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Short Note

3-(1-Cyclohexyl-2-(cyclohexylamino)-4-(4-ethoxyphenyl)-6-oxo-1,6-dihydropyrimidin-5-yl)-1-methylquinoxalin-2(1*H*)-one

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Abstract: The reaction of 3-cyclohexyl-2-(cyclohexylimino)-6-(4-ethoxyphenyl)-5-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-2,3-dihydro-4*H*-1,3-oxazin-4-one with ammonium acetate afforded 3-(1-cyclohexyl-2-(cyclohexylamino)-4-(4-ethoxyphenyl)-6-oxo-1,6-dihydropyrimidin-5-yl)-1- methylquinoxalin-2(1*H*)-one in a good yield. The compound was fully characterized.

Keywords: 1,3-oxazine; pyrimidine; quinoxaline

Citation: Khramtsova, E.E.; Kasatkina, S.O.; Dmitriev, M.V.; Maslivets, A.N. 3-(1-Cyclohexyl-2-(cyclohexylamino)-4-(4-ethoxyphenyl)-6-oxo-1,6-dihydropyrimidin-5-yl)-1-methylquinoxalin-2(1*H*)-one. *Molbank* **2022**, *2022*, M1421. https://doi.org/10.3390/M1421

Academic Editors: Fawaz Aldabbagh and René T. Boeré

Received: 8 June 2022
Accepted: 4 August 2022
Published: 5 August 2022

1. Introduction

2-(Pyrimidin-5-yl)quinoxalines are interesting nitrogen heterocycles for medical applications. For example, potential pharmaceutical substances, bearing a 2-(pyrimidin-5-yl)quinoxaline core, were developed for treating pain [1], inflammatory conditions [2], T-cell-mediated autoimmune disease [2], anemia [3], and cancer [2,4] (Figure 1).

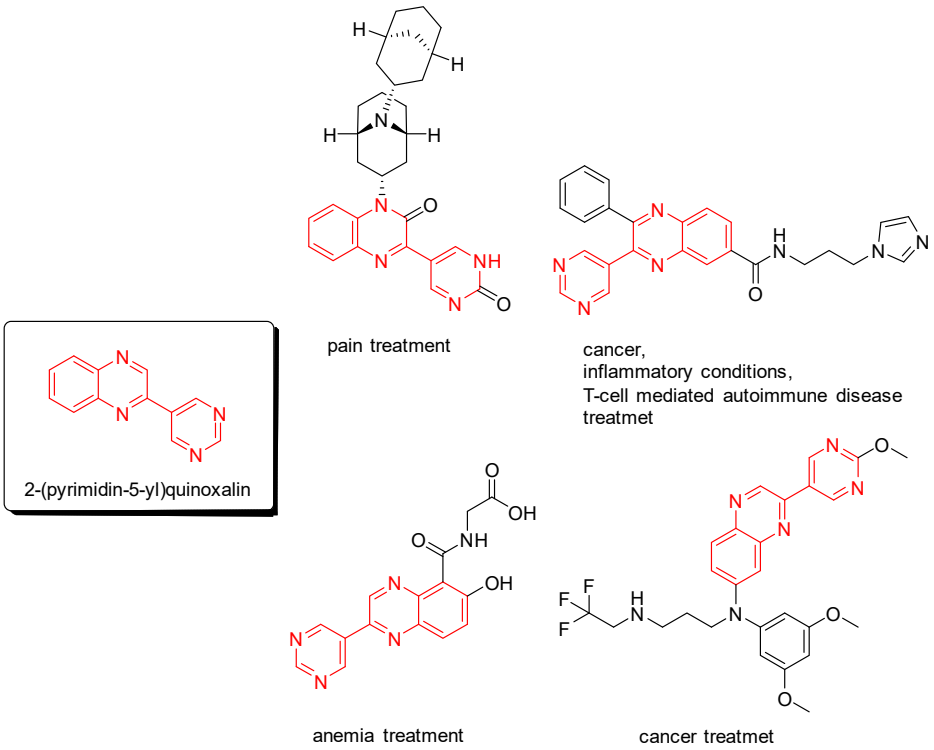
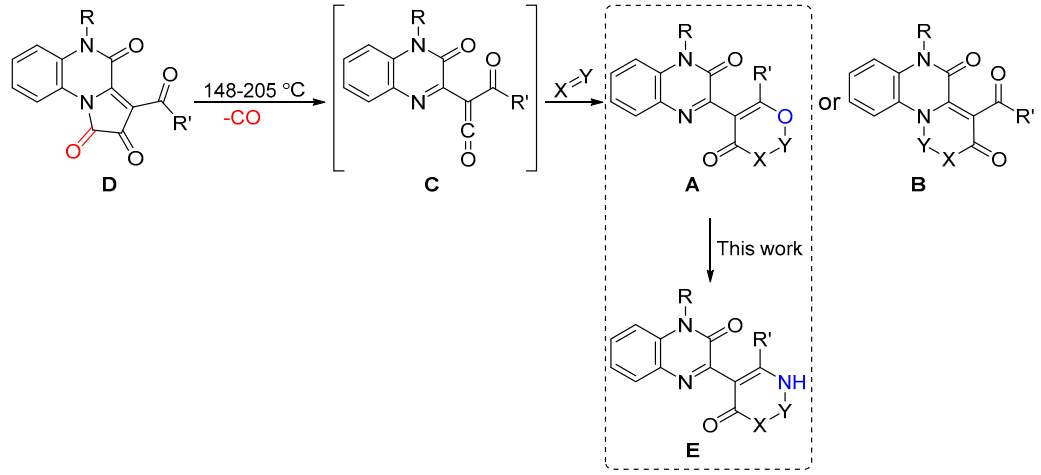


Figure 1. Potential pharmaceutical substances, bearing a 2-(pyrimidin-5-yl)quinoxaline core.

As a continuation of our study on the syntheses of quinoxaline-based heterocycles **A** and **B**, via reactions of acyl(quinoxalin-2-yl)ketenes **C**, generated by the thermolysis of [*e*]-fused 1*H*-pyrrole-2,3-diones **D** [5], we investigated the capacity of the conversion of

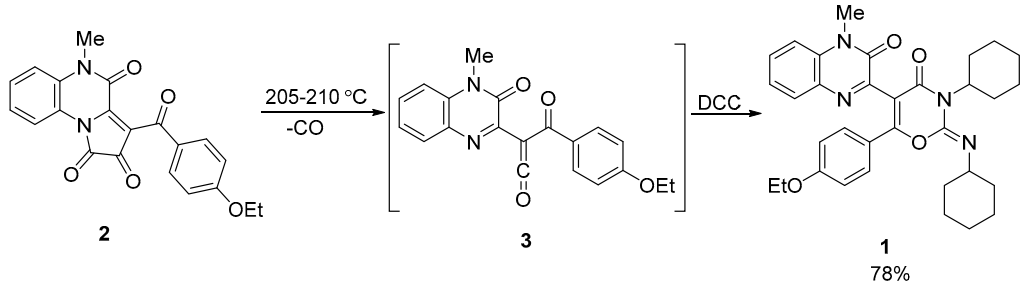
heterocycles **A** to their aza-analogs **E**, e.g., pyrimidinylquinoxalines (X = NR″; Y = CR‴$_2$) (Scheme 1).



Scheme 1. Syntheses of quinoxaline derivatives **A** and **B** via reactions of acyl(quinoxalin-2-yl)ketenes **C**.

2. Results and Discussion

The starting quinoxaline derivative **1** was synthesized according to the previously reported procedure [6] using the solvent-free reaction of [*e*]-fused 1*H*-pyrrole-2,3-dione **2** with dicyclohexylcarbodiimide (DCC) (Scheme 2). This transformation was completed in two steps through a one-pot procedure. First, pyrrole-2,3-dione **2** underwent thermal decomposition to form a highly reactive acyl(quinoxalin-2-yl)ketene **3** in situ. Second, ketene **3** was involved in a [4+2] cycloaddition reaction with DCC to afford the desired compound **1**.



Scheme 2. Synthesis of the starting quinoxaline derivative **1** [6].

It should be mentioned that compound **1** was chosen for this study, since its closest analogs had shown significant antihypoxic effects in vivo [7] (Figure 2).

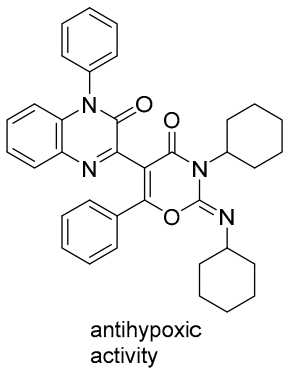
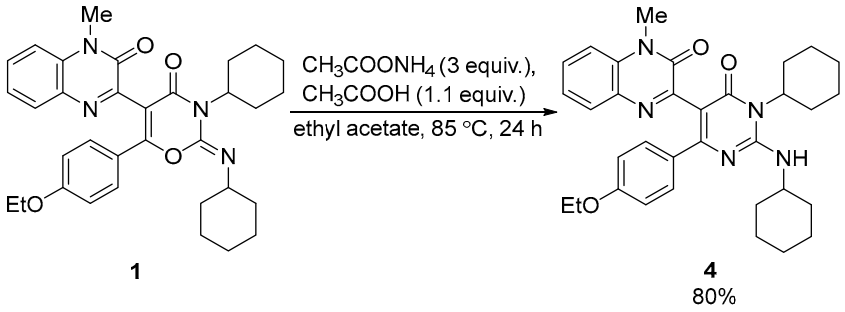


Figure 2. Close analog of quinoxaline derivative **1** [7].

The reaction of compound **1** with ammonium acetate afforded pyrimidinylquinoxaline derivative **4** in a good yield (80%) (Scheme 3). No other products were observed through the UPLC-UV-MS of the reaction mixture. The structure of compound **4** was unambiguously confirmed through single crystal X-ray analysis (CCDC Refcode = ZUNYIT, CCDC 2010489 [8]).



Scheme 3. Synthesis of pyrimidinylquinoxaline **4** from quinoxalinyl-1,3-oxazine **1**.

3. Materials and Methods

3.1. General Information

^{1}H and ^{13}C NMR spectra (Supplementary Materials) were acquired using a Bruker Avance III 400 HD spectrometer (at 400 and 100 MHz, respectively) in $CDCl_3$ (stab. with Ag) using the HMDS signal (in ^{1}H NMR) or solvent residual signal (in ^{13}C NMR, 77.00 for $CDCl_3$) as internal standards. The IR spectrum was recorded using a Perkin–Elmer Spectrum Two spectrometer from a mull in mineral oil. The melting point was measured on a Khimlabpribor PTP apparatus. Elemental analysis was carried out on a Vario MICRO Cube analyzer. The reaction conditions were optimized using UPLC-UV-MS (Waters ACQUITY UPLC I-Class system; Acquity UPLC BEH C18 column; grain size of 1.7 µm; acetonitrile–water as eluents; flow rate of 0.6 mL/min; ACQUITY UPLC PDA eλ Detector (wavelength range of 230–780 nm); Xevo TQD mass detector; electrospray ionization (ESI); positive and negative ion detection; ion source temperature of 150 °C; capillary voltage of 3500–4000 V; cone voltage of 20–70 V; vaporizer temperature of 200 °C). The single crystal X-ray analysis of compound **4** was performed on an Xcalibur Ruby diffractometer (Agilent Technologies). The empirical absorption correction was introduced by the multi-scan method using the SCALE3 ABSPACK algorithm [9]. Using OLEX2 [10], the structure was solved using the SUPERFLIP [11] program and refined by the full-matrix least-squares minimization in the anisotropic approximation for all non-hydrogen atoms with the SHELXL [12] program. Hydrogen atoms bound to carbon were positioned geometrically and refined using a riding model. The hydrogen atom of the NH group was refined freely with isotropic displacement parameters. Starting compound **1** was obtained according to the reported procedure [6] from DCC (purchased from commercial vendors) and 1*H*-pyrrole-2,3-dione **2** (obtained according to the reported procedure [6] from commercially available reagents). All other solvents and reagents were purchased from commercial vendors and used as received.

3.2. 3-(1-Cyclohexyl-2-(cyclohexylamino)-4-(4-ethoxyphenyl)-6-oxo-1,6-dihydropyrimidin-5-yl)-1-methylquinoxalin-2(1H)-one **4**

A mixture of 50 mg (90 µmol) of compound **1**, 21 mg (270 µmol) of ammonium acetate, and 6 mg (100 µmol) of acetic acid in 1 mL of ethyl acetate were stirred in a screw-capped vial at 85 °C for 24 h. Then, the reaction mixture was cooled to room temperature. The formed precipitate was filtered off and recrystallized from ethyl acetate to yield the title compound **4** (yield: 40 mg (80%); pale yellow solid; mp 289–291 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (m, 1 H), 7.50 (m, 3 H), 7.28 (m, 2 H), 6.73 (m, 2 H), 5.16 (br.s, 1 H), 4.92 (br.s, 1 H), 4.18 (m, 1 H), 3.97 (q, *J* 6.8 Hz, 2 H), 3.70 (s, 3 H), 2.16–1.12 (m, 25 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.8, 159.8, 156.9, 154.8, 152.0, 133.6, 133.1, 133.1, 130.4, 130.3, 130.0, 130.0, 123.2, 123.1, 113.9, 113.9, 113.4, 63.3, 50.4, 32.9, 29.8, 29.3, 26.5, 25.7, 24.6,

14.7 ppm. IR (mineral oil): 3366, 1654 cm^{-1}. Anal. Calcd. (%) for $C_{33}H_{39}N_5O_3$: C 71.58; H 7.10; N 12.65. Found: C 71.92; H 7.13; N 12.51. MS (ESI+): *m/z* calcd. for $C_{33}H_{39}N_5O_3+H^+$: 554.31 [M+H^+]; found: 554.30. The crystal structure of compound **4** was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2010489, CCDC Refcode = ZUNYIT [8].

Supplementary Materials: The following are available online: copies of NMR spectra for new compound.

Author Contributions: Conceptualization, E.E.K.; methodology, E.E.K.; validation, E.E.K.; investigation, E.E.K., S.O.K. (synthetic chemistry) and M.V.D. (X-ray analysis); writing—original draft preparation, E.E.K.; writing—review and editing, E.E.K. and M.V.D.; visualization, E.E.K.; supervision, E.E.K. and A.N.M.; project administration, E.E.K.; funding acquisition, A.N.M. All authors have read and agreed to the published version of the manuscript.

Funding: This study was performed under financial support by the Perm Research and Educational Center "Rational subsoil use", 2022.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The presented data are available in this article.

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

Sample Availability: Samples of all compounds are available from the authors.

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