# Discovery of novel orally active tetrahydro-naphthyl-*N*-acylhydrazones with in vivo anti-NO effect and remarkable anti-inflammatory properties

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## Abstract

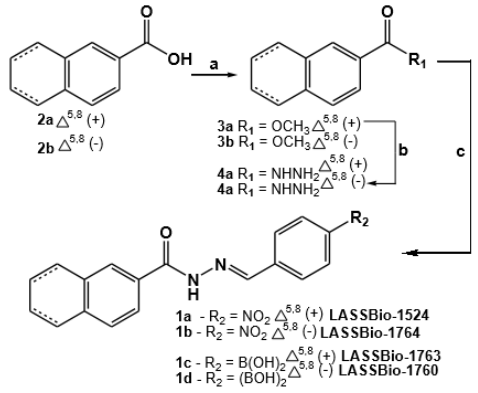
This work describes the design, the synthesis and the pharmacological evaluation of novel tetrahydro-naphthyl-*N*-acylhydrazones with in vivo anti-NO effect and anti-inflammatory properties.

## Introdução

Despite the benefit of inflammation to homeostasis of the organism, there are cases where chronic inflammation is exacerbated or unregulated for a long period, and inflammation itself cause deleterious effects, being associated with a large number of diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, among others[1]. Thus, there is an urgent need for new and more effective anti-inflammatory drugs with fewer side effects. In order to optimize the pharmacological activity of LASSBio-1524, a prototype with potent antiinflammatory properties, we proposed three new *N*-acylhydrazone derivatives based on the planned exchange of their structure.

## Resultados e Discussão

Commercially available carboxylic acids (**2a**-**b**) were used as the starting material; they were converted to the hydrazide intermediates (**4a**-**b**) after Fischer esterification and nucleophilic substitution at the carbonyl group of methyl esters (**3a**-**b**) with 80% hydrazine hydrate. The desired NAH derivatives (**1a**-**d**) were obtained in high yields from acid-catalyzed condensation of hydrazides (**4a**-**b**) with the appropriate aromatic aldehydes[2] (Scheme 1).




**Scheme 1:** a) MeOH, $H_2SO_4$, 70°C, 6 h, 90%; b) $NH_2NH_2$, EtOH, 80°C, 4 h, 84-88%; c) ArCHO, EtOH, HCl 10%, 3 h, 75-94%

In order to investigate the effect of the target compounds in the inflammatory mediators produced after an inflammatogenic stimuli, the amount of nitric oxide (NO) accumulated in the SAP exudate was quantified. Animals pretreated orally with vehicle and injected with PBS in subcutaneous air pouch (SAP) had a concentration of 13.4 ± 8.6 µM of NO; while in animals pretreated orally with vehicle and that received carrageenan injection, to promoted chemotaxis, the NO production increased almost 19-fold (243.3 ± 56.5 µM) (Figure 1). Our results indicate that pretreatment with all *N*-acylhydrazone derivatives (**1a**-**d**) reduced by more than 65 % NO production. At the lowest dose, 3 µmol/kg, it was observed a significant reduction in NO production for all compounds. LASSBio-1760 (**1d**) blocked almost completely NO production in the doses of 30 µmol/kg (Figure 1), suggesting that these substances could be acting as direct nitric oxide synthase inhibitors or perhaps inhibiting the biosynthesis/iNOS expression in cells.

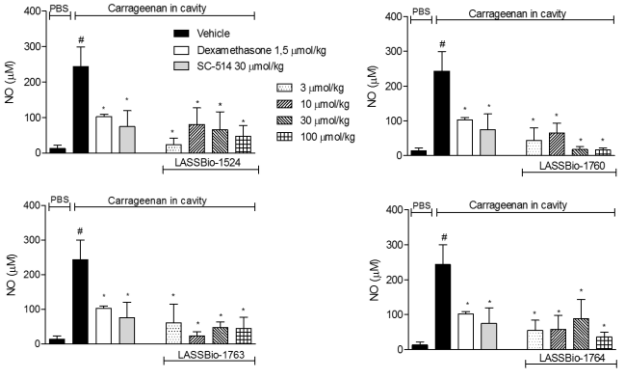



**Figure 1.** In vivo anti-NO effect of novel NAH derivatives (1a-d).

## Conclusões

New NAH derivatives were potent and orally active as anti-inflammatory agents. This profile may be correlated with their ability to inhibit leukocyte migration and reduce the biosynthesis of NO in vivo.

## Agradecimentos

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