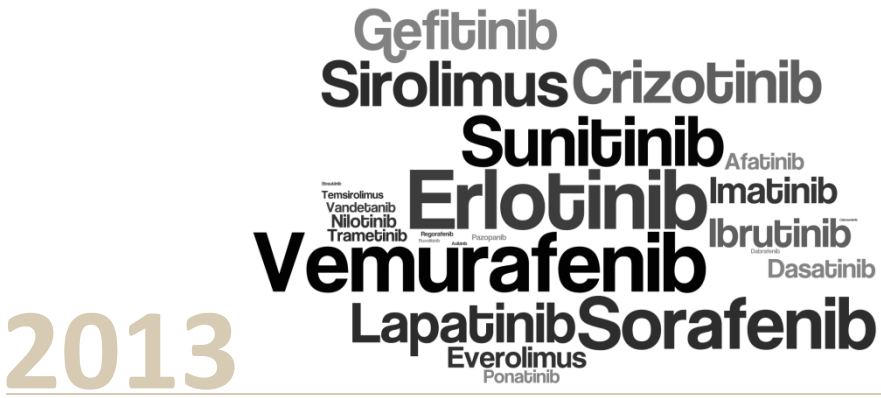
A 10-year summary of kinase small molecule research

Text mining AACR abstracts (white paper)



Approved Kinase Inhibitors

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A 10-year summary of kinase small molecule research; Text mining AACR abstracts

Introduction: Small molecule Protein Kinase Inhibitor (PKI) drug development has been successful with 14 FDA approvals since 2011 including crizotinib, ruxolitinib, vandetanib, vemurafenib approved in 2011, axitinib, bosutinib, cabozantinib, ponatinib, regorafenib, tofacitinib approved in 2012 and afatinib, dabrafenib, trametinib, ibrutinib approved to date in 2013. Here we used text mining to summarize a decade of PKI research using AACR abstracts covering the period of 2004-2013.

Method: Text mining has been performed on 57,000 AACR abstracts covering 10-years (2004 – 2013) using Hermetic Word Frequency Counter software (version 14.912). The frequency of occurrence, of hits, of approved drugs (DrugBank 3.0) and PKIs was determined using drug names, their synonyms and PubMed MESH terms. The PKIs were used, which are represented in the databases of the Computational Chemical Biology Group and Kinase SARfari of the European BioInformatics Institute, SelleckChem and the International Center for Kinase Profiling at the MRC Protein Phosphorylation Unit at Dundee Kinase Inhibitor.

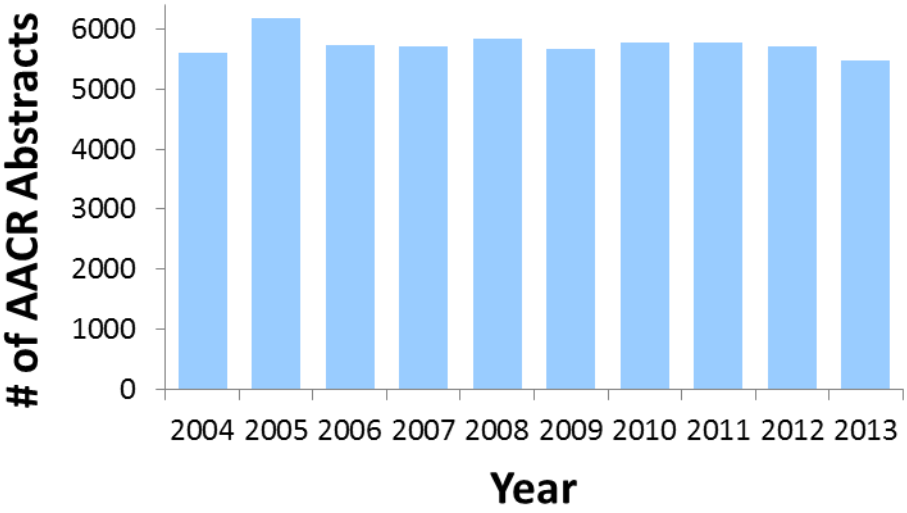
Results: Of the 1691 DrugBank drugs, 310 ± 10 drugs have been described in the abstracts each year. The top-4 most described drugs are cisplatin, paclitaxel, gemcitabine and doxorubicin. The highest ranked PKI is gefitinib at rank five. The frequency of DrugBank drugs described in the abstracts has remained stable over the last decade.

More than 90 companies and institutes provided abstracts on more than 300 PKIs with 30 companies and institutes covering more than 1 PKI. The top-4 companies being Pfizer, Novartis, AstraZeneca and GlaxoSmithKline cover 94 compounds and 50% of all PKI hits. In contrast to DrugBank drugs hits which have remained stable in the last decade, the number of PKIs has increased by 300% and the number of PKI hits by 200% in 2013 compared to 2004. Although these 300 PKIs address up to 69 kinase targets, the top-4, EGFR, HER, PDGFR and VEGFR already represent more than 50% of all targeted kinases. We see that ALK and BRAF have entered into the top-10 of most addressed targets. Details on all PKI's associated companies and kinase targets of 10-year of cancer research will be presented.

Conclusion In summary we describe a steady growth in the number of PKIs as well as companies involved in kinase small molecule research. With the advent of combination therapy and in view of the rich PKI pipeline we may expect more approvals in the years to come.

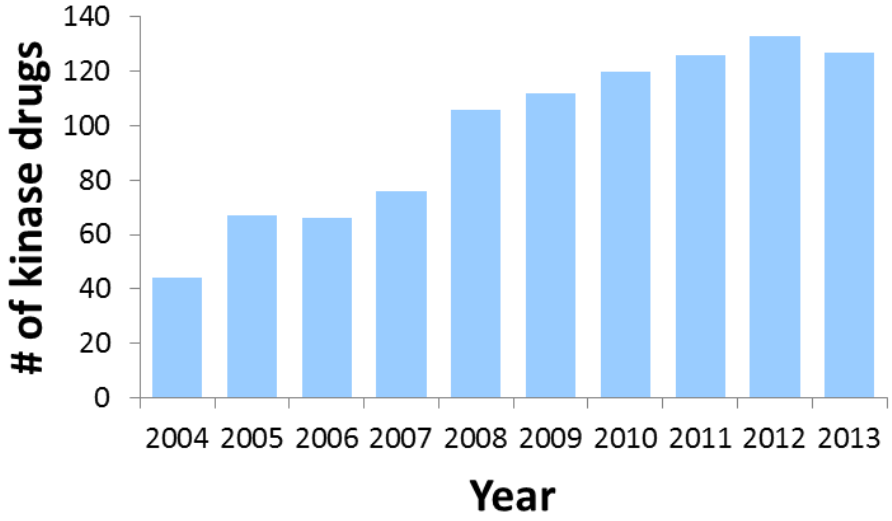
AACR abstracts over period of 2004-2013.

Outline: The number of AACR abstracts is constant over the period of 2004 – 2013 with about 5,750 ± 185 published abstracts each year.



Small molecule protein kinase inhibitors described in AACR abstracts.

Outline: However, the number of kinase small molecule inhibitor drugs described each year has tripled from 40 to 120. In total 266 small molecule kinase inhibitors have been described in the period 2004-2013.



FDA approved protein kinase inhibitors described in AACR abstracts.

Outline:

The number of FDA approved PKI small molecule drugs are ranked from 1 to 26 in the table below. The ranking is based on the average frequency of the term described in the AACR abstracts. These frequencies are expressed as a percentage of the maximum frequency observed. The small graphs show the frequency covering the period from 2004-2013. The arrow indicates the growth trend over the period of 2004-2013.

In 2013, vemurafenib and erlotinib shared the first place of most studied small molecule kinase inhibitors.

No	Kinase	FDA Approval	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Graph	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
1	Sirolimus	1999	24%	38%	55%	60%	93%	75%	59%	48%	43%	41%		4	4	3	2	1	1	1	2	2	5
2	Gefitinib	2003	89%	100%	79%	61%	57%	55%	49%	41%	29%	36%		1	1	1	1	3	4	3	5	6	7
3	Imatinib	2003	57%	63%	47%	47%	42%	51%	27%	19%	28%	24%		2	2	4	3	4	5	8	10	7	10
4	Erlotinib	2004	30%	39%	56%	43%	58%	64%	45%	46%	41%	54%		3	3	2	4	2	2	5	4	3	1
5	Sorafenib	2005		1%	11%	25%	37%	58%	51%	56%	59%	47%			14	8	8	7	3	2	1	1	3
6	Dasatinib	2006	9%	8%	16%	38%	26%	27%	25%	12%	22%	17%		8	9	5	5	10	8	9	11	10	12
7	Sunitinib	2006	0%	3%	9%	26%	40%	33%	46%	32%	37%	45%		11	12	9	7	5	7	4	6	5	4
8	Lapatinib	2007	11%	5%	5%	11%	27%	35%	32%	47%	38%	36%		7	10	11	11	9	6	7	3	4	8
9	Nilotinib	2007		10%	5%	17%	14%	8%	18%	2%	8%	12%			7	12	10	12	12	10	21	15	15
10	Temsirolimus	2007	18%	12%	12%	8%	19%	21%	12%	11%	11%	7%		5	6	7	12	11	11	12	12	12	18
11	Everolimus	2009	6%	10%	13%	22%	28%	23%	15%	24%	23%	19%		9	8	6	9	8	9	11	7	9	11
12	Pazopanib	2009			1%			3%	2%	8%	5%	5%				14			15	15	15	19	19
13	Crizotinib	2011					0%	2%	1%	10%	18%	39%						17	16	21	13	11	6
14	Ruxolitinib	2011									1%	3%										25	22
15	Vandetanib	2011	16%	14%	7%	28%	40%	21%	37%	21%	11%	9%		6	5	10	6	6	10	6	8	13	17
16	Vemurafenib	2011			1%	1%	2%	2%	2%	19%	26%	54%				15	15	14	17	17	9	8	1
17	Axitinib	2012		3%	2%	3%	2%	5%	4%	3%	8%	3%			11	13	14	14	13	13	18	17	23
18	Bosutinib	2012	1%	1%	1%	5%	1%	2%		0%	1%	3%		10	13	15	13	16	17		23	26	24
19	Cabozantinib	2012							0%		4%	2%								22		21	25
20	Ponatinib	2012						4%	2%	6%	4%	12%							14	17	17	20	14
21	Regorafenib	2012							3%	2%	3%	4%								14	20	22	21
22	Tofacitinib	2012							2%		2%									16		24	
23	Afatinib	2013						1%	1%	6%	8%	15%							20	19	16	14	13
24	Dabrafenib	2013								2%	8%	4%									21	15	20
25	Trametinib	2013								10%	3%	11%									13	23	16
26	Ibrutinib	2013					3%	2%	1%	2%	7%	26%						13	17	19	19	18	9

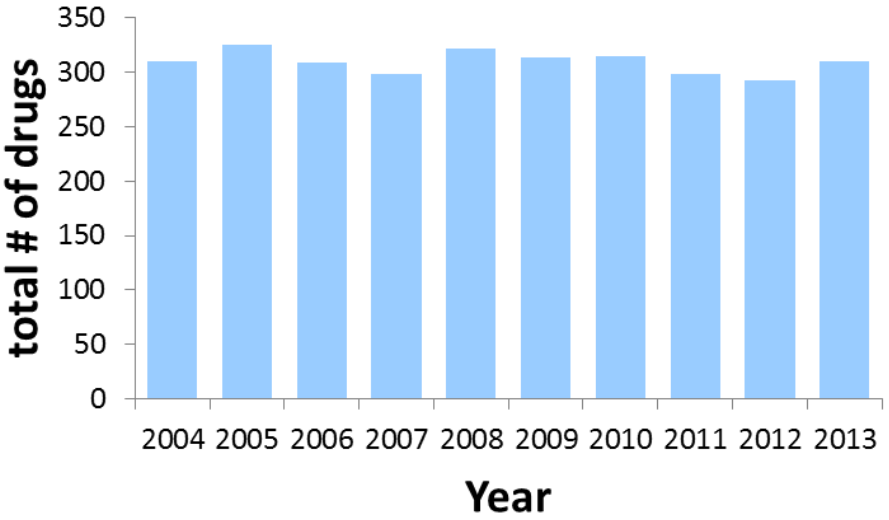
100% 0%

1 26

Drugbank approved drugs described in AACR abstracts.

Outline:

The number of DrugBank registered drugs described in AACR abstracts has remained constant over the years (top). The ranking of the top-15 (bottom) is based on the average frequency (in % of the max). The small graphs show the frequency covering the tested period. The arrow indicates the growth trend over the period of 2004-2013. Over the period of 2004-2013, 646 drugs have been described. The top-4 represent chemotherapeutic drugs. The top targeted small molecule kinase inhibitor is gefitinib on position 5.



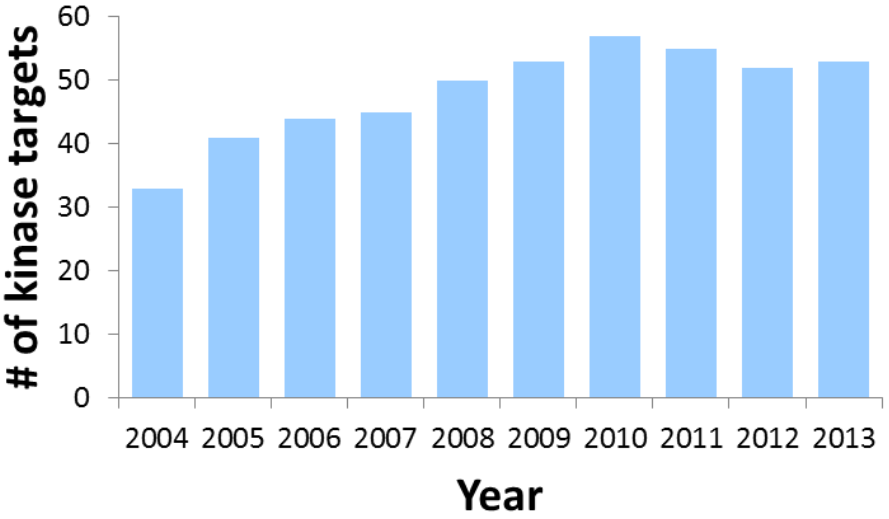
No	Drug	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Graph
1	cisplatin	76%	82%	76%	80%	84%	86%	86%	100%	92%	79%	
2	paclitaxel	70%	82%	64%	62%	78%	60%	61%	49%	51%	55%	
3	gemcitabine	44%	51%	53%	46%	53%	43%	53%	50%	55%	44%	
4	doxorubicin	44%	46%	40%	50%	41%	59%	47%	56%	46%	46%	
5	gefitinib	62%	69%	56%	43%	40%	38%	35%	29%	21%	25%	
6	docetaxel	50%	54%	37%	53%	42%	33%	36%	32%	34%	33%	
7	irinotecan	53%	48%	38%	36%	46%	29%	30%	28%	17%	23%	
8	trastuzumab	27%	26%	28%	38%	34%	43%	35%	39%	38%	35%	
9	erlotinib	21%	27%	40%	30%	41%	45%	32%	32%	29%	38%	
10	bortezomib	36%	32%	30%	36%	43%	39%	37%	33%	31%	17%	
11	tamoxifen	42%	32%	37%	27%	33%	26%	29%	42%	32%	34%	
12	imatinib	35%	41%	33%	33%	30%	36%	19%	13%	20%	17%	
13	sorafenib		0%	8%	17%	26%	41%	36%	40%	41%	33%	
14	cetuximab	7%	23%	21%	30%	26%	25%	30%	24%	19%	30%	
15	celecoxib	41%	48%	32%	20%	20%	17%	14%	5%	9%	8%	

2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
1	1	1	1	1	1	1	1	1	1
2	1	2	2	2	2	2	4	3	2
6	5	4	5	3	6	3	3	2	4
7	8	5	4	7	3	4	2	4	3
3	3	3	6	9	9	9	11	11	11
5	4	9	3	6	11	6	9	7	8
4	6	7	9	4	12	11	12	14	12
12	13	13	7	10	5	8	7	6	6
13	12	6	12	8	4	10	9	10	5
10	11	12	8	5	8	5	8	9	14
8	10	8	13	11	13	13	5	8	7
11	9	10	10	12	10	14	14	12	13
	15	15	15	14	7	7	6	5	9
14	14	14	11	13	14	12	13	13	10
9	7	11	14	15	15	15	15	15	15

Kinase targets described in AACR abstracts.

Outline:

The number of kinase targets being described in AACR abstracts from 2004-2013 has slowly increased from about 30 to 50 kinase targets each year. Out of the potential 518 kinase targets only 69 kinase targets have ever been described in the AACR abstracts over the period 2004-2013. The top-4, EGFR, PDGFR, HER and VEGFR cover more than 50% of all abstracts. In the table (bottom) the targets are ranked based on the 2013 frequency ranking. BRAF and PI3K pathway have recently gained most attention and currently have one or more FDA approved drugs.



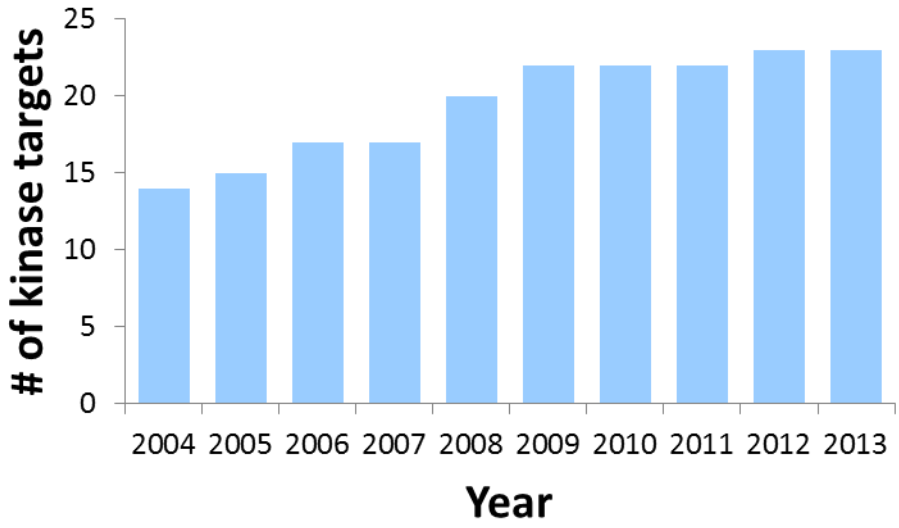
No	Kinase	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Graph
1	EGFR	58%	66%	63%	79%	100%	95%	84%	97%	81%	83%	
2	PDGFR	18%	24%	19%	31%	35%	41%	40%	35%	40%	38%	
3	HER	35%	39%	35%	34%	43%	42%	36%	38%	30%	37%	
4	VEGFR	13%	19%	13%	25%	38%	34%	40%	39%	35%	35%	
5	MEK	14%	9%	10%	12%	14%	15%	13%	19%	14%	24%	
6	PI3K	8%	8%	6%	10%	10%	12%	20%	17%	15%	24%	
7	BRAF			1%	0%	1%	1%	1%	5%	7%	13%	
8	ABL	12%	18%	12%	18%	15%	16%	11%	8%	10%	12%	
9	ALK		1%	0%	0%	1%	2%	1%	4%	5%	11%	
10	FGFR	3%	4%	1%	3%	2%	4%	1%	8%	6%	8%	
11	DDR1	12%	16%	11%	14%	12%	13%	10%	5%	8%	8%	
12	mTor		0%		1%	1%	2%	10%	8%	9%	6%	
13	JAK	0%	1%	1%	2%	1%	1%	3%	2%	3%	6%	
14	Btk					1%	0%	0%	1%	1%	6%	
15	TKI	13%	15%	15%	7%	8%	7%	6%	3%	4%	5%	

2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
1	1	1	1	1	1	1	1	1	1
3	3	3	3	4	3	3	4	2	2
2	2	2	2	2	2	4	3	4	3
6	4	5	4	3	4	2	2	3	4
4	8	8	7	6	6	6	5	6	5
9	9	10	8	10	8	5	6	5	6
		17	22	21	23	22	14	10	7
7	5	6	5	5	5	8	7	7	8
	16	23	23	20	19	24	17	15	9
13	11	19	16	16	15	20	8	11	10
8	6	7	6	8	7	9	15	9	11
	20		20	22	18	9	9	8	12
20	16	19	18	18	21	17	23	19	13
				23	24	26	25	24	13
5	7	4	11	12	10	12	19	16	15

Targets addressed by FDA approved small molecule kinase inhibitors.

Outline:

The number kinase targets inhibited by currently FDA approved small molecule kinase inhibitor drugs has grown from 14 to 23. As outlined on page 7 the total number of targets addressed by kinase inhibitors is 69.



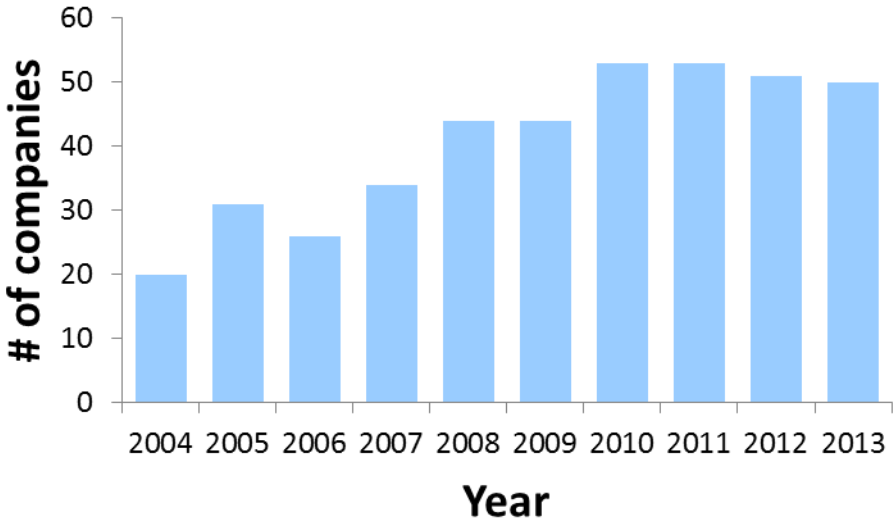
No	Kinase	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Graph
1	KIT	35%	48%	49%	84%	86%	100%	95%	72%	92%	84%	
2	EGFR	79%	85%	80%	77%	98%	95%	89%	87%	69%	81%	
3	PDGFR	31%	43%	40%	64%	73%	85%	81%	66%	80%	75%	
4	HER2	79%	85%	80%	77%	98%	94%	88%	84%	64%	73%	
5	VEGFR	9%	11%	16%	44%	64%	67%	77%	68%	69%	66%	
6	RAF		0%	6%	14%	21%	32%	30%	42%	47%	57%	
7	ABL	36%	45%	37%	58%	44%	50%	39%	21%	34%	37%	
8	mTOR	26%	32%	43%	49%	75%	64%	47%	45%	41%	36%	
9	MEK			1%	0%	1%	1%	1%	16%	16%	35%	
10	BRAF			1%	0%	1%	1%	1%	11%	18%	32%	
11	FLT	0%	2%	5%	14%	22%	20%	26%	21%	22%	31%	
12	Src	5%	5%	9%	23%	16%	17%	14%	8%	16%	25%	
13	MET					0%	1%	1%	5%	12%	22%	
14	ALK					0%	1%	0%	5%	10%	21%	
15	HER4	48%	54%	43%	33%	30%	29%	27%	22%	16%	20%	

2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
5	4	3	1	3	1	1	3	1	1
1	1	1	2	1	2	2	1	3	2
6	6	6	4	5	4	4	5	2	3
1	1	1	2	1	3	3	2	5	4
9	9	9	7	6	5	5	4	3	5
	15	11	15	14	8	8	7	6	6
4	5	7	5	7	7	7	9	8	7
8	8	4	6	4	6	6	6	7	8
		16	16	17	19	16	11	14	9
		16	16	17	19	16	14	11	10
14	14	12	14	10	11	10	10	9	11
13	13	10	10	15	12	15	17	13	12
				19	17	19	18	15	13
				19	17	22	18	17	14
3	3	5	9	8	10	9	8	12	15

Companies involved in small molecule kinase inhibitors research.

Outline:

The number pharmaceutical and biotech companies involved kinase small molecule research has grown from 21 in 2004 to 59 in 2011. In the period of 2004 to 2013 there have been 93 companies active in the field of kinase small molecule research.



No	Kinase	PKIs	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Graph
1	Pfizer	34	47%	51%	59%	72%	100%	91%	86%	71%	81%	91%	
2	AstraZeneca	21	65%	64%	54%	68%	69%	63%	66%	64%	39%	51%	
3	Novartis	23	39%	57%	44%	51%	48%	52%	48%	48%	51%	55%	
4	OSI	5	15%	23%	29%	22%	32%	35%	29%	28%	23%	30%	
5	Bayer	4		0%	6%	13%	21%	30%	27%	31%	32%	26%	
6	GlaxoSmithKline	16	6%	3%	6%	11%	20%	24%	19%	35%	30%	29%	
7	Bristol-Myers Squib	12	5%	9%	12%	27%	24%	23%	15%	10%	20%	13%	
8	Lilly	9	12%	11%	17%	14%	14%	10%	7%	6%	7%	8%	
9	Bristol-Myers Squib (Du Pont)	1	11%	12%	11%	10%	13%	10%	10%	11%	7%	7%	
10	Celgene	2	5%	9%	7%	6%	7%	11%	7%	6%	6%	6%	
11	Roche	6	0%	0%	1%	2%	2%	9%	1%	11%	13%	28%	
12	Merck	7		0%		6%	4%	6%	9%	16%	10%	9%	
13	Millennium Pharmaceuticals	5			2%	0%	9%	7%	1%	10%	7%	14%	
14	Sanofi-Aventis	2	10%	7%	5%	5%	2%	2%	2%	4%	5%	9%	
15	Cyclacel	2	4%	3%	2%	3%	12%	6%	2%	2%	1%		

2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
2	3	1	1	1	1	1	1	1	1
1	1	2	2	2	2	2	2	3	3
3	2	3	3	3	3	3	3	2	2
4	4	4	5	4	4	4	6	6	4
	12	9	7	6	5	5	5	4	7
8	10	9	8	7	6	6	4	5	5
10	7	6	4	5	7	7	10	7	9
5	6	5	6	8	10	10	12	12	12
6	5	7	9	9	9	8	8	11	13
9	8	8	10	12	8	11	13	13	14
12	13	14	14	15	11	14	9	8	6
	14		10	13	14	9	7	9	10
		12	15	11	12	15	11	10	8
7	9	11	12	14	15	13	14	14	11
11	11	13	13	10	13	12	15	15	