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Supplemental Material

Prioritizing Environmental Chemicals for Obesity and Diabetes Outcomes Research: A Screening Approach Using ToxCast High Throughput Data

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Figures S7-S12. Dendrograms representing hierarchy of structural similarity among ToxPi Top 30 lists of chemicals. The Tox21 set of chemicals (8307 InChIS) were imported into a Leadscope Enterprise v3.2 project, and subsequently exported as Leadscope "fingerprints". A chemical's fingerprint consists of a bitmap representing the presence or absence of ~27000 structural features. Fingerprints were extracted from the entire Tox21 set for each "top 30" list (Excel File Table S18). Features not present in any of the 30 members comprising a given list were eliminated, yielding fingerprints characterized by 611 – 843 chemical features. Fingerprints from ToxPi "top 30" lists were clustered (single linkage; tanimoto), yielding dendrograms, similarity scores, and heatmaps. Structure-activity classes are elucidated by inspecting line graphs of the tanimoto coefficients, plotted coincident with the dendrograms. Heatmaps (blue = feature present; grey = absent) align structural features common among the chemical sets. There are 30 chemicals in each structural hierarchy, having 29 similarity coefficients, each representing the structural similarity between nearest neighbors. Each dendrogram and similarity profile, together with an understanding of the biological effects of certain chemicals, enabled elucidation of number of enriched chemical classes within each of several "top 30" lists. Heatmaps contain alignments of structural features common among chemicals in the lists (not described here). Figures S7-S12 reveal chemical classes present in 3 of the 6 ToxPi Top 30 lists. Rodent feeding behavior (Figure S8) is clearly affected by both estrogens, and non-steroidal estrogenic compounds. Adipocyte differentiation (Figure S7) collects tin containing chemicals, along with glucocorticoids, and CPs. Finally, Islet Cell Model 2 (Figure S12) is clearly affected by estrogens (see also, Excel File Table S18). The remaining ToxPi top 30 lists reveal no discernible chemical classes.

Figure S7. Adipocyte differentiation

Figure S8. Feeding behavior (rodent)

Figure S9. Feeding behavior (*C. elegans*)

Figure S10. Insulin sensitivity

Figure S11. Islet cell function

Figure S12. Beta cell function

Figure S13. Chemical clustering based upon model of feeding behavior in *C. elegans*. The first three principal components (PCs) from the ToxPi model of feeding behavior in *C. elegans* are plotted in a pair-wise matrix of each PC. The points, each representing a single chemical, are colored according to the k-means clustering of the PC output. The three cluster insets show the mean ToxPi profile (plus overall ToxPi score) for chemicals in that cluster. The component assays in each slice are indicated in Table 1.

Additional Files

Supplemental Code and Data Zip File

Supplemental Code and Data Zip File Index

Excel File Tables S1-S18

Excel File Table S1. Description of Phase 2 ToxCast assays

Excel File Table S2. Phase 2 ToxCast assays used in prediction models

Excel File Table S3. Prediction model for adipocyte differentiation

Excel File Table S4. Prediction model for feeding behavior in rodents

Excel File Table S5. Prediction model for feeding behavior in *C. elegans*

Excel File Table S6. Prediction model for insulin sensitivity

Excel File Table S7. Prediction model for islet cell function

Excel File Table S8. Prediction model for pancreatic beta cell function

Excel File Table S9. Correlation analysis for chemicals having similar activity to troglitazone

Excel File Table S10. Correlation analysis for chemicals having similar activity to tributyltin chloride

Excel File Table S11. Correlation analysis for chemicals having similar activity to tributyltin methacrylate

Excel File Table S12. Correlation analysis for chemicals having similar activity to nicotine

Excel File Table S13. Correlation analysis for chemicals having similar activity to haloperidol

Excel File Table S14. Correlation analysis for chemicals having similar activity to chlorpromazine

Excel File Table S15. Correlation analysis for chemicals having similar activity to tolazamide

Excel File Table S16. Correlation analysis for chemicals having similar activity to amitraz

Excel File Table S17. Correlation analysis for chemicals having similar activity to dexamethasone

Excel File Table S18. Chemical structures represented in the top 30 lists

R Scripts

correlation_analysis.R

generate.allmodels.input.r

generate.inputs_v5.r

generate.inputs_v6.r

generate.inputs_v7.r

generate.inputs_v8.r

mapcheminfo.r

ToxPi

- Scripts
  - color.select.ind.R
  - color.select.R
  - data.parse.R
  - easy.colors.R
  - implement_vNIEHS.R
  - refchemlabel.R
  - server.implement.R
  - toxpi4_vNIEHS.R

ToxPi_Combined_140801.r

ToxPi_Models_140801.r

ToxPi_Models_150428.r

Figure S1. Adipocyte Differentiation

(a)

diallyl phthalate[131-17-9]
(0.306)
plasticizer
phthalate
RAR score = 0.115

methyl salicylate [119-36-8]
(0.293)
flavor, antiseptic
salicylate
RAR score = 0.180

melengestrol acetate [2919-66-6]
(0.289)
pharmaceutical
progestin: antineoplastic

rotenone [83-79-4]
(0.266)
insecticide
botanical
RAR score = 0.222

tebufenpyrad [119168-77-3]
(0.257)
insecticide
pyrazole
RAR score = 0.120

trans-retinoic acid [302-79-4]
(0.251)
pharmaceutical
RAR pan-agonist: acne, acute promyelocytic leukemia
RAR score = 1

isazofos[42509-80-8]
(0.0.248)
insecticide
organophosphate

aspirin [50-78-2]
(0.246)
pharmaceutical
analgesic, antipyretic, anti-inflammatory (suppresses prostaglandins and thromboxanes, COX-1 and COX-2 inhibition) nonsteroidal anti-inflammatory drugs (NSAIDs)
RAR score = 0.071

GW473178E methyl benzene sulphonic acid [263553-33-9]
(0.221)
pharmaceutical
thrombin inhibitor: thrombosis

bentazone [25057-89-0]
(0.221)
herbicide
carbamate

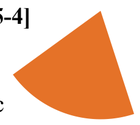
sodium abietate [14351-66-7]
(0.215)
coating
abietate

2-ethyl-2-hexenal [645-62-5]
(0.212)
intermediate,insecticide
aldehyde

AVE8923 [NOCAS_47381]
(0.207)
pharmaceutical
tryptase inhibitors

SR271425 [155990-20-8]
(0.205)
pharmaceutical
thioxanthone analog, cytotoxic DNA-interacting agent with broad antitumor activity, associated with cardiac toxicity in pre-clinical models
RAR score = 0.084

tributyltin benzoate [4342-36-3]
(0.200)
microbicide
organotin
RAR score = 0.145



farglitazar [196808-45-4]
(0.200)
pharmaceutical
PPARγ agonist: hepatic fibrosis

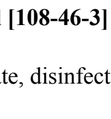
acrylamide [79-06-1]
(0.193)
reactant
acrylamide

1-(6-tert-butyl-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethanone [13171-00-1] "celestolide"
(0.180)
fragrance
phenyl ketone
RAR score = 0.143

tetrabutyltin [1461-25-2]
(0.176)
microbicide
organotin
RAR score = 0.157

triamcinolone [124-94-7]
(0.172)
pharmaceutical
corticosteroid (steroid)

pyridaben [96489-71-3]
(0.171)
insecticide
diazine phenyl sulfide halide ketone
RAR score = 0.063



resorcinol [108-46-3]
(0.167)
intermediate, disinfectant
phenol
RAR score = 0.162

dexamethasone sodium phosphate [2392-39-4]
(0.160)
pharmaceutical
corticosteroids

phenobarbital sodium [57-30-7]
(0.160)
pharmaceutical
barbiturate, nonselective central nervous system depressant, sedative hypnotic, anticonvulsant

CP-457677 [214535-77-0]
(0.159)
pharmaceutical

basic blue 7 [2390-60-5]
(0.156)
dye
aniline dye

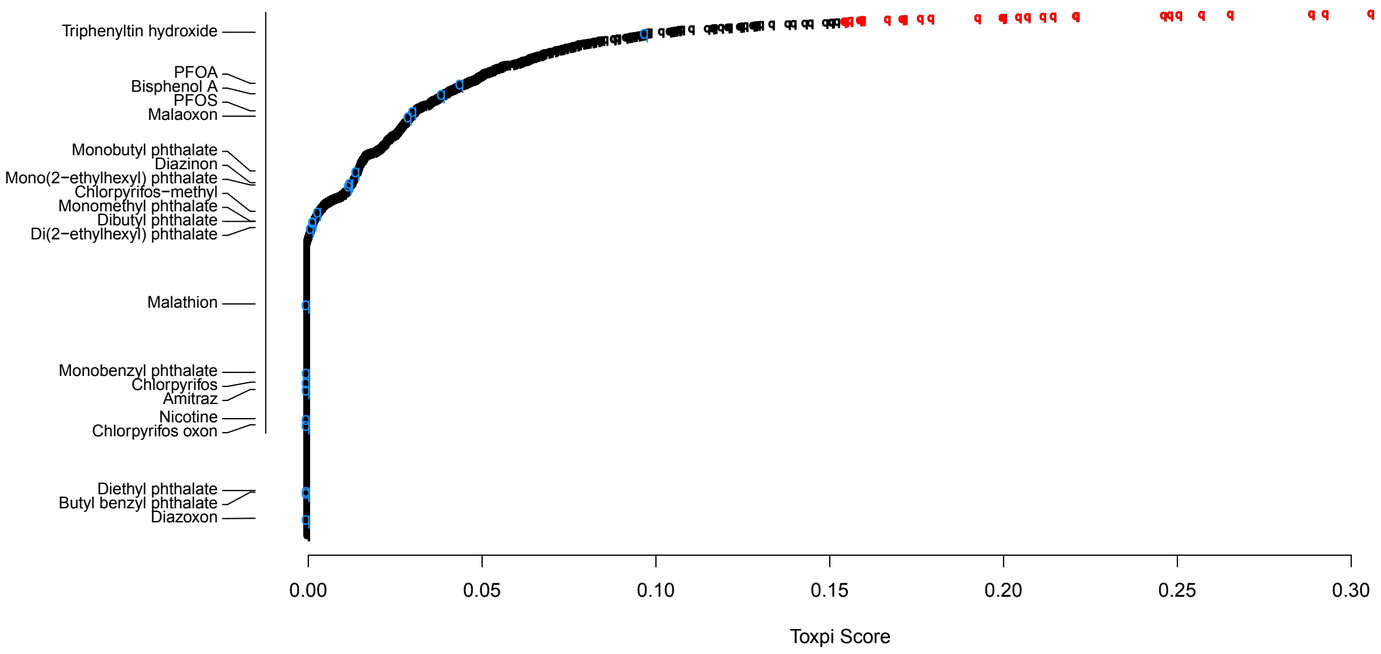
fenpyroximate (Z,E) [111812-58-9]
(0.156)
insecticide
pyrazole
RAR score = 0.235

CP-612372 [214535-77-0]
(0.155)
pharmaceutical

2-methyl-5-nitroaniline [99-55-8]
(0.155)
intermediate
aniline nitro

retinol acetate [127-47-9]
(0.154)
vitamin A
carboxylate

(b)



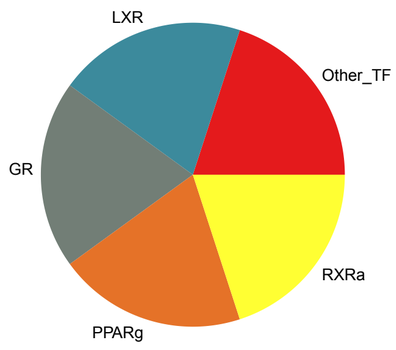


Figure S2. Feeding Behavior (rodents)

(a)

HMR1171 [328392-46-7]
(0.192)
pharmaceutical
lipid lowering

pharmaGSID_48511 [1062243-51-9]
(0.133)
pharmaceutical
polo-like kinase inhibitor

4-hydroxytamoxifen [68392-35-8]
(0.125)
pharmaceutical
selective estrogen receptor modulator (SERM), active metabolite of tamoxifen

niclosamide [50-65-7]
(0.114)
molluscicide
phenol halide

pharmaGSID_47337 [1061517-62-1]
(0.112)
pharmaceutical
cholecystokinin 1 receptor (CCK1R) agonist

acetic acid, C8-10-branched alkyl esters, C9-rich [108419-33-6]
(0.111)
solvent
carboxylate

methyl parathion [298-00-0]
(0.111)
insecticide
organophosphate

isopropyl triethanolamine titanate [36673-16-2]
(0.111)
coupling agent
organometallic

ilepatril [473289-62-2]
(0.111)
pharmaceutical
vasopeptidase inhibitor: hypertension

equilin [474-86-2]
(0.111)
pharmaceutical
estrogen, steroidal

triisononyl trimellitate [53894-23-8]
(0.111)
plasticizer
phthalate

cymoxanil [57966-95-7]
(0.110)
fungicide
acetamide carboxylate amine

AVE6324 [NOCAS_47377]
(0.108)
pharmaceutical
direct Xa inhibitor: deep vein thrombosis, acute coronary syndrome

zearalenone [17924-92-4]
(0.108)
mycotoxin

rifampicin [13292-46-1]
(0.102)
pharmaceutical
bactericidal antibiotic

mestranol [72-33-3]
(0.101)
pharmaceutical
estrogen, steroidal

meso-hexestrol [84-16-2]
(0.099)
pharmaceutical
estrogen, synthetic non-steroidal

estriol [50-27-1]
(0.098)
pharmaceutical
estrogen, steroidal

pirimiphos-methyl [29232-93-7]
(0.097)
insecticide
organophosphate

diethylstilbestrol [56-53-1]
(0.095)
pharmaceutical
estrogen, synthetic non-steroidal

raloxifene hydrochloride [82640-04-8]
(0.095)
pharmaceutical
selective estrogen receptor modulator (SERM): osterporosis

17beta-estradiol [50-28-2]
(0.095)
pharmaceutical
estrogen, steroidal

4,4'-methylenedianiline [101-77-9]
(0.093)
industrial intermediate
aniline

pyraflufen-ethyl [129630-19-9]
(0.092)
herbicide
pyridine alkoxy carboxylic acid halide

17alpha-ethinylestradiol [57-63-6]
(0.092)
pharmaceutical
estrogen, steroidal

nicotine [54-11-5]
(0.090)
pharmaceutical, pesticide, natural
pyridine amine

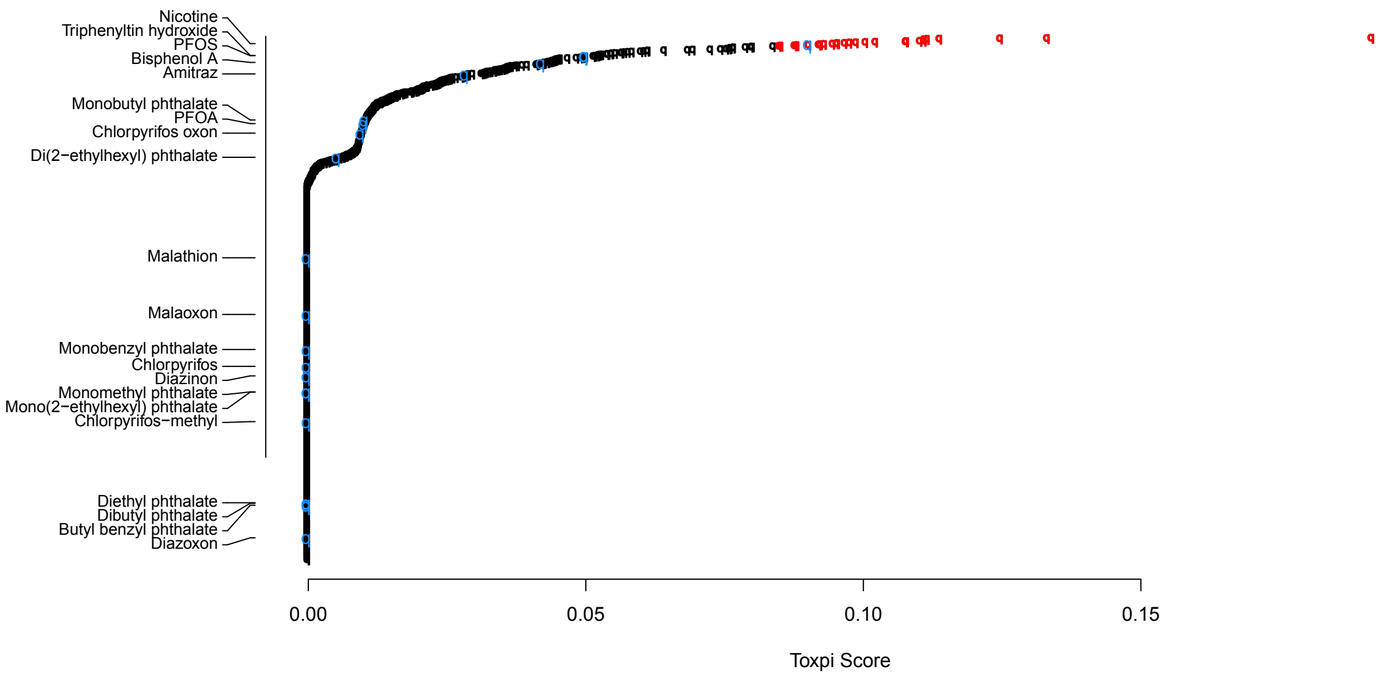
benzal chloride [98-87-3]
(0.088)
dye component/chemical reactant
phenyl halide

methyleugenol [93-15-2]
(0.088)
fragrance, flavor, anesthetic
phenol ethoxylate alkyl

17alpha-estradiol [57-91-0]
(0.085)
pharmaceutical
estrogen, steroidal

piperazine [110-85-0]
(0.085)
insecticide
amine

(b)



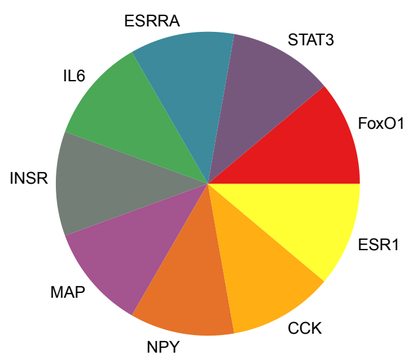
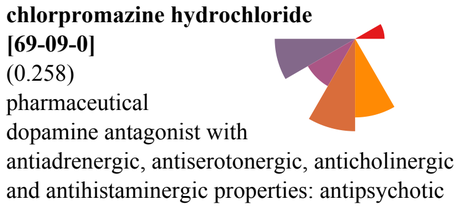


Figure S3. Feeding Behavior (C. elegans)

(a)



chlorpromazine hydrochloride [69-09-0]
(0.258)
pharmaceutical
dopamine antagonist with antiadrenergic, antiserotonergic, anticholinergic and antihistaminergic properties: antipsychotic

trelanserin [189003-92-7]
(0.241)
pharmaceutical
selective serotonin 5-HT2A antagonist

fabesetron hydrochloride [129299-90-7]
(0.239)
pharmaceutical
5-HT3 (serotonin M) receptor antagonist

volinanserin [139290-65-6]
(0.236)
pharmaceutical
5-HT2A receptor antagonist: antipsychotic, antidepressant and insomnia

PharmaGSID_47315 [444610-91-7]
(0.132)
pharmaceutical
PPARγ agonist

elzasonan [361343-19-3]
(0.130)
pharmaceutical
selective 5-HT1B and 5-HT1D receptor antagonist (discontinued)

volinanserin [139290-65-6]
(0.225)
pharmaceutical
5-HT2A receptor antagonist: antipsychotic, antidepressant and insomnia

SSR150106 [NOCAS_47362]
(0.222)
pharmaceutical
chemokine receptor antagonist (TNF alpha)

pharmaGSID_48511 [1062243-51-9]
(0.174)
pharmaceutical
polo like kinase inhibitor

raloxifene hydrochloride [82640-04-8]
(0.126)
pharmaceutical
selective estrogen receptor modulator (SERM): osterporosis

Allura red C.I.16035 [25956-17-6]
(0.117)
dye
phenyl sulfuric acid dye

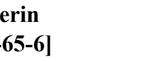
AVE6324 [NOCAS_47377]
(0.108)
pharmaceutical
direct Xa inhibitor: deep vein thrombosis, acute coronary syndrome

SSR241586 [NOCAS_47353]
(0.103)
pharmaceutical
a 2,2-disubstituted morpholine: schizophrenia and irritable bowel syndrome

mercuric chloride [7487-94-7]
(0.103)
bactericide
heavy metal salt

calcium neodecanoate [27253-33-4]
(0.099)
additive
carboxylic acid

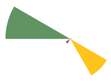
FD&C Yellow 6 [2783-94-0]
(0.095)
dye
phenyl sulfuric acid dye



aspirin [50-78-2]
(0.093)
pharmaceutical
analgesic, antipyretic, anti-inflammatory (suppresses prostaglandins and thromboxanes, COX-1 and COX-2 inhibition)
nonsteroidal anti-inflammatory drugs (NSAIDs)

diphenhydramine hydrochloride [147-24-0]
(0.090)
pharmaceutical ("Benadryl")
antihistomine

PD 0343701 [676116-04-4]
(0.089)
pharmaceutical
dopamine D2 receptor, 5HT2A



SSR240612 [NOCAS_47351]
(0.087)
pharmaceutical
kinin B1 receptor antagonist

farglitazar [196808-45-4]
(0.084)
pharmaceutical
PPARγ agonist: hepatic fibrosis

fomesafen [72178-02-0]
(0.084)
herbicide
diphenyl ether

diallyl phthalate [131-17-9]
(0.084)
plasticizer
phthalate

methyl parathion [298-00-0]
(0.083)
insecticide
organophosphate

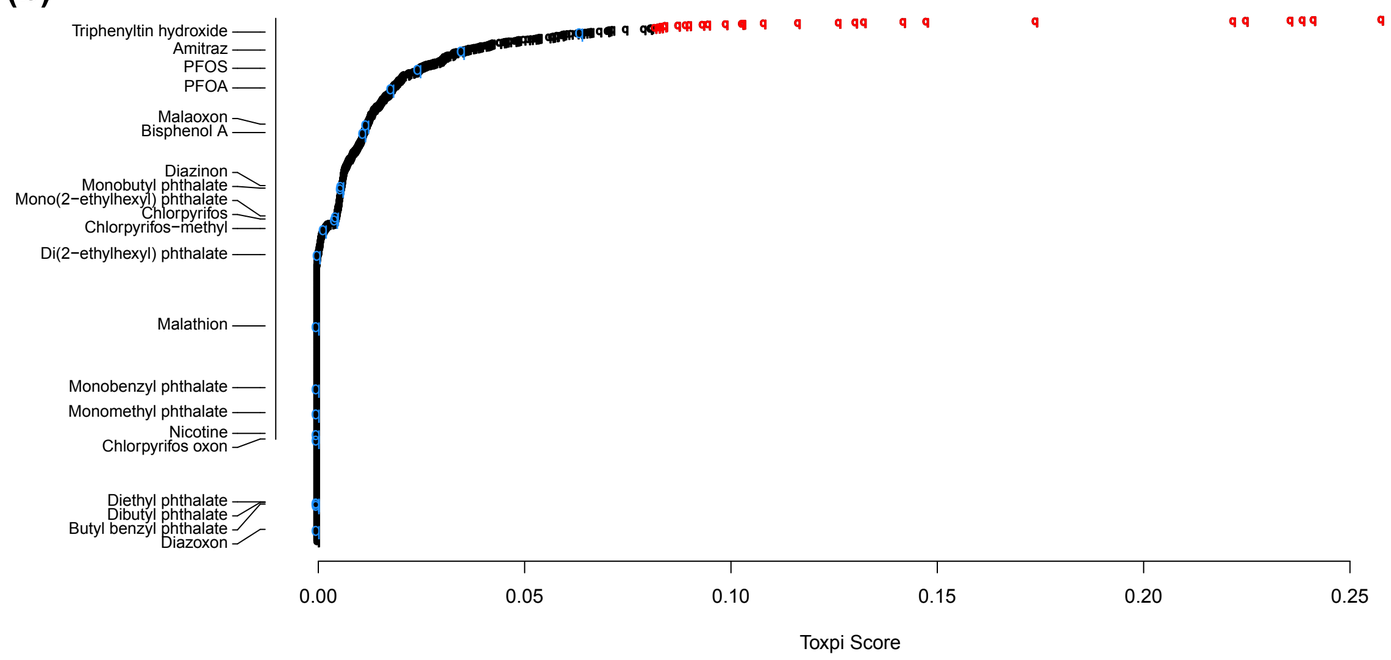
N-nitrosodipropylamine[621-64-7]
(0.083)
breakdown product, research compound
nitrosoamine

trioctyl trimellitate [89-04-3]
(0.083)
plasticizer
phthalate

rifampicin [13292-46-1]
(0.083)
pharmaceutical
bactericidal antibiotic

resorcinol [108-46-3]
(0.082)
intermediate, disinfectant
phenol

(b)



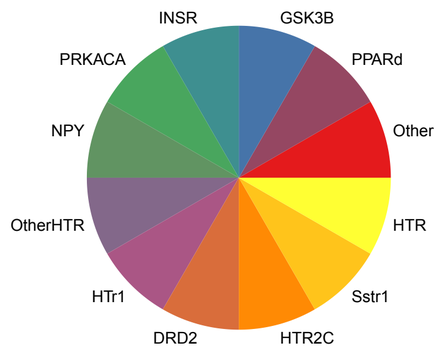


Figure S4. Insulin Sensitivity

(a)

farglitazar [196808-45-4]
(0.250)
pharmaceutical
PPARγ agonist: hepatic fibrosis

PharmaGSID_47315 [444610-91-7]
(0.221)
pharmaceutical
PPARγ agonist

basic blue 7 [2390-60-5]
(0.204)
dye
aniline

rotenone [83-79-4]
(0.203)
insecticide
botanical

tebufenpyrad [119168-77-3]
(0.197)
insecticide
pyrazole

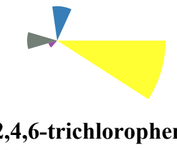
pharmaGSID_48511 [1062243-51-9]
(0.187)
pharmaceutical
polo-like kinase inhibitor

isopropyl triethanolamine titanate [36673-16-2]
(0.182)
coupling agent
organometallic

pyridaben [96489-71-3]
(0.177)
insecticide
diazine phenyl sulfide halide ketone

1,3-diphenyl-1,3-propanedione [120-46-7]
(0.165)
plasticizer
phenyl

fenamiphos [22224-92-6]
(0.156)
insecticide
organophosphate



2,4,6-trichlorophenol [88-06-2]
(0.153)
herbicide
chlorinated phenol

fenpyroximate (Z,E) [111812-58-9]
(0.151)
insecticide
pyrazole

2-ethyl-2-hexenal [645-62-5]
(0.150)
intermediate,insecticide
aldehyde

diuron [330-54-1]
(0.146)
herbicide
phenyl urea

propargite [2312-35-8]
(0.137)
insecticide
phenyl ether sulfate yne

1-(6-tert-butyl-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethanone [13171-00-1]
(0.130)
fragrance
phenyl ketone

isoxaben [82558-50-7]
(0.129)
herbicide
amide, oxazole

1,4-diaminoanthraquinone [128-95-0]
(0.129)
dye
anthraquinone

sodium abietate [14351-66-7]
(0.127)
coating
abietate

gyceryl monoricinoleate [11323-38-2]
(0.127)
intermediate, emulsifier
alcohol-3 carboxylate ene

troglitazone [97322-87-7]
(0.125)
pharmaceutical
thiazolidinediones: anti-diabetic, anti-inflammatory

isazofos [42509-80-8]
(0.123)
insecticide
organophosphate

famoxadone [42509-80-8]
(0.123)
fungicide
dicarboxamide

HMR1171 [328392-46-7]
(0.122)
pharmaceutical
lipid lowering

pirinixic acid [50892-23-4]
(0.121)
pharmaceutical
PPARα agonist that is under investigation for prevention of severe cardiac dysfunction, cardiomyopathy and heart failure

dinocap[39300-45-3]
(0.120)
fungicide
dinitrophenol derivative

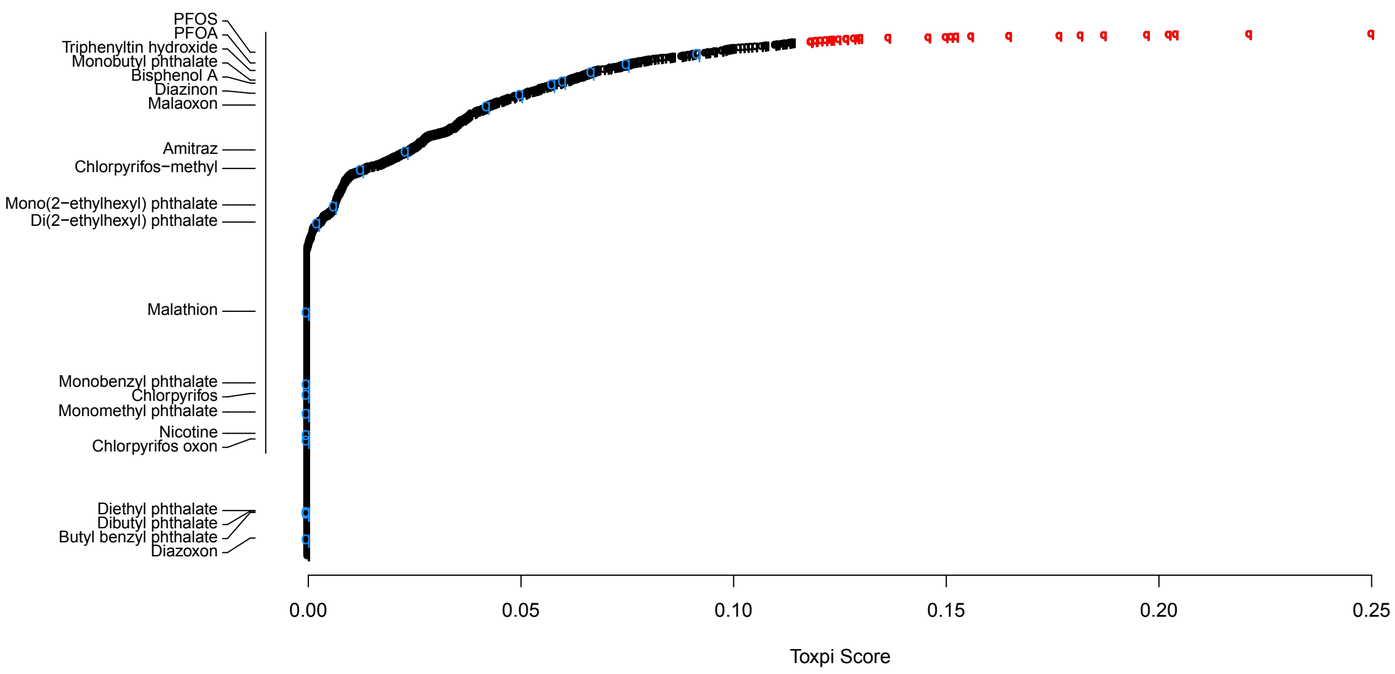
Z-tetrachlorvinphos [22248-79-9]
(0.119)
insecticide
organophosphate

apigenin [520-36-5]
(0.118)
flavone
genistein-like

sodium dodecyl sulfate [151-21-3]
(0.118)
surfactant
sulfuric acid alkyl

sodium 2,4,7-tri(propan-2-yl) naphthalene-1-sulfonate [1323-19-9]
(0.118)
pesticide adjuvant
naphthalene sulfuric acid

(b)



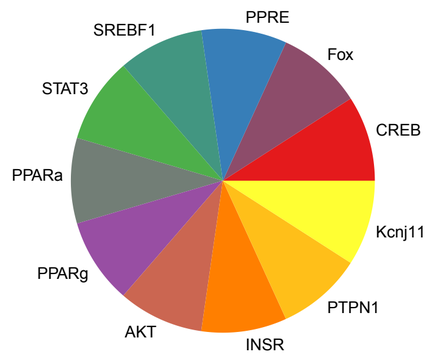


Figure S5. Islet Cell Function

(a)

isopropyl triethanolamine titanate [36673-16-2]
(0.177)
coupling agent
organometallic

basic blue 7 [2390-60-5]
(0.176)
dye
aniline

pharmaGSID_48511 1062243-51-9]
(0.130)
pharmaceutical
polo-like kinase inhibitor

spiromesifen [283594-90-1]
(0.106)
insecticide
phenyl tetronic acid

tris(2,3-dibromopropyl) phosphate [126-72-7]
(0.100)
flame retardant
phosphate alkyl halide

apigenin [520-36-5]
(0.097)
flavone
genistein-like

acetic acid, C8-10-branched alkyl esters, C9-rich [108419-33-6]
(0.091)
solvent
carboxylate

resorcinol [108-46-3]
(0.091)
intermediate, disinfectant
phenol

haloperidol [52-86-8]
(0.091)
pharmaceutical
inverse agonist of dopamine: schizoaffective disorders

dibenz(a,h)anthracene [53-70-3]
(0.091)
research chemical (no commercial use)
polycyclic aromatic hydrocarbon

caffeine [58-08-2]
(0.091)
pharmaceutical
receptor antagonist adenosine receptors

N-nitrosodipropylamine [621-64-7]
(0.091)
research chemical/by-product
nitrosoamine

dicyclopentadiene [77-73-6]
(0.091)
intermediate
alkene

rotenone[83-79-4]
(0.091)
insecticide
botanical

2,4,6-trichlorophenol [88-06-2]
(0.091)
herbicide, fungicide, reactant
phenol halide

silica [7631-86-9]
(0.087)
filler
silicate

tannic acid [1401-55-4]
(0.086)
natural product
phenol benzoic acid

perfluorooctane sulfonate PFOS [1763-23-1]
(0.086)
fluorosurfactant
perfluoro sulfuric acid

1-phenoxy-2-propanol [770-35-4]
(0.085)
pesticidal inert, solvent
phenol ethoxylate alcohol

dimethyl succinate [106-65-0]
(0.084)
intermediate
carboxylate

1,3-diphenyl-1,3-propanedione [106-65-0]
(0.083)
plasticizer
phenyl-phenyl

auramine hydrochloride [2465-27-2
(0.082)
dye, disinfectant
aniline-aniline [CN] alkylate

dibenzothiophene [132-65-0]
(0.081)
fragrance, flavor
benzofuran

2,4,6-tribromophenol [118-79-6]
(0.080)
intermediate, antiseptic
phenol halide

sulfasalazine [599-79-1]
(0.080)
pharmaceutical
sulfa drug: antirheumatic drug for rheumatoid arthritis, inflammatory bowel disease, Crohn's disease

1-(6-tert-butyl-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethanone [13171-00-1]
(0.078)
fragrance
phenyl ketone

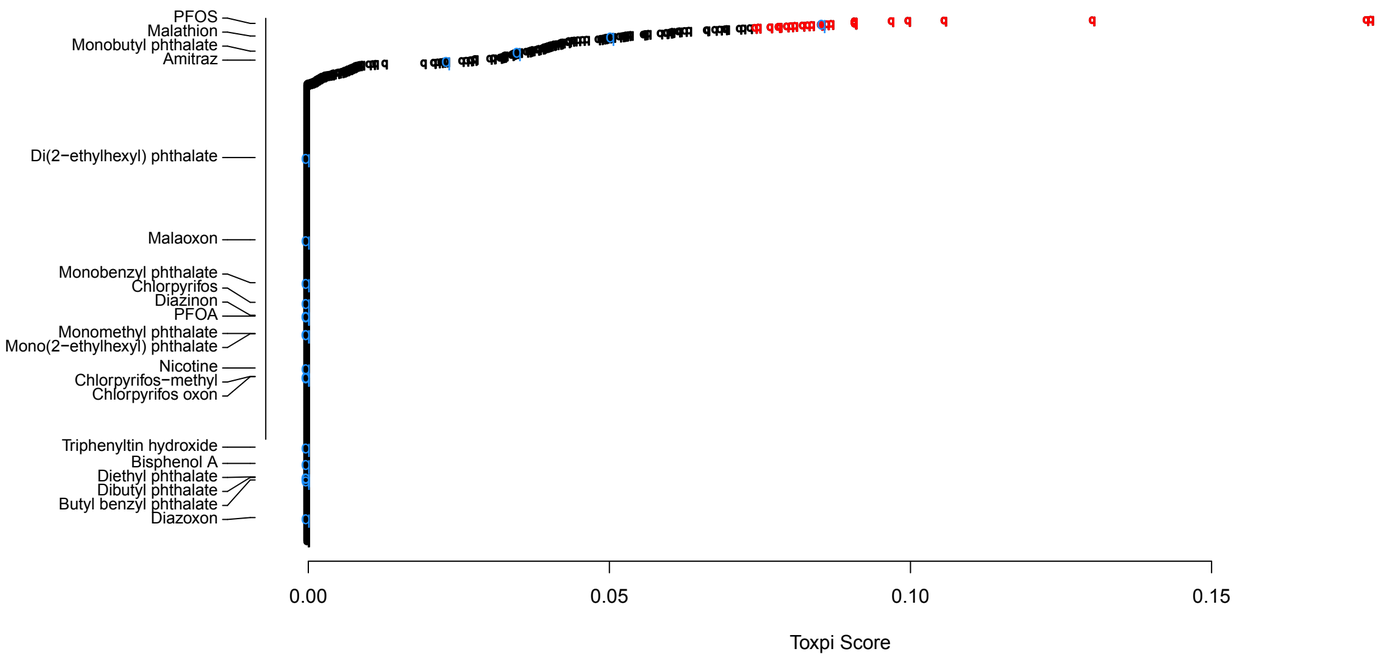
chlorpromazine hydrochloride [69-09-0]
(0.078)
pharmaceutical
dopamine antagonist with antiadrenergic, antiserotonergic, anticholinergic and antihistaminergic properties: antipsychotic

PharmaGSID_48505 [NOCAS_48505]
(0.077)
pharmaceutical
CDK2 inhibitor

ethyl butyrate [105-54-4]
(0.075)
flavor
carboxylate

tolazamide [1156-19-0]
(0.074)
pharmaceutical
sulfonylurea: type 2 diabetes

(b)



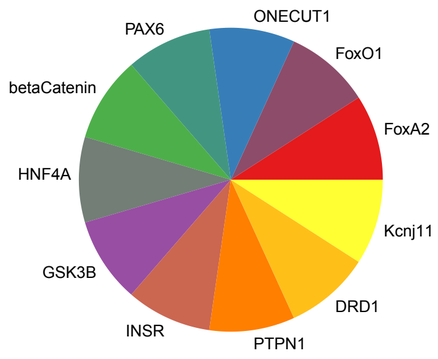


Figure S6. Beta Cell Function

(a)

raloxifene hydrochloride [82640-04-8]
(0.240)
pharmaceutical
selective estrogen receptor modulator (SERM): osterporosis

PharmaGSID_47315 [444610-91-7]
(0.225)
pharmaceutical
PPARγ agonist

SSR150106 [NOCAS_47362]
(0.223)
pharmaceutical
chemokine receptor antagonist (TNF alpha)

PharmaGSID_47259 [149062-75-9]
(0.221)
pharmaceutical
acetylcholinesterase inhibitor

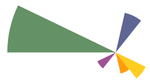
farglitazar [196808-45-4]
(0.203)
pharmaceutical
PPARγ agonist: hepatic fibrosis

chlorpromazine hydrochloride [69-09-0]
(0.192)
pharmaceutical
dopamine antagonist
with antiadrenergic, antiserotonergic, anticholinergic and antihistaminergic properties: antipsychotic

UK-416244 [402910-27-4]
(0.189)
pharmaceutical
sertraline analog, selective serotonin reuptake inbitor (SSRI)

volinanserin [139290-65-6]
(0.176)
pharmaceutical
5-HT2A receptor antagonist: antipsychotic, antidepressant and insomnia

haloperidol [52-86-8]
(0.163)
pharmaceutical
(inverse agonist of dopamine: schizoaffective disorders



pharmaGSID_48511 [1062243-51-9]
(0.149)
pharmaceutical
polo-like kinase inhibitor

meso-hexestrol [84-16-2]
(0.145)
pharmaceutical
estrogen, synthetic non-steroidal

trelanserin [189003-92-7]
(0.135)
pharmaceutical
selective serotonin 5-HT2A antagonist

4-hydroxytamoxifen [68392-35-8]
(0.123)
pharmaceutical
selective estrogen receptor modulator (SERM), active metabolite of tamoxifen

2,2-bis(4-hydroxyphenyl)-1,1,1-trichloroethane [2971-36-0]
(0.128)
degradate
phenol halide

glyceryl monoricinoleate [1323-38-2]
(0.119)
intermediate, emulsifier
alcohol carboxylate

17alpha-ethinylestradiol [557-63-6]
(0.122)
pharmaceutical
estrogen, steroidal

9-octadecenoic acid, 12 -hydroxy-, (9Z,12R)- [141-22-0] "ricinoleic acid"
(0.122)
pharmaceutical
unsaturated omega-9 fatty acid, major component of the seed oil from Castor plant seeds or in sclerotium of ergot

calcium neodecanoate [27253-33-4]
(0.121)
additive
carboxylic acid

17alpha-estradiol [57-91-0]
(0.120)
pharmaceutical
estrogen, steroidal

diphenhydramine hydrochloride [147-24-0] "Benadryl"
(0.119)
pharmaceutical
antihistamine

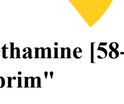
2,4,6-trichlorophenol [88-06-2]
(0.120)
herbicide
chlorinated phenol

clomiphene citrate [50-41-9] "Clomid"
(0.117)
pharmaceutical
selective estrogen receptor modulator (SERM) used for ovulation induction to reverse anovulation or oligoovulation

17beta-estradiol [50-28-2]
(0.115)
pharmaceutical
estrogen, steroidal

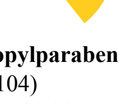
SAR150640 [NOCAS_47389]
(0.114)
pharmaceutical
selective β3-adrenoceptor agonist

N-dodecanoyl-N-methylglycine [97-78-9]
(0.111)
cosmetic, surfactant
carboxylic acid amide

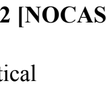


pyrimethamine [58-14-0] "Daraprim"
(0.111)
pharmaceutical
protozoal infections, antimalarial drug

2-naphthalenol [135-19-3]
(0.111)
antioxidant, reactant
naphthalene alcohol



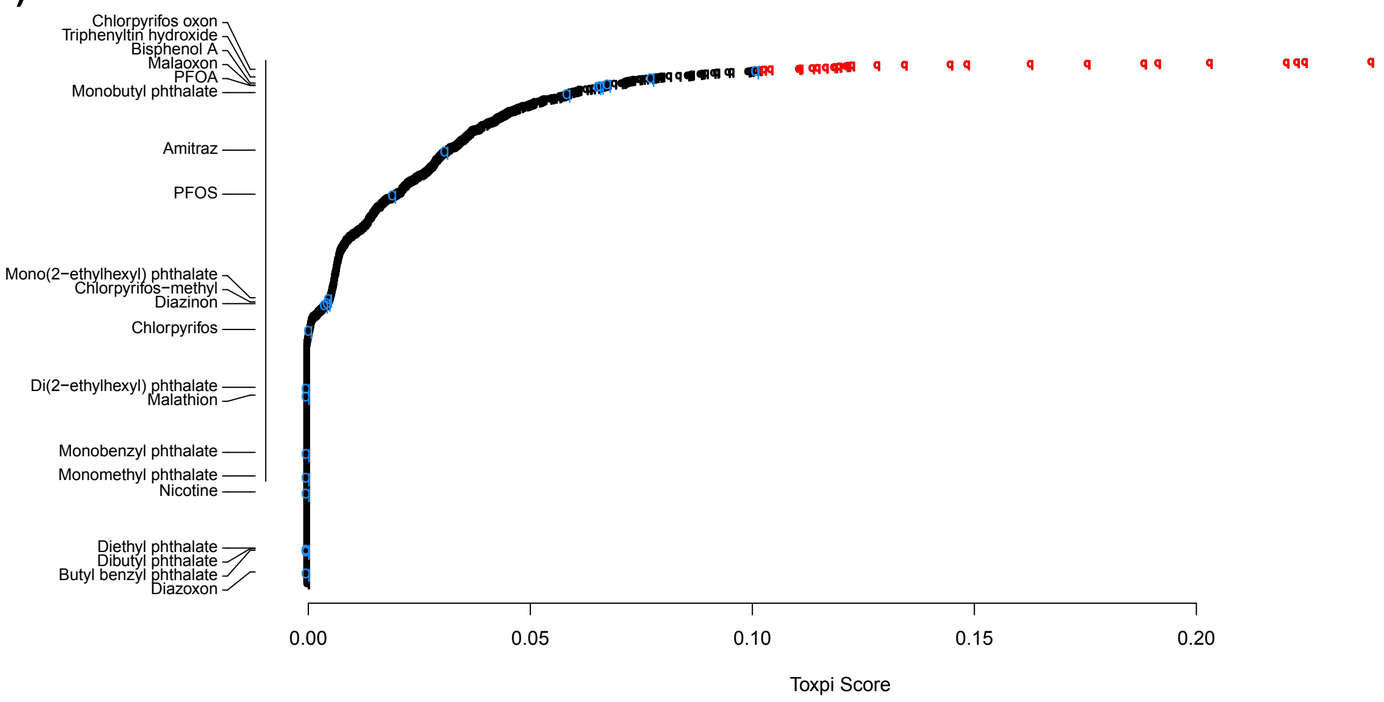
propylparaben [94-13-3]
(0.104)
microbicide
paraben

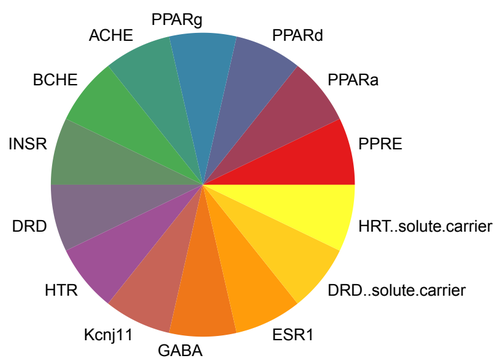


SAR377142 [NOCAS_47385]
(0.103)
pharmaceutical
factor Xa inhibitor

pirinixic acid [50892-23-4]
(0.102)
pharmaceutical
PPARα agonist that is under investigation for prevention of severe cardiac dysfunction, cardiomyopathy and heart failure

(b)





Figures S7-S12. Dendrograms representing hierarchy of structural similarity among ToxPi Top 30 lists of chemicals

The Tox21 set of chemicals (8307 InChIS) were imported into a Leadscope Enterprise v3.2 project, and subsequently exported as Leadscope "fingerprints". A chemical's fingerprint consists of a bitmap representing the presence or absence of ~27000 structural features. Fingerprints were extracted from the entire Tox21 set for each "top 30" list (Excel File Table S18). Features not present in any of the 30 members comprising a given list were eliminated, yielding fingerprints characterized by 611 – 843 chemical features. Fingerprints from ToxPi "top 30" lists were clustered (single linkage; tanimoto), yielding dendrograms, similarity scores, and heatmaps. Structure-activity classes are elucidated by inspecting line graphs of the tanimoto coefficients, plotted coincident with the dendrograms. Heatmaps (blue = feature present; grey = absent) align structural features common among the chemical sets. There are 30 chemicals in each structural hierarchy, having 29 similarity coefficients, each representing the structural similarity between nearest neighbors. Each dendrogram and similarity profile, together with an understanding of the biological effects of certain chemicals, enabled elucidation of number of enriched chemical classes within each of several "top 30" lists. Heatmaps contain alignments of structural features common among chemicals in the lists (not described here). Figures S7-S12 reveal chemical classes present in 3 of the 6 ToxPi Top 30 lists. Rodent feeding behavior (Figure S8) is clearly affected by both estrogens, and non-steroidal estrogenic compounds. Adipocyte differentiation (Figure S7) collects tin containing chemicals, along with glucocorticoids, and CPs. Finally, Islet Cell Model 2 (Figure S12) is clearly affected by estrogens (see also, Excel File Table S18). The remaining ToxPi top 30 lists reveal no discernible chemical classes.

Figure S7. Adipocyte Differentiation

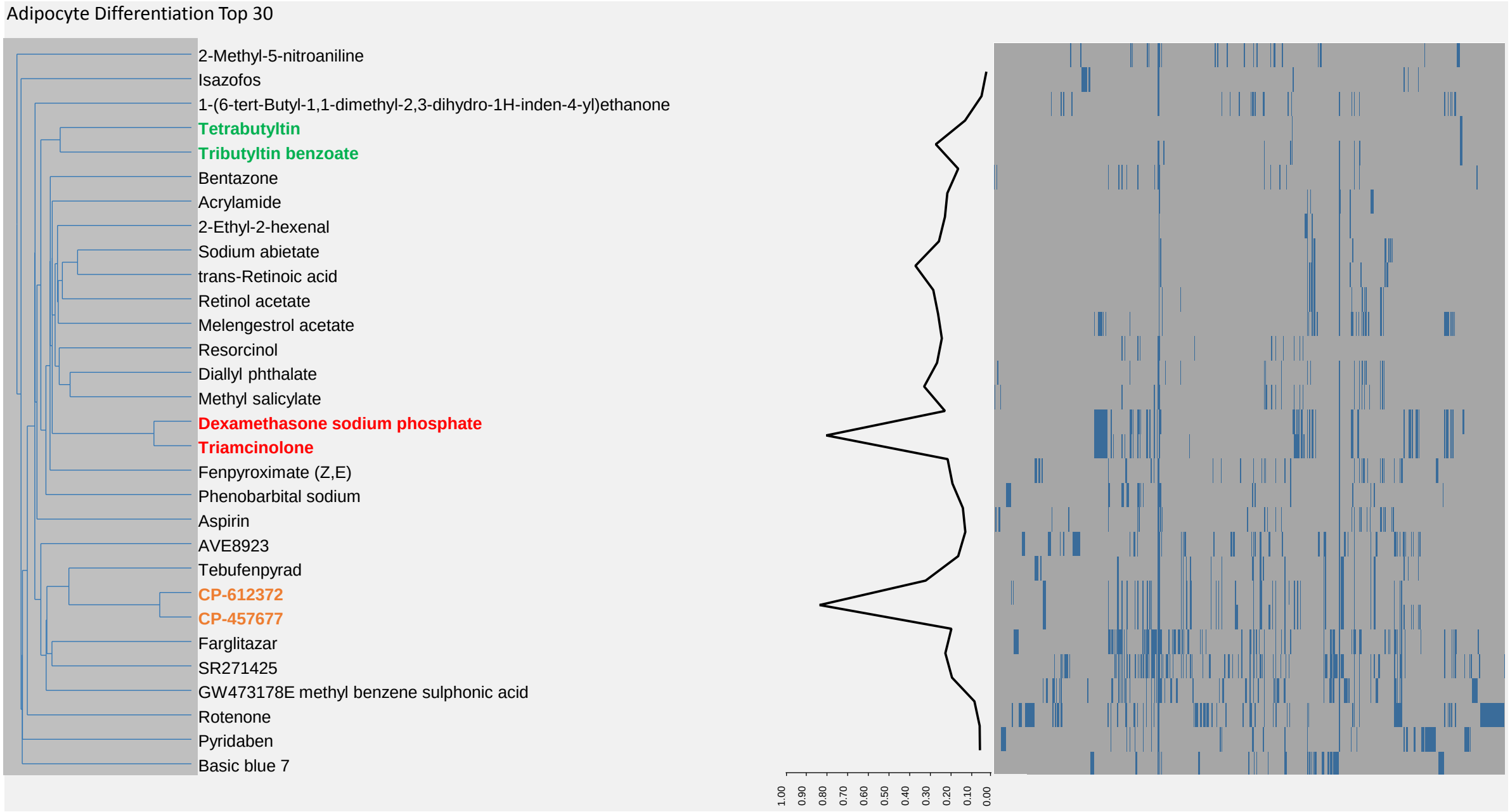


Figure S8. Feeding Behavior (rodent)

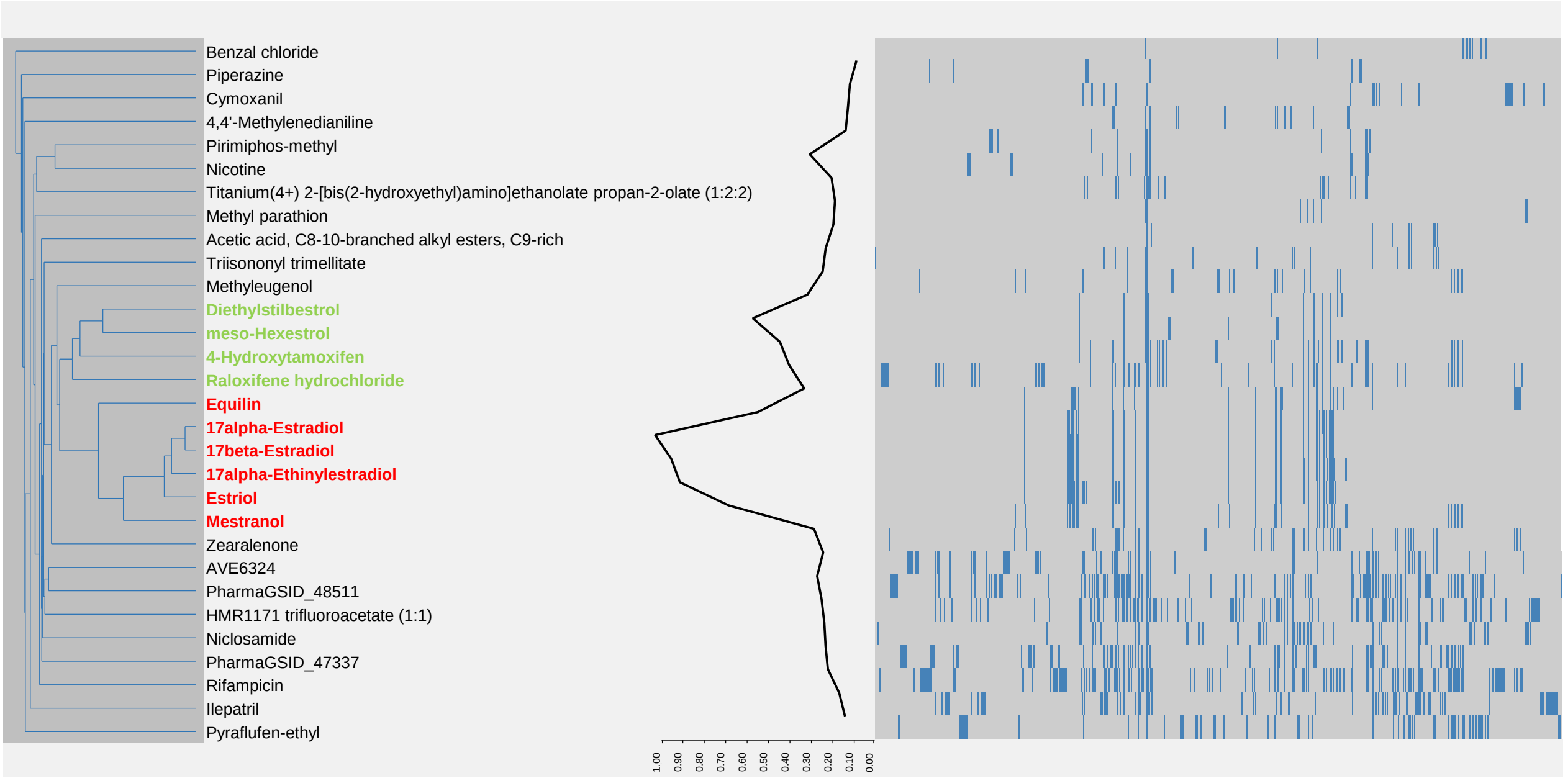


Figure S9. Feeding Behavior (*c. elegans*)

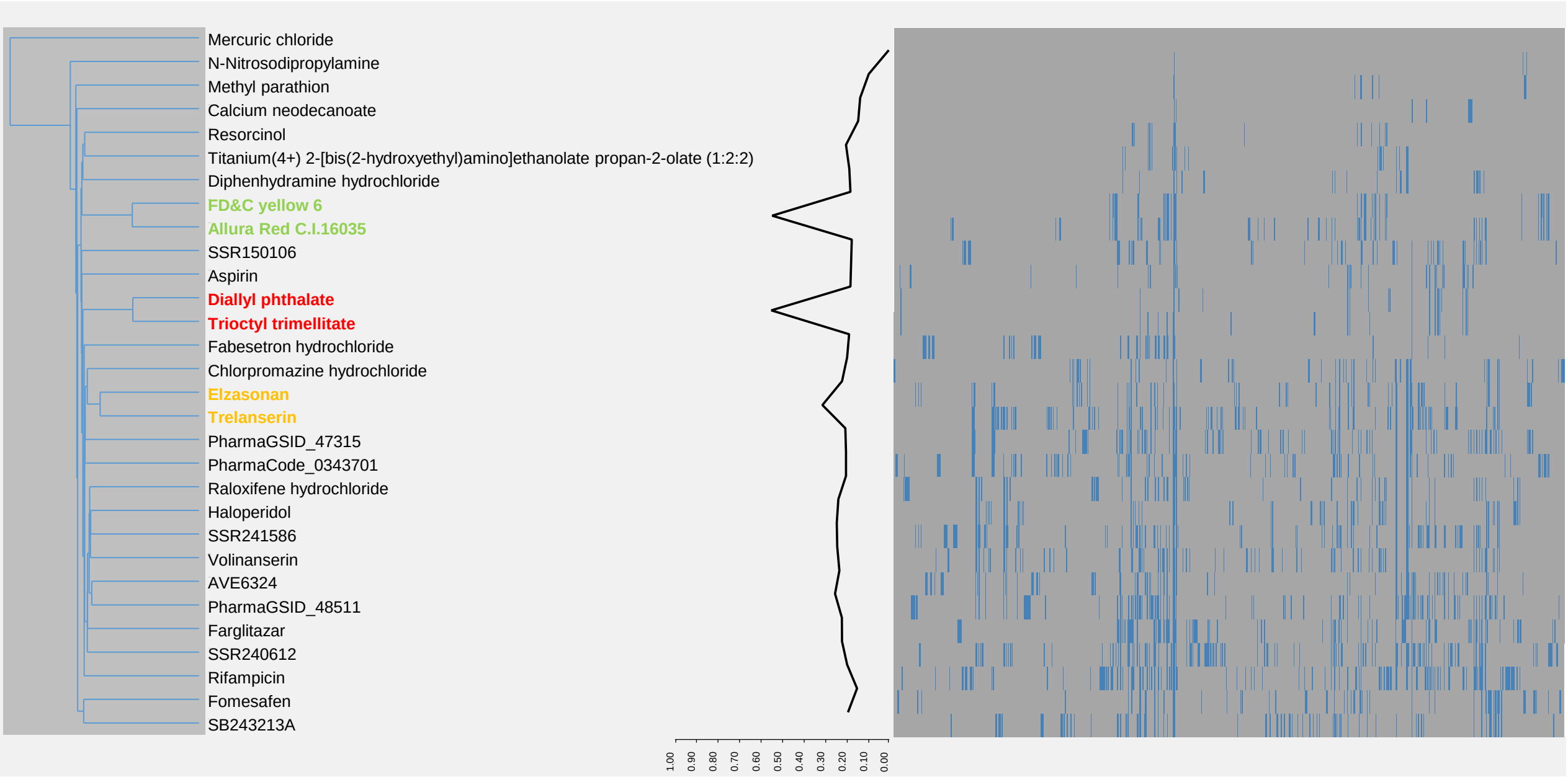


Figure S10. Insulin Sensitivity

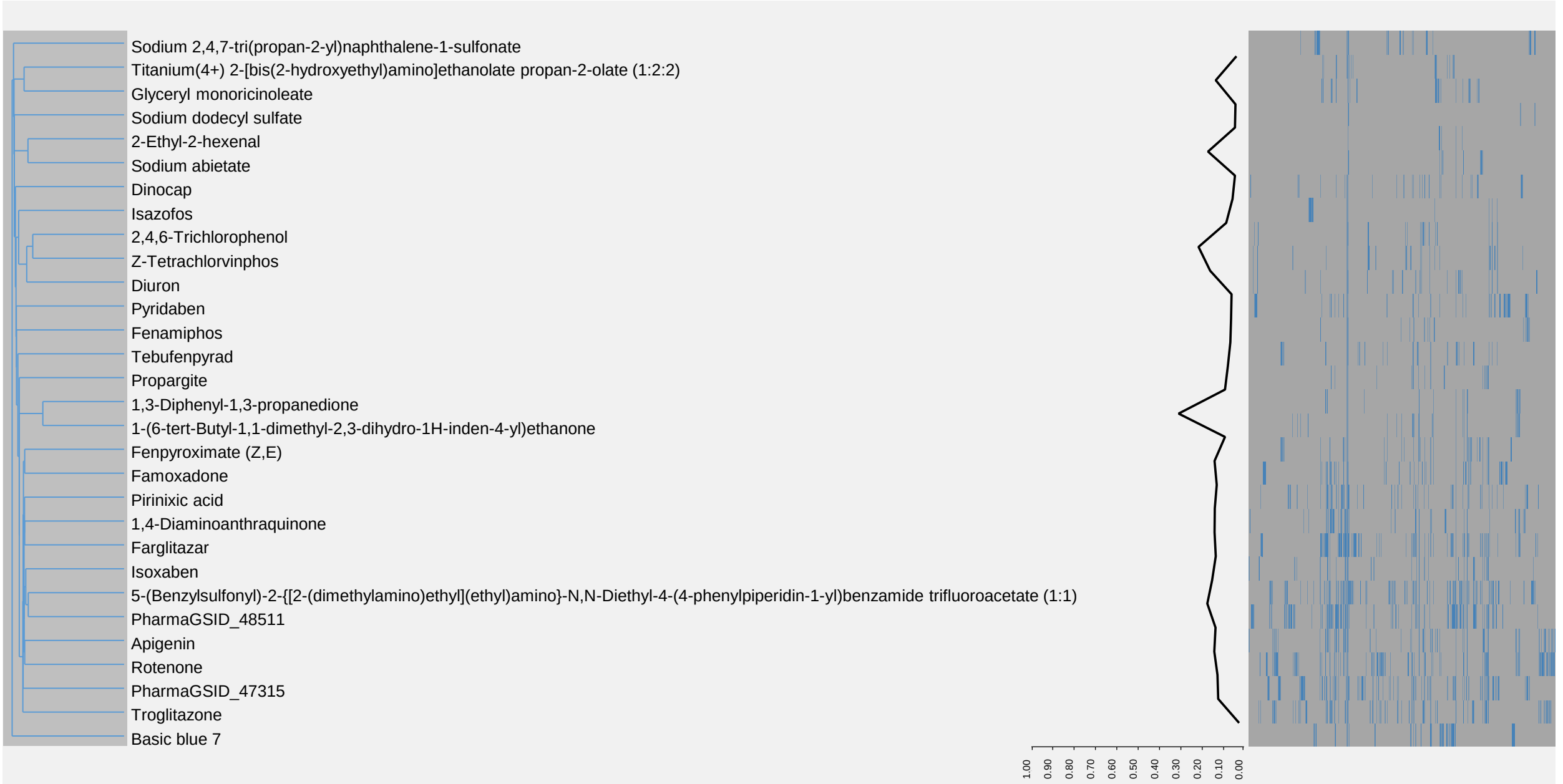


Figure S11. Islet Cell Function

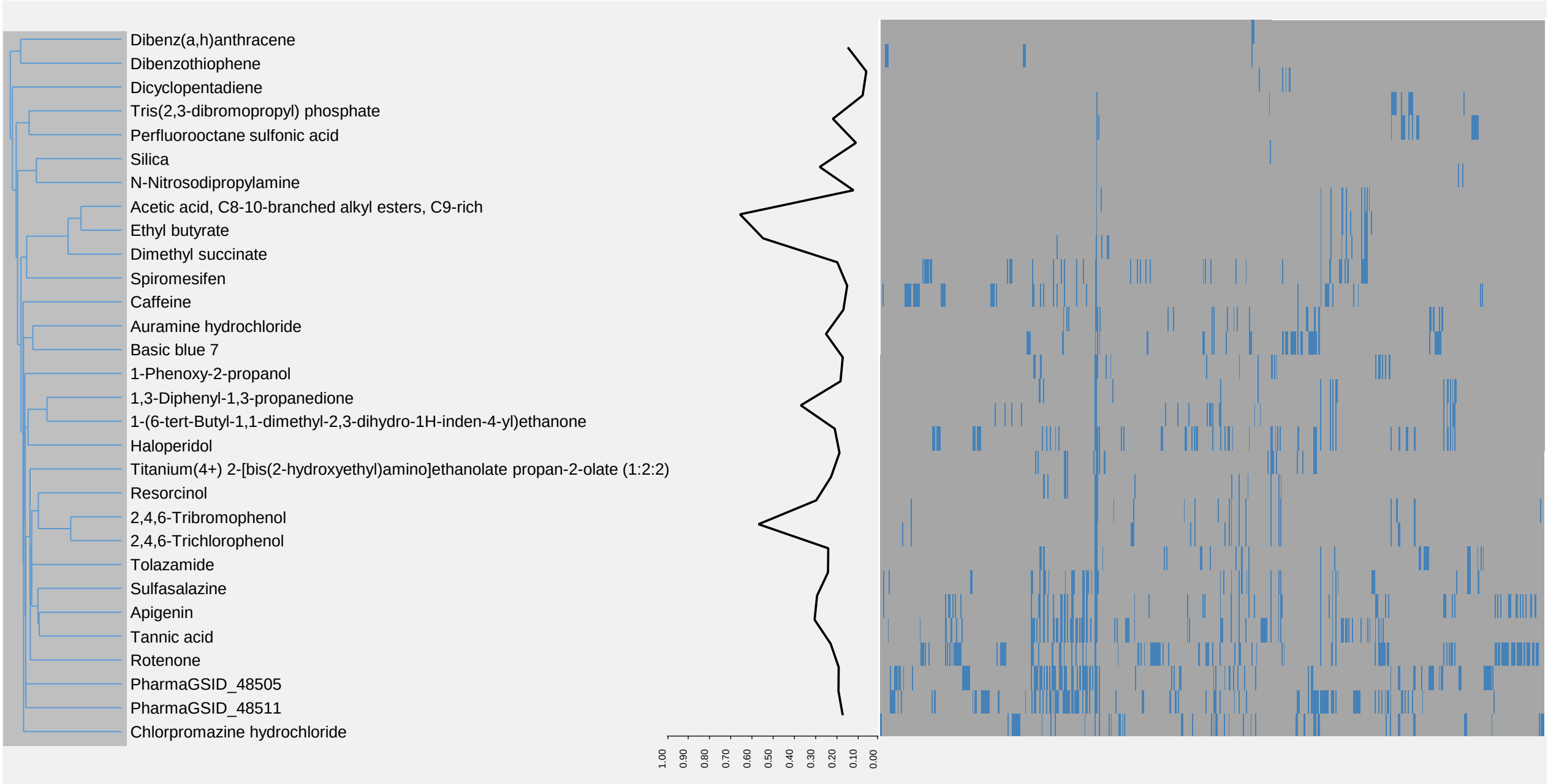


Figure S12. Beta Cell Function

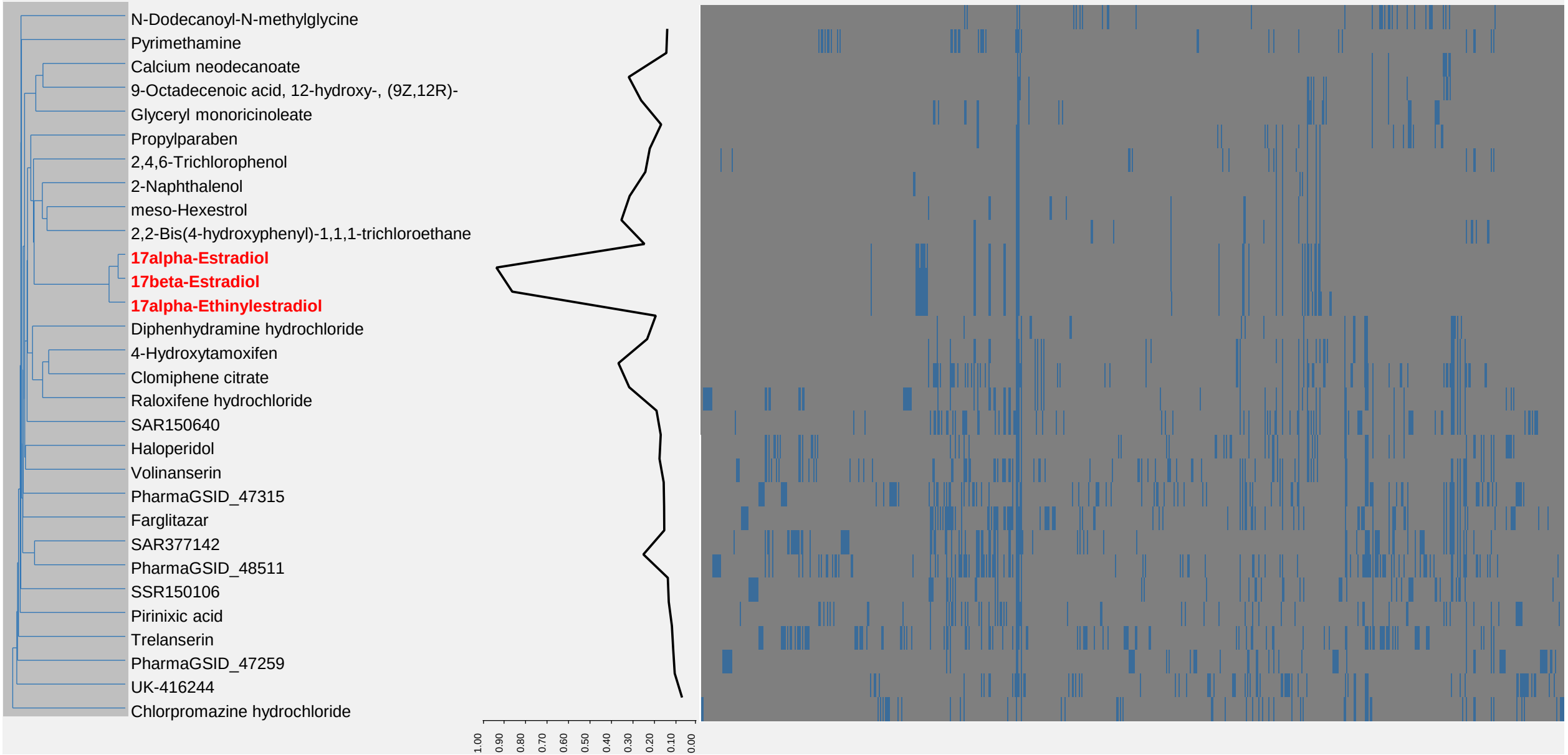


Figure S13. Chemical clustering based upon model of feeding behavior in C. elegans

The first three principal components (PCs) from the ToxPi model of feeding behavior in C. elegans are plotted in a pair-wise matrix of each PC. The points, each representing a single chemical, are colored according to the *k*-means clustering of the PC output. The three cluster insets show the mean ToxPi profile (plus overall ToxPi score) for chemicals in that cluster. The component assays in each slice are indicated in Table 1.

Figure S13. Chemical clustering based upon model of feeding behavior in C. elegans