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ORIGINAL ARTICLE

Synthesis and biological evaluation of schiff bases of 4-aminophenazone as an anti-inflammatory, analgesic and antipyretic agent

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Hypotonicity-induced haemolysis;
Albumin denaturation

Abstract A series of schiff base derivatives of 4-aminophenazone (4APZ-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one) with different aldehydes were synthesized. The synthetic compounds were screened for their anti-inflammatory, analgesic and antipyretic activities. The characterization of synthesized compounds was carried out by ^{1}H NMR, ^{13}C NMR and MS. Carrageenan-induced paw oedema (CIPO) and histamine induced paw oedema (HIPO) methods were used to determine the anti-inflammatory activity of commercial sample of 4APZ and its synthesized schiff bases in mice. The anti-inflammatory activity was in the order of 4APZAB > 4APZBB > 4APZCB > 4APZVn and all the test compounds exhibited considerable dose dependent inhibition of the paw oedema. The effect of the compounds on membrane stabilization was also determined which showed that compounds 4APZ (120 and 240 mg/kg doses), 4APZAB (160 mg/kg) and 4APZVn (600 mg/kg) produced highly significant inhibition ($P < 0.001$) of hypotonicity-induced haemolysis. Further, it was also observed that 4APZ (120 and 240 mg/kg doses), 4APZBB (500 mg/kg) and APZCB (150, 300 and 600 mg/kg dose) produced highly significant inhibition ($P < 0.001$) of albumin denaturation; a consistent dose dependent anti-inflammatory effect of test compounds as compared to the standard drug. Analgesic activity of the compounds was investigated by formalin-induced paw licking (FIPL) and acetic acid-induced writhing (AIW) methods in mice. It was observed that 4APZ (240 mg/kg), 4APZAB (160 mg/kg), 4APZBB (500 mg/kg), 4APZCB (600 mg/kg) and 4APZVn (600 mg/kg) showed analgesic effect with highly significant ($P < 0.001$) reduction of paw licking and writhing activity in the treated mice. The order of

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analgesic effect of the compounds was 4APZAB > 4APZBB > 4APZVn > 4APZCB. Moreover, phenobarbitone-induced sleeping time (PIST) in mice was also studied but only 600 mg/kg of 4APZVn significantly increased the duration of induced sleep which also suggested its sedative property. Brewer's yeast was used to induce fever in rabbits and analysed the compounds for their antipyretic activity. Different doses of 4APZ for different time durations (240 mg/kg-after 1 h, 120 and 240 mg/kg doses-after 2 h) produced highly significant ($P < 0.001$) inhibition of hyperpyrexia. Other compounds showed good antipyretic activity after 2, 3 and 4 h.

1. Introduction

Due to side effects of existing available anti-inflammatory, analgesic and antipyretic medicines that have been creating serious problems in their clinical applications, it is crucial to synthesize and develop novel and more potent anti-inflammatory, analgesic and antipyretic drugs with no or fewer side effects. Therefore, in the present study a known active compound "4-aminophenazone" was modified into its schiff bases with four different benzaldehydes. The biological applications of schiff bases like antibacterial, antifungal, antiviral and anticancer agents are well known particularly due to the azomethine group (–CH═N–) [30,6]. 4-Aminophenazone has pyrazol-3-one fragment (another important moiety) which also is found in several biologically active molecules that have important roles in the animal as well as plant kingdoms. Compounds bearing pyrazol-3-one possess antibacterial [53], anti-inflammatory [4], antihypertensive [20], antifungal [42], anti-HIV [9], antitumor [40] and anticonvulsant activities [41]. Pyrazol-3-one nucleus having azomethine linkage has engrossed much attention in the field of pharmacy due to their expected efficiency. Considering pyrazol-3-one as a possible pharmacophore in various pharmacologically active agents, it was decided to synthesize schiff bases of pyrazol-3-one and investigate their anti-inflammatory, analgesic and antipyretic activities.

Inflammation has acquired the attention of global research due to its implication in both human and animal diseases. Inflammatory abnormalities are considered as a giant group of disorders that trigger a huge variety of human diseases. Inflammation is a crucial aspect of host response that escorts to infection, and is requisite to keep healthy condition against microbial infections. However, excessive inflammation may contribute to acute or chronic human diseases. Acne vulgaris, asthma, glomerulonephritis, hypersensitivities, coeliac disease, chronic prostatitis, inflammatory bowel diseases, rheumatoid arthritis, sarcoidosis, pelvic inflammatory disease, reperfusion injury, transplant rejection, autoimmune diseases, interstitial cystitis and vasculitis [43,8] are some examples of disorders associated with inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) were the first group that was used to treat inflammatory diseases. These drugs lessen inflammation and assist to relieve pain, however, seldom entirely eradicate signs of active arthritis [26]. A wide variety of NSAIDs is available, many of which cause inhibition of cyclooxygenase (COX). The enzyme is responsible for the conversion of arachidonic acid into prostaglandins [51].

Commonly used anti-inflammatory drugs such as NSAIDs and analgesic agents are associated with some adverse effects such as myocardial infarction [21], congestive heart failure [37], nausea/vomiting, dyspepsia, gastric ulceration/bleeding, diarrhoea [52] hypertension and salt and fluid retention. The NSAIDs may also cause renal failure when used in combination with some diuretic and ACE inhibitors (triple whammy effect) [50], nephrotic syndrome, interstitial nephritis, acute tubular necrosis and acute renal failure. NSAIDs may also be causing analgesic nephropathy when used in combination with phenacetin and/or paracetamol [10], photosensitivity [28], premature birth [34], hepatotoxicity [56], raised liver enzymes, hyperkalaemia, bronchospasm, rash and allergy, headache, dizziness, confusion [46].

NSAIDs have been extensively used for the treatment of minor pain and for the management of oedema and tissue damage resulting from inflammatory joint disease (arthritis). Unlike NSAIDs which cure both inflammation and pain, analgesics purely target the pain. This property makes it safer for those who have allergic or stomach problems with NSAIDs. Many analgesic drugs have antipyretic activity as well and hence have effectiveness in the treatment of fever. Most of these drugs show their therapeutic actions by inhibition of prostaglandin biosynthesis [32].

2. Experimental

2.1. Materials

4-Aminophenazone (4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one, 4APZ) and 4-dimethylaminobenzaldehyde were purchased from BDH, 4-chlorobenzaldehyde and 4-bromobenzaldehyde from ACROS, and vanillin from Alfa. Piroxicam (Hovid, Malaysia). Acetylsalicylic acid (Reckit & Colman, Karachi), Phenobarbitone (Amros Pharmaceuticals, Karachi), Formalin (MERCK, Darmstadt, Germany), Acetic acid (BDH Laboratories, Poole, England), Dried yeast (Sigma Chemical Company, St. Louis, MO, USA), Gum Tragacanth (MERCK, Darmstadt, Germany), Carboxymethylcellulose (MERCK, Darmstadt Germany), Carrageenan (Sigma Chemical Company, St. Louis, MO, USA). Histamine (BDH Laboratories, Poole, England). Albumin kit (Randox Laboratories, United Kingdom). NMR spectra (300 MHz, in $CDCl_3$); Bruker AM-300; d(H) in ppm. Using $CDCl_3$ as an internal reference [^{1}H ($CDCl_3$) = 7.25 and ^{13}C ($CDCl_3$) = 77]. ESI-MS: solvent; MeOH, spray voltage 1.4 kV.

2.2. General procedure for the preparation of schiff bases

Schiff bases of 4-aminophenazone (4APZ) were prepared by standard procedure (Scheme 1). The solutions of 4APZ and