Synthesis of Azolines and Imidazoles and their Use in Drug Design

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Abstract

Heterocycles are very important functional groups, especially in medicinal chemistry. They are not only pivotal in the synthesis of drugs, but also form part of the structure of a diversity of drugs, vitamins, natural products and biomolecules. The importance of azolines and imidazoles in heterocycles lies in the fact that their derivatives are known for analgesic, antifungal, antihypertensive, antiobesity, anticancer, and other biological activity. Additionally, they can inhibit butyrylcholinesterase, acetylcholinesterase, carboxylesterase and quorum sensing. Due to these properties, the present contribution reviews the use of azoline and imidazole moieties in recent drug synthesis based on classic as well as non-classic methods, the latter employing microwave and sonication energies. Also included is the preparation from oxazoline of nanostructured material having biomedical applications. Hence, the present focus is on the synthesis of azolines and imidazoles that are directly involved in the preparation of drug precursors and potential drugs.

Keywords: Azolines and imidazoles synthesis; Azolines and imidazoles in drug design; Nanoparticles from oxazolines

Introduction

Heterocycles are a very important functional group, especially in medicinal chemistry, because they constitute a common structural moiety in many drugs [1-4]. Azolines and imidazoles are key groups inside heterocycles, as they are not only a cornerstone of the synthesis pathway of these compounds, but also form part of potential [5] and marketed drugs [2]. Furthermore, in some cases azolines and imidazoles are the pharmacophore in drugs [6,7]. Consequently, azoline and imidazole synthesis has great importance in drug research.

The various interesting reviews of azolines and imidazoles [8-10] either focus on synthetic methods for obtaining these compounds or their biological activity, or both of these topics but with greater emphasis given to one of them [10]. In the current review, we focus on the synthesis of azolines and imidazoles that are directly involved in the preparation of drug precursors and the synthesis of potential drugs. We first discuss azolines and then imidazoles.

Azolines

Azolines are five-membered heterocycles with one double bond in the ring and two heteroatoms at positions 1 and 3, one of which is always nitrogen. Whereas imidazolines also contain nitrogen, oxazolines include oxygen, and thiazolines sulfur. Figure 1 shows some imidazolines, oxazolines and thiazolines that are either potential drugs or have important biological activity.

Compound 1 acts as a COX-2 inhibitor precursor [11], compound 2, methoxy-idoaxan / RX821002 (a2), as an α-adrenergic antagonist [1], compounds 3 and 7 as quorum sensing inhibitors [12,13], compound 4, epi-oxazoline halipeptine D, as a potent anti-inflammatory agent [14], compound 5, (-)-spongotine A, as an antitumor agent with moderate cytotoxicity against human leukemia K-562 [15,16], and compound 6, brasilibactin A, as a cytotoxic siderophore [17].

Synthesis and pharmacological activity of azolines

The synthetic routes for building azolines can be divided into classic methods that use conventional energy, and non-classic methods accomplished with microwave (MW) or ultrasound energy.

Classical methods of synthesis: One commonly used method for the synthesis of azolines starts from an aldehyde and a source of heteroatoms, usually an ethylenediamine for imidazolines, an ethanolamine for oxazolines, and a cysteamine for thiazolines. After obtaining azolidines in this way, oxidants (e.g., I2, tert-buthyl hypochlorite (t-BuOCl), N-chlorosuccinimide (NCS), N-bromosuccinimide (NBS) and N-iodosuccinimide (NIS) are utilized to achieve azolines. For instance, NCS and t-BuOCl have been applied to the total synthesis of (-)-spongotine A, 5 [15]. In other reactions, oxidation with NCS gave an 88% yield, but spongotine was obtained at 52% yield (Scheme 1).

Scheme 1: Total synthesis of (-)-spongotine A, which displays moderate cytotoxicity against human leukemia K-562.

Figure 1: Examples of biologically active azolines, including blue imidazolines, pink oxazolines, and red thiazolines.

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NBS-mediated reactions have in some cases required some of the longest reaction times. Nevertheless, NBS was used to synthesize 30 imidazoline inhibitors of cyclooxygenase-2 (COX-2), with a consequent anti-inflammatory activity [11]. Scheme 2 shows an example of the synthesis of a COX-2 inhibitor precursor 13, which is then oxidized to a COX-2 inhibitor, imidazole [11].

Scheme 2: Synthesis of a COX-2 inhibitor precursor.

Amino alcohols and 4-ethoxy-4-iminobutanenitrile have also been employed to obtain new enantiomerically pure 2-cyanoethyl-oxazolines 18 in one step with good to excellent yields (73–96%). This was accomplished by following a procedure appropriate for the selective synthesis of mono-oxazolines, which display antioxidant, antimicrobial and analgesic activities [18] (Scheme 3).

Scheme 3: Synthesis of 2-cyanoethyl-oxazolines, with antioxidant, antimicrobial and analgesic activities.

Padmavathi et al. [19] reported a new class of sulfone-linked pyrrolyl oxazolines and thiazolines 20 and 21, the synthesis of which was carried out with a one-pot methodology using trans-arylsulfonylethenesulfonyl-acetic acid methyl ester and ethanolamine or cysteamine, respectively. In the presence of a lanthanide chloride, SmCl₃, aromatic compounds 22 and 23 were also obtained (Scheme 4). Compounds containing pyrrole and thiazoline possess excellent antimicrobial activity, while those including pyrrole and oxazoline show good antioxidant properties.

Scheme 4: Synthesis of pyrrolyl oxazolines and pyrrolyl thiazolines, with antioxidant and antimicrobial properties, respectively.

Altintop et al. [20] synthesized 40 compounds 29 by reacting α-thiophenoxy esters 25 with hydrazine and then followed by phenyl isothiocyanate. After wards, α-bromo acetophenone 28 derivatives were added to achieve 40 thiazolines having with one exo double bond (Scheme 5). The compounds were evaluated for as antibacterial, or antifungal activity agents, or and in the case of one compound, was tested as for anticancer activity against C6 glioma cells. All compounds significant antimicrobial activity against T. harzianum, A. ochraceus, F. solani, F. moniliforme, and/or F. culmorum. It was observed that the compound bearing 1-phenyl-1H-tetrazole and p-chlorophenyl moieties displays an inhibitory effect against P. aeruginosa, while it was also found that the compound having 1-phenyl-1H-tetrazole and non-substituted phenyl moieties (IC₅₀=8.3 +/- 2.6 mg/mL), was more effective than cisplatin (IC₅₀=13.7 +/- 1.2 mg/mL).

Scheme 5: Synthesis of thiazolines with antibacterial, antifungal and/or anticancer activity.

Thiazoline hydrohalide was also synthesized from N-allylthiourea, which is obtained from allylisothiocyanate 30 and the corresponding amine 31, as can be appreciated in Scheme 6. It is known that thiazines are formed in this type of reaction under conditions of polar solvents and high temperature. Conversely, thiazolines hydrohalide 34 were obtained in good yields (Scheme 6) [21]. They were evaluated as acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and carboxylesterase (CaE) inhibitors. Of the 30 compounds evaluated, only 5 were selective inhibitors of BChE, both BChE and ChE, or CaE [21].

Scheme 6: Starting from allylisothiocyanate, synthesis of thiazolines that are inhibitors of BChE, ChE, or CaE.

Non-classic methods of synthesis:

- **Microwave energy:** When synthesizing 2-aryloxy methyl oxazolines 37 with carboxylic acid derivatives 36 and ethanol amine via MW energy operating at 20% for 5-10 min, good yields were obtained [22] (Scheme 7). Since the time is very short and the MW power low, this can be considered a very good method (even though the authors did not mention the total MW power). Compounds 37a–n were screened for anti-inflammatory and ulcerogenic activities,
finding that compounds 37b (48.2%), 37h (48.5%) and 37l (46.5%) display significant anti-inflammatory activity. On the other hand, these compounds had lower ulcerogenic activity than the standard drugs, aspirin and phenylbutazone [22].

Ultrasound energy: Ultrasound energy has proven to minimize waste, decrease reaction times, and sometimes eliminate the use of solvents in organic chemistry synthesis. Since these are good properties for green chemistry [23], its use will undoubtedly increase. Ultrasound was utilized in one study on imidazoline synthesis by reacting aromatic aldehydes and ethylenediamine, with NBS as oxidant and water as solvent, to achieve good to excellent yields in 12-18 min. [24] (Scheme 8). The resulting imidazolines 40 were evaluated as monoamine oxidase (MAO) inhibitors, finding that they have activity in the micro molar (µM) range with good selectivity [24]. When applying ultrasound energy to mediate azoline synthesis, we verified the high efficiency of this methodology, attaining imidazoline 40 in 12 min (81% yield) and alklyphenoxy imidazolines in 20 min with moderate to good yields. Our interest in azolines lies in antimicrobial sensing activity [12,13].

Imidazoles

Imidazole (1,3-diaza-2,4-cyclopentadiene) is a five-membered organic compound having the formula C₄H₅N₂. As can be appreciated, it has three carbons and two nitrogens, the latter two atoms at positions 1 and 3. Its derivatives include an extensive variety of natural products such as histamine, histidine, biotin, alkaloids and nucleic acids [27].

In addition, this structure is present in a variety of pharmacologically active compounds. One example is 5-ethyl-1-beta-D-ribofuranosylimidazole-4-carboxamide (EICAR) 41. The most potent congener of this group has shown antiviral potency about 10- to 100-fold greater than that of ribavirin [28]. Other examples are etomidade (amide) 43 and cimetidine (tagamet) [44] (Figure 2).

Various imidazole derivatives had been discovered as early as the 1840s. However, it was not until 1858 that Heinrich Debus carried out the first imidazole synthesis, which was done by using glyoxal and formaldehyde in ammonia to yield imidazole [29]. Although imidazoles are of great pharmacological importance, there is no recent compendium of their current applications in the synthesis of new pharmacologically active compounds.

Pharmacological activity

The imidazole moiety is contained in the backbone of many drugs that have anticancer, antifungal, antibacterial, antitubercular, anti-inflammatory, antineuropathic, antihypertensive, antihistaminic, antiparasitic, antiseizis and antiviral activity.

Imidazoles in the synthesis of new biologically active compounds

Sharma et al. reported the utility of an imidazole moiety as the precursor of 2-(substituted phenyl)-1H-imidazoles 47, which has antibacterial activity. During the process of synthesis, the last step involves a direct acylation of a 2-phenylimidazole 45 with acyl chloride substituted 46 prepared in situ [30] (Scheme 9).

Nanoparticles from azolines

Recently, nanoparticles have come to light as entities with medical applications, including their possible use as carriers in drug delivery to the target site or gene delivery to tumors, as well as contrast agents in imaging [25]. In this context, 2-methyl-2-oxazoline was taken as the raw material for a nanostructural material (PMeOX-silica hybrid nanoparticles) [26] that can be used in biomedical applications.

PMeOX-silica hybrid nanoparticles were prepared by using the “grafting to” method and either click chemistry or silane coupling. The first step of the method is the synthesis of the 2-methyl-2-oxazoline polymer functionalized with azide. Afterwards, a microemulsion water oil containing SiO₂ is prepared separately, followed by the addition of the polymer of oxazoline. Finally, PMeOX-silica hybrid nanoparticles emerge.

![Figure 2: Examples of biologically active imidazoles.](image-url)
Synthesis route of 2-(substituted phenyl)-1H-imidazoles 7, with antibacterial activity.

Duran et al. synthesized a new series of 2-(4,5-dimethyl-1-(phenylamino)-1H-imidazol-2-ylthio)-N-(thiazol-2-yl) acetamide derivatives. The reaction implied a nucleophilic displacement of the chlorine of the chloroacacetamide intermediate 49, promoted by an imidazolene-2-thione derivative 48. This process used potassium carbonate as catalyst at room temperature. These compounds were among those accepted by the National Cancer Institute for anticancer activity tests. The most effective compound of the series showed selective activity against melanoma cell lines (SK-MEL-5) [31,32] (Scheme 10).

Scheme 9: Synthesis of 2-(substituted phenyl)-1H-imidazoles 7, with antibacterial activity.

Blunden et al. developed an amphiphilic block copolymer capable of self-assembling into polymeric micelles, which was successfully tested as a drug carrier for NAMI-A. This antitumorigenic agent, now in Phase II clinical trials, has low cytotoxicity and is inactive against primary tumors. A polymeric form of NAMI-A was synthesized by combining with suitable 2-chloro-aryl-substituted acetamides in order to improve the current anti-HIV drugs activity. The most effective compound is an aminoimidazole thioacetanilides in order to improve the current anti-HIV drugs activity. The most effective compound is an aminoimidazole thioacetanilides in order to improve the current anti-HIV drugs activity.

Recently, Patil et al. carried out the synthesis of 2,3-disubstituted-imidazolyl-quinazolin-4(3H)-one derivatives 63a-b with good yields. The synthesized compounds exhibited anti-inflammatory and antimicrobial activity. Through in vitro experiments, some 2,3-disubstituted-imidazolyl-quinazolin-4(3H)-one compounds found to be as active as prednisolone. Interestingly, the presence of electron-withdrawing groups on the quinazoline nucleus was related to biological activity. An in vivo anti-inflammatory assay showed that compounds having an electron-withdrawing group had an important pharmacological response. The synthesis is based on the reaction between 6,8-substituted-2-methyl-4H-3,1-benzoxazin-4-ones 61a or 6,8-substituted-2-phenyl-4H-3,1-benzoxazin-4-ones 61b and aminoimidazole 62, in refluxing glacial acetic acid and sodium acetate or in refluxing dry pyridine [36] (Scheme 14).

Scheme 10: Synthesis route of 2-(substituted phenyl)-1H-imidazoles 50, with anticancer activity.

On the other hand, Ramachandran et al. synthesized analogues of 1-[2-(1H-imidazo-1-yl)acetyl]-2,6-diarylpiperidin-4-ones 57. In this process imidazole was introduced via nucleophilic substitution with N-chloroacetyl-2,6-diarylpiperidin-4-ones 55 under reflux to achieve the desired compounds. It is noteworthy that imidazole is a critical motif for the antifungal activity of the new produgs [34] (Scheme 12).

Scheme 11: Synthesis route of NAMI-A copolymer micelles 54, with anticancer activity.

Scheme 12: Synthesis route of 1-[2-(1H-imidazo-1-yl)acetyl]-2,6-diarylpiperidin-4-ones 57, with antifungal activity.

Kantevari et al. synthesized 2-butyl-4-chloro-1-methylimidazoles 60 with embedded aryl- and heteroaryl-derived chalcones. These compounds were tested as inhibitors of angiotensin converting enzyme (ACE). The synthesis strategy involved the Claisen–Schmidt condensation of several aryl or heteroaryl methyl ketones of type 59 with imidazole-5-carbaldehyde 58. This procedure was catalyzed by means of 10% aqueous NaOH in methanol for 3.0-5.0 h at room temperature. When screening all the new compounds with the colorimetric ACE inhibition assay, the most active inhibitors, of type 60, were found to have an IC<sub>50</sub> of 2.24-3.60 μM. These values show that some derived chalcones are ~100 times more active than various chalcones and flavonoids of synthetic and natural origin [35] (Scheme 13).

Scheme 13: Synthesis route of 2-butyl-4-chloro-1-methylimidazolyl chalcones 60, with antihypertensive activity.

Kane et al. synthesized 2-butyl-4-chloro-1-methylimidazoles 60 with embedded aryl- and heteroaryl-derived chalcones. These compounds were tested as inhibitors of angiotensin converting enzyme (ACE). The synthesis strategy involved the Claisen–Schmidt condensation of several aryl or heteroaryl methyl ketones of type 59 with imidazole-5-carbaldehyde 58. This procedure was catalyzed by means of 10% aqueous NaOH in methanol for 3.0-5.0 h at room temperature. When screening all the new compounds with the colorimetric ACE inhibition assay, the most active inhibitors, of type 60, were found to have an IC<sub>50</sub> of 2.24-3.60 μM. These values show that some derived chalcones are ~100 times more active than various chalcones and flavonoids of synthetic and natural origin [35] (Scheme 13).

Scheme 14: Synthesis of 2,3-disubstitutedimidazolylquinazolin-4(3H)-one derivatives 63a-b, with anti-inflammatory activity.
microwave and ultrasound energies. Finally, we have mentioned the use of oxazolines for the preparation of nanostructural material with biomedical applications.

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References


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