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SYNTHESIS OF PYRROLO[2,3]PYRIDO[2,4-*d*]PYRIMIDIN-6-ONES AND RELATED NEW HETEROCYCLES

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Abstract – During our synthetic development work focused on new Bcl-2 inhibitor molecules an unexpected and interesting by-product was formed. Using this observation we have explored the synthesis of the hitherto unknown pyrrolo[2,3]pyrido[2,4-*d*]pyrimidin-6-one heterocyclic core. The study of the scope and limitations of this cyclisation resulted in other three new types of three membered heterocyclic ring systems.

INTRODUCTION

Resistance to apoptosis is a widely studied cancer hallmark that has inspired the development of targeted therapeutic approaches towards unlocking apoptotic signaling and selective induction of cancer cell death. The B-cell lymphoma-2 (Bcl-2) gene family encodes at least 20 proapoptotic and antiapoptotic proteins that are the key regulators of apoptosis in the mitochondria-mediated death pathway. The antiapoptotic protein family includes Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and A1 bearing four Bcl homology (BH) domains (BH1-4) and a transmembrane domain. Interplay of the proapoptotic (as Bax or Bak) and the antiapoptotic proteins modulates cell survival and death. In normal healthy cell, antiapoptotic proteins sequester their apoptotic counterparts through BH3 domain binding. To evade apoptosis, tumor cells can upregulate antiapoptotic protein Bcl-2 and block the normal apoptotic pathway. Therefore, a small molecule Bcl-2 inhibitor designed to bind to the BH3 binding groove in the antiapoptotic proteins may restore the normal apoptotic signaling and overcome the apoptosis resistance of cancer cells.¹

Drug development work over many years focused on Bcl-2 inhibitors has recently led to the clinical approval of Venetoclax (ABT-199, Figure 1) approved for the treatment of chronic lymphocytic leukemia in patients.² In parallel on the same research ground at Servier many potent Bcl-2 inhibitor has been developed, patented³ and put on clinic (S55746).⁴

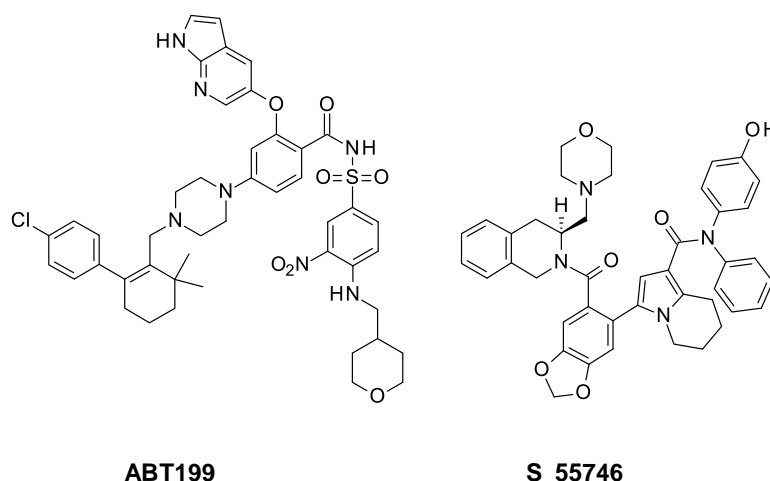
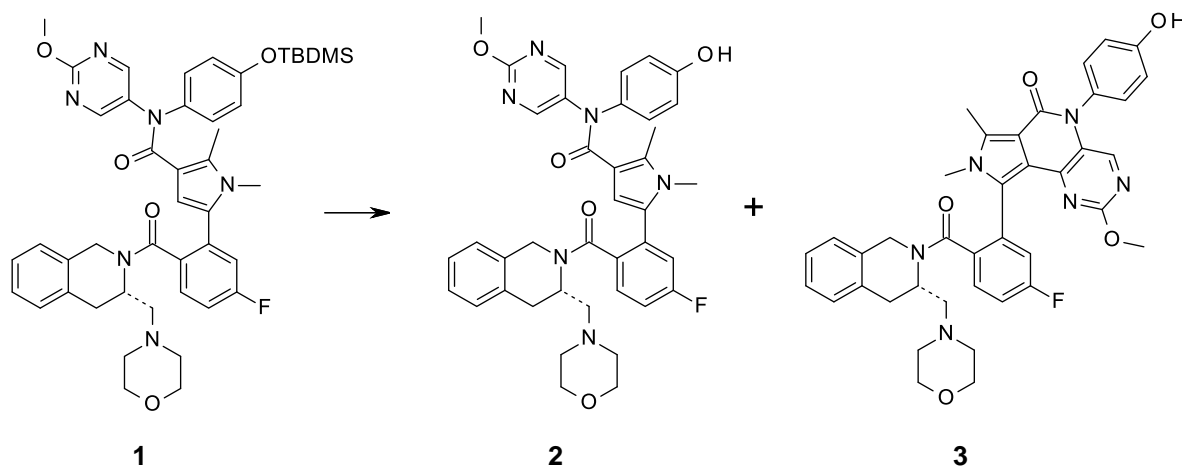


Figure 1. Structures of representative Bcl-2 inhibitors

During the synthetic development of this compound family in one particular example at the last synthetic step, an unexpected and interesting by-product **3** assumed to be formed under acidic conditions in a significant amount to make problematic the isolation of the targeted molecule **2**. The structure of **3** was not fully confirmed by spectroscopical methods, but it was suggested it is an interesting tricyclic derivative, with a heterocyclic core - pyrrolo[2,3]pyrido[2,4-*d*]pyrimidin-6-ones - hitherto unknown from the chemical literature (Scheme 1).

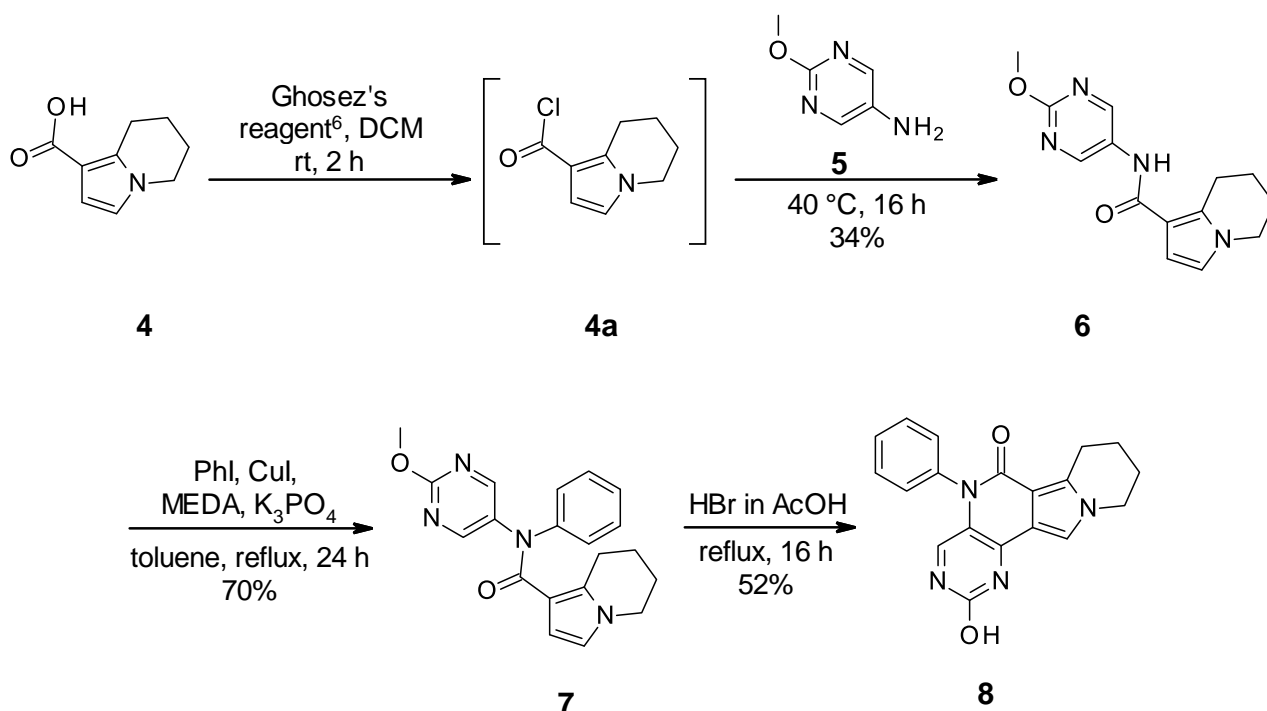


Scheme 1. Side reaction observed during drug discovery

RESULTS AND DISCUSSION

To prove this possible side reaction of this deprotection step, we have decided to check the reactivity on a smaller scaffold, namely on an unsubstituted 5,6,7,8-tetrahydroindolizine-1-carboxylic acid⁵ (**4**) which was readily available for the exemplification of our ongoing drug development program that time. The model substrate for the cyclisation **7** has been prepared by a two-steps sequence from commercially

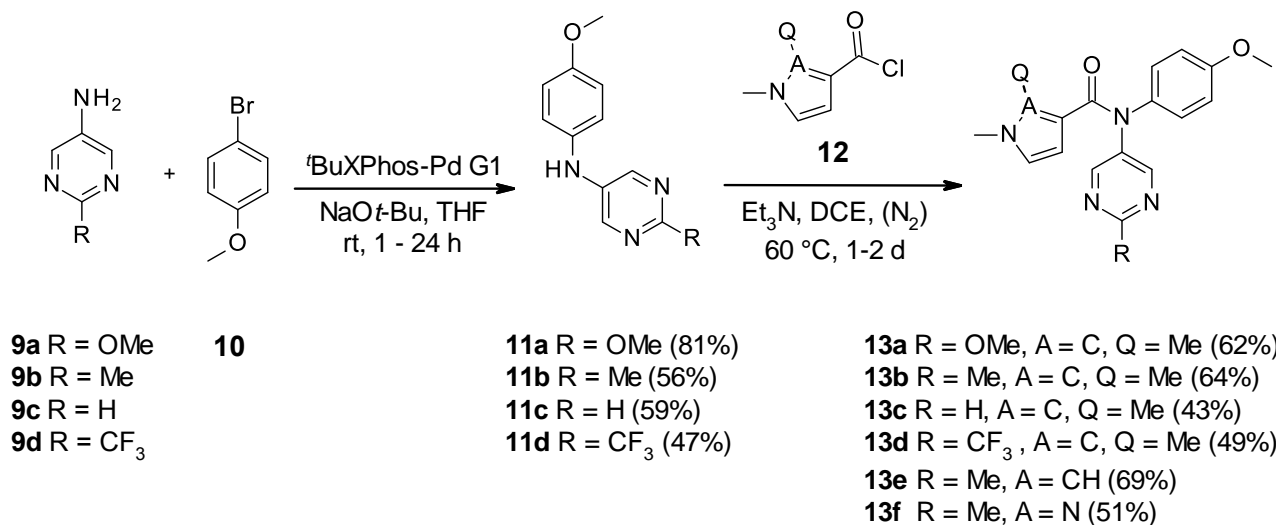
available reagents. Eventually, we have confirmed the reactivity initially observed on **1**, a more decorated molecule: when **7** indolizine-1-carboxamide was heated under strongly acidic conditions - excess hydrobromic acid in refluxing acetic acid overnight - the corresponding demethylated and cyclised analogue **8** is formed in one step (Scheme 2). Beside the standard spectroscopical validation the NOE and HMBC experiments have unambiguously confirmed the structure of **8**.



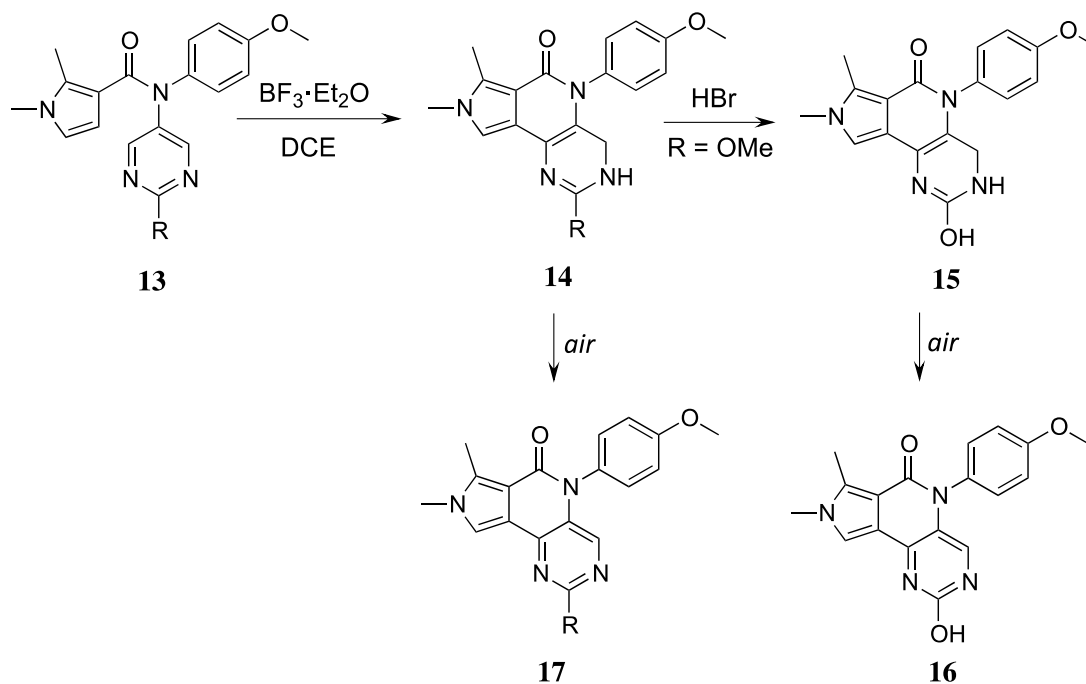
Scheme 2. First synthetic approach to the targeted tricyclic ring system

Encouraged by this fact, beside our ongoing medicinal chemistry program we have decided on to study (on a limited scale) the scope and limitations of these cyclisations in order to prepare some new representatives for this new heterocyclic ring system. We envisioned a small set of model compounds with some changes on the reacting heteroaromatic systems using the available reagents from our reserach program.

The **11a-d** diarylamines were synthesised in a Buchwald reaction from the appropriate 5-pyrimidinamine **9a-d** and 1-bromo-4-methoxybenzene **10** using *t*BuXPhos-Pd G1⁷ as a catalyst in tetrahydrofuran at room temperature with NaO*t*-Bu as base, usually in good yields. The acylation of the formed hindered and less nucleophilic amines **11a-d** were performed with the corresponding **12** acyl chlorides in the presence of triethylamine base (Scheme 3). The usual peptide coupling reagents for acid activation in these amide formations were not usable.



Scheme 3. Preparation of key intermediates for ring closure (yields in brackets)

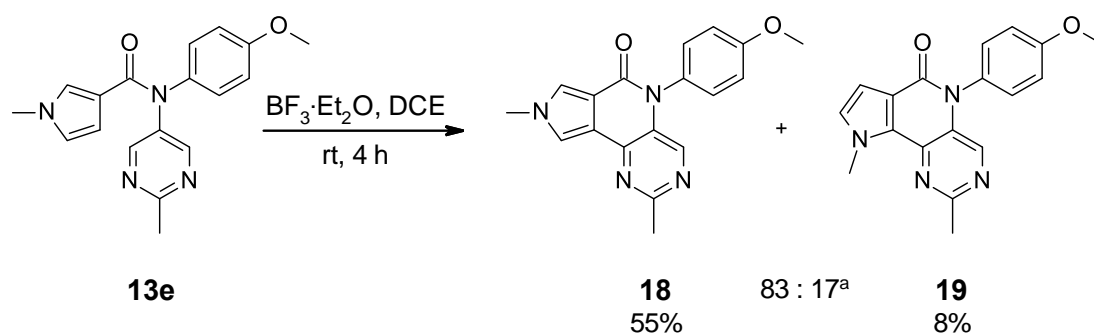


Entry	Starting material	R	BF ₃ ·Et ₂ O (equiv)	Reaction time (h)	Product	Yield
1	13a	MeO	2	2	17a	57%
2	13b	Me	1.5	2.5	17b	66%
3	13c	H	1	1	17c	50%
4	13d	CF ₃	1.5	5	17d	50%

Scheme 4. Effect of R substituent on Lewis acid-facilitated ring closure

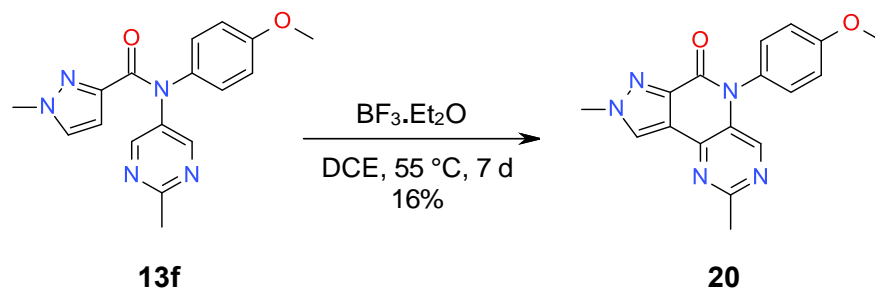
The initial ring closing experiments were performed with **13a** in DMSO at room temperature in the presence of trifluoroacetic acid. The expected product **17a** was isolated in 31% yield but many side products were observed by HPLC suggesting the reaction conditions are probably too harsh. The major by-product **16** even become the main component in this reaction using HBr as an acid, but the reaction profile was still poor, due to the cleavage of the amide bond, the yield remained low. Finally we have found that the application of boron trifluoride etherate as a catalyst resulted in the clean formation of **17a**. The transformation involves an oxidation step promoted by exposing the reaction mixture to open air. These conditions were used for the cyclisation of **13b-d** analogues giving the corresponding 5-(4-methoxyphenyl)-7,8-dimethylpyrrolo[2,3]pyrido[2,4-*d*]pyrimidin-6-ones **17b-d** in medium yield, there is no significant effect of the different R substituents (Scheme 4).

In the next reaction the unsubstituted *N*-methylpyrrole-3-carboxamide **13e** was investigated where two positions were available for the intramolecular cyclisation reaction. The 83:17 mixture of **18** and **19** were formed in the boron trifluoride etherate mediated reaction, both compounds were isolated and identified. The preferential formation of the main product (**18**) can be explained on the more steric accessibility of the pyrrole position-4 over the other alternative (Scheme 5).



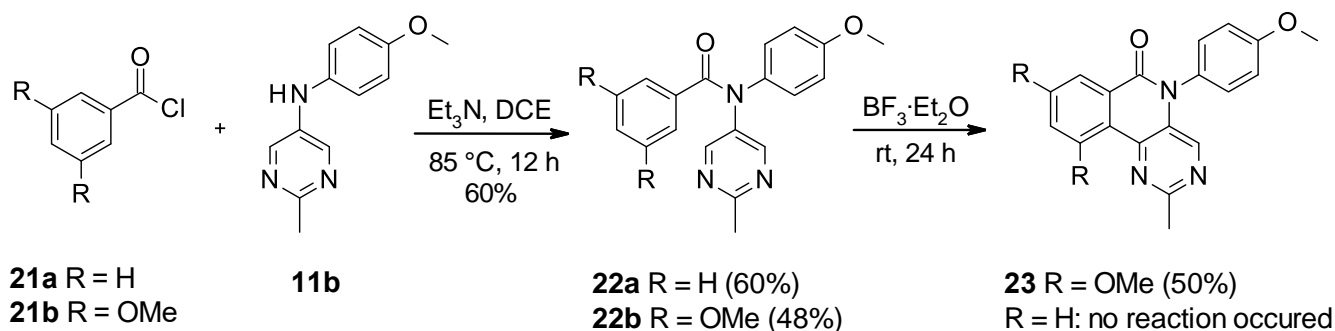
Scheme 5. Formation of regioisomers during the ring closure (^aIsomeric ratio was determined by HPLC)

The reaction of the **13f** pyrazole derivative was very sluggish in comparison with the above described pyrroles. No reaction occurred at room temperature and at 50 °C after one week reaction time using 20 fold excess of boron trifluoride etherate only 6% of 5-(4-methoxyphenyl)-2,8-dimethylpyrazolo[2,3]pyrido[2,4-*b*]pyrimidin-6-one **20** was isolated after chromatography. The low yield is probably the result of the coordination of pyrazole with the excess of Lewis acid which prevents the cyclisation (Scheme 6).



Scheme 6. Studying the nature of nucleophile partner during the ring closure: application of pyrazole instead of pyrrole

Finally the pyrrole ring was replaced by benzene ring, first with an unsubstituted phenyl group. Not surprisingly **22a** amide was reluctant to participate in the cyclisation reaction, while the dimethoxy substituted version **22b** with two strongly electron donating group gave the expected pyrimido[5,4-*c*]isoquinolin-6-one **23** in a moderate yield (Scheme 7).

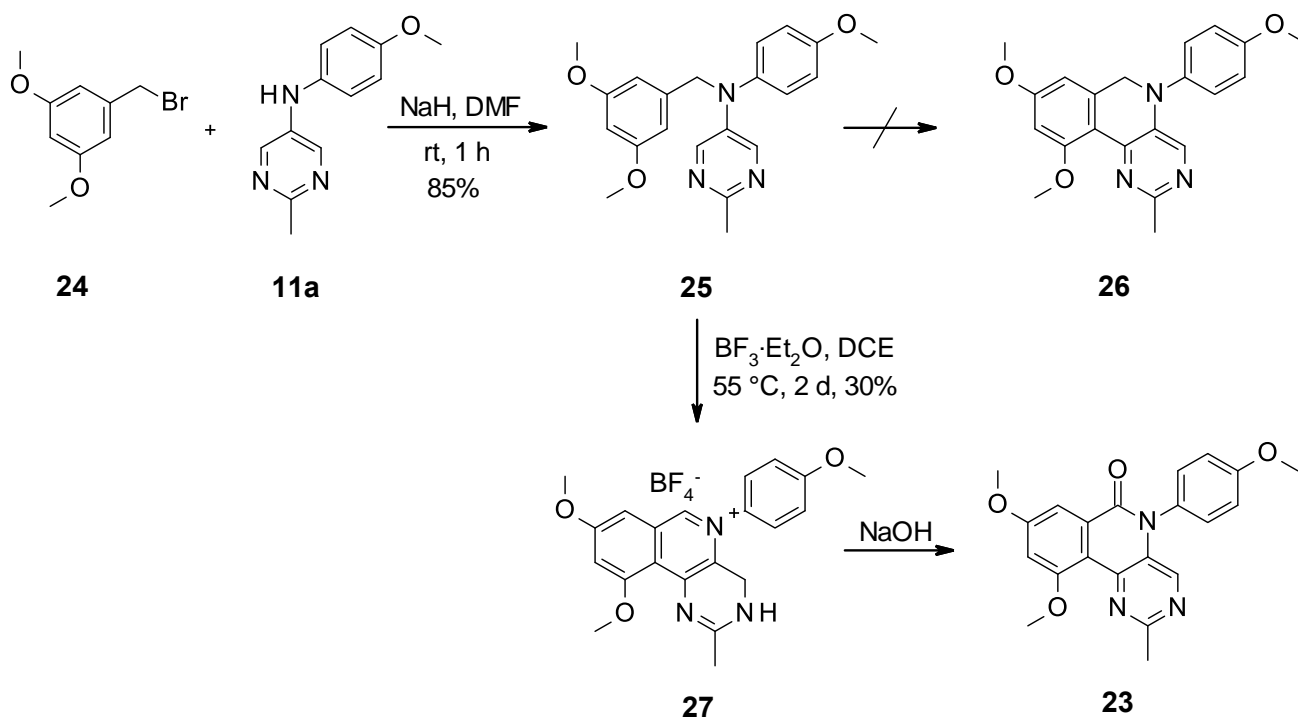


Scheme 7. Studying the nature of nucleophile partner during the ring closure: application of substituted benzene instead of five-membered heterocycle

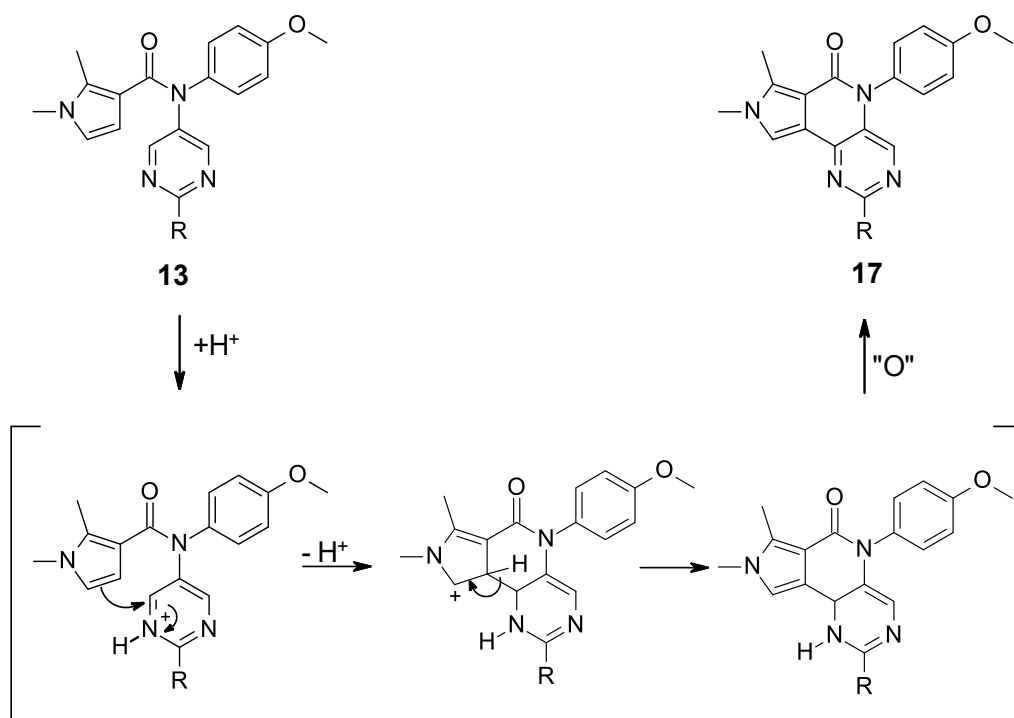
The attempted change in the linker between the diarylamine and benzene part (namely the removal of the amide carboxyl group) gave a very interesting result. To obtain the appropriate precursor **25** first the attempted reduction of **22b** amide to **25** amine was totally unsuccessful using a number of well-known, standard reaction conditions. Then, the **25** amine was finally prepared by the direct benzylation of **11a** with **24** benzyl bromide. The **25** intermediate after the usual treatment with boron trifluoride etherate gave an unstable salt **27** as a major product, which was transformed readily to the already synthesised **23** upon with the treatment with aqueous sodium hydroxide solution (Scheme 8).

To explain these results, we suggested a cationic ring closing step with the involvement of the protonated or boron trifluoride complex **13** with a subsequent oxidative rearomatization as described in Scheme 9. The protonation or complex formation of **13** is required, as no reaction of the unprotonated or uncomplexed starting materials occurred. Thus, the pyrimidine behaves as electrophile but it still needs a

good nucleophile partner as the pyrrole or dimethoxyphenyl ring for this electrophile substitution step to achieve good yields. The rearomatization is highly facilitated by the newly formed conjugated ring system.



Scheme 8. Effect of lack of carbonyl group on the outcome of the ring closure



Scheme 9. Plausible mechanism of acid facilitated oxidative ring closure

In conclusion in this work we have described the synthesis of six different pyrimidine containing heterocyclic system: while the last one, the pyrimido[5,4-*c*]isoquinoline⁸ with a few examples already represented in the literature, the other five (**8**, **17-20**) are completely new heterocycles.

EXPERIMENTAL

The starting materials were purchased from commercial sources. IR spectra were recorded with a Bruker Tensor 27 FT-IR spectrophotometer. ¹H, ¹³C, NMR spectra were recorded in DMSO-*d*₆ using TMS as an internal reference with a Bruker Avance III. spectrometer operating at 500 MHz and 125 MHz respectively (¹H-, DEPTQ-, HSQC-, HMBC-, NMR). High-resolution MS spectra were measured by Agilent 6230 TOF LC/MS spectrometer. All reagents and solvents were purchased and used without further purification.

N-(2-Methoxypyrimidin-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (**6**):

5,6,7,8-Tetrahydroindolizine-1-carboxylic acid (**4**, 1.00 g, 6.05 mmol) was dissolved in dry CH₂Cl₂ (20 mL) then 1-chloro-*N,N*,2-trimethyl-1-propenylamine (Ghosez reagent, 1.00 mL, 7.56 mmol) was added dropwise at room temperature. The reaction mixture was stirred under nitrogen for 2 h at room temperature then a solution of 2-methoxypyrimidin-5-amine (**5**, 1.00 g, 7.99 mmol) in dry toluene (15 mL) was added. The reaction mixture was stirred under nitrogen atmosphere at 40 °C overnight. When the reaction was completed it was diluted by addition of CH₂Cl₂ (15 mL) and a solution of saturated aqueous NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layer was dried over magnesium sulfate, concentrated to dryness and purified by flash chromatography over silica (eluent: EtOAc/CH₂Cl₂) to yield *N*-(2-methoxypyrimidin-5-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide **6** as a white solid (560 mg, 34%). IR (KBr, cm⁻¹): 3350, 3170, 1643. ¹H NMR (500 MHz, DMSO-*d*₆): δ 9.50 (s, 1H, NH), 8.85 (s, 2H, pyrimidine), 6.72 (d, *J* = 3.0 Hz, 1H, H-3), 6.69 (d, *J* = 3.0 Hz, 1H, H-2), 3.95 (t, *J* = 5.9 Hz, 2H, 5-CH₂), 3.91 (s, 3H, OMe), 3.00 (t, *J* = 6.4 Hz, 2H, 8-CH₂), 1.90 (m, 2H, 7-CH₂), 1.81 (m, 2H, 6-CH₂). HRMS [M+H]⁺_{found} = 273.1348, C₁₄H₁₇N₄O₂ required 273.1352.

N-(2-Methoxypyrimidin-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (**7**): To a solution of **6** (490 mg, 1.76 mmol) in toluene (20 mL), tetramethylethylenediamine (0.080 mL, 0.533 mmol), potassium phosphate (750 mg, 3.533 mmol) and iodobenzene (1.00 mL, 8.97 mmol) were added. The reaction mixture was degassed with argon, then copper(I) iodide (167 mg, 0.877 mmol) was added. The reaction mixture was heated under reflux for 24 h. After cooling activated charcoal was added (2 g) and the suspension was filtrated. The filtrate was concentrated to dryness and purified by flash chromatography over silica (eluent: EtOAc/CH₂Cl₂) to yield

N-(2-methoxypyrimidin-5-yl)-*N*-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide **8** as a sticky white solid (429 mg, 1.23 mmol, 70%). IR (KBr, cm^{-1}): 1619. ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.45 (s, 2H, pyrimidine), 7.40 (t, $J = 7.5$ Hz, 2H, Ph-3' and 5'H), 7.28 (m, 3H, Ph-2', 4' and 6'H), 6.38 (d, $J = 3.1$ Hz, 1H, H-3), 5.2 (d, $J = 3.1$ Hz, 1H, H-2), 3.92 (s, 3H, OMe), 3.81 (t, $J = 5.9$ Hz, 2H, 5- CH_2), 2.91 (t, $J = 6.4$ Hz, 2H, 8- CH_2), 1.85 - 1.71 (m, 4H, 6 and 7- CH_2). HRMS $[\text{M}+\text{H}]^+_{\text{found}} = 348.1583$, $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2$ required 348.1586.

4-Hydroxy-8-phenyl-3,5,8,16-tetrazatetracyclo[8.7.0.02,7.011,16]heptadeca-1(17),2(7),3,5,10-pentan-9-one (8): To a solution of **7** (200 mg, 0.574 mmol) in acetic acid (1 mL) was added a solution hydrobromic acid 33% in acetic acid (1 mL). The reaction mixture was allowed to stir at room temperature for 4 h and then overnight at reflux. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and a saturated aqueous solution of Na_2CO_3 was cautiously added until $\text{pH} > 7$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL) and the combined organic layers were dried over magnesium sulphate and concentrated to dryness. The residue was submitted to flash chromatography over silica (eluent: $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford the title product **8** as a sticky yellow solid (100 mg, 52%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 11.59 (brs, 1H, OH), 7.69 (s, 1H, H-17), 7.59 (m, 2H, Ph-H), 7.52 (m, 1H, Ph-H), 7.33 (m, 2H, Ph-H), 7.96-7.1 (brs, 1H, H-6), 4.21 (t, $J = 6.0$ Hz, 2H, 15- CH_2), 3.09 (t, $J = 6.45$ Hz, 2H, 12- CH_2), 1.97 - 1.82 (m, 4H, 13 and 14- CH_2). HRMS $[\text{M}+\text{H}]^+_{\text{found}} = 333.1347$, $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2$ required 332.1273.

Synthesis of diarylamines (11a-d) - General procedure: The appropriate pyrimidinamine (**9a-d**, 10 mmol), 1-bromo-4-methoxybenzene (**10**, 1.87 g, 10 mmol) and *t*BuXPhos-Pd G1 (200 mg, 3 mol%) were dissolved in THF (40 mL) at room temperature and a solution of $\text{NaO}i\text{Bu}$ (6 mL, 12 mmol, 2 M solution in THF) was added dropwise. The reaction mixture was stirred under nitrogen atmosphere at room temperature until the reaction was completed (by HPLC, 1 – 24 h). All the solvents were removed in vacuo and the residue was purified by flash chromatography over silica (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield the product.

2-Methoxy-*N*-(4-methoxyphenyl)pyrimidin-5-amine (11a): 1.87 g (81%); light brown solid; mp 100-103 $^\circ\text{C}$; IR (KBr, cm^{-1}): 3274, 1595, 1243, 1032. ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.30 (s, 2H, H-2 and 6), 7.80 (s, 1H, NH), 6.95 (dm, 2H, Ar-2' and 6'H), 6.84 (dm, 2H, Ar-3' and 5'H), 3.84 (s, 3H, OMe), 3.70 (s, 3H, OMe). ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 159.9 (q), 154.1 (q), 148.2 (2x CH), 137.0 (q), 134.8 (q), 118.8 (2 x CH), 115.2 (2 x CH), 55.7 (CH_3), 54.8 (CH_3). HRMS $[\text{M}+\text{H}]^+_{\text{found}} = 232.1085$, $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$ required 232.1086.

***N*-(4-Methoxyphenyl)-2-methylpyrimidin-5-amine (11b)**: 1.21 g (56%); light yellow solid; mp 110-112 $^\circ\text{C}$; IR (KBr, cm^{-1}): 3271, 1593, 1241, 1213, 1032. ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 8.32 (s,

2H, H-2 and 6), 8.06 (s, 1 H, NH), 7.07 (dm, 2H, Ar-2' and 6'H), 6.9 (dm, 2H, Ar-3' and 5'H), 3.72 (s, 3H, OMe), 2.48 (s, 3H, Me). ^{13}C NMR (125 MHz, DMSO- d_6): δ 157.4 (q), 155.0 (q), 143.6 (2 x CH), 137.6 (q), 135.2 (q), 120.8 (2 x CH), 115.2 (2 x CH), 55.7 (CH₃), 24.9 (CH₃). HRMS $[\text{M}+\text{H}]^+_{\text{found}} = 216.1137$, C₁₂H₁₃N₃O required 216.1137.

***N*-(4-Methoxyphenyl)pyrimidin-5-amine (11c)**: 1.19 g (59%); light brown solid, mp 95-6 °C; IR (KBr, cm⁻¹): 3035, 1601, 1241, 1032. ^1H NMR (500 MHz, DMSO- d_6): δ 8.53 (s, 1H, H-2), 8.38 (s, 2H, H-2 and 6), 8.26 (s, 1H, NH), 7.12 (m, 2H, Ar-3' and 5'H), 6.92 (m, 2H, Ar-2' and 6'H), 3.73 (s, 3H, OMe). ^{13}C NMR (125 MHz, DMSO- d_6): δ 155.4 (q), 148.9 (CH), 142.6 (2 x CH), 140.4 (q), 134.2 (q), 121.8 (2 x CH), 115.3 (2 x CH), 55.7 (CH₃). HRMS $[\text{M}+\text{H}]^+_{\text{found}} = 201.1023$, C₁₁H₁₁N₃O required 201.1019.

***N*-(4-Methoxyphenyl)-2-(trifluoromethyl)pyrimidin-5-amine (11d)**: 1.27 g (47%); yellow solid, yield : mp 105-6 °C; IR (KBr, cm⁻¹): 3095, 1606, 1242, 1030; ^1H NMR (500 MHz, DMSO- d_6): δ 8.89 (s, 1H, NH), 8.45 (s, 2H, H-2 and 6), 7.22 (m, 2H, Ar-3' and 5'H), 6.96 (m, 2H, Ar-2' and 6'H), 3.75 (s, 3H, OMe). ^{13}C NMR (125 MHz, DMSO- d_6): δ 156.4 (q), 144.3 (q), 142.3 (q), 141.8 (2 x CH), 132.5 (q), 123.3 (2 x CH), 120.7 (q), 115.4 (2 x CH), 55.7 (CH₃). HRMS $[\text{M}+\text{H}]^+_{\text{found}} = 270.0852$, C₁₂H₁₀F₃N₃O required 270.0854.

Acylation of diarylamines 11a-d – General procedure: The corresponding carboxylic acid **12** (1.5 mmol) has been dissolved in dry CH₂Cl₂ (30 mL) then 1-chloro-*N,N*,2-trimethyl-1-propenylamine (Ghosez reagent, 0.24 mL, 1.814 mmol) has been added at room temperature. The reaction mixture was stirred under nitrogen for 1 h then triethylamine (0.32 mL, 2.30 mmol) and the corresponding diarylamine **11a-d** (1.25 mmol) have been added. The reaction mixture was stirred under nitrogen atmosphere at 60 °C until the reaction was completed (by HPLC, 1 – 2 days). All the solvents were removed *in vacuo* and the residue was purified by flash chromatography over silica (eluent: CH₂Cl₂/MeOH) to yield the expected product.

***N*-(4-Methoxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethylpyrrole-3-carboxamide (13a)**: 0.27 g (62%); light yellow solid, mp 175-6 °C; IR (KBr, cm⁻¹): 1635, 1555, 1242, 1168, 1027 cm⁻¹. ^1H NMR (500 MHz, DMSO- d_6): δ 8.45 (s, 2H, pyrimidine 4' and 6'H), 7.2 (dm, 2H, Ph-2' and 6'H), 6.91 (dm, 2H, Ph-3' and 5'H), 6.41 (d, 1H, $J = 3$ Hz, H-5), 5.28 (d, 1H, $J = 3$ Hz, H-4), 3.89 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.44 (s, 3H, NMe), 2.35 (s, 3 H, CH₃). ^{13}C NMR (125 MHz, DMSO- d_6): δ 166.9 (q), 157.9 (2 x CH), 135.7 (q), 129.7 (2 x CH), 120.9 (CH), 114.9 (2 x CH), 114.1 (q), 108.8 (CH), 55.7 (CH₃), 54.9 (CH₃), 33.7 (CH₃), 11.4 (CH₃). HRMS $[\text{M}+\text{H}]^+_{\text{found}} = 353.1616$, C₁₉H₂₀N₄O₃ required 353.1614.

***N*-(4-Methoxyphenyl)-1,2-dimethyl-*N*-(2-methylpyrimidin-5-yl)pyrrole-3-carboxamide (13b)**: 0.27 g (64%), light yellow solid, mp 180-2 °C; IR (KBr, cm⁻¹): 1637, 1552, 1241, 1020. ^1H NMR (500 MHz, DMSO- d_6): δ 8.46 (s, 2H, pyrimidine 4' and 6'H), 7.18 (dm, 2H, Ph-2' and 6'H), 6.92 (dm, 2H, Ph-3' and 5'H), 6.42 (d, 1H, $J = 3$ Hz, H-5), 5.27 (d, 1H, $J = 3$ Hz, H-4), 3.75 (s, 3H, OMe), 3.44 (s, 3H, NMe),

2.58 (s, 3H, Me), 2.34 (s, 3 H, CH₃). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 166.9 (q), 163.7 (q), 158.4 (2 x CH), 154.8 (q), 138.0 (q), 136.5 (q), 135.9 (q), 130.0 (2 x CH), 121.1 (2 x CH), 120.8 (CH), 115.1 (2 x CH), 114.2 (q), 108.9 (CH), 55.8 (CH₃), 33.9 (CH₃), 25.6 (CH₃), 11.5 (CH₃). HRMS [M+H]⁺_{found} = 337.1656, C₁₉H₂₀N₄O₂ required 337.1664.

***N*-(4-Methoxyphenyl)-1,2-dimethyl-*N*-(pyrimidin-5-yl)pyrrole-3-carboxamide (13c):** 0.17 g (43%); brown solid, yield; mp 160-2 °C; IR (KBr, cm⁻¹): 1633, 1551, 1241, 1048, 1021. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.94 (s, 1H, pyrimidine-2'H), 8.59 (s, 2H, pyrimidine 4' and 6'H), 7.22 (dm, 2H, Ph-2' and 6'H), 6.95 (dm, 2H, Ph-3' and 5'H), 6.43 (d, 1H, *J* = 3 Hz, H-5), 5.28 (d, 1H, *J* = 3 Hz, H-4), 3.76 (s, 3H, OMe), 3.45 (s, 3H, NMe), 2.36 (s, 3H, Me). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 166.9 (q), 158.5 (q), 154.6 (CH), 154.5 (2 x CH), 140.4 (q), 136.2 (q), 136.1 (q), 130.1 (2 x CH), 121.1 (CH), 115.2 (2 x CH), 114.0 (q), 108.8 (CH), 55.8 (CH₃), 33.8 (CH₃), 11.4 (CH₃). HRMS [M+H]⁺_{found} = 323.1496, C₁₈H₁₈N₄O₂ required 323.1497.

***N*-(4-Methoxyphenyl)-1,2-dimethyl-*N*-[2-(trifluoromethyl)pyrimidin-5-yl]pyrrole-3-carboxamide (13d):** 0.24 g (49%); yellow solid, mp 166-8 °C; IR (KBr, cm⁻¹): 1637, 1551, 1242, 1078, 1020; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.74 (s, 2H, pyrimidine 4' and 6'H), 7.25 (dm, 2H, Ph-2' and 6'H), 6.97 (dm, 2H, Ph-3' and 5'H), 6.45 (d, 1H, *J* = 3 Hz, H-5), 5.30 (d, 1H, *J* = 3 Hz, H-4), 3.77 (s, 3H, OMe), 3.46 (s, 3H, NMe), 2.38 (s, 3H, Me). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 167.0 (q), 158.9 (q), 154.3 (CH), 149.9 (q), 142.2 (q), 137.1 (q), 135.2 (q), 130.3 (2 x CH), 121.4 (CH), 115.6 (2 x CH), 113.6 (q), 108.9 (CH), 55.8 (CH₃), 33.8 (CH₃), 11.4 (CH₃). HRMS [M+H]⁺_{found} = 391.1377, C₁₉H₁₇F₃N₄O₂ required 391.1381.

***N*-(4-Methoxyphenyl)-1-methyl-*N*-(2-methylpyrimidin-5-yl)pyrrole-3-carboxamide (13e):** 0.28 g (69%); yellow solid, mp 163-5 °C; IR (KBr, cm⁻¹): 1636, 1550, 1241, 1021. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.57 (s, 2H, pyrimidine 4' and 6'H), 7.33 (dm, 2H, Ph-2' and 6'H), 6.99 (dm, 2H, Ph-3' and 5'H), 6.71 (d, 1H, *J* = 1.5 Hz, H-2), 6.55 (dd, 1H, *J* = 1.5 and 3 Hz, H-5), 5.51 (dd, 1H, *J* = 1.5 and 3 Hz, H-4), 3.78 (s, 3H, OMe), 3.51 (s, 3H, NMe), 2.59 (s, 3H, Me); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 165.0 (q), 164.1 (q), 159.1 (q), 154.9 (2 x CH), 137.5 (q), 135.7 (q), 130.6 (2 x CH), 128.1 (CH), 122.7 (CH), 117.9 (q), 115.3 (2 x CH), 110.7 (CH), 55.9 (CH₃), 36.4 (CH₃), 25.5 (CH₃). HRMS [M+H]⁺_{found} = 323.1495, C₁₈H₁₈N₄O₂ required 323.1492.

***N*-(4-Methoxyphenyl)-1-methyl-*N*-(2-methylpyrimidin-5-yl)pyrazole-3-carboxamide (13f):** 0.21 g (51%); white solid; mp 155-9 °C; IR (KBr, cm⁻¹): 1632, 1550, 1347, 1240, 1017; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.60 (s, 2H, pyrimidine 4' and 6'H), 7.60 (d, 1H, *J* = 3 Hz, H-5), 7.29 (dm, 2H, Ph-2' and 6'H), 6.94 (dm, 2H, Ph-3' and 5'H), 6.71 (d, 1H, *J* = 1.5 Hz, H-2), 6.55 (dd, 1H, *J* = 1.5 and 3 Hz, H-5), 5.51 (dd, 1H, *J* = 1.5 and 3 Hz, H-4), 3.78 (s, 3H, OMe), 3.51 (s, 3H, NMe), 2.59 (s, 3H, Me), 6.11 (brs, 1H, H-4), 3.75 (s, 3H, OMe), 3.7 (s, 3H, NMe), 2.6 (s, 3H, Me). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 164.9 (q), 163.3 (q), 158.7 (q), 155.4 (2 x CH), 145.4 (q), 137.2 (q), 135.6 (q), 131.8 (CH), 129.9 (2 x CH),

115.0 (2 x CH), 108.8 (CH), 55.8 (CH₃), 39.4 (CH₃), 25.6 (CH₃). HRMS [M+H]⁺_{found} = 324.1455, C₁₇H₁₇N₅O₂ required 324.1460.

2-Hydroxy-5-(4-methoxyphenyl)-7,8-dimethylpyrrolo[2,3]pyrido[2,4-d]pyrimidin-6-one (16):

N-(4-Methoxyphenyl)-*N*-(2-methoxypyrimidin-5-yl)-1,2-dimethylpyrrole-3-carboxamide (**13a**, 0.42 g, 1.19 mmol) was dissolved in acetic acid (10 mL) and hydrogen bromide (1.1 mL, 33% in acetic acid) was added and the reaction mixture was stirred at room temperature for 1 h. The precipitated solid was filtered off and it was purified by flash chromatography over silica (eluent: CH₂Cl₂/MeOH) to yield the title product **11a** as a light brown solid (222 mg, 55%). mp 220-22 °C; IR (KBr, cm⁻¹): 3105, 2988, 1634, 1551, 1249, 1154, 1019; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.62 (brs, 1H, OH), 7.76 (s, 1H, H-9), 7.24 (dm, 2H, Ph-2' and 6'H), 7.11 (m, 2H, Ph-3' and 5'H), 7.08 (brs, 1H, H-4), 3.84 (s, 3H, OMe), 3.79 (s, 3H, NMe), 2.59 (s, 3H, Me); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 143.5 (CH), 131.1 (2 x CH), 119.9 (CH), 115.5 (2 x CH), 55.9 (CH₃), 34.9 (CH₃), 10.7 (CH₃). HRMS [M+H]⁺_{found} = 337.1288, C₁₈H₁₆N₄O₃ required 337.1300.

Cyclisation reactions with boron trifluoride etherate – General procedure: The corresponding pyrrole-3-carboxamide **13a-f** (0.5 mmol) was dissolved in CH₂Cl₂ (5 mL). At room temperature boron trifluoride etherate (0.061 mL, 0.50 mmol) was added and after one hour stirring another portion (0.061 mL, 0.50 mmol). When the reaction was completed (by HPLC) it was diluted with CH₂Cl₂ (10 mL) and washed with saturated aqueous Na₂CO₃ solution (3 x 15 mL) and brine. After drying over sodium sulfate all the solvents were removed in vacuo and the residue was purified by flash chromatography over silica (eluent: CH₂Cl₂/MeOH) to yield the cyclized products.

2-Methoxy-5-(4-methoxyphenyl)-7,8-dimethylpyrrolo[2,3]pyrido[2,4-d]pyrimidin-6-one (17a): 112 mg (64%); pale yellow solid, mp 192-4 °C; IR (KBr, cm⁻¹): 1656, 1585, 1248, 1156, 1030; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.82 (s, 1H, H-9), 7.53 (s, 1H, H-4), 7.26 (dm, 2H, Ph-2' and 6'H), 7.13 (dm, 2H, Ph-3' and 5'H), 3.90 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.81 (s, 3H, NMe), 2.61 (s, 3H, Me). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 160.6 (q), 159.5 (q), 145.2 (CH), 133.9 (q), 131.1 (2 x CH), 129.7 (q), 119.2 (CH), 115.5 (2 x CH), 111.9 (q), 56.4 (CH₃), 55.9 (CH₃), 34.8 (CH₃), 10.8 (CH₃). HRMS [M+H]⁺_{found} = 351.1455, C₁₉H₁₈N₄O₃ required 351.1456.

5-(4-Methoxyphenyl)-2,7,8-trimethylpyrrolo[2,3]pyrido[2,4-b]pyrimidin-6-one (17b): 94 mg (56%); white solid, mp 188-190 °C; IR (KBr, cm⁻¹): 1657, 1584, 1248, 1153, 1028. ¹H NMR (500 MHz, DMSO-*d*₆): 7.83 (s, 1H, H-9), 7.63 (s, 1H, H-4), 7.26 (m, 2H, Ar-2' and 6'H), 7.13 (m, 2H, Ar-3' and 5'H), 3.85 (s, 3H, OMe), 3.80 (s, 3H, NMe), 2.61 (s, 3H, Me), 2.57 (s, 3H, Me). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 160.3 (q), 159.5 (q), 159.4 (q), 143.2 (CH), 142.6 (q), 133.8 (q), 131.1 (2 x CH), 130.8 (q), 129.5 (q), 118.7 (CH), 118.3 (q), 115.5 (2 x CH), 112.0 (q), 55.9 (CH₃), 34.8 (CH₃), 25.4 (CH₃), 10.8 (CH₃). ¹⁵N-NMR: (50 MHz, DMSO-*d*₆): δ 285, 271, 172, 144. HRMS [M+H]⁺_{found} = 335.1507,

C₁₉H₁₈N₄O₂ required 335.1508.

5-(4-Methoxyphenyl)-7,8-dimethylpyrrolo[2,3]pyrido[2,4-*b*]pyrimidin-6-one (17c): 80 mg (50%); light brown solid; mp 191-194 °C; IR (KBr, cm⁻¹): 1647, 1582, 1209, 1151, 1028; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.78 (s, 1H, H-2), 7.85 (s, 1H, H-9), 7.72 (s, 1H, H-4), 7.28 (m, 2H, Ar-2' and 6'H), 7.14 (m, 2H, Ar-3' and 5'H), 3.85 (s, 3H, OMe), 3.82 (s, 3H, NMe), 2.63 (s, 3H, Me); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 159.6 (q), 159.5 (q), 151.8 (CH), 142.8 (CH), 134.0 (q), 132.9 (q), 131.1 (2 x CH), 129.4 (q), 118.7 (CH), 118.2 (q), 115.6 (2 x CH), 111.9 (q), 55.9 (CH₃), 34.8 (CH₃), 10.8 (CH₃). HRMS [M+H]⁺_{found} = 321.1346, C₁₈H₁₆N₄O₂ required 321.1341.

5-(4-Methoxyphenyl)-7,8-dimethyl-2-(trifluoromethyl)pyrrolo[2,3]pyrido[2,4-*d*]pyrimidin-6-one (17d): 105 mg (54%); white solid, mp 172-174 °C; IR (KBr, cm⁻¹): 1672, 1575, 1333, 1209, 1122. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.99 (s, 1H, H-9), 7.86 (s, 1H, H-4), 7.31 (dm, 2H, Ar-2' and 6'H), 7.16 (dm, 2H, Ar-3' and 5'H), 3.87 (s, 3H, OMe), 3.84 (s, 3H, NMe), 2.64 (s, 3H, Me); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 160.0 (q), 159.4 (q), 148.2 (q), 143.5 (q), 143.0 (CH), 134.7 (q), 134.3 (q), 131.1 (2 x CH), 129.1 (q), 120.0 (CH), 117.3 (q), 115.8 (2 x CH), 111.9 (q), 56 (CH₃), 34.9 (CH₃), 10.7 (CH₃). HRMS [M+H]⁺_{found} = 389.1212, C₁₉H₁₅F₃N₄O₂ required 389.1215.

5-(4-Methoxyphenyl)-2,8-dimethylpyrrolo[2,3]pyrido[2,4-*b*]pyrimidin-6-one (18): 88 mg (55%); white solid, mp 144-147 °C; IR (KBr, cm⁻¹): 1671, 1572, 1329, 1209, 1120. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.90 (d, *J* = 2.0 Hz, 1H, H-7), 7.78 (d, *J* = 2.0 Hz, 1H, H-9), 7.70 (s, 1H, H-4), 7.28 (d, *J* = 8.9 Hz, 2H, Ar-2' and 6'H), 7.14 (d, *J* = 8.9 Hz, 2H, Ar-3' and 5'H), 3.94 (s, 3H, OMe), 3.85 (s, 3H, NMe), 2.59 (s, 3H, Me). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 160.4 (q), 159.6 (q), 158.4 (q), 143.6 (CH), 142.3 (q), 131.0 (2 x CH), 130.9 (q), 129.4 (q), 124.4 (q), 120.2 (CH), 119.9 (q), 116.7 (q), 115.6 (2 x CH), 55.9 (CH₃), 37.7 (CH₃), 25.4 (CH₃); HRMS [M+H]⁺_{found} = 321.1342, C₁₈H₁₆N₄O₂ required 321.1351.

5-(4-Methoxyphenyl)-2,9-dimethylpyrrolo[4,5]pyrido[1,2-*b*]pyrimidin-6-one (19): 13 mg (8%), white sticky solid; IR (KBr, cm⁻¹): 1669, 1571, 1212, 1112. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.90 (s, 1H, H-4), 7.54 (d, *J* = 3.0 Hz, 1H, H-8), 7.29 (d, *J* = 9.0 Hz, 2H, Ar-2' and 6'H), 7.15 (d, *J* = 9.0 Hz, 2H, Ar-3' and 5'H), 6.78 (d, *J* = 3.0 Hz, 1H, H-7), 4.36 (s, 3H, NMe), 3.86 (s, 3H, OMe), 2.67 (s, 3H, Me). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 159.29 (q), 159.28 (q), 157.7 (q), 143.9 (CH), 137.3 (q), 132.2 (CH), 130.4 (2 x CH), 129.8 (q), 129.1 (q), 128.7 (q), 121.0 (q), 115.1 (2 x CH), 106.2 (CH), 55.5 (CH₃), 37.0 (CH₃), 25.2 (CH₃); HRMS [M+H]⁺_{found} = 321.1346, C₁₈H₁₆N₄O₂ required 321.1351.

5-(4-Methoxyphenyl)-2,8-dimethylpyrazolo[2,3]pyrido[2,4-*b*]pyrimidin-6-one (20): 25 mg (16%); light brown sticky solid, IR (KBr, cm⁻¹): 1672, 1574, 1210, 1174, 1112. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.97 (s, 1H, H-9), 7.83 (s, 1H, H-4), 7.35 (d, *J* = 8.5 Hz, 2H, Ar-2' and 6'H), 7.17 (d, *J* = 8.5 Hz, 2H, Ar-3' and 5'H), 4.20 (s, 3H, NMe), 3.86 (s, 3H, OMe), 2.64 (s, 3H, Me); ¹³C NMR (125 MHz,

DMSO-*d*₆): δ 161.0 (q), 159.9 (q), 150.9 (q), 144.4 (CH), 143.0 (q), 140.9 (q), 130.8 (2 x CH), 129.6 (CH), 128.9 (q), 120.2 (q), 115.7 (2 x CH), 56.0 (CH₃), 40.8 (CH₃), 25.4 (CH₃); HRMS [M+H]⁺_{found} = 322.1308, C₁₇H₁₅N₅O₂ required 322.1304.

***N*-(4-Methoxyphenyl)-*N*-(2-methylpyrimidin-5-yl)benzamide (22a):**

2-Methyl-*N*-(4-methoxyphenyl)pyrimidin-5-amine (**11b**, 0.50 g, 2.32 mmol) and triethylamine (0.5 mL, 3.59 mmol) were dissolved in dry CH₂Cl₂ (35 mL) and benzoyl chloride (0.407 mL, 3.5 mmol) was added. The reaction mixture was heated at 85 °C for 12 h under nitrogen. Then all the solvents were removed and the residue was purified by flash chromatography over silica (eluent: CH₂Cl₂/MeOH) to yield the title product as a sticky white solid (0.44 g, 60%). IR (KBr, cm⁻¹): 1665, 1544, 1211, 1174, 1109; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.62 (s, 2H, Py-4' and 6'H), 7.44 (d, *J* = 7.5 Hz, 2H, Ph-2' and 6'H), 7.34 (t, *J* = 7.5 Hz, 1H, Ph-4'H), 7.29 (d, *J* = 7.5 Hz, 2H, Ph-3' and 5'H), 7.25 (d, *J* = 8.0 Hz, 2H, Ar-2' and 6'H), 6.88 (d, *J* = 8.0 Hz, 2H, Ar-3' and 5'H), 3.71 (s, 3H, OMe), 2.59 (s, 3H, Me); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 170.4 (q), 164.8 (q), 158.5 (q), 155.2 (2 x CH), 137.0 (q), 135.8 (q), 135.5 (q), 130.6 (CH), 130.0 (2 x CH), 129.0 (2 x CH), 128.4 (2 x CH), 115.1 (2 x CH), 55.8 (CH₃), 25.6 (CH₃); HRMS [M+H]⁺_{found} = 320.1387, C₁₉H₁₇N₃O₂ required 322.1399.

3,5-Dimethoxy-*N*-(4-methoxyphenyl)-*N*-(2-methylpyrimidin-5-yl)benzamide (22b): From freshly prepared 3,5-dimethoxybenzoyl chloride (0.702 g, 3.5 mmol) and 2-methyl-*N*-(4-methoxyphenyl)pyrimidin-5-amine (**11b**, 0.50 g, 2.32 mmol) as described for **22a**. White powder (0.42 g, 48%); mp 118-120 °C; IR (KBr, cm⁻¹): 1668, 1544, 1211, 1172, 1111. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.64 (s, 2H, Py-4' and 6'H), 7.29 (d, *J* = 8.0 Hz, 2H, Ar²-2' and 6'H), 6.89 (d, *J* = 8.0 Hz, 2H, Ar²-3' and 5'H), 6.60 (s, 2H, Ar¹-2' and 6'H), 6.45 (s, 1H, Ar¹-4'H), 3.72 (s, 3H, OMe), 3.64 (s, 6H, OMe), 2.59 (s, 3H, Me); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.9 (q), 164.9 (q), 160.2 (q), 158.6 (q), 155.2 (2 x CH), 137.7 (q), 136.9 (q), 135.5 (q), 129.9 (2 x CH), 115.1 (2 x CH), 107.1 (2 x CH), 102.4 (CH), 55.8 (CH₃), 55.8 (CH₃), 25.6 (CH₃); HRMS [M+H]⁺_{found} = 380.1602, C₂₁H₂₁N₃O₄ required 380.1610.

8,10-Dimethoxy-5-(4-methoxyphenyl)-2-methylpyrimido[5,4-*c*]isoquinolin-6-one (23):

3,5-Dimethoxy-*N*-(4-methoxyphenyl)-*N*-(2-methylpyrimidin-5-yl)benzamide (**22b**, 0.17 g, 0.448 mmol) was dissolved in CH₂Cl₂ (5 mL). At room temperature boron trifluoride etherate (0.084 mL, 0.68 mmol) was added in two portions. When the reaction was completed (judged by HPLC) it was diluted with CH₂Cl₂ (10 mL) and washed with saturated aqueous Na₂CO₃ solution (3 x 15 mL) and brine. After drying over sodium sulfate all the solvents were removed in vacuo and the residue was purified by flash chromatography over silica (eluent: CH₂Cl₂/MeOH) to yield the cyclised product (**23**, 84 mg, 50%) as a pale yellow solid. mp 132-135 °C; IR (KBr, cm⁻¹): 1660, 1540, 1110. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.86 (s, 1H, H-4), 7.37 (d, *J* = 8.0 Hz, 2H, Ar-2' and 6'H), 7.20 (s, 1H, H-6), 7.18 (d, *J* = 8.0 Hz, 2H,

Ar-3' and 5'H), 7.15 (d, 1H, H-9), 4.02 (s, 3H, OMe), 3.96 (s, 3H, OMe), 3.87 (s, 3H, OMe), 2.66 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO- d_6): δ 162.9 (q), 161.3 (q), 160.2 (q), 159.9 (q), 159.6 (q), 144.1 (CH), 130.6 (2 x CH), 129.1 (q), 115.7 (2 x CH), 105.5 (CH), 103.0 (CH), 57.2 (CH₃), 56.3 (CH₃), 55.9 (CH₃), 25.9 (CH₃). HRMS $[\text{M}+\text{H}]^+$ _{found} = 378.1451, C₂₁H₁₉N₃O₄ required 378.1454.

***N*-[(3,5-Dimethoxyphenyl)methyl]-*N*-(4-methoxyphenyl)-2-methylpyrimidin-5-amine (25):**

2-Methyl-*N*-(4-methoxyphenyl)pyrimidin-5-amine (**11a**, 0.560 g, 2.60 mmol) was dissolved in dry DMF (10 mL) and cooled to 0 °C. Then sodium hydride (dispersion in mineral oil, 60%) was added (0.104 g, 2.6 mmol) and it was stirred for 1 h under nitrogen. Then 1-(bromomethyl)-3,5-dimethoxybenzene (0.60 g 2.60 mmol in 5 mL dry DMF) was added. The reaction mixture was stirred for 1 h. Then it was diluted with water and extracted with EtOAc and evaporated *in vacuo*. The remaining oil was purified by flash chromatography over silica (eluent: heptane/EtOAc) to yield the title product as a sticky yellow oil (0.81 g, 85%). IR (KBr, cm⁻¹): 1663, 1541, 1234, 1201, 1172, 1110. ^1H NMR (500 MHz, DMSO- d_6): δ 8.11 (s, 2H, Py-4' and 6'H), 7.23 (d, $J = 7.8$ Hz, 2H, Ar¹-2' and 6'H), 6.96 (d, $J = 7.8$ Hz, 2H, Ar¹-3' and 5'H), 6.48 (d, $J = 1.5$ Hz, 2H, Ar¹-2' and 6'H), 6.37 (s, 1H, Ar¹-4'H), 4.86 (s, 2H, CH₂), 3.74 (s, 3H, OMe), 3.69 (s, 6H, 2 x OMe), 2.44 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO- d_6): δ 161.1 (q), 157.0 (q), 156.9 (q), 143.7 (2 x CH), 141.0 (q), 140.3 (q), 139.0 (q), 126.6 (2 x CH), 115.7 (2 x CH), 105.2 (2 x CH), 98.9 (CH), 55.7 (CH₃), 55.6 (CH₃), 55.5 (CH₃), 24.8 (CH₃); HRMS $[\text{M}+\text{H}]^+$ _{found} = 366.1817, C₂₁H₂₃N₃O₃ required 366.1818.

8,10-Dimethoxy-5-(4-methoxyphenyl)-2-methyl-3,4-dihydropyrimido[5,4-*c*]isoquinolin-5-ium tetrafluoroborate (27):

N-[(3,5-Dimethoxyphenyl)methyl]-*N*-(4-methoxyphenyl)-2-methylpyrimidin-5-amine (**25**, 0.365 g, 1 mmol) was dissolved in dry CH₂Cl₂ (10 mL), then at room temperature boron trifluoride etherate (0.802 mL, 6.5 mmol) was added in two portions. The reaction mixture was stirred at 55 °C for 2 days. When the reaction was completed (by HPLC) it was diluted with CH₂Cl₂ (10 mL) and washed with saturated aqueous NaHCO₃ solution (3 x 15 mL) and brine. After drying over sodium sulfate all the solvents were removed *in vacuo* and the residue was purified by flash chromatography over silica (eluent: CH₂Cl₂/MeOH) to yield the cyclised product (**27**, 0.12 g, 30%) as a pale-yellow sticky solid. ^1H NMR (500 MHz, DMSO- d_6): δ 9.71 (s, 1H, H-6), 7.68 (d, $J = 7.5$ Hz, 2H, Ar-2' and 6'H), 7.51 (d, $J = 2.0$ Hz, 1H, H-9), 7.49 (d, $J = 2.0$ Hz, 1H, H-11), 7.30 (d, $J = 7.5$ Hz, 2H, Ar-3' and 5'H), 4.68 (s, 2H, CH₂-4), 4.17 (s, 3H, OMe), 3.99 (s, 3H, OMe), 3.9 (s, 3H, OMe), 2.54 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO- d_6): δ 162.4 (q), 162.2 (q), 161.7 (q), 156.3 (q), 147.1 (CH), 132.3 (q), 130.4 (q), 128.9 (q), 127.5 (2 x CH), 122.6 (q), 115.8 (2 x CH), 113.7 (q), 110.2 (CH), 101.7 (CH), 58.4 (CH₃), 56.9 (CH₃), 56.4 (CH₃), 42.0 (CH₂), 19.2 (CH₃); ^{15}N -NMR (50 MHz, DMSO- d_6): δ 205, 126, 120; HRMS $[\text{M}+\text{H}]^+$ _{found} = 364.1660, C₂₁H₂₁N₃O₃ required 364.1660.

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