Biomedicine & Pharmacotherapy 104 (2018) 437–450

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Synthetic chalcones as potential tool for acute- and chronic-pain control

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ARTICLE INFO

Keywords:
Nitrochalcone
Hypersensitivity
Persistent pain
In silico
Analysis

ABSTRACT

The purpose of this study was to validate the potential anti-hypersensitive activity of two chalcones, (2E)-1-(4-aminophenyl)-3-(4-nitrophenyl)prop-2-en-1-one (ANCh) and N-{4-[(2E)-3-(4-nitrophenyl)prop-2-enoil]phenyl} acetamide (AcANCh), by different models of acute and persistent pain in mice, besides in silico analysis. Molecules computational investigation for prediction of Lipinki's and Veber's rules to determine solubility, % absorption, drug likeness and toxicity liabilities was performed. Male and female C57BL/6 mice (20–30 g, n = 6) were used. Firstly, mice were pre-treated with the compounds ANCh or AcANCh and then submitted to the models of acute hypersensitivity by the intraplantar injection of different phlogistic agents. The mechanical sensitivity was assessed using von Frey hairs (0.6 g). The obtained data shows that both compounds presented important inhibitory effects on mechanical hypersensitivity induced by carrageenan (with oral bioavailability). The anti-hypersensitive effect was also accompanied by the interference in leukocyte migration, interleukin-1β (IL-1β) and tumour necrosis factor (TNF) levels reduction and by the absence of unspecific effects. Added to the in vivo results, the in silico analysis presented none violation in Lipinski's or Veber's rules, good probability to cell membrane permeability and oral bioavailability, positive values of drug likeness and few risk of computational toxicity. ANCh partially reduced the hypersensitivity induced by IL-1β and TNF, epinephrine and prostaglandin E_2 (PGE_2). AcANCh had similar effect, except for the absent of inhibition in PGE_2-injected mice. Both compounds were capable of reducing the mechanical hypersensitivity presented in all persistent models of hypersensitivity (inflammatory pain, chronic nerve constriction and cancer pain), with emphasis for ANCh. These results suggest that both chalcones could represent good strategies for the control of acute and chronic pain, without important side effects. ANCh seems to involve cell migration and cytokines production as the main mechanism, together with interference in PGE2 neuronal sensitization pathway. In vivo and in silico analyses reinforce the potential characteristics of the compounds to become future drugs.

1. Introduction

Pain is a complex experience that involves the neuronal stimulation by something harmful or potentially harmful, as well as emotional and physiological conditions related to this event. There is no doubt that chronic pain causes many losses, concerning individual suffering and social impact and, unfortunately, current therapies have limitations related to safety and efficacy [1,2]. Only 50–60% of patients with inflammatory pain achieve relief of this symptom by the use of current available medications, and it is even lower for patients suffering from neuropathic pain, 30–40% [3].

Chalcones (1,3-diaryl-2-propen-1-ones) are naturally occurring compounds commonly found in plant kingdom and belonging to the flavonoid family. Chemically, chalcones are open-chained molecules in which the two aromatic rings are joined by the three-carbon α-β-unsaturated carbonyl system. These compounds can be naturally obtained or synthetized and have been reported to present various pharmacological activities, including anti-tumor [4,5] antimalarial and antileishmanial [6], antifungal [7], anti-inflammatory [8], anti-hyperglycaemic [9] and antinociceptive effects [10–13].

Previous studies with the chalcones presented in Fig. 1(A and C) have demonstrated that both (2E) - 1 - (4-Aminophenyl) -3 - (4-nitrophenyl) prop-2-en-1-one (ANCh;) and N-{4 - [(2E) -3 - (4-nitrophenyl) prop-2-enoyl] phenyl} acetamide (AcANCh; unpublished

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https://doi.org/10.1016/j.biopha.2018.05.075
Received 23 February 2018; Received in revised form 16 May 2018; Accepted 16 May 2018
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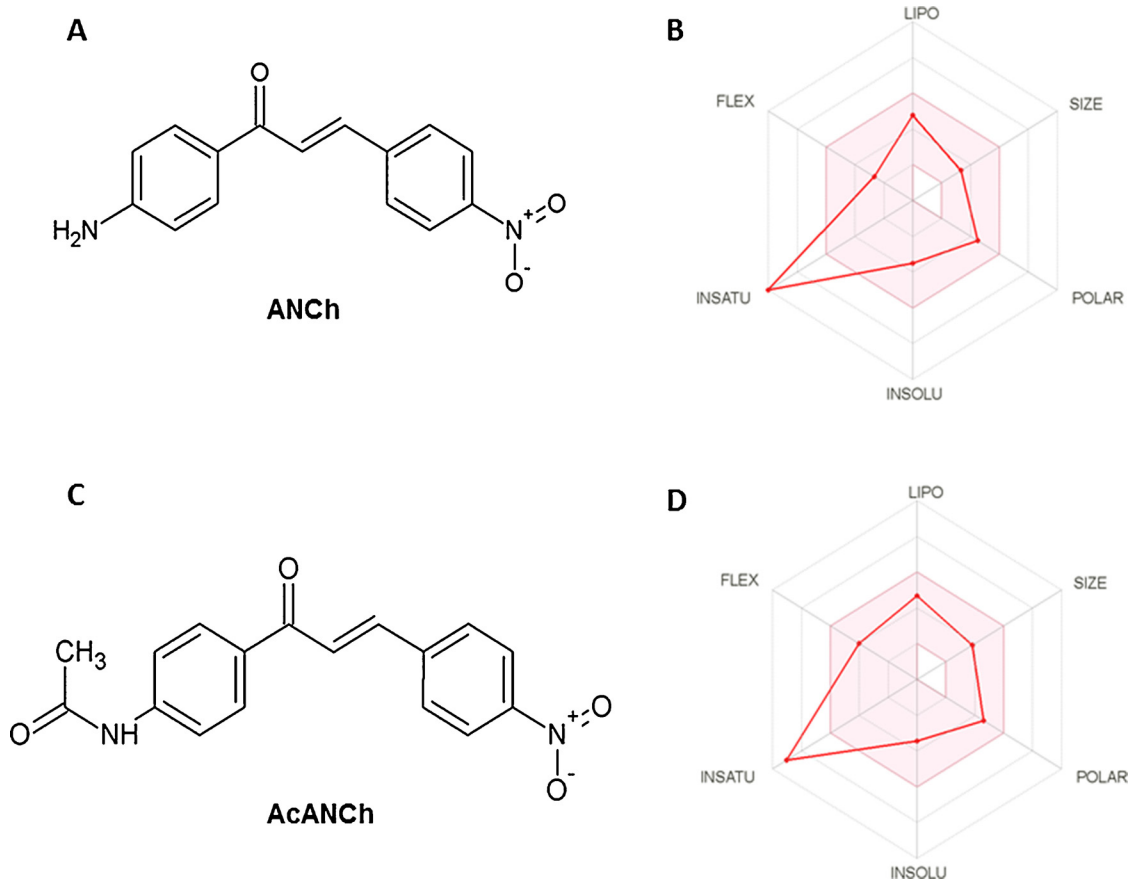

Fig. 1. Structures and bioavailability radar of N-{4 - [(2E) -3 - (4-nitrophenyl) prop-2-enoyl] phenyl} acetamide (AcANCh) and (2E) - 1 - (4-Aminophenyl) -3 - (4-nitrophenyl) prop-2-en-1-one (ANCh). Note: The pink area represents the optimal range for each properties according to Daina et al. [30] (lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 Å2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds).

data) presented antinociceptive activity in experimental models of acute pain in mice [13]. Due to these properties, both compounds were largely evaluated in this study with the aimed of investigating the anti-hypersensitive effect of ANCh and AcANCh throughout different experimental models of long-lasting inflammatory, neuropathic and cancer pain in mice. It was also performed *in silico* analyses to predict the bioavailability and toxicity of the compounds.

2. Material and methods

2.1. In silico evaluation

The two-dimensional chemical structure and canonical SMILES were performed using SwissADME, to calculate physicochemical descriptors as well as to predict bioavailability radar.

The methodology used by Molinspiration calculation as a sum of fragment-based contributions and correction factors is very robust and is able to process practically all organic and most organometallic molecules. Lipinski's rule of five acts as a filter for drug-like properties and states that a potential molecule is orally active if its molecular weight is ≤ 500 g, clog P ≤ 5, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5. Molecular Polar Surface Area (TPSA) is calculated as a sum of fragment contributions. S-, N-, I and Pd centred polar fragments are considered. PSA has been shown to be a great descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood–brain barrier penetration. Number of rotatable bonds (nrotb) is an important indicator for molecular flexibility and conformational change for binding to the receptor or channels.

Toxicity risks (mutagenicity, tumorigenicity, irritability, and reproductive effective) and physicochemical properties (solubility and drug-likeness) of compounds were calculated by the methodology developed by Data Warrior. The toxicity risk predictor locates fragments within a molecule which indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the specified risk category.

The percentage of absorption was calculated using the following equation: %ABS = 109 − [0.345 × TPSA] [14].

2.2. Drugs and reagents

The following drugs were used: ƛ-Carrageenan, prostaglandin E_2 (PGE_2), epinephrine, tetramethylbenzidine (TMB), phenylmethylsulphonyl fluoride (PMSF), hexadecyltrimethyl ammoniumbromide (HTAB), benzethonium chloride, aprotinin, EDTA, Tween 20, bradykinin (BK), lipopolysaccharide (LPS), complete Freund's adjuvant (CFA), hydrogen peroxide, methyl methanesulfonate (MMS) all came from Sigma Chemical Company (St Louis, MO, USA). NaH_2PO_4, Na_2HPO_4, NaCl, and glucose were supplied by Merck (Haar, Germany). Recombinant mouse (rm) tumour necrosis factor (TNF), rm-Interleukine-1β (IL-1 β), rm-keratinocyte-derived chemokine (KC) and Mouse IL-1β, TNF, KC/CXCL1 and IL-10 DuoSet kit were obtained from R&D Systems (Minneapolis, MN, USA). Lipopolysaccharide (LPS) derived from E. coli was bought from Sigma (St Louis, MO, USA).

2.3. Animals

The experiments were conducted using male and female C57BL/6

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