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Importance of Catalytic Asymmetric Synthesis of Saturated N-Heterocucles in Chemical Biology and Medicinal Chemistry

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The important requirement for approval of a new drug, in case it happens to be chiral, that both enantiomers of the drug be studied in detail [1], have focused the attention of synthetic organic and medicinal chemists on the development of new methods for catalytic asymmetric synthesis especially of relevant saturated N-heterocycles. Despite the success of chirally modified transition-metal catalysts in asymmetric synthesis, in the form of the Nobel Prize in Chemistry in 2001, the field of asymmetric organic synthesis has since then been dominated by organocatalysts due to their ability to catalyze a variety of fundamentally important transformations in medicinal chemistry and therefore chemical biology. One example is the Staudinger synthesis of β-lactams representing one class of saturated N-heterocycles and continuing to provide unique opportunities for the discovery of new derivatives with novel pharmacological profiles [2,3]. Specifically, β-lactams have recently been found to have potential as the basis for treatments for neurological disorders including amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease [4]. Although significant progress has been made in asymmetric organocatalytic Staudinger synthesis of β-lactams since the inaugural and pioneering investigations by Lectka and coworkers around the turn of the century [5,6], the same did not hold true regarding the development of a novel Gilman-Speeter process for the catalytic enantioselective synthesis of β-lactams [7]. Efforts directed at this latter goal are ongoing in this Laboratory.

On the other hand, the piperazine ring, besides defining a major class of saturated N-heterocycles, has been classified as a privileged structure in Medicinal Chemistry since it is more than frequently found in biologically active compounds including several marketed blockbuster drugs such as Glivec (Imatinib) and Viagra (Sildenafil) [8,9]. Actually, an analysis of all U.S. FDA approved small molecule drugs found that 21% contained saturated 6-membered N-heterocycles with an additional heteroatom (N, piperazines; O, morpholines; S, thiomorpholines) [10]. Indeed, 13 of the 200 best-selling small molecule drugs in 2012 contain a piperazine ring [11]. In the vast majority of these molecules, however, the piperazine ring is not substituted on any of its carbon atoms. Specifically, analysis of the piperazine substitution pattern reveals a luck of structural diversity, with almost every single drug in this category (83%) containing a substituent at both the N1- and N4-positions compared to only a few drugs having a substituent at any other position (C2, C3, C5 and C6) [11]. Significant chemical space that is closely related to that known to be biologically relevant, therefore, remains unexplored. In order to explore this chemical space, an efficient and enantioselective synthesis of C-substituted piperazines must be designed and developed [12,13]. Efforts toward the implementation of this particular target are ongoing in this Laboratory. It must be emphasized, however, that these latter efforts were initiated by considering a novel retrosynthetic analysis of the unique marine natural product Ecteinascidin-743 (**1**, Et-743 also known as Trabectidin or Yondelis™, a commercially available drug against soft-tissue sarcoma), centered at its piperazine ring shown in structure **1 (Figure 1)** [14-16].

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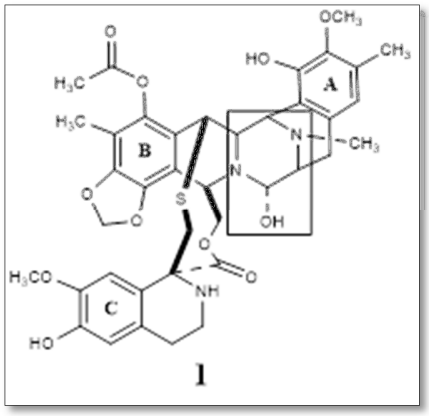

Figure 1. Structure **1** showing piperazine ring.

Since piperazine derivatives have been reported to elicit a broad spectrum of pharmacological activities including antidepressant, anticancer, anti-helminthic, anti-bacterial, antifungal, anti-mycobacterial, anti-malarial, anti-tuberculant, anti-convulsant [8] and anti-AIDS [17]; one can easily comprehend that the sky will be the limit, as far as novel drug development is concerned, once this catalytic enantioselective process will be fully developed [18].

Finally, aziridines are structurally fascinating, pharmaceutically important, and finding applications in synthetic organic and medicinal chemistry [19-20]. Thus, they can be readily converted into a variety of nitrogen-containing compounds due to the inherent reactivity of the constrained three-membered ring present in biologically active natural products such as the azinomycins [21] and the mitomycins [22]. Novel catalytic enantioselective synthesis of aziridines as well as their employment in piperazine syntheses is under active investigation in this Laboratory [23-25].

REFERNCES

1. Stinson SC (2001) Chiral Chemistry. Chem Eng News 79: 45-56.
2. Galletti P, Giacomini D (2011) Monocyclic β-lactams: New structures for new biological activities. Curr Med Chem 18: 4265-4283.
3. Magriotis PA (2014) Progress in asymmetric organocatalytic synthesis of β-lactams. Eur J Org Chem 2014: 2647-2657.
4. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, et al. (2005) Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 433: 73-77.
5. Lectka T, Taggi AE, Hafez AM, Wack H, Young B, et al. (2000) Catalytic, asymmetric synthesis of β-lactams. J Am Chem Soc 122: 7831-7832.
6. Lectka T, France S, Weatherwax A, Taggi AE (2004) Advances in the catalytic, asymmetric synthesis of β-lactams. Acc Chem Res 37: 592-600.
7. Magriotis PA (2001) Recent progress in the enantioselective synthesis of beta-lactams: development of the first catalytic approaches. Angew Chem Int Ed Engl 40: 4377-4379.
8. Alam M, Shaquiquzzaman M, Verma G, Marella A, Akhter M, et al. (2015) Piperazine scaffold: A remarkable tool in generation of diverse pharmacological agents. Eur J Med Chem 102: 487-529.
9. Ye Z, Gettys KE, Dai M (2016) Opportunities and challenges for direct C–H functionalization of piperazines. Beilstein J Org Chem 12: 702-715.
10. Vitaku E, Smith DT, Njardarson JT (2014) Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J Med Chem 57: 10257-10274.
11. Nelson A, James T, MacLellan P, Burslem GM, Simpson I, et al. (2014) A modular lead-oriented synthesis of diverse piperazine, 1,4-diazepane and 1,5-diazocane scaffolds. Org Biomol Chem 12: 2584-2591.
12. Gettys KE, Ye Z, Dai M (2017) Recent advances in piperazine synthesis. Synthesis 49: 2589-2604.
13. Vo CVT, Luescher MU, Bode JW (2014) SnAP reagents for the one-step synthesis of medium-ring saturated N-heterocycles from aldehydes. Nat Chem 6: 310-314.
14. Rinehart KL (2000) Antitumor compounds from tunicates. Med Drug Rev 20: 1-27.
15. Nikolaou KC, Montagnon T (2008) Molecules that changed the World. Wiley-VCH: Weinheim, pp: 241-250.

16. Magriotis PA (2017) Synthetic approaches to the stereochemically complex antitumor drug Ecteinascidin-743: A marine natural product by the name Yondelis® or Trabectidin. In: Stereochemistry and Global Connectivity: The Legacy of Ernest L Eliel.; Cheng et al. Ed. ACS Symposium Series, American Chemical Society: Washington, DC, 2: 61-78.

17. Nathans R, Cao H, Sharova N, Ali A, Sharkey M, et al. (2008) Small-molecule inhibition of HIV-1 Vif. Nat Biotechnol 26: 1187-1192.

18. Rathi AK, Syed R, Shin HS, Patel RV (2016) Piperazine derivatives for therapeutic use: a patent review (2010-present). Expert Opin Ther Pat 26: 777-797.

19. Jacobsen EN (1999) Asymmetric aziridination, In: Comprehensive Asymmetric Catalysis: Jacobsen EN, Pfaltz A, Yamamoto H (Eds). Springer: New York, Chapter 17.

20. McCuil W, Davis FA (2000) Recent synthetic applications of chiral aziridines. Synthesis 2000: 1347-1365.

21. Hodgkinson TJ, Shipman M (2001) Chemical synthesis and mode of action of the azinomycins. Tetrahedron 57: 4467-4488.

22. Kasai M, Kono M (1992) Studies on the chemistry of mitomycins. Synlett 1992: 778-790.

23. Osborn HM, Sweeny J (1997) The asymmetric synthesis of aziridines. Tetrahedron Asymmetry 8: 1693-1715.

24. Tanner D (1994) Chiral aziridines - Their synthesis and use in stereoselective transformations. Angew Chem Int. Ed 33: 599-619.

25. Pellissier H (2014) Recent developments in asymmetric aziridination. Adv Synth Catal 356: 1899-1935.