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Development of Therapeutics That Induce Mitochondrial Biogenesis for the Treatment of Acute and Chronic Degenerative Diseases

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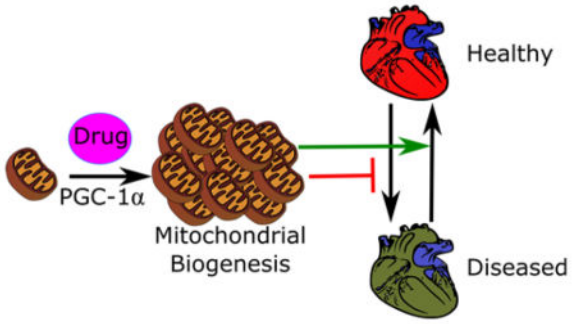
Abstract

Mitochondria have various roles in cellular metabolism and homeostasis. Because mitochondrial dysfunction is associated with many acute and chronic degenerative diseases, mitochondrial biogenesis (MB) is a therapeutic target for treating such diseases. Here, we review the role of mitochondrial dysfunction in acute and chronic degenerative diseases and the cellular signaling pathways by which MB is induced. We then review existing work describing the development and application of drugs that induce MB *in vitro* and *in vivo*. In particular, we discuss natural products and modulators of transcription factors, kinases, cyclic nucleotides, and G protein-coupled receptors.

Graphical Abstract



Keywords

Mitochondrial biogenesis; mitochondria; PGC-1α; degenerative disease; sirtuin 1; PPARγ; G protein-coupled receptor; cGMP; cAMP; AMPK; ERK1/2; beta-2 adrenergic receptor; 5-hydroxytryptamine

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Mitochondria, the metabolic powerhouses of the cell, have diverse functions including ATP production, biomolecule synthesis, ionic homeostasis and antioxidant defense. As cells age and accumulate damage, mitochondria less readily meet ATP demands, thereby diminishing the cells' functions and regenerative capacity. After toxicant exposure or cell stress, mitochondria can be damaged, and increased free radical production may be followed by persistent mitochondrial dysfunction. Diminished ATP and increased free radicals propagate injury and subsequent tissue and organ dysfunction (Figure 1). Indeed, many acute and chronic degenerative diseases across multiple organ systems are associated with a degree of mitochondrial dysfunction, often with suppression of electron transport chain proteins and activities.[1–4]

Because many diseases are associated with mitochondrial dysfunction, research is underway to develop therapeutics that target mitochondria to prevent disease progression. For example, numerous compounds have been studied that prevent cell death by interfering with the formation of the mitochondrial permeability transition pore (MPTP), reducing oxidative stress using mitochondrial-targeted antioxidants, or modulating mitochondrial dynamics by inhibiting mitochondrial fission or promoting mitochondrial networking.[5] However, whereas many of these strategies are effective for preventing injury in animal models, they target events that occur early in cellular dysfunction and therefore may be less efficacious for facilitating recovery after an insult. To address this problem, some groups have investigated compounds that induce mitochondrial biogenesis (MB), or the generation of new, functional mitochondria within cells to promote repair and regeneration.[1]

This perspective will describe the role of the peroxisomal proliferation activated receptor coactivator-1α (PGC-1α) in MB and the role of mitochondrial dysfunction in acute and chronic degenerative diseases. We will also describe existing compounds that induce MB, signaling pathways responsible for their effects, and finally, potential utility of these compounds for treating human acute and chronic degenerative diseases for which there are presently limited therapeutic options.

Regulation of MB

MB requires the activation of a complex transcriptional and translational program integrating both nuclear and mitochondrial genomes.[6–7] Nuclear encoded mitochondrial genes, such as the mitochondrial transcription factors and the mitochondrial DNA (mtDNA) replication complex, facilitate transcription, replication, and proofreading of the mitochondrial genome.[6] Integrity of mtDNA replication is particularly important in aging and chronic degenerative diseases, where deleterious mtDNA mutations and deletions can lead to dysfunctional mitochondria.[8–9] For example, the nuclear transcription factors estrogen receptor (ER) and estrogen related receptor-α (ERRα), nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2), peroxisome proliferator-activated receptor (PPAR) family of transcription factors, thyroid hormone receptor (TR), cAMP-responsive element binding protein (CREB), and yin yang-1 (YY-1)[10] increase expression of genes of the electron transport chain, mitochondrial transporters, antioxidant proteins, and other mitochondrial transcription factors. However, these transcription factors are pleotropic with effects on genes unrelated to MB. Selective induction of MB is typically regulated through

transcriptional co-activation proteins such as the PGC-1 family (Figure 2). PGC-1 proteins activate transcription and translation of mitochondrial genes and increase energy production in healthy cells, whereas in injured cells PGC-1 activation often normalizes overall mitochondrial function as measured by ATP production, mitochondrial membrane potential, and reactive oxygen species (ROS) generation.[11–13]

The PGC-1 family, composed of PGC-1α, PGC-1β, and PGC-1 related coactivator (PRC), facilitate the formation of complexes capable of activating the transcription of nuclear genes related to MB.[14] PRC is thought to play a role in redox-sensitive inflammatory responses and MB during cellular proliferation, whereas PGC-1β appears to contribute more to maintenance of mitochondrial mass. In contrast, PGC-1α has been shown to drive MB in response to various environmental cues. Because PGC-1α tends to be the most inducible and responsive member of the PGC-1 family, its activation has emerged as a key therapeutic strategy for MB induction. However, it is important to note that PGC-1α-independent mechanisms of MB have been reported.[15–18] Such mechanisms include compensatory activation of PGC-1β or PRC and direct activation of transcription factors that induce mitochondrial genes.

Through activation of PGC-1α and its associated transcription factors, multiple signaling pathways have been shown to regulate MB. PGC-1α can be directly activated by silent mating type information regulation 2 homolog 1 (SIRT1)-mediated deacetylation,[19] methylation by protein arginine methyltransferase 1 (PRMT1),[20] or phosphorylation by kinases such as p38,[21] protein kinase A (PKA),[22] and AMP-dependent kinase (AMPK).[23] Additionally, PGC-1α and other transcription factors associated with MB can be activated by NO/cGMP and calcium-dependent signaling.[24] In summary, these diverse signaling inputs allow exquisite control of mitochondrial homeostasis to meet cellular energy demands and to maintain proper cellular function.

The Importance of MB in Disease

Because mitochondria regulate many processes within cells, mitochondrial dysfunction or disruptions in mitochondrial homeostasis lead to severe deficits in cellular functions.[1–2] Injury to mitochondria following ischemia reperfusion injury, toxicant exposure, or severe inflammatory response leads to deficient ATP and disruption of ion homeostasis. Additionally, mitochondrial stress increases superoxide anion production and which causes damage to proteins and lipid membranes. These mitochondrial derangements disrupt cellular repair, proliferation, and differentiation status and increase cell death.

Mitochondrial dysfunction has been implicated in numerous acute and degenerative disease processes, such as myocardial infarction,[25] stroke,[26] and acute kidney injury (AKI).[27] These disease states may be attributed in part to the role of mitochondria and oxidative metabolism in cellular differentiation as observed in neurons,[28] myocytes,[29] and immune cells.[30] Chronic conditions causally linked to such acute insults (such as chronic kidney disease and heart failure) are also characterized by persistent mitochondrial dysfunction,[31–32] suggesting that the lack of mitochondrial recovery after an acute injury can also lead to chronic degenerative disease. For example, deficits in PGC-1 family proteins have been associated

with the development heart failure in both animal models and human patients.[33–34] Interestingly, mice that overexpress PGC-1 proteins also exhibit abnormal cardiac function,[35] indicating that a tight control over mitochondrial content is necessary for normal organ function. Similarly, animal models of chronic kidney disease demonstrate diminished renal mitochondrial function,[36] and animal models of mitochondrial dysfunction demonstrate chronic kidney disease.[37] Finally, human patients with chronic kidney disease have decreased mtDNA in skeletal muscle and peripheral mononuclear blood cells,[36] suggesting that mitochondrial defects in a single organ can lead to global mitochondrial dysfunction.

Other chronic diseases also have been associated with disruption of mitochondrial homeostasis. Type II diabetes mellitus and metabolic syndrome are characterized by mitochondrial dysfunction associated with insulin resistance.[38] In metabolic syndrome, pancreatic beta cells exhibit increases in UCP2, decreased ATP synthesis, and increased levels of ROS.[39–40] Additionally, reductions in complex IV of the electron transport chain have been associated with the development of diabetes in obese mice and patients.[41] Furthermore, epigenetic silencing of electron transport chain genes and mtDNA,[42–44] along with genes associated with MB such as PGC-1α and TFAM,[45–46] lead to decreased mitochondrial content and a greater proportion of dysfunctional mitochondria, thereby causing sustained deficiencies in cellular respiration.

Multiple neurodegenerative diseases also have been associated with decreased mitochondrial mass, altered mitochondrial dynamics, and dysregulation of MB. Parkinson disease has been linked to a panoply of mutations that lead to mitochondrial dysfunction. Defects in PINK1 and Parkin disrupt clearance of damaged mitochondria, permitting accumulation of oxidative damage in dopaminergic neurons and suppression of PGC-1α and decreased cellular respiration.[47–50] Mutations in DJ-1 increase ROS while decreasing anti-oxidant defenses,[51] leading to decreases in mitochondrial membrane potential, poor mitochondrial quality control, and altered mitochondrial morphology. Similarly, mutations in mTDNA,[52–55] TFAM,[56] mortalin,[57] and α-synuclein[58] lead to increased susceptibility to ROS and subsequent mitochondrial dysfunction. Additionally, huntingtin mutants associated with Huntington's disease bind to the PGC-1α promoter and prevent its transcription and the transcription of other nuclear transcription factors associated with MB, including CREB.[59–60] Huntingtin mutations also cause impaired mitochondrial calcium handling,[61] reduced respiration,[62–63] and disrupted mitochondrial dynamics.[64–65] Finally, genetic and toxicant-induced models of Alzheimer disease and samples from human patients confirm the suppression of mitochondrial proteins and the MB transcriptome in Alzheimer disease,[66–67] along with mtDNA damage and disruptions in mitophagy and mitochondrial morphology.[68–70] Thus, compounds that induce MB may alleviate cellular dysfunction associated with acute and chronic degenerative diseases and promote organ repair and recovery that leads to improvements in patient health.[71]

Natural Products

Because mitochondria and oxidative stress are associated with aging, populations with longer lifespans have been studied to identify a potential means for preventing deleterious

effects of aging. These studies have identified multiple chemicals capable of inducing MB (Figure 3), and these compounds have shown efficacy in multiple disease models by modulation of multiple signaling axes. Nonetheless, their therapeutic applicability in many cases is limited by poor absorption and low oral bioavailability.

Resveratrol

A widely studied nutritional activator of MB is the polyphenol resveratrol (**1**).[72] Compound **1** has been shown to induce MB by activating SIRT1 directly or indirectly through AMPK.[73] SIRT1 in turn deacetylates PGC-1α and allows it to exert its transcriptional effects. In particular, **1** activates AMPK by inhibiting components of the electron transport chain such as complex I and F1/F0 ATPase.[74–75] Docking studies with complex I suggest that resveratrol binds to the NAD^+ binding site of complex I through pi stacking interactions with its aromatic components and by hydrogen bond interactions through its hydroxyl group.[75] When binding F1/F0 ATPase, **1** prevents rotation of the ATP synthase complex through a network of hydrophilic and hydrophobic interactions.[74] Compound **1** can also directly activate PPARα via interactions with the 4′-hydroxyl group.[76] It also activates PPARγ by interactions between R280 and its 4′-hydroxyl group near the opening of the ligand binding pocket as well as Van der Waals interactions with F264, H266, and R288.[77] Together, protein-ligand interactions trigger signals that induce MB.

In models of diabetic cardiovascular disease, **1** induces MB and restores vascular reactivity *in vitro* and *in vivo*.[78] In cellular and animal models of neuronal radiation damage,[79] Alzheimer disease,[80] Parkinson disease,[81] and Huntington's disease,[82] **1** normalizes mitochondrial function and rescue cellular viability and function. Compound **1** also attenuates oxidative stress in fibroblasts from patients with Complex I deficiency by increasing SOD2 in a SIRT3-dependent manner.[83] Human clinical trials using **1** demonstrated improved lipid profiles, antioxidant defenses, and vascular reactivity in diabetic and obese subjects;[84–89] however, there are conflicting data regarding the effect of **1** on insulin sensitivity,[84, 88, 90] and **1** had no effect in non-obese subjects.[91]

Epicatechins

(−)-Epicatechin (**2**),[92] primarily found in cocoa, has been shown to induce MB through multiple signaling pathways, including Akt-dependent nitric oxide (NO) generation,[93–94] CREB phosphorylation, and δ-opioid receptor activation.[95] The epicatechin epigallocatechin-3-gallate (**3**),[96] promotes cAMP-dependent signaling to increase SIRT1 and PGC-1α.[97] Although there are limited data regarding the structural basis for **2** activation of cAMP-dependent signaling, Akt-dependent signaling is mediated by the 3″-, 3′-, and 4′-hydroxyl groups.[98] Following oxygen-glucose deprivation, neuronal viability is rescued by **2** via the Akt-eNOS pathway and CREB activation.[94] In a mouse model of diabetes, **2** reduces oxidative stress in cardiac tissue by inducing MB.[99] Similarly, in mouse models of cardiovascular disease, **2** acts through the δ-opioid receptor to prevent mitochondrial swelling and to increase respiration;[95, 100] it can also decrease cardiac ischemia-reperfusion injury through NO and cGMP generation. Even in aged mice, epicatechin increases expression of mitochondrial and antioxidant proteins.[101] Through its cAMP-dependent activation of SIRT1 and PGC-1α, **3** enhances MB in Down's syndrome patient fibroblasts

and enhances mitochondrial calcium handling by modulating mitochondrial tethering to the rough endoplasmic reticulum.[97] Compound **2** also induces MB in human diabetic patients to improve skeletal muscle metabolism.[102]

Curcumin

Curcumin (**4**),[103] a diarylheptanoid found in turmeric, has shown promise for promoting MB and improved function in several disease models. By activating multiple signaling molecules, including p38, PKA, AMPK, SIRT1, and NRF2, **4** can induce MB and protect cells against injury.[104–106] The *o*-methoxy group in compound **4** is important for increasing p38-mediated HO-1 expression, which confers cytoprotection in endothelial cells.[104] The unsubstituted 5′- and 5″-positions and its olefinic system allow **4** to inhibit NF-κB and activate the NRF2 pathway.[107] In cellular models of metabolic syndrome, **4** rescues hepatic mtDNA, NRF1, and TFAM and reduces inflammation and NFκB activity.[108] In white adipose tissue, **4** increases browning and markers of MB via increases in norepinephrine and β_3 adrenergic receptor expression.[109] Pretreatment with **4** improves mitochondrial membrane potential, oxygen consumption rates, and survival in cellular models of Parkinson disease.[110] Compound **4** attenuates neuronal death and reduces infarct size following cerebral ischemia-reperfusion injury with concomitant increases in mitochondria and improvements in neurological function.[111] In animal models of metabolic syndrome, **4** restores hepatocyte mitochondrial function to reduce hepatosteatosis.[112] Following gentamicin-induced nephrotoxicity, **4** can increase PGC-1α and NRF2, thereby elevating mitochondrial protein expression and improving mitochondrial structure.[105] In rat skeletal muscle, **4** increases mtDNA content and mitochondrial protein expression following endurance training via PKA-dependent activation of AMPK, SIRT1, and PGC-1α.[106]

Phytoestrogens

Phytoestrogens, such as genistein (**5**),[113] daidzein (**6**),[114] pyrroloquinoline quinone(**7**),[115] coumestrol (**8**),[116] and equol (**9**),[117] are natural products often found in legumes such as soybeans. They have been shown to exert their effects in part by modulation of estrogen receptors and partly via activation of SIRT1.[118–120] 5-hydroxyl groups prevent SIRT1 activation, whereas 7-hydroxyl groups are necessary for SIRT1 activation. Similarly, a 3-phenyl group appears to drive increased SIRT1 expression.[120] Compounds **5**–**8** have been shown to induce MB *in vitro*.[120–122] Additionally, through their biogenic effects, **5** and **6** rescued cultured renal proximal tubule cells from oxidant injury.[120] *In vivo*, **5** and **9** induce MB to improve bioenergetics in ovariectomized mice.[123–124] Both **5** and **6** increase mitochondrial markers with associated improvements in insulin sensitivity and glucose metabolism in diabetic mice.[125–126] Compound **5** also reduces the size of a myocardial infarct in mice by rescuing mitochondrial function.[118] Finally, **7** stimulates MB in both wild type mice and transgenic models of Alzheimer disease;[127–128] in the latter model, improvements in synaptosomal bioenergetics are correlated with cognitive improvement.

Transcription Factor Modulators

Although natural products have been useful in identifying biological targets for MB, their poor pharmacokinetic parameters limit their therapeutic potential. Modulators of the

transcriptional machinery responsible for MB can potently and efficaciously induce MB; however, because they activate transcriptional programs other than MB, these compounds can have severe side effects that limit their clinical utility. *Thiazolidinediones*

The thiazolidinediones (TZDs) are a class of hypoglycemic drugs used to treat diabetes mellitus that includes rosiglitazone (**10**),[129] pioglitazone (**11**),[130] troglitazone (**12**),[131] and ciglitazone (**13**) (Figure 4).[132] Classically, they act as agonists of the transcription factor peroxisome PPARγ, leading to increased insulin sensitivity. These effects are primarily mediated by the acidic head group, which engages in necessary hydrogen bonding interactions with PPARγ to stabilize its active conformation.[133–134] More recently, acute PPARγ-independent effects of TZDs have been discovered, including inhibition of the electron transport chain, which reduces the ATP/AMP ratio, leading to AMPK activation and subsequent MB.[135–137] TZDs have also been shown to exert anti-inflammatory effects and to upregulate the mitochondrial stress-response, leading to increased anti-oxidant defenses.[135] Although they upregulate multiple signaling pathways, the capacity of TZDs to sensitize tissues to the effects of insulin has been shown to correlate with increased expression of mitochondrial proteins, suggesting that induction of MB may be central to the clinical efficacy of these drugs.[138]

In vitro, **10**–**13** increase cell viability and improve neuronal function in models of ischemic injury,[139] Alzheimer disease,[140] Huntington's disease,[141–142] and multiple sclerosis.[143] Similarly, in animal models of neurodegenerative diseases, **10** and **11** improve both cellular and behavioral markers of neurological function.[144–145] In animal models of cardiac disease, **10** can rescue cardiac mitochondrial function following septic injury;[146] however, other studies indicate that **10** increases cardiac ROS and can be arrhythmogenic.[147–148] In models of metabolic syndrome, **10**–**13** induce MB in adipose tissue,[15, 149] pancreatic beta cells,[150] and skeletal muscle[137, 151] to enhance insulin sensitivity. In humans, **11** induces MB in subcutaneous adipose tissue,[152] and **10** can do so in skeletal muscle.[153]

Estrogens

To understand the underlying processes responsible for sex-dependent differences in lifespan and oxidative stress, multiple groups reported that estrogens can be protective in various tissues. Furthermore, reduced levels of estrogens, such as in ovariectomized mice, lead to increased ROS production.[154] Estrogens (Figure 5) can bind to the transcription factors estrogen receptor α (ERα) and estrogen receptor β (ERβ) to directly influence gene expression. 17β-Estradiol (**14**)[155] and progesterone (**15**)[156] are the principle biologically active estrogens. **14** and **15** interact with nuclear estrogen receptors by hydrogen bonding interactions between the ligands' hydroxyl groups and the receptors' polar residues and by hydrophobic interactions with the receptors' binding pockets.[157] ERα-selectivity, such as by the selective ligand 4,4′,4″-(4-propyl-[1*H*]-pyrazole-1,3,5-triyl)*tris*phenol (**16**),[158] is mediated by steric bulk to interact with a residue found in ERα but not ERβ.[158] Selectivity for ERβ by diarylpropionitrile (**17**)[159] is mediated by phenolic groups, while its efficacy is improved by its nitrile group.[159] Recently, it has also been shown that estrogens activate plasma membrane-bound estrogen receptors such as the G protein-coupled estrogen receptor (GPER). The GPER-selective ligand G-1(**18**)[160] is structurally similar to **14** but is unable to

form hydrogen bonds in the nuclear estrogen receptors;[160] however, **18**'s acetyl group and pseudosymmetry allows engagement of specific residues of the GPER to stabilize the active conformation.[161–162]

Compound **14** has been shown to induce MB in immortalized cell lines and in a cellular model of Leber hereditary optic neuropathy, a mitochondrial disease. [163–164] In animal models, **14** normalizes ROS production, increases antioxidant defenses, and enhances respiratory capacity in the heart and brain.[154, 165] Furthermore, **15** and synthetic estrogen receptor agonists such as **16** and **17** have been shown to enhance respiratory capacity in the brain and promote clearance of lipid peroxidation products.[166] Of note, the use of receptor subtype selective agonists suggests that ERα and ERβ differentially regulate the expression of electron transport chain proteins. Additionally, at least a portion of the cardioprotective effects of estrogen are mediated through the GPER, as shown by stimulation with the GPER-selective agonist **18**.[154] Despite the clear protective potential of estrogens, their proliferative and endocrine effects limit their use as a long-term therapy for chronic degenerative diseases. However, the development of selective ER and GPER ligands that drive specific signaling and transcriptional programs may improve the utility of such therapeutics.

SIRT1 activators

The identification of SIRT1 as a common target of natural product-induced increases in PGC-1α led to the development of multiple SIRT1 activators, such as SRT1720 (**19**),[167] SRT1460 (**20**),[167] SRT2183 (**21**),[167] and SRT2104 (**22**) (Figure 6).[168] In the initial synthesis of SIRT1 activators,[169] the basic methylamino ring at C-3 of the imidazothiazole ring of **19** and **20** enhanced water solubility, while derivatization of the amide group (such as with the 2-quinoxaline group of **19**) improved potency and efficacy. Interestingly, both **19** and **20** share a methylamino ring and have greater efficacy, whereas **19** and **21** have a 2-quinoxaline group and more potency,[167] suggesting that the two groups may play distinct roles in the pharmacodynamic qualities of these compounds. The direct mechanisms of action for the sirtuin class have been controversial. Assays with isolated fluorescent peptides were used for optimization, but direct proteomic assays indicate that **19–21** do not directly activate SIRT1 and, rather, act promiscuously to activate or inhibit numerous targets;[170] however, other work has shown that these compounds directly activate SIRT1 by binding to amino acid E230.[171]

Due to numerous SIRT1 targets, these activators can affect various cellular processes, including inflammation, lysosomal trafficking, and metabolism. Among its targets, SIRT1 deacetylates PGC-1α, facilitating nuclear import of and transcriptional regulation by PGC-1α, leading to MB. In models of type II diabetes mellitus, SIRT1 activators have been shown to improve lifespan, normalize pancreatic morphology, improve insulin, glucose, and fatty acid metabolism and increase mitochondrial markers;[167, 172–174] however, other studies have shown a lack of efficacy in diabetic mice, calling into question the beneficial effects of these compounds.[170] With respect to neurodegenerative diseases, SIRT1 activators prevent neurodegeneration and restore MB in animal models of Huntington's disease and multiple sclerosis.[175–176] SIRT1 activation has shown promise in renal disease, restoring renal function after AKI and preventing renal medullary damage in obstructive

nephropathy.[177–179] In models of cardiovascular disease, **19** reduces the size of myocardial infarction and preserves contractility,[180] as well as reducing ROS and improving contractility in mice with enhanced ALDH2 activity.[181] Compound **19** also preserves endothelial function in aged mice.[182] Even in healthy animals, **19** and other SIRT1 activators have been shown to extend lifespan and "healthspan" by preventing the development of age-associated diseases in multiple organ systems.[183] In human trials, **22** improved lipid profiles in diabetic patients but did not affect plasma glucose or insulin, likely due to large pharmacokinetic variability.[184] Additionally, **22** reduces cholesterol, LDL, and triglycerides in otherwise healthy smokers,[185] suggesting that SIRT1 activation is important to the human healthspan.

Kinase Modulators

Kinases either phosphorylate target proteins or function as scaffolds to co-localize other kinases and targets to regulate cellular signaling. Phosphorylation of specific targets can either activate or inhibit cellular signaling pathways in response to environmental cues. Because they are central signaling molecules, kinases are attractive therapeutic targets. In particular, activators of kinases that induce MB, such as AMPK, can be useful in multiple diseases. Unfortunately, inhibitors are easier to develop, and most kinase modulators are inhibitors. However, inhibitors of kinases that negatively regulate MB, such as extracellular signal-regulated kinases 1/2 (ERK1/2), also provide promise as therapeutics.

AMPK

AMPK is an energy sensing kinase involved in the modulation of metabolism through the cellular AMP/ATP ratio. AMPK activation is increased during exercise and induces MB, and it is decreased with aging and during multiple chronic degenerative diseases.[186] AMPK activation has been shown to be an upstream regulator of sirtuins and therefore PGC-1α.[187] Furthermore, pharmacologic activation of AMPK has been observed with multiple natural products that induce MB. Activators of AMPK (Figure 7), including the indirect activators AICAR (**23**),[188] metformin (**24**),[189] phenformin (**25**),[190] R419 (**26**),[191] and C24 (**27**),[192] and the direct activator A769662 (**28**),[193] have been developed and induce MB in multiple cell lines. Additionally, **23** has been shown to enhance proliferation and increase ATP in models of complex I deficiency and MELAS.[194–195] Compound **23** is biotransformed via phosphorylation within the cell and acts as an AMP mimetic to activate AMPK and other AMP-dependent processes.[188] The biguanides **24** and **25** activate AMPK in a LKB1-dependent manner and through inhibition of complex I;[191, 196] by inhibiting the electron transport chain, the AMP/ATP ratio is increased, leading to AMPK activation. Compound **26** also indirectly activates AMPK via complex I inhibition,[191] and **28** activates AMPK by binding to an allosteric site between the alpha and beta subunits of AMPK. **28** both allosterically activates and prevents Thr172 dephosphorylation.[197]

In models of diabetes and metabolic syndrome, **23** mimics high intensity exercise in skeletal muscle with accompanying increases in SIRT1 activation and PGC-1α activity. These improvements in MB decrease oxidative stress in both renal and endothelial cells,[198–200] preventing common comorbidities such as diabetic nephropathy and poor wound healing.

Compound **23** can also improve pancreatic morphology via AMPK activation to enhance insulin sensitivity and GLUT4 expression,[201] thereby decreasing plasma glucose. In hepatic cells, **27** reduces lipid biosynthesis to prevent lipid accumulation and preserve hepatic function.[192] In humans with gestational or type II diabetes, **23** and **25** prevents insulin resistance in multiple tissues.[202–204] In the heart, **23** reduces oxidative stress and improves contractility,[181] and it is associated with improvements in insulin sensitivity in diabetic mice as well as reductions in cold ischemic injury in mouse models of heart transplant.[205]

AMPK activators have also shown promise for treating neurodegenerative diseases. Neuronal activity has been shown to drive PGC-1α and NRF-1 expression in an AMPK-dependent manner,[206] leading to MB, and pharmacologic activation of AMPK has been shown to mimic these effects. Compound **23** has also been shown to impact neuronal development by promoting mitochondrial accumulation at axonal branch points, thereby facilitating branch formation and retention.[207] In models of Alzheimer disease, **23** ameliorated mitochondrial dysfunction and prevented neurotoxicity and tau hyperphosphorylation.[208–209] Compound **23** decreased amyloid beta, a protein implicated in Alzheimer disease, in a PPARγ dependent manner.[210] Compound **23** has also been shown to decrease inflammation in models of multiple sclerosis, attenuating pathological and behavioral changes. Furthermore, in models of ischemic brain injury, **23** diminishes ischemic neuronal damage.[211]

ERK1/2

Another means of inducing MB is the inhibition of negative regulators of MB, such as ERK1/2. Following its activation by MEK1/2, ERK1/2 regulates a variety of cellular processes, including differentiation, apoptosis, survival, proliferation, and motility.[212] Inhibition of MEK by U0126 (**29**)[213] or trametinib (**30**)[214] leads to a rapid suppression of ERK1/2 phosphorylation (Figure 7). Compound **29** can exist in the (*Z,Z*) or (*Z,E*) isomer; however, the (*Z,Z*) isomer provides better MEK inhibition, as does the presence of electron donating amino groups at *o*-positions of its phenyl groups.[213] The iodo- and cyclopropyl groups of Compound **30** improve potency for cancer cell growth inhibitory activity over its lead compound JTP-70902 **(31)**[214], while its methyl groups improve stability and its acetamide group improves solubility.[214] ERK1/2 has been shown to suppress PGC-1α in melanoma cells.[215] Additionally, in models of Parkinson disease ERK1/2 activation leads to phosphorylation of TFAM, impairing its ability to bind to mitochondrial DNA.[216] MEK1/2 inhibitors, such as **29** and **30**, have been developed for cancer chemotherapy. *In vitro* models of renal oxidative stress indicate that ERK1/2 is a mediator of oxidative damage in proximal tubule cells, and that its inhibition by **29** prevents oxidative damage.[217] Our laboratory has shown that ERK1/2 activation increases after AKI and that pre-treatment with the MEK1/2 inhibitor **30** rescues mitochondrial function and restores renal function in a mouse model of AKI.[218] These data indicate that inhibition of suppressors of MB can induce MB and restore organ function following injury.

Cyclic Nucleotide Modulators

The cyclic nucleotides cGMP and cAMP are cellular second messengers that are generated in response to extracellular signals. They activate downstream kinases or are hydrolyzed by phosphodiesterases (PDE). NO increases cGMP synthesis by binding to a heme group on soluble guanylate cyclase (sGC), while cAMP is increased through activation of adenylate cyclase by the stimulatory G-protein $G\alpha_s$. Because cyclic nucleotide generation is disrupted in multiple pathological states, cyclic nucleotide modulators are attractive targeted therapies for the induction of MB in various diseases.

NO-cGMP-PKG Axis

The NO-cGMP-PKG pathway can be modulated by: 1) nitric oxide (NO) donors, such as sodium nitroprusside (**32**), (±)S-nitroso-N-acetylpenicillamine (SNAP, **33**),[219] diethylamine NONOate (DEA-NONOate, **34**),[220] and diethylenetriamine-NONOate (DETA-NONOate, **35**)[220] which increase cellular NO (Figure 8); 2) sGC stimulators and activators, such as cinaciguat (**36**),[221] riociguat (**37**),[222] and BAY 41-2272 (**38**)[223] which directly increase cGMP production (Figure 8); and 3) phosphodiesterase (PDE) inhibitors, such as zaprinast (**39**),[224] sildenafil (**40**),[225] udenafil (**41**),[226] tadalafil (**42**),[227] and vardenafil (**43**)[228] which increase cGMP by preventing its hydrolysis (Figure 9). Clinically, these compounds are used to induce vasodilation to treat hypertension or erectile dysfunction. Activation of this pathway has been shown to increase PGC-1α and stimulate MB both through the activation of PKG and nitrosylation of transcription factors to increase their binding to the PGC-1α promoter.[229–230]

As their name implies, all NO donors have a group, usually a nitrate or a furoxan group, that can be liberated to form NO. Because the NO donating group is small, NO donors can be “fine-tuned” for multiple clinical uses and to slow the rate of NO release.[231–232] However, because NO generation causes such a dramatic drop in blood pressure, NO donors are of limited clinical use. However, these compounds readily confirm the importance of NO for preventing metabolic derangements and cell death, particularly in skeletal muscle. In hypoxia, dietary nitrate (a natural NO donor) prevents PGC-1α suppression, leading to increases in fatty acid oxidation and respiration. Even under normoxic conditions, nitrate stimulates MB in a cGMP/PKG-dependent manner.[233] Compound **33** has also been shown to induce MB in myoblasts and reduce the effects of caspase-dependent and –independent apoptotic molecules,[234] and **34** also improves synaptic conduction in models of Alzheimer disease in a cGMP-dependent manner.[235]

sGC activators and stimulators increase the activity of sGC in the absence of NO. Stimulators such as **37** and **38** increase sGC activity with a non-oxidized heme group, whereas activators increase sGC activity even if the heme prosthetic group is oxidized. Both classes of compounds have been approved for clinical use to treat pulmonary hypertension. Compound **38** was optimized for vasorelaxation through the addition of a 2-fluoro-phenyl group, a pyrazolo[3,4-*b*]pyridine ring, and a cyclopropyl group.[223] Compound **37** was optimized to increase oral bioavailability and half-life, and to reduce clearance via amino and N-methylcarbamate substitutions on the pyrimidine group.[222] On the other hand, sGC activators have shown greater utility beyond blood pressure control, likely due to their

capacity to activate sGC even under high oxidative stress. Compound **36** was identified using a high-throughput screen and was confirmed to displace the heme of sGC by interacting with its YXSXR motif through carboxylic acid moieties.[236] In pre-clinical studies, compounds **36**–**38** improve cardiac, renal, and neurological function across multiple disease models including ischemia reperfusion injury, sepsis, diabetes, and Alzheimer disease.[237–241] However, despite the efficacy of cGMP in promoting MB, few studies have examined the role of MB in these functional improvements. Compound **36** protects against myocardial infarction by increasing H_2S, a known inducer of MB,[242] suggesting that further investigation is warranted into the role of MB in these compounds' protective effects.

Inhibition of cGMP-selective PDEs prevents cGMP hydrolysis, promoting its accumulation in the cell and facilitating stimulation of MB. Compound **40** was designed from **39** by mimicking the guanosine dipole moment, adding an ethoxy group to improve potency, and adding a piperazine sulfonamide to improve solubility, selectivity, and potency.[243] However, both **40** and **41** discriminate poorly between PDE5 and PDE6, leading to visual side effects.[226] Compound **42** has better selectivity for PDE5 over PDE6 with the addition of more electron donating groups; however, relative to **40** and **43**, **42** is less selective for PDE11.[227, 244–245] Although these compounds have been extensively developed for treating pulmonary hypertension and erectile dysfunction, they also have been tested for treating other diseases.

Because cGMP-selective PDE inhibitors were designed to reduce blood pressure via increased vasodilation, it is reasonable that they have been tested for conditions characterized by endothelial dysfunction, such as diabetes. As expected, in models of diabetes, **40** improves endothelial function as measured by flow-mediated dilation.[246–247] In addition to their effects on vascular reactivity, **40**, **42**, and **43** reduce plasma markers of diabetes, such as lipids, serum glucose, and HbA_{1c}, and are associated with improvements in mitochondrial content.[248–251] In adipocytes and hepatocytes, **40** enhances lipid oxidation and increases insulin tolerance and cellular morphology.[248] cGMP-selective PDE inhibitors also reduce diabetic complications in other organs, such as the kidney and heart. In models of diabetic nephropathy, **40** reduces microalbuminuria, a predictor of renal and cardiac dysfunction.[249] Additionally, in diabetic mice, **42** rescues the expression of cardiac cytoskeletal and redox proteins to improve cardiac morphology and function.[251–252]

In addition to beneficial reductions in the development of diabetic cardiomyopathy, cGMP-selective PDE inhibitors also ameliorate non-diabetic cardiac dysfunction. In ischemic cardiomyopathy and myocardial infarction, **40**, **42**, and **43** increase survival and decrease infarct size by reducing cell death and preserving mitochondrial function.[253–255] Compound **42** also prevents cardiac remodeling and hypertrophy, stabilizing contractility rather than allowing progression to heart failure and pulmonary edema.[256] Similarly, in models of mitral regurgitation and doxorubicin toxicity, **40** inhibits cell death and preserves mitochondrial function by upregulating anti-apoptotic proteins and maintaining the mitochondrial membrane potential.[257–258]

cAMP-PKA-CREB axis

CREB regulates PGC-1α activity and expression to promote MB and is down-regulated in multiple disease states characterized by mitochondrial dysfunction. In Alzheimer disease, CREB phosphorylation is diminished due to impaired activation by PKA. This loss of activity leads to a downregulation of PGC-1α and an imbalance in tau protein, a driver of Alzheimer disease.[259] A similar decrease in CREB activity has been observed in Huntington's disease.[260] Additionally, ethanol decreases cellular cAMP, thereby reducing CREB activity to suppress PGC-1α and thereby exert its toxic effects.[261] Taken together, these data indicate that activation of the cAMP-PKA-CREB signaling pathway can promote MB and protect against neurodegenerative diseases.

The primary therapeutic approach for activating this signaling axis is with phosphodiesterase (PDE) inhibitors such as rolipram (**44**)[262] and cilostazol (**45**)[263] (Figure 9). Compound **44** inhibits PDE4, a cAMP-selective PDE, whereas **45** inhibits PDE3, a PDE capable of hydrolyzing both cAMP and cGMP; however, PDE3's V_{max} for cAMP is substantially higher than that of cGMP. Compound **44**'s selectivity arises in part from its optimized potency for PDE4 and the unfavorable orientation of a conserved glutamate residue in other PDEs.[264] In contrast, the lactam group of **45** engages in hydrogen bonding interactions with multiple receptor residues to promote PDE3 selectivity.[265] Both **44** and **45** can increase PGC-1α *in vitro*, indicating that they induce MB,[266] and both have shown potential for therapeutic use in pre-clinical disease models. However, in humans, **44**'s narrow therapeutic window limits its application, whereas **45** is approved for clinical use in the treatment of diabetic vascular complications.

Restoration of the cAMP-PKA-CREB pathway substantially reduces the effects of neurodegenerative diseases. In animal models of Huntington's disease, **44** improves neuronal function, morphology, and survival and decreases neurological impairment.[260, 267] Compound **44** also reduces synaptic conduction abnormalities associated with Alzheimer disease, improving cognition.[268–269] Interestingly, these effects and increased CREB phosphorylation lasted beyond the cessation of treatment. In ischemic brain injury, **45** reduces neuroinflammation, reducing infarction size and decreasing apoptosis and free radical production.[270–271] In models of Alzheimer disease, **45** increases SIRT1 expression, reducing symptoms and improving cognitition.[272] Furthermore, in a retrospective study, **45** improved cognition in human patients,[273] suggesting that PDE3 inhibition holds promise for treating Alzheimer disease.

Used clinically to treat claudication, the beneficial effects of **45** in models of diabetic cardiovascular disease are well studied. In models of limb ischemia, **45** increases angiogenesis by rescuing PPARγ, increasing angiogenic factors vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF);[274–275] this normalization of PPARγ also occurs in other tissues, such as the retina and the kidney.[276] Compound **45** also prevents endothelial cell senescence by increasing cAMP, leading to SIRT1 activation. In the heart, **45** reduces oxidant-induced mitochondrial dysfunction and significantly reduces myocardial infarction size.[277–279] Furthermore, **45** improves insulin sensitivity and reduces blood glucose and HbA_{1c} in diabetic mice and human subjects,[280–282] as well as reducing the

urinary excretion of albumin and renal inflammation, indicating that **45** improves diabetic nephropathy.

Despite these promising data, controversy exists regarding use of cAMP-selective PDEs in chronic degenerative diseases of the liver and kidney. On the one hand, **45** improves hepatic function after ischemic insult by inducing MB;[283] however, in models of lipotoxicity, increased cAMP acts synergistically to induce cell death despite concurrent stimulation of MB.[284] Additionally, despite the promising work in diabetic nephropathy described previously, we found that cAMP-selective PDE inhibitors do not induce MB in proximal tubule cells,[285] suggesting they are poor therapeutic options for treating AKI.

GPCR Ligands

G protein-coupled receptors (GPCRs) are well characterized plasma membrane receptors that are the target of a substantial portion of currently available drugs. By coupling to G proteins, GPCRs can modulate cAMP, calcium, and NO and activate various kinases and signaling pathways. Additionally, different ligands of the same receptor can cause activation of distinct signaling programs, a phenomenon known as “functional selectivity” or “biased agonism.”[286] By stabilizing different receptor conformations, different ligands can alter receptor interactions with G proteins, G protein-coupled receptor kinases (GRKs), and scaffolding proteins such as arrestins. One such scaffolding protein, GRK interacting protein 1 (GIT1), regulates MB in the heart, likely in an eNOS-dependent manner.[287–288] Biased agonism allows for the development of ligands that selectively stimulate signaling pathways that lead to MB while inhibiting negative regulators of MB. Many GPCRs are modulated by endogenous molecules, a fact which has facilitated the development of potent and selective agonists and antagonists for various receptors. Despite the potential of GPCRs to activate pathways known to induce MB and the availability of clinically approved GPCR ligands, little investigation has occurred to explore the potential of such compounds to induce MB.

Cannabinoid-1 receptor

Cannabinoid-1 receptor (CB1R) antagonists such as taranabant (**46**)[289] and rimonobant (**47**)[290] were studied for anorectic effects (Figure 10). Despite the lack of a cyclic linker, **46** binds in a similar mode to **47**; however, the amide group on **46** is able to engage in an extra hydrogen bonding interaction, leading to its enhanced affinity for the CB1R.[289, 291] By inhibiting CB1R activity in the brain, these compounds can suppress appetite and cause weight loss with concomitant improvements in plasma lipid profiles. Both **46** and **47** were efficacious for inducing weight loss in wild type mice, mice fed a high fat diet, and ob/ob mice.[292–293] Inhibition of CB1R by **47** or by genetic ablation induces MB in adipose tissue and MB in a cAMP- and eNOS-dependent manner, leading to decreases in body weight and fat content.[292] Interestingly, **47** increased mitochondrial energy consumption did not increase mitochondrial mass in rat livers, indicating improved mitochondrial efficiency.[294] Although both **46** and **47** were efficacious in animal models, investigation of **46** was halted in Phase III trials, and **46** was withdrawn from the market in the U.S. after initial approval as an anti-obesity drug. In humans, **47** reduced food intake and increased energy consumption

to promote weight loss but caused serious side effects such as suicidal ideation and severe depression.[295296]

5-Hydroxytryptamine receptors

Endogenous serotonin binds to the 5-hydroxytryptamine (5-HT) class of receptors (48, Figure 11)[297]. 5-HT receptors are primarily GPCRs that have been identified as therapeutic targets for neuropsychiatric, neurologic, and cardiac diseases. The synthetic ligand alpha-methyl-5-hydroxytryptamine (**49**)[298] possesses an extra methyl group that prevents its metabolism by monoamine oxidase.[299] The 5-HT_2 receptor agonist DOI (**50**)[300] has enhanced selectivity due to its primary amine, with the iodo-group adding to its potency.[301] Much work has been done to identify and characterize the pharmacophore of 5-HT_{2C} receptor agonists (e.g., CP809101, **51**)[302] and antagonists (e.g. SB242084, **52**)[303] and optimize their selectivity.[301–303] 5-HT_{2C} receptor agonists stabilize the TM6 domain of the receptor through its aromatic group, whereas antagonists interact with Asn331, Val354, and Ser334 through a positively ionizable group.[304]

In addition to direct 5-HT receptor antagonists, serotonin reuptake inhibitors such as fluoxetine (**53**)[305] prevent the uptake and degradation of **48** and prolong its actions at its receptors. The *p*-trifluoromethyl group of **53** confers selectivity for the serotonin reuptake transporter by binding to I172 in its transmembrane domain.[306–307] Treating rat pups with **53** improves mitochondrial membrane potential, respiratory capacity, and antioxidant defense in the heart, implicating **48** in mitochondrial health during development.[308]

Our laboratory identified multiple ligands that induce MB through various 5-HT receptors. In renal proximal tubule cells, we have shown that the non-selective 5-HT receptor agonist **49** induces MB.[309] The 5-HT_2 receptor agonist **50** increased cellular respiration *in vitro* and improved recovery from oxidant injury by *tert*-butyl hydrogen peroxide (TBHP); interestingly, induction of MB did not reduce initial injury by TBHP.[310] The 5-HT_{2C} selective ligands **51** and **52** induce MB *in vitro* and in naïve mice; interestingly, siRNA studies and work in knockout mice indicate that the ligands exert these effects through the 5-HT_{2A} receptor.[311]

In contrast to 5-HT_2 receptors, the 5-HT_{1F} receptor has few selective ligands-namely, LY334370 (**54**) and LY344864 (**55**) and limited data regarding its pharmacophore. Nevertheless, the selective 5-HT_{1F} agonists **54** and **55** induced MB *in vitro*, and **55** also improved recovery from ischemia-reperfusion-induced AKI *in vivo*.[309] Additionally, preliminary data suggest that **55** stimulates MB through the Gβγ-dependent activation of Akt and eNOS (Gibbs, W.; Beeson, C.C.; Schnellmann, R.G., unpublished results). These data indicate that the induction of MB by 5-HT agonists could be clinically useful for treating AKI and other acute organ injuries as they effectively promote recovery and regeneration even after initial injury.

Beta adrenergic receptors

The beta adrenergic receptor family is activated by endogenous stress hormones epinephrine (**56**)[312] and norepinephrine (**57**, Figure 12)[312] and the family comprises three receptors.

First, the beta-1 adrenergic receptor, primarily expressed in the heart, is targeted by drugs that affect cardiac contractility and heart rate. The beta-2 adrenergic receptor, which is ubiquitously expressed, is a target of bronchodilators to treat asthma and COPD. The beta-3 adrenergic receptor, which is primarily expressed in adipose tissue and the urinary bladder and is targeted to treat overactive bladder.[313]

Beta-adrenergic agonists contain distinct structural features, specifically a catechol or phenethanolamine core, whereas antagonists have a 3-aminophenoxypropan-2-ol core. However, while beta-adrenergic agonists have been extensively studied to optimize pharmacodynamics and pharmacokinetic parameters, there are few studies relating structural features to the induction of MB. Compounds **56**, **57**, and the non-selective beta adrenergic receptor agonist isoproterenol (**58**)[314] increase PGC-1α in brown adipose of naïve mice and in models of obesity in a cAMP- and p62-dependent manner.[315] Interestingly, in models of cardiac dysfunction, beta-1 adrenergic receptor stimulation by dobutamine (**59**)[316] increases cell death and inflammation,[317] but its blockade by the beta-1 selective antagonist metoprolol (**60**)[318] enhances PGC-1α activation and improves cardiac metabolism and function.[319–320] Our laboratory has studied beta-2 adrenergic receptor selective agonists in renal MB. In particular, formoterol (**61**),[321] fenoterol (**62**),[322] and procaterol (**63**)[323] induced MB *in vitro* at pharmacologically relevant doses.[324–325] Compound **61** has been confirmed to induce MB *in vivo* in naïve mice as well as in mice subjected to AKI,[326] and this was associated with improvements in renal function, indicating that formoterol has therapeutic promise for treating AKI. However, other beta-2 adrenergic receptor agonists such as clenbuterol (**64**)[327] and isoetharine (**65**)[328] did not induce MB *in vitro*,[324] suggesting that biased agonism can be exploited to develop more effective mitochondrial biogenic beta-2 adrenergic receptor agonists. Because both MB-inducing and non-MB-inducing beta-2 adrenergic receptor agonists increase cAMP, we suggest that the classical $G\alpha_s$-signaling pathway is not responsible for beta-2 adrenergic receptor-induced MB in the kidney. Preliminary data suggests that **61** but not **64** activates the Akt-eNOS pathway in a Gβγ-dependent manner (Cameron, R.B.; Beeson, C.C.; Schnellmann, R.G., unpublished results). In addition to its renal effects, **61** induces MB in multiple other tissues, including the heart and skeletal muscle.[325, 329] Together, these data indicate that certain beta-2 adrenergic receptor agonists such as **61** can be used to treat multiple diseases and improve mitochondrial function and ameliorate symptoms.

Perspectives

Because MB can arise from diverse signaling pathways, a number of drug classes have been identified to induce MB. The earliest identified inducers of MB are natural products, such as **1**–**9,** which are efficacious,[73, 97, 111, 120] but MB induction often occurs through multiple signaling pathways and these compounds may activate signaling programs unrelated to MB. Such promiscuity means that these compounds are poor therapeutic agents, particularly for chronic degenerative diseases for which a more targeted approach may be required.

Transcription factor activators such as TZDs (**10**–**13**), estrogens (**14**–**18**), and SIRT1 activators (**19**–**22**) induce MB by activating transcription factors that act on mitochondrial genes.[139, 163, 173] This selectivity facilitates the induction of relatively small gene sets.

Furthermore, transcription factor modulation can drive the recruitment of a select set of transcriptional machinery, increasing the specificity of the resulting transcriptome. However, ligands with that degree of specificity, particularly for MB, have not yet been designed. Thus, currently, activation of these transcription factors upregulates unwanted genes and causes detrimental neurological and hyperproliferative effects.

Similar to transcription factor modulators, kinase modulators such as **23** and **30** have been developed with a high activity for their targets. Although some kinase activators are available, many kinase inhibitors have been developed and are utilized clinically. These inhibitors will be of particular use as more negative regulators of MB, such as ERK1/2, are identified. Kinase signaling is fairly well-characterized, so acute downstream effects of such modulators are usually predictable. Nonetheless, because kinases have central roles in cellular processes, predicting longer-term effects of such drugs is not straightforward.

Cyclic nucleotide modulators such as sGC stimulators and activators and PDE inhibitors have recently been shown to be efficacious inducers of MB.[242, 266, 285, 330] However, as with kinase modulators, these drugs influence central signaling processes, often in a manner that prevents physiological feedback loops to prevent pathological signaling. Additionally, cyclic nucleotides can have tissue-specific effects that can give rise to either injurious or curative effects to different organ systems.

GPCR modulators are the most widely developed and prescribed drug class. Although few of these compounds have been tested for MB induction, several promising classes, have been identified to induce MB, such as cannabinoid, serotonergic, and adrenergic ligands.[292, 309–311, 324] These compounds can act through a single target and activate a particular signaling program. [286] Unlike the above-mentioned compound classes, GPCR ligands act at surface receptors and can retain cellular feedback mechanisms to limit signaling if necessary, so GPCR ligands represent promising chemical space for the induction of MB.

In vitro, *in vivo*, and human studies indicate that induction of MB promotes recovery from disease states among many organ systems due to myriad roles played by mitochondria in both physiological and pathophysiological states. However, relatively few drugs have been identified to induce MB, and much chemical space remains untested for MB. One domain of chemical space that may be promising for phenotypic screens to identify lead compounds is the so-called “dark chemical space,” as compounds derived from this space tend to have high specificity for a given target.[331] As more chemical space is investigated for MB, we will gain a better understanding of the role of mitochondria in health and disease and will provide researchers and clinicians with better tools for treating debilitating acute and chronic degenerative diseases.

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ABBREVIATIONS

ATP	adenosine triphosphate
AMP	adenosine monophosphate
MPTP	mitochondrial permeability transition pore
MB	mitochondrial biogenesis
PGC-1α	peroxisomal proliferation activated receptor coactivator-1α
mtDNA	mitochondrial DNA
ER	estrogen receptor
ERRα	estrogen related receptor-α
NRF-1	nuclear respiratory factor 1
NRF-2	nuclear respiratory factor 2
PPAR	peroxisome proliferator-activated receptor
TR	thyroid hormone
CREB	cAMP-responsive element binding protein
YY-1	yin yang-1
ROS	reactive oxygen species
PGC-1	peroxisomal proliferation activated receptor coactivator-1
PGC-1β	peroxisomal proliferation activated receptor coactivator-1β
PRC	PGC-1 related coactivator
PKA	protein kinase A
NO	nitric oxide
AMPK	growth stimulatory AMP-dependent kinase
SIRT1	silent mating type information regulation 2 homolog 1
AKI	acute kidney injury
Tfam	mitochondrial transcription factor A
UCP2	uncoupling protein 2

PINK1	PTEN-induced putative kinase 1
NAD^+	nicotinamide adenine dinucleotide
SOD2	superoxide dismutase 2
SIRT3	silent mating type information regulation 2 homolog 3
eNOS	endothelial nitric oxide synthase
TZD	thiazolidinedione
PPARγ	peroxisomal proliferation activated receptor-γ
ERα	estrogen receptor α
ERβ	estrogen receptor β
GPER	G protein-coupled estrogen receptor
ALDH2	aldehyde dehydrogenase 2
LDL	low density lipoprotein
ERK 1/2	extracellular signal-related kinases 1/2
MEK 1/2	mitogen-activated protein kinase kinase 1/2
sGC	soluble guanylate cyclase
PDE	phosphodiesterase
PKG	Protein kinase G
VEGF	vascular endothelial growth factor
HGF	hepatocyte growth factor
HbA_{1c}	glycated hemoglobin
GPCR	G protein-coupled receptor
GRK	G protein-coupled receptor kinase
GIT1	GRK interacting protein 1
CB1R	cannabinoid-1 receptor
5-HT	5-hydroxytryptamine
TBHP	*tert*-butyl hydrogen peroxide

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Biographies

Robert B. Cameron obtained his B.S. from Davidson College where he performed research on the synthesis and characterization of light-harvesting molecules under the direction of Dr. Durwin R. Striplin. He is currently an M.D./Ph.D. candidate at the Medical University of South Carolina studying the signaling mechanisms by which mitochondrial biogenesis occurs following G protein-coupled receptor stimulation under the direction of Rick G. Schnellmann at the University of Arizona.

Craig C. Beeson obtained his organic chemistry B.S. degree from CSU, Northridge, M.S. degree from San Diego State University and Ph.D. degree from U.C. Irvine. After studying the biophysics of T-cell activation under the direction of Harden M. McConnell at Stanford University, he started his academic career in the Chemistry Department at the University of Washington, Seattle and he is now a Professor in the Drug Discovery and Biomedical Sciences Department at the Medical University of South Carolina.

Rick G. Schnellmann obtained his B.S. in Pharmacy degree from the St. Louis College of Pharmacy, St. Louis, MO and his Ph.D. degree in pharmacology and toxicology from the University of Arizona, Tucson, AZ. After a postdoctoral fellowship at Duke University in mitochondrial biology and renal toxicity, he rose through the ranks at the University of Georgia and University of Arkansas for Medical Sciences, and became Eminent Scholar, Distinguished University Professor, and Chair in the Department of Drug Discovery and Biomedical Sciences at the Medical University of South Carolina. He currently serves as dean of the College of Pharmacy for the University of Arizona.

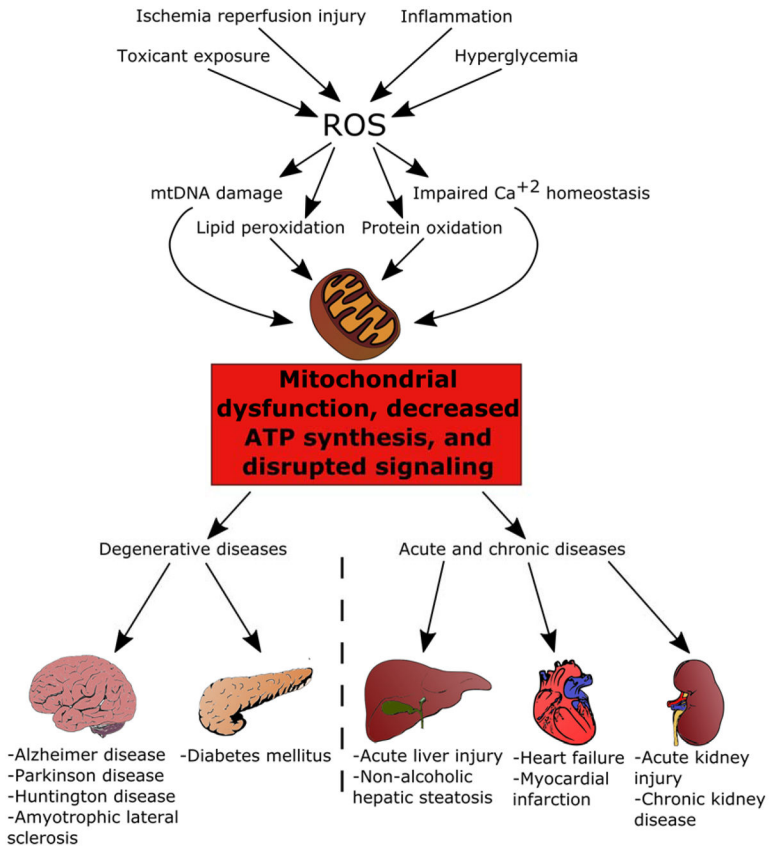


Figure 1.

Multiple insults converge upon the mitochondria, leading to mitochondrial dysfunction and subsequent organ injury and disease.

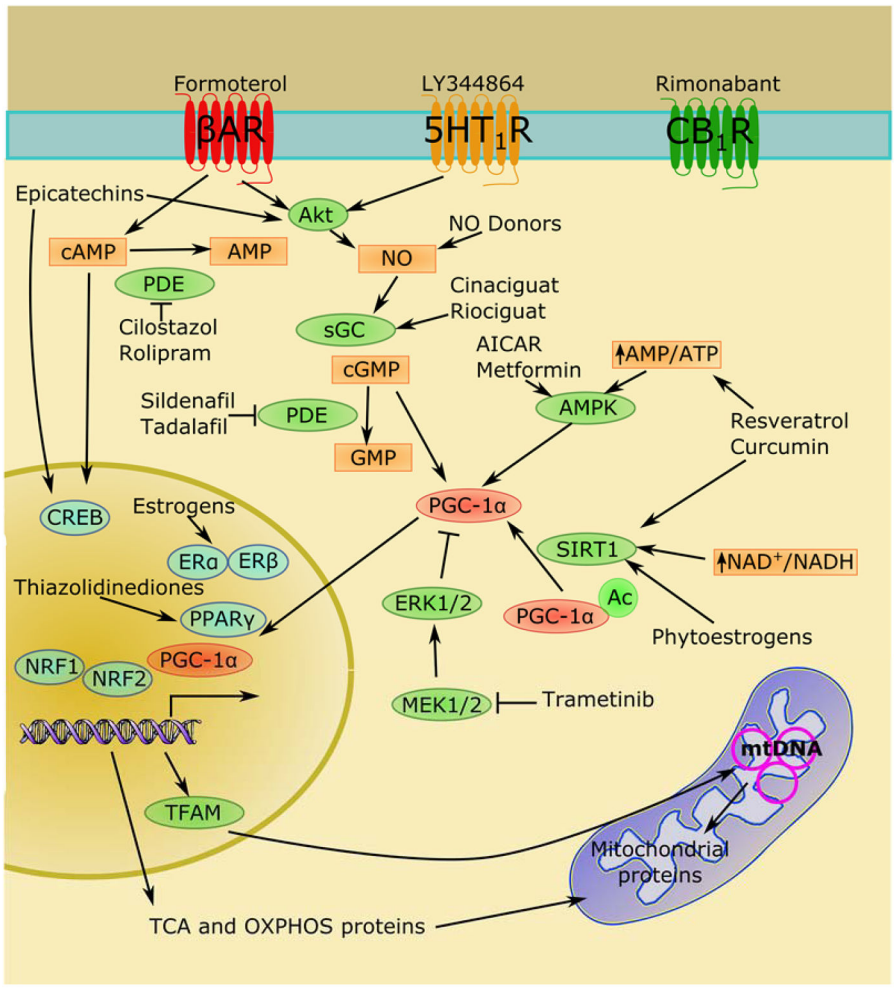


Figure 2.

PGC-1α integrates extracellular and cytosolic signaling inputs to selectively upregulate mitochondrial biogenesis.

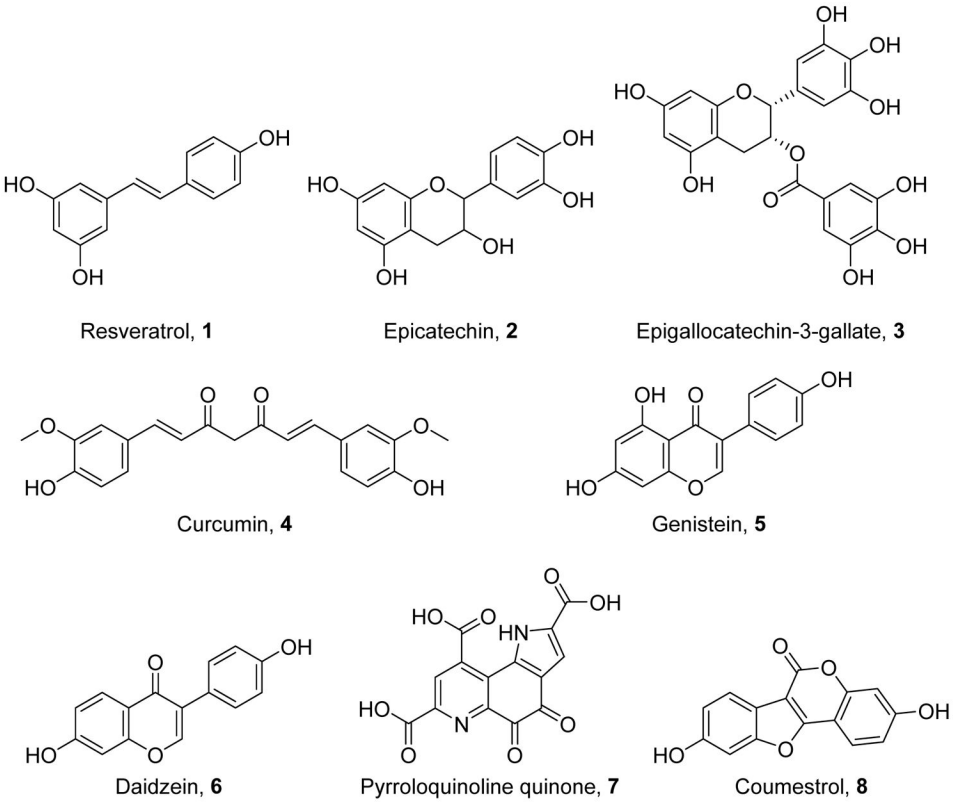


Figure 3.
Naturally occurring polyphenols capable of inducing MB.

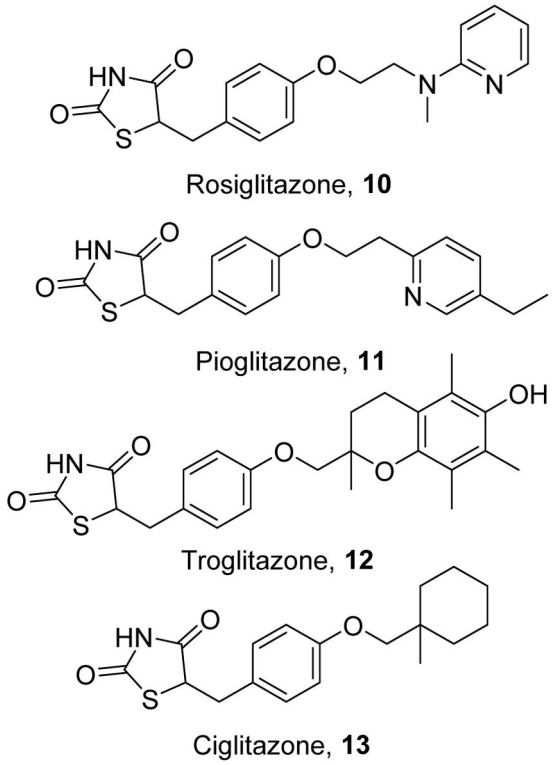


Figure 4.
Thiazolidinedione inducers of MB.

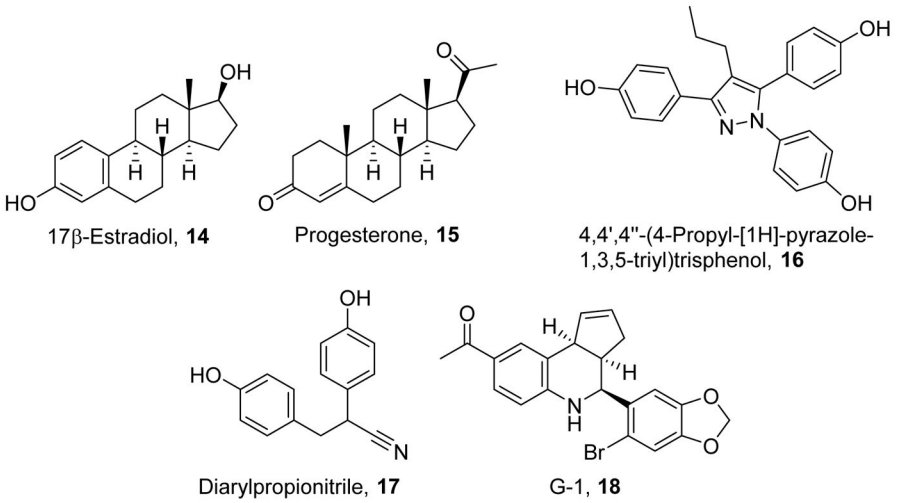


Figure 5.
Estrogen inducers of MB.

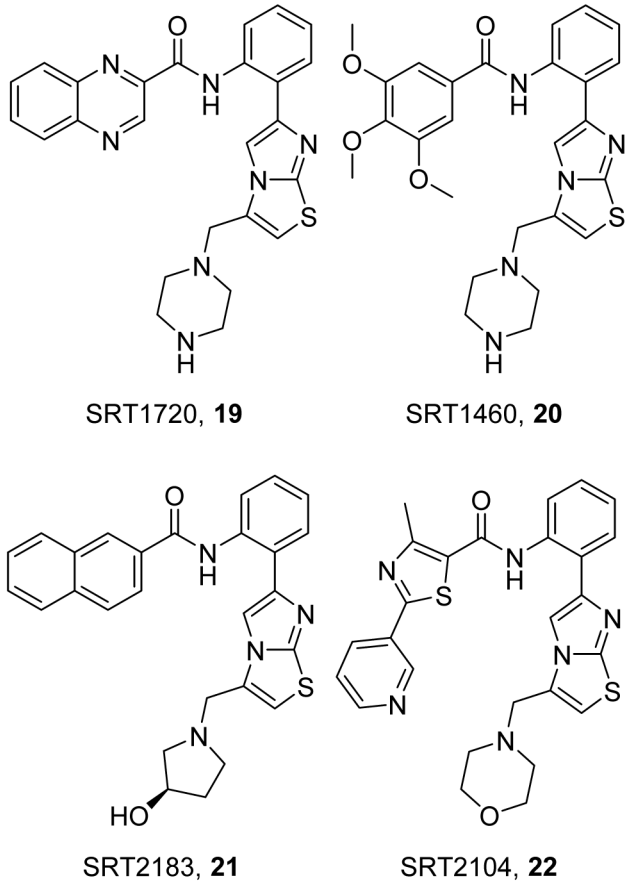


Figure 6.
Activators of SIRT1 that induce MB.

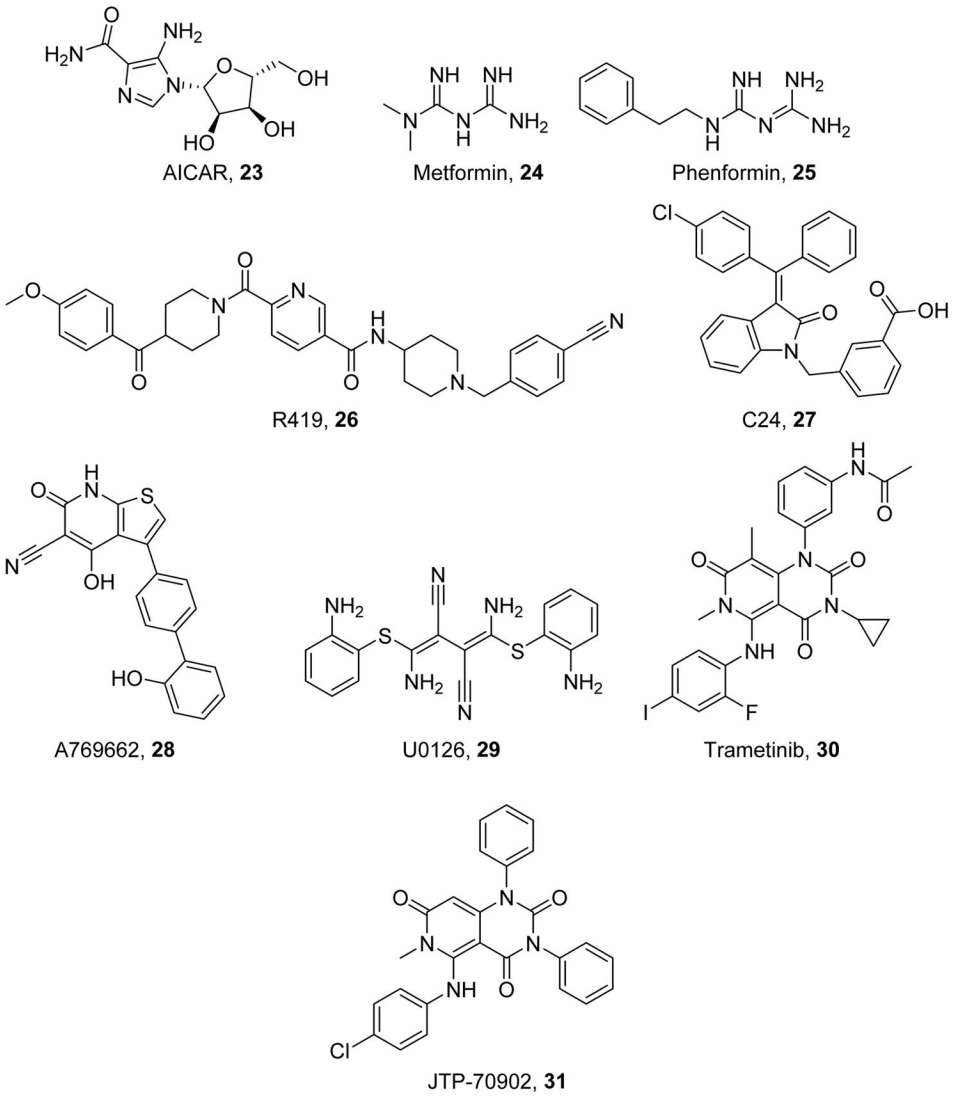


Figure 7.
Kinase modulators that induce MB.

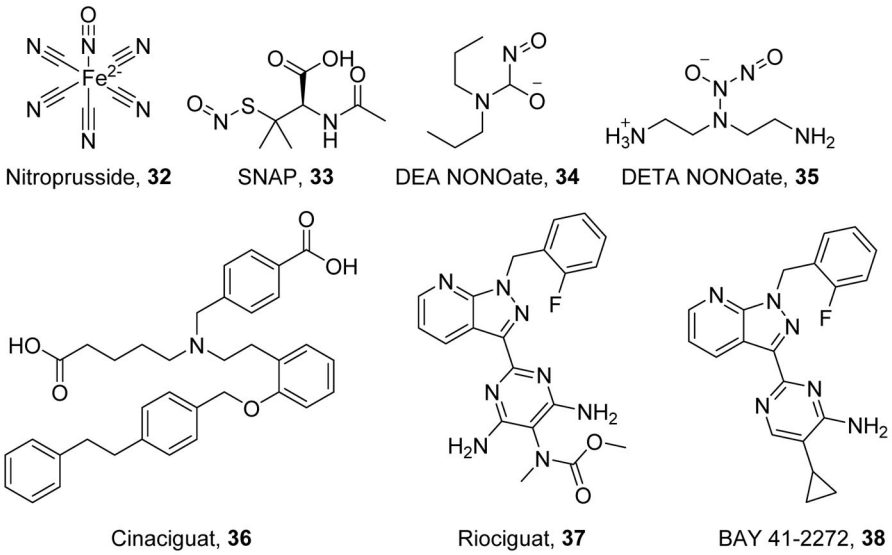


Figure 8.
Activators and stimulators of the NO/cGMP pathway.

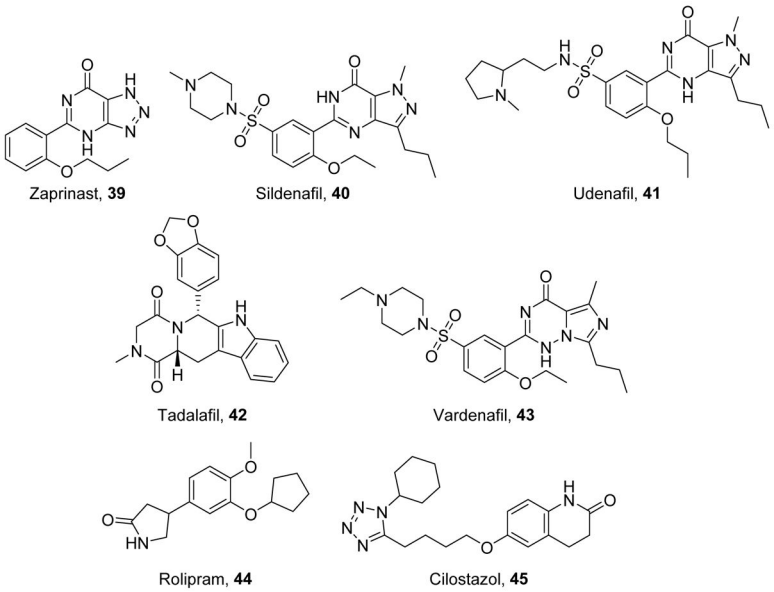
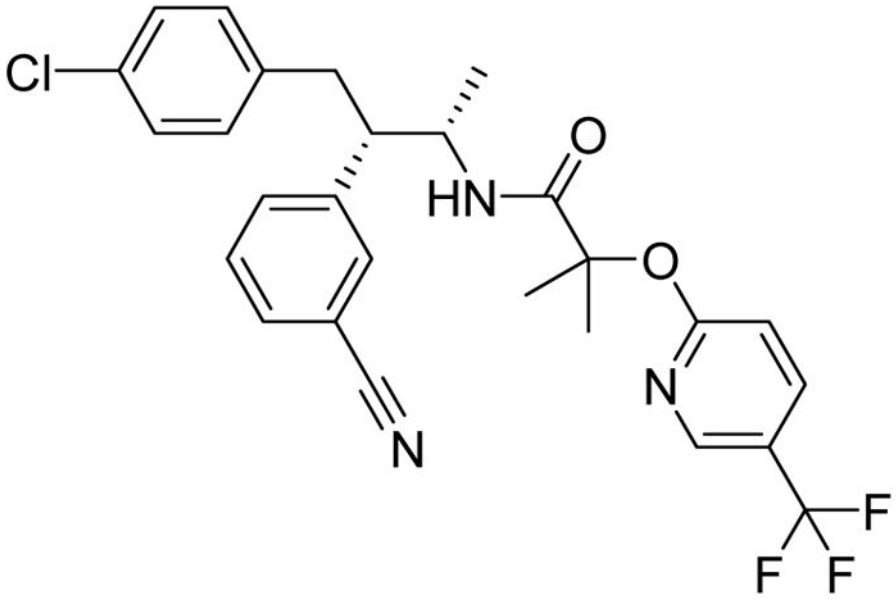
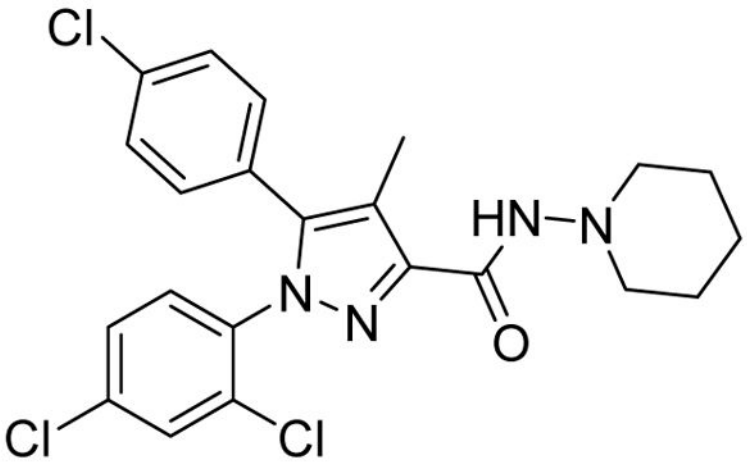


Figure 9.
Phosphodiesterase (PDE) inhibitors associated with MB.



Taranabant, **46**



Rimonabant, **47**

Figure 10.
Cannabinoid-1 Receptor antagonists.

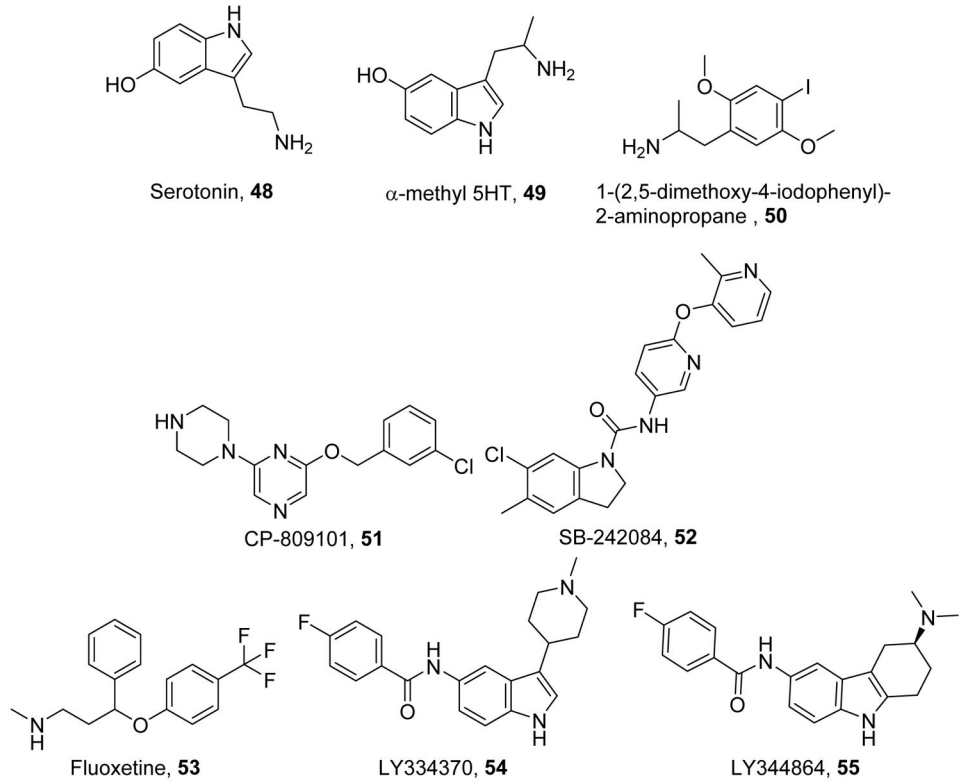


Figure 11.
5-Hydroxytryptamine receptor modulators that induce MB.

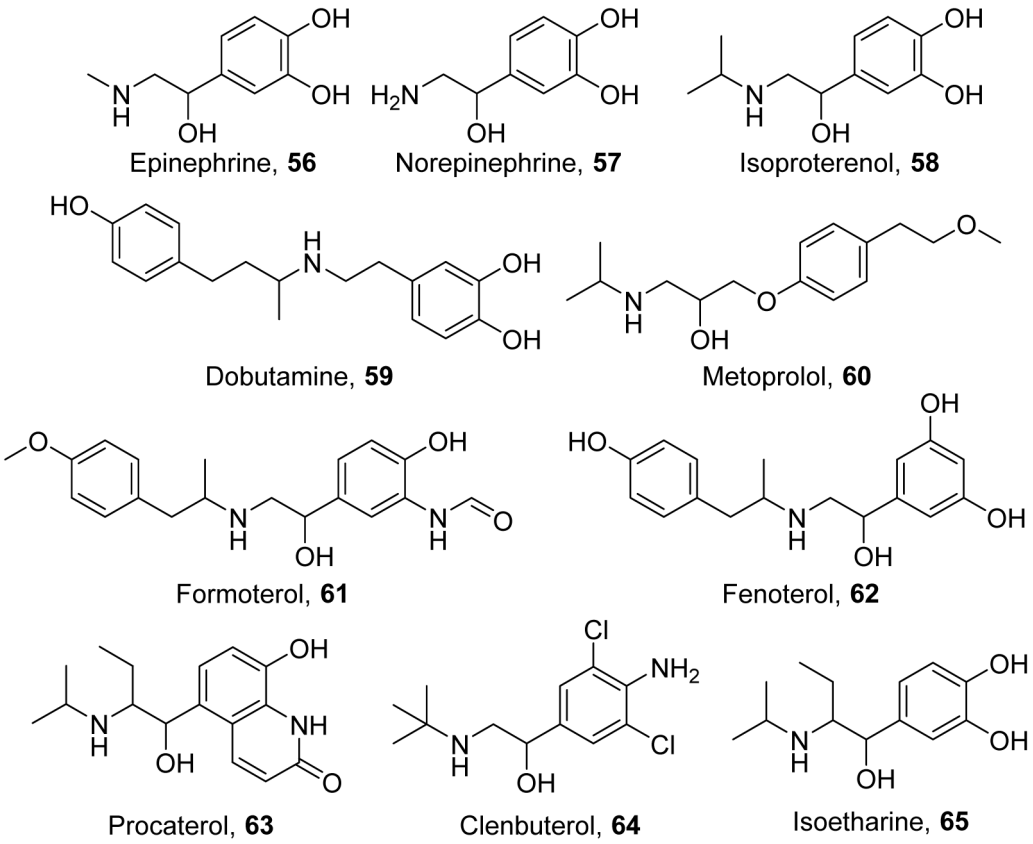


Figure 12.
Beta adrenergic receptor modulators tested for the induction of MB.