Arabian Journal of Chemistry (2015) 8, 307–312

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis, physicochemical and biological evaluation of 2-amino-5-chlorobenzophenone derivatives as potent skeletal muscle relaxants

Rajesh K. Singh *, **Sonia Devi** [1], **D.N. Prasad**

Pharmaceutical Chemistry Division, Shivalik College of Pharmacy, Nangal, Rupnagar, Punjab 140126, India

Received 7 June 2011; accepted 22 November 2011
Available online 3 December 2011

KEYWORDS

2-Aminobenzophenone;
Central Nervous System;
Skeletal muscle relaxant activity;
Physicochemical parameters;
Log *P*;
Rotarod test

Abstract A series of novel 2-amino-5-chlorobenzophenone derivatives (**3a**–**3g**) were prepared by the reaction of 2-(chloroacetamido)-5-chlorobenzophenone and different aniline derivatives by both conventional and microwave methods and structures were confirmed on the basis of their TLC, IR, 1H NMR and CHN elemental studies. Out of the two methods, microwave methods was found to give better yield. All the synthesized compounds were subjected to physicochemical parameters determination for BBB penetration through online software. The log *P* values of most of our test compounds indicate that test compounds have the potential to be CNS active. The experimentally determined and calculated values of log *P* are very much similar to values of log *P* calculated by the online software chemsilico and are in the range required for good CNS activity. The values of other physicochemical parameters like molecular weight, nON value, nOHNH value, *n*-violations and the number of rotatable bonds of all the test compounds also lie between the ranges that are required for good BBB penetration. The compounds were screened for the skeletal muscle relaxant activity and from the investigation, it is quite apparent that all the 2-amino-5-chlorobenzophenone derivatives (**3a**–**3g**) possess significant differences between control group and treated group, $P < 0.001$. Among these 2-amino-5-chlorobenzophenone derivatives, the compound bearing *o*-toluidine as a substituent (**3e**) possesses the highest skeletal muscle relaxant activity.

1. Introduction

2-Aminobenzophenone derivatives are important compounds in organic chemistry because of their application in heterocyclic synthesis and medicines (Walsh, 1980). 2-Aminobenzophenone has been used as starting material for the synthesis of 1, 4-benzodiazepines (Sternbach et al., 1962), proquazone and amfenac as anti-inflammatory agents (Coombs et al., 1973; Welstead et al., 1979; Ottosen et al., 2003). It has also been used for the synthesis of Peptidoaminobenzophenones, a novel class of ring open derivatives of 1, 4-benzodiazepines, evaluated for Central Ner-

* Corresponding author. Tel.: +91 01887 221276, mobile: +91 9417513730; fax: +91 01887 221276.
E-mail address: rksingh244@gmail.com (R.K. Singh).
[1] Present Address: Dept. of Pharmaceutical Chemistry, Laureate Institute of Pharmacy, Kathog, Kangra, Himachal Pradesh, India.
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1878-5352 © 2011 Production and hosting by Elsevier B.V. on behalf of King Saud University.
http://dx.doi.org/10.1016/j.arabjc.2011.11.013

vous System (CNS) activity. (Felix et al., 1974; Bodor et al., 1977; Hirai et al., 1980). 2-Aminobenzophenone derivatives were also evaluated as antimitotic agents (Liou et al., 2002) and a novel class of bradykinin B_1 receptor antagonists with excellent receptor occupancy in the CNS of hBK B_1 transgenic rats but not a substrate for P-glycoprotein (P-gp) mediated efflux and hence good brain penetration (Su et al., 2008). All these drugs synthesized from 2-aminobenzophenones possess CNS activity. 2-aminobenzophenone derivatives were considered to be of our interest because they fulfill all the structure activity requirements as the benzodiazepine contains. According to SAR study rings A and C and substitutions at these rings and the substitution at the amide nitrogen of ring B are important for the activity of benzodiazepines as shown in Fig. 1. So it was considered to be of interest to synthesize the 2-aminobenzophenones derivatives having all the important pharmacophores required for the CNS activity of benzodiazepines to obtain drugs with high therapeutic index than diazepam. In this 2-amino-5-chlorobenzophenones are subjected to acetylation by treating with chloroacetylchloride to obtain 2-chloroacetamidobenzophenones which are then reacted with different aniline derivatives in the presence of potassium carbonate and DMF by conventional and microwave irradiation methods to obtain different derivatives (Scheme 1).

2. Materials and methods

2.1. Experimental

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (^{1}H) nuclear magnetic resonance (^{1}H NMR) spectra were obtained using Brucker AC-400 F, 400 MHZ spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as internal standard. The spin multiplicities are indicated by the symbols: s (singlet), d (doublets), t (triplet), q (quartet), m (multiplet) and br (broad). Infrared (IR) spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using potassium bromide pellets (in cm^{-1}). The ultraviolet spectra were recorded on Shimadzu, UV-1800 spectrophotometer. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN elemental analyzer. Syntheses related to microwave irradiation were carried out in domestic LG little chef microwave oven. Reactions were monitored and the homogeneity of the products was checked by TLC which were prepared with silica gel G and activated at 110 °C for 30 min. The plates were developed by exposure to iodine vapors. Anhydrous sodium sulfate was utilized as drying agents. All solvents were dried and freshly distilled prior to use according to standard procedure.

2.2. Synthesis of 2-(chloroacetamido)-5-chlorobenzophenone

2.2.1. Conventional method

The syntheses of 2-amino-5-chlorobenzophenone and 2-(chloroacetamido)-5-chlorobenzophenone were carried out by literature methods (Sternbach et al., 1961, 1962). In this method, 2-amino-5-chlorobenzophenone **(1)** (1 mole) and chloroacetylchloride (2 mole) in toluene was refluxed for 2.5 h to expel most of the formed hydrogen chloride. The solution was then cooled, washed with ice cold dilute aqueous ammonia solution, dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The recrystallization of the crude residue from alcohol afforded 82% of 2-(chloroacetamido)-5-chlorobenzophenone **(2)**; mp 119–122 °C, lit. (Sternbach et al., 1961) 119–121 °C.

2.2.2. Microwave irradiation method

A solution of 2-amino-5-chlorobenzophenone **(1)** (0.464 g, 2 mmole) and chloroacetylchloride (0.318 ml, 4 mmole) in toluene (20.0 ml) was irradiated for 1 minute in a microwave oven (360 W). The solution was then cooled, washed with ice cold dilute aqueous ammonia solution, dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The recrystallization of the crude residue from alcohol afforded 88% of 2-(chloroacetamido)-5-chlorobenzophenone **(2)**; mp 118–120 °C, lit. (Sternbach et al., 1961) 119–121 °C.

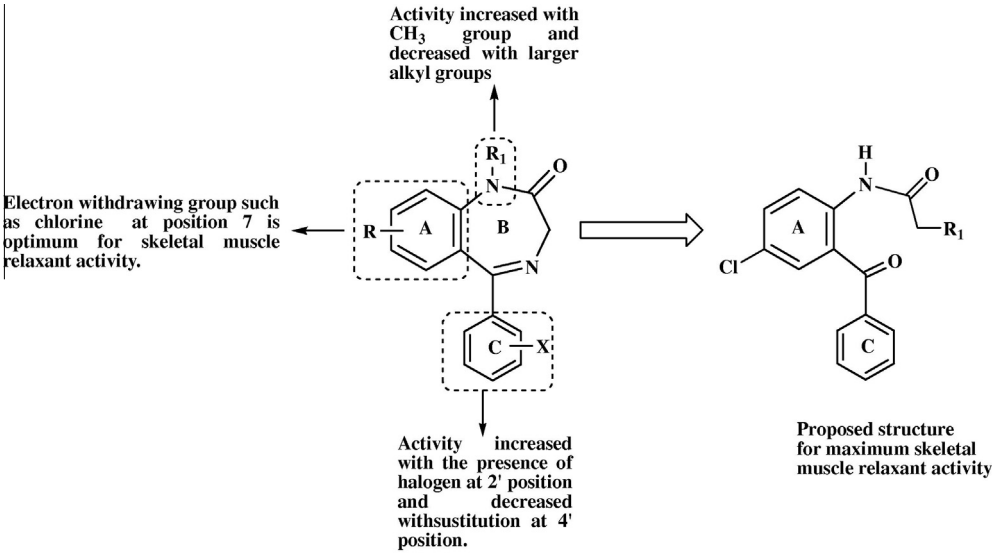

Figure 1 Important pharmacophore of 1,4-benzodiazepine nucleus.