Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5129

www.rsc.org/obc

PAPER

Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors *via* one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence†‡

Eugen Merkul,[a] Fabian Klukas,[a] Dieter Dorsch,[b] Ulrich Grädler,[b] Hartmut E. Greiner[b] and Thomas J. J. Müller*[a]

Received 12th April 2011, Accepted 13th May 2011
DOI: 10.1039/c1ob05586k

The one-pot, three-component Sonogashira coupling–TMS-deprotection–CuAAC ("click") sequence is the key reaction for the rapid synthesis of triazolyl substituted *N*-Boc protected NH-heterocycles, such as indole, indazole, 4-, 5-, 6-, and 7-azaindoles, 4,7-diazaindole, 7-deazapurines, pyrrole, pyrazole, and imidazole. Subsequently, the protective group was readily removed to give the corresponding triazolyl derivatives of these tremendously important NH-heterocycles. All compounds have been tested in a broad panel of kinase assays. Several compounds, **8f**, **8h**, **8k**, and **8l**, have been shown to inhibit the kinase PDK1, a target with high oncology relevance, and thus they are promising lead structures for the development of more active derivatives. The X-ray structure analysis of compound **8f** in complex with PDK1 has revealed the detailed binding mode of the molecule in the kinase.

Introduction

Indoles represent one of the most prominent privileged structures[1] because they are widespread in nature[2] and pharmaceutically relevant compounds.[3] Among them, indoles bearing 5- and 6-membered heterocycles as substituents in the 3-position represent a conspicuously frequently occurring substitution pattern. In particular, the heterocyclic ring found in natural products or their bioactive analogues can be pyrimidine (meridianins,[4] hyrtinadine A[5]), tetrahydropyrimidine (aplicyanins[6]), piperazine and (dihydro)pyrazine (dragmacidins,[7] hamacanthins[8]), oxazinone (oxazinins[9]), oxadiazinone (alboinon[10]), imidazole (nortopsentins,[11] topsentins[12]), imidazolone,[13,14] oxazole (diazonamides,[15] martefragin A,[16] almazoles,[17] pimprinine,[18] and labradorins[19]), thiazole (camalexins,[20] BE-10988[21]), imidazoline (spongotines,[22] discodermindoles,[23] trachycladindoles[24]), oxazoline,[25] maleimide (didemnimides[26]), isoquinolinequinone (mensouramycin D[27]), β-carboline (eudistomin U,[28] hyrtioerectine A[29]), pyrrole (chromopyrrolic acid,[30] lynamicins[31]), pyrrolinone (violacein[32]), or another indole.[33] Besides indoles, their aza analogues, *i.e.* indazole and azaindoles, apparently play an increasingly important role as scaffolds for biologically active molecules.[34] In particular, 7-azaindoles are predestined to be promising scaffolds for investigations as kinase inhibitors due to their pronounced ability to bind to the hinge region of kinases.[35] Again, heterocyclic substituents at the C-3 position are very common. The most prominent examples are the marine natural products variolins[36] and the simplified synthetic analogues of variolin B, *i.e.* the meriolins[37] (Fig. 1).

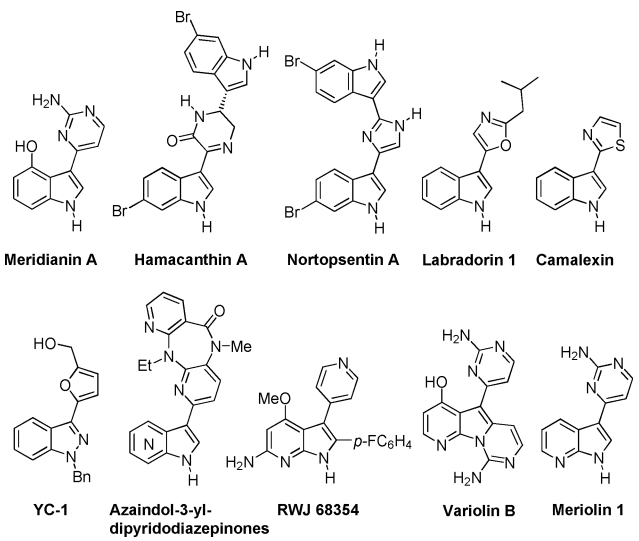


Fig. 1 Biologically active (aza)indoles with 5- and 6-membered heterocycles at C-3 (corresponds to C-5 in variolin B).

Recently, we reported a practical approach to indoles and 7-azaindoles substituted with azines *via* a one-pot Masuda borylation–Suzuki coupling sequence.[38] Using this approach,

[a]*Lehrstuhl für Organische Chemie, Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, D-40225, Düsseldorf, Germany. E-mail: ThomasJJ.Mueller@uni-duesseldorf.de; Fax: ++49 (0)211 8114324; Tel: ++49 (0)211 8112298*
[b]*Merck Serono Research & Development, Merck KGaA, D-64271, Darmstadt, Germany*

† Dedicated to Prof. K. Barry Sharpless on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: experimental procedures and analytical data of compounds **1a–l**, **1n**, **8a–s**, **9a–b**, **10**, and **11**. See DOI: 10.1039/c1ob05586k

concise total syntheses of meridianins A and G could be realized. Previously, we synthesized some members of the meridianin family and a 7-azaindole analogue of variolin B (later called meriolin 1),[37] using a carbonylative Sonogashira coupling as a key step.[39] In these compounds, as well as in variolin B, the key structural feature responsible for the observed biological activity is the 2-aminopyrimidine ring at C-3, even though meridianins, meriolins, and variolins bind differently to the hinge region of kinases.[37,40] Notably, isomeridianins,[41] possessing the 2-aminopyrimidine moiety at C-2, and variolin D, lacking a heterocycle substituent at C-5, are not biologically active.

Surprisingly, triazolyl substituted indoles have hardly been explored,[42] although the 1,2,3-triazole ring as an electron-poor metabolically stable[43] 5-membered heterocyclic substituent has attracted considerable attention in bioconjugate chemistry, medicinal chemistry, and drug discovery.[44] In addition to its function as a convenient linker,[45] 1,4-disubstituted 1,2,3-triazole is a peptidomimetic,[46] has a large dipole moment and is an H-acceptor over N-2 and N-3 atoms. Here, we report a diversity-oriented synthetic concept to access 3-triazolyl-substituted (aza)indole scaffolds in a one-pot fashion. In addition, the potential of the title compounds as kinase inhibitors[47,48] and cytostatics is explored.

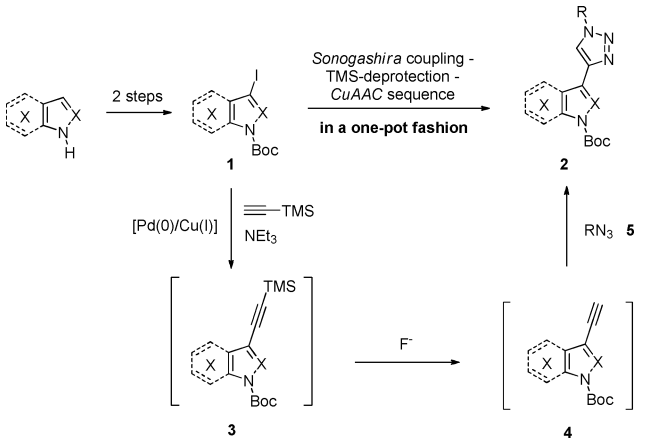
Results and discussion

The Sonogashira coupling–TMS-deprotection–CuAAC sequence

The Sonogashira–Hagihara cross-coupling[49] is among the most reliable C–C bond forming reactions and has become the method of choice for the construction of internal alkynes from (hetero)aryl halides and terminal alkynes.[50] Upon coupling halides with trimethylsilylacetylene (TMSA), TMS-protected alkynes are formed, which can be easily deprotected to give (hetero)aromatic terminal alkynes.[51] The latter are perfectly suited for the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[52,53] the most remarkable Cu(I)-catalyzed process developed in the last decade. The transformation belongs to click-type reactions,[54] which proceed with a high degree of atom economy.[55] This process is also very reliable, mild, general, and highly tolerant to diverse functional groups. All these features render this reaction highly practical.[56] In the past, many efforts have been made to develop one-pot methodologies based upon the *in situ* generation of the azide component,[57] the *in situ* utilization of TMS-acetylenes,[58] or the direct sequential Cu(I)-catalyzed C–H-bond arylation of the obtained triazoles.[59] Surprisingly, only little attention has been paid to the *in situ* construction of terminal alkynes.[60]

As a continuation of our program directed to develop new one-pot multi-component reactions initiated by metal-catalyzed cross-coupling as an entry for the synthesis of heterocycles[61,62] we envisioned the possibility of performing Sonogashira coupling and CuAAC in a one-pot fashion. Coupling of *N*-Boc protected 3-iodo NH-heterocycles **1** with TMSA would furnish the intermediate TMS-protected heterocyclic alkynes **3**, which after *in situ* deprotection would give terminal alkynes **4**, the starting material to accomplish CuAAC with an azide **5**, resulting in another Cu(I)-catalyzed reaction. It was hoped the strategy would give direct access to triazoles **2** in the sense of sequential catalysis (Scheme 1).

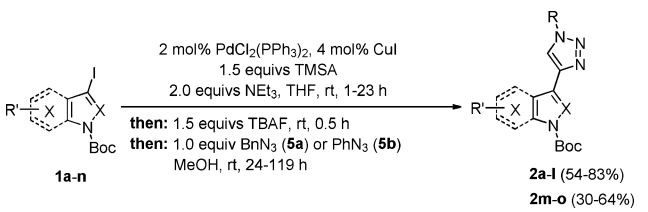
Boc (*tert*-butoxycarbonyl) is one of the cheapest and most frequently used nitrogen protective groups.[63] Either it can be



Scheme 1 Synthetic concept for triazolyl *N*-Boc protected heterocycles (X = CH or N; R = alkyl or aryl, may be generated *in situ*).

easily introduced on the nitrogen atoms of 5-membered NH-heterocycles[64] or it can be installed directly in the course of their synthesis.[65,66] If not further required, this group can be removed easily and cleanly under various conditions.[67] Previously, we have demonstrated the enormous utility and versatility of 3-iodo *N*-Boc protected indoles, 7-azaindoles, and pyrroles as easily accessible synthetic building blocks.[38,39,66]

The Sonogashira coupling of iodo *N*-Boc NH-heterocycles[68] **1** with TMSA proceeded smoothly under standard Sonogashira conditions ($PdCl_2(PPh_3)_2/CuI/NEt_3$).[69] The obtained TMS-alkynes were not isolated but directly deprotected with TBAF and subsequently reacted with one equivalent of the commercially available and stable benzyl azide (**5a**) to furnish *N*-Boc 3-triazolyl (aza)indoles **2a–l** and azoles **2m–o** in a one-pot fashion (Scheme 2). The yields were very similar for (aza)indoles and pyrrole regardless of the number and position of nitrogen atoms.

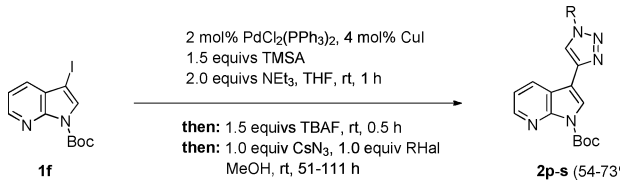


Scheme 2 Sonogashira coupling–TMS-deprotection–CuAAC sequence for the synthesis of *N*-Boc 3-triazolyl (aza)indoles **2a–l** and azoles **2m–o** (X = CH or N; R = Bn, Ph; R′ = Me, OMe, $O(CH_2)_2OMe$, *p*-$MeOC_6H_4$).

No further addition of CuI was required in the CuAAC step. The reaction progress can be conveniently monitored by TLC and the steps cleanly proceed as "spot-to-spot" reactions without noticeable amounts of byproducts. No Glaser-type homodimerization products[70] were detected because the CuAAC reaction was performed under an argon atmosphere. It is worth mentioning that the electron-withdrawing Boc protective group renders the (aza)indolyl iodides **1** stable to storage,[71] whereas the unprotected iodides are frequently sensitive to light and temperature and therefore inconvenient to handle.[72] Moreover, the Sonogashira coupling is greatly facilitated, or even becomes feasible, due to the diminished electron density of these heterocycles.

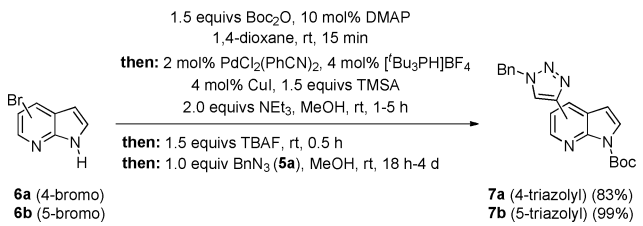
For the synthesis of triazoles with different substituents on the N-1 atom of the triazole moiety, the sequence was extended

to a four-component reaction with *N*-Boc protected 3-iodo 7-azaindole (**1f**) as a substrate. This sequence additionally includes the *in situ* generation of the azide **5** *via* nucleophilic substitution of a halide with caesium azide (Scheme 3). Hence, not only electronically diverse benzyl substituents (**2p** and **2q**), and even α-phenylethyl substituents (**2s**), but also the homobenzyl group can be introduced with a comparable yield (**2r**).



Scheme 3 Four-component Sonogashira coupling–TMS-deprotection–Finkelstein-type reaction–CuAAC sequence for the synthesis of *N*-Boc protected triazolyl 7-azaindoles **2p–s** (R = alkyl; Hal = Br, Cl).

For 4- and 5-bromo 7-azaindoles (**6a** and **6b**), which are commercially available and stable compounds, a four-component Boc-protection–Sonogashira coupling–TMS-deprotection–CuAAC sequence was developed to give *N*-Boc protected 4- and 5-triazolyl azaindoles (**7a** and **7b**) in very good yields (Scheme 4). The Sonogashira coupling was performed at room temperature using Fu's catalytic system.[73]

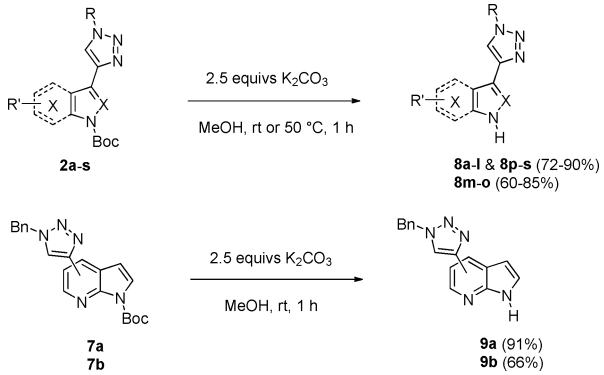


Scheme 4 Boc-protection–Sonogashira coupling–TMS-deprotection–CuAAC sequence for the synthesis of *N*-Boc 4- and 5-triazolyl 7-azaindoles **7a** and **7b**.

The possibility to easily adopt the whole synthesis to a specific substrate and a flexible incorporation of additional steps into the sequence is an additional advantage of this one-pot methodology.

The obtained *N*-Boc protected triazolyl NH-heterocycles **2** and **7** were readily deprotected under extremely mild conditions using potassium carbonate in methanol at room temperature or slightly above (Scheme 5). It should be mentioned that although the Boc protective group could be removed after the completed sequence in a one-pot fashion, we preferred to perform the Boc-deprotection in a separate step to ensure the high purity of the final products **8** and **9** (as determined by HT-LC-MS analysis, the UV purity was 99.9–100% for all presented compounds). The content of Pd and Cu in compound **8f** was determined to be $< 1\ \mu g\ g^{-1}$ (< 3 ppm) and $< 2\ \mu g\ g^{-1}$ (< 9 ppm), respectively. Thus, no additional removal of these heavy metals is required.[74]

The scope of the presented methodology includes indole (**8a**) and its bioisosters[75] such as indazole (**8b**), all azaindoles (**8c–i**, **8p–s**, and **9**), diazaindole (**8j**), deazapurines (**8k–l**), as well as pyrrole (**8m**), pyrazole (**8n**), and imidazole (**8o**) (Fig. 2).



Scheme 5 Deprotection of *N*-Boc 3-triazolyl heterocycles **2** and **7** to 3-triazolyl NH-heterocycles **8** and **9** (X = CH or N; R = Me, OMe, $O(CH_2)_2OMe$, *p*-$MeOC_6H_4$; R′ = Ph, homobenzyl, Bn, or benzyl derivatives).

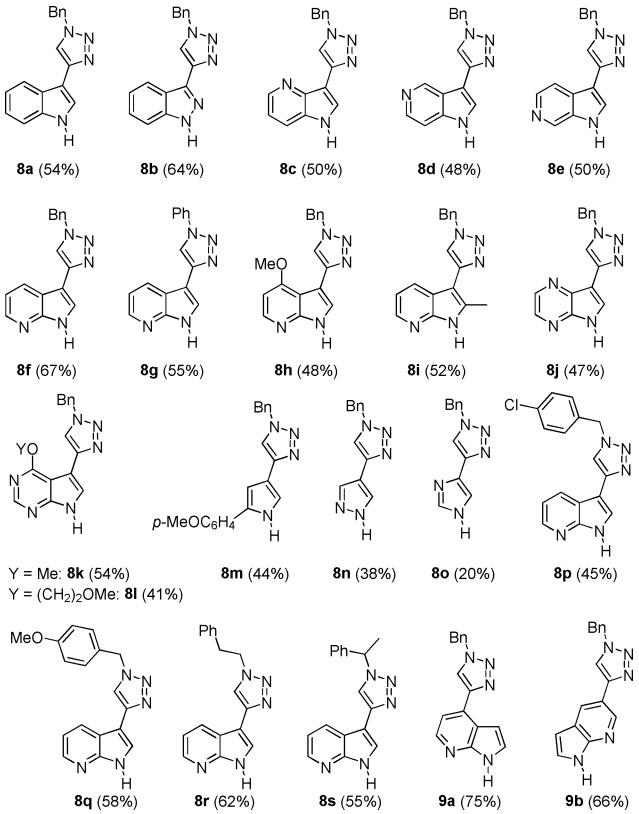


Fig. 2 Scope of the synthetic strategy towards triazolyl NH-heterocycles **8** and **9** (isolated yields over two steps).

The yields are fair to good and are very similar for all indole analogues **8a–l**. They are little affected by the position and number of additional nitrogen atoms, which is not self-evident (according to personal observations experienced with other coupling reactions of these substrates) and emphasizes the synthetic power gained from the combination of two very general methods, Sonogashira coupling and CuAAC. Only the azoles **8n** and **8o** gave poor yields due to the increased lability of the Boc protective group in the corresponding starting materials. Moreover, with *tert*-butyl 4-iodo-1*H*-imidazole-1-carboxylate (**1n**) the Sonogashira coupling proceeded very sluggishly and required

15 d reaction time. The structures of the obtained triazoles **8** and **9** were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis, and later by an X-ray structure analysis of compound **8f**, cocrystallized with kinase PDK1 (*vide infra*).

The sequences are very straightforward and preparatively extremely simple to perform. Generally, all steps proceed at room temperature, which is especially important if less stable azides are to be used. However, they can even be generated *in situ* with comparable efficiency. It should be noted that while these studies were in progress two reports appeared in the literature which described the same synthetic approach with simple aryl iodides.[76] However, we used this strategy to synthesize triazolyl NH-heterocycles, which are more sophisticated chemical targets and show promising biological activity, thus illustrating the synthetic utility of this practical synthesis. Since a variety of diverse NH-heterocycles, which are of paramount importance in many areas of research, can be decorated with triazoles in a very straightforward fashion, the sequence is quite general. Starting from these small lead structures, more potent derivatives can be readily developed using this synthetic approach.

Biological data

All compounds **8** and **9** were tested for inhibition of a broad panel of kinases at the Division of Signal Transduction Therapy (DSTT) at the University of Dundee, UK. The compounds were screened against 95–121 kinases at a concentration of 1 μM. In addition, for all compounds, IC_{50} values for the inhibition of the kinase PDK1, a target of high relevance for oncology,[77] were determined. The results for compounds that showed submicromolar activity on at least one kinase are summarized in Table 1.

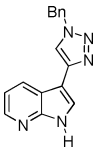
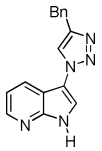
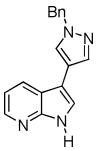
For the compounds described here, a hydrogen donor/acceptor pattern of the 7-azaindole core that can interact with the hinge region of kinases, is a prerequisite for kinase inhibitory activity. All compounds in this table possess such a pattern whereas the great majority of the inactive compounds **8a**, **8c**, **8d**, **8e**, **8m**, **8n**, and **8o**, lack this peculiar structural feature. In particular, compounds with a benzyltriazole group in the 3-position of a 7-azaindole-like template turned out to be broad kinase inhibitors with **8h**, **8k**, and **8l** having the broadest activity. In contrast, compounds **9a** and **9b**, which possess a benzyltriazole substituent at C-4 and C-5 of the 7-azaindole, are much less active, thus emphasizing the importance of C-3 substitution. Furthermore, substitution at C-2 or a nitrogen atom in the *para*-position to N-7 of the 7-azaindole seem to reduce the biological activity of compounds **8i** and **8j**.

Table 1 Biological data of selected compounds **8** and **9**

	Number of kinases with >50% inhibition @ 1 μM/number of kinases tested	IC_{50}[PDK1] (μM)
8b	4/121	>10
8f	22/121	0.8
8g	10/120	5.2
8h	48/95	0.1
8i	2/120	2.3
8j	11/95	4.9
8k	54/120	0.2
8l	60/102	0.3
8p	15/95	1.8
8q	3/121	>10
8r	17/121	>10
8s	11/120	1.1
9a	12/110	7.9
9b	4/110	>10

IC_{50}: concentration inhibiting kinase activity or reducing cell proliferation by 50%.

Table 2 Comparison of IC_{50} values of PDK1 inhibition between isomeric 3-triazolyl 7-azaindole compounds **8f** and **10**, as well as 3-pyrazolyl 7-azaindole **11**

PDK1 inhibition/IC_{50} (μM)		
		
8f	**10**	**11**
0.8	>10	2.6

For determining whether the triazole unit is merely a linker or possesses an additional function, an analogue of compound **8f** was prepared *via* the recently reported Masuda borylation–Suzuki coupling sequence.[38] This compound bears a pyrazole moiety instead of a triazole. Interestingly, the triazole unit seems to be important for the biological activity, since the pyrazole compound **11** was significantly less active with an IC_{50} value of 2.6 μM for PDK1 compared with 0.8 μM for the triazole **8f**. Therefore, triazole does not simply seem to be a linker, as in many applications of this heterocycle, but rather displays a pharmacophore character. However, even more exciting was the observation that the isomeric compound **10**,[78] differing from **8f** only in the permutation of substituents on N-1 and C-4 of the triazole unit, showed no activity on kinases, including PDK1 (Table 2).

X-ray structure of 8f in complex with PDK1

For further characterization of the binding mode, compound **8f** was soaked in crystals of the kinase domain of PDK1. Broad kinase activity of triazole derivatives is related to PDK1 activity (Table 1), which suggests that the binding mode in this kinase may be representative for several other kinases. The crystal structure was solved at 1.7 Å (Table 3) and reveals the detailed binding mode of **8f** within the ATP-binding site (Fig. 3).

Compound **8f** shows two canonical hydrogen bonds to the hinge region, an H-bond donor contact from azaindole N-1 to Ser160, and an H-bond acceptor contact from azaindole N-7 to Ala162. The triazole nitrogen atoms are also involved in hydrogen bonding interactions: N-3 to the Thr222 side chain (which may explain the lower activity of the pyrazole **11**) and N-2 to a water molecule. This water molecule is also in the H-bond distance to the catalytic amino acids Lys111 and Asp223. The molecule binds in an overall bent conformation with the benzyl group forming hydrophobic interactions with the glycine-rich region (GC-loop). The reason for the inactivity of compound **10**, which is a bioisostere of compound **8f** and differs only in the relative position of the substituents on N-1 and C-4 of the triazole unit and consequently in the dipole moment

Table 3 Crystallographic data of compound **8f**

PDB ID	**3RCJ**
Total number of reflections collected	110193
Number of unique reflections	33266
Space group	*C*2
Cell dimensions *a*, *b*, *c* (Å)	148.87, 44.39, 47.10
Cell dimensions α, β, γ (°)	90, 101.01, 90
R_{merge} overall, highest resolution shell (%)	55.4, 7.2
I/σ overall, highest resolution shell	20.58, 2.81
Completeness (%)	99.0
Redundancy	3.31
Resolution range used in refinement (Å)	70–1.7
Number of unique reflections used in refinement	33266
R_{factor} (%)	19.8
R_{free} (%)	21.7
Number of molecules per asymmetric unit	1
Number of ligands per asymmetric unit	1
Number of protein atoms	2278
Number of ligand atoms	21
Number of water molecules	162

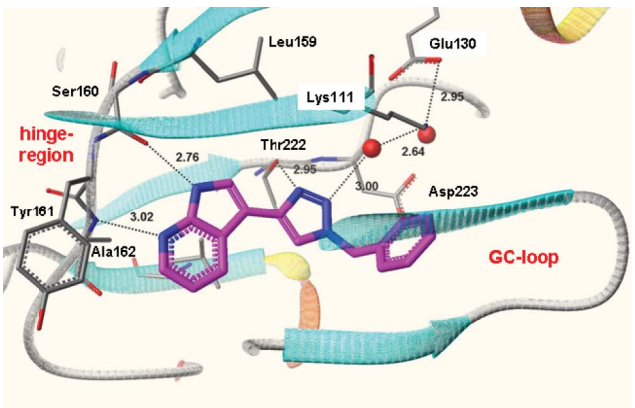


Fig. 3 X-ray structure of the complex of **8f** with PDK1 at 1.7 Å resolution. The 7-azaindole ring forms H-bonds to the hinge region (Ser160 & Ala162); two of the triazole N-atoms form H-bonds to Thr222 and a water molecule. The benzyl ring is oriented towards the GC-loop.

of the molecule, cannot be deduced from this X-ray structure and still remains obscure.

Conclusions

A practical and preparatively simple one-pot three-component Sonogashira coupling–TMS-deprotection–CuAAC sequence was developed to synthetically access a variety of triazolyl NH-heterocycles **8** and **9** in high purity and a very concise fashion. The sequence works very reliably for substrates with nitrogen atoms in different positions of various indole isosters, arising from the robustness, the versatility, and the generality of both Sonogashira coupling and CuAAC. The title compounds were tested for inhibition of a broad panel of kinases to reveal their kinase inhibitory activities. Compounds **8f**, **8h**, **8k**, and **8l** were found to inhibit PDK1 kinase with IC_{50} values below 1 µM. The X-ray structure analysis of compound **8f** in complex with PDK1 reveals the importance of the benzyl substituent for the binding. The phenyl and homobenzyl derivatives **8g** and **8r** were considerably less active, indicating a suboptimal position of their aromatic rings for favorable interaction towards the GC-loop compared with the benzyl substituent in **8f**. Since all synthesized compounds are small molecules, more potent analogues can be envisioned by derivatization, which can be achieved easily with the presented method.

Experimental

Synthesis of 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (8f)

(Compound **2f**): $PdCl_2(PPh_3)_2$ (71 mg, 0.10 mmol, 2 mol%) and CuI (39 mg, 0.20 mmol, 4 mol%) were placed in a dry screw-cap Schlenk vessel with a septum. Then, *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1f**) (1.72 g, 5.00 mmol) was added in 25 mL of dry tetrahydrofuran under an argon atmosphere and the reaction mixture was degassed with argon. After that, trimethylsilylacetylene (1.08 mL, 7.50 mmol, 1.50 equiv.) and dry triethylamine (1.39 mL, 10.0 mmol, 2.00 equiv.) were added and the mixture was stirred at room temperature (in a water bath) for 1 h until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (7.50 mL, 1.50 mmol, 1.50 equiv.) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, benzyl azide (**5a**) (679 mg, 5.00 mmol, 1.00 equiv.) in 5 mL of dry methanol was added and the mixture was stirred at room temperature for 40 h until the complete conversion to the product (monitored by TLC). After removal of the solvents *in vacuo* the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40–60 °C)–ethyl acetate PE–EtOAc = 2 : 1 (R_f (PE–EtOAc = 2 : 1): 0.20) to give 1.56 g (4.15 mmol, 83%) *tert*-butyl 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**2f**) as a yellow foam. The obtained compound was deprotected without characterization and further purification.

(Compound **8f**): *tert*-Butyl 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**2f**) (1.56 g, 4.15 mmol) was placed in 21 mL of methanol. Then, potassium carbonate (1.45 g, 10.4 mmol, 2.50 equiv.) was added and the mixture was stirred at room temperature (in a water bath) for 1 h (monitored by TLC). A precipitate formed after a few min. The mixture was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane–methanol–aqueous ammonia DCM–MeOH–NH_3 = 100 : 1 : 1 → 100 : 2 : 1 → 100 : 3 : 1 (stepwise gradient). After drying *in vacuo* overnight, 930 mg (3.38 mmol, 81%) of a pale yellow solid were obtained. The product was additionally purified by suspension in dichloromethane, sonication in ultrasonic bath for 0.5 h, filtration and drying *in vacuo* at 70 °C overnight to obtain the analytically pure 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**8f**) as a colorless solid. UV purity (HT-LC-MS): 100%. M.p. 234–237 °C.^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 5.66 (s, 2 H), 7.17 (dd, J = 7.9 Hz, J = 4.7 Hz, 1 H), 7.32–7.43 (m, 5 H), 7.92 (d, J = 2.5 Hz, 1 H), 8.29 (dd, J = 4.7 Hz, J = 1.6 Hz, 1 H), 8.44 (dd, J = 7.9 Hz, J = 1.6 Hz, 1 H), 8.54 (s, 1 H), 11.9 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 52.8 (CH_2), 105.0 (C_{quat}), 115.9 (CH), 116.9 (C_{quat}), 119.8 (CH), 123.2 (CH), 127.8 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 136.1 (C_{quat}), 142.4 (C_{quat}), 143.1 (CH), 148.5

(C_{quat}). EI + MS (*m*/*z* (%)): 275 (M^+, 100), 248 (13), 247 (74), 246 (87), 220 (11), 219 (35), 170 (15), 156 (24), 142 (10), 129 (17), 91 ($C_7H_7^+$, 19), 44 (19). IR (KBr): $\tilde{\nu}$ 1584 (s) cm^{-1}, 1458 (m), 1420 (m), 1220 (m), 941 (m), 799 (m), 771 (s), 722 (s). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.71, H 5.02, N 25.44.

PDK1 biochemical kinase assay

The PDK1 (3-phosphoinositide-dependent protein kinase-1) assay was carried out in 384-well streptavidin-coated FlashPlates (PerkinElmer). 3.4 nM His6-PDK1(Δ1-50), 400 nM biotinylated PDKtide (Biotin-βA-βA-KTFCGTPEYLAPEVRREPRILS-EEEQEMFRDFDYIADWC), and 4 μM ATP (spiked with 0.25 μCi ^{33}P-ATP per well) were incubated in a total volume of 50 μL (50 mM TRIS, 10 mM magnesium acetate, 0.1% mercaptoethanol, 0.02% Brij35, 0.1% bovine serum albumin, pH 7.5) with or without test compound (7–10 concentrations) for 60 min at 30 °C. The reaction was stopped by the addition of 25 μL 200 mM EDTA. After 30 min at room temperature the liquid was removed and each well washed three times with 100 μL 0.9% sodium chloride solution. Nonspecific reaction was determined in the presence of 100 nM staurosporine. Radioactivity was measured in a Topcount (PerkinElmer). Results (IC_{50} values) were calculated with *e.g.* AssayExplorer (Symyx).

DSTT kinase assays

The kinase assays[79] were carried out at room temperature. Compounds were pre-incubated in the presence of the enzyme and peptide/protein substrate for 5 min before initiation of the reaction by adding ATP. Assays were incubated at room temperature before termination by the addition of 5 μL orthophosphoric acid. The assay plates were then harvested onto P81 Unifilter Plates (wash buffer was 50 mM orthophosphoric acid) and dried in air. The dry Unifilter plates were then sealed on the addition of MicroScint O and were counted in Packard Topcount NXT scintillation counters.

Cocrystallization of compound 8f with PDK1 and X-ray structure determination

Crystallization of PDK1 was performed as previously described[80] and crystals were used for soaking with compound **8f**. X-Ray diffraction data were collected at the PXIII beamline equipped with a Pilatus detector at the Paul Scherrer Institut in Villingen, Switzerland. With the detector set at 270 mm, data were collected in 720 contiguous 0.25° oscillation images at 1 Å wavelength. The data for compound **8f** extends to 1.7 Å resolution, has an R_{merge} of 7.2% and 3.31-fold multiplicity. The structure was refined using CNX (Accelrys Inc.) to an R_{factor} of 19.8%.

Acknowledgements

The support of this work by the Merck Serono, Darmstadt, the Deutsche Forschungsgemeinschaft DFG, and by the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Daniel Schröder, Merck Serono, for conducting the crystallization experiments.

Notes and references

1 For a review on indole scaffold as a privileged structure, see: F. R. de Sá Alves, E. J. Barreiro and C. A. M. Fraga, *Mini-Rev. Med. Chem.*, 2009, **9**, 782; For a general review on bicyclic privileged structures, see: D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; For a comprehensive listing of privileged scaffolds, see: M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347.
2 For a recent review on halogenated marine indole alkaloids, see: P. M. Pauletti, L. S. Cintra, C. G. Braguine, A. A. S. Filho, M. L. A. Silva, W. R. Cunha and A. H. Januário, *Mar. Drugs*, 2010, **8**, 1526.
3 For recent reviews on indole alkaloid marine natural products as a source of drug leads, see: A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; W. Gul and M. T. Hamann, *Life Sci.*, 2005, **78**, 442; For a recent review on anticancer properties of indole compounds, see: A. Ahmad, W. A. Sakr and K. M. W. Rahman, *Curr. Drug Targets*, 2010, **11**, 652.
4 M. D. Lebar and B. J. Baker, *Aust. J. Chem.*, 2010, **63**, 862 (note authors' claim that the compound isolated from *Psammopemma* sp. as described in M. S. Butler, R. J. Capon and C. C. Lu, *Aust. J. Chem.*, 1992, **45**, 1871, is meridianin A and not psammopemmin A, which apparently does not exist); A. M. Seldes, M. F. R. Brasco, L. Hernández Franco and J. A. Palermo, *Nat. Prod. Res.*, 2007, **21**, 555; L. Hernández Franco, E. Bal de Kier Joffé, L. Puricelli, M. Tatian, A. M. Seldes and J. A. Palermo, *J. Nat. Prod.*, 1998, **61**, 1130.
5 T. Endo, M. Tsuda, J. Fromont and J. Kobayashi, *J. Nat. Prod.*, 2007, **70**, 423.
6 F. Reyes, R. Fernández, A. Rodríguez, A. Francesch, S. Taboada, C. Ávila and C. Cuevas, *Tetrahedron*, 2008, **64**, 5119.
7 R. J. Capon, F. Rooney, L. M. Murray, E. Collins, A. T. R. Sim, J. A. P. Rostas, M. S. Butler and A. R. Carroll, *J. Nat. Prod.*, 1998, **61**, 660; A. E. Wright, S. A. Pomponi, S. S. Cross and P. McCarthy, *J. Org. Chem.*, 1992, **57**, 4772; S. A. Morris and R. J. Andersen, *Tetrahedron Lett.*, 1990, **46**, 715; S. Kohmoto, Y. Kashman, O. J. McConnell, K. L. Rinehart, Jr., A. Wright and F. Koehn, *J. Org. Chem.*, 1988, **53**, 3116.
8 B. Bao, Q. Sun, X. Yao, J. Hong, C.-O. Lee, H. Y. Cho and J. H. Jung, *J. Nat. Prod.*, 2007, **70**, 2; B. Bao, Q. Sun, X. Yao, J. Hong, C.-O. Lee, C. J. Sim, K. S. Im and J. H. Jung, *J. Nat. Prod.*, 2005, **68**, 711; K.-B. Oh, W. Mar, S. Kim, J.-Y. Kim, M.-N. Oh, J.-G. Kim, D. Shin, C. J. Sim and J. Shin, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4927; A. Casapullo, G. Bifulco, I. Bruno and R. Riccio, *J. Nat. Prod.*, 2000, **63**, 447; S. P. Gunasekera, P. J. McCarthy and M. Kelly-Borges, *J. Nat. Prod.*, 1994, **57**, 1437.
9 P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, L. Grauso, F. U. Santelia, L. Tartaglione, V. I. Moutsos, E. N. Pitsinos and E. A. Couladouros, *Eur. J. Org. Chem.*, 2007, 5434, and references therein.
10 T. Bergmann, D. Schories and B. Steffan, *Tetrahedron*, 1997, **53**, 2055.
11 S. Sakemi and H. H. Sun, *J. Org. Chem.*, 1991, **56**, 4304.
12 J. Shin, Y. Seo, K. W. Cho, J.-R. Rho and C. J. Sim, *J. Nat. Prod.*, 1999, **62**, 647; L. M. Murray, T. K. Lim, J. N. A. Hooper and R. J. Capon, *Aust. J. Chem.*, 1995, **48**, 2053, and references therein; K. Bartik, J.-C. Braekman, D. Daloze, C. Stoller, J. Huysecom, G. Vandevyver and R. Ottinger, *Can. J. Chem.*, 1987, **65**, 2118.
13 M. Guyot and M. Meyer, *Tetrahedron Lett.*, 1986, **27**, 2621.
14 A. Loukaci, M. Guyot, A. Chiaroni and C. Rieche, *J. Nat. Prod.*, 1998, **61**, 519.
15 N. Lindquist, W. Fenical, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 2303.
16 S. Takahashi, T. Matsunaga, C. Hasegawa, H. Saito, D. Fujita, F. Kiuchi and Y. Tsuda, *Chem. Pharm. Bull.*, 1998, **46**, 1527.
17 G. Guella, I. Mancini, I. N'Diaye and F. Pietra, *Helv. Chim. Acta*, 1994, **77**, 1999; F. Miyake, M. Hashimoto, S. Tonsiengsom, K. Yakushijin and D. A. Horne, *Tetrahedron*, 2010, **66**, 4888.
18 B. S. Joshi, W. I. Taylor, D. S. Bhate and S. S. Karmarkar, *Tetrahedron*, 1963, **19**, 1437.
19 G. R. Pettit, J. C. Knight, D. L. Herald, R. Davenport, R. K. Pettit, B. E. Tucker and J. M. Schmidt, *J. Nat. Prod.*, 2002, **65**, 1793.
20 L. M. Browne, K. L. Conn, W. A. Ayer and J. P. Tewari, *Tetrahedron*, 1991, **47**, 3909.
21 H. Oka, T. Yoshinari, T. Murai, K. Kawamura, F. Satoh, K. Funaishi, A. Okura, H. Suda, M. Okanishi and Y. Shizuri, *J. Antibiot.*, 1991, **44**, 486; H. Suda, K. Matsunaga, S. Yamamura and Y. Shizuri, *Tetrahedron Lett.*, 1991, **32**, 2791.

22 S. Tsujii, K. L. Rinehart, S. P. Gunasekera, Y. Kashman, S. S. Cross, M. S. Lui, S. A. Pomponi and M. C. Diaz, *J. Org. Chem.*, 1988, **53**, 5446.
23 H. H. Sun and S. Sakemi, *J. Org. Chem.*, 1991, **56**, 4307; J. Cohen, G. K. Paul, S. P. Gunasekera, R. E. Longley and S. A. Pomponi, *Pharm. Biol.*, 2004, **42**, 59.
24 R. J. Capon, C. Peng and C. Dooms, *Org. Biomol. Chem.*, 2008, **6**, 2765.
25 K. Motohashi, M. Takagi and K. Shin-ya, *J. Nat. Prod.*, 2010, **73**, 226.
26 H. C. Vervoort, S. E. Richards-Gross, W. Fenical, A. Y. Lee and J. Clardy, *J. Org. Chem.*, 1997, **62**, 1486.
27 U. W. Hawas, M. Shaaban, K. A. Shaaban, M. Speitling, A. Maier, G. Kelter, H. H. Fiebig, M. Meiners, E. Helmke and H. Laatsch, *J. Nat. Prod.*, 2009, **72**, 2120.
28 A. Badre, A. Boulanger, E. Abou-Mansour, B. Banaigs, G. Combaut and C. Francisco, *J. Nat. Prod.*, 1994, **57**, 528.
29 D. T. A. Youssef, *J. Nat. Prod.*, 2005, **68**, 1416.
30 T. Hoshino, Y. Kojima, T. Hayashi, T. Uchiyama and K. Kaneko, *Biosci., Biotechnol., Biochem.*, 1993, **57**, 775.
31 K. A. McArthur, S. S. Mitchell, G. Tsueng, A. Rheingold, D. J. White, J. Grodberg, K. S. Lam and B. C. M. Potts, *J. Nat. Prod.*, 2008, **71**, 1732.
32 N. Durán, G. Z. Justo, C. V. Ferreira, P. S. Melo, L. Cordi and D. Martins, *Biotechnol. Appl. Biochem.*, 2007, **48**, 127.
33 N. K. Kubota, H. Iwamoto, Y. Fukazawa and Y. Uchio, *Heterocycles*, 2005, **65**, 2675; A. A. El-Gamal, W.-L. Wang and C.-Y. Duh, *J. Nat. Prod.*, 2005, **68**, 815.
34 For YC-1, see: K. W. Hering, J. D. Artz, W. H. Pearson and M. A. Marletta, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 618; J.-C. Lien, F.-Y. Lee, L.-J. Huang, S.-L. Pan, J.-H. Guh, C.-M. Teng and S.-C. Kuo, *J. Med. Chem.*, 2002, **45**, 4947; F.-Y. Lee, J.-C. Lien, L.-J. Huang, T.-M. Huang, S.-C. Tsai, C.-M. Teng, C.-C. Wu, F.-C. Cheng and S.-C. Kuo, *J. Med. Chem.*, 2001, **44**, 3746; For azaindol-3-yl-dipyridodiazepinones, see: T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih and P. M. Grob, *J. Med. Chem.*, 1997, **40**, 2430.
35 For selected examples of kinase inhibitors with (hetero)aryl substituents at C-3, see: S. Hong, S. Lee, B. Kim, H. Lee, S.-S. Hong and S. Hong, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7212; M. Hammond, D. G. Washburn, T. H. Hoang, S. Manns, J. S. Frazee, H. Nakamura, J. R. Patterson, W. Trizna, C. Wu, L. M. Azzarano, R. Nagilla, M. Nord, R. Trejo, M. S. Head, B. Zhao, A. M. Smallwood, K. Hightower, N. J. Laping, C. G. Schnackenberg and S. K. Thompson, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4441; S. Huang, R. Li, P. J. Connolly, S. Emanuel and S. A. Middleton, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4818; H.-C. Zhang, H. Ye, B. R. Conway, C. K. Derian, M. F. Addo, G.-H. Kuo, L. R. Hecker, D. R. Croll, J. Li, L. Westover, J. Z. Xu, R. Look, K. T. Demarest, P. Andrade-Gordon, B. P. Damiano and B. E. Maryanoff, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3245; For RWJ 68354, see: J. R. Henry, K. C. Rupert, J. H. Dodd, I. J. Turchi, S. A. Wadsworth, D. E. Cavender, B. Fahmy, G. C. Olini, J. E. Davis, J. Lee Pellegrino-Gensey, P. H. Schafer and J. J. Siekierka, *J. Med. Chem.*, 1998, **41**, 4196; J. R. Henry, K. C. Rupert, J. H. Dodd, I. J. Turchi, S. A. Wadsworth, D. E. Cavender, P. H. Schafer and J. J. Siekierka, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3335.
36 N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin and H. Hope, *Tetrahedron*, 1994, **50**, 3987; G. Trimurtulu, D. J. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro and G. B. Jameson, *Tetrahedron*, 1994, **50**, 3993; For a recent review on variolins and related alkaloids, see: S. R. Walker, E. J. Carter, B. C. Huff and J. C. Morris, *Chem. Rev.*, 2009, **109**, 3080.
37 A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clément, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. A. Endicott, B. Joseph and L. Meijer, *J. Med. Chem.*, 2008, **51**, 737; K. Bettayeb, O. M. Tirado, S. Marionneau-Lambot, Y. Ferandin, O. Lozach, J. C. Morris, S. Mateo-Lozano, P. Drueckes, C. Schächtele, M. H. G. Kubbutat, F. Liger, B. Marquet, B. Joseph, A. Echalier, J. A. Endicott, V. Notario and L. Meijer, *Cancer Res.*, 2007, **67**, 8325.
38 E. Merkul, E. Schäfer and T. J. J. Müller, *Org. Biomol. Chem.*, 2011, **9**, 3139.
39 A. S. Karpov, E. Merkul, F. Rominger and T. J. J. Müller, *Angew. Chem., Int. Ed.*, 2005, **44**, 6951.
40 According to an X-ray structure analysis of meridianin C and meriolin 1 in the kinase TGFβ, which will be published elsewhere.
41 A. Seggio, G. Priem, F. Chevallier and F. Mongin, *Synthesis*, 2009, 3617; M. Gompel, M. Leost, E. Bal de Kier Joffé, L. Puricelli, L. Hernández Franco, J. Palermo and L. Meijer, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1703; L. Hernández Franco and J. A. Palermo, *Chem. Pharm. Bull.*, 2003, **51**, 975.
42 For triazole as a linking element in an indole salicylic acid based library, see: X. Zhang, Y. He, S. Liu, Z. Yu, Z.-X. Jiang, Z. Yang, Y. Dong, S. C. Nabinger, L. Wu, A. M. Gunawan, L. Wang, R. J. Chan and Z.-Y. Zhang, *J. Med. Chem.*, 2010, **53**, 2482.
43 D. K. Dalvie, A. S. Kalgutkar, S. C. Khojasteh-Bakht, R. S. Obach and J. P. O'Donnell, *Chem. Res. Toxicol.*, 2002, **15**, 269.
44 W.-T. Li, W.-H. Wu, C.-H. Tang, R. Tai and S.-T. Chen, *ACS Comb. Sci.*, 2011, **13**, 72, and references therein; S. K. Mamidyala and M. G. Finn, *Chem. Soc. Rev.*, 2010, **39**, 1252; K. A. Kalesh, K. Liu and S. Q. Yao, *Org. Biomol. Chem.*, 2009, **7**, 5129; G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba and A. A. Genazzani, *Med. Res. Rev.*, 2008, **28**, 278; A. D. Moorhouse and J. E. Moses, *ChemMedChem*, 2008, **3**, 715; A. Dondoni, *Chem.–Asian J.*, 2007, **2**, 700; K. B. Sharpless and R. Manetsch, *Expert Opin. Drug Discovery*, 2006, **1**, 525; H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128; R. Breinbauer and M. Köhn, *ChemBioChem*, 2003, **4**, 1147.
45 J.-F. Lutz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1018.
46 Y. L. Angell and K. Burgess, *Chem. Soc. Rev.*, 2007, **36**, 1674.
47 D. Dorsch, M. Wucherer-Plietker, T. J. J. Müller and E. Merkul, *PCT Int. Appl.* 2010, WO 2010127754 A1 20101111; D. Dorsch, M. Wucherer-Plietker, T. J. J. Müller and E. Merkul, *Ger. Offen.* 2010, DE 102009019962 A1 20101111.
48 For a recent synthesis of kinase inhibitors based on 3-triazolyl substituted pyrazolo[3,4-*d*]pyrimidines, see: M. Klein, P. Dinér, D. Dorin-Semblat, C. Doerig and M. Grøtli, *Org. Biomol. Chem.*, 2009, **7**, 3421.
49 For seminal publications, see: K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; Y. Tohda, K. Sonogashira and N. Hagihara, *Synthesis*, 1977, 777.
50 For recent reviews, see: R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874; H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834; For general reviews, see: H. Plenio and A. Datta, in *Handbook of C-H Transformations*, Wiley, Weinheim, 2005, ch. 1.2; J. A. Marsden and M. M. Haley, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley, Weinheim, 2nd edn, 2004, ch. 6; K. Sonogashira, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley, Weinheim, 1998, ch. 5.
51 S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *Synthesis*, 1980, 627.
52 For seminal publications on CuAAC, see: V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.
53 For recent reviews on CuAAC, see: V. V. Fokin, in *Catalyzed Carbon-Heteroatom Bond Formation*, Wiley, Weinheim, 2011, ch. 7; J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302; C. Spiteri and J. E. Moses, *Angew. Chem. Int. Ed.*, 2010, **49**, 31; M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952; P. Wu and V. V. Fokin, *Aldrichimica Acta*, 2007, **40**, 7; V. D. Bock, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51; W. H. Binder and C. Kluger, *Curr. Org. Chem.*, 2006, **10**, 1791.
54 For the philosophy of click chemistry, see: M. G. Finn and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1231; C. J. Hawker, V. V. Fokin, M. G. Finn and K. B. Sharpless, *Aust. J. Chem.*, 2007, **60**, 381; H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004; For recent reviews on click chemistry, see: G. Franc and A. K. Kakkar, *Chem. Soc. Rev.*, 2010, **39**, 1536; J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; M. V. Gil, M. J. Arévalo and Ó. López, *Synthesis*, 2007, 1589.
55 For the concept of atom economy, see: B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259; B. M. Trost, *Science*, 1991, **254**, 1471.
56 W. D. Sharpless, P. Wu, T. V. Hansen and J. G. Lindberg, *J. Chem. Educ.*, 2005, **82**, 1833.
57 F. Alonso, Y. Moglie, G. Rodivoy and M. Yus, *Adv. Synth. Catal.*, 2010, **352**, 3208; D. Kumar and V. B. Reddy, *Synthesis*, 2010, 1687; L. S. Campbell-Verduyn, W. Szymański, C. P. Postema, R. A. Dierckx, P. H. Elsinga, D. B. Janssen and B. L. Feringa, *Chem. Commun.*, 2010, **46**, 898; Y. Huang, G. L. Gard and J. M. Shreeve, *Tetrahedron Lett.*, 2010, **51**, 6951; V. Bénéteau, A. Olmos, T. Boningari, J. Sommer and P. Pale, *Tetrahedron Lett.*, 2010, **51**, 3673; C.-T. Lee, S. Huang and B. H. Lipshutz, *Adv. Synth. Catal.*, 2009, **351**, 3139; S. Maisonneuve and J. Xie, *Synlett*, 2009, 2977, and references therein; K. Odlo, E. A. Høydahl and T. V. Hansen, *Tetrahedron Lett.*, 2007, **48**, 2097; J. Andersen, S. Bolvig and X. Liang, *Synlett*, 2005, 2941; K. Kacprzak, *Synlett*, 2005,

943; P. Appukkuttan, W. Dehaen, V. V. Fokin and E. Van der Eycken, *Org. Lett.*, 2004, **6**, 4223; A. K. Feldman, B. Colasson and V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897.
58 F. Cuevas, A. I. Oliva and M. A. Pericàs, *Synlett*, 2010, 1873, and references therein.
59 L. Ackermann, H. K. Potukuchi, D. Landsberg and R. Viante, *Org. Lett.*, 2008, **10**, 3081.
60 I. R. Baxendale, S. V. Ley, A. C. Mansfield and C. D. Smith, *Angew. Chem., Int. Ed.*, 2009, **48**, 4017; D. Luvino, C. Amalric, M. Smietana and J.-J. Vasseur, *Synlett*, 2007, 3037.
61 For recent reviews, see: T. J. J. Müller, *Top. Heterocycl. Chem.*, 2010, **25**, 25; B. Willy and T. J. J. Müller, *Curr. Org. Chem.*, 2009, **13**, 1777; B. Willy and T. J. J. Müller, *ARKIVOC*, 2008, **Part I**, 195; D. M. D'Souza and T. J. J. Müller, *Chem. Soc. Rev.*, 2007, **36**, 1095.
62 For selected examples of syntheses of other 5-membered heterocycles, see: A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Eur. J. Org. Chem.*, 2006, 2991; A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Chem. Commun.*, 2005, 2581 (furans); E. Merkul and T. J. J. Müller, *Chem. Commun.*, 2006, 4817; E. Merkul, O. Grotkopp and T. J. J. Müller, *Synthesis*, 2009, 502 (oxazoles); B. Willy and T. J. J. Müller, *Eur. J. Org. Chem.*, 2008, 4157 (pyrazoles); B. Willy, F. Rominger and T. J. J. Müller, *Synthesis*, 2008, 293 (isoxazoles).
63 P. G. M. Wuts and T. W. Greene, in *Green's Protective Groups in Organic Synthesis*, Wiley, New York, 4th edn, 2007, ch. 7.
64 Boc_2O/CsF method: N. Inahashi, A. Matsumiya and T. Sato, *Synlett*, 2008, 294; for the standard protocol (Boc_2O/DMAP), see: L. Grehn and U. Ragnarsson, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 296.
65 For some examples, see: J. J. Richards and C. Melander, *J. Org. Chem.*, 2008, **73**, 5191; R. Martín, C. H. Larsen, A. Cuenca and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 3379; M. R. Rivero and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 973; Y.-Q. Fang, J. Yuen and M. Lautens, *J. Org. Chem.*, 2007, **72**, 5152; R. Martín, M. R. Rivero and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7079; F. S. Al-Hajjar and S. S. Sabri, *J. Heterocyclic Chem.*, 1986, **23**, 727.
66 For a one-pot synthesis of 2-substituted *N*-Boc 4-iodo pyrroles, see: E. Merkul, C. Boersch, W. Frank and T. J. J. Müller, *Org. Lett.*, 2009, **11**, 2269.
67 Cleavage with boiling water: J. Wang, Y.-L. Liang and J. Qu, *Chem. Commun.*, 2009, 5144; cleavage with fluorinated alcohols: J. Choy, S. Jaime-Figueroa, L. Jiang and P. Wagner, *Synth. Commun.*, 2008, **38**, 3840; cleavage with NaOMe/dry MeOH: K. Ravinder, A. V. Reddy, K. C. Mahesh, M. Narasimhulu and Y. Venkateswarlu, *Synth. Commun.*, 2007, 281; cleavage with aqueous K_2CO_3/MeOH under reflux: M. Chakrabarty, T. Kundu and Y. Harigaya, *Synth. Commun.*, 2006, **36**, 2069, see also references therein; cleavage using TBAF: U. Jacquemard, V. Bénéteau, M. Lefoix, S. Routier, J.-Y. Mérour and G. Coudert, *Tetrahedron*, 2004, **60**, 10039; thermolytic cleavage: V. H. Rawal and M. P. Cava, *Tetrahedron Lett.*, 1985, **26**, 6141.
68 Compounds **1a**, **1d–k**, and **1n** were prepared as described in: B. Witulski, N. Buschmann and U. Bergsträßer, *Tetrahedron*, 2000, **56**, 8473.
69 Although numerous efficient catalytic systems have been described for the Sonogashira-type alkynylations, this standard catalytic system is still by far the most widely used one: H. Plenio, *Angew. Chem., Int. Ed.*, 2008, **47**, 6954; R. R. Tykwinski, *Angew. Chem., Int. Ed.*, 2003, **42**, 1566.
70 E. Merkul, D. Urselmann and T. J. J. Müller, *Eur. J. Org. Chem.*, 2011, 238.
71 *N*-Boc protected 3-iodo (aza)indoles and 4-iodo pyrroles are storable for years in the refrigerator under an argon atmosphere without decomposition.
72 3-Iodo (aza)indoles can be prepared in large quantities without need for argon atmosphere, but they should be promptly protected with Boc to avoid decomposition and for convenient handling and storage.
73 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295; T. Hundertmark, A. F. Littke, S. L. Buchwald and G. C. Fu, *Org. Lett.*, 2000, **2**, 1729.
74 For some strategies developed to remove Pd from pharmaceutically active ingredients, see a review: C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889.
75 For a recent review on the role of bioisosterism in rational drug design, see: L. M. Lima and E. J. Barreiro, *Curr. Med. Chem.*, 2005, **12**, 23.
76 F. Friscourt and G.-J. Boons, *Org. Lett.*, 2010, **12**, 4936; K. Lörincz, P. Kele and Z. Novák, *Synthesis*, 2009, 3527.
77 J. R. Bayascas, *Curr. Top. Microbiol. Immunol.*, 2010, **346**, 9; A. Mora, D. Komander, D. M. F. van Aalten and D. R. Alessi, *Sem. Cell Dev. Biol.*, 2004, **15**, 161.
78 J. Andersen, S. Bolvig and X. Liang, *Synlett*, 2005, 2941.
79 J. Bain, L. Plater, M. Elliott, N. Shpiro, C. J. Hastie, H. McLauchlan, J. Klevernic, J. S. C. Arthur, D. R. Alessi and P. Cohen, *Biochem. J.*, 2007, **408**, 297; J. Bain, H. McLauchlan, M. Elliott and P. Cohen, *Biochem. J.*, 2003, **371**, 199.
80 V. Hindie, A. Stroba, H. Zhang, L. A. Lopez-Garcia, L. Idrissova, S. Zeuzem, D. Hirschberg, F. Schaeffer, T. J. D. Jørgensen, M. Engel, P. M. Alzari and R. M. Biondi, *Nat. Chem. Biol.*, 2009, **5**, 758.

