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Review article

1,3,5-Triazines: A promising scaffold for anticancer drugs development

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ABSTRACT

This review covering literature reports from the beginning of this century to 2016 describes the synthetic pathways, the antitumor activity, the structure-activity relationship and, whenever reported, the possible mechanism of action of 1,3,5-triazine derivatives as well as of their hetero-fused compounds. Many 1,3,5-triazine derivatives, both uncondensed and hetero-fused, have shown remarkable antitumor activities and some of them reached clinical development.

Contents

1. Introduction

1,3,5-Triazine, also referred as *s*-triazine (symmetric triazine), is one of the three possible isomers of a six membered ring containing three nitrogen atoms in an alternate sequence with carbon atoms (Fig. 1).

The 1,3,5-triazine scaffold was extensively studied due to a wide variety of biological properties such as antimicrobial [1], antiviral [2], anti-inflammatory [3] activities etc. Moreover, a great deal of attention has been paid to 1,3,5-triazine derivatives endowed with antitumor activity [4].

In the latest years literature reported four reviews dealing with the chemistry and the biological properties of 1,3,5-triazine derivatives [4–7]. Three of them deal with uncondensed 1,3,5-triazine derivatives with various biological activities [5–7], whereas, the first one deals with uncondensed derivatives possessing antitumor

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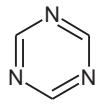

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Fig. 1. 1,3,5-Triazine.

activity mainly dedicated to kinases inhibitors [4].

This monograph covers the literature from the beginning of this century to 2016, and deals, through a comprehensive approach, with 1,3,5-triazine and their hetero-fused derivatives having antitumor activity. Herein, the synthesis, the antitumor activity, the Structure Activity Relationship (SAR) and, whenever reported, the possible mechanism of action, of the most promising 1,3,5-triazine derivatives will be described.

The first derivatives to be described are the disubstituted 1,3,5-triazines then the trisubstituted ones followed by the hetero-fused systems (fused with five and six membered rings and polycyclic systems).

2. Disubstituted 1,3,5-triazines

Kuo et al. discovered a new series of [1,3,5]triazine-pyridine as potent CDK inhibitors [8]. The assembly of different biheteroaryl molecules was carried out taking adavantage of palladium-catalysed C-C bond formation reactions, and, in particular of the Negishi coupling reaction [9].

The most active compound of the series, the 3-{4-[4-(3-chloro-phenylamino)-[1,3,5]triazin-2-yl]-pyridin-2-ylamino}-propan-1-ol **2** (Fig. 2), elicited IC_{50} values of 0.021, 0.007 and 0.308 μM against CDK1, CDK2 and CDK4, respectively. Compound **2** showed high potency also toward the glycogen synthase kinase GSK-3β (IC_{50} = 0.02 μM), a key enzyme involved in glycogen metabolism and recently described for its implication in the molecular pathways of different diseases including cancer [10].

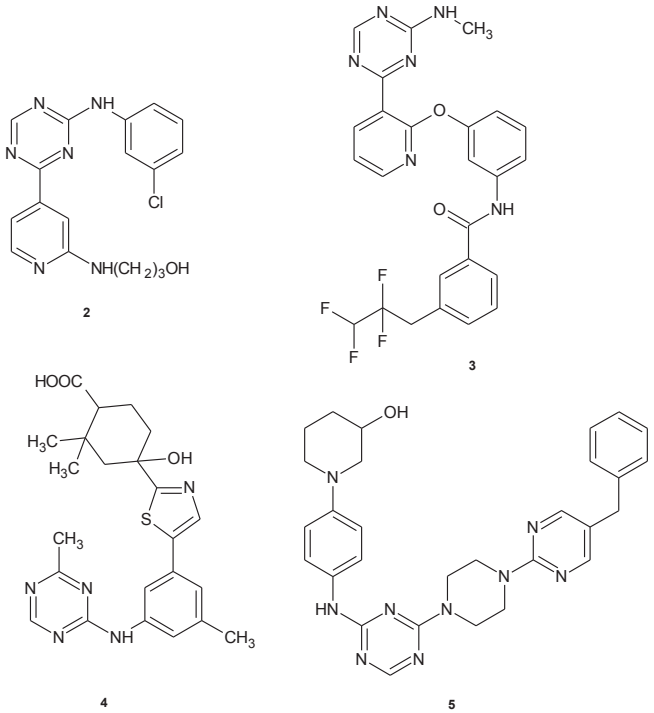

Fig. 2. Structure of disubstituted 1,3,5-triazines **2**–**5**.

Derivative **2** displayed potent antiproliferative activity, both *in vitro,* against various cancer cell lines, including HeLa, HCT-116, U937 and A375 with IC_{50} values ranging from 23 to 33 nM, and *in vivo*, in a human melanoma A375 xenograft model.

In U937 cells, compound **2** resulted able to induce apoptosis via activation of caspases in a dose-dependent manner. The antiproliferative activity of **2** was also evaluated against the drug-sensitive cell line MES-SA and the multidrug-resistant, P-glycoprotein overexpressing, MES-SA/Dx5 and the fact that the compound **2** showed the same activity against both cell lines, highlighted that it is not a substrate of the multidrug resistance pump P-glycoprotein.

The highly fluorinated derivative **3** (Fig. 2) was reported as potent Tie-2 inhibitor (IC_{50} = 16 nM) [11]. Angiopoietin (Ang)/Tie-2 pathway is considered critical for tumor angiogenesis and a challenging target for the development of new anticancer compounds [12,13].

Compound **3** resulted also able to inhibit the phosphorylation of the serine/threonine kinase p38α and the non-receptor tyrosine kinase Lck with IC_{50} values of 47 and 146 nM, respectively, and it showed interesting rat pharmacokinetic parameters with a half-life of 1.7 h and a clearance of 889 ml/h/kg.

Recently other two classes of disubstituted 1,3,5-triazines were described as anticancer agents endowed with kinase inhibitory activity [14,15].

Among a large number of synthesized compounds, **4** [14] and **5** [15] (Fig. 2) elicited the highest activity (IC_{50} values in the nanomolar range) against human Syk and the receptor tyrosine kinase KIT, respectively. These derivatives resulted useful for treating conditions associated with aberrant activity of the two enzymes including cancer.

Compound **11**, in particular the (+) enantiomer of 4-(4-fluoro-2-methoxyphenyl)-*N*-{3-[(S-methylsulfonilimidoyl)methyl]phenyl}-1,3,5-triazin-2-amine, is currently in clinical development for treatment of acute myeloid leukemia (AML). The synthesis of the disubstituted triazine **10** involves the reaction of 2,4-dichloro-1,3,5-triazine with substituted aniline **7** to give intermediate **8** which undergoes a Pd catalysed coupling with boronic acid **9** producing triazine **10**. The latter, upon deprotection, afforded triazine **11** (Scheme 1) [16,17].

3. Trisubstituted 1,3,5-triazines

Trisubstituted 1,3,5-triazines are easily obtained by substitution of chlorine atoms of commercially available 2,4,6-trichloro-1,3,5-triazine, also called cyanuric chloride **12** with various nucleophilic groups.

In a bid to develop novel unconventional antitumor agents targeting hypoxic cancer cells, Garaj et al. synthesized a series of benzenesulfonamide derivatives bearing triazine moieties as carbonic anhydrase inhibitors [18,19].

The target sulfonamides were obtained by reaction of cyanuric chloride **12** with sulfanilamide **13**, homosulfanilamide **14** or 4-aminoethylbenzensulfonamide **15** to give the dichlorotriazinyl-benzenesulfonamides **16**–**18**, which were, subsequentely, reacted with various nucleophiles such as water, methylamine or aliphatic alcohols (Scheme 2). These series of compounds were tested for the inhibition of three physiologically relevant carbonic anhydrases: the cytosolic hCA I and II, and the *trans*-membrane, tumor-associated hCA IX. Some of them (**16**, **28** and **29**) showed sub-nanomolar affinity for isozyme IX with K_Is ranging from 0.12 to 0.34 nM and selectivity ratio values (K_I hCA II/K_I hCA IX) in the range 166–706. Compounds **16**, **28** and **29** are among the most potent and selective inhibitors of hCA IX known. The introduction