

**Final Report**  
**Short-Term Scientific Mission (STSM)**  
**COST Action BM0806**

**Host Institution: Trinity College Dublin, Ireland**

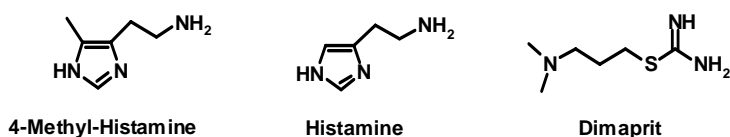
**Dr. Marco Eleopra**

### **Introduction**

I spent three months at Trinity College Dublin (Ireland) within a short-term-scientific mission under the supervision of Dr. Astrid Sasse. The aim of this STSM was the synthesis and characterization of new selective histamine H4 receptor ligands.

### **Background and Purpose**

Histamine acts through interactions with four G protein-coupled receptor subtypes, histamine H1, H2, H3, and H4 receptors (H1R, H2R, H3R, H4R). Whereas H1R and H2R antagonists became blockbuster drugs in recent years,<sup>1</sup> H3R was detected in the 1980s as an autoreceptor regulating histamine synthesis and release in the central nervous system.<sup>2</sup> In recent years, histamine H<sub>3</sub> and H<sub>4</sub> receptors have been studied extensively. Bioinformatic analysis on human genome databases resulted in the identification of the gene encoding the human H4R based on its sequence homology to the H3R gene (37%). In contrast to structural similarities, expression patterns of H3R and H4R strongly differ.<sup>3</sup> The H3R is mainly present in the nervous system, whereas H4R is expressed in hematopoietic cells. However, recent studies provided strong evidence that H4R is expressed and is functionally active on neurons in the mammalian CNS.<sup>4</sup> Although H3R and H4R exhibit a different pharmacological profile, many H<sub>4</sub>R ligands also interact with the H3R and there is limited selectivity for the H<sub>4</sub>R subtype.<sup>5</sup> Thus, in these years the development of H4R selective ligands became a major goal in this exciting new research field to better understand the pathophysiological role of these G protein-coupled receptors. Even though several research efforts produced different compounds, there is still a lack of receptor selectivity.<sup>6</sup> Hence, aim of this STSM was the synthesis and characterization of new histamine related compounds with high selectivity for H4 histamine receptors. Starting from 4-methyl-histamine and Dimaprit, we synthesized novel linear and cyclic compounds, optimizing a suitable synthetic pathway (**Figure1**).

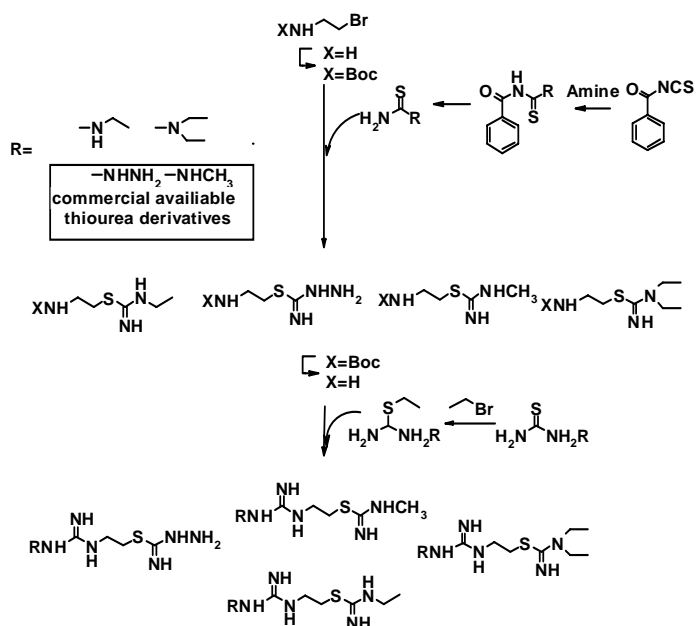


**Figure 1.** H4 receptors agonists.

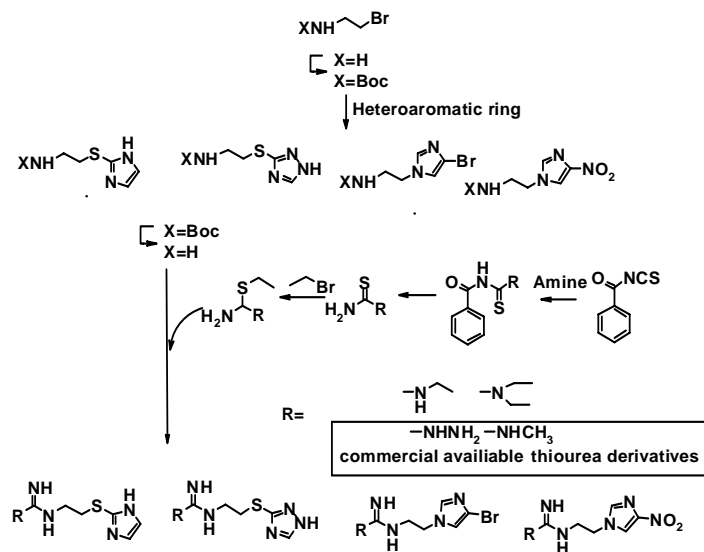
### **Work carried out**

During the three months of this STSM, three general synthetic routes were planned (**Routes A-C**). Due to common intermediates, these synthetic pathways are suitable for the development of different series of compounds in a convenient and cost-effective way. In addition, the synthetic routes described herein are suitable for microwave synthesis as well as scale-up processes, making them suitable for potential further development.

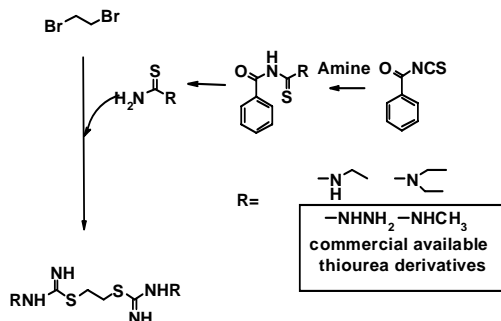
**Route A.** Synthetic pathway to obtain asymmetrical, linear compounds:



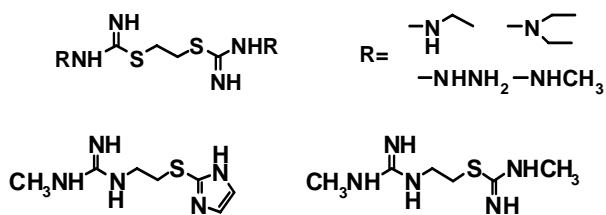
**Route B.** Synthetic pathway to develop asymmetrical, heterocyclic compounds:



**Route C.** Simple synthesis of symmetrical linear compounds.

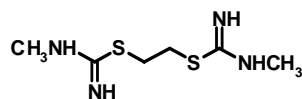


The synthesized final compounds (**Figure 2**) will be sent to the Prof. Stark's lab at the University of Frankfurt (COST BM0806 MC member and WG4 chair) for biological evaluation on histamine receptors, focusing the attention on the selectivity between H3R and H4R.



**Figure 2.** First synthesized compounds.

### Example



### Synthesis of 1,2-methylthiourea-ethane:

1-Methyl-2-thiourea (2 eq.) was added to a solution of dibromoethane (1 eq.) in ethanol and the reaction was heated at reflux overnight. After cooling, the solvent was evaporated in vacuo and the crude material was crystallized by ethanol/ethyl ether to give the desired product as white solid. Yield: 65%  $^1\text{H}$  NMR: (400 MHz,  $\text{D}_2\text{O}$ ) 2.89 (s, 6H), 3.36 (s, 4H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ) 31.14, 45.78.

### Future collaboration

In this three months work, our synthetic procedures showed an exciting potential to develop several sets of histamine related compounds. In collaboration with Prof. Stark and other scientists of the COST Action BM0806, we will be able to develop subtype- and species-selective H4 receptor agonists and antagonists. I applied to EU and national funding bodies to continue my postdoctoral studies in Dr.Sasse's Lab at Trinity College Dublin. In addition, our results will be object of international contributions to conferences, as well as publications in peer-reviewed journals in the field of medicinal chemistry.

### Reference

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