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Squarate-based carbocyclic nucleosides: Syntheses, computational analyses and anticancer/antiviral evaluation

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ABSTRACT

Squaric acid and its derivatives are versatile synthons and have demonstrated applications in medicinal chemistry, notably as non-classical bioisosteric replacements for functional groups such as carboxylic acids, alpha-amino acids, urea, guanidine, peptide bonds and phosphate/pyrophosphate linkages. Surprisingly, no reports have appeared concerning its possible application as a nucleobase substitute in nucleosides. A preliminary investigation of such an application is reported herein. 3-Amino-4-((1*R*,4*S*)-4-(hydroxymethyl)cyclopent-2-en-1-yl)amino-cyclobut-3-ene-1,2-dione, 3-((1*R*,4*S*)-4-(hydroxymethyl)cyclopent-2-en-1-yl)amino-4-methoxycyclobut-3-ene-1,2-dione, and 3-hydroxy-4-((1*R*,4*S*)-4-(hydroxymethyl)cyclopent-2-en-1-yl)amino-cyclobut-3-ene-1,2-dione sodium salt were synthesized. Computational analyses of their structures and preliminary antitumor and antiviral screening results are reported.

Nucleoside analogues play critical roles in medicinal chemistry and have found applications as anticancer, antiviral and antiparasitic agents.[1–7] For example, nucleoside analogues such as AraC, floxuridine, deoxycoformycin, and gemcitabine are approved anticancer nucleoside analogues.[1] In the antiviral arena, ribavirin, trifluridine, and azidothymidine are approved antiviral agents.[1,2,4,8] However the need for the discovery of other novel nucleoside structures with expanded therapeutic potential or new mechanisms of action has spurred intense synthetic efforts.[9–14] One area of research interest has focused on carbocyclic-based modifications and has included investigations on aristeromycin (**1**), neoplanocin A (**2**), carbovir (**3**), and abacavir (**4**).[4,15–18] The discovery of new nucleobase replacements is of continuing importance in this field as well and compounds such as ribavirin (**5**), pyrazofurin (**6**), showdomycin (**7**) and tiazofurin (**8**) have shown interesting biological and therapeutic activities (Fig. 1).[8,9,13,14,19–21]

Due to their interesting molecular structures, 3,4-dihydroxycyclobut-3-ene-1,2-dione (squaric acid, (**9**)) and its analogues have been applied to various areas of medicinal and biological chemistry (Fig. 2).[22–27] For example, we and others have demonstrated the versatility of the squarate moiety as a non-classical bioisosteric replacement for the carboxylic acid moiety in the potent AMPA agonist **10**,[28] the phosphate monoester in inhibitors of protein tyrosine phosphatases such as **11**,[29] the α-amino acid moiety in the NMDA antagonist **12**,[30] as a replacement for the guanidine function in the HIV-1 Tat-TAR interaction inhibitor **13**,[31] and as a phosphate ester and phosphodiester surrogate in nucleotides such as **14**.[32–35] Other studies have also employed the squarate nucleus as a substitute for ureas,[22,36] carboxylic acids,[22,24,37] glutamines,[38] and the lipid head group.[39] A number of squarate/squaramide-containing compounds have been reported to exhibit antiplasmodial,[40,41] anticancer,[42–44] antileishmanial,[45] antitrypanosomal,[46] and antibacterial[47] properties among other biological activities. CXCR2 and histamine H2 receptor antagonist activities have also been reported.[48,49]

Although a rich repertoire of chemical reactions has been reported for these interesting molecules, it is surprising that their investigation as components of a nucleoside has not been explored to our knowledge, except as a phosphate or phosphodiester bioisostere.[32–35,50] This report outlines a preliminary investigation of squarate and squaramide (squarate with at least one amine substitution) functional groups as nucleobase replacements within a carbocyclic nucleoside framework. Herein the syntheses, computational studies and preliminary anticancer and antiviral activities of squarate-based carbocyclic nucleoside analogues 3-amino-4-((1*R*,4*S*)-4-(hydroxymethyl)cyclopent-2-en-1-yl)amino-cyclobut-3-ene-1,2-dione (**15**), 3-((1*R*,4*S*)-4-(hydroxymethyl)cyclopent-2-en-1-yl)amino-4-methoxycyclobut-3-ene-1,2-dione (**16**), and 3-hydroxy-4-((1*R*,4*S*)-4-(hydroxymethyl)cyclopent-2-en-1-yl)

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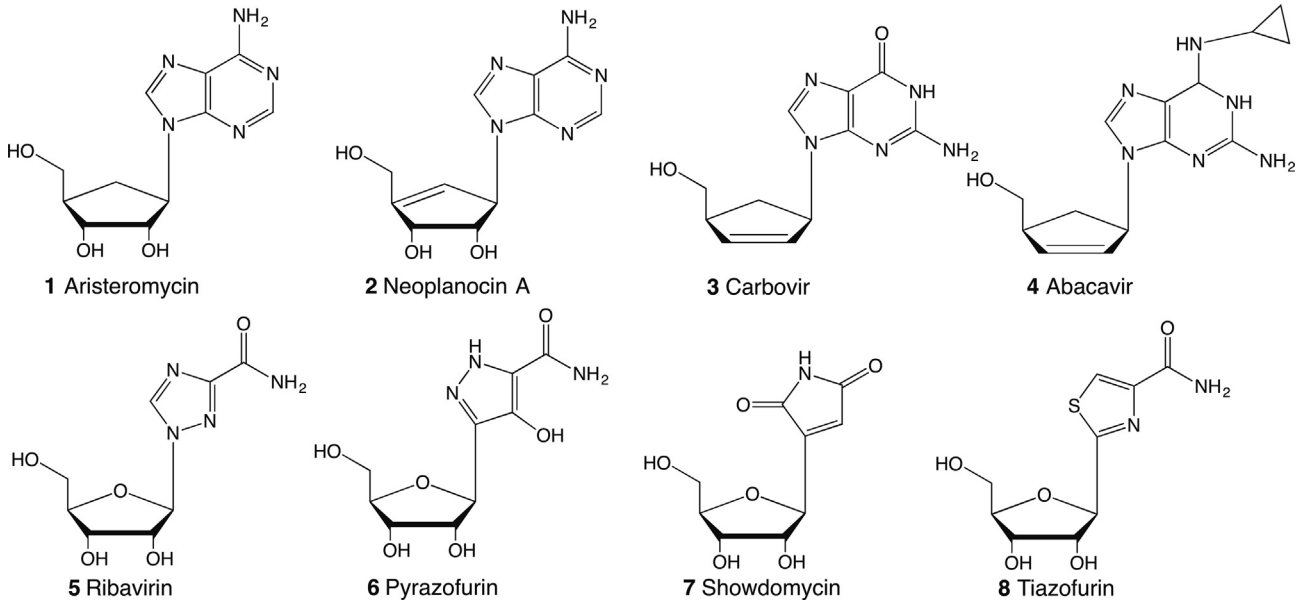

Fig. 1. Select nucleosides exhibiting anticancer, antiviral or antimicrobial activities mentioned in the text.

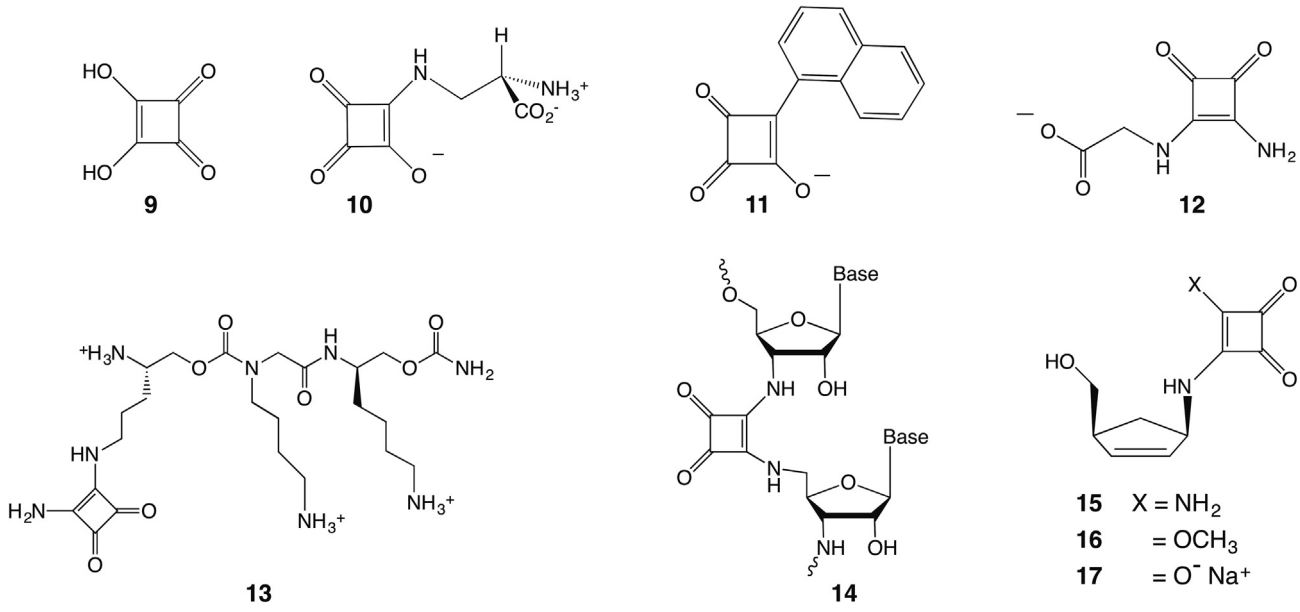

Fig. 2. Squaric acid (**9**) and various squarate/squaramate-containing bioactive molecules (**10**–**14**). Analogues synthesized in this study (**15**–**17**).

amino-cyclobut-3-ene-1,2-dione sodium salt (**17**) are presented (Fig. 2). The rational for incorporation of these three specific functionalities on the squarate was to: a) maintain an amino moiety (**15**) that might resemble the exocyclic amines found in adenine or guanine; b) provide a hydroxyl (actually a negatively charged oxygen since the pKa of squaryl monoamides have been determined to be approximately 2.3)[33,37] to possibly interact electrostatically with a molecular target; c) supply a potentially reactive methyl ester as dimethyl and diethyl squarate have been synthetically useful as crosslinking agents in the areas of protein bioconjugation and carbohydrate chemistry.[51,52]

Comparison of the structural and electronic properties of the various squarate-based analogues with standard nucleic acid bases and several nucleobase analogues were undertaken to determine if structural/electron similarities might exist. Computational analyses of simpler models of the squarate/squaramide base replacements were undertaken utilizing 3-amino-4-(methylamino)cyclobut-3-ene-1,2-dione (**18**), 3-methoxy-4-(methylamino) cyclobut-3-ene-1,2-dione (**19**), and 3-hydroxy-4-(methylamino) cyclobut-3-ene-1,2-dione (**20**) (Fig. 3). The electrostatic potentials mapped onto the electron densities at the B3LYP/6-311+G**// B3LYP/6-311+G** level[53] for **18**–**20** as well as models of the standard nucleic acid bases: 9-methyladenine (**21**), 9-methylguanine (**22**), 1-methylcytidine (4-amino-2-hydroxy-1-methylpyrimidine) (**23**), 1-methyluracil (**24**) and models (**25**–**28**) of the nucleobases found in ribavirin, pyrazofurin, showdomycin and tiazofurin were compared (Figs. 3 and 4) (Supplementary Information). From these initial computations it appeared that limited steric and electronic similarities do exist between the squarate-based nucleobase analogues and several other nucleobases. This similarity was also seen in a series of superpositions of the model squarates with models of the other nucleobases listed above (Supplementary Information,