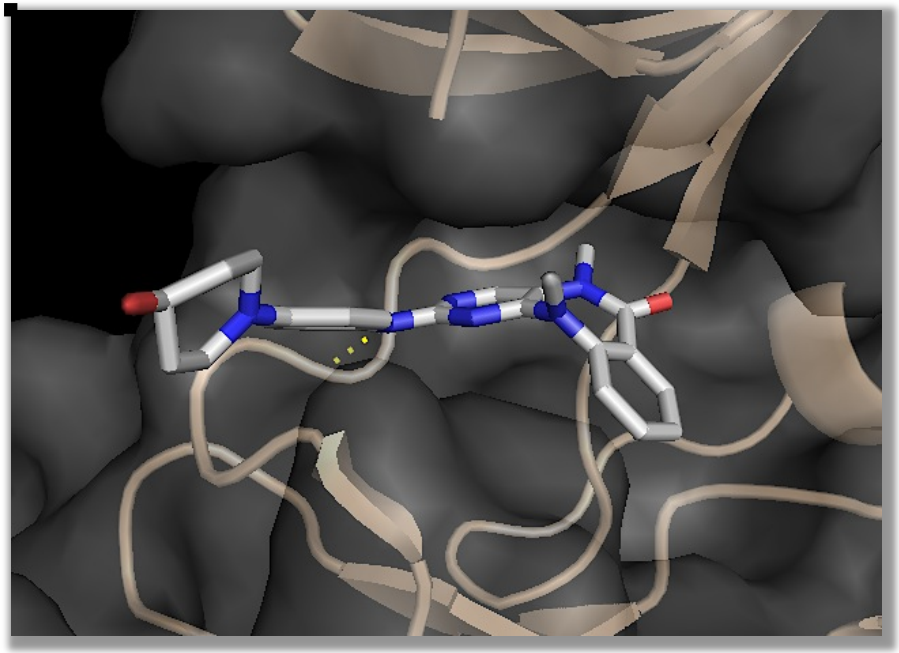
Selective Aurora Kinase Inhibitors Identified Using a Taxol-Induced Checkpoint Sensitivity Screen

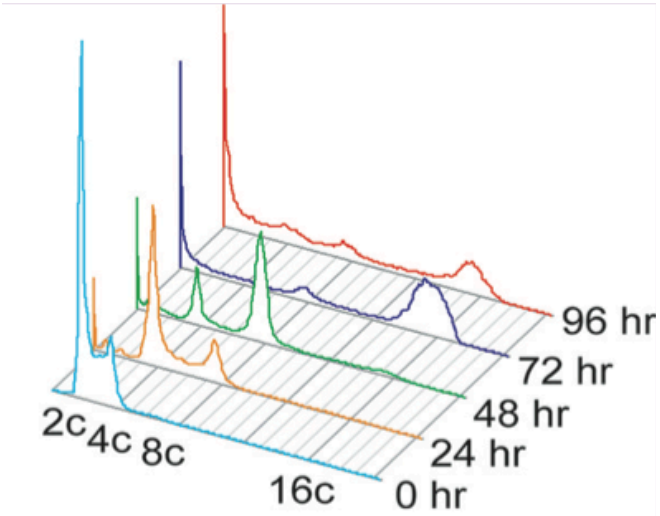
N. Kwiatkowoski *et al*. *ACS Chem. Biol.* **2012**, 7, 185-196.



Evan Carder
Wipf Group Current Literature
18 January 2014

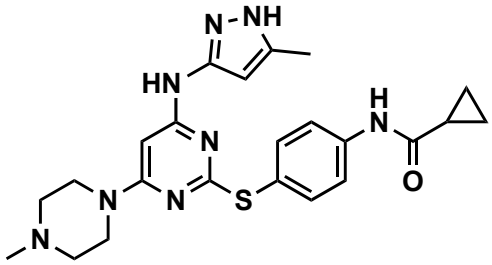
Aurora Kinases

- A family of three serine/threonine protein kinases – Aurora Kinase A, Aurora Kinase B, Aurora Kinase C.
- Aurora kinases play an important role in centrosome duplication, mitotic spindle formation, chromosome alignment, and the spindle checkpoint.[1]
- Inhibition of Aurora kinases have been shown to reduce tumor growth in nude mice xenograft models evaluating human colon cancer and leukemia.[2]

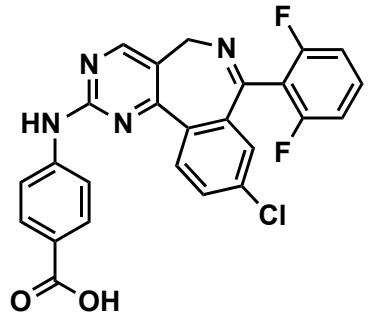


[1] Keen, N.; Tayler, S. *Nat. Rev.* **2004**, 4, 927.
[2] E. Harrington *et al. Nat. Med.* **2004**, 10, 262.

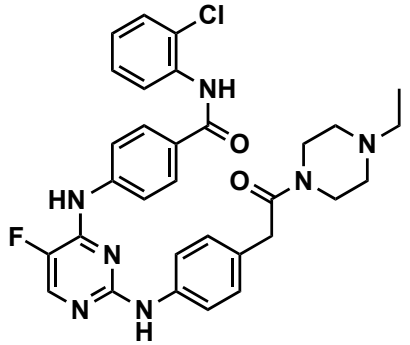
Known Aurora Kinase Inhibitors



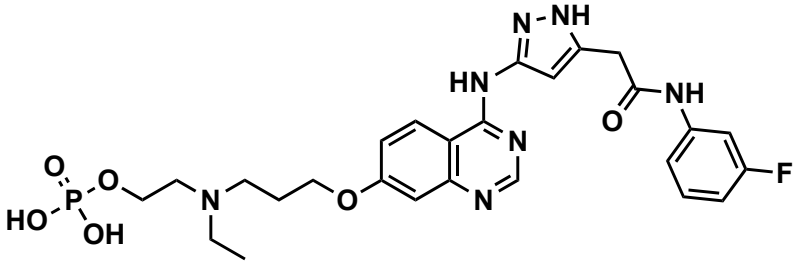
VX-680/MK-0457
Vertex/Merck
Pan-Aurora Kinase Inhibitor
Phase II - Discont. QT longation



MLN8054
Milennium
Aurora A/C Kinase Inhibitor
Phase I - Discont. Sedation

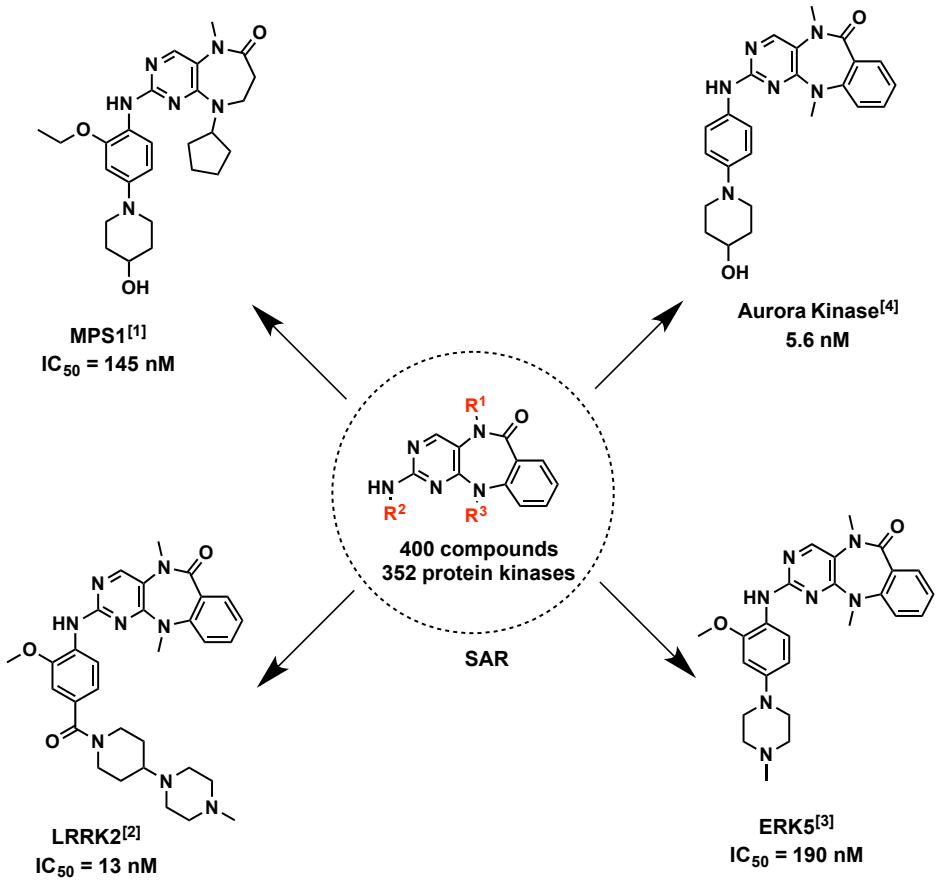


35
Genetech
Aurora A Kinase Inhibitor



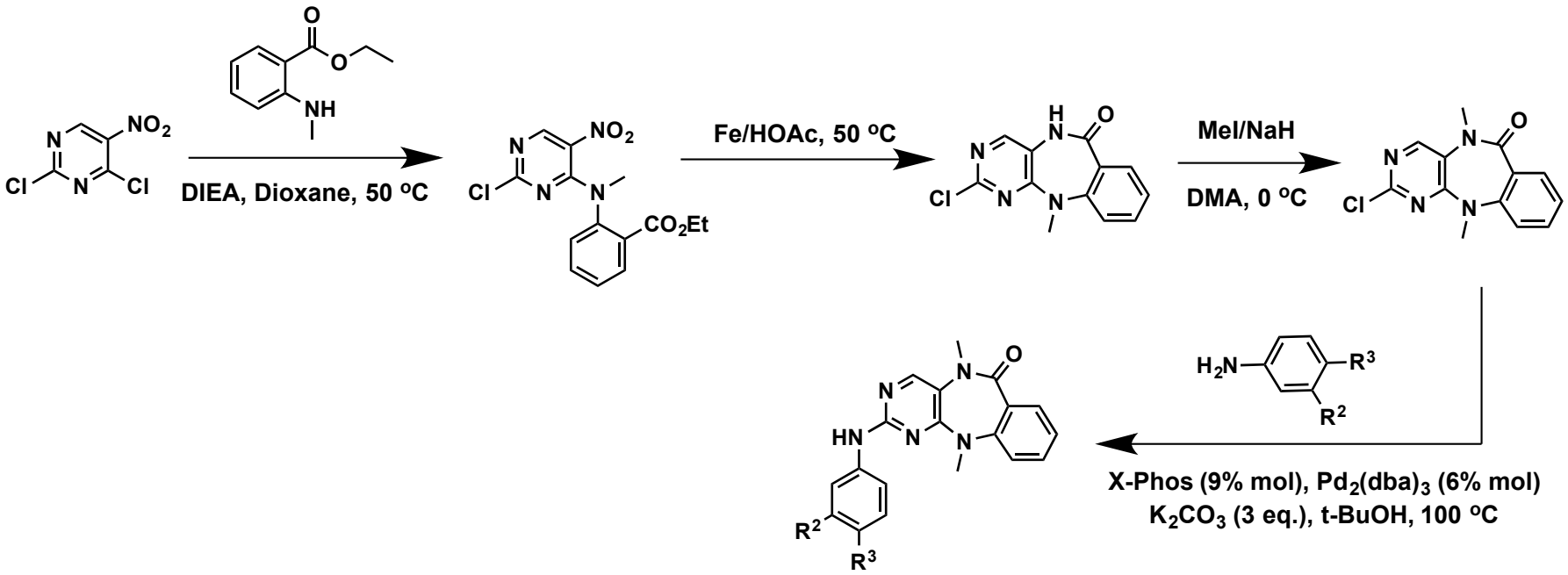
AZD1152
AstraZeneca
Aurora B/C Kinase Inhibitor
Phase II, Neutropenia

Privileged Scaffold



[1] N. Kwiatkowski *et al. Nat. Chem. Biol.* **2010**, 6, 359.
[2] X. Deng *et al. Nat. Chem. Biol.* **2011**, 7, 203.
[3] X. Deng *et al. ACS Med. Chem. Lett.* **2011**, 2, 195.
[4] N. Kwiatkowski *et al. ACS Chem. Biol.* **2012**, 7, 185.

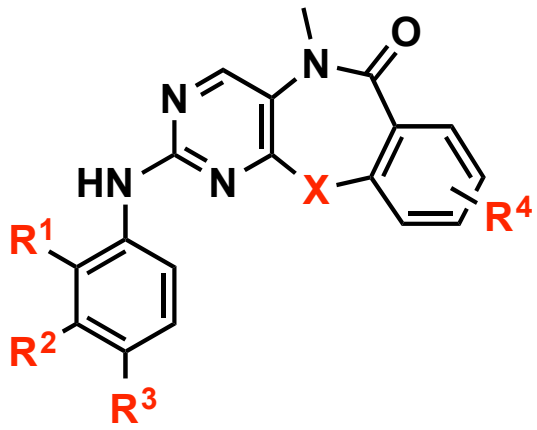
Synthetic Scheme



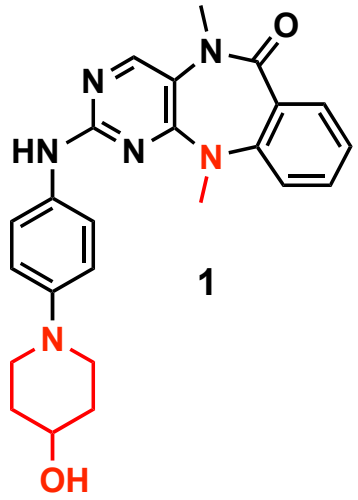
X. Deng *et al. ACS Med. Chem. Lett.* **2011**, 2, 195.

Structure-Activity Relationship Summary

- **R^1**
  - Substitution reduces activity
- **R^2 & R^3**
  - Diverse substitutions tolerated
    - Amines, amides, sulfonamides
  - Disubstitutions contribute toward isoform specificity
- **R^4**
  - Me or F at the 3-position improves selectivity and maintains activity
- **X**
  - N-Alkylation is better than O or S
  - N-Me it prefered

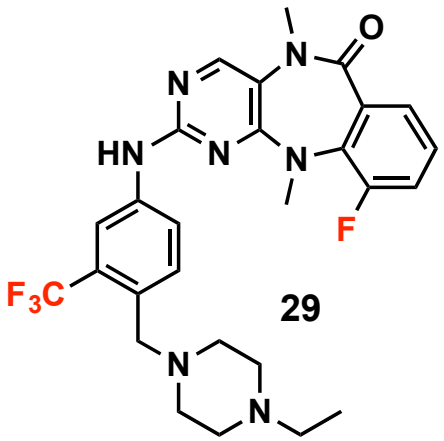


Structure-Activity Relationship Results



1

Potent Pan-Aurora Kinase Inhibitor



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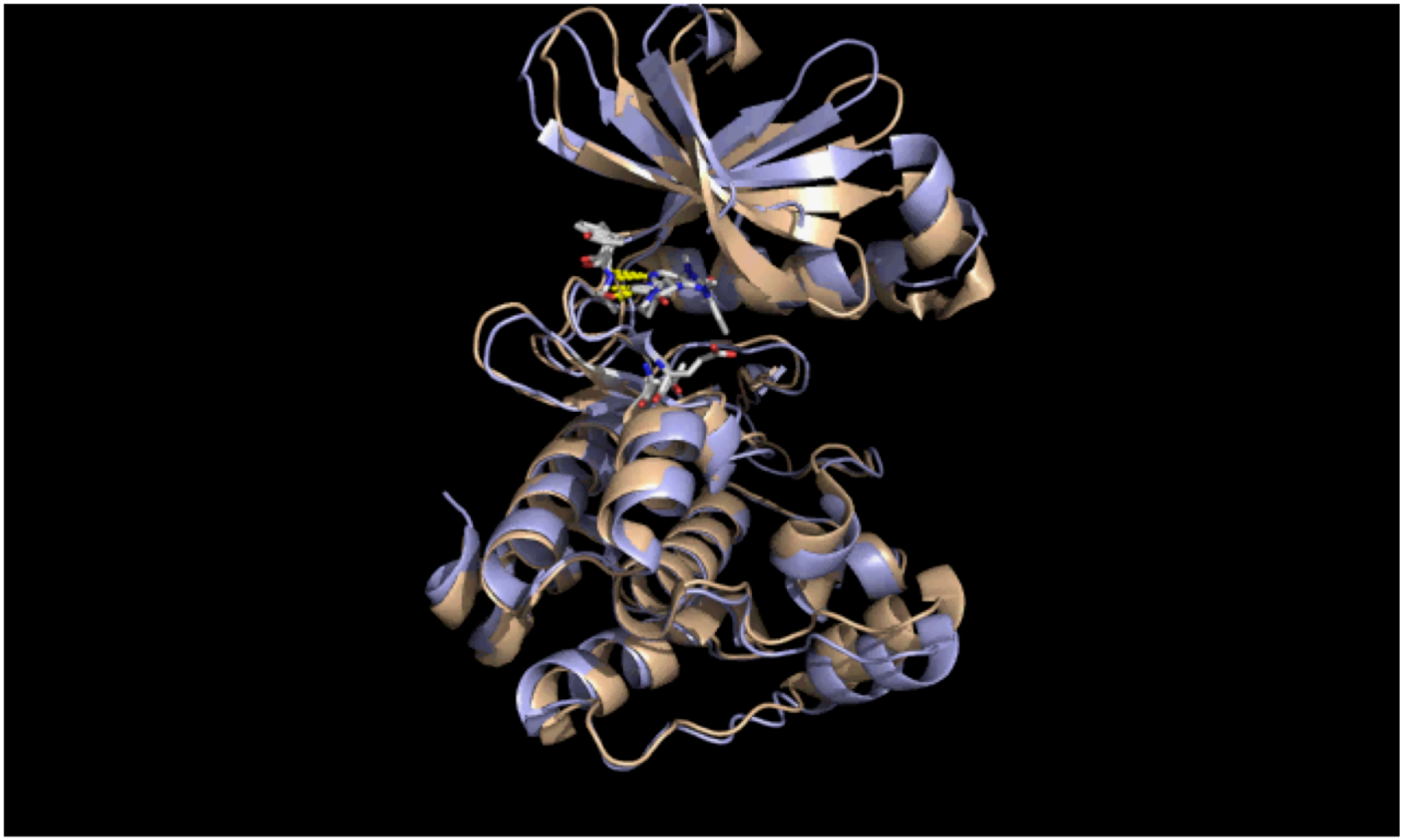
Potent Aurora Kinase A Inhibitor

Isoform Selectivity

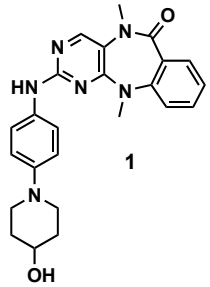


Gold – Aurora Kinase A; PDB: 1OL5
Blue – Aurora Kinase B; PDB: 2BFX

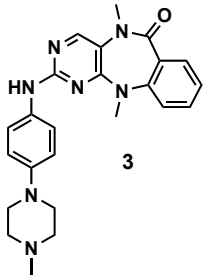
Characterization of Aurora Kinase Inhibitors

	1	3	23	29	32	33	34	35
				Enzyme IC_{50} (nM)[a]				
Aur A	5.6	7.2	16.8	13.4	5.6	193	3.0	3.2
Aur B	18.4	25.9	194	487	19.8	15.5	23.2	1380
Aur C	24.6	40.5	419	595	18.3	25.3	9.1	432
				Cell EC_{50} (nM)[b]				
HCT116	9.5	19	553	449	15.8	17.4	50.3	377.6
HT29	55	68	951	1577	118.8	239.2	687.8	5600
HeLa	16.7	10.9	1300	792	16.4	3.8	214	416

[a]The required concentration to inhibit 50% of enzyme activity. [b]The required concentration for inhibiting cell growth at 50%.



1



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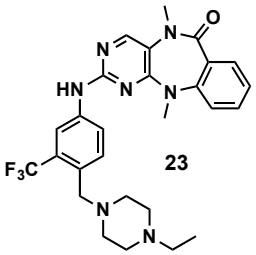

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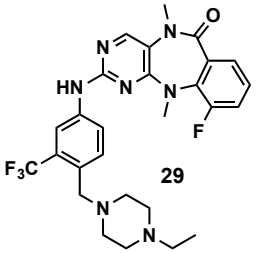

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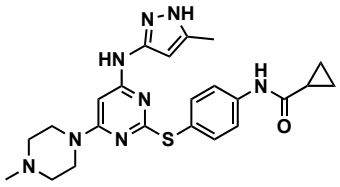

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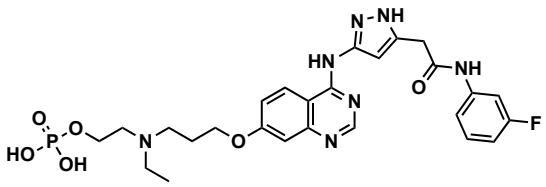

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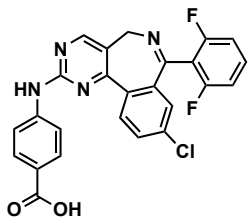

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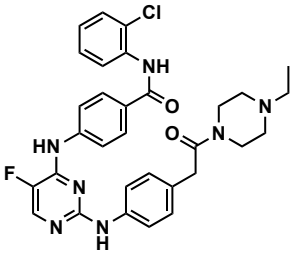

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Conclusion

- Developed a novel and potent aurora kinase inhibitor employing a pyrimidodiazepinone based scaffold.
- Structural-activity relationship supported the “fine-tuning” of the privileged scaffold toward aurora kinase specificity.
- Structural evidence helped in the investigation of isoform specific inhibition – compound 29 has a 36-fold biochemical selectivity for aurora kinase A.
- Combinational treatment with aurora kinase inhibitors and Taxol desensitized cancer cells and reduced Taxol-independent apoptosis.