Supporting Information, Methods

Mutagens (-S9) with concentration data

A set of NTP genotoxicity data with dose information was obtained from Leadscope SAR Genetox Database. The dose information (unit, micro-g/plate) was converted to the concentration assuming that volume is 700 μL per plate. Positive (-S9) data for the respective strains (see Methods for the strain names)) were collected. For a mutagen, if the lowest concentration in the bacterial mutagenicity (BM) test is lower or within the assay potency variation range (1SD, 0.17 $\log_{10}$ unit) compared with the highest tested concentration of the chemical in the p53 qHTS assay, the positive mutagenicity result is considered to fall within the qHTS concentration range. The Fisher's exact test was used to check the significance of the association ($\alpha < 0.05$) between the BM assay concentration and the p53 activity (Supplemental Material, Table 4).

Generation of a list of consensus bacterial mutagens (-S9) with their lowest positive concentration within the qHTS concentration range

For assay validation purposes, we wanted to create a subset of bacterial mutagens that not only have their lowest effective concentration within the qHTS concentration range but also are widely accepted as mutagens in the literature. The information on the number of genotoxicity related studies per Tox21 chemical, grouped either by Registry of Toxic Effects of Chemical Substances (RTECS) associated or by non-RTECS associated sources, was retrieved from the Leadscope database. Chemicals with the greatest number of genotoxicity related studies within the top 10% of both the RTECS-associated and the non-RTECS associated lists were collected. In total, 25 chemicals in this category were identified (Supplemental Material, Table 5)

Definitions of categories from DrugBank and DrugMatrix databases

Mechanism: One or more descriptive phrases were established in DrugMatrix™ to classify a compound based on phenotypic or physiological effect such as “Inhibit platelet aggregation”, “Increase lipid catabolism” or “Block neural transmission.” A list of 75 Mechanism terms was established for compound curation.

Mode Class: One or more descriptive phrases were established in DrugMatrix™ to describe a compound based on how it affects its molecular target. A list of 75 Modes have been created for the assignment of the Mode Class, such as “Enzyme Inhibitor”, “Receptor Agonist, Selective” or “Channel Blocker.”

Activity Class: Each compound studied in DrugMatrix™ is grouped into an activity class, which represents a more generic compound annotation than structure activity class. Compounds are grouped together based on having structure activity class annotations that are related by a common therapeutic activity (i.e. anti-inflammatory) or toxicological activity (DNA damager). Structures are not considered when grouping compounds, such that unrelated structures that act through a common molecular target are grouped together. Likewise, compounds with distinct, but pharmacologically related, targets are also grouped together under a single activity class term. Compounds with a structure activity annotation unrelated by therapeutic or toxicological activity are simply annotated with their structure activity until such time that related compounds are added to the database.

Product Class: Product class, such as “Hormones, Endocrine and Metabolic”, “Central Nervous System (CNS)”, or “Anti-infectives” is a general industry classification of the drug. A vocabulary list of 24 terms was established for product class. Each therapeutic class is pre-associated with a product class in the curation database so that when a therapeutic class is selected, the product class is determined automatically.

Therapeutic Class: The purpose of the “therapeutic class” category is to classify a compound based on its therapeutic uses with respect to its indications. A comprehensive list of 120 therapeutic classes, such as “Antidiabetic Agents”, “General Anesthetics, Intravenous” or “Antibacterials, Systemic”, was established for this purpose. During the process of curating drug indications, each indication is associated with an appropriate therapeutic class term from this list of 120. The same therapeutic class may be associated with several indications of a given compound. For example, the therapeutic class “Antibacterials, Systemic” may be associated with the indications “Mycobacterium tuberculosis”, “Erythema Nodosum Leprosum (ENL)”, “Leprosy”, and “Atypical Mycobacterial Diseases” for the same compound.

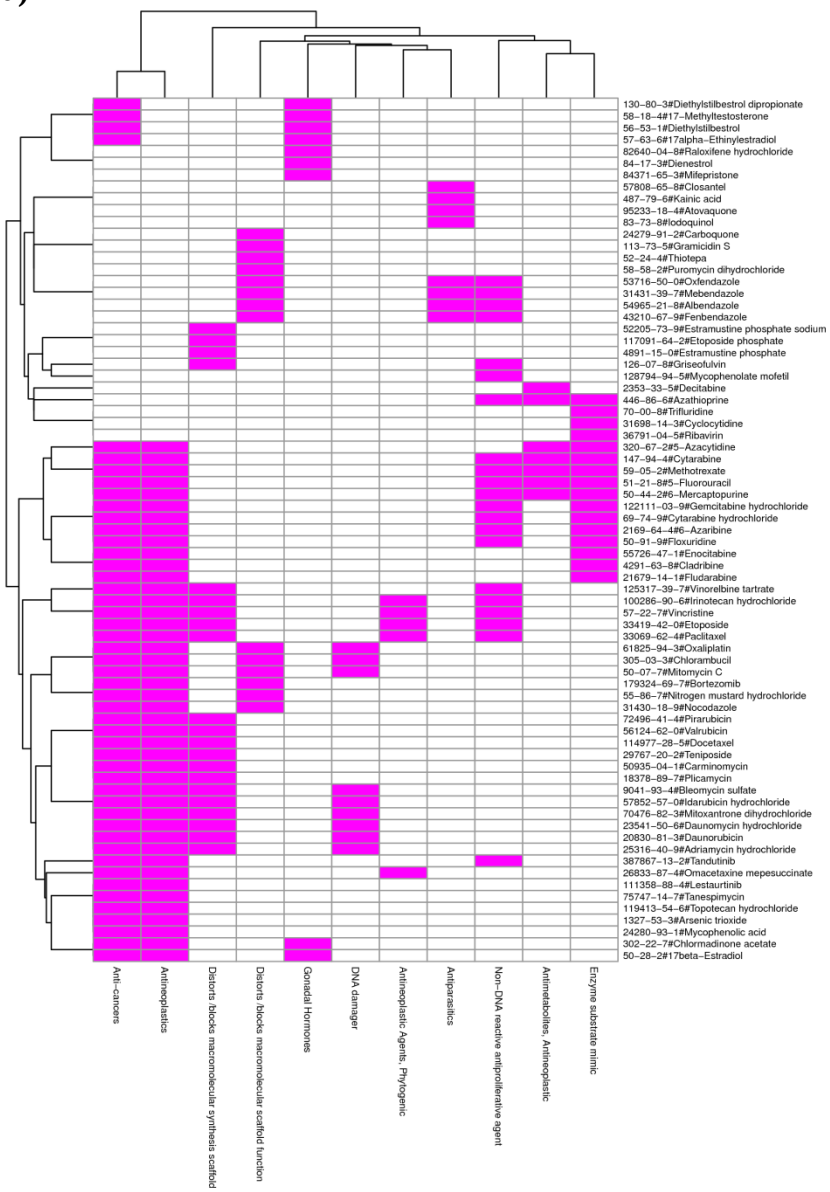
Drugbank Target: A protein, macromolecule, nucleic acid, or small molecule to which a given drug binds, resulting in an alteration of the normal function of the bound molecule and a desirable therapeutic effect. Drug targets are most commonly proteins such as enzymes, ion channels, and receptors.

Drugbank ATC Code: WHO drug classification system (ATC) identifiers. These are used identify therapeutic classes and uses of drugs

Supporting Information, Figures

Supporting Information, Figure 1. The chemical annotations associated with chemical activity in the p53RE assay. (a: class group; b: functional group; magenta cell: chemical that is active in the p53 assay and has the respective annotation)

a)



b)


147-94-4#Cytarabine
36791-04-5#Ribavirin
446-86-6#Azathioprine
122111-03-9#Gemcitabine hydrochloride
50-44-2#6-Mercaptopurine
69-74-9#Cytarabine hydrochloride
51-21-8#5-Fluorouracil
70-00-8#Trifluridine
152946-68-4#Nolatrexed dihydrochloride
112887-68-0#Raltitrexed
24280-93-1#Mycophenolic acid
128794-94-5#Mycophenolate mofetil
50-91-9#Floxuridine
2169-64-4#6-Azaribine
59-05-2#Methotrexate
58-14-0#Pyrimethamine
56124-62-0#Valrubicin
119413-54-6#Topotecan hydrochloride
61825-94-3#Oxaliplatin
18378-89-7#Plicamycin
20830-81-3#Daunorubicin
52-24-4#Thiotepa
305-03-3#Chlorambucil
50-07-7#Mitomycin C
117091-64-2#Etoposide phosphate
9041-93-4#Bleomycin sulfate
57852-57-0#Idarubicin hydrochloride
24279-91-2#Carboquone
72496-41-4#Pirarubicin
100286-90-6#Irinotecan hydrochloride
98631-95-9#Sobuzoxane
70476-82-3#Mitoxantrone dihydrochloride
23541-50-6#Daunomycin hydrochloride
25316-40-9#Adriamycin hydrochloride
55-86-7#Nitrogen mustard hydrochloride
29767-20-2#Teniposide
50935-04-1#Carminomycin
33419-42-0#Etoposide
123318-82-1#Clofarabine
50-65-7#Niclosamide
54-91-1#Pipobroman
2353-33-5#Decitabine
320-67-2#5-Azacytidine
4291-63-8#Cladribine
55726-47-1#Enocitabine
31698-14-3#Cyclocytidine
21679-14-1#Fludarabine
53716-50-0#Oxfendazole
31431-39-7#Mebendazole
54965-21-8#Albendazole
43210-67-9#Fenbendazole
125317-39-7#Vinorelbine tartrate
126-07-8#Griseofulvin
57-22-7#Vincristine
52205-73-9#Estramustine phosphate sodium
4891-15-0#Estramustine phosphate
114977-28-5#Docetaxel
33069-62-4#Paclitaxel
31430-18-9#Nocodazole
Inhibit DNA synthesis, repair, and function
DNA
Inhibit precursor synthesis
DNA-directed DNA polymerase
Incorporate into DNA/RNA/Protein
Inhibit mitosis
Inhibit microtubule dependent glucose uptake
Microtubule / tubulin

Supporting Information, Tables

Supporting Information, Table 1. The structural fingerprints (FP) enriched with p53RE actives and the underlying p53 activity data and genotoxicity data used in Figure 4

FP name	Representative p53 actives[1]	p-value	# of p53 actives in the FP	# of chemicals in the FP	# of chemicals active in p53 and genotoxic	# of genotoxic chemicals	PPV	% compounds with no genotoxicity data	Median of POD of p53 actives	Median of E_{max} of p53 actives
benzene, 1-(3-oxopropyl)-,2-oxymethyl-	Daunorubicin,|Carminomycin|,Etoposide	1.06E-11	10	13	7	7	0.70	0.46	7.4	**187.7**
benzene, 1-(2-oxyethyl)-,2-oxymethyl-	Daunorubicin,|Carminomycin|,Valrubicin	1.75E-10	8	9	5	5	0.63	0.44	7.4	**248.6**
benzene, 1-hydroxy-,2-(3-oxopropyl)-	Daunorubicin|, Carminomycin,| Valrubicin	3.42E-09	7	8	5	5	0.71	0.38	7.5	**265.2**
benzimidazole, 2-amino-	Nocodazole,| Parbendazole, |Mebendazole	3.60E-09	9	15	1	2	0.11	0.47	6.7	**67.5**
benzene, 1-carbonyl-,3-oxymethyl-	Hycanthone|, Daunorubicin, |Carminomycin	3.60E-09	9	15	6	8	0.67	0.47	7.4	**265.2**
amine, di-(2-haloethyl)	Trichlomethine,| Nitrogen mustard HCl,| Chlorambucil	2.51E-07	6	8	2	3	0.33	0.63	5.2	57.5
pyridine(H), 3-oxymethyl-	Topotecan HCl, |Vincristine,|Rubitecan	2.88E-07	7	12	1	1	0.14	0.92	7.6	58.9
D-arabinofuranose	Enocitabine,|Fludarabine, Cytarabine	1.22E-06	5	6	2	2	0.40	0.67	6.1	42.0
1,4-naphthoquinone, 5-alkoxy-	Daunorubicin,|Valrubicin, |Pirarubicin	1.22E-06	5	6	4	4	0.80	0.33	7.4	**231.9**
1,3-diazine(H), 1-(2-oxyethyl)-	Doxifluridine, |Cyclocytidine, |Cytarabine	1.74E-06	6	10	2	3	0.33	0.70	5.8	40.2
indole, 2-(t-alkyl)-	Vincristine|,Vinorelbine tartrate,|Vinblastine sulfate	4.60E-06	4	4	1	1	0.25	0.75	8.7	51.8
benzene, 1-alkoxy-,2-(2-oxoethyl)-	Vincristine,|Vinorelbine tartrate|,Vinblastine sulfate	1.06E-05	5	8	1	1	0.20	0.75	8.6	52.0
aziridine	Carboquone,|Fotretamine, |Thiotepa	2.28E-05	5	9	3	4	0.60	0.56	6.5	60.8
quinoline, 3-(alkyl, cyc)-	Topotecan HCl,|Irinotecan HCl, Rubitecan	6.41E-05	4	6	0	0	0.00	0.67	6.5	109.3
quinazoline, 6-(alkyl, acyc)-	Trimetrexate trihydrochloride,| Nolatrexed dihydrochloride,| Raltitrexed	9.98E-05	3	3	0	0	0.00	1.00	6.2	41.5
pyridine, 2-(alkenyl, cyc)-	Topotecan HCl, |Irinotecan HCl, Rubitecan	9.98E-05	3	3	0	0	0.00	1.00	7.1	135.3
benzene, 1-amino-,3-arylthio-	Hycanthone,|Febantel,	9.98E-05	3	3	1	1	0.33	0.67	5.5	367.6

	|SR271425									
thiazole, 4-carbonyl-	Thiostrepton,|Peplomycin sulfate,|Bleomycin sulfate	9.98E-05	3	3	1	1	0.33	0.67	7.0	56.6
any 9-ring-Z	Vincristine,|Vinblastine sulfate,|Vindesine sulfate salt	9.98E-05	3	3	1	1	0.33	0.67	8.7	51.6
1,3-dioxane, 4-hydroxymethyl-	Teniposide,|Etoposide phosphate,|Etoposide	9.98E-05	3	3	2	2	0.67	0.33	6.4	**51.3**
purine, 2-halo-	Clofarabine,|Fludarabine,|Cladribine	9.98E-05	3	3	2	2	0.67	0.33	6.8	**99.0**
1,4-benzoquinone, 2-alkylamino-	Mitomycin C|, Tanespimycin, |Carboquone	9.98E-05	3	3	2	2	0.67	0.33	6.9	**91.2**
benzene, 1-hydroxy-,4-iodo-	Iodoquinol, |Rafoxanide, |Closantel	3.85E-04	3	4	0	0	0.00	1.00	4.9	24.1
1,2,4-triazine(H), 3-oxo-	6-Azaribine, |Diclazuril, |6-Azacytidine	3.85E-04	3	4	0	0	0.00	1.00	6.0	52.6
benzene, 1-carbonyloxy-,4-heteroamino-	Binapacryl, |Dinobuton, |2-Acetoxy-5-nitrobenzyl Cl	3.85E-04	3	4	0	1	0.00	0.75	4.9	58.7
naphthalene, 2-(alkyl, cyc)-	Geliomycin, |Chromomycin A3, |Plicamycin	3.85E-04	3	4	0	0	0.00	0.75	7.4	82.4
cytidine(NS)	Enocitabine|, Cytarabine HCl, Cytarabine	3.85E-04	3	4	2	2	0.67	0.50	7.2	**42.0**
benzene, 1-(N-iminomethyl)-,4-amino-	Toluidine blue, |Methylene blue trihydrate, |Methylene blue	3.85E-04	3	4	2	2	0.67	0.25	5.2	**43.0**

[1]Maximum of 3 p53RE actives are reported; p-value was calculated based on the data of # of p53 actives in the FP, # of chemicals in the FP, # of p53 actives (365), and # of Tox21 chemicals (7849); bold text: data-rich structural FPs (i.e., % with no genotoxicity data $\leq$ 50%); POD value (log10(M)*-1)

Supporting Information, Table 2. Association analysis between chemical activity in the p53RE assay and presence of Leadscope structural alerts (SA) for mutagenicity

SA name	p-value	N_P	N	n_p	n
3: N-methylol [P450 metabolism->formaldehyde]	**6.35E-15**	**365**	**7849**	**48**	**292**
37: urethane derivatives [Alkylation of DNA]	**2.65E-09**	**365**	**7849**	**27**	**157**
38: urethane or thiocarbamate	**9.09E-09**	**365**	**7849**	**24**	**134**
26: methylamine	**1.34E-08**	**365**	**7849**	**83**	**974**
81: polycyclic planar system	**1.24E-07**	**365**	**7849**	**28**	**199**
116: 1,2-dialkyl phenols [Metabolized to electrophillic 1,2-quinone methides]	**1.29E-06**	**365**	**7849**	**32**	**275**
33: NS mustard [(1) SN2 internal cyclization (2) SN2 ring-opening, formation of episulfonium ion]	**3.68E-06**	**365**	**7849**	**6**	**11**
123: 1,4-dihydroxybenzene [Oxidation->electrophilic 1,4-quinone]	**1.09E-05**	**365**	**7849**	**8**	**25**
30: aziridine	**2.28E-05**	**365**	**7849**	**5**	**9**
87: aryl aldehyde	**3.43E-05**	**365**	**7849**	**89**	**1283**
115: 1,4-dialkyl phenols [Metabolized to electrophillic 1,4-quinone methides]	**9.01E-05**	**365**	**7849**	**33**	**353**
98: Haloethylamines	**2.16E-04**	**365**	**7849**	**6**	**20**
83: polycyclic planar system	**2.17E-04**	**365**	**7849**	**15**	**113**
88: quinone [Electrophilic-nucleophilic reaction with a nucleophile]	1.17E-03	365	7849	4	11
85: aliphatic halogen [Alkylation of DNA]	1.33E-03	365	7849	50	701
101: a-Halocarbonyl	2.58E-03	365	7849	14	129
124: Imides [Production of imide radical]	3.44E-03	365	7849	11	92
31: epoxide [Ring opening via SN2 reaction with nucleophilic DNA center]	4.86E-03	365	7849	9	70
94: isothiocyanate [Direct acylation]	6.79E-03	365	7849	3	9
133: Thiazole [P450 epoxidation->...->electrohpilic carbonyl species]	1.30E-02	365	7849	11	110
79: polycyclic planar system	1.42E-02	365	7849	8	69
86: alpha,beta unsaturated carbonyls	1.47E-02	365	7849	31	444
119: Arenes [Epoxidation->ring opening->oxidation->electrophilic 1,2-quinone]	1.60E-02	365	7849	3	12
29: primary alkyl halide	2.62E-02	365	7849	26	375
80: polycyclic planar system	2.74E-02	365	7849	6	50
135: Thiophenes [P450 sulfoxidation->electrophile, SN2-01 - P450 epoxidate->electrophilic epoxide]	3.18E-02	365	7849	8	80
125: Methylenedioxyphenyl	3.53E-02	365	7849	6	53
73: aliphatic N-nitro	5.01E-02	365	7849	2	8
50: unsubst het-het	6.76E-02	365	7849	40	678
22: amine generating	8.05E-02	365	7849	6	65
138: a,b-Unsaturated carbonyls (C[H=0]=O) [Michael addition reaction]	8.28E-02	365	7849	47	827
78: polycyclic planar system	9.08E-02	365	7849	1	2
70: bay region [P450 oxidation->...->electrophilic carbenium ion]	9.82E-02	365	7849	3	24
71: K region	9.82E-02	365	7849	3	24

117: Allyl benzenes [Hydroxylation->Sulfation->electrophilic carbenium ion]	1.69E-01	365	7849	2	16
136: Thioureas [P450 sulfoidation->SN2-capable electrophilic intermediate]	1.69E-01	365	7849	2	16
82: polycyclic planar system	1.85E-01	365	7849	3	32
75: alpha,beta unsaturated alkoxy	2.55E-01	365	7849	2	21
72: alpha, beta unsaturated aldehyde	2.64E-01	365	7849	6	93
142: 1,4-quinone methides [Michael addition reaction]	2.84E-01	365	7849	1	7
122: Furan [P450 ring opening->reactive a,b-unsaturated dial]	3.06E-01	365	7849	5	79
139: 1,2-hydroquinone [Oxidation->electrophilic 1,2-quinone]	3.26E-01	365	7849	4	62
109: 1,1,-Dihaloalkanes [Metabolized->acyl halides (binds covalently to DNA)]	3.36E-01	365	7849	3	44
97: Benzylic halides	3.55E-01	365	7849	8	144
121: Formamide [P450 metabolism->DNA-reactive isocyanate]	3.79E-01	365	7849	1	10
118: a,b,-Dicarbonyl [Direct acting schiff based formers]	4.25E-01	365	7849	3	51
16: mixed alkyl esters of phosphoric acid	4.26E-01	365	7849	2	31
144: 1,2-dihaloalkane [Metabolic step->episulfonium ion]	4.55E-01	365	7849	5	95
34: nitrosamine	4.74E-01	365	7849	2	34
11: 1-aryl, 2-monoalkyl hydrazine	4.75E-01	365	7849	3	55
5: hydrazine [Metab. conversion->...->electrophilic carbenium ion, C radical species]	4.79E-01	365	7849	10	204
104: Allylic alkoxides	6.26E-01	365	7849	4	92
76: polycyclic planar system	6.50E-01	365	7849	1	22
96: coumarins and furocoumarins [P450 expoxidation->electrophilic epoxide]	6.96E-01	365	7849	1	25
15: alkyl esters of phosphoric acids	7.10E-01	365	7849	3	78
137: a,b-Unsaturated carbonyls (CH=O) [Michael addition reaction]	7.11E-01	365	7849	1	26
9: alkyl hydrazine(RNHNH2) [Metab. conversion->...->electrophilic carbenium ion, C radical species]	7.12E-01	365	7849	4	103
4: alkyl aldehyde [Direct acting schiff based formers]	7.44E-01	365	7849	108	2434
140: 1,2-dimethoxy-quinone [Demethylation->oxidation->electrophilic 1,2-quinone]	7.49E-01	365	7849	3	83
112: Aliphatic tertiary amine [Metabolic conversion->electrophilic carbenium ion/iminium ion]	8.11E-01	365	7849	24	600
84: polycyclic planar system	8.12E-01	365	7849	1	35
14: alkyl esters of phosphonic acids	8.45E-01	365	7849	1	39
146: Phosphonic ester (O-alkyl) [Alkylation of DNA]	9.70E-01	365	7849	1	73
100: Haloalkylethers (ethyl)	NA	365	7849	0	6
102: a-Halohydroxy	NA	365	7849	0	7
103: Allylic halides (Cl, Br or I)	NA	365	7849	0	8
105: Halogenated methanes	NA	365	7849	0	3
107: Halogenated methanes	NA	365	7849	0	5
108: Halogenated methanes	NA	365	7849	0	4
10: alkyl hydrazine(RNHNHR)	NA	365	7849	0	6
110: 3-Methylindole [P450-mediated steps -> quinone-imine species]	NA	365	7849	0	1
113: Alkyl carbamyl halides [Direct acylation]	NA	365	7849	0	1
120: Benzylamine [P450 metab.->DNA-reactive isocyanates, P450 metab.->electrophilic carbonyl species]	NA	365	7849	0	50

129: Pyrrolizidine alkaloids (1) [Metabolic conversion->electrophilic carbenium ion]	NA	365	7849	0	1
12: alkyl alkane sulphonate [Alkylation of DNA]	NA	365	7849	0	8
131: 1,2-quinone methides [Michael addition reaction]	NA	365	7849	0	2
132: Sulfonylurea [P450 metabolism->DNA-reactive isocyanate]	NA	365	7849	0	27
134: Thiazolidinediones [P450 sulfoxidation->DNA-reactive isothiocyanates]	NA	365	7849	0	6
13: dialkyl sulphate [Alkylation of DNA]	NA	365	7849	0	3
141: 1,4-dimethoxybenzene [demethylation->oxidation->electrophilic 1,4-quinone]	NA	365	7849	0	24
143: Acycl halides [Direct acylation]	NA	365	7849	0	11
145: Phosphonic ester (Alkyl) [Alkylation of DNA]	NA	365	7849	0	12
148: Diazonium (aryl) [Loss of N to produce aryl radical]	NA	365	7849	0	2
1: N-chloramine	NA	365	7849	0	12
23: amine generating	NA	365	7849	0	6
2: haloamine	NA	365	7849	0	13
32: monohaloalkenes	NA	365	7849	0	5
35: propriolactone [Ring opening SN2 reaction]	NA	365	7849	0	3
36: propiosultones [Ring opening SN2 reaction]	NA	365	7849	0	1
40: N-nitroso-N-dialkylamines [Alpha-hydroxylation->...->electrophilic carbenium ion]	NA	365	7849	0	15
42: N-nitroso-N-alkylureas	NA	365	7849	0	5
43: N-nitroso-N-alkylcarbamates	NA	365	7849	0	1
45: N-nitroso-N-hydroxylamines	NA	365	7849	0	2
46: alkyl nitrite	NA	365	7849	0	10
47: azide	NA	365	7849	0	3
48: diazoalkane [Metabolic conversion->...->electrophilic carbenium ion]	NA	365	7849	0	1
49: triazene [Metabolic conversion into a carbenium ion]	NA	365	7849	0	8
51: carboxylic acid halide	NA	365	7849	0	28
6: alkyl hydrazine(R2NNH2) [Metab. conversion->...->electrophilic carbenium ion, C radical species]	NA	365	7849	0	35
77: polycyclic planar system	NA	365	7849	0	4
7: alkyl hydrazine(R2NNHR)	NA	365	7849	0	4
8: alkyl hydrazine(R2NNR2)	NA	365	7849	0	4
90: aliphatic azo	NA	365	7849	0	4
91: aliphatic azo	NA	365	7849	0	7
93: isocyanate [Direct acylation]	NA	365	7849	0	13
99: Haloalkylethers (methyl) [Dissociation of halide ion producing carbenium ion stabilized by oxonium ion]	NA	365	7849	0	3

Bold text: significant association after Bonferroni correction; N_P: number of p53 actives; N: number of Tox21 chemicals in p53 assay; n_p: number of chemicals having the alert and active in p53 assay; n: number of Tox21 chemicals having the alert; p-value is based on Fisher's exact test.

Supporting Information, Table 3. Compounds active in the p53RE assay that also evidenced cytotoxicity over the concentration range tested

CASRN	Chemical Name	EC_{50} of ratio (log10(M)*-1)	EC_{50} of viability (log10(M))	Log10 difference	EC_{50} of viability/EC_{50} of ratio
NOCAS_48505	PharmaGSID_48505	6.77	-4.56	2.21	162.93
23541-50-6	Daunomycin hydrochloride	6.26	-4.21	2.05	112.21
24279-91-2	Carboquone	6.68	-4.94	1.73	54.15
128794-94-5	Mycophenolate mofetil	6.91	-5.20	1.72	52.04
179324-69-7	Bortezomib	7.87	-6.21	1.66	45.28
105624-86-0	5HPP-33	5.80	-4.21	1.59	39.06
24280-93-1	Mycophenolic acid	7.11	-5.55	1.56	36.35
123318-82-1	Clofarabine	6.99	-5.52	1.48	29.93
111358-88-4	Lestaurtinib	7.12	-5.77	1.35	22.32
135080-03-4	CP-100829	5.48	-4.21	1.27	18.70
380315-80-0	Tenovin-1	6.08	-4.81	1.27	18.50
102409-92-7	FR073317	5.77	-4.56	1.21	16.23
50-07-7	Mitomycin C	5.71	-4.71	0.99	9.88
6317-18-6	Methylene bis(thiocyanate)	5.06	-4.21	0.85	7.12
141505-33-1	Levosimendan	5.64	-4.86	0.78	6.01
643-79-8	1,2-Benzenedicarboxaldehyde	5.32	-4.56	0.76	5.81
148477-71-8	Spirodiclofen	4.97	-4.21	0.76	5.75
55-86-7	Nitrogen mustard hydrochloride	5.23	-4.51	0.72	5.26
21564-17-0	2-(Thiocyanomethylthio)benzothiazole	5.27	-4.56	0.71	5.13
563-68-8	Thallium acetate	4.91	-4.21	0.70	5.00
91421-42-0	Rubitecan	6.50	-5.82	0.68	4.76
521-74-4	Broxyquinoline	5.19	-4.51	0.68	4.75
5026-74-4	Oxiranemethanamine, N-[4-(oxiranylmethoxy)phenyl]-N-(oxiranylmethyl)-	4.89	-4.21	0.68	4.74
119413-54-6	Topotecan hydrochloride	5.92	-5.29	0.63	4.25
96686-51-0	2-Chloro-N-(2-methyl-4-bromophenyl)acetamide	5.09	-4.47	0.62	4.20
72496-41-4	Pirarubicin	5.47	-4.86	0.61	4.09
868540-17-4	Carfilzomib	7.02	-6.42	0.59	3.93
84-16-2	meso-Hexestrol	4.80	-4.21	0.58	3.85
6898-97-1	(Z,E)-Diethylstilbestrol	5.09	-4.51	0.58	3.83
28772-56-7	**Bromadiolone**	**4.29**	**-4.82**	**-0.53**	**0.29**
57808-65-8	**Closantel**	**4.86**	**-5.43**	**-0.56**	**0.27**
128517-07-7	**Romidepsin**	**5.07**	**-5.67**	**-0.59**	**0.26**
50-44-2	**6-Mercaptopurine**	**5.07**	**-5.71**	**-0.64**	**0.23**
4776-06-1	**Fluorosalan**	**5.29**	**-6.05**	**-0.76**	**0.18**
60506-81-2	**Dipentaerythritol pentaacrylate**	**4.26**	**-5.53**	**-1.27**	**0.05**
3236-71-3	**4,4'-(9H-Fluorene-9,9-diyl)diphenol**	**4.53**	**-6.44**	**-1.91**	**0.01**

Bold text: cytotoxicity is more potent than p53 activation for at least half log_{10} unit; normal text: cytotoxicity is less potent than p53 activation for at least half log_{10} unit; CASRN: CAS Registry Number; EC_{50}: half-maximal effect concentration

Supporting Information, Table 4. Actives in the p53RE assay that showed "single-humped" or "double-humped" dose response curve patterns not associated with cytotoxicity

CASRN	Chemical Name	# of masked points	Mask*	log10(POD) -1
57-22-7	Vincristine	12	0 0 0 1 1 1 1 1 1 1 1 1 1 1 1	8.78
59917-39-4	Vindesine sulfate salt	11	0 0 0 0 1 1 1 1 1 1 1 1 1 1 1	8.71
18556-44-0	Vinblastine sulfate	12	0 0 0 1 1 1 1 1 1 1 1 1 1 1 1	8.64
50935-04-1	Carminomycin	4	0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1	7.72
57852-57-0	Idarubicin hydrochloride	4	0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1	7.72
26833-87-4	Omacetaxine mepesuccinate	8	0 0 0 1 0 0 0 0 1 1 1 1 1 1 1 1	7.57
7059-24-7	Chromomycin A3	8	0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1	7.56
25316-40-9	Adriamycin hydrochloride	6	0 0 0 1 0 0 0 0 0 0 0 1 1 1 1 1	7.49
18378-89-7	Plicamycin	8	0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1	7.42
14255-87-9	Parbendazole	6	0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1	7.41
20830-81-3	Daunorubicin	4	0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1	7.39
114977-28-5	Docetaxel	7	0 0 1 1 1 1 1 0 0 0 0 0 0 1 1	7.36
75443-99-1	Aclarubicin hydrochloride	5	0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1	7.21
43210-67-9	Fenbendazole	7	0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1	7.07
125317-39-7	Vinorelbine tartrate	7	0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1	7.07
31430-18-9	Nocodazole	6	0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1	7.03
83-79-4	Rotenone	6	0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1	6.89
54965-21-8	Albendazole	5	0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1	6.79
31431-39-7	Mebendazole	5	0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1	6.69
20559-55-1	Oxibendazole	5	0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1	6.68
152044-54-7	Epothilone B	7	0 0 0 1 1 1 1 0 0 0 0 0 0 1 1 1	6.35
149647-78-9	Suberoylanilide hydroxamic acid	4	0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1	6.33

141517-21-7	Trifloxystrobin	4	0 0 0 0 0 0 0 0 0 0 0 1 1 1 1	6.00
1239-45-8	Ethidium bromide	4	0 1 0 0 0 0 0 0 0 0 0 0 1 1 1	5.73
5153-67-3	(E)-beta-Nitrostyrene	4	0 0 0 0 0 0 0 0 0 0 0 1 1 1 1	5.60
33069-62-4	Paclitaxel	5	0 0 0 0 1 1 1 1 1 0 0 0 0 0 0	5.14

* number represents the concentration points in qHTS; 1: represents the data points that present non-monotonic behavior; CASRN: CAS Registry Number.

Supporting Information, Table 5. The association between activity in the p53RE assay and concentration that elicited activity in the bacterial mutation (BM) assay

	Active in the p53 assay	Not active in the p53 assay
lowest positive dose in BM assay within qHTS range	15	107
lowest positive dose in BM assay beyond qHTS range	3	122

*p-value = 0.003 by Fisher's exact test

Supporting Information, Table 6. Consensus mutagens (-S9) having the lowest active dose in the bacterial mutation (BM) assay within the p53RE qHTS assay concentration range

CAS Registry Number	Chemical Name	lowest positive conc. in BM (µM)	highest tested conc. in qHTS range (µM)	Hit call in p53 assay	chromosome aberration (-S9)	in vivo micronucleus test
30516-87-1	3'-Azido-3'-deoxythymidine	0.02	94.34	inactive	negative	positive
320-67-2	5-Azacytidine	0.06	92.17	active	positive	positive
67-20-9	Nitrofurantoin	0.06	92.17	inactive	positive	negative
133-06-2	Captan	0.14	91.84	active	positive	*no data*
15663-27-1	Cisplatin	0.14	92.77	inactive	positive	positive
59-87-0	Nitrofurazone	0.22	92.17	inactive	positive	negative
99-56-9	4-Nitro-1,2-phenylenediamine	0.28	92.17	inactive	negative	*no data*
26628-22-8	Sodium azide	0.66	98.66	inactive	negative	*no data*
117-39-5	Quercetin	1.42	92.83	inactive	positive	negative
7778-50-9	Potassium dichromate	1.46	92.88	active	*no data*	*no data*
57-57-8	beta-Propiolactone	1.98	46.08	inactive	positive	*no data*
613-13-8	2-Aminoanthracene	7.39	93.53	active	negative	*no data*
121-14-2	2,4-Dinitrotoluene	7.84	92.17	inactive	positive	*no data*
56-49-5	3-Methylcholanthrene	17.56	47.18	inactive	negative	*no data*
556-52-5	Glycidol	19.28	93.44	inactive	positive	positive
443-48-1	Metronidazole	25.03	94.50	inactive	positive	positive
106-93-4	1,2-Dibromoethane	25.09	93.09	inactive	positive	positive
119-90-4	3,3'-Dimethoxybenzidine	29.24	92.17	inactive	positive	*no data*
148-82-3	Melphalan	31.36	46.08	*inconclusive*[1]	positive	positive
759-73-9	1-Ethyl-1-nitrosourea	36.60	90.70	inactive	positive	positive
66-27-3	Methyl methanesulfonate	42.82	95.08	inactive	*no data*	positive
79-44-7	Dimethylcarbamoyl chloride	43.85	92.17	inactive	negative	*no data*
106-89-8	Epichlorohydrin	46.32	89.43	inactive	positive	negative
111-30-8	Glutaraldehyde	47.10	92.16	active	positive	negative
5307-14-2	2-Nitro-1,4-phenylenediamine	93.31	92.17	*inconclusive*[2]	negative	*no data*

[1] potentially confounded by compound auto-fluorescence

[2] non-increasing signals in the reporter gene readout despite the significant increase in the ratio data after normalization