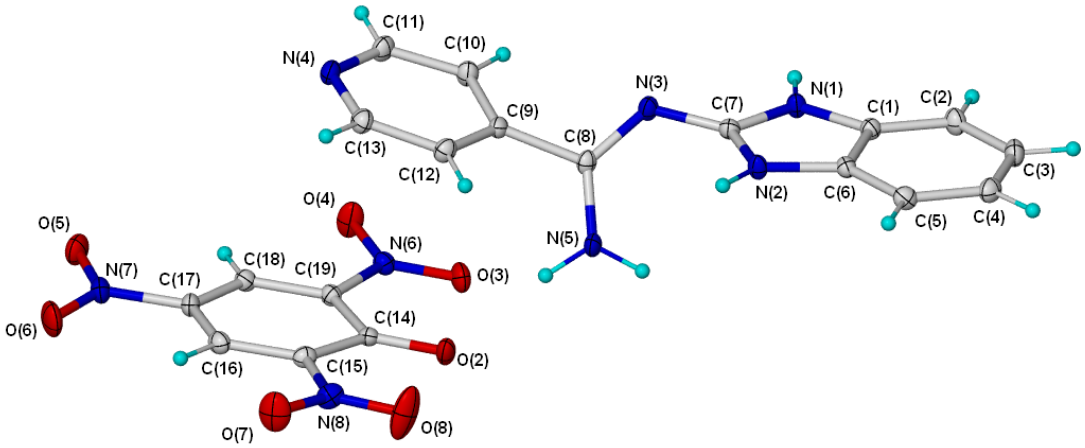
(*Z*)-*N*'-(1*H*-benzo[*d*]imidazol-2-yl)-arylimidamide adducts of 2-aminobenzimidazole and aromatic nitriles: Structural and spectroscopic proof of regiochemical and stereochemical outcomes.

Martin J. Stoermer[1*], Simon Egan[2], Craig M. Forsyth[3], and Gerard P. Moloney[2]

[1] Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, The University of Queensland, St. Lucia, 4072, Queensland, Australia; [2]Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University (now Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville Victoria, 3052, Australia. [3]School of Chemistry, Monash University Clayton Victoria 3800, Australia.

*Corresponding author
Dr. Martin J. Stoermer
Division of Chemistry and Structural Biology, Institute for Molecular Bioscience
University of Queensland
Brisbane, Queensland 4072, Australia
E-mail: martin.stoermer@uq.edu.au
Twitter: @MartinStoermer

Abstract



The selection of a core scaffold or template is of enormous importance in medicinal chemistry. Benzimidazoles are a recurring fragment in medicinal chemistry, and the 2-amino derivative is a versatile example in lead generation. Alkylated and acylated examples abound, however, alternative linkage chemistries leading do more diverse structures are needed. Here we discuss the regiochemistry of nucleophilic addition of 2-aminobenzimidazole to nitriles, leading to imidamide (amidine) adducts. Additionally, we use extensive NMR analysis and ultimately X-ray crystallography to demonstrate both the regiochemistry and stereochemistry of the addition products, arising from derivatisation of the exocylic 2-amino group.

Keywords: aminobenzimidazole, nucleophilic addition, X-ray crystallography, regiochemistry, imidamide.

Introduction

Benzimidazoles are common fragments and scaffolds found in drug discovery and development programs and in several marketed drugs including omeprazole, telmisartan, and albendazole. Their combination of synthetic tractability, hydrophobic B ring and heterocyclic A ring containing up to 3 attachment points for elaboration into drug-like molecules make benzimidazoles attractive synthons for medicinal chemistry (Figure 1). The 2-amino derivative (**1**) is similarly frequently found in the medicinal chemistry literature as a starting material or scaffold with the additional virtue of being a low-basicity guanidine mimetic[1] with a pKa some 5 log units lower than a free guanidine group such as that found in the amino acid arginine.

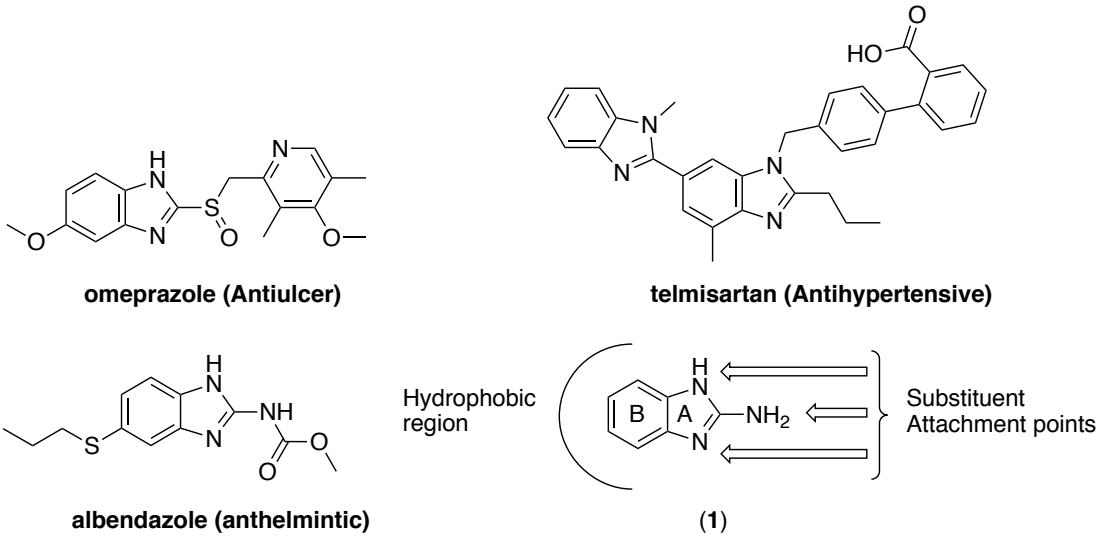


Figure 1. Marketed drugs containing benzimidazoles and 2-aminobenzimidazole (**1**), a scaffold for medicinal chemistry

As mentioned above, 2-aminobenzimidazole (**1**) can in principal be used as a scaffold for the attachment of up to 3 substituents, based upon relatively straightforward alkylation and acylation chemistries at both ring nitrogen atoms and the exocyclic amine. The general trends of this reactivity have been examined in some detail and reviewed in journals[2] and monographs[3]. Interestingly much of the literature dates from the pre-NMR era and relied on infra-red spectroscopy for confirmation of the regiochemical outcomes. Later work unequivocally confirmed the regiochemistry of initial alkylation or acylation reactivity by using small-molecule crystal structure determination (see Table S1, Supporting Information for examples). Sometimes additional crystallographic evidence is obtained where the lead or drug candidate has been co-crystallised in complex with its biological target, e.g. for HIV-1 protease[4] (Figure 2) and IRAK-4 kinase[5], although in the latter case the compounds were prepared by alternative routes to avoid structural ambiguity.

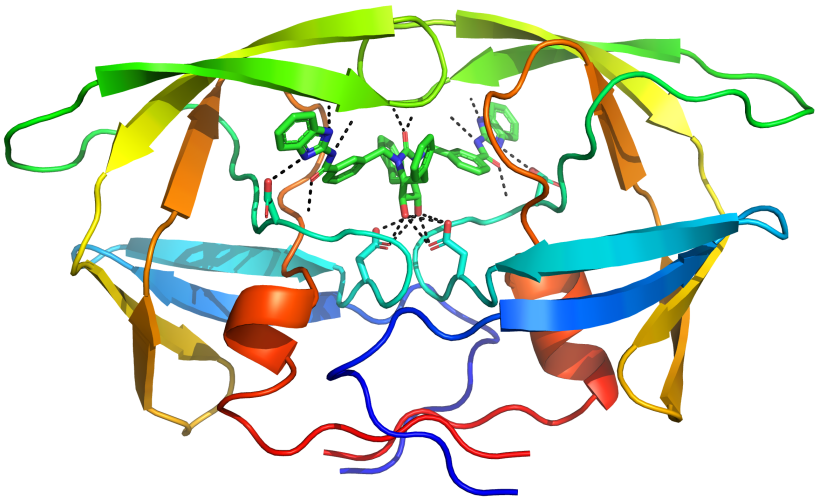


Figure 2. 2-aminobenzimidazole-containing inhibitor SD146 bound to HIV protease[4] (PDB code 1QBT). Inhibitor and hydrogen-bonded aspartate residues shown in stick format. Hydrogen bonds displayed as dashed lines. Figure prepared using Pymol (www.schrodinger.com).

In brief alkylation occurs first on one endocyclic nitrogen to produce compounds of general structure (**2**) (Figure 3). A subsequent second alkylation step generally produces the 1,3-disubstituted compounds (**3**)[3a]. If the second reaction is an acylation then the products obtained (**4**) have the 1,2-regiochemistry[3b]. If the initial reaction is an acylation then initially the most electrophilic endocyclic nitrogen N(3) reacts with the acylating agent to produce benzimidazolinium intermediates of type (**5**) which undergo an acyl migration to produce the 2-acylamino compounds (**6**)[6].

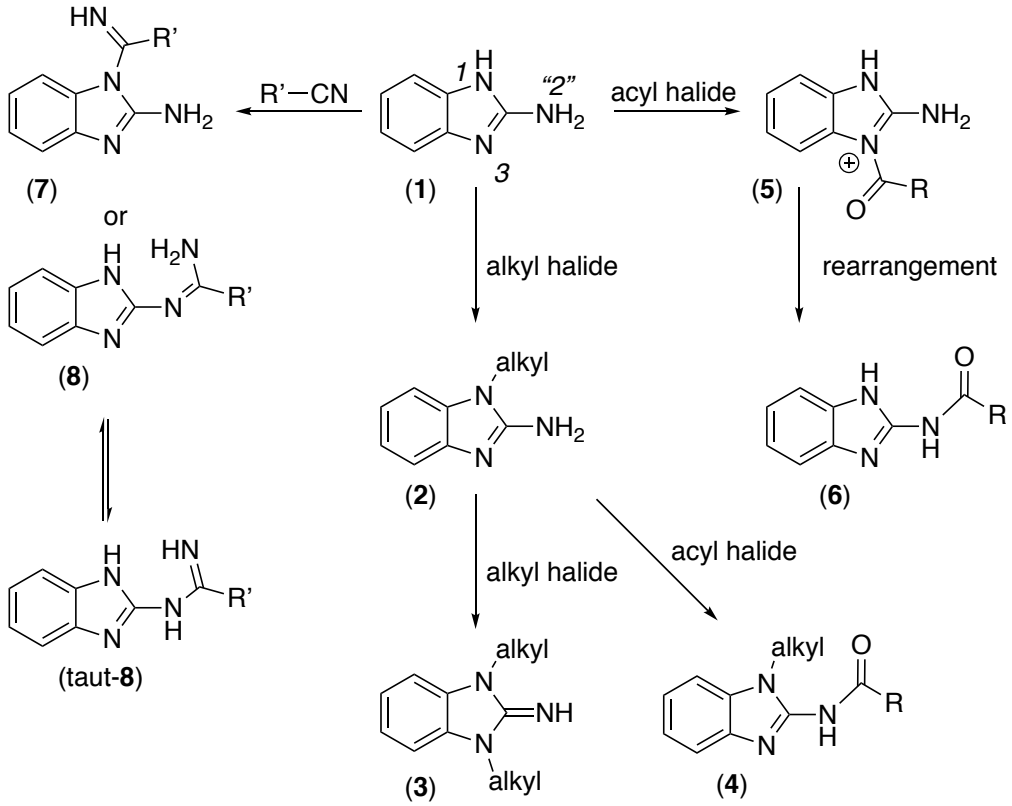
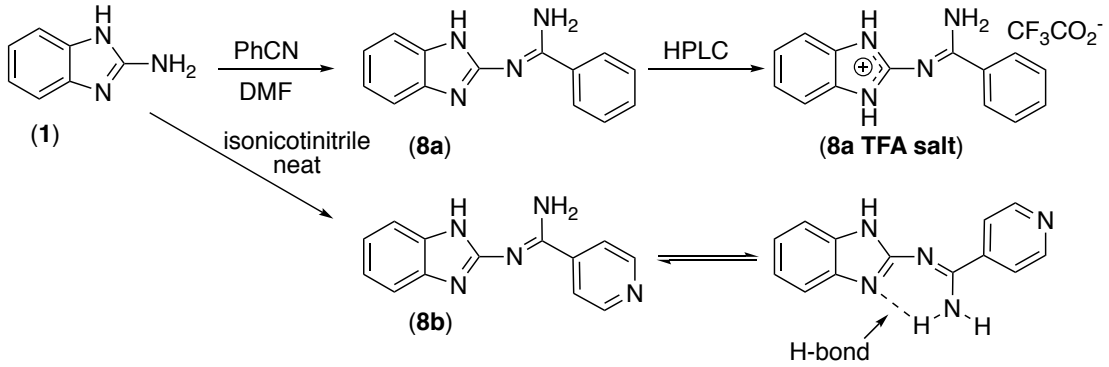


Figure 3. Regiochemical outcomes of alkylation/acylation of 2-aminobenzimidazole

We were interested in using alternative methodologies to simple acylation and alkylation, thus broadening the range of linkage methods available to the medicinal chemist. In this study we wished to produce imidamide (amidine) analogues (**7** or **8**) of compounds such as (**4**) and (**6**). These products are isosteric with those produced by acylation, however have different hydrogen bonding capabilities. For example, replacing (**6**) with (**8**) adds an additional hydrogen bond donor, and depending on the tautomeric state, relocates a hydrogen bond acceptor. For more information on the effects of these changes on physiochemical properties such as octanol/water partition coefficient (LogP), and polar surface area (PSA) see the Supporting Information. The amidine products could be conceptually derived most simply by thermal or acid-catalysed addition of (**1**) to nitriles. There are few literature examples[7,8] of such compounds, which have been proposed to react at N2 giving (**taut-8**), a tautomer of (**8**). Of concern to us however was the lack of any structural or conclusive spectroscopic evidence for this tautomeric, regiochemical or stereochemical outcome. The NMR spectra provided in the two publications for the single compound (**8a**, R'=Ph) were somewhat contradictory and the regiochemistry of addition was implied from the products obtained after subsequent reactions steps, often under harsh oxidative or heating conditions which may have promoted rearrangement.

Results and Discussion

In our hands the previous report[7] using tin(IV) chloride catalysis suffered from extensive hydrolysis of the desired product (**8a**) to the simple benzoyl derivative. We therefore chose initially to prepare compounds derived from 2-aminobenzimidazole (**1**) and benzonitrile and isonicotinitrile by simple thermal addition in the absence of tin (IV) catalyst thus avoiding the harsh alkaline workup (Scheme 1). The reactions proceeded smoothly albeit in moderate yields both in solution (**8a**) and the melt (**8b**).



Scheme 1. Preparation of aromatic nitrile adducts with 2-aminobenzimidazole

Compounds such as (**8**) are complex organic bases, consisting of a heterocyclic guanidine fused to a benzamidine moiety. We were particularly interested to study the regiochemistry of protonation of compounds (**8**) and the effect of this upon imine-amine tautomerism that has previously been studied for acylation products (**6**)[9]. Accordingly, the simple benzonitrile product (**8a**) was most conveniently purified by HPLC in acidic medium yielding the product as a TFA salt. Analysis of the resultant ^{1}H and ^{13}C NMR spectra clearly indicated the presence of symmetry on both the benzimidazole and phenyl rings as only 5 aromatic CH signals and 4 quaternary carbons were observed, whereas in the neutral adduct (**8b**), asymmetry in the benzimidazole ring resulted in 6 aromatic CH and 5 quaternary carbons being observed. In addition, the neutral adduct (**8b**) was also analysed by natural abundance

^{15}N NMR (HSQC/HMBC/DEPT) spectroscopy which clearly indicated that the two NH protons at 10.47 and 8.86 ppm were attached to the same nitrogen atom (at 102.4 ppm). The difference in chemical shift of these two NH protons is likely attributable to the presence of an internal hydrogen bond for one NH to N3 of the benzimidazole scaffold (Scheme 1). This strongly implied that the addition products were obtained with the *Z*-geometry about the amidine double bond. Macromodel analysis of the possible *E*- and *Z*-isomers (Supporting Information) strongly supported the NMR observation of the stabilising intramolecular hydrogen bond for the *Z*-isomers, whereas in the *E*-isomers this hydrogen bond is absent and the additional steric clash of the phenyl or pyridyl rings results in an out of plane twist in the structures. This also has significant effects on the molecular volume and polar surface area. A similarly downfield shifted NH had been reported for a neutral form of (**8a**) without comment[7]. These results strongly support the amidation reaction occurring at the exocyclic NH_2 group, analogous to acylation chemistry[3b], although here also an intermediate N(3) benzimidazolinium species followed by rearrangement to (**8**) cannot be ruled out. Further compounds (**8c-e**) were prepared, purified and characterised in the same manner as (**8a**), albeit in lower yields (Figure 4). Analogues (**8c-e**) were all found by NMR to possess the same symmetry in the benzimidazole ring, indicating uniform initial protonating on the N3 nitrogen.

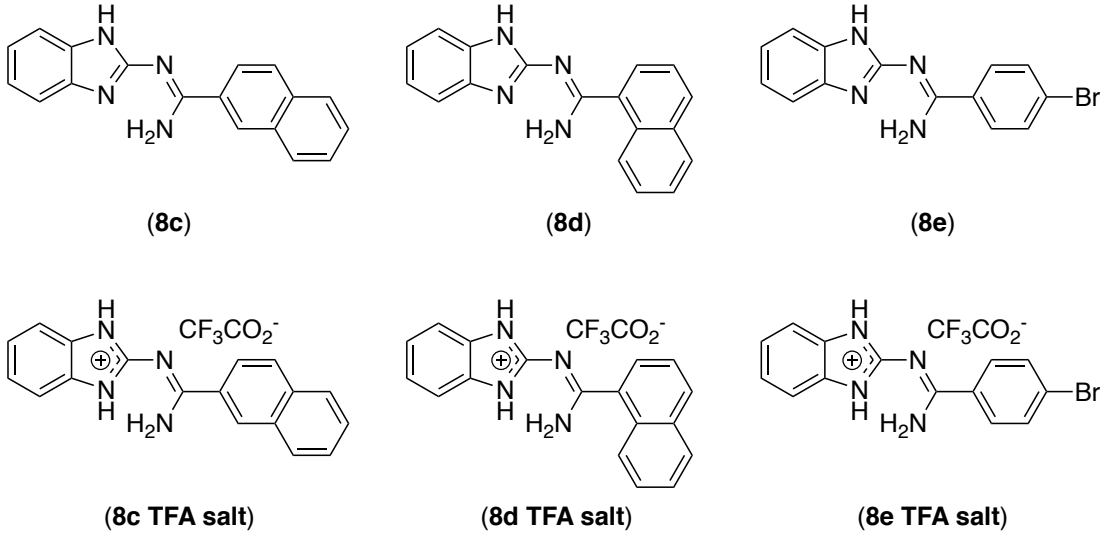


Figure 4. Further arylimidamide adducts (**8c-e**) of 2-aminobenzimidazole prepared in this work as their TFA salts.

As ultimate proof for the regiochemistry of addition and protonation states for adducts of type (**8**), we undertook a small molecule crystal structure analysis of (**8b**), prepared as the picrate salt[10]. As well as confirming the regiochemistry of addition, the X-ray structure also showed that the amidine double bond was in the *Z*-configuration. The picrate ring is involved in an offset π-π interaction with the B ring of two benzimidazole moieties. Near symmetry in the benzimidazole B ring is revealed as both nitrogen atoms are protonated, and all the ring bond lengths with the exception of the two A ring benzimidazole C-N bonds (0.011Å) are all within 0.006Å of the symmetrical pair. One of these is involved in a hydrogen bond with the 2-nitro group of the picrate molecule (H-O distances 2.013, 2.545Å), whilst the one proton from the amidino NH_2 group is hydrogen bonded (H-O distances 2.059Å) to the picrate phenoxide oxygen (Figure 5). The amidino group itself displays evidence of

delocalisation. Whilst the tautomer with two hydrogens on one nitrogen appears preferred, the two C-N bonds are of similar length (1.320, 1.316Å), and the N(3)-C(8)-N(5) group is out of plane with the pyridine ring.

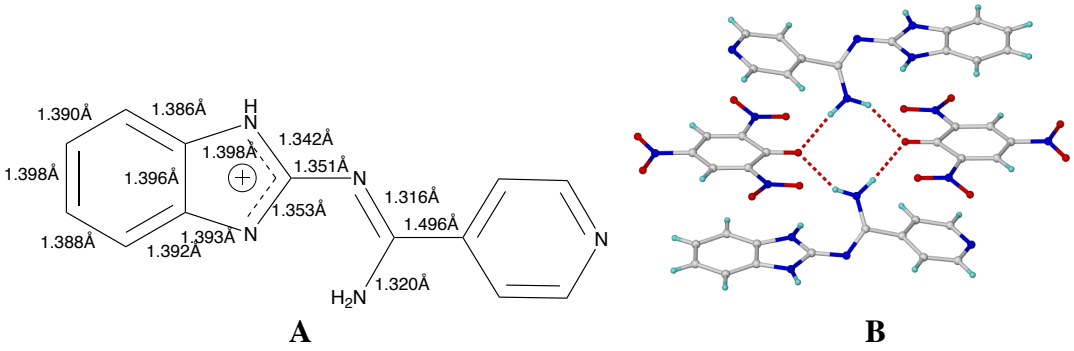


Figure 5. Crystal structure of (**8b**), picrate salt[10]. A: Bond lengths observed for the imidamide in the crystal structure. B: Hydrogen bonds (red dotted lines) between amidine NH_2 group and picrate phenoxide anion.

Conclusion

Thermal addition of 2-aminobenzimidazole to aromatic nitriles gives products analogous to acylation reactions, with substitution occurring on the exocyclic NH_2 group. The products are obtained in the *Z*-configuration about the amidine double bond. Initial protonation of these complex fused guanidine-amidine products occurs on the benzimidazole.

References

1a. Peyman, A.; Gourvest, J.-F.; Gadek, T. R.; Knolle, J., Vitronectin Receptor Antagonists: Purine-Based Peptidomimetics. *Angew. Chem.* **2000,** *112* (16), 2996-2999. DOI:10.1002/1521-3757(20000818)112:16<2996::AID-ANGE2996>3.0.CO;2-H.

1b. Zechel, C.; Backfisch, G.; Delzer, J.; Geneste, H.; Graef, C.; Hornberger, W.; Kling, A.; Lange, U. E.; Lauterbach, A.; Seitz, W.; Subkowski, T., Highly potent and selective alphaVbeta3-receptor antagonists: solid-phase synthesis and SAR of 1-substituted 4-amino-1H-pyrimidin-2-ones. *Biorg. Med. Chem. Lett.* **2003,** *13* (2), 165-169. DOI:10.1016/S0960-894X(02)00931-9.

1c. Scheffer, U.; Strick, A.; Ludwig, V.; Peter, S.; Kalden, E.; Göbel, M. W., Metal-Free Catalysts for the Hydrolysis of RNA Derived from Guanidines, 2-Aminopyridines, and 2-Aminobenzimidazoles. *J. Am. Chem. Soc.* **2005,** *127* (7), 2211-2217. DOI:10.1021/ja0443934.

2. Rastogi, R.; Sharma, S., 2-Aminobenzimidazoles in Organic Syntheses. *Synthesis* **1983,** *1983* (11), 861-882. DOI: 10.1055/s-1983-30546

3. Katritzky, A. R.; Rees, C. W., *Comprehensive heterocyclic chemistry : the structure, reactions, synthesis and uses of heterocyclic compounds*. Oxford

New York, Sydney : Pergamon Press: 1984. a) pp382-383, b) pp 438-439. DOI:10.1016/c2009-0-15932-9.

4. Jadhav, P. K.; Ala, P.; Woerner, F. J.; Chang, C.-H.; Garber, S. S.; Anton, E. D.; Bacheler, L. T., Cyclic Urea Amides: HIV-1 Protease Inhibitors with Low Nanomolar Potency against both Wild Type and Protease Inhibitor Resistant Mutants of HIV. *J. Med. Chem.* **1997,** *40* (2), 181-191. DOI: 10.1021/jm960586t

5a. Powers, J. P.; Li, S.; Jaen, J. C.; Liu, J.; Walker, N. P. C.; Wang, Z.; Wesche, H., Discovery and initial SAR of inhibitors of interleukin-1 receptor-associated kinase-4. *Bioorg. Med. Chem. Lett.* **2006,** *16* (11), 2842-2845. DOI: 10.1016/j.bmcl.2006.03.020

5b. Wang, Z.; Liu, J.; Sudom, A.; Ayres, M.; Li, S.; Wesche, H.; Powers, J. P.; Walker, N. P., Crystal structures of IRAK-4 kinase in complex with inhibitors: a serine/threonine kinase with tyrosine as a gatekeeper. *Structure* **2006,** *14* (12), 1835-44. DOI: 10.1016/j.str.2006.11.001

6. Khristich, B. I.; Suvorova, G. M.; Simonov, A. M. Benzimidazole derivatives. XXXII. Synthesis ad transformations of 2-amino-3-acyl-1-methylbenzimidazolium. *Khim. Geterotsikl. Soedin.* **1974**, *10*, 1398-401.

7. Reddy, B. S.; Sambaiah, T.; Reddy, K. K., A facile synthesis of 2-aryl[1,2,4]triazolo[1,5-a]benzimidazoles. *Indian J. Chem., Sect. B* **1992,** *31B* (3), 191-192.

8. Reddy, B. S.; Sambaiah, T.; Reddy, K. K., A convenient approach to the synthesis of 2-aryl-4-alkyl-1,3,5-triazino[1,2-a]benzimidazoles. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1998,** *37B* (12), 1283-1285.

9. Gründemann, E.; Graubaum, H.; Martin, D.; Schiewald, E., NMR investigations on benzheteroazoles. 2—NMR investigations of N-acylated 2-aminobenzimidazoles. *Magn. Reson. Chem.* **1986,** *24* (1), 21-30.

10. Crystallographic data for compound (**8b**) have been deposited at the Cambridge Crystallographic Data Centre (Accession code 1891428). These data can be obtained free of charge from the CCDC.