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Abstract for the 256th National Meeting of the American Chemical Society – 19 – 23 Aug 2018

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Title: Towards brighter bioluminescence: Synthesis and properties of rigid infra-luciferins

Bioluminescence is produced by the luciferin-luciferase reaction in the bodies of fireflies. Firefly bioluminescence has found many applications in research such as in reporter assays, and *in-vivo* imaging.

The native luciferin-luciferase reaction produces light of wavelength 558 nm. Research in oncology and regenerative medicine requires nIR (650 – 1000 nm) probes as blood and tissue adsorb light of ≤ 600 nm. In recent years, many efforts have been devoted to the development of bright nIR luciferin probes with limited success. Our group has previously reported Infra-luciferin; a synthetic luciferin that is one of the most red-shifted luciferin to-date (λ_{max} = 706 nm). Like other analogues infra-luciferin is also dimmer than D-luciferin. The loss in brightness is most likely due to radiation less decay caused by amongst other things, rotation around single bonds. In this project we investigated whether making rigid infra-luciferin structures would improve the quantum yield of the bioluminescence reaction.

A rationally designed modification of infra-luciferin resulted in the development of a novel series of rigid infra-luciferin structures bearing pyridobenzimidazole and dibenzothiophene scaffolds and their non-rigid counterparts bearing benzimidazole and benzothiophene scaffolds. In-silico docking studies into *Photinus pyralis* luciferase were carried out to determine the suitability of the proposed analogues. This presentation will focus on the design, synthesis and biological activity of these structures. Preliminary results indicate that the rigid compounds are brighter than their non-rigid counterparts. Studies are currently underway to understand the mechanism of light output using DFT calculations and inspecting the co-crystal of infra-luciferin with luciferase. Our work is the first example of its kind that explores the effect of conformational restraint on infra-luciferin structures.