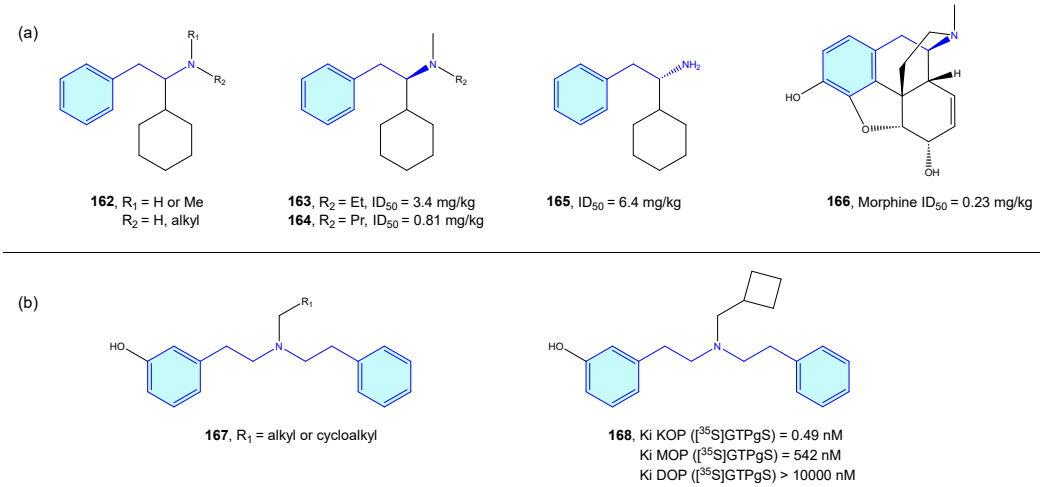


Figure 20. 2-Phenethylamines with 5-HT receptor activity.

2.15. Peroxisome Proliferator-Activated (PPAR) Receptors

Peroxisome proliferator-activated (PPAR) receptors are peroxisome receptors and subcellular organelles performing several tasks related to cholesterol and fatty acid metabolism. Three members, named PPAR-α, PPAR-δ, and PPAR-γ, form this family, with different levels of expression and functionalities in diverse tissues, from energy storage in endothelial and vascular smooth muscle cells (type γ) to energy expenditure across all bodies (type δ). Several agents have been developed in relation to PPAR to address obesity, inflammation or neurodegenerative disorders (Figure 21, Table 8) [233,234].

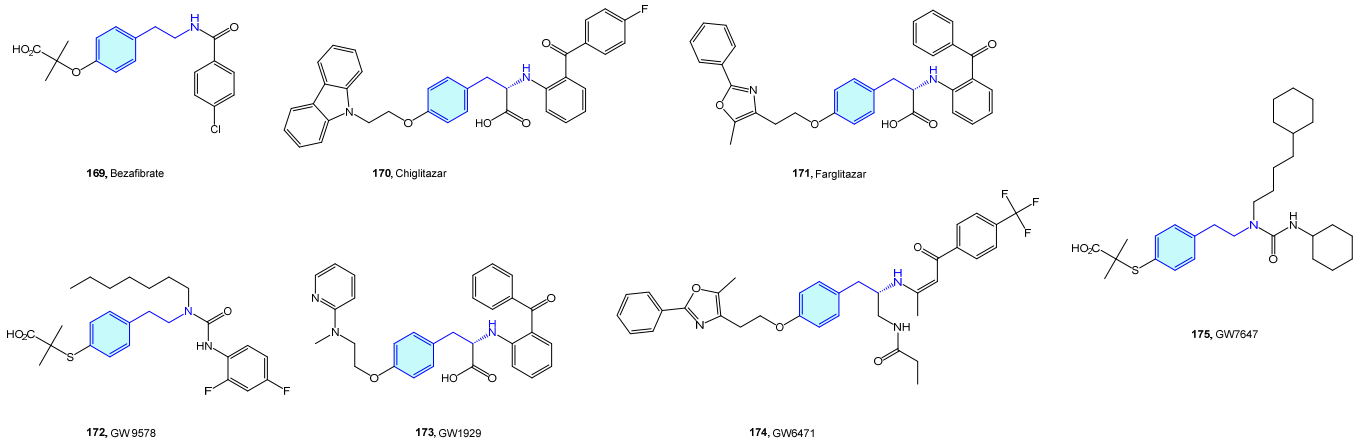


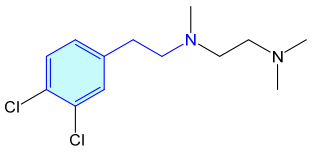
Figure 21. 2-Phenethylamine PPAR medicinal chemistry leads.

Table 8. PPAR medicinal chemistry leads.

Molecule	Name	Primary Targets	Secondary Targets	References
169	Bezafibrate	PPAR		[235,236]
170	Chiglitazar	PPAR		[237]
171	Farglitazar	PPAR-γ		[238]
172	GW 9578	PPAR-α		[239]
173	GW1929	PPAR-γ		[240]
174	GW6471	PPAR-α		[241]
175	GW7647	PPAR-α		[242]

2.16. Sigma Receptors

Initially described as opioid receptors, sigma receptors conform their own family, unrelated to other receptors. Both members σ1R and σ2R are primarily found at the endoplasmic reticulum, and participate in diverse conditions, such as cancer, pain, neurodegenerative diseases or depression [243]. BD-1047 (Figure 22) is an open-chain, flexible 2-phenethylamine acting as antagonist of σ1R [244].

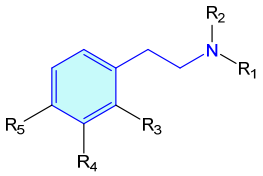


176, BD-1047

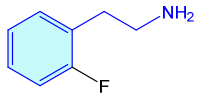
Figure 22. A 2-Phenethylamine Sigma-1 receptor hit.

2.17. Trace Amine-Associated Receptors (TAAR)

Relatively recently discovered, trace amine-associated receptors (TAAR) are a GPCR family composed of nine members (TAAR1 to 9) with prospective therapeutic applications in the field of schizophrenia and metabolic disorders [245]. Lewin et al. [246] carried out SAR explorations with simple 2-phenethylamines to envisage improved pharmacological hits (Figure 23).



177, R_1=H or Me
R_2=H or Me
R_3=H, F, Cl or Br
R_4=H, F, Cl or Br
R_5=H, F, Cl or Br



178, EC_{50} hTAAR1=65 nM

Figure 23. 2-Phenethylamines with hTAAR1 bioactivity.

3. Methods

All described compounds, targets and activities were retrieved using "2-phenethylamine" as title or keyword term in the chemical databases SciFinder [247] and Scopus [248]. Additionally, a SciFinder and Scopus structure search, with the scope described early in this review (Figure 2), was employed.

4. Conclusions

This review represents a concise, central summary of relevant 2-phenethylamine-based leads and research hits, which spans receptors and their corresponding therapeutic indications. This report serves as a guide to researchers interested in medicinal chemistry to identify suitable ligand–target associations displaying the aforementioned motif, as well as help to identify prospective targets of brand-new molecules with the 2-phenethylamine core embedded.

Future directions will include both a complementary report covering synthetic strategies to access 2-phenethylamine derivatives and a second, satellite review of 2-heteroarylethylamines in medicinal chemistry.

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