**Introduction**

- The ability of enaminone (E121-Figure 1) to decrease the pro-inflammatory mediators (TNF-alpha and IL-6) in macrophages stimulated with lipopolysaccharide encouraged us to examine its structural scaffold as a novel anti-inflammatory agent.
- Pro-inflammatory mediators regulate the immune response when infection is present. However, overproduction cause severe tissue injury seen in autoimmune diseases such as Crohn’s disease.
- JODI series were designed where an N-arylpiperazine motif was incorporated into the aromatic side of the enaminone (JODI 18 and 19; Figure 1).
- JODI 18 and 19 (Figure 1) has shown to suppress TNF-alpha and IL-6 and were more effective in reducing TNF-alpha after LPS stimulation when compared to dexamethasone (Figure 2).
- Positive results of JODI encouraged further exploration of the chemical scaffold, hence JOAB series was developed.

**Objective**

- To explore four possible chemical modification of the original enaminone scaffold to identify the structural features responsible for their activity.

**Results & Discussion**

- Sixteen compounds were synthesized and tested on their ability to reduce TNF-alpha and IL-6 in LPS-stimulated macrophages (Figures 4 and 5).
- Size of R₁ play a major role of the ability of JOAB series to reduce TNF-alpha and IL-6.
- Phenyl ring in R₁ position is more favorable than its methyl counterpart.
- High lipophilicity at R₁ play a major role on the ability to interact with the target site (s).
- R₁ size and lipophilicity might not be determining factors in the ability of the piperazino-enaminone to suppress the pro-inflammatory mediators.
- The effect of the position of the piperazine ring is less consistent. However, the para or meta positions are more favorable than the ortho counterpart.

**Conclusion**

- Piperazino-enaminones (JODI and JOAB series) represent potential pro-inflammatory mediator suppressants.
- Reduction of IL-6 seems to be more significant than reduction of TNF-alpha, indicative of an effect on a differential signaling mechanism or a transcription factor (future experiments).

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