New Calcineurin Inhibiting 3-Dimethylaminopropyl Substituted Diarylheterocycles by Sonogashira Reactions and Catalytic Hydrogenation

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A series of calcineurin inhibiting compounds **1** consisting of a central aromatic N-heterocycle, two aryl substituents and a 3-dimethylaminopropyl chain was synthesized by introduction of the side chain. A corresponding haloheterocycle **3** was transformed into a 3-dimethylaminopropynylheterocycle **2** by Sonogashira coupling and was in turn hydrogenated in the presence of Pd/C to afford the 3-dimethylaminopropyl-substiuted heterocycles **1**. Some of the products showed calcineurin inhibiting activity.

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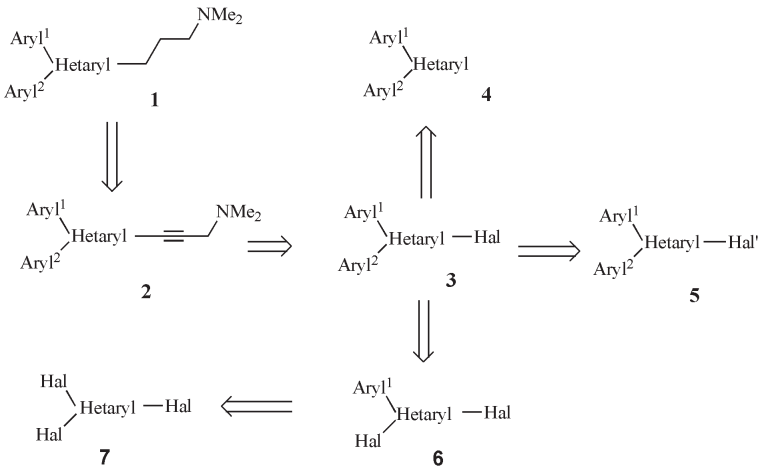
Inhibitors of the protein phosphatase calcineurin represent an important class of compounds which are used as immunosuppressive drugs in the prevention of allograft rejections after transplantation of organs or bone marrow and for the treatment of autoimmune diseases [1-3]. So far, the most potent compounds in these fields are of natural origin and produced by microorganisms, such as the cyclic undecapeptide Cyclosporin A (CsA) or the macrolacton FK506 [4,5]. However, both immunosuppressants do not inhibit the enzymatic activity of calcineurin on their own. It was shown that CsA and FK506 bind to and inhibit calcineurin only in complex with cyclophilins and FK506-binding proteins respectively. Both proteins are members of the enzyme class of peptidyl *cis/trans* proline isomerases (PPIases) [6,7]. PPIases are involved in many cellular processes such as protein folding, receptor signaling and apoptosis [8-10]. The simultaneous inhibition of PPIases and calcineurin by CsA and FK506 could be a reason for the number of side effects, such as neurotoxicity, nephrotoxicity and carcinogenity [11-13]. Until now, cellular proteins and polypeptides are known as potent and specific calcineurin inhibitors [14,15]. However, peptidic and protein-based drugs have a short half life time in the organism conditioned by a rapid proteolytic degradation *in vivo*. Another aspect is the limited cell permeability for peptides and proteins due to the fact that charged molecules cannot readily cross the cell membrane. Therefore, there is a high requirement for a monospecific non-peptidic calcineurin inhibitor.

We recently found that compounds of the general structure **1** and related products, which are composed of a central heterocyclic ring, two peripheral aryl groups and one ω-functionalized aliphatic side chain exhibit an interesting inhibition of calcineurin. This class of products **1** represents a novel motif for calcineurin inhibition. So far, the central heterocycle of these compounds was pyrazolo[1,5-*a*]tri-

Scheme 1



Retrosynthesis of potential calcineurin-inhibitors **1**

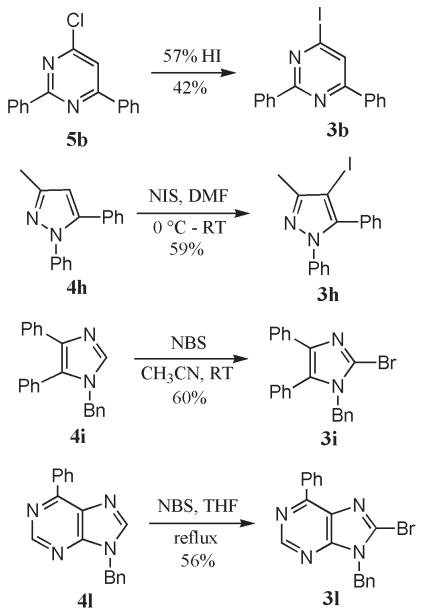
azine, [16] pyrazolo[1,5-*a*]pyrimidine, [16-18] and pyrido[2,3-*b*]pyrazine. [19] In order to investigate the effect of the central heterocycle on the calcineurin inhibitory activity, it was necessary to develop such products **1**.

As a synthetic strategy (see Scheme 1), we chose a two steps procedure starting from suitable diaryl haloheterocycles **3**. The side chain is introduced by Sonogashira coupling [20] with *N*,*N*-dimethylpropargylamine and the resulting heterocyclic propargylamines **2** are finally hydrogenated to the corresponding aminopropylheterocycles **1**. The precursors **3** can either be obtained by ring closure or starting from diarylheterocycles **4** or **5** by substitution. On the other hand one or two aryl groups can be introduced into dihaloheterocycles **6** or trihaloheterocycles **7**, respectively to achieve precursors **3** for Sonogashira coupling.

The sequence **3** → **2** → **1** was used by us in the pyrazolo[1,5-*a*]pyrimidine series [18]. So far, the single steps, *i.e.*, introduction of a dimethylaminopropargyl group into heterocycles by Sonogashira reaction [21] or reduction of a dimethylaminopropargyl to a dimethylaminopropyl group [22] were applied to other heterocycles. Both steps can be crucial when applied to new heterocyclic systems, for example the Sonogashira coupling can fail, *e.g.*, in the case of 7-halopyrazolo[1,5-*a*]pyrimidines [23], or hydrogenation affects the central heterocyclic ring [24] or the intermediate allyl amine side chains [25] or the substituents at the aryl groups.

Here, we chose haloheterocycles **3a – 3m** as starting materials (Figure 1). Compounds **3c**, [26] **3f**, [27] **3g**, [28] and **3m**, [29] were known and prepared by corresponding literature. The haloheterocycles **3h**, **3i** and **3l** were obtained by halogenation of halogen free analogues of **4** with NIS or NBS, respectively, while the 4-iodopyrimidine **3b** was synthesized from the corresponding chloropyrimidine **5** and hydroiodic acid (Scheme 2).

Scheme 2



Synthesis of **3b**, **3h**, **3i** and **3l**

The bicyclic compounds **3j** and **3k** were prepared from the corresponding 6-membered aminoheterocycles by ring closure with desylbromide. (Scheme 3)

We further started with 6-membered dihaloheterocycles **6a** or the trihaloheterocycle **7a** and introduced one or both aryl substituents, respectively to get access to Sonogashira coupling precursors **3e** and **3d**. Compound **3a** was prepared by twofold Suzuki coupling but the starting material **8** contained an amino group. The resulting 2-amino-3,5-diphenylpyridine **9** was transformed into the iodo compound **3a** *via* diazotization and iodination. (Scheme 4)

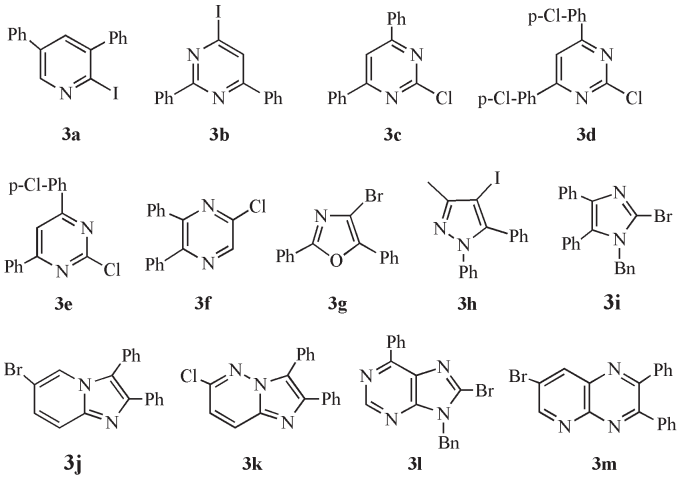
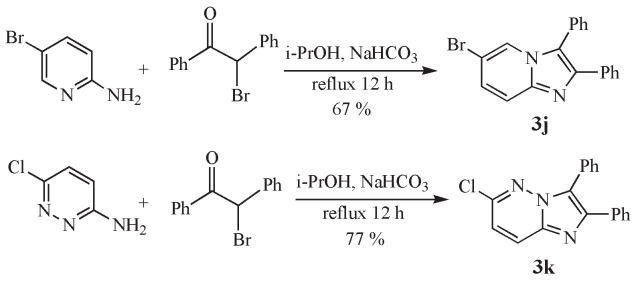


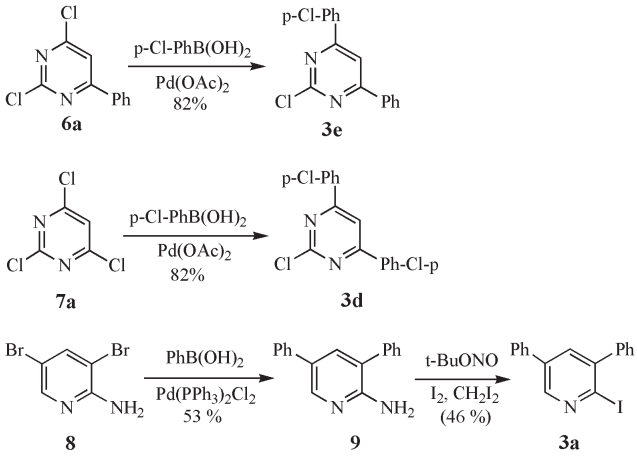
Figure 1. Diaryl-haloheterocycles

Scheme 3



Synthesis of **3j** and **3k**

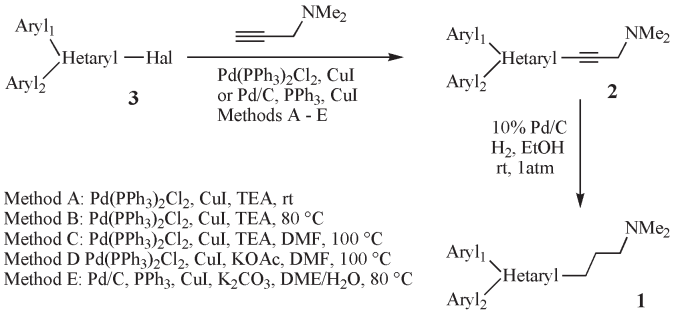
Scheme 4



Introduction of aryl groups by Suzuki coupling

With all these haloheterocycles **3** in hand, Sonogashira coupling was approached to introduce the *N*,*N*-dimethylaminopropynyl side chain (Scheme 5). Five different methods were applied: Method A – D using $Pd(PPh_3)_2Cl_2$, CuI with different bases or solvents and Method E applying Pd/C, PPh_3, CuI.

Scheme 5



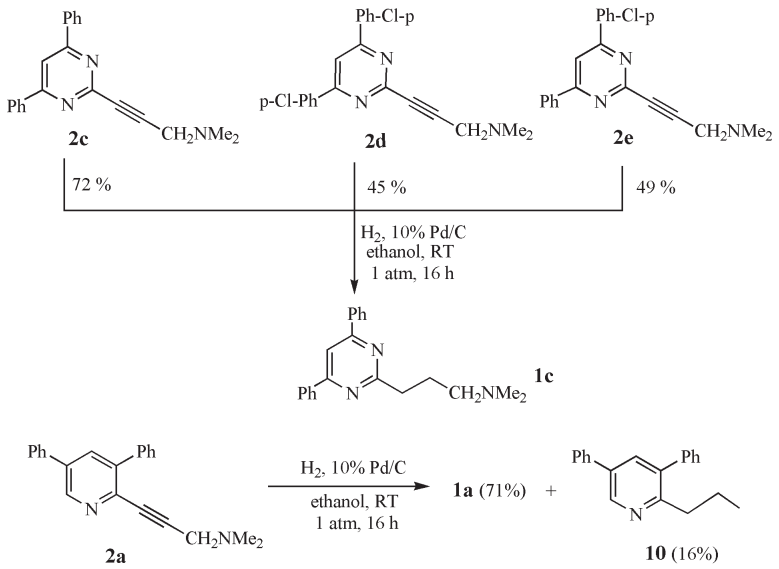
Synthesis of **2** and **1**

In most cases (see Table 1) $Pd(PPh_3)_2Cl_2$ was successful, but the 4-iodopyrazole **3g** gave no coupling product, when method A ($Pd(PPh_3)_2Cl_2$/CuI) was used, while high yields of **2g** were obtained with Pd/C (method E, see entry 7). A reversed situation was found with the bromoimidazopyridine **3j** where method E failed while with $Pd(PPh_3)_2Cl_2$/CuI (Method C) product **2j** was obtained in 74 % yield (entry 10). Thus it is not possible to predict useful methods for a specific case of heterocycle. The products **2** are stable, mostly solid compounds and can be stored without any precaution. Reduction of the C-C triple bond of the aminoalkynylheterocycles **2** could be achieved by hydrogenation at atmospheric pressure and room temperature in the presence of 10 % Pd/C. In all cases, but the chlorophenyl compounds **2d** and **2e**, the expected aminopropyl products **1** could be obtained (Table 1). In the latter two cases the chloro-substituents got lost under the hydrogenation conditions and thus the same chloro-free product **1c** was obtained like starting from **2c** (see Scheme 4 and Table 1, entry 3). Similar hydrodehalogenations are found in literature for other chloro substituted arenes when amines are used as base [30]. Presumably, the dimethylaminopropyl substitutents of the products **1** act as bases in our case. Deamination of the side chain was another side reaction observed in the hydrogenation of the dimethylaminoalkyn-3-ylheterocycles **2** affording propylheterocycles such as product **10** formed along with the expected dimethylaminopropylpyridine **1a** (Scheme 6). In the literature hydrogenolytic hydrodeamination was observed for allylamine moieties in alkaloide-like tetrahydopyridine and open chained compounds in the presence of acid [25]. This side reaction could also be the reason that in general the yields in the reduction of **2** are moderate.

Measurement of Calcineurin Activity.

The influence of compounds **1** and their precursors **2** on the enzymatic activity of calcineurin was investigated in a phosphopeptide based calcineurin activity assay [31]. The biotinylated 19-residue peptide of a partial sequence of the RII subunit of the bovine protein kinase A was phosphorylated with [γ-^{33}P]ATP. For all measurements of calcineurin activity, the labeled RII phosphopeptide was used as substrate in a scintillation proximity assay. In brief, preincubation of 50 nM calmodulin, 2 nM calcineurin, and 20 µM compound in phosphatase assay buffer (40 mM Tris/HCl, pH 7.5; 100 mM NaCl, 6 mM $MgCl_2$, 0.5 mM DTT, 1 mM $CaCl_2$, 0.1 mg/ml BSA) was carried out at 22 °C for 30 min. 10 pmol biotinylated [^{33}P] RII phosphopeptide was added to each sample in a final assay volume of 100 µl. After dephosphorylation of RII phosphopeptide by calcineurin at 30 °C for 20 min, 90 µl of the reaction mixture were transferred to a

Scheme 6



Hydrodechlorination and deamination as side reaction of the catalytic reduction of the alkynyl group

Table 1

Sonogashira Coupling Products **2** and 3-Dimethylaminopropylheterocycles **1** and the Remaining Activity of Calcineurin in the Presence of Selected Compounds

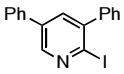
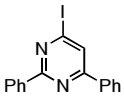
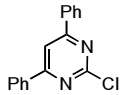
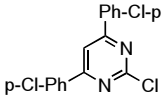
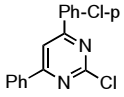
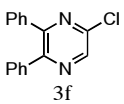
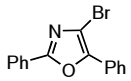
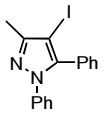
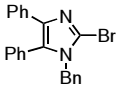
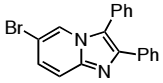
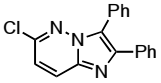
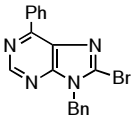
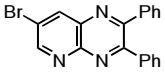
Entry	Reactant **3**	Coupling product **2** / yield (%) [a] / method [b]	Calcineurin Activity [c]	Dimethylamino propyl-product **1** / yield (%)	Calcineurin Activity [c]
1	 3a	2a/89/A	100 %	**1a**/71	100 %
2	 3b	**2b**/76/A	53 %	**1b**/76	50 %
3	 3c	**2c**/38/C 71/D	75 %	**1c**/72 /45 [d] /49 [e]	46 %
4	 3d	**2d**/51/C	100 %		
5	 3e	**2e**/51/C	100 %		
6	 3f	**2f**/27/C 52/D	81 %	**1f**/58	62 %

Table 1 (continued)

Entry	Reactant **3**	Coupling product **2** / yield (%) [a] / method [b]	Calcineurin Activity [c]	Dimethylamino propyl-product **1** / yield (%)	Calcineurin Activity [c]
7	 3g	**2g**/10/B 42/C 66/D	78 %	**1g**/58	88 %
8	 3h	**2h**/0/A 97/E	100 %	**1h**/76	72 %
9	 3i	**2i**/43/B 27/C	87 %	**1i**/63	71 %
10	 3j	**2j**/0/E 74/C	100 %	**1j**/47	57 %
11	 3k	**2k**/86/C	94 %	**1k**/73	67 %
12	 3l	**2l**/86/B	95 %	**1l**/70	87 %
13	 3m	**2m**/76/C	90 %	**1m**/54	53 %

[a] Isolated yield; [b] Conditions: Method A: $Pd(PPh_3)_2Cl_2$, CuI, TEA, RT; Method B: $Pd(PPh_3)_2Cl_2$, CuI, TEA, 80 °C; Method C: $Pd(PPh_3)_2Cl_2$, CuI, TEA, DMF, 100 °C; Method D: $Pd(PPh_3)_2Cl_2$, CuI, KOAc, DMF, 100 °C; Method E: Pd/C, PPh_3, CuI, K_2CO_3, DME-H_2O, 80 °C; [c] Remaining activity of calcineurin after incubation with 20 μM compound (% of control); [d] Starting from **2d**; [e] Starting from **2e**.

scintillation well coated with streptavidin. Biotinylated RII phosphopeptide was allowed to bind to streptavidin for 20 min at 22 °C. The well was washed once with water, and the RII phosphopeptide associated [^{33}P] was measured in a MicroBeta top-counter.

It turned out that some of the products **1** showed a moderate inhibitory activity at a concentration of 20 μM. Remarkably even corresponding precursors **2** were active to a similar degree. Thus, in extension to our previous experiences with aminoalkylheterocycles of the general structure **1**, where the side chains were saturated, now it turned out that the aliphatic side chain can also contain C-C triple bonds.

EXPERIMENTAL

All cross-coupling reactions were carried out under argon in oven-dried glassware. Solvents were dried and deoxygenated by standard procedures. Starting materials were purchased from Aldrich, Lancaster, Acros, and Merck. The known compounds **3c**, [26] **3f**, [27] **3g**, [28] and **3m** [29] were prepared according to literature. TLC analysis was performed on Merck silica gel 60F254 plate or Merck Al_2O_3 $60F_{254}$ neutral (Typ E) plates and visualized with UV illumination. Column chromatography was conducted with Merck silica gel 60 (400-639 mesh) or Merck neutral Al_2O_3 (90 standard). Melting points were determined on a Boetius hot-stage apparatus and are reported uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz,

respectively, on a Bruker AC-300 in $CDCl_3$ with TMS as internal standard. Mass spectra were measured at 70 eV.

2-Amino-3,5-diphenyl-pyridine (**9**).

The compound was prepared adopting a reported procedure [32]. 2-Amino-3,5-dibromopyridine **8** (2.52 g, 10.0 mmol) and phenylboronic acid (2.53 g, 21.0 mmol) were dissolved in MeOH (20 ml). Na_2CO_3 (25 g) in water (50 ml) and then toluene (100 ml) was added. The suspension was degassed under vacuum for 10 min and then flashed with argon. $Pd(PPh_3)_2Cl_2$ (177 mg, 0.25 mmol) was added and the mixture was heated at reflux under argon with vigorous stirring for 66 h. The organic solvents were removed under reduced pressure, followed by extraction with EtOAc (3 x 50ml), washing of the combined organic layers with water (2 x 50ml) and drying with anhydrous $MgSO_4$. The solvents were evaporated and the residue was purified by column chromatography on silica (Et_2O) to provide of **9** (1.37 g, 53%) as a light brown solid, mp 106 °C. ^{1}H nmr ($CDCl_3$), δ(ppm): 4.83 (s, 2 H, NH_2), 7.39-7.64 (m, 10 H, Ph-H), 7.69 (d, 1 H, *J* = 2.3 Hz, H-4), 7.81 (d, 1 H, *J* = 2.3 Hz, H-6). ^{13}C nmr ($CDCl_3$), δ(ppm): 121.7 C, 126.3 CH, 126.9 CH, 127.9 CH, 127.9 CH, 128.8 CH, 128.9 CH, 129.2 CH, 136.6 CH(C-4), 138.0 C, 138.2 C, 145.5 CH(C-6), 155.21 C.

Anal. Calcd. for $C_{17}H_{14}N_2$ (246.30): C, 82.90; H, 5.73; N, 11.37. Found: C, 82.83; H, 5.93; N, 11.41.

2-Iodo-3,5-diphenylpyridine (**3a**).

2-Amino-3,5-diphenyl-pyridine (**9**) (1.00 g, 4.0 mmol) was dissolved in CH_2I_2 (13 ml) aided by ultrasound. *tert*-Butyl nitrite (0.65 g, 6.0 mmol) and I_2 (1.02 g, 4.0 mmol) were added and the reaction mixture was stirred at room temperature for 24 h under exclusion of light. To complete the reaction (TLC monitoring), the addition of *tert*-butyl nitrite (0.32 g, 3.0 mmol) was repeated and the mixture was stirred for further 12 h. The reaction was stopped by the addition of saturated Na_2CO_3 solution (30 ml) and an excess of solid $Na_2S_2O_3$. The solvents were evaporated to dryness under reduced pressure, followed by addition of water (40 ml) and extraction with EtOAc (3 x 40 ml). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel, eluting with cyclohexane/EtOAc (10:1-3:1). 660 mg (46 %) of **3a** was obtained as a light brown solid, mp 86-7 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 7.31-7.44 (m, 10 H, Ph-H), 7.54 (d, 1 H, *J* = 2.6 Hz, H-4), 8.43 (d, 1 H, *J* = 2.6 Hz, H-4). ^{13}C nmr ($CDCl_3$), δ (ppm): 120.8 C, 127.1 CH, 128.4 CH, 128.5 CH, 128. 7 CH, 129.3 CH, 129.4 CH, 135.4 CH(C-4), 136.1 C, 136.3 C, 141.4 C, 144.1 C, 147.5 CH(C-6).

Anal. Calcd. for $C_{17}H_{12}IN$ (357.19): C, 57.16; H, 3.39; I, 35.53; N, 3.93. Found: C, 57.48; H, 3.60; I, 35.30; N, 3.98.

Further elution with ethyl acetate gave 3,5-diphenyl-1*H*-pyridin-2-one (161 mg, 16 %) as a light yellow solid by-product, mp 192-3 °C (ref. [33] mp 202 °C).

4-Iodo-2,6-diphenylpyrimidine (**3b**).

This new compound was prepared adopting a reported procedure [34]. A mixture of 4-chloro-2,6-diphenyl-pyrimidine (**5b**) [35] (3.0 g, 8.3 mmol) and 57 % HI (30 ml, 0.23 mol) was stirred at room temperature for 20 h. Then cold 10 % NaOH (100 ml) was added, the precipitate was collected and washed with cold water, the crude product was recrystallized with petroether (40-60 °C), to give a light brown solid 1.70 g, yield 42 %, mp 98 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 7.41-7.48 (m, 6 H, Ph-H), 7.95 (s, 1 H, H-5), 8.06-8.10 (m, 2H, Ph-H), 8.44-8.48 (m, 2H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 125.6 CH (C-5), 127.3 CH, 128.5 CH, 128.6 CH, 129.0 CH, 130.8 C (C-4) 131.3 CH, 131.4 CH, 135.5 C, 136.3 C, 163.4 C, 164.0 C.

Anal. Calcd for $C_{16}H_{11}IN_2$ (358.18): C, 53.65; H, 3.10; I, 35.43; N, 7.82. Found: C, 53.79; H, 3.24; I, 35.27; N, 7.58.

2-Chloro-4,6-bis-(4-chlorophenyl)-pyrimidine (**3d**).

This new compound was prepared adopting a reported procedure [26]. To a solution of 2,4,6-trichloropyrimidine (1.0 g, 5.5 mmol) in DME (50 ml), 4-chlorophenylboronic acid (1.72 g, 11.0 mmol) and Na_2CO_3 (3.61 g, 34.1 mmol, dissolved in a minimium amount of water) were added. The active catalyst was generated by the addition of palladium (II) acetate (31 mg, 0.14 mmol) and triphenylphosphine (72 mg, 0.28 mmol) to the mixture. Argon was passed through, and the mixture was heated to 70 °C for 24 h. The solvent was removed by rotary evaporation and the residue was dissolved in CH_2Cl_2 (100 ml), washed with water (2 x 50 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with cyclohexane/ethyl acetate (15:1 5:1). A white solid (1.65 g) was obtained, yield 82 %, mp 151-3 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 7.42 (d, 4 H, *J* = 8.7 Hz. Ph-H), 7.85 (s, 1 H, H-5), 8.01 (d, 4 H, *J* = 8.7 Hz, Ph-H). ^{13}C nmr ($CDCl_3$), δ (ppm): 110.3 CH (H-5), 128.7 CH, 129.4 CH, 133.8 C, 138.2 C, 162.2 C, 166.5 C.

Anal. Calcd. for $C_{16}H_9Cl_3N_2$ (335.62): C, 57.26; H, 2.70; Cl, 31.69; N, 8.35. Found: C, 57.23; H, 2.61; Cl, 31.80; N, 8.44.

2-Chloro-4-(4-chlorophenyl)-6-phenyl-pyrimidine (**3e**).

This new compound was prepared adopting a reported procedure [26]. To a solution of 2,4-dichloro-6-(4-phenyl)-pyrimidine [26] (293 mg, 1.1 mmol) in DME (15 ml), 4-chlorophenylboronic acid (134 mg, 1.1 mmol, 1.0 equivalents), Na_2CO_3 (360 mg, 3.4 mmol, 3.1 equivalents, dissolved in a minimium amount of water) were added. The active catalyst was generated by the addition of palladium (II) acetate (12 mg, 0.055 mmol, 5 % equivalents) and triphenylphosphine (29 mg, 0.11 mmol, 10 % equivalents) to the mixture. Argon was passed through and the mixture was heated to 70 °C for 24 h. The solvent was removed by rotary evaporation and the residual product was dissolved in CH_2Cl_2 (50 ml). The solution was washed with water (2 x 20 ml), and dried over anhydrous $MgSO_4$. The solvent was evaporated, the residue was purified by flash column chromatography on silica gel, eluting with cyclohexane/CH_2Cl_2 (5:1 1:1). The compound was obtained as a white solid (274 mg, yield 82 %), mp 97-9 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 7.39-7.46 (m, 5 H, Ph-H), 7.87 (s, 1 H, H-5), 7.98-8.05 (m, 4 H, Ph-H). ^{13}C nmr ($CDCl_3$), δ (ppm): 110.6 CH(C-5), 127.5 CH, 128.7 CH, 129.1 CH, 129.4 CH, 131.8 CH, 134.1 C, 135.8 C, 138.0 C, 162.1 C, 166.3 C, 167.9 C.

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; Cl, 23.54; N, 9.30. Found: C, 63.71; H, 3.46; Cl, 23.66; N, 9.13.

4-Iodo-3-methyl-1,5-diphenyl-pyrazole (**3h**).

This new compound was prepared adopting a reported procedure [36]. A 100 ml flask was charged with 4-methyl-1,2-diphenyl-pyrrole (**4h**) [37] (2.34 g,10.0 mmol) and DMF (50 ml). The solution was cooled to 0 °C and argon was passed through. NIS (2.70 g, 12.0 mmol) was added and the mixture was stirred at

room temperature overnight (16 h). After cooling the solution was cooled again to 0 °C. NIS (0.13 g, 0.5 mmol) was added and stirring at room temperature was continued for another 12 h. Water (250 ml) was added, the mixture was extracted with ether (2 x 120 ml), ethyl acetate (100 ml) and hexane (100 ml) and the combined extracts were washed with water (50 ml), 10 % aq. $Na_2S_2O_3$ (50 ml), water (50 ml), and dried with anhydrous $MgSO_4$. The solvent was evaporated providing a brown solid 2.12 g, yield 59 %, mp 94-6 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 2.33 (s, 3 H, CH_3), 7.08-7.19 (m, 10 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 14.4 CH_3, 66.2 C, 124.6 CH, 127.3 CH, 128.3 C, 128.4 CH, 128.8 CH, 128.9 CH, 130.2 CH, 139.9 C, 144.0 C, 151.6 C; HRMS (EI) calcd for $C_{16}H_{13}IN_2$ (M^+) 360.0123, found 360.0124.

1-Benzyl-2-bromo-4,5-diphenylimidazole (**3i**).

This new compound was prepared adopting a reported procedure [38]. A 50 ml flask was charged with 1-benzyl-4,5-diphenylimidazole (**4i**) [39] (1.25 g, 4.0 mmol), NBS (0.89 g, 5.0 mmol) and acetonitrile (30 ml), the mixture was stirred at room temperature for 4 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with cyclohexane/ethyl acetate (6:1 2:1). A yellow solid 929 mg was obtained, yield 60 %; mp 106-8 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 5.09 (s, 2 H, CH_2), 6.98-7.55 (m, 15 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 49.0 CH_2, 120.6 C(C-2), 126.3 CH, 126.5 CH, 126.8 CH, 127.7 CH, 128.2 CH, 128.7 CH, 129.0 CH, 129.2 CH, 130.2 C, 130.9 CH, 131.4 C, 133.5 C, 136.1 C, 139.2 C.

Anal. Calcd. for $C_{22}H_{17}BrN_2$ (389.29): C, 67.88; H, 4.40; Br, 20.53; N, 7.20. Found: C, 67.59; H, 4.49; Br, 20.91; N, 7.42.

6-Bromo-2,3-diphenyl-imidazo[1,2-a]pyridine (**3j**).

This new compound was prepared adopting a reported procedure [40]. A 50 ml flask was charged with 2-amino-5-bromopyridine (892 mg, 5 mmol), 2-bromo-2-phenyl-acetophenone (desyl bromide) (1.70 g, 6 mmol), $NaHCO_3$ (491 mg, 6 mmol) and *i*-PrOH (15 ml). The mixture was heated under reflux for 12 h, the alcohol was evaporated, then water (30 ml) and dichloromethane (60 ml) were added. The organic phase was separated, washed with water (2 x 30 ml) and dried with anhydrous $MgSO_4$. After evaporating the solvent, the residue was purified by column chromatography on silica gel, eluting with cyclohexane/ethyl acetate (3:1). The compound **3j** was obtained as a white solid 1.17 g, yield 67 %, mp 198-9 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 7.23-7.66 (m, 12 H, Ph-H, H-7 and H-8), 8.05 (dd, 1 H, J_1 = 1.8 Hz, J_2 = 0.8 Hz, H-5); ^{13}C nmr ($CDCl_3$), δ (ppm): 107.1 C, 118.2 CH(C-8), 121.4 C(C-7), 123.3 CH(C-5), 127.8 CH, 128.0 CH, 128.1 CH, 128.3 CH, 129.2 C, 129.3 CH, 129.8 CH, 130.6 CH(C-5), 133.6 C, 143.2 C.

Anal. Calcd. for $C_{19}H_{13}BrN_2$ (349.22): C, 65.35; H, 3.75; Br, 22.88; N, 8.02. Found: C, 65.09; H, 3.97; Br, 23.17; N, 7.91.

6-Chloro-2,3-diphenyl-imidazo[1,2-b]pyridazine (**3k**).

This new compound was prepared adopting a reported procedure [40]. A 50 ml flask was charged with 3-amino-6-chloropyridazine (1.30 g, 10 mmol), 2-bromo-2-phenyl-acetophenone (desyl bromide) (3.40 g, 12 mmol), $NaHCO_3$ (982 mg, 12 mmol) and *i*-PrOH (30 ml). The mixture was heated under reflux for 12 h, the alcohol was evaporated, then water (50 ml) and dichlomethane (100 ml) were added. The organic phase was separated and washed with water (2 x 30 ml), dried with anhydrous $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography on silica gel, eluting with cyclohexane/ethyl acetate (2:1). Compound **3k** was obtained as yellow needles 2.35 g, yield 77 %, mp 207-8 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 7.07 (d, 1 H, J = 9.0 Hz, H-7), 7.31-7.67 (m, 10 H, Ph-H), 7.94 (d, 1 H, J = 9.0 Hz, H-8); ^{13}C nmr ($CDCl_3$), δ (ppm): 118.8 CH, 126. 6 CH, 128.0 C, 128.2 CH, 128.4 CH, 128.5 CH, 128. 8 CH, 129.0 CH, 130.4 CH, 133.6 C, 137.3 C, 144.1 C, 146.5 C.

Anal. Calcd. for $C_{18}H_{12}ClN_3$ (305.76): C, 70.71; H, 3.96; Cl, 11.60; N, 13.74. Found: C, 70.64; H, 3.93; Cl, 11.80; N, 13.63.

9-Benzyl-8-bromo-6-phenyl-purine (**3l**).

A 50 ml flask was charged with 9-benzyl-6-phenyl-purine (**4l**) [41] (358 mg, 1.25 mmol), NBS (1.35 g, 7.5 mmol) and THF 20 ml. The mixture was heated under reflux for 2 days. The solvent was evaporated, the residue was separated by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (3:1). Compound **3l** was obtained as a white solid (255 mg, yield 56 %), mp 112-4 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 5.43 (s, 2 H, CH_2), 7.23-8.69 (m, 10 H, Ph-H), 8.91 (s, 1 H, H-2); ^{13}C nmr ($CDCl_3$), δ (ppm): 47.6 CH_2, 127.8 CH, 128.4 CH, 128.7 CH, 128.9 CH, 129.7 CH, 131.2 CH, 131.3 C, 133.1 C, 134.8 C, 135.1 C, 152.1 CH(H-2), 153.6 C, 153.7 C.

Anal. Calcd for $C_{18}H_{13}BrN_4$ (365.23): C, 59.19; H, 3.59; Br, 21.88; N, 15.34. Found**:** C, 59.45; H, 3.75; Br, 22.06; N, 15.13

Propargylamines **2** by Sonagashira Cross-coupling Reaction of Halogenated Diarylheterocycles **3**.

General Procedure, Method A**.**

A 25 ml Schlenk flask was charged with the appropriate iodoarene **3** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), TEA (10 ml) and *N*,*N*-dimethylpropargylamine (83 mg, 1.0 mmol). The flask was flushed with argon three times and the mixture was stirred at room temperature for 24 h. The solvent was evaporated under vacuum, the residue was purified by column chromatography.

General Procedure, Method B.

A 25 ml Schlenk flask was charged with the appropriate aryl halide **3** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), TEA (10 ml) and *N*,*N*-dimethylpropargylamine (83 mg, 1.0 mmol). The flask was flushed with argon three times and the mixture was stirred at 80 °C for 24 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography.

General Procedure, Method C.

A 25 ml Schlenk flask was charged with the appropriate halide **3** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), TEA (5 ml)**,** DMF (5 ml) and *N*,*N*-dimethyl-propargylamine (83 mg, 1.0 mmol). The flask was flushed with argon three times and the mixture was heated at 100 °C for 24 h. The solvent was evaporated under vacuum, the residue was purified by column chromatography.

General Procedure, Method D.

A 25 ml Schlenk flask was charged with the appropriate aryl halide **3** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), KOAc (80 mg, 0.8 mmol), DMF (10 ml) and *N*,*N*-dimethylpropargylamine (83 mg, 1.0 mmol). The flask was flushed with argon three times and the mixture was heated at 100

°C for 24 h, the solvent was evaporated under vacuum, the residue was purified by column chromatography.

General Procedure, Method E.

A 25 ml Schlenk flask was charged with the appropriate aryl halide **3** (0.5 mmol), K_2CO_3 (166 mg, 1.2 mmol), CuI (10 mg, 0.05 mmol), 10% Pd/C (22 mg, 0.02 mmol), PPh_3 (21 mg, 0.08 mmol), dimethoxyethane (5 ml) and water (5 ml). Argon was passed through the flask three times and the mixture was stirred at 25°C for 0.5 h, then *N*,*N*-dimethylpropargylamine (50 mg, 0.6 mmol) was added *via* a syringe . The mixture was heated at 80 °C for 24 h, then cooled to room temperature, filtered through a pad of celite and washed with EtOAc. The combined organic layers were washed with water (30 ml) twice. The organic layer was dried with anhydrous $MgSO_4$, concentrated under vacuum and the residue was purified by flash column chromatography.

3-(3,5-Diphenyl-pyridin-2-yl)-prop-2-ynyl]-dimethyl-amine (**2a**).

According to Method A, the product was purified by column chromatography on silica gel eluting with EtOAc/MeOH (6:1). Compound **2a** was obtained as a light brown crystals, yield 89 %, mp 82-83 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 2.08 (s, 6 H, 2 x CH_3), 3.35 (s, 2 H, CH_2), 7.28-7.51 (m, 10H, Ph-H), 7.74 (d, 1H, *J* = 1.8 Hz, H-4), 8.70 (d, 1 H, *J* = 1.8 Hz, H-6); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.0 CH_3, 48.5 CH_2, 84.7 C, 88.3 C, 127.1 CH, 128.1 CH, 128.3 CH, 128.4 CH, 129.2 CH, 129.3 CH, 135.1 CH(C-4), 135.5 C, 137.0 C, 138.3 C, 139.6 C, 139.8 C, 147.0 CH(C-6); HRMS (EI) calcd for $C_{22}H_{20}N_2$ (M^+) 312.1627, found 312.1626.

Anal. Calcd. for $C_{22}H_{20}N_2$ (312.41): C, 84.58; H, 6.45; N, 8.97. Found: C, 84.52; H, 6.50; N, 8.94.

[3-(2,6-Diphenyl-pyrimidin-4-yl)-prop-2-ynyl]-dimethyl-amine (**2b**).

According to Method A, the product was purified by column chromatography on silica gel, eluting with EtOAc/MeOH (8:1). Compound **2b** was obtained as a light brown solid, yield 76 %, mp 62-3 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.29 (s, 6 H, 2 x CH_3), 3.44 (s, 2 H, CH_2), 7.35-7.37 (m, 6 H, Ph-H), 7.51 (s, 1 H, H-5), 8.05 (m, 2 H, Ph-H), 8.48 (m, 2H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.5 CH_3, 48.6 CH_2, 84.2 C, 89.1 C, 116.9 CH(H-5), 127.2 CH, 128.5 CH, 128.5 CH, 128.9 CH, 130. 9 CH, 132.2 CH, 136.4 C, 137.4 C, 151.4 C, 164.0 C, 164.7 C.

Anal. Calcd. for $C_{21}H_{19}N_3$ (313.40): C, 80.48; H, 6.11; N, 13.41. Found: C, 80.30; H, 6.35; N, 13.24.

[3-(4,6-Diphenyl-pyrimidin-2-yl)-prop-2-ynyl]-dimethyl-amine (**2c**).

Purification by column chromatography on silica gel and eluting with EtOAc/MeOH (5:1) provided a light brown solid, yield 38 % (Method C), yield 71 % (Method D), mp 101-3 °C; ^{1}H nmr ($CDCl_3$), δ (ppm): 2.39 (s, 6 H, 2 x CH_3), 3.54 (s, 2H, CH_2), 7.43-7.46 (m, 6H, Ph-H), 7.93 (s, 1 H, H-5), 8.06-8.10 (m, 4H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.4 CH_3, 48.4 CH_2, 83.1 C, 85.4 C, 111.6 CH(H-5), 127.4 CH, 129.0 CH, 131.1 CH, 136. 6C, 153.1 C, 165.2 C; HRMS (EI) calcd for $C_{21}H_{19}N_3$ (M^+) 313.1579, found , 313.1579.

Anal. Calcd. for $C_{21}H_{19}N_3$ (313.40) C, 80.48; H, 6.11; N, 13.41. Found: C, 80.14; H, 6.12; N, 13.37.

{3-[4,6-Bis-(4-chloro-phenyl)-pyrimidin-2-yl]-prop-2-ynyl}-dimethyl-amine (**2d**).

According to Method C**,** the product was purified by column chromatography on silica gel, eluting with EtOAc gave a light brown solid 98 mg, yield 51 %, mp: 112-4 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.35 (s, 6 H, 2 x CH_3), 3.50 (s, 2 H, CH_2), 7.37 (d, 4 H, *J* = 8.7 Hz), 7.80 (s, 1 H, H-5), 7.98 (d, 4 H, *J* = 8.7 Hz, Ph-H). ^{13}C nmr ($CDCl_3$), δ (ppm): 44.4 CH_3, 48.4 CH_2, 83.7 C, 85.1 C, 111.8 CH(H-5), 128.6 CH, 129.18 C, 134. 7 CH, 137.5 C, 153.1 C, 164.0 C.

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3$ (382.28): C, 65.98; H, 4.48; Cl, 18.55; N, 10.9. Found: C, 65.84; H, 4.61; Cl, 18.73; N, 10.81.

{3-[4-(4-Chloro-phenyl)-6-phenyl-pyrimidin-2-yl]-prop-2-ynyl}-dimethyl-amine (**2e**).

According to Method C, the product was purified by column chromatography on neutral Al_2O_3, eluting with cyclohexane/EtOAc (1:1) provided a light brown solid 88 mg. yield 51 %, mp 86-8 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.35 (s, 6 H, 2 x CH_3), 3.50 (s, 2 H, CH_2), 7.36-7.42 (m, 5 H, Ph-H), 7.84(s, 1 H, H-5), 7.97-8.05 (m, 4 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.4 CH_3, 48.4 CH_2, 83. 5 C, 85.2 C, 111.1 CH(H-5), 127.3 CH, 128.6 CH, 129.0 CH, 129.2 CH, 131.2 CH, 134. 9 C, 136.3 C, 137.3 C, 153.1 C, 163.8 C, 165.3 C.

Anal. Calcd. for $C_{21}H_{18}ClN_3$ (347.84): C, 72.51; H, 5.22; Cl, 10.19; N, 12.08. Found: C, 72.66; H, 5.41; Cl, 10.26; N, 11.94.

[3-(5,6-Diphenyl-pyrazin-2-yl)-prop-2-ynyl]-dimethyl-amine (**2f**).

Purification by column chromatography on neutral Al_2O_3, eluting with cyclohexane/EtOAc (1:1) provided a light brown oil, yield 27 % (Method C), yield 52 % (Method D). ^{1}H nmr ($CDCl_3$), δ (ppm): 2.31 (s, 6 H, 2 _ CH_3), 3.48 (s, 2 H, CH_2), 7.18-7.37 (m, 10 H, Ph-H), 8.58 (s, 1 H, H-3); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.4 CH_3, 48.6 CH_2, 82.5 C, 89.2 C, 128.3 CH, 128.8 CH, 128.9 CH, 129.6 CH, 129.7 CH, 137.0 C, 138.1 C, 138.1 C, 144.7 CH(C-3), 150.8 C, 152.3 C; HRMS (EI) calcd for $C_{21}H_{19}N_3$ (M^+) 313.1579, found 313.1576.

[3-(2,5-Diphenyl-oxazol-4-yl)-prop-2-ynyl]-dimethyl-amine (**2g**).

Purification by column chromatography on silica gel, eluting with EtOAc:MeOH (6/1) gave light brown glassy material. Yields were 10 % (Method B), 42 % (Method C) and 56 % (Method D), respectively. ^{1}H nmr($CDCl_3$), δ (ppm): 2.35 (s, 6 H, 2 x CH_3), 3.58 (s, 2 H, CH_2), 7.37-8.02 (m, 10 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.1 CH_3, 48.6 CH_2, 77.9 C, 91.1 C, 119.2 C, 125.0 CH, 126.6 CH, 128.8 CH, 129.0 CH, 130.8 CH, 132.0 CH, 133.1 C, 135.2 C, 151. 8 C, 159.6 C; HRMS (EI) calcd for $C_{20}H_{18}N_2O$ (M^+) 302.1419, found 302.1419.

Dimethyl-[3-(3-methyl-1,5-diphenyl-pyrazol-4-yl)-prop-2-ynyl]-amine (**2h**).

According to Method E, the product was purified by flash column chromatography on silica gel, eluting with EtOAc: MeOH(1:0 6:1) gave a light brown solid. Yield 153 mg (97 %), mp 66-7 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.23 (s, 6 H, 2 x CH_3), 2.36 (s, 3 H, CH_3), 3.40 (s, 2 H; CH_2), 7.14-7.61 (m, 10H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 12.6 CH_3, 44.0 CH_3, 48.7 CH_2, 88.1 C, 104.1 C, 125.0 CH, 127.3 CH, 128.3 CH, 128.5 CH, 128. 9 CH, 129.4 CH, 132.0 C, 133.2 C, 139.8 C, 144.2 C, 152.0 C.

Anal. Calcd. for $C_{21}H_{21}N_3$ (315.41): C, 79.97; H, 6.71; N, 13.32. Found: C, 80.12; H, 6.72; N, 13.15.

[3-(1-Benzyl-4,5-diphenyl-imidazol-2-yl)-prop-2-ynyl]-dimethyl-amine (**2i**).

The product was purified by column chromatography on neutral Al_2O_3, eluting with cyclohexane/EtOAc (5:1 1:1) provided a light brown oil. Yield were 43 % (Method B) and 27 % (Method C), respectively. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.20 (s, 6 H, 2 x CH_3), 3.49 (s, 2 H, CH_2), 5.09 (s, 2 H, CH_2), 6.88-7.48 (m, 15 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.0 CH_3, 48.3 CH_2, 48.4 CH_2, 75.6 C, 89.2 C, 126.6 CH, 126.7 CH, 126.8 CH, 126.9 C, 127.6 CH, 128.1 CH, 128.6 C, 128.8 CH, 128.9 CH, 130.3 C, 130.8 CH, 131.6 C, 133.9 C, 136.6 C, 138.5 C; HRMS (EI) calcd for $C_{27}H_{25}N_3$ (M^+) 391.2049, found 391.2046.

[3-(2,3-Diphenyl-imidazo[1,2-*a*]pyridin-6-yl)-prop-2-ynyl]-dimethyl-amine (**2j**).

According to Method C, the product was purified by column chromatography on silica gel, eluting with EtOAc/MeOH (4:1). The compound **2j** was obtained as a light yellow solid, yield 74 %, mp 136-7 °C. 1H nmr ($CDCl_3$), δ (ppm): 2.27 (s, 6 H, 2 x CH_3), 3.34 (s, 2 H, CH_2), 7.15-7.59 (m, 12 H, Ph-H, H-7 and H-8), 7.98 (s, 1 H, H-5); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.4 CH_3, 48.6 CH_2, 81.4 C, 86.3 C, 108. 9 C, 117.2 CH(C-8), 126.2 CH(C-7), 127.7 CH, 127.8 CH, 128.0 CH, 128.3 CH, 129.2 CH, 129. 7 CH, 130.7 CH(C-5), 132.0 C, 132.2 C, 133.8 C, 143.1 C, 143.6.

Anal. Calcd. for $C_{24}H_{21}N_3$ (351.44): C, 82.02; H, 6.02; N, 11.96. Found: C, 82.06; H, 6.26; N, 11.78.

[3-(2,3-Diphenyl-imidazo[1,2-b]pyridazin-6-yl)-prop-2-ynyl]-dimethyl-amine (**2k**).

According to Method C, the product was purified by column chromatography on silica gel, eluting with EtOAc/MeOH (6:1). The compound **2k** was obtained as a light yellow solid, yield 86 %, mp 144-5 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.38 (s, 6 H, 2 x CH_3), 3.50 (s, 2 H, CH_2), 7.15 (d, 1 H, *J* = 9.2 Hz, H-7), 7.28-7.66 (m, 10 H, Ph-H), 7.98 (d, 1H, *J* = 9.2 Hz, H-8); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.5 CH_3, 48.5 CH_2, 81.7 C, 88.6 C, 121.0 CH, 124.7 CH, 125.3 C, 128.1, 128.3 CH, 128. 5 CH, 128.7 CH, 128.7 CH, 130.6 CH, 133.7 C, 137.6 C, 138.0, 143.9 C, 146.6 C.

Anal. Calcd. for $C_{23}H_{20}N_4$ (352.43): C, 78.38; H, 5.72; N, 15.90. Found: C, 78.22; H, 5.91; N, 15.86.

[3-(9-Benzyl-6-phenyl-purin-8-yl)-prop-2-ynyl]-dimethyl-amine (**2l**).

According to Method B, purification by column chromatography on silica gel, eluting with EtOAc → EtOAc/MeOH (8:1) provided a light brown solid (158 mg, 86 %), mp 134-6 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.34 (s, 6 H, 2 x CH_3), 3.63 (s, 2 H, CH_2), 5.58 (s, 2 H, CH_2), 7.29-8.80 (m, 10 H, Ph-H), 9.03 (s, 1 H, H-2). ^{13}C nmr ($CDCl_3$), δ (ppm): 44.2 CH_3, 46.9 CH_2, 47.6 CH_2, 75.1 C, 94.2 C, 127.6 CH, 128.2 CH, 128.7 CH, 128.8 C, 128.9 CH, 129.9 CH, 130.9 C, 131.1 CH, 135.5 C, 138.4 C, 152.3 C, 152.1 CH(H-2), 154.6 C.

Anal. Calcd for $C_{23}H_{21}N_5$ (367.45): C, 75.18; H, 5.76; N, 19.06. Found: C, 75.05; H, 5.98; N, 19.01.

[3-(2,3-Diphenyl-pyrido[2,3-*b*]pyrazin-7-yl)-prop-2-ynyl]-dimethyl-amine (**2m**).

According to general Method C, the product was purified by column chromatography on silica gel, eluting with EtOAc/MeOH (4:1). The compound **2m** was obtained as a light yellow solid (133 mg, 76 %), mp 101-3 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 2.32 (s, 6 H, 2 x CH_3), 3.47 (s, 2 H, CH_2), 7.20-7.27 (m, 6 H, Ph-H), 7.42 (m, 2 H, Ph-H), 7.51 (m, 2 H, Ph-H), 8.40 (d, 1 H, *J* = 2.3 Hz, H-8), 8.40 (d, 1 H, *J* = 2.3 Hz, H-6); ^{13}C nmr ($CDCl_3$), δ (ppm): 44.3 CH_3, 48.6 CH_2, 81. 7 C, 91.0 C, 121.7 C, 128.1 CH, 128.4 CH, 129.4 CH, 129.5 CH, 129.8 CH, 129.8 CH, 130.2 CH, 135.3 C, 137.9 C, 138.3 C, 139.6 CH(C-8), 148.6 C, 155.2 C, 156.1 CH(C-6).

Anal. Calcd. for $C_{24}H_{20}N_4$ (364.44): C, 79.10; H, 5.53; N, 15.73. Found: C, 78.94; H, 5.69; N, 15.36.

Catalytic Hydrogenation of Alkynes **2**.

General Procedure.

A flask was charged with the corresponding 3-dimethylaminopropyn-1-yl substituted diaryl-heterocycle **2** (0.2-0.5 mmol), 10 % Pd/C (0.2 equivalent) and EtOH (15 ml). The mixture was stirred under hydrogen at room temperature and atmospheric pressure for 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of celite, washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on neutral Al_2O_3.

3,5-Diphenyl-2-(3-dimethylaminopropyl)-pyridine (**1a)** and 3,5-Diphenyl-2-propyl-pyridine (**10**).

Purification by column chromatography on neutral Al_2O_3 eluting with EtOAc/MeOH (1:0→10:1) gave at first (elution with EtOAc) the hydrodeaminated side product **10** as a light yellow liquid (17 mg, 16%) followed by the fraction of **1a** as a light brown oil, yield 71 %. **1a**: ^{1}H nmr ($CDCl_3$), δ (ppm): 1.73-1.83 (m, 2 H, CH_2), 2.08 (s, 6 H, 2 x CH_3), 2,20 (t, 2 H, *J* = 7.5 Hz, CH_2), 2.73 (t, 2 H, *J* = 7.9 Hz, CH_2), 7.26-7.52 (m, 10 H, Ph-H), 7.61 (d, 1 H, *J* = 2.3 Hz, H-4), 8.70 (d, 1 H, *J* = 2.3 Hz, H-6); ^{13}C nmr ($CDCl_3$), δ (ppm): 27.4 CH_2, 33.1 CH_2, 45.0 CH_3, 59.3 CH_2, 127.0 CH, 127.6 CH, 127.9 CH, 128.5 CH, 129.0 CH, 129.1 CH, 133.9 C, 135.9 C, CH(C-4), 136.8 C, 137.6 C, 139.7 C, 146.5 CH(C-6), 158.0 C; HRMS (EI) calcd for $C_{22}H_{24}N_2$ (M^+) 316.1939, found 316.1937. **10**: ^{1}H nmr ($CDCl_3$), δ (ppm): 0.80 (t, 3 H, *J* = 7.3 Hz, CH_3), 1.60-1.69 (m, 2 H, CH_2), 2.71 (t, 2 H, *J* = 7.9 Hz, CH_2), 7.27-7.55 (m, 10 H, Ph-H), 7.63 (d, 1 H, *J* = 2.3 Hz, H-4), 8.72 (d, 1 H, *J* = 2.3 Hz, H-6); ^{13}C nmr ($CDCl_3$), δ (ppm): 14.1 CH_3, 23.1 CH_2, 37.2 CH_2, 127.0 CH, 127.5 CH, 127.9 CH, 128.4 CH, 129.0 CH, 129.1 CH, 133.7 C, 135.9 CH(C-4), 136.8 C, 137.7 C, 139.9 C, 146.4 CH(C-6). 158.4 C; HRMS (EI) calcd for $C_{20}H_{19}N$ (M^+) 273.1518, found 273.1517.

[3-(2,6-Diphenyl-pyrimidin-4-yl)-propyl]-dimethyl-amine (**1b**).

Purification by column chromatography on neutral Al_2O_3 using EtOAc/MeOH (10:1) as eluting solvent gave a light brown oil, yield 76 %. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.91-2.01 (m, 2 H, CH_2), 2.17 (s, 6 H, 2 x CH_3), 2.31 (t, 2 H, *J* = 7.3 Hz, CH_2), 2.79 (t, 2 H, *J* = 7.5Hz, CH_2), 7.35 (s, 1 H, H-5), 7.38-7.41 (m, 6 H, Ph-H), 8.11 (m, 2H, Ph-H), 8.51(m, 2H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 26.5 CH_2, 35.8 CH_2, 45.4 CH_3, 59.0 CH_2, 113.5 CH(C-5), 127.1 CH, 128.4 CH, 128.4 CH, 128.9 CH, 130.5 CH, 130.7 CH, 137.3 C, 138.2 C, 163.7 C, 164.2 C, 171.0 C; HRMS (EI) calcd for $C_{21}H_{23}N_3$ (M^+) 317.1892, found 317.1892.

[3-(4,6-Diphenyl-pyrimidin-2-yl)-propyl]-dimethyl-amine (**1c**).

Purification by column chromatography on neutral Al_2O_3 using EtOAc/cyclohexane (1:1) as eluting solvent gave a light brown oil (55 mg, 72 %). ^{1}H nmr ($CDCl_3$), δ (ppm): 2.04-2.14 (m, 2 H, CH_2), 2.20 (s, 6 H, 2 x CH_3), 2.37 (t, 2 H, *J* = 7.5 Hz, CH_2), 3.03 (t, 2 H, *J* = 7.7 Hz, CH_2), 7.41-7.44 (m, 6 H, Ph-H),

7.81 (s, 1H, H-5), 8.05-8.08 (m, 4 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 26.5 CH_2, 37.5 CH_2, 45.6 CH_3, 59. 6 CH_2, 110.0 CH(C-5), 127.3 CH, 128.9 CH, 130.6 CH, 137.6 C, 164.7 C, 171.3 C; HRMS (EI) calcd for $C_{21}H_{23}N_3$ (M^+) 317.1892, found 317.1890.

Catalytic hydrogenation of **2d** and **2e** gave **1c** in 45 % and 49 % yield, respectively. The expected chlorophenyl-containing products were not observed.

[3-(5,6-Diphenylpyrazin-2-yl)-propyl]-dimethyl-amine (**1f**).

The residue was purified by column chromatography on neutral Al_2O_3 eluting with EtOAc/MeOH (10:1). The compound **1f** was obtained as a light brown oil, yield 58 %. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.89-1.99 (m, 2 H, CH_2), 2.18 (s, 6 H, 2 _ CH_3), 2.32 (t, 2H, *J* = 7.3 Hz, CH_2), 2.86 (t, 2 H, *J* = 7.7Hz, CH_2),7.20-7.36 (m, 10 H, Ph-H), 8.40 (s, 1 H, H-3); ^{13}C nmr ($CDCl_3$), δ (ppm): 27.3 CH_2, 32.8 CH_2, 45.5 CH_3, 59.1 CH_2, 128.2 CH, 128.3 CH, 128.5 CH, 129.6 CH, 129.7 CH, 138.8 C, 138.9 C, 141.6 CH(C-3), 150.0 C, 151.6 C, 154.5 C; HRMS (EI) calcd for $C_{21}H_{23}N_3$ (M^+) 317.1892, found 317.1890.

[3-(2,5-Diphenyl-oxazol-4-yl)-propyl]-dimethyl-amine (**1g**).

Purification by column chromatography on neutral Al_2O_3 eluting with cyclohexane/EtOAc (1:1) gave a light yellow oil, yield 58 %. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.78-1.88 (m, 2 H, CH_2), 2.09 (s, 6 H, 2 x CH_3), 2.25 (t, 2 H, *J* = 7.4 Hz, CH_2), 2.70 (t, 2 H, *J* = 7.7 Hz, CH_2), 7.17-7.95 (m, 10 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 25.1 CH_2, 26.8 CH_2, 45.5 CH_3, 59.2 CH_2, 125.6 CH, 126.3 CH, 127.6 C, 127.7 CH, 128.7 CH, 128.8 CH, 129.1 C, 130.1 CH, , 133.1 C, 137.5 C, 145.4 C, 159.5 C; HRMS (EI) calcd for $C_{20}H_{22}N_2O$ (M^+) 306.1173, found 306.1173.

Dimethyl-[3-(3-methyl-1,5-diphenyl-pyrazol-4-yl)-propyl]-amine (**1h**).

Purification by column chromatography on neutral Al_2O_3 eluting with EtOAc/MeOH (10:1) gave a light brown oil, yield 76 %. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.48-1.58 (m, 2 H, CH_2), 2.06 (s, 3 H, CH_3), 2.12 (t, 2 H, *J* = 7.4 Hz, CH_2), 2.28 (s, 3 H, CH_3), 2.37 (t, 2 H, *J* = 7.9 Hz, CH_2), 7.07-7.62 (m,10 H, Ph-H); ^{13}C nmr ($CDCl_3$), δ (ppm): 12.2 CH_3, 21.3 CH_2, 28.9 CH_2, 45.4 CH_3, 59. 4 CH_2, 119.4 C, 124.4 CH, 126.3 CH, 128.1 CH, 128.4 CH, 128.6, 129.8 CH, 131.1 C, 140.1 C, 140.4 C, 148.3 C; HRMS (EI) calcd for $C_{21}H_{25}N_3$ (M^+) 319.2049, found 319.2046.

Anal. Calcd. for $C_{21}H_{25}N_3$ (319.44): C, 78.96; H, 7.89; N, 13.15. Found: C, 78.83; H, 8.02; N, 13.07.

[3-(1-Benzyl-4,5-diphenyl-imidazol-2-yl)-propyl]-dimethyl-amine (**1i**).

Purification by column chromatography on neutral Al_2O_3 eluting with EtOAc gave a light brown oil, yield 63 %. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.92-2.02 (m, 2 H, CH_2), 2.19 (s, 6 H, 2 x CH_3), 2,35 (t, 2 H, *J* = 7.8 Hz, CH_2), 2,70 (t, 2 H, *J* = 7.58 Hz, CH_2), 5.01 (s, 2 H, CH_2), 6.92-7.52 (m, 15 H, Ph-H). ^{13}C nmr ($CDCl_3$), δ (ppm): 25.1 CH_2, 26.0 CH_2, 45.3 CH_3, 46.8 CH_2, 59.1 CH_2, 125.8 CH, 126.1 CH, 126.7 CH, 127.5 CH, 128.1 C, 128.5 CH, 128. 8 CH, 128.9 CH, 131.0 CH, 132.4 C, 134.8 C, 136.7 C, 137.4 C, 148.3; HRMS (EI) calcd for $C_{27}H_{29}N_3$ (M^+) 395.2362, found 395.2359.

[3-(2,3-Diphenylimidazo[1,2-*a*]pyridin-6-yl)-propyl]-dimethyl-amine (**1j**).

Purification by column chromatography on neutral Al_2O_3 eluting with AcOEt/MeOH (10:1) gave a light brown solid, yield 47 %, mp 70-1 °C. 1H nmr ($CDCl_3$), δ (ppm): 1.67 (m, 2 H, CH_2), 2.12 (s, 3 H, 2 x CH_3), 2.19 (t, 2 H, *J* = 7.2 Hz, CH_2), 2.49 (t, 2 H, *J* = 7.7 Hz, CH_2), 7.01 (dd, 1 H, J_1 = 9.0 Hz, J_2 =1.5 Hz , H-7), 7.16-7.58 (m, 11 H, Ph-H and H-8), 7.67 (s, 1 H, H-5); ^{13}C nmr ($CDCl_3$), δ (ppm): 28.7 CH_2, 30.4 CH_2, 45.4 CH_3, 58.7 CH_2, 117.9 CH, 120.8 CH, 126.3 C, 126.9 CH, 127.3 CH, 128.0 CH, 128.2 CH, 128.8 Ch, 129.5 CH, 130.1 C,130.7 CH,132.2 C, 134.3 C, 142.4 C, 142.4 C, 144.1 C; HRMS (EI) calcd for $C_{24}H_{25}N_3$ (M^+) 355.2049, found 355.2045.

[3-(2,3-Diphenylimidazo[1,2-*b*]pyridazin-6-yl)-propyl]-dimethyl-amine (**1k**).

Purification by column chromatography on neutral Al_2O_3, eluting with EtOAc/MeOH (10:1) gave a light brown solid, yield 73 %, mp 112-3 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.80 (m, 2 H, CH_2), 2.11 (s, 6H, 2 x CH_3), 2.23 (t, 2 H, *J* = 7.3 Hz, CH_2), 2,73 (t, 2 H, *J* = 7.7 Hz, CH_2), 6.85 (d, 1 H, *J* = 9.1 Hz, H-7), 7.19-7.60 (m, 10H, Ph-H), 7.79 (d, 1 H, *J* = 9.1 Hz, H-8); ^{13}C nmr ($CDCl_3$), δ (ppm): 26.6 CH_2, 33.3 CH_2, 45.5 CH_3, 58.9 CH_2, 118.5 CH, 124.9 CH, 127.7 CH, 128.3 CH, 128.3 CH, 128.4 CH, 128.4 CH, 129.1 C, 130.5 CH,134.4 C, 137.9 C, 142.9 C, 154.9 C.

Anal. Calcd. for $C_{23}H_{24}N_4$ (356.46): C, 77.50; H, 6.79; N, 15.72. Found: C, 77.52; H, 6.82; N, 15.62.

[3-(9-Benzyl-6-phenyl-purin-8-yl)-propyl]-dimethyl-amine (**1l**).

Purification by column chromatography on neutral Al_2O_3 eluting with cyclohexane/EtOAc (1:1) gave a light yellow solid, yield 70 %, mp 81-3 °C. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.94-2.02 (m, 2 H, CH_2), 2.13 (s, 6 H, 2 x CH_3), 2.27 (t, 2H, *J* = 7.2 Hz, CH_2), 2.82 (t, 2 H, *J* = 7.4 Hz, CH_2), 5.45 (s, 2H, CH_2), 7.07-8.78 (m, 10 H, Ph-H), 8.91 (s, 1H, H-2); ^{13}C nmr ($CDCl_3$), δ (ppm): 25.0 CH_2, 25.5 CH_2, 45.4 CH_3, 45.5 CH_2, 58.7 CH_2, 126.9 CH, 128.1 CH, 128.6 CH, 129.0 C, 129.7 CH, 130.6 CH, 130.9 C, 132.2 C, 135.8 C, 151.8 CH(H-2), 152.9 C, 154.1 C, 157.4 C.

Anal. Calcd for $C_{23}H_{21}N_5$ (371.48): C, 74.36; H, 6.78; N, 18.85. Found: C, 74.56; H, 6.91; N, 18.77

N'-(2,3-Diphenylpyrido[2,3-*b*]pyrazin-7-yl)-*N*,*N*-dimethyl-propane-1,3-diamine (**1m**).

Purification by column chromatography on neutral Al_2O_3 eluting with EtOAc/MeOH (10:1), gave a light brown oil, yield 54 %. ^{1}H nmr ($CDCl_3$), δ (ppm): 1.85-1.92 (m, 2 H, CH_2), 2.18 (s, 6 H; 2 x CH_3), 2.30 (t, 2 H, *J* = 7.2 Hz, CH_2), 2.88 (t, 2 H, *J* = 7.2 Hz, CH_2), 7.26-7.30 (m, 6 H, Ph-H), 7.46 (m, 2 H, Ph-H), 7.51 (m, 2 H, Ph-H), 8.2 (d, 1 H, $J_{6,8}$ = 2.3 Hz, H-8), 8.96 (d, 1 H, $J_{6,8}$ = 2.3 Hz, H-6); ^{13}C nmr ($CDCl_3$), δ (ppm): 28.7 CH_2, 30.7 CH_2, 45.4 CH_3, 58. 7 CH_2, 128.1 CH, 128.4 CH, 129.2, CH, 129.2 CH, 129.8 CH, 130.2 CH, 135.8 CH(C-8), 136.0 C, 138.2 C, 138.7 C, 140.2 C, 148.4 C, 154.5 C, 155.3 C, 155.8 CH(C-6); HRMS (EI) calcd for $C_{24}H_{24}N_4$ (M^+) 368.2001, found 368.2001.

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