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Review article

Phthalazin-1(2H)-one as a remarkable scaffold in drug discovery

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ABSTRACT

Phthalazinones are an important kind of nitrogen atom containing heterocyclic compounds due to their synthetic and pharmacological versatility. This fused heterocycle system represents a common structural feature for many bioactive compounds showing a variety of pharmacological activities such as anticancer, anti-diabetic, anti-asthmatic, antihistaminic, antihypertensive, antithrombotic, anti-inflammatory, analgesic, antidepressant or antimicrobial agents, which makes it an attractive scaffold for the design and development of new drugs. This review summarizes detailed and updated information, described in recent non-patent literature, about the most relevant pharmacological properties of phthalazinone derivatives, highlighting the application of this potent pharmacophore in drug discovery.

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1. Introduction

Heterocyclic compounds constitute a huge group of organic compounds playing a key role in drug discovery because of their biological properties. Therefore, several heterocycles are fundamental for life of plants and animals, such as the heme group of chlorophylls and haemoglobin or the nitrogen bases and sugars of nucleic acids, and many of them are nitrogen containing heterocycles [1].

Phthalazin-1(2H)-one (**1**), also called 2H-benzo[d]pyridazin-1-one, is a benzo-fused heterocycle that presents a 1,2-diazine ring with two adjacent nitrogen atoms exhibiting a tautomeric equilibrium in solution which has been the subject of many studies. This heterobicyclic system can exist either in the lactam form (**1A**) or in the lactime structure (**1B**) (Scheme 1), with the first one (**1A**) being the predominant one despite its minor aromaticity [2]. In this regard, recent theoretical studies in the gas phase of different heterocyclic lactams and their benzo-fused derivatives show that benzo-fusion stabilizes the lactam form reducing the aromaticity difference between the two tautomeric forms [3]. Thus, in the crystal structure of phthalazin-1(2H)-one the benzene and pyridazine rings are almost coplanar [4].

Natural products are a traditional source of nitrogen-rich heterocycles as lead structures for drug development like indole, quinoline or quinazoline derivatives [5]. However, the presence of a 1,2-diazine ring is not very common in compounds isolated from living organisms and the biosynthesis of this structural unit is poorly understood. Pyridazomycin (**2**), antrimycin (**3**), cirratiomycin (**4**), L 365209 (**5**) and azamerone (**6**), all of them isolated from *Streptomyces* culture, are representative examples of natural products containing a 1,2-diazine ring with different pharmacological activities [6], with azamerone being the only one with a pyridazino-fused ring structure like phthalazinone (Fig. 1).

Despite its small presence in natural products phthalazinone nucleus and especifically phthalazin-1(2H)-one system is a versatile scaffold in Medicinal Chemistry providing derivatives able to interact with different kinds of biological targets. They were developed as enzyme inhibitors, such as aldose reductase (AR) inhibitors [7], poly-[ADP-ribose] polymerase (PARP) inhibitors [8] or phosphodiesterase (PDE) inhibitors [9], as ligands acting at G protein-coupled receptors (GPCRs), in particular histamine receptors [10], adrenoceptors [11], dopamine/serotonin receptors [12], or adenosine receptors [13], or even as modulators of ion channel-coupled receptors [14] or ligands for nuclear receptors [15]. Thus, phthalazinone derivatives have a wide variety of biological properties like antidiabetic [16], anticancer [17], anti-asthmatic [18], anti-inflammatory and analgesic [19], antihistaminic [20], antihypertensive and antithrombotic [21],

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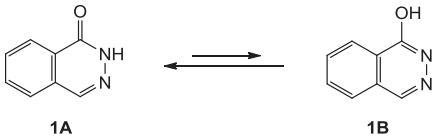

Scheme 1. Tautomeric equilibrium of phthalazin-1(2H)-one.

anticonvulsant [22], antimicrobial [23], antiviral [24], antiparasitic [25], as well as antidepressant and antipsychotic activities [26,12]. Their use as diagnostic agents [27] or even as herbicides [28] was also described. Moreover, a number of bioactive compounds are accessible using the phthalazinone nucleus as synthetic intermediates [29]. Some important established drugs which are related to the phthalazinone scaffold are detailed in Fig. 2.

A compilation of reports on the different biological activities associated with the phthalazine nucleus has been recently reported [30] and the therapeutic potential of phthalazinone derivatives for some activities was also mentioned in this review. However, a comprehensive report on different activities of phthalazinone based compounds is not available in literature till now. The present review summarizes the current information about the relevant pharmacological applications of phthalazinone derivatives in different therapeutic fields and described in non-patent literature, highlighting the application of this potent pharmacophore in drug discovery.

2. Chemistry

Synthesis of phthalazin-1(2H)-one derivatives is a research field of continuing interest not only because of their diverse pharmacological properties but also because of their potential as synthetic intermediates. A number of methods have been developed for obtaining phthazin-1(2H)-ones, especially referred to analogues substituted at C4 because this position along with N2 represent two key positions to modulate and optimize the biological activity of phthalazinone derivatives [31].

The chemistry of phthalazin-1(2H)-one was reviewed by Haider and Holzer in an interesting paper about phthalazines describing the different methodologies followed for phthalazine derivatives synthesis, in which most of analyzed strategies involve obtaining different precursors of phthalazinone structure [2]. Other review papers about chemistry of diazines and their benzo-fused systems were also recently published [32].

The most habitual methods for phthalazinone nucleus synthesis consist of cyclocondensation reactions of phthalic acid derivatives, such as phthalic anhydrides and phthalimides, or 2-formyl and 2-acylbenzoic acids with hydrazine or substituted hydrazines (Scheme 2), in a polar solvent and in the presence of an acid or basic catalyst [2]. Functionalization at N2 with several acyl, aryl or alkyl groups can also be achieved by substitution of the hydrogen atom and using different and specific conditions [2].

In addition, phthalimides are suitable to react under Friedel–-Crafts conditions [33] or with organometallic compounds [33,34] giving 2-keto benzoic acids hydrazides or 3-substituted 3-hydroxy indolinones, good building blocks to synthesize phthalazin-1(2H)-ones substituted at C4 with aryl, heteroaryl, aralkyl or alkyl groups (Scheme 3).

A frequent approach to 4-substituted phthalazin-1(2H)-ones involves 3-substituted benzofuran-1-ones or their tautomeric 2-acylbenzoic acids as synthetic intermediates [7,31a-b]. The synthesis of these key intermediates starts from the corresponding phthalic anhydrides and follows different pathways, such as condensation with active methylene compounds [35], Wittig-type alkenylation [7], a Friedel–Crafts reaction [31a,36] or through a metallation process [31a,37], depending on the selected substituents (Scheme 4).

Moreover, the reaction of 2-substituted 1,3-indanediones with hydrazine or hydrazine derivatives represents another useful method, also based on ring transformations, for the preparation of 4-diarylmethyl phthalazin-1(2H)-one core [38]. Likewise, an interesting approach based on hydrazine induced ring contraction of β-dicarbonyl functionalized tropolones was recently described for the synthesis of 2,4 disubstituted phthalazin-1(2H)-one derivatives [39].

Finally, microwave-assisted synthesis [40], palladium-catalyzed intramolecular cross-coupling reactions [41], one-pot synthesis [42] and other multicomponent syntheses, such as palladium-catalyzed carbonylation or isocyanide insertion on haloarenes [43], provide significant progress in phthalazinone derivatives chemistry. Green chemistry procedures have also been recently described. For example, reactions performed using ionic liquids

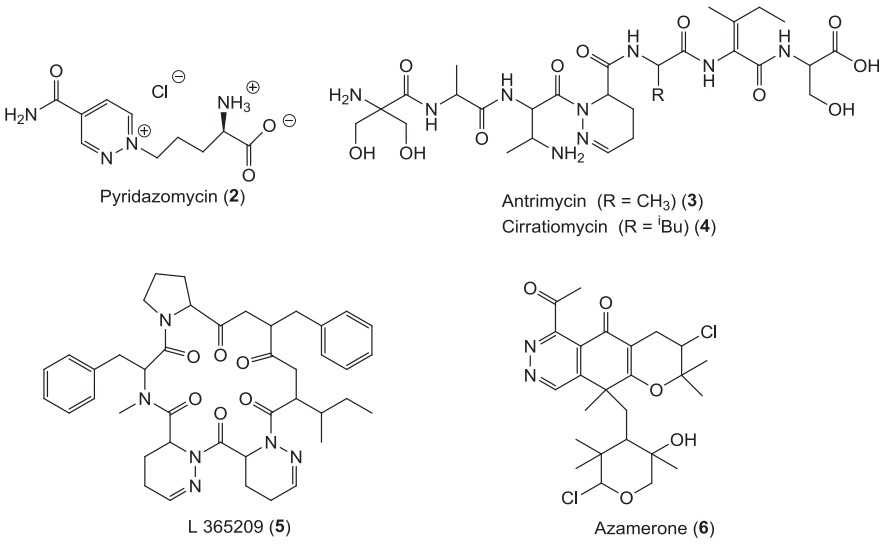

Fig. 1. Several natural products containing a 1,2-diazine ring in their structure.

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