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Natural Products and Other Inhibitors of F_1F_O ATP Synthase

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Abstract

F_1F_O ATP synthase is responsible for the production of >95% of all ATP synthesis within the cell. Dysregulation of its expression, activity or localization is linked to various human diseases including cancer, diabetes, and Alzheimer's and Parkinson's disease. In addition, ATP synthase is a novel and viable drug target for the development of antimicrobials as evidenced by bedaquiline, which was approved in 2012 for the treatment of tuberculosis. Historically, natural products have been a rich source of ATP synthase inhibitors that help unravel the role of F_1F_O ATP synthase in cellular bioenergetics. During the last decade, new modulators of ATP synthase have been discovered through the isolation of novel natural products as well as through a ligand-based drug design process. In addition, new data has been obtained with regards to the structure and function of ATP synthase under physiological and pathological conditions. Crystal structure studies have provided a significant insight into the rotary function of the enzyme and may provide additional opportunities to design a new generation of inhibitors. This review provides an update on recently discovered ATP synthase modulators as well as an update on existing scaffolds

Graphical Abstract

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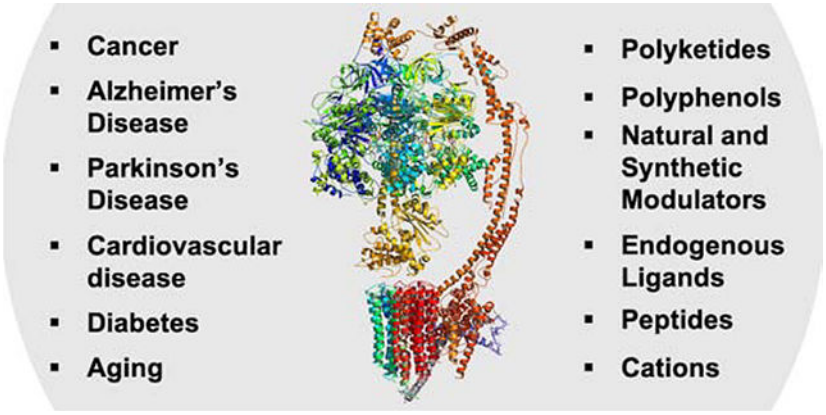
8. Declaration of competing interest

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Keywords

F_1F_O; ATP synthase; ATPase; inhibitors; oligomycin; anticancer

1. Introduction

F_1F_O ATP synthase (F_1F_O-ATPase) is a well-documented and highly studied enzyme due to its critical role in the synthesis of ATP, the primary currency for energy used in life, but also for its role in various diseases including cancer, neurodegenerative disorders, and mitochondrial disease resulting from genetic mutations. Since isolation of the F_1 portion of ATP synthase by Racker in 1961, followed by identification of the chemiosmotic mechanism of ATP synthesis in the same year by Mitchell, significant efforts have been invested to improve our understanding of F_1F_O-ATPase's structure, its function, and its role in disease.[1] In addition, extensive research has been pursued to develop compounds that modulate F_1F_O-ATPase activity. In 2008, a review was published by Hong and Pedersen, which identified over 250 compounds that target this molecular machine.[2] The purpose of this review is to provide a more recent update that outlines F_1F_O-ATPase research that has primarily occurred since 2008.

2. F_1F_O ATP Synthase

F_1F_O-ATPase is a membrane-bound multiprotein complex that is responsible for producing the majority of ATP synthesis within the cell via exploitation of the proton motive force that can drive the phosphorylation of ADP to ATP under aerobic conditions (oxidative phosphorylation). Although predominantly located within the mitochondria in the inner mitochondrial membrane (IMM), F_1F_O-ATPase is also expressed on the surface of various cell types (ectopic F_1F_O-ATPase) and can play various roles to modulate lipid metabolism, cell differentiation, survival and proliferation, angiogenesis and cancer, as well as intracellular pH.[3]

3. F_1F_O ATP Synthase Structure

F_1F_O-ATPase is a heteroprotein complex that is composed of 29 subunits, with each subunit comprised of a single protein.[4,5] The DNA code for 27 of the proteins are nuclear genes,

which are synthesized by cytosolic ribosomes and then transported into the mitochondria for assembly into the heteroprotein complex. The other 2 proteins (subunits 6 and 8) are encoded by mitochondrial DNA and are synthesized by ribosomes within the mitochondria. The genes associated with each subunit are provided in Table 1.

F_1F_O-ATPase is comprised of two major regions, which consists of the F_1 and F_O domains (Fig. 1). The F_1 domain is derived from the name “Fraction 1”. The F_O domain is named with the subscript “O”, due to the binding of oligomycin to this region. The F_1 domain can be subdivided into two additional subunits, the F_1 catalytic head and the F_1 central stalk. The F_1 catalytic head is composed of three alternating α and β subunits and the F_1 central stalk contains one γ, δ, and ε subunits. The F_O domain is subdivided into three groups: the F_O rotor, the F_O peripheral stalk, and the F_O supernumerary subunits. The F_O rotor consists of the subunits 6 (‘a’ or ATP6) and 8 (ATP8) and the c-ring (c_8-ring) composed of eight identical c subunits. Inhibitory Factor 1 (IF1) is a inhibitory protein that can also regulate the activity of F_1F_O ATP synthase.

4. F_1F_O ATP Synthase Function

F_1F_O-ATPase is an ATP synthase and is solely dependent upon a proton gradient that is generated by the electron transport chain (ETC). The catalytic phosphorylation of ADP begins via the movement of a proton into F_1F_O-ATPase and ends with the release of ATP into the mitochondrial matrix. A proton from the IMS binds to an influx channel that exists between the c-ring and subunit 6, which ultimately leads to protonation of a hydrophilic residue. This change in hydrophobicity results in a counterclockwise rotation (as seen from the matrix) of the c-ring. Each proton that binds to subunit c will elicit a full rotation of the c-ring before it reaches the efflux channel. When the protonated c subunit reaches the efflux channel, it is readily deprotonated, and the proton is released into the matrix. This rotation of the c-ring is very rapid and occurs at a rate of approximately 130 revolutions per second.[6]

Rotation of the c-ring imparts a torque on the F_1 central stalk that results in its rotation within the F_1 catalytic head and is facilitated by the δ and ε subunits to provide additional support for the c-ring.[7] The F_1 catalytic head is anchored by the F_O peripheral stalk and held in a stationary position relative to the rotating F_1 central stalk. The hexameric F_1 catalytic head ($\alpha_3\beta_3$) is the site of ATP catalysis, specifically within the β subunits.

Rotation of the F_1 central stalk results in perturbations of the F_1 catalytic head that subsequently result in small conformational changes (Fig. 2). The catalytic sites exist in three unique binding states; β_E (open or empty), β_{DP} (loose or ADP bound) and β_{TP} (tight or ATP bound).[8] When the catalytic site is in an open state, ADP and phosphate (P_i) can occupy the site. During the next 120° rotation, the catalytic site changes from an open state to a loose state wherein bound ADP + P_i are bound more closely. The next 120° rotation results in transformation of the catalytic site into a tight state wherein the synthesis of ATP occurs. During the final 120° rotation, the catalytic site returns to an open state and newly synthesized ATP is released. Hydrolysis of ATP occurs in a similar manner, but in which rotation is reversed.[9]

The F_O subunits are not directly involved in the synthesis of ATP, but perform supporting roles for the function of ATP synthase, which includes structural support (particularly the peripheral stalk), dimerization, and oligomerization. Cristae formation within the mitochondria has been shown to be influenced by dimerization and oligomerization of F_1F_O-ATPase to increase the overall surface area of IMM for the respiratory chain.[10] Moreover, knockdown studies of DAPIT and the 6.8PL subunits have demonstrated a decrease in both the population of ATP synthase and ATP production, demonstrating their importance in the biogenesis and proper functioning of the ATP synthase.[4,11]

5. Implications for Disease

Given the complexity of the molecular machinery of F_1F_O-ATPase in terms of interconnectivity and interactions among subunits, minor disruptions to the structure or conformation inhibit or impair ATP synthesis and/or hydrolysis. Mitochondrial diseases which often result from genetic mutations, lead to disruption of F_1F_O-ATPase biogenesis and an underdeveloped cristae, insufficient F_1F_O-ATPase populations and ATP synthesis, and poor prognosis for those affected. The therapeutic role of F_1F_O-ATPase spans various areas of human health including cancer, neurodegenerative disorders (Alzheimer's and Parkinson's), cardiovascular and other metabolic diseases as diabetes.[2,12] The aberrant ectopic expression of the β subunit has been demonstrated in various cancers, including non-small cell lung cancer, acute myeloid leukemia and prostate cancer.[13–15] Inhibition of the ectopic β subunit by a monoclonal antibody (Mc178-Ab) led to apoptosis via the MAPK and Akt pathways.[16] Downregulation of the mitochondrial β subunit in tumors such as breast, lung, colon and squamous lung carcinomas was affected at the translation step, which may be regulated by the AMPK and/or GCN2–ATF4 pathway.[17,18] It was also shown that mitochondrial F_1F_O-ATPase translocates to cell surface in hepatocytes and has high activity in tumor-like acidic and hypoxic environments.[19] In addition, overexpression of the ε subunit was shown to promote metastasis in colorectal cancer.[20] Endogenous p53 has also been shown to interact with a subunit OSCP and may play an important role in tumor suppression via the regulation of F_1F_O-ATPase activity.[21] In neurodegeneration, the α subunit of the ATP-synthase is targeted for oxidative damage in the very early stages (Braak stages I/II) of AD pathology.[22] Moreover, Aβ in Alzheimer's and α synuclein in Parkinson disease, interact with the F_1F_O-ATPase to open the mitochondrial permeability transition pore (mPTP).[23,24] F_1F_O-ATPase-Cyclophilin D (CyPD) interactions were also shown to increase during diabetic encephalopathy.[25]

6. Compounds Targeting F1FO ATP Synthase

6.1. Polyketides Inhibitors

Polyketides are a group of secondary metabolites produced by various microorganisms. Many polyketides have shown antibacterial, antifungal, and/or immunosuppressive activities. Some of these polyketides such as oligomycin, aurovertin, apoptolidin, mandelalide and cruentaren have been shown to manifest inhibitory activity against F_1F_O ATP synthase, and thus, exhibiting anti-cancer activity (Fig. 3–6).

Oligomycins, which are produced by *Streptomyces* sp. constitute a class of 26-membered macrolactones that contain a spiroketal. Oligomycin targets the c subunit, which blocks ATP synthesis and inhibits oxidative phosphorylation.[26] There is a strong interest to develop oligomycin as an anticancer therapeutic due to its selective cytotoxic activity against tumor cells, however, high toxicity and low water solubility hinder its clinical application and development. In addition, oligomycin also inhibits P-glycoprotein (P-gp), and prevents oncogenic K-Ras activation by disrupting its localization to the plasma membrane, further complicating the development of this class of molecules.[27,28]

Limited structure-activity relationship (SAR) studies for oligomycin A have been performed in an effort to overcome these shortcomings (Fig. 3). Side-chain substitutions (azide, triazole and formyl) onto the spiroketal ring resulted in compounds that retained activity against cancer cell lines (human leukemia cell line K562 and colon carcinoma cell line HCT116; IC_{50} = 0.1–1 μM, excepting a COOH derivative) similar to that of oligomycin A.[29,30] 33-Dehydrooligomycin A was ~3.7 times more potent against K-562 cells and ~1.7 times less potent against HCT116 cells when compared to oligomycin A.[31] Enantioselective reduction of the C7 and C11 ketones at provided (7*S*)-dihydrooligomycin A and (7*S*,11*R*)-tetrahydrooligomycin A derivatives that also maintained inhibitory activity against K562 and the doxorubicin-resistant subline, K562/4, but were slightly less active against HCT116 (~3.5-fold) and its doxorubicin-resistant subline HCT116(−/−) (~1.8-fold).[32] The IC_{50} values of a tri-O-acetyl derivative of oligomycin A were 3.1 μM (HCT116 cell line) and 0.9 μM (K562 cell line), while oligomycin A exhibited IC_{50} values of 1 μM (HCT116 cell line) and 0.2 μM (K562 cell line).[33]

YO-001A is a recently identified antifungal macrolide from the oligomycin family that was isolated via a soil sample collected at Toyama Prefecture in Japan (Fig. 3). Compared to oligomycin A, YO-001A does not contain functionalities at C13, C14 and C24. However, YO-001A was shown to inhibit F_1F_O-ATPase with an IC_{50} of 1 μM against isolated bovine heart mitochondria, and demonstrated modest cytotoxicity in the HeLa (IC_{50} = 8.2 μM) and HL-60 (IC_{50} = 5.8 μM) cancer cell lines.[34]

Aurovertins A-E are secondary metabolites that are produced by the fungus *Calcarisporium arbuscular* and contain a polyketide structure, a 2,6-dioxabicyclo[3.2.1]octane ring system and an α-pyrone moiety.[35–39] Aurovertins F-U have recently been isolated from other fungi (Fig. 4).[40–43] Reports of the synthesis and production of aurovertins and structurally related compounds were recently reviewed.[44]

Aurovertin B binds to the β subunits wherein β(Arg412) and β(Tyr458) are responsible for making important interactions that result in the inhibition of F_1F_O-ATP synthase.[45,46] Aurovertin is a mixed, noncompetitive inhibitor of F_1F_O-ATPase. In fact, it inhibits ATP synthesis more strongly than ATP hydrolysis. Interestingly, inhibition of ATP hydrolysis by aurovertin is never complete, even under saturating conditions. A mechanistic study attempted to address the basis for the inhibitory behavior of aurovertin using F_1F_O-ATPase complex from bovine heart mitochondria and *E. coli* membrane.[47] Stoichiometric experiments suggested that two molecules of aurovertin are required to bind the F_1 domain at low substrate concentration, while cooperativity decreases to one at higher concentrations.

This data may explain the differential activity observed for ATP hydrolysis ($K_{i(ES)}$ = 120 nM) vs synthesis ($K_{i(ES)}$ = 25 nM), illustrating the fact that aurovertin exhibits a higher affinity for the F_1 binding site during ATP synthesis. In contrast, loosely bound aurovertin appears to hinder catalytic interactions during ATP hydrolysis, and thus, prolonging ADP-release, which is the rate-limiting step.

Aurovertin B targets the β subunit of ectopic F_1F_O-ATPase in the breast cancer cell lines T-47D, MDA-MB-231 and MCF-7, which also inhibits cellular proliferation with IC_{50} values of 0.89, 5.52, and 0.09 μM, respectively, while remaining relatively non-toxic to the normal MCF-10A human breast cell line at 10 μM.[2,48] In addition, aurovertin B was able to sensitize colorectal cancer cells to recognition and lysis by natural killer cells.[49] Aurovertin P displayed moderate cytotoxicity against various tumor cell lines (SMMC-7721; IC_{50} = 18.3 μM and SW480; IC_{50} = 14.4 μM) whereas aurovertin U inhibited the growth of MDA-MB-231 cells with an IC_{50} of 5.43 μM.[42,43] Interestingly, aurovertin T was ineffective in a cytotoxicity assay, which illustrates the importance of the 2,6-dioxabicyclo[3.2.1]octane system for anti-cancer activity.[43]

Mandelalides are marine macrocyclic polyketides produced by *Lissoclinum* sp; a rare ascidian or sea squirt species (Fig. 5). Mandelalides A-L manifest cytotoxicity against the HeLa cervical and NCI-H460 lung cancer cells with mandelalides A, B, F and L manifesting EC_{50}s at the nanomolar concentration range (2.8 nM to 270 nM).[50–52] Mandelalides A and B, which are similar to oligomycin and apoptolidin, were found to be selective inhibitors of the ATP synthase. The IC_{50} values for inhibition of F_1F_O-ATPase by mandelalides A and C were 2.2 nM and 3.4 μM, respectively.[47] A synthetic ring-expanded isomandelalide A analog exhibited an EC_{50} value of 17 nM and 30 nM against HeLa and NCI-H460 cells, respectively.[53]

Apoptolidin A, a 20-membered macrolide was first isolated by the Seto group in 1993 from the culture broth of *Nocardiopsis* sp.[54,55] Later, Wender's group extracted compounds with a similar structure, which they referred to as Apoptolidins B-D.[56,57] Isolation of apoptolidin E-H followed (Fig. 6) and subsequent studies determined that mitochondrial F_1F_O-ATPase was the molecular target of apoptolidin A.[58–61] Semisynthetic analogs of apoptolidin have also been prepared and evaluated with hopes that compounds exhibiting superior stability and pharmacokinetic properties could be identified.[62–65]

Growth inhibition of human lung carcinoma H292 cells by apoptolidins has been reported to occur at concentrations between 7–150 nM, when the glycoside is present.[56,57] Less active compounds 2′-O-succinyl-apoptolidin A and 3′-O-succinyl-apoptolidin A, were also isolated from *Amycolatopsis* sp. Serrill and co-workers confirmed that apoptolidin A and C activate AMPK, which triggers autophagy in cells containing the sensitive metabolic phenotype.[66,67] Isoapoptolidin A is 10-fold less potent at the inhibition of F_1F_O-ATP synthase as compared to apoptolidin A.[68] The synthetic aglycones, apoptolidinones A and D, were inactive against the H292 cell line highlighting the need for the sugar appendages.[69]

Cruentaren A and B are members of the benzolactone class of macrolides, which were isolated from Myxobacterium *Byssovorax cruenta* and exhibit both antifungal and anticancer activities (Fig. 6). Cruentaren A manifested high cytotoxicity (IC_{50} = 1.2 ng/mL) towards the L929 mouse fibroblast cell line, while congener B was inactive (1 μg/mL).[70] Cruentaren A showed growth inhibition against multiple human cancer cells including cervix carcinoma KB-3–1, multi-drug resistant KB-V1, chronic myelogenous leukemia K-562 and kidney carcinoma A498. Cruentaren A was shown to bind the F_1 domain and to selectively inhibit ATP synthesis with an IC_{50} of 15–20 nM, but without inhibition of Na^+/K^+ ATPase or V-ATPase up to 1 μM concentration.[71] It was reported that F_1F_O ATP synthase acts as an ancillary protein during the Hsp90-mediated protein folding process, which is a promising target for anti-cancer therapy.[72,73] A number of groups have reported the total synthesis and biological evaluation of cruentaren A and a few analogs, which led to the identification of a few key functional groups that are important for inhibitory activity.[74–77]

6.2. Polyphenols

Polyphenols represent a class of natural products found in plants that appear to play a vital role in human health. The protective effects of polyphenols have been widely demonstrated in various diseases such as obesity, neurodegenerative disease, type 2 diabetes, and cardiovascular disease.[78] Polyphenols such as resveratrol, dihydromyricetin and curcumin can affect multiple targets while continuing to inhibit F_1F_O ATP synthase (Fig. 7A).

Resveratrol was shown to interact with a hydrophobic pocket in the F_1 domain that is created between the γ subunit and the β_{TP} subunits. Upon binding, resveratrol blocks rotation of the γ subunit, thereby inhibiting the catalytic activity of the F_1F_O complex.[79] The acetyl and methyl capped analogs (RDA compounds) were also shown to inhibit ATPase at 50 μM, while R-3BTPI and R-4′BTPI did not affect the hydrolytic activity.[80] Resveratrol derivatives with heterocyclic extensions were also synthesized and evaluated for anticancer activity against MCF-7 cells. A synthetic derivative that contains a furan (IC_{50} = 42.7 μM) was 2-fold more potent than resveratrol and appears to inhibit F_1F_O-ATPase.[81]

Dihydromyricetin is a bioactive component that can be isolated from the medicinal plant species, *Ampelopsis*, and exhibits a variety of pharmacological effects such as antioxidant, antibacterial, anticancer, antiobesity and neuroprotective activity. Dihydromyricetin (DHM), a natural flavonoid, inhibits F_1F_O-ATPase activity and increases the AMP/ATP ratio which activates AMPK. The inhibitory activity manifested by DHM induces autophagy and prevents insulin-resistant related metabolic diseases.[82]

Curcumin, found in the rhizome of *Curcuma* sp. has also been reported to inhibit F_1F_O-ATP synthase.[2,83] A synthetic analog, dimethoxycurcumin exhibits cytotoxic activity against MCF-7 cells via induction of reactive oxygen species (ROS), DNA damage, mitochondrial dysfunction, and disruption of the p53/p21/CDK4 pathway. It also decreases cellular ATP levels by suppressing the α, β, γ and ε subunits of the ATPase complex.[84]

6.3. Cationic Inhibitors

Cationic compounds have been shown to accumulate selectively in the mitochondria due to the negative potential that exists across the IMM (Fig. 7B). Therefore, compounds that contain triphenylphosphine moiety or a choline ester that is positively charged are often used to aid uptake into the mitochondria. Some cationic compounds have also been shown to possess favorable pharmacokinetic properties, enhancing their potential for clinical activity.[85]

The alkylphosphocholine or alkylphospholipid (APL) analogs constitute a class of anticancer agents that manifest various medicinal properties and include promising lead compounds/drugs, such as miltefosine, edelfosine, erufosine and perifosine. Miltefosine, sold as Impavido, is the first orally-active treatment for visceral leishmaniasis.[86] Miltefosine is also an ingredient of Miltex, which is used topically for the treatment of skin metastases resulting from breast cancer.[87]

Erucylphosphohomocholine (ErPC3, Erufosine) was shown to target the mitochondria by activating an apoptotic pathway via the 18 kDa Translocator Protein (TSPO).[88] Effects on ROS generation and mitochondrial membrane potential ($\Delta\psi m$) have also been observed with Erufosine. Concomitant treatment of cells with respiratory chain inhibitors and F_1F_O complex inhibitors support a role for the F_O subunit in this apoptotic pathway.[89] Erufosin induced selective apoptosis of a highly apoptosis-resistant malignant glioma cell line, but not normal cells.[90]

The induction of apoptosis by edelfosine was shown to involve the mitochondria and cholesterol-rich lipid rafts. Edelfosine was the most active APL, followed by perifosine, miltefosine and erufosine. These compounds exhibited promising anti-cancer activity against several human cancer cell lines and include leukemia (HL-60, Jurkat and CEM-C7H2), multiple myeloma (MM144), and cervical cancers (HeLa). Genetic deletion in *S. cerevisiae* and other experiments indicate F_1F_O-ATPase plays a critical role in the generation of ROS. Proteomic analysis demonstrated a translocation of the F_1F_O-ATPase β subunit to the lipid raft in drug-treated Jurkat cells. The exact mechanism has not been established, however it appears that edelfosine may perturb membrane integrity, which alters the proton gradient and thus, stimulates the ATP hydrolase activity and cell death.[91]

Fluorone dyes like rhodamine 123 have been reported to inhibit F_1F_O-ATP synthase by binding the F_1 domain.[2,92] Rosamines are a structurally related class of molecules that lack a carboxylic acid at the meso-position on the phenyl ring. Lim and co-workers synthesized 16 rosamine derivatives, two of which contained a thiofuran or a para-iodophenyl substitution at the meso position, which were found to inhibit human leukemia HL-60 at an IC_{50} of ~0.1 μM.[93] These compounds showed potent anti-proliferative activity against several cancers such as colon, breast, oral and nasopharynx. It was proposed that the rosamine derivatives localize specifically to the mitochondria to affect both complex II and the ATP synthase. The thiofuran and para-iodophenyl derivatives inhibited ATP synthase activity with IC_{50} values of 3 and 3.9 μM, respectively. Unfortunately, the thiofuran compounds showed very modest activity in 4T1 murine breast cancer-bearing female BALB/c mice model in terms of tumor growth delay.[94]

A high-throughput screen with primary glioblastoma cells identified the imidazole-based small molecule, Gboxin as an F_1F_O-ATPase inhibitor. It was determined that gboxin binds ATP synthase through various biochemical and pull-down assays. Gboxin also selectively inhibited the growth of cancer cells (IC_{50} = 150 nM against high-throughput GBM sphere cells), while sparring normal embryonic fibroblasts and neonatal astrocytes. Structure-activity relationship studies led to the discovery of S-Gboxin (IC_{50} = 470 nM), which contains a 3-trifluoromethylphenyl group. S-Gboxin decreased the tumor volume in in vivo studies, but failed to ablate the tumor.[95]

6.4. Natural Peptides and Endogenous Ligands

A variety of natural peptides and endogenous ligands have shown diverse activities against F_1F_O ATP synthase on the cell surface, which stimulates downstream effects that ultimately, induce anticancer activity (Fig. 8 and 9).

Efrapeptins are peptaibiotics that contain a 15-mer linear peptide rich in Cα-dialkyl amino acids that are produced non-ribosomally by the fungi, *Tolypocladium*. Structurally, these metabolites consist of non-proteinogenic amino acids such as α-aminoisobutyric acid, isovaline, β-alanine or pipecolic acid, and have an acetylated N-terminus and an unusual cationic C-terminal cap. The co-crystal structure determined efrapeptin to bind the F_1 domain. Efrapeptin inhibits F_1F_O catalytic activity by preventing the β_E subunit to assemble into a conformation that is amenable for nucleotide binding.[96] Efrapeptin displayed potent cytotoxic activity against a variety of organisms via inhibition of the 20S proteasome, F_1F_O synthase and/or other ATPases.[97,98] Efrapeptin F displays preferential cytotoxicity (IC_{50} = 52 nM) to pancreatic cancer cells (PANC-1) under nutrient-deprived conditions in vitro and in vivo.[99] Efrapeptin was also shown to selectively eliminate liver cancer cells that express high levels of SALL4.[100] In addition, interactions between F_1F_O-ATPase and Hsp90 are perturbed by efrapeptins, which resulted in the degradation of select Hsp90 clients as well as decreased levels of Hsp70, Hsp90, and Hsp27.[101]

Yaku'amide A and B are anticancer tetradecapeptides produced by the rare deep-sea sponge, *Ceratopsion*, and contain four β,β-dialkylated α,β-unsaturated amino acid residues.[102] Analysis with synthetic chemical probes of Yaku'amide B revealed it to predominantly localize in the mitochondria and to interact with the F_1F_O-ATP synthase complex, resulting in the growth arrest of MCF-7 (IC_{50} = 10 nM) and P388 mouse leukemia cell lines (IC_{50} = 0.51 nM). Moreover, an unnatural enantiomer of Yaku'amide B was synthesized that inhibited MCF-7 cell growth at 3-fold lower potency as compared to the natural peptide. Yaku'amide B acts via two distinct modes of action; inhibition of ATP synthesis and increased ATP hydrolysis. Yaku'amide B inhibits ATP synthesis 9-fold more effectively than its enantiomer. In contrast, Yaku'amide B enhances the hydrolytic activity of the ATPase complex by 300%, whereas the enantiomer is completely inactive.[103] In addition, 14 stereoisomers of Yaku'amide B were synthesized and evaluated, the results from which indicate non-specific hydrophobic interactions contribute to their inhibitory activity.[104]

Amycolatopsis alba and *Streptomyces* sp. produce ribosomally processed and post-translationally modified peptides (RiPPs), which include thioviridamide, prethioviridamide, JBIR-140, neothioviridamide (thiostreptamide S87 or thioholgamide A), thioalbamide,

thiostreptamide S4, and thioholgamide B. All of these natural products manifest cytotoxicity against various human cancer cell lines and serve as starting points for modern drug discovery efforts.[105–112] These unique peptides contain an unusual thioamide bond. It was determined that prethioviridamide induced the integrated stress response (ISR) via the GCN2-eIF2α-ATF4 pathway by inhibition of the F_1F_O-ATP synthase complex. Thioviridamide and prethioviridamide both exhibit >25-fold selective cytotoxicity towards E1A-3Y1 (transfected with adenovirus oncogene E1A) cells over 3Y1 (rat fibroblasts) cells and were also active against the HeLa S3 human cervical carcinoma cell line.[106,113]

Leucinostatin (LCS)-A, a nanopeptide from the fungi, *Paecilomyces lilacinus*, and its synthetic derivative LCS-7 were shown to inhibit ATP synthase activity (IC_{50} = 2.8 μg/mL). Inhibition of mitochondria ATP synthase activity suppressed the growth of prostate cancer DU-145 cells in vitro and in vivo via reduction of insulin-like growth factor-1 secretion by prostate stromal cells. This activity resulted in strong antiproliferative effects by LCS-A and LCS-7 on DU-145 (androgen-unresponsive) and LNCaP (androgen-responsive) cells in cultures and included prostate stromal cells (PrSCs).[114,115]

PEDF is a multifunctional 50 kDa protein that belongs to the serpin superfamily and is secreted by most cell types. PEDF was shown to bind the β-subunit of ectopic F_1F_O-ATPase on endothelial cells.[116] Structure-activity relationship studies demonstrated that a PEDF-derived 34-mer peptide composed of amino acids 44–77 performed similar to the full-length PEDF peptide as a measurement of ATP synthase inhibiton and anti-tumor activity.[117] The anti-tumor activity against neuroblastoma was first reported by Crawford and coworkers wherein the ganglionic and Schwann cells produced PEDF that inhibited angiogenesis while promoting the growth of Schwann cells.[118] PEDF exhibits promising anti-cancer activity against multiple cancer types such as glioma, breast, lung, prostate, pancreatic carcinomas, ovarian, melanoma, and osteosarcoma.[119] PEDF also modulates interactions between macrophages and prostate cancer cells to induce tumor cell apoptosis and phagocytosis.[120] Moreover, PEDF acts as a tumor-suppressor in fibroblasts as well as in nasopharyngeal carcinoma during epithelial– mesenchymal transition (EMT) and metastasis.[121,122]

Human alpha-lactalbumin made lethal to tumor cells (HAMLET) is a proteolipid complex that manifests anti-tumor activity in in vitro and in vivo studies.[123] HAMLET reduced cellular ATP levels in A549 lung carcinoma cells and was found to localize the α and β subunits of F_1F_O-ATPase. Upon binding to the F_1 domain with a K_D value of 20.5 μM, HAMLET led to reduced rotation rates of the molecular motor.[124]

3-iodothyronamine (T1AM) is an endogenously produced signaling molecule that manifests various physiological properties by the modulation of various extra- and intra-cellular targets (Fig. 9). T1AM was found to be a non-competitive inhibitor of F_1F_O-ATP synthase and binds two different sites; one within the IF1 binding site in the F_1 domain and the other at the aurovertin binding site. The binding of T1AM was mutually exclusive with IF1 and aurovertin B. T1AM increases mitochondrial respiration in H9c2 cardiomyocytes at low nanomolar concentrations by displacing IF1 (high affinity site) at micromolar concentrations, it also binds to the aurovertin site to inhibit enzymatic activity.[125]

α-ketoglutarate (α-KG), an important intermediate in the Krebs cycle was shown to inhibit ATP synthase in bovine heart mitochondria and to extend the lifespan of C. elegans. In a similar manner, both 2-Hydroxyglutarate (2-HG) enantiomers, which are produced by mutant IDH1/2, were also demonstrated to act on F1FO-ATPase in U87 human glioblastoma cells. Accordingly, inhibition of F1FO-ATPase by α-KG or 2-HG was sufficient for antiproliferative and cytotoxic activity in glioblastoma cells under low glucose conditions. [126,127]

6.5. Natural and Synthetic Miscellaneous Modulators

Small molecules from natural as well as synthetic origins have been successfully developed to act on diverse biological targets, including F_1F_O-ATPase (Fig. 10 and 11). In addition, the repurposing of approved drugs has gained momentum to reduce the cost and time needed for lengthy clinical trials. Alternatively, RNA oligonucleotides have been viewed as a potential therapeutic approach due to their high affinity and specificity (Fig. 11).

Fungi such as Penicillium and Aspergillus produce citreoviridin which has been shown to inhibit F_1F_O-ATPase activity by binding to the β subunit at a site different than that of aurovertin.[128,129] Further, it was determined that it acts as an uncompetitive inhibitor of ATP hydrolysis and as a noncompetitive inhibitor of ATP synthesis.[130] Ectopic F_1F_O-ATPase and ETC on lung adenocarcinoma and breast cancer cells has been shown to contribute to tumor growth. Citreoviridin, which inhibits ectopic F_1F_O-ATPase activity, increased the unfolded protein response (UPR) and ROS to selectively block cancer cell proliferation.[131,132] Proteomic analysis of citreoviridin administered in a lung cancer xenograft model suggested that gluconeogenesis is activated by upregulating the expression of gluconeogenic enzymes, namely UDP-glucose pyrophosphorylase, inositol-3-phosphate synthase 1 and aldose reductase. Reduced glycolytic intermediates that are required for macromolecule synthesis resulted in the inhibition of cell proliferation.[133]

Nerolidol or peruviol is a sesquiterpene alcohol present in the essential oils from various plants. Nerolidol is approved by the FDA for use as a flavoring agent in food. Nerolidol also manifests various biological activities including antitumor, antioxidant, anti-inflammatory, antiulcer, and antimicrobial.[134] Nerolidol may affect the activity of F_1F_O-ATPase to decrease ATP/ADP levels in a concentration-dependent manner, as it was shown that nerolidol inhibits F_1F_O ATPase activity at low micromolar concentrations.[135]

A multi-disciplinary study based on chemical proteomics, molecular modelling and bio-organic assays concluded that deglucoruscin, a spirostanol component isolated from an extract of *Ruscus aculeatus*, interacts with F_1F_O-ATP synthase with a K_i value of 10 μM. [136,137] Docking studies suggested that it may bind similar to 8-chloroadenosine and resveratrol and serve as a competitive inhibitor to trap the enzyme in an inactive conformation.[137]

Benzodiazepine (Bz)-423 has been shown to selectively induce apoptosis in $CD4^+$ T cells in an animal model of lupus.[138] The binding site for Bz-423 was localized to a shoulder region of OSCP via NMR spectroscopy and exhibit an allosteric mode of inhibition.[139] This binding site, which is also shared by cyclophilin D, was recently confirmed as the

mechanism by which Bz-423 sensitizes the mPTP to Ca^{2+}.[140–142] Bz-423 reduces the rate of both ATP synthesis and hydrolysis and promotes superoxide formation, which leads to inactivation of anti-apoptotic PI3K-Akt signaling and selective upregulation of Noxa and Bak pro-apoptotic proteins in pathogenic lymphocytes.[143] Bz-423 was also shown to selectively kill alloreactive T cells manifesting graft-versus-host disease in bone marrow transplant models without affecting hematopoietic engraftment or lymphocyte reconstitution both in vitro and in vivo.[144] Two analogs (**1002**, **1118**) that differ by substitutions on the diazepinone ring were reported to manifest comparable activity to Bz-423.[145]

PK11195 inhibits both ATP synthesis (EC_{50} = 33 μM) and hydrolysis (EC_{50} = 230 μM) by presumably by binding the OSCP subunit.[146,147] As a consequence, PK11195 alters the mitochondrial integrity and selectively targets Bcl-2 knockdowned in HeLa cells and chronic lymphocytic leukemia (CLL) cells.[148,149] In comparison, JM-20 inhibits only the hydrolytic activity of F_1F_O-ATPase and increases cellular ATP levels, and thus, manifests cytoprotective activity. This was confirmed by a JM-20 mediated rescue of PC-12 cells at low nanomolar concentrations.[150]

Dexpramipexole is the R-enantiomer of the antiparkinsonian drug, pramipexole, which binds to subunits b and OSCP to increase the rate of ATP synthesis and improve mitochondrial bioenergetics. It was also hypothesized that dexpramipexole binding to the F_O domain could inhibit opening of the mPTP pore.[151] Unfortunately, the cytoprotective effects of dexpramipexole did not yield positive outcomes in a Phase III clinical trial for the treatment of amyotrophic lateral sclerosis (ALS).[152]

Leflunomide is an anti-inflammatory drug that is used for the treatment of rheumatoid arthritis. During an investigation of its off-target effects, it was found that leflunomide and its active metabolite, A771726, inhibited the ATP synthase with IC_{50} values of 35.0 μM and 63.7 μM respectively. The ensuing depletion of ATP levels led to cytotoxic response in HepG2 cells, and provides rationale for the adverse effects manifested by leflunomide on the liver.[153]

A phenotypic screening assay based on age-associated pathologies identified a small molecule (J147) that showed neuroprotective activity in vitro and in vivo.[154,155] J147 was found to localize in the mitochondria and to partially inhibit the ATP synthase (EC_{50} = 20 nM) via modulation of the α subunit. In vivo, J147 prevented age-associated drift in mice and extended the lifespan of drosophila.[155] Based on the structure of J147, a pharmacophore model was built to identify additional compounds (ZINC04549531, ZINC70656000 and ZINC70656005) that exhibited similar biological profiles.[154–157]

ATR-101 (Nevanimibe or PD132301–02) is a urea derivative and a potent acetyl-CoA acetyltransferase (ACAT1) inhibitor. It exhibits anti-tumor activity against the adrenocortical carcinoma (ACC)-derived H295R xenograft model in vivo. Nevanimibe was also found to inhibit F_1F_O-ATP synthase, resulting in mitochondrial hyperpolarization.[158] Evaluation of nevanimibe in a Phase I study concluded that the requisite drug concentrations needed to induce apoptosis was not achieved and thus, resulting in its discontinuation for the treatment of ACC.[159]

BTB06584 was discovered in a chemoinformatic screen based on the structure of BMS199264, which was previously shown to exhibit cardioprotective effects.[160,161] BTB06584 inhibited F_1F_O-ATPase hydrolytic activity while having no effect on ATP synthesis as illustrated by $\Delta\Psi m$ and O_2 consumption. The activity manifested by BTB06584 was dependent upon the expression of IF_1. Docking experiments suggested interactions between BTB06584 and the F_1 portion of F_1F_O-ATPase.[162] Recently, it was shown that BTB06584 increased the sensitivity of non-small cell lung cancer cells to radiotherapy via the inhibition of ATP hydrolysis.[163]

The 1,3,8-triazaspiro[4.5]decane-scaffold represents a first-in-class small molecule mPTP inhibitor that was designed to target subunit c of F_1F_O-ATPase. The triazaspiro core was identified via a high-throughput screen based on a similar region of oligomycin, a well-known inhibitor of mPTP opening.[26] Proximity ligation assay (PLA)-based studies indicated the spiro compounds (**PP11** and analog) to stabilize ATP synthase dimers and desensitize mPTP for protection against cell death in a cardiovascular model of disease.[164]

8-chloroadenosine (8-Cl-Ado) is a ribonucleoside analog that integrates into RNA and inhibits polyadenylation to impede transcription.[165,166] In addition, it decreases cellular ATP levels suggesting an interference with ATP synthase. Molecular docking and functional assays indicated that 8-Cl-ADP and 8-Cl-ATP may act as a substrate and inhibitor of F_1F_O ATP synthase, respectively.[167] This hypothesis is supported by both basal mitochondrial respiration and glycolysis measurements following 8-Cl-Ado treatment.[166] Depletion of ATP levels by 8-Cl-Ado was shown to induce AMPK phosphorylation and inhibit mTOR activity in sensitive clear cell renal cell carcinoma cells.[168] 8-Cl-Ado has entered Phase I/II clinical trial as a single agent for the treatment of relapsed or refractory acute myeloid leukemia (AML) (ClinicalTrials.gov identifier: NCT02509546). Unfortunately, adverse effects of 8-chloroadenosine were recently reported on human coronary artery endothelial cells and macrophages, which may affect clinical advancement.[169,170]

Sorafenib (Nexavar) is a marketed multikinase inhibitor used for the treatment of advanced renal-cell carcinoma and liver cancer.[171] Sorafenib was found to activate ubiquitin E3 ligase Parkin to result in mitochondrial damage. The PINK1-Parkin pathway is activated as a result of dual inhibition of complex II/III (~10 μM) and ATP synthase (~2.5 μM).[172]

Apt63 was identified via a differential Cell-SELEX (Systematic Evolution of Ligands by EXponential enrichment) RNA aptamer that distinguishes ligands based on their selective targeting of the metastatic cancer cells (LN3) in preference to normal and non-metastatic cells (LNCaP and Pro5). The Apt63 aptamer was shown to target ectopic F_1F_O-ATPase at the β-subunit, which led to the translocation of endonuclease G from the mitochondria and into the nucleus, DNA fragmentation, and apoptosis in tumor cells (IC_{50} = 1.030 nM, LN3 cells). Apt63 induced no signs of toxicity to non-transformed epithelial cells in vitro and adjacent normal tissue in vivo.[173]

7. Summary and Outlook

F_1F_O-ATPase is a promising target for the treatment of human disease, as it plays a central role in cellular bioenergetics. During the last decade, new structural and functional information has emerged to help understand the role played by F_1F_O-ATPase during cell growth and survival. While post-translational modifications help to regulate the ATP synthase activity under normal and pathological conditions, additional studies are needed to further deconvolute their effects. For example, Cys244 and Cys294 in the α subunit are S-sulfhydrated by endogenous H_2S to maintain ATP synthase activity under physiological condition.[174] In obese individuals, the phosphorylation of Thr213 and Tyr361 in the β subunit results in an impaired insulin-stimulated glucose disposal, clearly highlighting the opposing roles of post-translational modifications on F_1F_O-ATPase function.[175]

The involvement of F_1F_O-ATPase in mPTP formation is an area of debate. Giorgio and co-workers reported that Ca^{2+} binding to the β subunit can trigger opening of mPTP, which appears to be formed by dimers of the ATP synthase.[142,176] In addition, it was reported that the c subunit is required for mPTP formation along with an uncoupling channel within the c-subunit ring that acts as mPTP.[177–179] In contrast, Walker and coworkers reported persistence of a mitochondrial permeability transition (mPT) in the absence of F_O subunits.[180–182] Bonora et al suggested dissociation of the ATP synthase dimer during mPT.[183]

There is a great deal of published research regarding various small molecule modulators of F_1F_O ATP synthase (Table 2).[2] In fact, ATP synthase modulators can be classified into various classes, such as polyketide, polyphenols, cationic, peptides, endogenous ligands, natural small molecules and synthetic modulators. Endogenous ligands such as IF1 and PEDF play a crucial role in regulating cell survival and tumor growth. IF1 has been shown to exhibit both antiapoptotic and tumorigenic function whereas the silencing of IF1 inhibits bladder cancer growth.[184,185] The overexpression of IF1 inhibits ATP synthase activity in neurons and promotes metabolic reprogramming, highlighting its role in neuroprotection.[186] Inhibition of ectopic ATP synthase leads to intracellular acidification and contributes to the inhibition of cell proliferation. Coupled with the inhibition of ATP synthesis, ectopic ATP synthase inhibitors can induce apoptosis.[187] Ligands such as aurovertin, cruentaren A, resveratrol, efrapeptin, prethioviridamide, PEDF, HAMLET, α-KG, citreoviridin, J147, and Apt63 bind the F_1 domain to modulate ATP synthase activity, whereas oligomycin A, leucinostatins, Bz-423 and dexpramipexole target the F_O subunit.

Combination therapy with ATP synthase inhibitors have also been suggested. In fact, it was shown that citreoviridin along with the 26S proteasome inhibitor, bortezomib, caused higher endoplasmic reticulum (ER) stress and resulted in effective anticancer activity.[132] Similar results were obtained with a combination of efrapeptins and the glycolysis inhibitor, 2-deoxyglucose. However, they acted as an antagonist in vivo, most likely due to the downregulation of F_1F_O-ATPase.[98] Moreover, it was found that acquired resistance to HER2-targeted therapies may render cancer vulnerable to ATP synthase inhibition, suggesting another potential combination strategy.[188]

This new data underscores the role played by ATP synthase in various diseases and highlights new opportunities for drug discovery. In fact, the current work provides a solid foundation for the development of new ATP synthase modulators for the treatment of diseases ranging from cancer to neurodegeneration.

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10. References

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Highlights

- F_1F_O ATP synthase, being the generator of cell energy currency (ATP), plays a pivotal role in cell survival and growth in disease states.
- No current drug has been approved that specifically targets mitochondrial F_1F_O ATP synthase.
- Natural and synthetic modulators of F_1F_O ATP synthase are covered in this review.
- The biological data for small molecule modulators of F_1F_O ATP synthase is presented.

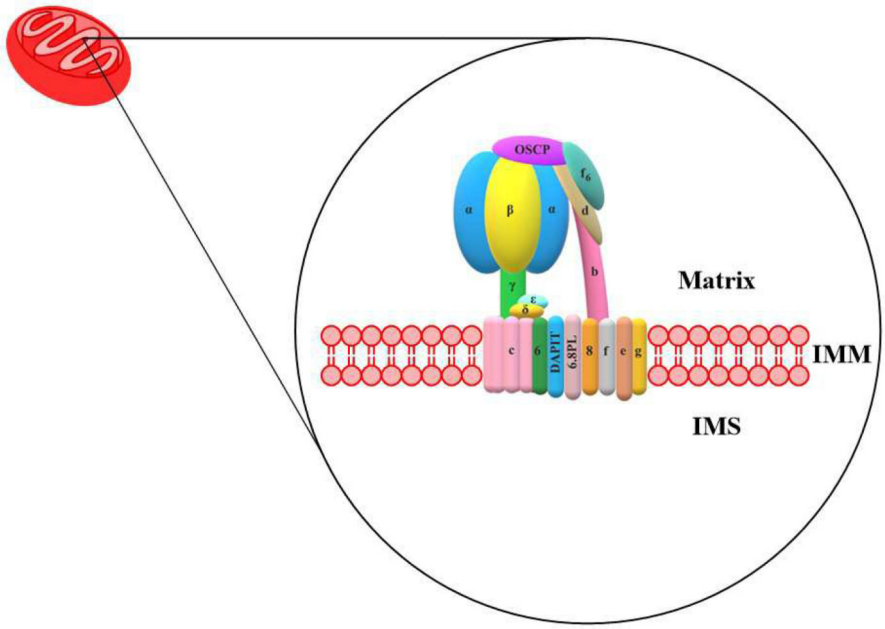


Fig. 1.
Human mitochondria F_1F_O-ATPase.

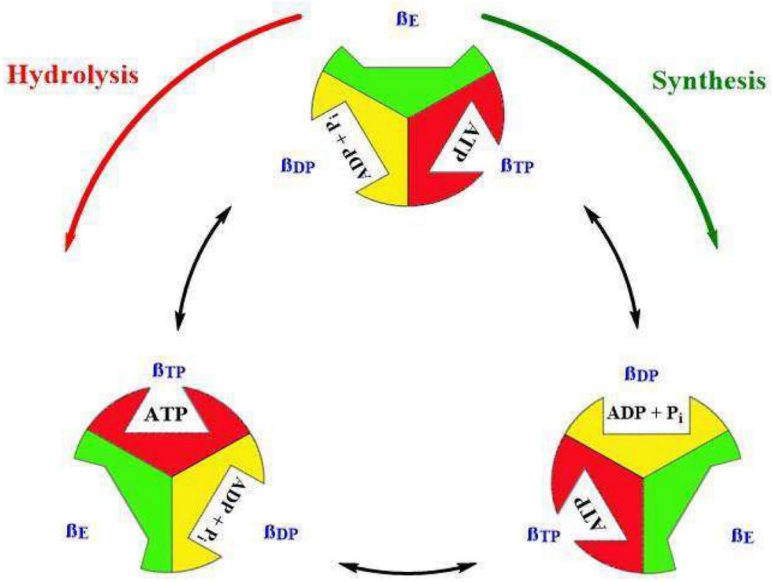


Fig. 2.

F_1F_O-ATPase catalytic states. Open states are shown in green, loose states in yellow, and tight states in red.

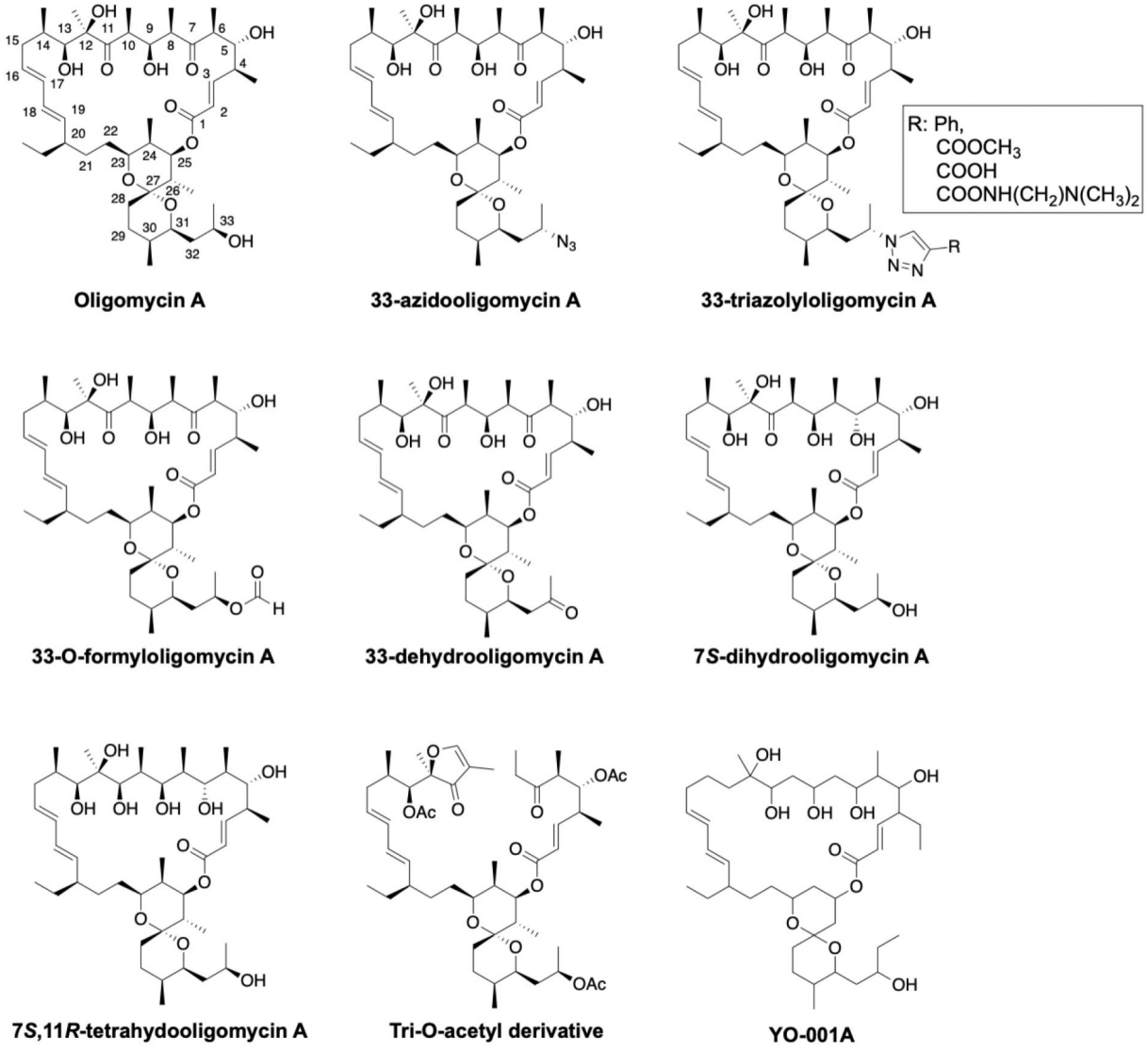
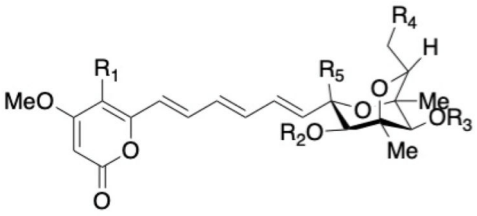
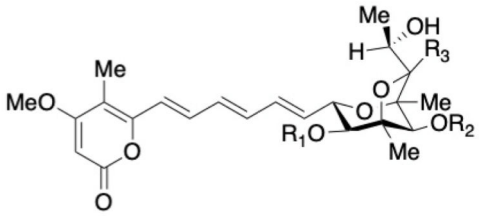


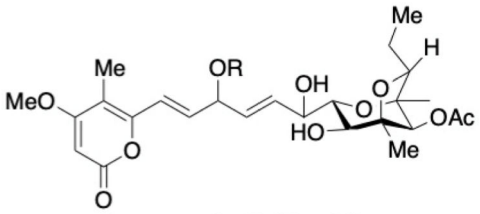
Fig. 3:
Structures of oligomycin A and derivatives



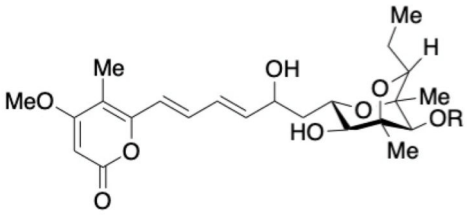
	R_1	R_2	R_3	R_4	R_5
Aurovertin A	Me	Ac	Ac	Me	H
Aurovertin B	Me	H	Ac	Me	H
Aurovertin C	Me	H	Ac	H	H
Aurovertin E	Me	H	H	Me	H
Aurovertin I	Me	H	H	H	H
Aurovertin J	H	H	Ac	Me	H
Aurovertin K	H	H	H	H	Me
Aurovertin M	Me	H	EtCOO	Me	H
Aurovertin U	Me	H	H	H	Me



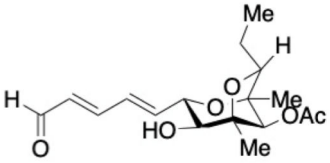
	R_1	R_2	R_3
Aurovertin D	H	Ac	H
Aurovertin F	H	H	H
Aurovertin G	H	Ac	OH
Aurovertin H	Ac	H	OH



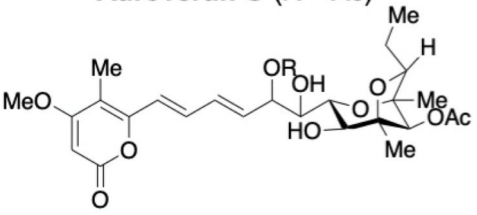
Aurovertin P (R = H)
Aurovertin Q (R = Me)



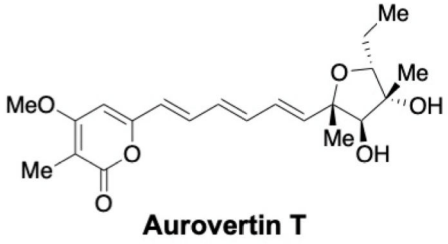
Aurovertin N (R = H)
Aurovertin O (R = Ac)



Aurovertin L



Aurovertin R (R = H)
Aurovertin S (R = Me)



Aurovertin T

Fig. 4:
Structures of aurovertins A-U

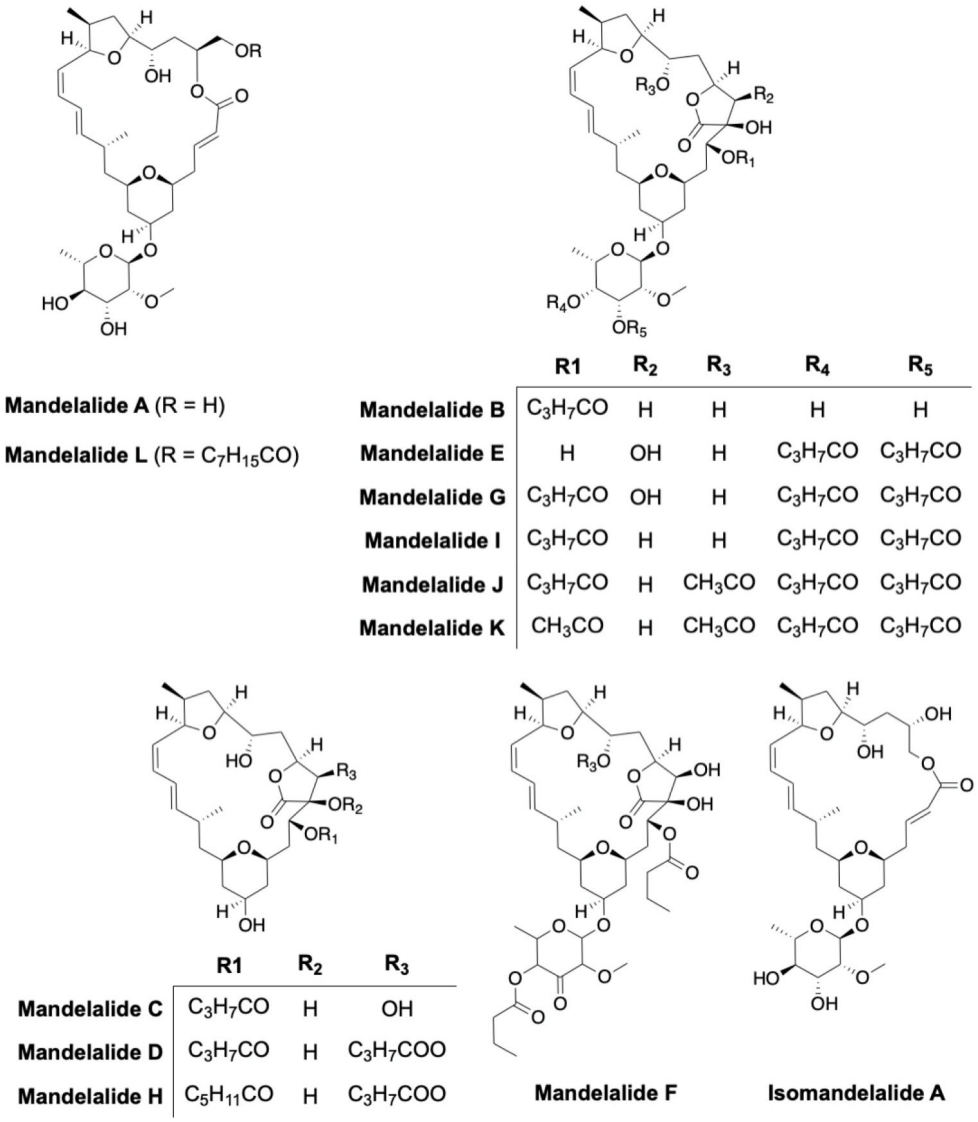
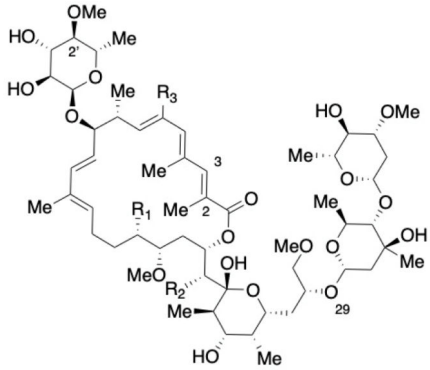
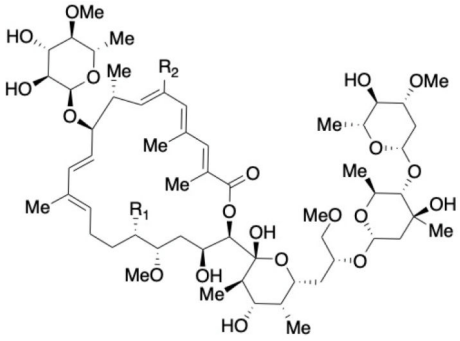


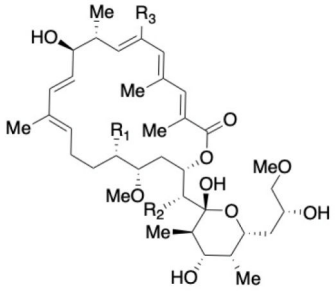
Fig. 5:
Structures of mandelalides A-L and isomandelalide A



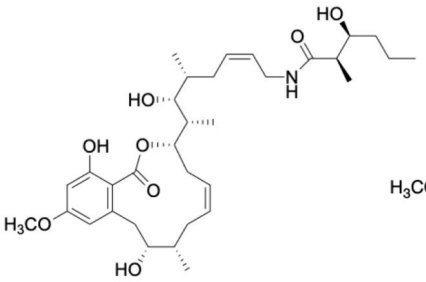


Apotolidin A (R_1 = OH, R_2 = OH, R_3 = Me)
Apotolidin B (R_1 = H, R_2 = OH, R_3 = Me)
Apotolidin C (R_1 = H, R_2 = H, R_3 = Me)
Apotolidin D (R_1 = OH, R_2 = OH, R_3 = H)
Apotolidin E (R_1 = H, R_2 = H, R_3 = Me, C2' = *S*-isomer)
Apotolidin F (R_1 = H, R_2 = H, R_3 = Me, C2' = *S*-isomer, O29 lacks disaccharide)
Apotolidin G (R_1 = OH, R_2 = OH, R_3 = Me, C2-C3 = z-isomer)

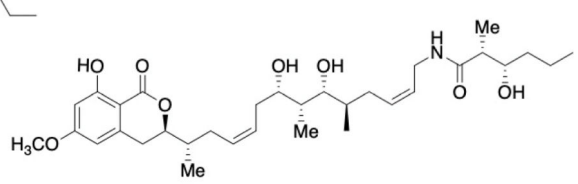
Isoapotolidin A (R_1 = OH, R_2 = Me)
Isoapotolidin B (R_1 = H, R_2 = Me)
Isoapotolidin D (R_1 = OH, R_2 = H)



Apotolidinone A (R_1 = OH, R_2 = OH, R_3 = Me)
Apotolidinone B (R_1 = H, R_2 = OH, R_3 = Me)
Apotolidinone C (R_1 = H, R_2 = H, R_3 = Me)
Apotolidinone D (R_1 = OH, R_2 = OH, R_3 = H)



Cruentaren A



Cruentaren B

Fig. 6:
Structures of apoptolidins A-G, Isoapoptolidin A, B and D, Apoptolidinone A-D and Cruentaren A-B

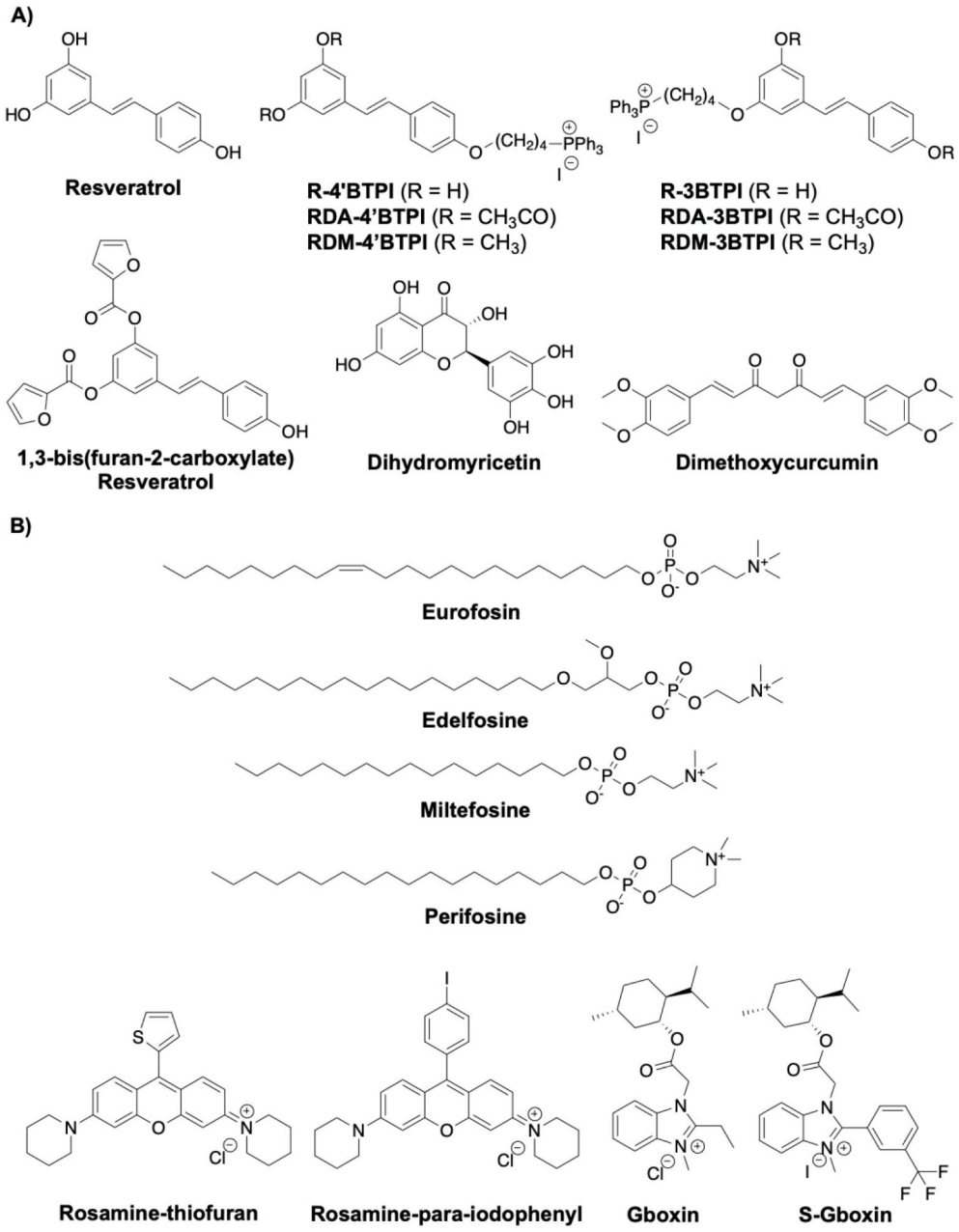


Fig. 7:
Structures of polyphenols and cationic compounds

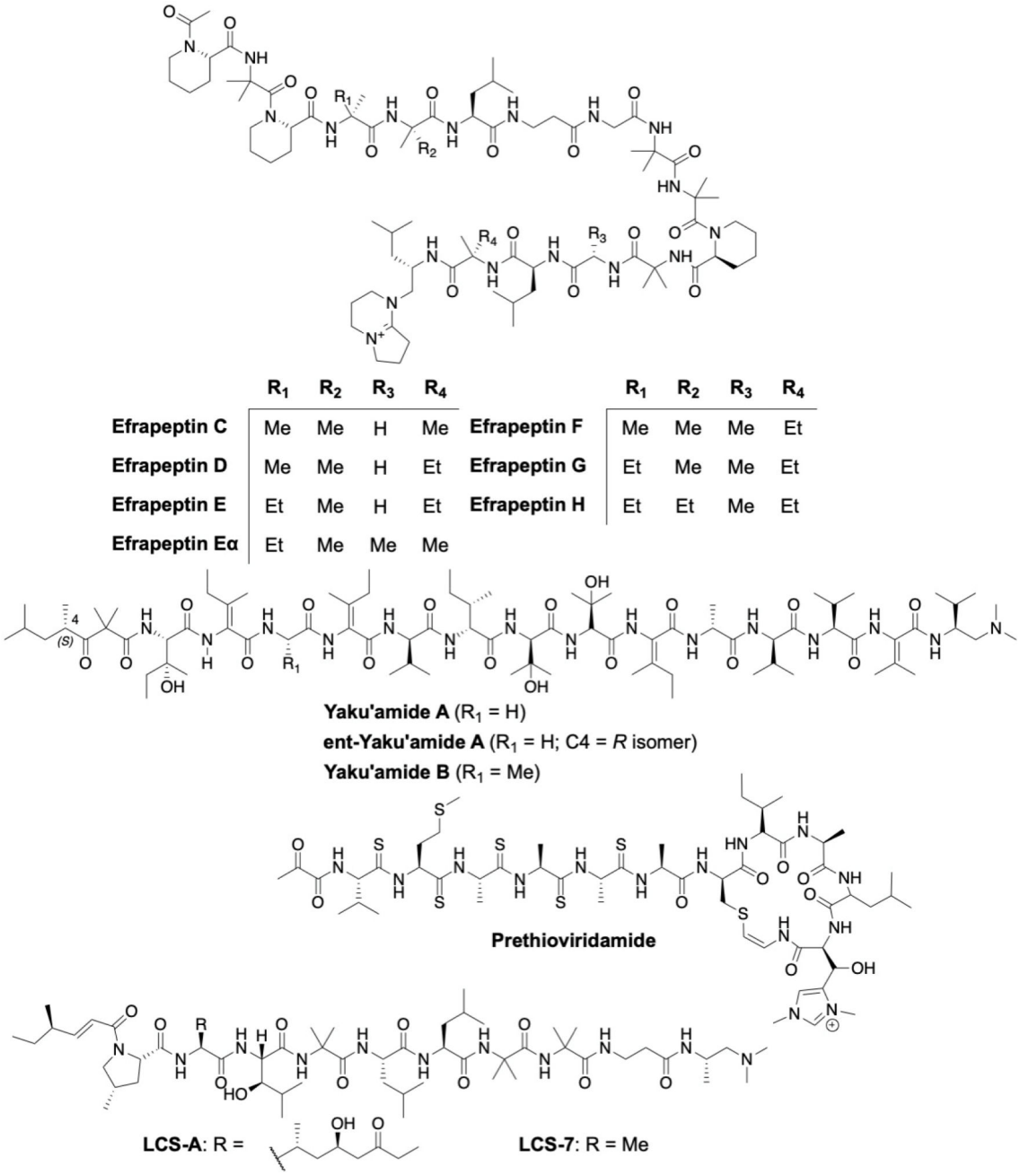


Fig. 8:
Structures of natural peptides

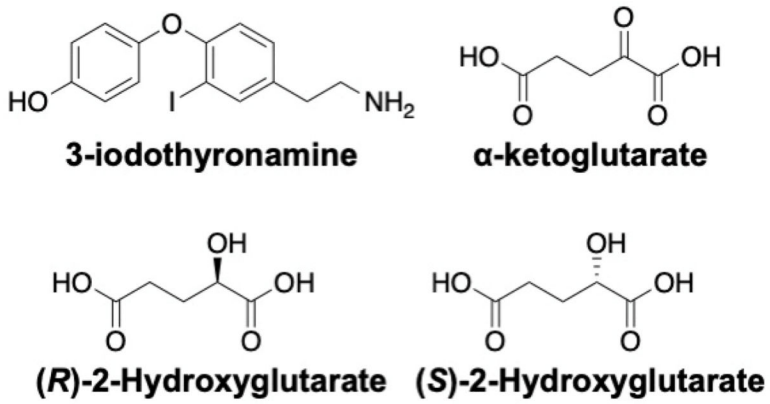


Fig. 9:
Structures of endogenous ligands

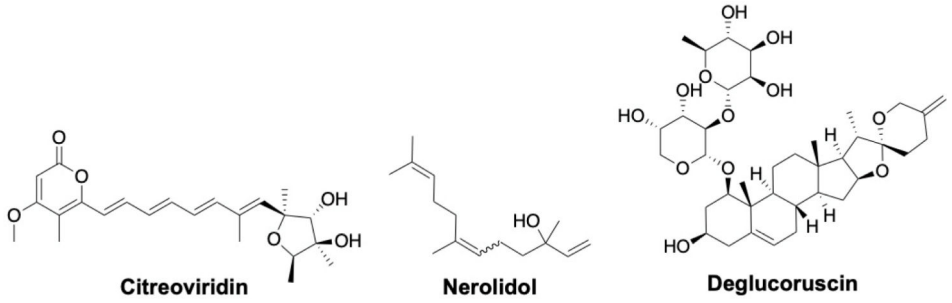


Fig. 10:
Structures of natural small molecules

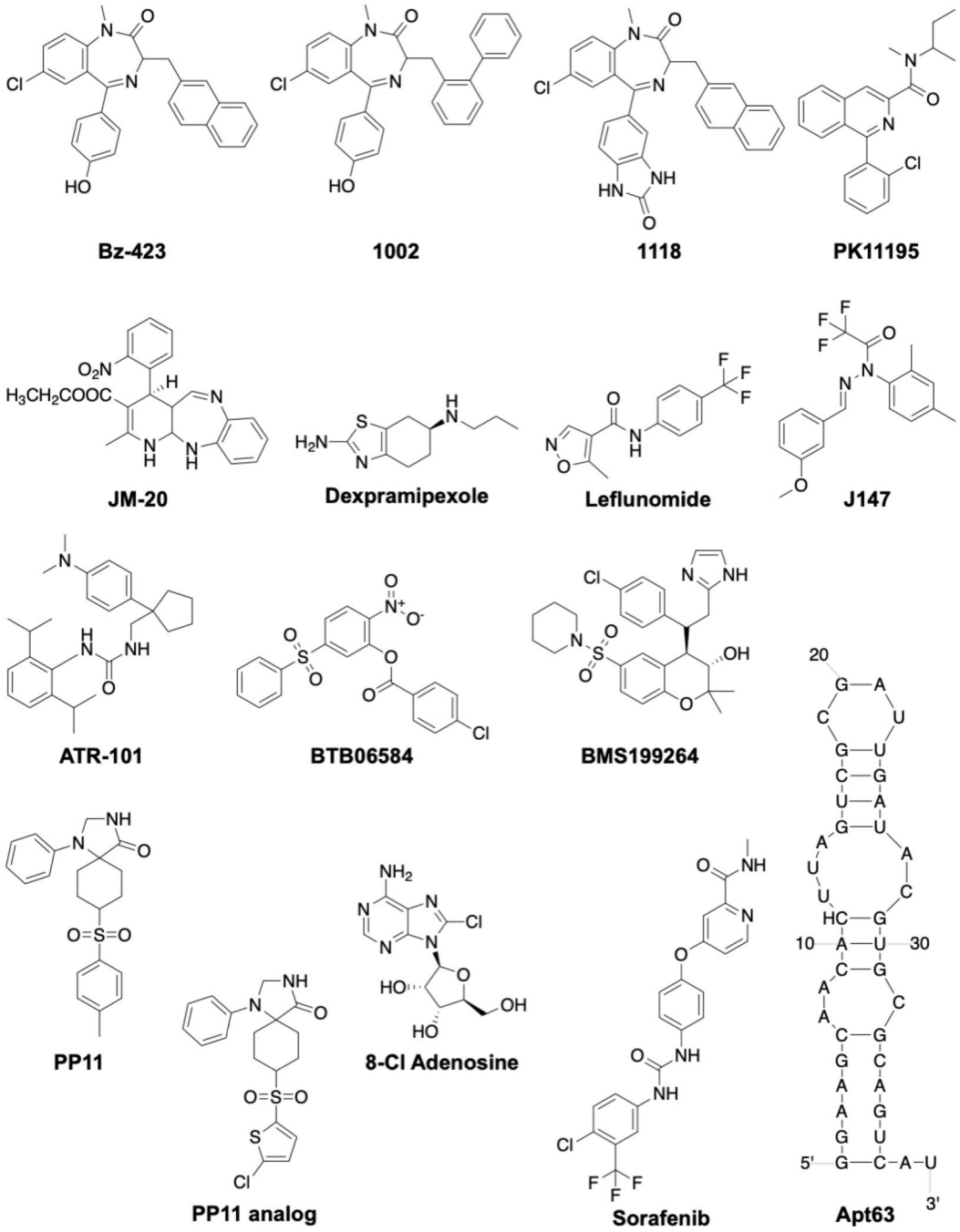


Fig. 11:
Structures of synthetic modulators

Table 1.

Mitochondrial F_1F_O-ATPase subunits and associated genes

Groups	Subunit	Ratio	HGNC Symbol
F_1 Catalytic Head	α	3	ATP5F1A
	β	3	ATP5F1B
F_1 Central Stalk	γ	1	ATP5F1C
	δ	1	ATP5F1D
	ε	1	ATP5F1E
F_O Rotor	6 (ATP6)	1	MT-ATP6
	8 (ATP8)	1	MT-ATP8
	c	8	ATP5MC1
			ATP5MC2
			ATP5MC3
F_O Peripheral Stalk	b	1	ATP5PB
	d	1	ATP5PD
	f_6	1	ATP5PF
	OSCP	1	ATP5PO
F_O Supernumerary Subunits	e	1	ATP5ME
	f	1	ATP5MF
	g	1	ATP5MG
			ATP5MGL
	6.8PL	1	ATP5MPL
	DAPIT	1	ATP5MD
Inhibitory Factor 1	IF1	1	ATP5IF1

Table 2:

Summary of biological activities of F_1F_O ATP synthase modulators

Modulators	Mechanism of action[a]	Biological activity
Polyketide		
Oligomycin A	Targets subunit c to inhibit ATP synthesis and hydrolysis[26]	IC_{50} values: 0.2 μM (K-562), 0.9 μM (HCT116)[31]
YO-001A	Inhibits ATP synthase from isolated bovine heart mitochondria with an IC_{50} of 1 μM[34]	IC_{50} values: 8.2 μM (HeLa), 5.8 μM (HL-60)[34]
Aurovertin B	Aurovertin B and D binds βTP and β_E subunits; Aurovertin B inhibits ATP synthesis (K_i = 25 nM), slows rate of ATP hydrolysis (K_i = 120 nM)[46]	IC_{50} values: 0.89 μM (T-47D), 5.52 μM (MDA-MB-231), 0.09 μM (MCF-7), 14.7 μM (HL-60), 10.8 μM (SMMC-7721), 14.7 μM (A-549), 18.8 μM (MCF-7), 22.4 μM (SW480)[42,43,48]
Aurovertin D		IC_{50} values: 0.08 μM (MDA-MB-231)[43]
Aurovertin E		IC_{50} values: 8.79 μM (MDA-MB-231)[43]
Aurovertins J-S (except P)		IC_{50} values: >40 μM (HL-60, SMMC-7721, A-549, MCF-7, SW480)[42]
Aurovertin P		IC_{50} values: >40 μM (HL-60), 18.2 μM (SMMC-7721), >40 μM (A-549), >40 μM (MCF-7), 14.4 μM (SW480)[42]
Aurovertin T		IC_{50} values: >50 μM (MDA-MB-231)[43]
Aurovertin U		IC_{50} values: 5.43 μM (MDA-MB-231)[43]
Mandelalide A	Mandelalides A and C inhibits ATP synthase with an IC_{50} of 2.2 nM and 3.4 μM respectively[52]	IC_{50} values: 9.9 nM (HeLa), 12 nM (NCI-H460), 44 nM (Neuro-2A)[50,52]
Mandelalide B		IC_{50} values: 23 nM (HeLa), 44 nM (NCI-H460), 84 nM (Neuro-2A), 61 nM (U87-Mg), 54 nM (HCT116)[50–52]
Mandelalide C		IC_{50} values: >3000 nM (HeLa, NCI-H460)[51,52]
Mandelalide D		IC_{50} values: 660 nM (HeLa), 1700 nM (NCI-H460)[52]
Mandelalide E		IC_{50} values: 1900 nM (HeLa), 2000 nM (NCI-H460), >3000 nM (U87-MG), >3000 nM (HCT116)[51,52]
Mandelalide F		IC_{50} values: 50 nM (HeLa), 270 nM (NCI-H460)[52]
Mandelalide G		IC_{50} values: >3000 nM (HeLa, NCI-H460)[52]
Mandelalide H		IC_{50} values: 330 nM (HeLa), 2600 nM (NCI-H460)[52]
Mandelalide I		IC_{50} values: 2000 nM (HeLa), 910 nM (NCI-H460)[52]
Mandelalide J		IC_{50} values: >3000 nM (HeLa), 790 nM (NCI-H460)[52]
Mandelalide K		IC_{50} values: >3000 nM (HeLa), 2400 nM (NCI-H460)[52]
Mandelalide L		IC_{50} values: 2.8 nM (HeLa), 9.8 nM (NCI-H460)[52]
Apoptolidin A	Apoptolidin A inhibits mitochondrial ATP synthase with IC_{50} value of 0.7 μM in mitochondria[62]	IC_{50} values: 32 nM (H292)[56]
Apoptolidin B		IC_{50} values: 7 nM (H292)[56]
Apoptolidin C		IC_{50} values: 24 nM (H292)[56]
Apoptolidin D		IC_{50} values: 110 nM (H292)[57]
Apoptolidin E		IC_{50} values: <100 nM (H292)[58]
Apoptolidin F		IC_{50} values: >1000 nM (H292)[58]

Modulators	Mechanism of action[a]	Biological activity
Apoptolidin G		IC_{50} values: 150 nM (H292)[59]
Isoapoptolidin		17 μM (K_i against isolated yeast mitochondria)[68]
2′-O-succinyl-apoptolidin A		IC_{50} values: 91 nM (H292), 240 nM (HeLa)[66]
3′-O-succinyl-apoptolidin A		IC_{50} values: 82 nM (H292), 260 nM (HeLa)[66]
Cruentaren A	Cruentaren A binds F_1 domain inhibiting beef and yeast ATP synthase with IC_{50} values of 15–30 nM[71]	IC_{50} values: 0.3 ng/mL (KB-3-1), 0.6 ng/mL (KB-V1), 0.6 ng/mL (K-562), 0.1 ng/mL (U-937), 0.4 ng/mL (A-549), 1.0 ng/mL (SK-V-3), 0.4 ng/mL (A-498), 1.2 ng/mL (L929)[70,71]
Cruentaren B		IC_{50} >1000 ng/mL (L929)[70]
Polyphenols		
Resveratrol	Resveratrol binds F_1 and inhibits ATP synthase activity[79]	IC_{50} = 80 μM (MCF-7)[81]
Resveratrol derivatives		RDM and RDA analogs inhibit >40% ATPase activity at 50 μM
Furan-resveratrol		IC_{50} = 42.7 μM (MCF-7)[81]
Dihydromyricetin	Inhibits F_1F_O ATP synthase activity to induce autophagy[82]	Improved skeletal muscle insulin resistance in rat skeletal muscle L6 myoblast cells[82]
Dimethoxycurcumin	Suppressed levels of the α, β, γ and ε subunits[84]	Cytotoxic to MCF-7 cells at 5–50 μM[84]
Cationics		
Alkylphosphocholines	Translocates β subunit to lipid raft[91]	Induced apoptosis-like cytotoxicity in HL-60, Jurkat, CEM-C7H2, MM144, HeLa cells[91]
Rosamines	Inhibits ATP synthase activity with IC_{50} of 3–4 μM[94]	IC_{50} = 0.1 μM (HL-60)[93]
Gboxin	Inhibits ATP synthase activity[95]	Gboxin: IC_{50} = 150 nM and S-Gboxin: IC_{50} = 470 nM (high-throughput GBM sphere cells)[95]
Natural peptides		
Efrapeptin D	Binds F_1 preventing β_E to assume nucleotide binding conformation and disrupts interactions between F_1F_O-ATPase and Hsp90[96,101]	IC_{50} = 15 nM (SNU-398 with $SALL4^{hi}$)[100]
Efrapeptin Eα		IC_{50} = 5 nM (SNU-398 with $SALL4^{hi}$)[100]
Efrapeptin G		IC_{50} = 9 nM (SNU-398 with $SALL4^{hi}$)[100]
Efrapeptin H		IC_{50} = 6 nM (SNU-398 with $SALL4^{hi}$)[100]
Efrapeptin F		IC_{50} = 52 nM (PANC-1)[96,99]
Yaku’amide A	Yaku’amide B inhibits ATP synthesis and increases rate of ATP hydrolysis[103]	IC_{50} = 0.88 nM (P388)[102]
Yaku’amide B		IC_{50} = 0.51 nM (P388), IC_{50} = 10 nM (MCF-7 and P388)[102,103]
Thioviridamide	Prethioviridamide binds β subunit in the F_1 domain[113]	IC_{50} values: 3.9 ng/mL (Ad12-3Y1), 32 ng/mL (E1A-3Y1), 630 ng/mL (SR-3Y1), 460 ng/mL (SV-3Y1), 200 ng/mL (HR-3Y1), 38 μM (SKOV-3), 27.8 μM (Meso-1), 12.5 μM (Jurkat)[105,107]
Thioalbamide		IC_{50} values: 48 nM (A549), 59 nM (MCF7), 72 nM (MDA-MB-231), 50 nM (HeLa), 65 nM (PA-TU-8988T)[110]

Modulators	Mechanism of action[a]	Biological activity
Neothioviridamide/ Thioholgamide A/ thiostreptamide S87		IC_{50} values: 2.1 μM (SKOV-3), 0.7 μM (Meso-1), 0.4 μM (Jurkat), 0.176 μM (HCT116), 0.141 μM (Huh7), 0.48 μM (MCF7), 1.16 μM (A549), 0.157 μM (RIL175)[108,111,112]
JBIR-140		IC_{50} values: 10.8 μM (SKOV-3), 14.3 μM (Meso-1), 5.4 μM (Jurkat)[107]
Prethioviridamide		IC_{50} values: 0.36 μM (HeLa S3), 16 nM (Ad12-3Y1), 21 nM (E1A-3Y1)[106,113]
Thioholgamide B		IC_{50} values: 1.47 μM (HL60), 0.83 μM (MCF-7), 5.02 μM (H1299), 1.18 μM (LOVO), 20.89 μM (SKOV-3), 5.28 μM (Jurkat), 0.51 μM (HCT116), 4.49 μM (KB-3-1), 12.17 (SW480), 16.94 μM (U937)[109,111]
Thiostreptamide S4		IC_{50} values: 0.61 μM (HL60), 4.98 μM (MCF-7), 5.08 μM (H1299), 1.83 μM (LOVO)[109]
Leucinostatins (LCS-A and LCS-7)	Binds the F_O domain of ATP synthase; IC_{50} = 2.8 μg/mL[114]	DU-145 cells cocultured with PrSCs vs DU-145 cells monoculture (LCS-A: coculture IC_{50} = 0.045 μg/ml, monoculture IC_{50} > 1 μg/ml; LCS-7: coculture IC_{50} = 0.21 μg/ml, monoculture IC_{50} > 1 μg/ml); Maximum tolerated dose in mice: LCS-A (2.5 mg/kg) and LCS-7 (12.5 mg/kg)[114,115]
Endogenous ligands		
Pigment epithelium-derived factor (PEDF)	Binds β subunit on the ectopic ATP synthase[116]	Showed anticancer activity in vitro and in vivo against lung, breast, prostatic, ovarian and pancreatic carcinomas, melanoma, glioma, as well as osteosarcoma[119]
HAMLET	Binds F_1 domain with K_D value of 20.5 μM[124]	A peroral agent for colon cancer, with APC mutation, prevention and treatment[123]
3-iodothyronamine	Non-competitive inhibition of ATP synthase (IC_{50} = 27.5 μM), binds at two different sites (IF1 and aurovertin binding sites)	Increased ATP synthesis at low concentration (50 nM) in H9c2 cells by displacing IF1[125]
α-KG and 2-HG	Binds the β subunit of ATP synthase	Extends the lifespan of adult Caenorhabditis elegans[126,127]
Natural small molecules		
Citreoviridin	Binds β subunit and inhibits ecto-F_1F_O-ATPase; uncompetitive inhibitor of ATP hydrolysis and as a noncompetitive inhibitor of ATP synthesis[128,130]	IC_{50} values: 1.5 μM (A549), 4.65 μM (CL1-0); cytotoxic to MCF7, T47D, and MDA-MB-231 cells[131–133]
Nerolidol	Inhibits ATP synthesis at 1.2 and 2.4 μM	Inhibited cell proliferation of HepG2 cells[135]
Deglucoruscin	Inhibits F_1F_O-ATPase with K_i = 10 μM[137]	Reduced thrombin-induced hyperpermeability of endothelial cells (HMEC-1) by 41.9%[137,189]
Synthetic modulators		
Bz-423	Binds OSCP disrupting OSCP-F_1 interactions[139]	Keratinocyte EC_{50} Bz-423: 3.1 μM 1002: 2.2 μM 1118: 2.1 μM[145]
PK11195	Inhibits ATP synthesis (EC_{50} = 33 μM) and hydrolysis (EC_{50} = 230 μM)[146]	IC_{50} values: 5.4 nM (MCF-7) 6 nM (T47D)[190]

Modulators	Mechanism of action[a]	Biological activity
JM-20	Inhibits 67% ATP hydrolytic activity at 5 μM concentration	Rescued PC-12 cells from glutamate and KCN induced damage with IC_{50} of 29 nM and 8 nM respectively[150]
Dexpramipexole	Binds subunits b and OSCP[151]	Increased mitochondrial ATP production and resistance to in vitro ischemia of primary cultures of neurons or glia[152]
Leflunomide	Inhibits ATP synthase activity, IC_{50} = 35 μM	IC_{50} = 109.5 μM (HepG2)[153]
J147	Targets α subunit; EC_{50} = 20 nM[155]	Rescued primary embryonic cortical cells with an EC_{50} of 25 nM; Blocked extracellular amyloid toxicity using rat hippocampal neurons with an EC_{50} of about 200 nM[154]
ATR-101	Depletes ATP levels by inhibiting ATP synthase	Inhibited proliferation of H295R cells in vitro and in vivo[158]
BTB06584	Selectively inhibits ATP hydrolysis[162]	Enhanced radiosensitivity in non-small lung cancer cell[163]
1,3,8-Triazaspiro[4.5]decane	May bind subunit c to affect mPTP	Inhibited mPTP opening and protected against cell death in cardiovascular model[164]
8-Cl adenosine	8-Cl ADP may act as a substrate and 8-Cl ATP as an inhibitor of ATP synthase[167]	IC_{50} = 2 μM (CAKI-1), tumoricidal to MCF-7 and active in in vivo BT-474 tumor[166,168]
Sorafenib	Dual inhibition of complex II/III and ATP synthase (IC_{50} = 2.5 μM)	Broad spectrum marketed anti-tumor drug for treatment of renal-cell carcinoma and liver cancer[171,172]
Apt63	Targets β subunit on ectopic ATP synthase	IC_{50} = 1.030 nM (LN3)[173]

[a]For certain modulator classes, mechanism of action was tested only for one or two members. It is assumed that compounds from the same class act via similar mechanism of action.