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Short communication

New orally effective 3-(2-nitro)phenylpropanamide analgesic derivatives: Synthesis and antinociceptive evaluation

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ABSTRACT

A series of substituted 6-nitrophenylpropanamide derivatives (**1**–**20**) were synthesized using either the TDAE strategy or classical organic reactions. All these compounds were characterized by fusion point, ^{1}H NMR, ^{13}C NMR, elemental analysis or mass spectrometry data. Because of their structural analogy with recently published compounds possessing antinociceptive properties, our derivatives were screened for peripheral analgesic activities on acetic acid-induced writhing in mice. Compound **13** showed the best result at 100 μmol/kg *ip* (50% inhibition *vs* 59% for aspirin). This antinociceptive activity was maintained after oral administration (40% inhibition *vs* 31.6% for aspirin). Both hot-plate and actimetry-based tests were non-significant suggesting the analgesic activity of **13** linked to a peripheral mechanism.

1. Introduction

Pain is an unpleasant and a subjective sensation resulting from a harmful sensorial stimulation that alerts the body about current or potential damage to its tissues and organs [1]. Prescribing analgesics is the first response of health professionals, before removal of the underlying causes. The World Health Organization classifies analgesic drugs into three categories, by analgesic strength [2]. The first category includes paracetamol, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). The second and the third are composed of opioid drugs such as codeine and morphine acting against moderate and severe pain respectively.

Among the non-steroidal anti-inflammatory agents, arylalkanoic acids are the most widely investigated compounds. A typical molecule offer valuable features like a carboxyl group separated by one or more carbon atoms from an aromatic nucleus. The lead compound for aryl acetic acids is ibuprofen.

However, although these drugs are very effective and abundantly prescribed, they have revealed some gastric or intestinal adverse effects leading to numerous hospitalizations or death [3].

As a solution, many research groups transformed the carboxylic acid moiety of commercially available NSAIDs into carboxamide or ester forms in order to increase their cyclooxygenase-2 selectivity and their oral absorption, and to hide the irritant carboxylic acid group. Derivatizations studies of this kind were performed on indometacine [4] and mefenamic acid [5,6], profens [7], and phenylacetic acids [8].

In parallel, three research groups developed alternative arylalkanoic scaffolds bearing a carboxamide moiety which showed promising analgesic and anti-inflammatory activity combined with a safe ulcerogenic profile (Fig. 1, formula A, B and C) [9–14]. Kwak

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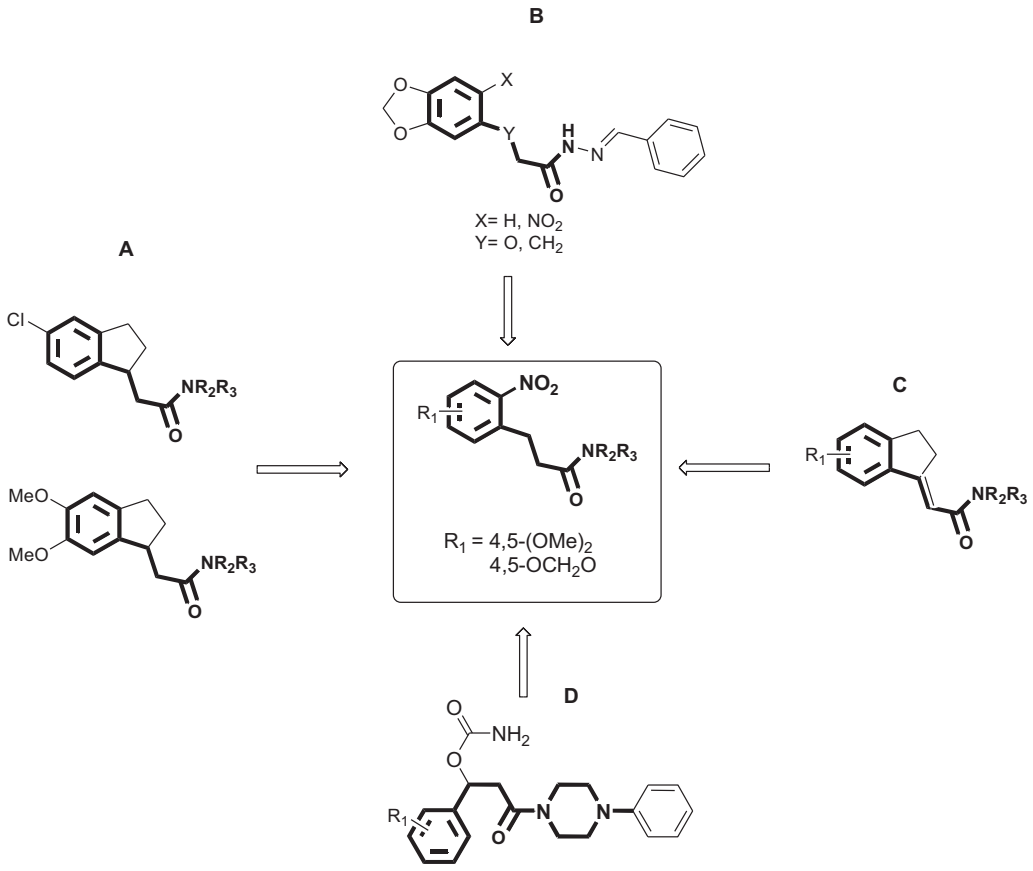

Fig. 1. Design of 3-(2-nitrophenyl)propanamides.

et al. developed carbamic acid derivatives bearing similar scaffolds and phenylpiperazinyl moiety (Fig. 1 formula D). These derivatives not only showed peripheral antinociceptive property but also anti-anxiety and antidepressant activities on mice [15].

Combining these promising structures enabled us to reveal the N-substituted 3-(2-nitrophenyl)propanamide skeleton as a new potentially analgesic scaffold (Fig. 1).

Recently, we developed a new synthesis methodology using tetrakis(dimethylamino)ethylene (TDAE) to prepare *N*,*N*-disubstituted 3-(6-nitrobenzo[*d*][1,3]dioxol-5-yl)propanamide and 3-(4,5-dimethoxy-2-nitrophenyl)propanamide derivatives [16]. This and previous studies [17,18] demonstrated the nitro group requirement in *ortho*- or in *para*- position from chloride to performed the carbon-halide reduction *via* the TDAE strategy. Consequently, we focus our interest on the synthesis of nitrated compounds. In continuation of our work directed towards the development of original synthetic methods in medicinal chemistry [19–25] and the preparation of new potentially analgesic active compounds [26,27], we report herein the synthesis of new 3-(2-nitrophenyl)propanamide derivatives and their analgesic properties.

2. Results–discussion

2.1. Chemistry

Preparation of the 3-(2-nitrophenyl)propanamides and esters (**1**–**20**) was realized *via* two different pathways (Scheme 1).

First, we used the S_N2 initiated by TDAE. This methodology led us to previously synthesize compounds **1**–**6** [16].

The second pathway used phenylpropanoic acids as starting materials using classical organic reactions. This yielded more synthesis alternatives such as un-nitrated derivatives or 2-substituted amides, *via* a simple, quick and cost-effective strategy. The 3-(benzo[*d*][1,3]dioxol-5-yl)propanoic acid was first reacted with nitric acid in dichloromethane, leading to nitrated derivatives in quantitative yield. These, or the starting propanoic acid, were reacted with thionyl chloride to obtain acyl chlorinated intermediates. After evaporation of the solvent, the crude was reacted with the corresponding amine reagent, leading to the expected products **7**–**17** in moderate to good yields (34–95%) (Table 1).

To complete the pharmacomodulation of compound **13**, reduction of its nitro group appeared an attractive option and was performed using molecular hydrogen in dioxane leading to compound **20** in 36% yield.

2.2. Analgesic activity

2.2.1. Antinociceptive screening

Antinociceptive activity of synthesized compounds was first assessed through the acetic acid-induced writhing test. A screening protocol was used to select structures possessing analgesic activity after 3 mg/kg intra-peritoneal (*ip*) administration in mice (Table 2). No toxic effect was observed during the protocol.

In 6-nitrobenzo[*d*][1,3]dioxol-5-yl series (**1**–**4**, **8**–**20**), non-significant results were observed with the non-substituted carboxamide derivative **8** or with compounds bearing an aromatic ring (**9**, **10**). However, substitution by aliphatic groups such as *n*-hexyl (**11**), piperidinyl (**1**), morpholinyl (**2**), piperazinyl (**12**, **13**) led to better results. Focusing on compound **13**, analogous derivatives with periodic structural changes were synthesized and screened (**3**, **14**–**17**, **20**). These compounds did not show improved antinociceptive activity. We can observe that derivatives **17** and **20**, the