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Short Note

(*E*)-4-Oxo-3,4-dihydroquinazoline-2-carbaldehyde Oxime

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Abstract: Reaction of 4-oxo-3,4-dihydroquinazoline-2-carbaldehyde with hydroxylamine hydrochloride (1.1 equiv) in the presence of K_2CO_3 (1 equiv) gave (*E*)-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde oxime (**8**) in 58% yield. The compound was fully characterized and the conformation of the oxime was supported by single crystal x-ray diffractometry.

Keywords: heterocycle; polyfunctionalized; quinazoline; oxime

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1. Introduction

Quinazolines are important aromatic N-heterocycles that have wide pharmaceutical applications. Among the 6-membered aromatic nitrogen-containing heterocycles, quinazolines rank 3rd in the most frequently used U.S. FDA-approved drugs [1]. Examples of quinazoline-containing drugs are the anticancer drug erlotinib and the antihypertensive prazosin (Figure 1). The chemistry and applications of quinazolines have been reviewed [2].

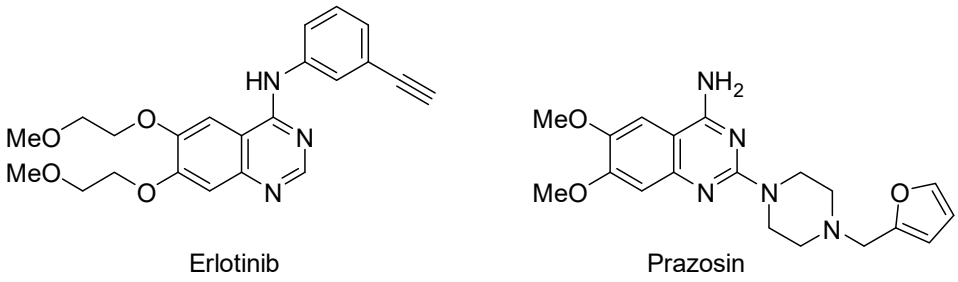


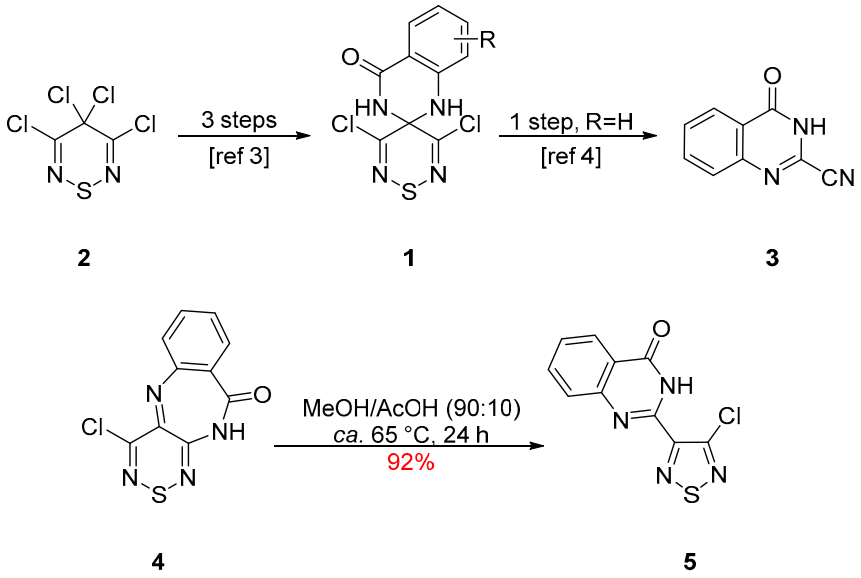
Figure 1. Quinazolines in drugs.

2. Results and Discussion

Our interest in quinazolines began with 3′,5′-dichloro-1*H*-spiro(quinazoline-2,4′-[1,2,6]thiadiazin)-4(3*H*)-ones **1** that can be synthesized in 3 steps starting from tetrachlorothiadiazine **2** [3] (Scheme 1). Interestingly, spirocycle **1a** (R = H) can also be decomposed to 4-oxo-3,4-dihydroquinazoline-2-carbonitrile (**3**) [4] (Scheme 1). More recently, while investigating the stability of 4-chlorobenzo[e][1,2,6]thiadiazino[3,4-b][1,4]diazepin-10(11*H*)-one (**4**), we found that upon heating in MeOH/AcOH (90:10), it was converted in 92% yield to the isomeric 2-(4-chloro-1,2,5-thiadiazol-3-yl)quinazolin-4(3*H*)-one (**5**) [5] (Scheme 1). We attributed this transformation to an acid-catalyzed nucleophilic addition to the thiadiazine **4** followed subsequent Wagner–Meerwein shifts leading to the observed ring contractions [5].

We were interested in developing an independent synthesis for thiadiazole **5** to investigate its chemistry. The proposed independent synthesis started from 2-aminobenzamide **6,** which can be converted to quinazolinone-2-carbaldehyde **7** in two steps with 51% overall yield [6] (Scheme 2). The conversion of aldehyde **7** into oxime **8**, followed by the addition

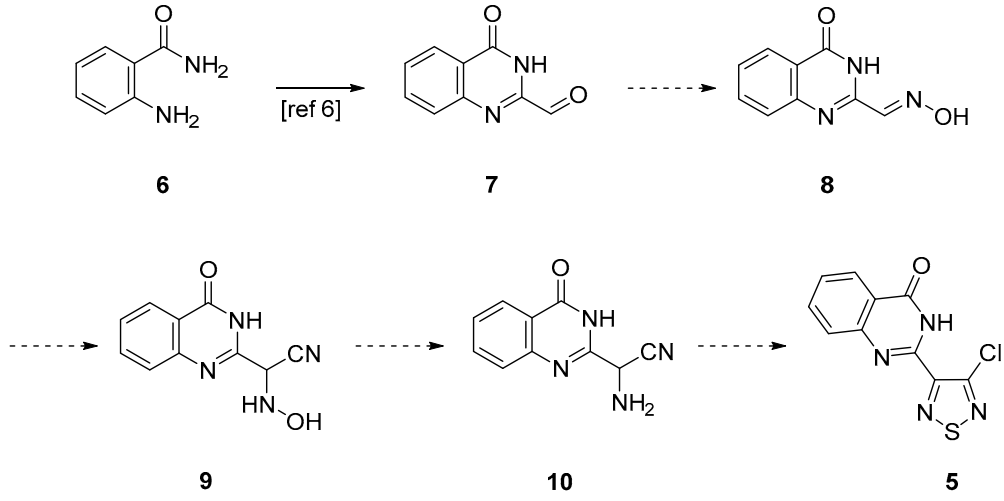
of cyanide should give hydroxylamine **9** [7]. The subsequent reduction to aminoacetonitrile **10** [8] followed by reaction with S_2Cl_2 was expected to give the desired thiadiazole **5** [9].



2 **1** **3**

4 **5**

Scheme 1. Synthesis of spirocycles **1** and quinazolinone **3** and isolation of thiadiazole **5** from diazepine **4**.



6 **7** **8**

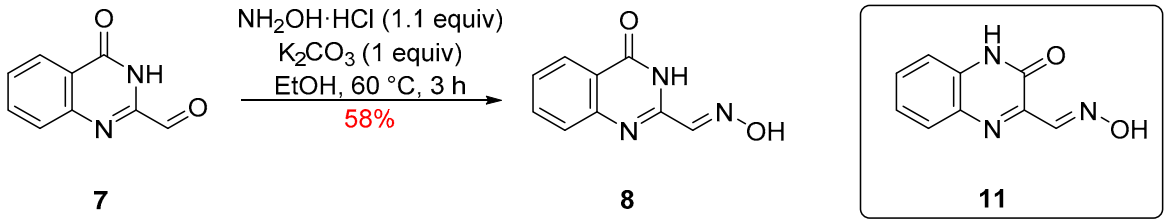
9 **10** **5**

Scheme 2. Proposed synthesis for thiadiazole **5**.

The reaction of quinazolinone-2-carbaldehyde **7** with hydroxylamine hydrochloride (1.1 equiv), in the presence of K_2CO_3 (1 equiv), in EtOH, at ca. 60 °C led after 3 h to complete consumption of the starting aldehyde and on work-up isolation of oxime **8** in 58% yield (Scheme 3).

Product **8** was isolated as colorless needles, mp 237–238 °C (from EtOH/H_2O). FTIR spectroscopy showed an oxime ν(O-H) stretch at 3280 cm^{-1} along with an amide ν(N-H) stretch at 3173 cm^{-1}, an oxime ν(C-H) stretch at 2876 cm^{-1} and a broad ν(C=O) stretch at 1678 cm^{-1}. Meanwhile, mass spectrometry revealed a molecular ion (MH^+) peak of m/z 190, agreeing with the addition of NH_2OH and loss of H_2O from the starting aldehyde **7**. ^{13}C NMR spectroscopy showed the presence of five CH resonances and four quaternary carbon resonances (see Supplementary Materials for the complete spectra). At the same time, a correct elemental analysis (CHN) was obtained for the molecular formula $C_9H_7N_3O_2$, agreeing with the structure shown above. Structural support was also provided by single-crystal X-ray

diffraction studies (Figure 2). To the best of our knowledge, compound **8** has not been reported in the literature and could have many potential uses. Importantly, the structurally similar isomer quinoxalin-2(1*H*)-one-3-carbaldoxime (**11**) (Scheme 3) has been used as a scaffold for the preparation of benzimidazoles [10]. At the same time, other analogs were investigated as neurologically active compounds for the treatment of Alzheimer's disease [11] or as ligands to ruthenium and osmium complexes with anticancer properties [12].



Scheme 3. Synthesis of (*E*)-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde oxime (**8**) and structure of the isomeric (*E*)-3-oxo-3,4-dihydroquinoxaline-2-carbaldehyde oxime (**11**).

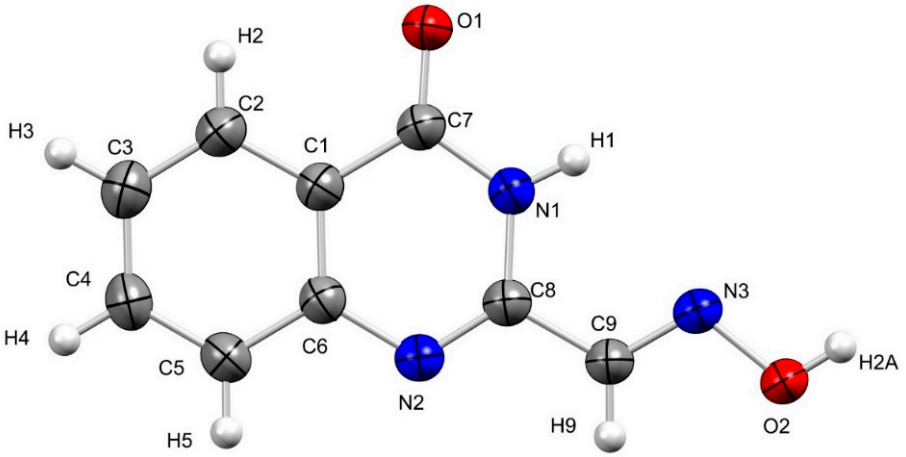


Figure 2. Geometry of (*E*)-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde oxime (**8**) in the crystal; crystallographic atom numbering. Thermal ellipsoids at 50% probability.

X-ray crystallography indicated that quinazoline **8** is planar in the crystalline state and forms sheets (intersheet distance is 4.03 Å) of off-set dimers held together by hydrogen bond interactions [$d_{(O\text{-}H\ldots O)}$ ~2.60 Å, $\Theta_{(O\text{-}H\ldots O)}$ 173.41°] (Figure 3). Notable intramolecular bond lengths include the C7-O1 and N2-C8 bond lengths typical of double bonds; $d_{(C7=O1)}$ = 1.23 Å and $d_{(C8=N2)}$ = 1.29 Å, respectively.

After the synthesis of oxime **8**, the addition of cyanide was attempted, but unfortunately, no reaction occurred with KCN (10 equiv), in dry DMF at ca. 20 °C for 2 d, as well as, with 18-crown-6 (1 equiv) at ca. 100 °C for 3 d. This reaction will be further investigated in the future.

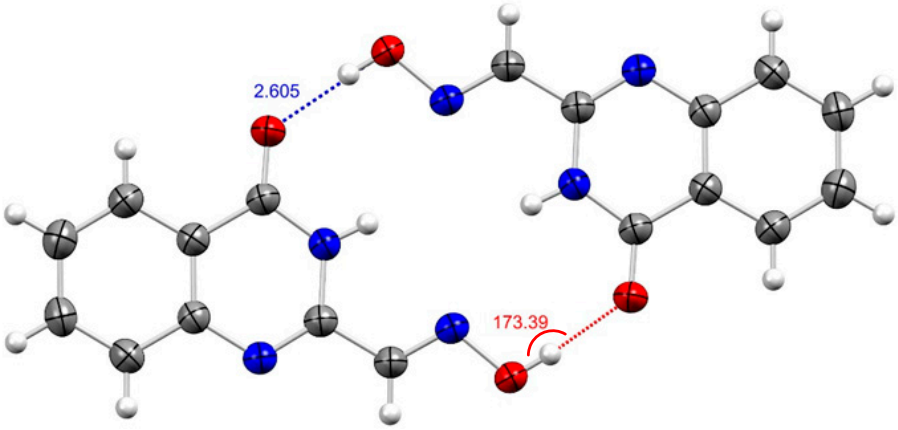


Figure 3. ORTEP view of notable intermolecular interactions (Å, in blue) and related bond angles (°, in red) from the crystal structure of (*E*)-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde oxime (**8**); thermal ellipsoids at 50% probability.

3. Materials and Methods

The reaction mixture was monitored by TLC using commercial glass-backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}, Darmstadt, Germany). The plates were observed under UV light at 254 and 365 nm. The melting point was determined using a PolyTherm-A, Wagner & Munz, Kofler–Hotstage Microscope apparatus (Wagner & Munz, Munich, Germany). The solvent used for recrystallization is indicated after the melting point. The UV-vis spectrum was obtained using a Perkin-Elmer Lambda-25 UV-vis spectrophotometer (Perkin-Elmer, Waltham, MA, USA) and inflections are identified by the abbreviation "inf". The IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with Pike Miracle Ge ATR accessory (Pike Miracle, Madison, WI, USA), and strong, medium, and weak peaks were represented by s, m, and w, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 machine [at 500 and 125 MHz, respectively, (Bruker, Billerica, MA, USA)]. Deuterated solvents were used for homonuclear lock, and the signals are referenced to the deuterated solvent peaks. Attached proton test (APT) NMR studies were used to assign the ^{13}C peaks as CH_3, CH_2, *C*H, and *C*q (quaternary). The Matrix-Assisted Laser Desorption/Ionization-Time Of Flight (MALDI-TOF) mass spectrum (+ve mode) was recorded on a Bruker Autoflex III Smartbeam instrument (Bruker). The elemental analysis was run by the London Metropolitan University Elemental Analysis Service. 4-Oxo-3,4-dihydroquinazoline-2-carbaldehyde (**7**) was prepared according to the literature procedure [6].

(E)-4-Oxo-3,4-dihydroquinazoline-2-carbaldehyde oxime (**8**). To a stirred mixture of 4-oxo-3,4-dihydroquinazoline-2-carbaldehyde (**7**) (87 mg, 0.50 mmol) in EtOH (2 mL) at ca. 20 °C was added $NH_2OH{\cdot}HCl$ (38 mg, 0.55 mmol) followed by K_2CO_3 (69 mg, 0.50 mmol) and the mixture was then warmed to ca. 60 °C and stirred at this temperature until complete consumption of the starting material (TLC, 3 h). The mixture was then cooled to ca. 20 °C and then H_2O (5 mL) was added. The red precipitate formed was filtered, washed with H_2O (5 mL) and dried in vacuo to give the title compound **8** (55 mg, 58%) as colorless needles, mp 237–238 °C (from EtOH/H_2O); R_f 0.25 (DCM/*t*-BuOMe 90:10); (found: C, 57.21; H, 3.69; N, 22.21. $C_9H_7N_3O_2$ requires C, 57.14; H, 3.73; N, 22.21%); λ_{max}(THF)/nm 306 inf (log ε 3.98), 316 (4.04), 346 (3.80), 364 inf (3,50); υ_{max}/cm^{-1} 3281 w (O-H), 3173 w (N-H), 3065 w and 3003 w (C-H arom), 2876 w and 2799 w (oxime C-H), 1678 s (C=O), 1599 m, 1564 w, 1510 w, 1470 m, 1344 m, 1275 w, 1260 w, 1142 w, 1038 m, 1020 m, 1003 m, 922 w, 878 m, 808 m, 781 m, 748 m, 733 m; δ_H(500 MHz; DMSO-d_6) 12.43 (1H, br. s, OH), 12.01 (1H, br. s, NH), 8.13 (1H, d, *J* = 7.6, Ar CH), 7.87 (1H, s, NCH), 7.83 (1H, dd, *J* = 7.4, 7.4, Ar CH), 7.69 (1H, d, *J* = 8.2, Ar CH), 7.54 (1H, dd, *J* = 7.4, 7.4, Ar CH); δ_C(125 MHz; DMSO-d_6) 160.9 (Cq), 148.2 (Cq), 148.1 (Cq), 143.4 (CH), 134.7 (CH), 127.4 (CH), 127.3 (CH), 126.0 (CH), 122.0 (Cq); *m*/*z* (MALDI-TOF) 228 ($M + K^+$, 100%), 212 ($M + Na^+$, 82), 190 (MH^+, 93), 113 (35).

X-ray crystallographic studies on (E)-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde oxime (**8**). Data were collected on an Oxford-Diffraction Supernova diffractometer, equipped with a CCD area detector utilizing Cu-Kα radiation (λ = 1.5418 Å). A suitable crystal was attached to glass fibers using paratone-N oil and transferred to a goniostat, where they were cooled for data collection. Unit cell dimensions were determined and refined using 6738 ($4.485^\circ \leq \theta \leq 77.063^\circ$) reflections. Empirical absorption corrections (multi-scan based on symmetry-related measurements) were applied using CrysAlis RED software.[17] The structures were solved by direct method and refined on F^2 using full-matrix least-squares using SHELXL97.[18] Software packages used: CrysAlis CCD[17] for data collection, CrysAlis RED[17] for cell refinement and data reduction, WINGX for geometric calculations,[19] and DIAMOND[20] for molecular graphics. The non-H atoms were treated anisotropically. The hydrogen atoms were placed in calculated, ideal positions and refined as riding on their respective carbon atoms.

Crystal refinement data for (E)-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde oxime (**8**): isolated as colorless needles (from EtOH/H_2O vapor diffusion), $C_9H_7N_3O_2$, M = 189.18, Monoclinic, space group $P2_1/c$, a = 10.0944(12) Å, b = 9.8586(8) Å, c = 9.2424(10) Å, $\alpha = 90^\circ$, β = 11.696 (13)°, $\gamma = 90^\circ$, V = 854.61(17) Å^3, Z = 4, T = 100(2) K, ρ_{calcd} = 0.908 g·cm^{-3}, θ_{max} = 77.063°. Refinement of 128 parameters on 1780 independent reflections out of 6738 measured reflections (R_{int} = 0.0789) led to R_1 = 0.1182 [I > 2σ(I)], wR_2 = 0.3004 (all data), and S = 1.087 with the largest difference peak and hole of 0.581 and −0.326 e·Å^{-3}, respectively. (CCDC: 2083591).

Supplementary Materials: Supplementary materials are available online. Mol file, ^{1}H and ^{13}C NMR spectra, and IR spectrum.

Author Contributions: P.A.K. and A.S.K. conceived the experiments; A.S.K. designed and performed the experiments, analyzed the data, and wrote the paper; A.K. collected the X-ray crystallography data. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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