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# (Z)-1-Benzyl-5-(4-bromophenyl)-5-hydroxy-4-(2-oxomorpholin-3-ylidene)pyrrolidine-2,3-dione

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**Abstract:** The reaction of 8-(4-bromobenzoyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6,7-trione with benzylamine in acetonitrile at room temperature afforded a good yield of (*Z*)-1-benzyl-5-(4-bromophenyl)-5-hydroxy-4-(2-oxomorpholin-3-ylidene)pyrrolidine-2,3-dione. The compound was fully characterized.

**Keywords:** 1,4-oxazine; pyrrolidine; pyrrolidine-2,3-dione; heterocyclization



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## 1. Introduction

Compounds whose structures are based on a morpholine moiety associated with an azole heterocyclic system are of particular interest to the pharmaceutical industry as substances with anti-bacterial [1], anti-neurodegenerative [2], neuroprotective [3], anti-infective [4] and analgesic activity [5] (Figure 1).

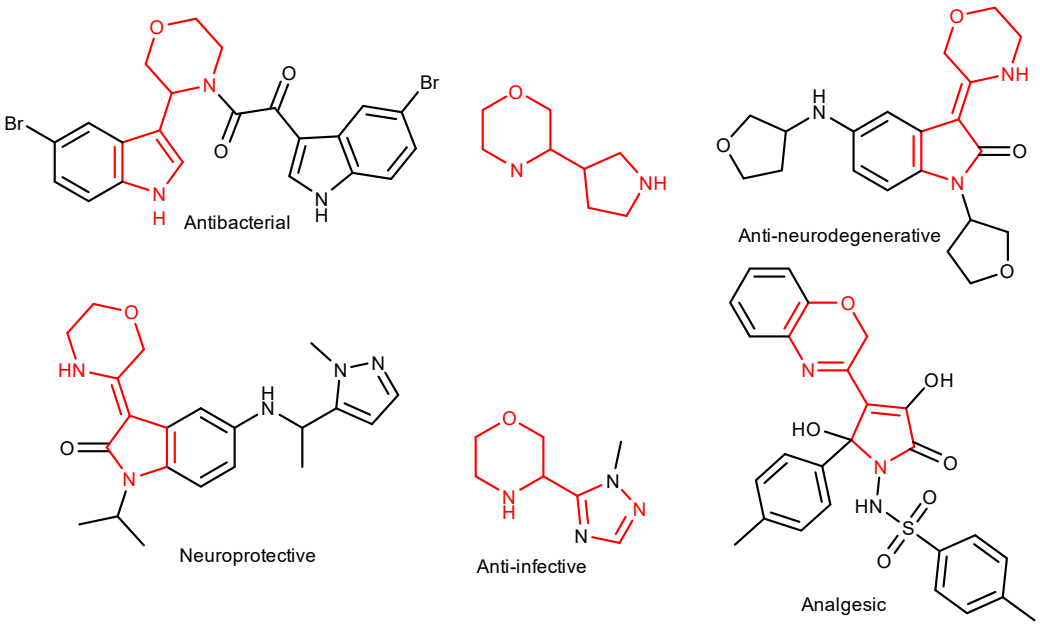
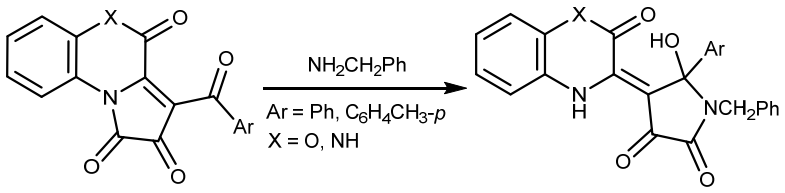
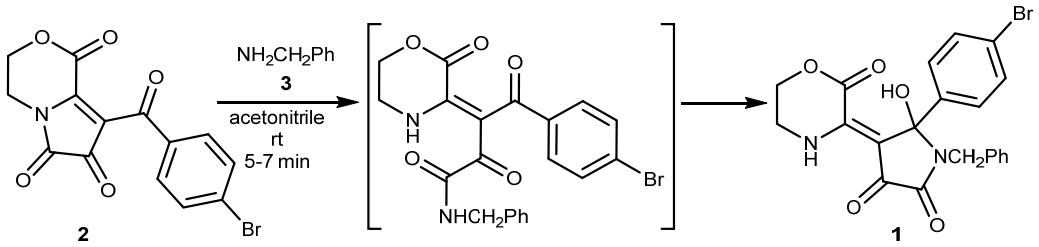



**Figure 1.** Potential pharmaceutical substances bearing a core.

In continuation of our research on the development of methods for the synthesis of pyrrolidine-2,3-diones directly linked to a heterocyclic fragment via the reaction of hetereno[*e*]pyrrolediones with substituted amines (Scheme 1) [6,7], we synthesized a new representative of the functionally substituted 4-(2-oxomorpholin-3-ylidene)pyrrolidine-2,3-dione **1** via the reaction of 8-(4-bromobenzoyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6,7-trione and benzylamine (Scheme 2).




**Scheme 1.** Synthesis of pyrrolidine-2,3-diones via reaction of hetereno[*e*]pyrroldiones and amines.




**Scheme 2.** Synthesis of (*Z*)-1-benzyl-5-(4-bromophenyl)-5-hydroxy-4-(2-oxomorpholin-3-ylidene) pyrrolidine-2,3-dione **1**.

## 2. Results and Discussion

The target compound, compound **1**, was synthesized via the reaction of 8-(4-bromobenzoyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6,7-trione **2** and benzylamine **3**. (*Z*)-1-Benzyl-5-(4-bromophenyl)-5-hydroxy-4-(2-oxomorpholin-3-ylidene)pyrrolidine-2,3-dione **1** (Scheme 2); the target compound was obtained for the first time.

The structure of compound **1** was unambiguously confirmed via an X-ray diffraction analysis of a single crystal (CCDC 2310760) (Figure 2).

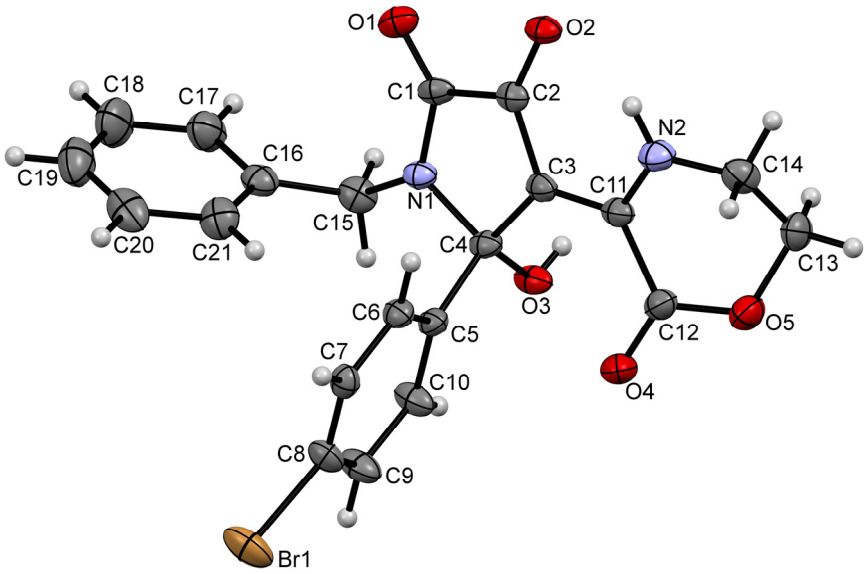



**Figure 2.** Structure of (*Z*)-1-benzyl-5-(4-bromophenyl)-5-hydroxy-4-(2-oxomorpholin-3-ylidene) pyrrolidine-2,3-dione **1** according to X-ray diffraction data.

## 3. Materials and Methods

### *3.1. General Information*

$^{1}$H and $^{13}$C NMR spectra (Supplementary Materials) on a Bruker Avance III 400 HD spectrometer (Fällanden, Switzerland) (at 400 and 100 MHz, respectively) were acquired in DMSO-$d_6$ using the solvent residual signal (in $^{1}$H NMR, 2.50 for DMSO-$d_6$; in $^{13}$C NMR, 39.51 for DMSO-$d_6$) as an internal standard. The IR spectrum was recorded on Perkin Elmer Spectrum Two Spectrometer (Shelton, CT, USA) as mulls in mineral oil. The melting

point was measured on the device Khimlabpribor PTP (USSR). Elemental analysis was carried out on a Vario MICRO Cube analyzer (Langenselbold, Germany). The single-crystal X-ray analysis of compound 1 was performed on an Xcalibur Ruby diffractometer (Agilent Technologies, Wroclaw, Poland). The empirical absorption correction was introduced via the multi-scan method using the SCALE3 ABSPACK algorithm [8]. Using OLEX2 [9], the structure was solved with the olex2.solve [10] program and refined via full-matrix least-squares minimization in an anisotropic approximation for all non-hydrogen atoms with the SHELXL [11] program. Hydrogen atoms bound to carbon were positioned geometrically and refined using a riding model. Hydrogen atoms of OH and NH groups were refined independently with isotropic displacement parameters. Thin-layer chromatography (TLC) was performed on Alugram Sil G/UV$_{254}$ plates using EtOAc/MeOH, 3:1 *v*/*v*, as an eluent and manifested an iodine vapor. The starting compound, compound 3, was obtained in accordance with the reported, commercially available reagents. All procedures with compound 3 were performed in oven-dried glassware. All other solvents and reagents were purchased from commercial vendors and used as received.

### *3.2. (Z)-1-Benzyl-5-(4-bromophenyl)-5-hydroxy-4-(2-oxomorpholin-3-ylidene)pyrrolidine-2,3-dione 1*

To a solution of 0.350 g of (1.0 mmol) 8-(4-bromobenzoyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6,7-trione 2 in 10 mL of anhydrous acetonitrile, a solution of 0.109 mL (1.0 mmol, 0.107 g, $\rho$ = 0.981 g/mL) of benzylamine 3 in 5 mL of anhydrous acetonitrile at room temperature and after stirring for 5 min (until the color of the solution changes) was added; the solvent was evaporated, and 5 mL of ethyl acetate was added. The resulting precipitate was filtered off to obtain the title compound 1. Yield: 0.306 g (67%); yellow solid; mp 168–170 °C (decomp.). $^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 3.58–3.76 (m, 2 H), 4.10 (d, *J* = 15 Hz, 1 H), 4.25 (d, *J* = 15 Hz, 1 H), 4.35–4.51 (m, 2 H), 6.72 (s, 1 H), 6.99–7.08 (m, 2 H), 7.09–7.17 (m, 3 H), 7.25 (d, *J* = 8.56 Hz, 2 H), 7.35 (d, *J* = 8.56 Hz, 2 H), and 11.22 (br. s., 1 H) ppm. $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ = 39.3, 42.2, 67.2, 87.5, 110.0, 120.1, 126.3, 127.6 (2 C), 127.7 (2 C), 128.4 (2 C), 130.2 (2 C), 137.2, 141.1, 143.8, 156.7, 161.0, 183.0 ppm. IR (mineral oil): 3295, 3184, 1763, 1716, 1644 cm$^{-1}$. Anal.Calcd (%) for $C_{21}H_{17}BrN_2O_5$: C 55.16; H 3.75; N 6.13. Found: C 55.28; H 3.69; N 6.09.

Crystal data of compound 1: $C_{21}H_{17}BrN_2O_5$, *M* = 457.27, monoclinic, space group $P2_1/n$, *a* = 15.426(5) Å, *b* = 6.5325(15) Å, *c* = 19.972(5) Å, β = 107.62(3)°, *V* = 1918.1(9) Å$^3$, *T* = 295(2) K, *Z* = 4, and μ(Mo Kα) = 2.180 mm$^{-1}$. The final refinement parameters were as follows: $R_1$ = 0.0586 (for observed 2514 reflections with $I > 2\sigma(I)$_; $wR_2$ = 0.1553 (for all independent 4517 reflections, $R_{int}$ = 0.0532); *S* = 1.060. The largest diff. peak and hole values were 0.455 and –0.636 ēÅ$^{-3}$. The crystal structure of compound 1 was deposited in the Cambridge Crystallographic Data Centre with the deposition number CCDC 2310760.

**Supplementary Materials:** The following supporting information can be downloaded online; copies of NMR spectra for the new compound are provided.

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

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