Targeting the Resistance of Pancreatic Cancer Cells to Nutrient Deprivation: Anti-Austerity Compounds

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ABSTRACT

The emerging "anti-austerity" anti-cancer therapeutic strategy targets the ability of certain cancer cell lines, particularly pancreatic cancer, to survive nutrient deprivation. While biochemical pathways for the tolerance to nutrient deprivation are still not well understood, a growing number of inhibitors of this process are being discovered. A number of natural products have been isolated, structurally characterized and evaluated as inhibitors of austerity, thereby providing valuable initial structure-activity relationship data.

KEY WORDS

pancreatic cancer, nutrient deprivation, natural product, anti-austerity

INTRODUCTION

Our efforts toward the chemical synthesis and discovery of anti-pancreatic cancer compounds with novel modes of action led us recently to complete the first total synthesis of anti-austerity agent (+)-angelmarin. [1] First proposed by the Esumi group in 2000, the anti-austerity therapeutic strategy targets the extraordinary ability of some cancers to survive and proliferate in conditions of extreme nutrient deprivation. [2] In particular, pancreatic cancers demonstrate remarkable in vitro austerity, or resistance to starvation, relative to other cancer cell lines and non-cancerous tissue cells. [2] In the past few years some details of the biochemical mechanisms and components of the austerity process have been elucidated and dozens of small molecule inhibitors of austerity have been identified. This review offers an overview of the research in this field to date; with a focus on the structural characteristics of known anti-austerity agents.

PANCREATIC CANCER IS A TRAGIC UNSOLVED HEALTH PROBLEM

The overall 5-year survival rate for pancreatic cancer patients is less than all other major cancers at 3–5%. Globally, more than 232,000 new cases of pancreatic cancer are diagnosed each year. In the United States this cancer is the fourth leading cause of cancer death for men and women. Risk factors include smoking and age, but primary causes of the disease are poorly understood. [3-5]

A number of factors contribute to the extremely poor prognosis of pancreatic cancer. Firstly, this cancer is one of the most insidious and aggressive of all human malignancies and most patients are suffering from advanced metastatic disease at first diagnosis. Fewer than 10% of cases present with the disease locally confined to the pancreas. Secondly, there is a terrible paucity of effective therapies for pancreatic cancer. The administration of conventional anti-cancer therapeutic agents has little impact on the disease. Currently, surgical resection is the only potentially curative therapy, yet just 15–20% of patients have operable tumors and a high incidence of recurrence leaves just 20% of surgery patients

surviving for 5 years. [3] Since its approval in 1996, gemcitabine has been the standard palliative treatment for metastatic or advanced pancreatic cancer, however it offers very little survival benefit. [6, 7]

The limited clinical trial successes of various chemotherapeutic combinations, chemoradiation, adjuvant and neo-adjuvant therapies, second-line therapies, and novel targeted therapies have been reviewed recently. [8, 9] Notably, erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, has demonstrated modest survival benefit in combination with gemcitabine in a phase III clinical trial. [10] Continued trials of chemotherapeutic combinations and adjuvant therapy are ongoing. However, it is clear that any prospects for a major improvement in prognosis will likely rely on much improved early detection methods, or novel drugs based on new therapeutic strategies resulting from an improved understanding of the pathogenesis of pancreatic cancer.

PANCREATIC CANCERS ARE DEPRIVED OF NUTRIENTS AND OXYGEN

Despite their aggressive and rapidly growing nature, pancreatic tumors are known to be chronically deprived of nutrients and oxygen. Angiographic, [11] sonographic, [12, 13] and computed tomographic [14] investigations indicate that most pancreatic cancers are hypovascular. Indeed, as a general characteristic, in contrast to normal tissues, many rapidly growing solid tumors exhibit abnormal and inadequate vasculature resulting in the development of microenvironments characterized by fluctuating oxygen and nutrient supply and low pH. [15-18]

Ironically, rather than hinder cancer progression, these hostile metabolic conditions are correlated with poor outcomes for patients. [19] Metabolic stress contributes to genomic instability, impaired cellular repair functions, and mutagenesis, fostering the development of malignant and increasingly aggressive cancer cells. [20, 21] Furthermore, nutrient deficiency has been linked to the induction of resistance to

chemotherapy, [22, 23] photodynamic therapy, [24] and radiation-induced oxidative stress. [25] Nutrient deprivation also contributes to the formation of quiescent regions in tumors that are immune to many chemotherapeutics that target proliferating cells. [26] Hypoxia triggers a number of cellular responses that enhance cancer progression and contribute to treatment failure. Activation of hypoxia-inducible factor (HIF-1) regulates a large panel of genes that are exploited by tumor cells for survival. [27-31]

A primary cellular response to hypoxia is the recruitment of new blood vessels - angiogenesis. [32-36] Inhibition of this malignancy-associated process has now become a well-established strategy in novel chemotherapeutic development. [37-41] In addition, the inherent differences between tumor blood vessels and those of normal tissue offer an additional potential target for novel therapeutics termed vascular targeting agents. [42] Both angiogenesis inhibitors and vascular targeting agents endeavor to kill tumor cells by selectively depriving them of oxygen and nutrients which are pivotal to the maintenance of cellular function and integrity. In this light, highly aggressive cancers that are already chronically hypoxic and nutrient deprived, such as pancreatic cancer, present a curious dilemma. Despite considerable evidence of angiogenesis, [43-52] many pancreatic tumors remain hypovascular, hypoxic, and starved for nutrients, and they not only survive in these conditions, but are able to grow aggressively.

THE ANTI-AUSTERITY THERAPEUTIC STRATEGY

Two obvious questions emerge from these observations. 1) How do these cancers survive and proliferate with seemingly insufficient nutrient supply? 2) How do pancreatic cancers compare to other cancers or non-cancerous cells in this respect? These issues were addressed by means of an elegant

experiment by Esumi and co-workers in 2000. [2] The researchers cultured various liver, pancreas, gastric, and colon cancer cell lines in nutrient deprived media, free of serum, glucose, and amino acids and measured cell viability against time. Under these conditions, in which 100% of normal human fibroblasts underwent apoptosis within 24 hours, pancreatic cancer cells demonstrated an extraordinary capacity for survival. Of the sixteen cancer cell lines tested, four pancreatic cancer cell lines (PANC-1, AsPC-1, BxPC-1, and KP-3) were most resistant to starvation with >50% survival after 48 hours and a small portion of cells even functioning after 72 hours. One gastric (MNKN45) and three colon cancer cell lines (SW480, WiDr, and DLD-1) also showed notable survival ability with >50% cell survival after 36 hours.

Explaining this remarkable resistance to starvation, labeled ‘austerity’ by Esumi, and identification of the specific biochemical components of the process has subsequently proven to be a challenging task. Tumor cells acquire numerous modifications that allow for unregulated growth and the bypass of endogenous control mechanisms. Resistance to starvation may certainly benefit rapidly proliferating cells that, despite functioning angiogenesis, are likely to encounter nutrient shortages. Along with inhibition of apoptosis, it is reasonable to assume that such resistance may involve modifications to cellular metabolism and may yield novel targets for selective chemotherapeutic agents. [53, 54] Indeed, the significance of cellular energy metabolism and metabolic adaptation in cancers has not only been long recognized, [55-57] but has also recently begun to emerge as a prominent theme in cancer biology. [58-60] In fact, a dedicated issue of *Seminars in Cancer Biology* titled ‘The Warburg Effect’, after the German Nobel Laureate Otto Heinrich Warburg who first described the vital link between cancer and cellular metabolism, appeared in 2009 with a number of review articles describing the re-emergence of metabolism research in cancer. [61-69]

The details of the biochemical mechanisms that enable pancreatic cancer cells to resist nutrient starvation continue to be elucidated and a large number of proteins and pathways have been implicated in recent years. Among these, hypoxia-inducible factor 1 (HIF-1) [38, 65, 70-74] and the serine/threonine kinase Akt, also known as protein kinase B, (PKB) [64, 75-82] have been prominent. Esumi and co-workers identified phosphorylation of Akt/PKB as a characteristic of starvation resistance among their initial observations [2]. Other proteins and pathways that have been related to tolerance to nutrient deprivation include: AMPK [83-86] and related family member ARK5 [87-93], hexokinase-2 [68], the Bcl-2 family of proteins [62, 94], the phosphatidylinositol 3-kinase (PI3k)/AKT/survivin pathway [95-98], insulin-like growth factor-1 receptor tyrosine kinase (IGF-1)[99-102], mammalian target of rapamycin (mTOR) [103], p53 tumor suppressor [67], glucose transporters GLUT 1, 3 and 4 [104, 105], peroxisome proliferator-activated receptors γ (PPAR γ) [106-108], angiotensin II type 1 (AT1) receptor [109], NF-E2-related factor-2 (Nrf2) [110], protease-activated receptor (PAR)-2, [111], protein kinase Cζ (PKCζ) [112], class I and II histone deacetylases (HDACs) [113], N-myc [114], Abl kinases [115], , type II hexokinase (HKII) and aldolase B (ALDOB) [116], Uev1A and the NF-kappaB signaling pathway [117], matrix metalloproteinase-9 (MMP-9) [118], cyclin-dependent kinase inhibitor 1B (CDKN1B or p27Kip1) [119], glucose regulated protein-78 (GRP78) and transcription factor c-Myb [120, 121], hepatocyte growth factor/scatter factor (HGF/SF) [122], the unfolded protein response (UPR) pathway [123, 124], and mucin 1 (MUC1). [125]

Furthermore, the role of autophagy, a process of self-cannibalism by which cells recycle constituents or eliminate damaged organelles, has been a controversial topic in this field. Autophagy is known to play a role in tumor suppression via programmed cell death [126, 127] but can also act as a pro-survival mechanism by providing a source of energy to cells under metabolic stress. [128-132] This interesting dichotomy of autophagy in cancer has been recently reviewed. [129, 133, 134] The potential survival

value of the related phagic process of xeno-cannibalism, the engulfing and digestion of entire cell siblings, was also recently reviewed. [135, 136]

INHIBITORS OF AUSTERITY

While elucidation of the relevant biochemical process has been underway, the search for anti-austerity agents, or inhibitors of the exceptional tolerance of pancreatic cancers to nutrient deprivation, also began as soon as this tolerance was identified. Esumi and co-workers described a simple high-throughput screening method for anti-austerity activity. [137] In parallel, two PANC-1 cell cultures (this has been the cell line of choice for anti-austerity screening) are grown in two different growth media: one in nutrient deprived medium free of glucose, serum, and amino-acids (NDM) and the other to ordinary nutrient rich medium (Dulbecco's modified Eagle's medium, DMEM). The cells are then treated with serial dilutions of the test samples and incubated for 24 hours, at which point cell survival is measured using one of various available methods. Compounds that are cytotoxic in NDM, without cytotoxicity in DMEM are judged to be anti-austerity agents. The results of this assay are generally presented as either an *observed* preferential cytotoxicity (PC_{100}) corresponding to the lowest concentration (μM) of test compound at which 100% cell death occurs or as a *calculated* PC_{50} concentration (μM) determined from the cell viability vs. concentration curve in nutrient deprived medium. In most cases, compounds with $PC_{100} > 100$ μM are described as inactive.

This simple assay method allows for the identification of anti-austerity agents without the isolation or even knowledge of specific protein targets. The first two compounds identified with anti-austerity activity were troglitazone (**1**, 20 μM), a known insulin sensitizer and LY294002 (**2**, 50 μM), a phosphatidylinositol-3-kinase (PI3K) inhibitor (**Fig. 1**). [2] Interestingly, troglitazone caused necrotic

cell death while LY294002 induced apoptosis. Furthermore, a second and more potent PI3K inhibitor, wortmannin, did not display anti-austerity activity, indicating a complexity beyond a simple direct relationship between PI3K activity and austerity.

Recently, Momose and co-workers tested more than fifty established small molecule inhibitors of known protein targets, for anti-austerity activity against PANC-1. Just two compounds were identified, the IGF-1R inhibitors AG1024 (**3**) and I-OMe-AG538 (**4**), to be selectively toxic in nutrient deprived medium at 1 μM (**Fig. 1**). [100] The remainder of the ligands screened by Momose, none of which displayed anti-austerity activity at 1 μM, are listed in Table 1.

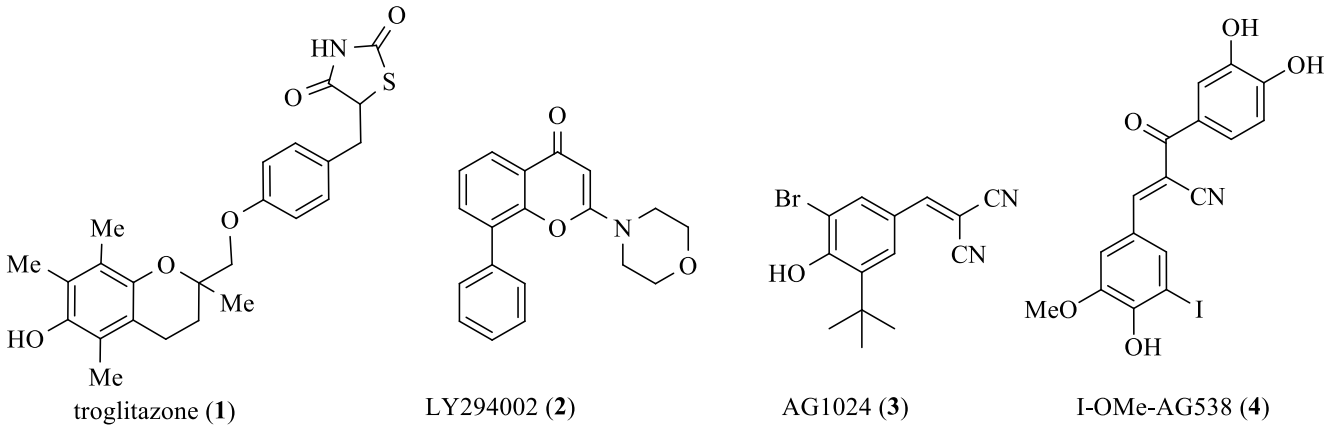
Table 1. Bioactive Compounds Acting on Established Targets That Do Not Inhibit Austerity of PANC-1 at 1μM. [100]

Target (detail)	**Compound**	**Target**	**Compound**
antitumor (thymidylate synthetase)	5-FU	HMG-CoA reductase	Lovastatin
antitumor (aminopeptidase B)	Bestatin	HSP90	Radicicol
antitumor (DNA)	Bleomycin	HSP90	17-AAG
antitumor (DNA)	Cisplatin	iNOS	1400W, HCl
antitumor (DHFR)	Methotrexate	iNOS	AMT, HCl
antitumor (DNA)	Mitomycin C	Jak-2	AG490
antitumor (tubulin)	Vinblastine	Jak-2	Cucurbitacin I
antitumor (tubulin)	Paclitaxel	JNK	SP600125
antitumor (AR)	Flutamide	lck (p56), TYK	Damnacanthal
antitumor (DNA)	Daunorubicin	MEK	PD 98059
antitumor (DNA)	Doxorubicin	MEK	U0126
antitumor (ER)	Tamoxifen	methionine aminopeptidase	Fumagillin
antitumor (RNA)	Actinomycin D	MMP	GM 6001
antitumor (topo I)	Camptothecin	NF-kB	N-Acetyl-L-cysteine
antitumor (topo I/II)	Aclarubicin	NOS	Aminoguanidine
antitumor (topo II)	Etoposide (VP-16)	NOS	L-NMMA
actin filament	Cytochalasin D	p38 (MAPK)	PD169316
adenylcyclase	2',5'-dideoxyadenosine	p38 (MAPK)	SB 203580
AKT	AKT inhibitor	p70 S6K	Rapamycin

AKT	NL-71-101	PARP	NU1025
Bcr-Abl	AG957	PARP-1	Benzamide
CAMKII	KN93	PC-PLC	D609
caspase	Z-VAD-FMK	PDE	IBMX
CDC2	Kenpaullone	PDE (cAMP)	Ro-20-1724
CDK2	Purvalanol A	PDE (cGMP)	Zaprinast
CDK4	3-ATA	PDGFR	AG1296
CDKs	Olomoucine	PI3K	LY294002
CKII	TBB	PI3K	Wortmannin
COX-1	Sulindac sulfide	PKA	H-89, HCl
COX-1	Valeryl salicylate	PKC	Bisindolymaleimide I
COX-2	NS-398	PKC, PKA	H-7
COX	Sodium salicylate	PKC, PKA, PKG, MLCK	Staurosporine
cyclicphosphodiesterase	Theophylline	PLA2	cPLA2inhibitor
DNA methyltransferase	Azacytidine	PLA2	OBAA
DNA polymerase	Aphidicolin	PP2A	Cantharidin
EGFR	AG1478	PP2A	Cytostatin
EGFR, topoII	Genistein	PP2B/cyclophilin	Cyclosporin A
farnesyltransferase	Manumycin A	PP2B/FKBP	FK-506
farnesyltransferase	FTI-276	proteasome	MG-132
Flk-1	SU1498	proteasome	Lactacystin
geranylgeranyltransferase I	GGTI-286	ribonucleotide reductase	Hydroxyurea
GR	Dexamethasone	ROCK	HA1077
GSK-3	GSK-3 inhibitor II	ROCK	Y27632
HDAC	Scriptaid	Src, Fyn, Lck	PP1 (analog)
HDAC	Trichostatin A	Src, Fyn, Lck	PP-H
HER2 (erbB2/neu), EGFR	AG825	tubulin depolymerization	Nocodazole
protein synthesis	Cycloheximide		

Notably, none of the sixteen conventional anticancer drugs included in the study demonstrated anti-austerity activity, nor were any of them cytotoxic to PANC-1 cells in nutrient rich conditions at 1 μM. In addition, at this concentration, the PI3K inhibitor LY294002 (**2**, **Fig. 1**) also did not inhibit austerity.

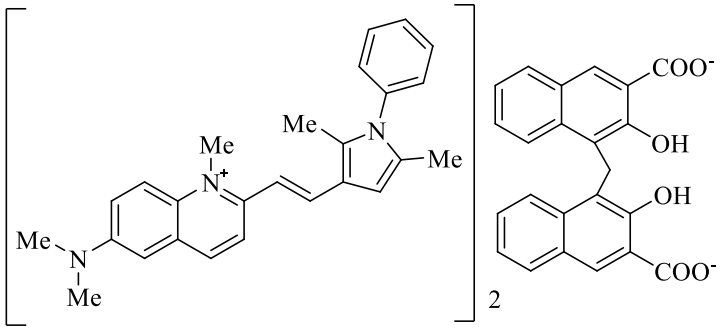
Figure 1: Four Anti-Austerity Inhibitors with Previously Known Protein Targets



troglitazone (**1**) LY294002 (**2**) AG1024 (**3**) I-OMe-AG538 (**4**)

Only a few other presently known anti-austerity agents are small-molecules with established biochemical targets. Recently, two autophagy inhibitors, 8-aminoadenosine [138] and 3-methyladenine [125], have been shown to enhance cell death selectively under glucose-deprived conditions. Furthermore, 3-methyladenine was demonstrated to inhibit the action of the MUC1 oncoprotein under these conditions. [125] Melformin, an antidiabetic drug that acts via indirect activation of AMPK, has also been shown to enhance the susceptibility of two colon cancer cell lines to apoptosis under nutrient deprivation. [139]

Figure 2: Pyrvinium Pamoate



pyrvinium pamoate (**5**)

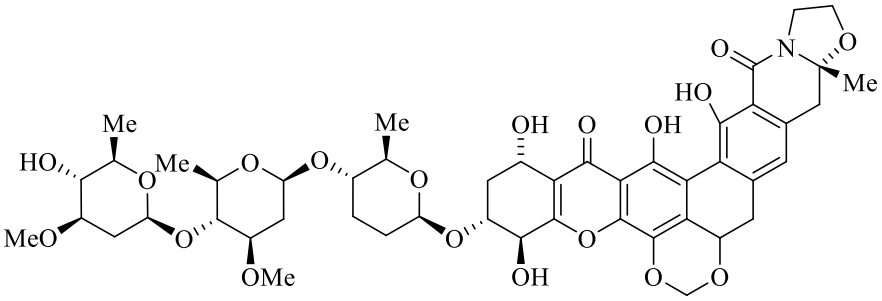
In 2004, Esumi and co-workers demonstrated that pyrvinium pamoate (**5, Fig. 2**), an anthelminthic drug, induced necrosis *in vitro* in three nutrient deprived pancreatic cancer cell lines and inhibited

spheroid growth of a colon cancer cell line under these conditions. Furthermore, pyrvinium pamoate also significantly suppressed tumor growth of PANC-1 *in vivo* in both nude mice and Severe Combined Immunodeficient (SCID) mice xenograft experiments upon both subcutaneous and oral administration. [137] More recently, Yu and co-workers have provided evidence that pyrvinium pamoate targets the unfolded protein response (UPR) by inhibition of transcriptional activation of GRP78 and GRP94 and other UPR pathways induced by glucose deprivation. [124] Xenograft experiments also demonstrated that a combination of pyrvinium pamoate and doxorubicin is significantly more effective *in vivo* than monotherapy.

NATURAL PRODUCTS AS ANTI-AUSTERITY AGENTS

In the past five years, dozens of compounds isolated from natural sources have been found to inhibit austerity of PANC-1 *in vitro*. The first of these was kigamicin D (**6, Fig. 3)**, identified by Esumi and coworkers after high throughput screening of over 2000 culture media of actinomycetes. [140]

Figure 3: Kigamicin D



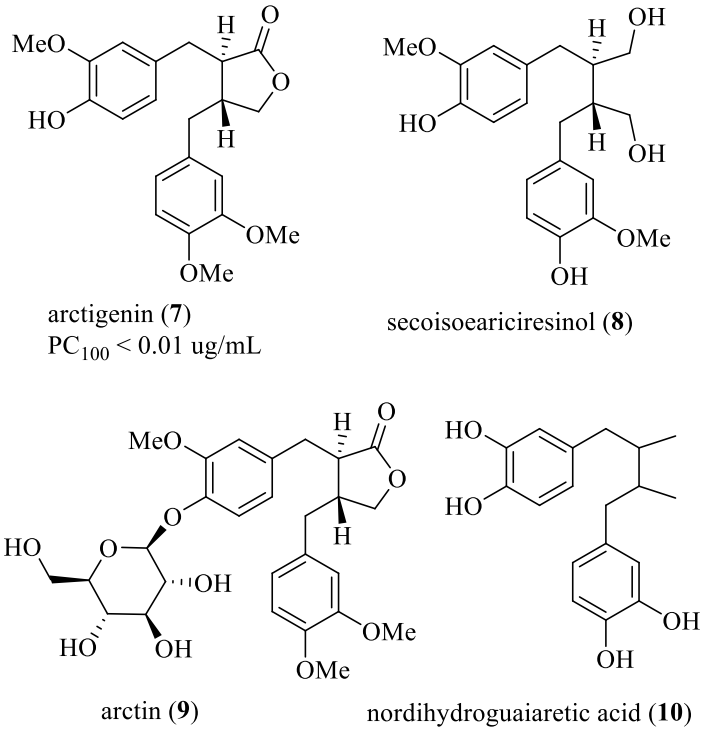
kigamicin D (**6**)

Like pyrvinium pamoate (**5**), kigamicin D (**6**) induces necrosis in PANC-1 cells *in vitro* under nutrient starvation conditions. *In vivo*, kigamicin D also suppressed tumor growth of human xenograft PANC-1 tumors in nude mice upon both subcutaneous and oral administration. [140] More extensive investigations of the spectrum of activity of kigamicin D against multiple human cancer xenograft

models have recently indicated that tumor growth inhibitory activity of this compound is limited to pancreatic and murine syngeneic tumors. [141]

Beginning in 2006, Kadota, Awale and co-workers have made rapid progress in the bioassay-guided isolation and identification of novel anti-austerity agents from natural sources. In particular, this group has focused on extracts of plants with a history of use as traditional medicines in Japan and Myanmar including *Arctium lappa,* [142] *Angelica pubescens,* [143] *Boesenbergia pandurata,* [144, 145] *Kayea assamica,* [146, 147] *Soymida febrifuga*, [148]. They have also isolated a number of anti-austerity agents from Pine Resin, [149] a natural resin obtained from conifers, and propolis, [150-152] a honeybee hive resin, both having a history of use in traditional medicine.

Figure 4: Arctigenin and Related Lignans [142]

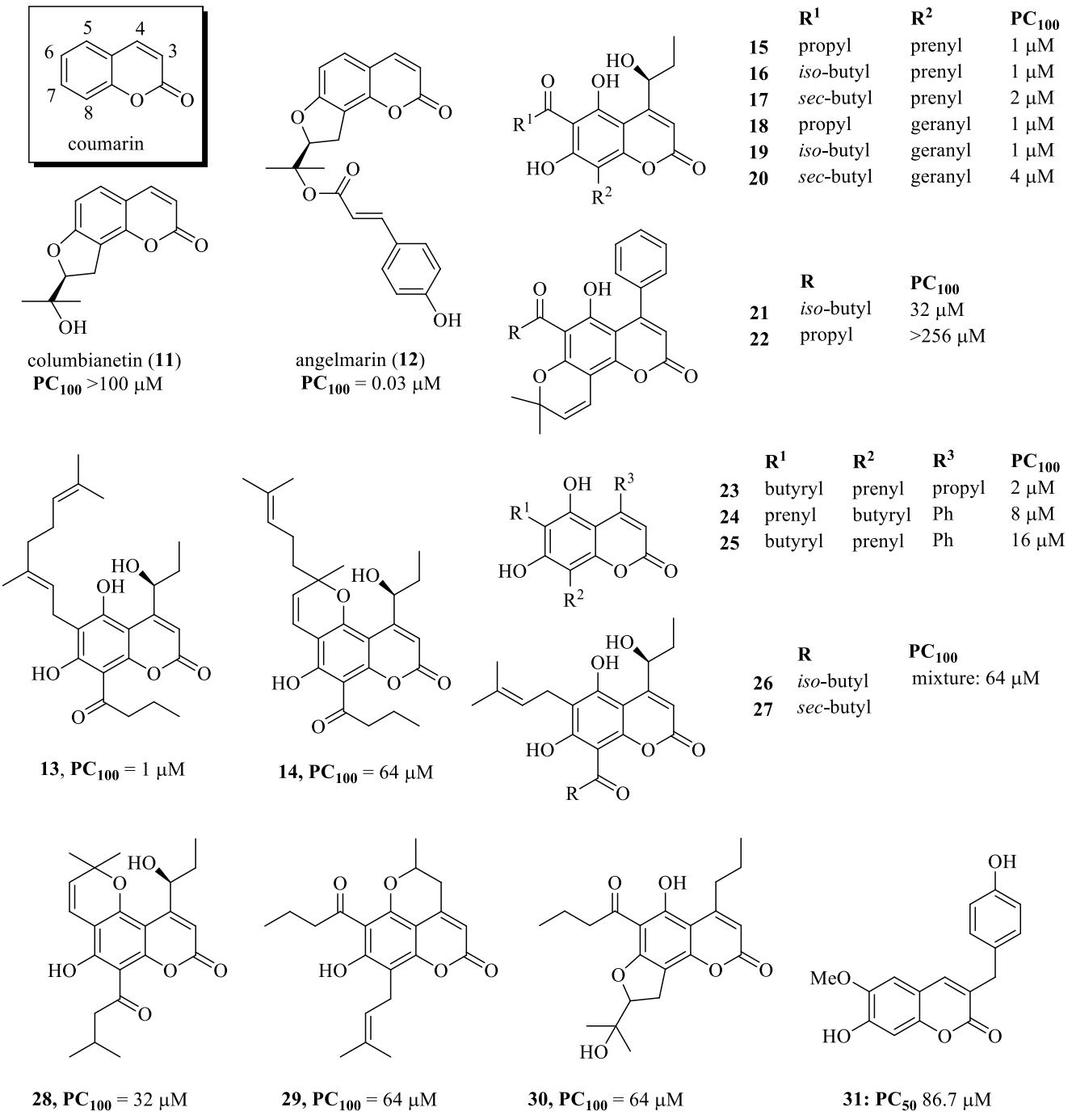


The first anti-austerity natural product reported by Kadota was a previously known butyrolactone lignan, arctigenin (**7**, **Fig. 4**), from *Arctinum lappa*. [142] Arctigenin exhibited 100% preferential

cytotoxicity against nutrient deprived PANC-1 at 0.01 μg/mL (PC_{100} = 0.03 μM) in a concentration-dependent and time-dependent manner. It also inhibited the austerity of four other cancer cell lines at higher concentrations. Like pyrvinium pamoate and kigamicin D, arctigenin also induced necrotic cell death. Furthermore, Esumi also showed that it was the absence of glucose in particular, and not serum or amino acids, that makes PANC-1 cells susceptible to arctigenin, kigamicin D, and pyrvinium pamoate. Arctigenin also strongly suppressed *in vivo* xenograph PANC-1 tumor growth in nude mice upon subcutaneous injection (50 μg per day) with mean tumor doubling time increased to 49 days from 23 days in the control group.

Three structurally related lignans: secoisoeariciresinol (**8**), arctin (**9**), and nordihydroguaiaretic acid (**10**), showed no anti-austerity activity in vivo.

Figure 5: Coumarin Anti-Austerity Agents (PANC-1)



	R1	R2	PC100
15	propyl	prenyl	1 μM
16	*iso*-butyl	prenyl	1 μM
17	*sec*-butyl	prenyl	2 μM
18	propyl	geranyl	1 μM
19	*iso*-butyl	geranyl	1 μM
20	*sec*-butyl	geranyl	4 μM

	R	PC100
21	*iso*-butyl	32 μM
22	propyl	>256 μM

	R1	R2	R3	PC100
23	butyryl	prenyl	propyl	2 μM
24	prenyl	butyryl	Ph	8 μM
25	butyryl	prenyl	Ph	16 μM

	R	PC100
26	*iso*-butyl	mixture: 64 μM
27	*sec*-butyl	

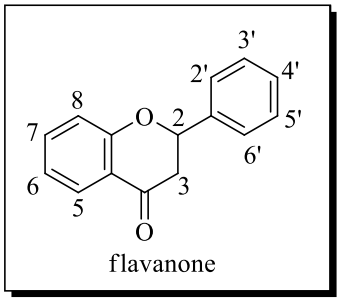
Angelmarin (**12, Fig. 5**), isolated from *Angelica pubescens* in 2006, was the first, and most potent, of nearly twenty coumarin based natural products with anti-austerity activity identified to date, with a reported PC_{100} of 0.01 μg/mL (0.03 μM). [143] Angelmarin is the *p*-hydroxycinnamate ester of a previously identified natural product, columbianetin (**11**). [153] Both columbianetin (**11**) and *p*-

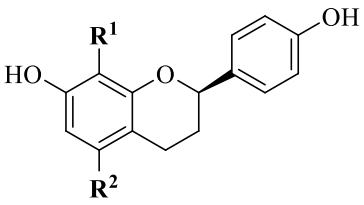
hydroxycinnamic acid were inactive in the anti-austerity assay (PC_{100} > 100 μg/mL, PANC-1). The fused tricyclic dihydrofuranocoumarin substructure of angelmarin (**12)** is unique among austerity inhibitors, however C-7 oxygenation and C-8 alkylation (or acylation) is common to all but one of the coumarins found to exhibit anti-austerity activity.

The flower of an evergreen tree found in Myanmar, *Kayea assimica*, has yielded 18 coumarins, known as kayeassamins and mammeas, with anti-austerity activity including 5 compounds with PC_{100} values of 1 μM (**Fig. 5**). [146, 147] In contrast to the effects of pyrvinium pamoate, kigamicin D, and arctigenin, cell death induced by these coumarins was characterized by apoptosis-like morphological changes. All of the kayeassamins and mammeas have characteristic C-5, C-7 oxygenation and C-3, C-6, C-8 alkylation around the coumarin nucleus. The moderate degree of structural diversity among many of these coumarins offers a modest amount of SAR information particularly with respect to C-4, C-6, and C-8 substitution. For instance, at the C-6 position, three acyl substituents can be compared. *n*-Propyl ketones kayeassamin E (**15)** and kayeassamin B (**18)** and *iso*-butyl ketones kayeassamin G (**16)** and kayeassamin D (**19**) show superior activity to the corresponding *sec*-butyl ketones kayeassamin F (**17**) and kayeassamin C (**20**). An additional pair of compounds: mammea A/AA cyclo D (**21)** and mammea A/AC cyclo D (**22)**, reveals that of the two preferred groups, the *iso*-butyl ketone group is superior to the propyl ketone. At the C-8 position, a direct comparison of kayeassamin F (**17)** and kayeassamin C (**20)** indicates prenyl substitution at C8 is preferable to geranyl. Direct comparison of mammea B/AC (**23**) with mammea A/AC (**25)** reveals an 8-fold higher potency for a propyl substituent at C-3 over a phenyl. Comparison of **24** and **25** shows that C-6-prenyl and C-8-butyryl substitution (as in **24)** results in enhanced activity compared to the reversed C6-butyryl and C8-prenyl substitution (**25)**. It is apparent that the presence of a third ring fused to the coumarin core, at the expense of a hydroxyl moiety, leads to a dramatic decrease in activity. This is supported by four direct comparisons: **15** is more active than **29**, **13** is more active than **14**, **23** is more active than **30**, and **25** is

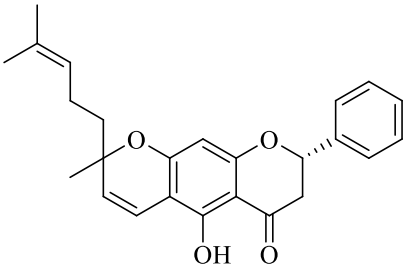
more active than **22**. Finally, the five most potent austerity inhibitors from *Kayea assimica* (**13**, **15**, **16**, **18**, and **19**) all share a C-4 hydroxypropyl substituent along with C-5 and C-7 phenols.

Figure 6. Flavanone and Flavan Anti-Austerity Agents (PANC-1)

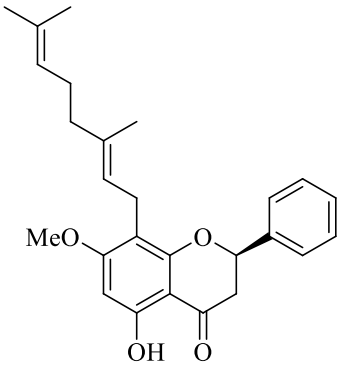




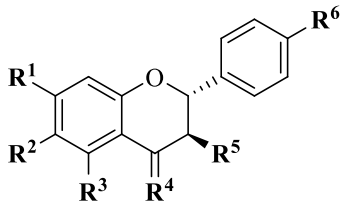
	R^1	R^2	PC_{50}
32	Me	OMe	70 μM
33	Me	H	86 μM
34	H	H	>100 μM



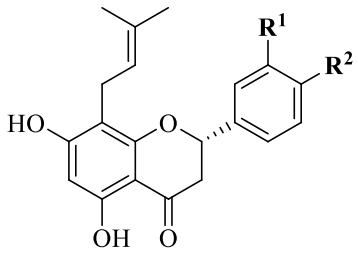
35, PC_{100} = 64 μM



36, PC_{100} 128 μM



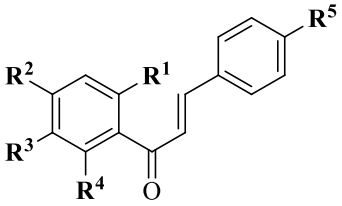
	R^1	R^2	R^3	R^4	R^5	R^6	PC_{100}
37	OH	geranyl	OH	O	H	H	8 μM
38	OMe	geranyl	OH	O	H	H	>100 μM
39	OH	H	OH	O	H	H	64 μM
40	OH	H	OH	H,H	H	H	73 μM (PC_{50})
41	OMe	H	OH	O	H	H	>256 μM
42	OH	H	OMe	O	H	H	>256 μM
43	OH	H	H	O	H	H	>100 μM
44	OH	H	OH	O	H	OH	>100 μM
45	OH	H	H	O	H	OH	>100 μM
46	OH	H	OMe	O	H	OH	>256 μM
47	OH	H	H	O	OH	OH	>100 μM
48	OMe	H	H	H,H	H	OH	74 μM (PC_{50})
49	OH	H	H	O	OH	H	>100 μM
50	OH	OMe	H	O	H	H	50 μM
51	OH	OMe	OH	O	H	H	>100 μM
52	OH	OMe	H	O	OH	H	>100 μM
53	OH	OMe	OH	O	OH	H	>100 μM
54	OH	OH	OH	O	H	H	>100 μM



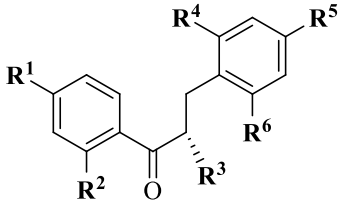
	R^1	R^2	PC_{50}	PC_{100}
55	prenyl	OMe	8 μM	13 μM
56	prenyl	OH	20 μM	25 μM
57	H	OMe	37 μM	50 μM
58	H	OH	39 μM	50 μM

A number of flavanone and flavan natural products with weak anti-austerity activity have been isolated from *Boesenbergia pandurata*,(**35-37, 39**) [144], *Soymida febrifuga* (**32, 33, 40, 48**) [148], and propolis (**50, 55-58**) [150, 152]. These compounds, along with inactive structural analogues offered by the same natural sources are illustrated in **Figure 6**. The most efficacious compound in this structural class is (-)-6-geranylpinocembrin (**37**, 8 μM). A number of inactive or less active structural analogues offer structure-activity relationship insight: replacement of hydroxyl with methyl ether yields inactive compounds (**38, 42**); the geranyl-free analogue (**39***)* is also less active than **37** as is the corresponding flavan (**40**). Cyclization of the C-6 geranyl moiety onto the C-7 hydroxyl to yield the corresponding fused pyran (**35)** also results in decreased activity in comparison to **37**.

Figure 7. Chalcone and Dihydrochalcone Anti-Austerity Agents (PANC-1)



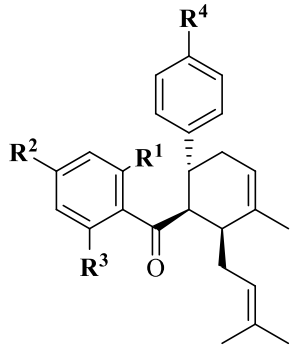
	R^1	R^2	R^3	R^4	R^5	PC_{100}	PC_{50}
59	H	OH	H	OH	H	>100 μM	19 μM
60	H	OH	H	OH	H	-	>100 μM
61	H	OH	H	OMe	OH	-	>100 μM
62	H	OH	H	OH	OH	>100 μM	-
63	H	OH	H	OMe	OH	>100 μM	-
64	OMe	H	H	OH	H	>100 μM	-
65	OMe	OH	geranyl	OH	H	16 μM	-
66	OMe	OMe	H	OH	OH	>100 μM	-



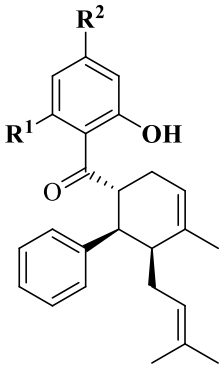
	R^1	R^2	R^3	R^4	R^5	R^6	PC_{50}
67	OH	H	H	H	OMe	OMe	83 μM
68	OH	H	H	OMe	OH	OMe	83 μM
69	OMe	H	H	OMe	OH	OMe	86 μM
70	OH	H	H	H	OMe	OH	>100 μM
71	OH	H	H	H	OH	OH	>100 μM
72	OH	OH	OH	H	OH	H	>100 μM (PC_{100})

Eight chalcones (**59-66**) and six dihydrochalcones (**67-72**), isolated from three natural sources (*Boesenbergia pandurata,* [144] Brazilian red propolis, [150] and *Soymida febrifuga* [148]) have been screened for anti-austerity activity against PANC-1 (**Fig. 7**). Of these, the most active compound is chalcone **65** with PC_{100} of 16 μM. [144] The most distinguishing structural feature of **65** among these compounds is the presence of alkyl (geranyl) substituent on one of the phenyl rings. Notably, compound **59** has a PC_{50} of 19 μM but does not achieve 100% preferential cytotoxicity at 100 μM. [148, 150] Three dihydrochalcones (**67-69**) showed very mild anti-austerity activity. [148]

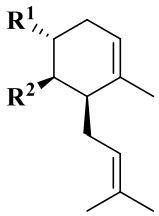
Figure 8. Prenyl Cyclohexene Anti-Austerity Agents (PANC-1)



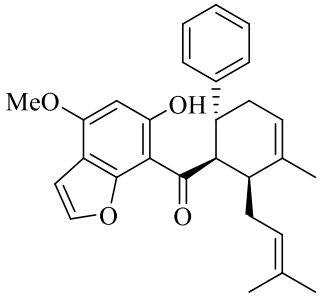
	R^1	R^2	R^3	R^4	PC_{100}
73	OH	OMe	OH	H	2.5 μM
74	OH	OH	OMe	H	16 μM
75	OH	OH	OH	H	16 μM
76	OMe	OMe	OH	H	64 μM
77	OMe	OH	OH	OH	>256 μM



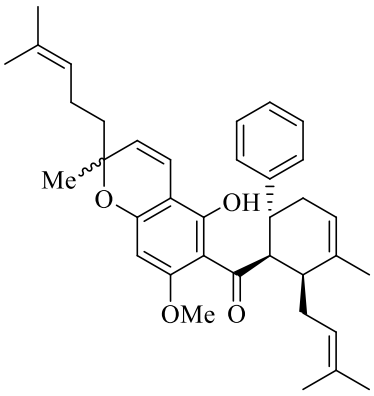
	R^1	R^2	PC_{100}
78	OH	OMe	2.5 μM
79	OMe	OH	8 μM
80	OH	OH	16 μM



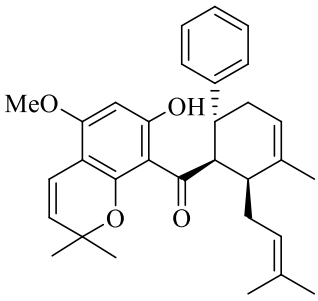
	R^1	R^2	PC_{100}
81	Ph	CO_2Me	128 μM
82	CO_2Me	Ph	128 μM



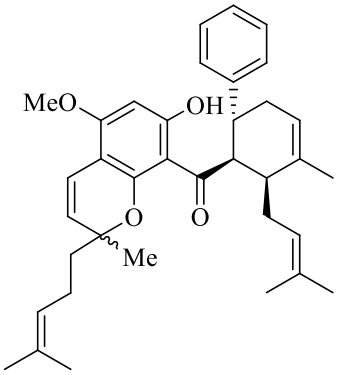
83, PC_{100} = 128 μM



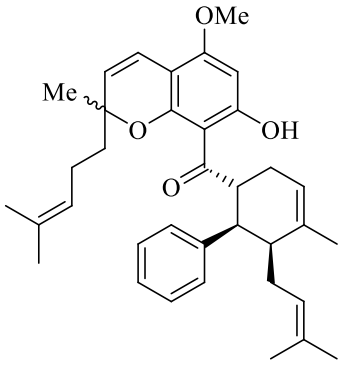
84, PC_{100} = 128 μM



85, PC_{100} = 128 μM



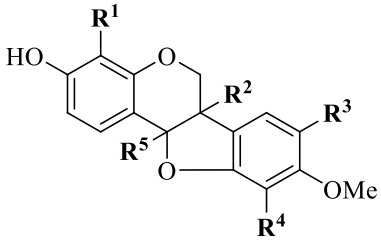
86, PC_{100} = 128 μM



87, PC_{100} = 128 μM

The perennial herb *Boesenbergia pandurata* has yielded fifteen highly substituted cyclohexene natural products (**73-87**) that have been screened for anti-austerity activity against PANC-1 (**Fig. 8**). [144, 145] The most active among these were (-)-panduratin A (**73**) and (-)-nicolaioidesin B (**78**), both with PC_{100} values of 2.5 μM. Both of these compounds have a 2,6-hydroxy-4-methoxy substituted phenyl ketone moiety. Other compounds in this class, isolated from the same source, illustrate that a number of modifications to the substitution pattern around the phenyl ketone portions of these compounds result in decreased activity (**74-76, 79, 80**). Introduction of a *p*-hydroxy functionality to the second aromatic ring appears to eliminate activity completely (**77**). Two structurally related methyl esters (**81,82**) showed PC_{100} values of 128 μM as did five tetracyclic derivatives containing benzofuran (**83**) and benzopyran (**84-87**) fragments.

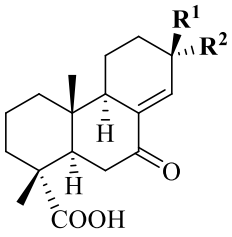
Figure 9. Pterocarpan Anti-Austerity Agents (PANC-1)



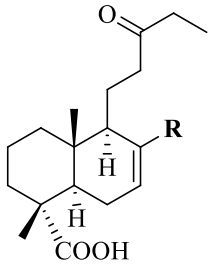
	R^1	R^2	R^3	R^4	R^5	PC_{100}
88	H	α-H	OH	H	α-H	12.5 μM
89	OH	α-H	H	H	α-H	25 μM
90	H	β-H	H	H	β-H	50 μM
91	H	β-H	H	OH	β-H	50 μM
92	H	α-H	OMe	H	α-H	>100 μM
93	OMe	α-H	H	H	α-H	>100 μM
94	H	α-OEt	H	H	α-H	>100 μM

Seven pterocarpans (**88-94**), also isolated from Brazillian red propolis, [150] have been screened for anti-austerity activity against PANC-1 (**Fig. 9**). The most active of these was (6a*R*,11a*S*)-3,10-dihydroxy-9-methoxypterocarpan (**88**) with PC_{100} of 12.5 μM. **88** induced necrosis of PANC-1 under nutrient deprived conditions.

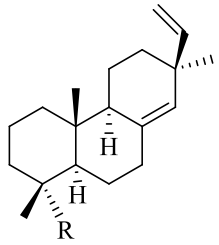
Figure 10. Diterpene Anti-Austerity Agents from Pine Resin (PANC-1)



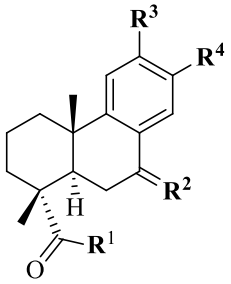
	R^1	R^2	PC_{100}
95	*i*-Pr	OH	>200 μg/mL
96	OH	*i*-Pr	200 μg/mL



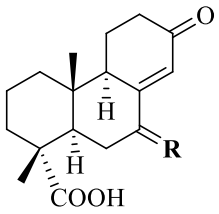
	R	PC_{100}
97	COOH	>200 μg/mL
98	CHO	200 μg/mL



	R	PC_{100}
99	COOH	50 μg/mL
100	CH_2OH	50 μg/mL



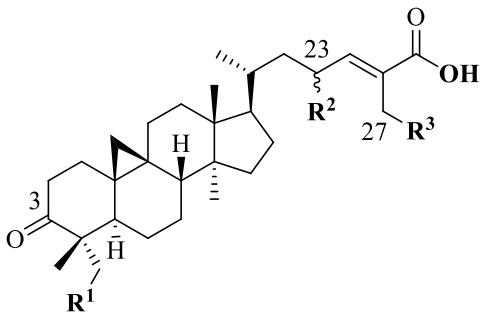
	R^1	R^2	R^3	R^4	PC_{100}
101	OH	O	H	*i*-Pr	200 μg/mL
102	OH	O	H	*i*-Pr	50 μg/mL
103	OMe	H,H	H	*i*-Pr	10 μg/mL
104	OH	H,H	OH	*i*-Pr	200 μg/mL
105	OH	H,H	H	*i*-Pr	50 μg/mL
106	OH	H,H	H	Ac	50 μg/mL



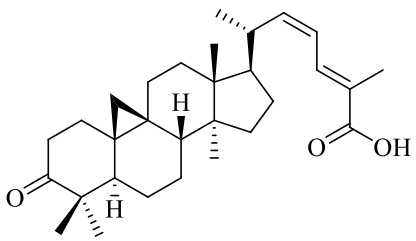
	R	PC_{100}
107	O	200 μg/mL
108	H,H	50 μg/mL

Pine Resin has yielded a series of anti-austerity compounds (**95-108**) with weak activity as shown in **Figure 10** [149]. The most active compound in this class is methyl abieta-8,11,13-trien-18-oate (**103**, 10 μg/mL, 32 μM). Five closely related carboxylic acids show decreased activity (**101, 102, 104-106**).

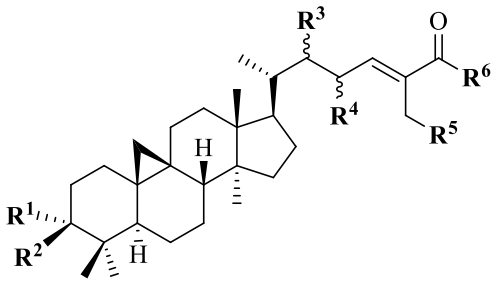
Figure 11. Cycloartane Anti-Austerity Agents (PANC-1)



	R1	R2	R3	PC100	PC50
109	H	OH	H	50 μM	28 μM
110	H	H	OH	50 μM	39 μM
111	H	H	H	>100 μM	>100 μM
112	OH	H	H	>100 μM	>100 μM
113	OH	H	OH	>100 μM	>100 μM



114, PC_{100} = 6.3 μM
PC_{50} = 4.3 μM

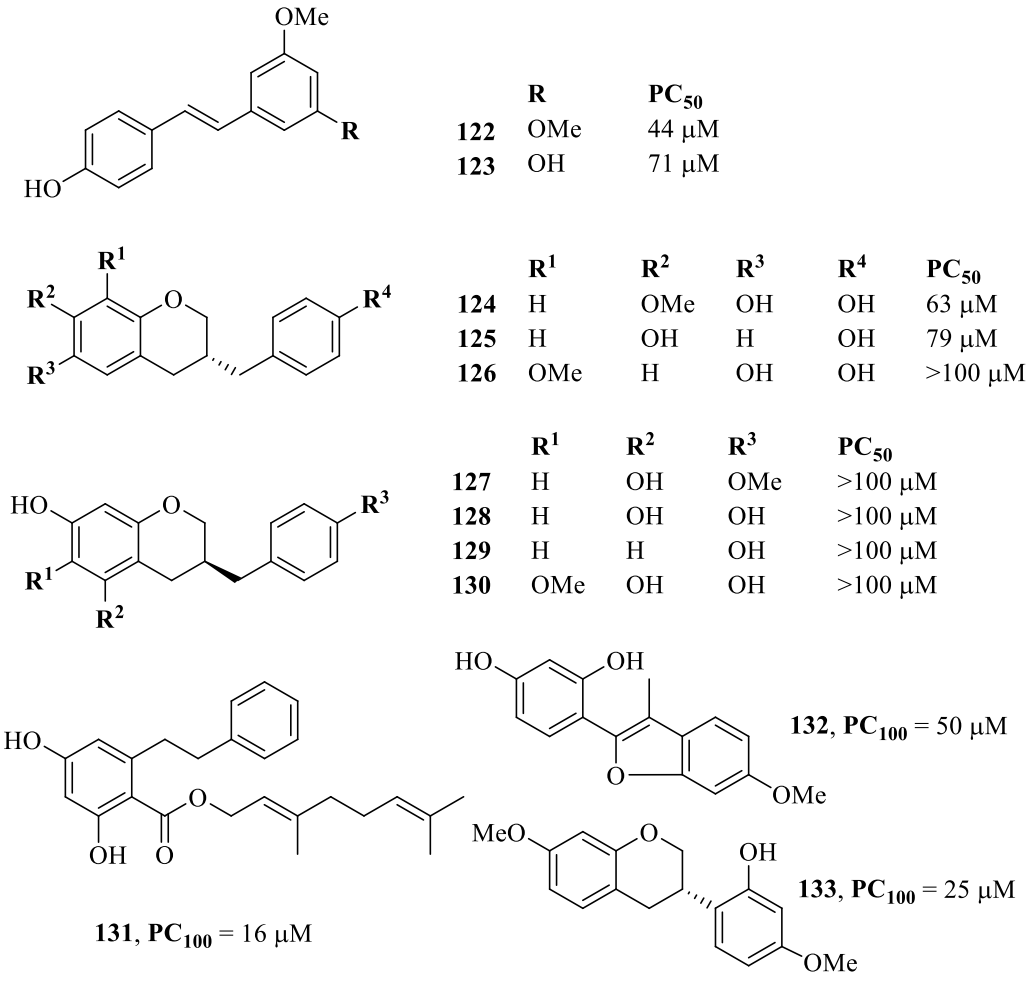


	R1	R2	R3	R4	R5	R6	PC100	PC50
115	OH	H	H	H	H	OH	25 μM	13.7 μM
116	OH	H	OH	H	H	OH	25 μM	13.4 μM
117	OH	H	H	H	OH	OH	25 μM	15.5 μM
118	H	OH	H	H	H	H	>100 μM	>100 μM
119	H	OH	H	H	H	OH	>100 μM	>100 μM
120	H	OH	H	H	OH	OH	>100 μM	>100 μM
121	H	OH	H	OH	H	OH	>100 μM	>100 μM

A propolis from Myanmar has recently yielded six cycloartane type triterpenoids that inhibit austerity in PANC-1 (**Fig. 11**). [152] The most active austerity inhibitor among these is keto acid **114** (PC_{100} = 6.3 μM, PC_{50} = 4.3 μM). Like the kayeassamins discussed above, **114** induced apoptotic cell death under nutrient deprived conditions. Removal of the conjugated cis-olefin leads to an inactive compound (**111**). Notably, the stereochemical configuration of the secondary alcohol at C-3 appears to be very significant. The α-hydroxyl group is present solely in three active compounds (**115-117**) while

the β-hydroxyl appears in four inactive ones (**118-121**). Furthermore hydroxylation of **111** at C-23 or C-27 results in active compounds (**109, 110**).

Figure 12. Other Anti-Austerity Agents (PANC-1)



	R	PC_{50}
122	OMe	44 μM
123	OH	71 μM

	R^1	R^2	R^3	R^4	PC_{50}
124	H	OMe	OH	OH	63 μM
125	H	OH	H	OH	79 μM
126	OMe	H	OH	OH	>100 μM

	R^1	R^2	R^3	PC_{50}
127	H	OH	OMe	>100 μM
128	H	OH	OH	>100 μM
129	H	H	OH	>100 μM
130	OMe	OH	OH	>100 μM

131, PC_{100} = 16 μM

132, PC_{100} = 50 μM

133, PC_{100} = 25 μM

Two stilbenes (**122** and **123**, **Fig. 12**) [148] and two benzylchromans (**124**, **125**) [150] with weak anti-austerity activity have been identified. Five additional benzylchromans (**126-130**) were inactive. Geranyl dihydroxy benzoate **131** from *Boesenbergia pandurata* [144] and benzofuran **132** from Brazilian red propolis [150] were also inhibitors of austerity in PANC-1 with PC_{100} values of 16 μM and 50 μM respectively. An isoflavan isolated from Brazilian red propolis, (3*S*)-7-*O*-methyl vesitol (**133**), has demonstrated weak anti-austerity activity with PC_{100} of 25 μM. [150] Fourteen additional

isoflavans, isoflavanones, and isoflavones also isolated from the same propolis, were found to be inactive.

CONCLUSIONS

In light of the urgent need for effective pancreatic cancer therapies, the authors feel that the recently established ‘anti-austerity’ strategy which targets the resistance of pancreatic cancer cells to nutrient deprivation warrants the consideration of the broader medicinal chemistry community. We hope that the comprehensive review of presently known anti-austerity inhibitors provided herein may inspire the interest and curiosity of investigators in this field. To date there has been relatively little synthetic chemistry directed towards anti-austerity compounds and no synthetic medicinal chemistry efforts appear in the literature. In 2009, two syntheses of (+)-angelmarin were published by the Coster and Hamada groups. [1, 154] These efforts have opened promising synthetic avenues for medicinal chemistry efforts investigating structure activity relationships (SAR) for angelmarin. The numerous other active compounds identified to date offer additional drug discover leads. Biological investigations to decipher the mechanisms of austerity will undoubtedly continue. This complex process is likely to incorporate multiple biochemical pathways and yield various protein targets for drug discovery. Our continuing efforts in this exciting field of research will be reported in due course.

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