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N-(4-Bromobenzyl)-2-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)benzeneamine

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Abstract: *N*-(4-Bromobenzyl)-2-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)benzeneamine was obtained by condensation of *N*-(4-bromobenzyl)-3,1-benzoxazine-2,4-dione (*N*-(4-bromobenzyl)isatoic anhydride) with 4,5-dimethyl-1,2-phenylenediamine in refluxing acetic acid. This is a rare example of condensation of *N*-substituted 3,1-benzoxazine-2,4-dione with 1,2-phenylenediamine, which resulted in the formation of a benzimidazole derivative with a moderate yield. Crystallographic studies and initial biological screening were performed for the obtained product.

Keywords: substituted benzimidazoles; 3,1-benzoxazine-2,4-dione; isatoic anhydride; 1,2-phenylenediamine; crystallographic studies; cytotoxicity

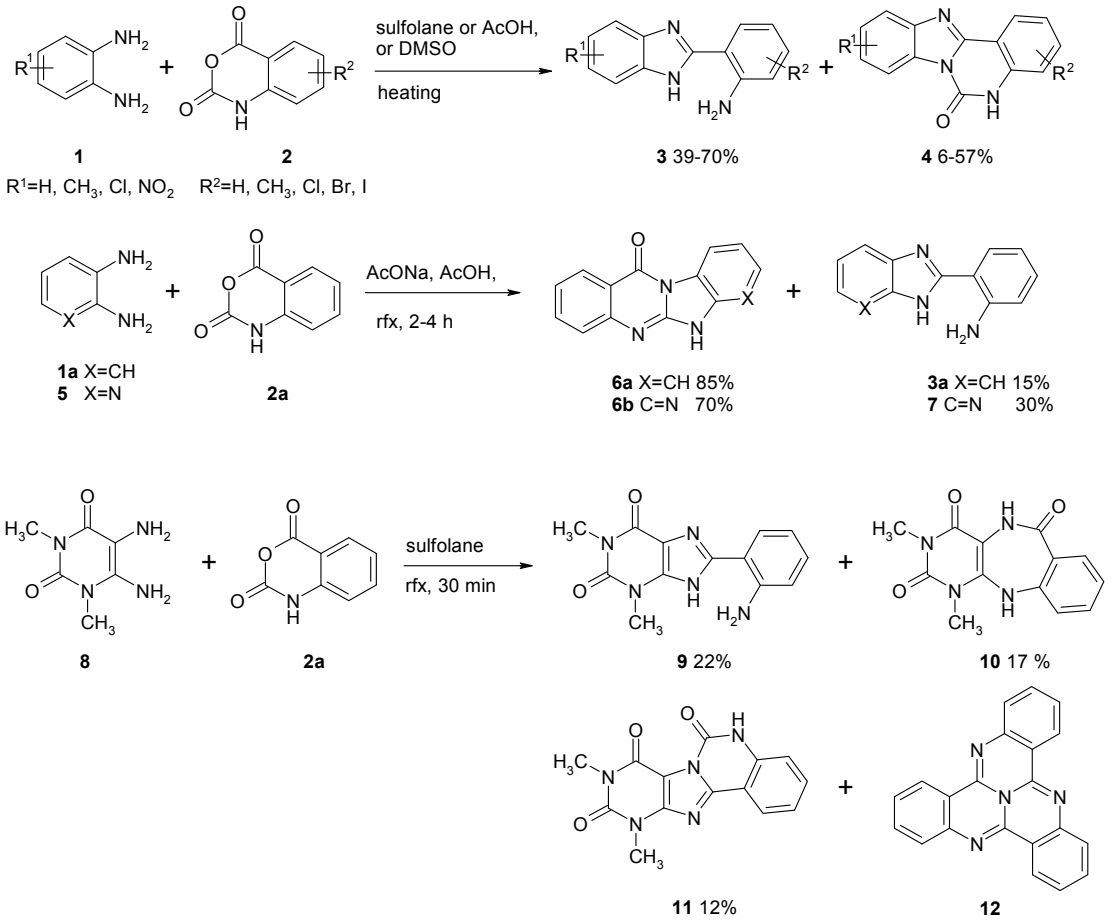
1. Introduction

Benzimidazole derivatives are extremely popular structural scaffolds in drug design and discovery, and provide a wide spectrum of biological activities and therapeutic effects. Their synthesis and applications have been recently reviewed in several articles [1–8]. Their great importance in medicinal chemistry has resulted in a large number of patent applications and has attracted great interest of the pharmaceutical industry [9,10].

3,1-Benzoxazine-2,4-diones (isatoic anhydrides) are versatile heterocyclic intermediates used in the synthesis of a wide range of heterocyclic scaffolds [11–13]. Based on the literature reports [14–17], the condensation of 1,2-phenylenediamines **1** with 3,1-benzoxazine-2,4-diones **2** could lead to the formation of substituted benzimidazole derivatives, featuring 2-(1*H*-benzo[*d*]imidazol-2-yl) benzenamines **3** as the main products, which are accompanied by various amounts of 6,7-dihydrobenzimidazo [l,2-*c*]quinazolin-6-ones **4** (Scheme 1).

Such a condensation can be performed in various solvents, such as sulfolane [14], acetic acid [15,16], or DMSO [14,17]. Fadda reported [18] that heating isatoic anhydride (**2a**) with 1,2-phenylenediamine (**1a**) or 2,3-diaminopyridine (**5**) in acetic acid and in the presence of sodium acetate leads predominantly to the formation of benzoimidazolo[2,3-*b*]-quinazoline-6-one (6a) and pyridooxazolo[2,3-*b*]quinazolin-6-one (**6b**), while the 2-(1*H*-benzo[*d*]imidazol-2-yl)benzenamine (**3a**) and 2-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)benzenamine (**3b**) are formed in minor amounts. The condensation of 5,6-diamino-1,3-dimethyluracil (**8**) with isatoic anhydride (**2a**) leads to four distinct products. The first report [14] described the formation of 8-(2-aminophenyl)theophiline (**9**) and 1,3-dimethyl-11*H*-pyrido[4,5-*b*][1,4]benzodiazepine-2,4,6(1*H*,3*H*,5*H*)-trione (**10**) with 22% and

17% yield, respectively. Furthermore, further investigation of the reaction [19] revealed formation of two additional products: 2,6-dimethylpurino[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione (**11**) (12% yield) and small amounts of tricycloquinazoline (**12**).



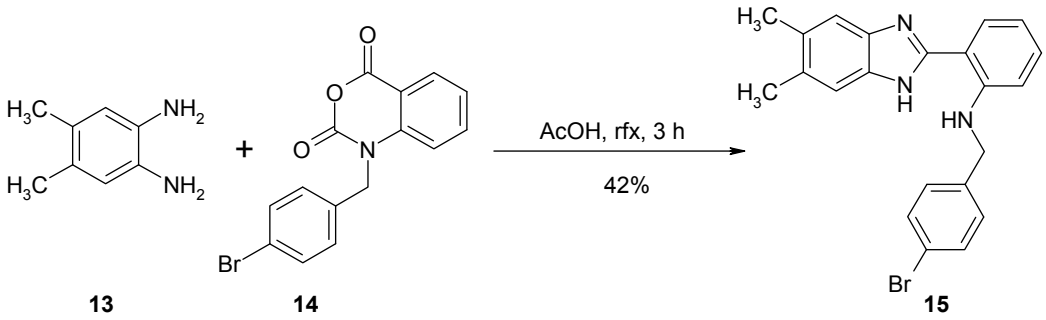
Scheme 1. Reactions of isatoic anhydrides with aromatic 1,2-diamines.

2. Results and Discussion

During our continuous efforts in the investigation of various heterocyclic derivatives as possible antiproliferative and potentially anticancer compounds [20–22], we decided to perform a reaction between 4,5-dimethyl-1,2-phenylenediamine (**13**) and *N*-(4-bromobenzyl)-3,1-benzoxazine-2,4-dione (*N*-(4-bromobenzyl)-isatoic anhydride) (**14**) in refluxing acetic acid (Scheme 2). We found only one example of a condensation involving of *N*-benzylated isatoic acid with 1,2-phenylenediamine in the literature [14], and decided to investigate this reaction as a possible pathway for the synthesis of complex, biologically-relevant compounds. Thus, 4,5-dimethyl-1,2-phenylenediamine (**13**) was mixed with an equimolar amount of *N*-(4-bromobenzyl)-3,1-benzoxazine-2,4-dione (**14**), synthesized from 3,1-benzoxazine-2,4-dione and bromobenzyl bromide according to the literature procedure, [23] and the reaction mixture was refluxed in the acetic acid for 3 h. After the usual workup and column purification (see Materials and Methods section), we isolated the main product in 42% yield and identified it as *N*-(4-bromobenzyl)-2-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)benzeneamine (**15**).

The identity of **15**, crystallized from acetonitrile, was proven by the single-crystal X-ray diffraction analysis. It turned out that the investigated compound crystallizes in the orthorhombic space group $P2_12_12_1$, with one molecule of the compound in the asymmetric part of the unit cell (Figure 1). The details of the crystallographic data and the refinement parameters are summarized in Table S1

(Supplementary Material). The full list of values of bond lengths, valence and torsion angles can be found in the Supplementary Information (Tables S2–S4).



Scheme 2. Synthesis of *N*-(4-bromobenzyl)-2-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)benzeneamine (**15**).

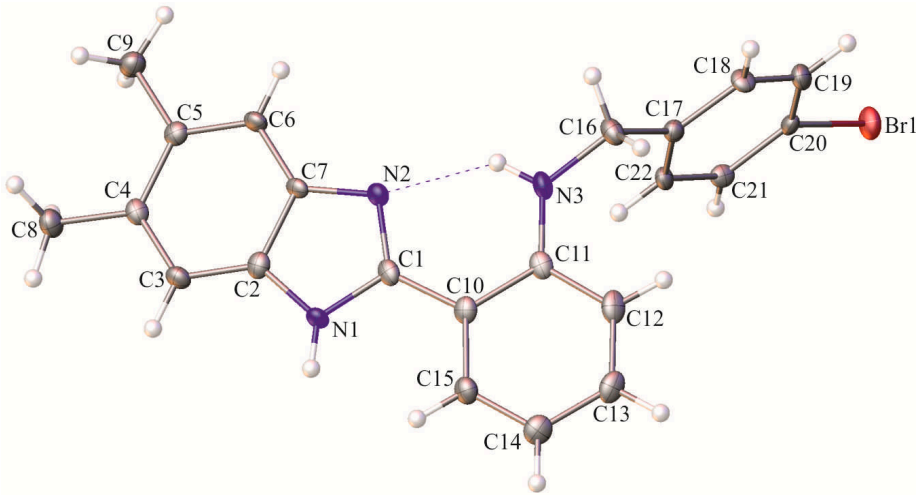


Figure 1. Molecular structure of **15** with crystallographic numbering. Displacement ellipsoids are drawn at the 50% probability level and the H-atoms are shown as small spheres of arbitrary radius. The intramolecular N–H···N hydrogen bond is represented by a dashed line.

With respective average deviations from planarity of 0.034 and 0.014 Å, the benzimidazole ring system and the phenyl ring, which is directly attached to the above-mentioned moiety, are oriented at a 13.2(2)° angle. The least-squares planes defined by the non-hydrogen atoms of the adjacent phenyl rings of the 2-amino(4-bromobenzyl)phenyl substituent are inclined to each other at the angle of 84.6(2)°.

Hydrogen atom linked to the N3-atom is involved in an intramolecular N–H···N hydrogen bond, where the imidazole N2-atom acts as a donor (d(D···A) = 2.705(5) Å; <D–H···A = 138(5)°) (Figure 1, Table S5, the Supplementary Material).

The packing of molecules in a crystal of the investigated compound is dominated by the formation of weak C–H···π and C–Br···π short contacts between the neighboring molecules (Figure 2, Tables S6 and S7, the Supplementary Material). The full list of molecular interactions identified using PLATON (version 130614, Utrecht University, Utrecht, The Netherlands) [24] can be found in the Supplementary Material (Tables S5–S7, the Supplementary Material).

The toxicity of the studied compound **15** was different for different cell lines studied. It was least effective for glioblastoma U87 cells, for which 250 μM concentration of **15** caused a decrease in survival only to 80% of untreated cells. Compound **15** was however toxic to other cell lines studied,

including one epidermal cell line A431, and two non-cancer cell lines, embryonic kidney cell line HEK293 and telomerase-immortalized fibroblasts K21. The toxicity was similar to both the cancerous epidermal as well as the non-cancer cells, and, at a concentration 250 μM, the survival rate dropped to 30% (Figure 3). Thus, the toxicity of **15** probably depends on the characteristics of the organ from which the cells derive.

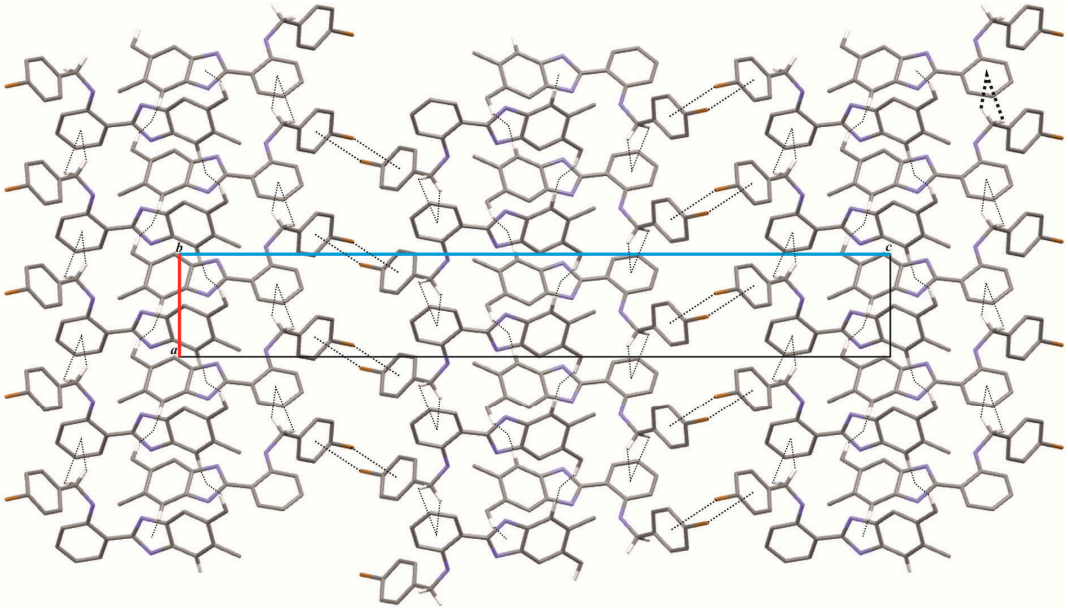


Figure 2. The arrangement of molecules in the crystal of **15**, viewed along the *b*-direction. The H-atoms not involved in the intermolecular interactions have been omitted for clarity. The C–H···π and the C–Br···π short contacts are represented by dotted lines.

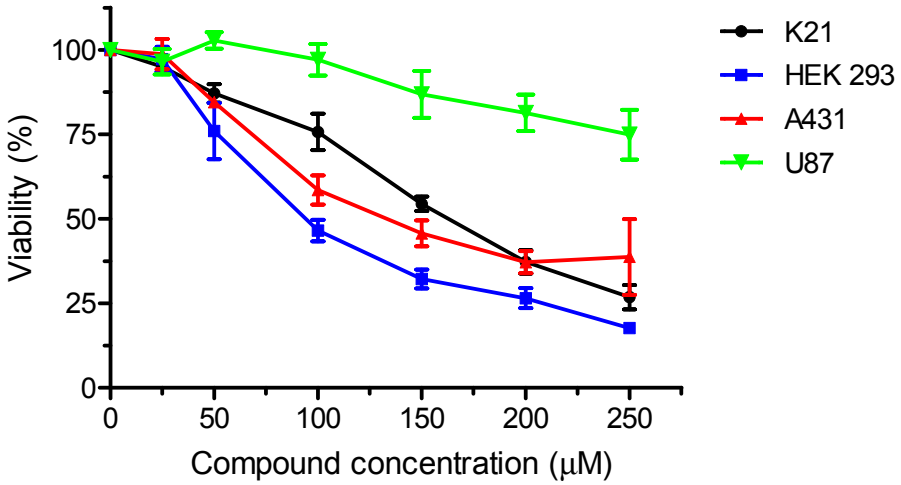


Figure 3. Viability plots of cell lines K21, HEK 293, A431 and U87 in response to *N*-(4-bromobenzyl)-2-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)benzeneamine (**15**).

3. Materials and Methods

Commercially available chemicals were of reagent grade and used as received. The reactions were monitored by thin layer chromatography (TLC), using silica gel plates (Kieselgel $60F_{254}$, E. Merck, Darmstadt, Germany). Column chromatography was performed on silica gel 60 M (0.040–0.063 mm, E. Merck, Darmstadt, Germany). Melting points are uncorrected and were measured on a Büchi

(New Castle, DE, USA) Melting Point B-540 apparatus. The ^{1}H and ^{13}C-NMR spectra, in $CDCl_3$, were recorded at the Department of Chemistry, Warsaw University, using the Bruker AVANCE III HD (Billerica, MA, USA) 500 MHz spectrometer; shift values in parts per million are relative to the $SiMe_4$ internal reference. The resonance assignments were based on peak integration, peak multiplicity, and 2D correlation experiments. Multiplets were assigned as bs (broad singlet), s (singlet), d, (doublet), dd (doublet of doublet), and m (multiplet). High resolution mass spectra were performed by the Laboratory of Mass Spectrometry, Institute of Biochemistry and Biophysics PAS, on a LTQ Orbitrap Velos instrument, Thermo Scientific (Waltham, MA, USA). IR spectra were recorded with a Jasco 6200 (Easton, MD, USA) FT/IR spectrometer in the Laboratory of Optical Spectroscopy, Institute of Organic Chemistry PAS (Warsaw, Poland).

A good quality single-crystal of **15** was selected for X-ray data collection at T = 100(2) K. Diffraction data were collected on an Agilent Technologies SuperNova Dual Source diffractometer (Rigaku OD, Wrocław, Poland) with Cu$K\alpha$ radiation (λ = 1.54184 Å), using the CrysAlis RED software (version 1.171.38.46, Rigaku OD, Wrocław, Poland) [25]. The multi-scan empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm, was applied [25]. The structural determination procedure was carried out using the SHELX package (version 2014/7, University of Göttingen, Göttingen, Germany) [26]. The structures were solved with direct methods and then successive least-square refinement was carried out based on the full-matrix least-squares method on F^2 using the SHELXL program [26]. All H-atoms linked to the N-atoms were located on a Fourier difference map and refined as riding with U_{iso}(H) = 1.2U_{eq}(N). Other H-atoms were positioned geometrically, with C–H equal to 0.93, 0.96 and 0.97 Å for the aromatic, methylene and methyl H-atoms, respectively, and constrained to ride on their parent atoms with U_{iso}(H) = xU_{eq}(C), where x = 1.2 for the aromatic and methylene H-atoms, and x = 1.5 for the methyl H-atoms. All presented molecular interactions were found using PLATON program [24]. The figures for this publication were prepared using the Olex2 (version 1.2.6, OlexSys Ltd., Durham University, Durham, UK) and Mercury programs (version 3.9, Cambridge Crystallographic Data Centre, Cambridge, UK) [27,28].

Crystal Data for $C_{22}H_{20}BrN_3$ (M = 406.32 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.70329(14) Å, b = 8.37203(17) Å, c = 37.9019(9) Å, V = 1809.75(7) Å^3, Z = 4, T = 100(2) K, μ(Cu$K\alpha$) = 3.163 mm^{-1}, D_{calc} = 1.491 g/cm^3, 5443 reflections measured (4.6° $\leq 2\Theta \leq$ 134.2°), 3199 unique (R_{int} = 0.023, R_{sigma} = 0.029) which were used in all calculations. The final R_1 was 0.0293 ($I > 2\sigma(I)$) and wR_2 was 0.0768 (all data).

The cytotoxic activity of **15** was verified against two cancer cell lines: A431 (human epidermoid carcinoma), U87 (human glioblastoma) and two non-cancer cell lines: K21 (human fibroblast) and HEK 293 (human embryonic kidney). One day before treatment, cells were seeded in 96-well plates at density of 3000 cells per well and then treated with increasing concentrations (25–250 μM) of tested compound dissolved in a complete growth medium. After 48 h of incubation, cells were assayed to measure their viability using the alamarBlue assay (Invitrogen by Life Technologies, Carlsbad, CA, USA) according to the manufacturer's instructions. Each experiment was repeated three times.

Synthesis of N-(4-Bromobenzyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)benzeneamine (**15**)

4,5-Dimethylphenylene-1,2-diamine (**13**) (830 mg, 6 mmol, 1 equiv.) was dissolved in 150 mL of glacial acetic acid. After dissolution of the starting material, *N*-(4-bromobenzyl)-3,1-benzoxazine-2,4-dione (**14**) (2.01 g, 6 mmol, 1 equiv.) was added and reaction mixture was refluxed for 3 h. TLC analysis showed disappearance of the substrates and the formation of several new products. The reaction mixture was cooled down, and acetic acid was evaporated under the reduced pressure. The residue was co-evaporated with toluene (3 × 50 mL), then dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate. The organic phase was dried with magnesium sulfate, filtrated, evaporated with silica gel (2 g), and purified by column chromatography using hexane:ethyl acetate 9:1 *v*/*v* mixture. The first, least polar fraction, was collected and concentrated under the reduced pressure, which led to the crystallization of the requested product **15**. Yield: 1.02 g (42%). m.p. 162.5–163.5 °C.

^{1}H NMR (500 MHz, $CDCl_3$): 9.32 (bs, 2H, 2 × NH); 7.49 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.0 Hz, H_{Ar}); 7.43–7.37 (m, 2H, H_{Ar}); 7.31 (bs, 2H, H_{Ar}); 7.24–7.20 (m, 2H, H_{Ar}); 7.20–7.14 (m, 1H, H_{Ar}); 6.69–6.63 (m, 1H, H_{Ar}); 6.59 (d, 1H, ^3J = 8.5 Hz, H_{Ar}); 4.47 (s, 2H, CH_2); 2.34 (s, 6H, 2 × CH_3); ^{13}C-NMR (125 MHz, MHz, $CDCl_3$):151.3, 147.5, 138.6, 131.5, 130.9, 128.6, 126.5, 120.5, 115.5, 111.9, 111.5, 46.6, 20.4; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{22}H_{20}BrN_3$: 406.09134, 408.08929, found: 406.09129, 408.08907; IR (KBr): cm^{-1} 3420, 3235, 3042, 2984, 2927, 1897, 1628, 1591, 1533, 1512, 1481, 1444, 1401, 1328, 1307, 1271, 1244, 1217, 1167, 1146, 1109, 1067, 1050, 1009.

4. Conclusions

The straightforward synthesis of a novel *N*-(4-bromobenzyl)-2-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)benzeneamine was performed by condensation of *N*-(4-bromobenzyl)-3,1-benzoxazine-2,4-dione with 4,5-dimethyl-1,2-phenylenediamine in refluxing acetic acid. The identity of product was proven by the single-crystal X-ray diffraction analysis. The toxicity of the studied compound was similar to both the cancerous as well as the non-cancer cells.

Supplementary Materials: The following are available online www.mdpi.com/1422-8599/2018/1/M979/s1. Copies of the ^{1}H-NMR, ^{13}C-NMR, IR, HRMS-ESI mass spectra and detailed crystallographic data are available in the supplementary information. The CCDC 1811923 (**15**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

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Author Contributions: A.M. conducted synthesis planning and writing of the manuscript; M.D. did experimental synthetic work; J.C. and B.M. completed screening of biological activity D.T. handled crystallographic analysis and writing of the manuscript; K.W. and B.T. were responsible for writing of the manuscript.

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

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