molbank

MDPI

Short Note

1-[2-(1*H*-Pyrrole-2-carbonyl)phenyl]-3-(4-methoxyphenyl)urea

Antonia G. Sarantou and George Varvounis *

Section of Organic Chemistry and Biochemistry, Department of Chemistry, University of Ioannina, 451 10 Ioannina, Greece
* Correspondence: gvarvoun@uoi.gr

Abstract: For the synthesis of 1-(2-(1*H*-pyrrole-2-carbonyl)phenyl)-3-(4-methoxyphenyl)urea, the final product, two different methods were used, in one or two steps, from (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone. The one-step synthesis entailed a carbonylation reaction with 1/3 equivalent of triphosgene in the presence of two equivalents of trimethylamine, followed by the addition of 4-methoxyaniline to the in situ generated aryl isocyanate. The two-step synthesis required first the preparation of phenyl(2-(1*H*-pyrrole-2-carbonyl)phenyl)carbamate and then a substitution reaction by 4-methoxyaniline. The first method produced the final product in 72% yield, which was the best yield. The structure of the final product was confirmed by FTIR, UV-VIS, ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectrometry.

Keywords: heterocycle; unsymmetrical *N*,*N*′-diaryl urea; carbonylation; triphosgene; carbamate

1. Introduction

Unsymmetrical *N*,*N*′-diaryl ureas are particularly important in anticancer drug design because the urea moiety is capable of forming hydrogen bonds with biological receptors, the NH groups being the hydrogen bond donors, while the urea oxygen atom is the acceptor [1,2]. Sorafenib (Nexavar®) and Regorafenib (Stivarga®) (Figure 1) are FDA-approved anticancer drugs in the U.S. used for treating advanced renal cancer and hepatocellular carcinoma [3,4], as well as metastatic colorectal cancer and gastrointestinal stromal tumor [5,6], respectively. Elubrixin (Figure 1) is undergoing clinical trials, as a CNS penetrant and CXCR2 antagonists, for the treatment of multiple sclerosis [7], the cannabinoid 1 receptor negative allosteric.

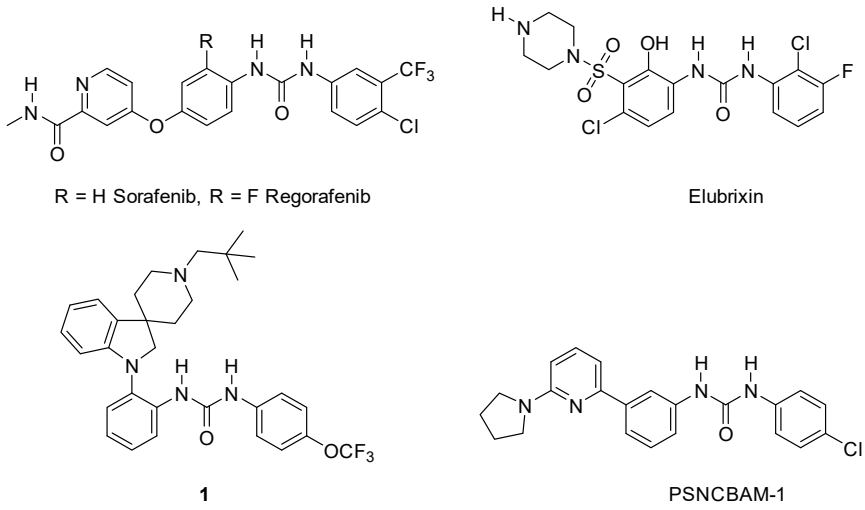


Figure 1. Bioactive unsymmetrical *N*,*N*′-diaryl ureas.

Bioactive unsymmetrical *N*,*N*′-diaryl ureas modulator PSNCBAM-1 (Figure 1) is used to treat obesity and addiction [8], while urea **1** (Figure 1) is the first $P2Y_1$ antagonist to give

Citation: Sarantou, A.G.; Varvounis, G. 1-[2-(1*H*-Pyrrole-2-carbonyl)phenyl]-3-(4-methoxyphenyl)urea. *Molbank* **2023**, *2023*, M1531. https://doi.org/10.3390/M1531

Academic Editor: Fawaz Aldabbagh

Received: 1 December 2022
Revised: 9 December 2022
Accepted: 17 December 2022
Published: 22 December 2022

a potent oral antithrombotic effect with mild bleeding accountability in the thrombosis and hemostasis models in rats [9]. Many more pharmaceutical applications have been found for these types of compounds, including antitrypanosomal [10], antimalarial [11], antibacterial [12,13], anti-inflammatory [14], and antimycobacterial [15] agents, and they were extensively studied as anticancer agents [2].

The occurrence of unsymmetrical *N*,*N*′-diaryl ureas in a variety of biologically active molecules has led to the development of several efficient synthetic methods for their preparation. The earliest method of preparing these compounds involved the reaction of an aryl amine with toxic gaseous phosgene in the presence of a base to form an aryl isocyanate that was then reacted with a different aryl amine. In 1987, Eckert and Forster [16] showed that crystalline triphosgene, first synthesized in 1880, was a safe alternative product of phosgene. The first non-toxic mild and efficient phosgene substitute was 1,1′-carbonylbisbenzotriazole. It reacted with an aryl amine to give an aryl carbamoyl benzotriazole intermediate that reacted with another aryl amine to afford the appropriate *N*,*N*′-diaryl urea. Another phosgene substitute that reacted similarly with two different aryl amines was 1,1′carbonyldiimidazole. Aryl carbamate intermediates are mostly stable and have been used as an alternative to aryl isocyanates. They were prepared by reacting ethylene carbonate, diethyl carbonate, or a chloroformate with an aryl amine. Earlier synthetic methodologies for unsymmetrical *N*,*N*′-diaryl ureas also involved the Curtius rearrangement to produce the aryl isocyanate and the reaction of aryl amines with carbon monoxide or carbon dioxide in the presence of various metal and non-metal catalysts [17]. The Curtius rearrangement continued to be a popular reaction to synthesize *N*,*N*′-diaryl ureas, although the methodology differed in the way the aroyl azide was formed, including microwave irradiation of aryl acids and aryl amines with diphenylphosphoryl azide [18], Pd-catalyzed carbonylation of aryl iodides with chromium hexacarbonyl [19], diphenyl phosphinic chloride activation of aryl carboxylic acids [20], and *s*-trichlorotriazine-mediated activation of aryl carboxylic acids [21], followed by azidation. All were one-pot reactions, while the last step was nucleophilic addition of the aryl amine to the aryl isocyanate. The photocatalyzed oxidative decarboxylation of aryl oxamic acids to aryl carbamoyl radicals in the presence of a hypervalent iodine reagent and (polyaniline)-g-C_3N_4-TiO_2 composite was another example that produced aryl isocyanates, which were trapped by aryl amines [22]. Another interesting one-pot synthesis of *N*,*N*′-diaryl ureas, via aryl isocyanate intermediates, was visible-light-initiated activation of aryl hydroxamic acids in the presence of CBr_4, DMF and $Ru(bpy)_3Cl_2$ that initiated the Lossen rearrangement that was followed by a reaction with aromatic amines [23].

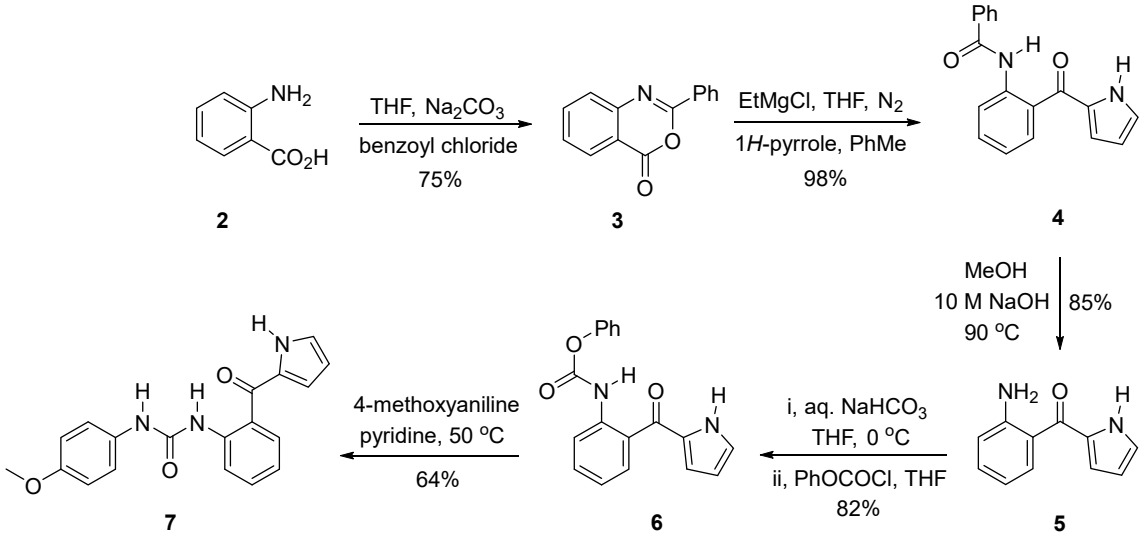
Novel methods, not involving aryl isocyanate intermediates, for the synthesis of *N*,*N*′-diaryl ureas were the palladium-catalyzed amidation of aryl halides by *N*-aryl ureas [24], the Pd-catalyzed coupling of *p*-methoxybenzyl urea and aryl chlorides, in situ hydrolysis to monoaryl ureas and coupling with different aryl chlorides [25], the Pd-catalyzed cross-coupling of aryl chlorides or triflates with sodium cyanate [26], and the nucleophilic addition of 2-aminobenzamides to aryl isothiocyanates followed by iodine-catalyzed intramolecular rearrangement [27].

2. Results

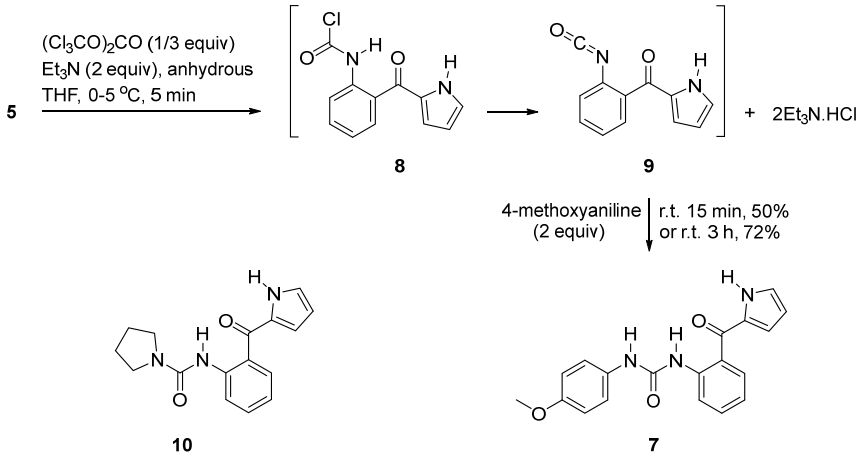
In light of the above, we became interested in synthesizing the unsymmetrical *N*,*N*′-diaryl urea (**7**) with a 2-(1*H*-pyrrole-2-carbonyl)phenyl group attached to one NH moiety and a 4-methoxyphenyl group attached to the other NH moiety of the urea functionality.

The synthesis of 1-(2-(1*H*-pyrrole-2-carbonyl)phenyl)-3-(4-methoxyphenyl)urea (**7**) was accomplished by two methods, via a common starting material (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone (**5**), using a two-step synthetic procedure as described in Scheme 1 and a one-step synthetic procedure as shown in Scheme 2. Compound (**5**) was synthesized from commercially available starting materials in three steps (Scheme 1). Benzoyl chloride was reacted with anthranilic acid (**2**) in tetrahydrofuran containing sodium carbonate to afford, after workup and without the need for further purification, 2-phenyl-4*H*-3,1-benzooxazin-4-one (**3**) in good yield. Pyrrolyl anion, produced in situ from the deproto-

nation of freshly distilled pyrrole by a dry solution of EtMgCl in THF, was reacted with 2-phenyl-4*H*-3,1-benzooxazin-4-one (**3**) by nucleophilic addition and gave the ring-opened *N*-(2-(1*H*-pyrrole-2-carbonyl)phenyl)benzamide (**4**) in excellent yield. The amide group of compound (**4**) was hydrolyzed by heating in methanol-containing aqueous sodium hydroxide to afford (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone (**5**) in very good yield. Compound (**5**) was converted to phenyl (2-(1*H*-pyrrole-2-carbonyl)phenyl)carbamate (**6**), in very good yield, by reaction with phenyl chloroformate in anhydrous THF-containing dry pyridine. The target compound, urea (**7**), was synthesized in moderate yield by the reaction of carbamate (**6**) with 4-methoxyaniline in pyridine at 50 °C.



Scheme 1. Synthesis of 1-(2-(1*H*-pyrrole-2-carbonyl)phenyl)-3-(4-methoxyphenyl)urea (**7**) from aminophenyl pyrrole (**5**) via carbamate (**6**).



Scheme 2. Synthesis of 1-(2-(1*H*-pyrrole-2-carbonyl)phenyl)-3-(4-methoxyphenyl)urea (**7**) directly from aminophenyl pyrrole (**5**).

An alternative method of synthesizing urea (**7**) from aminophenyl pyrrole (**5**) was carbonylation at low temperature using 1/3 equivalent of triphosgene with two equivalents of Et_3N in anhydrous THF under an atmosphere of nitrogen, followed by the addition of two equivalents of 4-methoxyaniline and then stirring at room temperature for 15 min (Scheme 2). Urea (**7**) was obtained in moderate yield. This reaction was repeated exactly but instead of stirring the reaction mixture for 15 min after the addition of 4-methoxyaniline, it was stirred for 3 h so that urea (**7**) was produced in good yield.

3. Discussion

There is a plethora of synthetic protocols for the preparation of unsymmetrical *N*,*N*′-diaryl ureas (vide supra). For the synthesis of urea (**7**), aminophenyl pyrrole (**5**) was first prepared in three steps from anthranilic acid (**2**) by using, essentially, the methodology first published by Varvounis and co-workers in 2011 [28]. The overall yield from compound (**2**) to aminophenyl pyrrole (**5**) was 62%. The first synthesis to obtain urea (**7**) was via its carbamate (**6**), which was chosen because carbamates are usually high-yielding and phenyl chloroformate is cheap (Scheme 1). Carbamate (**6**) was obtained in 82% yield without the need for purification with flash column or dry column vacuum chromatography. Nucleophilic acyl substitution of phenoxide from carbamate (**6**) by 4-methoxyaniline produced urea (**7**) in 64% yield. The overall yield from aminophenyl pyrrole (**5**) to urea (**7**) was 52%. Rotas and Varvounis recently published [29] the carbonylation of aminophenyl pyrrole (**5**) with 1/3 equivalent of triphosgene with and two equivalents of Et_3N in THF at 5 °C under argon to the non-isolable aryl isocyanate (**9**), followed by addition of two equivalents of pyrrolidine and then stirring for 15 min at room temperature, which gave *N*-[2-(1*H*-pyrrole-2-carbonyl)phenyl]pyrrolidine-1-carboxamide (**10**) in 83% yield (Scheme 2). The reaction was repeated to the letter, except that instead of adding pyrrolidine to the reaction mixture, 4-methoxyaniline was added. In this case the yield of urea (**7**) was only 50%. We postulated that the lower yield of this reaction could be due to the weaker nucleophilic character of 4-methoxyaniline compared to pyrrolidine. The reaction using 4-methoxyaniline was, therefore, repeated exactly but this time the reaction mixture was stirred for 3 h instead of 15 min. In this case, urea (**7**) was isolated in 72% yield, clearly showing that the less nucleophilic 4-methoxyaniline required a longer period of reaction time to react with the intermediate aryl isocyanate (**9**). The carbonylation step in these reactions most probably involved, first the intermediacy of aryl carbamoyl chloride (**8**), followed by the intermediacy of aryl isocyanate (**9**), while two equivalents of triethylamine hydrochloride were also formed (Scheme 2).

The structure of aryl carbamate (**6**) was confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. In the FTIR spectrum, the absorption bands at 3327 (s), 3254 (m) and 3122 (m) cm^{-1} were assigned to the N-H str. in pyrrole and to the two carbamate N-H str. vibrations, respectively, while the absorption bands at 1751 (s) and 1608 (s) cm^{-1} were assigned to the carbamate C=O str. and ketone C=O str. vibrations, respectively. In the ^{1}H NMR spectrum of aryl carbamate (**6**) in $CDCl_3$, the single peak at 10.60 ppm represented the NH proton of pyrrole, whereas the broad singlet at 10.14 ppm was assigned to the NH proton of the carbamate group. In the aromatic region, in the range of 8.80–6.81 ppm, there was a total of 12 protons, nine protons belonging to the two substituted benzene rings and three protons to the pyrrole ring. The ^{13}C NMR spectrum in $CDCl_3$ showed 16 signals. Signals at 128.86 ppm and 121.20 ppm contained two equivalent carbon atoms each, bringing the total number of carbon atoms to 18 as expected. High-resolution mass spectrometry analysis by ESI confirmed the expected molecular ion at m/z = 307.1082 $[M + H]^+$, which was calculated for $C_{18}H_{15}N_2O_3$ m/z = 307.1077. The structure of urea (**7**) was confirmed by UV-VIS, IR and ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The UV–VIS spectrum showed two strong absorptions at 252 nm and 305 nm, which are within the range of the absorptions found in mono- and di-substituted benzenes. In the FTIR spectrum, the absorption band at 3327 (w) cm^{-1} was assigned to the pyrrole N-H str. vibrations, while the two N-H str. vibrations at 3273 (w) and 3134 (w) cm^{-1} were indicative of a urea group. Furthermore, the absorption bands at 1734 (m) and 1639 (m) cm^{-1} were assigned to the urea C=O str. and ketone C=O str. vibrations, respectively. In the ^{1}H NMR spectrum of urea (**7**) in DMSO-d_6 the singlet at 12.05 ppm was assigned to the N-H proton of pyrrole, whereas the two singlets at 9.42 and 9.09 ppm corresponded to the two N-H protons of the urea group. In the aromatic region, in the range of 8.17–6.26 ppm, there were a total of 11 protons, eight protons belonging to the two substituted benzene rings and three protons to the pyrrole ring. Pyrrolic C-H protons are usually more upfield than substituted benzene C-H protons. The characteristic

singlet of the methyl group was found at 3.71 ppm. The ^{13}C NMR spectrum in DMSO-d_6 showed 17 signals. Signals at 121.07 ppm and 113.97 ppm contained two equivalent carbon atoms each, bringing the total number of carbon atoms to 19 as expected. High-resolution mass spectrometry analysis that was recorded by ESI confirmed the expected molecular ion at m/z = 336.1342 $[M + H]^+$, which was calculated for $C_{19}H_{18}N_3O_3$ m/z = 336.1342.

The synthesized urea derivative (**7**) inhibited rabbit platelet aggregation in vitro and ex vivo and effectively prevented thrombus formation and carotid artery occlusion in a rabbit model of arterial thrombosis in vivo [30]. Urea (**7**) is a useful lead compound that could be used in the design of novel urea analogues; potentially useful in the inhibition of platelet aggregation.

4. Materials and Methods

All reactions were carried out under a N_2 atmosphere. Solvents and reagents were used as received from the manufacturers (Aldrich, Acros and Alfa Aesar) except for DCM, EtOAc, hexane and toluene that were purified and dried according to recommended procedures. Organic solutions were concentrated by rotary evaporation at 23–40 °C under reduced pressure (15 Torr). Melting points were taken on a Büchi 510 apparatus (Büchi Labortechnik AG, Switzerland). The IR spectra were acquired on a Perkin-Elmer GX FTIR spectrophotometer (Perkin-Elmer, 68 Elm St. Hopkinton, MA, USA) as KBr disks and were reported in wave numbers (cm^{-1}). The UV spectrum was recorded using a Jasco V-630 UV-Vis spectrophotometer (Jasco Europe s.r.l., Cremella, Italy). The sample was measured in a 1 cm quartz cell at room temperature with an 8.95 $\times \cdot 10^{-6}$ mol/L concentration in MeCN. Samples for ^{1}H and ^{13}C NMR experiments were dissolved in dry DMSO-d_6 or $CDCl_3$ and were recorded on a Brüker Avance 400 MHz spectrometer (Brüker BioSpin GmbH, Rheinstetten, Germany). The chemical shifts (δ) were reported in ppm and referenced to residual solvent signals. Coupling constants (J) were given in Hz. The high-resolution ESI mass spectrum was measured on a ThermoFisher Scientific Orbitrap XL system (Thermo Fisher Scientific, Waltham, MA, USA). Analytical thin layer chromatography (TLC) was performed with Merck 70–230-mesh silica gel precoated TLC aluminium plates. TLC plates were observed under UV light at 254 and 365 nm. Preparative flash chromatography was carried out using Merck 9385 silica gel.

*4.1. 2-Phenyl-4H-3,1-benzooxazin-4-one (**3**)*

To a stirred solution of anthranilic acid (**2**) (4.57 g, 33.3 mmol, 1 equiv) in anhydrous THF (40 mL) at 5 °C under nitrogen, was added powdered sodium carbonate (7.06 g, 66.6 mmol, 2 equiv), followed by the dropwise addition of a solution of freshly distilled benzoyl chloride (11.70 g, 4.60 mL, 83.2 mmol, 2.5 equiv) in dry anhydrous THF (25 mL). The reaction mixture was stirred at room temperature for 24 h. TLC examination revealed the absence of the starting material spot and the presence of a new spot (visualized under a UV lamp). Water (50 mL) was added and stirring was continued for 15 min after which the solvent was evaporated under reduced pressure until an off-white solid precipitated. The solid was filtered, washed with water, cold 50% aqueous methanol and cold propan-2-ol, and then dried at 35 °C overnight under high vacuum to give the title compound (9.8 g, 75%) as an off-white solid, m.p. = 121–123 °C (lit. [31], m.p. = 122–125 °C); R_f = 0.57 (33% ethyl acetate in hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.31–8.34 (m, 2H), 8.25 (d, 1H, J = 7.8 Hz) 7.84 (t, 1H, J = 7.5 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.50–7.62 (m, 4H) (in accordance with the NMR data that were previously reported for this compound) [31].

*4.2. N-(2-(1H-pyrrole-2-carbonyl)phenyl)benzamide (**4**)*

Under an atmosphere of nitrogen, a solution of freshly distilled 1*H*-pyrrole (2.76 g, 41.2 mmol, 2.3 equiv) in dry toluene (3 mL) was added dropwise over 15 min to a stirred solution of EtMgCl (2.8 M in THF, 13.42 mL, 37.6 mmol, 2.1 equiv) in anhydrous THF (5 mL) at 3 °C. The reaction mixture was stirred at room temperature for 30 min before a suspension of 2-phenyl-4*H*-3,1-benzooxazin-4-one (**3**) (4.0 g, 17.9 mmol, 1 equiv) in anhydrous THF

(5 mL) was slowly added. Stirring was continued at room temperature for an additional 8 h and then the reaction mixture was heated at 60 °C for 5 h. TLC examination revealed the absence of the starting material spot and the presence of a new spot (visualized under a UV lamp). A saturated aqueous NH_4Cl solution (4 mL) was slowly added to the hot mixture; stirring was continued for 30 min at room temperature and then Na_2SO_4 (4 g) was added. After another 30 min of stirring, the reaction mixture was filtered and the collected solid washed with THF. The combined organic filtrates were evaporated under reduced pressure. The oily residue was suspended in toluene (20 mL), cooled in an ice bath and the solid was collected by filtration, washed with hexane/toluene (1:1) and dried under high vacuum overnight at room temperature to give the title compound as light green microcrystals (5.10 g, 98%) m.p. = 140–141 °C (lit. [28], m.p. = 141–142 °C); R_f = 0.33 (25% ethyl acetate in hexane); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 12.18 (br s, 1H), 11.11 (s, 1H), 8.28 (d, 1H, J = 8.0 Hz), 7.90–7.83 (m, 3H), 7.66–7.51 (m, 4H), 7.33–7.24 (m, 2H), 6.74 (dd, 1H, J = 3.8, 1.0 Hz), 6.28 (d, 1H, J = 2.5 Hz) (in accordance with the NMR data that were previously reported for this compound) [31].

*4.3. (2-Aminophenyl)(1H-pyrrol-2-yl)methanone (**5**)*

A mixture of *N*-[2-(1*H*-pyrrol-2-ylcarbonyl)phenyl]benzamide (**4**) (4.8 g, 16.5 mmol), methanol (30 mL) and aqueous 10 M NaOH (8 mL) was heated to reflux for 24 h. TLC examination, after neutralizing a few drops of the reaction mixture, revealed the absence of the starting material spot and the presence of a new spot (visualized under a UV lamp). To the warm reaction mixture water (25 mL) was added, stirred for 3 h at room temperature, and the precipitate filtered off and washed with cold water. The residue was dried at 35 °C under vacuum overnight and then crystallized from toluene to give the title compound (2.62 g, 85%) as off-white microcrystals; m.p. = 124–126 °C (lit. [31], m.p. = 125–127 °C); R_f (33% EtOAc/hexane) 0.41; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.46 (br s, 1H), 7.86 (dd, 1H, J = 8.3, 1.0), 7.36–7.30 (m, 1H), 7.13–7.05 (m, 1H), 6.88–6.80 (m, 1H), 6.74–6.68 (m, 2H), 6.33 (d, 1H, J = 3.5 Hz), 5.54 (br s, 2H, NH_2) (in accordance with the NMR data that were previously reported for this compound [31].

*4.4. Phenyl (2-(1H-pyrrole-2-carbonyl)phenyl)carbamate (**6**)*

To a stirred mixture of (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone (**5**) (1 g, 5.4 mmol) and dry pyridine (0.48 mL, 0.47 g, 6.0 mmol), in anhydrous THF (15 mL) at 0 °C and under an atmosphere of nitrogen, a solution of phenyl chloroformate (0.84 g, 5.4 mmol) in anhydrous THF (15 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h after which TLC examination revealed the absence of the starting material spot and the presence of a new spot (visualized under a UV lamp). THF was evaporated under reduced pressure from the reaction mixture and to the remaining oily residue, ethyl acetate (60 mL) was added and the solution was washed successively with 1 M HCl (10 mL), water (10 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (3 × 10 mL). The ethyl acetate extract was dried (Na_2SO_4) and the solvent was evaporated in vacuo. The solid residue was crystallized from IPA to afford the title compound (1.35 g, 82%) as pale yellow microcrystals, m.p. = 125–126 °C; R_f = 0.44 (20% ethyl acetate in hexane); FTIR (KBr) cm^{-1}: 3327 (s), 3254 (m), 3122 (m), 1751 (s), 1608 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.60 (s, 1H), 10.14 (br s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H), 7.99 (t, J = 8.4 Hz, 1H), 7.84–7.80 (m, 2H), 7.69–7.57 (m, 5H), 7.32 (t, J = 3.6 Hz, 1H), 6.81 (dd, J = 3.6, 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 185.10, 151.40, 150.14, 138.48, 132.69, 130.93, 130.74, 128.90, 128.86 (2C), 125.49, 125.12, 121.63, 121.20 (2C), 120.14, 119.64, 111.09; HRMS (ESI): m/z [M + H]$^+$ calcd. for $C_{18}H_{15}N_2O_3$: 307.1077. Found: 307.1082. m/z [M + Na]$^+$ calcd. for $C_{18}H_{14}N_2O_3Na$: 329.0897. Found: 329.0902.

*4.5. 1-(2-(1H-Pyrrole-2-carbonyl)phenyl)-3-(4-methoxyphenyl)urea (**7**)*

Method A. 4-Methoxyaniline (0.16 g, 1.30 mmol) was dissolved in dry pyridine (8 mL) at room temperature and under an atmosphere of nitrogen, and to the stirred mixture, a

solution of phenyl [2-(1*H*-pyrrole-2-carbonyl)phenyl]carbamate (**6**) (0.4 g, 1.30 mmol) in dry pyridine (8 mL) was added dropwise. The resulting reaction mixture was stirred at 50 °C for 8 h. TLC examination revealed the absence of the starting material spot and the presence of a new spot (visualized under a UV lamp). The solvent was removed under reduced pressure, the oily residue was triturated with dry toluene (10 mL), and then the solvents were removed under reduced pressure. The residue was suspended in water (30 mL), extracted with DCM (3 × 10 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The solid residue was purified by flash chromatography (20%, 33% ethyl acetate in hexane) to afford the title compound (0.28 g, 64%) as pale yellow microcrystals (ethyl acetate/hexane), m.p. = 131–132 °C; R_f = 0.29 (33% ethyl acetate in hexane); UV-VIS (MeCN) λ_{max}/nm: 252 (log ε 4.41), 305 (4.11); FTIR (KBr disc) cm^{-1}: 3327 (w), 3273 (w), 3134 (w), 1734 (m), 1639 (m); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.05 (s, 1H), 9.42 (s, 1H), 9.09 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 3.3 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.72–6.67 (m, 1H), 6.32–6.26 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 184.56, 154.55, 152.49, 138.87, 132.73, 131.54, 131.13, 130.25, 127.10, 126.47, 121.40, 121.07 (2C), 120.25, 120.22, 113.97 (2C), 110.50, 55.15; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd. for $C_{19}H_{18}N_3O_3$: 336.1342. Found: 336.1342. *m*/*z* $[M + Na]^+$ calcd. for $C_{19}H_{17}N_3O_3Na$: 358.1156. Found: 358.1156. (see Supplementary Materials)

Method B. To a stirred solution containing (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone (**5**) (0.40 g, 2.15 mmol) and freshly distilled triethylamine (0.60 mL, 0.43 g, 4.30 mmol) in anhydrous THF (30 mL) at 0−5 °C and under an atmosphere of nitrogen, a solution of triphosgene (0.21 g, 0.72 mmol) in anhydrous THF (25 mL) was added dropwise, maintaining the temperature in the range of 0–5 °C. The reaction mixture was stirred at this temperature for 5 min and then 4-methoxyaniline (0.53 g, 4.30 mmol) was added in small portions, the ice bath was removed and stirring was continued at room temperature for 15 min. TLC examination revealed the absence of the starting material spot and the presence of two new spots (visualized under a UV lamp). The reaction mixture was poured into a saturated solution of $NaHCO_3$ (80 mL) and extracted with DCM (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The solid residue was purified by flash chromatography (20%, 33%, 50% ethyl acetate in hexane) to afford the title compound (0.36 g, 50%) as pale yellow microcrystals (ethyl acetate/hexane), identical in all respects to the sample prepared by Method A.

Method C. The experimental procedure of Method B was repeated with exact precision until the ice bath was removed, and stirring was continued at room temperature for 3 h instead of 15 min. TLC examination revealed the absence of the starting material spot and the presence of two new spots (visualized under a UV lamp). A similar workup of the reaction mixture was afforded the title compound (0.52 g, 72%) as pale yellow microcrystals (ethyl acetate/hexane), identical in all respects to the sample prepared by Method A.

Supplementary Materials: The following supporting information can be downloaded online. Figure S1: ^{1}H NMR spectrum of compound **3**; Figure S2: ^{1}H NMR spectrum of compound 4; Figure S3: ^{1}H NMR spectrum of compound **5**; Figure S4: ^{1}H NMR spectrum of compound **6**; Figure S5: ^{13}C NMR spectrum of compound **6**; Figure S6: IR spectrum of compound **6**; Figure S7: HRMS (ESI) spectrum of compound **6**. Figure S8: ^{1}H NMR spectrum of compound **7**; Figure S9: ^{13}C NMR spectrum of compound **7**; Figure S10: IR spectrum of compound **7**; Figure S11: UV spectrum of compound **7**; Figure S12: HRMS (ESI) spectrum of compound **7**.

Author Contributions: Conceptualization, G.V.; methodology, A.G.S. and G.V.; investigation, A.G.S. and G.V.; writing—original draft preparation, G.V.; writing—review and editing, A.G.S. and G.V.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Acknowledgments: We appreciate the use of NMR and mass spectrometry facilities funded by the Network of Research Supporting Laboratories of the University of Ioannina and thank Athanassios Karkabounas and Vasiliki I. Boti for providing high-resolution mass spectra.

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

Sample Availability: Samples of the compounds (**6**) and (**7**) are available from the authors.

References

1. Ghosh, A.K.; Brindisi, B. Urea Derivatives in Modern Drug Discovery and Medicinal Chemistry. *J. Med. Chem.* **2020**, *63*, 2751–2788. [CrossRef]
2. Garuti, L.; Roberti, M.; Bottegoni, G.; Ferraro, M. Diaryl Urea: A Privileged Structure in Anticancer Agents. *Curr. Med. Chem.* **2016**, *23*, 1528–1548. [CrossRef] [PubMed]
3. Wilhelm, S.; Carter, C.; Lynch, M.; Lowinger, T.; Dumas, J.; Smith, R.A.; Schwartz, B.; Simantov, R.; Kelley, S. Discovery and development of sorafenib: A multikinase inhibitor for treating cancer. *Nat. Rev. Drug Discov.* **2006**, *5*, 835–844. [CrossRef] [PubMed]
4. Hsu, C.H.; Shen, Y.C.; Shao, Y.Y.; Hsu, C.; Cheng, A.L. Sorafenib in advanced hepatocellular carcinoma: Current status and future perspectives. *J. Hepatocell. Carcinoma* **2014**, *1*, 85–99.
5. Strumberg, D.; Scheulen, M.E.; Schultheis, B.; Richly, H.; Frost, A.; Buchert, M.; Christensen, O.; Jeffers, M.; Heinig, R.; Boix, O.; et al. Regorafenib (BAY 73-4506) in advanced colorectal cancer: A phase I study. *Br. J. Cancer* **2012**, *106*, 1722–1727. [CrossRef] [PubMed]
6. Crona, D.J.; Keisler, M.D.; Walko, C.M. Regorafenib: A novel multitargeted tyrosine kinase inhibitor for colorectal cancer and gastrointestinal stromal tumors. *Ann. Pharmacother.* **2013**, *47*, 1685–1696. [CrossRef] [PubMed]
7. Xu, H.; Lu, H.; Xu, Z.; Luan, L.; Li, C.; Xu, Y.; Dong, K.; Zhang, J.; Li, X.; Li, Y.; et al. Discovery of CNS Penetrant CXCR2 Antagonists for the Potential Treatment of CNS Demyelinating Disorders. *ACS Med. Chem. Lett.* **2016**, *7*, 397–402. [CrossRef]
8. Jing, L.; Qiu, Y.; Zhang, Y.; Li, J. −X. Effects of the cannabinoid CB1 receptor allosteric modulator ORG 27569 on reinstatement of cocaine- and methamphetamine-seeking behavior in rats. *Drug Alcohol. Depend.* **2014**, *143*, 251. [CrossRef]
9. Qiao, J.X.; Wang, T.C.; Ruel, R.; Thibeault, C.; L'Heureux, A.; Schumacher, W.A.; Spronk, S.A.; Hiebert, S.; Bouthillier, G.; Lloyd, J.; et al. Conformationally Constrained *ortho*-Anilino Diaryl Ureas: Discovery of 1-(2-(1′-Neopentylspiro[indoline-3,4′-piperidine]-1-yl)phenyl)-3-(4-(trifluoromethoxy)phenyl)urea, a Potent, Selective, and Bioavailable $P2Y_1$ Antagonist. *J. Med. Chem.* **2013**, *56*, 9275–9295. [CrossRef]
10. Steverding, D. The development of drugs for treatment of sleeping sickness: A historical review. *Parasites Vectors* **2010**, *3*, 15. [CrossRef]
11. Anderson, J.W.; Sarantakis, D.; Terpinski, J.; Kumar, T.R.S.; Tsai, H.-C.; Kuo, M.; Ager, A.L.; Jacobs, W.R., Jr.; Schiehser, G.A.; Ekins, S.; et al. Novel diaryl ureas with efficacy in a mouse model of malaria. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1022–1025. [CrossRef] [PubMed]
12. Keche, A.P.; Hatnapure, G.D.; Tale, R.H.; Rodge, A.H.; Kamble, V.M. Synthesis, anti-inflammatory and antimicrobial evaluation of novel 1-acetyl-3,5-diaryl-4,5-dihydro(1*H*)pyrazole derivatives bearing urea, thiourea and sulfonamide moieties. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6611–6615. [CrossRef] [PubMed]
13. Keche, A.P.; Hatnapure, G.D.; Tale, R.H.; Rodge, A.H.; Birajdar, S.S.; Kamble, V.M. A novel pyrimidine derivative with aryl urea, thiourea and sulfonamide moieties: Synthesis, anti-inflammatory and antimicrobial evaluation. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3445–3448. [CrossRef] [PubMed]
14. Kulkarni, R.G.; Laufer, S.; Mangannavar, C.; Garlapati, A. Design, synthesis and characterization of *N*′,*N*″-diaryl ureas as p38 kinase inhibitors. *Med. Chem.* **2013**, *9*, 213–221. [CrossRef] [PubMed]
15. Velappan, A.B.; Raja, M.R.C.; Datta, D.; Tsai, Y.T.; Halloum, I.; Wan, B.; Kremer, L.; Gramajo, H.; Franzblau, S.G.; Mahapatra, S.K.; et al. Attenuation of Mycobacterium species through direct and macrophage mediated pathway by unsymmetrical diaryl urea. *Eur. J. Med. Chem.* **2017**, *125*, 825–841. [CrossRef] [PubMed]
16. Eckert, H.; Forster, B. Triphosgene, a Crystalline Phosgene Substitute. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 894–895. [CrossRef]
17. Gallou, I. Unsymmetrical Ureas. Synthetic Methodologies and Application in Drug Design. *Org. Prep. Proced. Int.* **2007**, *39*, 355–383. [CrossRef]
18. Kulkarni, A.R.; Garai, S.; Thakur, G.A. Scalable, One-Pot, Microwave-Accelerated Tandem Synthesis of Unsymmetrical Urea Derivatives. *J. Org. Chem.* **2017**, *82*, 992–999. [CrossRef]
19. Mozaffari, M.; Nowrouzi, N. Palladium-Catalyzed Synthesis of Symmetrical and Unsymmetrical Ureas Using Chromium Hexacarbonyl as a Convenient and Safe Alternative Carbonyl Source. *Eur. J. Org. Chem.* **2019**, 7541–7544. [CrossRef]
20. Kumar, A.; Kumar, N.; Sharma, R.; Bhargava, G.; Mahajan, D. Direct Conversion of Carboxylic Acids to Various Nitrogen-Containing Compounds in the One-Pot Exploiting Curtius Rearrangement. *J. Org. Chem.* **2019**, *84*, 11323–11334. [CrossRef]
21. Ahmed, R.; Gupta, R.; Akhter, Z.; Kumara, M.; Singh, P.P. TCT-mediated click chemistry for the synthesis of nitrogen-containing functionalities: Conversion of carboxylic acids to carbamides, carbamates, carbamothioates, amides and amines. *Org. Biomol. Chem.* **2022**, *20*, 4942–4948. [CrossRef] [PubMed]

22. Wanga, L.; Wang, H.; Wang, Y.; Shen, M.; Li, S. Photocatalyzed synthesis of unsymmetrical ureas via the oxidative decarboxylation of oxamic acids with PANI-g-C_3N_4-TiO_2 composite under visible light. *Tetrahedron Lett.* **2020**, *61*, 151962. [CrossRef]
23. Yadav, A.K.; Srivastava, V.P.; Yadav, L.D.S. An easy access to unsymmetrical ureas: A photocatalytic approach to the Lossen rearrangement. *RSC Adv.* **2014**, *4*, 24498–24503. [CrossRef]
24. Kotecki, B.J.; Fernando, D.P.; Haight, A.R.; Lukin, K.A. A General Method for the Synthesis of Unsymmetrically Substituted Ureas via Palladium-Catalyzed Amidation. *Org. Lett.* **2009**, *11*, 947–950. [CrossRef] [PubMed]
25. Breitler, S.; Oldenhuis, N.J.; Fors, B.P.; Buchwald, S.L. Synthesis of Unsymmetrical Diarylureas via Pd-Catalyzed C−N Cross-Coupling Reactions. *Org. Lett.* **2011**, *13*, 3262–3265. [CrossRef]
26. Vinogradova, E.V.; Fors, B.P.; Buchwald, S.L. Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Triflates with Sodium Cyanate: A Practical Synthesis of Unsymmetrical Ureas. *J. Am. Chem. Soc.* **2012**, *134*, 11132–11135. [CrossRef]
27. Shamanth, S.; Chaithra, N.; Gurukiran, M.; Mamatha, M.; Lokanath, N.K.; Rangappa, K.S.; Mantelingu, K. I_2-Catalyzed transformation of *o*-aminobenzamide to *o*-ureidobenzonitrile using isothiocyanates. *Org. Biomol. Chem.* **2020**, *18*, 2678–2684. [CrossRef]
28. Rotas, G.; Kimbaris, A.; Varvounis, G. Synthesis of a novel pyrrolo [1,2-*c*][1.3]benzodiazepine analogue of VPA-985. *Tetrahedron* **2011**, *67*, 7805–7810. [CrossRef]
29. Rotas, G.; Varvounis, G. Tunable Reactivity of Triphosgene-Triethylamine: A study on the synthesis of pyrrole-based tricyclics. *Tetrahedron* **2020**, *76*, 131527. [CrossRef]
30. Papadaki, S.; Moschonas, I.; Peroulis, M.; Tatsidou, P.; Sarantou, A.; Tellis, C.; Varvounis, G.; Tselepis, A. Investigation of the Antithrombotic and Antiplatelet Effect of a New Urea Analog, on Carotid Artery Thrombosis in Rabbits. *Thromb. Res.* **2016**, *141* (Suppl. 1), S2.
31. Qurban, J.; Elsherbini, M.; Alharbi, H.; Wirth, T. Synthesis, characterisation, and reactivity of novel pseudocyclic hypervalent iodine reagents with heteroaryl carbonyl substituents. *Chem. Commun.* **2019**, *55*, 7998–8000. [CrossRef] [PubMed]