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Millions of people suffer from thyroid hormone disorders. However, many more are unaware of their condition. Symptoms of thyroid conditions fall into two basic categories: hyperthyroidism with excessive thyroid hormone (TH) levels and hypothyroidism with lower TH levels. The thyroid gland is responsible for the synthesis and secretion of the (TH), which includes both thyroxine (T_4) and triiodothyronine (T_3). The predominant TH produced by the thyroid gland is T_4, which is the inactive form. Recent studies have shown, that T_3 is a metabolite of T_4. This typically takes place at the target tissue or in the liver. The active hormone, T3, is then transported into the cell and binds to a thyroid nuclear receptor (TR). Normally, T_3 mediated TR activation leads to the control of various biological processes: core body temperature, heart rate and metabolism. This activation process is typically slow ranging anywhere from hours to days. In the case of hyperthyroidism, patients exhibit increases in their core body temperature, heart rate and metabolism. Alternatively, patients with hypothyroidism experience a decrease in these biological processes.

Recently, a naturally occurring metabolite, 3-iodothyronamine (T_1AM) was discovered to elicit a rapid physiological response in mice. These include a decrease in core body temperature, metabolism and heart rate. T_1AM is a potent agonist of an orphan G-protein coupled receptors (GPCR) known as the trace amine-associated receptor ($TAAR_1$). GPCRs are known to mediate rapid cellular responses. If we consider these opposing physiological effects of T_1AM and TH it is possible that T_1AM and T_3 work in conjunction to provide a regulatory mechanism of TH activity including cardiac output, body temperature, and metabolism.

Studying this mechanism may lead to a greater understanding of TH biology. Our lab has been interested in developing novel derivatives of T_1AM as a means of examining this mechanism. Previously, we have found that incorporating a urea functional group in place of the ether linkage of T_1AM has led to significant $TAAR_1$ activation. These derivatives contained a para-linked aromatic system. The goal of this project is to expand on this structure activity relationship by examining a meta-linked aromatic system. Additionally, the length between the two aryl groups will be examined by insert 0 to 4 methylenes. To this end, the five targeted meta-linked ureas were synthesized utilizing a four step synthesis. These compounds now await biological evaluation in the next phase of the project. By achieving a greater understanding of T_1AMs role in thyroid hormone biology there may be more opportunities for treatments of patients who are suffering from thyroid hormone disorders.

*This scholar and faculty mentor have requested that only an abstract be published.