

Structural and thermal properties of 3-substituted quinazoline Schiff base conjugates

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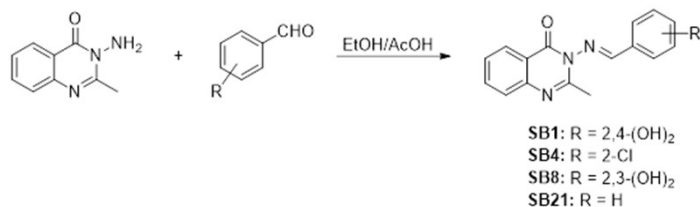
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INTRODUCTION

The excellent pharmaceutical, biological and physicochemical properties of both quinazolines and Schiff bases along with the undemanding synthetic procedure resulted in the development of a large number of quinazoline-Schiff base conjugates [1]. Recent research in this particular area has shown that quinazoline-Schiff base conjugates are potential inhibitors of SARS-CoV-2 proteins [2], antioxidants, anti-cancer agents [3], and perspective chelating ligands for the preparation of structurally diverse coordination compounds [4]. Although it is quite obvious that these compounds have enormous potential in many different fields, there is a surprisingly small number of investigations dealing with the solid-state structure. Moreover, none of these studies explore the relationship between solid-state properties and biological or physicochemical properties. The above-mentioned properties of these compounds and the lack of structural investigations led us to study the molecular and crystal structure of 4 quinazoline Schiff base conjugates (**SB1**= 3-*(E)*-[(2,4-dihydroxyphenyl)methylidene]amino)-2-methylquinazolin-4(3*H*)-one, **SB4**= 3-*(E)*-[(2-chlorophenyl)methylidene]amino)-2-methylquinazolin-4(3*H*)-one, **SB8**= 3-*(E)*-[(2,3-dihydroxyphenyl)methylidene]amino)-2-methylquinazolin-4(3*H*)-one, and **SB21**= 3-*(E)*-[*(E)*-benzylideneamino)-2-methylquinazolin-4(3*H*)-one).

EXPERIMENTAL METHODS

Compounds were prepared by previously reported procedures (Scheme 1.) [5], and single crystals were obtained by simple recrystallization from different organic solvents. The molecular and crystal structures were determined by the single-crystal X-ray diffraction method (XtaLAB Synergy, Dualflex, HyPix diffractometer). The thermal properties of compounds were investigated by TG/DSC methods (Mettler-Toledo TGA/DSC 1). Intermolecular interactions were further studied by Hirshfeld surface analysis, and interaction and lattice energies were calculated.



Scheme 1. Synthesis of quinazolinone Schiff bases.

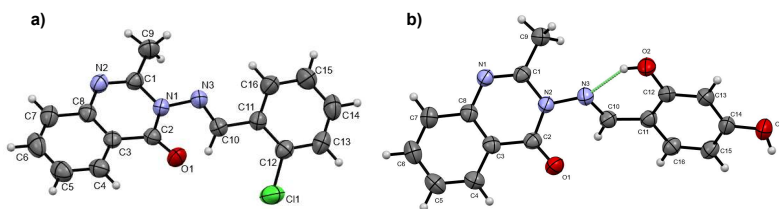


Figure 1. a) Molecular structure of **SB4**. b) Molecular structure of **SB1**. Intramolecular O-H...N interaction is represented by the green dashed line.

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RESULTS & DISCUSSION

Herein reported compounds are rare examples of structurally characterized quinazoline Schiff base conjugates. Compounds can be described as Schiff bases composed of 2-methyl-quinazoline-4-one moiety and substituted benzene moiety connected by the imine bond (Cl substituted (**SB4**), 2,4-OH substituted (**SB1**), 2,3-OH-substituted (**SB8**), and unsubstituted (**SB21**)). Considering molecular structure, herein reported compounds are similar, with the most pronounced difference found in the dihedral angle between the two aromatic systems (Figure 1.). In the crystal, compounds with –OH groups on the benzene ring are primarily connected by strong O–H...N hydrogen bonds, and unsubstituted and Cl-substituted compounds *via* N–H...O hydrogen bonds and π -stacking interactions (Figure 2.). Thermal analysis results have shown that among these compounds the 2,4-OH substituted **SB1** has the highest melting point (226 °C), followed by 2,3-OH substituted **SB8** (201 °C), unsubstituted **SB21** (192 °C), and the Cl-substituted **SB4** (159 °C). Additional Hirshfeld surface analysis and intermolecular energy calculations (Table 1) indicate that hydrogen bonds have the largest impact on thermal stability and that dispersive interactions are important for stability, but can be sterically hindered by bulky substituents on aromatic systems.

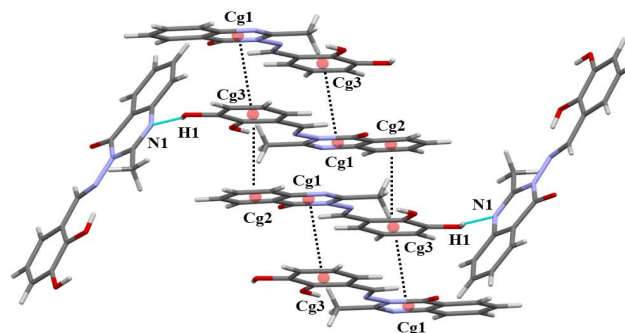


Figure 2. Representation of intermolecular O–H...N hydrogen bonds (blue dashed lines) and offset π – π interactions (black dashed lines) in **SB8**

Table 1. Intermolecular interaction energies (electrostatic (E_{ele}), polarization (E_{pol}), dispersion (E_{dis}), repulsion (E_{rep}) in kJ/mol) for all compounds, and sum of attractive interactions ($E_{attractive}$). The percentage contribution of individual attractive interaction energies to total energies is given in brackets.

Compound	E_{ele}	E_{pol}	E_{dis}	$E_{attractive}$	E_{rep}	E_{tot}	Melting point /°C
SB4	-96.5 (30.1%)	-46.2 (14.4%)	-176.9 (55.3%)	-319.6	142.3	-177.3	226
SB8	-86.3 (27.2%)	-39.8 (12.5%)	-190.4 (60.0%)	-316.5	160.9	-155.6	201
SB21	-55.9 (23.2%)	-23.5 (9.7%)	-160.9 (66.9%)	-240.3	93.3	-147.0	192
SB1	-30.4 (12.1%)	-61.7 (24.6%)	-158.3 (63.2%)	-250.4	85.2	-165.2	159

CONCLUSION(S)

The herein presented results within this group of compounds can be used to set a useful guidelines for crystal engineering of thermally stable organic compounds: (i) the primary source of crystal stability comes from strong electrostatic interactions. (ii) dispersive interactions are important for stability, but easily sterically hindered by bulky substituents; (iii) weak hydrogen bond acceptors (Cl, Br) show a negative effect on crystal stability by reducing the ability and strength of intermolecular interactions and hindering the formation of desirable dispersive interactions.