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Short Communication

Analgesic activity of cyclic imides: 1,8-naphthalimide and 1,4,5,8-naphthalenediimide derivatives

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Abstract

In early studies, we have reported the synthesis and biological activities of several cyclic imides. The present study describes the analgesic activity of 1,8-naphthalimide and 1,4,5,8-naphthalenediimide derivatives in a standard murine model of analgesia. The pharmacological results show that all compounds studied, given intraperitoneally, produced significant inhibition of acetic acid-induced abdominal constrictions. At the ID_{50} (μmol/kg) level, these cyclic imide derivatives were about 40–270-fold more potent in this assay than aspirin and acetaminophen, two well-known and widely used analgesics. These results extend previous studies on the analgesic activity of cyclic imides.

Keywords: Cyclic imides; Analgesic activity; Naphthalimides; Writhing test

1. Introduction

Previously, our research group has studied the chemical and biological properties of cyclic imides, which were synthesized using phyllantimide, an alkaloid extracted from *Phyllantus sellowianus* [1], as a model. Several analogues were obtained that exhibit a spectrum of biological activities [2–8], including analgesic action [9–13].

In order to extend our research program concerning the biological properties of cyclic imides, we have now evaluated a series of 1,8-naphthalimide and 1,4,5,8-naphthalenediimide derivatives as analgesics. Previous studies provide evidence that these compounds exerted analgesic action at 10 mg/kg in mice [12].

2. Results and discussion

In order to extend our research program to discover molecules which could be used as starting points for the discovery of new analgesic drugs, a series of 1,8-naphthalimides and 1,4,5,8-naphthalenediimides was prepared and their analgesic properties evaluated by using the writhing test in mice. For comparison, we have also included the analgesic effects of aspirin and acetaminophen [14]. The compounds studied here are shown in Scheme 1. The substituent group in the aromatic ring was selected according to the Topliss method [15], which aids in the prediction of new, more active compounds.

Table 1 shows the analgesic potency of these compounds, and of aspirin and acetaminophen. As can be seen, all of them exhibit potent and structure-dependent analgesic effects, being several times more potent than aspirin and acetaminophen, two comparative standard drugs used in our studies. The most active compound (**10**) is approximately 270-fold more active on a molar

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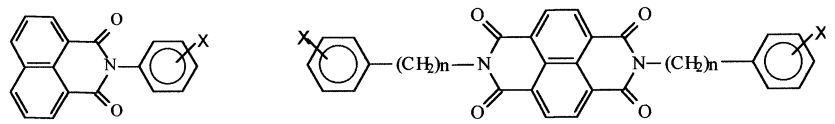

X = H (1)
X = 4-CH_3 (2)
X = 4-OCH_3 (3)
X = 4-Cl (4)
X = 3,4-Cl_2 (5)

n = 0, X = H (6)
n = 1, X = H (7)
n = 2, X = H (8)
n = 0, X = 4-CH_3 (9)
n = 0, X = 4-OCH_3 (10)
n = 0, X = 4-Cl (11)
n = 0, X = 3,4-Cl_2 (12)

Scheme 1.

basis than the standard drugs. Comparison of the 1,4,5,8-naphthalenediimides **6** and **10** indicates that the introduction of an electron-donating methoxy group in position 4 of the aromatic ring significantly increased the analgesic activity. This suggests that resonance donation plays a significant role in the binding of these molecules, and results in enhanced inhibition of the acetic acid-induced abdominal constrictions in mice. Similarly, comparison between 1,8-naphthalimides **1** and **3** confirms that the introduction of a 4-methoxy group improves the analgesic potency.

The distance between the aromatic and the imido ring seems to be another important factor related to analgesic activity of the 1,4,5,8-naphthalenediimides. Comparing data for structures **6**–**8**, the compound containing the aromatic ring directly attached to the imido ring (**6**) is the most potent. It was, therefore, used as a point of departure to achieve more active derivatives, such as compound **10**, the most potent cyclic imide synthesized by our research group to the present time.

The promising analgesic effects demonstrated here for these cyclic imides suggest that this class of organic compounds may be useful for the design of novel cyclic imides having improved analgesic activity. This communication confirms previous studies concerning the activity of cyclic imides [10–13]. Studies are currently in progress to evaluate these compounds in other pharmacological models of pain as well to characterize their mechanism of analgesic action.

3. Experimental

3.1. Chemical procedures

Compounds were prepared by adding the appropriate aniline or aniline derivative to a solution of the respective anhydride in acetic acid, as previously described [12].

3.2. Pharmacological analysis: writhing test

Female Swiss mice (25–30 g) were kept at an automatically controlled temperature (23 ± 2°C) with 12 h light–dark cycles. Food and water were freely available. The abdominal constriction induced by intraperitoneal injection of acetic acid (0.6%; 15 ml/kg) was carried out according to the procedures described previously [16]. Animals were pretreated with the compounds (0.06–30 mg/kg; 0.21–97.7 μmol) intraperitoneally 30 min before the acetic acid injection. Control animals received a similar volume of 0.9% NaCl (10 ml/kg). All experiments were carried out at 20–22°C. After challenge, pairs of mice were placed in separate boxes and the number of abdominal constrictions was cumulatively counted over a period of 20 min. The results are reported in Table 1.

Table 1
Analgesic effects of a series of 1,8-naphthalimides and 1,4,5,8-naphthalenediimides given intraperitoneally, against acetic acid-induced abdominal constriction in mice [a]

Comp.	ID_{50} (μmol/kg)	ID_{50} (mg/kg)	MI (%)
1	1.69 (1.28–2.27)	0.46 (0.35–0.62)	88 ± 8
2	0.60 (0.21–1.18)	0.17 (0.06–0.34)	99 ± 1
3	0.79 (0.40–0.99)	0.24 (0.12–0.30)	99 ± 1
4	3.20 (2.08–5.28)	0.98 (0.64–1.62)	93 ± 2
5	1.00 (0.79–1.37)	0.34 (0.27–0.48)	92 ± 4
6	1.00 (0.67–1.48)	0.42 (0.25–0.63)	90 ± 3
7	1.50 (0.29–1.91)	0.67 (0.13–0.85)	98 ± 1
8	1.29 (0.69–2.40)	0.61 (0.33–1.14)	91 ± 2
9	1.19 (0.62–2.42)	0.53 (0.28–1.10)	99 ± 1
10	0.48 (0.40–0.79)	0.23 (0.19–0.38)	99 ± 1
11	1.60 (0.99–2.89)	0.78 (0.48–1.41)	92 ± 6
12	1.10 (0.79–1.69)	0.61(0.44–0.94)	90 ± 6
Aspirin [14]	133.0 (73–243)	24.0 (13.1–43.8)	83 ± 2
Acetaminophen [14]	125.0 (104–150)	18.8 (15.7–22.6)	88 ± 1

[a] ID_{50} values are accompanied by 95% confidence limits. MI indicates the maximal inhibition (%) of abdominal constrictions (at 30 mg/kg). Each group represents the mean of six to ten animals.

3.3. Drugs

The cyclic imides were dissolved in Tween 80 (Merck) plus 0.9% NaCl solution. The final concentration of Tween 80 did not exceed 5% and did not cause any effect per se.

3.4. Statistical analysis

The results are presented as mean ± SEM, except the ID_{50} values (the dose of compound that reduced responses by 50% relative to control value) which are reported as geometric means followed by their corresponding 95% confidence limits. The statistical significance between groups was calculated by means of analysis of variance followed by Dunnett's multiple comparison test. *P* values less than 0.05 were considered as indicative of significance. The ID_{50} values were determined by linear regression from individual experiments using linear regression GraphPad software.

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