Cheminformatic comparison of approved drugs from natural product versus synthetic origins

Christopher F. Stratton,[1] David J. Newman,[2] and Derek S. Tan[1,3]

[1]Tri-Institutional PhD Program in Chemical Biology,
[3]Chemical Biology Program and Tri-Institutional Research Program
Memorial Sloan Kettering Cancer Center,
1275 York Ave, Box 422, New York, NY 10065, USA

[2]Natural Products Branch, Developmental Therapeutics Program,
Division of Cancer Treatment and Diagnosis, National Cancer Institute
Frederick, P.O. Box B, Frederick, Maryland 21702 USA

Supplementary Information

I. SUPPLEMENTARY TABLES AND FIGURES

	Natural product drugs (NP)	*NP-derived drugs (ND)*	*NP-inspired synthetic drugs (S*, S*/NM)*	*Completely synthetic drugs (S, S/NM)*
MW	414	467	345	337
N	1	2	2	2
O	6	5	4	3
HBD	4	2	2	1
HBA	7	6	5	4
RotB	7	7	6	5
nStereo	7	5	1	1
nStMW	0.013	0.010	0.004	0.002
Fsp^3	0.67	0.59	0.48	0.33
tPSA	140	113	91	67
VWSA	646	657	517	478
relPSA	0.19	0.18	0.15	0.14
Rings	3	4	3	3
RngAr	0	1	2	2
RngSys	2	2	2	2
RngLg	6	6	6	6
RRSys	1.0	1.5	1.3	1.0
ALOGPs	2.0	2.4	1.9	2.9
ALOGpS	−3.6	−4.3	−3.4	−3.8
LogD	−0.4	0.5	0.2	1.6

Table S1. Median values for analysis of approved drugs. ALOGPs = logP; ALOGpS = logS; Fsp^3 = fraction sp^3 carbons; HBA = hydrogen-bond acceptors; HBD = hydrogen-bond donors; MW = molecular weight; N = nitrogens; nStereo = stereocenters; nStMW = stereochemical density (nStereo ÷ MW); O = oxygens; relPSA = relative polar surface area; RngAr = aromatic rings; RngLg = largest ring size; RngSys = ring systems; RRSys = rings per ring system (Rings ÷ RngSys), VWSA = van der Waals surface area; tPSA = topological polar surface area.

	Natural product drugs (NP)	*NP-derived drugs (ND)*	*NP-inspired synthetic drugs (S*, S*/NM)*	*Completely synthetic drugs (S, S/NM)*
N ÷ MW	0.007 (0.002)	0.007 (0.004)	0.008 (0.006)	0.007 (0.006)
O ÷ MW	0.015 (0.015)	0.013 (0.011)	0.011 (0.012)	0.008 (0.009)
HBD ÷ MW	0.010 (0.010)	0.008 (0.004)	0.006 (0.006)	0.004 (0.003)
HBA ÷ MW	0.016 (0.017)	0.015 (0.013)	0.014 (0.015)	0.012 (0.012)
RotB ÷ MW	0.018 (0.017)	0.020 (0.015)	0.020 (0.017)	0.015 (0.015)
nStereo ÷ MW	**0.013 (0.017)**	**0.011 (0.011)**	**0.005 (0.003)**	**0.002 (0.003)**

Table S2. Molecular weight normalization for size-dependent parameters. Mean and (median) values for molecular weight-normalized parameters are shown. For each compound class, nitrogen atom count (N), oxygen atom count (O), hydrogen bond donor count (HBD), hydrogen bond acceptor count (HBA), rotatable bond count (RotB), and stereocenter count (nStereo) were normalized by dividing average parameter values (mean or median) by the average molecular weight (mean or median).

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Standard deviation	3.062	1.868	1.609	1.158	0.941	0.820	0.696	0.502	0.487	0.466
Proportion of Variance	0.469	0.175	0.129	0.067	0.044	0.034	0.024	0.013	0.012	0.011
Cumulative Proportion	0.469	0.643	0.773	0.840	0.884	0.917	0.942	0.954	0.966	0.977

Table S3. Standard deviation and percent contribution for each principal component in the PCA of approved drugs (R Summary). The first three principal components (PC1–PC3) retain 77% of the information in the full 20-dimensional dataset, while >90% of the information in the full dataset is represented in the first six principal components (PC1–PC6).

Group	Period	MW	N	O	HBD	HBA	RotB	tPSA	vWSA	relPSA	nStereo	nStMW	Fsp³	Rings	RngAr	RngSys	RngLg	RRSys	ALOGPs	ALOGPs	LogD
Natural product drugs (NP)	1981–1985	613	3.7	9.4	5.3	10.4	11.1	196	930	0.23	9.2	0.014	0.71	3.2	0.8	2.5	8.5	1.3	1.4	-3.2	-2.2
	1986–1990	456	1.4	7.2	3.9	7.5	8.7	134	708	0.20	7.8	0.013	0.73	2.7	0.3	1.7	5.4	1.4	2.1	-3.2	-0.03
	1991–1995	864	8.3	11.9	11.4	14.5	16.6	325	1247	0.24	9.0	0.012	0.60	3.6	1.6	2.6	14.3	1.6	0.6	-3.5	-4.1
	1996–2000	352	0.8	5.3	1.3	5.0	3.0	89	557	0.21	5.0	0.009	0.70	2.0	0.0	0.8	9.0	1.5	0.5	-2.6	0.6
	2001–2005	1526	17.7	21.3	21.7	25.0	26.3	644	2145	0.27	11.7	0.005	0.54	3.3	1.7	2.0	27.7	1.8	0.02	-3.9	-18.1
	2006–2010	651	3.5	8.5	4.0	8.5	3.0	156	891	0.18	5.5	0.008	0.56	5.5	1.5	1.0	13.0	5.5	2.0	-3.9	2.4
NP-derived drugs (ND)	1981–1985	482	3.6	5.7	2.8	7.0	9.0	137	681	0.20	4.1	0.009	0.53	3.5	1.4	2.1	6.1	1.9	1.7	-4.1	-1.0
	1986–1990	539	3.3	7.1	3.7	7.8	9.1	155	771	0.20	6.0	0.011	0.58	3.8	1.4	2.1	6.9	2.1	2.1	-3.8	-0.3
	1991–1995	494	3.2	5.6	3.1	6.7	8.9	130	727	0.20	4.8	0.010	0.61	3.6	1.1	2.0	6.4	2.0	2.2	-4.0	0.5
	1996–2000	691	4.7	9.5	5.7	10.1	14.3	218	1007	0.20	7.5	0.012	0.64	3.6	1.1	2.3	7.4	2.0	1.9	-3.9	-1.5
	2001–2005	954	8.4	12.9	10.2	14.3	22.1	344	1389	0.22	10.3	0.012	0.66	4.0	1.5	2.3	9.3	2.0	1.7	-3.5	-4.9
	2006–2010	821	4.5	11.8	6.6	12.3	16.9	250	1194	0.19	10.0	0.012	0.64	4.7	1.3	2.3	10.7	2.5	2.6	-4.4	-1.8
NP-inspired synthetic drugs (S*, S*/NM)	1981–1985	321	2.2	3.6	2.7	4.5	7.4	84	498	0.18	1.3	0.004	0.49	2.0	1.5	1.5	6.0	1.4	1.9	-3.2	0.02
	1986–1990	340	2.1	3.9	2.5	4.8	7.8	87	520	0.18	1.9	0.005	0.52	2.0	1.3	1.6	5.7	1.2	1.4	-3.3	-0.3
	1991–1995	415	2.7	4.9	1.8	5.7	8.2	97	611	0.19	2.3	0.006	0.48	3.1	2.0	2.2	6.0	1.5	1.6	-3.6	0.2
	1996–2000	378	3.3	3.1	2.2	4.5	6.1	89	552	0.17	1.4	0.003	0.41	3.1	2.2	2.2	6.4	1.5	2.4	-3.7	1.0
	2001–2005	435	4.0	4.5	2.7	6.0	8.2	119	631	0.20	2.2	0.005	0.46	3.3	2.2	2.3	6.0	1.6	1.6	-3.5	0.2
	2006–2010	456	4.3	4.9	3.9	6.4	9.4	136	658	0.23	2.6	0.006	0.45	2.9	2.1	2.5	6.0	1.1	1.6	-3.4	0.7
Completely synthetic drugs (S, S/NM)	1981–1985	319	2.3	2.6	1.1	3.7	4.8	62	453	0.15	0.6	0.002	0.35	2.6	1.8	2.1	5.9	1.3	2.7	-3.6	1.7
	1986–1990	335	2.3	3.1	1.4	4.3	5.3	73	473	0.17	0.9	0.002	0.37	2.6	1.8	2.0	5.9	1.3	2.6	-3.7	1.5
	1991–1995	334	2.3	2.9	1.1	4.1	5.0	68	469	0.16	0.8	0.002	0.39	2.6	1.7	2.0	5.8	1.3	2.6	-3.5	1.3
	1996–2000	345	2.5	2.9	1.4	4.4	5.5	73	497	0.16	0.8	0.003	0.39	2.8	1.9	2.2	5.8	1.3	2.7	-3.7	1.3
	2001–2005	380	2.9	3.1	1.4	4.8	5.4	80	524	0.17	0.8	0.002	0.30	3.4	2.5	2.9	6.0	1.2	2.8	-4.0	1.7
	2006–2010	387	2.8	2.7	1.5	4.4	5.9	73	558	0.14	1.1	0.003	0.38	3.3	2.3	2.5	6.2	1.4	3.1	-3.9	1.8

Table S4. Mean values of physicochemical parameters for NCEs 1981–2010 parsed in five-year intervals. Mean values of each chemical descriptor are shown for natural product drugs (NP), natural product-derived drugs (ND), natural product-inspired synthetic drugs (S*, S*/NM) and completely synthetic drugs (S, S/NM) in five-year time blocks from 1981–2010.

Natural product drugs (NP)

	MW	N	O	HBD	HBA	RotB	tPSA	VWSA	relPSA	nStereo	nStMW	FSP3	Rings	RngAr	RngSys	RngLg	RRSys	ALOGPS	ALOGPS	LogD
1981–1985	470	1.0	7.5	4.0	10.0	7.5	177.4	720	0.18	10.5	0.016	0.72	3.0	0.0	2.5	6.0	1.0	2.3	-3.9	0.5
1986–1990	313	0.5	4.5	3.0	4.0	7.5	81.5	533	0.17	4.5	0.015	0.74	3.0	0.0	1.5	6.0	1.0	2.2	-3.5	-0.7
1991–1995	553	1.0	9.5	4.0	9.0	6.0	166.0	826	0.23	7.0	0.012	0.55	4.0	1.5	2.0	7.0	1.2	0.3	-4.4	-1.6
1996–2000	189	1.0	3.0	1.0	3.0	3.0	60.3	288	0.16	2.5	0.008	0.71	2.0	0.0	0.5	3.5	1.0	0.0	-2.4	-0.6
2001–2005	1621	17.0	26.0	22.0	27.0	35.0	702.0	2289	0.31	13.0	0.008	0.53	4.0	1.0	2.0	31.0	2.0	-0.5	-3.8	-18.9
2006–2010	651	3.5	8.5	4.0	8.5	3.0	155.7	891	0.18	5.5	0.008	0.56	5.5	1.5	1.0	13.0	5.5	2.0	-3.9	2.4

NP-derived drugs (ND)

	MW	N	O	HBD	HBA	RotB	tPSA	VWSA	relPSA	nStereo	nStMW	FSP3	Rings	RngAr	RngSys	RngLg	RRSys	ALOGPS	ALOGPS	LogD
1981–1985	445	2.00	6.0	2.0	6.0	8.0	107.0	620	0.18	4.0	0.007	0.51	4.0	1.0	2.0	6.0	1.3	1.4	-4.0	-0.5
1986–1990	475	1.00	7.0	2.0	6.0	7.0	111.6	646	0.18	5.0	0.010	0.57	4.0	1.0	2.0	6.0	1.5	2.5	-4.2	1.2
1991–1995	413	3.00	5.0	2.0	6.0	6.0	112.7	645	0.18	3.0	0.009	0.60	3.0	1.0	2.0	6.0	1.5	2.6	-4.4	0.7
1996–2000	450	1.00	5.0	3.0	6.0	7.0	113.5	710	0.18	6.5	0.011	0.63	3.0	0.5	2.0	6.0	1.3	2.4	-4.3	1.2
2001–2005	492	1.50	6.0	3.0	5.0	7.0	116.0	686	0.22	6.0	0.012	0.69	4.0	1.0	2.0	6.0	1.5	1.9	-4.3	-1.2
2006–2010	518	1.00	7.0	3.0	8.0	10.0	133.9	786	0.14	8.0	0.013	0.61	4.0	1.0	2.0	6.0	1.7	3.3	-4.6	2.1

NP-inspired synthetic drugs (S*, S*/NM)

	MW	N	O	HBD	HBA	RotB	tPSA	VWSA	relPSA	nStereo	nStMW	FSP3	Rings	RngAr	RngSys	RngLg	RRSys	ALOGPS	ALOGPS	LogD
1981–1985	292	2.00	3.0	2.0	4.0	6.0	73.7	488	0.14	1.0	0.003	0.54	2.0	1.0	1.0	6.0	1.0	2.1	-3.2	-0.2
1986–1990	342	2.00	4.0	2.0	5.0	8.0	95.8	524	0.15	1.5	0.004	0.55	2.0	1.0	2.0	6.0	1.0	1.6	-3.5	-0.1
1991–1995	358	2.00	4.0	2.0	5.0	7.0	95.9	485	0.15	2.0	0.006	0.50	3.0	2.0	2.0	6.0	1.5	1.8	-3.3	0.0
1996–2000	335	3.00	3.0	2.0	4.0	5.0	75.1	517	0.14	1.0	0.003	0.43	3.0	2.0	2.0	6.0	1.5	2.2	-3.6	1.0
2001–2005	391	3.50	4.0	2.0	6.0	7.0	113.5	553	0.17	2.0	0.005	0.47	3.0	2.0	2.0	6.0	1.5	1.7	-3.2	0.3
2006–2010	368	2.50	4.5	3.0	5.0	6.0	99.1	514	0.18	2.5	0.006	0.42	2.5	2.0	2.0	6.0	1.0	1.9	-4.2	0.4

Completely synthetic drugs (S, S/NM)

	MW	N	O	HBD	HBA	RotB	tPSA	VWSA	relPSA	nStereo	nStMW	FSP3	Rings	RngAr	RngSys	RngLg	RRSys	ALOGPS	ALOGPS	LogD
1981–1985	321	2.00	2.0	1.0	3.0	4.0	59.2	440	0.14	0.0	0.000	0.33	3.0	2.0	2.0	6.0	1.0	2.9	-3.8	1.6
1986–1990	321	2.00	3.0	1.0	4.0	5.0	66.4	449	0.15	0.0	0.000	0.33	3.0	2.0	2.0	6.0	1.0	2.6	-3.7	1.5
1991–1995	320	2.00	3.0	1.0	4.0	4.0	64.3	473	0.14	1.0	0.002	0.36	3.0	2.0	2.0	6.0	1.0	2.8	-3.7	1.3
1996–2000	351	2.00	3.0	1.0	4.0	5.0	70.9	495	0.15	1.0	0.002	0.35	3.0	2.0	2.0	6.0	1.0	2.7	-3.8	1.5
2001–2005	373	3.00	3.0	1.0	5.0	5.0	76.7	507	0.13	1.0	0.002	0.31	3.0	2.0	3.0	6.0	1.0	3.2	-4.2	1.9
2006–2010	403	3.00	3.0	1.0	4.0	5.0	73.8	551	0.14	1.0	0.002	0.36	3.0	2.0	3.0	6.0	1.3	3.0	-4.1	2.2

Table S5. Median values of physicochemical parameters for NCEs 1981–2010 parsed in five-year intervals. Median values of each chemical descriptor are shown for natural product drugs (NP), natural product-derived drugs (ND), natural product-inspired synthetic drugs (S*, S*/NM) and synthetic drugs (S, S/NM) in five-year time blocks from 1981–2010.
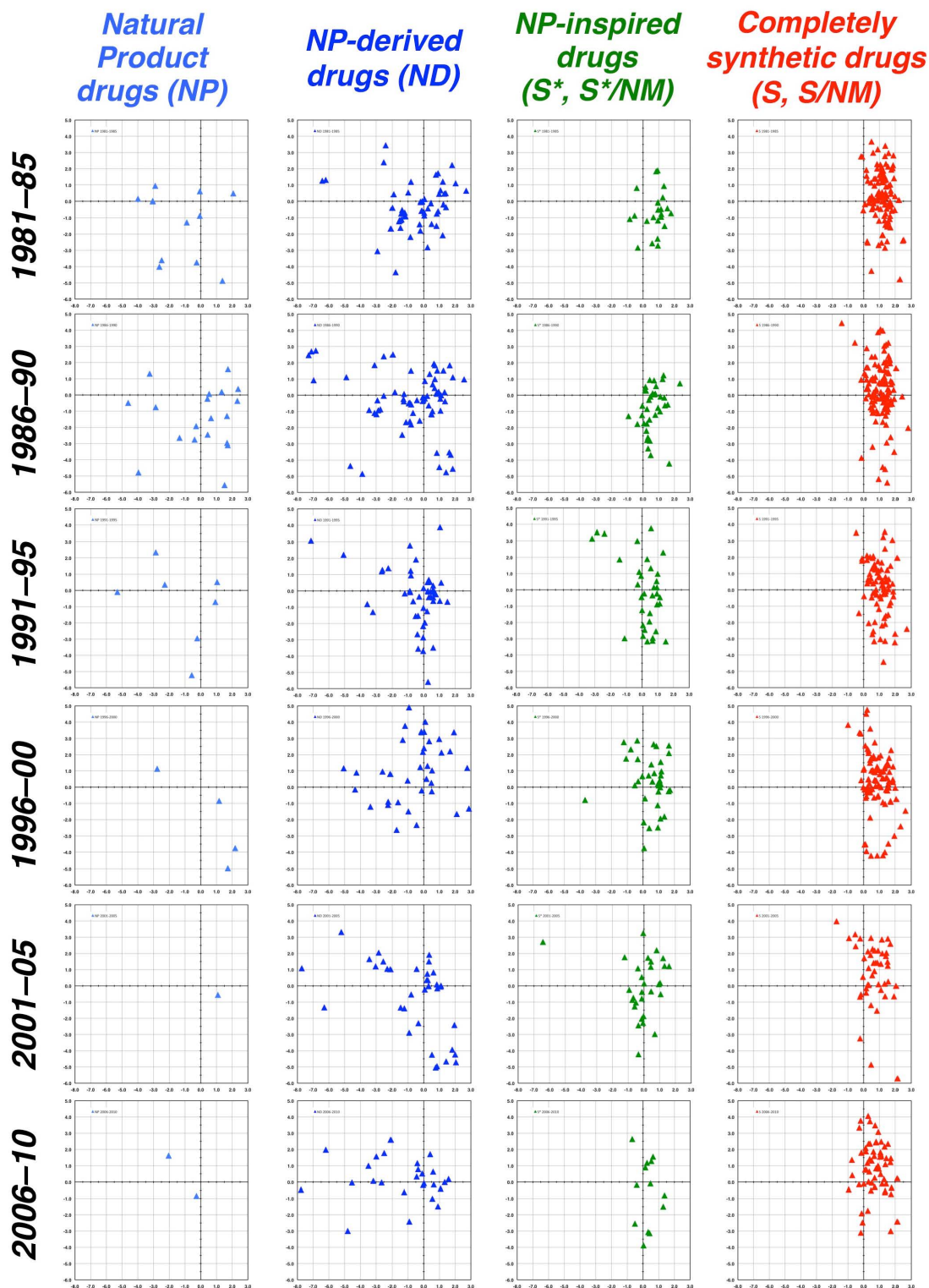
Figure S1. Time-resolved PCA plots for NCEs 1981–2010. Data from a single analysis are presented in five year blocks for natural product drugs (NP), natural product derived drugs (ND), natural product-inspired drugs (S*, S*/NM), and completely synthetic drugs (S, S/NM).

II. LIST OF COMPOUNDS USED IN THE ANALYSIS

Small-molecule drugs included in the analysis are listed below. The drugs are organized by year of approval, generic and trade names, and compound source (N = natural product, ND = natural product-derived, S* = natural product inspired synthetic, S = completely synthetics, NM = natural product mimic, NB = natural product botanical).

Year	Generic Name	Trade Name	Source
1981	aclarubicin	Aclacin	N
1981	netilimicin sulfate	Netromicine	N
1981	peplomycin	Pepleo	N
1982	isotrentoin	Accutane	N
1982	micronomicin sulfate	Sagamicin	N
1983	chenodiol	Chenix	N
1983	cyclosporine	Sandimmun	N
1983	meglutol	Lipoglutaren	N
1984	mizoribine	Bredinin	N
1985	miokamycin	Miocamycin	N
1985	mupirocin	Bactroban	N
1985	podophyllotoxin	Condyline	N
1986	dronabinol	Marinol	N
1987	anabasine_HCl	Gamibasin	N
1987	artemisinin	Artemisin	N
1987	bucillamine	Rimatil	N
1987	ganglioside_GM1	Sygen	N
1987	ivermectin	Mectizan	N
1987	lovastatin	Mevacor	N
1987	plaunotol	Kelnac	N
1987	ubenimex	Bestatin	N
1988	carumonam	Amasulin	N
1988	fosfomycin trometamol	Monuril	N
1988	gamolenic acid	Epogam	N
1988	isepamicin	Isepacin	N
1988	simvastatin	Zocor	N
1989	adenosine	Adenocard	N
1989	azelaic acid	Skinoren	N
1989	pravastatin	Mevalotin	N
1989	RV-11	Zalig	N
1992	masoprocol	Actinex	N
1992	pentostatin	Nipent	N
1993	paclitaxel	Taxol	N
1993	tacrolimus	Prograf	N
1994	angiotensin II	Delivert	N

1994	voglibose	Basen	N
1995	carperitide	Hanp	N
1995	galanthamine HBr	Nivalin	N
1996	betain anhydrous	Cystadane	N
1999	arglabin	arglabin	N
1999	sirolimus	Rapamune	N
2000	aminolevulinic acid HCl	Levulan	N
2003	daptomycin	Cubicin	N
2003	mycophenolate sodium	Myfortic	N
2005	ziconotide	Prialt	N
2007	trabectedin	Yondelis	N
2010	romidepsin	Istodax	N
1987	guglipid	Guglip	NB
1989	solamargines	Curaderm	NB
1981	budesonide	Pulmicort	ND
1981	cefoperazone sodium	Cefobis	ND
1981	cefotiam HCl	Pansporin	ND
1981	cefsoludin sodium	Takesulin	ND
1981	desogestrel/ethinylestradiol	Marvelon	ND
1981	sulprostone	Nalador	ND
1981	testosterone undecanoate	Restandol	ND
1982	apalcillin sodium	Lumota	ND
1982	atracurium besilate	Nimbex	ND
1982	ceftizoxime sodium	Epocelin	ND
1982	ceftriaxone sodium	Rocephin	ND
1982	lisuride maleate	Dopergin	ND
1982	moxalactam disodium	Shiomarin	ND
1982	vecuronium bromide	Norcuron	ND
1983	cefmenoxime HCl	Tacef	ND
1983	ceftazidime	Fortam	ND
1983	elliptinium acetate	Celiptium	ND
1983	epoprostenol sodium	Flolan	ND
1983	gemeprost	Cervagem	ND
1983	halometasone	Sicorten	ND
1983	hydrocortisone butyrate	Pandel	ND
1983	oxitropium bromide	Oxivent	ND
1983	promegestrone	Surgestone	ND
1984	aztreonam	Azactam	ND
1984	buserelin acetate	Suprefact	ND
1984	cefonicid sodium	Monocid	ND
1984	ceforanide	Precef	ND
1984	cefotetan disodium	Yamatetan	ND
1984	epirubicin HCl	Farmorubicin	ND
1984	ibopamine HCl	Inopamil/Scandine	ND
1984	leuprolide acetate	Enantone	ND

1984	melinamide	Artes_Oil	ND
1984	naltrexone HCl	ReVia	ND
1984	nicorandil	Sigmart	ND
1984	sofalcone	Solon	ND
1984	temocillin disodium	Temopen	ND
1984	teprenone	Selbex	ND
1985	alclometasone dipropionate	Vaderm	ND
1985	astromycin sulfate	Fortimicin	ND
1985	cefbuperazone sodium	Tomiporan	ND
1985	cefpiramide sodium	Sepatren	ND
1985	cimetropium bromide	Alginor	ND
1985	doxofylline	Ansimar	ND
1985	enprostil	Gardrin	ND
1985	imipenem/cilastatin	Zienam	ND
1985	mefloquine HCl	Fansimef	ND
1985	misoprostol	Cytotec	ND
1985	nabumetone	Relifex	ND
1985	rifaximin	Rifacol	ND
1985	rosaprostol	Rosal	ND
1985	thymopentin	Sintomodulina	ND
1986	brovincamine fumarate	Sabromin	ND
1986	deflazacort	Deflan	ND
1986	gestrinone	Dimetrose	ND
1986	gonadoreline-6-D-trp acetate	Decapeptyl	ND
1986	idebenone	Avan	ND
1986	levacecarnine HCl	Nicetile	ND
1986	nedocromil sodium	Tilade	ND
1986	nomegestrol acetate	Lutenyl	ND
1986	norgestimate	Cilest	ND
1986	prednicarbate	Dermatop	ND
1986	rokitamycin	Ricamycin	ND
1986	sulbactam sodium	Sulperazone	ND
1986	triptorelin	Decapeptyl	ND
1987	amlexanox	Solfa	ND
1987	artemether	Artemetheri	ND
1987	artenusate	Arinate	ND
1987	aspoxicillin	Doyle	ND
1987	cefixime	Cefspan	ND
1987	cefminox sodium	Meicelin	ND
1987	cefpimizole	Ajicef	ND
1987	cefteram pivoxil	Tomiron	ND
1987	cefuroxime axetil	Zinnat	ND
1987	cefuzonam sodium	Cosmosin	ND
1987	gestodene/ethinylestradiol	Femodene	ND
1987	goserelin	Zoladex	ND

1987	hidrosmin	Venosmil	ND
1987	lenampicillin HCl	Veracillin	ND
1987	metergolin	Liserdol	ND
1987	micinicate	Micivas	ND
1987	midoriamin	Midoriamine	ND
1987	mometasone furoate	Elocon	ND
1987	ornoprostil	Alloca	ND
1987	rifamixin	Normix	ND
1987	roxithromycin	Rulid	ND
1987	sultamycillin tosylate	Unasyn	ND
1988	azithromycin	Sumamed	ND
1988	choline alfoscerate	Delecit	ND
1988	erythromycin acistrate	Erasis	ND
1988	flomoxef sodium	Flumarin	ND
1988	flutropium bromide	Flubron	ND
1988	halopredone acetate	Haloart	ND
1988	hydrocortisone aceponate	Retef	ND
1988	limaprost	Opalmon	ND
1988	mifepristone	Mifegyne	ND
1988	octreotide	Sandostatin	ND
1988	pergolide mesylate	Permax	ND
1988	pirarubicin	Pinorubicin	ND
1988	propentofylline propionate	Hextol	ND
1988	rifapentine	Rifampin	ND
1988	secalciferol	Osteo_D	ND
1988	tibolone	Livial	ND
1989	acitretin	Neotigason	ND
1989	cefpodoxime proxetil	Banan	ND
1989	deslorelin	Somagard	ND
1989	ipriflavone	Osten	ND
1989	tiopronin	Thiola	ND
1989	vigabatrin	Sabril	ND
1989	vinorelbine	Navelbine	ND
1990	acarbose	Glucobay	ND
1990	arbekacin	Habekacin	ND
1990	cefodizime sodium	Neucef	ND
1990	clarithromycin	Klaricid	ND
1990	eflornithine HCl	Ornidyl	ND
1990	ethyl icosapentate	Epadel	ND
1990	fluticasone propionate	Flixonase	ND
1990	idarubicin hydrochloride	Zavedos	ND
1990	nafarelin acetate	Synarel	ND
1990	rebamipide	Mucosta	ND
1991	calcipotriol	Daivonex	ND
1991	cefdinir	Cefzon	ND

1991	cloricromene	Proendotel	ND
1991	halobetasol propionate	Ultravate	ND
1991	romurtide	Nopia	ND
1992	beraprost sodium	Dorner	ND
1992	cefetamet pivoxil HCl	Globocef	ND
1992	cefpirome sulfate	Cefrom	ND
1992	cefprozil	Cefzil	ND
1992	ceftibuten	Seftem	ND
1992	deprodone propionate	Eclar	ND
1992	finasteride	Proscar	ND
1992	iloprost	Ilomedin	ND
1992	loracarbef	Lorabid	ND
1992	rifabutin	Mycobutin	ND
1992	sapropterin hydrochloride	Biopten	ND
1992	tazobactam sodium	Tazobac	ND
1993	alendronate sodium	Alendros	ND
1993	cabergoline	Dostinex	ND
1993	cefepime	Maxipime	ND
1993	cladribine	Leustatin	ND
1993	cytarabine ocfosfate	Starasid	ND
1993	dirithromycin	Nortron	ND
1993	ecabet sodium	Gastrom	ND
1993	formestane	Lentaron	ND
1993	histrelin	Supprelin	ND
1993	miltefosine	Miltex	ND
1993	tacalcitol	Bonalfa	ND
1993	tretinoin tocoferil	Olcenon	ND
1994	betamethasone butyrate propion	Antebate	ND
1994	cefditoren pivoxil	Meiact	ND
1994	docarpamine	Tanadopa	ND
1994	gusperimus trihydrochloride	Spanidin	ND
1994	irinotecan hydrochloride	Campto	ND
1994	meropenem	Merrem	ND
1994	panipenem/betamipron	Carbenin	ND
1994	polaprezinc	Promac	ND
1994	quinagolide hydrochloride	Norprolac	ND
1994	rocuronium bromide	Zemuron	ND
1994	trimetrexate glucuronate	Neutrexin	ND
1994	unoprostone isopropyl ester	Rescula	ND
1994	zinostatin stimalamer	Smancs	ND
1995	cefozopran HCl	Firstcin	ND
1995	docetaxel	Taxotere	ND
1995	lanreotide acetate	Somatuline	ND
1995	mycophenolate mofetil	CellCept	ND
1995	nalmefene HCl	Revex	ND

1995	rimexolone	Vexol	ND
1995	tirilazad mesylate	Freedox	ND
1996	etoposide phosphate	Etopophos	ND
1996	glycopin	Licopid	ND
1996	latanoprost	Xalatan	ND
1996	prezatide copper acetate	Lamin_gel	ND
1996	topotecan HCl	Hycamtin	ND
1997	cefcapene pivoxil	Flomox	ND
1997	flurithromycin ethylsuccinate	Ritro	ND
1997	fropenam	Farom	ND
1998	cefoselis	Wincef	ND
1998	loteprednol etabonate	Lotemax	ND
1998	miglitol	Diastabol	ND
1998	orlistat	Xenical	ND
1998	paricalcitol	Zemplar	ND
1998	sermorelin acetate	Geref	ND
1999	alitretinoin	Panretin	ND
1999	cetrorelix	Cetrotide	ND
1999	colforsin dapropate HCl	Adehl	ND
1999	dalfopristin	Synercid	ND
1999	doxercalciferol	Hectorol	ND
1999	exemestane	Aromasin	ND
1999	melevodopa (CHF-1301)	Levomet	ND
1999	oseltamivir	Tamiflu	ND
1999	quinupristin	Synercid	ND
1999	rapacuronium bromide	Raplon	ND
1999	valrubicin	Valstar	ND
1999	zanamivir	Relenza	ND
2000	arteether	Artemotil	ND
2000	atosiban	Tractocile	ND
2000	bivalrudin	Angiomax	ND
2000	dosmalfate	Diotul	ND
2000	drospirenone	Yasmin	ND
2000	egualen sodium	Azuloxa	ND
2000	ganirelix acetate	Orgalutran	ND
2000	gemtuzumab ozogamicin	Mylotarg	ND
2000	maxacalcitol	Prezios	ND
2000	medroxyprogesterone/estradiol	Lunelle	ND
2000	taltirelin	Ceredist	ND
2000	trimegesrone/estradiol	Totelle Sekvens	ND
2001	aminolevulinic acid me ester	Metvix	ND
2001	bimatoprost	Lumigan	ND
2001	caspofungin acetate	Cancidas	ND
2001	dutaseride	Duagen	ND
2001	falecalcitriol	Horner/Fulstan	ND

2001	fudosteine	Cleanal/Spelear	ND
2001	nesiritide	Natrecor	ND
2001	norelgestromin/ethinylestradio	Ortho_Evra	ND
2001	telithromycin	Ketek	ND
2001	travoprost	Travatan	ND
2002	amrubicin HCl	Calsed	ND
2002	biapenem	Omegacin	ND
2002	eplerenone	Inspra	ND
2002	ertapenem sodium	Invanz	ND
2002	etonogestrel/ethinylestradiol	NuvaRing	ND
2002	fondaparinux sodium	Arixtra	ND
2002	fulvestrant	Faslodex	ND
2002	micafungin sodium	Funguard	ND
2002	pimecrolimus (SDZ-ASM-981)	Elidel	ND
2002	sodium oxybate	Xyrem	ND
2002	teriparatide	Forteo	ND
2002	treprostinil sodium	Remodulin	ND
2003	carglumic acid	Carbaglu	ND
2003	drospirenone/estradiol	Angeliq	ND
2003	enfuvirtide	Fuzeon	ND
2003	estradiol/nomegestrol acetate	Naemis	ND
2003	miglustat	Zavesca	ND
2004	belotecan hydrochloride	Camtobell	ND
2004	estradiol/levonorgestrel	Climara Pro	ND
2004	everolimus	Certican	ND
2004	hexyl aminolevulinate	Hexvix	ND
2004	pregabalin	Lyrica	ND
2004	talaporfin sodium	Laserphyrin	ND
2004	vapreotide acetate	Docrised	ND
2005	ciclesonide	Alvesco	ND
2005	doripenem	Finibax	ND
2005	extenatide	Byetta	ND
2005	L-alanyl-L-glutamine	Dipeptiven	ND
2005	pralmorelin	GHRP_Kaken_100	ND
2005	tigecycline	Tygacil	ND
2005	triproamylin acetate	Normylin	ND
2005	zotarolimus	Endeavor	ND
2006	anecortave acetate	Retaane	ND
2006	anidulafungin	Eraxis	ND
2006	lubiprostone	Amitiza	ND
2007	fluticasone furoate	Allermist	ND
2007	ixabepilone	Ixempra	ND
2007	lisdexamfetamine mesilate	Vyvanse	ND
2007	retapamulin	Altabax	ND
2007	temsirolimus	Torisel	ND

2008	biolimus a9	BioMatrix	ND
2008	ceftobiprole medocaril	Zeftera	ND
2008	dienogest	Dinagest	ND
2008	difluprednate	Durezol	ND
2008	icatibant acetate	Firazyr	ND
2008	methylnaltrexone bromide	Relistor	ND
2008	sugammadex sodium	Bridion	ND
2008	tafluprost	Taflotan	ND
2009	liraglutide	Victoza	ND
2009	nalfurafine HCl	Remitch	ND
2009	pralatrexate	Folotyn	ND
2009	telavancin HCl	Vibativ	ND
2009	uliprisnil acetate	ellaOne	ND
2010	cabazitaxel	Jevtana	ND
2010	diquafosol tetrasodium	Diquas	ND
2010	eribulin	Halaven	ND
2010	fingolimod HCl	Gilenya	ND
2010	laninamivir octanoate	Inavir	ND
2010	mifamurtide	Junovan	ND
2010	vinflunine	Javlor	ND
2010	zucapsacin	Civanex	ND
1981	acyclovir	Zovirax	S*
1981	carmofur	Mifurol	S*
1981	indoramin HCl	Wydora	S*
1981	inosine pranobex	Imunovir	S*
1983	befunolol HCl	Bentox	S*
1983	celiprolol HCl	Selectol	S*
1983	enocitabine	Sunrabin	S*
1984	fosfosal	Disdolen	S*
1984	mitoxantrone HCl	Novantrone	S*
1985	progabide	Gabrene	S*
1987	doxifluridine	Furtulon	S*
1987	eptazocine HBr	Sedapain	S*
1987	zidovudine	Retrovir	S*
1988	epervudine	Hevizos	S*
1988	ganciclovir	Cymevene	S*
1989	acamprosate	Aotal	S*
1989	ethanolamine oleate	Ethamolin	S*
1991	didanosine	Videx	S*
1991	doxacurium chloride	Nuromax	S*
1991	fludarabine phosphate	Fludara	S*
1992	atovaquone	Mepron	S*
1992	mivacurium chloride	Mivacron	S*
1992	zalcitabine	Hivid	S*
1993	gabapentin	Neurontin	S*

1993	sorivudine	Usevir	S*
1994	famciclovir	Famvir	S*
1994	stavudine	Zerit	S*
1995	cisatracurium besilate	Nimbex	S*
1995	gemcitabine HCl	Gemzar	S*
1995	lamivudine	Epivir	S*
1995	topiramate	Topamax	S*
1995	valaciclovir HCl	Valtrex	S*
1996	cidofovir	Vistide	S*
1996	penciclovir	Vectavir	S*
1998	capecitabine	Xeloda	S*
1999	abacavir sulfate	Ziagen	S*
1999	kinetin	Kinerase	S*
1999	nateglinide	Starsis	S*
2000	bulaquine / chloroquine	Aablaquin	S*
2001	tenofovir disoproxil fumarate	Viread	S*
2001	valganciclovir	Valcyte	S*
2002	adefovir dipivoxil	Hepsera	S*
2002	timodepressin	Thymodepressin	S*
2003	emtricitabine	Emtriva	S*
2004	azacytidine	Vidaza	S*
2004	ximelagatran	Exanta	S*
2005	clofarabine	Clolar	S*
2005	entecavir	Baraclude	S*
2006	decitabine	Dacogen	S*
2006	nelarabine	Arranon	S*
2006	telbivudine	Sebivo	S*
2007	clevudine	Levovir	S*
2008	etravirine	Intelence	S*
1981	cloranolol HCl	Tobanum	S*/NM
1981	mepindolol sulfate	Corindolan	S*/NM
1981	penbutanol sulfate	Betapressin	S*/NM
1981	tulobuterol HCl	Berachin	S*/NM
1982	carteolol HCl	Teoptic	S*/NM
1982	methypranolol	Minims_metipranolol	S*/NM
1983	betaxolol HCl	Kerlone	S*/NM
1983	pirbuterol HCL	Exirel	S*/NM
1984	bucladesine sodium	Actosin	S*/NM
1984	enalapril maleate	Renitec	S*/NM
1985	bopindolol	Sandonorm	S*/NM
1985	levobunolol HCl	Betagan	S*/NM
1986	arotinolol HCl	Almarl	S*/NM
1986	bisoprolol fumarate	Concor	S*/NM
1986	formoterol fumarate	Atock	S*/NM
1986	mabuterol HCl	Broncholin	S*/NM

1987	bevantolol HCl	Ranestol	S*/NM
1987	enalaprilat	Renitec	S*/NM
1987	esmolol HCl	Brevibloc	S*/NM
1987	lisinopril	Prinivil	S*/NM
1987	tertatolol HCl	Artex	S*/NM
1988	alacepril	Cetapril	S*/NM
1988	amosulalol	Lowgan	S*/NM
1988	denopamine	Kalgut	S*/NM
1988	nipradilol	Hypadil	S*/NM
1988	perindopril	Coversyl	S*/NM
1988	xamoterol fumarate	Corwin	S*/NM
1989	citalopram	Cipramil	S*/NM
1989	delapril	Adecut	S*/NM
1989	dilevalol	Levadil	S*/NM
1989	dopexamine	Dopacard	S*/NM
1989	droxidopa	DOPS	S*/NM
1989	quinapril	Accupro	S*/NM
1989	ramipril	Triatec	S*/NM
1990	argatroban	Slonnon	S*/NM
1990	bambuterol	Bambec	S*/NM
1990	benazepril hydrochloride	Cibacen	S*/NM
1990	cilazapril	Inhibace	S*/NM
1990	ondansetron hydrochloride	Zophren	S*/NM
1990	remoxipride hydrochloride	Roxiam	S*/NM
1990	salmeterol xinafoate	Serevent	S*/NM
1991	carvedilol	Dilatrend	S*/NM
1991	centchroman	Choice_7	S*/NM
1991	fosinopril sodium	Staril	S*/NM
1991	granisetron hydrochloride	Kytril	S*/NM
1991	moxonidine	Cynt	S*/NM
1991	sumatriptan succinate	Imigran	S*/NM
1992	tilisolol hydrochloride	Daim	S*/NM
1992	tropisetron	Novaban	S*/NM
1993	acetorphan	Tiorfan	S*/NM
1993	brodimoprin	Hyprim	S*/NM
1993	imidapril HCl	Tanatril	S*/NM
1993	trandolapril	Odrik	S*/NM
1994	fluvastatin sodium	Lescol	S*/NM
1994	nazasetron hydrochloride	Serotone	S*/NM
1994	temocapril hydrochloride	Acecol	S*/NM
1995	itopride HCl	Ganaton	S*/NM
1995	moexipril HCl	Univasc	S*/NM
1995	pranlukast	Onon	S*/NM
1995	saquinavir mesylate	Invirase	S*/NM
1995	spirapril HCl	Setrilan	S*/NM

1996	indinavir sulfate	Crixivan	S*/NM
1996	loprinone HCl	Coretec	S*/NM
1996	raltitrexed	Tomudex	S*/NM
1996	ramosetron	Nasea	S*/NM
1996	ritonavir	Norvir	S*/NM
1996	ropinirole HCl	ReQuip	S*/NM
1996	sertindole	Serdolect	S*/NM
1996	tiagabine	Gabitril	S*/NM
1997	anagrelide HCl	Agrylin	S*/NM
1997	atorvastin calcium	Lipitor	S*/NM
1997	cerivastatin	Lipobay	S*/NM
1997	naratriptan HCl	Naramig	S*/NM
1997	neflinavir mesylate	Viracept	S*/NM
1997	tazarotene	Zorac	S*/NM
1997	tolcapone	Tasmar	S*/NM
1997	zomitriptan	Zomig	S*/NM
1998	dolasetron mesylate	Anzemet	S*/NM
1998	entacapone	Comtess	S*/NM
1998	rizatriptan benzoate	Maxalt	S*/NM
1998	sildenafil citrate	Viagra	S*/NM
1999	amprenavir	Agenerase	S*/NM
1999	eptilfibatide	Integrilin	S*/NM
1999	levalbuterol HCl	Xopenex	S*/NM
1999	temozolomide	Temodal	S*/NM
2000	almotriptan	Almogran	S*/NM
2000	alosetron HCL	Lotronex	S*/NM
2000	bexarotene	Targretin	S*/NM
2000	cevimeline HCl	Evoxac	S*/NM
2000	lopinavir	Aluviran	S*/NM
2000	ziprasidone HCl	Zeldox	S*/NM
2000	zofenapril calcium	Zantipres	S*/NM
2001	eletriptan	Relpax	S*/NM
2001	perspirone hydrochloride	Lullan	S*/NM
2001	tegaserod maleate	Zelmac	S*/NM
2002	escitalopram	Cipralex	S*/NM
2002	frovatriptan	Frova	S*/NM
2002	landiolol	Onoact	S*/NM
2002	tiotropium bromide	Spiriva	S*/NM
2003	atazanavir	Reyataz	S*/NM
2003	atomoxetine	Strattera	S*/NM
2003	fosamprenevir	Lexiva	S*/NM
2003	palonosetron	Aloxi	S*/NM
2003	pitavastatin	Livalo	S*/NM
2003	rosuvastatin	Crestor	S*/NM
2003	tadalafil	Cialis	S*/NM

2003	vardenafil	Levitra	S*/NM
2004	abarelix	Plenaxis	S*/NM
2004	indisetron hydrochloride	Sinseron	S*/NM
2004	pemetrexed disodium	Alimta	S*/NM
2005	tamibarotene	Amnoid	S*/NM
2005	tipranavir	Aptivus	S*/NM
2005	udenafil	Zydena	S*/NM
2006	vorinostat	Zolinza	S*/NM
2007	aliskiren fumarate	Tekturna	S*/NM
2007	arformoterol tartrate	Brovana	S*/NM
2008	alvimopan hydrate	Entereg	S*/NM
2008	dabigatran etexilate	Pradaxa	S*/NM
2008	lacosamide	Vimpat	S*/NM
2008	rivaroxaban	Xarelto	S*/NM
2009	degarelix	Firmagon	S*/NM
2009	indacaterol maleate	Onbrez	S*/NM
1981	alizapride	Liticum	S
1981	amezinium methylsulfate	Supratonin	S
1981	aminoglutethimide	Cytadren	S
1981	azurene	Impromen	S
1981	bepridil HCl	Cordium	S
1981	carprofen	Rimadyl	S
1981	clinofibrate	Lipoclin	S
1981	isosorbide 5-mononitrate	Ismo	S
1981	ketoconazole	Nizoral	S
1981	lonazolac calcium	Lonax	S
1981	morniflumate	Niflam	S
1981	nicardipine HCl	Perpidine	S
1981	nifurzide	Ricridene	S
1981	oxatomide	Tinset	S
1981	piretanide	Tauliz	S
1981	ranitidine HCl	Zantac	S
1981	tocainide HCl	Tonocard	S
1981	trifusal	Disgren	S
1981	urapidil	Ebrantil	S
1981	valproate sodium	Depacon	S
1982	albendazole	Eskazole	S
1982	ciclopirox olamine	Loprox	S
1982	ethyl loflazepate	Victan	S
1982	flecainide	Tambocor	S
1982	flumecinol	Zixoryn	S
1982	gemfibrozal	Lopid	S
1982	halazepam	Paxipam	S
1982	memantine HCl	Akatinol	S
1982	midazolam maleate	Versed	S

1982	pirprofen	Rengasil	S
1982	pranoprofen	Niflan	S
1982	talniflumate	Lomucin	S
1982	tranilast	Rizaben	S
1982	zotepine	Zoleptil	S
1983	acetohydroxamic acid	Lithostat	S
1983	afloqualone	Arofuto	S
1983	alfentanil HCl	Rapifen	S
1983	alminoprofen	Minalfene	S
1983	amineptine	Maneon	S
1983	astemizole	Hismanal	S
1983	auranofin	Ridaura	S
1983	bifonazole	Mycospor	S
1983	brotizolam	Lendormin	S
1983	budralazine	Buteraxine	S
1983	butyl flufenamate	Fenazole	S
1983	divalproex sodium	Depakote	S
1983	eperisone HCl	Myonal	S
1983	fenbuprol	Valbil	S
1983	flutamide	Drogenil	S
1983	gallopamil HCl	Procorum	S
1983	guanadrel sulfate	Hylorel	S
1983	indalpine	Upstene	S
1983	isoxicam	Pacyl	S
1983	linsidomine	Corvasal	S
1983	loprazolam mesylate	Dormonoct	S
1983	meptazinol HCl	Meptid	S
1983	muzolimine	Edrul	S
1983	nefopam HCl	Acupan	S
1983	nitrefazole	Altimol	S
1983	norfloxacin	Noroxin	S
1983	oxaprozin	Duraprox	S
1983	oxiconazole nitrate	Oceral	S
1983	sufentanil	Sufenta	S
1983	suprofen	Maldocil	S
1983	terconazole	Gyno-Terazol	S
1983	tianeptine sodium	Stablon	S
1983	tioconazole	Trosyl	S
1983	tiropramide	Maiorad	S
1984	butoctamide	Listomin_S	S
1984	detomidine HCl	Domosedan	S
1984	emorfazone	Pentoil	S
1984	etizolam	Depas	S
1984	flutazolam	Coreminal	S
1984	indobufen	Ibustrin	S

1984	isofezolac	Sofenac	S
1984	lidamidine HCl	Lidaral	S
1984	mepixanox	Pimexone	S
1984	mesalamine	Asacol	S
1984	metapramine	Timaxel	S
1984	mexazolam	Melex	S
1984	naftifine HCl	Exoderil	S
1984	piketoprofen	Calmatel	S
1984	quinfamide	Amenox	S
1984	terazocin HCl	Hytrin	S
1984	timiperone	Tolopelon	S
1984	tiquizium bromide	Thiaton	S
1985	acipimox	Olbetam	S
1985	buspirone HCl	Bespar	S
1985	cibenzoline succinate	Cipralan	S
1985	ciprofibrate	Lipanor	S
1985	diacerein	Artrodar	S
1985	doxefaxepam	Doxans	S
1985	etodolac	Lodine	S
1985	famotidine	Gaster/Pepcid	S
1985	flupirtine maleate	Katadolon	S
1985	malotilate	Kantec	S
1985	nimesulide	Aulin	S
1985	nimodipine	Nimotop	S
1985	nitrendipine	Bayotensin	S
1985	ofloxacin	Tarivid	S
1985	pefloxacin mesylate	Peflacine	S
1985	quazepam	Selepam	S
1985	sulconazole nitrate	Exelderm	S
1986	adrafinil	Olmifon	S
1986	amfenac sodium	Fenazox	S
1986	azelastine HCl	Azeptin	S
1986	azosemide	Luret	S
1986	beclobrate	Beclosclerin	S
1986	binifibrate	Biniwas	S
1986	butoconazole	Femstat	S
1986	carboplatin	Paraplatin	S
1986	ciprofloxacin	Ciprobay	S
1986	cloconazole HCl	Pilzcin	S
1986	clodronate disodium	Bonefos	S
1986	enoxacin	Flumark	S
1986	felbinac	Napageln	S
1986	flutoprazepam	Restas	S
1986	lobenzarit sodium	Carfenil	S
1986	loxoprofen sodium	Loxonin	S

1986	medifoxamine fumarate	Cledail	S
1986	osalazine sodium	Dipentum	S
1986	piproxen	Piproxen	S
1986	propacetamol HCl	Pro-dafalgan	S
1986	propofol	Diprivan	S
1986	ronifibrate	Cloprane	S
1986	roxatidine acetate HCl	Altat	S
1986	trientine HCl	Cuprid	S
1986	troxipide	Aplace	S
1986	zopiclone	Imovane	S
1987	amsacrine	Amsakrin	S
1987	benexate HCl	Lonmiel	S
1987	bifemelane HCl	Alnert	S
1987	cetirizine HCl	Zyrtec	S
1987	disodium pamidronate	Aminomux	S
1987	encainide HCl	Enkaid	S
1987	fenticonazole nitrate	Lomexin	S
1987	flunoxaprofen	Priaxim	S
1987	flurbiprofen sodium	Ocufen	S
1987	ibuprofen guaiacol ester	Benflogin	S
1987	lonidamine	Doridamina	S
1987	lumefantrine	lumefantrine	S
1987	metaclazepam	Talis	S
1987	nilutamide	Anandron	S
1987	nizatidine	Axid	S
1987	oxiracetam	Neuromet	S
1987	pinacidil	Pindac	S
1987	ranimustine	Cymerine	S
1987	repirinast	Romet	S
1987	rimantadine HCl	Roflual	S
1987	setastine HCl	Loderix	S
1987	spizofurone	Maon	S
1987	tenoxicam	Tilcotil	S
1987	zuclopenthixol acetate	Clopixol_Acutard	S
1988	acrivastine	Semprex	S
1988	alfuzosin HCl	Xatral	S
1988	cadralazine	Cadraten	S
1988	cicletanine	Tenstaten	S
1988	cisapride	Prepulsid	S
1988	clobenoside	Arvigol	S
1988	exifone	Adlone	S
1988	felodipine	Plendil	S
1988	fluconazole	Diflucan	S
1988	guaimesal	Bronteril	S
1988	halofantrine	Halfan	S

1988	indeloxazine HCl	Elen	S
1988	itraconazole	Sporanox	S
1988	levodropropizine	Levotuss	S
1988	loratadine	Claritin	S
1988	nizofenone fumarate	Ekonal	S
1988	omepraxole	Losec	S
1988	piroxicam cinnamate	Sinartrol	S
1988	rilmenidine	Hyperium	S
1988	taurolidine	Taurolin	S
1988	tiamenidine HCl	Sundralen	S
1988	tinazoline	Varsyl	S
1988	zinc acexamate	Copinal	S
1988	zolpidem hemitartrate	Stilnox	S
1989	bupropion HCl	Wellbutrin	S
1989	fepradiinol	Flexidol	S
1989	foscarnet sodium	Foscavir	S
1989	fotemustine	Muphoran	S
1989	indecainide	Decabid	S
1989	irsogladine	Gaslon-N	S
1989	isradipine	Prescal	S
1989	lomefloxacin	Uniquin	S
1989	nilvadipine	Nivadil	S
1989	rilmazafone	Rhythmy	S
1989	zonisamide	Excegran	S
1990	aminoprofen	Aldospray	S
1990	amlodipine besylate	Istin	S
1990	bisantrene hydrochloride	Zantrene	S
1990	colfosceril palmitate	Exosurf_Neonatal	S
1990	droxicam	Ombolan	S
1990	ebastine	Ebastel	S
1990	ketorolac tromethamine	Toradol_IM	S
1990	lamotrigine	Lamictal	S
1990	manidipine hydrochloride	Calslot	S
1990	moricizine hydrochloride	Ethmozine	S
1990	nisoldipine	Baymycard	S
1990	oxcarbazepine	Trileptal	S
1990	sevoflurane	Sevofrane	S
1990	tazanolast	Tazalest	S
1990	tiracizine hydrochloride	Bonnecor	S
1990	tosufloxacin	Ozex	S
1990	tropesin	Repanidal	S
1990	vesnarinone	Arkin-Z	S
1991	amorolfine hydrochloride	Loceryl	S
1991	benidipine hydrochloride	Coniel	S
1991	gallium nitrate	Ganite	S

1991	lacidipine	Lacipil	S
1991	levocabastine hydrochloride	Livostin	S
1991	pemirolast potassium	Pemilaston	S
1991	pilsicainide hydrochloride	Sunrythm	S
1991	temafloxacin hydrochloride	Temac	S
1992	aceclofenac	Airtal	S
1992	barnidipine hydrochloride	Hypoca	S
1992	butibufen	Butilopan	S
1992	desflurane	Suprane	S
1992	dexrazoxane	Cardioxane	S
1992	fleroxacin	Quinodis	S
1992	flosequinan	Manoplax	S
1992	lansoprazole	Ogast	S
1992	lodoxamide tromethamine	Aolmide	S
1992	lofexidine	Britlofex	S
1992	propiverine hydrochloride	Mictonorm	S
1992	rufloxacin hydrochloride	Qari	S
1992	sertaconazole nitrate	Dermofix	S
1992	telmesteine	Reolase	S
1993	aniracetam	Draganon	S
1993	cinolazepam	Gerodorm	S
1993	emedastine difumarate	Daren	S
1993	felbamate	Felbatol	S
1993	levofloxacin	Floxacin	S
1993	nadifloxacin	Acuatim	S
1993	neltenexine	Tenoxol	S
1993	neticonazole HCl	Atolant	S
1993	pidotimod	Polimod	S
1993	pramiracetam H2SO4	Remen	S
1993	sparfloxacin	Spara	S
1993	torasemide	Unat	S
1993	zaltoprofen	Soleton	S
1994	actarit	Orcl	S
1994	ampiroxicam	Nacyl	S
1994	dexibuprofen	Seractyl	S
1994	efonidipine hydrochloride	Landel	S
1994	epinastine hydrochloride	Alesion	S
1994	lanoconazole	Astat	S
1994	modafinil	Modiodal	S
1994	mofezolac	Disopain	S
1994	pantoprazole sodium	Pantozol	S
1994	pimobendan	Acardl	S
1994	pirmenol hydrochloride	Pimenol	S
1994	sobuzoxane	Perazolin	S
1995	amifostine	Ethyol	S

1995	cinildipine	Cinalong	S
1995	defeiprone	Kelfer	S
1995	erdosteine	Edirel	S
1995	fasudil HCl	Eril	S
1995	flutrimazole	Micetal	S
1995	glimepiride	Amaryl	S
1995	nedaplatin	Aqupla	S
1995	ranitidine bismuth citrate	Pylorid	S
1995	suplatast tosylate	IPD	S
1995	tenidap sodium	Enablex	S
1995	tiludronate disodium	Skelid	S
1996	aranidipine	Bec/Sapresta	S
1996	dexketoprofen trometamol	Enantyum	S
1996	fexofenadine	Allegra	S
1996	fosphenytoin sodium	Cerebyx	S
1996	ibandronic acid	Bondronat	S
1996	ibutilide fumarate	Corvert	S
1996	nevirapine	Viramune	S
1996	oxaliplatin	Eloxatin	S
1996	remifentanil HCl	Ultiva	S
1996	riluzole	Rilutek	S
1996	ropivacaine	Naropin	S
1996	sodium phenylbutyrate	Buphenyl	S
1997	balsalazide disodium	Colazide	S
1997	bromfenac sodium	Duract	S
1997	delavirdine mesylate	Rescriptor	S
1997	ebrotidine	Ebrocrit	S
1997	grepafloxacin	Vaxar	S
1997	imiquimod	Aldara	S
1997	incadronic acid	Bisphonal	S
1997	lercanidipine	Lerdip	S
1997	lornoxicam	Xefo	S
1997	mibefradil hydrochloride	Posicor	S
1997	olopatadine HCl	Patanol	S
1997	pivagabine	Tonerg	S
1998	amtolmetin guacil	Eufans	S
1998	efavirenz	Sustiva	S
1998	lobaplatin	Lobaplatin	S
1998	mizolastine	Mizollen	S
1998	rabeprazole sodium	Pariet	S
1998	repaglinide	Prandin	S
1998	risedronate sodium	Actonel	S
1998	trovafloxacin mesylate	Trovan	S
1999	gatilfloxacin	Tequin	S
1999	heptaplatin /SK-2053R	Sunpla	S

1999	lomerizine HCl	Terranas	S
1999	mivotilate	mivotilate	S
1999	moxifloxacin HCl	Avelox	S
1999	nifekalant HCl	Shinbit	S
1999	pioglitazone NCl	Actos	S
1999	zaleplon	Sonata	S
2000	arsenic trioxide	Trisenox	S
2000	betotastine besilate	Talion	S
2000	dofetilide	Tikosyn	S
2000	esomeprazole magnesium	Nexium	S
2000	lafutidine	Stogar	S
2000	levetiracetam	Keppra	S
2000	levobupivacaine	Chirocaine	S
2000	linezolid	Zyvox	S
2000	ramatroban	Baynas	S
2000	zoledronic acid	Zometa	S
2001	desloratadine	Clarinex/Neoclarityn	S
2001	edarvarone	Radicut	S
2001	levocetirizine	Xyzal/Xusal	S
2001	rupatadine fumarate	Rupafin	S
2002	balofloxacin	Q-Roxin	S
2002	dexmethylphenidate	Focalin	S
2002	ezetimibe	Zetia	S
2002	neridronic acid	Nerixia	S
2002	nitisinone	Orfadin	S
2002	pazufloxacin	Pasil	S
2002	prulifloxacin	Sword	S
2002	voriconazole	Vfend	S
2003	azelnipidine	Calblock	S
2003	fosfluconazole	Prodif	S
2003	gemifloxacin mesilate	Factive	S
2004	cinacalcet	Sensipar	S
2004	mitiglinide calcium hydrate	Glufast	S
2004	solifenacin succinate	Vesicare	S
2004	strontium ranelate	Protelos	S
2005	deferasirox	Exjade	S
2005	eberconazole	Ebernet	S
2005	eszopiclone	Lunesta	S
2005	ivabrandin hydrochloride	Procoralan	S
2005	lanthanum carbonate	Fosrenol	S
2005	lenalidomide	Revlimid	S
2005	luliconazole	Lulicon	S
2005	nepafenac	Nevanac	S
2005	posaconazole	Noxafil	S
2005	rasagline mesilate	Azilect	S

2005	sorafenib	Nexavar	S
2006	ranolazine	Ranexa	S
2006	silodosin	Urief	S
2007	garenoxacin	Geninax	S
2007	imidafenacin	Uritos	S
2007	maraviroc	Celsentri	S
2007	raltegravir potassium	Isentress	S
2007	revaprazan hydrochlorie	Revanex	S
2007	rufinamide	Xilep	S
2007	stiripentol	Diacomit	S
2008	choline fenofibrate	Trilipix	S
2008	clevidipine butyrate	Cleviprex	S
2008	eltrombopag olamine	Promacta	S
2008	pirfenidone	Pirespa	S
2008	sitafloxacin hydrate	Gracevit	S
2009	armodafinil	Nuvigil	S
2009	besifloxacin	Besivance	S
2009	dexlansoprazole	Dexilant	S
2009	dronedarone HCl	Multaq	S
2009	eslicarbazepine acetate	Zebinix	S
2009	minodronate	Bonoteo	S
2009	plerixafor hydrochloride	Mozobil	S
2010	3,4-diaminopyridine phosphate	Firdapse	S
2010	4-aminopyridine	Ampyra	S
2010	bilastine	Bilatex	S
2010	miriplatin hydrate	Miripla	S
2010	vernakalant HCl	Brinavess	S
1981	selegiline HCl	Jumex	S/NM
1983	amrinone	Inocor	S/NM
1983	fluvoxamine maleate	Floxyfral	S/NM
1984	tizanidine	Sirdalud	S/NM
1984	toloxatone	Humoryl	S/NM
1985	bunazosin HCl	Detandol	S/NM
1985	camostat mesylate	Foipan	S/NM
1985	ketanserin	Serefrex	S/NM
1985	trimazosin HCl	Supres	S/NM
1986	amisulpride	Socian	S/NM
1986	fluoxetine HCl	Prozac	S/NM
1986	nafamostat mesylate	Futhan	S/NM
1987	dapiprazole HCl	Glamidolo	S/NM
1987	flumazenil	Anexate	S/NM
1987	levosulpiride	Levopraid	S/NM
1987	picotamide	Plactidil	S/NM
1988	apraclonidine HCl	Iopidine	S/NM
1988	cilostazol	Pletal	S/NM

1988	doxazosin mesylate	Carduran	S/NM
1988	enoximone	Perfan	S/NM
1988	ozagrel sodium	Xanbon	S/NM
1989	ibudilast	Ketas	S/NM
1989	milrinone	Corotrope	S/NM
1989	setiptiline	Tecipul	S/NM
1989	tolrestat	Alredase	S/NM
1989	toremifene	Fareston	S/NM
1990	cinitapride	Cidine	S/NM
1990	moclobemide	Aurorix	S/NM
1990	setraline hydrochloride	Lustral	S/NM
1991	alpidem	Ananxyl	S/NM
1991	clospipramine hydrochloride	Cremin	S/NM
1991	dezocine	Dalgan	S/NM
1991	nemonapride	Emilace	S/NM
1991	paroxetine	Seroxat	S/NM
1991	terbinafine hydrochloride	Lamisil	S/NM
1992	butenafine hydrochloride	Mentax	S/NM
1992	epalrestat	Kinedak	S/NM
1993	risperidone	Risperdal	S/NM
1993	sarpogrelate HCl	Anplag	S/NM
1993	tacrine HCl	Cognex	S/NM
1993	tamsulosin HCl	Harnal	S/NM
1994	broxaterol	Summair	S/NM
1994	losartan potassium	Cozaar	S/NM
1994	mirtazapine	Remeron	S/NM
1994	nefazodone hydrochloride	Serzone	S/NM
1994	venlafaxine	Effexor	S/NM
1995	anastrozole	Arimidex	S/NM
1995	bicalutamide	Casodex	S/NM
1995	dorzolamide HCl	Trusopt	S/NM
1995	fadrozole HCl	Afema	S/NM
1995	seratrodast	Bronica	S/NM
1996	brimonidine	Alphagan	S/NM
1996	letrazole	Femara	S/NM
1996	meloxicam	Mobec	S/NM
1996	olanzapine	Zyprexa	S/NM
1996	talipexole	Domin	S/NM
1996	tandospirone	Sediel	S/NM
1996	valsartan	Diovan	S/NM
1996	zafirlukast	Accolate	S/NM
1997	budipine	Parkinsan	S/NM
1997	candesartan cilexetil	Atacand	S/NM
1997	dexfenfluramine	Redux	S/NM
1997	donepezil HCl	Aricept	S/NM

1997	eprosartan	Teveten	S/NM
1997	irbesartan	Avapro	S/NM
1997	milnacipran	Ixel	S/NM
1997	nebivolol	Nebilet	S/NM
1997	pramipexole HCl	Mirapex	S/NM
1997	quetiapine fumarate	Seroquel	S/NM
1997	reboxetine	Edronax	S/NM
1997	rivastigmin	Exelon	S/NM
1997	tolterodine	Detrusitol	S/NM
1997	troglitazone	Rezulin	S/NM
1997	zileuton	Zyflo	S/NM
1998	brinzolamide	Azopt	S/NM
1998	clopidogrel hydrogensulfate	Plavix	S/NM
1998	fenoldopam mesylate	Corlopam	S/NM
1998	fomepizole	Antizol	S/NM
1998	lefunomide	Arava	S/NM
1998	montelukast sodium	Singulair	S/NM
1998	mosapride citrate	Gasmotin	S/NM
1998	raloxifene HCl	Evista	S/NM
1998	sibutramine	Meridia	S/NM
1998	tirofiban HCl	Aggrastat	S/NM
1999	celecoxib	Celebrex	S/NM
1999	naftopidil	Flivas	S/NM
1999	rofecoxib	Vioxx	S/NM
1999	rosiglitazone maleate	Avandia	S/NM
1999	telmisartan	Micardis	S/NM
2000	dexmedetomidine HCl	Precedex	S/NM
2000	levosimendan	Simdax	S/NM
2000	liranaftate	Zefnart	S/NM
2001	bosentan	Tra-cleer	S/NM
2001	imatinib mesilate	Gleevec	S/NM
2002	aripiprazole	Abilify	S/NM
2002	etoricoxib	Arcoxia	S/NM
2002	gefitinib	Iressa	S/NM
2002	olmesartan medoxil	Benicar	S/NM
2002	parecoxib sodium	Dynastat	S/NM
2002	sivelestat sodium hydrate	Elaspol	S/NM
2002	temoporfin	Foscan	S/NM
2002	valdecoxib	Bextra	S/NM
2003	aprepitant	Emend	S/NM
2003	bortezomib	Velcade	S/NM
2004	duloxetine hydrochloride	Cymbalta	S/NM
2004	erlotinib hydrochloride	Tarceva	S/NM
2005	darifenacin hydrobromide	Emselex	S/NM
2005	lumiracoxib	Prexige	S/NM

2005	ramelteon	Rozerem	S/NM
2006	conivaptan HCl	Vaprisol	S/NM
2006	darunavir	Prezista	S/NM
2006	dasatinib	Sprycel	S/NM
2006	mozavaptan	Physuline	S/NM
2006	rimonabant	Acomplia	S/NM
2006	rotigotine	Neupro	S/NM
2006	sitagliptin	Januvia	S/NM
2006	sitaxsentan sodium	Thelin	S/NM
2006	sunitinib malate	Sutent	S/NM
2006	varenicline tartrate	Chantix	S/NM
2007	ambrisentan	Letairis	S/NM
2007	lapatinib ditosylate	Tykerb	S/NM
2007	nilotinib hydrochloride	Tasigna	S/NM
2007	paliperidone	Invega	S/NM
2007	vildagliptin	Galvus	S/NM
2008	blonanserin	Lonasen	S/NM
2008	desvenlafaxine succinate	Pristiq	S/NM
2008	fesoterodine fumarate	Toviaz	S/NM
2008	fosaprepitant dimeglumine	Ivemend	S/NM
2009	asenapine maleate	Saphris	S/NM
2009	dapoxetine HCl	Priligy	S/NM
2009	febuxostat	Adenuric	S/NM
2009	lasofoxifene tartrate	Fablyn	S/NM
2009	niacin/laropiprant	Tredaptive	S/NM
2009	pazopanib	Votrient	S/NM
2009	prasugrel	Efient	S/NM
2009	saxagliptin	Onglyza	S/NM
2009	tapentadol HCL	Nucynta	S/NM
2009	tolvaptan	Samsca	S/NM
2010	alogliptin benzoate	Nesina	S/NM
2010	bazedoxifene acetate	Conbriza	S/NM
2010	iloperidone	Fanapt	S/NM
2010	peramivir	PeramiFlu	S/NM
2010	prucalopride	Resolor	S/NM
2010	roflumilast	Daxas	S/NM

III. CALCULATION OF STRUCTURAL AND PHYSICOCHEMICAL PARAMETERS

A. CALCULATION OF PARAMETERS USING INSTANTJCHEM

Physicochemical parameters for approved small-molecule drugs were calculated using the InstantJChem platform for cheminfomatic analysis developed by ChemAxon.[1] Our procedure for the calculation of physicochemical descriptors using InstantJChem has been reported in detail previously.[2] The protocol for this analysis is as follows:

1) SMILES codes for drugs were saved as a tab delimited text (.txt) file in MS Excel with two columns: Column A contained compound names and Column B contained the SMILES codes. A header row was not included.

2) SMILES codes were imported into InstantJChem.

> a) Clicked "**File**" > "**New Project**" > "**Next**."
>
> b) Specified name and location for the project folder, then clicked "**Finish**."
>
> c) Clicked "**File**" > "**Import File**" > "**Next**."
>
> d) Clicked on the folder icon next to the "**File to Import**" field and located the file containing the SMILES codes. Under "**File Format**" chose "**Delineated text files (*.csv, *.tab, *.txt)**." InstantJChem scanned the file and indicated the number of fields found. Once the file was scanned, clicked "**Next**."
>
> e) The "**Field Details**" panel gave a summary of the fields to be imported from the text file. The structure, molecular weight, molecular formula, and compound name of each entry were displayed by default. Undesired term fields were removed using the "**< Remove**" button. When finished, clicked "**Next**."
>
> f) The "**Monitor Import**" window gave a summary of the imported data. Once fully processed, clicked "**Finish**.

3) New chemical terms were added by clicking "**Data**" > "**New Chemical Terms Field**." Some chemical terms were manually defined in the expression window. User-defined chemical terms can be saved to the "Expression" menu by clicking on the yellow star to the right of the menu.

> Molecular weight (MW): mass()
>
> N atom count (N): atomCount("7")
>
> O atom count (O): atomCount("8")
>
> H-bond donor count (HBD): donorCount()
>
> H-bond acceptor (HBA): acceptorCount()
>
> Rotatable bond count (Rot): rotatableBondCount()
>
> Stereocenter count (nStereo): chiralCenterCount()
>
> Topological polar surface area (tPSA): PSA()
>
> Number of rings (Rings): ringCount()
>
> Aromatic ring count (RngAr): aromaticRingCount()
>
> Ring system count (RngSys): ringSystemCount()
>
> Size of largest ring (RngLg): largestRingSize()

Fraction of sp3-hybridized carbons (Fsp3): count(filter('atno()==6 && connections()==4'))/atomCount("6")

n-Octanol/water partition coefficient at pH=7.4 (LogD): logd('7.4')

van der Waals surface area (VWSA): vanDerWaalsSurfaceArea()

Relative polar surface area (relPSA): PSA()/vanDerWaals SurfaceArea()

4)   Once all desired chemical terms were added to the grid, used "**File**" > "**Export to File**" to export the data as an Excel file (.xls).

5)   Once the export process completed, clicked "**Finish.**"

B. BATCH CALCULATION OF ALOGPS / ALOGpS

Calculation of the ALOGPs and ALOGpS parameters was carried out using the Virtual Computational Chemistry (VCC) Laboratory.[3,4] Our procedure for the calculation of ALOGPs and ALOGpS has been reported in detail previously.[2] The protocol for this analysis is as follows:

1)   SMILES codes for drugs were saved as a single-column tab delimited text (.txt) file in MS Excel. Compound names and a header row were not included.

2)   The VCC Lab website was accessed at URL: "http://www.vcclab.org/lab/alogps/start.html"

3)   Clicked "**upload file.**"

4)   Selected "**smiles -- SMILES file – default**" from the dropdown menu and clicked "**Proceed with file uploading**."

5)   A new browser window opened. Followed "**Step 1: Click Browse and select a file**."

6)   Followed "**Step 2: Click Upload File**."

7)   The window displayed "Your file "yourfile.txt" was uploaded as "smiles" successfully. Please, close this page in your browser now."

8)   A new browser window open entitled "results.txt."

9)   Saved the results page as a text (.txt) file.

10)   Opened the text file containing the results using MS Excel. Here, "logP" = "ALOGPs" and "logS" = "ALOGpS." The output for SMILES codes with errors will be shown as "error in..."

IV. PRINCIPAL COMPONENT ANALYSIS

Principal component analysis (PCA) on the physicochemical features of approved drugs was carried out using the "R" open source statistical computing software package.[5] Our procedure for PCA using R has been reported previously for both Mac[2] and Windows[6] operating systems. The current analysis was carried out using R and MS Excel for Mac OSX (10.8.5). The protocol is as follows:

1) In MS Excel, a "Raw" worksheet was created with compounds in rows and descriptors in columns. Drugs were sorted by compound source (*i.e.,* natural product drugs (NP), natural product-derived drugs (ND), natural product-inspired drugs (S*, S*/NM), and completely synthetic drugs (S, S/NM)), and by date of approval (ascending). Note that compound names must not have spaces or other punctuation.

2) Mean values and standard deviation values were calculated for each column.

3) A "Norm" worksheet was created and mean-centered, standardized values were generated for each column using the equation:

$$normval = (val - Column\ Mean)\ /\ Column\ Standard\ Deviation$$

4) With the upper left cell blank (R requires this to recognize a header row), the Number format was designated for all data columns to 4 decimal places.

5) The Excel workbook was saved.

6) The "Norm" worksheet was saved as "Data.txt" (Text–Tab Delimited) on the Desktop (Mac).

7) The Excel workbook was closed and the changes discarded.

8) The "R" open source computing package was opened and the following commands were entered:

9) R> read.table("~/Desktop/Data.txt") -> a   # read data into dataframe a

10) R> prcomp(a) -> b   # PCA of dataframe a, results to b

11) R> summary(b)   # prints summary of %contributions

12) R> b   # prints the rotation (loading) matrix

13) R> b$x   # prints the rotated data (scores)

14) R > b$x - > c   # defines the scores as c

15) R > write.table(c, "~/Desktop/scores.txt", sep = "\t")   # saves scores as tab delimited txt file to the Desktop.

16) The scores were imported into a new Excel worksheet "Scores".

17) The first three columns (compound names, PC1, and PC2) where copied into a new worksheet "PCA", and the Number format was designated to 3 decimal places.

18) To maintain the resemblance of these PCA plots with our previous analyses,[6-11] scores for PC2 were inverted by multiplying each value by (–1); this is feasible because the signs and units of each principal component are arbitrary

19) PCA plots were generated by plotting PC1 and PC2 on XY scatter plots in MS Excel or GraphPad Prism.

20) The loading plot was generated by plotting the loadings for PC1 and PC2 in GraphPad Prism. Loadings on PC2 were inverted by multiplying each value by (–1) to remain consistent with the inversion of scores along PC2.

V. SUPPLEMENTARY REFERENCES

1. ChemAxon – InstantJChem Suite; https://www.chemaxon.com/products/instant-jchem-suite/instant-jchem/

2. Wenderski, T. A.; Stratton, C. F.; Bauer, R. A.; Kopp, F.; and Tan, D. S. *Methods Mol. Biol.* **2015**, *1263*, 225–242.

3. Tetko, I. V., Virtual Computational Chemistry Laboratory; http://www.vcclab.org/lab/alogps/

4. Tetko, I. V.; Tanchuk, V. Y.; Kasheva, T. N.; and Villa, A. E. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 246–252.

5. The R Project for Statistical Computing; http://www.r-project.org/

6. Davis, T. D.; Gerry, C. J.; and Tan, D. S. *ACS Chem. Biol.* **2014**, *9*, 2535–2544.

7. Bauer, R. A.; DiBlasi, C. M.; and Tan, D. S. *Org. Lett.* **2010**, *12*, 2084–2087.

8. Bauer, R. A.; Wenderski, T. A.; and Tan, D. S. *Nat. Chem. Biol.* **2013**, *9*, 21–29.

9. Bauer, R. A.; Wurst, J. M.; and Tan, D. S. *Curr. Opin. Chem. Biol.* **2010**, *14*, 308–314.

10. Kopp, F.; Stratton, C. F.; Akella, L. B.; and Tan, D. S. *Nat. Chem. Biol.* **2012**, *8*, 358–365.

11. Moura-Letts, G.; DiBlasi, H. M.; Bauer, R. A.; and Tan, D. S. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6745–6750.