Ring Distortion of Vincamine Leads to Complex and Diverse Compounds for Drug Discovery

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Introduction

High-Throughput Screening (HTS) is the primary driver in modern drug discovery. Despite the success of HTS in drugging certain biological targets (e.g. tyrosine kinases), current screening libraries have been ineffective at targeting more sophisticated biological targets of therapeutic relevance (e.g. protein-protein interactions) due to a lack of chemical diversity. HTS libraries consist mainly of structurally simple organic molecules that lack stereochemical complexity and other features found in biologically active natural products (e.g. fused ring systems). As such, complex and diverse small molecules are of significant interest to the discovery of new therapeutic agents. Complexity to Diversity (CtD) is a chemical synthesis strategy aimed to rapidly generate complex and diverse molecules from complex NPs with fused ring systems for HTS and drug discovery. This is accomplished through dramatic ring-altering synthetic manipulations of select NPs, by utilizing ring distortion reactions (e.g. ring cleavage).[1,2] The goal of this venture is to create a structurally diverse screening library from the indole alkaloid vincamine (**V**), which is commercially available on decagram scale.

Experimental

Solid stock of vincamine derivatives (1-30 milligrams) were dissolved into ~ 500 µL of appropriate deuterated solvent containing 0.03% trimethylsilane. NMR experiments at the AMRIS facility provided key ^{1}H, ^{13}C, COSY, HSQC, HMBC, and 2-D NOESY data for the elucidation of molecules within this library. The Avance II 600 MHz and Avance III 500 MHz instruments were used regularly for the analysis of compounds.

Results and Discussion

To date more than 100 complex and diverse derivatives have been synthesized from vincamine, which we are attempting to publish at this time. Preliminary anti-cancer screens found that multiple compounds from this library activate the anti-oxidant response element (ARE), which is involved in many disease areas (e.g. cancer, inflammation). Additionally, other compounds within this library have been identified as having antimalarial and GPCR antagonistic activities. One novel, ring distorted analogue has been identified as a hypocretin receptor 2 (HCRTR2) antagonist. Antagonists of this receptor have been implicated in drug addiction, that is, studies have indicated efficacious molecules have attenuated the effects of heroin addiction in mouse models.[3] We have collaborated with an abuse expert in our College of Pharmacy and have demonstrated that this new vincamine analogue inhibits morphine-seeking behaviors in acute and reinstatement models of addiction.

The AMRIS facility has enabled us to streamline our synthetic, ring distortion efforts regarding vincamine. HMBC correlations were used to elucidate a novel ring fused scaffold, which inhibits morphine-seeking behaviors. This data was key in elucidating the ring closure due to HMBC correlations observed in this product, but not the starting material. Of course, other supporting data were acquired on the Avance III 500 MHz instrument such as ^{1}H, ^{13}C, COSY, and HSQC. Overall, these data provided our lab the capabilities to unambiguously characterize a library of highly complex and diverse small molecules with several molecular architectures. This compound library continues to be screened for biological activities at the University of Florida and other Universities.

Conclusions

The AMRIS facility has enabled a detailed characterization of several novel vincamine-derived small molecules that are currently being used to screen against new drug targets. Future compounds will need to be elucidated on AMRIS spectrometers, thus the need for these facilities is imperative.

Acknowledgements

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References

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