A Connectivity Mapping (CMap) Based Assessment of BHT for Endocrine Disruption (ED)

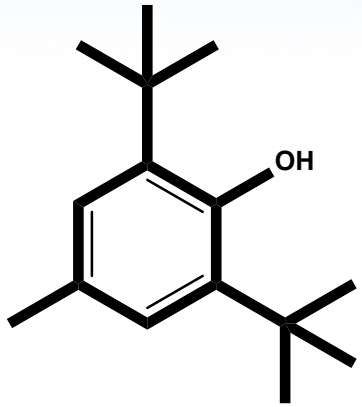
Nadira De Abrew

Human Safety
Ensuring Safe Products

Agenda

- Perceived Safety of BHT
- Connectivity Map (CMap)
- Connectivity Analysis of BHT
- SAR Analysis of BHT
- Conclusions

Butylated Hydroxytoluene (BHT)



BHT is listed as a CORAP substance with Endocrine Disruption in Human as one of the concerns. These concerns are based on:

- Comparisons made to BHA
- Borderline thyroid effects seen at high doses in one species
- Other in vitro results from mostly academic labs

BHT CMap Study

5 doses of BHT

4 cell lines

Run in triplicate

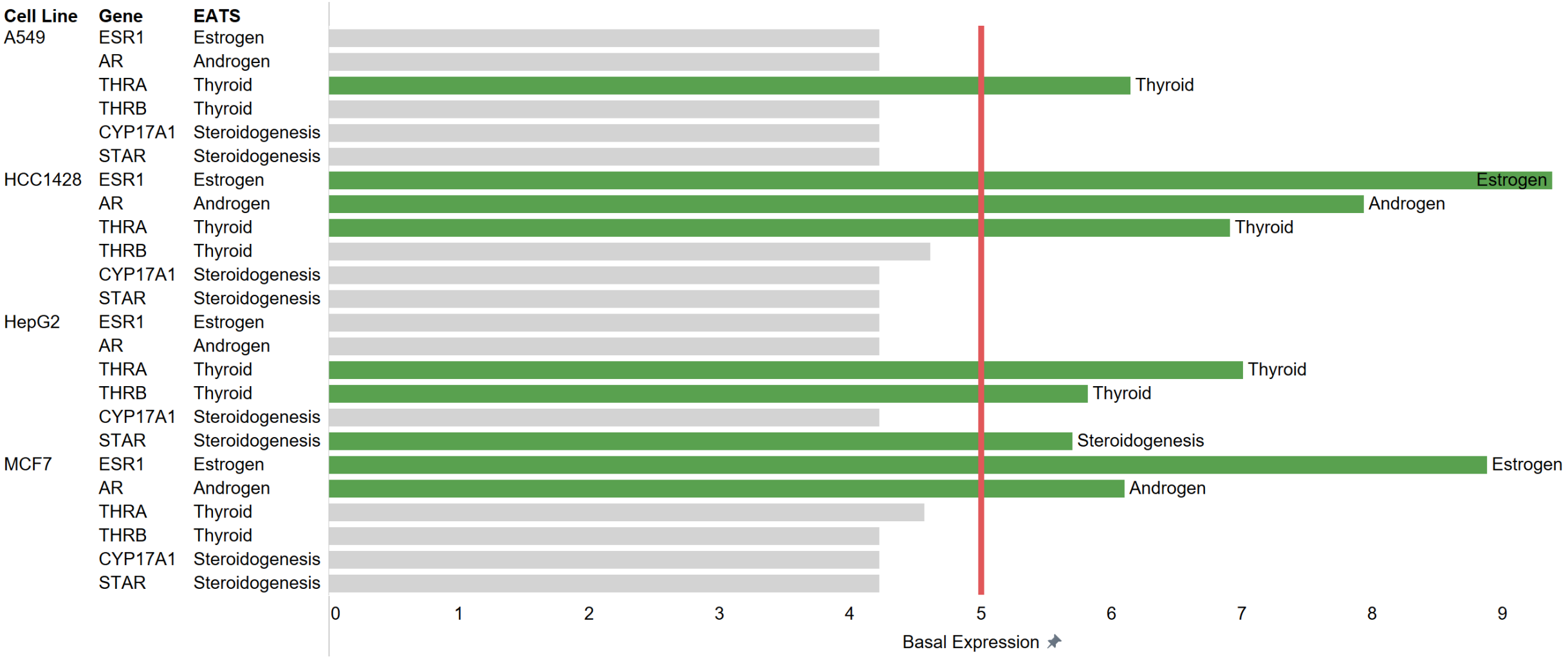
5 X 4 X 3 = 60

60 samples

EATS

- **E**strogenic
- **A**ndrogenic
- **T**hyroidal
- **S**teroidogenic

EATS Expression in 4 Cell lines



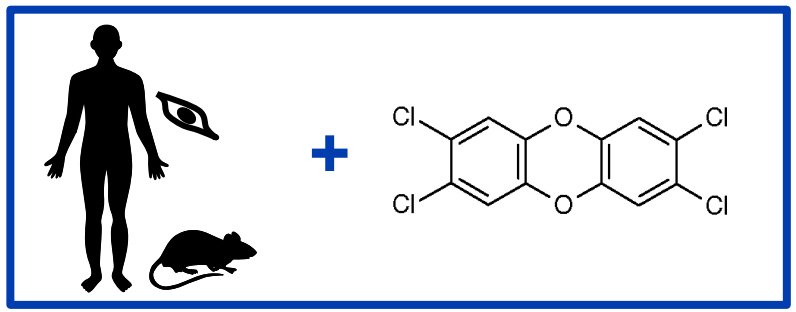
The Concept of a Biological Signature

Biological System

Chemical

Gene array analysis

Rank order fold change



This "signature" is unique to the biological system and chemical of interest

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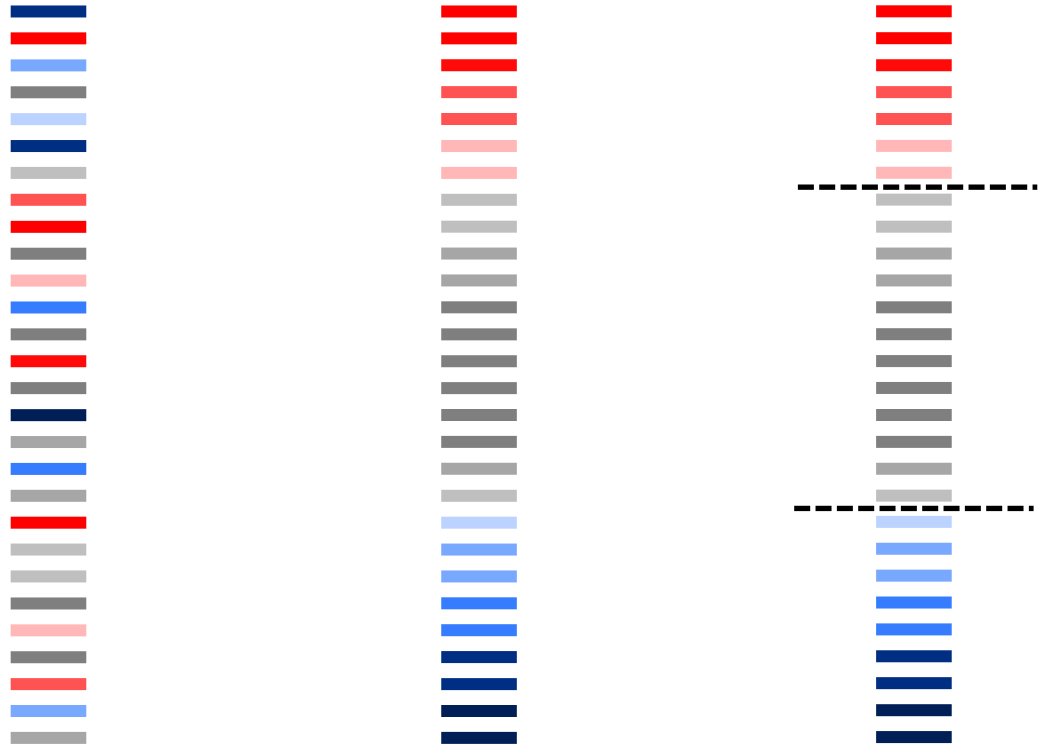
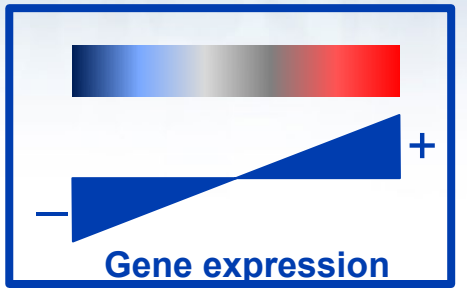
CMap Signature

C1D1 differential gene expression

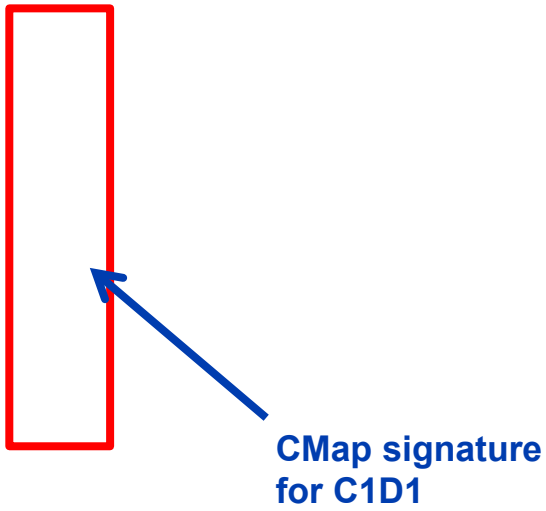
C1D1 rank ordered by fold change

C1D1 define CMap signature





C: Chemical
D: Dose

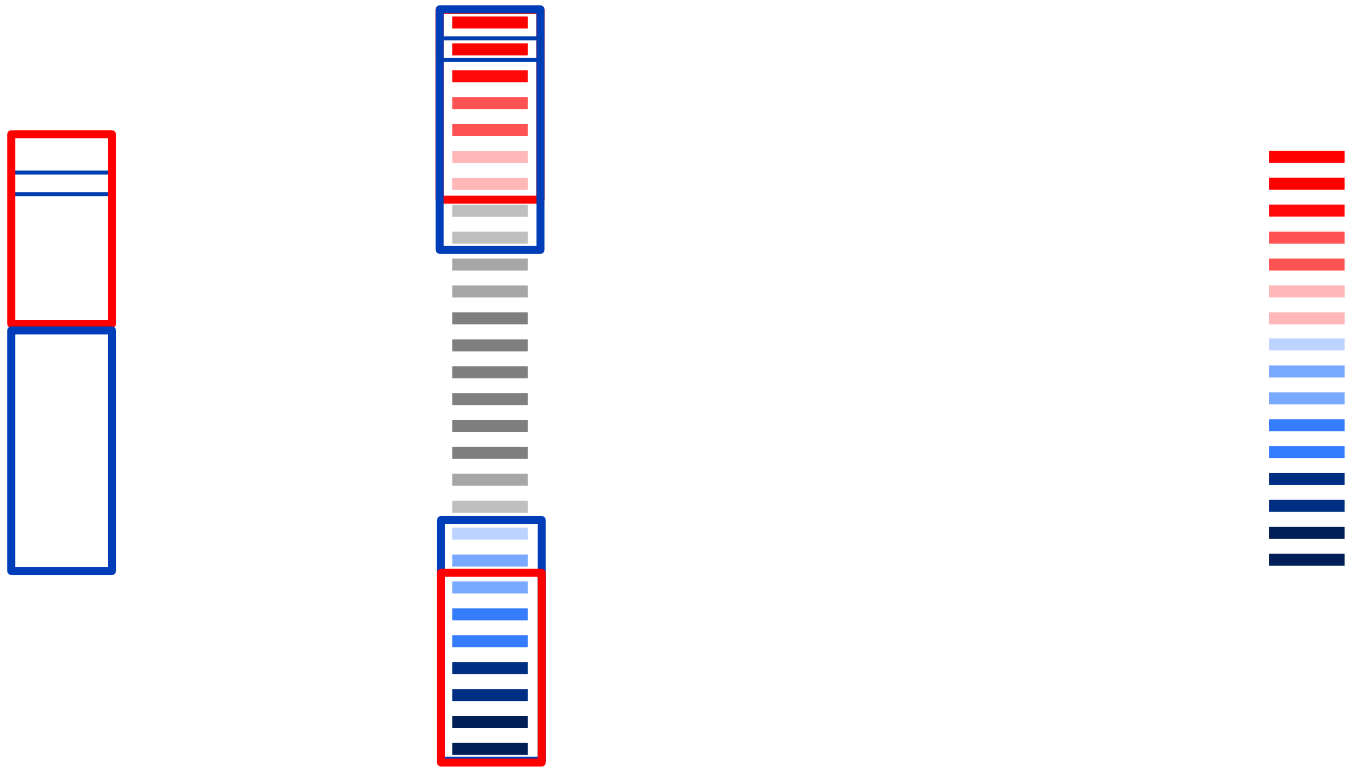


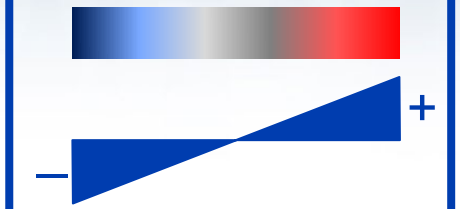
CMap signature for C1D1

CMap Signature

C1D1
CMap
Signature

C2D2
rank ordered
by
fold change

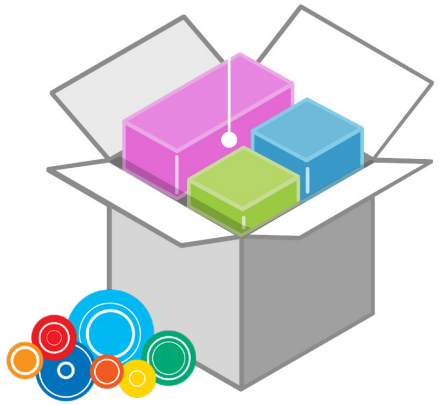




C: Chemical
D: Dose

Ask the question:
At what positions are genes from C1DI CMap signature present in C2D2 list of rank ordered genes
Give a CMap Score between -100 and +100

Broad Institute Next Generation CMap

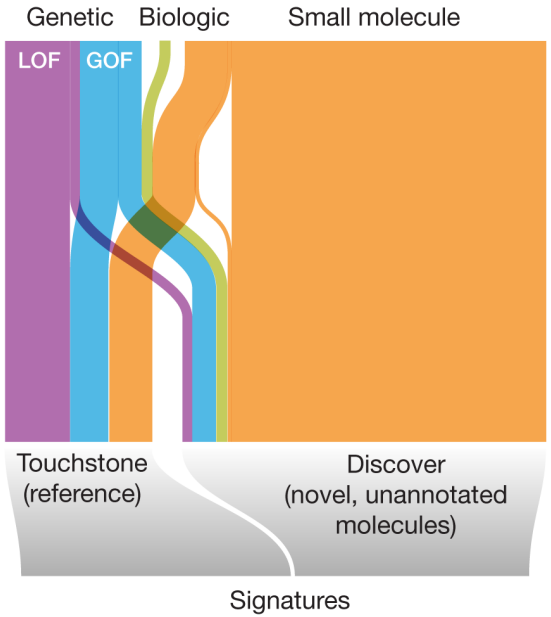


L1000

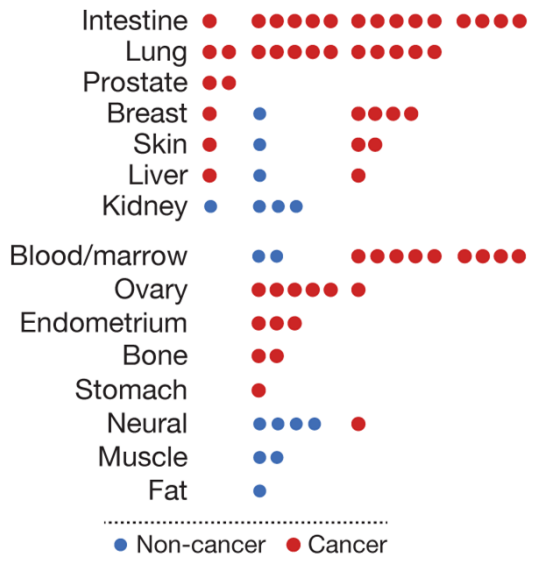
Pattern-recognition algorithms

2.2M profiles

28,000 (9000) perturbagens



80 Cell lines



Subramanian et al, Cell, 2017
Slide credit: Broad Institute

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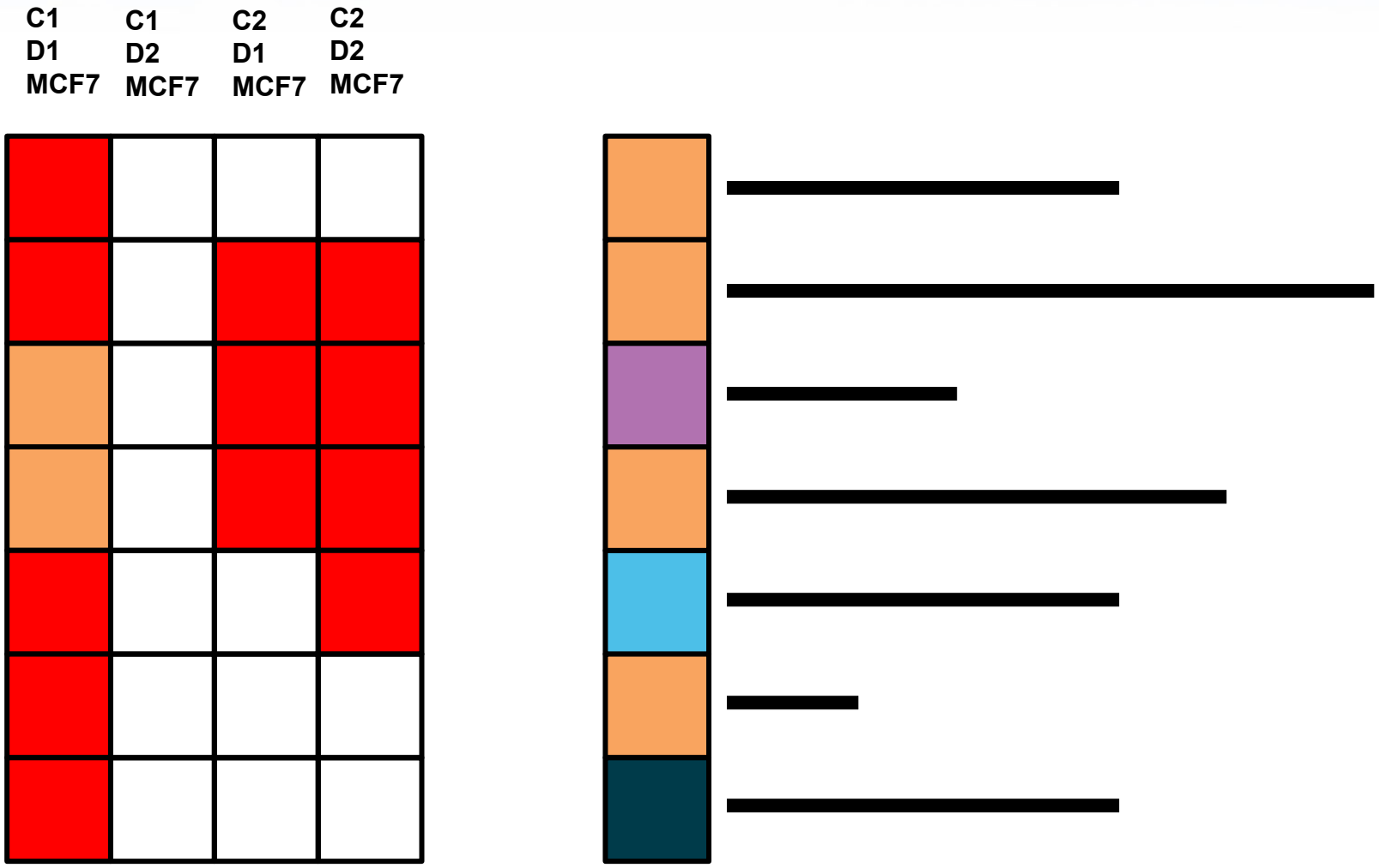

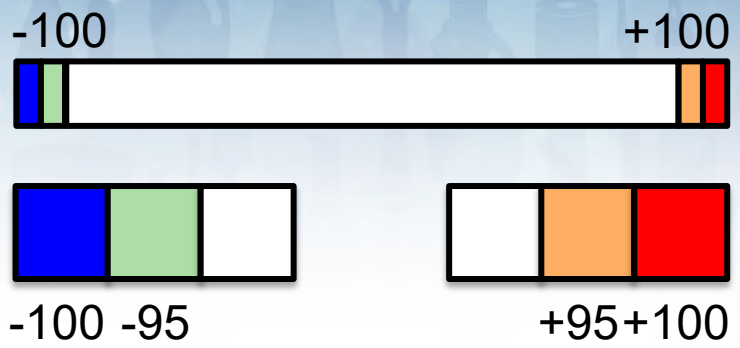

C: Chemical
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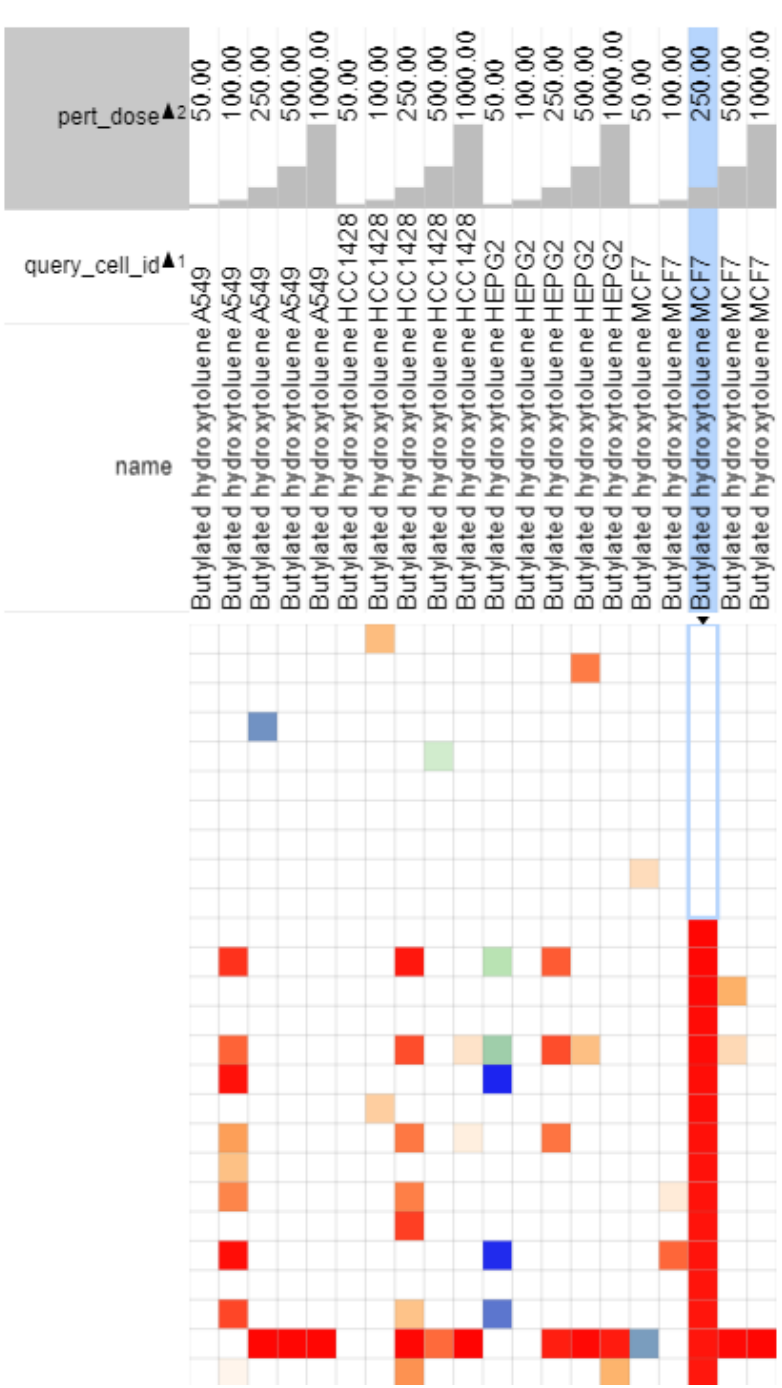
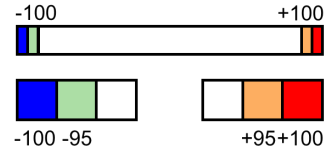
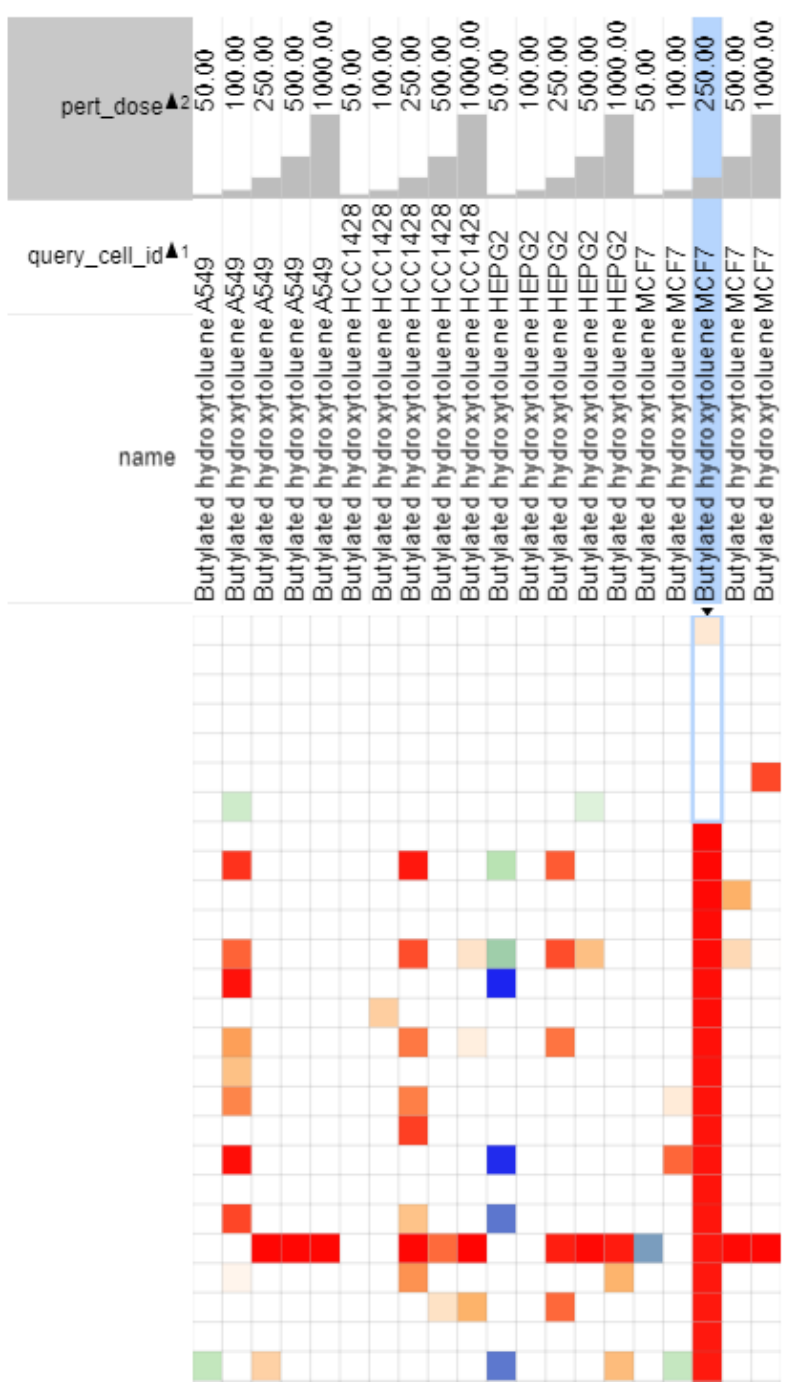
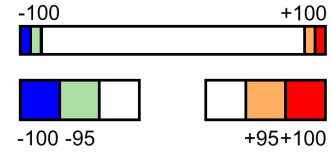




- **MCF7**
- **250 µM**
- **Search Term “estrogen receptor agonist”**

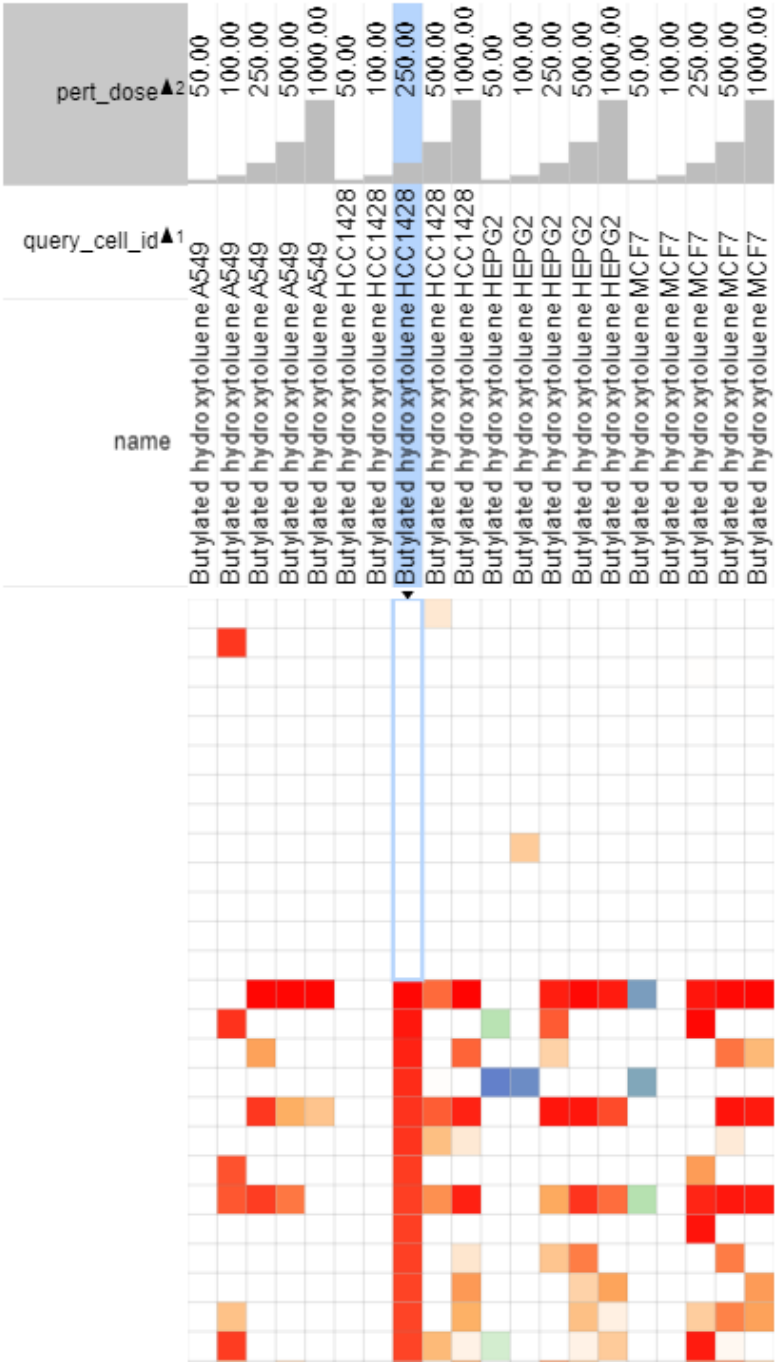
type	name	description
	estradiol-benzoate	contraceptive agent
	ethinyl-estradiol	DNA directed DNA polymerase stimunlant, estrogen receptor agonist, estrogenic component in oral contraceptives
	ethinylestradiol	DNA directed DNA polymerase stimunlant, estrogen receptor agonist
	17-beta-estradiol	estrogen receptor agonist
	estradiol	estrogen receptor agonist
	alpha-estradiol	estrogen receptor agonist
	estradiol	estrogen receptor agonist
	estradiol-cypionate	estrogen receptor agonist
	estradiol	estrogen receptor agonist
	estradiol-valerate	estrogen receptor agonist
	ERLIN1	ER lipid raft associated 1
	menadione	CDC inhibitor, mitochondrial DNA polymerase inhibitor, phosphatase inhibitor, pyruvate kinase isozyme inhibitor
	G2E3	Zinc fingers, PHD-type, G2/M-phase specific E3 ubiquitin protein ligase
	SNX11	Sorting nexins, sorting nexin 11
	BRD-K98824517	tyrosine phosphatase inhibitor
	Protein synthesis inhit	
	MRGPRF	GPCR / Class A : Orphans, MAS-related GPR, member F
	ryuvidine	histone lyinse methyltransferase inhibitor
	SERPINC1	Serine (or cysteine) peptidase inhibitors, serpin peptidase inhibitor, clade C (antithrombin), member 1
	penfluridol	dopamine receptor antagonist, T-type calcium channel blocker
	TNFRSF1A	Tumour necrosis factor (TNF) receptor family, tumor necrosis factor receptor superfamily, member 1A
	IFNG	Interferons, interferon, gamma
	RNPS1	RNA binding motif (RRM) containing, RNA binding protein S1, serine-rich domain
	QL-XII-47	BMX inhibitor, Bruton's tyrosine kinase (BTK) inhibitor, bruton's tyrosine kinase inhibitor, cytoplasmic tyrosine protein kinase BM
	celastrol	anti-inflammatory agent, antioxidant, HSP90 Inhibitor, NFKB pathway inhibitor, topoisomerase inhibitor
	NEK6	NIMA (never in mitosis gene a)- related kinase (NEK) family, NIMA (never in mitosis gene a)-related kinase 6

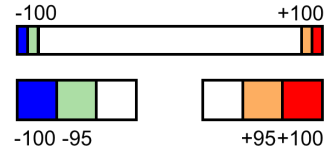




- **MCF7**
- **250 µM**
- **Search Term “androgen receptor agonist”**

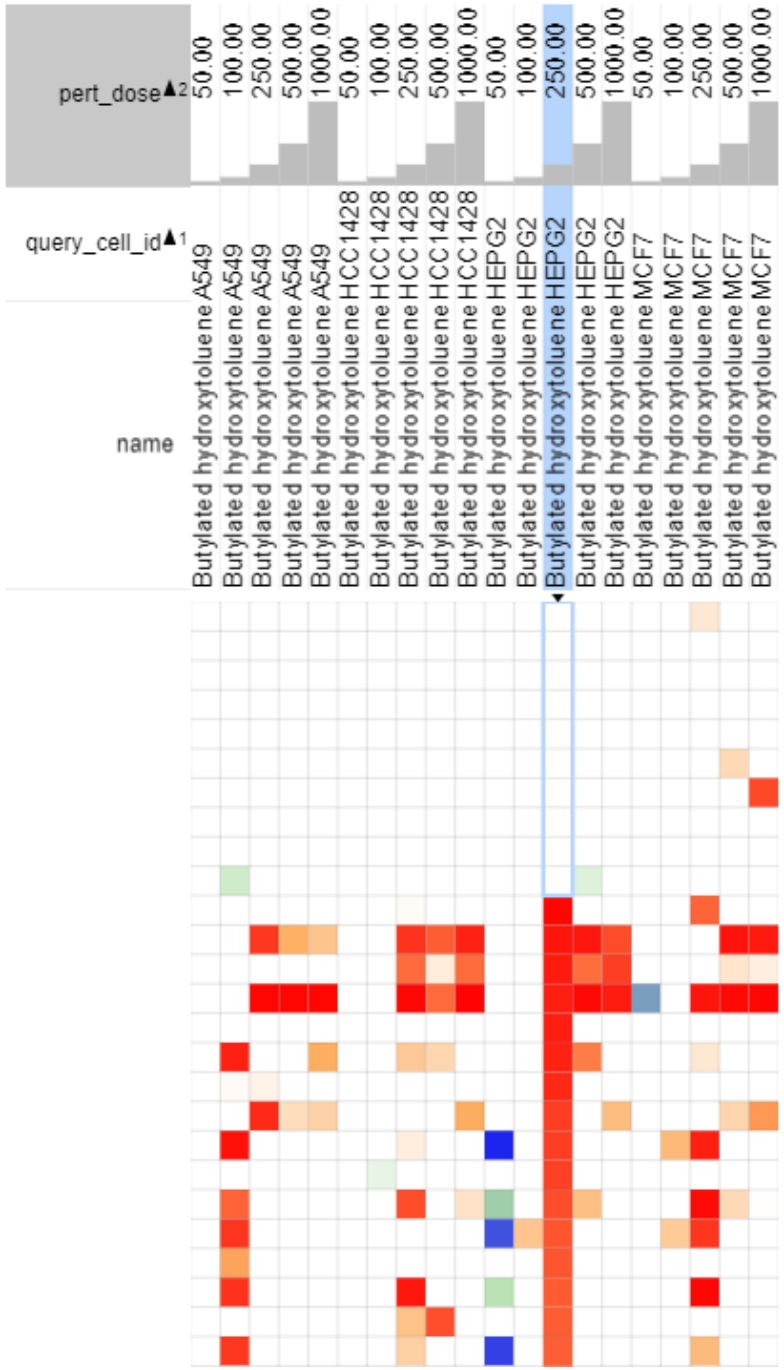
type	name	description
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	clomifene	estrogen receptor antagonist, estrogen receptor modulator, selective estrogen receptor modulator (SERM), testosterone recepto
	clomifene	estrogen receptor antagonist, estrogen receptor modulator, selective estrogen receptor modulator (SERM), testosterone recepto
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	ERLIN1	ER lipid raft associated 1
	menadione	CDC inhibitor, mitochondrial DNA polymerase inhibitor, phosphatase inhibitor, pyruvate kinase isozyme inhibitor
	G2E3	Zinc fingers, PHD-type, G2/M-phase specific E3 ubiquitin protein ligase
	SNX11	Sorting nexins, sorting nexin 11
	BRD-K98824517	tyrosine phosphatase inhibitor
	Protein synthesis inhit	
	MRGPRF	GPCR / Class A : Orphans, MAS-related GPR, member F
	ryuvidine	histone lyinse methyltransferase inhibitor
	SERPINC1	Serine (or cysteine) peptidase inhibitors, serpin peptidase inhibitor, clade C (antithrombin), member 1
	penfluridol	dopamine receptor antagonist, T-type calcium channel blocker
	TNFRSF1A	Tumour necrosis factor (TNF) receptor family, tumor necrosis factor receptor superfamily, member 1A
	IFNG	Interferons, interferon, gamma
	RNPS1	RNA binding motif (RRM) containing, RNA binding protein S1, serine-rich domain
	QL-XII-47	BMX inhibitor, Bruton's tyrosine kinase (BTK) inhibitor, bruton's tyrosine kinase inhibitor, cytoplasmic tyrosine protein kinase BM
	celastrol	anti-inflammatory agent, antioxidant, HSP90 Inhibitor, NFKB pathway inhibitor, topoisomerase inhibitor
	NEK6	NIMA (never in mitosis gene a)- related kinase (NEK) family, NIMA (never in mitosis gene a)-related kinase 6
	CCDC86	coiled-coil domain containing 86
	NDUFV1	Mitochondrial respiratory chain complex / Complex I, NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa
	CALCOCO2	calcium binding and coiled-coil domain 2

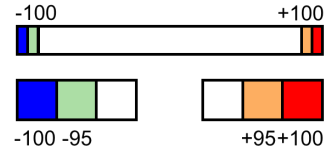




- **HCC1428**
- **250 µM**
- **Search Term**
  “thyroid hormone receptor”

type	name	description
	TRIP10	thyroid hormone receptor interactor 10
	TRIP10	thyroid hormone receptor interactor 10
	TRIP13	ATPases / AAA-type, thyroid hormone receptor interactor 13
	BRD-A89049230	thyroid-stimulating hormone receptor agonist
	PTHLH	Endogenous ligands, parathyroid hormone-like hormone
	THRAP3	thyroid hormone receptor associated protein 3
	THADA	thyroid adenoma associated
	methimazole	antithyroid Drugs
	liothyronine	thyroid hormone function stimulant
	BRD-A61599461	thyroid-stimulating hormone receptor inverse agonist
	TRIP13	ATPases / AAA-type, thyroid hormone receptor interactor 13
	THRAP3	thyroid hormone receptor associated protein 3
	PTHLH	Endogenous ligands, parathyroid hormone-like hormone
	celastrol	anti-inflammatory agent, antioxidant, HSP90 Inhibitor, NFKB pathway inhibitor, topoisomerase inhibitor
	menadione	CDC inhibitor, mitochondrial DNA polymerase inhibitor, phosphatase inhibitor, pyruvate kinase isozyme inhibitor
	FADD	Fas (TNFRSF6)-associated via death domain
	USP12	Ubiquitin-specific peptidases, ubiquitin specific peptidase 12
	SU-11652	FGFR inhibitor, PDGFR tyrosine kinase receptor inhibitor, tyrosine kinase receptor & angiogenic inhibitor, VEGFR inhibitor
	SLC35A1	SLC35 family of nucleotide sugar transporters, solute carrier family 35 (CMP-sialic acid transporter), member A1
	MAGEB6	melanoma antigen family B, 6
	auranofin	disease modifying antirheumatic drug, immunosuppressant, NFkB pathway inhibitor, prostanoid receptor inhibitor, thioredoxin re
	TNFRSF1A	Tumour necrosis factor (TNF) receptor family, tumor necrosis factor receptor superfamily, member 1A
	RRP8	ribosomal RNA processing 8, methyltransferase, homolog (yeast)
	SKAP2	Pleckstrin homology (PH) domain containing, src kinase associated phosphoprotein 2
	GADD45A	growth arrest and DNA-damage-inducible, alpha
	IFNB1	Interferons, interferon, beta 1, fibroblast

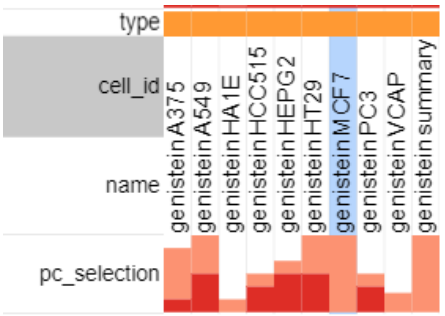




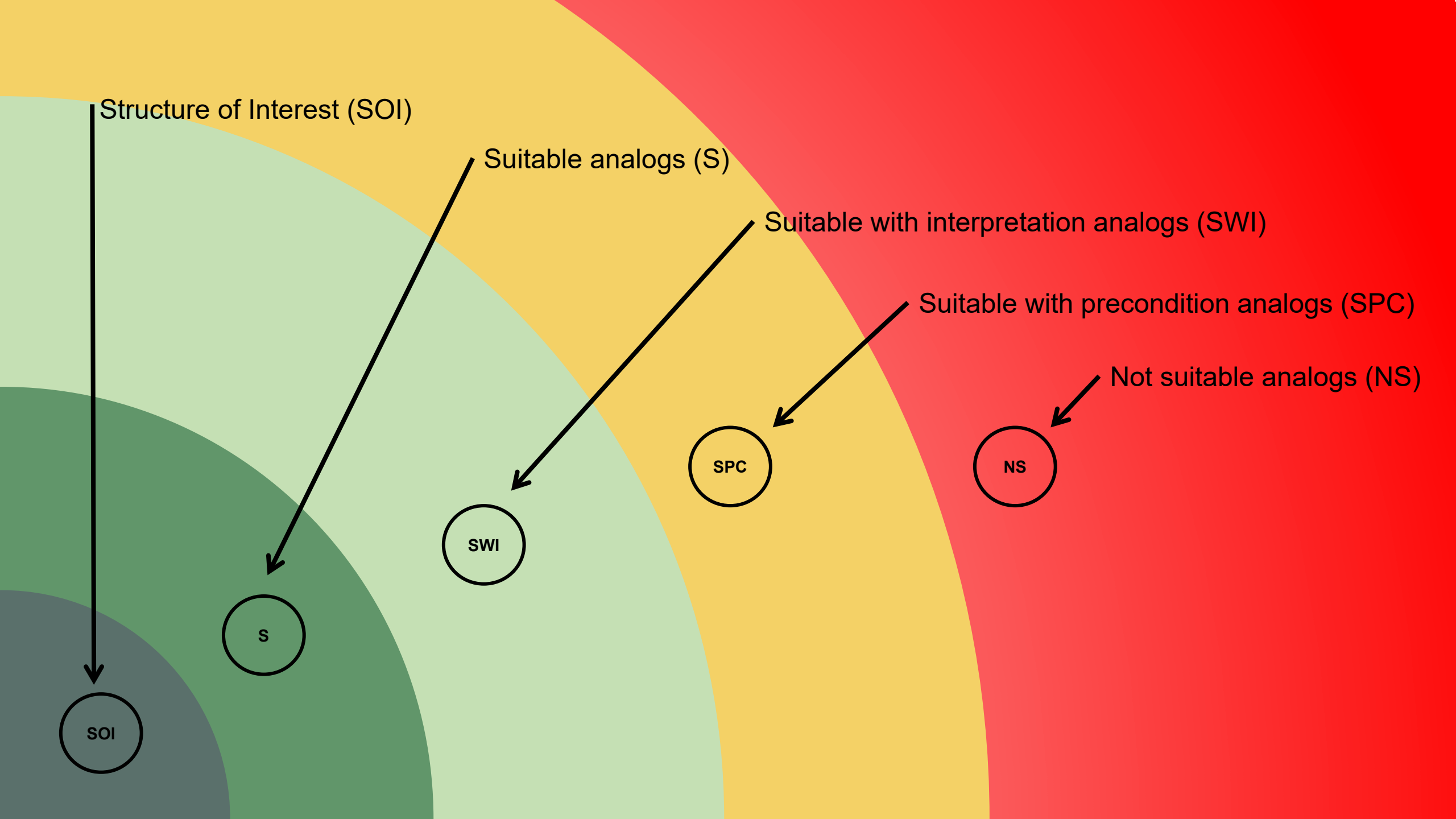
- **HepG2**
- **250 µM**
- **Search Term “testosterone”**

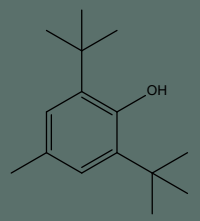
type	name	description
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	clomifene	estrogen receptor antagonist, estrogen receptor modulator, selective estrogen receptor modulator (SERM), testosterone recepto
	clomifene	estrogen receptor antagonist, estrogen receptor modulator, selective estrogen receptor modulator (SERM), testosterone recepto
	cyproterone	androgen receptor antagonist, DNA directed DNA polymerase stimunlant, Estradiol 17 beta dehydrogenase stimulant, estrone s
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	epitestosterone	inactive testosterone analog
	epitestosterone	inactive testosterone analog
	testosterone	androgen receptor (AR) agonist, androgen receptor agonist, testosterone receptor agonist
	PUF60	RNA binding motif (RRM) containing, poly-U binding splicing factor 60KDa
	SU-11652	FGFR inhibitor, PDGFR tyrosine kinase receptor inhibitor, tyrosine kinase receptor & angiogenic inhibitor, VEGFR inhibitor
	DCTN6	dynactin 6
	celastrol	anti-inflammatory agent, antioxidant, HSP90 Inhibitor, NFKB pathway inhibitor, topoisomerase inhibitor
	DUSP6	Protein tyrosine phosphatases / Class I Cys-based PTPs : MAP kinase phosphatases, dual specificity phosphatase 6
	NUP133	nucleoporin 133kDa
	RFC2	ATPases / AAA-type, replication factor C (activator 1) 2, 40kDa
	ARNT2	Basic helix-loop-helix proteins, aryl-hydrocarbon receptor nuclear translocator 2
	ATPase inhibitor	
	PDLIM4	PDZ and LIM domain 4
	BRD-K98824517	tyrosine phosphatase inhibitor
	digoxin	ATPase inhibitor, ROR antagonist
	NUDCD3	NudC domain containing 3
	menadione	CDC inhibitor, mitochondrial DNA polymerase inhibitor, phosphatase inhibitor, pyruvate kinase isozyme inhibitor
	RBM15B	RNA binding motif (RRM) containing, RNA binding motif protein 15B
	HU-211	glutamate receptor antagonist, apoptosis stimulant, NFkB pathway inhibitor, reducing agent

CMap Database search for Genistein



type	name	description	ts_pc
	FDX1L	ferredoxin 1-like	
	avrainvillamide-analog-6	nucleophosmin inhibitor	
	WFDC2	WAP four-disulfide core domain containing, WAP four-disulfide core domain	
	Nucleophosmin inhibitor		
	CDK6	Cyclin-dependent kinases, CDK4 subfamily, cyclin-dependent kinase 6	
	C5ORF62	chromosome 5 open reading frame 62	
	KCNQ1	Voltage-gated potassium channels, potassium voltage-gated channel, KQT-	
	dienestrol	estrogen receptor agonist	
	PRMT2	Protein arginine N-methyltransferases, protein arginine methyltransferase 2	
	alpha-estradiol	estrogen receptor agonist	
	TAL2	Basic helix-loop-helix proteins, T-cell acute lymphocytic leukemia 2	
	MRGPRX3	GPCR / Class A : Orphans, MAS-related GPR, member X3	
	EDN1	Endogenous ligands, endothelin 1	
	ITPK1	inositol-tetrakisphosphate 1-kinase	
	genistein	tyrosine kinase inhibitor, angiogenesis inhibitor, CFTR channel activator, EC	
	equol	estrogen receptor agonist	
	USP12	Ubiquitin-specific peptidases, ubiquitin specific peptidase 12	
	equilin	estrogen receptor agonist	
	rilmenidine	adrenergic receptor agonist, imidazoline receptor agonist	
	AT-9283	Aurora kinase inhibitor, JAK inhibitor, Abl kinase inhibitor, Bcr-Abl kinase inh	
	CDKN1C	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	
	RSU1	Ras suppressor protein 1	
	DUSP3	Protein tyrosine phosphatases / Class I Cys-based PTPs : Atypical dual spe	
	trequinsin	phosphodiesterase inhibitor, platelet aggregation inhibitor, potassium chann	
	diethylstilbestrol	estrogen receptor agonist, chloride channel blocker	
	CHN1	Rho GTPase activating proteins, chimerin (chimaerin) 1	
	PRKACA	Protein kinase A, protein kinase, cAMP-dependent, catalytic, alpha	


Structure of Interest (SOI)
Suitable analogs (S)
Suitable with interpretation analogs (SWI)
Suitable with precondition analogs (SPC)
Not suitable analogs (NS)
SOI
S
SWI
SPC
NS



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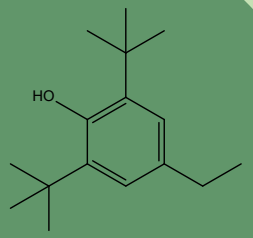

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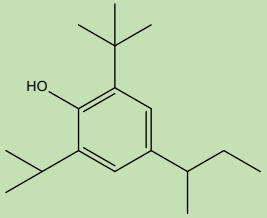

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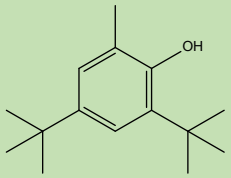

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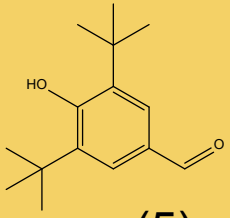

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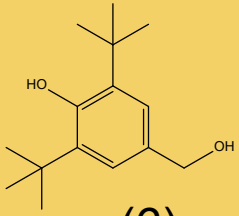

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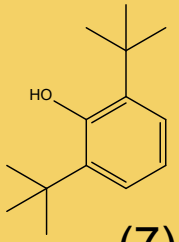

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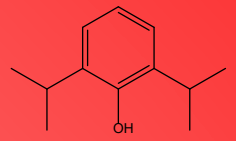

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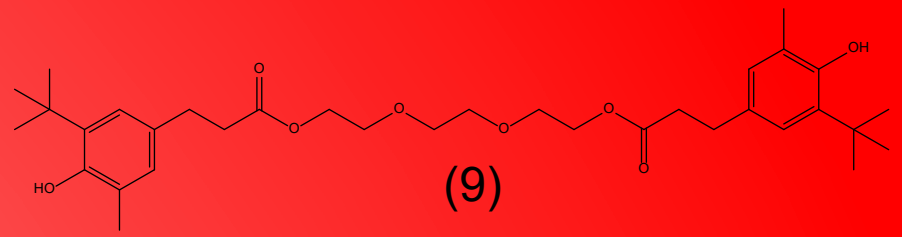

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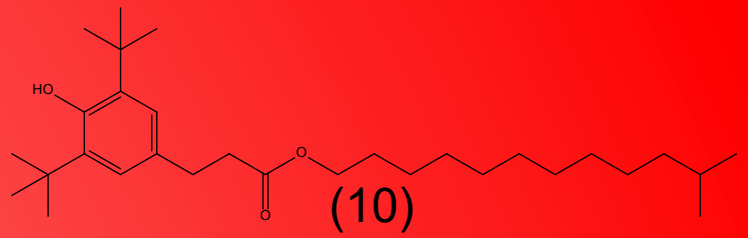

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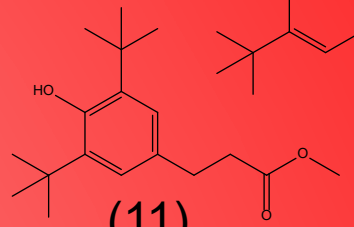

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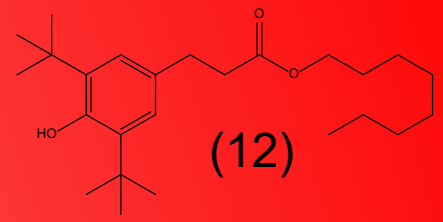

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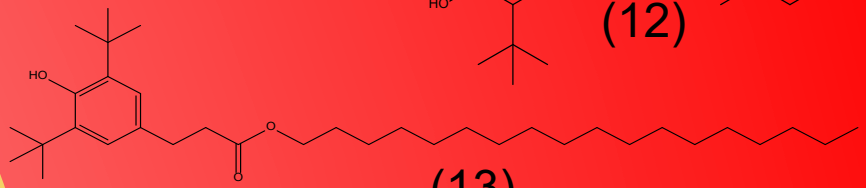

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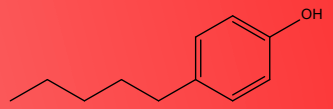

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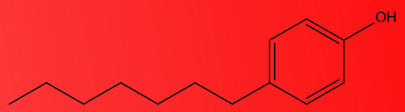

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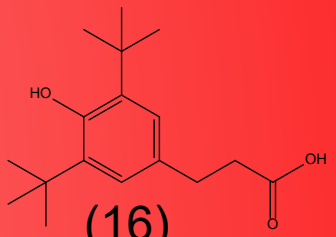
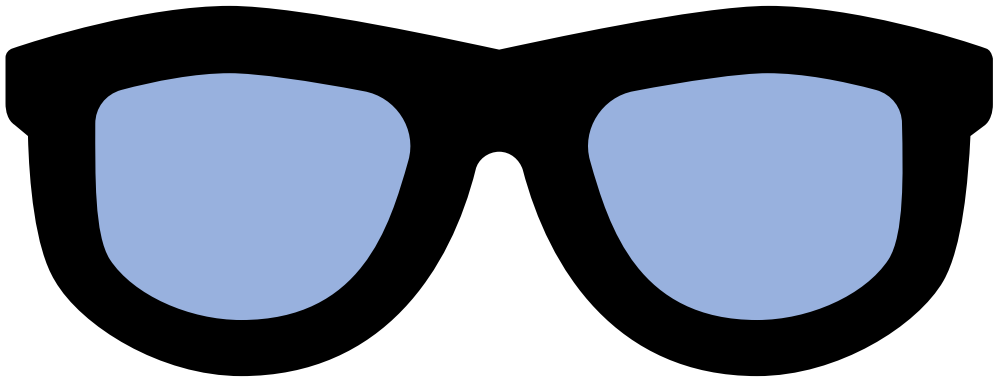
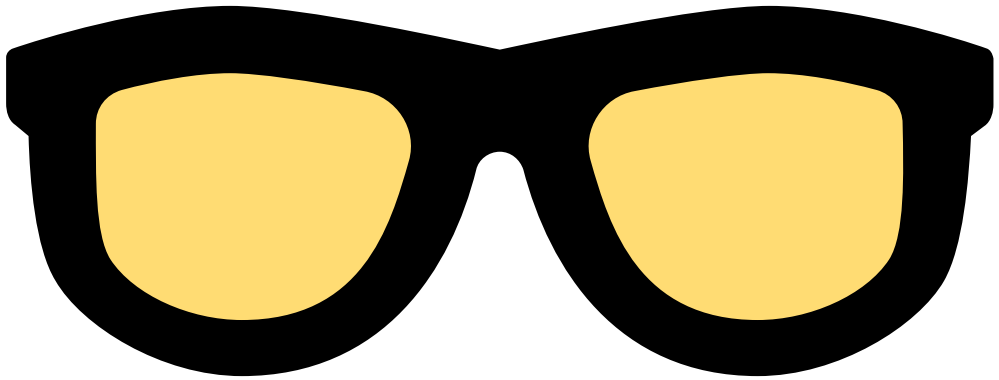


(16)

Chemistry
(structural similarity)

Biology
(functional similarity)





Do they align?

Human Safety
Ensuring Safe Products

BHT CMap Study

16 chemicals

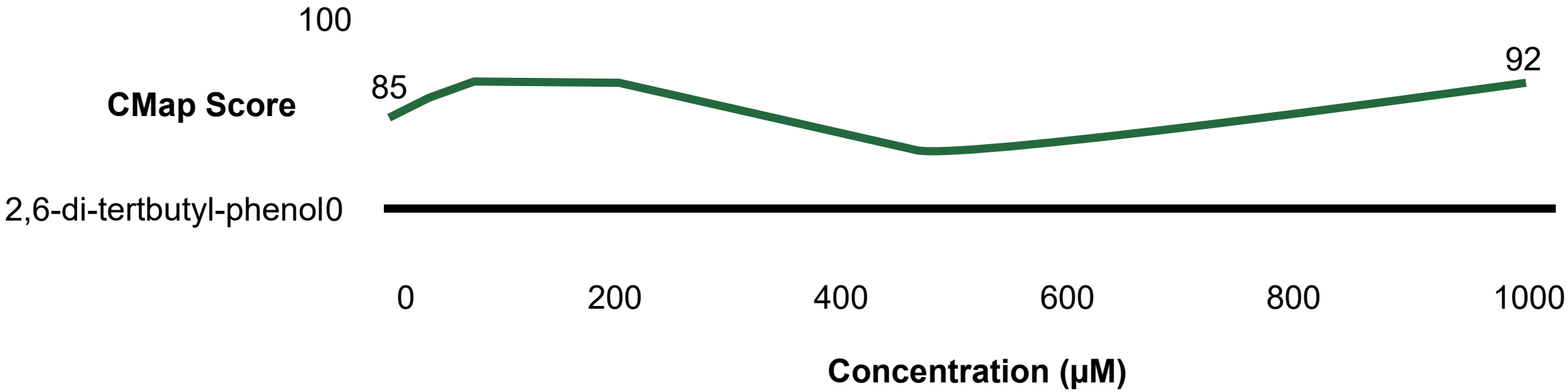
5 doses per chemical

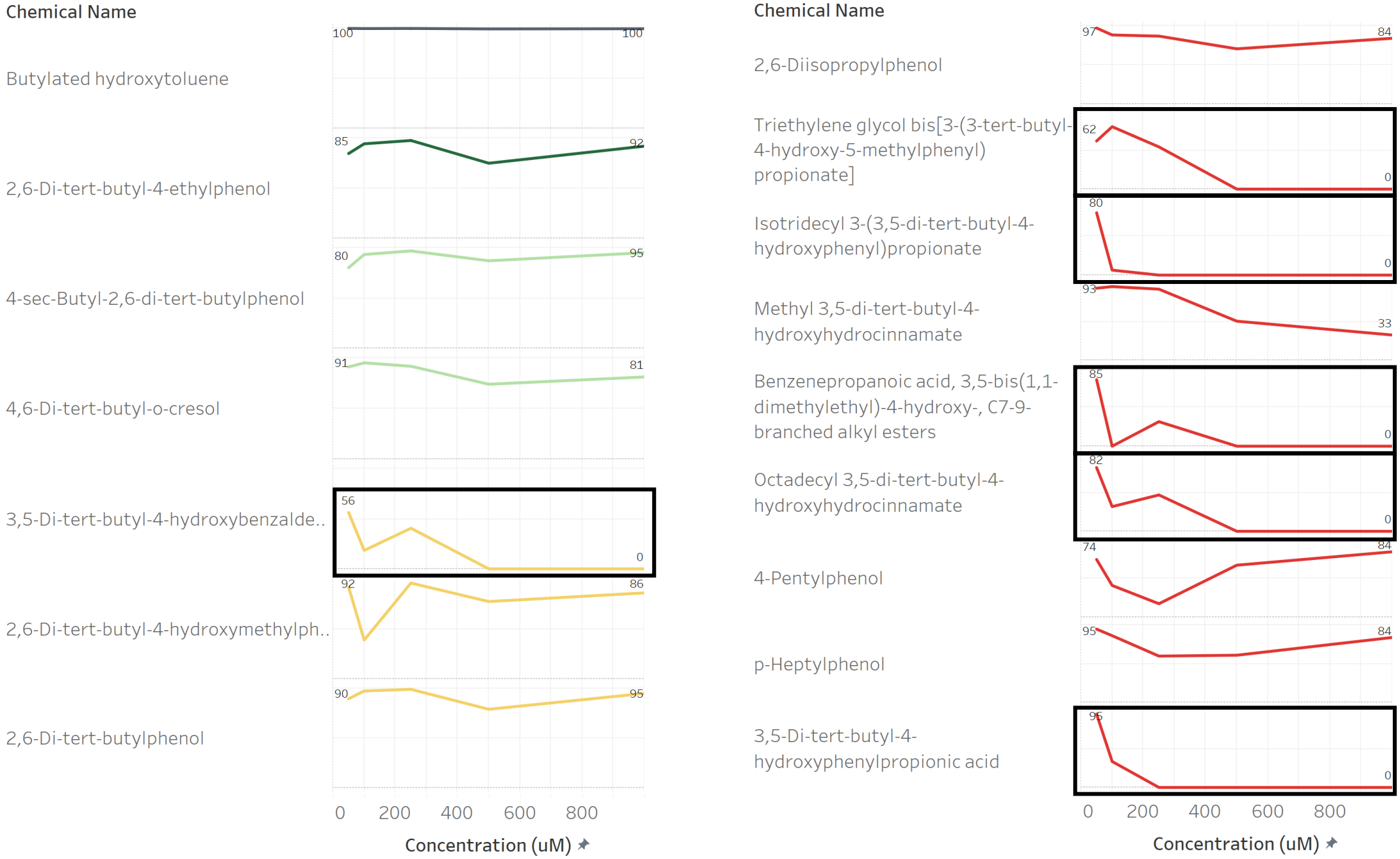
4 cell lines

Run in triplicate

16 X 5 X 4 X 3 = 960

960 samples




Chemical Name
Butylated hydroxytoluene
2,6-Di-tert-butyl-4-ethylphenol
4-sec-Butyl-2,6-di-tert-butylphenol
4,6-Di-tert-butyl-o-cresol
3,5-Di-tert-butyl-4-hydroxybenzalde..
2,6-Di-tert-butyl-4-hydroxymethylph..
2,6-Di-tert-butylphenol
100
100
85
92
80
95
91
81
56
0
92
86
90
95
0
200
400
600
800
Concentration (uM)
Chemical Name
2,6-Diisopropylphenol
Triethylene glycol bis[3-(3-tert-butyl-4-hydroxy-5-methylphenyl) propionate]
Isotridecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate
Methyl 3,5-di-tert-butyl-4-hydroxyhydrocinnamate
Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, C7-9-branched alkyl esters
Octadecyl 3,5-di-tert-butyl-4-hydroxyhydrocinnamate
4-Pentylphenol
p-Heptylphenol
3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid
97
84
62
0
80
0
93
33
85
0
82
0
74
84
95
84
96
0
0
200
400
600
800
Concentration (uM)
SOI
S
SWI
SPC
NS


Butylated hydroxytoluene
2,6-Di-tert-butyl-4-ethylphenol
4-sec-Butyl-2,6-di-tert-butylphenol
4,6-Di-tert-butyl-o-cresol
3,5-Di-tert-butyl-4-hydroxybenzaldehyde
2,6-Di-tert-butylphenol
2,6-Di-tert-butyl-4-hydroxymethylphenol
2,6-Diisopropylphenol
Triethylene glycol bis[3-(3-tert-butyl-4-hydroxy-5-methylphenyl)propionate]
Isotridecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate
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Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, C7-9-branched alkyl esters
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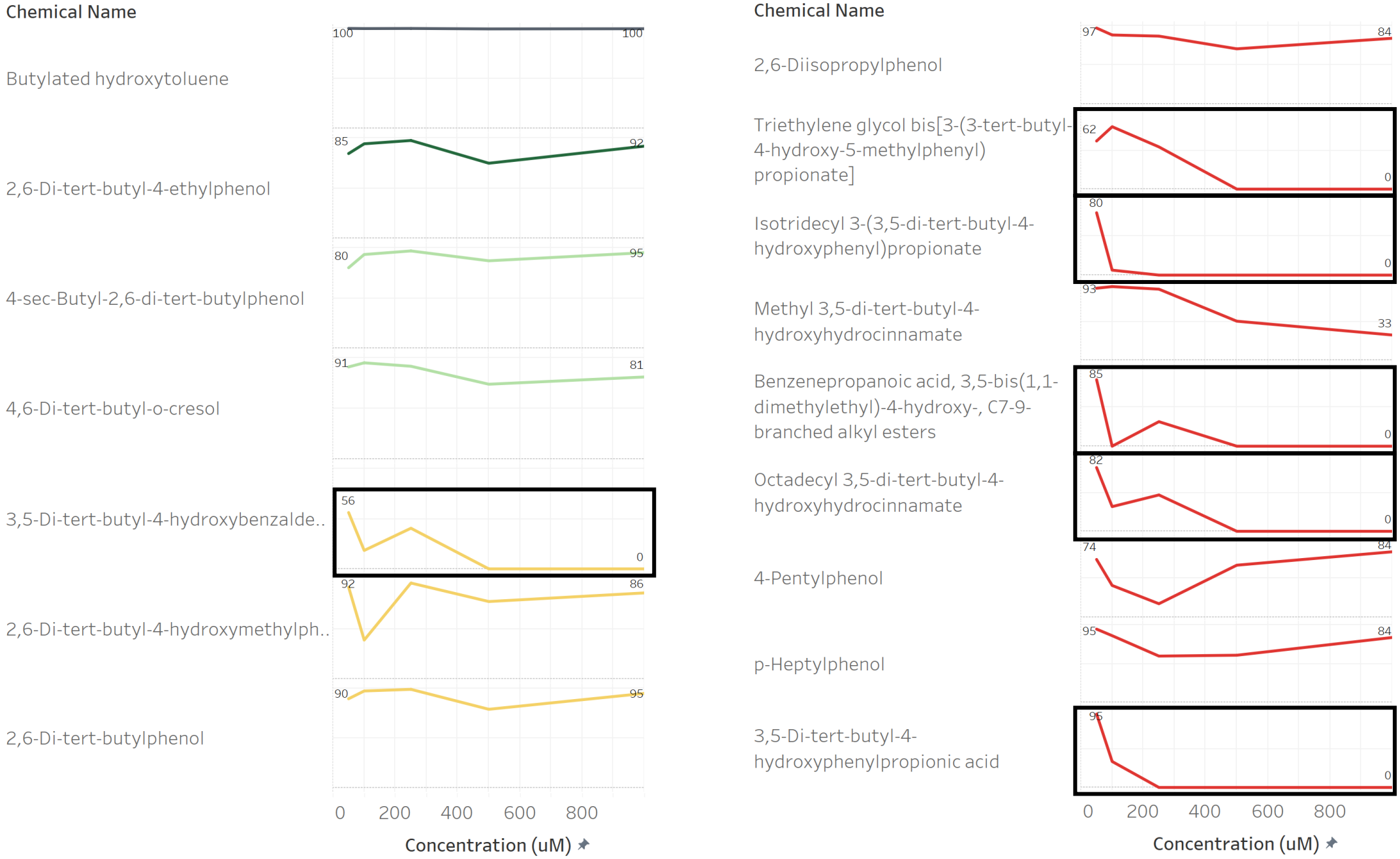
4-Pentylphenol
p-Heptylphenol
3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid
SOI
S
SWI
SPC
NS
0
100
200
300
400
500
600
700
800
900
Number of Landmark Genes Expressed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2,6-Di-tert-butyl-4-hydroxymethylph..
2,6-Di-tert-butylphenol
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97
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93
33
85
0
82
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74
84
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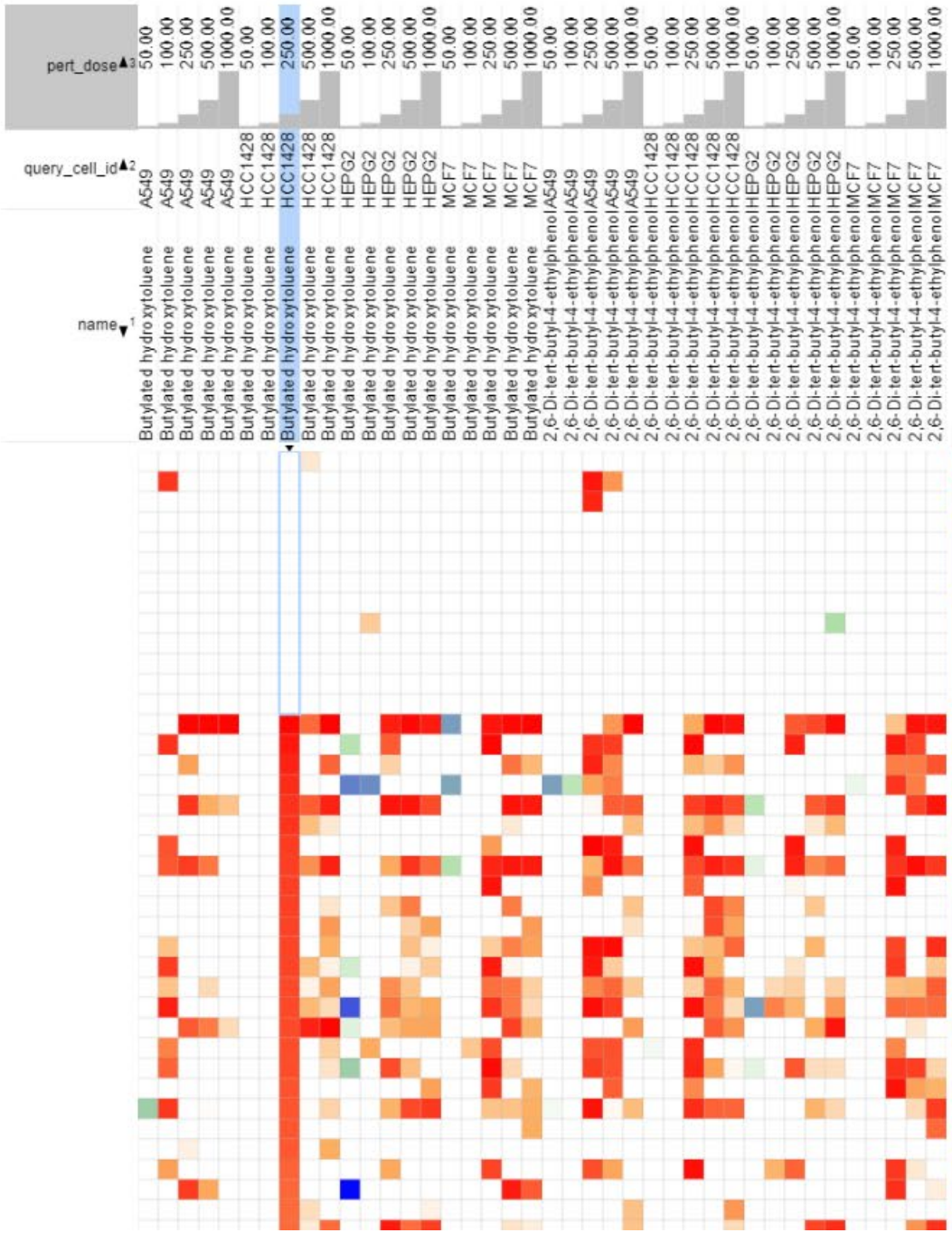
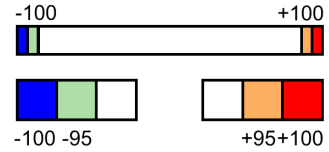
96
0
0
200
400
600
800
Concentration (uM)
SOI
S
SWI
SPC
NS





- **HCC1428**
- **250 µM**
- **Search Term “thyroid hormone receptor”**

type	name	description
	TRIP10	thyroid hormone receptor interactor 10
	TRIP10	thyroid hormone receptor interactor 10
	TRIP13	ATPases / AAA-type, thyroid hormone receptor interactor 13
	BRD-A89049230	thyroid-stimulating hormone receptor agonist
	PTHLH	Endogenous ligands, parathyroid hormone-like hormone
	THRAP3	thyroid hormone receptor associated protein 3
	THADA	thyroid adenoma associated
	methimazole	antithyroid Drugs
	liothyronine	thyroid hormone function stimulant
	BRD-A61599461	thyroid-stimulating hormone receptor inverse agonist
	TRIP13	ATPases / AAA-type, thyroid hormone receptor interactor 13
	THRAP3	thyroid hormone receptor associated protein 3
	PTHLH	Endogenous ligands, parathyroid hormone-like hormone
	celastrol	anti-inflammatory agent, antioxidant, HSP90 Inhibitor, NFKB pathway inhibitor, topoisomerase inhibitor
	menadione	CDC inhibitor, mitochondrial DNA polymerase inhibitor, phosphatase inhibitor, pyruvate kinase isozyme inhibitor
	FADD	Fas (TNFRSF6)-associated via death domain
	USP12	Ubiquitin-specific peptidases, ubiquitin specific peptidase 12
	SU-11652	FGFR inhibitor, PDGFR tyrosine kinase receptor inhibitor, tyrosine kinase receptor & angiogenic inhibitor, VEGFR inhibitor
	SLC35A1	SLC35 family of nucleotide sugar transporters, solute carrier family 35 (CMP-sialic acid transporter), member A1
	MAGEB6	melanoma antigen family B, 6
	auranofin	disease modifying antirheumatic drug, immunosuppressant, NFkB pathway inhibitor, prostanoid receptor inhibitor, thioredoxin reductase inhibitor
	TNFRSF1A	Tumour necrosis factor (TNF) receptor family, tumor necrosis factor receptor superfamily, member 1A
	RRP8	ribosomal RNA processing 8, methyltransferase, homolog (yeast)
	SKAP2	Pleckstrin homology (PH) domain containing, src kinase associated phosphoprotein 2
	GADD45A	growth arrest and DNA-damage-inducible, alpha
	IFNB1	Interferons, interferon, beta 1, fibroblast
	TIRAP	toll-interleukin 1 receptor (TIR) domain containing adaptor protein
	LDN-193189	ALK inhibitor, serine/threonine protein kinase inhibitor
	SLC36A1	SLC36 family of proton-coupled amino acid transporters, solute carrier family 36 (proton/amino acid symporter), member 1
	importazole	importin-beta transport receptor inhibitor
	BRD-K98824517	tyrosine phosphatase inhibitor
	BIRC5	Inhibitors of apoptosis (IAP) protein family, baculoviral IAP repeat containing 5
	OVOL2	Zinc fingers, C2H2-type, ovo-like 2 (Drosophila)
	FABP5	Fatty acid-binding proteins, fatty acid binding protein 5 (psoriasis-associated)
	TPD52L2	tumor protein D52-like 2
	NSC-663284	CDC inhibitor
	RAVER1	RNA binding motif (RRM) containing, ribonucleoprotein, PTB-binding 1
	CLPB	Ankyrin repeat domain containing, ClpB caseinolytic peptidase B homolog (E. coli)
	DCTN6	dynactin 6

Conclusions

- BHT does not show positive connections to endocrine related
  - Pathways
  - Compounds

  in EATS cell lines
- Structural analogs of BHT (S, SWI, SPC) show functional connections (CMap connections) to BHT

SCCS Opinion on BHT “Neither the *in silico* nor *in vitro* data give indication of endocrine disrupting properties of BHT”

- Level 1: Non-test information, in silico, read across, in chemico,
- Level 2: In vitro studies
- Level 3-5: In vivo assays
- Help further interpret in vivo result

CMap Publications

Grouping 34 Chemicals Based on Mode of Action Using Connectivity Mapping

K. Nadira De Abrew,*,[1] Raghunandan M. Kainkaryam,* Yuqing K. Shan,* Gary J. Overmann,* Raja S. Settivari,‡ Xiaohong Wang,* Jun Xu,* Rachel L. Adams,* Jay P. Tiesman,* Edward W. Carney,‡,† Jorge M. Naciff,* and George P. Daston*

*Mason Business Center, The Procter & Gamble Company, Cincinnati, Ohio 45040 and ‡Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan 48674
†Deceased.

Use of connectivity mapping to support read across: A deeper dive using data from 186 chemicals, 19 cell lines and 2 case studies

K. Nadira De Abrew[a,*], Yuqing K. Shan[a], Xiaohong Wang[a], Jesse M. Krailler[a], Raghunandan M. Kainkaryam[a], Cathy C. Lester[a], Raja S. Settivari[b], Matthew J. LeBaron[b], Jorge M. Naciff[a], George P. Daston[a]

[a] *Mason Business Center, The Procter & Gamble Company, Cincinnati, OH, 45040, USA*
[b] *Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, 48674, USA*

A New Approach Methodology (NAM) Based Assessment of Butylated hydroxytoluene (BHT) for Endocrine Disruption Potential

K. Nadira De Abrew,*,[1] Ted Natoli,† Cathy C. Lester,‡ Xiaohong Wang,‡ Mahmoud Shobair,‡ Arvind Subramanian,† and George P. Daston‡

Procter & Gamble uses non-animal tools to test suspected EDC

NEWS | 13 October 2022

Results indicate absence of endocrine activity for Corap substance BHT

United States | Personal care | Chemical industry | EDCs | Alternatives to testing

An industry study based on the 'next generation risk assessment' (NGRA) concept has found no evidence of endocrine disruption for widely used antioxidant butylated hydroxytoluene (BHT).

Developed in 2020 by the cosmetics industry, NGRA is an exposure-led approach based on new approach methodologies (NAMs), such as *in vitro* tests, that aims to be 'human relevant' and 'hypothesis driven'. The conclusions drawn by the study authors, therefore, challenge the traditional belief that NAMs are generally of limited regulatory use for endocrine disruption, which is a notoriously complex hazard endpoint.

P&G Human Safety
Ensuring Safe Products

Acknowledgements

P&G Human Safety

- Cathy Lester
- ElLantae Byrd
- Mahmoud Shobair

Broad Institute

- Ted Natoli
- Aravind Subramanian
- John Davis

- Xiaohong Wang
- Yuching Shan
- Jorge Naciff
- George Daston

Human Safety
Ensuring Safe Products