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# 3-Benzoyl-2-hydroxy-3a-[(3-methylquinoxalin-2-yl)methyl]-1*H*-pyrrolo[2,1-*c*][1,4]benzothiazine-1,4(3a*H*)-dione

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**Abstract:** The reaction of 3-benzoylpyrrolo[2,1-*c*][1,4]benzothiazine-1,2,4-trione with 2,3-dimethylquinoxaline afforded 3-benzoyl-2-hydroxy-3a-[(3-methylquinoxalin-2-yl)methyl]-1*H*-pyrrolo[2,1-*c*][1,4]benzothiazine-1,4(3a*H*)-dione in a moderate yield. The compound was fully characterized.

**Keywords:** 1,4-thiazine; 2,3-dimethylquinoxaline; 1*H*-pyrrole-2,3-dione

## 1. Introduction

3a-(Quinoxalin-2-ylmethyl)pyrrolo[2,1-*c*][1,4]benzothiazine **A** (Figure 1) core is a heterocyclic hybrid of two pharmacologically promising scaffolds, 1,4-thiazine [1] and quinoxaline [2]. For example, several heterocyclic compounds with a 1,4-thiazine core were reported to show good antibacterial [3–5] and antihypertensive [6–8] activities (Figure 1). In addition, several quinoxaline-based structures were used to develop antimicrobial [9] and cytotoxic [10] agents, inhibitors of platelet-derived growth factor receptor tyrosine kinase (PDGFR) [11], acetylcholinesterase (AChE), and butyrylcholinesterase (BChE) [12] (Figure 1). Thus, structures with a 3a-(quinoxalin-2-ylmethyl)pyrrolo[2,1-*c*][1,4]benzothiazine **A** scaffold are attractive objects for medicinal and pharmaceutical studies.

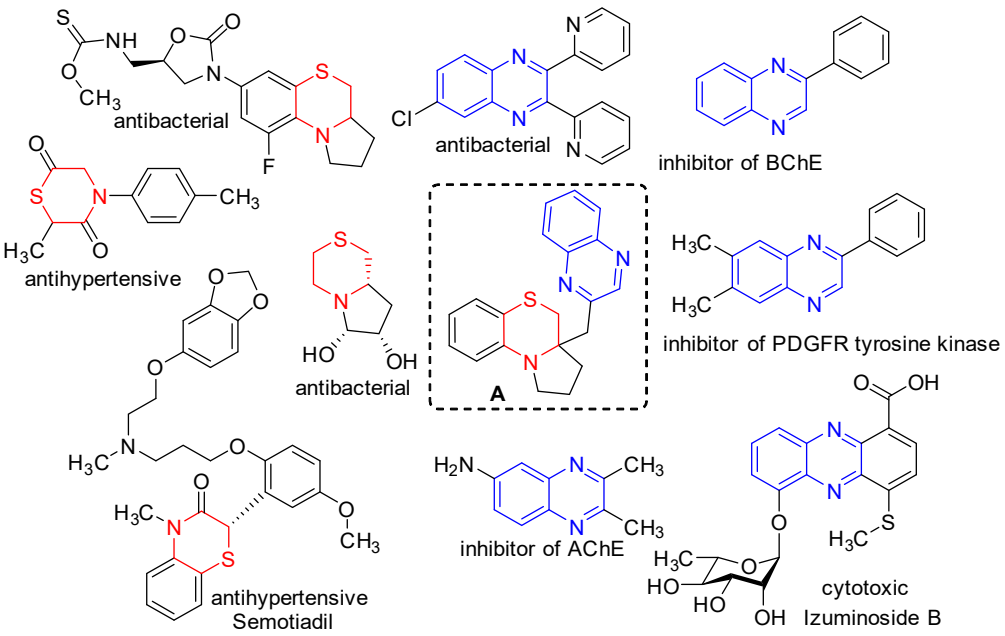


**Figure 1.** 3a-[(Quinoxalin-2-yl)methyl]pyrrolo[2,1-*c*][1,4]benzothiazine core **A** and selected examples of pharmacologically active molecules based on the thiazine and quinoxaline scaffolds.

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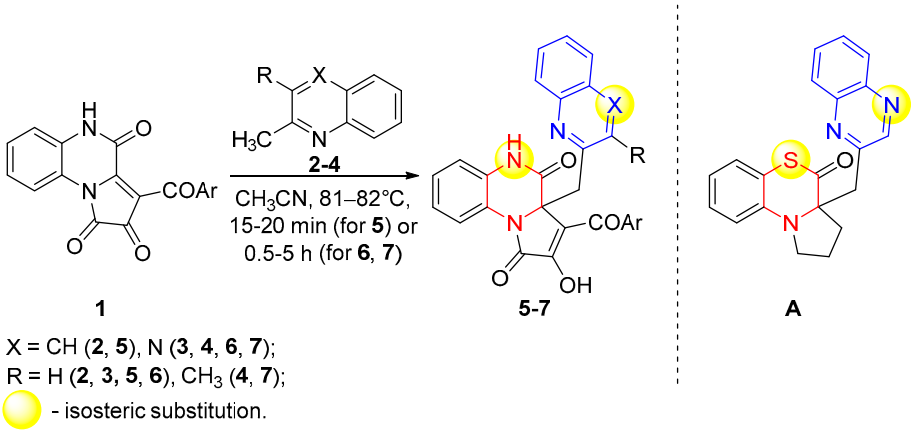
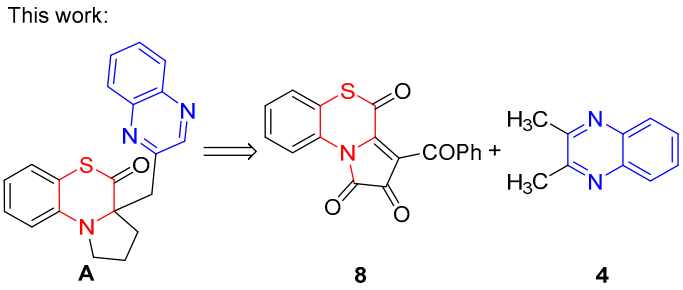
Recently, 3-aroylpyrrolo[1,2-*a*]quinoxaline-1,2,4(5*H*)-triones **1** ([*e*]-fused 1*H*-pyrrole-2,3-diones (FPDs) [13–15] bearing a quinoxaline core) were reported to react with quinaldine **2** or 2-methylquinoxalines **3**, **4** to afford corresponding 3a-(quinolin-2-ylmethyl)pyrrolo[1,2-*a*]quinoxalines **5** or 3a-(quinoxalin-2-ylmethyl)pyrrolo[1,2-*a*]quinoxalines **6**, **7** under mild conditions (Scheme 1) [16]. Compounds **5–7** bear isosteric moieties of the pharmacologically attractive 3a-(quinoxalin-2-ylmethyl)pyrrolo[2,1-*c*][1,4]benzothiazine **A** (Scheme 1).




**Scheme 1.** Reaction of FPDs **1** with quinaldine **2** and 2-methylquinaxalines **3**, **4** [13].

In order to achieve pharmacologically valuable 3a-(quinoxalin-2-ylmethyl)pyrrolo[2,1-*c*][1,4]benzothiazine **A** derivatives, we studied the reaction of an exemplar of a recently emerged class of FPDs bearing a 1,4-thiazine moiety (3-aroylpyrrolo[2,1-*c*][1,4]benzothiazine-1,2,4-triones (APBTTs) [17–19]), compound **8**, with 2,3-dimethylquinoxaline **4** (Scheme 2).

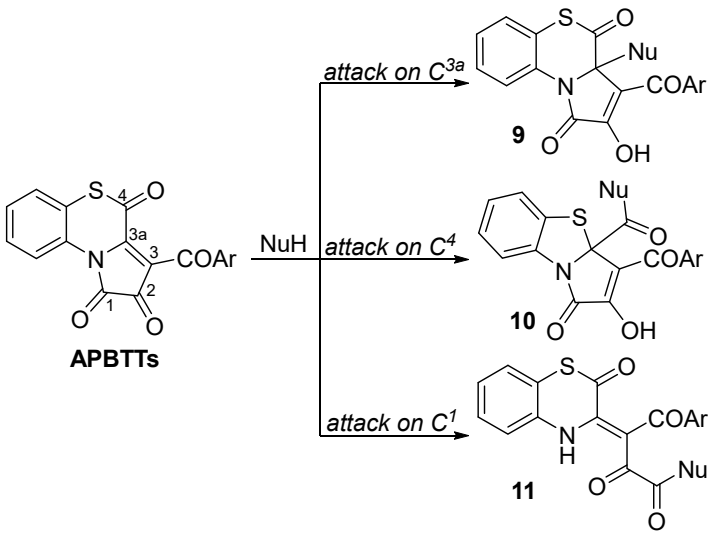



**Scheme 2.** Retrosynthetic analysis of 3a-(quinoxalin-2-ylmethyl)pyrrolo[2,1-*c*][1,4]benzothiazine **A**.

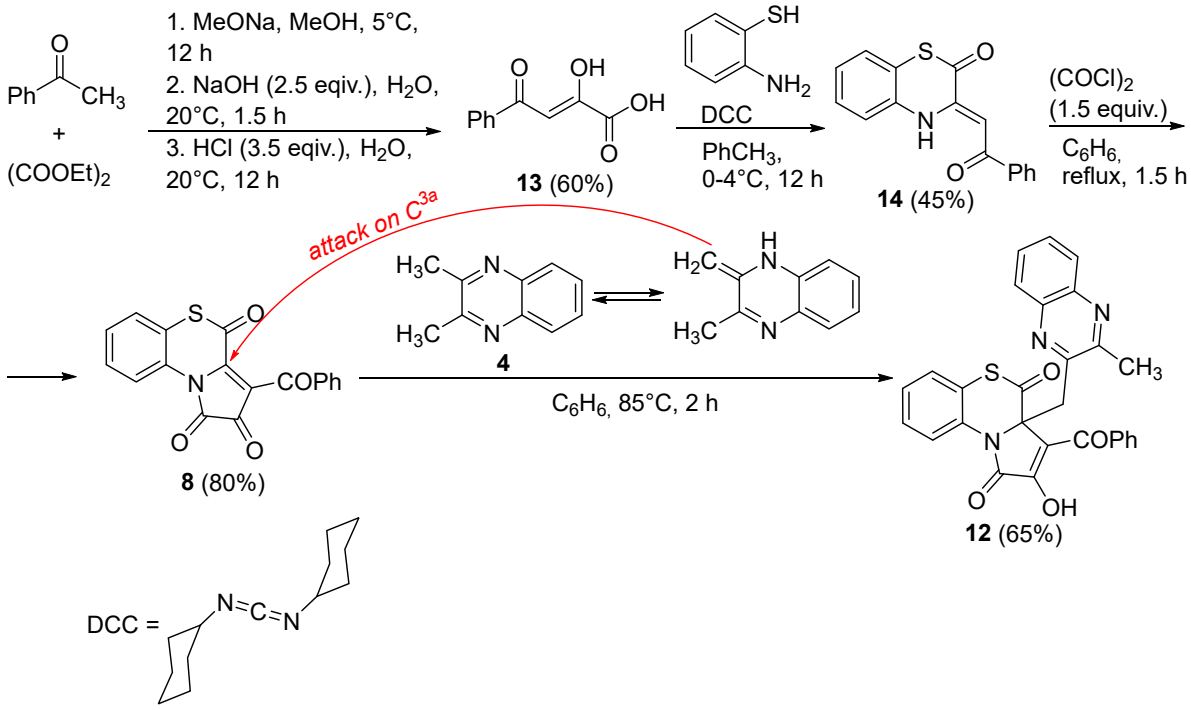
## 2. Results and Discussion

APBTTs are known to be prone to react with mononucleophiles NuH at three various electrophilic centers ($C^1$, $C^{3a}$, and $C^4$), resulting in three types of products **9–11** [18] (Scheme 3). The reaction direction is highly dependent on the structure of NuH [18]. Thus, a study on the reactions of APBTTs with various nucleophiles is of high theoretical and practical interest.

The title product **12** bearing a pursued 3a-(quinoxalin-2-ylmethyl)pyrrolo[2,1-*c*][1,4]benzothiazine **A** core was obtained in several steps (Scheme 4). Initially, benzoylpyruvic acid **13** was obtained via the Claisen condensation of acetophenone and diethyl oxalate in the presence of sodium methoxide [20]. Then, the reaction of compound **13**, *o*-aminophenol, and dicyclohexylcarbodiimide (DCC) afforded 1,4-benzothiazinone **14** [21]. After that, acylation of compound **14** via oxalyl chloride resulted in APBTT **8** [17]. And finally, the reaction of APBTT **8** and 2,3-dimethylquinoxaline **4** afforded the title compound **12** in a moderate yield.




**Scheme 3.** Possible pathway reactions of APBTTs with mononucleophiles.




**Scheme 4.** Synthesis of 3-benzoyl-2-hydroxy-3a-[(3-methylquinoxalin-2-yl)methyl]-1*H*-pyrrolo-[2,1-*c*][1,4]benzothiazine-1,4-(3a*H*)-dione **12**.

Obviously, the formation of compound **12** proceeded via a nucleophilic attack of the $CH_2$ group of the enamino–tautomer of 2,3-dimethylquinoxaline **4** on the $C^{3a}$ electrophilic center of APBTT **8** (Scheme 4).

The structure of compound **12** was confirmed using single-crystal X-ray analysis (CCDC 2307237, Figures 2–4), IR, and NMR spectra.

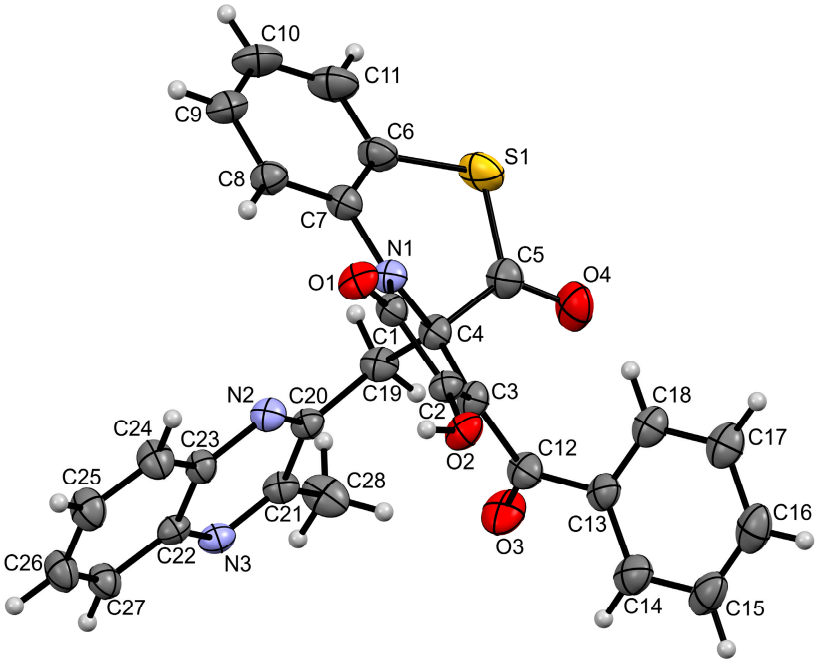



**Figure 2.** Molecular structure of compound **12** showing a 30% probability amplitude displacement ellipsoids (view 1).

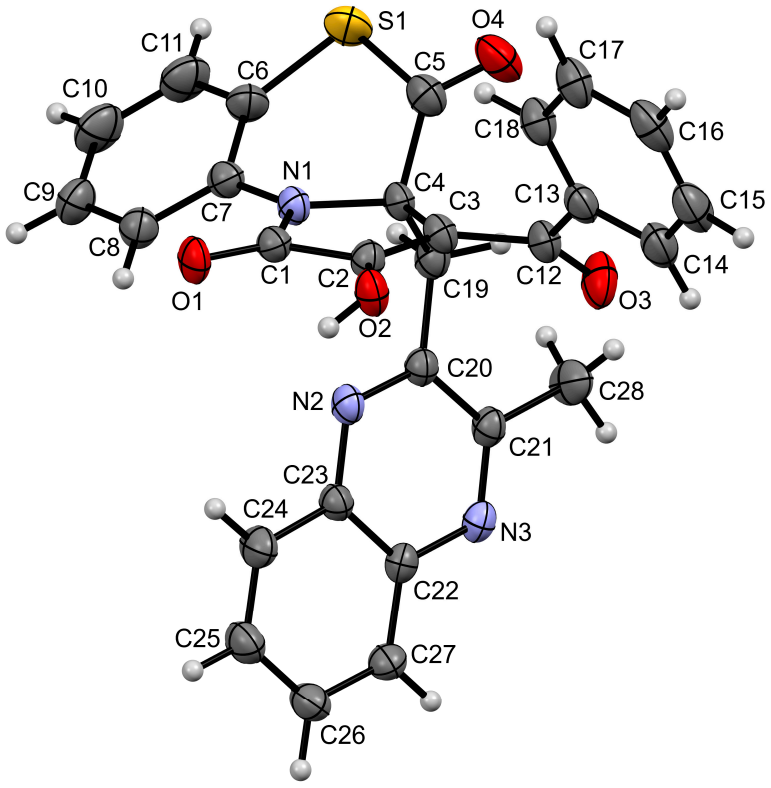



**Figure 3.** Molecular structure of compound **12** showing a 30% probability amplitude displacement ellipsoids (view 2).

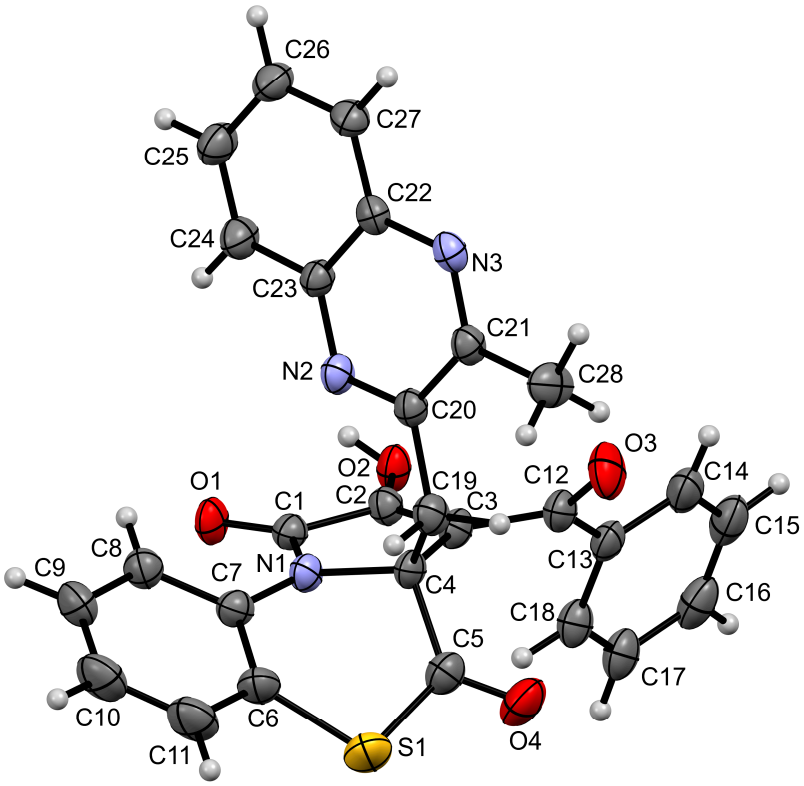



**Figure 4.** Molecular structure of compound **12** showing a 30% probability amplitude displacement ellipsoids (view 3).

## 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 (Bruker BioSpin AG, Faellanden, Switzerland) (at 400 and 100 MHz, respectively) in DMSO-$d_6$ using the solvent residual signal (in $^{1}$H NMR, 2.50; in $^{13}$C NMR, 39.52) as an internal standard. The IR spectrum was recorded using a Perkin–Elmer Spectrum Two spectrometer (PerkinElmer Inc., Waltham, MA, USA) from a mull in mineral oil. Melting points were measured using a Mettler Toledo MP70 apparatus (Mettler-Toledo (MTADA), Schwerzenbach, Switzerland). Elemental analysis was conducted on a Vario MICRO Cube analyzer (Elementar Analysensysteme GmbH, Langenselbold, Germany). The single-crystal X-ray analysis of compound **12** was performed on an Xcalibur Ruby diffractometer (Agilent Technologies) (Oxfordshire, UK). The empirical absorption correction was introduced using a multi-scan method using the SCALE3 ABSPACK algorithm [22]. Using OLEX2 [23], the structures were solved with the SHELXS [24] program and refined using the full-matrix least-squares minimization in the anisotropic approximation for all non-hydrogen atoms with the SHELXL [25] program. Hydrogen atoms were positioned geometrically and refined using a riding model. All procedures with compound **8** were performed in oven-dried glassware. Benzene for procedures with compound **8** was distilled over Na before the use.

### *3.2. 3-Benzoyl-2-hydroxy-3a-[(3-methylquinoxalin-2-yl)methyl]-1H-pyrrolo[2,1-c][1,4]-benzothiazine-1,4-(3aH)-dione 12*

A mixture of 50.0 mg (149 µmol) of APBTT 8 and 23.5 mg (149 µmol) of 2,3-dimethylquinaxaline 4 in 2 mL of anhydrous benzene was stirred in a screw-capped vial at 85 °C for 2 h (until a yellow transparent solution was formed instead of a dark violet suspension characteristic of APBTT 8). Then, the reaction mixture was cooled to room temperature. About 1 mL of the solvent was evaporated. The formed precipitate was filtered off. Then, it

was stirred in 1 mL of benzene at 85 °C for 5 min. Then, the formed precipitate was filtered off to yield the title compound **12**. Yield: 48 mg (65%); white powder; mp 161–163 °C (decomp.). $^{1}$H NMR (DMSO-$d_6$, 400 MHz): δ = 11.88 (br. s, 1H), 8.08 (m, 1H), 7.91–7.84 (m, 2H), 7.74 (m, 4H), 7.57 (m, 2H), 7.50–7.41 (m, 3H), 7.34 (m, 1H), 4.12 (m, 1H), 3.24 (m, 1H), 2.66 (s, 3H) ppm. $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ = 192.2 ($C^4$), 191.2 (COPh), 163.8 ($C^1$), 153.5 ($C^2$), 152.2 ($C^{2'}$=N), 151.5 ($C^{3'}$=N), 139.7, 139.5, 137.6, 132.8, 129.6, 129.4, 129.1 (2C), 128.9, 128.3, 128.1 (2C), 128.1, 127.9, 126.6, 126.5, 123.3, 123.2, 111.6 ($C^3$), 70.9 ($C^{3a}$), 31.9 ($CH_2$), 22.2 ($CH_3$) ppm. IR (mineral oil): 3060, 1723, 1694, 1645 cm$^{-1}$. Anal. Calcd. (%) for $C_{28}H_{19}N_3O_4S$: C 68.14; H 3.88; N 8.51. Found: C 68.10; H 3.96; and N 8.59. The crystal structure of compound **12** was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2307237.

**Supplementary Materials:** The following supporting information can be downloaded online: copies of NMR spectra and crystallographic data for new compounds.

**Author Contributions:** Conceptualization, E.E.K. and E.A.L.; methodology, E.A.L.; investigation, E.A.L. (synthetic chemistry); writing—original draft preparation, E.E.K. and E.A.L.; writing—review and editing, E.E.K. and E.A.L.; supervision, E.E.K.; project administration, E.E.K.; funding acquisition E.E.K. All authors have read and agreed to the published version of the manuscript.

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

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

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