

Supplementary Information

Natural product and natural product derived drugs in clinical trials

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Table S1 (1 of 3) NP and NP-derived launched since 2000 by year with reference to their lead compound, classification, disease area, developer, first launch company and route of administration. **The blue coloured rows are new human drug classes.**

Drug name	Year Launched	Lead compound	Lead Source	Classification	Disease	Developer	First launch	Administration
arteether	2000	artemisinin	plant	SS NP	antimalarial	Artecef BV	EU	IV
ertapenem	2001	thienamycin	actino	NP derived	antibacterial	Merck	USA	IV
telithromycin	2001	erythromycin	actino	SS NP	antibacterial	Aventis	Germany	oral
pimecrolimus	2001	ascomycin	actino	SS NP	atopic dermatitis	Novartis	USA	topical
casprofungin	2002	pneumocandin B0	fungus	SS NP	antifungal	Merck	USA	IV
galantamine	2002	galantamine	plant	NP	Alzheimer's disease	J&J	EU	oral
micafungin	2002	FR901379	fungus	SS NP	antifungal	Fujisawa	Japan	IV
amrubicin	2002	doxorubicin	actino	NP derived	oncology	Sumitomo	Japan	IV
biapenem	2002	thienamycin	actino	NP derived	antibacterial	Meiji Seika	Japan	IV
nitisinone	2002	leptospermon	plant	NP derived	antityrosinaemia	Rare Diseases Therapeutics	USA	oral
miglustat	2003	1-deoxynojirimycin	plant	SS NP	type 1 Gaucher disease	Actelion	UK	oral
mycophenolate sodium	2003	mycophenolic acid	fungus	NP	immunosuppression	Novatis	Switzerland	oral
rosuvastatin	2003	mevastatin	fungus	NP derived	dyslipidemia	AstraZeneca	EU	oral
pitavastatin	2003	mevastatin	fungus	NP derived	dyslipidemia	Sankyo/ Kowa	Japan	oral
daptomycin	2003	daptomycin	actino	NP	antibacterial	Cubist	USA	IV
everolimus	2004	sirolimus	actino	SS NP	immunosuppression	Novartis	Germany	oral
dronabinol / cannabidiol	2005	dronabinol / cannabidiol	plant	NP / NP	pain	GWPharma	Canada	oral
fumagillin	2005	fumagillin	fungus	NP	antiparasitic	Sanofi-Aventis	EU	oral
doripenem	2005	thienamycin	actino	NP derived	antibacterial	Shionogi	Japan	IV
tigecycline	2005	tetracycline	actino	SS NP	antibacterial	Wyeth	USA	IV
ziconotide	2005	ziconotide	cone shell	NP	pain	Elan	USA	IV
zotarolimus	2005	sirolimus	actino	SS NP	cardiovascular surgery	Medtronic	EU	stent
anidulafungin	2006	echinocandin B	fungus	SS NP	antifungal	Pfizer	USA	IV
exenatide	2006	exenatide-4	lizard	NP	diabetes	Lilly/ Amylin	USA	IV
varenicline	2006	cytisine	plant	NP derived	nicotine dependence	Pfizer	USA	oral

Table S1 (2 of 3) NP and NP-derived launched since 2000 by year with reference to their lead compound, classification, disease area, developer, first launch company and route of administration. **The blue coloured rows are new human drug classes.**

Drug name	Year Launched	Lead compound	Lead Source	Classification	Disease	Developer	First launch	Administration
lisdexamfetamine	2007	amphetamine	plant	NP derived	ADHD	Shire	USA	oral
retapamulin	2007	pleuromutilin	fungus	SS NP	antibacterial (topical)	GSK	USA	topical
temsirolimus	2007	sirolimus	actino	SS NP	oncology	Wyeth	USA	IV
trabectedin	2007	trabectedin	ascidian	NP	oncology	Pharmamar	EU	IV
ixabepilone	2007	epothilone B	myxobacteria	SS NP	oncology	BMS	USA	IV
ceftobiprole medocaril	2008	cephalosporin	fungus	SS NP	antibacterial	J&J / Basilea	Canada	IV
methylnaltrexone	2008	morphine	plant	NP derived	opioid-induced constipation	Wyeth / Progenics	Canada	IV
umirolium	2008	sirolimus	actino	SS NP	anti-restenotic	Biosensors	EU	stent
tebipenem pivoxil	2009	thienamycin	actino	SS NP	antibacterial	Meiji Seika	Japan	oral
telavancin	2009	vancomycin	actino	SS NP	antibacterial	Theravance	USA	IV
romidepsin	2009	romidepsin	eubacteria	NP	Cancer	Celgene	USA	IV
vinflunine	2009	vinblastine	plant	SS NP	cancer	Pierre Fabre	EU	IV
nalfurafine	2009	morphine	plant	SS NP	pruritus	Toray Industries	Japan	oral
cabazitaxel	2010	paclitaxel	plant	SS NP	cancer	Sanofi-Aventis	US	IV
fingolimod	2010	myriocin	fungus	NP-derived	multiple sclerosis	Novartis	US	oral
ceftaroline fosamil	2010	cephalosporin	fungus	SS NP	antibacterial	Forest	US	IV
eribulin	2010	halichondrin B	sponge	NP-derived	cancer	Eisai	US	IV
mifamurtide	2010	mifamurtide	bacteria	NP-derived	oncology	Takeda	EU	IV
zucapsaicin	2010	capsaicin	plant	NP-derived	pain	Winston	Canada	topical
fidaxomicin	2011	tiacumicin	actino	NP	antibacterial	Optimer	USA	topical (oral)
spinosad	2011	spinosyn A : D 5:1	actino	NP	head lice	ParaPRO	USA	topical
brentuximab vedotin	2011	dolastatin 10	cyanobacteria	ADC	oncology	Seattle Genetics	USA	IV

Table S1 (3 of 3) NP and NP-derived launched since 2000 by year with reference to their lead compound, classification, disease area, developer, first launch company and route of administration. **The blue coloured rows are new human drug classes.**

Drug name	Year Launched	Lead compound	Lead Source	Classification	Disease	Developer	First launch	Adminis- tration
ingenol mebutate	2012	ingenol mebutate	plant	NP	actinic keratose	Leo Pharma	USA	topical
dapagliflozin	2012	phlorizin	plant	NP-derived	type II diabetes	BMS/AstraZeneca	EU	oral
omacetaxine mepesuccinate	2012	omacetaxine mepesuccinate	plant	NP	oncology	Teva	USA	IV, infusion
carfilzomib	2012	epoxomicin	actino	SS NP	oncology	Onyx	USA	IV
arterolane / piperazine	2012	artemisinin	plant	NP-derived	antiparasitic	Ranbaxy	India	oral
novolimus	2013	sirolimus	actino	NP	cardiovascular surgery	Elixir Medical Corporation	EU	stent
canagliflozin	2013	phlorizin	plant	NP-derived	type II diabetes	Janssen Pharmaceuticals	USA	oral
ado-trastuzumab emtansine	2013	maytansine	plant	ADC	oncology	Roche/Genentech	USA	IV

Table S2 Halted or Discontinued NP-derived Compounds from Infectious Diseases Clinical Trials from 2008 to 2013.

Disease area Name (synonym) [classification]	Lead compound (source)	Mode of Action	Company (Comment)
Antibacterial			
friulimicin [NP]	friulimicin (actino)	cell wall synthesis (Lipid II)	MerLion (Discontinued drugs in 2008 anti-infectives EOID 1 10)
CBR-2092 [NP-derived]	rifampicin (actino) / “quinolone” hybrid	RNA polymerase inhibition and TopoIV/Gyrase	Cumbre
TD 1414 (zibrofusidic acid) [NP-derived]	fusidic acid (fungi)	protein synthesis (elongation factor G)	Leo Pharma
NXL-103 (XRP2868) mixture: flopristin / linopristin [NP-derived]	streptogramin type A and B (actino)	protein synthesis (23S rRNA)	Sanofi-Aventis
razupenem (PZ-601) [NP-derived]	thienamycin (actino)	cell wall synthesis (PBP)	Novartis / Protez Pharmaceuticals
PF-3709270 (sulopenem prodrug) [NP-derived]	thienamycin (actino)	cell wall synthesis (PBP)	Pfizer
sulopenem (CP 65,207) [NP-derived]	thienamycin (actino)	cell wall synthesis (PBP)	Pfizer
tomopenem (CS-023) [NP-derived]	thienamycin (actino)	cell wall synthesis (PBP)	Daiichi Sankyo (Discontinued drugs in 2008 anti-infectives EOID 1 10)
faropenem daloxate [NP-derived]	carbapenem (actino)	cell wall synthesis (PBP)	Replidyne
cethromycin [NP-derived]	erythromycin (actino)	protein synthesis (70s rRNA)	Advanced Life Sciences
BAL-19403 [SS-NP]	erythromycin (actino)	protein synthesis (70s rRNA)	Basilea
PF-04287881	ketolide (actino)	protein synthesis	Pfizer, phase I (Discontinued drugs in 2010 rheumatology, allergy and dermatology, pulmonary EOID 1175 11)

CB-182,804 [SS-NP]	polymyxin (bacteria)	membrane	Cubist
omiganan [NP-derived]	indolicidin (bovine)	cytoplasmic membrane interaction	MIGENIX
Antifungal			
aminocandin [SS-NP]	echinocandin (fungi)	1,3- β -D-glucan synthesis	Indevus Pharmaceuticals
SPK-843 [SS-NP]	polyene (bacteria)	membrane	Kaken / Aparts
Antiparasitic			
artemisono [SS-NP] / mefloquine	artemisinin (plant)	under argument; malaria	MMV, Bayer, University of Hong Kong
Antiviral			
bevrimat (MPC-4326, PA-457) [SS-NP]	betulinic acid (plant)	Gag processing inhibition; HIV	Myriad Genetics
taribavirin (viramidine, ribamidine) [NP-derived]	pyrazomycin (actino)	viral RNA replication, interaction of ribavirin 5'-triphosphate with the viral polymerase, and IMPDH inhibition; HSV	Valeant

Table S3 Halted or Discontinued NP-derived Compounds from Neurological Disease Clinical Trials from 2008 to 2013.

Name (synonym) [classification]	Lead compound (source)	Mode of Action	Comment
M6G (morphine 6-glucuronide) [SS NP; metabolite]	morphine (plant)	opioid receptor; pain	Paion / CeNes
mimopezil (Debio-9902, ZT-1) [SS NP]	huperzine (plant)	AChE inhibitor; Alzheimer's disease	Debio
XEN-2174 [NP derived]	χ -M ₁ IA (cone shell)	norepinephrine transporter (NET) inhibitor; pain	Xenome
ALKS 37 (RDC 1036) [unknown]	<i>morphine (plant) ??</i>	opioid receptor; opioid induced constipation	Alkermes, (Discontinued drugs in 2012 endocrine and metabolic EOID 1305 13)
ILS-920 [NP]	sirolimus (actino)	mTOR; Acute Ischemic Stroke	Wyeth
leconotide (CNSB004, AM-336) [NP]	ω -Conotoxin CVI (cone shell)	blocks voltage sensitive calcium channels; pain	Relevare

Table S4 Halted or Discontinued NP-derived Compounds from Cardiovascular and Metabolic Diseases Clinical Trials from 2008 to 2013.

Name (synonym) [classification]	Lead compound (source)	Mode of Action	Comment
eritoran (E5564) [NP-derived]	lipid A (bacteria)	TLR 4 antagonist; sepsis	Eisai
lancovutide (Moli1901, duramycin) [NP] ¹⁰³	lancovutide (actino)	chloride channel modulation, Cystic Fibrosis	AOP Orphan Pharmaceuticals AG and Lantibio; Completed phase II (NCT00671736) in Oct2009 but no update since
sergliflozin etabonate (GW869682, KGT-1251)	phlorizin (plant)	SGLT2; Type 2 Diabetes, obesity	GlaxoSmithKline (Discontinued drugs in 2008 endocrine EOID 1243 09)
T-1095 [NP derived]	phlorizin (plant)	SGLT2	Tanabe Pharma Corp.
TS-033 [NP derived]	phlorizin (plant)	SGLT2	Taisho (Discontinued drugs in 2008 endocrine EOID 1243 09)
AVE 2268 [NP derived]	phlorizin (plant)	SGLT2	Sanofi-Aventis (Discontinued drugs in 2008 endocrine EOID 1243 09)
BI 44847 [NP derived]	phlorizin (plant)	SGLT2	Boehringer Ingelheim
NCX-4016 [NP derived]	salicylic acid (plant)	nitric oxide (NO) and aspirin	Nicox (Discontinued drugs in 2008 endocrine EOID 1243 09)
isofagomine (AT2101)	sugar (various)	β -glucocerebrosidase stabilisation; Gaucher Disease	Amicus
ilepatril (AVE-7688, MDL-107688) [NP derived]		neutral endopeptidase and angiotensin converting enzyme (ACE)	Sanofi-Aventis (Discontinued drugs in 2008 cardiovascular EOID 875 09)
mitemcinal fumarate (GM-611) [SS NP]	erythromycin (actino)	motilin agonist	Chugai Pharma
PF-04548043 (KOS-2187) [NP ?]	<i>erythromycin (actino) ??</i>	motilin agonist	Pfizer / Kosan

Name (synonym) [classification]	Lead compound (source)	Mode of Action	Comment
MC-1 [SS NP]	vitamin B6 (plant)	P2X receptor antagonist	Medicure
ruboxistaurin (Arxxant™) (LY333531) [NP-derived]	staurosporine (action)	protein kinase C β	Lilly (Discontinued drugs in 2012 endocrine and metabolic EOID 1305 13)
PPD10558 [NP derived]	mevastatin (fungus)	HMG CoA	Furiex (Discontinued drugs in 2011 cardiovascular EOID 1449 12)
trodusquemine (MSI-1436) [NP]	trodusquemine (shark)	appetite suppression	MedImmune

Table S5 Halted or Discontinued NP-derived Compounds from Immunological, Inflammatory and Related Diseases Clinical Trials from 2008 to 2013.

Name (synonym) [classification]	Lead compound (source)	Mode of Action	Comment
TAFA-93 [NP-derived]	sirolimus (actino)	mTOR inhibitor	Isotechnika
E6201 [SS NP]	radicicol (LL-Z1640-2) (fungus)	MEK Kinase-1 inhibition; psoriasis and cancer	Eisai

Table S6 Halted or Discontinued NP-derived Compounds from Oncology Clinical Trials from 2008 to 2013.

Name (synonym)	Lead compound	Mode of action	Comments
Plant			
saridegib (IPI-926) [SS NP]	cyclopamine (plant)	Hedgehog signalling pathway.	Infinity (Discontinued drugs in 2012 oncology drugs EOID 1627 13)
phenoxodiol [NP-derived]	daidzein (plant)	protein-tyrosine kinase inhibitor, antioxidant	Marshall Edwards (Novogen)
triphendiol (NV-196, phenoxodiol analogue) [NP-derived]	daidzein (plant)	protein-tyrosine kinase inhibitor, antioxidant	Marshall Edwards (Novogen)
terameprocol (EM-1421, tetra-O-methyl nordihydroguaiaretic acid) [NP]	3'-O-methyl nordihydroguaiaretic acid (plant)	transcription inhibitor	Erimos (John Hopkins)
tenifatecan (SN2310)	camptothecin (plant) / tocopherol (vitamin E)	topoisomerase I	OncoGenex Pharmaceuticals, Inc. (Sonus) Phase I (Discontinued drugs in 2011 oncology EOID 9 13)
TP-300 [NP-derived]	camptothecin (plant)	topoisomerase I	Chugai
DRF 1042 [NP-derived]	camptothecin (plant)	topoisomerase I	Dr Reddy/ClinTec International
diflomotecan (BN80915) [NP-derived]	camptothecin (plant)	topoisomerase I	Ipsen phase 2 (NCT00080015) finish Jul 2009 and not in pipeline
BN80927 (elomotecan) [NP-derived]	camptothecin (plant)	topoisomerase I	Ipsen phase I (NCT01435096) finish Sep 2011 and not in pipeline
AR-67 (DB-67) [NP-derived]	camptothecin	topoisomerase I	Arno Therapeutics phase II (completed); Discontinued drugs in 2012 oncology drugs EOID 1627 13
ombrabulin (AVE-8062, AC-7700) [NP-derived]	combretastatin A-4 (plant)	tubulin binding	Sanofi Aventis

Name (synonym)	Lead compound	Mode of action	Comments
tafluposide [SS NP ?]	epipodophyllotoxin (plant)	topoisomerase II	Pierre Fabre
larotaxel (XRP-9881, RPR-109881A) [SS NP]	paclitaxel (plant)	tubulin stabilisation	Sanofi-Aventis
tesetaxel (DJ-927) [SS NP]	paclitaxel (plant)	tubulin stabilisation	Genta (Daiichi Sankyo)
BMS-188797 [SS NP]	paclitaxel (plant)	tubulin stabilisation	BMS
DHA-paclitaxel (Taxoprexin®) [SS NP]	paclitaxel (plant)	tubulin stabilisation	
milataxel (MAC-321) [SS NP]	paclitaxel (plant)	tubulin stabilisation	Wyeth; completed Phase II but update since 2009
LC-1 (DMAPT) [SS NP]	parthenolide (plant)	NF-κB suppression	
CB3304 (noscapine) [NP]	noscapine (plant)	tubulin binding	Cougar Biotechnology
bardoxolone methyl (RTA 402; CDDO-Me) [SS NP]	oleanolic acid (plant)	NF-κB, STAT3 and STAT5 inhibition	Reata (Discontinued drugs in 2010 oncology drugs EOID 1479 11)
betulinic acid [NP]	betulinic acid (plant)	transcription factor specificity protein 1 (Sp1), Sp3, and Sp4 activation	Advanced Life Sciences (Discontinued drugs in 2011 oncology EOID 9 13)
ASA404 (DMXAA, ASA1404) [NP-derived]	flavone-8-acetic acid (plant)	vascular targeting and angiogenesis inhibition	Antisoma (Discontinued drugs in 2010 oncology drugs EOID 1479 11)
β-lapachone (ARQ-501) [NP]	β-lapachone (plant)	E2F1 pathway activator	ArQule
Bacteria/Actinomycetes			
obatoclax (GX15-070) [NP-derived]	streptorubin B (prodigiosin) (bacteria)	Bcl-2 inhibition	pan Bcl-2 antagonism phase II (IV) Teva (Cephalon, Gemin X); discontinued drugs in 2012 oncology drugs EOID 1627 13; Teva website ““People get old. That's nature””
E7107 [SS NP]	pladienolide (actino)	splicing factor SF3b inhibition	Eisai; phase I trial halted

Name (synonym)	Lead compound	Mode of action	Comments
ECO-4601 (TLN-4601, diazepinomicin) [NP]	ECO-4601 (actino)	MAPK pathway inhibitor and inhibition of the peripheral benzodiazepine receptor	Thallion (Ecopia)
KRX-0601 (UCN-01, KW-2401)	UCN-01 (actino)	CDK1 inhibition	Keryx (Kyowa Hakko/NCI)
tanespimycin (17-AAG, KOS-953, NSC-330507)BMS-188797	geldanamycin (actino)	HSP90 inhibitor	BMS (Kosan)
alvespimycin (17-DMAG, BMS-826476, KOS-1022, NSC-707545)	geldanamycin (actino)	HSP90 inhibitor	BMS (Kosan)
retaspimycin (IPI-504, 17-AAG hydroquinone salt)	geldanamycin (actino)	HSP90 inhibitor	Infinity
berubicin (RTA744, WP744)	doxorubicin (actino)	topoisomerase II inhibition	Reata
L-annamycin	doxorubicin (actino)	topoisomerase II inhibition	Callisto
FCE-28068 (doxorubicin-HPMA complex)	doxorubicin (actino)	topoisomerase II inhibition	Pharmacia Upjohn, Phase II (Discontinued drugs in 2008 oncology EOID 1581 09)
FCE-28069 (doxorubicin-HPMA complex)	doxorubicin (actino)	topoisomerase II inhibition	Pharmacia Upjohn, Phase II (Discontinued drugs in 2008 oncology EOID 1581 09)
elsamitrucin (SPI 28090, elsamicin A) [NP]	elsamicin (actino)	topoisomerase I and II inhibition	Spectrum
ridaforolimus (deforolimus, MK-8669, AP-23573) [SS NP]	sirolimus (actino)	mTOR	Merck
patupilone (epothilone B, EPO-906) [NP]	epothilone (myxo)	tubulin stabilisation	Novartis

Name (synonym)	Lead compound	Mode of action	Comments
sagopilone (BAY86-5302, ZK-EPO, epothilone (myxo ZK-219477) [NP-derived]	epothilone (myxo)	tubulin stabilisation	Schering AG
9,10-didehydroepothilone D (KOS-1584) [NP]	epothilone D (myxo)	tubulin stabilisation	Kosan (Memorial Sloan-Kettering)
epofolate (BMS-753493) [SS NP]	epothilone (myxo)	tubulin stabilisation	BMS
Fungi			
irofulven (E7850, MGI-114, HMAF) [NP-derived]	illudin S (fungi)	DNA synthesis inhibition	Eisai; Discontinued drugs in 2012 oncology drugs EOID 1627 13; Discontinued drugs in 2012 pulmonary EOID 1453 13
plinabulin (NPI-2358) [NP-derived]	halimide, phenylahistin (fungi)	tubulin binding	Nereus
Marine			
E7974 [NP-derived]	hemiasterlin (sponge)	tubulin assembly inhibition	Eisai
elisidepsin (Irvalec®, PM02734) [NP-derived ?]	kahalalide F (mollusc/green algae)	alters lysosomal membrane function	PharmaMar; Discontinued drugs in 2012 oncology drugs EOID 1627 13; Discontinued drugs in 2012 pulmonary EOID 1453 13
tasidotin (synthadotin, ILX-651) [NP-derived]	dolastatin 15 (cyanobacteria)	tubulin assembly inhibition	Genzyme
soblidotin (YHI-501, TZT-1027, auristatin PE) [NP-derived]	dolatstain 10 (cyanobacteria)	tubulin assembly inhibition	Yakult Honsha (ASKA Pharmaceutical)

Table S7 Halted or Discontinued ADCs from Oncology Clinical Trials from 2008 to 2013.

Name (synonym)	Lead compound (source)	Mode of Action	Comment
vorsetuzumab mafodotin (SGN75) [MMAF / CD70]	dolastatin 10 (sea hare/ cyanobacteria)	tubulin assembly inhibition	Seattle Genetics
MDX-1203 [RCC CD70]	duocarmycin (actino)	DNA minor groove binding alkylating agents	Bristol-Myers Squibb
BIIB015 DM4	maytansine (plant/bacteria)	tubulin assembly inhibition	
BAY79-4620 [MMAF]	dolastatin 10 (sea hare/ cyanobacteria)	tubulin assembly inhibition	Bayer