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Review article

Triazine as a promising scaffold for its versatile biological behavior

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ABSTRACT

Among all heterocycles, the triazine scaffold occupies a prominent position, possessing a broad range of biological activities. Triazine is found in many potent biologically active molecules with promising biological potential like anti-inflammatory, anti-mycobacterial, anti-viral, anti-cancer etc. which makes it an attractive scaffold for the design and development of new drugs. The wide spectrum of biological activity of this moiety has attracted attention in the field of medicinal chemistry. Due to these biological activities, their structure–activity relationship has generated interest among medicinal chemists and this has culminated in the discovery of several lead molecules. The outstanding development of triazine derivatives in diverse diseases within very short span of time proves its magnitude for medicinal chemistry research. Therefore, these compounds have been synthesized as target structure by many researchers, and were further evaluated for their biological activities. In this review, we have compiled and discussed the biological potential of *s*-triazine derivatives, which could provide a low-height flying bird's eye view of the triazine derived compounds to a medicinal chemist, for a comprehensive and target oriented information for the development of clinically viable drugs.

1. Introduction

The designing, synthesis and evaluation of molecules with some human therapeutic values, remain one of the main objective of organic and medicinal chemistry. During the past decades, combinatorial chemistry has provided access to chemical libraries based on privileged heterocyclic motifs with utility in medicinal chemistry [1]. Synthesis of nitrogen containing heterocyclic compounds has been attracting increasing interest because of their utility for various biological receptors with a high degree of binding affinity. In the present review, the triazine moiety with a broad spectrum of biological profile has been matured into an indispensable heterocyclic scaffold that makes it one of the extensively studied heterocycle. The triazine structure is a heterocyclic ring analog to the six-membered benzene ring with three carbons replaced by nitrogens. The isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and referred to as 1,2,3-triazine (**1**), 1,2,4-triazine (**2**) and 1,3,5-triazine (**3**) (Fig. 1).

1,3,5-Triazine (*s*-triazine) has been widely used in organic reactions [2–7] that offers access to a multitude of useful molecules [8,9] due to its specific structure and electronic properties. Increased interest in this scaffold lies in the different reactivity of the chlorine atoms at 2-, 4- and 6-positions that are controlled by temperature, allows the sequential introduction of various substitutes for the preparation of mono-, di- and tri-substituted triazines [10,11]. Owing to the immense synthetic importance and varied bioactivities, efforts have been made from time to time to generate libraries of these compounds (Scheme 1).

Nitrogen containing triazine heterocyclic motif is the 'Master Key', as acting at different targets to elicit varied pharmacological properties by inhibiting the action of an inducible membrane protein that normally function to increase the efflux of the cytotoxic agents. The triazine scaffold provides the basis for the design of biologically relevant molecules with widespread applications like antiprotozoal [12], anticancer [13–16], antimalarial [17], antiviral [18] and antimicrobial [19,20]. Triazine is also the basic structure of some herbicides like amitole, atrazine, cyanazine, simazine, trietazine, and resin modifiers like melamine and benzoguanamine [21,22]. There are also some compounds containing 1,3,5-triazine nucleus, that are available in the market as shown in Fig. 2.

In the present review, we are intending to describe the structural and biological importance of this moiety in the development of drugs by investigating recent publications about the diverse range of triazine ring. These revealed that the substitution of various groups on the ring imparts different activity.

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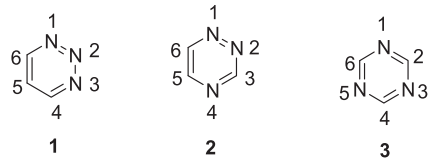


Fig. 1. Various isomers of triazine.

2. Biological activities

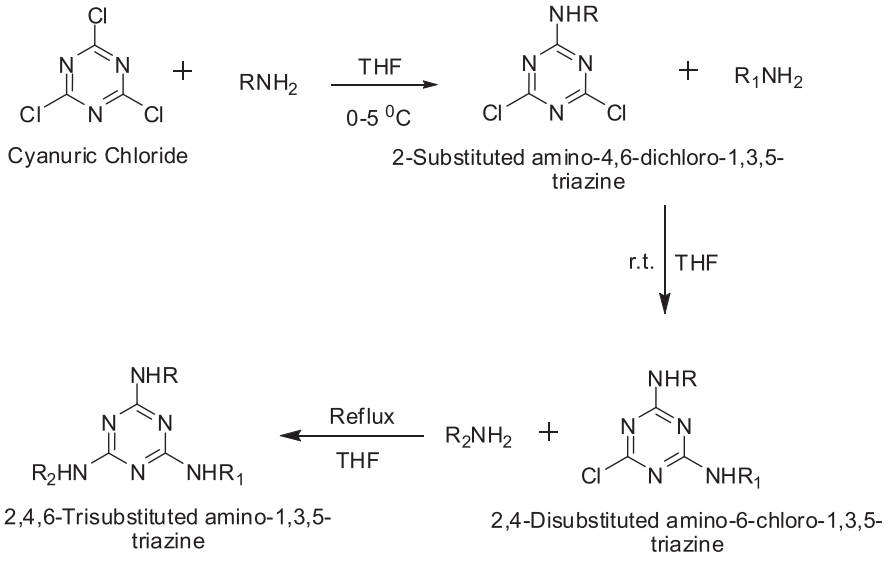
2.1. Antitumor activity

Triazine is widely explored for the development of anticancer agent due to its importance in various biological active molecules like triethylenemelamine, furazil and dioxadet [23]. Smith et al. [24] has been designed and synthesized a highly selective series of inhibitors of the class I phosphatidylinositol 3-kinases (PI3Ks) that showed the dual PI3K/mTOR inhibitor **4**. A structure-based approach was used to improve potency and selectivity. This resulted in the identification of compound **5**, by the replacement of benzimidazole with pyridyl moiety and introduction of the methylsulphonylpiperazine group at 5-position of the pyridine ring [25]. It acted as a potent inhibitor of the class I PI3Ks with excellent selectivity over mechanistic target of rapamycin (mTOR) and a broad panel of protein kinase. Replacement of phenyl with pyridyl ring at 2-position of pyridyl moiety at triazine ring **6** showed potent, selective, and efficacious activities in both biochemical and cellular assays (Fig. 3). To pursue hybrid strategy for second generations, potent pan class I PI3K/mTOR inhibitors were exemplified by generic structure **8** that addressed the shortcomings of compound **6** and improved solubility over compound **7** [26]. The chloropyridyl sulfonamide affinity pocket moiety of **7** has been replaced with 2-methoxypyridyl group of **6** to give a pan class I PI3K inhibitor **8** with a moderate (>10-fold) selectivity over the mammalian target of rapamycin [27].

2-(Difluoromethyl)-1-[4,6-di-(4-morpholinyl)-1,3,5-triazin-2-yl]-1*H*-benzimidazole [28] (ZSTK474), **9a** is a potent ATP competitive pan class I PI3K inhibitor [29–32]. Replacement of both morpholines in ZSTK474, a dual PI3K/mTOR inhibitor with 2,6-bridged morpholines (**9b**) was obtained, that led to 19-fold increase in mTOR selectivity due to the deeper binding pocket in mTOR relative to PI3K as compared to one bridged morpholine (**9c**). Substitution at 4- and 6-positions of the benzimidazole ring with 6-amino-4-methoxy analog **10a** displayed greater than 1000-fold potency enhancement over the corresponding 6-aza-4-methoxy analog **10b** (Fig. 4) against all three PI3K enzymes (p110α, p110β, and p110δ) and also showed significant potency against two mutant forms of p110α isoform (H1047R and E545K) [33].

Peterson et al. [34] aimed at developing ATP-competitive mTOR inhibitors by transposing benzimidazole nitrogen (**11**) to imidazopyridine (**12**) that maintained the broader planarity between the triazine hinge-binder and the imidazopyridine ring, which was essential for good potency (Fig. 5). These *s*-triazine derivatives were screened for phototoxicity as well as the cytotoxic activities by interacting with DNA that caused extensive DNA damage, leading to induction of cell death against leukemia and adenocarcinoma derived cell lines in comparison to the normal human keratinocytes.

Venkatesan and co-workers [35,36] have been reported a series of mono-morpholino triazine derivatives bearing 3-oxa-8-azabicyclo[3.2.1]octane, as potent dual PI3K/mTOR inhibitors by increasing the clog P (Fig. 6). Morpholine in **13** was kept, as it formed a pivotal hinge region hydrogen bond interaction with



Scheme 1. Synthetic strategies for triazine derivatives.

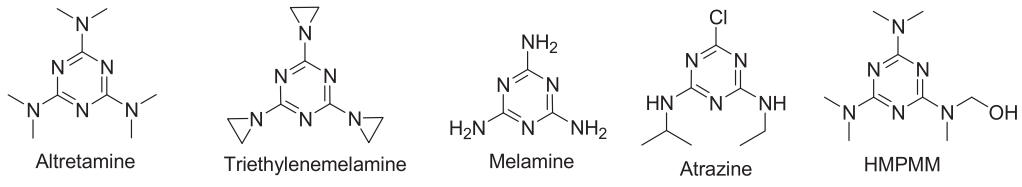


Fig. 2. Drugs containing triazine nucleus.