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Published in:
European Journal of Organic Chemistry

DOI:
[10.1002/ejoc.202000933](https://doi.org/10.1002/ejoc.202000933)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Konstantinidou, M., Boiarska, Z., Butera, R., Neochoritis, C. G., Kurpiewska, K., Kalinowska-Tluscik, J., & Doemling, A. (2020). Diaminoimidazopyrimidines: Access via the Groebke–Blackburn–Bienaymé Reaction and Structural Data Mining. *European Journal of Organic Chemistry*, 2020(34), 5601-5605.
<https://doi.org/10.1002/ejoc.202000933>

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MCR Chemistry

Diaminoimidazopyrimidines: Access via the Groebke–Blackburn–Bienaymé Reaction and Structural Data Mining

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Dedicated to the memory of Professor Rolf Huisgen.

Abstract: Imidazopyrimidines with diverse substitution patterns are a prime class of heterocycles, present in many commercially available or late-stage clinical trials drugs. Here, we describe a fast access to diaminoimidazopyrimidines by means of a powerful multicomponent reaction; the Groebke–Blackburn–Bienaymé reaction. We provide the design of such libraries of compounds, identifying all the structural motifs, and subsequently their synthesis. Scope and limitations are discussed,

in addition to data mining in the Cambridge Structural Database and pharmacophore search with Crossminer. The presented approach highlights the vast amount of data available in the databases and provides potential future scaffold hopping alternatives for compounds with similar binding patterns. Further studies are ongoing to introduce more “drug-like” properties into this scaffold and to investigate cellular mechanism-based anti-cancer behaviours.

Multicomponent reactions (MCR) combining at least three starting materials in a single reaction step are powerful convergent chemical transformations to access complex scaffolds.^[1–4] Among the many advantages are the diversity of building blocks that can be utilized and the functional group tolerance allowing for plenty of post-MCR modifications.^[5,6] One of the youngest MCR reactions, the three component Groebke–Blackburn–Bienaymé reaction (GBB-3CR) was first described in 1998^[7–9] and a detailed overview of the chemistry, as well as applications of the GBB reaction was recently published.^[10] The GBB reaction, typically occurring between an aldehyde, an isocyanide and 2-aminopyridine, leads to fused imidazo[1,2-*a*]pyrimidines, a privileged scaffold,^[11] present in many commercial and clinical trials drugs, such as the zolpidem, miroprofen, minon-dronic acid and olprinone. It is noteworthy, that the choice of the starting materials in GBB reactions, in particular the aminopyridine component variation can be used to introduce more diversity and functional groups on the flat fused bis-heterocyclic ring system.^[12–14] As a result, certain potential ligand-

protein binding interactions can be incorporated in the design of the GBB reaction, including hydrogen bonds, electrostatic interactions, as well as hydrophobic interactions.

In medicinal chemistry, one of the most explored targets with clear structural understanding are kinases.^[15] Type I-active site kinase inhibitors bear the characteristic binding motif of a hydrogen-bond donor in close proximity to a hydrogen-bond acceptor. This common motif can be observed for instance in dabrafenib (a reversible ATP-competitive kinase inhibitor targeting the BRAF, PDB ID 5CSW),^[16] lorlatinib (a macrocyclic kinase inhibitor targeting ALK, PDB ID 5A9U),^[17] an aminopyridine inhibitor targeting GLK kinase (PDB ID 5J5T)^[18] and ibrutinib (a covalent inhibitor of Bruton's tyrosine kinase, PDB ID 5P9J).^[19] A similar motif of hydrogen-bond donor in adjacent position to a hydrogen-bond acceptor is also observed in ganciclovir (a guanine analogue targeting thymidine kinase, PDB ID 1K12)^[20] and trimethoprim (an antifolate antibacterial inhibiting bacterial dihydrofolate reductase, PDB ID 1DG5)^[21] (Figure 1). We are very interested to access the binding motifs of those marketed drugs (the specific combination of hydrogen-bond donors-hydrogen-bond acceptors in a relatively flat system, Figure 1), utilizing suitably substituted aminopyrimidines as starting materials in a GBB reaction.

Therefore, we wish to explore the scope and limitations of accessing polysubstituted aminopyrimidines and in particular diaminoimidazopyrimidines via the GBB-3CR. Despite the usefulness of this MCR reaction in providing in a single step drug-like heterocycles, diaminoimidazopyrimidines have not been previously thoroughly studied. One exception includes the work of Lavilla et al.^[22] where the 2,4-diaminopyrimidine **1** is used without protection in a GBB-3CR, leading selectively to the substituted imidazo[1,2-*a*]pyrimidin-7-amine derivatives **2**

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <https://doi.org/10.1002/ejoc.202000933>.

Figure 1. The common binding motif of H-B donor (blue) and H-B acceptor (red) on heterocyclic ring systems in marketed drugs and in a cocrystal structure of GLK kinase with aminopyridine inhibitor (PDB ID 5J5T).

(Scheme 1). That work served as inspiration for us since the use of this diamine **1** could potentially lead also to the scaffold of imidazo[1,2-*c*]pyrimidin-5-amine **3**, which is our targeted scaffold (Scheme 1). This scaffold which is comprised of a flat substituted 2-aminopyrimidine ring fused with a substituted imidazole ring with distinct hydrogen donors (blue) and acceptors (red) bears exactly the desired hydrogen donor-acceptor structural motif (Figure 1). Moreover, the two possibilities of an intramolecular hydrogen bond (the 5-amino group could serve both as hydrogen-bond acceptor and donor), in a pseudo *peri* position enhancing the conformational rigidity of the scaffold and potentially increasing the permeability of the molecule, made the whole design quite attractive. The structural motif of the scaffold could potentially be of interest not only for kinase inhibitors, but also for protein-protein interactions due to the flatness of the bicyclic ring system and the specific polar interactions that can be rationally introduced by choosing appropriate starting materials. Establishing a suitable synthetic route would facilitate future biological applications of the scaffold. The retrosynthetic analysis led us to two possible strategies based on one common moiety; the protected diaminopyrimidine **4**, which could be accessed either by a simple monoamine protection, followed by the GBB-3CR and finally a deprotection (Scheme 1, strategy I) or by employing the 2-chloropyrimidin-4-amine **5** (Scheme 1, strategy II). The latter could be directly employed in the GBB-3CR, followed by a nucleophilic aromatic substitution with ammonia or be used first in the syn-

thesis of the protected diaminopyrimidines **4** via an aromatic nucleophilic substitution and then in GBB-3CR, followed by deprotection (Scheme 1, strategy II).

Initially, 2,4-diaminopyrimidine **1** was protected with Boc₂O as described previously^[23] and the obtained product **4a** was used in the GBB-3CR. However, the Boc group turned out to be unstable in this step (data not shown), leading to the formation of a mixture of products (Scheme 2, strategy I). The trityl group

Scheme 2. Syntheses pursued in this work towards diaminimidazopyrimidines.

Scheme 1. The targeted scaffold, which consists of the flat (green circle), fused 2-aminopyrimidine ring with distinct hydrogen donors (blue) and acceptors (red) and the proposed retrosynthetic pathways towards it.

was not included in the study due to unfavorable atom economy. The –Cbz group was also excluded, since utilizing a hydrogenation reaction as the deprotecting step would probably partially dearomatize the imidazopyrimidine ring. For that reason, 2,4-dimethoxybenzylamine appeared as an attractive alternative.

Trials using 2-chloropyrimidin-4-amine **5** in the GBB-3CR as the amine component led to the desired product **6** but with low yields in both the GBB step and the nucleophilic aromatic substitution with ammonia, even after thorough investigation of the reaction conditions (Scheme 2, strategy II). It is noteworthy, that with 2,6-dichloropyrimidin-4-amine in the GBB-3CR, only starting materials were obtained even by using harsh conditions and large amounts of catalyst (data not shown). The hypothesis is that the presence of the chlorine substituents significantly inactivated the ring in the GBB reaction. For this reason, we turned our focus on accessing the protected 2,4-diaminopyrimidine **4a** in a different way. Therefore, an aromatic nucleophilic substitution of the 2-chloropyrimidin-4-amine **5** with the (2,4-dimethoxyphenyl)methanamine proved to be the best strategy (Scheme 2, strategy II). The protected aminopyr-

imidine **5a** proved to be stable under the GBB-3CR reaction conditions and successfully gave rise to compounds **7** and finally the desired adducts **3**. Via this route, a series of protected aminopyrimidines **5a–j** were prepared under microwave irradiation (Supporting Information, SI, Scheme S1).

After selecting the protecting group, the optimization of the GBB reactions was performed (SI, Table S1). It was found out that microwave irradiation at 120 °C for 1 h with catalytic amount of Sc(OTf)₃ (20 mol-%) was beneficial. The protected aminopyrimidines were stable in the GBB reaction, although significant variations in the reactivity were noted (see SI for details). Regarding the final deprotection step, trials with hydrochloric acid or mixtures of DCM/TFA resulted in slow and incomplete transformations. Performing the deprotection with refluxing TFA overnight led to the desired products, which were isolated as free amines after column chromatography.

Next, we turned our focus on aminopyrimidines **5a** and **5b** and further explored the scope and limitations of the aldehyde and isocyanide components. Regarding the aldehyde component, aromatic aldehydes with electron withdrawing and electron donating groups, as well as heterocyclic aldehydes were

Scheme 3. Obtained products **3a–n** and isolated yields (the yield of the second step is noted in the parenthesis). Reaction conditions in the GBB step: aldehyde (1.5 equiv.), aminopyrimidine (1 equiv.), isocyanide (1.5 equiv.), scandium triflate (20 mol-%), acetonitrile (0.5 M), MW 1 h 120 °C. Reaction conditions in the deprotection step: TFA (0.1 M), reflux overnight.

well tolerated in the GBB reaction. On the other hand, aliphatic aldehydes reacted with lower yields and led to more complex reaction mixtures. The main issue with aliphatic aldehydes was the instability of the deprotected GBB products. Regarding the isocyanide component, both aliphatic and aromatic variations were well tolerated and no instability was observed in those cases. An overview of the obtained products and isolated yields is provided in the next scheme (Scheme 3).

A single-crystal X-ray structure was solved for compound **3f** (Figure 2). To our delight, the anticipated intramolecular hydrogen bond of 2.1 Å between the exocyclic amine groups was observed in which the 5-amino group serves as hydrogen-bond donor (H–N–H...N–H). In addition, the designed structural motif was achieved as intermolecular hydrogen bonding of 2.0 Å between the pyridine type nitrogen and the exocyclic amino group was observed. Finally, as expected, the fused heterocyclic system is relatively rigid.

Figure 2. X-ray structure of compound **3f** (CCDC 1986084).

At that point, it would be very interesting to check similar structural motifs and extract useful insights that would potentially be utilized in drug discovery. One of the best tools to get those insights is the Cambridge Structural Database (CSD).^[24] The CSD provides the ultimate reference for evaluating the geometry and interactions of a putative drug design bound to its protein target. Thus, data mining in CSD-ConQuestTM showed 824 derivatives of 2-aminopyrimidines (Figure 3A). We are highly interested in the features of the hydrogen bond that forms the N–H with any atoms such as O, N (QA). Interestingly, it was revealed that the mean value of such hydrogen bond is 2.2 Å (dist1, red color) with the angle (ang1, blue color) at 162° (Figure 3B). As the distance of the hydrogen bond gets to the value of 2.0 Å, the angle becomes linear ($\approx 170^\circ$ – 180°).^[25]

Next, we wanted to query both CSD and the Protein Data Bank (PDB)^[26] utilizing the aforementioned structural motif of our compounds. CSD-Crossminer^[27] is a tool that allows such types of pharmacophore investigations giving us the opportunity to identify patterns and ideas for lead optimization and scaffold hopping. Matching crystal structures are overlaid onto the pharmacophore query and visualized as soon as they are available. Consequently, we employed two crystal structures, both from the CSD and PDB with the representative binding pattern (as it is seen both in our obtained crystal structure and the literature). Firstly, we used as pharmacophore query the CSD X-ray structure UFOJEF^[28] (the structure was mined from the 824 different crystal structures of the CSD, Figure 3). Thus, we wanted to search for similar structures in PDB with the

Figure 3. Geometrical features of the intermolecular hydrogen bond of the 2-aminopyrimidines (824 hits in CSD) between the amino group and a heteroatom (O or N, QA). The angle N–H–QA (ang1) is depicted with blue color and the distance H–QA (dist1) with red color.

following characteristics (Figure 4, A); flat, fused (green sphere) 2-aminopyrimidine structures with the NH₂ as hydrogen donor (blue sphere) and a N as donor acceptor (red sphere). The query revealed 28 different cocrystal structures of 2-aminopyrimidines with a very similar binding mode as shown from the alignment (SI). As a second pharmacophore query, we employed as “pharmacophore template” the 8-aminoimidazo[1,2-*a*]pyrazine with Hsp90 inhibitory activity from a cocrystal structure (PDB ID 4R3M) with very similar binding pattern to our GBB scaffold **3**. Noteworthy, this pyrazine is also synthesized by a GBB reaction.^[29] The pharmacophore query is depicted in Figure 4, B and consists of a flat, fused (green sphere) heterocycle with the –NH₂ as hydrogen donor (blue sphere) and a N as hydrogen acceptor (red sphere). Moreover, we searched a –NH group adjacent to the pyridine ring (blue sphere), a similar motif with our scaffold with the exocyclic NH (derived from the isocyanide moiety). The query revealed 37 different cocrystal structures of fused aminopyrimidines which are nicely aligned (SI). By this exercise, we implement the binding pattern to various scaffolds not only demonstrating the usefulness of our synthesized library but also offering alternative type of pharmacophores for future scaffold hopping against similar targets.^[30]

Figure 4. Pharmacophore search in PDB with CSD-Crossminer; (A) based on CSD number UFOJEF and (B) based on PDB ID4R3M. Green sphere depicts flat, fused structures, whereas hydrogen donors and acceptors are depicted as blue and red spheres, respectively.

A new and facile synthetic pathway towards the privileged structure of diaminoimidazopyrimidines via GBB-3CR is described. A library of 14 derivatives is synthesized in just 2-steps, after performing the protecting step on big scale (up to 10 mmol). The structural design of the molecules including a hydrogen-bond donor in close proximity to a hydrogen-bond

acceptor on a flat bicyclic ring system and an intramolecular hydrogen bond introducing a third flat ring, was verified via a crystal structure. Furthermore, the usefulness of the scaffold was hardened by data mining and pharmacophore query exercise in the CDC and PDB. The obtained scaffold, as well as the structural analysis provided is a useful addition in the area of fused nitrogen-containing heterocycles with potential applications in drug design and medicinal chemistry. A clear understanding of binding patterns and structural features is highly beneficial in addressing novel drug targets and this is the main advantage of combining computational tools and data mining analysis with fast and straightforward synthetic routes. Further studies on improving the physicochemical properties of the compounds in order to be screened against certain targets will be reported in due course.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental Details, general procedures, characterization data ($^1\text{H-NMR}$, $^{13}\text{C-NMR}$, HRMS), single X-ray details, data mining in CSD and pharmacophore search with Crossminer (PDF file).

Deposition Number 1986084 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgments

This research has been supported (to AD) through ITN "Accelerated Early stage drug dIScovery" (AEGIS, grant agreement No 675555). Moreover, funding was received by the National Institute of Health (NIH) (2R01GM097082-05), the European Lead Factory (IMI) (grant agreement number 115489), the Qatar National Research Foundation (NPRP6-065-3-012) and COFUNDs ALERT (grant agreement No 665250), Prominent (grant agreement No 754425) and KWF Kankerbestrijding grant (grant agreement No 10504). K.K and J.K-T. acknowledge the financial support of the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08) for equipment purchase.

Keywords: Diaminoimidazopyrimidines · Heterocycles · Multicomponent reactions · GBB · Data mining

- [1] A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.
- [2] A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083–3135.
- [3] C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80.
- [4] E. Ruijter, R. V. A. Orru, *Drug Discovery Today Technol.* **2013**, *10*, e15–e20.
- [5] T. Zarganes-Tzitzikas, A. L. Chandgude, A. Dömling, *Chem. Rec.* **2015**, *15*, 981–996.
- [6] T. Zarganes-Tzitzikas, A. Dömling, *Org. Chem. Front.* **2014**, *1*, 834–837.
- [7] H. Bienaymé, K. Bouzid, *Angew. Chem. Int. Ed.* **1998**, *37*, 2234–2237; *Angew. Chem.* **1998**, *110*, 2349.
- [8] K. Groebke, L. Weber, F. Mehlin, *Synlett* **1998**, *6*, 661–663.
- [9] C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.* **1998**, *39*, 3635–3638.
- [10] A. Boltjes, A. Dömling, *Eur. J. Org. Chem.* **2019**, *2019*, 7007–7049.
- [11] N. Devi, D. Singh, R. K. Rawal, J. Bariwal, V. Singh, *Curr. Top. Med. Chem.* **2016**, *16*, 2963–2994.
- [12] C. G. Neochoritis, S. Stotani, B. Mishra, A. Dömling, *Org. Lett.* **2015**, *17*, 2002–2005.
- [13] C. G. Neochoritis, S. Shaabani, M. Ahmadianmoghaddam, T. Zarganes-Tzitzikas, L. Gao, M. Novotná, T. Mitriková, A. R. Romero, M. I. Irianti, R. Xu, et al., *Sci. Adv.* **2019**, *5*, eaaw4607.
- [14] C. Neochoritis, J. Zhang, A. Dömling, *Synthesis* **2015**, *47*, 2407–2413.
- [15] R. Roskoski, *Pharmacol. Res.* **2016**, *103*, 26–48.
- [16] I. C. Waizenegger, A. Baum, S. Steurer, H. Stadtmüller, G. Bader, O. Schaaf, P. Garin-Chesa, A. Schlattl, N. Schweifer, C. Haslinger, et al., *Mol. Cancer Ther.* **2016**, *15*, 354–365.
- [17] A. T. Shaw, L. Friboulet, I. Leshchiner, J. F. Gainor, S. Bergqvist, A. Brooun, B. J. Burke, Y.-L. Deng, W. Liu, L. Dardaei, et al., *N. Engl. J. Med.* **2016**, *374*, 54–61.
- [18] D. Marcotte, M. Rushe, R. M. Arduini, C. Lukacs, K. Atkins, X. Sun, K. Little, M. Cullivan, M. Paramasivam, T. A. Patterson, *Protein Sci.* **2017**, *26*, 152–162.
- [19] A. T. Bender, A. Gardberg, A. Pereira, T. Johnson, Y. Wu, R. Grenningloh, J. Head, F. Morandi, P. Haselmayer, L. Liu-Bujalski, *Mol. Pharmacol.* **2017**, *91*, 208–219.
- [20] J. N. Champness, M. S. Bennett, F. Wien, R. Visse, W. C. Summers, P. Herdewijn, E. de Clercq, T. Ostrowski, R. L. Jarvest, M. R. Sanderson, *Proteins Struct., Funct., Genet.* **1998**, *32*, 350–361.
- [21] R. Li, R. Sirawaraporn, P. Chitnumsub, W. Sirawaraporn, J. Wooden, F. Athappilly, S. Turley, W. G. Hol, *J. Mol. Biol.* **2000**, *295*, 307–323.
- [22] O. Ghashghaei, S. Caputo, M. Sintes, M. Revés, N. Kielland, C. Estarellas, F. J. Luque, A. Aviñó, R. Eritja, A. Serna-Gallego, et al., *Chem. Eur. J.* **2018**, *24*, 14513–14521.
- [23] A. Jonczyk, D. Dorsch, F. Zenke, C. Amendt, **2011**, WO2011/101069, A2.
- [24] C. R. Groom, I. J. Bruno, M. P. Lightfoot, S. C. Ward, *Acta Crystallogr., Sect. B Struct. Sci. Cryst. Eng. Mater.* **2016**, *72*, 171–179.
- [25] B. Kuhn, P. Mohr, M. Stahl, *J. Med. Chem.* **2010**, *53*, 2601–2611.
- [26] S. K. Burley, H. M. Berman, C. Bhikadiya, C. Bi, L. Chen, L. Di Costanzo, C. Christie, K. Dalenberg, J. M. Duarte, S. Dutta, et al., *Nucleic Acids Res.* **2019**, *47*, D464–D474.
- [27] O. Korb, B. Kuhn, J. Hert, N. Taylor, J. Cole, C. Groom, M. Stahl, *J. Med. Chem.* **2016**, *59*, 4257–4266.
- [28] P. Dübon, M. Schelwies, G. Helmchen, *Chem. Eur. J.* **2008**, *14*, 6722–6733.
- [29] J. Ren, M. Yang, H. Liu, D. Cao, D. Chen, J. Li, L. Tang, J. He, Y.-L. Chen, M. Geng, B. Xiong, J. Shen, *Org. Biomol. Chem.* **2015**, *13*, 1531–1535.
- [30] H.-J. Böhm, A. Flohr, M. Stahl, *Drug Discovery Today Technol.* **2004**, *1*, 217–224.

Received: July 6, 2020