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Synthesis and reactivity of 4-, 5- and 6-azaindoles

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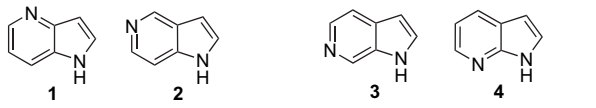
1. Introduction

Azaindole ring systems have attracted considerable interest from the chemistry community as they represent promising building blocks with potential applications in the field of pharmaceuticals, natural product synthesis and also diverse key synthetic intermediates. Azaindoles can be considered as bioisosteres of an indole moiety with variation of the position of the nitrogen atom on the benzene core. In this paper, we wish to report the synthesis and reactivity of 4-, 5- and 6-azaindoles **1**–**3** updated from 2000 (Fig. 1).[1] Organometallic methods for the synthesis and functionalization of azaindoles were recently reviewed.[2] The synthesis and reactivity of the 7-azaindoles **4** have been already reported in a previous review.[3]



4-azaindole or pyrrolo[3,2-*b*]pyridine **1** 6-azaindole or pyrrolo[2,3-*c*]pyridine **3**
5-azaindole or pyrrolo[3,2-*c*]pyridine **2** 7-azaindole or pyrrolo[2,3-*b*]pyridine **4**

Figure 1. Structures of 4-, 5-, 6- and 7-azaindoles **1**–**4**.

Contrary to their 7-azaindole analogues that have been widely studied for their luminescence properties as inorganic complexes, the 4-, 5- and 6-azaindoles have been far less studied for their inorganic properties.

The photophysical properties of 6-azaindole **3** and 6-azatryptophan have been studied and a strong dependence on the pH has been pointed out. The biosynthetic incorporation of 6-azatryptophan into the Y99W mutant of rat calmodulin allowed protein structural studies via fluorescence from this protein.[4]

A novel stable organic radical, 2-(4-azaindol-2-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazol-1-oxyl-3-oxide **5**, was synthesized with the aim of studying its magnetic properties (Fig. 2).[5]

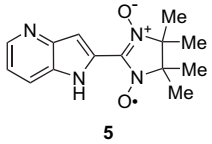


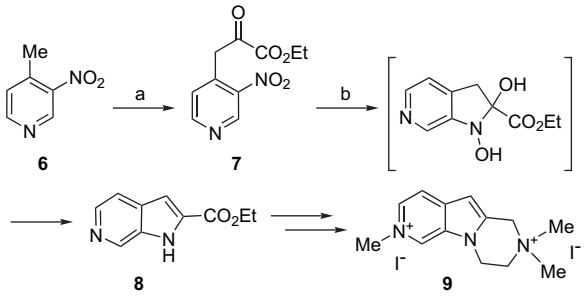
Figure 2. Compound **5**.

2. Synthesis of 4-, 5- and 6-azaindoles

Miscellaneous synthetic methods have been reported for the preparation of substituted indoles,[6] but relatively few have been applied to the preparation of substituted 4-, 5- and 6-azaindoles.[7] This fact could be explained by the electron-deficient nature of the pyridine ring. The electronics of the π-system are altered in such a way that many classical indole formation methods do not work or are not efficient (e.g., Fischer indolization). Besides the classical methods, alternative synthetic strategies to reach 4-, 5- and 6-azaindole derivatives have been developed and reported in the literature.

2.1. Reissert synthesis[7g]

Commercially available 4-methyl-3-nitropyridine **6** was treated with diethyl oxalate in the presence of sodium ethoxide providing intermediate **7**. Subsequent hydrogenation in a Parr apparatus allowed the intramolecular cyclization, generating ethyl 6-azaindole-2-carboxylate **8**. Further functionalization was performed on **8** to provide compound **9**, which was evaluated for its potential activity as a nicotinic ligand (Scheme 1).[8]



Scheme 1. *Reagents and conditions*: (a) diethyl oxalate, EtONa/EtOH, rt, 2.5 h, 42%; (b) H_2, Pd/C 10%, CH_2Cl_2, 35 psi, rt, 72 h, 84%.

This experimental procedure was repeated recently in two patents with miscellaneous applications such as access to new glycogen phosphorylase inhibitors (e.g., **10**) with therapeutic application for diabetes[9] and human casein kinase 1 epsilon inhibitors for the treatment of central nervous system diseases (e.g., **11**) (Fig. 3).[10]

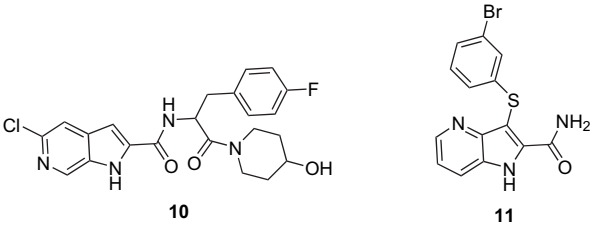
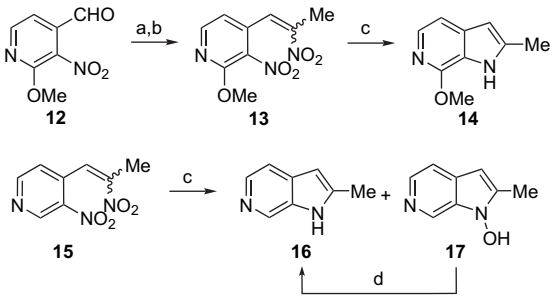


Figure 3. Compounds **10** and **11**.

A general large-scale synthesis of 2-alkyl-7-methoxy-6-azaindoles from 2-methoxy-3-nitro-4-formylpyridine **12** was described by Leftheris and co-workers (Scheme 2).[11] Aldehyde **12** was subjected to a Henry reaction in the presence of $EtNO_2$, followed by dehydration, affording nitroalkene **13** in good yield. The catalytic hydrogenation of **13** afforded the desired 6-azaindole **14** in 66% yield. The same procedure was applied to 3-nitro-4-formylpyridine. In this case, the reduction of nitroalkene **15** gave a mixture of the desired indole **16** and *N*-hydroxy-6-azaindole **17** (ratio 3:1), which was easily reduced by zinc in AcOH.

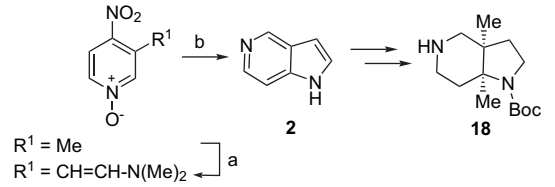
2.2. Batcho–Leimgruber synthesis

5-Azaindole **2** was prepared through the Batcho–Leimgruber synthesis[7a,e,i] by Shah and co-workers[12] as a precursor



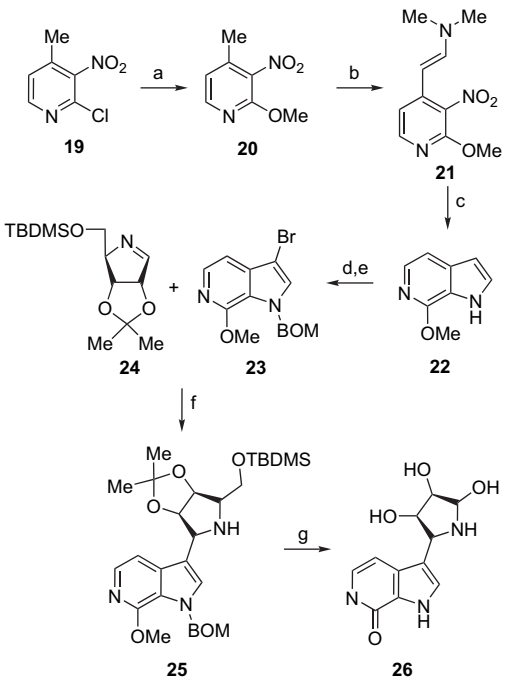
Scheme 2. *Reagents and conditions*: (a) $EtNO_2$, KF, 18-crown-6, *i*-PrOH, rt, 16 h, 97%; (b) Ac_2O, AcONa, KF, 18-crown-6, rt, 64 h, 89%; (c) H_2, Pd/C 10%, EtOH, AcOH, EtOAc, rt, 3 h, **14**=66%; (d) Zn, AcOH, reflux, 3 h, **16**=94%.

of bicyclic piperidine **18**, which was evaluated for its biological properties as a CCR5 antagonist (Scheme 3).



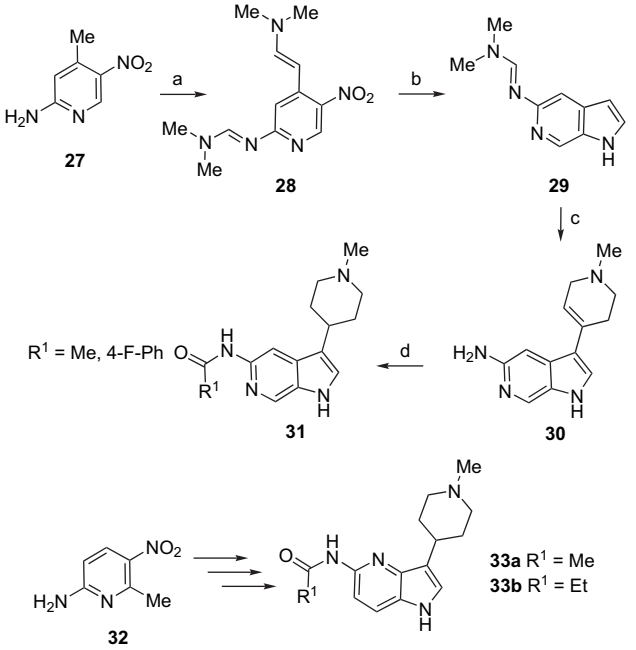
Scheme 3. *Reagents and conditions*: (a) DMF/DMA, DMF, 90 °C; (b) H_2, Pd/C 10%, EtOH, 60 °C.

In the same manner, 7-methoxy-6-azaindole **22** could be obtained from 2-chloro-4-methyl-3-nitropyridine **19**. Starting from **22**, the synthesis of aza-C-nucleoside immucillins, as potential inhibitors of human purine nucleoside phosphorylase (PNP), was developed (Scheme 4).[13] Compound **19** was subjected to SN_{Ar} in the presence of MeONa to provide 2-methoxypyridine **20**. Subsequent treatment with DMF/DMA gave the enamine **21**, which upon hydrogenation allowed the cyclization reaction to afford **22**. *N*-BOM protection of **22**, followed by regioselective bromination in the C-3 position, provided compound **23** in 46% overall yield (five steps). Lithium/halogen exchange on **23** with *n*-BuLi in THF at −78 °C afforded a lithiated species, which reacted immediately with iminoribitol **24** to give adduct **25** in 69% yield. Acid hydrolysis afforded the immucillin analogue **26** in 9% yield.



Scheme 4. *Reagents and conditions*: (a) MeONa/MeOH, reflux, 2 h, 98%; (b) DMF/DMA, DMF, 130 °C, 18 h, 99%; (c) H_2, Pd/C 10%, EtOH, 15 psi, rt, 15 min, 89%; (d) NaH, BOMCl, THF, rt, 2 h, 72%; (e) Br_2, $CHCl_3$, <10 °C, 74%; (f) (i) *n*-BuLi, Et_2O, −78 °C, (ii) imine, Et_2O, 0 °C, 69%; (g) HCl, MeOH, reflux, 48 h, 9%.

A structure–activity relationship study in the search for new 5-HT_{1F} receptor agonists was dedicated to the synthesis of indole bioisosteres, 6-azaindole and 4-azaindole. These derivatives were obtained following a modification of the Batcho–Leimgruber procedure (Scheme 5).[14]

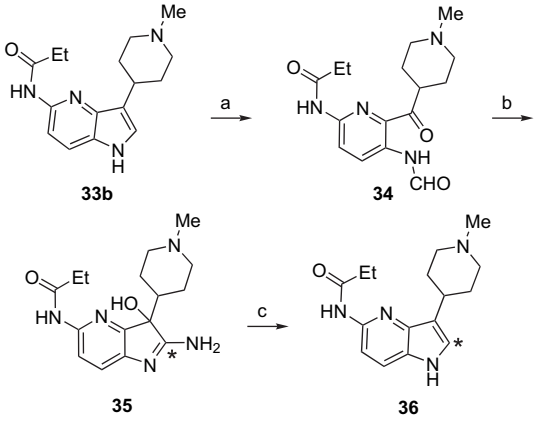


Scheme 5. *Reagents and conditions*: (a) DMF/DMA, DMF, 110 °C, overnight, quant; (b) H_2, 10% Pd/C, EtOH, 40 psi, 24 h, rt, 60%; (c) MeONa/MeOH, 1-methyl-4-piperidone, 75 °C, overnight, 86%; (d) (i) H_2, 10% Pd/C, EtOH, 60 psi, 40 °C, 24 h, 80%, (ii) R^1COCl, pyridine, rt, 4 h, 77%.

Treatment of 2-amino-4-methyl-5-nitropyridine **27** with DMF/DMA in DMF provided the enamine **28**. Reductive cyclization (H_2, Pd/C) of **28** afforded the pyrrolo[2,3-*c*]-pyridine derivative **29**. Condensation of **29** with 1-methyl-4-piperidone in the presence of freshly prepared MeONa introduced the 1,2,5,6-tetrahydropyridyl moiety in the C-3 position with concomitant hydrolysis of the amidine group to afford **30**. The desired 5-acylaminopyrrolo[2,3-*c*]pyridine analogues **31** were prepared from **30** by hydrogenation of the olefin, followed by acylation with an appropriate acid chloride in pyridine. In a similar way, the 5-acylaminopyrrolo[3,2-*b*]pyridine analogues **33** were obtained starting from the 2-amino-6-methyl-5-nitropyridine **32**. Biological evaluations pointed out the compounds **33a** and **33b** as potent and selective 5-HT_{1F} receptor agonists.

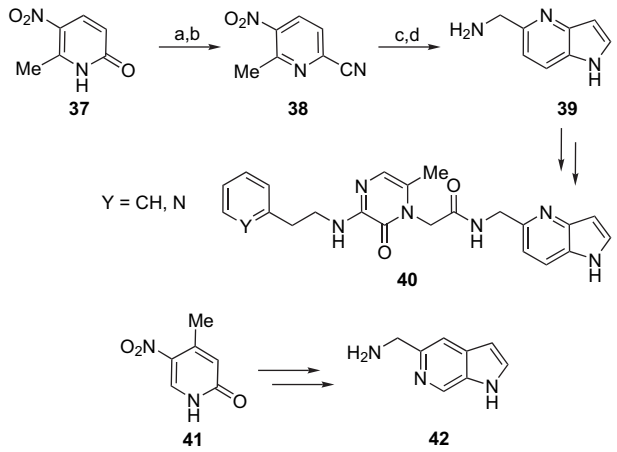
Wheeler and co-workers have developed an original strategy to obtain carbon-14-labelled compound **36**. The latter

derivative was prepared from unlabelled **33b** (Scheme 6).[15] Oxidation of **33b** with $OsO_4/NaIO_4$ in MeOH/H_2O yielded the opened keto derivative **34** in 16% yield. Treatment of **34** with $K^{14}CN$ afforded the intermediate **35** labelled in the C-2 position. Finally $NaBH_4$ reduction followed by dehydration gave the radiolabelled 4-azaindole **36** in 47% yield.



Scheme 6. *Reagents and conditions*: (a) $OsO_4/NaIO_4$, MeOH/H_2O, 63 h, rt, 16%; (b) $K^{14}CN$, EtOH, H_2O, 3 h, rt; (c) $NaBH_4$, THF/AcOH, 0–5 °C, 2 h; 47% (two steps).

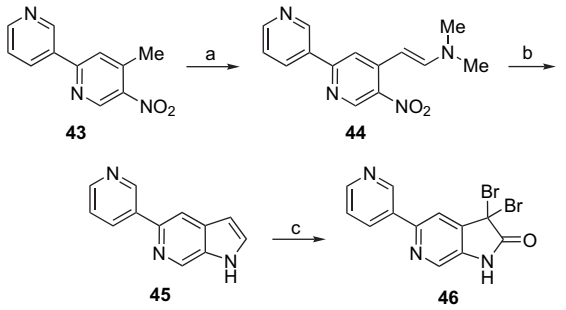
6-Methyl-5-nitropyridin-2-one **37** was converted in a two-step procedure into the corresponding nitrile **38**. The latter compound was subjected to a Batcho–Leimgruber procedure with concomitant reduction of the nitrile, providing the 5-aminomethyl-4-azaindole **39**. A reaction sequence led to the final compounds **40** bearing the azaindole moiety, which were evaluated for their biological properties as thrombin inhibitors (Scheme 7).[16]



Scheme 7. *Reagents and conditions*: (a) $POBr_3$, $(CHCl_2)_2$, reflux, 4 h; (b) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80 °C, 5 h; (c) DMF/DMA, DMF, 90 °C, 2 h; (d) H_2, Pd/C 10%, MeOH/6 M HCl, 16 h; yields not given.

Following the same pathway, 5-aminomethyl-6-azaindole **42** was prepared from 4-methyl-5-nitropyridin-2-one **41**.

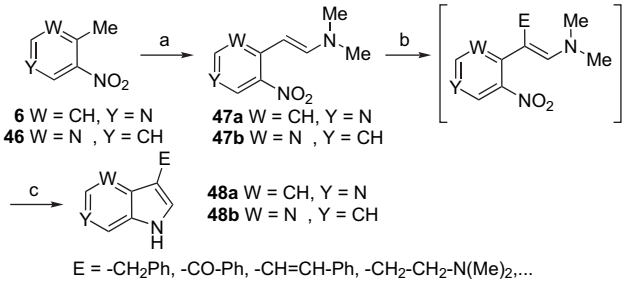
According to the same methodology, 5-pyridinyl-6-azaindole **45** was prepared as precursor of a potential Janus kinase 3 inhibitor (Scheme 8). Starting from 2,3-bipyridine **43**, the nitroalkene **44** was obtained in 52% yield. Cyclization of **44** occurred in the presence of H_2 and Pd/C to give **45**.[17] Bromination of **45** in *t*-BuOH/H_2O afforded **46** in 88% yield.



Scheme 8. *Reagents and conditions*: (a) $(EtO)_2CHNMe_2$, DMF, reflux, 52%; (b) H_2, Pd/C, IMS, 81%; (c) NBS, *t*-BuOH/H_2O, 88%.

The efficiency of the Batcho–Leimgruber indole synthesis could be enhanced by microwave irradiation. This optimization was applied in order to give access to 4-azaindoles. The presence of Lewis acids reduces considerably the reaction times, when compared with conventional heating methods.[18]

A practically convenient, one-pot process has been reported for the synthesis of 3-substituted 4- and 6-azaindoles. Condensation of 4-methyl-3-nitropyridine **6** or 2-methyl-3-nitropyridine **46** with DMF/DMA gave **47**. The enamines were reacted with various electrophiles, and then cyclized via reduction of the nitro group and elimination of dimethylamine (Scheme 9) to afford the 3-substituted azaindoles **48** in 30–69% overall yield.[19]



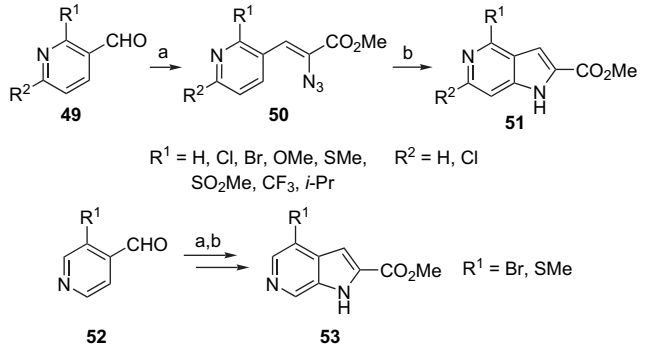
Scheme 9. *Reagents and conditions*: (a) DMF/DMA; (b) E^+, *i*-Pr_2NEt, dioxane, 115 °C, 14 h; (c) Fe, MeOH/dioxane/1 N HCl, 115 °C, 3 h, 30–69% (three steps).

The Batcho–Leimgruber synthesis was recently described in a Chinese patent for the industrial preparation of 5-azaindole **2**.[20]

2.3. Hemetsberger–Knittel synthesis

In 2000, the Hemetsberger–Knittel reaction was used by Fresneda and co-wrokers[21] to build up ethyl 4-methoxy-7-azaindole-2-carboxylate, representing the first example of its application to indole bioisosteres. Roy and co-workers[22] decided to investigate the generality of this reaction for the preparation of a series of methyl 4-substituted 5- or 6-azaindole-2-carboxylates (Scheme 10). The pyridine-3- and 4-carboxaldehydes **49** and **52** were treated with methyl azidoacetate in the presence of MeONa, affording the azidopyridineacrylates (e.g., **50**). Thermal cyclization of

these intermediates generated the azaindoles **51** and **53** in fair yields.



Scheme 10. *Reagents and conditions*: (a) methyl azidoacetate, MeONa/MeOH, −10 to 0 °C, 2 h, 55–83%; (b) mesitylene, reflux, 1 h, 32–93%.

The promising antiviral activity of BMS-488043[23] **54** (Fig. 4) encouraged Barret and co-workers to develop a new route to obtain 4,7-dimethoxy-5- or 6-azaindoles (Scheme 11).[24] The investigation was first made on the preparation of both 3- and 4-formylpyridines.

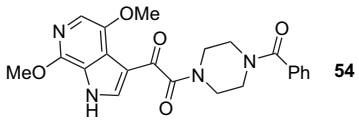
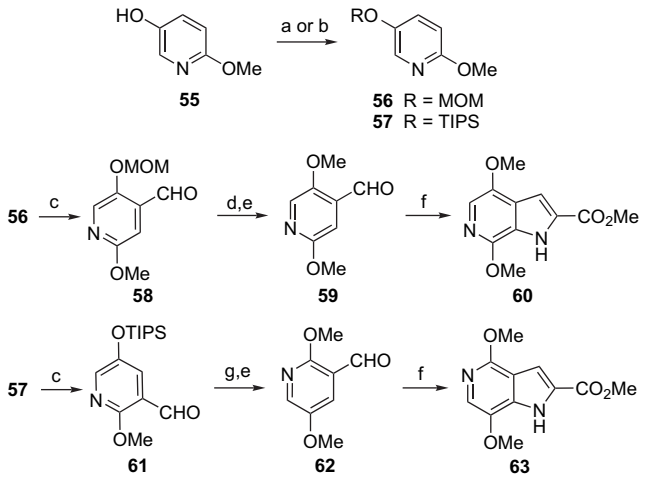


Figure 4. BMS-488043 **54**.



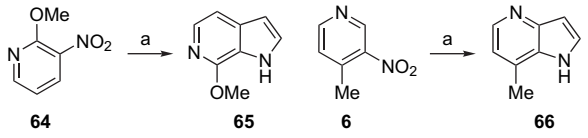
Scheme 11. *Reagents and conditions*: (a) NaH, MOMCl, DMF, rt, 3 h, **56**=92%; (b) TIPSCl, imidazole, DMF, rt, 24 h, **57**=quant; (c) (i) MeLi, DIPA, THF, 0 °C, 3 h, (ii) *N*-formylpiperidine, −40 °C, 2 h; **58**=62%, **61**=64%; (d) 3 N HCl, THF, 50 °C, 3 h, 95%; (e) MeI, K_2CO_3, DMF, 50 °C, 3 h, **59**=89%, **62**=97%; (f) (i) methyl azidoacetate, MeONa/MeOH, 30 °C, 2 h, (ii) xylene, 140 °C, 1 h, **60**=27%, **63**=47%; (g) TBAF, THF, 0 °C to rt, 2 h, 87%.

The formylation of 2,5-dimethoxypyridine was not regioselective, leading to a mixture of the 3- and 4-formyl derivatives in 70% yield (19:81 ratio). The reaction was next investigated on 5-hydroxy-2-methoxypyridine **55**. The lithium-based metalation procedure could be orientated either in the C-3 position or in the C-4 position by the choice of an appropriate protecting alcohol group on the C-5 position. The regioselectivity of the formylation would lead to the access of either 5- or 6-azaindole derivatives.

The *ortho*-directing methoxymethyl (MOM) group on **56** led to the regioselective formation of the 4-formylpyridine **58** as expected. Acidic cleavage of the MOM group followed by O-methylation afforded the 4-formyl-2,5-dimethoxypyridine **59**. The sterically hindered triisopropylsilyl (TIPS) ether on **57** led to the *C*-3 regioisomer **61**, pointing out the importance of a bulky protecting group. In this case, no trace of the *C*-4 regioisomer was detected. Desilylation of **61** followed by O-methylation afforded 3-formyl-2,5-dimethoxypyridine **62** in good yield. Both regioisomers **59** and **62** were subjected to a classical Hemetsberger–Knittel reaction, allowing the 6- and 5-azaindoles **60** and **63**.

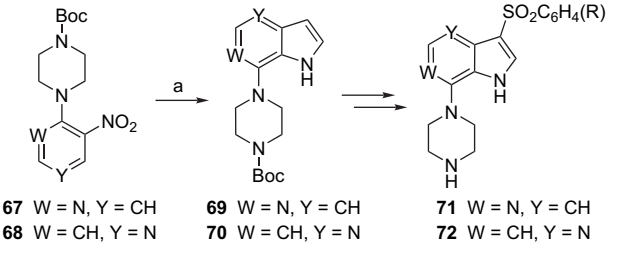
2.4. Bartoli synthesis

The Bartoli cyclization has been extensively studied in the synthesis of indole derivatives from nitrobenzene derivatives. This straightforward approach was applied to the synthesis of 7-substituted 4- and 6-azaindoles (Scheme 12).[25] 2-Methoxy-3-nitropyridine **64** was treated with 3–4 equiv of 1 M vinylmagnesium bromide in THF at −78 °C, providing the desired 7-methoxy-6-azaindole **65** in 20% yield. Although modest, this yield was similar to that obtained during the preparation of the corresponding indole. Miscellaneous nitropyridines were engaged to provide 4- and 6-azaindoles in 18–50% yields. As an example, 4-methyl-3-nitropyridine **6** gave 7-methyl-4-azaindole **66** in 18% yield. 5-Azaindole was not prepared, but the authors reported the probable application by the use of an appropriate nitropyridine.



Scheme 12. *Reagents and conditions*: (a) 1 M vinylmagnesium bromide (3–4 equiv), THF, −78 to −20 °C, 8 h, **65**=20%, **66**=18%.

The same experimental procedure was applied to the synthesis of heteroarylpiperazines (Scheme 13).[26] Nitropyridines **67** and **68** (obtained from reaction of the appropriate fluoro compound with *N*-Boc-piperazine) were successfully treated with vinylmagnesium bromide, as described above, to afford the desired azaindoles **69** and **70**, respectively, in 17 and 51% yield. The heteroarylpiperazines **71** and **72** were evaluated for their biological activity as potential brain



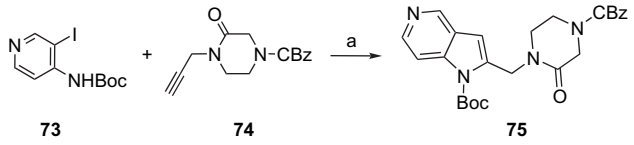
Scheme 13. *Reagents and conditions*: (a) 1 M vinylmagnesium bromide, THF, −40 °C, 40 min, **69**=17%, **70**=51%.

5-HT_6 receptor antagonists. Unfortunately, these ligands had a markedly lower 5-HT_6 affinity, compared to the reference compound.

This experimental procedure was applied recently in a patent relating to the design of 4- and 6-azaindolyloxoacetylpiperazines as anti-HIV drugs.[27]

2.5. Organometallic syntheses: Pd, Ru, Zr, Ti and Cu

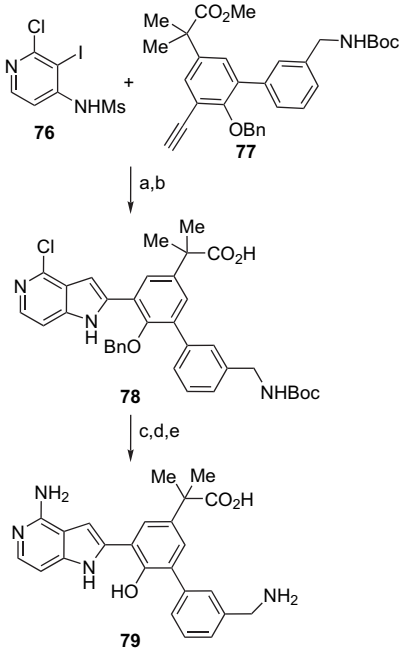
2.5.1. Azaindoles from terminal alkynes. A Sonogashira reaction of an aminohalopyridine and a terminal alkyne afforded the alkynylpyridine, which was cyclized into the azaindole using a variety of methods. Thus, palladium-catalyzed reaction of 4-(*N*-Boc-amino)-3-iodopyridine **73** with alkyne **74** followed by cyclization in the presence of DBU provided the 5-azaindole derivative **75** as a precursor of selective Factor Xa inhibitors (Scheme 14).[28]



73 **74** **75**

Scheme 14. *Reagents and conditions*: (a) (i) $PdCl_2(PPh_3)_2$, Et_3N, CuI, DMF, 100 °C, 1.5 h, (ii) DBU, 50 °C, 30 min, 77%.

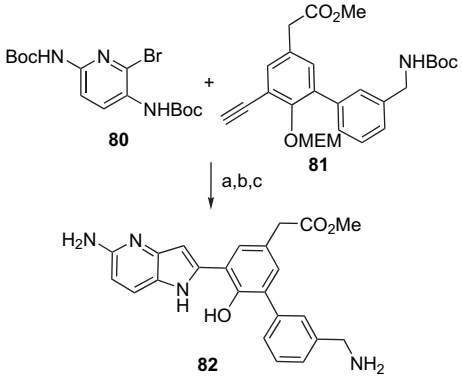
In the search for potent Factor VIIa inhibitors as anticoagulants, Hu and co-workers have performed a Sonogashira reaction between 4-(mesylamino)-2-chloro-3-iodopyridine **76** and alkyne **77** followed by basic cyclization (50% NaOH) to afford the 4-chloro-5-azaindole derivative **78** (Scheme 15). The chloro atom on the C-4 position was then replaced by an amino group to reach the desired inhibitor **79**.[29]



76 **77** **78** **79**

Scheme 15. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, MeCN, 80 °C; (b) 50% NaOH, MeOH, 60 °C, 63% (two steps); (c) $AcONH_4$, PhOH, 105 °C; (d) 6 N HCl, reflux; (e) H_2, $Pd(OH)_2$/C, EtOH, 15% (three steps).

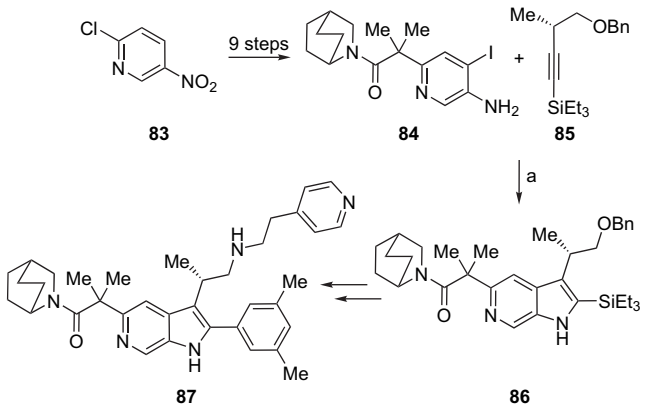
In a similar approach,[30] the synthesis of 5-amino-4-azaindole derivatives was also reported. 3,6-Bis(*N*-Boc-amino)-2-bromopyridine **80** was coupled with **81** to reach the alkyne intermediate, which was cyclized in the presence of TBAF (Scheme 16). Subsequent removal of the protecting groups afforded the 2-substituted 5-amino-4-azaindole **82**.



80 **81** **82**

Scheme 16. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, MeCN, 80 °C, 75%; (b) TBAF, THF; (c) 4 N HCl in dioxane, MeOH, 55% (two steps).

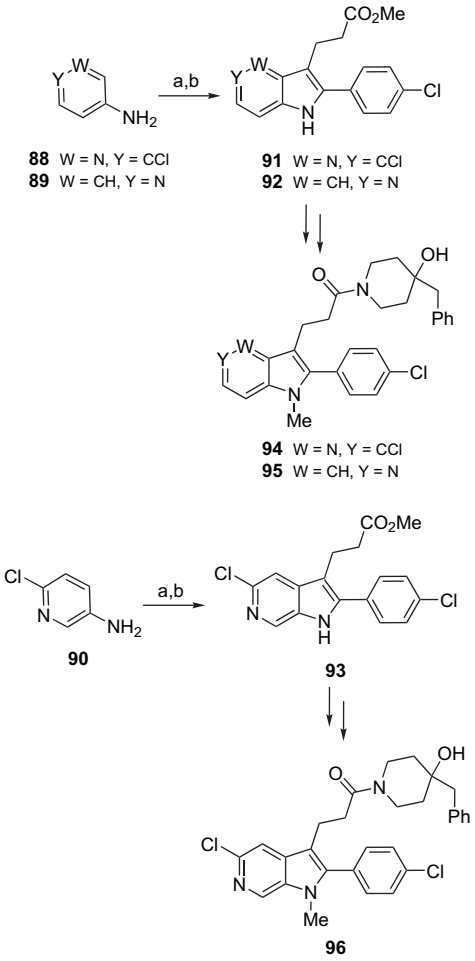
2.5.2. Heteroannulation using internal alkynes. Larock and Babu[31] reported an easy pathway to the indole nucleus involving palladium-catalyzed heteroannulation of internal alkynes and 2-haloanilines. This synthetic strategy was applied towards the preparation of azaindoles. In the first studies that were performed by Gronowitz and co-workers,[32] 2,3-disubstituted 4- and 5-azaindoles were obtained in 20–40% yields. The reaction conditions were optimized by Yum and co-workers[7k] for the specified 7-azaindole. Despite the limited literature precedent, the interest in this strategy was enhanced by the choice of $PdCl_2$(dppf) as the reference catalyst.[71] The Larock heteroannulation was, therefore, applied to more complicated azaindole systems of biological interest such as the potential GnRH antagonist 6-azaindole **87** (Scheme 17).[33] Thus, 2-chloro-5-nitropyridine **83** was converted within nine steps and 23% overall yield into the target aminopyridine **84**. Palladium-catalyzed heteroannulation of **84** and (*S*)-(4-benzyloxy-3-methylbut-1-ynyl)-triethylsilane **85** in the presence of $PdCl_2$(dppf), LiCl and Na_2CO_3 provided the desired 6-azaindole **86** in 62% yield.



83 **84** **85** **86** **87**

Scheme 17. *Reagents and conditions*: (a) $PdCl_2(dppf)\cdot CH_2Cl_2$, LiCl, Na_2CO_3, DMF, 100 °C, 15 h, 62%.

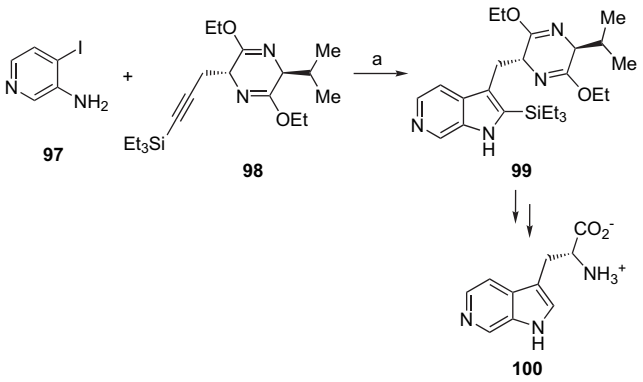
In the course of a search for new molecules with high affinity for the human neurokinin-1 (hNK_1) receptor, the Larock heteroannulation provided access to a new series of 4- or 5-azaindoles (Scheme 18).[34] Iodination of the aminopyridines **88–90** followed by palladium-catalyzed coupling with methyl 5-(4-chlorophenyl)pent-4-ynoate afforded the azaindoles **91–93**. The in vitro NK_1 binding results for the azaindole derivatives **94–96** pointed out the excellent affinity of 4- and 6-azaindoles. The compound derived from 5-azaindole did not give good results, which is in accordance with preliminary studies showing the importance of the substituent in the C-5 position.



Scheme 18. *Reagents and conditions*: (a) I_2, Ag_2SO_4, EtOH, rt, 24 h; (b) methyl 5-(4-chlorophenyl)pent-4-ynoate, $Pd(OAc)_2$, LiCl, Na_2CO_3, DMF, 70 °C, 24 h, 20–25%.

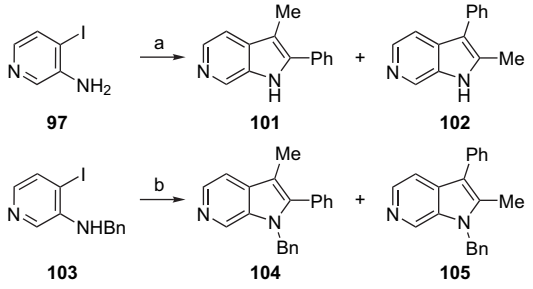
The synthesis of tryptophan analogues as potential indolamine 2,3-dioxygenase (IDO) inhibitors has also been reported by the reaction of 3-amino-4-iodopyridine **97** and the propargyl-substituted Schöllkopf chiral auxiliary **98** in the presence of $Pd(OAc)_2$, Na_2CO_3 and LiCl in DMF at 100 °C to give **99** (42% yield). The 2,3-regioisomer was also isolated in 15% yield. 6-Aza-D-tryptophan **100** was obtained in optically active form from **99** for biological evaluation (Scheme 19).[35]

Heteroannulation of 3-amino-4-iodopyridines and aromatic internal alkynes was developed to reach trisubstituted



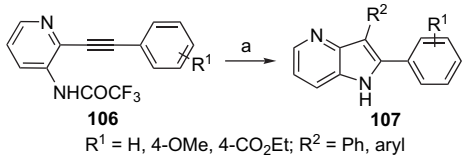
Scheme 19. *Reagents and conditions*: (a) $Pd(OAc)_2$ (5 mol %), Na_2CO_3, LiCl, DMF, 100 °C, 42%.

6-azaindoles (Scheme 20). The initial reaction was performed between **97** and 1-phenylpropyne in order to optimize the reaction conditions.[36a] Different sources of palladium were used, but the azaindole derivatives **101** and **102** were isolated in 13% yield (2:1 ratio). The best reaction conditions were found when 3-(*N*-benzylamino)-4-iodopyridine **103** was treated with $Pd(OAc)_2$ and AcOK. In all cases, two regioisomers **104** and **105** were obtained with a 2.3:1 ratio in favour of the phenyl substituent in the C-2 position. The same strategy was used to reach tetracyclic 5-azaindole analogues.[36b]



Scheme 20. *Reagents and conditions*: (a) 1-phenylpropyne, $Pd(OAc)_2$ (5 mol %), LiCl, AcOK, DMF, 110 °C, 24 h, **101**+**102**=13% (2:1); (b) 1-phenylpropyne, $Pd(OAc)_2$ (5 mol %), LiCl, AcOK, DMF, 110 °C, 10 h, **104**+**105**=78% (2.3:1).

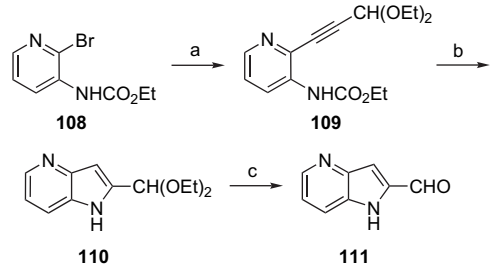
Recently, an aminopalladation–reductive elimination procedure was applied by Cacchi for the synthesis of 2,3-disubstituted 4-azaindole libraries (Scheme 21).[37] Starting from the readily available precursors **106**, a large diversity of 2-phenyl-4-azaindoles **107** were prepared.



Scheme 21. *Reagents and conditions*: (a) R^2X or R^2OTf (1.5 equiv), $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100 °C, 38–96%.

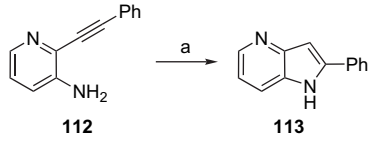
Sonogashira cross-coupling reaction between ethyl (2-bromopyridin-3-yl)carbamate **108** and propargylaldehyde

diethylacetal afforded alkyne **109**.[5] The cyclization of **109** occurred in the presence of EtONa at 100 °C to give the derivative **110**. Hydrolysis of the acetal led to 2-formyl-4-azaindole **111** in 70% yield (Scheme 22).



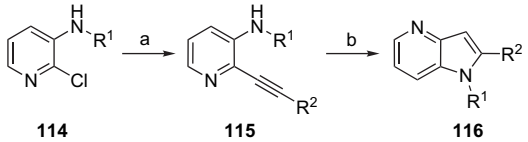
Scheme 22. *Reagents and conditions*: (a) propargylaldehyde diethylacetal, $PdCl_2(PPh_3)_2$, Et_3N, CuI, 100 °C, 5 h, 55%; (b) Na, EtOH, 100 °C, 24 h, 52%; (c) 1 M H_2SO_4, 100 °C, 15 min, 70%.

Knochel and co-workers reported the 5-*endo-dig*-cyclization mediated by potassium or cesium bases of 3-amino-2-alkynylpyridines obtained by a Sonogashira reaction (Scheme 23).[38] As an example, the 2-phenylethynylpyridin-3-ylamine **112** afforded the subsequent 2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine **113** in 74% yield.



Scheme 23. *Reagents and conditions*: (a) KH, NMP, rt, 1 h, 74%.

Recently, a two-step sequence of copper-free Sonogashira alkynylation between alkynes and 3-amino-2-chloropyridines **114** followed by a base-mediated cyclization reaction of **115** was reported (Scheme 24).[39] A catalytic system such as $PdCl_2(MeCN)_2$ or $Pd(OAc)_2$ could be used with dppb or X-Phos as phosphine ligand in the presence of potassium carbonate as a base. The 4-azaindoles **116** were obtained in good yields.



R^1 = Bn, cyclopentyl, cyclohexyl, 4-(ethoxycarbonyl)piperidinyl
R^2 = Ph, butyl, cyclohexenyl, chloropropyl

Scheme 24. *Reagents and conditions*: (a) terminal alkynes, $PdCl_2(MeCN)_2$, X-Phos, K_2CO_3, MeCN, 60 °C, 16 h or terminal alkynes, $Pd(OAc)_2$, dppb, K_2CO_3, MeCN, 80 °C, 16 h; (b) 1 M *t*-BuOK, THF, rt, 83–91% (two steps).

In a similar way, a DBU-mediated cyclization of *o*-(*N*-Boc-amino)alkynylpyridines was reported, affording 4-, 5- and 6-azaindoles **117a–c** under mild conditions, in high yields and allowing a wide variety of functionality (Fig. 5).[40] Larock heteroannulation was largely used in different patents for the construction of azaindole skeletons.[41]

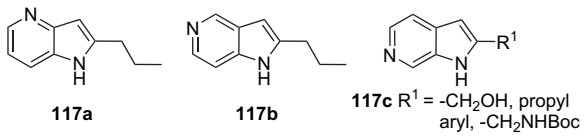
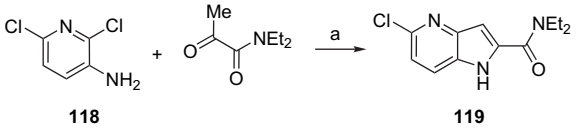


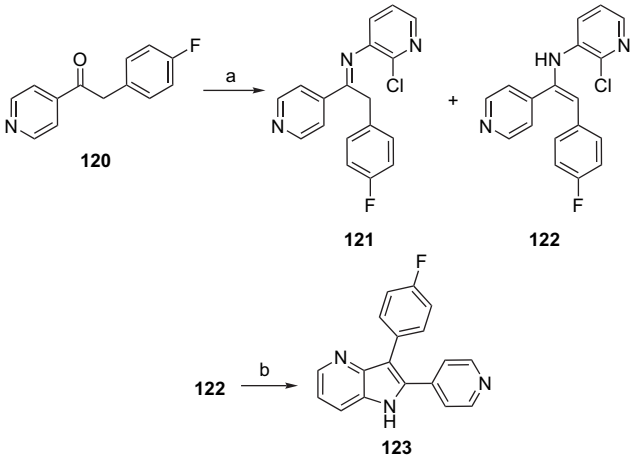
Figure 5. Structures of **117**.

2.5.3. Other palladium-catalyzed cyclizations. A flexible palladium-catalyzed 4-azaindole synthesis was investigated by direct annulation of 3-amino-2-chloropyridines and ketones (Scheme 25).[42] An extensive screening of palladium catalysts revealed that $Pd(t\text{-}Bu_3P)_2$ in combination with a base such as K_3PO_4 or AcOK and $MgSO_4$ as a water scavenger was able to catalyze annulation in DMA at 140 °C. Addition of AcOH to the reaction medium allowed almost quantitative conversion into the expected bicyclic system. Thus, 2,6-dichloro-3-aminopyridine **118** led to the 5-chloro-4-azaindole derivative **119** in 60% yield.



Scheme 25. *Reagents and conditions*: (a) $Pd(t\text{-}Bu_3P)_2$, K_3PO_4, AcOH, $MgSO_4$, DMA, 140 °C, 16 h, 60%.

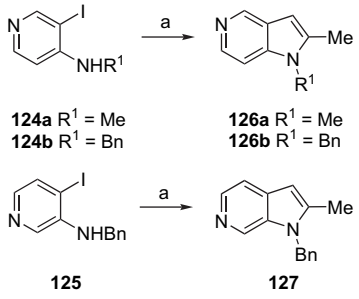
Ketone **120** could be converted into an imine **121**/enamine **122** mixture (ratio 1:4) via condensation with 3-amino-2-chloropyridine with azeotropic removal of water. The desired azaindole **123** was then formed from **122** through an intramolecular palladium coupling reaction (Scheme 26).[43]



Scheme 26. *Reagents and conditions*: (a) 3-amino-2-chloropyridine, *p*-TSA, toluene, reflux, 24 h; (b) $PdCl_2(PPh_3)_2$, DABCO, DMF, 120 °C, 4 h, yields not given.

Palladium-catalyzed annulation of 3-iodopyridines **124a**,**b** or 4-iodopyridine **125** in the presence of $Pd(OAc)_2$ (5 mol %) and allyl acetate afforded the 5-azaindoles **126a**,**b** or 6-azaindole **127** in fair yields (Scheme 27).[44]

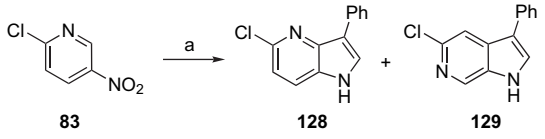
Azatryptophan derivatives have been recently prepared by Zhu and Jia [45] by a palladium-catalyzed annulation of *o*-haloanilines and aldehydes.



Scheme 27. *Reagents and conditions*: (a) allyl acetate, $Pd(OAc)_2$, LiCl, K_2CO_3, DMF, 120 °C, 13 h, **126a**=56%, **126b**=53%, **127**=45%.

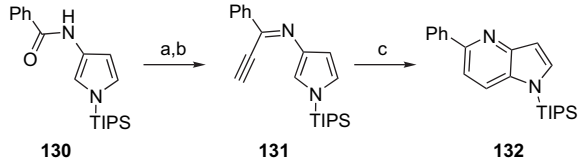
Under microwave-irradiation conditions, the Hegedus–Mori–Heck reaction was extended to the synthesis of 4-, 5- and 6-azaindoles with good yields, reducing significantly the reaction time and promoting the palladium coupling with more traditional palladium catalysts.[46]

2.5.4. Ruthenium approach. Ruthenium-catalyzed reductive annulation of nitroaromatics with alkynes was applied to the preparation of the azaindole core.[47] Indoles can be prepared, due to the ability of metals to induce C–N bond formation combined with the reduction of nitroaromatic compounds with carbon monoxide. In this paper, a sole example was reported for the synthesis of azaindoles (Scheme 28). 2-Chloro-5-nitropyridine **83** was reacted with phenylacetylene and ruthenium-complex catalyst in a stainless steel reactor charged with 750 psi of carbon monoxide. Both regioisomers were obtained, depending on the cyclization process: 4-azaindole **128** and 6-azaindole **129** in a 3.5:1 ratio.



Scheme 28. *Reagents and conditions*: (a) phenylacetylene, CO, $[(\eta^5\text{-}C_5Me_5)Ru(CO)_2]_2$, molecular sieves 4 Å, dioxane or benzene, 750 psi, 170 °C, 48–72 h, **128**+**129**=53% (3.5:1).

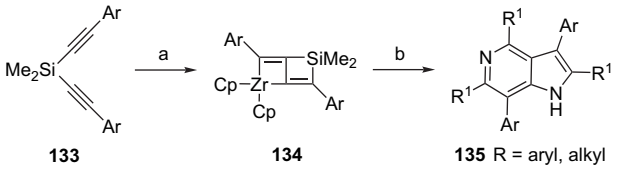
The ruthenium-catalyzed cycloisomerization of azadienynes was also investigated, allowing a general approach for the access of 4-azaindoles (Scheme 29).[48] Amide **130** was converted into the corresponding alkynylimine **131** by treatment with trifluoromethanesulfonic anhydride followed by copper trimethylsilylacetylide. Compound **131** was subjected to cycloisomerization in the presence of chlorocyclopentadienylbis(triphenylphosphine)ruthenium $[CpRu(PPh_3)_2Cl]$ as catalyst to afford 5-phenyl-4-azaindole **132**. The combination of $[CpRu(PPh_3)_2Cl]$ (5 mol %), SPhos (5 mol %) and



Scheme 29. *Reagents and conditions*: (a) (i) Tf_2O, 2-chloropyridine, CH_2Cl_2, −78 to 0 °C, 5 min, (ii) copper trimethylsilylacetylide, THF, −78 to 0 °C, 10 min, 82%; (b) K_2CO_3, MeOH, 23 °C, 15 min, 94%; (c) $[CpRu(PPh_3)_2Cl]$ (5 mol %), SPhos, NH_4PF_6, toluene, 90 °C, 4 h, 65%.

ammonium hexafluorophosphate (1 equiv) in toluene (0.2 M) at 90 °C was identified as the best conditions.

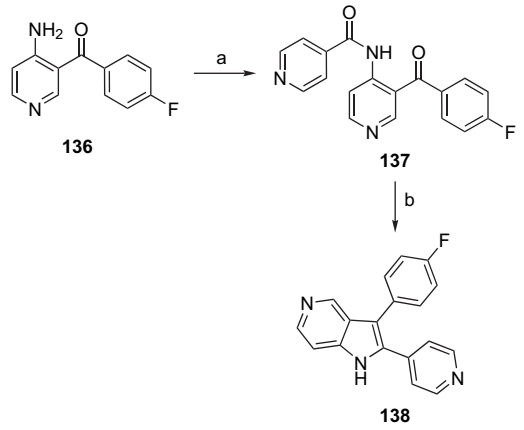
2.5.5. Zirconocene-mediated intermolecular coupling. The zirconocene-mediated coupling reaction of organonitriles with alkynes, in which one Si-tethered diyne is coupled in one pot with three molecules of nitrile promoted by a low-valent zirconocene species, provided the 5-azaindole derivatives (Scheme 30).[49]



Scheme 30. *Reagents and conditions*: (a) Cp_2ZrBu_2, 50 °C, 3 h; (b) (i) R^1CN, 50 °C, 1 h, (ii) aq $NaHCO_3$, 46–81% (two steps).

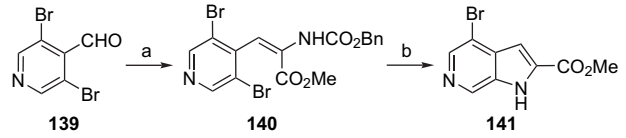
When treated with the Negishi reagent (Cp_2ZrBu_2), the bis(arylethynyl)dimethylsilane **133** reacted to afford a zirconacyclobutene-silacyclobutene fused-ring intermediate **134**. This organometallic compound was treated in the presence of R^1CN, and then hydrolyzed with aqueous $NaHCO_3$ to furnish 5-azaindoles **135** in 46–81% yields.

2.5.6. Titanium cyclization. The titanium cyclization approach was applied to the preparation of 5-azaindole derivatives (Scheme 31). Compound **136** treated with isonicotinoyl chloride in CH_2Cl_2 in the presence of pyridine afforded the oxoamide **137**. Reductive coupling with $TiCl_3$/Mg under the conditions described by Fürstner and coworkers[50] gave the corresponding 5-azaindole **138**.[43]



Scheme 31. *Reagents and conditions*: (a) isonicotinoyl chloride, pyridine, CH_2Cl_2, 0 °C to rt, 4 h; (b) $TiCl_3$, Mg, pyridine, DME, reflux, 1 h, yields not given.

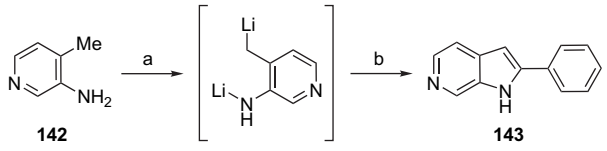
2.5.7. Copper cyclization. Ene-carbamate **140** was synthesized by a Horner–Wadsworth–Emmons reaction between *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester and 3,5-dibromo-4-formylpyridine **139** (Scheme 32). The cyclization of **140** occurred in the presence of CuI and L-proline to afford the 6-azaindole derivative **141** in 85% yield.[51] It should be noted that amino acids accelerated the Cu-mediated self-coupling with aryl halides.



Scheme 32. *Reagents and conditions*: (a) DBU, *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester, CH_2Cl_2, rt, 2 h, 77%; (b) K_2CO_3, dioxane, L-proline, CuI, 100 °C, 24 h, 85%.

2.6. Dilithiation

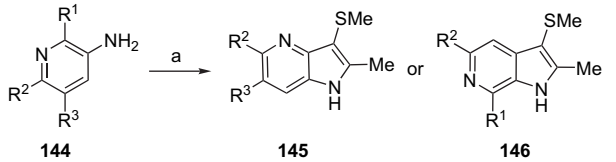
3-Amino-4-picoline **142** was used as a building block for the synthesis of 2-substituted 6-azaindoles (Scheme 33).[52] First, the dilithiation of pyridine was achieved in the presence of 3 equiv of *s*-BuLi. The addition of ethyl benzoate at −78 °C was essential to avoid the formation of *N*-(4-methylpyridin-3-yl)benzamide derived from the lone nitrogen attack on the ester. Compound **143** was obtained in 88% yield. The scope of this reaction was explored by the use of a wide range of aryl carboxylic esters, providing the corresponding 2-substituted 6-azaindoles with moderate-to-excellent yields (33–88%). The challenge of this strategy relies on the direct dilithiation of unprotected 3-amino-4-picoline, which provided 6-azaindoles in a single step.[53]



Scheme 33. *Reagents and conditions*: (a) *s*-BuLi, THF, −78 °C to rt, 3 h; (b) ethyl benzoate, −78 °C, 1 h, 88%.

2.7. Sommelet–Hauser rearrangement

Recently, Merck researchers enhanced the Sommelet–Hauser-type rearrangement, expanding it to the construction of 4-azaindoles **145** and 6-azaindoles **146** from 3-aminopyridines **144** (Scheme 34).[54] 6-Azaindoles were prepared using 2-substituted 3-aminopyridines as starting materials, whereas the use of 2-unsubstituted 3-aminopyridines provided the corresponding 4-azaindoles exclusively (Table 1).



Scheme 34. *Reagents and conditions*: (a) (i) *t*-BuOCl (2 equiv), CH_2Cl_2, −78 °C, 10–15 min, (ii) $MeCOCH_2SMe$, −78 °C, 90 min, then Et_3N, −78 °C to rt.

Table 1. Preparation of 4-azaindoles **145a–d** and 6-azaindoles **146e–f**

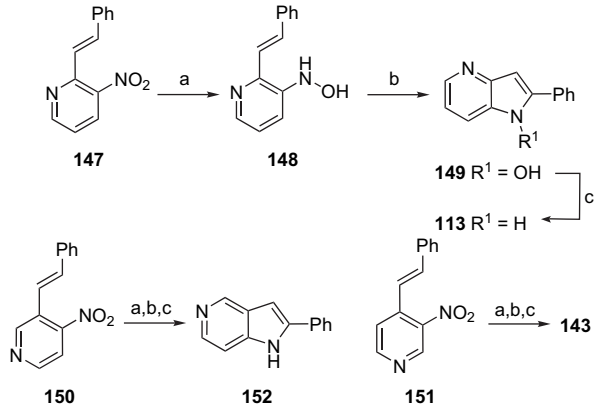
Compd	R^1	R^2	R^3	Temp (°C)	**145** (%)	**146** (%)
144a	H	–CH(CH$_2$)$_2$CH–		0	91	—
144b	H	Cl	H	−78	70	—
144c	H	CF_3	H	−10	41	—
144d	H	H	H	−40	25	—
144e	Cl	H	H	−78	—	94
144f	OMe	H	H	−78	—	35

When a solution of 3-aminopyridines **144** was treated with *t*-BuOCl followed by the addition of methylthioacetone and Et_3N, either the 4-azaindoles **145** or the 6-azaindoles **146** were isolated in moderate-to-good yields (25–94%).

The same reaction conditions were applied to 4-aminopyridines to obtain the 5-azaindole core. In this case, 4-aminopyridines have been found unreactive, even at room temperature.

2.8. Oxidation of *o*-hydroxyaminostyrylpyridines

The use of acetylenic aminopyridines for the synthesis of substituted azaindoles was first reported by Xu and co-workers.[7m] The scope of the cyclization of *o*-hydroxyaminostyrylpyridines was investigated and significantly improved by Boehringer–Ingelheim researchers (Scheme 35).[55] 3-Nitro-2-styrylpyridine **147** was reduced in the presence of stannous chloride, providing an intermediate hydroxylamine **148**, which upon oxidation with DDQ was converted into 1-hydroxy-2-phenyl-4-azaindole **149** in 93% yield. Reduction of the hydroxylamine function afforded 2-phenyl-4-azaindole **113** in 75% yield. The same pathway was applied for the synthesis of 2-phenyl-5-azaindole **152** and 2-phenyl-6-azaindole **143** from **150** and **151**, respectively (58 and 72% yield, three steps).



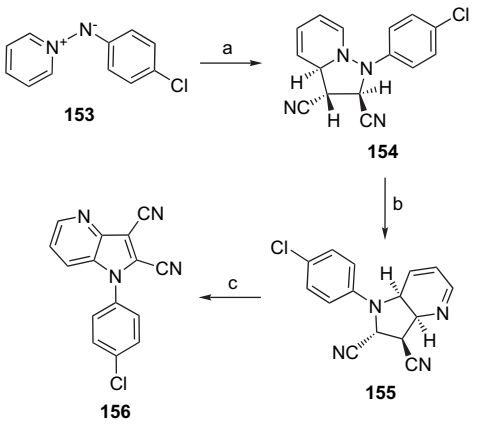
Scheme 35. *Reagents and conditions*: (a) $SnCl_2\cdot 2H_2O$, $AcONa\cdot 3H_2O$, THF/MeOH, 0 °C, 5 h, **148**=98%; (b) DDQ, $MeCN/H_2O/AcOH$, −10 °C, 20 min, **149**=93%; (c) Fe, AcOH/EtOH, reflux, 45 min, **113**=75%, **152**=58%, **143**=72% (three-step yield for the last two compounds).

2.9. Dipolar cycloaddition

A 1,3-dipolar cycloaddition reaction allowed access to the unexpected 4-azaindoles (Scheme 36).[56] Pyridinium *N*-arylimide **153** reacted with fumaronitrile, providing the cycloadduct **154** that underwent rearrangement in toluene at reflux to provide the tetrahydropyrrolo[3,2-*b*]pyridine **155**. Subsequent oxidation with DDQ afforded the 1,2,3-trisubstituted 4-azaindole **156**.

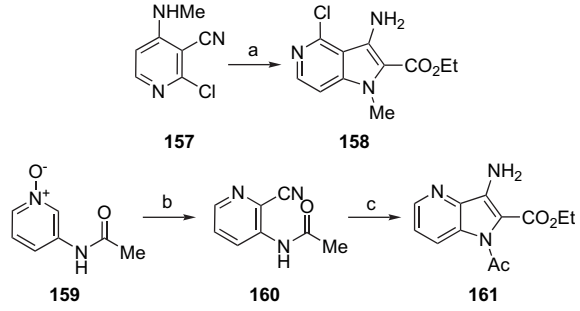
2.10. Other methods

2-Chloro-3-cyano-4-methylaminopyridine **157** was alkylated in the presence of ethyl bromoacetate and NaH (Scheme 37). In the meantime, cyclization proceeded smoothly, providing ethyl 3-amino-4-chloro-1-methyl-5-



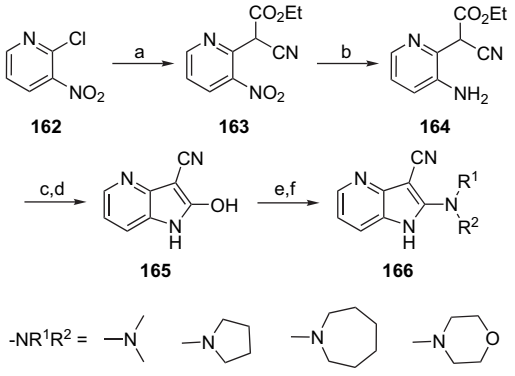
Scheme 36. *Reagents and conditions*: (a) fumaronitrile, Et_2O, rt, 20 min, 53%; (b) toluene, reflux, 2 h, 28%; (c) DDQ, toluene, reflux, 2 h, 86%.

azaindole-2-carboxylate **158**.[57,58] The 4-azaindole skeleton was obtained in a different way.[57] First, the acetamidopyridine *N*-oxide **159** was subjected to a cyanation procedure, providing the intermediate **160**. Subsequent alkylation and cyclization furnished the 4-azaindole **161**. Both 4- and 5-azaindoles **158** and **161** were further engaged in the preparation of azaindolopyrimidines.



Scheme 37. *Reagents and conditions*: (a) ethyl bromoacetate, NaH, DMF, 40 °C, 61%; (b) Me_2NCOCl, TMSCN, CH_2Cl_2, rt, 92%; (c) NaH, ethyl bromoacetate, THF, 0 °C to rt, 88%.

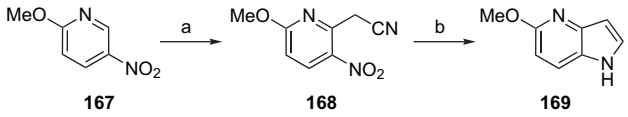
The synthesis of 2-amino-3-cyano-4-azaindoles was initiated by the reaction of 2-chloro-3-nitropyridine **162** with the enolate of ethyl cyanoacetate to obtain **163** (Scheme 38).[59] Catalytic hydrogenation of the nitro group of **163** provided



Scheme 38. *Reagents and conditions*: (a) ethyl cyanoacetate, *t*-BuOK, *i*-PrOH, rt, 30 min then 80 °C, 6 h, 74%; (b) H_2, Pd/C, EtOH, 50 psi, 3 h, 99%; (c) xylene, reflux, 20 h; (d) NaOH then CO_2(g), 46% (two steps); (e) $POCl_3$, 105 °C, 2 h, 45%; (f) R^1R^2NH, 110 °C, 18 h.

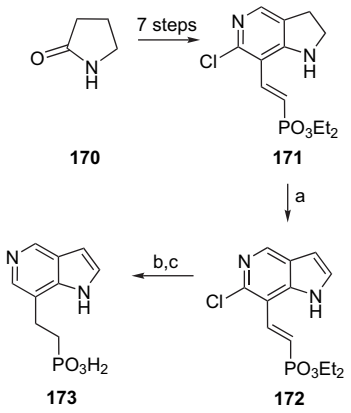
the 3-amino derivative **164**. Thermal cyclization of **164**, followed by subsequent treatment with NaOH and CO_2(g), afforded the 2-hydroxyazaindole **165**. A wide variety of 2-amino-4-azaindoles were obtained by functionalization of the C-2 position of **165**. Treatment of **165** with phosphorus oxychloride afforded the 2-chloro derivative. Displacement of the halogen with primary and secondary amines gave the corresponding 2-amino-4-azaindoles **166** in moderate yields. These compounds were evaluated as a potential class of BK_{Ca} channel openers.

2-Methoxy-5-nitropyridine **167** underwent a vicarious nucleophilic aromatic substitution of hydrogen upon treatment with the anion of 4-chlorophenoxyacetonitrile,[60] providing the intermediate **168** in 86% yield (Scheme 39). Subsequent hydrogenation of **168** in classical conditions afforded the cyclization, providing the 5-methoxy-4-azaindole **169** in 57% yield.[61]



Scheme 39. *Reagents and conditions*: (a) *t*-BuOK, 4-chlorophenoxyacetonitrile, THF, −10 °C, 3 h, 86%; (b) H_2, Pd/C, EtOH, 57%.

The synthesis of the 5-azaindole phosphonic acid **173** was accomplished in ten steps from pyrrolidin-2-one **170** (Scheme 40).[62] The pyridine nucleus was first prepared from **170** and the lateral side chain was then introduced in the C-7 position to give 5-azaindoline **171**. Pyrrole aromatization of **171** was effective in the presence of $Ce(NH_4)_2(NO_3)_5$ (CAN) to afford 5-azaindole **172** in 50% yield.

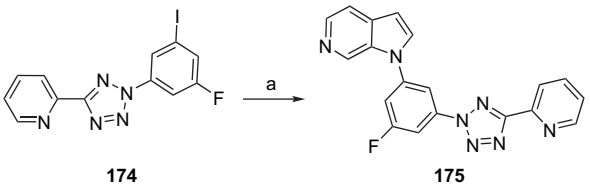


Scheme 40. *Reagents and conditions*: (a) CAN, 50%; (b) H_2, Pd/C, MeOH, 97%; (c) HCl, 94%.

3. Functionalization and reactivity of 4-, 5- and 6-azaindoles

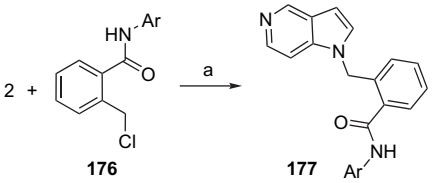
3.1. Functionalization of N-1 position

3.1.1. N-Arylation. N-Arylation between the iodo derivative **174** and 6-azaindole **3** was performed in the presence of $Pd_2(dba)_3$ and biphenyl-2-yl(dicyclohexyl)phosphine to reach a new selective mGlu5 receptor antagonist **175** (Scheme 41).[63]



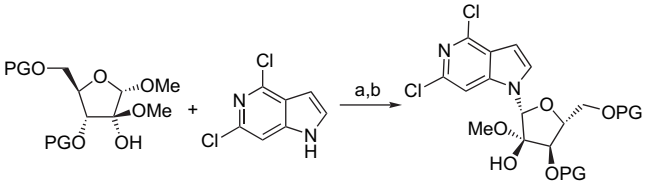
Scheme 41. *Reagents and conditions*: (a) **3**, *t*-BuONa, biphenyl-2-yl(dicyclohexyl)phosphine, $Pd_2(dba)_3$, dioxane, 110 °C, yield not given.

3.1.2. N-Alkylation. Novel inhibitors **177** of VEGFR-1/2 kinases were synthesized by N-alkylation of 5-azaindole **2** with chloroamide **176** in basic conditions (Scheme 42).[64]



Scheme 42. *Reagents and conditions*: (a) K_2CO_3, DMF, rt, 12 h, yield not given.

The bromo derivative of compound **178** was coupled with the anion of 4,6-dichloro-5-azaindole **179** providing the corresponding ribonucleoside **180** (Scheme 43).[65]

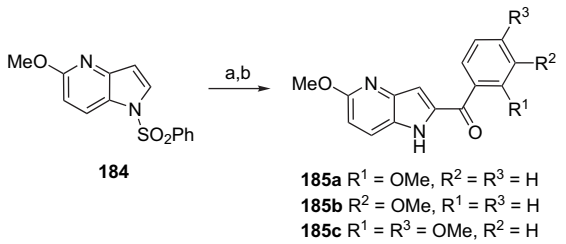


Scheme 43. *Reagents and conditions*: (a) HBr, CH_2Cl_2, 0 °C, 30 min; (b) NaH, NMP, rt, 1 h, 37% (two steps).

3.2. Functionalization of C-2 position

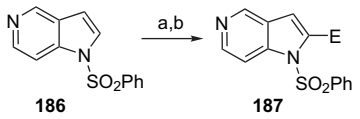
2-Iodo-3-substituted azaindoles **182** were obtained by the reaction of 2-trimethylsilyl-3-substituted azaindoles **181** with ICl at room temperature (Scheme 44). Palladium-catalyzed coupling reactions (Suzuki, Heck, Stille reactions) were performed with miscellaneous 2-iodo-3-methyl-5-azaindoles **182a** and boronic acids, acrylates and organostannane derivatives to give the 2-substituted 3-methyl-5-azaindoles **183**. The catalytic system used for all the palladium-catalyzed reactions was $Pd(OAc)_2$ (5 mol %) in the presence of LiCl and AcOK in DMF at 110 °C. The 2-substituted 5-azaindoles were obtained in moderate-to-good yields (49–81%). No reaction was observed when the *N*-free azaindole was used.[66]

The synthesis of 2-aroylazaindoles as potential antimitotic agents was explored (Scheme 45). 1-Benzenesulfonyl-5-methoxy-4-azaindole **184** was lithiated in the C-2 position and condensed with methoxybenzoyl chlorides, providing the methoxyphenyl-(1-benzenesulfonyl-5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl)methanones **185a–c**.[67]



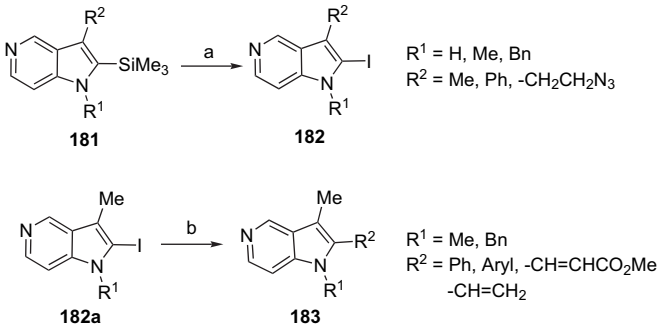
Scheme 45. *Reagents and conditions*: (a) LDA, THF, 0 °C, 30 min; (b) 2-methoxybenzoyl chloride or 3-methoxybenzoyl chloride or 2,4-dimethoxybenzoyl chloride, THF, −78 °C to rt, overnight, **185a**=44%, **185b**=66%, **185c**=14%.

2-Lithio-1-benzenesulfonyl-5-azaindole was also prepared from 1-benzenesulfonyl-5-azaindole **186** by the addition of LDA. Trapping by various electrophiles [Me_3SnCl, I_2, MeI, DMF, $B(OMe)_3$] afforded the 2-substituted 5-azaindoles **187** in good yields (62–95%) (Scheme 46).[68]



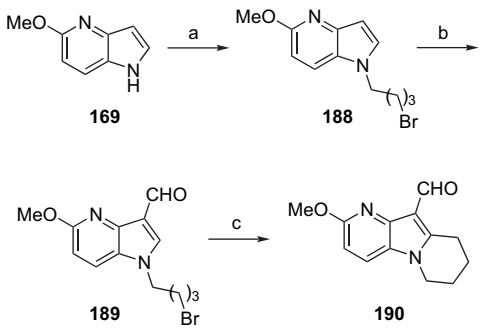
Scheme 46. *Reagents and conditions*: (a) LDA, THF, −20 °C, 30 min; (b) electrophile, THF, −20 °C, E=$SnMe_3$=95% (30 min), E=I=62% (30 min), E=Me=86% (2 h), E=CHO=84% (3 h), E=$B(OH)_2$, 71% (5 h).

5-Methoxy-4-azaindole **169** was alkylated with 1,4-dibromobutane by the use of sodium hydride in DMF. Formylation of **188** under Vilsmeier–Haack conditions provided



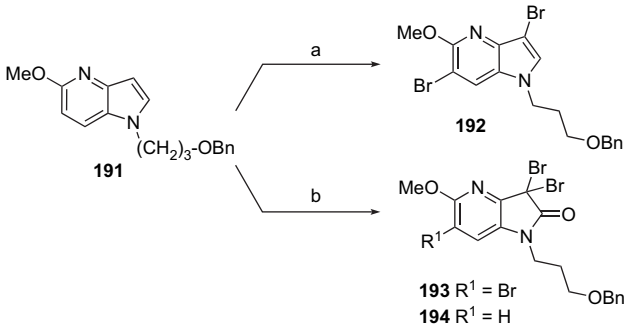
Scheme 44. *Reagents and conditions*: (a) ICl, CH_2Cl_2, 0 °C to rt, 1 h, 75–93%; (b) boronic acids, acrylates or organostannanes, $Pd(OAc)_2$, LiCl, AcOK, DMF, 110 °C, 49–81%.

the desired substrate **189**, which was subjected to the radical cyclization (Scheme 47). The 6,7,8,9-tetrahydropyrido[3,2-*b*]indolizine ring system **190** was obtained in 65% yield.[69]



Scheme 47. *Reagents and conditions*: (a) 1,4-dibromobutane, NaH, DMF, rt, 79%; (b) $POCl_3$, DMF, rt, 91%; (c) Bu_3SnH, AIBN, toluene, reflux, 65%.

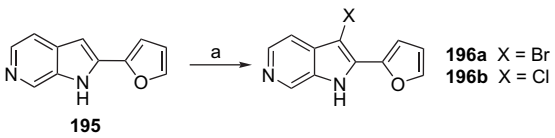
In the same paper,[69] the 1-[3-(benzyloxy)propyl]pyrrolopyridine **191** was oxidized by an excess of pyridinium bromide perbromide (PBPB) in *t*-BuOH to furnish the dibromide **192** in 94% yield (Scheme 48). The tribromo derivative **193** was prepared in 50% yield when **191** (by-product **194**=25%) was reacted with 4 equiv of bromine in *t*-BuOH and H_2O.



Scheme 48. *Reagents and conditions*: (a) PBPB, *t*-BuOH, rt, 94%; (b) Br_2, *t*-BuOH/H_2O, rt, **193**=50%, **194**=25%.

3.3. Functionalization of C-3 position

3.3.1. Regioselective halogenation. A mild and efficient synthesis of 2-substituted 3-halo-6-azaindoles was developed for 6-azaindole systems (Scheme 49).[70] The 2-(2-furyl)-6-azaindole **195** was a challenging substrate for selective halogenation, as conventional bromination methods led to various mixtures of mono-and dibrominated compounds at the C-3 position and in the C-1 position of the furan ring. Side reactions were minimized by use of $CuBr_2$ or $CuCl_2$ (3 equiv), which provided the 3-halo-6-azaindoles **196a**,**b** with excellent yields (85–90%). This halogenation was extended to 2-methyl-, 2-phenyl-, 2-(thien-3-yl)-, 2-phenylethyl- and 2-adamantyl-6-azaindoles and pointed out the regioselectivity and high yields of this method (74–90%).



Scheme 49. *Reagents and conditions*: (a) $CuBr_2$ or $CuCl_2$, MeCN, rt, 85–90%.

This regioselective bromination was recently extended by the same authors to the substrates **1–3** and 2-substituted 4- and 5-azaindoles **197a**,**b** (Fig. 6).[71] 3-Iodo-5-azaindole **198** was also prepared in 91% yield by treatment of **2** with KOH in DMF.[68]

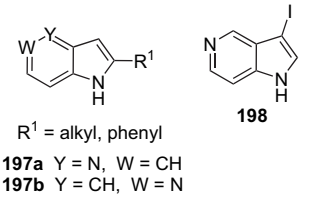
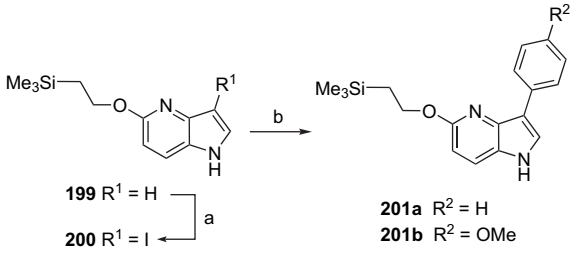


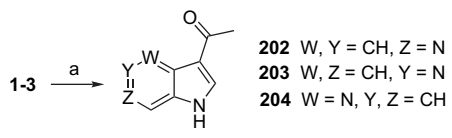
Figure 6. Compounds **197** and **198**.

Iodination of **199** on the C-3 position in the presence of NIS afforded almost quantitatively compound **200**. This intermediate was further functionalized via a Suzuki palladium-catalyzed coupling reaction. Using phenylboronic acid and 4-methoxyphenylboronic acid, the 3-arylazaindoles **201a**,**b** were obtained, respectively, in 26 and 71% yield (Scheme 50).[61]

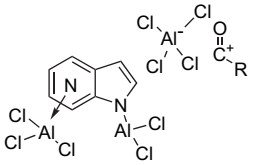


Scheme 50. *Reagents and conditions*: (a) NIS, THF, rt, 2 h, 97%; (b) 4-R^2-$ArB(OH)_2$, $PdCl_2(dppf)$, 2 N Na_2CO_3, EtOH, reflux, 3 h, **201a**=26%, **201b**=71%.

3.3.2. Regioselective acylation. In pursuit of a Friedel–Crafts-type approach that relies upon activation of the electrophile, a convenient acylation of azaindoles **1–3** was reported by Wang and co-workers.[72] As example, compounds **202–204** were prepared from **1–3** in good yields (Scheme 51). It was found that a minimum of 3 equiv of $AlCl_3$ in CH_2Cl_2 was required to achieve the best results. Use of additional $AlCl_3$ did not improve the yield further. The requirement for greater-than-stoichiometric quantities of $AlCl_3$ could be interpreted by the formation of complex **205** (Fig. 7). The first equivalent of $AlCl_3$ coordinates with the pyridine nitrogen atom, resulting in a decrease of the pK_a of the pyrrole NH. Reaction of the second equivalent of $AlCl_3$ may lead to deprotonation and the formation of an aluminium salt. Finally, the third equivalent of $AlCl_3$ forms an 'ate' complex with the acyl chloride, the active intermediate engaged for the Friedel–Crafts reaction.



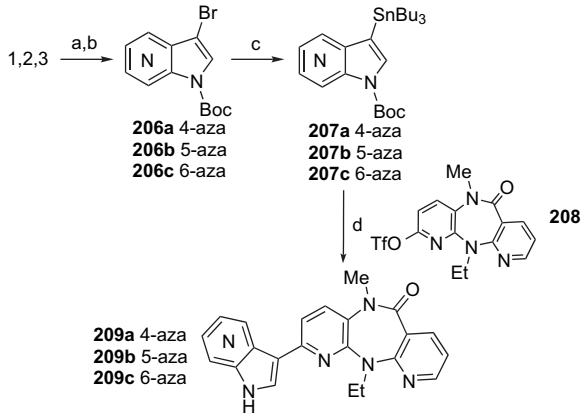
Scheme 51. *Reagents and conditions*: (a) $AlCl_3$ (5 equiv), CH_2Cl_2, rt, 1 h then acetyl chloride, rt, 8 h, **202**=63%, **203**=94%, **204**=70%.



205

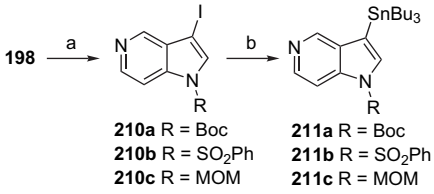
Figure 7. Complex **205**.

3.3.3. Stannylation followed by Stille coupling. Bromination of azaindoles **1–3** with Br_2 in CCl_4 produced the 3-bromoazaindoles, which were immediately converted into their *N*-Boc derivatives **206a–c** by treatment with Boc_2O in the presence of DMAP (Scheme 52). Lithium/halogen exchange in the presence of *n*-BuLi and TMEDA generated the lithiated species, which upon immediate reaction with Bu_3SnCl furnished the corresponding organostannanes **207a–c** in 14–20% yield. These latter compounds were engaged in a Stille palladium-catalyzed coupling reaction in the presence of triflate **208**,[73] $PdCl_2(PPh_3)_2$ and LiCl, providing the 2-azaindol-3-yl-dipyridodiazepinones **209a–c** in low yield. The same synthetic strategy was applied to 4- and 5-azaindoles within the same range of yields. The low isolated yields observed at each stage of the synthesis are due to significant difficulties encountered during the purifications.[74]



Scheme 52. *Reagents and conditions*: (a) Br_2, CCl_4, *i*-Pr_2NEt, 0 °C; (b) Boc_2O, DMAP, dioxane, **206a**=76%, **206b**=42%, **206c**=42% two steps; (c) (i) *n*-BuLi, TMEDA, THF, −78 °C, 15 min, (ii) Bu_3SnCl, −78 °C to rt, 2 h, **207a**=18%, **207b**=14%, **207c**=20%; (d) triflate **208**, $PdCl_2(PPh_3)_2$, LiCl, DMF, 110 °C, overnight, **209a**=5%, **209b**=11%, **209c**=14%.

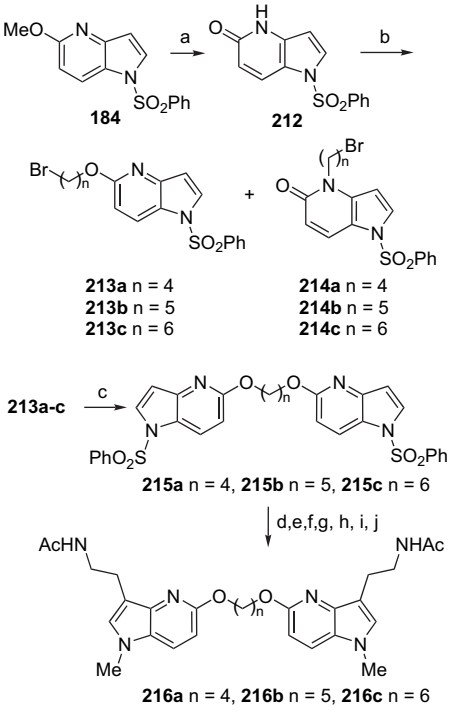
Stannylation of 3-iodo-5-azaindole derivatives from compound **198** was described by Mérour and co-workers (Scheme 53).[68] 3-Iodo-5-azaindole **198** was first subjected to N-protection to afford compounds **210a–c** in good yields. Reaction of **210a–c** with hexamethylditin in the presence of $PdCl_2(PPh_3)_2$ and LiCl gave organostannanes **211a–c** in excellent yields. Organostannane **211a** was also prepared in 93% yield by a lithium/halogen exchange of **210a** and addition of trimethyltin chloride.



Scheme 53. *Reagents and conditions*: (a) Boc_2O, DMAP, THF, rt, 16 h, **210a**=quant; NaH, $PhSO_2Cl$, THF, 0 °C to rt, 2 h, **210b**=78%; NaH, THF, 0 °C to rt, 15 min, **210c**=77%; (b) $PdCl_2(PPh_3)_2$, LiCl, Me_6Sn_2, THF, reflux, 2 h, **211a**=90%, **211b**=97%, **211c**=95%.

3.4. Functionalization of pyridine ring

Dimers linked by an alkoxy spacer have been prepared from a 5-methoxy-4-azaindole **184** (Scheme 54).[75] Subsequent treatment of **184** with $AlCl_3$ led to the pyridone **212**, which was subjected to an alkylation procedure with an alkyl dibromide in the presence of potassium carbonate in DMF, providing a mixture of the expected *O*-alkylated compounds **213a–c** in moderate yields and *N*-alkylated compounds **214a–c** in lower yields. Compound **212** was condensed with bromoalkoxy derivatives **213a–c** leading to the bis-4-azaindoles **215a–c**. After a deprotection–protection sequence to afford the N-position protected with a methyl group, a lateral side chain was introduced in the C-3 position by formylation under Vilsmeier–Haack conditions. The bis-aldehydes were engaged in a Henry reaction with nitromethane followed by reduction with $NaBH_4$ and hydrogenation over Raney nickel. Final acetylation gave the desired derivatives **216a–c**.



Scheme 54. *Reagents and conditions*: (a) $AlCl_3$, CH_2Cl_2, reflux, 12 h, 83%; (b) $Br–(CH_2)_n–Br$, K_2CO_3, DMF, rt, 12 h, **213a**=54%, **213b**=54%, **213c**=53%, **214a**=23%, **214b**=24%, **214c**=29%; (c) **212**, K_2CO_3, DMF, rt, 24 h, **215a**=57%, **215b**=60%, **215c**=50%; (d) 2.5 M NaOH, MeOH, CH_2Cl_2, reflux, 12 h; (e) NaH, MeI, DMF, rt, 4 h; (f) $POCl_3$, DMF, rt, 2 h; (g) $MeNO_2$, NH_4OAc, 120 °C, 4 h; (h) *i*-PrOH, $CHCl_3$, SiO_2, $NaBH_4$, rt, 20 min; (i) H_2, Raney Ni, MeOH, 60 °C, 12 h; (j) Ac_2O, CH_2Cl_2, pyridine, rt, 12 h, **216a**=11%, **216b**=8%, **216c**=6% (six steps).

4. Design of 4-, 5- and 6-azaindoles as biological targets

The diversity of biological targets is a good criterion of interest in medicinal chemistry of the azaindole core. Numerous

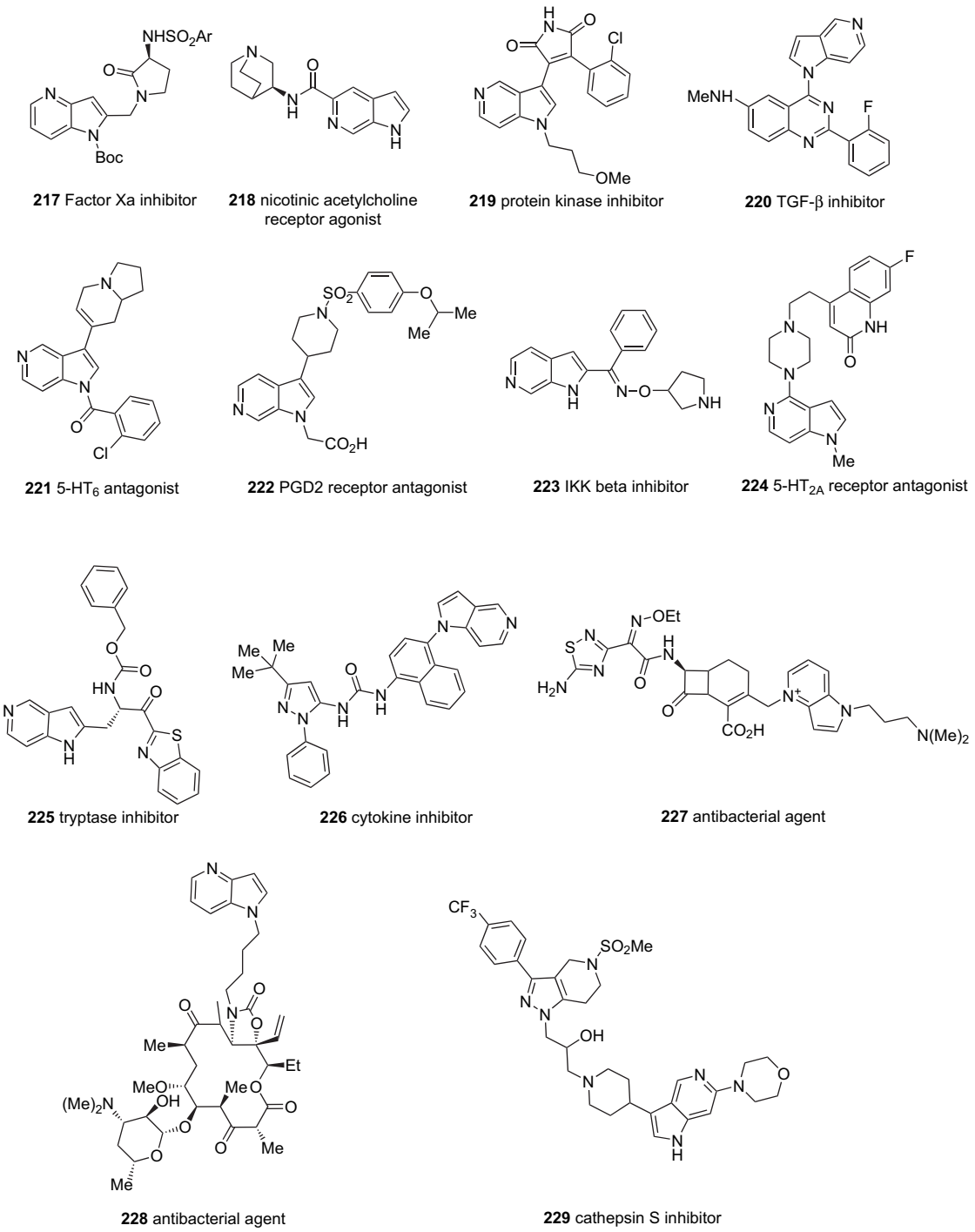


Figure 8. Compounds **217**–**229**.

compounds are described in the literature,[76–94] and a few examples are given in Figure 8 (**217**,[76] **218**,[77] **219**,[78] **220**,[79] **221**,[80] **222**,[81] **223**,[82] **224**,[83] **225**,[84] **226**,[85] **227**,[86] **228**[87] and **229**[88]).

5. Conclusions

In a similar manner to the 7-azaindole field, the expanding use of 4-, 5- and 6-azaindoles in medicinal chemistry makes them attractive tools for the drug discovery. The main efforts have been devoted to new synthetic methods, extending the scope of the preparation of 4-, 5- and 6-azaindoles, as well as functionalization of the nuclei.

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Biographical sketch

Florence Popowycz was born in Auxerre (France) on October 25, 1976. She graduated from the Ecole Nationale Supérieure de Chimie de Paris in 1999. The same year, she obtained a master degree in organic chemistry at the Université Pierre et Marie Curie and worked in the laboratory of Professor J.-P. Genêt. She received her Ph.D. degree in 2003 from the Ecole Polytechnique Fédérale de Lausanne (Switzerland) after working on mannosidase inhibitors in the laboratory of Professor P. Vogel. After a post-doctoral year in Geneva (Switzerland) studying aminolevulinic acid derivatives and their use in photodynamic therapy under the supervision of Dr. N. Lange, she joined the group of Professor B. Joseph in October 2004 as an assistant Professor at the Université Claude Bernard—Lyon 1.

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Jean-Yves Mérour graduated with a chemistry engineer diploma Ecole Nationale Supérieure de Chimie de Paris; he received his Ph.D. from the University of Paris VI (France) under the supervision of Professor P. Cadiot. Then he moved to the University of Orléans (France) as 'assistant'. In 1979 he joined Dr. J. L. Roustan's group at the University of Ottawa (Canada) as a post-doctoral fellow to work on the synthesis of iron carbonyl complexes. Back to the Université d'Orléans he started his work in the field of nitrogen heterocycles with Professors A. Buzas and F. Tatibouët. In 1992 he became full Professor at the Université d'Orléans. His main research interests are in the synthesis and reactivity of indole and 7-azaindole derivatives. More recently his work at the Institut de Chimie Organique et Analytique has focused on the synthesis of new indolic anticancer agents, which included marine natural products analogues.