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Review article

An integrated overview on pyrrolizines as potential anti-inflammatory, analgesic and antipyretic agents

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ABSTRACT

Despite the existence of huge number of NSAIDs, the quest for safer drugs is still in the focus of several drug discovery programs. Pyrrolizine heterocyclic system is among the privileged scaffolds utilized in this regard. At least one of these pyrrolizines, ketorolac, has reached the market. The current review represents a collective effort to highlight the reported pyrrolizines with anti-inflammatory and analgesic potential and categorize them into eight different classes. Furthermore, the various synthetic approaches, structure-activity relationship as well as metabolic pathways have been discussed. Taken together, this review sets a base for researchers to design and synthesize novel pyrrolizine-based libraries for further development into safer and efficient anti-inflammatory and analgesic agents.

Contents

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List of abbreviations

Asp	aspirin
CDI	1,1′-carbonyldiimidazole
conc.	concentration
COXs	cyclooxygenase enzymes (COX-1 and COX-2)
DADHP	6,7-diphenyl-2,3-dihydro-1*H*-pyrrolizine
DMSO	dimethyl sulfoxide
Gluc	glucuronic acid
HPLC	high performance liquid chromatography
IP	inhibition percent
5-LOX	5-lipoxygenase
M	metabolite
MOA	mechanism of action
MOE	molecular operating environment
mPGES-1	microsomal prostaglandin E2 synthase-1
n.d.	not determined
n.i.	no inhibition
nAChR	nicotinic acetylcholine receptor
NBS	*N*-bromosuccinimide
NLC	nanostructured lipid carrier
NSAIDs	non-steroidal anti-inflammatory drugs
n.t.	not tested
PB	phenylbutazone
Ph	phenyl
PMNL	polymorphonuclear leukocyte
RA	residual activity
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
Tol	tolyl
UI	ulcer index

1. Introduction

1.1. Pyrrolizine nucleus

Pyrrolizine nucleus **1** found in many natural and synthetic compounds is a bicyclic ring system consisting of two fused pyrrole rings. Pyrrolizine alkaloids exist in hundreds of plant species and herbs [1]. In the literature, three names were used to describe this bicyclic systems; 4-azabicyclo[3.3.0]octane [2] which is less common, pyrrolo[1,2-*a*]pyrrole [3] and finally, pyrrolizine [4]. The pyrrolizine nuclei exist in four different forms **1**–**4**, with different degree of (un)saturation. Chemical names and the directions of numbering of these forms were presented in Fig. 1 [5–7].

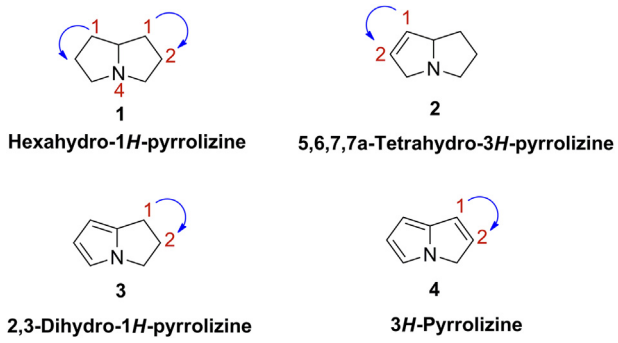

Fig. 1. Chemical nomenclature and numbering of different forms of the pyrrolizine nuclei.

1.2. Pharmacological activities of the pyrrolizine derivatives

Pyrrolizine derivatives displayed various types of biological activities such as nootropic activity [8], reversal of amnesia and treatment of senility [9], anticonvulsant activity [10], antineoplastic activity [11], antiarrhythmic activity [12], antibacterial activity [13] and antiviral activity [14,15]. Moreover, several pyrrolizine derivatives were found to exhibit potent anti-inflammatory, analgesic and antipyretic activities [16–24]. However, the investigation of the reported pyrrolizine derivatives with anti-inflammatory, analgesic or antipyretic revealed that the substitution of the pyrrolizine nucleus with at least one aromatic or heteroaromatic ring is essential for activity. In the presented work, it was focused on reviewing pyrrolizine derivatives that were reported to have anti-inflammatory, analgesic and/or antipyretic activities, their various synthetic schemes and some representative metabolic pathways.

1.3. Chemical classification of pyrrolizine-based anti-inflammatory and analgesic agents

The pyrrolizine derivatives with anti-inflammatory, analgesic and antipyretic activities that would be covered in this review could be classified into eight chemical classes based on the type of the various substituents on the pyrrolizine nucleus in order to find a proper correlation between their chemical structure and their activities, Fig. 2.

2. Synthetic approaches of the pyrrolizine derivatives

2.1. Construction of the pyrrolizine nucleus

The great advance in the last three decades in the field of