Communication

Expedient Access to Type II Kinase Inhibitor Chemotypes by Microwave-Assisted Suzuki Coupling

Lorenza Destro, Ross Van Melsen, Alex Gobbi, Andrea Terzi, Matteo Genitoni and Alfonso Zambon*

Department of Chemical and Geological Sciences, University of Modena and Reggio Emilia, Via G. Campi 103, 41125 Modena, Italy; lorenza.destro@unimore.it (L.D.); rvanmels@unimore.it (R.V.M.); 256915@studenti.unimore.it (A.G.); 229348@studenti.unimore.it (A.T.); 227048@studenti.unimore.it (M.G.)

* Correspondence: alfonso.zambon@unimore.it

Abstract: Functionalized pyrazole-urea scaffolds are a common type II chemotype for the inhibition of protein kinases (PKs), binding simultaneously into the ATP-binding pocket with an ATP bioisostere and into a vicinal allosteric pocket with a pyrazole group. Standard approaches to the scaffold require multi-step synthesis of the ATP bioisostere followed by phosgene or triphosgene-mediated coupling with the substituted pyrazole group. Here we report an expedient approach to the chemotype, characterized by an optimized MW-assisted Suzuki coupling on easily accessed bromo-phenyl pyrazole ureas. The new protocol allowed quick access a large library of target analogues covering a broad chemical space of putative protein kinases inhibitors (PKIs).

Keywords: protein kinase inhibitors; pyrazole-ureas; microwave synthesis

1. Introduction

Protein phosphorylation in eukaryotes plays a key role in cell signaling, gene expression, and differentiation. Protein phosphorylation is also involved in the global control of DNA replication during the cell cycle, as well as in the mechanisms that cope with stress-induced replication blocks [1]. The role of kinases is to phosphorylate serine, threonine, or tyrosine residues of specific protein substrates via the transfer of the γ-phosphate group of adenosine triphosphate (ATP) or, in specific cases, GTP [2]. Protein kinases are, therefore, key enzymes in the function of cellular signaling pathways and are crucial in the regulation of key functions such as cell proliferation, differentiation, and apoptosis [3].

Aberration of PK-mediated cellular pathways is a most common factor in the onset and progression of cancer [4,5], and starting from the early 2000s PKs have emerged as prominent targets for the development of cancer therapies, with 43 protein kinase inhibitors (PKI) approved by FDA for the treatment of solid and liquid tumors [6]. To date, an estimated 20–33% of the global drug discovery efforts are directed at the development of protein kinase inhibitors [7–11]. Depending on their binding mode within the ATP binding site and in proximal or distal allosteric pockets, PKIs are classified as Type I, Type I 1/2, and Type II-VI, with Type I and Type II being first binding modes identified and the most common ones [12]. Type II inhibitors, in particular, bind simultaneously to the ATP-binding pocket and to an adjacent allosteric pocket when the kinase in an inactive, DFG-out conformation and into the ATP-binding pocket. Of the 27 co-crystal structures of FDA-approved PKIs available in 2019, eight were Type II [6]. As inactive protein kinase conformations exhibit greater structural variation than the conserved active conformation to which Type I PKIs bind, Type II PKIs are considered potentially more selective than Type I ones [13,14]. Most Type II PKIs share a common chemotype enticing a hydrophobic element that forms Van der Waals interactions with the allosteric pocket and a bridge system (e.g., an amine or a urea) able to form hydrogen bonds with the conserved...
salt bridge adjacent to the PK active site and an ATP bioisostere that occupies the ATP binding pocket [15–18].

The introduction of a pyrazole-urea moiety as an allosteric binder in Type II PKIs has been shown to confer activity against a range of protein targets and to improve the pharmacokinetic properties of the scaffold, allowing for the progression to the clinic of several compounds of this type. The general structure of pyrazole-urea PKIs entices a central pyrazole-phenyl urea core substituted on the pyrazole by aliphatic (X) and aromatic and aliphatic (Y) groups and bearing on the phenyl ring a range of substituents usually comprising a variously substituted aromatic group (Z), as depicted in Figure 1 [19–21].

![Figure 1](image)

**Figure 1.** General structure of Type II pyrazole-urea PKI.

In general, access to this chemotype requires the multi-step synthesis of the aniline ATP isostere followed by phosgene or triphosgene-mediated coupling to urea with the pyrazole group. This approach requires lengthy synthetic and purification procedures, the optimization of reaction conditions for each analogue, and the use of hazardous reagents for the coupling step, which often occurs with sub-optimal yields [22–27]. We posit that direct reaction of the pyrazole group with commercial Bromophenyl Isocyanates followed by a Suzuki coupling (Scheme 1) would provide an expedient access to this chemotype. Diversity points can be easily introduced at each step, allowing for the rapid synthesis of a library of analogues [28,29].

![Scheme 1](image)

**Scheme 1.** Proposed route to pyrazole-ureas analogues.

Suzuki-Miyaura coupling allows the formation of new C-C bonds between an aryl halide and an aryl boron species and is particularly suitable for our purpose due to its robustness and tolerance of functional groups. Although this reaction has already been extensively investigated, reactions on substrates containing an aromatic urea group are scantily reported, and no examples in which one of the two aromatic rings is a pyrazole are reported in the literature [30,31] The affinity of palladium for the urea group suggests a possible coordination of the catalyst by our substrate, and thus possible deactivation of the former. Here we report the optimization of the problematic Suzuki-Miyaura reaction on pyrazole ureas, and the consequent synthesis of a library of analogues easily accessed by the variation of substituents on the pyrazole and phenylboronic reagents.

2. Materials and Methods

General Methods: Commercial building blocks, reagents, and solvents for reactions were reagent grade and used as purchased or purified according to methods in the literature. Reactions were monitored by Pre-coated TLC sheets ALUGRAM® Sil G/UV254 (0.20 mm thickness). Dry solvents were prepared by overnight standing on freshly activated 4 Å molecular sieves under argon atmosphere or purchased. Flash chromatography was
conducted using a Merk 60, 230–400 mesh silica gel. \(^1\)H- and \(^{13}\)C-NMR spectra were recorded at 298K on Bruker FT-NMR Advance 400 (400.13 MHz) e Bruker FT-NMR Advance III HD 600 (600.13 MHz). Chemical shift values are given in ppm relative to TMS and were determined by taking as reference the isotopic impurity signals of CDCl\(_3\) (7.26 ppm for \(^1\)H and 77.16 for \(^{13}\)C) and DMSO-d\(_6\) (2.50 ppm for \(^1\)H and 39.52 ppm for \(^{13}\)C). Data are presented as follows: chemical shift (\(\delta\)) in ppm, multiplicity, coupling constants (J) given in hertz. LCMS data were acquired using a 6130A quadrupole ion trap analyzer Ion Trap LC-MS(n) by Agilent Technologies. Docking analysis was carried out using the Glide Docking Module of Maestro (Schroedinger) in the standard precision (SP) mode.

Detailed synthetic procedures and full characterization of all the synthesized compounds are reported in Supplementary Information.

3. Results

As discussed above, Suzuki coupling on aromatic ureas is rarely reported, and to our knowledge never on a substituted pyrazole scaffold [30,31]. We thus set out to optimize the coupling step using as model reaction the coupling of easily obtained 1-(4-bromophenyl)-3-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)urea \(1\)a with boronic 3,4-dimethoxyphenylboronic acid \(2\)a as coupling partner to 1-(3-(tert-butyl)-1-phenyl-1H-pyrazol-5-yl)-3-(3′,4′-dimethoxy-[1,1′-biphenyl]-4-yl)urea \(3\)a (Table 1). We first tried the protocol reported by Al-Masoudi et al. [30] for structurally close bis-phenyl ureas, carrying out the reaction under reflux with readily available reagents (Entry 1) but did not observe any product formation after 18h. We then tried varying base, catalyst, and solvent system replacing K\(_2\)CO\(_3\) with Na\(_2\)CO\(_3\) (Entry 2), Pd(PPh\(_3\))\(_4\) with Pd(dppf)Cl\(_2\) (Entry 3) and finally the solvent with a 1:1=H\(_2\)O:DMF mixture (Entry 4). Again, under all the conditions explored we did not observe any conversion to product, suggesting a considerable deactivation of the substrate towards Suzuki coupling under thermal conditions.

We then set out to explore a range of conditions starting from those reported by Brunner et al. [31] in which coupling of phenyl bromo ureas is carried out under microwave (MW) irradiation. The use of MW is known to improve the reaction rates and thus could overcome the deactivation of the system observed under thermal conditions [32]. As the starting conditions, we used MeCN as solvent, Pd(PPh\(_3\))\(_4\) as catalyst, Na\(_2\)CO\(_3\) as base and run the reaction for 1 h at 100 °C under microwave condition as reported (Entry 5) [32]. Unfortunately, this reaction did not lead to the desired results, most likely due to the poor solubility of urea \(1\)a in the solvent medium. We then changed the solvent system by replacing the MeCN with a mixture of a 2M aqueous solution of K\(_2\)CO\(_3\) and 1,4-dioxane in a ratio of 1:2, in which our urea proved more soluble (Entry 6). Encouragingly, we observed the formation of some product in the reaction mixture, albeit with incomplete conversion and 30% isolated yield. After several attempts, we were then able to further optimize the reaction conditions by changing both the base by switching K\(_2\)CO\(_3\) with Na\(_2\)CO\(_3\), a slightly stronger base, and the catalyst by replacing Pd(PPh\(_3\))\(_4\) with Pd(dppf)Cl\(_2\) (Entry 7–8), a catalyst that was proven stable and effective under microwave conditions [33]. We finally identified the best conditions with the use of Pd(dppf)Cl\(_2\) as catalyst and Na\(_2\)CO\(_3\) as base with complete spectroscopic conversion and 50% yield after chromatography (Entry 9).

After identifying the optimal solvent, base, and catalyst, we decided to investigate if the reaction could be performed at lower temperatures (70 °C instead of 100 °C, Entry 10) and with shorter reaction times (45 min instead of 1.25 h, Entry 11). Lowering the temperature significantly affected the conversion, with only 15% of urea \(1\)a converted to \(3\)a, but we found that reaction times could be shortened to 30 min (Entry 11), with ~99% conversion of urea \(1\)a to \(3\)a, in line with that observed for Entry 9.
Table 1. Optimization of the reaction conditions for the Suzuki coupling of 1a and 2a.

| Entry | Conditions | Time (h) | T (°C) | Solvent | Catalyst | Base | Yield     |
|-------|------------|----------|--------|---------|----------|------|-----------|
| 1     | T₁         | 18       | 101    | 1,4-dioxane | Pd(PPh₃)₄ | K₂CO₃ | N.R.      |
| 2     | T₂         | 18       | 101    | 1,4-dioxane | Pd(PPh₃)₄ | Na₂CO₃ | N.R.      |
| 3     | T₃         | 18       | 101    | 1,4-dioxane | Pd(dppf)Cl₂ | K₂CO₃ | N.R.      |
| 4     | T₄         | 18       | 100    | 1:1 DMF/H₂O | Pd(PPh₃)₄ | K₂CO₃ | N.R.      |
| 5     | MW         | 1        | 100    | MeCN    | Pd(PPh₃)₄ | Na₂CO₃ | N.R.      |
| 6     | MW         | 1.25     | 100    | 1:2 H₂O/1,4-dioxane | Pd(PPh₃)₄ | Na₂CO₃ | 30% ¹   |
| 7     | MW         | 1.25     | 100    | 1:2 H₂O/1,4-dioxane | Pd(PPh₃)₄ | K₂CO₃ | N.R.      |
| 8     | MW         | 1.25     | 100    | 1:2 H₂O/1,4-dioxane | Pd(dppf)Cl₂ | K₂CO₃ | N.R.      |
| 9     | MW₅        | 1.25     | 100    | 1:2 H₂O/1,4-dioxane | Pd(dppf)Cl₂ | Na₂CO₃ | 50% ²   |
| 10    | MW₆        | 1.25     | 70     | 1:2 H₂O/1,4-dioxane | Pd(dppf)Cl₂ | Na₂CO₃ | 15% ²   |
| 11    | MW₇        | 0.5      | 100    | 1:2 H₂O/1,4-dioxane | Pd(dppf)Cl₂ | Na₂CO₃ | ~99% ²   |

¹ Isolated yield (column purification) ² spectroscopic yield (¹H-NMR) N.R. = Not reacted; only Starting materials recovered.

We then set out to perform the synthesis of a small library of analogues of 1a taking advantage of the newly optimized Suzuki procedure. Although reaction time could be lowered at 30 min, we deemed it preferable to keep it at 1.25 h to account for the potential lower reactivity of the alternative boronic agents.

The overall synthetic route to this library of compounds is depicted in Scheme 2 and involves the condensation of an oxo nitrile 4a-b with a hydrazine 5a-c to give pyrazole 6a-f, followed by the formation of Br-substituted ureas 1a-h by reaction with isocyanates 7a-b. These steps are already well reported in the scientific literature and gave high yields for all the substrates explored [34].

Ureas 1a-l were finally reacted following the optimized Suzuki protocol with selected boronic acids 2a-e to afford para-substituted (3a-f) and meta-substituted (3g-l) final compounds in good 35–60% yields as reported in Table 2 (para-substituted compounds) and Table 3 (meta-substituted compounds).

For a preliminary evaluation of the potential of our compounds as PKIs, we carried out docking of 3a-l in the co-crystal structure (pdb code 1KV2) of p38, a validated target for autoimmune diseases, with pyrazole-urea BIRB-796 [21]. All compounds faithfully mirrored the binding mode of BIRB-796 and registered high docking scores, suggesting a high affinity of the library for p38 (Figure 2). The best affinities were calculated for compounds 3g, 3h, 3l and 3a, with docking scores ranging from −11.7 and −8.9 kcal/mol.
Scheme 2. General synthetic route to pyrazole urea 3a-l. Reagents and conditions: (a) Toluene, 116 °C, 72 h; (b) anhydrous DCM, room temperature, 24 h; (c) 1:2 H2O/1,4-dioxane, 100 °C, 1.25 h.

Table 2. Structures and yields of the final step of compounds 3a-f.

| Compound | R1 | R2 | R3 | Yield |
|----------|----|----|----|-------|
| 3a       |    |    |    | 35%   |
| 3b       |    |    |    | 43%   |
| 3c       |    |    |    | 36%   |
Table 2. Cont.

![Structures and yields of the final step of compounds 3a-f.](image)

| Compound | R₁ | R₂ | R₃       | Yield |
|----------|----|----|----------|-------|
| 3d       |   |   | -Me      | 52%   |
| 3e       |   |   | -Me      | 48%   |
| 3f       |   |   | -Me      | 58%   |

Table 3. Structures and yields of the final step of compounds 3g-l.

![Structures and yields of the final step of compounds 3g-l.](image)

| Compound | R₁ | R₂ | R₃       | Yield |
|----------|----|----|----------|-------|
| 3g       |   |   | -Me      | 36%   |
| 3h       |   |   | -Me      | 48%   |
Table 3. Cont.

![Chemical structures and yields of the final step of compounds 3g-l.](image)

| Compound | R₁ | R₂ | R₃ | Yield |
|----------|----|----|----|-------|
| 3i       |    |    |    | 36%   |
| 3l       |    |    | -Me | 41%   |

**Figure 2.** Docking pose of compound 3g (gray) into the binding pocket of p38 (pdb code 1KV2) superposed to BIRB-796 (pink).

4. Conclusions

In conclusion, we report a novel, efficient synthetic route to a privileged scaffold for protein kinase inhibitors based on a novel, robust microwave-assisted protocol for the Suzuki reaction of pyrazole ureas, which allowed quick to access a structurally varied library of putative kinase inhibitors. Although this route is limited to the synthesis of biphenyl pyrazole ureas, it compares favorably with previous literature in terms of yields and overall ease of synthesis.
Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/applbiosci1010004/s1.

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