Cancer Theraputics Course

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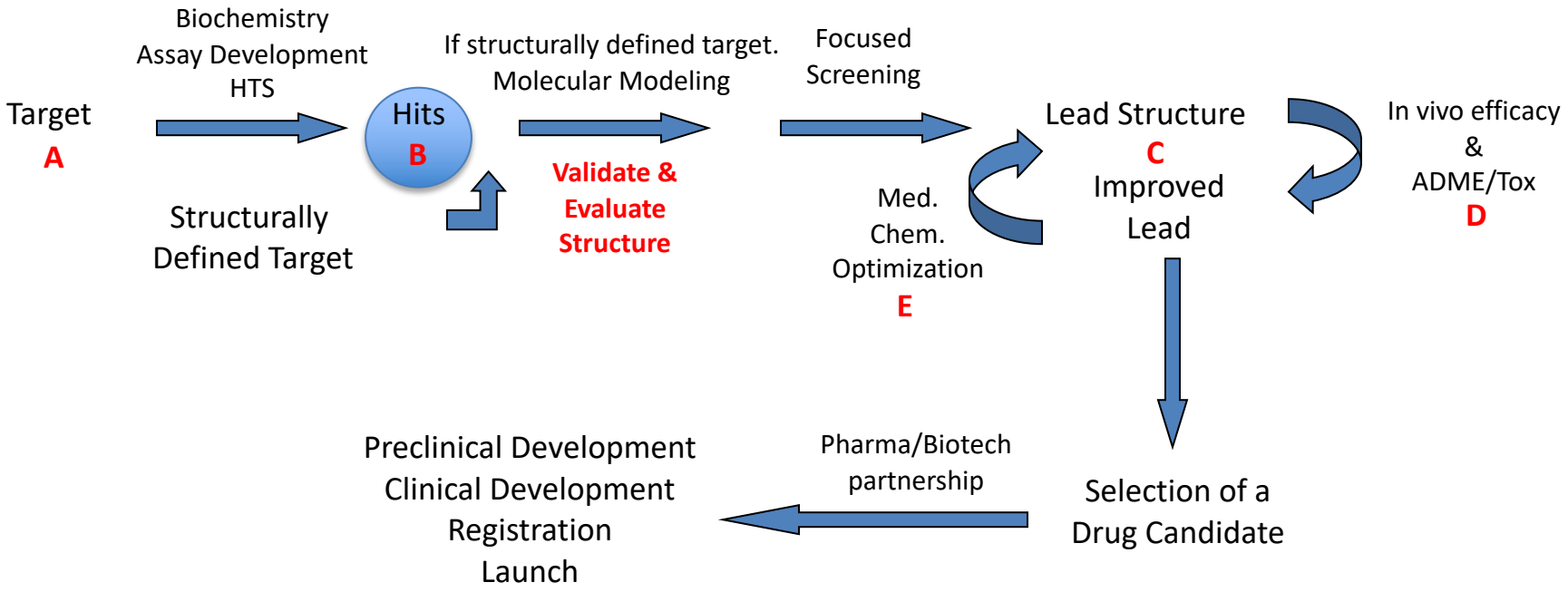
UNIVERSITY of HOUSTON

Drug Discovery Pipeline



Validation and Evaluation of Hits

Validate structure and purity by independent synthesis.

Purchase from another source is often not that.

Evaluate structure for the ability to modify and optimize.

Drug likeness. Not necessarily Lipinski's rules but if molecule has poor solubility or stability things will be hard!

Synthetic tractability

Can someone get you the diverse structures you will need to advance the hit?

How we learned this the hard way!

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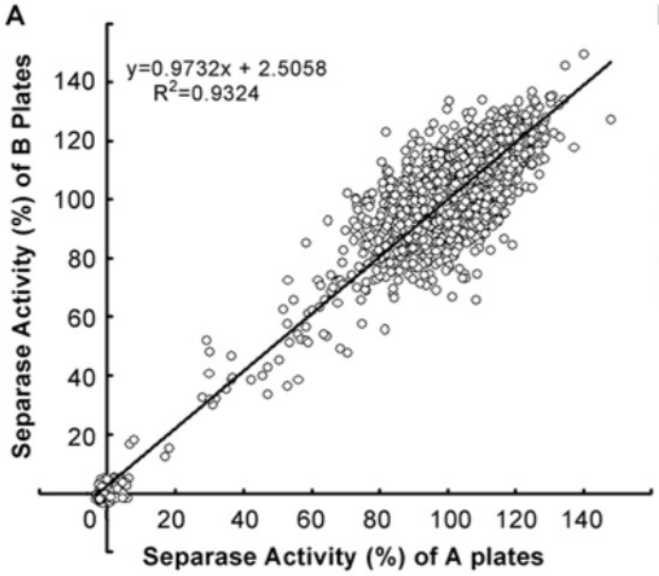
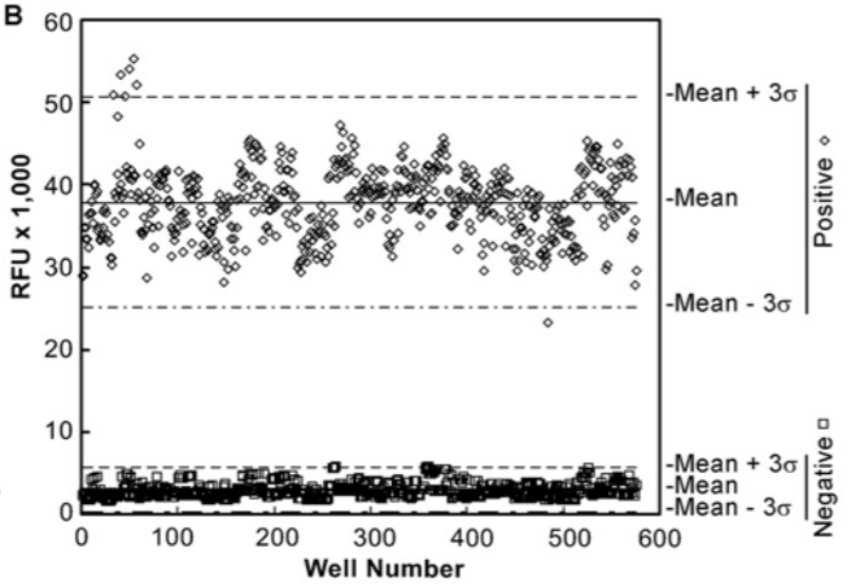
Target: Separase

- Separase is a protease important for cell division, is overexpressed in over 60% of breast tumor specimens, and 50% of TNBC and 65% of Luminal B tumors. Separase overexpression strongly correlates with aneuploidy, high incidence of relapse, metastasis, and a lower 5-year overall survival rate. In mouse models, Separase overexpression has been shown to induce aneuploidy and mammary tumorigenesis.

- Our colleage developed a HTS assay for this enzyme.

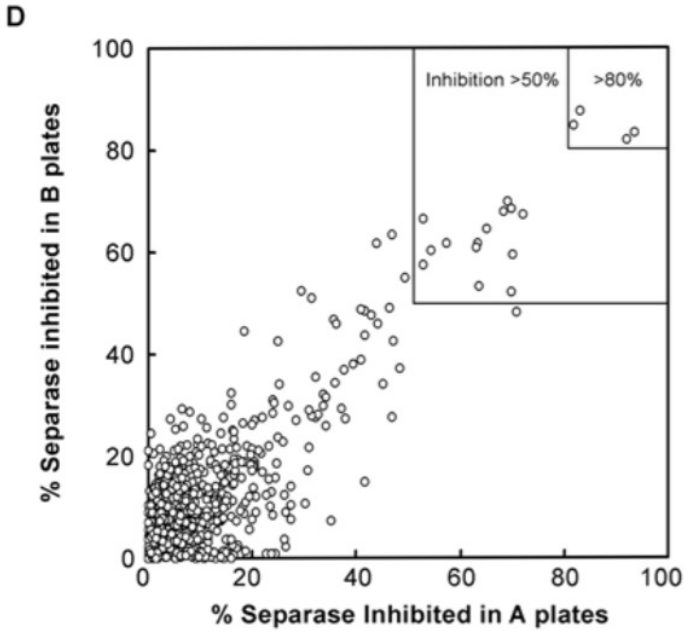
- That screen was done in the GCC screening center.

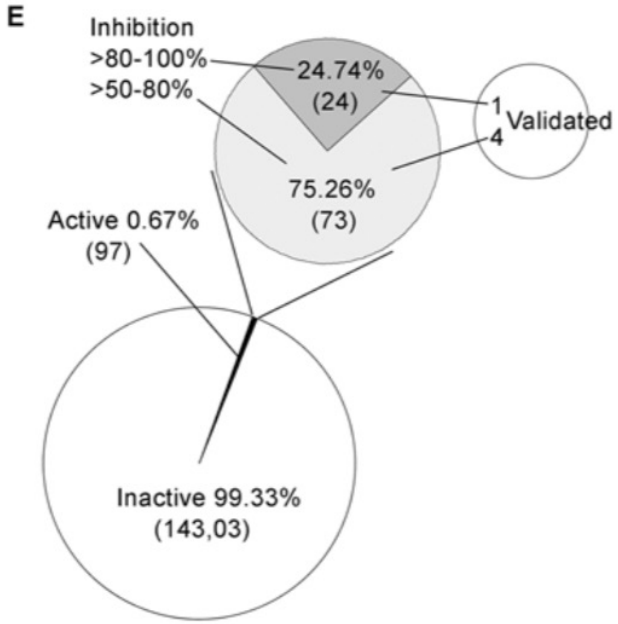




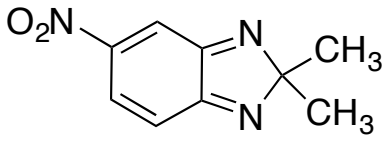
C

	S:B	S:B Range (A : B)	S:N	S:N Range (A : B)	Z'	Z' Range (A : B)
Mean	10.54	(10.75 : 10.34)	46.35	(47.92 : 44.77)	0.55	(0.57 : 0.54)
σ	2.69	(3.06 : 3.03)	15.77	(20.38 : 18.70)	0.10	(0.12 : 0.12)





Lead Compound from HTS of Maybridge Library



Synthesis of the structure provided by Maybridge gave a molecule that was not stable and was the wrong color.

So the first issue was the structure provided by the company was incorrect. Another common problem can be impurities in the sample leading to activity that is not related to the expected structure.

Identification and Characterization of Separase Inhibitors (Sepins) for Cancer Therapy

2014, Vol. 19(6) 878–889

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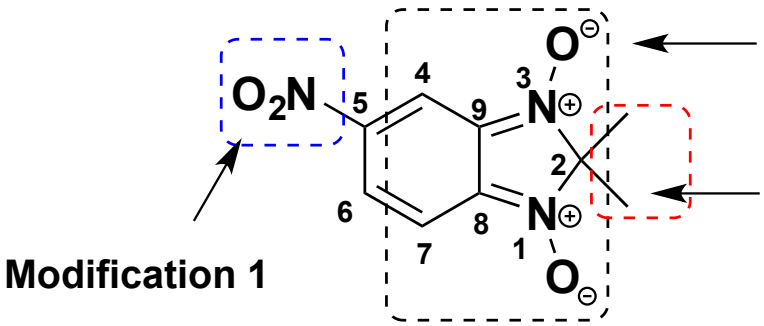
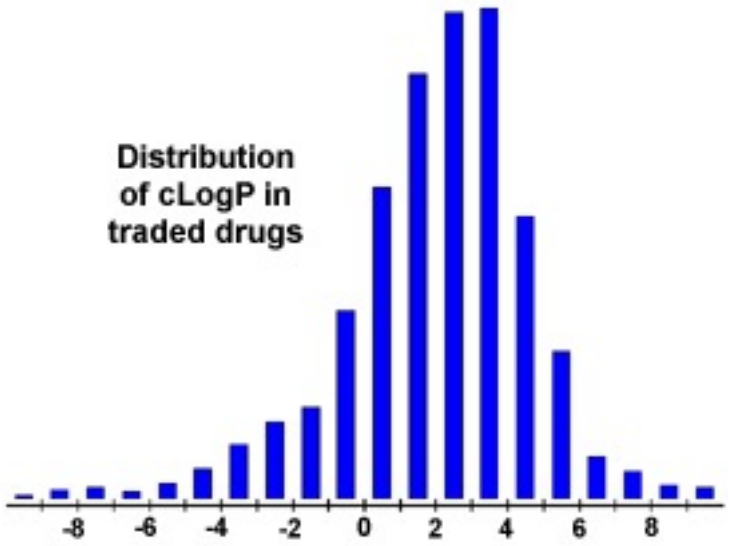
SAGE

Nenggang Zhang[1], Kathleen Scorsone[1], Gouqing Ge[1], Caterina C. Kaffes[1], Lacey E. Dobrolecki[2], Malini Mukherjee[1], Michael T. Lewis[2], Stacey Berg[1], Clifford C. Stephan[3], and Debananda Pati[1]

Three Sites for Optimization





Issues to address

Nitro groups are generally not a good functional group for drugs.

They are converted to reactive molecules such as nitroso compounds.

Not a very drug like structure

Highly charged cLogP -5.3 (Chemicalize.org)

May be an acceptor of nucleophiles (stability issue)

Moderate activity

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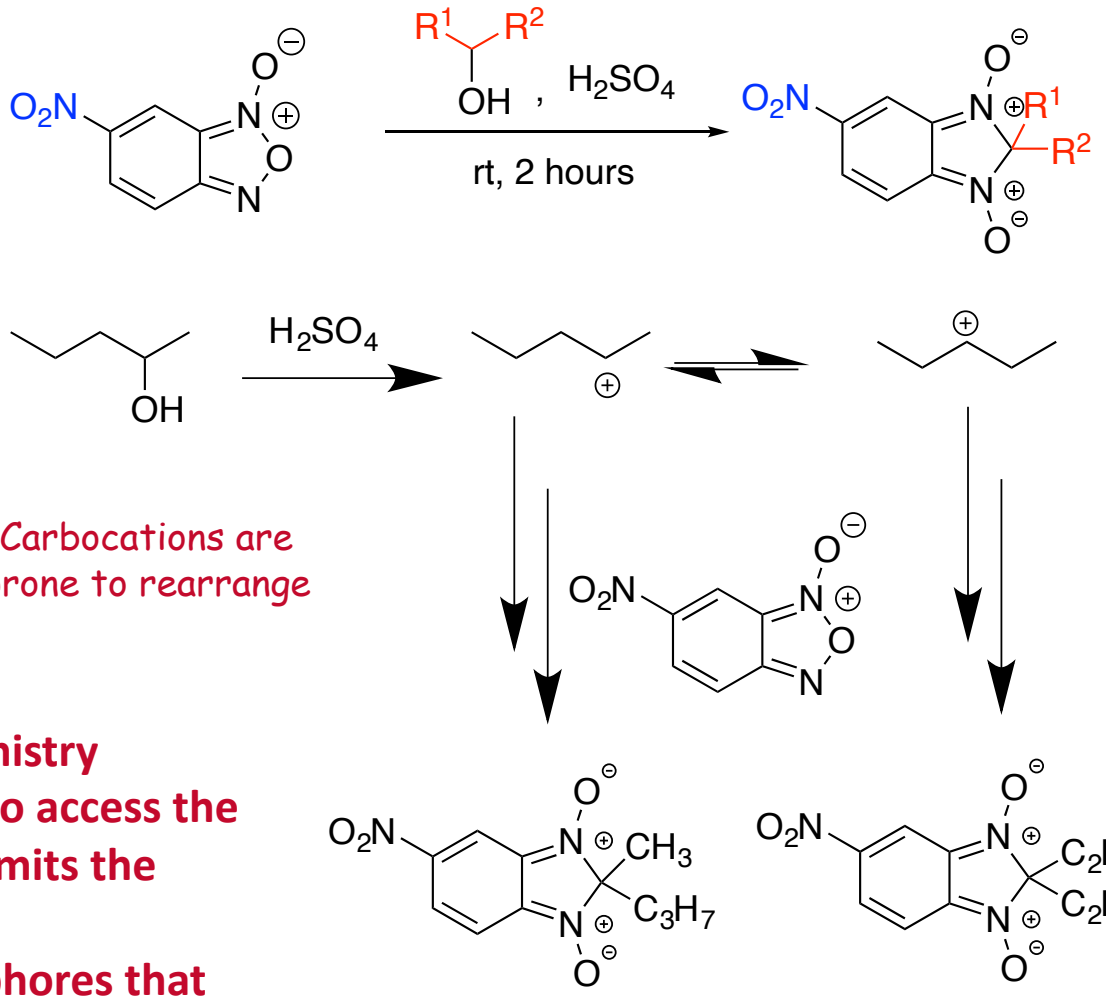
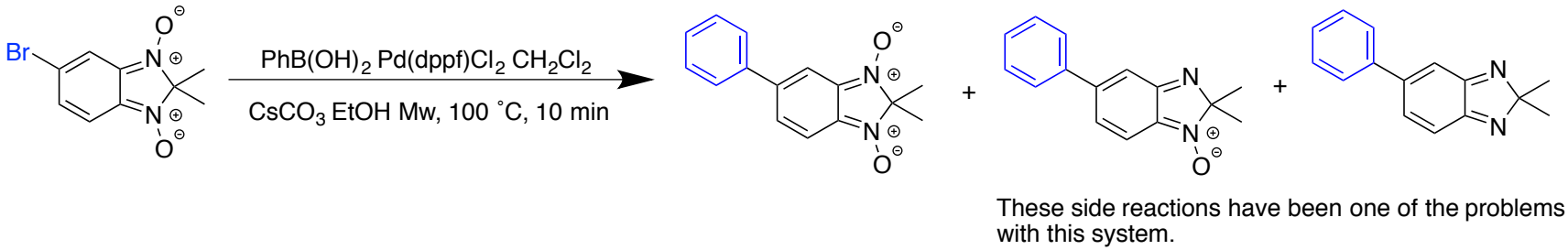
Reaction Conditions Lead to Multiple Products with Some Substrates

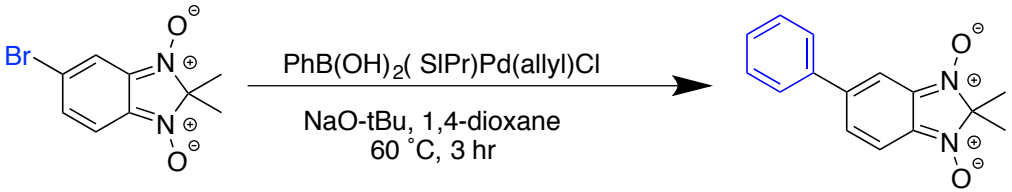


Harsh chemistry necessary to access the molecule limits the types of pharmacophores that can be attached.

Modification of the Bromide Would Allow for the Synthesis of Version After the Problem Step



These side reactions have been one of the problems with this system.



Reoxidation of the reduced biproducts was not consistent

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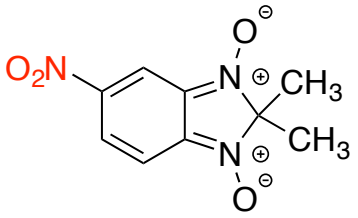
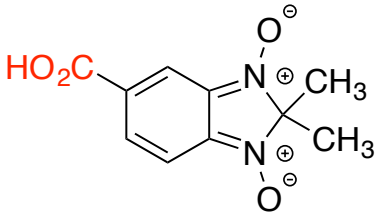
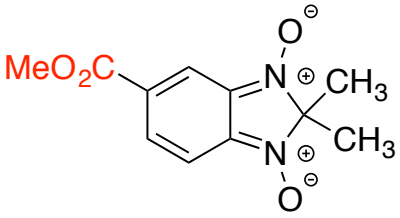
Replacement of the Nitro Group



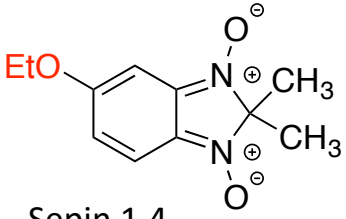
Sepin 1.1



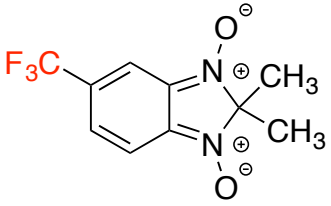
Sepin 1.2



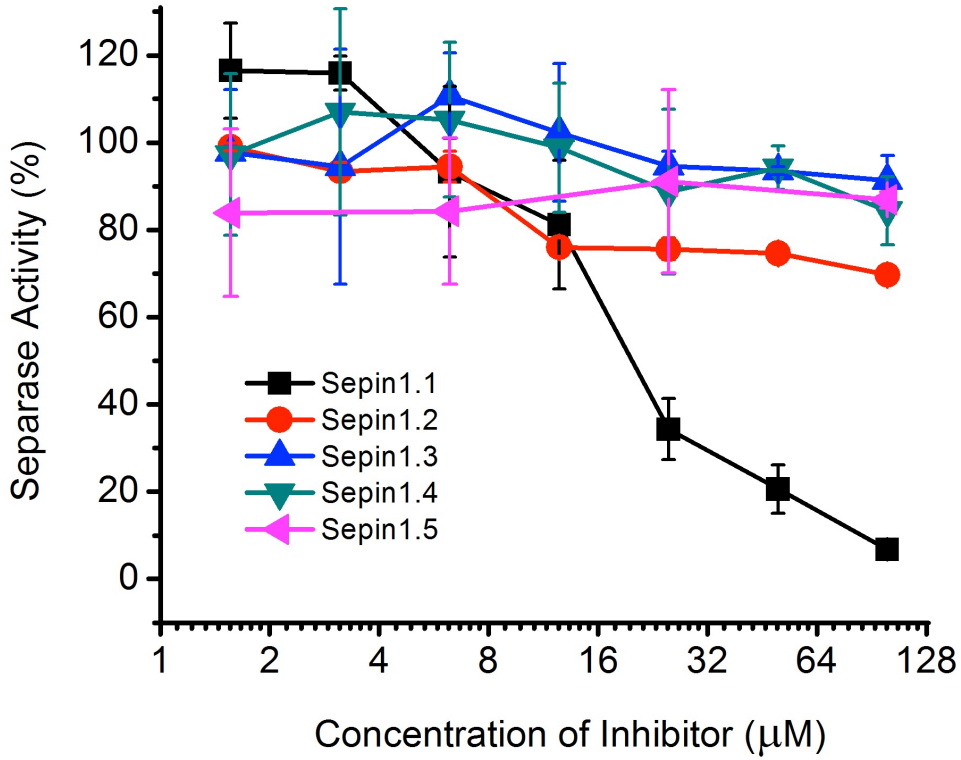
Sepin 1.3



Sepin 1.4



Sepin 1.5



Every version without the nitro group is less active
Both electron withdrawing and H-bond acceptor groups

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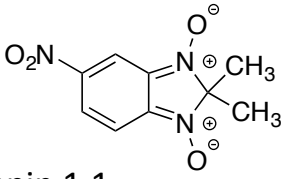
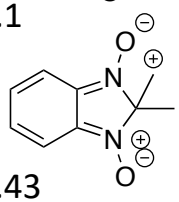
Miscellaneous Changes



Sepin 1.1



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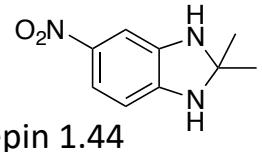

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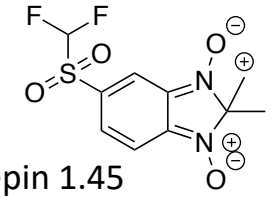
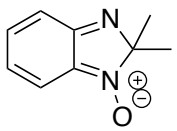


Sepin 1.45



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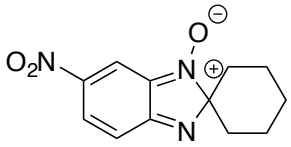

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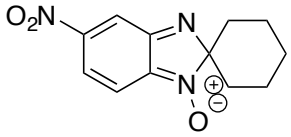

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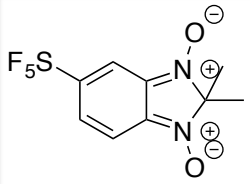

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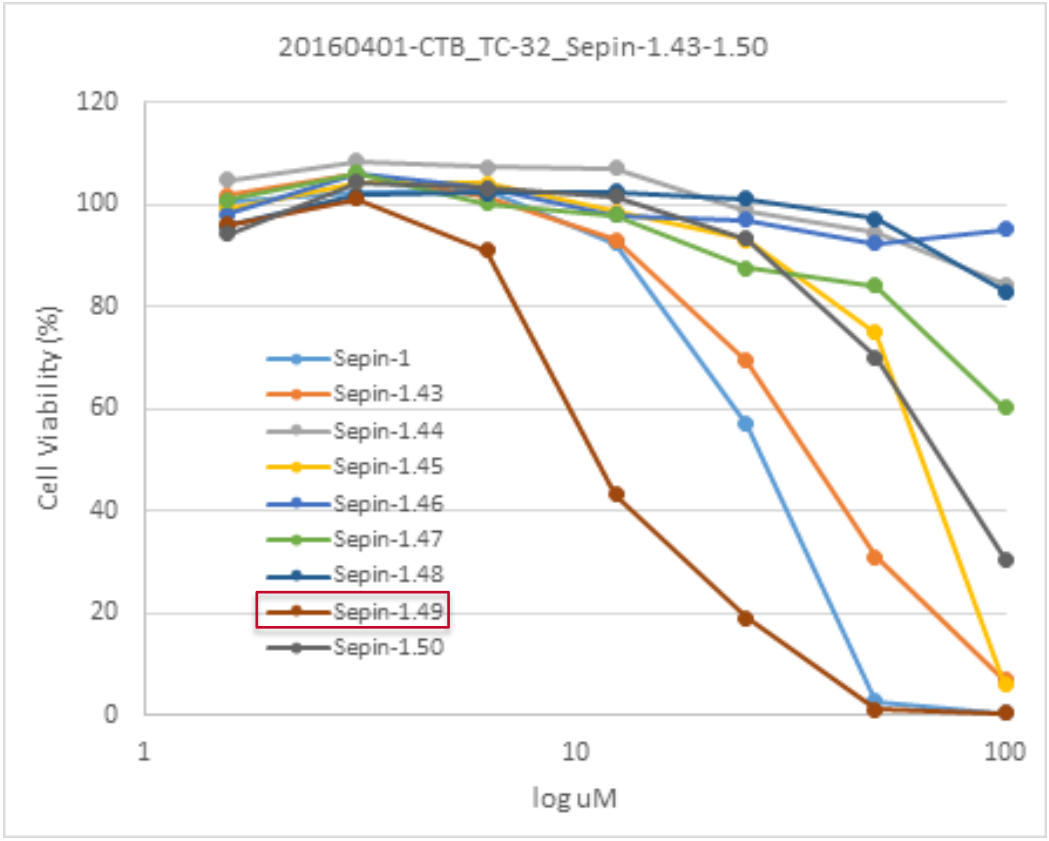

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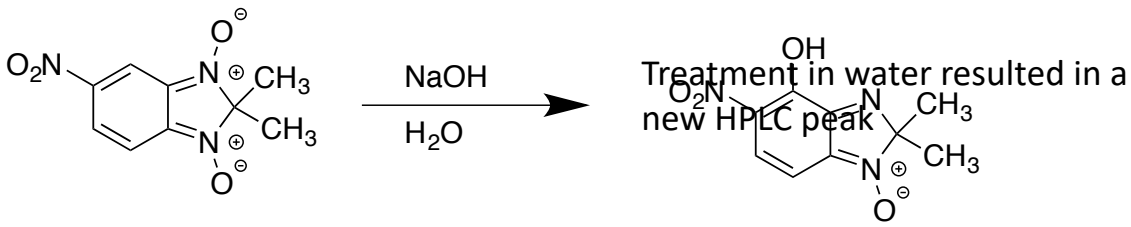
Final Nail in the Coffin

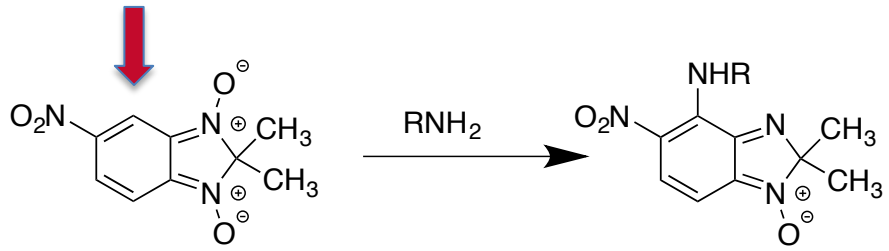


Treatment in water resulted in a new HPLC peak

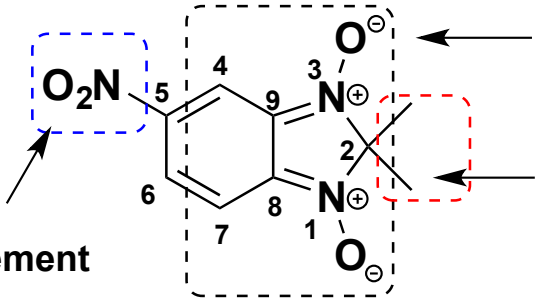
MW 233.06
$C_9H_9N_3O_4$

MW 233.06
$C_9H_9N_3O_4$

This site readily reacts with nucleophiles



Summary to date



Must have at least one N-O
Other heterocycles are not active

Hydrophobic groups are good

Required
SF_5 maybe a replacement

Acknowledgements

- Dr. Ha Do
- Silviya Demerzhan
- Dr. Debananda Pati
- Dr. Anton Agarkov
- Dr. Zhang Nenggang

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