A Greener and Efficient Method for Nucleophilic Aromatic Substitution of Nitrogen-Containing Fused Heterocycles

Joana F. Campos 1, Mohammed Loubidi 1, Marie-Christine Scherrmann 2 and Sabine Berteina-Raboin 1,*

1 Institute of Organic and Analytical Chemistry (ICOA), University of Orleans, UMR-CNRS 7311, BP 6759 F-45067 Orleans CEDEX 2, France; joana-filomena.mimoso-silva-de-campos@univ-orleans.fr (J.F.C.); m.loubidi@gmail.com (M.L.)
2 Institute of Molecular Chemistry and Materials of Orsay, UMR CNRS 8182, University of Paris-Sud, Building 420, 91400 Orsay, France; marie-christine.scherrmann@u-psud.fr
* Correspondence: sabine.berteina-raboin@univ-orleans.fr; Tel.: +33-238-494-856

Received: 27 February 2018; Accepted: 16 March 2018; Published: 18 March 2018

Abstract: A simple and efficient methodology for the nucleophilic aromatic substitution of nitrogen-containing fused heterocycles with interesting biological activities has been developed in an environmentally sound manner using polyethylene glycol (PEG-400) as the solvent, leading to the expected compounds in excellent yields in only five minutes.

Keywords: PEG-400; nucleophilic aromatic substitution; nitrogen fused heterocycles

1. Introduction

Environmentally sustainable practices are increasingly being taken into consideration in medicinal chemistry and applied as far as possible by the various pharmaceutical companies and laboratories [1–3]. It is therefore necessary to provide chemists with effective methods for the development of complex structures under mild and green conditions. Green chemistry refers to the design of a process that minimizes the use and generation of hazardous substances [4]. As pointed out in [5–7], the solvent often represents the major part of the mass used in a reaction or a process, and chemists are therefore encouraged to use greener alternatives [8–11]. In this context, polyethylene glycols (PEGs), compounds with widespread industrial and medical applications [12,13], have attracted special attention as green solvents in various chemical transformations [14–16]. These rather inexpensive polymers are available in a wide range of molecular weights and are mainly produced from ethylene glycol, a by-product of the petrochemical industry, but can also be obtained from agricultural waste [17]. PEG400 is a viscous sustainable liquid soluble in water and many organic solvents. It has the advantage of being readily biodegradable as well as non-toxic, odourless, neutral, non-volatile, and non-irritating, which explains its use in a variety of pharmaceuticals and medications [12,13,18].

Substituted pyrimidine and pyrazine derivatives are a significant class of nitrogen-fused heterocycles, which are ubiquitous in many natural products and biologically active compounds in agrochemistry as well as in the pharmaceutical area. Over the past few decades, more and more drugs with fused bicyclic pyrimidine and pyrazine scaffolds have been approved by the Food and Drug Administration (FDA) for their significant biological activities, such as antitumor activities [19–21] and insomnia disorder [22]. In the major cases, the fused bicyclic pyrimidines exhibit an anticancer function by targeting different kinases [20,21], such as epidermal growth factor receptor (EGFR), Bruton’s tyrosine kinase (BTK), Janus kinase (JAK), and phosphatidylinositol 3 kinase (PI3K), (Figure 1).
These compounds play an important role in drug discovery and development [23,24]. In view of our interest in the development of green chemistry procedures [25–34], we report herein the use of PEG400 as an efficient medium for nucleophilic aromatic substitution (SNAr) of some nitrogen-containing fused heterocycles with various amines. SNAr involving amines have been carried out and studied in conventional organic solvents [35–39] but also in non-volatile alternative media such as ionic liquids [40–44], but, to the best of our knowledge, this reaction has never been reported using PEG as the solvent.

2. Results and Discussion

For this study the chloro compounds were chosen as starting materials. In all cases the reactions were conducted without additional base and the results obtained are given by class of heterocycles. In the first attempts, we explored the temperature parameter, however attempts performed below 120 °C did not give the desired product and this was consistent for all the scaffolds chosen as the starting material. This is likely due to the poor solubility problem of the reagents at temperatures below 120 °C.

2.1. From 4-Chloro-2-methylimidazo[1,5-a]pyrimidine-8-carbonitrile

Commercially available 4-chloro-2-methylimidazo[1,5-a]pyrimidine-8-carbonitrile was reacted with various primary or secondary amines in PEG 400 as the solvent without additional base, initially at room temperature. However, these conditions were not appropriate due to the lack of solubility of the mixture of starting materials. At 120 °C, all the reactants were soluble and we were pleased to observed the formation of 2-methylimidazo[1,5-a]pyrimidine-8-carbonitrile with an amino group in position 4 within only 5 min.

Compounds 2 to 6 were obtained with good yields (81 to 95%). The lowest yield (70%, entry 6, compound 1) is due to the strong electro-withdrawing effect of the trifluoromethyl group in the ortho position of the aniline, which is an amine that is already less nucleophilic than aliphatic amines (Scheme 1, Table 1). PEG-400 is a very effective solvent to generate these amino substituted heterobicyclic compounds which can be used as fungicides [45].
Molecules contain valuable biological properties. Some [1,2,4]-triazolo[1,5-a]pyrimidine systems containing a [1,2,4]triazolo[1,5-a]pyrimidine moiety are reported as antitumor agents [53,54], as corticotropin releasing factor 1 receptor antagonists [55] or calcium channel modulators [56] and they can also be used for the treatment of Alzheimer’s disease [57] and insomnia [58].

Compounds 2 to 6 were obtained with good yields (81 to 95%). The lowest yield (70%, entry 6, Table 1) was obtained with amines that are already less nucleophilic than aliphatic amines (Scheme 1).

Scheme 1. Synthesis of 1–6. Reagents and conditions: (i) amino derivative (2 equiv.), PEG400, 120 °C, 5 min, 70–95%.

Table 1. Results of the S_NAr on 4-chloro-2-methylimidazo[1,5-a]pyrimidine-8-carbonitrile with various amines.

| Entry | Amine Reagent | Product | Yield   |
|-------|---------------|---------|---------|
| 1     |               | ![Image](https://example.com/image1.png) | 1; 87%  |
| 2     |               | ![Image](https://example.com/image2.png) | 2; 92%  |
| 3     |               | ![Image](https://example.com/image3.png) | 3; 95%  |
| 4     |               | ![Image](https://example.com/image4.png) | 4; 81%  |
| 5     |               | ![Image](https://example.com/image5.png) | 5; 85%  |
| 6     |               | ![Image](https://example.com/image6.png) | 6; 70%  |
These reaction conditions with amine derivative (2 equiv.) in PEG 400 at 120 °C for 5 min were applied to other nitrogen-containing fused heterocycles.

2.2. From 7-Chloro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine

[1,2,4]Triazolo[1,5-a]pyrimidines are a highly interesting class of fused heterocycles due to their valuable biological properties. Some [1,2,4]-triazolo[1,5-a]pyrimidines possess herbicidal activity [46,47], while others can act as antifungal [48,49], antitubercular [50,51] and antibacterial [52] agents. Polycyclic systems containing a [1,2,4]triazolo[1,5-a]-pyrimidine moiety are reported as antitumor agents [53,54], as corticotropin releasing factor 1 receptor antagonists [55] or calcium channel modulators [56] and they can also be used for the treatment of Alzheimer’s disease [57] and insomnia [58].

The commercially available 7-chloro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine was submitted to the same conditions as 4-chloro-2-methylimidazo[1,5-a]pyrimidine in PEG-400 as solvent at 120 °C without additional base. In this case also we were able to synthesize the desired compounds 7 to 10 in only 5 min in good yields (Scheme 2, Table 2).

![Scheme 2. Synthesis of 7–10. Reagents and conditions: (i) amino derivative (2 equiv.), PEG400, 120 °C, 5 min, 79–89%.

| Entry | Amine Reagent | Product | Yield |
|-------|---------------|---------|-------|
| 1     | ![Amine 1](image1.png) | ![Product 1](image2.png) | 7, 79% |
| 2     | ![Amine 2](image3.png) | ![Product 2](image4.png) | 8, 88% |
| 3     | ![Amine 3](image5.png) | ![Product 3](image6.png) | 9, 89% |
| 4     | ![Amine 4](image7.png) | ![Product 4](image8.png) | 10, 88% |

Table 2. Results of S_NAr on 7-chloro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine with various amines.
2.3. From 8-Chloro-[1,2,4]triazolo[4,3-a]pyrazine

The fused triazole-moiety can be found in a variety of biologically active compounds including antibacterial [59], anti-inflammatory [60,61], antimicrobial [62], antiplatelet [63], anticonvulsant and antidiabetic [64] agents. In particular, bicyclic fused 1,2,4-triazole derivatives are an important group of heterocycles and have been the subject of studies from various academic and industrial groups in the recent past due to their biological versatility [65]. The commercially available 8-chloro-[1,2,4]triazolo[4,3-a]pyrazine underwent the analogue nucleophilic aromatic substitution in the same conditions with various amines, leading to the expected compounds in good yields (73% to 99%). The reactions were rapid as for the previous examples (Scheme 3, Table 3).

Scheme 3. Synthesis of 11–14. Reagents and conditions: (i) amino derivative (2 equiv.), PEG400, 120 °C, 5 min, 73–99%.

Table 3. Results of the SNAr on 8-chloro-[1,2,4]triazolo[4,3-a]pyrazine with various amines.

| Entry | Amine Reagent | Product | Yield |
|-------|---------------|---------|-------|
| 1     |               | ![Image](image1.png) | 11; 92% |
| 2     |               | ![Image](image2.png) | 12; 99% |
| 3     |               | ![Image](image3.png) | 13; 73% |
| 4     |               | ![Image](image4.png) | 14; 75% |

2.4. From 4-Chlorofuro and thieno[3,2-d]pyrimidine

Thienopyrimidines are fused heterocyclic ring systems; structurally they resemble purines, and they have considerable pharmacological potential. They are known to play a crucial role in
various disease conditions. Thieno[2,3-$d$]pyrimidine derivatives have been explored for their inhibitory activities towards various protein kinase enzymes [66]. Furopyrimidine heterocyclic ring systems are structural analogues of purines which have been subjected to biological investigations to assess their potential therapeutic usefulness [67]. Furopyrimidines have attracted considerable attention because of their great practical potential as antiviral [68–70], antimicrobial [71] and antitumor agents [72,73]. Starting from commercially available 4-chlorofuro and thieno[3,2-$d$]pyrimidine we obtained the same results, good to excellent yields (71% to 99%), for the desired compounds 15 to 24 under the same conditions (Scheme 4, Table 4).

![Scheme 4](image-url)

**Scheme 4.** Synthesis of 15–24. Reagents and conditions: (i) amino derivative (2 equiv.), PEG400, 120 $^\circ$C, 5 min, 71–99%.

**Table 4.** Results of the aromatic nucleophilic substitution (SNAr) on 4-chlorofuro and thieno[3,2-$d$]pyrimidine.

| Entry | Amine Reagent | Product | Yield |
|-------|---------------|---------|-------|
| 1     |               | 15: $X = O$, 99% |
|       |               | 16: $X = S$, 86% |
| 2     |               | 17: $X = O$, 99% |
|       |               | 18: $X = S$, 90% |
| 3     |               | 19: $X = S$, 83% |
| 4     |               | 20: $X = S$, 96% |
were visualized by UV irradiation. Flash column chromatography was performed on silica gel stirred at 120 °C.

3.2. General Procedure for the Synthesis of 4G by the “Federation de Recherche” ICOA/CBM (FR2708) pFlatform.

Table 4. Results of the aromatic nucleophilic substitution (SNAr) on 4-chlorofuro and thieno[3,2-]

| Entry | Amine Reagent | Product | Yield |
|-------|----------------|---------|-------|
| 5     |                | 21; X = S, 77% |
| 6     |                | 22; X = S, 71% |
| 7     |                | 23; X = S, 79% |
| 8     |                | 24; X = S, 88% |

3. Materials and Methods

3.1. General Methods

All reagents were purchased from commercial suppliers and were used without further purification. THF was dried with a GT S100 drying station immediately prior to use. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp (°C)) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds were recorded on a Nicolet iS10 spectrophotometer (Thermo Scientific, Villebon-sur-Yvette, France). 1H- and 13C-NMR spectra were recorded on an Avance II spectrometer at 250 MHz (13C, 62.9 MHz) and on an Avance III HD nanobay 400 MHz (13C 100.62 MHz) (Bruker, Wissembourg, France). Chemical shifts are given in parts per million from tetramethylsilane (TMS) or deuterated solvent (MeOH-d4, Chloroform-d) as internal standard. The following abbreviations were used for the proton spectra multiplicities: b: broad, s: singlet, d: doublet, t: triplet, q: quartet, p: pentuplet, m: multiplet. Coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra (HRMS (ESI)) were performed on a Maxis Bruker 4G by the “Federation de Recherche” ICOA/CBM (FR2708) pPlatform.

3.2. General Procedure for the Synthesis of 1 to 24

A mixture of chloro compound (50 mg) and amine derivative (2 equiv.) in PEG 400 (2 mL) was stirred at 120 °C for 5 min. After completion the reaction was then cooled to room temperature.
DCM and water were added and the phases were separated. The aqueous phase was extracted with DCM and the organic phase was dried and filtered. The removal of solvent gave the product as a white solid.

2-Methyl-4-(piperidin-1-yl)imidazo[1,5-alpyrimidine-8-carbonitrile (1) [74]. From 4-chloro-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (50 mg; 0.260 mmol) and piperidine (44 mg; 0.520 mmol), (54 mg, 87%), m.p 164–166 °C. $^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 1.74–1.81 (m, 6H), 2.51 (s, 3H), 3.25–3.29 (m, 4H), 6.04 (s, 1H), 7.80 (s, 1H) ppm. $^{13}$C-NMR (63 MHz, CDCl$_3$) $\delta$ 24.0 (2xCH), 25.2 (2xCH), 50.4 (2xCH), 96.5 (CH), 100.8 (C), 115.1 (C), 123.8 (CH), 145.9 (C), 149.5 (C), 162.7 (C) ppm.

2-Methyl-4-morpholinoimidazo[1,5-alpyrimidine-8-carbonitrile (2). From 4-chloro-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (50 mg; 0.260 mmol) and morpholine (45 mg; 0.520 mmol), (58 mg, 92%), m.p 178–180 °C. $^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 2.60 (s, 3H), 3.29–3.32 (m, 4H), 3.94–3.98 (m, 4H), 6.11 (s, 1H), 7.88 (s, 1H) ppm. $^{13}$C-NMR (63 MHz, CDCl$_3$) $\delta$ 25.2 (CH), 49.5 (2xCH), 66.0 (2xCH), 96.9 (CH), 100.0 (C), 114.7 (C), 123.4 (CH), 145.6 (C), 148.8 (C), 162.6 (C) ppm. HRMS: calcd for C$_{12}$H$_{14}$N$_3$O [M + H]$^+$ 244.1193, found 244.1192.

4-((2R,6S)-2,6-Dimethylmorpholin-2-yl)imidazo[1,5-alpyrimidine-8-carbonitrile (3). From 4-chloro-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (50 mg; 0.260 mmol) and cis-2,6-dimethylmorpholine (60 mg; 0.520 mmol), (67 mg, 95%), m.p 252–254 °C. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.27 (d, $J = 6.3$ Hz, 6H), 2.56 (s, 3H), 2.68–2.73 (m, 2H), 3.44 (d, $J = 11.8$ Hz, 2H), 3.91–3.95 (m, 4H), 6.08 (s, 1H), 7.84 (s, 1H) ppm. $^{13}$C-NMR (100.6 MHz, CDCl$_3$) $\delta$ 18.7 (2xCH), 25.2 (CH), 54.5 (2xCH), 71.1 (2xCH), 96.9 (CH), 101.4 (C), 114.8 (C), 123.5 (CH), 145.7 (C), 148.4 (C), 162.7 (C) ppm. HRMS: calcd for C$_{14}$H$_{18}$N$_5$O [M + H]$^+$ 272.1506, found 272.1503.

4-(Dibutylamino)-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (4) [74]. From 4-chloro-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (50 mg; 0.260 mmol) and di-n-butylamine (67 mg; 0.520 mmol), (60 mg, 81%), m.p 145–147 °C. $^1$H-NMR (250 MHz, CDCl$_3$) $\delta$ 0.9 (t, $J = 7.3$ Hz, 6H), 1.22–1.38 (m, 4H), 1.53–1.65 (m, 4H), 2.51 (s, 3H), 3.29–3.35 (m, 4H), 6.01 (s, 1H), 7.85 (s, 1H) ppm. $^{13}$C-NMR (63 MHz, CDCl$_3$) $\delta$ 13.7 (2xCH), 20.1 (2xCH), 25.1 (CH), 29.0 (2xCH), 50.2 (2xCH), 96.9 (CH), 100.6 (C), 115.2 (C), 123.9 (CH), 146.6 (C), 148.2 (C), 162.3 (C) ppm.

4-(((3S,5S,7S)-Adamantan-1-yl)amino)-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (5). From 4-chloro-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (50 mg; 0.260 mmol) and adamantylamine (78 mg; 0.520 mmol), (68 mg, 85%), m.p 293–295 °C. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.74–1.81 (m, 6H), 2.13 (s, 6H), 2.25 (s, 3H), 2.54 (s, 3H), 4.88 (s, 1H), 6.03 (s, 1H), 7.90 (s, 1H) ppm. $^{13}$C-NMR (100.6 MHz, CDCl$_3$) $\delta$ 25.6 (CH), 29.4 (3xCH), 35.9 (2xCH), 41.8 (3xCH), 54.07 (C), 80.0 (CH), 90.3 (CH), 100.2 (C), 115.3 (C), 120.2 (CH), 142.12 (C), 145.9 (C), 161.93 (C) ppm. HRMS: calcd for C$_{18}$H$_{22}$N$_5$ [M + H]$^+$ 308.1869, found 308.1870.

2-Methyl-4-(2-(trifluoromethyl)phenyl)amino)imidazo[1,5-alpyrimidine-8-carbonitrile (6). From 4-chloro-2-methylimidazo[1,5-alpyrimidine-8-carbonitrile (50 mg; 0.260 mmol) and 2-trifluoromethylaniline (83 mg; 0.520 mmol), (57 mg, 70%), m.p 205–207 °C. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.23 (s, 3H), 5.25 (s, 1H), 6.94 (d, $J = 7.9$ Hz, 1H), 7.20 (t, $J = 7.6$ Hz, 1H), 7.52 (t, $J = 7.6$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 8.25 (s, 1H), 10.30 (s, 1H) ppm. $^{13}$C-NMR (100.6 MHz, CDCl$_3$) $\delta$ 19.0 (CH), 90.6 (CH), 92.4 (C), 114.9 (C), 122.1 (CH), 123.4 (CH), 126.8 (C), 126.9 (CH), 126.9 (CH), 127.5 (CH), 132.7 (CH), 139.2 (C), 143.5 (C), 146.2 (C), 146.4 (C) ppm. $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ –61.9 ppm. HRMS: calcd for C$_{15}$H$_{13}$F$_3$N$_5$ [M + H]$^+$ 318.0961, found 318.0964.

5-Methyl-7-(piperidin-1-yl)-1,2,4-triazolo[1,5-alpyrimidine (7) [75]. From 7-chloro-5-methyl-1,2,4-triazolo[1,5-alpyrimidine (50 mg; 0.297 mmol) and piperidine (50 mg; 0.594 mmol), (51 mg, 79%), m.p 153–155 °C. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.71–1.79 (m, 6H), 2.52 (s, 3H), 3.62 (s, 1H), 3.71–3.75 (m, 3H), 6.09 (s, 1H), 8.24 (s, 1H) ppm. $^{13}$C-NMR (100.6 MHz, CDCl$_3$) $\delta$ 24.2 (CH), 25.1 (2xCH), 25.4 (CH), 49.4 (2xCH), 94.4 (CH), 150.4 (C), 154.0 (CH), 157.3 (C), 164.5 (C) ppm.
(2R,6S)-2,6-Dimethyl-4-(5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)morpholine (9). From 7-chloro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine (50 mg; 0.297 mmol) and morpholine (52 mg; 0.594 mmol), (57 mg, 88%), m.p 164–166 °C. 1H-NMR (400 MHz, methanol-d4) δ 2.55 (s, 3H), 3.90 (s, 8H),6.49 (s, 1H), 8.32 (s, 1H) ppm. 13C-NMR (100.6 MHz, methanol-d4) δ 23.3 (CH), 65.9 (4xCH), 94.4 (CH), 150.4 (C), 152.9 (CH), 156.7 (C), 165.5 (C) ppm.

N,N-Di butyl-5-methyl-[1,2,4]triazolo[1,5-alpyrimidin-7-amine (10). (69 mg, 88%), m.p 130–132 °C. 1H-NMR (400 MHz, CDCl3) δ 0.94 (t, J = 7.4 Hz, 6H), 1.33–1.39 (m, 4H), 1.66 (s, 2H), 2.50 (s, 3H), 3.64 (s, 2H), 3.74–3.78 (m, 4H), 5.90 (s, 1H), 8.18 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 13.8 (2xCH), 20.0 (2xCH), 25.1 (CH), 30.1 (CH), 51.6 (2xCH), 70.5 (CH), 92.3 (CH), 149.1 (C), 153.7 (CH), 157.9 (C), 163.7 (C) ppm. HRMS: calcld for C14H24N5 [M + H]+ 262.2026, found 262.2027.

8-(Piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine (11). From 8-chloro-[1,2,4]triazolo[4,3-a]pyrazine (50 mg; 0.323 mmol) and piperedine (55 mg; 0.646 mmol), (61 mg, 92%), m.p 180–182 °C. 1H-NMR (400 MHz, CDCl3) δ 1.68 (s, 6H), 4.24 (s, 4H), 7.25 (d, J = 4.5 Hz, 1H), 7.36 (d, J = 4.5 Hz, 1H), 8.68 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 24.7 (CH), 26.2 (2xCH), 47.4 (2xCH), 106.0 (CH), 129.8 (CH), 136.6 (CH), 140.5 (C), 147.9 (C) ppm. CAS:1878022-44-6; Distributor Name: Sigma-Aldrich, F 38297 Saint-Quentin Fallavier, France.

(2R,6S)-4-((1,2,4]triazolo[4,3-a]pyrazin-8-yl)-2,6-dimethylmorpholine (12). From 8-chloro-[1,2,4]triazolo[4,3-a]pyrazine (50 mg; 0.323 mmol) and cis-2,6-dimethyl-morpholine (74 mg; 0.646 mmol), (74 mg, 99%), m.p 172–174 °C. 1H-NMR (400 MHz, CDCl3) δ 1.22 (d, J = 6.3 Hz, 6H), 2.73–2.81 (m, 2H), 3.57–3.59 (m, 1H), 3.66–3.73 (m, 2H), 5.33 (s, 1H), 7.27 (d, J = 4.5 Hz, 1H), 7.41 (d, J = 4.5 Hz, 1H), 8.71 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 18.8 (2xCH), 71.9 (2xCH), 106.8 (CH), 129.5 (CH), 136.7 (CH), 140.3 (C), 147.7 (2xCH), 160.6 (C) ppm. CAS: 2127319-44-0; Distributor Name: Aurora Fine Chemicals Ltd., A-8010 Graz, Austria.

N,N-Di butyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (13). From 8-chloro-[1,2,4]triazolo[4,3-a]pyrazine (50 mg; 0.323 mmol) and di-n-butylamine (83 mg; 0.646 mmol),(58 mg, 73%), m.p 106–108 °C. 1H-NMR (400 MHz, CDCl3) δ 0.92 (t, J = 7.4 Hz, 6H), 1.34–1.41 (m, 4H), 1.67 (t, J = 7.7 Hz, 4H), 4.00 (s, 4H), 7.27 (d, J = 4.5 Hz, 1H), 7.32 (d, J = 4.5 Hz, 1H), 8.67 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ14.0 (3xCH), 20.1 (2xCH), 30.4 (CH), 49.5 (2xCH), 105.3 (CH), 130.1 (CH), 136.5 (CH), 140.4 (C), 148.0 (C) ppm. HRMS: calcld for C13H22N5 [M + H]+ 248.1870, found 248.1871.

N-(2-(Trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (14). From 8-chloro-[1,2,4]triazolo[4,3-a]pyrazine (50 mg; 0.323 mmol) and 2-trifluoromethylalanine (104 mg; 0.646 mmol), (68 mg, 75%), m.p 169–171 °C. 1H-NMR (400 MHz, CDCl3) δ 7.29 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 4.7 Hz, 1H), 7.60 (d, J = 4.7 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 8.39 (s, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.82 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ109.2 (CH), 121.0 (C), 124.3 (2xCH), 125.4 (C), 126.6 (CH), 129.2 (CH), 132.7 (CH), 135.6 (C), 137.4 (CH), 139.2 (C), 145.4 (C) ppm. 19F-NMR (376 MHz, CDCl3) δ −60.7 ppm. HRMS: calcld for C12F6H4F3N5 [M + H]+ 280.0805, found 280.0805.

4-(Piperidin-1-yl)furo[3,2-d]pyrimidine (15). From 4-chlorofuro[3,2-d]pyrimidine (50 mg; 0.323 mmol) and piperedine (55 mg; 0.646 mmol), (65 mg, 99%), m.p 140–142 °C. 1H-NMR (400 MHz, CDCl3) δ 1.64–1.73 (m, 6H), 3.94–3.98 (m, 4H), 6.80 (d, J = 2.2 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H), 8.41 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 24.7 (CH),26.0 (2xCH), 46.3 (2xCH), 107.8 (CH), 134.4 (C),
4-(Piperidin-1-yl)thieno[3,2-d]pyrimidine (16). From 4-chlorothieno[3,2-d]pyrimidine (50 mg; 0.293 mmol) and piperidine (50 mg; 0.586 mmol), (55 mg, 86%), m.p 154–156 °C. 1H-NMR (400 MHz, CDCl3) δ 1.10–1.61 (m, 6H), 3.87–3.90 (m, 4H), 7.33 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 8.49 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 24.7 (CH), 26.1 (2xCH), 47.4 (2xCH), 114.2 (C), 125.1 (CH), 131.1 (CH), 154.2 (CH), 157.8 (C), 161.0 (C) ppm. HRMS: calcd for C15H13N6O [M + H]+ 204.1131, found 204.1135.

4-Morpholinofuro[3,2-d]pyrimidine (17). From 4-chlorofuro[3,2-d]pyrimidine (50 mg; 0.323 mmol) and morpholine (56 mg; 0.646 mmol), (65 mg, 99%), m.p 185–187 °C. 1H-NMR (400 MHz, CDCl3) δ 3.81–3.85 (m, 4H), 3.91–3.97 (m, 4H), 7.39 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 8.56 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 46.3 (2xCH), 66.7 (2xCH), 114.4 (C), 125.3 (CH), 131.5 (CH), 154.2 (CH), 157.8 (C), 161.3 (C) ppm. CAS: 676119-22-5; Distributor Name: Aurora Fine Riga, Latvia.

4-(Thieno[3,2-d]pyrimidin-4-yl)morpholine (18) [77]. From 4-chlorothieno[3,2-d]pyrimidine (50 mg; 0.293 mmol) and methyl 4-aminobenzoate (88 mg; 0.586 mmol), (66 mg, 79%), m.p 227–229 °C. 1H-NMR (400 MHz, CDCl3) δ 3.78–3.82 (m, 4H), 3.91–3.97 (m, 4H), 7.39 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.6 Hz, 1H), 8.54 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 46.3 (2xCH), 66.7 (2xCH), 114.4 (C), 125.3 (CH), 131.5 (CH), 154.2 (CH), 157.8 (C), 161.3 (C) ppm. CAS: 676119-22-5; Distributor Name: Aurafine Chemicals Ltd., A-8010 Graz, Austria.

N,N-Dibutylthieno[3,2-d]pyrimidin-4-amine (20). From 4-chlorothieno[3,2-d]pyrimidine (50 mg; 0.293 mmol) and di-n-butylamine (76 mg; 0.586 mmol), (60 mg, 83%), m.p 121–123 °C. 1H-NMR (400 MHz, CDCl3) δ 0.92 (t, J = 7.4 Hz, 6H), 1.32–1.40 (m, 4H), 1.64 (dd, J = 6.6, 16.9 Hz, 4H), 3.64–3.68 (m, 4H), 7.31 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 8.45 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 13.9 (2xCH), 20.1 (2xCH), 30.8 (2xCH), 49.3 (2xCH), 113.3 (C), 124.9 (CH), 130.9 (CH), 154.3 (CH), 157.5 (C), 160.6 (C) ppm. HRMS: calcd for C14H22N3S [M + H]+ 264.1529, found 264.1532.

N-((3s,5s,7s)-Adamantan-1-yl)thieno[3,2-d]pyrimidin-4-amine (21). From 4-chlorothieno[3,2-d]pyrimidine (50 mg; 0.293 mmol) and adamantylamine (88 mg; 0.586 mmol), (64 mg, 77%), m.p 238–240 °C. 1H-NMR (400 MHz, CDCl3) δ 1.70–1.77 (m, 6H), 2.14 (s, 3H), 2.24 (dd, J = 2.6 Hz, 6H), 4.52 (s, 1H), 7.36 (d, J = 5.4 Hz, 1H), 7.61 (d, J = 5.4 Hz, 1H), 8.57 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 29.6 (3xCH), 36.4 (3xCH), 41.9 (3xCH), 53.6 (C), 115.6 (C), 125.6 (CH), 129.7 (CH), 154.6 (CH), 156.9 (C), 159.5 (C) ppm. HRMS: calcd for C14H22N3S [M + H]+ 286.1372, found 286.1375.

N-(2-(Trifluoromethyl)phenyl)thieno[3,2-d]pyrimidin-4-amine (22). From 4-chlorothieno[3,2-d]pyrimidine (50 mg; 0.293 mmol) and 2-trifluoromethylaniline(94 mg; 0.586 mmol), (61 mg, 71%), m.p 122–124 °C. 1H-NMR (400 MHz, CDCl3) δ 7.37 (t, J = 7.7 Hz, 1H), 7.45 (d, J = 5.4 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.71–7.75 (m, 2H), 7.99 (d, J = 8.1 Hz, 1H), 8.70 (s, 1H) ppm. 13C-NMR (100.6 MHz, CDCl3) δ 122.5 (C), 124.2 (C), 124.5 (C), 125.1 (CH), 126.0 (CH), 126.7 (CH), 127.8 (CH), 132.6 (CH), 132.9 (CH), 135.3 (C), 154.5 (CH), 155.9 (C), 161.5 (C) ppm. 19F-NMR (376 MHz, CDCl3) δ –60.8 ppm. HRMS: calcd for C13H14F3N3S [M + H]+ 296.0464, found 296.0467.

Methyl 4-(thieno[3,2-d]pyrimidin-4-ylamino)benzoate (23). From 4-chlorothieno[3,2-d]pyrimidine (50 mg; 0.293 mmol) and methyl 4-aminobenzoate (88 mg; 0.586 mmol), (66 mg, 79%), m.p 227–229 °C. 1H-NMR
(400 MHz, CDCl$_3$) $\delta$ 3.93 (s, 3H), 6.97 (d, $J = 19.8$ Hz, 1H), 7.51 (d, $J = 5.4$ Hz, 1H), 7.84–7.79 (m, 3H), 8.09 (d, $J = 8.7$ Hz, 2H), 8.82 (s, 1H) ppm. $^{13}$C-NMR (100.6 MHz, CDCl$_3$) $\delta$ 29.7 (C), 52.1 (CH), 116.2 (C), 120.5 (2xCH), 125.6 (CH), 130.9 (2xCH), 132.1 (C), 142.4 (C), 154.6 (CH), 154.9 (C), 161.2 (C), 166.6 (C) ppm. HRMS: calcd for $\text{C}_{14}\text{H}_{12}\text{N}_{3}\text{O}_{2}\text{S}$ [M + H]$^+$ 286.0644, found 286.0646.

N-(4-Methoxyphenyl)thieno[3,2-d]pyrimidin-4-amine (24) [78]. From 4-chlorothieno[3,2-d]pyrimidine (50 mg; 0.293 mmol) and methyl 4-methoxyaniline (72 mg; 0.586 mmol), m.p 154–156 $^\circ$C.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.85 (s, 3H), 6.93–6.95 (m, 2H), 7.36 (d, $J = 5.4$ Hz, 1H), 7.39–7.41 (m, 2H), 7.64 (d, $J = 5.4$ Hz, 1H), 7.93 (s, 1H), 8.60 (s, 1H) ppm. $^{13}$C-NMR (100.6 MHz, CDCl$_3$) $\delta$ 55.5 (CH), 114.3 (2xCH), 114.4 (C), 124.6 (2xCH), 128.2 (CH), 129.7 (C), 133.2 (CH), 154.6 (CH), 157.3 (C), 158.6 (C), 161.2 (C) ppm.

4. Conclusions

We have developed an efficient, environmentally sound method for the nucleophilic aromatic substitution in PEG400 of chlorine atoms by primary and secondary amines on various nitrogen-containing fused heterocycles. The salient feature of our method is the facile introduction of amino derivatives on commercially available starting materials in an environmentally friendly alternative solvent. Several precursors of potential biologically active compounds have been synthetized in good to excellent yields and the conditions used are applicable to a large panel of heterocycles and amines, with similar yields and reaction time.

Acknowledgments: We acknowledge the Region Centre for financial support.

Author Contributions: Joana F. Campos, Mohammed Loubidi, Marie-Christine Scherrmann and Sabine Berteina-Raboin conceived and designed the experiments; Joana F. Campos and Mohammed Loubidi performed the experiments; Joana F. Campos, Marie-Christine Scherrmann and Sabine Berteina-Raboin analyzed the data and wrote the paper.

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

References

1. Bryan, M.C.; Dillon, B.; Hamann, L.G.; Hughes, G.J.; Kopach, M.E.; Peterson, E.A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; et al. Sustainable Practices in Medicinal Chemistry: Current State and Future Directions. *J. Med. Chem.* 2013, **56**, 6007–6021. [CrossRef] [PubMed]

2. Watson, W.J.W. How do the fine chemical, pharmaceutical, and related industries approach green chemistry and sustainability? *Green Chem.* 2012, **14**, 251–259. [CrossRef]

3. Lombardino, J.G.; Lowe, J.A., III. A Guide to drug discovery: The Role of Medicinal Chemist in Drug Discovery-Then and Now. *Nat. Rev. Drug Discov.* 2004, **3**, 853–862. [CrossRef] [PubMed]

4. Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, NY, USA, 1998; p. 30. ISBN 9780198506980.

5. Ashcroft, C.P.; Dunn, P.J.; Hayler, J.D.; Wells, A.S. Survey of Solvent Usage in Papers Published in Organic Process Research & Development 1997–2012. *Org. Process Res. Dev.* 2015, **19**, 740–747. [CrossRef]

6. Jimenez-Gonzalez, C.; Ponder, C.S.; Broxtermann, Q.B.; Manley, J.B. Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes. *Org. Process Res. Dev.* 2011, **15**, 912–917. [CrossRef]

7. Jimenez-Gonzalez, C.; Curzons, A.D.; Constable, D.J.C.; Cunningham, V.L. Expanding GSK’s Solvent Selection Guide—application of life cycle assessment to enhance solvent selections. *Clean Technol. Environ. Policy* 2005, **7**, 42–50. [CrossRef]

8. Clarke, C.J.; Tu, W.-C.; Levers, O.; Brohl, A.; Hallett, J.P. Green and Sustainable Solvents in Chemical Processes. *Chem. Rev.* 2018, **118**, 747–800. [CrossRef] [PubMed]

9. Laird, T. Green Chemistry is Good Process Chemistry. *Org. Process Res. Dev.* 2012, **16**, 1–2. [CrossRef] [PubMed]

10. Bisz, E.; Szostak, M. 2-Methyltetrahydrofuran: A Green Solvent for Iron-Catalyzed Cross-Coupling Reactions. *ChemSusChem* 2018. [CrossRef] [PubMed]
11. Bisza, E.; Szostak, M. Cyclic ureas (DMI, DMPU) as efficient, sustainable ligands in iron-catalyzed C(sp2)–C(sp3) coupling of aryl chlorides and tosylates. Green Chem. 2017, 19, 5361–5366. [CrossRef]

12. Harris, J.M.; Zalipsky, S. Polyethylene Glycol: Chemistry and Biological Application; ACS Books: Washington, DC, USA, 1997; ISBN 9780841235373.

13. Harris, J.M. Polyethylene Glycol Chemistry. Biotechnological and Biomedical Applications; Plenum Press: New York, NY, USA, 1992; ISBN 9781489907035.

14. Vafaeezadeh, M.; Hashemi, M.M. Polyethylene glycol (PEG) as a green solvent for carbon–carbon bondformation reactions. J. Mol. Liq. 2015, 207, 73–79. [CrossRef]

15. Colacino, E.; Martinez, J.; Lamaty, F.; Patrikeeva, L.S.; Khemchyan, L.L.; Ananikov, V.P.; Beletskaya, I.P. PEG as an alternative reaction medium in metal-mediated transformations. Coord. Chem. Rev. 2012, 256, 2893–2920. [CrossRef]

16. Chen, J.; Spear, S.K.; Huddleston, J.G.; Rogers, R.D. Polyethylene glycol and solutions of polyethylene glycol as green reaction media. Green Chem. 2005, 7, 64–82. [CrossRef]

17. Zhu, Y.; Romain, C.; Williams, C.K. Sustainable polymers from renewable resources. Nature 2016, 540, 354–362. [CrossRef] [PubMed]

18. Knop, K.; Hoogenboom, R.; Fischer, D.; Schubert, U.S. Poly(ethylene glycol) in Drug Delivery: Pros and Cons as Well as Potential Alternatives. Angew. Chem. Int. Ed. 2010, 49, 6288–6308. [CrossRef] [PubMed]

19. Parrott, M.; Rule, S.; Kelleher, M.; Wilson, J. A Systematic Review of Treatments of Relapsed/Refractory Mantle Cell Lymphoma. Clin Lymphoma Myeloma Leuk. 2018, 18, 13–25. [CrossRef] [PubMed]

20. Samadder, P.; Aithal, R.; Belanc, O.; Krejci, L. Cancer TARGETases: DSB repair as a pharmacological target. Pharm. Ther. 2016, 161, 111–131. [CrossRef] [PubMed]

21. Mortlock, A.; Foote, K.; Kettle, J.; Aquila, B. Kinase Inhibitors in Cancer Reference Module in Chemistry. Mol. Sci. Chem. Eng. Kinase Inhib. Cancer 2014. [CrossRef]

22. Cherukupalli, S.; Hampannavar, G.A.; Chinnam, S.; Chandrasekaran, B.; Sayyad, N.; Kayamba, F.; Aleti, R.R.; Prosa, N.; Turgis, R.; Piccardi, R.; Scherrmann, M.-C. Soluble Polymer-Supported Flow Synthesis: A Green Process for the Preparation of Heterocycles. Eur. J. Org. Chem. 2012, 11, 2188–2200. [CrossRef]
33. Fresneau, N.; Hiebel, M.-A.; Agrofoglio, L.A.; Berteina-Raboin, S. Efficient Synthesis of Unprotected C-5-Aryl/Heteroaryl-2′-deoxyuridine via a Suzuki-Miyaura Reaction in Aqueous Media. *Molecules* **2012**, *17*, 14409–14417. [CrossRef] [PubMed]

34. Fresneau, N.; Hiebel, M.-A.; Agrofoglio, L.A.; Berteina-Raboin, S. One-pot Sonogashira-cyclization protocol to obtain substituted furopyrimidine nucleosides in aqueous conditions. *Tetrahedron Lett.* **2012**, *53*, 1760–1763. [CrossRef]

35. Alarcón-Espósito, J.; Tapia, R.A.; Contreras, R.; Campodónico, P.R. Changes in the SNAr reaction mechanism brought about by preferential solvation. *RSC Adv.* **2015**, *5*, 99322–99328. [CrossRef]

36. Ormazabal-Toledo, R.; Santos, J.G.; Rios, P.; Castro, E.A.; Campodónico, P.R.; Contreras, R. Hydrogen Bond Contribution to Preferential Solvation in SNAr Reactions. *J. Phys. Chem. B* **2013**, *117*, 5908–5915. [CrossRef] [PubMed]

37. Wang, X.; Salaski, E.J.; Berger, D.M.; Powell, D. Dramatic Effect of Solvent Hydrogen Bond Basicity on the Regiochemistry of SNAr Reactions of Electron-Deficient Polyfluoroarenes. *Org. Lett.* **2009**, *11*, 5662–5664. [CrossRef] [PubMed]

38. Um, I.H.S.; Min, W.; Dust, J.M. Choice of Solvent (MeCN vs H2O) Decides Rate-Limiting Step in SNAr Aminolysis of 1-Fluco-2,4-dinitrobenzene with Secondary Amines: Importance of Brønsted-Type Analysis in Acetonitrile. *J. Org. Chem.* **2007**, *72*, 8797–8803. [CrossRef] [PubMed]

39. Nudelman, N.S.; Mancini, P.M.E.; Martinez, R.D.; Vottero, L.R. Solvents effects on aromatic nucleophilic substitutions. Part 5. Kinetics of the reactions of 1-fluro-2,4-dinitrobenzene with piperidine in aprotic solvents. *J. Chem. Soc. Perkin Trans.* **1987**, *2*, 951–954. [CrossRef]

40. Alarcón-Espósito, J.; Contreras, R.; Tapia, R.A.; Campodónico, P.R. Gutmann’s Donor Numbers Correctly Assess the Effect of the Solvent on the Kinetics of SNAr Reactions in Ionic Liquids. *Chem. Eur. J.* **2016**, *22*, 13347–13351. [CrossRef] [PubMed]

41. Tanner, E.E.L.; Hawker, R.R.; Yau, H.M.; Croft, A.K.; Harper, J.B. Probing the importance of ionic liquid structure: A general ionic liquid effect on an SNAr process. *Org. Biomol. Chem.* **2013**, *11*, 7516–7521. [CrossRef] [PubMed]

42. Weber, C.C.; Masters, A.F.; Maschmeyer, T. Steric, hydrogen-bonding and structural heterogeneity effects on the nucleophilic substitution of N-(p-fluorophenyldiphenylmethyl)-4-picolinium chloride in ionic liquids. *Org. Biomol. Chem.* **2013**, *11*, 2534–2542. [CrossRef] [PubMed]

43. D’Anna, F.; Marullo, S.; Noto, R. Aryl Azides Formation under Mild Conditions: A Kinetic Study in Some Ionic Liquid Solutions. *J. Org. Chem.* **2010**, *75*, 767–771. [CrossRef] [PubMed]

44. Newington, I.; Perez-Arlandis, J.M.; Welton, T. Ionic Liquids as Designer Solvents for Nucleophilic Aromatic Substitutions. *Org. Lett.* **2007**, *9*, 5247–5250. [CrossRef] [PubMed]

45. Tormo, I.B.J.; Blettner, C.; Muller, B.; Gewehr, M.; Grammenos, W.; Grote, T.; Gypser, A.; Rheinheimer, J.; Schaefer, P.; Schieweck, F.; et al. Research Advances in Synthesis and Antifungal Activity of Pyrimidine Compounds. PCT/EP2004/004067, WO 2004092175 A1, 28 October 2004.

46. Tang, W.; Shi, D.-Q. Synthesis and herbicidal activity of O,O-dialkyl N-[2-(5,7-dimethyl-1,2,4]triazolo[1,5-a]pyrimidin-2-yloxy)benzoxyl]-1-amino-1-substitutedbenzyl phosphonates. *J. Heterocyclic Chem.* **2010**, *47*, 162–166. [CrossRef]

47. Jiang, L.; Chen, C.; Zhou, Y.; Chen, Q.; Yang, G. Synthesis and Herbicidal Activities of Novel 1,2,4-Triazolo[1,5-a]pyrimidineContaining Oxime Ether Moiety. *Chin. J. Org. Chem.* **2009**, *29*, 1392–1404. [CrossRef]

48. Qizhong, X.; Xuanfu, L.; Junhu, L.; Liang, B.; Xiaoping, B. Synthesis and Bioactivities of Novel 1,2,4-triazolo[1,5-a]Pyrimidine Derivatives Containing 1,2,4-triazole-5-thione Schiff Base Unit. *Chin. J. Org. Chem.* **2012**, *32*, 1255–1260. [CrossRef]

49. Chen, Q.; Zhu, X.-L.; Jiang, L.-L.; Liu, Z.-M.; Yang, G.-F. Synthesis, antifungal activity and CoMFA analysis of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives. *Eur. J. Med. Chem.* **2008**, *43*, 595–603. [CrossRef] [PubMed]

50. Bhattacharyya, C.; Saha, A.; Paul, K.; Syed, C.; Pati, P.K. Pyrazole clubbed triazolo[1,5-a]pyrimidine hybrids as an anti-tubercular agents: Synthesis, in vitro screening and molecular docking study. *Bioorg. Med. Chem.* **2015**, *23*, 7711–7716. [CrossRef] [PubMed]

51. Abdel-Rahman, H.M.; El-Koussi, N.A.; Hassan, H.Y. Fluorinated 1,2,4-Triazolo[1,5-a]pyrimidine-6-carboxylic Acid Derivatives as Antimycobacterial Agents. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 94–99. [CrossRef] [PubMed]
52. Wang, H.; Lee, M.; Peng, Z.; Blázquez, B.; Lastochkin, E.; Kumaraśiri, M.; Bouley, R.; Chang, M.; Mobashery, S. Synthesis and Evaluation of 1,2,4-Triazolo[1,5-a]pyrimidines as Antibacterial Agents Against Enterococcus faecium. *J. Med. Chem.* 2015, 58, 4194–4203. [CrossRef] [PubMed]

53. Zhao, X.-L.; Zhao, Y.-F.; Guo, S.-C.; Song, H.-S.; Wang, D.; Gong, P. Synthesis and Anti-tumor Activities of Novel 1,2,4-triazolo[1,5-a]pyrimidines. *Molecules* 2007, 12, 1136–1146. [CrossRef] [PubMed]

54. Hassan, G.S.; El-Sherbeny, M.A.; El-Ashmawy, M.B.; Bayomi, S.M.; Maarouf, A.R.; Badria, F.A. Synthesis and Antimicrobial Activity of 3-(2H)-pyridin-2(3H)-one Base. *Can. J. Chem.* 2017, 10, S1345–S1355. [CrossRef]

55. Uryu, S.; Tokuiro, S.; Murasugi, T.; Oda, T. A novel compound, RS-1178, specifically inhibits neuronal cell death mediated by β-amyloid-induced macrophage activation in vitro. *Brain Res.* 2002, 946, 298–306. [CrossRef]

56. Hougaard, C.; Hammami, S.; Eriksen, B.L.; Sørensen, U.S.; Jensen, M.L.; Stroøbæk, D.; Christophersen, P. Evidence for a Common Pharmacological Interaction Site on KCa2 Channels Providing Both Selective Activation and Selective Inhibition of the Human KCa2.1 Subtype. *Mol. Pharmacol.* 2012, 81, 210–219. [CrossRef] [PubMed]

57. Saito, T.; Obitsu, T.; Minamoto, C.; Sugiura, T.; Matsumura, N.; Ueno, S.; Kishi, A.; Katsumata, S.; Nakai, H.; Toda, M. Pyrazolo[1,5-a]pyrimidines, triazolo[1,5-a]pyrimidines and their tricyclic derivatives as corticotropic-releasing factor 1 (CRF1) receptor antagonists. *Bioorg. Med. Chem.* 2011, 19, 5955–5966. [CrossRef] [PubMed]

58. Mustazza, C.; Del Giudice, M.R.; Borioni, A.; Gatta, F. Synthesis of pyrazolo[1,5-a]-, 1,2,4-triazolo[1,5-a]- and imidazo[1,2-a]pyrimidines related to zaleplon, a new drug for the treatment of insomnia. *J. Heterocycl. Chem.* 2001, 38, 1119–1129. [CrossRef]

59. Sadana, A.K.; Mirza, Y.; Anjea, K.R.; Prakash, O. Hypervalent iodine mediated synthesis of 1-arlyl/hetryl-1,2,4-triazolo[4,3-a] pyridines and 1-arlyl/hetryl 1,2,4-triazolo[4,3-a]quinolines as antibacterial agents. *Eur. J. Med. Chem.* 2003, 38, 533–536. [CrossRef]

60. Kalgutkar, A.S.; Hatch, H.L.; Kosea, F.; Nguyen, H.T.; Choo, E.F.; McClure, K.F.; Taylor, T.J.; Henne, K.R.; Kuperman, A.V.; Dombroski, M.A.; et al. Preclinical pharmacokinetics and metabolism of 6-(4-(2,5-difluorophenyl)oxazol-5-yl)-3-isopropyl-[1,2,4]-triazolo[4,3-a]pyridine, a novel and selective p38alpha inhibitor: Identification of an active metabolite in preclinical species and human liver microsomes. *Biopharm. Drug Dispos.* 2006, 27, 371–386. [CrossRef] [PubMed]

61. McClure, K.F.; Abramov, Y.A.; Laird, E.R.; Barberia, J.T.; Cai, W.; Carty, T.J.; Cortina, S.R.; Danley, D.E.; Dipesa, A.J.; Donahue, K.M.; et al. Theoretical and Experimental Design of Atypical Kinase Inhibitors: Application to p38 MAP Kinase. *J. Med. Chem.* 2005, 48, 5728–5737. [CrossRef] [PubMed]

62. Bektas, H.; Karaali, N.; Sahin, D.; Demirbas, A.; Karaoglu, S.A.; Demirbas, N. Synthesis and Antimicrobial Activities of Some New 1,2,4-Triazole Derivatives. *Molecules* 2010, 15, 2427–2438. [CrossRef] [PubMed]

63. Lawson, E.C.; Hoekstra, W.J.; Addo, M.F.; Andrade-Gordon, P.; Damiano, B.P.; Kauffman, J.A.; Mitchell, J.A.; Maryanoff, B.E. 1,2,4-Triazolo[3,4-a]pyridine as a novel, constrained template for fibrinogen receptor (GPIIb/IIIa) antagonists. *Bioorg. Med. Chem. Lett.* 2001, 11, 2619–2622. [CrossRef]

64. Moreau, S.; Coudert, P.; Rubat, C.; Vallee-Goyet, D.; Gardette, D.; Gramain, J.-C.; Couquellet, J. Synthesis and anticonvulsant properties of triazolo- and imidazopyridazinyl carboxamides and carboxylic acids. *Bioorg. Med. Chem.* 1998, 6, 983–991. [CrossRef]

65. Nitlikar, L.H.; Darandale, S.N.; Shinde, D.B. Exploring the Unexplored Practical and Alternative Synthesis of 3-(Trifluoromethyl)-Triazolopiperazine the Key Intermediate for Sitagliptin. *Lett. Org. Chem.* 2013, 10, 348–352. [CrossRef]

66. Elrazaz, E.Z.; Serya, R.A.T.; Ismail, N.S.M.; El Ella, D.A.A.; Abouzid, K.A.M. Thieno[2,3-d]pyrimidine based derivatives as kinase inhibitors and anticancer agents. *Future J. Pharm. Sci.* 2015, 1, 33–41. [CrossRef]

67. Dinakaran, V.S.; Bomma, B.; Srinivasan, K.K. Fused pyrimidines: The heterocycle of diverse biological and pharmacological significance. *Der Pharma Chem.* 2012, 4, 255–265.

68. Janeba, Z.; Holý, A.; Pohl, R.; Snoeck, R.; Andrei, G.; De Clercq, E.; Balzarini, J. Synthesis and biological evaluation of acyclic nucleotide analogues with a furo[2,3-d]pyrimidin-2(3H)-one base. *Can. J. Chem.* 2010, 88, 628–638. [CrossRef]
69. Robins, M.J.; Nowak, I.; Rajwanshi, V.K.; Miranda, K.; Cannon, J.F.; Peterson, M.A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Synthesis and Antiviral Evaluation of 6-(Alkyl-heteroaryl)furo[2,3-d]pyrimidin-2(3H)-one Nucleosides and Analogues with Ethynyl, Ethenyl, and Ethyl Spacers at C6 of the Furopyrimidine Core. *J. Med. Chem.* 2007, 50, 3897–3905. [CrossRef] [PubMed]

70. McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J.T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Highly Potent and Selective Inhibition of Varicella-Zoster Virus by Bicyclic Furopyrimidine Nucleosides Bearing an Aryl Side Chain. *J. Med. Chem.* 2000, 43, 4993–4997. [CrossRef] [PubMed]

71. Bhuiyan, M.M.H.; Rahman, K.M.M.; Hossain, M.K.; Rahim, M.A.; Hossain, M.I. Fused Pyrimidines. Part II: Synthesis and Antimicrobial activity of Some Furopyrimidine Nucleosides Bearing an Aryl Side Chain. *J. Med. Chem.* 2005, 58, 5260–5264. [CrossRef] [PubMed]

72. Gangjee, A.; Devraj, R.; McGuire, J.J.; Kisliuk, R.L.; Queener, S.F.; Barrows, L.R. Classical and Nonclassical Furopyrimidines as Novel Antifolates: Synthesis and Biological Activities. *J. Med. Chem.* 1994, 37, 1169–1176. [CrossRef] [PubMed]

73. Pyo, J.I.; Lee, S.H.; Cheong, C.S. A facile synthesis of some substituted furopyrimidine derivatives. *J. Heterocycl. Chem.* 2006, 43, 1129–1133. [CrossRef]

74. Novinson, T.; O’Brien, D.E.; Robins, R.K. Synthesis of certain 8-cyano-2,4-disubstituted imidazo[1,5-a]pyrimidines. *J. Heterocycl. Chem.* 1974, 11, 873–878. [CrossRef]

75. Levin, Y.A.; Sergeeva, E.M.; Kukhtin, V.A. Condensed heterocycles. V. Reaction of 4-chloro-6-methyl-1,2,4-triazolo[2,3-a] pyrimidine with some nitrogenous bases. *Zhurnal Obshchei Khimii* 1964, 34, 205–209.

76. Reynolds, G.A.; VanAllan, J. A Structure of certain polyazaindenes. VII. 4-Amino-6-methyl-1,3,3a,7-tetraazaindene and its derivatives. *J. Org. Chem.* 1961, 26, 115–117. [CrossRef]

77. Barelier, S.; Eidam, O.; Fish, I.; Hollander, J.; Figaroa, F.; Nachane, R.; Irwin, J.J.; Shoichet, B.K.; Siegal, G. Increasing Chemical Space Coverage by Combining Empirical and Computational Fragment Screens. *ACS Chem. Biol.* 2014, 9, 1528–1535. [CrossRef] [PubMed]

78. Kemnitzer, W.; Sirisoma, N.; May, C.; Tseng, B.; Drewe, J.; Cai, S.X. Discovery of 4-anilino-N-methylthieno[3,2-d]pyrimidines and 4-anilino-N-methylthieno[2,3-d]pyrimidines as potent apoptosis inducers. *Bioorg. Med. Chem. Lett.* 2009, 19, 3536–3540. [CrossRef] [PubMed]

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

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).