New Ring Systems for New Drugs

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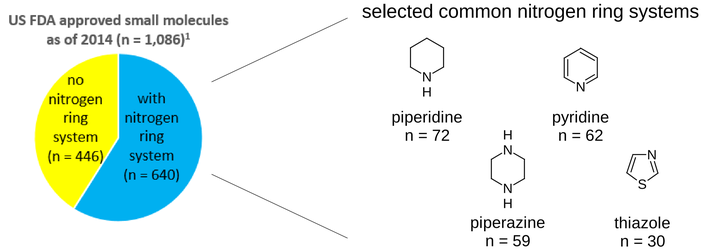
Few nitrogen rings, many drugs

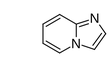
A study in 2014 found that of the 1,086 small molecule drugs approved by the US FDA, 640, or nearly 60%, contain a ring with at least one nitrogen atom.[1] Of these 640 structures, almost half were built around just seven different nitrogen-containing ring systems. With such high dependence on a small number of core structures, **discovering new drugs with these structures is increasingly more difficult**.[2]



1

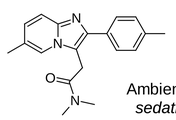
Identifying underutilized nitrogen ring systems

The usual suspect nitrogen rings are used frequently because they are easy to make. We decided to find nitrogen ring systems that are known to be useful in drugs but less often used. We then designed new reactions to make the less common systems easier to access for drug development. We ultimately studied the imidazopyridine (**1**) and imidazothiazole (**2**) based on their relationship to existing drugs, such as Ambien (**3**)**.**



imidazopyridine (**1**)

imidazothiazole (**2**)

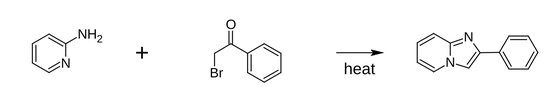


Ambien (**3**)
sedative

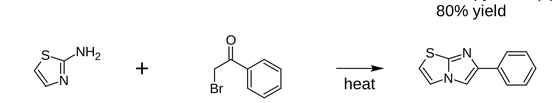
2

Starting to imidazopyridines and -thiazoles

Routes to imidazopyridines and -thiazoles are known in the literature.[3] To start, we followed these procedures, which are simple processes and rely upon inexpensive reagents.



2-aminopyridine + 2-bromoacetophenone → heat → an imidazopyridine (**4**) 80% yield

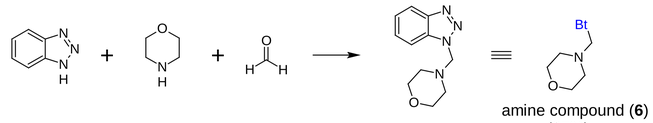


2-aminothiazole + 2-bromoacetophenone → heat → an imidazothiazole (**5**) 84% yield

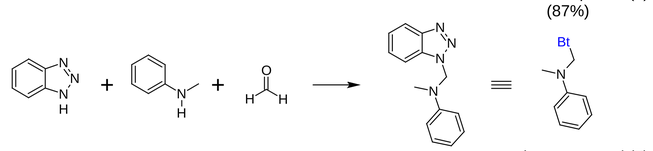
3

A little side chemistry

In order to further elaborate our imidazopyridine (**4**) and -thiazole (**5**)**,** we prepared two additional compounds through known chemistry.[4] These new compounds (**6** and **7**) were intended to react with **4** and **5** to make structures that contain drug-like features.



amine compound (**6**) (87%)

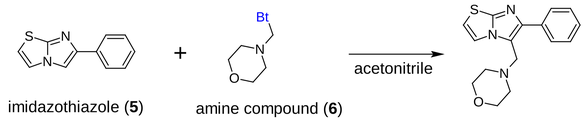


amine compound (**7**) (88%)

4

Putting everything together

Both **4** and **5** were reacted with both **6** and **7** with a variety of different solvents, including chloroform, acetonitrile, methanol, DMSO, and no solvent, in order to determine the optimal conditions for the reaction. The best combination between **5** and **6** in acetonitrile is shown below. The purified yield is disappointing, but the crude recovery implies the final yield may be improved dramatically.



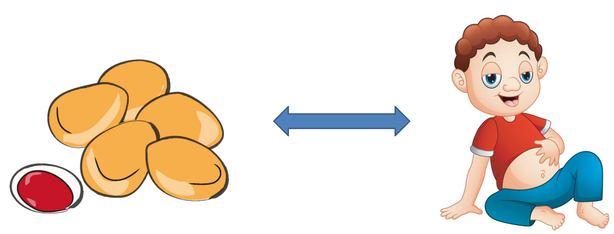
imidazothiazole (**5**) + amine compound (**6**)

product **8**
crude yield = 93%
purified yield = 15%

5

Student connections – stoichiometry

Stoichiometry addresses the proportions of different chemicals used when performing a reaction. Stoichiometry is a topic of daily importance in a synthetic laboratory for chemists who are setting up a reaction and deciding on amounts of different reagents to add. Parallels in day-to-day life can be found in cooking recipes and serving portions.



Images: iStock.com and dkcoin8.com

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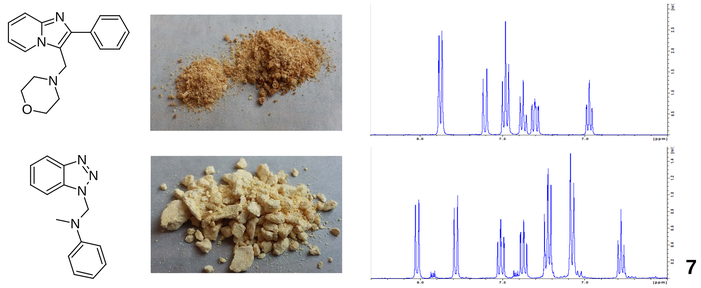
Student connections – using data

Small molecules often appear as beige powders, so other data is needed to identify the products. Two compounds from this project are shown below. Their spectroscopic data, in this case information on hydrogen atoms (^{1}H NMR), can distinguish the two compounds.



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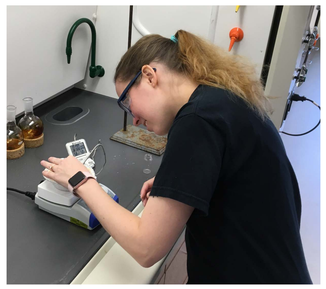
CTI Fellows in action

All the work presented on this poster was performed by outstanding teachers in the Charlotte-Mecklenburg School system with support from Davidson College and the Charlotte Teachers Institute.



Kassie gets the temperature right.

Josh checks on a reaction.

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References

1. Njardarson, J. T.; Vitaku, E.; Smith, D. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014,** *57,* 10257-10274.
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4. Burckhalter, J. H.; Stephens, V. C.; Hall, L. A. R. Proof of structures derived from the hydroxy- and aminomethylation of benzotriazole. *J. Am. Chem. Soc.* **1952,** *74,* 3868-3870.

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