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Synthesis and reactivity of 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine)

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Contents

1. Introduction

Contrary to indoles, the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) nucleus is present only in a few natural products such as alkaloids from the variolin family. Nevertheless, 7-azaindole derivatives have attracted much attention due to their physicochemical and pharmacological properties. 7-Azaindole can be considered as a bioisostere of an indole or purine moiety. Substitution of the C-7 position of indole by an sp^2-hybridized nitrogen provides a skeleton containing a hydrogen-bond donor and acceptor in a rigid three-atom

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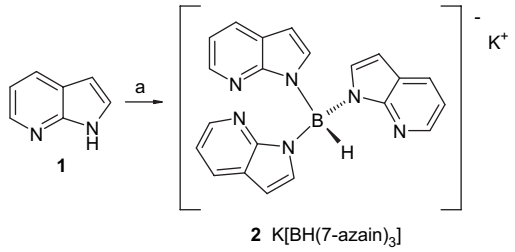
arrangement. This review aims to update our preceding report[1] in 2001 that was further completed by a short review[2] by Nora de Souza et al. on 4-, 5-, 6- and 7-azaindoles for the period 2001–2006. First, the use of 7-azaindole in inorganic chemistry is described. In the second part, its synthesis and uses in organic synthesis are reported.

2. Inorganic complexes

2.1. Mononuclear complexes

A wide range of 7-azaindole complexes have been synthesized in order to evaluate the luminescence properties of these derivatives. Amongst them, some of the 7-azaindole derivatives developed by Wang et al.[3] have been used as blue emitters in organic light emitting devices. The luminescent properties of 7-azaindole complexes with miscellaneous metals have been reviewed previously.[4–6] The blue emission of the 7-azaindol-1-yl anion was commonly reported as being unstable towards air and moisture.

Some efforts have been devoted to improve the stability and performance of compounds based on the 7-azaindole skeleton. The first approach concerned the direct use of the pyrrole nitrogen atom in a C–metal bond. It has been shown also that the 7-azaindol-1-yl anion could be stabilized by central ions such as aluminium, zinc or, more recently, boron.[7] The incorporation of a 7-azaindol-1-yl anion with a single electron-deficient boron atom through an N–B bond results in the formation of a new stable blue-luminescent scorponiate ligand. The borate ligand K[BH(7-azaindol-1-yl)$_3$] **2**, obtained from the reaction of KBH_4 with an excess of commercially available 7-azaindole **1** (Scheme 1),[8] was found to generate complexes with Zn^{II} and Cu^{I} ions. The cuprous complex [BH(7-azaindol-1-yl)$_3$](CuPPh$_3$) did not show blue emission, while compound **2** and complex [BH(7-azaindol-1-yl)$_3$](ZnCl) display bright blue emission.



Scheme 1. Reagents and conditions: (a) KBH_4, 180 °C, 1 h, 87%.

The synthesis of 1-diphenylphosphino-7-azaindole **3** (dppai) was performed either by reacting $PClPh_2$ with **1** in DMF in the presence of Et_3N in 36% yield[9] or in a two-step process involving the lithium 7-azaindol-1-yl salt and $PClPh_2$ (72% yield). 1-Diphenylphosphino-7-azaindole **3** (dppai) was coordinated as a *P,N* bidentate ligand [$PtCl_2$(dppai-*P,N*)] **4** by reaction with [$PtCl_2$(cod)] in dichloromethane. New palladium complex **5** with azaindolylphosphine as ligand was also developed as an active catalyst for the co-polymerization of CO and ethene (Fig. 1).[10]

One major modification was the replacement of the proton of the indole nitrogen atom by an aromatic group, providing

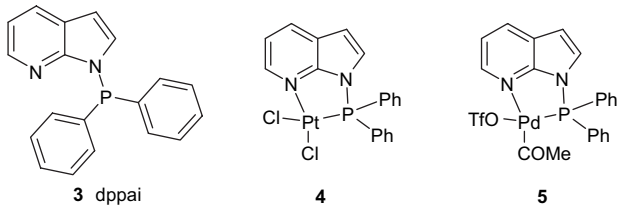
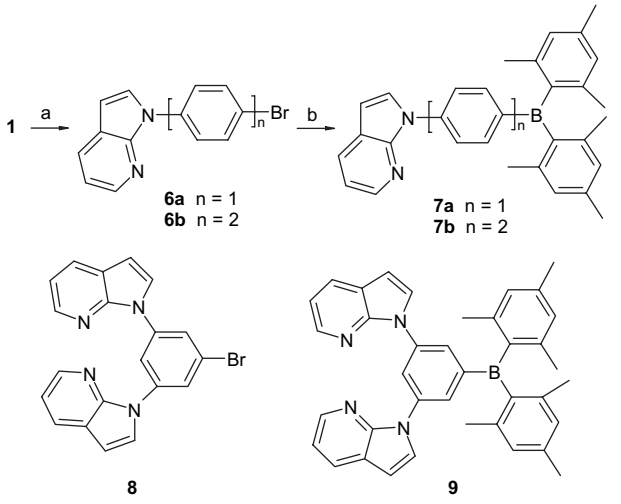


Figure 1. Ligand dppai and derivatives.

a series of stable and highly luminescent 1-aryl-7-azaindole derivatives.[11,12] Wang et al. have also carried out intensive studies on three-coordinate boron compounds that have emerged as promising materials for electroluminescent devices. These new organoboron compounds **7** (BAr_2L in which Ar is mesityl and L is 7-azaindol-1-yl) have been synthesized in two steps (Scheme 2).[13] First, an Ullman condensation between 7-azaindole **1** and 1,4-dibromobenzene or 1,4-dibromobiphenyl afforded compounds **6a** or **6b**. Subsequent treatment of **6a**,**b** with *n*-BuLi followed by addition of the electrophilic reagent (mesityl)$_2$BF afforded **7a**,**b**. The same procedure was applied to **8** to obtain the functionalized phenyl organoboron **9**.



Scheme 2. Reagents and conditions: (a) KOH, $CuSO_4$, 1,4-dibromobenzene or 1,4-dibromobiphenyl, 210 °C, 43%; (b) *n*-BuLi, Mes_2BF, −78 °C, **7a**=85%, **7b**=78%, **9**=67%.

In the same investigation, the metal could be changed. Luminescent organic/organometallic complexes **10** of group 15 metals of general structure M[4-C_6H_4(7-azaindol-1-yl)]$_3$ with M=P, Sb, Bi have been synthesized [14] by halogen–metal exchange of 1-(4-bromophenyl)-7-azaindole by *n*-BuLi followed by reaction of MCl_3 (Fig. 2). Cyclometallated compounds from group 7 and especially rhenium complexes

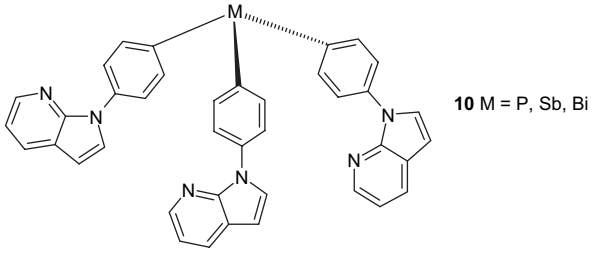
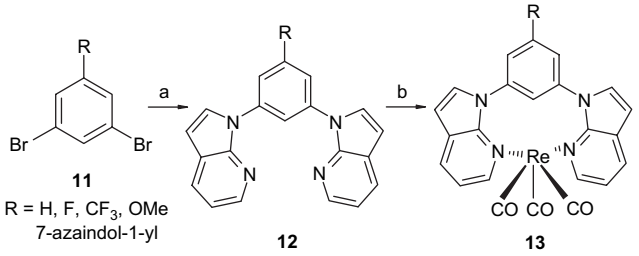


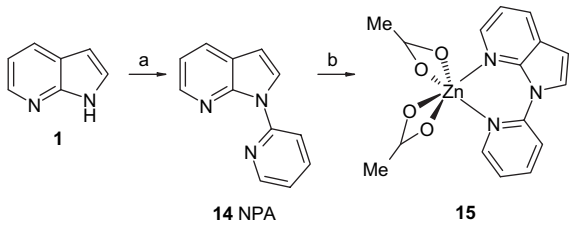
Figure 2. M[4-C_6H_4(7-azaindol-1-yl)]$_3$ complexes.

have been studied for photochemistry (Scheme 3). The Re(I) complexes **13** bearing a 2,6-bis(7-azaindol-1-yl)phenyl tridentate ligand were synthesized by complexation of 1,3-bis(7-azaindol-1-yl)-5-phenyl derivatives **12** (prepared from **11**) with $Re_2(CO)_{10}$ and exhibited green luminescence.[15]



Scheme 3. Reagents and conditions: (a) **1**, K_2CO_3, $CuSO_4$, 180–200 °C, 5–24 h, 12–85%; (b) $Re_2(CO)_{10}$, diglyme, reflux, 24 h, 62–85%.

Che et al. reported[16] Zn_4O(7-azaindol-1-yl)$_6$ derivative as a blue emitter. In view of this work, the blue-luminescent/electroluminescent properties of promising Zn(II) complexes of 7-azaindole **1** and *N*-(2-pyridyl)-7-azaindole (NPA) **14** such as Zn(7-azaindole)$_2$(MeCO$_2$)$_2$, Zn(NPA)-(MeCO$_2$)$_2$ and Zn(NPA)((*S*)-(+)-MeCH$_2$CH(Me)CO$_2$)$_2$ have been examined. In particular, the ligand **14** was prepared and complexed with zinc acetate to form a bright blue-luminescent complex **15** (Scheme 4). The use of a 2-pyridyl moiety improves the stability of the complex by chelating the metal centre.[17]

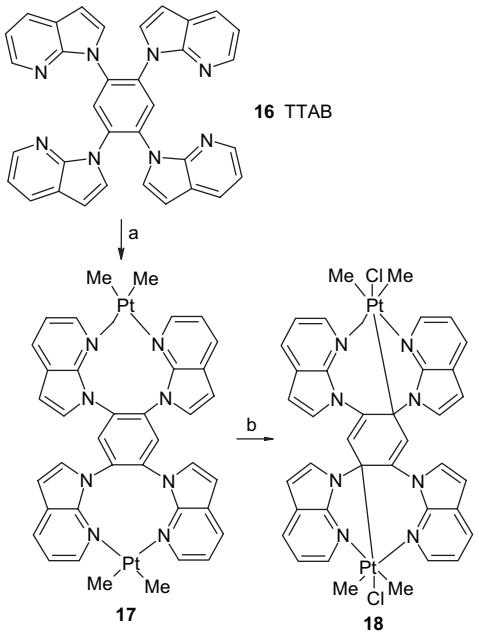


Scheme 4. Reagents and conditions: (a) 2-bromopyridine, K_2CO_3, $CuSO_4$, 200 °C, 4 h, 64%; (b) Zn(OAc)$_2$, EtOH, 2 h, 66%.

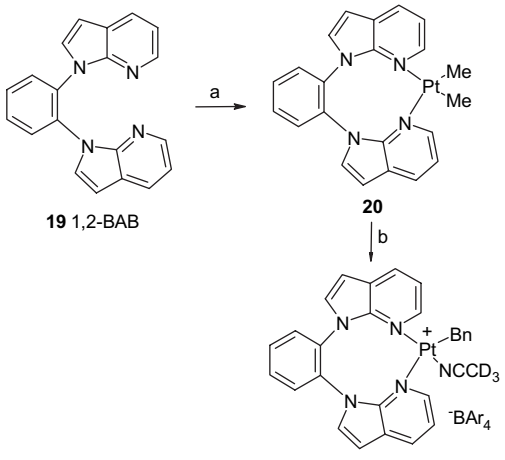
Organoplatinum complexes are also an important class of molecules because of their well-established roles in catalysis and photochemistry. The synthesis of the binuclear complex $Pt_2(Me)_4$(TTAB) **17** has been conducted by reaction of ligand **16** (TTAB) with $Pt_2(Me)_4(SMe_2)_2$ (Scheme 5).[18] The compound **17** was found to react readily with halogenated solvents such as $CFCl_3$, CCl_4, $CHCl_3$ and CH_2Cl_2 at room temperature to afford quantitatively a binuclear platinum(IV) complex **18** ($Pt_2(Me)_4$(TTAB)Cl_2). Elucidation of the structure of **18** by single-crystal X-ray diffraction analysis pointed to the formation of two internal Pt–C bonds as well as the transformation of the benzene ring into a 1,4-cyclohexadienyl dianion.

Song and Wang recently reported the facile benzene C–H bond activation by two isomeric platinum(II) complexes that contain a bis(7-azaindol-1-yl)methane ligand (BAM).[19,20] To further enhance the rigidity of the chelate, 1,2-bis(7-azaindol-1-yl)benzene (1,2-BAB) **19** has been synthesized (Scheme 6).

The new ligand **19** resembles one half of TTAB **16**, therefore allowing the synthesis of a mononuclear platinum(II)



Scheme 5. Reagents and conditions: (a) $Pt_2(Me)_4(SMe_2)_2$, THF, rt, 3 h, 74%; (b) $CHCl_3$, rt, 2 h, 95%.

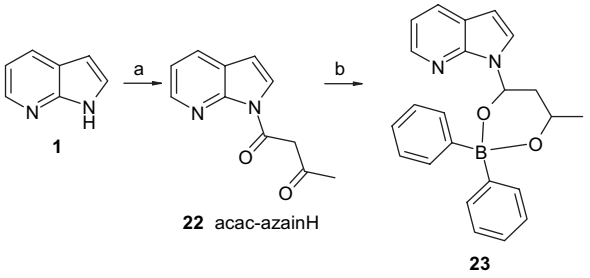


Scheme 6. Reagents and conditions: (a) $Pt_2Me_4(SMe_2)_2$, Et_2O, 5 h, rt, 57%; (b) $[H(Et_2O)_2][B(ArF)_4]$, toluene, rt, then CD_3CN, rt, 81%.

complex. The major advantage is the coordination environment close to that of the TTABPt_2 complex without the complication of a cooperative effect by a second platinum(II) centre leading to studies on the resulting steric effect.[21] A mixture of 1,2-diiodobenzene, **1**, CuI and caesium carbonate was heated in DMF at 150 °C to afford 1,2-bis(7-azaindol-1-yl)benzene **19** (1,2-BAB) in 75% yield. Complex **20** was prepared in 57% yield by the reaction of ligand 1,2-BAB **19** with $Pt_2Me_4(SMe_2)_2$ in Et_2O. The Pt(II) complex **21** was then generated in situ by the treatment of **20** with 1 equiv of $[H(Et_2O)_2][B(ArF)_4]$ (ArF=3,5-bis(trifluoromethyl)phenyl) followed by the addition of deuterated acetonitrile (CD_3CN) (Scheme 6).

The synthesis of a novel blue-luminescent ligand **22** (acacazainH=1-(7-azaindol-1-yl)butan-1,3-dione) was carried out by heating a solution of **1** and 4-methylene-2-oxetanone

in toluene at 90 °C. Addition of triphenylboron in a THF solution of **22** led to the boron complex **23** in 83% yield (Scheme 7). 7-Azaindole **1** emits at 360 nm in toluene solution and in the solid state, whereas compound **22** has a broad emission band at λ=420 nm in the solid state and at λ=429 nm in CH_2Cl_2. Nevertheless, the boron complex **23** has very weak blue luminescence in solution and in the solid state, which makes it unsuitable for electroluminescent applications.[22]



Scheme 7. Reagents and conditions: (a) 4-methylene-2-oxetanone, toluene, 90 °C, 2 h, 92%; (b) BPh_3, THF, reflux, 4 h, 83%.

2.2. Dinuclear complexes

The highly reactive acetone imine, obtained from acetone and ammonia, can be stabilized by coordination to a silver atom itself bound to the N-1 nitrogen atom of a 7-azaindole moiety stabilized by a tris(pentafluorophenyl)-platinum(II).[23]

7-Azaindole derivatives were also involved in a different fields of investigation, suggesting potential ferromagnetic interactions of some new complexes such as heterobridged μ-alkoxo-μ-7-azaindole dicopper(II) complexes.[24]

2.3. Physical and spectroscopic properties

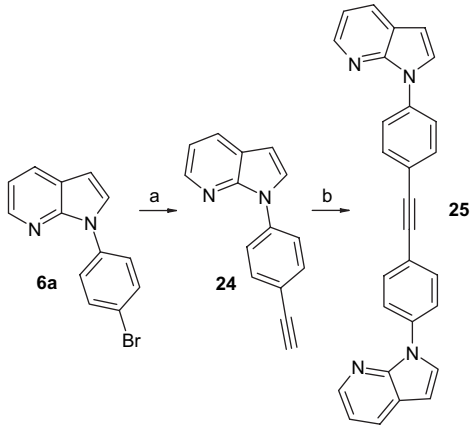
Hydrogen bonding in diruthenium(II,III) tetraacetate complexes with biologically relevant axial ligands has been examined.[25] Di-adduct complexes of the mixed-valent form of diruthenium tetraacetate, $[Ru_2(\mu\text{-}O_2CMe)_4L_2](PF_6)$, where L is 7-azaindole, were synthesized. In order to further elucidate the potential interactions of these dimers with DNA, the nature of the ligand coordination and the secondary inter- and intramolecular hydrogen-bonding interaction in the complex were assessed.

The molecular symmetry and electronic spectroscopy of the 7-azaindole dimer have been studied.[26] The excited-state double proton transfer (ESDPT) of the 7-azaindole dimer has been investigated with picosecond time-resolved resonance-enhanced multiphoton ionization spectroscopy.[27] A vibrational analysis of the 7-azaindole–water complex has been calculated.[28]

The molecular structure and properties of 7-azaindole **1** in its first four singlet states were studied with a view to improve the current understanding of the photophysical behaviour of its C_{2h} dimer.[29] This compound, which exhibits a double proton transfer via its two hydrogen bonds upon electronic excitation, has been used as a model for the photophysical behaviour of DNA base pairs. Electronic excitation of 7-azaindole simultaneously increases its acidity and basicity. These changes facilitate a concerted mechanism for the double proton transfer in the dimer. The methanol-catalyzed double proton transfer of excited 7-azaindole in reverse-micellar methanol nanopools[30] and in the gas phase was examined.[31,32]

A theoretical study of the ground and first excited singlet state proton-transfer reaction in isolated 7-azaindole–water complexes has been developed.[33] The absorption and fluorescence of 7-azaindole-3-acetic acid have been examined.[34] The excited-state double proton transfer in 3-formyl-7-azaindole has been studied and the role of the $n\pi^*$ state in proton-transfer dynamics was evaluated.[35] In this area, a full investigation of its tautomerism and proton-transfer solution has been reported.[36] The intrinsic proton-transfer dynamics of cyclic H-bonded 1/1 7-azaindole/alcohol complexes in *n*-alkanes were studied.[37]

In concluding, this part of the report and as an introduction to the use of the 7-azaindole core in organic chemistry, it was indicated that 1-aryl-7-azaindole derivatives could be used for their photoluminescence properties. Thus, rigid-rod [38] conjugated compounds such as **25** have been prepared by two successive Sonogashira reactions (Scheme 8). Compound **6a** was first submitted to a palladium-mediated coupling reaction with trimethylsilylacetylene followed by removal of the trimethylsilyl group in basic conditions. The alkyne **24** obtained in excellent yield was engaged subsequently in a second Sonogashira reaction, providing dimeric compound **25**. The photoluminescence properties of this new molecule have been investigated, leading to promising results in the field of molecular electronic devices.



Scheme 8. Reagents and conditions: (a) (i) trimethylsilylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, 80–100 °C, 12 h, 83%; (ii) KOH in excess, MeOH/THF 2:1, rt, 20 min, 94%; (b) **6a**, $Pd(PPh_3)_4$, CuI, Et_3N, 80–100 °C, 24 h, 60–75%.

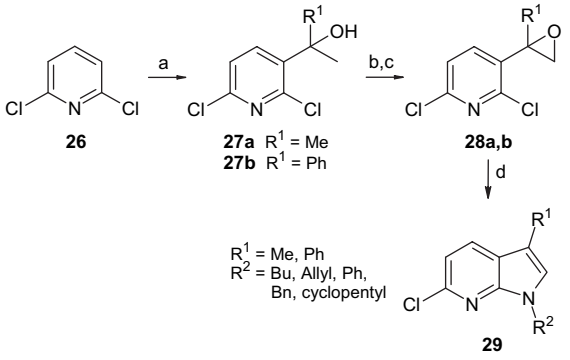
3. Synthesis of the 7-azaindole core

The conventional synthetic strategies (Fischer, Madelung or Reissert reaction) for the easy preparation of the indole core, applied to the synthesis of 7-azaindole, suffer from poor yields, limited scope or availability of the appropriate starting materials. In our preceding review in 2001, a great effort was devoted to the summary of all the synthetic approaches

to 7-azaindole.[1] Innovative pathways have been developed to improve the access to such derivatives.

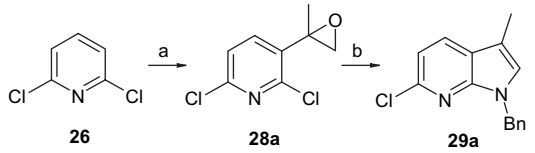
3.1. Pyrrole generation by nucleophilic cyclization of 2-chloro-3-ethylaminopyridine derivatives[39]

After deprotonation at the C-3 position of 2,6-dichloropyridine **26** with LDA, the addition of acetone or acetophenone occurred smoothly to afford, respectively, the tertiary alcohols **27a** or **27b** in 71% yield. In agreement with the literature, small amounts of regioisomeric adducts resulting from lithiation at the C-4 position of the pyridine **26** were detected. Dehydration of alcohols **27** at 130 °C provided α-styrene derivatives (84–98%). Epoxidation of alkenes with *m*-CPBA (**28a**,**b**=73–81%) was followed by opening of the oxirane ring at the sterically less hindered position by primary amines, leading to the 7-azaindole nucleus **29** in good yield (63–95%) (Scheme 9). The rate of the annelation reaction was determined by the steric hindrance of the primary amine.



Scheme 9. Reagents and conditions: (a) LDA, THF, −78 °C, 2 h then R^1COMe, −78 °C to rt, **27a**=71%, **27b**=71%; (b) H_2SO_4/AcOH 1:3, 130 °C, 30 min, 84–98%; (c) *m*-CPBA, CH_2Cl_2, rt, **28a**=81%, **28b**=73%; (d) R^2NH_2, *n*-BuOH, 110 °C, then aq HCl, 63–95%.

A shorter approach was reported by condensation of **26** on chloroacetone, which directly led to common intermediate **28a**. Ensuing treatment with benzylamine and then aq HCl gave 7-azaindole **29a** as described previously (Scheme 10).[39]

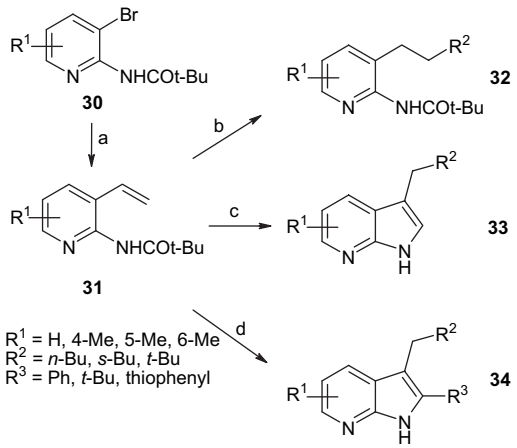


Scheme 10. Reagents and conditions: (a) LDA, THF, −78 °C then chloroacetone; (b) $BnNH_2$, *n*-BuOH, 120 °C, then aq HCl, 50% overall yield.

3.2. Carbolithiation of 3-vinylpyridine[40]

A new route to 7-azaindole based on a vinylcarbolithiation of 2-amino-3-vinylpyridines as the key synthetic step has been described (Scheme 11). The methodology involves a novel cascade reaction sequence of controlled carbolithiation of the vinyl double bond followed by addition of a suitable electrophile, leading to a supposed molecular diversity.

The synthesis of substituted 3-vinyl-pyridin-2-ylamines **31** was achieved in high yield (75–85%) by a Suzuki coupling



Scheme 11. Reagents and conditions: (a) 2,4,6-trivinylcyclotriboroxane/pyridine, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, reflux, 20 h, 75–85%; (b) (i) R^2Li (4 equiv), THF, −78 °C; (ii) H_2O, 70–88%; (c) (i) PhLi (1.5 equiv), THF, −30 °C; (ii) R^2Li (2 equiv), −78 °C; (iii) DMF, −78 °C; (iv) 3 M HCl, reflux, 40–85%; (d) (i) PhLi (1.5 equiv), Et_2O, −30 °C; (ii) R^2Li (2 equiv), −78 °C; (iii) R^3CN, 0 °C; (iv) 12 M HCl, reflux, 38–70%.

reaction between 3-bromo-2-aminopyridines **30** and 2,4,6-trivinylcyclotriboroxane–pyridine complex. The carbolithiation of **31** was highly effective with primary, secondary and tertiary alkyllithiums without addition on the pyridine ring. The reaction of **31** with PhLi failed. Aqueous quenching led to compounds **32** in 70–88% yields. The reaction of **31a** (R^1=H) with *t*-BuLi followed by trapping with DMF and acidification generated the 7-azaindole **33a** (R^1=H, R^2=*t*-Bu) in 40% yield. Abstraction of the hydrogen on the nitrogen atom with PhLi (1.5 equiv) prior to treatment with *t*-BuLi (2 equiv) increased the yield of **33a** to 69%. The sequence was extended to the reaction of **31** with *t*-, *s*- or *n*-BuLi and DMF leading to compounds **33** in a broad variety of yields. Substitution of DMF by nitriles opened the access to a wide range of 2,3-difunctionalized 7-azaindoles **34** in 38–70% yields.

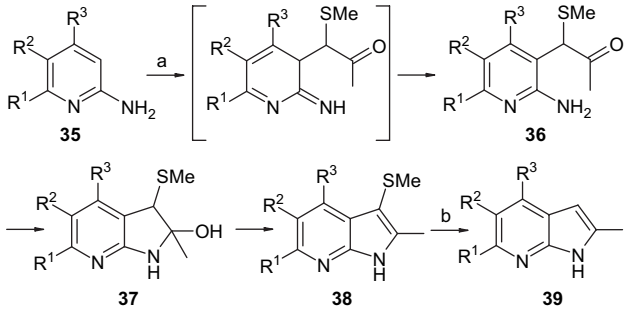
3.3. From 2-aminopyridine and methylthioacetone

Gassman et al.[41] reported a convenient, but underused, process to prepare 7-azaindole in low yield from 2-aminopyridine and keto sulfides via a Sommelet–Hauser-type rearrangement. Recently, Merck researchers enhanced the previously developed method, expanding it to the construction of 4- and 6-azaindole.[42]

When a solution of 2-amino-6-methylpyridine **35a** was treated with *t*-BuOCl at −78 °C followed by the addition of methylthioacetone and Et_3N, the 7-azaindole **38a** was isolated in 87% yield (intermediates **36** and **37** are described in Scheme 12). Reactions with other substituted 2-aminopyridines gave **38b–f** in moderate to good yields (Table 1). When desired, treatment with Raney nickel in ethanol provided the desulfurized material **39** in a near-quantitative yield (Scheme 12).[41a]

3.4. From 3-ethynyl-2-aminopyridine

Knochel et al.[43] reported the 5-*endo-dig* cyclization mediated by potassium or caesium bases of heteroaromatic

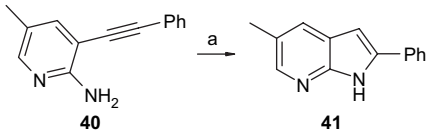


Scheme 12. Reagents and conditions: (a) *t*-BuOCl (2 equiv), CH_2Cl_2, −78 °C or −40 °C, $MeCOCH_2SMe$, then Et_3N, 44–87%; (b) Raney Ni, EtOH, rt, 15 min, >90%.

Table 1

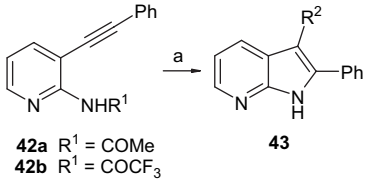
Compound	R^1	R^2	R^3	Yield (%)
38a	Me	H	H	87
38b	Br	H	H	59
38c	Me	H	Me	46
38d	OMe	H	H	56
38e	CF_3	H	H	44
38f	H	Me	H	63

nucleophiles bearing an acetylenic substituent. As an example, 5-methyl-3-(phenylethynyl)-2-pyridinylamine **40** afforded the subsequent 5-methyl-2-phenyl-1*H*-pyrrolo-[2,3-*b*]pyridine **41** with 72% yield (Scheme 13).



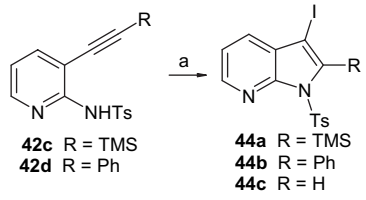
Scheme 13. Reagents and conditions: (a) KH, NMP, rt, 1 h, 72%.

Recently, an aminopalladation–reductive elimination procedure was applied by Cacchi et al.[44] for the synthesis of 2,3-disubstituted 7-azaindole libraries, starting from readily available precursors, allowing a large diversity of 2-phenyl-7-azaindoles **43** (Scheme 14).



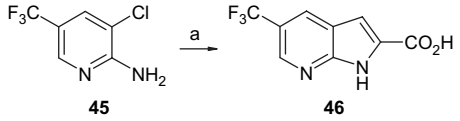
Scheme 14. Reagents and conditions: (a) $Pd(PPh_3)_4$, Cs_2CO_3, MeCN, 100 °C, R^2X or R^2OTf (1.5 equiv), 37–93%.

The acidity of the nitrogen–hydrogen bond plays a crucial role in the cyclization via the aminopalladation–reductive elimination process. Reaction between acetamido derivative **42a** and ethyl 4-iodobenzoate in the presence of $Pd(PPh_3)_4$ and caesium carbonate in acetonitrile at 100 °C afforded the desired derivative **43** (R^2=4-EtO_2C–C_6H_4) in 37% yield with recovery of the starting material **42a** (49%). This result pointed out the beneficial role of the pyridine moiety in favouring the formation of the free NH pyrrole ring, when compared to the benzene series, where no indole was obtained. Under the same conditions, derivative **42b** led to **43** in 83% yield making the trifluoroacetamido group an appropriate protecting group in this synthetic strategy. A similar method enabling the cyclization of *N*-Boc-2-amino-3-alkynylpyridines has been reported using a milder base such as DBU in a mixture of $MeOH/H_2O$.[45] 5-*endo-dig* Iodocyclization of *N*-tosyl-2-alkynylpyridines **42c**,**d** in the presence of molecular iodine and anhydrous potassium carbonate in acetonitrile afforded 3-iodo-7-azaindoles **44** in excellent yield (Scheme 15).[46] In the case of **42c**, the 7-azaindole nucleus was obtained in 90% yield, but with a 1:1 ratio of the 2-trimethylsilyl derivative **44a** and the desilylated derivative **44c**. An excellent yield was observed for the conversion of **42d** into **44b**.



Scheme 15. Reagents and conditions: (a) I_2 (3 equiv), anhyd K_2CO_3 (3 equiv), MeCN, 0–20 °C, 24 h, **44a**=45%, **44c**=45% from **42c**; **44b**=89% from **42d**.

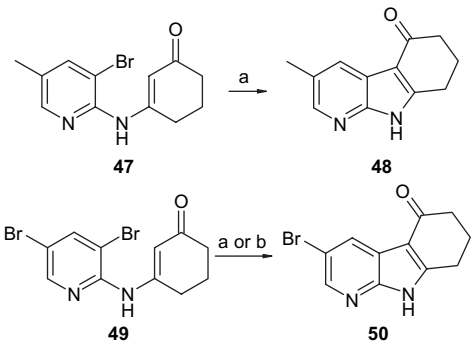
A flexible palladium-catalyzed 7-azaindole synthesis by direct annulation of 2-amino-3-chloro-5-trifluoromethylpyridine **45** with ketones has been also reported (Scheme 16).[47] This study involves an enamine formation in the first step followed by a Heck reaction. An extensive screening of palladium catalysts and ligands indicated that $Pd(Pt\text{-}Bu_3)_2$ in combination with a base (K_3PO_4 or KOAc) and 0.5 equiv of $MgSO_4$ as a water scavenger in acetic acid and dimethylacetamide (DMA) was able to perform the cyclization to **46** in high yield.



Scheme 16. Reagents and conditions: (a) $MeCOCO_2H$ (3 equiv), $Pd(Pt\text{-}Bu_3)_2$, K_3PO_4, $MgSO_4$ (0.5 equiv), AcOH/DMA, 140 °C, 4 h, 97%.

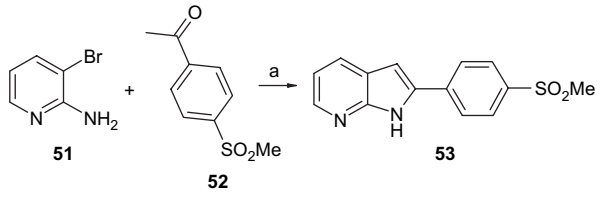
The application of the Hegedus–Mori–Heck reaction (intramolecular coupling) to the synthesis of 7-azaindoles was investigated on enamines in the presence of $Pd(PPh_3)_4$ and $NaHCO_3$ in HMPA at 140 °C, but the reaction was not effective.[48] Recently, Lachance et al. have developed a rapid and efficient one-pot microwave synthesis of the 7-azaindole nucleus.[49] A 3-halo-2-aminopyridine was first treated with an appropriate ketone, to provide the corresponding enamine **47** or **49** and then an intramolecular palladium-catalyzed Heck reaction on the enamine was subsequently carried out to afford the 7-azaindole derivatives **48** or **50** (Scheme 17). Optimization of the coupling reaction revealed that $Pd(PPh_3)_4$ and pyridine are, respectively, the best palladium source and solvent under microwave conditions.

A one-pot synthesis of 7-azaindole was also reported by the formation of the enamine followed by the Heck reaction.[49]



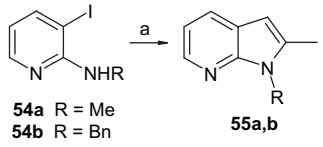
Scheme 17. Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol %), Cy_2NMe, pyridine, μwave, 160 °C, 20 min, **48**=89%, **50**=43%; (b) $Pd(PPh_3)_4$ (5 mol %), Cy_2NMe, pyridine, μwave, 160 °C, 40 min, 57%.

This approach was illustrated by the in situ formation of the enamine resulting from the condensation of (4-methylsulfonylphenyl)acetone **52** on 3-bromo-2-aminopyridine **51** in the presence of tetraethoxysilane, PPTS and pyridine under microwave irradiation (heated successively for 20 min at 160, 180 and 200 °C) followed by the addition of $Pd(PPh_3)_4$ (5 mol %) and Cy_2NMe. The 2-(4-methylsulfonyl)phenyl-7-azaindole **53** was obtained in 41% yield (Scheme 18).



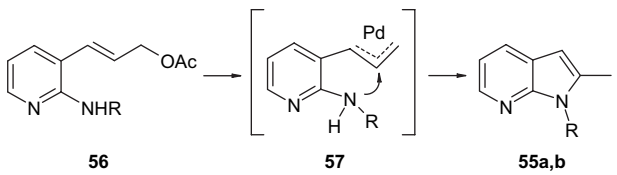
Scheme 18. Reagents and conditions: (a) (i) PPTS, $Si(OEt)_4$, pyridine, μwave (sequential heating); (ii) $Pd(PPh_3)_4$, Cy_2NMe, μwave, 160 °C, 6×20 min, 41%.

2-Methyl-7-azaindoles **55** were prepared by palladium-catalyzed annulation of various 2-iodoarylamines **54a**,**b** with allylic substrates (Scheme 19).[50]



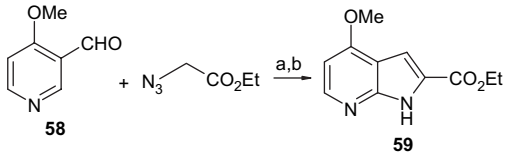
Scheme 19. Reagents and conditions: (a) allyl acetate, $Pd(OAc)_2$ (5 mol %), LiCl, K_2CO_3, DMF, 120 °C, 12–48 h, **55a**=47%, **55b**=65%.

The same compounds were synthesized by a Heck reaction between **54** and allyl acetate, which afforded the 3-alkenylpyridines **56**. Formation of the π-allyl complex **57** followed by internal nucleophilic attack generated the pyrrole ring to give **55a**,**b** (Scheme 20).



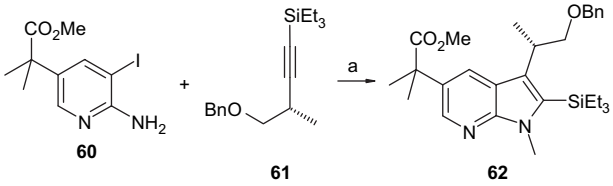
Scheme 20. Mechanism for 7-azaindole formation.

In 2000, Molina and Fresneda[51] reported the use of a modified Hemetsberger indole synthesis for the preparation of 2,4-disubstituted 7-azaindoles as starting materials for the synthesis of variolin alkaloids and analogues, to which a later part of this report is further dedicated. Thus, ethyl 4-methoxy-7-azaindole-2-carboxylate **59** was obtained by condensation of 4-methoxypyridine-3-carboxaldehyde **58** with ethyl azidoacetate in the presence of sodium ethylate, followed by thermal cyclization (Scheme 21).



Scheme 21. Reagents and conditions: (a) EtONa, EtOH, −15 °C, 72 h, 61%; (b) *o*-xylene, reflux, 25 min, 67%.

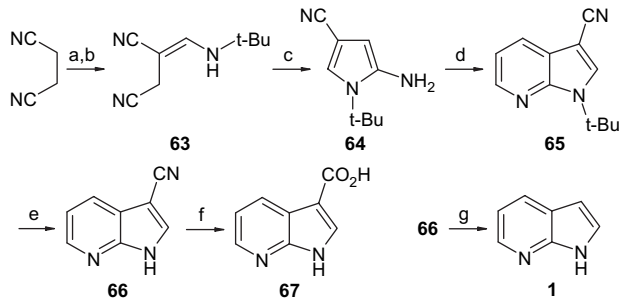
Recently, Roy et al.[52] expanded the Hemetsberger–Knittel reaction to the synthesis of 7-azaindoles. In the total synthesis of 7-azaindole-derived GnRH antagonists,[53] the Larock synthesis of indole[54] may be directly applied to 7-azaindole syntheses with moderate success. Palladium(0)-catalyzed heteroannulation of alkyne **61** with 2-amino-3-iodopyridine **60** under Larock conditions ($Pd(OAc)_2$, PPh_3, LiCl, Na_2CO_3, DMF, 100 °C, 15 h) generated the desired 7-azaindole **62** in only 10% yield with significant recovery of the starting material **60**, whereas using $Pd(dppf)Cl_2$ as catalyst provided **62** in 95% yield (Scheme 22).



Scheme 22. Reagents and conditions: (a) $Pd(dppf)Cl_2$, CH_2Cl_2, Na_2CO_3, LiCl, DMF, 100 °C, 15 h, 95%.

3.5. From pyrrole derivatives

A new optimized cost-effective synthesis of 7-azaindole was achieved recently and can be regarded, from now on, as a convenient way for its industrial production (Scheme 23).[55] The inexpensive starting materials, succinonitrile and ethyl formate, were condensed in the presence of MeONa

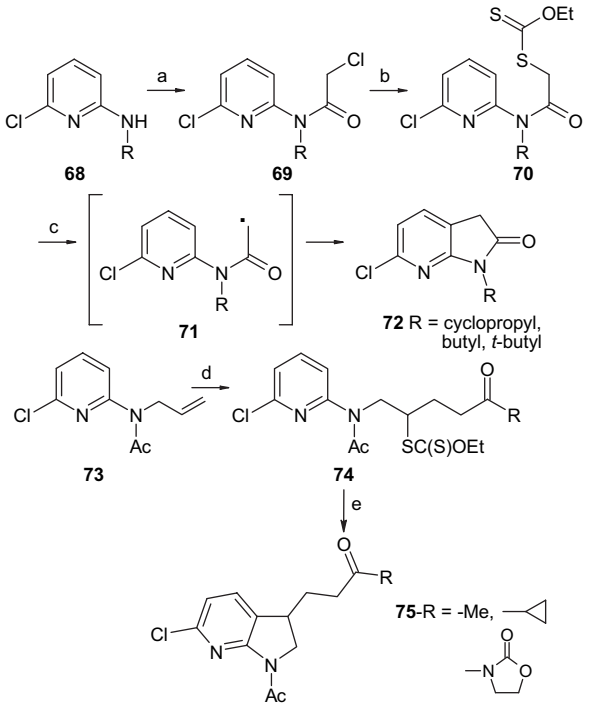


Scheme 23. Reagents and conditions: (a) MeONa, HCO_2Et, toluene, 5 °C to rt, 2.5 h; (b) *t*-$BuNH_2$, reflux, 2.5 h; (c) KOH, EtOH, 50 °C to rt, 4 h, 60% (three steps); (d) 1,1,3,3-tetramethoxypropane, toluene, *p*-TSA, reflux, 1 h, 80%; (e) $AlCl_3$, toluene, reflux, 8 h, 91%; (f) concd HCl, 70 °C, 20 h, 94%; (g) concd HCl, reflux, 48 h, 73%.

to give the corresponding 2-hydroxymethylenebutanenitrile salt. The latter compound was treated with *t*-$BuNH_2$ to obtain the enaminonitrile **63**. The base-catalyzed internal condensation of **63** led to the cyanopyrrole **64** in high yield. The 7-azaindole **65** was easily built up by reaction of the intermediate **64** with 1,1,3,3-tetramethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA). Removal of the *tert*-butyl group was conducted with $AlCl_3$ to afford the 3-cyano-7-azaindole **66** in 91% yield. An acidic hydrolysis at 70 °C led to the acid **67** in 94% yield. The last reaction was also carried out at reflux, leading to **1**.

3.6. Radical cyclization of xanthate derivatives

A radical cyclization onto the pyridine[56] ring has appeared as a potential general approach towards 7-azaindole derivatives (Scheme 24). Xanthate-mediated radical cyclization has numerous advantages such as experimental simplicity and the absence of heavy or toxic metals, as well as compatibility with a wide range of functionality. Reaction of chloroacetyl chloride with 2-alkylamino-6-chloropyridines **68** gave the amides **69**, which were then reacted with potassium *O*-ethyldithiocarbonate to afford the xanthate derivatives **70**. Addition of lauroyl peroxide (DLP) to a refluxing solution of the xanthates **70** in dichloromethane furnished the 7-azaoxindoles **72** in good yield via the radicals **71** (Scheme 24).

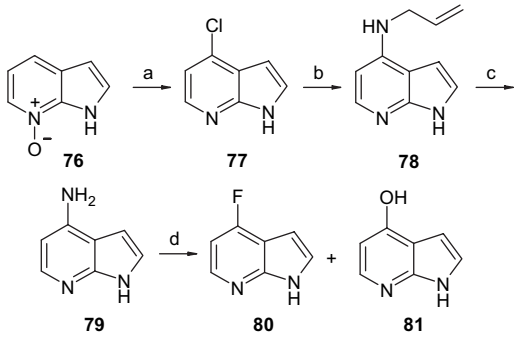


Scheme 24. Reagents and conditions: (a) $ClCH_2COCl$, toluene or $ClCH_2CH_2Cl$, reflux; (b) KSCSOEt, acetone, rt, 1 h, R=cyclopropyl 64%, R=*t*-Bu 88%, R=*n*-Bu 87% (two steps); (c) DLP, $ClCH_2CH_2Cl$, reflux, R=cyclopropyl 57%, R=*t*-Bu 82%, R=*n*-Bu 73%; (d) $RCH_2SCSOEt$, DLP, $ClCH_2CH_2Cl$, reflux, R=Me 84%, R=cyclopropyl 77%, R=oxazolidinone 87%; (e) DLP, PhCl, reflux, R=Me 50%, R=cyclopropyl 57%, R=oxazolidinone 66%.

Similarly, the 7-azaindolines **75** were obtained from *N*-allyl-*N*-acetyl-2-amino-6-chloropyridine **73**, which was subjected to the radical step via formation of the xanthates **74**.

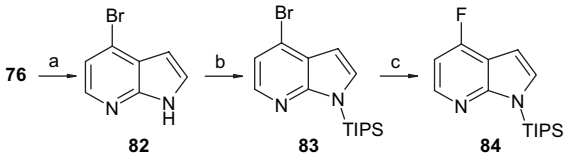
4. Functionalization of the pyridine ring of 7-azaindole

The regioselective synthesis of 7-azaindoles functionalized on the pyridine ring remains a significant challenge that has been faced so far by two main approaches: (i) formation of the pyrrole ring via the cyclization of an appropriate functionalized pyridine precursor or (ii) ring substitution starting from 7-azaindole *N*-oxide. This latter approach was fully examined by Thibault et al.[57] in their investigations of the selective fluorination of the C-4 position (Scheme 25). Regioselective chlorination occurred at the C-4 position of 7-azaindole *N*-oxide **76** using methanesulfonyl chloride in DMF to afford **77**. Buchwald palladium-catalyzed amination of 4-chloro-7-azaindole **77** with *N*-allylamine gave **78** with 76% yield. Subsequent deallylation by palladium on carbon in an acidic medium generated the 4-amino-7-azaindole **79** in 75% yield. The diazonium tetrafluoroborate salt was obtained from the amine **79** at 0 °C and some decomposition occurred spontaneously in the aqueous tetrafluoroboric acid solution affording a 1:1.3 mixture of 4-fluoro-7-azaindole **80** and 4-hydroxy-7-azaindole **81**. In this case, the desired fluoride compound **80** was isolated in 40% yield by basic aqueous extractions.



Scheme 25. Reagents and conditions: (a) $MeSO_2Cl$, DMF, 86%; (b) *N*-allylamine, $Pd(OAc)_2$, NaO*t*-Bu, (*o*-biphenyl)PCy_2, dioxane, 100 °C, 16 h, sealed tube, 76%; (c) Pd/C, $MeSO_3H$, EtOH, 105 °C, 12 h, 75%; (d) 48% aq HBF_4, $NaNO_2$, rt, 22 h, **80**=40%.

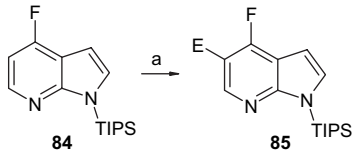
Another approach based on an efficient halogen–lithium exchange followed by quenching with an electrophilic fluorine source was considered to increase the global yield for preparing the 4-fluoro derivative **80** (Scheme 26).[57]



Scheme 26. Reagents and conditions: (a) $(MeSO_2)_2O$, Me_4NBr, DMF, rt, 4 h, 54%; (b) NaH, TIPSCl, THF, reflux, 3 h, 99%; (c) *t*-BuLi, NFSI, THF, −78 °C, 45 min, 84%.

The 4-bromo-7-azaindole **82** was obtained from 7-azaindole *N*-oxide **76** in 54% yield with methanesulfonic anhydride and tetramethylammonium bromide. Protection of the nitrogen atom as the *N*-TIPS derivative **83** (99% yield) to avoid lithiation at C-2 was followed by a halogen–lithium exchange at C-4 with *t*-BuLi in THF at −78 °C. Addition of *N*-fluorobenzenesulfinimide (NFSI) generated 4-fluoro-1-triisopropylsilyl-7-azaindole **84** in 84% yield.

Another promising strategy for the functionalization of the pyridine moiety is to use the property of the halogen substituent as an *ortho*-metalating group, providing 4,5-disubstituted 7-azaindoles (Scheme 27). *ortho*-Metallation[58] of **84** occurred in the presence of 1.5 equiv of *s*-BuLi at −78 °C for 1 h. Addition of various electrophiles on the resulting anion allowed the introduction of a wide diversity of substituents in the C-5 position (derivatives **85**, Table 2). The hydroxyl group can be introduced either by using Davies reagent (camphorsulfonyloxaziridine) or Ti(O*i*-Pr)$_4$/*t*-BuO$_2$Li.

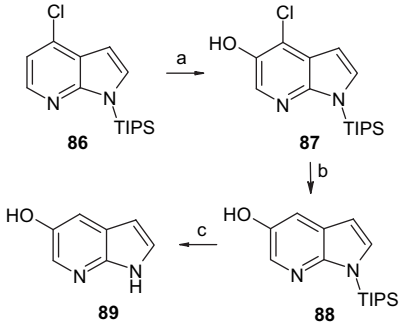


Scheme 27. Reagents and conditions: (a) (i) *s*-BuLi (1.5 equiv), THF, −78 °C, 1 h; (ii) electrophile.

Table 2

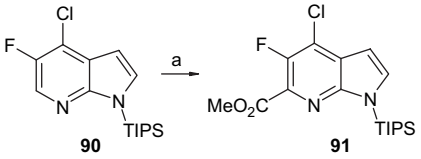
Electrophile	NFSI	$(CCl_3)_2$	CBr_4	NBS
E	F	Cl	Br	Br
85, Yield (%)	70	68	63	26
Electrophile	$ClCO_2Me$	$TosN_3$	Davies reagent	
E	CO_2Me	N_3	OH	
85, Yield (%)	87	50	58	

The same methodology was also used to improve the synthesis of 5-hydroxy-7-azaindole **89** (Scheme 28).[58] The protected 4-chloro-7-azaindole **86** was first hydroxylated with Davies reagent, giving **87** in 65% yield. Reduction of 4-chloro-5-hydroxy-1-triisopropylsilanyl-7-azaindole **87** with zinc in ethanol/acetic acid provided the dechlorinated derivative **88** in 65% yield. Finally, the silicon group was removed using TBAF to afford **89** in 70% yield and in three steps with 26% overall yield.



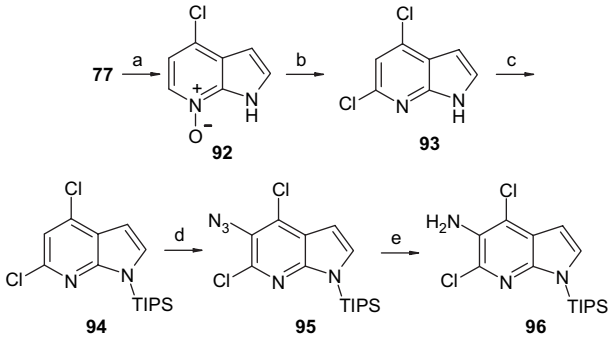
Scheme 28. Reagents and conditions: (a) *s*-BuLi, THF, −78 °C, Davies reagent, 65%; (b) Zn, AcOH/EtOH, 65%; (c) TBAF, THF, 70%.

Iterative lithiation leading to 4,5,6-trisubstituted-7-azaindoles can also be carried out when an *ortho*-directing group is introduced at the C-5 position, although alkyllithium bases could not be used, due to aromatic nucleophilic substitution of fluorine or chlorine.[58] As an example, 4-chloro-5-fluoro-1-triisopropylsilyl-7-azaindole **90** was deprotonated with LiTMP, followed by the addition of methyl chloroformate, to generate compound **91** in 61% yield (Scheme 29).



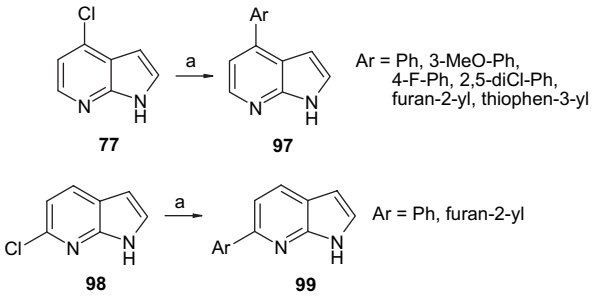
Scheme 29. Reagents and conditions: (a) LiTMP, THF, −78 °C, $ClCO_2Me$, 61%.

Chlorination at the C-6 position was performed on **92** to afford dichloro derivative **93** in 58% yield (Scheme 30).[58] This latter compound was protected to afford 4,6-dichloro-1-triisopropylsilyl-7-azaindole **94**. Lithiation on C-5 position of **94** followed by addition of tosylazide gave 4,6-dichloro-5-azido-1-triisopropylsilyl-7-azaindole **95** in 46% yield. The azido group was submitted to catalytic hydrogenation to generate the 5-amino substituent of compound **96** quantitatively.



Scheme 30. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2; (b) $MeSO_2Cl$, DMF, 80 °C, 58%; (c) NaH, TIPSCl, THF, 80 °C, 76%; (d) *s*-BuLi, THF, −78 °C, tosylazide, 46%; (e) H_2, Pd/C, EtOAc, quant.

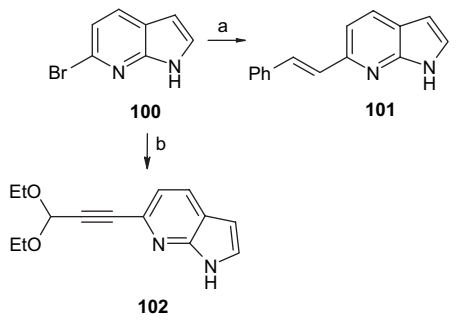
Functionalization at the C-4 and C-6 positions of 7-azaindoles has been investigated through palladium-catalyzed coupling reactions (Heck, Suzuki and Sonogashira reactions) of the corresponding 4- or 6-halo-7-azaindole (Scheme 31). For example the 4- and 6-chloro-7-azaindoles **77** and **98** undergo a Suzuki reaction with aryl/heteroarylboronic acids to afford the corresponding 4- and 6-substituted 7-azaindoles **97** and **99**.[59]



Scheme 31. Reagents and conditions: (a) $ArB(OH)_2$, KF, dioxane, $Pd_2(dba)_3$, P(*t*-Bu)$_3$, 100 °C, 2–24 h, 40–94%.

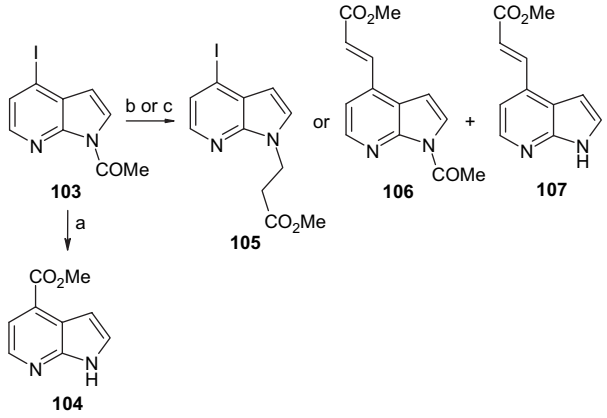
The chloro derivatives **77** and **98** were inert towards Sonogashira or Heck reaction. This drawback was overcome by the use of the more reactive 6-bromo-7-azaindole **100** or 4-iodo-7-azaindole.[59] As an example, the compound **100** was converted into alkene **101** (40% yield) by treatment with styrene in the presence of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$. In the same way,

a Sonogashira reaction between **100** and 3,3-diethoxypropyne in the presence of $Pd(PhCN)_2Cl_2$ and P(*t*-Bu)$_3$ afforded the alkyne **102** in good yield (Scheme 32).



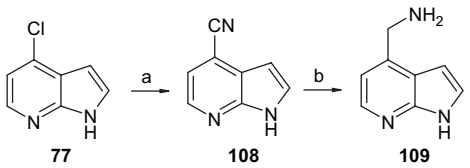
Scheme 32. Reagents and conditions: (a) styrene, $Pd_2(dba)_3$, P(*t*-Bu)$_3$, Cs_2CO_3, dioxane, 120 °C, 12 h, 40%; (b) 3,3-diethoxypropyne, $Pd(PhCN)_2Cl_2$, P(*t*-Bu)$_3$, CuI, piperidine, dioxane, 100 °C, 6 h, 84%.

Under carbonylative basic conditions, the acetyl group of 1-acetyl-4-iodo-7-azaindole **103** was also removed providing the ester **104** in 80% yield (Scheme 33).[59]



Scheme 33. Reagents and conditions: (a) $Pd(PPh_3)_4$, CO, MeOH, Et_3N, 60 °C, 80%; (b) methyl acrylate, $Pd(OAc)_2$, KOAc, K_2CO_3, DMF, 70 °C, **105**=58%; (c) idem with P(*o*-tol)$_3$, Et_3N, 80 °C, **106**=38%, **107**=45%.

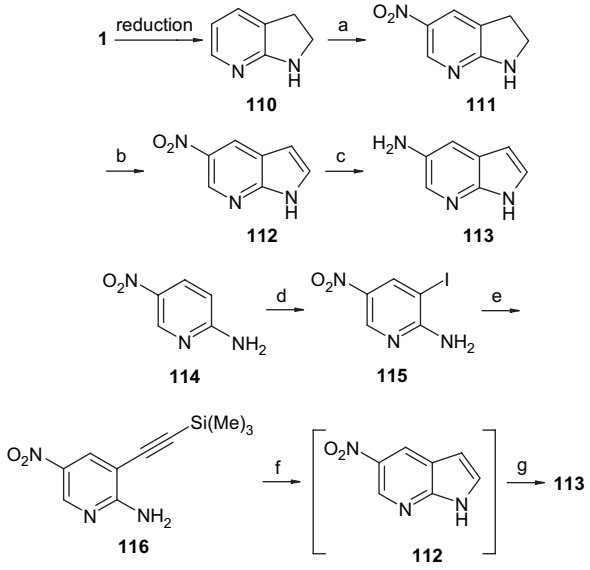
A Heck reaction applied on derivative **103** in the presence of methyl acrylate and a catalytic amount of $Pd(OAc)_2$ provided the adduct **105** in 58% yield as the sole product. The nature of the base strongly affected the reaction course. Indeed, using Et_3N as a base in the presence of tri-tolylphosphine and $Pd(OAc)_2$ led to a mixture of the derivatives **106** and **107** (Scheme 34).



Scheme 34. (a) Zn, $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMA, 120 °C, 2 h, 70%; (b) $LiAlH_4$, THF, 40 °C, 1 h, 74%.

Introduction of the aminomethyl group of **109** requires selective functionalization of 7-azaindole. The 4-chloro-7-azaindole **77** is obtained in 80% yield from the *m*-chlorobenzoate salt of **76** with $POCl_3$. Introduction of the methylamino group was accomplished by a two-step sequence: palladium-catalyzed coupling of the chloride **77** with zinc cyanide led to **108** in 70% yield, which was then subjected to LAH reduction, affording 4-aminomethyl-7-azaindole **109** in 74% yield (Scheme 34).[60]

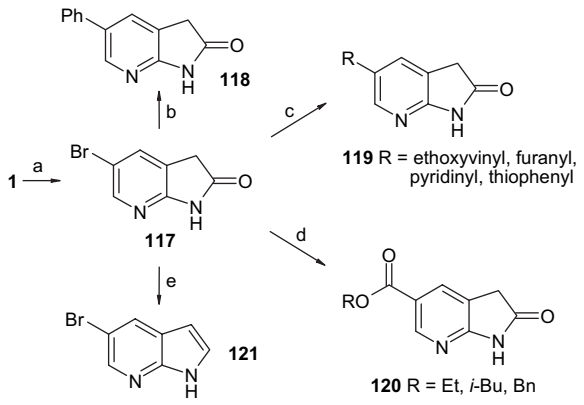
A synthesis of 5-amino-7-azaindole **113** has recently been reported based on a modification of an original Robison procedure described in 1959 (Scheme 35).[61] 7-Azaindole **1** was reduced to 7-azaindoline **110**, which reacted with ferric nitrate nonahydrate in refluxing ethanol to give the 5-nitro derivative **111**. This compound proved to be somewhat unstable on silica gel. Dehydrogenation was achieved using manganese dioxide in refluxing toluene, leading to 5-nitro-7-azaindole **112** in 51% yield. Hydrogenation of the nitro group was performed at room temperature in the presence of 10% Pt/C to give 5-amino-7-azaindole **113** (80%). The purifications at each stage were troublesome and an alternative procedure was developed. In the new strategy, the pyrrole unit was built up through a Sonogashira reaction. The 2-amino-5-nitropyridine **114** was iodinated at the C-3 position with a mixture of KI and KIO_3 affording **115** in 95% yield. A Sonogashira reaction between **115** and TMS/acetylene in the presence of $PdCl_2(PPh_3)_2$, CuI and Et_3N provided the acetylenic product **116** in excellent yield. Subsequent cyclization was achieved using catalytic copper(I) iodide either under thermal heating of **116** or, more conveniently, under microwave irradiation. Desilylation occurred under the reaction conditions to give the 5-nitro-7-azaindole **113**, which was placed on a short pad of silica and eluted with hot THF. This procedure removed copper residues and other insoluble impurities, which were found to poison the hydrogenation catalyst used in the next stage to recover the amino moiety.



Scheme 35. Reagents and conditions: (a) $Fe(NO_3)_3\cdot 9H_2O$, EtOH, reflux, 16 h, 35%; (b) MnO_2, toluene, reflux, 6 h, 51%; (c) H_2, Pt/C, THF, rt, 5 h, 80%; (d) KI, KIO_3, H_2SO_4, H_2O, 100 °C, 1 h, 95%; (e) TMS/acetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF/DMA, rt, overnight, 93%; (f) CuI, NMP, μwave, 190 °C, 30 min; (g) H_2, Pt/C, THF, rt, 5 h, 75% (two steps).

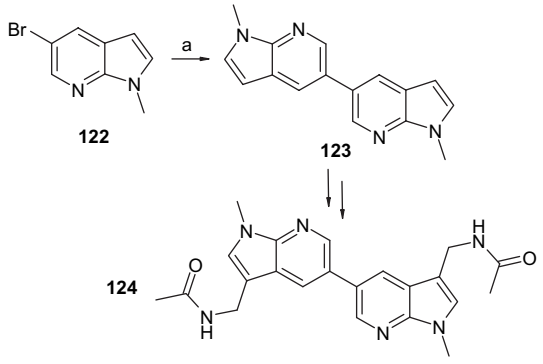
The synthesis of new melatonin analogues has reached the attention of several groups, with the challenge to solve the

main two drawbacks encountered with this hormone: (1) rapid catabolism and (2) lack of selectivity. Great efforts were devoted to the preparation of azaindole derivatives, e.g., 5-bromo-7-azaoxindole **117** was prepared from **1** by a bromination/debromination sequence (Scheme 36).[62] Compound **117** was submitted to palladium-catalyzed coupling reactions (Suzuki, Stille and carbonylation reactions) to introduce diversity at the C-5 position of the azaoxindole (**118–120** obtained in moderate yields).[63] Reduction of the amide function of **117** was realized with the $BH_3 \cdot THF$ complex. The resulting indoline was oxidized with $Mn(OAc)_3$ in acetic acid to provide 5-bromo-7-azaindole **121**.



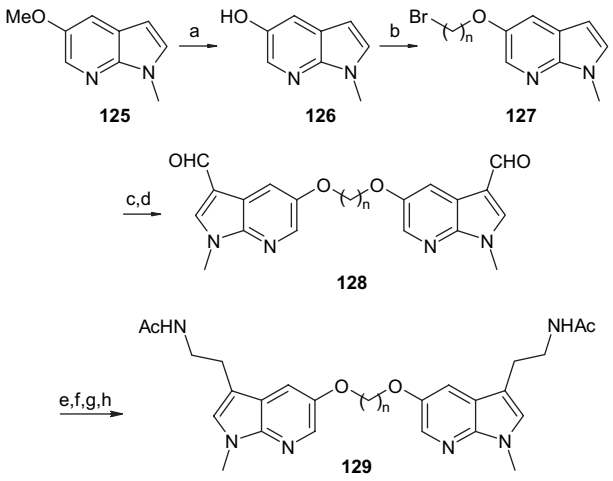
Scheme 36. Reagents and conditions: (a) (i) Br_2, *t*-BuOH, rt, 19 h, 85%; (ii) Zn, AcOH, 94%; (b) $PhB(OH)_2$, $Pd(PPh_3)_2Cl_2$, toluene/EtOH, LiCl, aq Na_2CO_3, 95 °C, 18 h, 51%; (c) $RSnBu_3$, $Pd(PPh_3)_2Cl_2$, Et_4NCl, MeCN, 95 °C, 22 h, 36–66%; (d) ROH, 40 psi CO, $Pd(OAc)_2$, dppp, Et_3N, DMSO, 95 °C, 18 h, 24–53%; (e) (i) $BH_3 \cdot THF$, THF, rt, 35 min; (ii) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, 75 °C, 45 min, 50% (two steps).

In addition, the synthesis of 7-azaindole dimers as new melatonin analogues has been reported via a modified in situ Suzuki homocoupling reaction (Scheme 37).[64] 5-Bromo-1-methyl-7-azaindole **122** was first converted into the corresponding boronic ester with bis(pinacolato)diborane in the presence of $Pd(dppf)Cl_2$ to give the corresponding dimer **123** in 83% yield. The expected amide **124** was synthesized using standard chemistry procedures in a 17% overall yield.



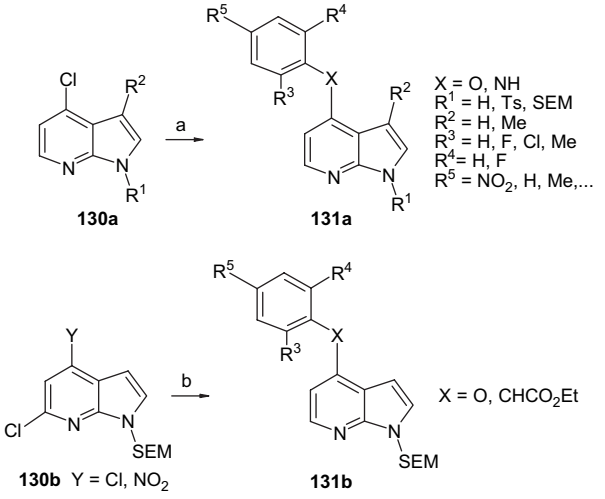
Scheme 37. Reagents and conditions: (a) bis(pinacolato)diborane, $Pd(dppf)Cl_2$, KOAc, DMF, 80 °C, 2 h then **122**, aq Na_2CO_3, H_2O, 80 °C, 2 h, 83%.

In the same way, dimers **129** linked by an alkoxy spacer have been prepared from 5-methoxy-1-methyl-7-azaindole **125** (Scheme 38).[65] Demethylation of **125** occurred with BBr_3 to generate the 5-hydroxy derivative **126**, which reacted with various dibromoalkanes in DMF to afford the bromoalkoxy derivatives **127**. A second alkylation of **127** with **126** led to bis-7-azaindole derivatives. A lateral side chain was introduced in the C-3 position by formylation under Vilsmeier–Haack conditions. The bis-aldehydes **128** 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 **129**.



Scheme 38. Reagents and conditions: (a) BBr_3, CH_2Cl_2, 0 °C, 1 h, 85%; (b) K_2CO_3, DMF, $Br(CH_2)_nBr$, *n*=4–6, rt, 4 h, 82–88%; (c) K_2CO_3, DMF, **126**, 80 °C, 6 h, 71–99%; (d) $POCl_3$, DMF, rt, 3 h, 82–88%; (e) $MeNO_2$, NH_4OAc, 120 °C, 4 h; (f) $NaBH_4$, SiO_2, *i*-PrOH/$CHCl_3$, rt, 12 h; (g) H_2, Raney Ni, MeOH, 60 °C, 6 h; (h) Ac_2O, CH_2Cl_2, rt, 12 h, 5–15% (four steps).

A Pd-mediated synthesis of 4-anilino- and 4-phenoxy-7-azaindole derivatives **131a** from protected 4-chloro-7-azaindoles **130a** has been reported as leading to promising intermediates for further medicinal chemistry programs for Bayer Healthcare (Scheme 39).[66]



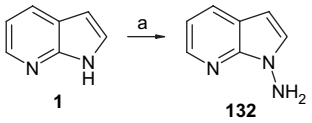
Scheme 39. Reagents and conditions: (a) anilines, $Pd_2(dba)_3$, K_2CO_3, *t*-BuOH, 100 °C, sealed tube, 3 h, 26–84% or phenols, $Pd_2(dba)_3$, K_2CO_3, toluene, 110 °C, sealed tube, overnight, 22–73%; (b) phenols or activated methylene nucleophiles, K_2CO_3, DMSO, 100 °C, 49–91%.

Recently, the same authors have also developed a straightforward synthetic strategy that allows access to 4-*O*- or

C-substituted 7-azaindole derivative **131b** by nucleophilic aromatic substitution of **130b** (Scheme 39).[67]

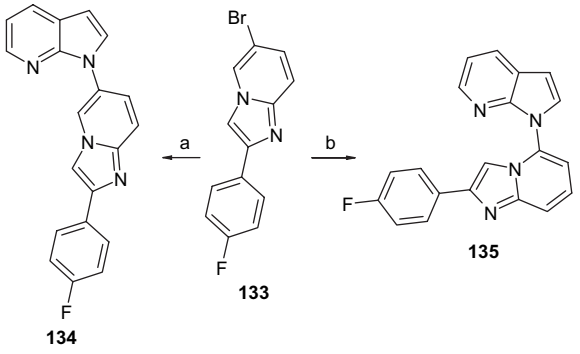
4.1. Functionalization of the pyrrole moiety of 7-azaindole

4.1.1. Reactions at the N-1 position. Heterocyclic N-aminations have been reported with various reagents, most of them derived from hydroxylamine. A study of several electrophilic ammonia reagents for the N-amination of **1** pointed out the high efficiency of monochloramine (NH_2Cl) in a basic medium to quickly generate 1-amino-7-azaindole **132** in 97% yield (Scheme 40).[68]



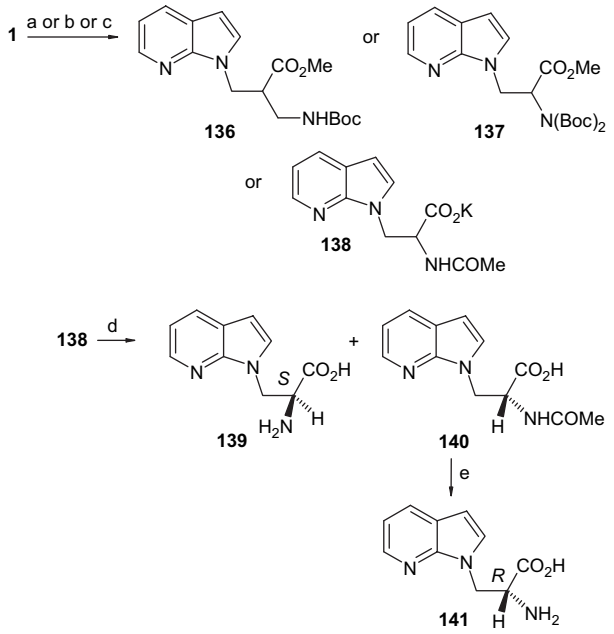
Scheme 40. Reagents and conditions: (a) *t*-BuOK, DMF, rt, 2 h then NH_2Cl, rt, 97%.

As discussed in the first part of this report, the reactivity of 6-bromoimidazo[1,2-*a*]pyridine **133** towards **1** has been examined due to its highly condition-dependent reactivity.[69] Using a copper(I) catalyst and *trans*-*N*,*N*′-dimethyl-1,2-diaminocyclohexane as a ligand, the product **134** (*ipso*-substitution) was obtained in 94% yield, while, in the absence of copper, with a stronger base such caesium carbonate, *cine*-substitution took place, affording **135** in 55% yield (Scheme 41).



Scheme 41. Reagents and conditions: (a) **1**, CuI (5 mol %), *trans N*,*N*′-dimethyl-1,2-diaminocyclohexane (15 mol %), K_3PO_4, DMF, 112 °C, 24 h, 94%; (b) **1**, Cs_2CO_3, DMF, 112 °C, 24 h, 55%.

The Michael addition of **1** on methyl 2-[(*N*-Boc-amino)-methyl]acrylate has been successfully described (Scheme 42).[70] Compound **136** was obtained with excellent yield (96% vs 20% for indole **1**). Other Michael additions of nitrogen nucleophiles to dehydroalanine derivatives have been reported. In particular, compound **137** has been obtained from the methyl ester of *N*,*N*-bis(Boc)dehydroalanine in 93% yield. Reaction of an excess of **1** on commercially available methyl 2-acetamidoacrylate in the presence of K_2CO_3 led directly to the potassium salt **138**. Resolution of azaindolylalanine **138** with acylase from *Aspergillus* sp. gave (*S*)-**139** in 38% yield. The non-reactive amide **140** was cleaved in an acidic medium (6 N HCl) to yield (*R*)-**141** in moderate yield (Scheme 42).[71]



Scheme 42. Reagents and conditions: (a) K_2CO_3, methyl 2-[(*N*-Boc-amino)-methyl]acrylate, MeCN or DMF, reflux, 6 h, **136**=96%; (b) K_2CO_3, MeCN, $CH_2{=}C(NBoc_2)CO_2Me$, **137**=93%; (c) $CH_2{=}C(NHCOMe)CO_2Me$, K_2CO_3, MeCN/H_2O, **138**=78%; (d) *Aspergillus* sp. acylase, phosphate buffer pH 7.2, **139**=38%; (e) 6 N HCl, 35%.

Michael addition of **1** to dehydroalanine methyl ester derivatives PG-ΔAla(*N*-Boc)-OMe [with PG=Boc, Bz, Z, Z(NO_2), Bz(NO_2)] afforded 1-substituted 7-azaindoles **142** with 54–99% yields. Similarly, the tosyl analogue reacted with **1** to afford the dipeptide **143** in 90% yield (Fig. 3).[72]

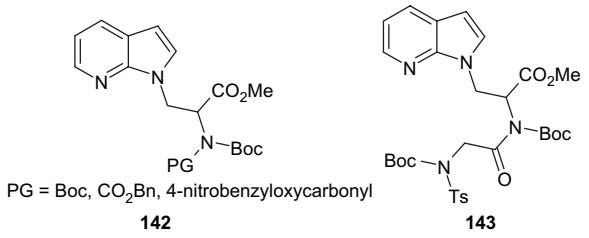
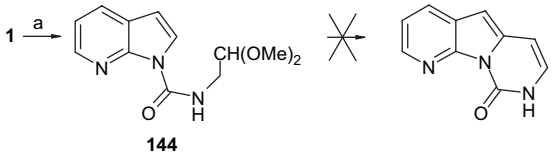


Figure 3. Structures of **142** and **143**.

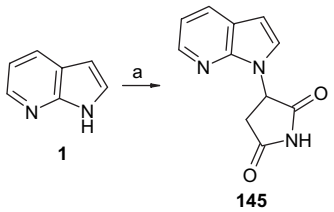
Reaction of **1** with triphosgene in dichloromethane at 0 °C followed by treatment with aminoacetaldehyde dimethyl acetal and DIPEA afforded dimethoxyethylcarbamoyl-7-azaindole **144** in moderate yield. Preliminary tests for cyclization at the C-2 position on the pyrrole ring under different conditions (Lewis or protic acid) were unsuccessful (Scheme 43).[73]



Scheme 43. Reagents and conditions: (a) triphosgene, CH_2Cl_2, 0 °C then $NH_2CH_2CH(OMe)_2$, *i*-Pr_2NEt, rt, 10 min, 46%.

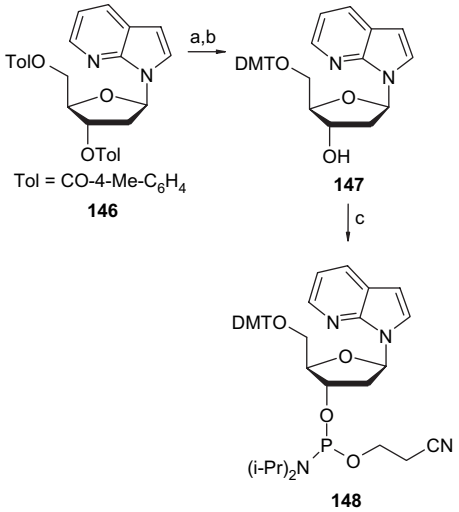
Michael addition of maleimide was observed on **1** in refluxing acetic acid, generating compound **145** in low yield

(Scheme 44). No trace of the Michael addition adduct was detected on the C-3 position as desired.[74]



Scheme 44. Reagents and conditions: (a) maleimide, AcOH, reflux, 60 h, 10%.

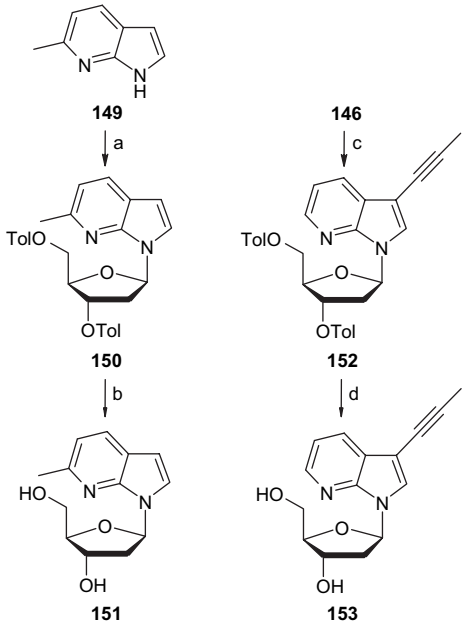
The use of a non-natural 'base' to replace one of the natural nucleic acid bases in DNA has been an important tool for studying biological events such as DNA–protein interaction, DNA structure and dynamics. As mentioned in the first part of this report, fluorescence has been one of the very useful techniques for studying DNA structure. As a reminder, 7-azaindole is weakly fluorescent in water, due to dimer formation. After methylation to prevent dimerization, 1-methyl-7-azaindole is strongly fluorescent. DNA oligonucleotides containing the 7-azaindole moiety as a replacement for the purine base were prepared as described below.[75] The sodium salt of 7-azaindole in acetonitrile was reacted on 1-α-chloro-3,5-di-*O*-(*p*-toluoyl)-2-deoxy-D-ribose to afford **146** in 66% yield. After basic hydrolysis, the residual primary alcohol was selectively protected with 4,4-dimethoxytrityl chloride, affording derivative **147**. The last step was the synthesis of phosphoramidite **148** that was afterwards engaged for an automated DNA synthesis (Scheme 45).



Scheme 45. Reagents and conditions: (a) MeONa/MeOH, rt, 3 h, 75%; (b) 4,4-dimethoxytrityl chloride, pyridine, DMAP, rt, 2.5 h, 75%; (c) 2-cyanoethyl diisopropylaminochlorophosphoramidite, *i*-Pr_2NH, CH_2Cl_2, rt, 1 h, 77%.

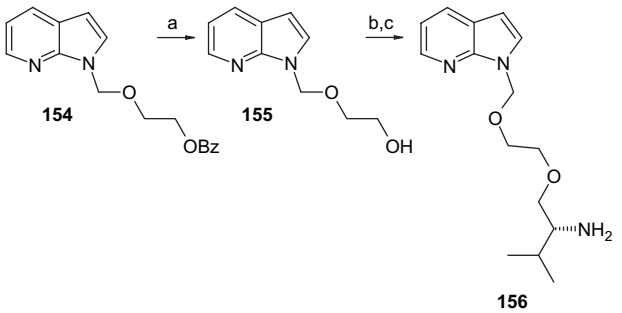
In the course of designing non-natural nucleobases, the sodium salt of 6-methyl-7-azaindole **149** was treated with bis-toluoyl-protected chloroglycoside at 0 °C to afford the coupling adduct **150**. Cleavage under basic methanolic conditions afforded the fully deprotected **151**.

Selective iodination at the C-3 position of **146**, followed by a Sonogashira coupling reaction with propyne, furnished the alkyne **152**. This compound treated in a basic medium yielded **153** (Scheme 46).[24c] These unnatural nucleosides have been characterized to form stable base pairs in duplex DNA.



Scheme 46. Reagents and conditions: (a) (i) NaH, DMF, 0 °C, 15 min then chloroglycoside, 0 °C, 1 h, 51%; (b) MeONa/MeOH, rt, 58%; (c) (i) ICl, CH_2Cl_2, 50 °C, 1 min; (ii) propyne, CuI, $Pd(PPh_3)_2Cl_2$, Et_3N, −78 °C to rt, 4 h; (d) MeONa/MeOH, rt, 45 min, 59% (three steps).

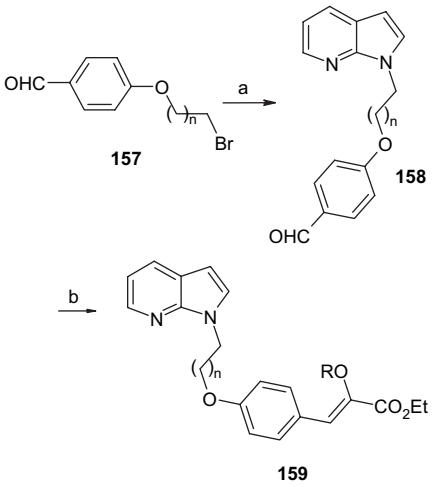
Analogues of the prodrug, L-valacyclovir, derived from 7-azaindole have been prepared (Scheme 47).[76] The protected 7-azaindole **154** was easily obtained from the sodium salt of 7-azaindole and 2-(chloromethoxy)ethyl benzoate in 47% yield. The primary alcohol **155**, resulting from the cleavage of the benzoyl protective group, was submitted to esterification with *N*-Boc-L-valine in classical conditions. Final cleavage of residual Boc in an acidic medium provided the compound **156** in a quantitative yield.



Scheme 47. Reagents and conditions: (a) 40% aq $MeNH_2$, rt, 1.5 h, 77%; (b) *N*-Boc-L-valine, EDCI, DMAP, DMF/CH_2Cl_2, 80 °C, 16 h, 92%; (c) TFA, CH_2Cl_2, rt, 3 h, 100%.

A novel series of azaindole-α-alkyloxyphenylpropionic acid analogues **159** has been designed and evaluated for biological properties as PPARα/γ agonists (Scheme 48).[77] Bromoaldehydes **157** were treated with **1** in a basic medium to

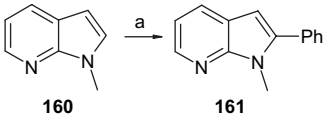
afford the 1-alkylated derivatives **158**. Condensation of **158** with ethyl α-alkyloxyacetates, in the presence of *t*-BuOK, gave **159** in 30–60% yields.



Scheme 48. Reagents and conditions: (a) **1**, KOH, DMSO, 2 h, 60–70%; (b) ethyl α-alkyloxyacetates, *t*-BuOK, DMF, 2 h, 30–60%.

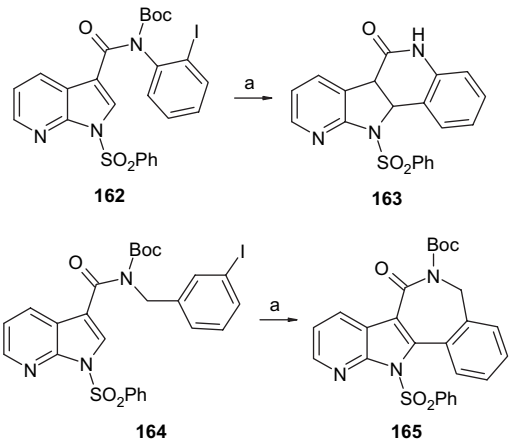
4.2. Reactions at the C-2 position

The direct intermolecular reaction of 1-substituted 7-azaindoles with aryl halides has not been really developed so far. A new practical method of arylation of the C-2 position of 1-protected 7-azaindoles has been reported.[78] The standard conditions used for palladium-catalyzed arylation proved to be unsuitable, especially due to the critical role played by the base. One major drawback of such a reaction was the competitive process of the biphenyl derivative formation. The supposed mechanism was, first, an oxidative addition that proceeds through an aryl-palladium halide intermediate, which may then undergo two competing pathways: (i) cross coupling with 7-azaindole **1** or (ii) formation of biphenyl. Thus, decreasing the catalyst loading favours the C-2 arylation. As demonstrated for indole, both 1-alkyl- and 1-arylindoles proved to be suitable substrates while 1-sulfonyl- or 1-acetylindole was inert. These results clearly pointed out the need for sufficient electron density on the pyrrole ring. Applying this methodology to 1-methyl-7-azaindole **160** afforded 1-methyl-2-phenyl-7-azaindole **161** in 85% yield (Scheme 49).



Scheme 49. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, PhI, CsOAc, DMA, 125 °C, 24 h, 85%.

Functionalization at the C-2 position was achieved through an intramolecular Heck coupling reaction on compound **162** using $Pd(OAc)_2$ in the presence of PPh_3 and silver carbonate as a base (Scheme 50).[79] The cyclic compound **163** was obtained in 72% yield. Very recently, compound **164** with homologation of one carbon was cyclized under the same Heck conditions, leading to compound **165** in 86% yield.[80]

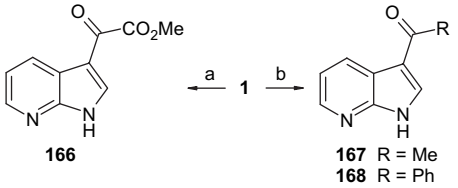


Scheme 50. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 100 °C, 24 h, **163**=72%; 2 h, **164**=86%.

4.3. Reactions at the C-3 position

3-Acylated-7-azaindoles have been reported to exhibit a wide range of biological activities. The relative inertness of the C-3 position of 7-azaindole, compared to indole, is probably the result of the electron-deficient nature of the pyridine moiety, which reduces the overall nucleophilicity of the heterocyclic system. The reaction of **1** with oxalyl chloride failed. As a direct consequence, functionalization of the C-3 position was restricted to halogenation reactions,[81,82] Mannich reaction,[83] carbonylation[84] and condensation with an aldehyde.[85]

Two main strategies for the direct C-3 acylation of 7-azaindole have been reported: either enhancing the nucleophilicity of 7-azaindole or activating the electrophile. The first approach is illustrated by the reaction of the 7-azaindolyl Grignard reagent with diethyl oxalate to form an α-keto ester.[86] The second approach is, for instance, reported by Gálvez and Viladoms[87] by activating acetic anhydride in CS_2 with an excess of $AlCl_3$. The main limitations pointed out were the use of elevated temperature as well as the use of noxious CS_2. In pursuit of a Friedel–Crafts-type approach that relies upon activation of the electrophile, a convenient acylation of azaindole was reported by Wang et al. (Scheme 51).[88] Compounds **166**, **167** and **168** were prepared from **1** in very good yield.



Scheme 51. Reagents and conditions: (a) $AlCl_3$ (5 equiv), CH_2Cl_2, rt, 1 h then methyl oxalyl chloride, rt, 8 h, 76%; (b) $AlCl_3$ (5 equiv), CH_2Cl_2, rt, 1 h then acetyl chloride or benzoyl chloride, rt, 8 h, **167**=93%, **168**=92%.

It was found that a minimum of 3 equiv of $AlCl_3$ in dichoromethane 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 $AlCl_3$ can be attributed to the formation of complex **169** (Fig. 4). The first equivalent of $AlCl_3$ coordinates with the

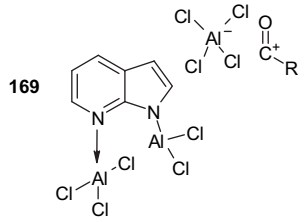
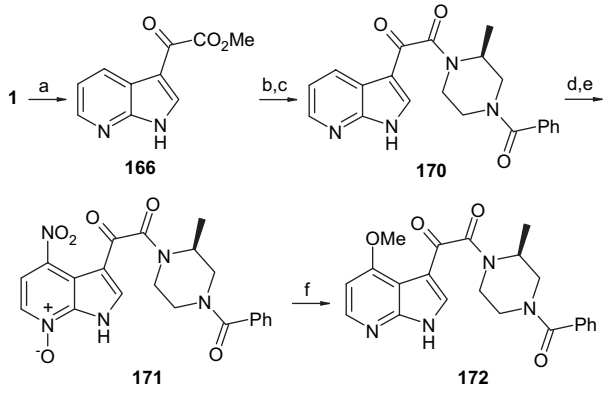


Figure 4. Complex **169**.

pyridine nitrogen atom, meaning 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.

The synthesis of 4-benzoyl-1-[(4-methoxy-1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl)oxoacetyl]-2-(*R*)-methylpiperazine **172** (BMS-378806)[89] was initiated by acylating **1** with methyl chlorooxoacetate by a Friedel–Crafts-type reaction in 79% yield (Scheme 52). The resulting ester **166** could also be obtained by an alternative procedure from the 7-azaindolyl Grignard reagent, followed by an exchange with $ZnCl_2$ and condensation with methyl chlorooxoacetate, but only with 41% yield. Hydrolysis of the ester **166** was performed with K_2CO_3 in MeOH/H_2O (90%). The potassium salt was then engaged in a coupling reaction with the 1-benzoyl-piperazine, which was mediated by 3-(diethoxy-phosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) in the presence of Hünig's base in DMF to afford **170** in 81% yield. Incorporation of the methoxy group in the C-4 position was next accomplished by a multistep procedure, initiated by the formation of the *N*-oxide derivative with *m*-CPBA in acetone, directly followed by nitration with fuming nitric acid in trifluoroacetic acid to afford **171**. Interestingly, compound **171** heated with an excess of MeONa/MeOH underwent an *ipso* displacement of the nitro group. Final transformation consisted of the reduction of the *N*-oxide using PCl_3 in EtOAc, giving **172** in 50% yield for three steps (26% overall yield from **1**).



Scheme 52. Reagents and conditions: (a) $ClCOCO_2Me$, $AlCl_3$, CH_2Cl_2, rt, 8 h, 79%; (b) K_2CO_3, MeOH/H_2O, 8 h, 90%; (c) *N*-benzoyl-3-(*R*)-methyl-piperazine, DEPBT, *i*-Pr_2NEt, DMF, rt, 8 h, 81%; (d) *m*-CPBA, acetone, rt, 8 h, 91%; (e) HNO_3/CF_3CO_2H 1:1, rt, 8 h; (f) (i) 2 N MeONa/MeOH, reflux, 8 h; (ii) PCl_3, EtOAc, rt, 8 h, 50% (three steps).

The 7-aza-analogue of meriadinin G[90] (Fig. 5) has first been prepared by Fresneda et al. (Scheme 53).[91] Acylation of **1** with acetyl chloride in the presence of $SnCl_4$ in benzene at room temperature afforded a white solid, which probably arose from N-acylation on the most nucleophilic pyridinic nitrogen atom according to the authors. This salt remained unchanged by heating in THF, either alone or in the presence of additional acetyl chloride. However, when a solution of this salt in THF was treated with additional $SnCl_4$ and acetyl chloride, compound **167** was successfully obtained in 45% yield after 3 days at room temperature. Subsequent protection of the nitrogen atom of **167** in the presence of NaH and tosyl chloride (TsCl) afforded **173**. *N*-Tosyl-3-acetyl-7-azaindole **173** reacted with DMF/DMA, yielding the enaminone **174**. Pyrimido-annelation with concomitant *N*-deprotection by treatment with guanidine hydrochloride in a basic medium led, finally, to pyrimidine **175**.

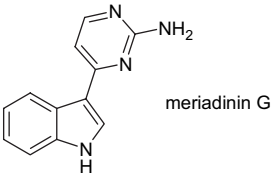
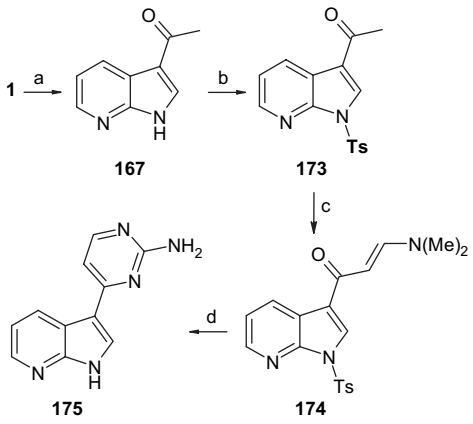
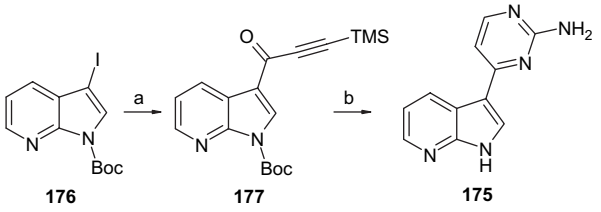


Figure 5. Structure of meriadinin G.



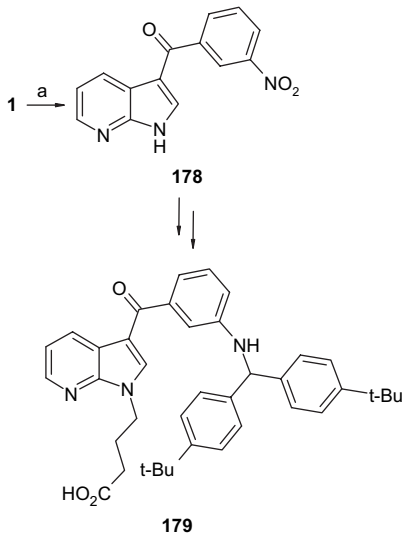
Scheme 53. Reagents and conditions: (a) MeCOCl, $SnCl_4$, benzene then THF, rt, 3 days, 45%; (b) NaH, DMF, rt, 1 h, then TsCl, 0 °C to rt, 2 h, 87%; (c) DMF/DMA, 110 °C, 4 h, 60%; (d) guanidine hydrochloride, K_2CO_3, 2-methoxyethanol, reflux, 24 h, 70%.

The preparation of the meriadinin G analogue **175** was also carried out through a carbonylative alkynylation with 1-Boc-3-iodo-7-azaindole **176**, in the presence of TMS/acetylene and $Pd(PPh_3)_2Cl_2$, in THF under 1 atm of CO affording **177** in 63% yield.[92] The alkynone **177** was treated with guanidine in a basic medium to furnish aza-meriadinin G **175** in 59% yield (Scheme 54).



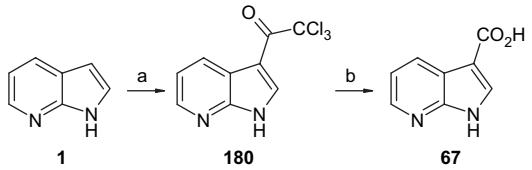
Scheme 54. Reagents and conditions: (a) TMS/acetylene, $Pd(PPh_3)_2Cl_2$, Et_3N, CuI, CO (1 atm), THF, rt, 48 h, 63%; (b) guanidine, Na_2CO_3, H_2O, MeCN/*t*-BuOH, 80 °C, 40 h, 59%.

In the search for novel non-steroidal inhibitors of steroid 5α-reductase, Sawada et al.[93] prepared a novel series of 4-substituted butyric acids (Scheme 55). 7-Azaindole **1** was acylated with 3-nitrobenzoyl chloride in the presence of $AlCl_3$, affording 3-benzoyl-7-azaindole **178** with only 19% yield. N-Alkylation of **178** with ethyl 4-bromobutyrate in the presence of K_2CO_3 in DMF provided the corresponding ester in 84% yield. The last steps involved saponification, reduction of the nitro function by hydrogenolysis and final N-alkylation in the presence of bis(4-*t*-BuPh)chloromethane, leading to **179** (three steps, 54%).



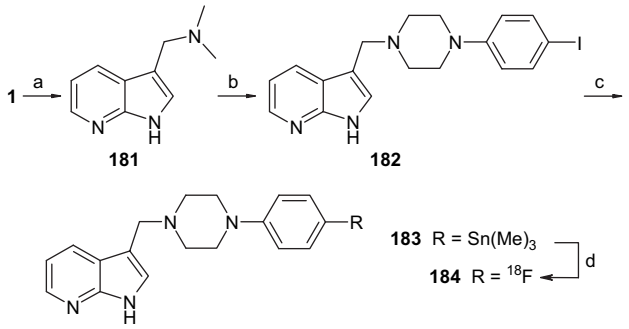
Scheme 55. Reagents and conditions: (a) 3-nitrobenzoyl chloride, $AlCl_3$ (1.8 equiv), CH_2Cl_2, rt, 1 h, 19%.

In the synthesis of DF-1012,[94] a new antitussive drug, it has been pointed out that, in a halogenated solvent and in the presence of a suitable catalyst such as $AlCl_3$, 7-azaindole reacted with trihaloacetyl halides (preferably with trichloroacetyl chloride) to give 3-trichloroacetyl-7-azaindole **180** in 58% yield. This latter compound underwent haloform transposition under a basic medium into the corresponding acid derivative **67** in 92% yield (Scheme 56).



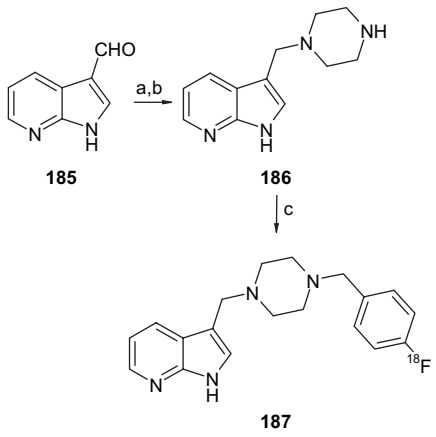
Scheme 56. Reagents and conditions: (a) CCl_3COCl, $AlCl_3$, CH_2Cl_2, 58%; (b) KOH, H_2O, 92%.

The radiolabelled fluorinated compound **184**, a dopamine D_4 receptor radiotracer candidate,[95] was synthetized in four steps (Scheme 57). Compound **181** was prepared from **1** by a Mannich reaction in the presence of dimethylammonium chloride and paraformaldehyde. A coupling reaction between **181** and 1-(4-iodophenyl)piperazine was performed in refluxing xylene to afford **182** in 56% yield. A Stille reaction between **182** and hexamethyldistannane gave **183** in 57% yield. The radioligand **184** was obtained by electrophilic fluorodestannylation of **183**.



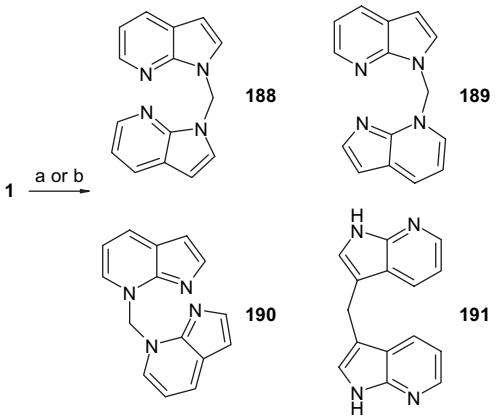
Scheme 57. Reagents and conditions: (a) dimethylammonium chloride, $(CH_2O)_n$, *n*-BuOH, reflux; (b) 1-(4-iodophenyl)piperazine, xylene, reflux, 56%; (c) $Sn_2(Me)_6$, $Pd(PPh_3)_4$, dioxane, reflux, 3 h, 57%; (d) CCl_3F, AcOH, $^{18}F[F_2]$.

In addition, the benzyl analogue of **184**, i.e., **187**, has been prepared by two successive reductive amination reactions (4-formylpiperazine in the presence of $NaBH_3CN$ followed by acidification leading to compound **186**, then 4-[^{18}F]benzaldehyde in the presence of $NaBH_3CN$) from 3-formyl-7-azaindole **185** (Scheme 58).[96–99]



Scheme 58. Reagents and conditions: (a) 4-formylpiperazine, $NaBH_3CN$, MeOH/AcOH, 60 °C, 3 h, 65%; (b) 4 M H_2SO_4, 80 °C, 8 h, 77%; (c) 4-[^{18}F]benzaldehyde, $NaBH_3CN$, MeOH/AcOH, 135 °C, 15 min.

The synthesis of compounds **188–191** was carried out by the reaction of dibromomethane with **1** in the presence of potassium hydroxide and Bu_4NBr in a refluxing toluene/water mixture (Scheme 59). When the reaction was carried out at 120 °C in the presence of a large excess of KOH, compounds **188** and **189** were obtained after 72 h as the major products (90% yield, 3:2 approximate ratio), while only a trace of compound **190** was detected. When a diluted solution of 1.5 equiv of KOH was used, compound **191** was isolated in poor yield. 7-Azaindole **1** is known to have multiple active sites towards electrophilic substitution. Since the 7-azaindol-1-yl anion intermediate is more stable than the 7-azaindol-7-yl anion, one would expect isomer **188** to be the major product. However, both isomers **188** and **189** were obtained and the isomer **190** was not observed. The results from ab initio calculations indicate that **188** is the most stable, whereas **189** seems to be the least stable. Compound **191** results from an attack on the most nucleophilic C-3 atom, which is usually observed under acidic conditions. The three isomers synthesized show distinct absorption and emission spectra.[3]



Scheme 59. Reagents and conditions: (a) KOH excess, CH_2Br_2, NBu_4Br, toluene/H_2O, 120 °C, 72 h, 90%, **188**=54%; **189**=36%; (b) KOH, CH_2Br_2, toluene/H_2O, 120 °C, 72 h, **191**=25%.

Reaction of **1** with erbium and mercury in 1,2,4,5-tetramethylbenzene (durene) under drastic conditions (170 °C, several days under vacuum) led to the unexpected compound **192**, which was the result of an unusual bond formation between a methyl group of durene and the C-3 position of two azaindole molecules (Fig. 6).[100]

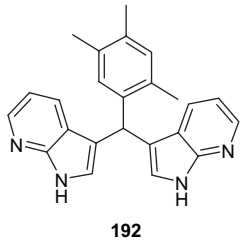
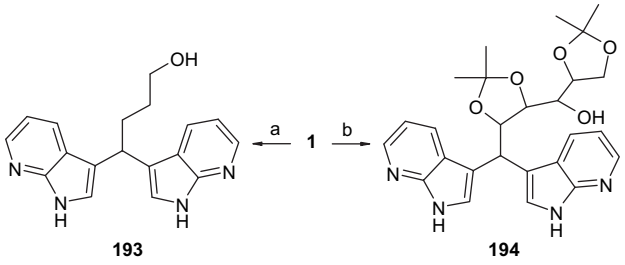


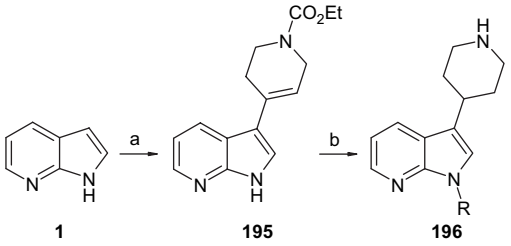
Figure 6. Compound **192**.

Treatment of 7-azaindolylmagnesium bromide with 2-ethoxytetrahydrofuran in the presence of $SnCl_4$ as a catalyst led to **193** in low yield (13%), compared to the results obtained with indole (42%).[101] The same procedure applied to a protected sugar (i.e., 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose) produced **194** in 22% yield (Scheme 60).



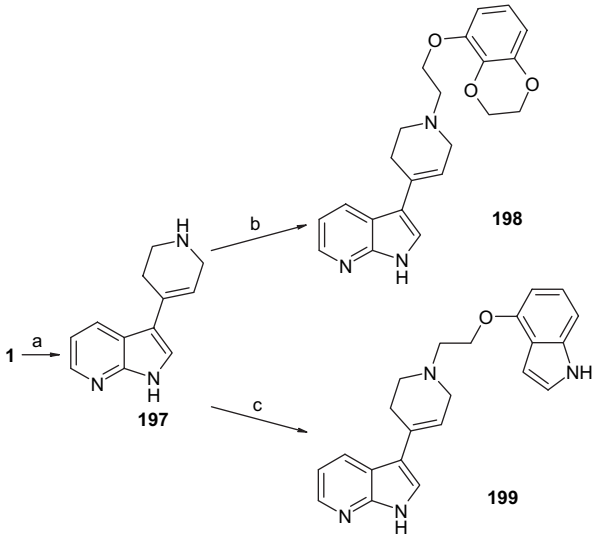
Scheme 60. Reagents and conditions: (a) (i) EtMgBr, Et_2O or THF, rt, 5 min; (ii) 2-ethoxytetrahydrofuran, $SnCl_4$, 50 °C to 80 °C, 12–24 h, 13%; (b) (i) EtMgBr, Et_2O or THF, rt, 5 min; (ii) 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose, $SnCl_4$, 50 °C to 80 °C, 12–24 h, 22%.

Regioselective alkylation on the C-3 position[102] of **1** was successfully achieved in a methanolic solution of potassium hydroxide in the presence of 1-ethoxycarbonyl-4-piperidone to give compound **195**. The reaction could also be performed with a non-protected piperidone. Potent and selective H_1 antagonists have been synthesized from 3-(4-piperidinyl)-7-azaindole **196** by introducing functional diversity on the secondary amine (Scheme 61).



Scheme 61. Reagents and conditions: (a) KOH, MeOH, 1-ethoxycarbonyl-4-piperidone, 60 °C, 15 h; (b) (i) H_2 (30 psi), PtO_2, MeOH, 1 h; (ii) NaH, RX, DMF, 25 °C; (iii) KOH, *i*-PrOH, 60 °C, 15 h.

Much attention has been devoted to the synthesis of azaindole analogues of the 5-HT reuptake inhibitor, indalpine (Scheme 62).[103] The design and synthesis of 7-azaindole derivatives having dual serotonin (5-HT) transporter reuptake and 5-HT_{1A} antagonist activity have been reported. The first step of the synthesis was the basic condensation of 7-azaindole **1** with 4-piperidone to provide **197** (no yield reported), which was further condensed either with 5-(2-chloroethoxy)benzo[1,4]dioxane or with 4-(2-chloroethoxy)indole to afford **198** or **199**.



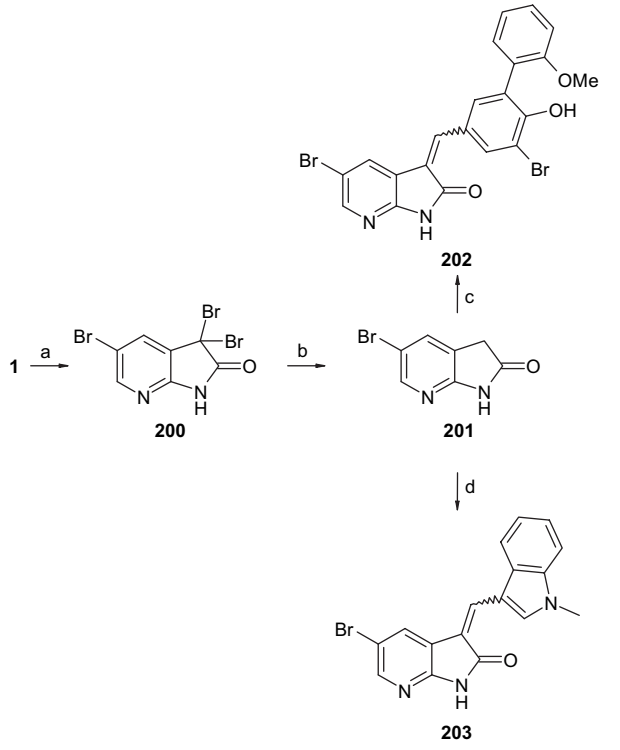
Scheme 62. Reagents and conditions: (a) 2 N KOH, MeOH, 4-piperidone; (b) 5-(2-chloroethoxy)benzo[1,4]dioxane, DMSO, Et_3N, 80 °C; (c) 4-(2-chloroethoxy)indole, DMSO, Et_3N, 80 °C.

Regioselective C-3 alkylation on 7-azaindole derivatives through a gold-catalyzed conjugate addition-type reaction was also reported.[104]

5. Oxidation to 7-azaoxindoles or 7-azaisatins

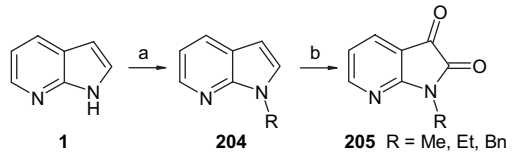
The survival rate of patients with pancreatic ductal adenocarcinoma is amongst the poorest for all cancers. TrkA kinase inhibitors such as **202** and **203** could provide beneficial biological effects in this disease (Scheme 63).[105] 5-Bromo-7-azaoxindole **201** was first obtained in two steps from **1** by a sequence of bromination (compound **200**)/reduction.

Aldol condensation of **201** with various aromatic or heteroaromatic aldehydes in an acidic medium gave **202** or **203**.



Scheme 63. Reagents and conditions: (a) Br_2, *t*-BuOH, $NaHCO_3$, H_2O; (b) Zn, NH_4Cl, THF/H_2O; (c) HCl/AcOH, 3-bromo-4-hydroxy-5-(2-methoxyphenyl)benzaldehyde, 100 °C; (d) HCl/AcOH, 3-formyl-1-methyl-7-azaindole, 100 °C.

1-Alkyl-7-azaindoles **204** were prepared in excellent yields by reaction of the sodium salt of **1** with the appropriate alkyl halides in DMA at room temperature. Subsequent oxidation of **204** with NBS/DMSO performed at 60 °C at atmospheric pressure and then at 80 °C under reduced pressure in order to remove the generated hydrogen halide led to an improved synthesis of isatins **205** (Scheme 64).[106]



Scheme 64. Reagents and conditions: (a) NaH, RX, DMA, rt, 12 h, 92–96%; (b) NBS, DMSO, 60 °C, 6 h then 80 °C for 20 h, 92–95%.

6. Synthesis of variolin B

Variolins, isolated by Munro et al.[107] from the antartic red sponge *Kirckpatrickia varialosa*, are alkaloids that exhibit antitumor and antiviral properties (Fig. 7). Their structures are organized around a common pyrido[3,2:4,5]pyrrolo-[1,2-*c*]pyrimidine skeleton with variations of the substituent at the C-5 position. Variolin B, the most active molecule of the group, has attracted considerable interest. Different research groups have developed strategies to allow the synthesis of variolins and their analogues. Alvarez and Joule have reported their work in a recent review.[108]

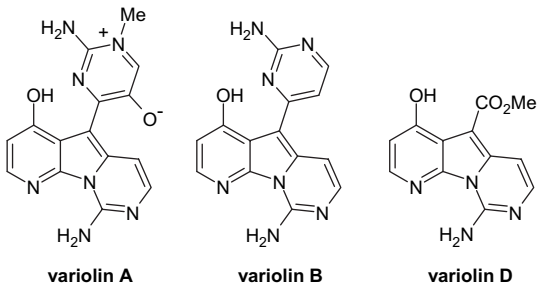
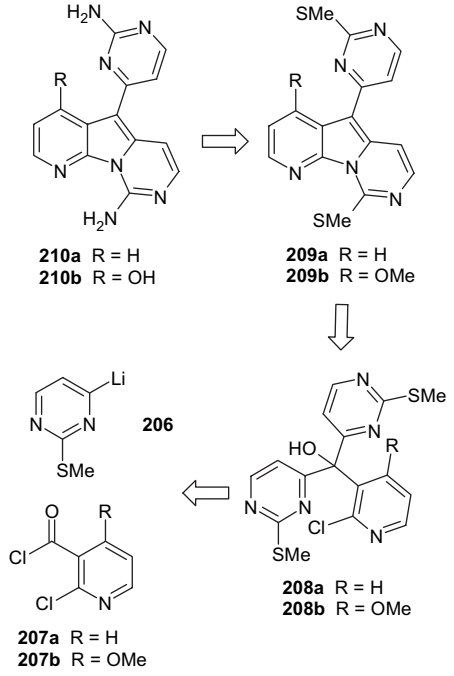


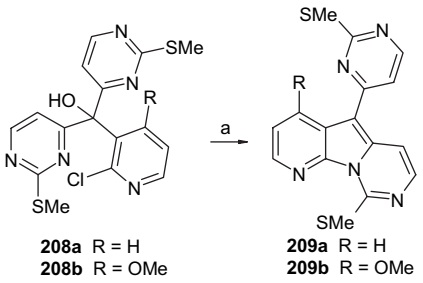
Figure 7. Structures of variolins A, B and D.

The first total synthesis of variolin B (**210b**) was reported by Anderson and Morris[109] in 2001 followed by a full paper[110] in 2005. The synthetic approach is based on the recognition of a symmetry element present in variolin B. The 7-azaindole core is generated as indicated in Scheme 65. The 4-lithio-2-methylthiopyridine **206** was prepared in two steps from the commercially available, 4-chloro-2-methylthiopyrimidine, which was converted into 4-iodo-2-methylthiopyrimidine by HI treatment. Iodine–lithium exchange of 4-iodo-2-methylthiopyrimidine by *n*-BuLi at −95 °C generated the lithiated species **206**. The latter compound was then added to 2-chloronicotinoyl chloride **207a** to form the triarylmethanol **208a** in a 56% optimized yield. The key reaction step involved the tandem deoxygenation/cyclization of **208a** using a combination of Et_3SiH and TFA (Scheme 66). This reaction was carried out successfully on compound **208a**, leading to the variolin core **209a** in 34% yield. The triarylmethanol **208b** was obtained in only poor yield from **206** reacting with a nicotinyl chloride **207b**, which precluded the development of the synthesis.



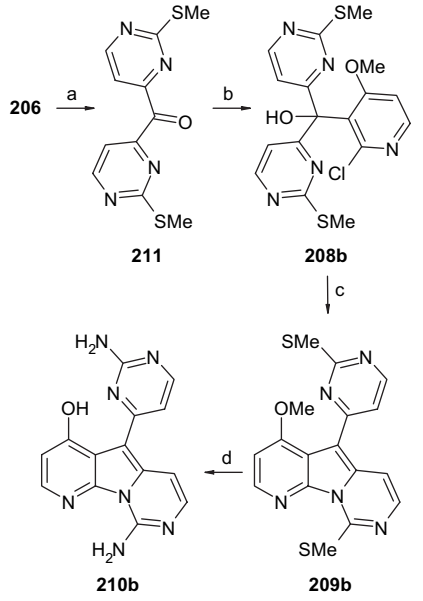
Scheme 65. Retrosynthetic synthesis of deoxyvariolin B and variolin B.

Similarly, the synthesis of a variolin analogue was performed by the use of diethyl carbonate as electrophile, leading to the symmetrical ketone **211** in 61% yield (Scheme 67).



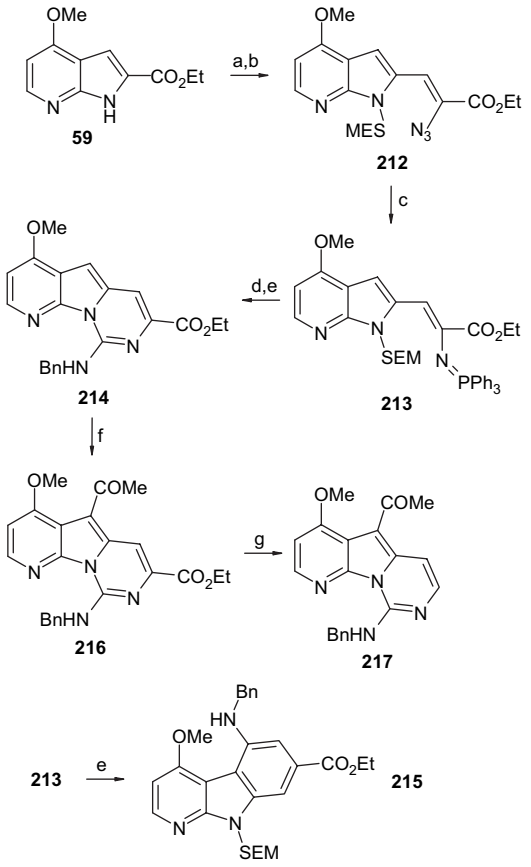
Scheme 66. Reagents and conditions: (a) TFA (4.3 equiv), Et_3SiH (8.1 equiv), 70 °C, **209a**=34%, **209b**=9%; TFA (2 equiv), Et_3SiH (8 equiv), $ClCH_2CH_2Cl$, 100 °C, **209b**=47%.

2-Chloro-4-methoxypyridine was lithiated at −95 °C and condensed with the ketone **211** to afford the triarylmethanol **208b** in 76% yield. The previous cyclization conditions applied to **208b** resulted in the formation of the tricyclic core **209b** in a very low yield, which could be improved to 47% with the previously optimized conditions: Et_3SiH (8 equiv) and TFA (2 equiv) in 1,2-dichloroethane. In addition, protection of the tertiary hydroxyl group as an acetate increased the yield of **209b** to 75% (69% for **209a**). Further oxidation of the thiomethyl ether **209b** into the bis-sulfoxide, displacement with 4-methoxybenzylamine ($PMBNH_2$), demethylation with sodium ethanethiolate and TFA removal of the PMB group afforded variolin B **210b** in an acceptable 17% overall yield from 6-chloro-2-methylthiopyrimidine. The same reactions applied to compound **209a** afforded the deoxyvariolin B **210a** in 23% overall yield.



Scheme 67. Reagents and conditions: (a) $OC(OEt)_2$, THF, −95 °C, 61%; (b) (i) 2-chloro-4-methoxypyridine, *n*-BuLi, THF, −95 °C; (ii) 2-chloro-3-lithio-4-methoxypyridine, THF, −78 °C, 76%; (c) TES (8 equiv), TFA (2 equiv), dichloroethane, 100 °C, 47%; (d) (i) *m*-CPBA, −40 °C; (ii) $PMBNH_2$, 90 °C, 78% (two steps); (iii) NaSEt, DMF, 55 °C, 95%; (iv) TFA, rt, 80%.

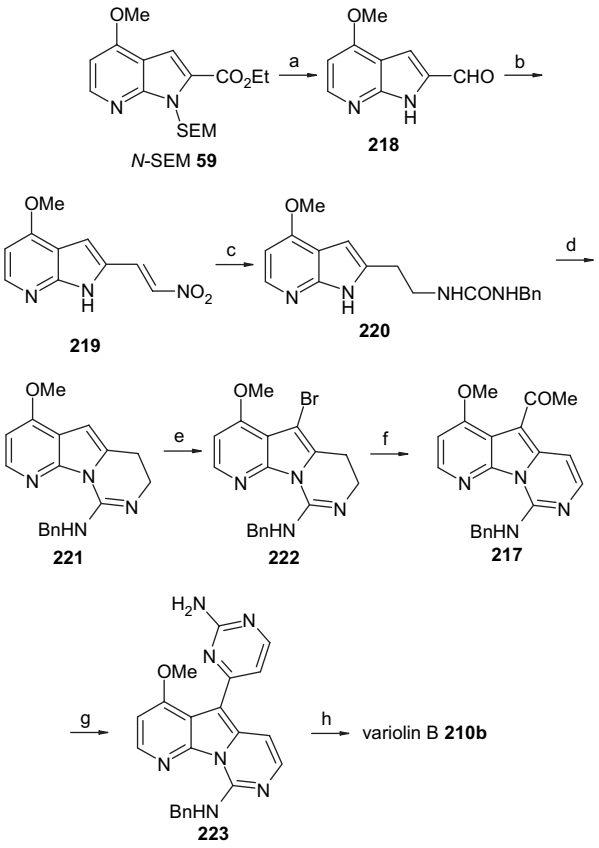
Two other total syntheses of variolin B or deoxyvariolin B, respectively reported by Molina et al.[111] (Scheme 68) and Alvarez et al.[73,112] (Scheme 69), have designed the tricyclic core in a linear pathway starting from **1**. The first synthetic approach involved a combined three-step reaction consisting of *N*-SEM protection of 2-ethoxycarbonyl-4-methoxy-7-azaindole **59** followed by $LiAlH_4$ reduction of the ester group and oxidation of the resulting alcohol with MnO_2, affording the intermediate aldehyde in 75% yield (Scheme 68). The condensation of the aldehyde derivative with ethyl azidoacetate in the presence of sodium ethoxide gave the vinyl azide **212** in 85% yield. The Staudinger reaction performed on **212** provided the iminophosphorane **213** in good yield. Treatment of **213** with Bu_4NF/SiO_2 under microwave irradiation cleanly removed the SEM group and allowed an aza-Wittig reaction in the presence of benzyl isocyanate to afford compound **214** in a near-quantitative yield as a result of a pyrimidino-annelation. It should be noted that the *N*-SEM protected compound **213** led to the linear tricyclic derivative **215** in 90% yield under the same conditions. Introduction of the acetyl group at the C-4 position of **214** occurred by heating in the presence of $POCl_3$ and dimethylacetamide. Quantitative saponification of **216** with LiOH followed by decarboxylation led to **217** in 50% yield (two steps).



Scheme 68. Reagents and conditions: (a) (i) NaH, SEMCl, DMF, 94%; (ii) $LiAlH_4$, THF, 93%; (iii) MnO_2, CH_2Cl_2, 86%; (b) $N_3CH_2CO_2Et$, EtONa, EtOH, −15 °C, 85%; (c) PPh_3, CH_2Cl_2, rt, 82%; (d) Bu_4NF/SiO_2, μwave, 1 min, 70%; (e) BnNCO, THF, 50 °C, **214**=97%, **215**=90%; (f) DMA, $POCl_3$, 90%; (g) (i) LiOH, THF/H_2O, 100%; (ii) Ph_2O, 225 °C, 50%.

The second synthetic approach focused on the preparation of the tricyclic framework without the ester group at the C-7 position (Scheme 69).

2-Formyl-4-methoxy-7-azaindole **218**, obtained by a three-step reaction sequence, reduction ($LiAlH_4$) of *N*-SEM

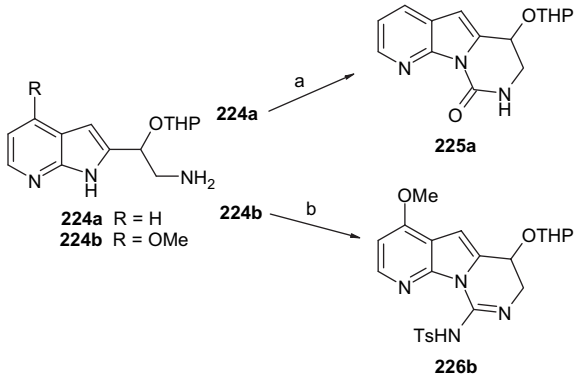


Scheme 69. Reagents and conditions: (a) (i) $LiAlH_4$, THF, 93%; (ii) MnO_2, CH_2Cl_2, 86%; (iii) $BF_3{\cdot}Et_2O$, 95%; (b) $MeNO_2$, NH_4OAc, EtOH, 75 °C, 80%; (c) (i) $LiAlH_4$, THF, 0 °C; (ii) BnNCO, CH_2Cl_2, rt, 60% (two steps); (d) CCl_4, PPh_3, Et_3N, CH_2Cl_2, 90%; (e) NBS, THF, 70%; (f) (i) ethoxyvinyltributylstannane, $PdCl_2(PPh_3)_2$, DMF, 70 °C; (ii) 1 M HCl, acetone, rt, 65% (two steps); (iii) DBU, $CBrCl_3$, 32% or DDQ, 40%; (g) (i) DMF-D*t*BA, DMF, 70 °C, 85%; (ii) guanidine hydrochloride, K_2CO_3, 2-methoxyethanol, reflux, 90%; (h) (i) MeSNa, DMF, 80 °C, 85%; (ii) TFA, 50 °C, 74%.

protected **59** (see Scheme 68), oxidation (MnO_2) and *N*-SEM deprotection with $BF_3{\cdot}Et_2O$, was condensed with nitromethane under Henry conditions, leading to the 2-nitrovinyl-7-azaindole **219**. Reduction of **219** with $LiAlH_4$ afforded the unstable primary amine, which was condensed, as previously, on benzyl isocyanate to produce the urea derivative **220**. Consequent treatment of **220** with Appel reagent (CCl_4, PPh_3, Et_3N) led to the cyclization of the carbodiimide intermediate in mild conditions, affording **221**, in contrast with the indole series, which needed drastic conditions. All attempts to promote the aromatization of the dihydropyrimidine **221** failed. Introduction of the crucial 2-aminopyrimidine ring at the C-5 position using an acetyl side chain for the construction of the desired ring was next investigated. Direct acylation proved to be problematic, since the tricyclic core did not stand up to the conditions employed.

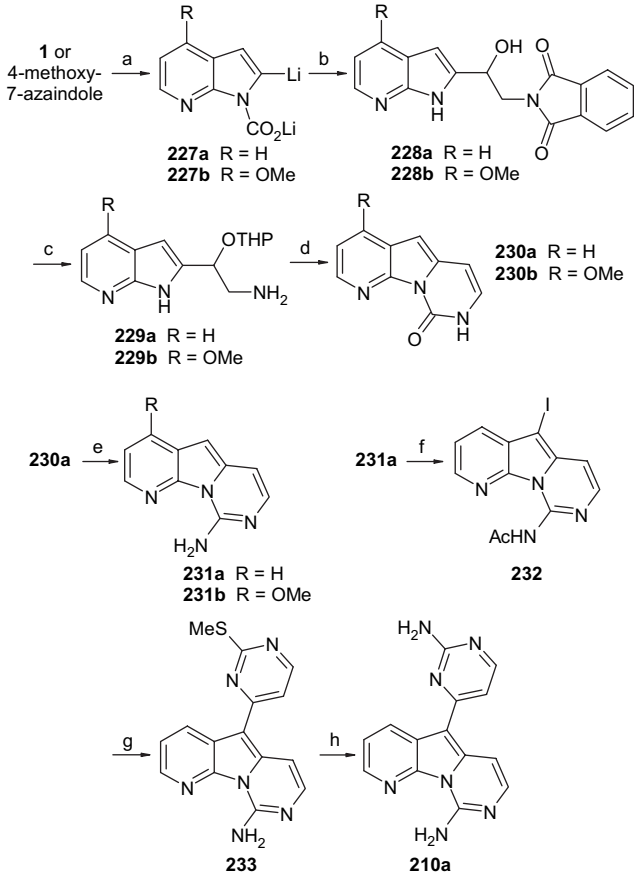
Thus, a two-step procedure was also envisaged involving bromination reaction at the C-5 position under classical conditions (NBS) to give **222** followed by a Stille reaction with 1-ethoxyvinyltributylstannane for the introduction of the acetyl functionality. Oxidative conversion of the intermediate dihydroheterocyclic compound into the corresponding heteroaromatic derivative **217** was achieved by using bromotrichloromethane in combination with DBU or DDQ in low yield (32–40%). The 2-aminopyrimidine ring was built up by treatment of acetyl derivative **217** with *N*,*N*-dimethylformamide di-*tert*-butylacetal (DMF-D*t*BA) then guanidine hydrochloride to afford **223** in 76% yield (two steps). *O*-Methyl deprotection occurred with sodium methanethiolate and, finally, the *N*-benzyl group was removed with neat TFA to yield variolin B **210b**.

Alvarez et al.[113] focused their efforts on the preparation of the aminopyrimidine ring and proposed an alternative synthesis (Scheme 70). In a first step, introduction of a protected aminoethyl chain at the C-2 position of 7-azaindole derivatives generated amines **224a**,**b**. For the synthesis of deoxyvariolin B, the cyclization of **224a** was achieved in 76% yield with triphosgene to furnish the tetrahydropyrimidone **225a**. Further chemical transformations led to the 2-aminopyrimidine moiety. A more convergent strategy was used for the synthesis of variolin B by employing *N*-tosyldichloromethanimine ($TsN{=}CCl_2$) as a cyclization reagent, generating directly the 2-aminopyrimidine unit from **224b** (compound **226b**, 65% yield).



Scheme 70. Reagents and conditions: (a) $(Cl_3CO)_2CO$, *i*-Pr_2NEt, CH_2Cl_2, rt, 76%; (b) $TsN{=}C(Cl)_2$, *i*-Pr_2NEt, CH_2Cl_2, 65%.

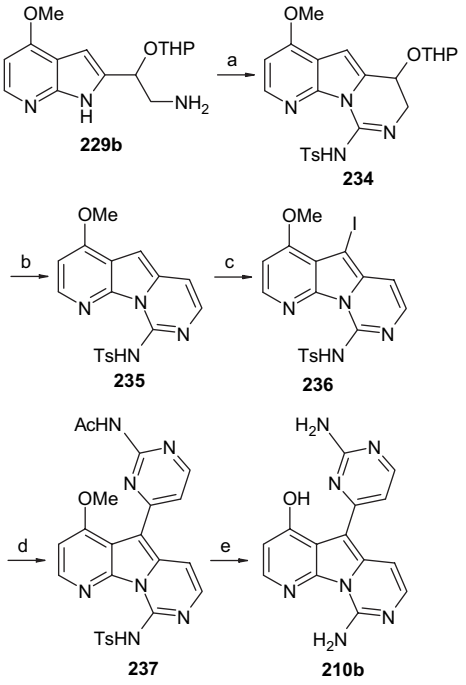
As a novelty, the synthesis of variolin B and deoxyvariolin B was also developed on the construction of the tricyclic core starting from **1**, followed by functionalization at the C-5 position, allowing the introduction of the D ring by a palladium-mediated cross-coupling reaction (Scheme 71).[73,113] 7-Azaindole **1** or 4-methoxy-7-azaindole were converted into a 2-lithiated species **227a**,**b** according to the Katritzky method. The nitrogen atom of 7-azaindole was first blocked by the temporary CO_2Li group and then the in situ lithiation was achieved with *t*-BuLi to abstract the C-2 hydrogen. Reaction with 2-phthalimidoacetaldehyde as electrophile gave the alcohols **228a**,**b** in 43–44% yields. Protection of the alcohols **228** as a tetrahydropyranyl ether offered the advantage of being orthogonal to the phthalimide protecting group as well as avoiding the competitive formation of an oxazolidinone. Cleavage of the phthaloyl protecting group by hydrazinolysis afforded **229a** and **229b**. The tetrahydropyrimidine intermediate was obtained as a 1:1 diastereomeric mixture by reaction of triphosgene on **229**. Removal of the THP group was achieved by treatment with 4 N HCl (80–100% yields). During the next step, the mesylation of the alcohol was followed by an in situ elimination at 0 °C to yield **230a** (95%) and **230b** (78%).



Scheme 71. Reagents and conditions: (a) (i) *n*-BuLi, THF, CO_2, −78 °C; (ii) *t*-BuLi, THF, −78 °C; (b) 2-phthalimidoacetaldehyde, THF, **228a**=44%, **228b**=43%; (c) (i) DHP, 6 N HCl, benzene, $CHCl_3$; (ii) $NH_2NH_2 \cdot H_2O$, EtOH, reflux, **229a**=87% (two steps), **229b**=62% (two steps); (d) (i) $(Cl_3CO)_2CO$, *i*-Pr_2NEt, CH_2Cl_2, rt; (ii) 4 N HCl, CH_2Cl_2; (iii) MsCl, TEA, CH_2Cl_2, 0 °C, **230a**=72% (three steps), **230b**=51% (three steps); (e) (i) HMDS, TMSCl, 2,6-lutidine; (ii) NH_3, 150 °C, 60 psi, 30% (two steps); (f) (i) Ac_2O, THF, rt, 75%; (ii) NIS, CH_2Cl_2, 0 °C, 93%; (g) (2-methylthiopyrimidin-4-yl)trimethyltin, $Pd_2(dba)_3$, CuI, PPh_3, LiCl, dioxane, reflux; (ii) HCl, MeOH, reflux, 45% (two steps); (h) (i) *m*-CPBA, CH_2Cl_2, 91%; (ii) 23% aq NH_4OH, dioxane, 80 °C, 90%.

To achieve the synthesis of deoxyvariolin B **210a**, the construction of the 9-aminopyrimidine system required the conversion of the carbonyl group of **230** into a leaving group for further displacement with ammonia. The use of $POCl_3$ was unproductive under various conditions. *O*-Silylation of **230a** with hexamethyldisilazane followed by treatment with ammonia under pressure at 150 °C afforded the attempted 2-aminopyrimidine **231a** in 30% yield. Following the same pathway, the methoxy derivative led to a complex mixture requiring an alternative route to generate the 2-aminopyrimidine **231b**. Introduction of the D ring on **231a** was envisaged by a Stille coupling reaction. *N*-Acetyl protection of **231a** followed by iodination on the C-5 position afforded **232** in good yield. A coupling reaction was next carried out between the iodo derivative **232** and (2-methylthiopyrimidin-4-yl)trimethyltin in the presence of $Pd_2(dba)_3$, PPh_3, CuI and LiCl. The desired product **233** was obtained in 45% yield after *N*-deacetylation in an acidic medium. Oxidation of the methylthio group of **233** proceeded in the presence of *m*-CPBA in 91% yield. Finally, the substitution of the sulfone group was performed in the presence of aqueous NH_4OH in a sealed tube in dioxane at 80 °C to give deoxyvariolin B **210a** in excellent yield.

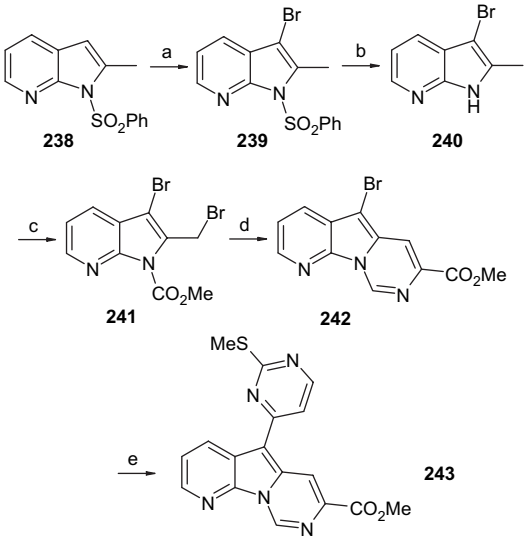
As discussed previously, numerous efforts were also necessary to improve the yield of the total synthesis of variolin B (Scheme 72).[73,112] As an intermediate in the global synthesis, the use of $TsN{=}CCl_2$ on substrate **229b** appeared to be very efficient to directly form the 2-tosylaminopyrimidine **234** in 65% yield. Removal of the THP group, followed by elimination of the hydroxyl group by formation of its mesylate, provided **235**. Regioselective iodination with NIS led to the 5-iodo derivative **236**. A Stille reaction between **236** and 2-acetylamino-4-trimethylstannylpyrimidine gave **237** in 75% yield. Acidic treatment of **237** resulted in simultaneous deprotection of the methoxy and acetyl protecting groups (60% yield). The reductive photolysis with a high-pressure Hg lamp (in the presence of hydrazine as a reducing agent and 1,4-dimethoxybenzene as an electron source) removed the tosyl group to give variolin B **210b** in moderate yield.



Scheme 72. Reagents and conditions: (a) $TsN{=}CCl_2$, *i*-Pr_2NEt, CH_2Cl_2, 65%; (b) (i) 4 N HCl, CH_2Cl_2, 95%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 71%; (c) (i) NIS, CH_2Cl_2, 95%; (d) (i) 2-acetylamino-4-trimethylstannylpyrimidine, $Pd_2(dba)_3$, CuI, PPh_3, LiCl, dioxane, reflux, 75%; (e) (i) 48% HBr, reflux, 60%; (ii) $NH_2NH_2 \cdot H_2O$, 1,4-dimethoxybenzene, hν, MeOH, 30%.

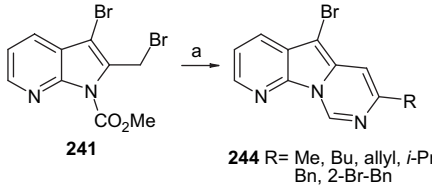
Vaquero et al.[114] has reported considerable efforts devoted to a new strategy to obtain the heterocyclic core of variolins (Scheme 73). The pyrido[3,2:4,5]pyrrolo[1,2-*c*]pyrimidine system was elaborated from 2-bromomethyl-7-azaindole and tosylmethyl isocyanide (TosMic). In preliminary studies, the 2-methyl-1-phenylsulfonyl-7-azaindole **238** was brominated in the C-3 position with NBS in CCl_4 to give **239** in 67% yield. A radical bromination of the 2-methyl group of compound **239** was achieved with NBS in the presence of benzoyl peroxide to afford the dibromo derivative in 81% yield. The latter compound treated with TosMic afforded the desired product in 37% yield as an unstable derivative. As an alternative, the carbamate protecting group

was considered with the hope of preserving the stability of the products generated. Deprotection of **239** was effective in a basic medium and led to **240** (80%). This step was immediately followed by quantitative protection of the nitrogen atom by treatment with LiHMDS and $ClCO_2Me$. Subsequent radical bromination afforded the dibromo derivative **241**, which, upon reaction with TosMic under phase-transfer conditions, led to the pyrimidine **242** with an unexpected methoxycarbonyl group transfer on the pyrimidine ring. A Stille reaction between **242** and (2-methylthiopyrimidin-4-yl)trimethyltin, using $Pd(PPh_3)_4$ in toluene/methanol at 110 °C, afforded **243** in 63% yield. In addition, arylation or heteroarylation on the 5-bromo derivative **242** was also investigated by the same laboratory to explore the reactivity of the halogen atom and also to complete the study.[115]



Scheme 73. Reagents and conditions: (a) NBS, CCl_4, rt, 12 h, 67%; (b) K_2CO_3, $MeOH/H_2O$, reflux, 7 h, 80%; (c) (i) LiHMDS, THF, −78 °C to rt, 2 h then $ClCO_2Me$, −78 °C, 2 h, 89%; (ii) NBS, benzoyl peroxide, CCl_4, reflux, 91%; (d) TosMic, TBAI, aq NaOH, CH_2Cl_2, −10 °C, 65%; (e) (2-methylthiopyrimidin-4-yl)trimethyltin, $Pd(PPh_3)_4$, toluene/MeOH, 110 °C, 63%.

Recently, Vaquero et al. has expanded the TosMic chemistry to the synthesis of substituted azolopyrimidines starting from the previous compound **241** (Scheme 74).[116] The use of substituted TosMic derivatives CN–CH(R)–Tos (R=Me, *i*-Pr, *n*-Bu, allyl, Bn, 2-Br–Bn) under phase-transfer conditions (Bu_4NCl, NaOH) allowed the formation of a large diversity of pyrido[3,2:4,5]pyrrolo[1,2-*c*]pyrimidines **244** (34–83% yields).



Scheme 74. Reagents and conditions: (a) CN–CH(R)–Tos, $(Et)_3NBnCl$, 30% NaOH, CH_2Cl_2, 4–24 h, 34–83%.

The synthesis and biological evaluation of new variolin B derivatives have been recently described by Fresneda and Molina. Some of the tested derivatives have similar activity to the natural compound, variolin B **210b**.[117]

7. 7-Azaindolocarbazoles

Indolocarbazole (or indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole) alkaloids form a class of compounds endowed with potent antitumor, antiviral and/or antimicrobial activities. This family (and especially rebeccamycin and staurosporine) has attracted considerable attention, due to their central role in the regulation of cell cycle progression and specific enzymatic inhibitions (Fig. 8). Other natural products such as granulatimide (see Fig. 10), which do not possess a sugar moiety inhibit the cell cycle checkpoint in the G2 phase.

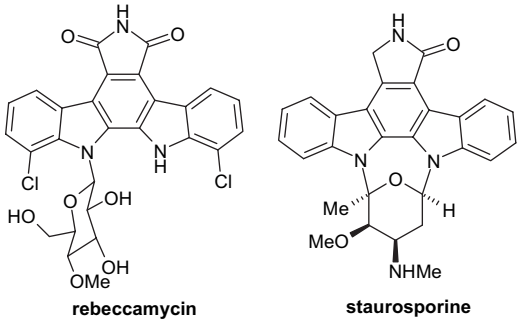
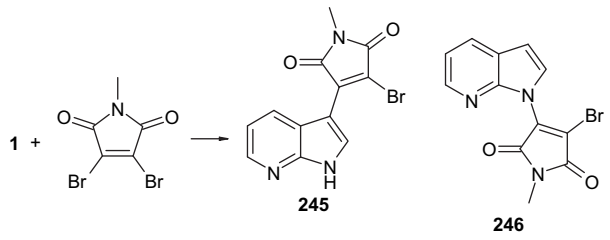


Figure 8. Structures of rebeccamycin and staurosporine.

Numerous analogues have been synthesized either by modifying the maleimide unit or by removal of the sugar moiety. Such aglycone derivatives named arcyriaflavins have been investigated due to their kinase inhibitory properties (GSK-3, CDK, etc.). Our laboratory has focused on the modification of the heterocyclic core highlighting the bioisosteric replacement of one or two indole moieties by a 7-azaindole unit as related below. First, we examined the anionic condensation of **1** on 2,3-dibromo-*N*-methylmaleimide (Scheme 75; Table 3).[118] Different conditions were attempted to orientate the regioselectivity of the anionic reaction towards the C-3 alkylated product **245**. The lithium derivative of 7-azaindole **1** obtained by treatment with LiHMDS reacted with the dibromomaleimide, affording only the *N*-alkylated derivative **246**, but in low yield (25%). The Grignard reagent EtMgBr in a 2:1 mixture of toluene and CH_2Cl_2 led to the C-3 alkylated derivative **245** in 65% yield.



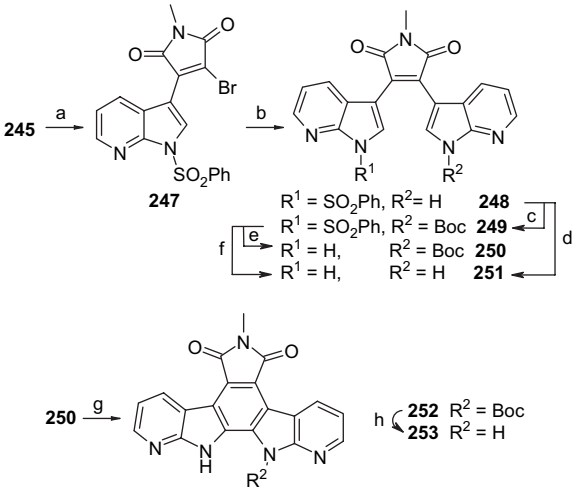
Scheme 75. Reagents and conditions: see Table 3.

Phenylsulfonyl group protection of **245** led to *N*-phenylsulfonyl-7-azaindolomaleimide **247** in 74% yield (Scheme 76).

Table 3

Base	Solvent	Temp	**245**	**246**
LiHMDS (2 equiv)	THF	0 °C	—	25
LiHMDS (2 equiv)	THF/hexane	0 °C	—	15
EtMgBr (2 equiv)	Et_2O then CH_2Cl_2	rt	14	—
EtMgBr (2 equiv)	Toluene	rt	—	—
EtMgBr (2 equiv)	Toluene	50 °C, 12 h	15	—
EtMgBr (2 equiv)	Toluene/CH_2Cl_2 2:1	50 °C, 24 h	65	—

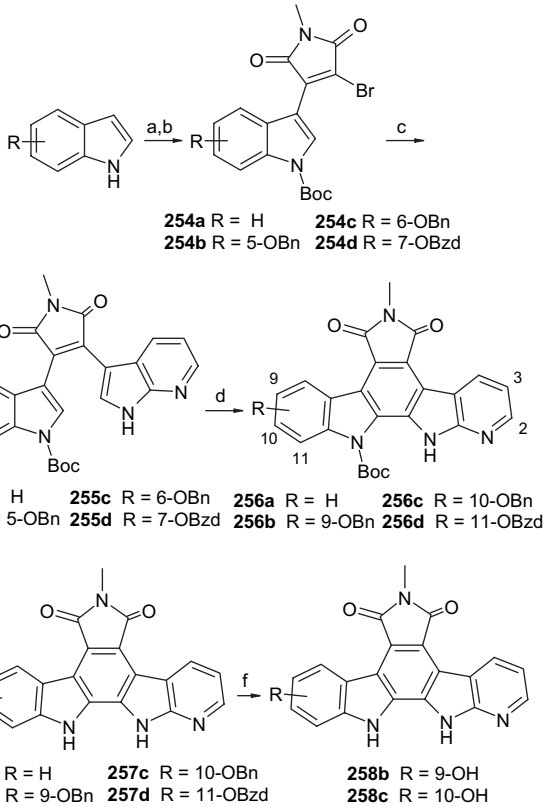
Anionic condensation of **247** with the lithium salt of **1** generated the bis-substituted maleimide **248** in 64% yield. The coupling reaction performed on the monophenylsulfonyl derivative **248** using $Pd(OAc)_2$, $Pd(OCOCF_3)_2$ or DDQ was unproductive. The fully deprotected bis-7-azaindole **251**, obtained from **248**, was submitted to cyclization into the carbazole in the presence of various palladium species, but ran to failure, due to the precipitation of palladium complexes with the nitrogen atoms.



Scheme 76. Reagents and conditions: (a) NaH, $PhSO_2Cl$, THF/DMF, rt, 74%; (b) **1**, LiHMDS, toluene, rt, 12 h, 64%; (c) Boc_2O, DMAP, THF, 30 °C, 92%; (d) TBAF (2 equiv), THF, reflux, 2 h, 83%; (e) TBAF (2 equiv), THF, rt, 2 h, 80%; (f) TBAF (10 equiv), THF, reflux, 1 h, 100%; (g) I_2, UV lamp TQ-718 DEMA (500 W), benzene, 3.5 h, 74%; (h) HCO_2H, rt, 2 h, 100%.

The Boc protection of the residual nitrogen atom of **248** afforded **249** in 92% yield. The phenylsulfonyl group of **249** was selectively cleaved using Bu_4NF to afford the mono *N*-Boc protected bis-7-azaindole **250** in 80% yield. By the use of an excess of Bu_4NF in THF at reflux, the fully deprotected bis-7-azaindole **251** was also obtained from **249** in quantitative yield. Oxidative photocyclization of **250** was successfully performed in the presence of molecular iodine to afford the 7-azacarbazole **252** in 74% yield. The choice of protecting groups also appeared to be crucial for the photoirradiation step, leading in other cases to the decomposition of starting materials. Final deprotection afforded aza-arcyriaflavin A **253** in quantitative yield.[118,119]

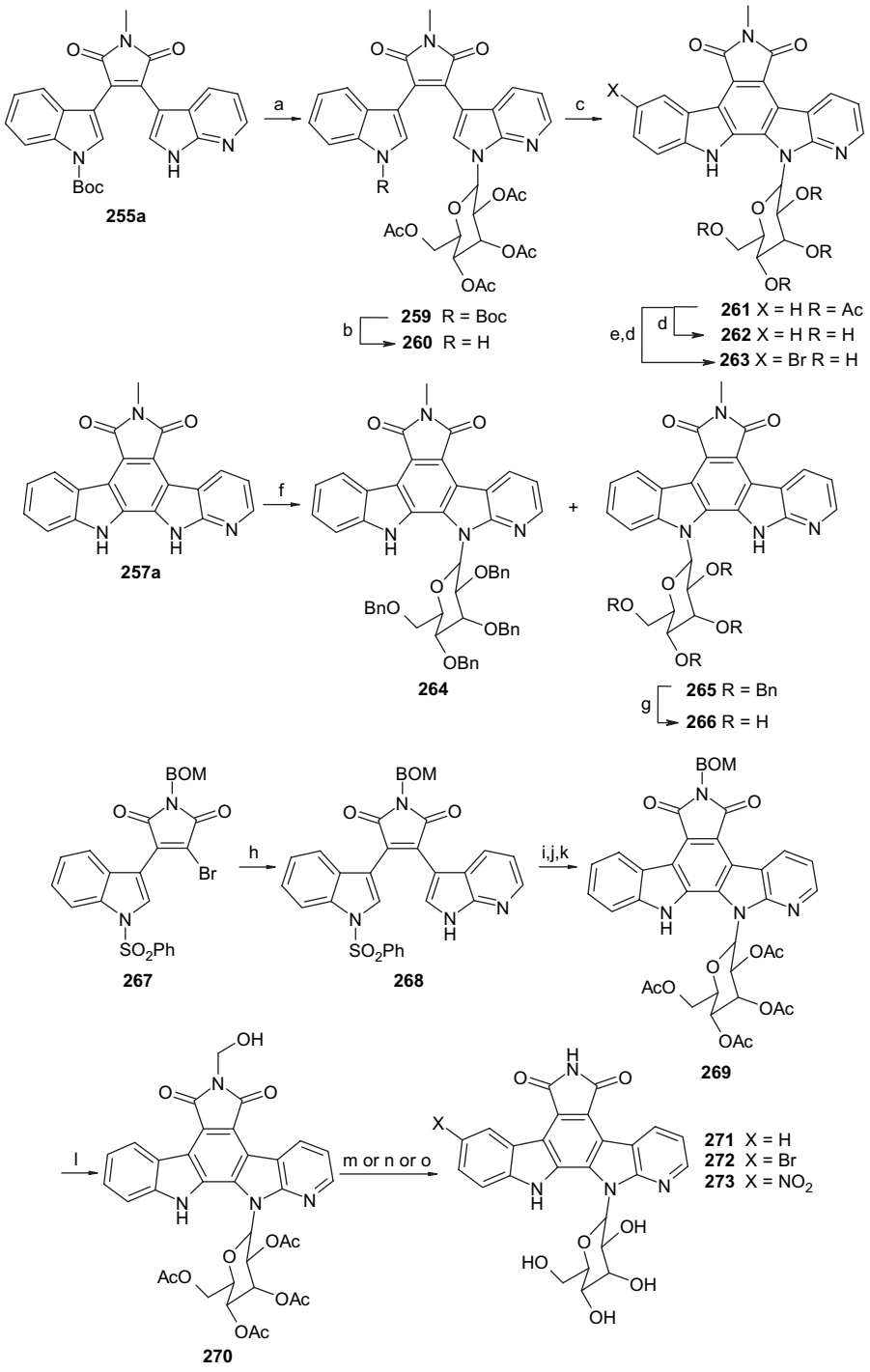
A similar approach was studied with a view to the preparation of mixed 7-azacarbazoles where only one indole unit was replaced by one 7-azaindole moiety (Scheme 77).[119,120] The lithio derivative of **1** was condensed at −20 °C in toluene with the 2-bromo-3-(*N*-Boc-indol-3-yl)-1-methylmaleimide **254a** to afford the bis-maleimide **255a** in 53% yield. In the presence of a benzyloxy- (BnO–) or benzhydryloxy- (BzdO–) substituent on the indole ring, the bis-maleimides **255b–d** were obtained in 48–74% yields. Photocyclization of **255a–d** afforded the 7-azacarbazole derivatives **256a–d** in 75–88% yields. *N*-Boc deprotection with Bu_4NF afforded **257a–d** and removal of the benzyl group of **257b**,**c** was effective with BBr_3 (6 equiv) to yield **258b** and **258c** in 100 and 85% yields, respectively. Unfortunately, decomposition of **257d** was observed either by hydrogenolysis or by reaction with BBr_3.



Scheme 77. Reagents and conditions: (a) *N*-methyl-2,3-dibromomaleimide, LiHMDS, THF; (b) Boc_2O, DMAP, MeCN; (c) **1** (3 equiv), LiHMDS (4 equiv), toluene, −20 °C, **255a**=53%, **255b**=60%, **255c**=48%, **255d**=74%; (d) I_2, UV lamp TQ-718 DEMA (500 W), benzene, 75–88%; (e) Bu_4NF, THF, reflux, 82–100%; (f) BBr_3, CH_2Cl_2, rt, **258b**=100%, **258c**=85%.

Further functionalization by a sugar moiety on the nitrogen atom either of the indole or of the 7-azaindole unit was next achieved by Prudhomme et al. (Scheme 78), starting from the previously synthesized aglycones **248** and **255a** with a view to the preparation of aza-rebeccamycin analogues.[120–123]

Amongst the various methods of N-glycosylation of indolocarbazole moieties described in the literature, a Mitsunobu reaction was performed on **255a** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose in the presence of DEAD and PPh_3, providing the β-*N*-glycosylated **259** in 61% yield. As attempted, treatment of **259** with Bu_4NF led to the fully deprotected product (Boc and acetate groups removed), giving a sparingly soluble derivative, inappropriate for further steps. Therefore, an alternative method using formic acid selectively removed the Boc protecting group, affording **260** in 72% yield. Oxidative photocyclization by irradiation



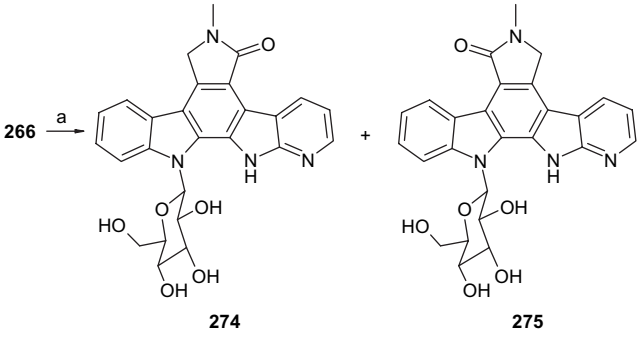
Scheme 78. Reagents and conditions: (a) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose, PPh_3, DEAD, THF, −78 °C to rt, 15 h, 61%; (b) HCO_2H, rt, 24 h, 72%; (c) I_2, Hg lamp (400 W), benzene, 1.5 h, 84%; (d) 28% aq NH_4OH, MeOH, 65 °C, 22 h, **262**=69%; rt, 22 h, **263**=53%; (e) NBS, THF, 0 °C then rt, 4 days, 44%; (f) KOH, Na_2SO_4, MeCN, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride, rt, 15 h, **264**=11%; **265**=42%; (g) H_2 (1 bar), Pd/C, EtOAc, rt, 3 days, 85%; (h) LiHMDS, **1**, toluene, rt, 24 h, 46%; (i) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose, PPh_3, DEAD, THF, −78 °C to rt, 15 h, 61%; (j) Bu_4NF, THF, rt, 2.5 h, 72%; (k) I_2, Hg lamp (400 W), benzene, 1.5 h, 78%; (l) H_2 (1 bar), Pd/C, EtOAc/MeOH, rt, 24 h, 46%; (m) 28% aq NH_4OH, MeOH, rt, 19 h, **271**=57%; (n) (i) NBS, THF, 0 °C then rt, 5 days; (ii) 28% aq NH_4OH, MeOH, rt, 22 h, **272**=53% (two steps); (o) (i) Fuming HNO_3, THF, 0 °C then rt, 21 h; (ii) 28% aq NH_4OH, MeOH, rt, 16 h, **273**=38% (two steps).

in the presence of iodine gave **261** in 84% yield. Subsequent cleavage of the acetate moieties was performed by treatment with aqueous ammonia in methanol at 65 °C, giving rebeccamycin analogue **262** in 69% yield.

To improve the solubility and to induce stronger interactions with the target biomolecules, a bromo substituent was introduced on the indole ring by reaction of **261** with NBS. Ammonia treatment released the bromo derivative **263** in 53% yield. N-Glycosylation was also performed on the deprotected aglycone **257a** in a heterogeneous medium with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride. In this case, the glucose moiety was introduced on the azaindole (**264**, 11% yield) and on the indole (**265**, 42% yield).

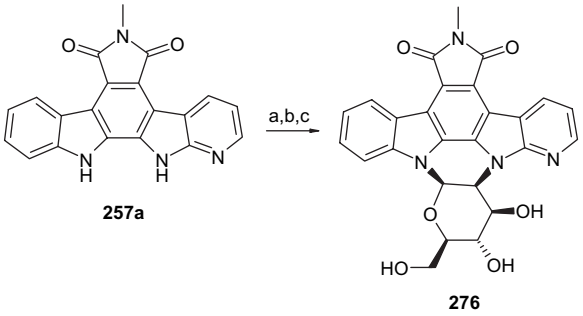
Removal of the benzyl group of the sugar moiety of **265** by hydrogenolysis in EtOAc/MeOH in the presence of a catalytic amount of Pd/C provided **266** in 85% yield. The synthesis of analogues of **262** and **263** with a free imide nitrogen in replacement of the methyl substituent was investigated. The use of the removable benzyloxymethyl (BOM) protecting group was found to be suitable (Scheme 78). 1-Benzyloxymethyl-3-bromo-4-(*N*-phenylsulfonyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione **267** reacted on lithiated 7-azaindole, generating **268** in 46% yield. A Mitsunobu reaction introduced the sugar moiety on the free nitrogen atom of 7-azaindole in 61% yield. The phenylsulfonyl group was removed using TBAF in THF at reflux in 82% yield. Oxidative photocyclization afforded **269** and was followed by hydrogenolysis of the BOM group to give the derivative **270**. Aminolysis removed the hydroxymethyl and acetate groups and provided compound **271** in 57% yield. Bromination and nitration on the indole moiety of **270** were achieved, respectively, with NBS and fuming nitric acid at 0 °C. Final deprotection of the sugar moiety led to compounds **272** and **273**.

A Clemensen reduction of compound **266** using zinc amalgam afforded **274** and **275** in a mixture of regioisomers (1:1 ratio, 40% yield) (Scheme 79).[123]



Scheme 79. Reagents and conditions: (a) Zn/Hg, HCl, EtOH, 40%.

Aza-staurosporines with an azaindolocarbazole core were also easily obtained from the coupling reaction between the aglycone **257a** and 1-chloro-2-*O*-tosyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (Scheme 80). The reaction was carried out using KOH and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as a phase-transfer reagent in acetonitrile. Treatment of the glycosyl derivative with sodium azide in DMF led to the bridged compound in 12% yield (two steps). Removal of the benzyl group was achieved with BBr_3 in dichloromethane to give **276** in 90% yield.[124,125]



Scheme 80. Reagents and conditions: (a) KOH, TDA-1, 1-chloro-2-*O*-tosyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose, MeCN, rt, 48 h; (b) NaN_3, DMF, 70 °C, 48 h, 12% (two steps); (c) BBr_3, CH_2Cl_2, −78 °C to rt, 90%.

Following the same strategy, the preparation of compounds **277** and **278** has been published (Fig. 9).[125] The synthesis of **277** from starting material **279** is depicted in Scheme 81 (intermediates **280** and **281** are described). The aza-bridged rebeccamycin **278**, isomer of **277**, was obtained from **268**.

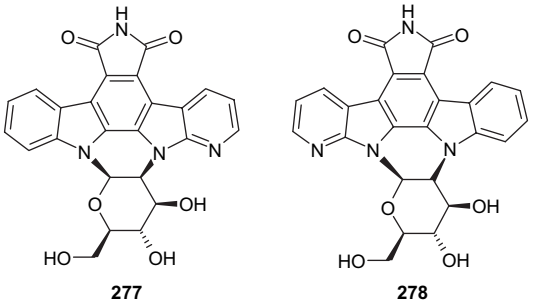
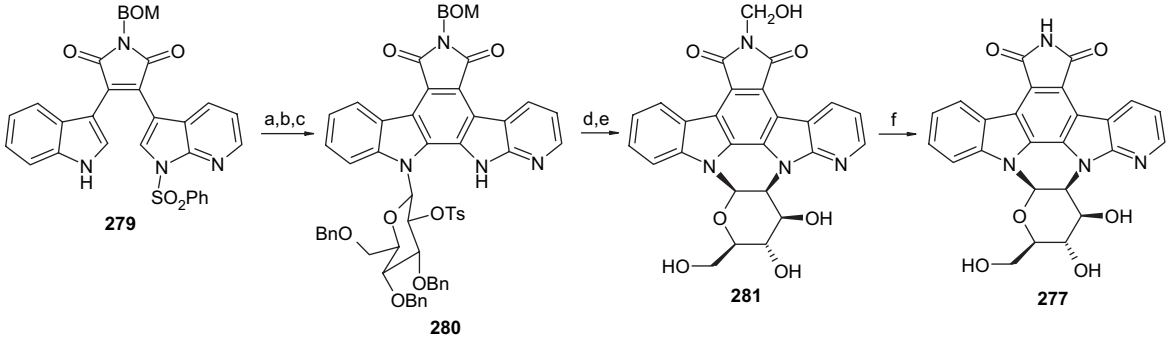


Figure 9. Compounds **277** and **278**.

8. Granulatimide and isogranulatimide analogues

Indolocarbazole derivatives were commonly associated with granulatimide, isogranulatimide and isogranulatimides A and B (Fig. 10), which are structurally related to staurosporine aglycone. The synthesis of isogranulatimides A and B analogues bearing a 7-azaindole moiety instead of the indole



Scheme 81. Reagents and conditions: (a) 2-*O*-tosyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose, PPh_3, THF, DIAD, −78 °C to rt, 18 h, 88%; (b) Bu_4NF, THF, rt, 2.5 h, 81%; (c) I_2, Hg lamp (400 W), benzene, 1.5 h, 62%; (d) NaN_3, DMF, 70 °C, 48 h, 72%; (e) H_2 (40 psi), $Pd(OH)_2$/C, EtOH/EtOAc, rt, 3 days, 52%; (f) 28% aq NH_4OH, THF, rt, overnight, 71%.

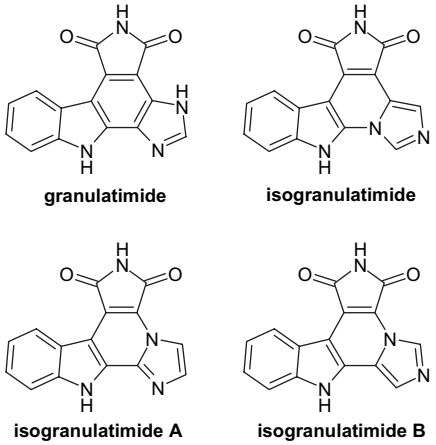


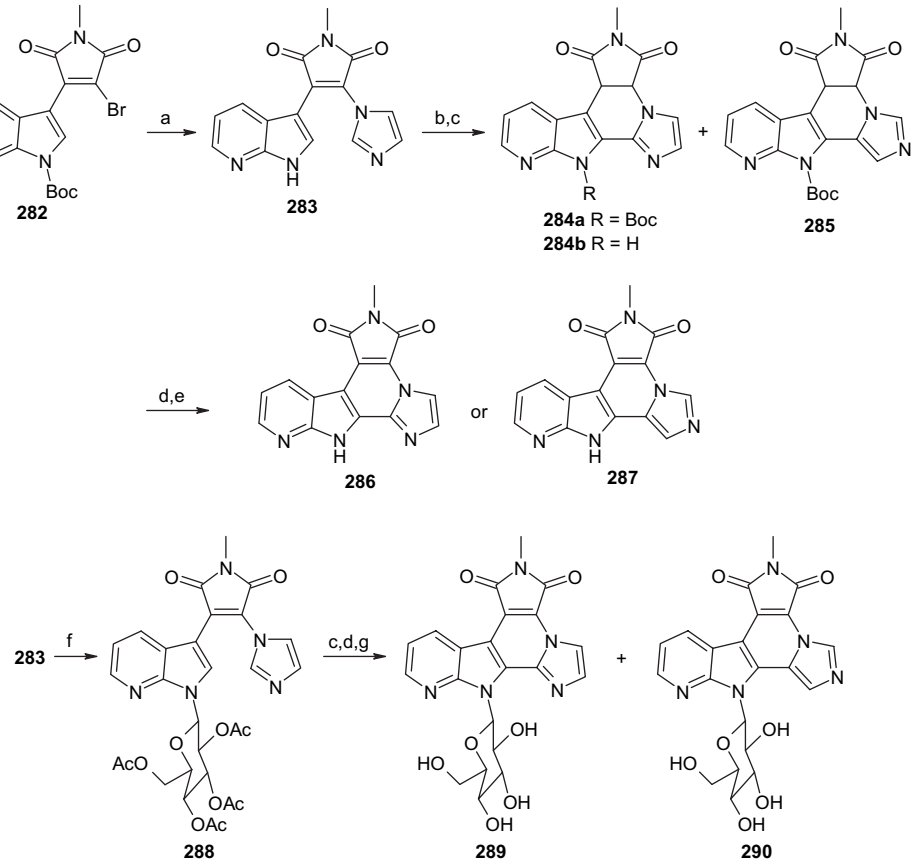
Figure 10. Structures of granulatimide and isogranulatimides.

moiety has been reported recently by the group of Prudhomme et al.(Scheme 82).[126]

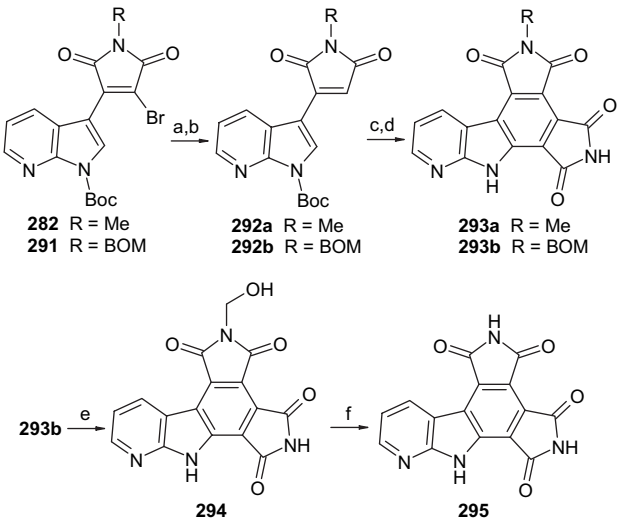
Compound **282** was treated with imidazole magnesium bromide, leading to the adduct **283** with a concomitant removal of the Boc group. Due to its insolubility, the product **283** was again protected into the carbamate. Irradiation with a 500 W lamp led to **284** (as a mixture of two derivatives) and **285** in low yield. Compounds **284** were separated and characterized as **284a** (21% yield) and the *N*-Boc derivative **284b** (24% yield). Further oxidation of **284** and **285** with MnO_2 followed by Boc group cleavage with formic acid led easily to the isogranulatimide A analogue **286** (77% yield) and isogranulatimide B analogue **287** (47% yield). Introduction of the glucose moiety was next carried out on compound **283** under Mitsunobu reaction conditions to give **288** in 65% yield. Photocyclization of **288** followed by oxidation and final deprotection afforded the two regioisomers **289** and **290** in 20 and 5% yields, respectively, for the last three steps.

Granulatimide bis-imide analogues have recently been prepared (Scheme 83).[74] As a novel feature, the key step of the synthesis was an intermolecular Diels–Alder reaction. Hydrogenolysis of the bromo substituent of compounds **282** and **291** in methanol led to the imides in 90 and 68% yields, respectively. Further treatment by DDQ generated the imide moiety in 94% yield for **292a**, and quantitatively for **292b**. Diels–Alder reactions with the maleimide were carried out in refluxing *p*-xylene and led to an unseparable mixture of isomers. Non-aromatic isomers were further oxidized with DDQ to yield **293a** and **293b** in 77–83% yields. Due to the lack of efficiency of the hydrogenolysis, the BOM group was removed in a two-step procedure from **293b** by treatment with TFA (**294**) and subsequent reflux in *p*-xylene to afford the compound **295**.

As an extension of this work, the synthesis of an isogranulatimide analogue bearing a pyrrole and a 7-azaindole moiety

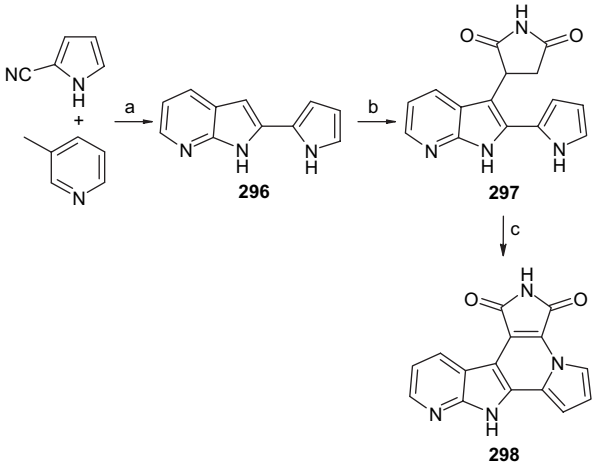


Scheme 82. Reagents and conditions: (a) EtMgBr, THF, imidazole; (b) Boc_2O, DMAP, THF; (c) UV lamp TQ-718 DEMA (500 W), MeCN, **284a**=21%, **284b**=24%, **285**=19%; (d) MnO_2, CH_2Cl_2; (e) HCO_2H, **286**=77%, **287**=47%; (f) 2,3,4,6-tetra-*O*-acetyl-α-glucopyranose, PPh_3, DEAD, THF, 65%; (g) MeONa/MeOH, **289**=20% (three steps), **290**=5% (three steps).



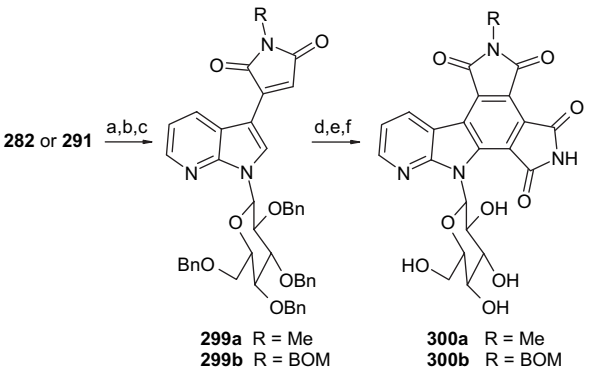
Scheme 83. Reagents and conditions: (a) H_2 (1 bar) Pd/C, MeOH, rt, 3 h; (b) DDQ, dioxane, rt, 15 h, **292a**=85% (two steps), **292b**=68% (two steps); (c) maleimide, *p*-xylene, reflux, 20–24 h; (d) DDQ, dioxane, reflux, 3 days, **293a**=83% (two steps); 40 h, **293b**=77% (two steps); (e) TFA, reflux, 3 days; (f) *p*-xylene, reflux, 7 days, 63% (two steps).

instead of an imidazole and an indole has been reported in 2006 (Scheme 84).[127] Compound **296** was obtained in 42% yield by coupling 3-picoline and 2-cyanopyrrole in the presence of LDA. Treatment of **296** with maleimide was successfully performed in MeOH/H_2O, providing the Michael adduct **297** in 54% yield. Compound **298** was obtained in a poor yield by cyclization of **297** in refluxing nitrobenzene in the presence of Pd/C. This step probably involves the oxidation of the succinimide into the corresponding maleimide prior to the cyclization.



Scheme 84. Reagents and conditions: (a) LDA, THF, 5 h, 42%; (b) maleimide, MeOH/H_2O, 50 °C, 48 h, 54%; (c) Pd/C, nitrobenzene, reflux, 7 h, 14%.

A similar strategy was used for the synthesis of the glycosyl derivatives **300a**,**b** from **299a**,**b** (Scheme 85).[74] The debenzylation step was quite reluctant in classical conditions. The use of dimethyldioxirane allowed the removal of the benzyl group in 59% yield for the *N*-methyl derivative and 76% yield for the BOM derivative.



Scheme 85. Reagents and conditions: (a) 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose, PPh_3, DEAD, THF, −78 °C to rt, 15 h, 46–64%; (b) H_2 (1 bar), Pd/C, EtOAc, $NaHCO_3$, rt, 24 h, 46–48%; (c) DDQ, dioxane, rt, 48 h, 61–64%; (d) maleimide, toluene, reflux, 14 h; (e) MnO_2, $CHCl_3$, reflux, 24 h, 61–86% (two steps); (f) dimethyldioxirane, CH_2Cl_2, rt, 48 h, 59–76%.

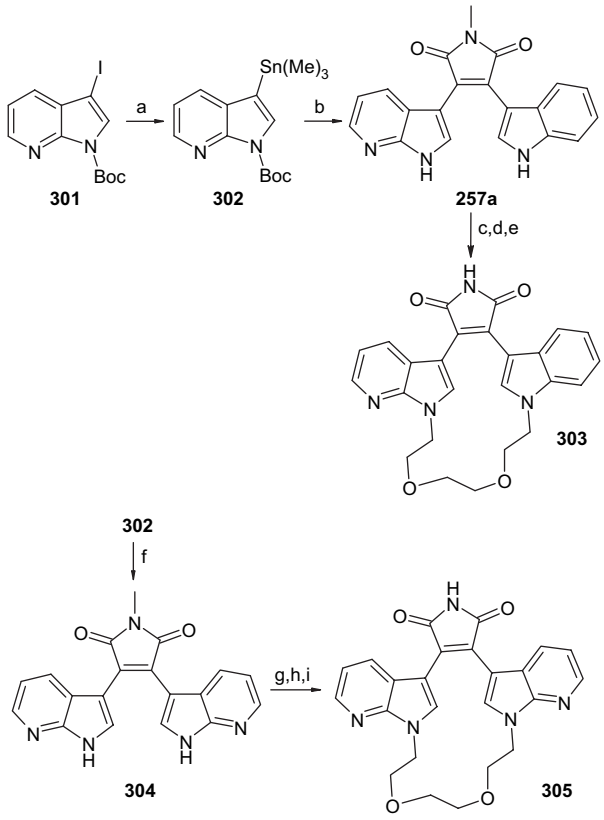
9. Bis-azaindolylmaleimides and derivatives

Glycogen synthase kinase (GSK-3) is a serine/threonine proteine kinase involved in diverse cellular processes. Related inhibitors may play a role for the treatment of Alzheimer's disease as well as diabetes. As an example, macrocyclic polyoxygenated bis-7-azaindolylmaleimides **303** and **305** have been discovered as a novel series of potent and highly selective GSK-3β inhibitors (Scheme 86).[128]

1-Boc-3-iodo-7-azaindole **301** was mixed with trimethyltin chloride at −78 °C before the addition of *n*-BuLi providing the stannyl derivative **302** with 60% yield. A Stille reaction with chloroindolylmaleimide in the presence of $PdCl_2(PPh_3)_2$ gave the deprotected 7-azaindoleindolylmaleimide **257a** in 31% yield. Alkylation of the coupling product **257a** with bismesylates gave the cyclic *N*-methylmaleimide. Hydrolysis of the *N*-methylimide ring by KOH in refluxing ethanol, directly followed by ammonolysis with HMDS, furnished the targeted molecule **303**. In a previous paper, Joule et al.[81] studied the influence of the diversity of 3-trimethylstannyl *N*-substituted 7-azaindole derivatives in the palladium-mediated cross-coupling reaction. In a similar approach, 2,3-dichloro-*N*-methylmaleimide reacted with the stannyl derivative **302** in excess to afford the desired symmetrical product **304,** which was then alkylated in the same way with bismesylates to afford compound **305**.

The same reasearch group reported the synthesis of macrocyclic polyoxygenated bis-7-azaindolylmaleimides with the incorporation of a ketone (**306**), a pyridine (**307**), or a thiophene unit in the macrocyclic chain (Fig. 11).[129] A novel series of 3-(7-azaindolyl)-4-arylmaleimide derivatives **310**, **311** and **312** were synthesized and evaluated for their biological activity against GSK-3β and selectivity versus protein kinase C-βII (Scheme 87).[130] Methyl 7-azaindole-3-glyoxylate **166** was obtained from the magnesium salt of 7-azaindole and methyl oxalyl chloride in 24% yield. N-Alkylation of **166** was carried out with iodoethane in the presence of caesium carbonate in DMF.

As an alternative to target such structures, the acetamide **308** could be synthesized from the glyoxal **166** by reduction of the keto group using Et_3SiH in TFA and followed by an



Scheme 86. Reagents and conditions: (a) Me_3SnCl, −78 °C, *n*-BuLi, −78 °C to rt, overnight, 60%; (b) chloroindolylmaleimide, $Pd(PPh_3)_2Cl_2$, LiCl, toluene, 95 °C, overnight, 31%; (c) $MsO(CH_2)_2O(CH_2)_2O(CH_2)_2OMs$, Cs_2CO_3, DMF, 100 °C, 20 h, 49%; (d) 10 N KOH, ethanol, reflux, overnight; (e) HMDS, DMF, 80 °C, overnight, 33% (two steps); (f) 2,3-dichloro-*N*-methylmaleimide, $Pd(PPh_3)_2Cl_2$, LiCl, toluene, 95 °C, overnight, 41%; (g) $MsO(CH_2)_2O(CH_2)_2O(CH_2)_2OMs$, Cs_2CO_3, DMF, 100 °C to 20 °C, 15 h, 67%; (h) 10 N KOH, ethanol, reflux, overnight; (i) HMDS, DMF, 80 °C, 6 h, 60% (two steps).

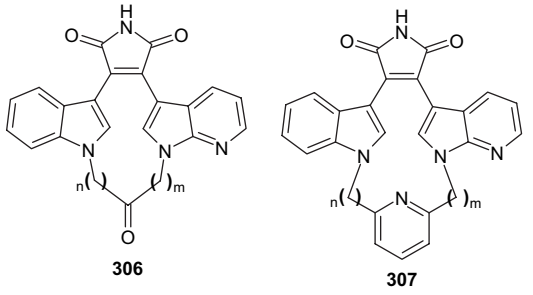
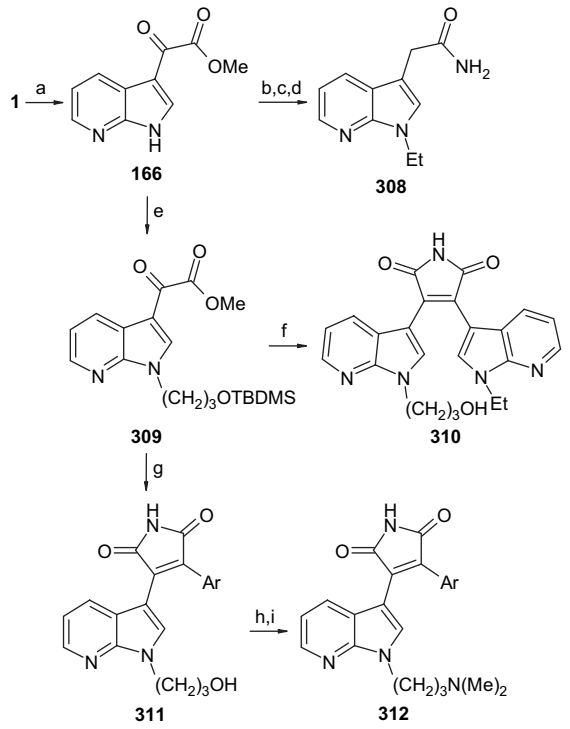


Figure 11. Structures of **306** and **307**.

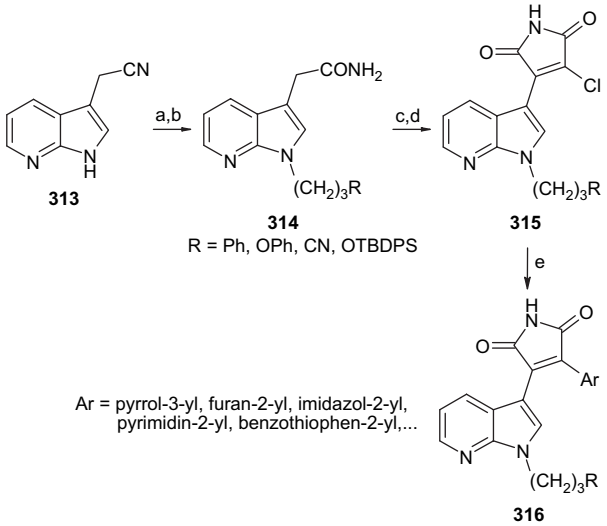
aminolysis of the ester in 34% yield (three steps). Compound **166** was also N-alkylated with 3-(*t*-butyldimethylsilyloxy)-propyl bromide in DMF at 50 °C to give the α-keto ester **309** in 44% yield. The maleimide condensation of **309** and amide **308** proceeded smoothly in the presence of *t*-BuOK at 0 °C, providing **310** after the removal of the TBDMS group with concd HCl. The α-keto ester **309** was next subjected to maleimide condensation with various commercially available arylacetamides (phenyl, naphthyl, thienyl and pyridyl) to afford **311**. Compound **312** was obtained in two steps from **311**.

The derivatives **316** were also obtained from 7-azaindole-3-acetonitrile **313** (Scheme 88).[131] Hydroxylation of **313**



Scheme 87. Reagents and conditions: (a) EtMgBr, THF, −65 °C, then MeO_2CCOCl, −78 °C, 24%; (b) EtI, Cs_2CO_3, DMF, 50 °C; (c) Et_3SiH, TFA, 55 °C; (d) NH_3, MeOH, 90 °C, 34% (three steps); (e) $Br(CH_2)_3OSiMe_2$-*t*-Bu, Cs_2CO_3, DMF, 50 °C, 44%; (f) **308**, *t*-BuOK, THF, 0 °C, then concd HCl, 39%; (g) $ArCH_2CONH_2$, *t*-BuOK, THF, 0 °C then concd HCl, 17–62%; (h) (i) Ms_2O, pyridine, THF, 50 °C; (ii) Me_2NH, THF, 50–65 °C, 22–31% (two steps).

afforded the acetamide, which was then N-alkylated to give **314**. The compounds **314** were reacted with diethyl oxalate in the presence of *t*-BuOK to afford the 2-hydroxymaleimides in good yield, which were then treated with oxalyl chloride to provide **315**. Suzuki or Stille reaction of **315** with various arylboronic acids or arylstannanes gave the desired coupling products **316** in moderate to good yields.



Scheme 88. Reagents and conditions: (a) H_2O_2, K_2CO_3, DMSO, 0 °C, 10 min, 84%; (b) $Br(CH_2)_3R$, Cs_2CO_3, DMF, 70 °C, 2–6 h, 27–60%; (c) $(CO_2Et)_2$, *t*-BuOK, THF, 0 °C, 20 min, 53–81%; (d) $(COCl)_2$, DMF/CH_2Cl_2 1:1, rt, 1 h, 73–89%; (e) *Method A*: $Pd(P(t\text{-}Bu_3))_2$, $Pd_2(dba)_3$, $ArB(OH)_2$, KF, THF, rt, 18 h; *Method B*: $Pd(P(t\text{-}Bu_3))_2$, $ArSnBu_3$, THF, reflux, 18 h.

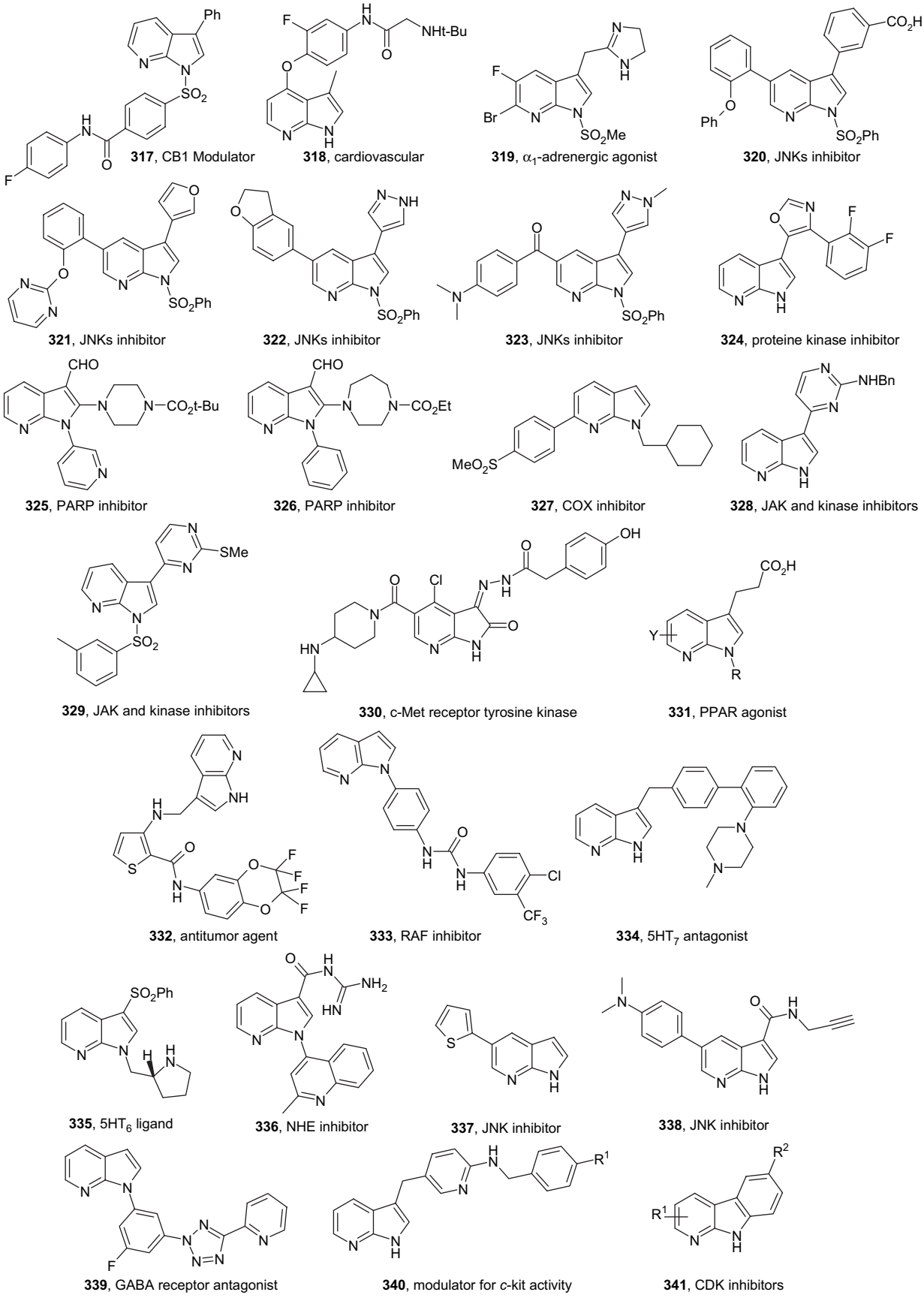


Figure 12. Structures of **317**–**341**.

10. Patents

The diversity of biological targets is a good criterion of the interest in medicinal chemistry of the 7-azaindole core. Numerous compounds were described in the patent literature, but only a few examples are given in this review (Fig. 12, **317**,[132] **318**,[133] **319**,[134] **320–322**,[135] **323**,[136] **324**,[137] **325–326**,[138] **327**,[139] **328–329**,[140] **330**,[141] **331**,[142] **332**,[143] **333**,[144] **334**,[145] **335**,[146] **336**,[147] **337**,[148] **338**,[149] **339**,[150] **340**,[151] **341**[152]).

11. Conclusions

Since 2000, the chemistry of 7-azaindole derivatives has increased tremendously, allowing the functionalization of almost all the positions of the nucleus and leading to a wide variety of substrates used for the synthesis of biologically active molecules. New methods for the design of 7-azaindole derivatives are currently under investigation, leading to a better knowledge of this heterocycle.

References and notes

1. Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471–506.
2. Le Hyaric, M.; Vieira de Almeida, M.; Nora de Souza, M. V. *Quim. Nova* **2002**, *25*, 1165–1171.
3. Song, D.; Schmider, H.; Wang, S. *Org. Lett.* **2002**, *4*, 4049–4052.
4. Wang, S. *Coord. Chem. Rev.* **2001**, *215*, 79–98.
5. Liu, S.-F.; Wu, Q.; Schmider, H. L.; Aziz, H.; Hu, N.-X.; Popović, Z.; Wang, S. *J. Am. Chem. Soc.* **2000**, *122*, 3671–3678.
6. Ashenhurst, J.; Wu, G.; Wang, S. *J. Am. Chem. Soc.* **2000**, *122*, 2541–2547.
7. Wu, Q.; Esteghamatian, M.; Hu, N.-X.; Popović, Z.; Enright, G.; Breeze, S. R.; Wang, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 985–988.
8. Song, D.; Jia, W. L.; Wu, G.; Wang, S. *J. Chem. Soc., Dalton Trans.* **2005**, *3*, 433–438.
9. Milton, H. L.; Wheatley, M. V.; Slawin, A. M. Z.; Woollins, J. D. *Inorg. Chem. Commun.* **2004**, *7*, 1106–1108.
10. Burrows, A. D.; Mahon, M. F.; Varrone, M. *J. Chem. Soc., Dalton Trans.* **2003**, *24*, 4718–4730.
11. Wu, Q.; Lavigne, J. A.; Tao, Y.; D'Iorio, M.; Wang, S. *Chem. Mater.* **2001**, *13*, 71–77.
12. Wu, Q.; Hook, A.; Wang, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3933–3935.
13. Jia, W.-L.; Bai, D.-R.; McCormick, T.; Liu, Q.-D.; Motala, M.; Wang, R.-Y.; Seward, C.; Tao, Y.; Wang, S. *Chem.—Eur. J.* **2004**, *10*, 994–1006.
14. Kang, Y.; Song, D.; Schmider, H.; Wang, S. *Organometallics* **2002**, *21*, 2413–2421.
15. Tani, K.; Sakurai, H.; Fujii, H.; Hirao, T. *J. Organomet. Chem.* **2004**, *689*, 1665–1674.
16. Ma, Y.; Chao, H.-Y.; Wu, Y.; Lee, S. T.; Yu, W.-Y.; Che, C.-M. *Chem. Commun.* **1998**, 2491–2492.
17. Wu, Q.; Lavigne, J. A.; Tao, Y.; D'Iorio, M.; Wang, S. *Inorg. Chem.* **2000**, *39*, 5248–5254.
18. Song, D.; Sliwowski, K.; Pang, J.; Wang, S. *Organometallics* **2002**, *21*, 4978–4983.
19. Song, D.; Wang, S. *Organometallics* **2003**, *22*, 2187–2189.
20. Song, D.; Wang, S. *Comments Inorg. Chem.* **2004**, *25*, 1–18.
21. Zhao, S.-B.; Song, D.; Jia, W.-L.; Wang, S. *Organometallics* **2005**, *24*, 3290–3296.
22. Song, D.; Liu, S.-F.; Wang, R.-Y.; Wang, S. *J. Organomet. Chem.* **2001**, *631*, 175–180.
23. Casas, J. M.; Forniés, J.; Martín, A.; Rueda, A. J. *Organometallics* **2002**, *21*, 4560–4563.
24. (a) Chou, Y.-C.; Huang, S.-F.; Koner, R.; Lee, G.-H.; Wang, Y.; Mohanta, S.; Wei, H.-H. *Inorg. Chem.* **2004**, *43*, 2759–2761; (b) Chou, P.-T.; Wu, G.-R.; Wei, C.-Y.; Cheng, C.-C.; Chang, C.-P.; Hung, F.-T. *J. Phys. Chem. B* **2000**, *104*, 7818–7829; (c) Wu, Y.; Ogawa, A. K.; Berger, M.; McMinn, D. L.; Schultz, P. G.; Romesberg, F. E. *J. Am. Chem. Soc.* **2000**, *122*, 7621–7632.
25. Bland, B. R. A.; Gilfoy, H. J.; Vamvounis, G.; Robertson, K. N.; Cameron, T. S.; Aquino, M. A. S. *Inorg. Chim. Acta* **2005**, *358*, 3927–3936.
26. Catalán, J.; de Paz, J. L. G. *J. Chem. Phys.* **2005**, *123*, 114302/1–114302/8.
27. Sakota, K.; Okabe, C.; Nishi, N.; Sekiya, H. *J. Phys. Chem. A* **2005**, *109*, 5245–5247.
28. Taketsugu, T.; Yagi, K.; Gordon, M. S. *Int. J. Quantum Chem.* **2005**, *104*, 758–772.
29. Catalán, J.; de Paz, J. L. G. *J. Chem. Phys.* **2005**, *122*, 244320/1–244320/7.
30. Kwon, O.-H.; Jang, D.-J. *J. Phys. Chem. B* **2005**, *109*, 8049–8052.
31. Sakota, K.; Sekiya, H. *J. Phys. Chem. A* **2005**, *109*, 2718–2721.
32. Sakota, K.; Sekiya, H. *J. Phys. Chem. A* **2005**, *109*, 2722–2727.
33. Casadesus, R.; Moreno, M.; Lluch, J. M. *Chem. Phys.* **2003**, *290*, 319–336.
34. Caric, D.; Tomisic, V.; Kveder, M.; Galic, N.; Pifat, G.; Magnus, V.; Soskic, M. *Biophys. Chem.* **2004**, *111*, 247–257.
35. Chou, P.-T.; Wu, G.-R.; Wei, C.-Y.; Shiao, M.-Y.; Liu, Y.-I. *J. Phys. Chem. A* **2000**, *104*, 8863–8871.
36. Chou, P.-T.; Yu, W.-S.; Wei, C.-Y.; Cheng, Y.-M.; Yang, C.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 3599–3600.
37. Kwon, O.-H.; Lee, Y.-S.; Park, H. J.; Kim, Y.; Jang, D.-J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5792–5796.
38. Kang, Y.; Wang, S. *Tetrahedron Lett.* **2002**, *43*, 3711–3713.
39. Schirok, H. *Synlett* **2005**, 1255–1258.
40. Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935–1938.
41. (a) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 590–591; (b) Gassman, P. G.; Huang, C. T. *J. Am. Chem. Soc.* **1973**, *95*, 4453–4455.
42. Debenham, S. D.; Chan, A.; Liu, K.; Price, K.; Wood, H. B. *Tetrahedron Lett.* **2005**, *46*, 2283–2285.
43. (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488–2490; (b) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571–1587.
44. Cacchi, S.; Fabrizi, G.; Parisi, L. M. *J. Comb. Chem.* **2005**, *7*, 510–512.
45. Harcken, C.; Ward, Y.; Thomson, D.; Riether, D. *Synlett* **2005**, 3121–3125.
46. Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539–541.
47. Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4256–4258.

48. Blache, Y.; Sinaldi-Troin, M.-E.; Hichour, M.; Benezech, V.; Chavignon, O.; Gramain, J.-C.; Teulade, J.-C.; Chapat, J.-P. *Tetrahedron* **1999**, *55*, 1959–1970.
49. Lachance, N.; April, M.; Joly, M.-A. *Synthesis* **2005**, 2571–2577.
50. Hong, C. S.; Seo, J. Y.; Yum, E. K.; Sung, N.-D. *Heterocycles* **2004**, *63*, 631–639.
51. Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2000**, *41*, 4777–4780.
52. Roy, P. J.; Dufresne, C.; Lachance, N.; Leclerc, J.-P.; Boisvert, M.; Wang, Z.; Leblanc, Y. *Synthesis* **2005**, 2751–2757.
53. Ujjainwalla, F.; Walsh, T. F. *Tetrahedron Lett.* **2001**, *42*, 6441–6445.
54. Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690.
55. Allegretti, M.; Anacardio, R.; Cesta, M. C.; Curti, R.; Mantovanini, M.; Nano, G.; Topai, A.; Zampella, G. *Org. Process Res. Dev.* **2003**, *7*, 209–213.
56. Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671–3674.
57. Thibault, C.; L'Heureux, A.; Bhide, R. S.; Ruel, R. *Org. Lett.* **2003**, *5*, 5023–5025.
58. L'Heureux, A.; Thibault, C.; Ruel, R. *Tetrahedron Lett.* **2004**, *45*, 2317–2319.
59. Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* **2001**, 609–612.
60. Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006**, *71*, 4021–4023.
61. Pearson, S. E.; Nandan, S. *Synthesis* **2005**, 2503–2506.
62. Mazéas, D.; Guillaumet, G.; Viaud, M.-C. *Heterocycles* **1999**, *50*, 1065–1080.
63. Cheung, M.; Hunter, R. N., III; Peel, M. R.; Lackey, K. E. *Heterocycles* **2001**, *55*, 1583–1590.
64. Guillard, J.; Larraya, C.; Viaud-Massuard, M.-C. *Heterocycles* **2003**, *60*, 865–877.
65. Larraya, C.; Guillard, J.; Renard, P.; Audinot, V.; Boutin, J. A.; Delagrange, P.; Bennejean, C.; Viaud-Massuard, M.-C. *Eur. J. Med. Chem.* **2004**, *39*, 515–526.
66. Thutewohl, M.; Schirok, H.; Bennabi, S.; Figueroa-Pérez, S. *Synthesis* **2006**, 629–632.
67. Figueroa-Pérez, S.; Bennabi, S.; Schirok, H.; Thutewohl, M. *Tetrahedron Lett.* **2006**, *47*, 2069–2072.
68. Hynes, J., Jr.; Doubleday, W. W.; Dyckman, A. J.; Godfrey, J. D., Jr.; Grosso, J. A.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368–1371.
69. Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 5614–5617.
70. Huck, J.; Duru, C.; Roumestant, M.-L.; Martinez, J. *Synthesis* **2003**, 2165–2168.
71. Rolland-Fulcrand, V.; Haroune, N.; Roumestant, M.-L.; Martinez, J. *Tetrahedron: Asymmetry* **2000**, *11*, 4719–4724.
72. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J.; Sebastião, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3317–3324.
73. Ahaidar, A.; Fernández, D.; Danelón, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Alvarez, M. *J. Org. Chem.* **2003**, *68*, 10020–10029.
74. Hénon, H.; Messaoudi, S.; Hugon, B.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 5599–5614.
75. Wang, K.; Stringfellow, S.; Dong, S.; Jiao, Y.; Yu, H. *Spectrochim. Acta, Part A* **2002**, *58*, 2595–2603.
76. Friedrichsen, G. M.; Chen, W.; Begtrup, M.; Lee, C.-P.; Smith, P. L.; Borchardt, R. T. *Eur. J. Pharm. Sci.* **2002**, *16*, 1–13.
77. Cai, Z.; Feng, J.; Guo, Y.; Li, P.; Shen, Z.; Chu, F.; Guo, Z. *Bioorg. Med. Chem.* **2006**, *14*, 866–874.
78. Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897–2900.
79. Mouaddib, A.; Joseph, B.; Hasnaoui, A.; Mérour, J.-Y. *Synthesis* **2000**, 549–556.
80. Joucla, L.; Putey, A.; Joseph, B. *Tetrahedron Lett.* **2005**, *46*, 8177–8179.
81. Alvarez, M.; Fernández, D.; Joule, J. A. *Synthesis* **1999**, 615–620.
82. Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29*, 359–367.
83. Doisy, X.; Dekhane, M.; Le Hyaric, M.; Rousseau, J.-F.; Singh, S. K.; Tan, S.; Guilleminot, V.; Schoemaker, H.; Sevrin, M.; George, P.; Potier, P.; Dodd, R. H. *Bioorg. Med. Chem.* **1999**, *7*, 921–932.
84. (a) Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1956**, *78*, 1247–1251; (b) Kruber, O. *Berichte der Deutschen Chemischen Gessellschaft* **1943**, *76B*, 128–143.
85. Cornia, M.; Casiraghi, G.; Zetta, L. *J. Org. Chem.* **1991**, *56*, 5466–5468.
86. Shadrina, L. P.; Dormidontov, Y. P.; Ponomarev, V. G.; Lapkin, I. I. *Khim. Geterotsikl. Soedin.* **1987**, *9*, 1206–1209.
87. Gálvez, C.; Viladoms, P. *J. Heterocycl. Chem.* **1982**, *19*, 665–667.
88. Zhang, Z.; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2002**, *67*, 6226–6227.
89. (a) Wang, T.; Zhang, Z.; Wallace, O. B.; Deshpande, M.; Fang, H.; Yang, Z.; Zadjura, L. M.; Tweedie, D. L.; Huang, S.; Zhao, F.; Ranadive, S.; Robinson, B. S.; Gong, Y.-F.; Ricarrdi, K.; Spicer, T. P.; Deminie, C.; Rose, R.; Wang, H.-G. H.; Blair, W. S.; Shi, P.-Y.; Lin, P.-F.; Colonno, R. J.; Meanwell, N. A. *J. Med. Chem.* **2003**, *46*, 4236–4239; (b) Wang, J.; Le, N.; Heredia, A.; Song, H.; Redfield, R.; Wang, L.-X. *Org. Biomol. Chem.* **2005**, *3*, 1781–1786.
90. (a) Jiang, B.; Yang, C.-G.; Xiong, W.-N.; Wang, J. *Bioorg. Med. Chem.* **2001**, *9*, 1149–1154; (b) Gompel, M.; Leost, M.; Bal De Kier Joffe, E.; Puricelli, L.; Hernandez Franco, L.; Palermo, J.; Meijer, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1703–1707.
91. Fresneda, P. M.; Molina, P.; Bleda, J. A. *Tetrahedron* **2001**, *57*, 2355–2363.
92. Karpov, A. S.; Merkul, E.; Rominger, F.; Muller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6951–6956.
93. Sawada, K.; Okada, S.; Kuroda, A.; Watanabe, S.; Sawada, Y.; Tanaka, H. *Chem. Pharm. Bull.* **2001**, *49*, 799–813.
94. Mantovanini, M.; Mellilo, G.; Daffonchio, L. Appl. Int. WO 9504742, 1995; *Chem. Abstr.* **1995**, *122*, 314537.
95. Eskola, O.; Bergman, J.; Lehikoinen, P.; Haaparanta, M.; Grönroos, T.; Forsback, S.; Solin, O. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 687–696.
96. Tian, H.-B.; Yin, D.; Zhang, C.; Zhang, L.; Wang, L.; Li, J.; Zhou, W.; Wang, Y.; Wu, C. *Zhongguo Yaolixue Tongbao* **2003**, *19*, 265–270; *Chem. Abstr.* **2004**, *141*, 343309.
97. Tian, H.-B.; Yin, D.-Z.; Zhang, L.; Wang, L.-H.; Zhang, C.-F.; Li, J.-L.; Zhou, W.; Wu, C.-Y.; Wang, Y.-X. *J. Radioanal. Nucl. Chem.* **2004**, *262*, 383–389.
98. Tian, H.-B.; Yin, D.-Z.; Li, J.-L.; Zhang, L.; Zhang, C.-F.; Wang, Y.-X.; Zhou, W. *Radiochim. Acta* **2003**, *91*, 241–245.
99. Oh, S.-J.; Lee, K. C.; Lee, S.-Y.; Ryu, E. K.; Saji, H.; Choe, Y. S.; Chi, D. Y.; Kim, S. E.; Lee, J.; Kim, B.-T. *Bioorg. Med. Chem.* **2004**, *12*, 5505–5513.

100. Deacon, G. B.; Junk, P. C.; Leary, S. G. *Adv. Synth. Catal.* **2003**, *345*, 1115–1117.
101. Giannini, G.; Marzi, M.; Moretti, G. P.; Penco, S.; Tinti, M. O.; Pesci, S.; Lazzaro, F.; De Angelis, F. *Eur. J. Org. Chem.* **2004**, *11*, 2411–2420.
102. Fonquerna, S.; Miralpeix, M.; Pagès, L.; Puig, C.; Cardús, A.; Antón, F.; Vilella, D.; Aparici, M.; Prieto, J.; Warrellow, G.; Beleta, J.; Ryder, H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1165–1167.
103. Mewshaw, R. E.; Meagher, K. L.; Zhou, P.; Zhou, D.; Shi, X.; Scerni, R.; Smith, D.; Schechter, L. E.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 307–310.
104. Alfonsi, M.; Arcadi, A.; Bianchi, G.; Marinelli, F.; Nardini, A. *Eur. J. Org. Chem.* **2006**, 2393–2402.
105. Wood, E. R.; Kuyper, L.; Petrov, K. G.; Hunter, R. N., III; Harris, P. A.; Lackey, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 953–957.
106. (a) Tatsugi, J.; Zhiwei, T.; Amano, T.; Izawa, Y. *Heterocycles* **2000**, *53*, 1145–1150; (b) Tatsugi, J.; Zhiwei, T.; Izawa, Y. *ARKIVOC* **2001**, *1*, 67–73.
107. (a) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987–3992; (b) Trimurtulu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993–4000.
108. Fernández, D.; Ahaidar, A.; Danelón, G.; Cironi, P.; Marfil, M.; Pérez, O.; Cuevas, C.; Albericio, F.; Joule, J. A.; Alvarez, M. *Monatsh. Chem.* **2004**, *135*, 615–627.
109. Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, *42*, 8697–8699.
110. Anderson, R. J.; Hill, J. B.; Morris, J. C. *J. Org. Chem.* **2005**, *70*, 6204–6212.
111. (a) Molina, P.; Fresneda, P. M.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2002**, *43*, 1005–1007; (b) Molina, P.; Fresneda, P. M.; Delgado, S. *J. Org. Chem.* **2003**, *68*, 489–499.
112. Ahaidar, A.; Fernández, D.; Pérez, O.; Danelón, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Álvarez, M. *Tetrahedron Lett.* **2003**, *44*, 6191–6194.
113. Alvarez, M.; Fernández, D.; Joule, J. A. *Tetrahedron Lett.* **2001**, *42*, 315–317.
114. Mendiola, J.; Baeza, A.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2004**, *69*, 4974–4983.
115. Mendiola, J.; Castellote, I.; Alvarez-Builla, J.; Fernández-Gadea, J.; Gómez, A.; Vaquero, J. J. *J. Org. Chem.* **2006**, *71*, 1254–1257.
116. Baeza, A.; Mendiola, J.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2005**, *70*, 4879–4882.
117. Fresneda, P. M.; Delgado, S.; Francesch, A.; Manzanares, I.; Cuevas, C.; Molina, P. *J. Med. Chem.* **2006**, *49*, 1217–1221.
118. Routier, S.; Coudert, G.; Mérour, J.-Y.; Caignard, D. H. *Tetrahedron Lett.* **2002**, *43*, 2561–2564.
119. Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621–6630.
120. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Joubert, A.; Bailly, C.; Renard, P.; Hickman, J.; Prudhomme, M. *J. Med. Chem.* **2003**, *46*, 609–622.
121. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 679–687.
122. Prudhomme, M. *Eur. J. Med. Chem.* **2003**, *38*, 123–140.
123. Messaoudi, S.; Anizon, F.; Léonce, S.; Pierré, A.; Pfeiffer, B.; Prudhomme, M. *Eur. J. Med. Chem.* **2005**, *40*, 961–971.
124. Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Golsteyn, R.; Prudhomme, M. *Tetrahedron Lett.* **2004**, *45*, 4643–4647.
125. Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 7304–7316.
126. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 4607–4611.
127. Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron Lett.* **2006**, *47*, 433–436.
128. Kuo, G.-H.; Prouty, C.; DeAngelis, A.; Shen, L.; O'Neill, D. J.; Shah, C.; Connolly, P. J.; Murray, W. V.; Conway, B. R.; Cheung, P.; Westover, L.; Xu, J. Z.; Look, R. A.; Demarest, K. T.; Emanuel, S.; Middleton, S. A.; Jolliffe, L.; Beavers, M. P.; Chen, X. *J. Med. Chem.* **2003**, *46*, 4021–4031.
129. Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Look, R. A.; Chen, X.; Beavers, M. P.; Roberts, J.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem.* **2004**, *12*, 1239–1255.
130. Zhang, H.-C.; Ye, H.; Conway, B. R.; Derian, C. K.; Addo, M. F.; Kuo, G.-H.; Hecker, L. R.; Croll, D. R.; Li, J.; Westover, L.; Xu, J. Z.; Look, R.; Demarest, K. T.; Andrade-Gordon, P.; Damiano, B. P.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3245–3250.
131. O'Neill, D. J.; Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Zhang, H.-C.; Maryanoff, B. E.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem.* **2004**, *12*, 3167–3185.
132. Allen, J. R.; Amegadzie, A. K.; Gardinier, K. M.; Gregory, G. S.; Hitchcock, S. A.; Hoogestraat, P. J.; Jones, W. D., Jr.; Smith, D. L. Appl. Int. WO 066126, 2005; *Chem. Abstr.* **2005**, *143*, 133274.
133. Bennabi, S.; Heckroth, H.; Schirok, H.; Mittendorf, J.; Kast, R.; Stasch, J.-P.; Gnoth, M. J.; Muenter, K.; Lang, D.; Perez, S. F.; Bauser, M.; Feurer, A.; Ehmke, H. Appl. Int. WO 058891, 2005; *Chem. Abstr.* **2005**, *143*, 97339.
134. Dillon, M. P.; Lin, C. J. J.; Moore, A. G.; O'Yang, C.; Zhai, Y. U.S. Patent Appl. 224,973, 2004; *Chem. Abstr.* **2004**, *141*, 410926.
135. Graczyk, P.; Khan, A.; Bhatia, G.; Iimura, Y. Appl. Int. WO 078756, 2004; *Chem. Abstr.* **2004**, *141*, 277498.
136. Medland, D. P.; Graczyk, P. P.; Bhatia, G. S. Appl. Int. WO 085244, 2005; *Chem. Abstr.* **2005**, *143*, 306184.
137. Aronov, A.; Lauffer, D. J.; Li, P.; Tomlinson, R. C. Appl. Int. WO 028475, 2005; *Chem. Abstr.* **2005**, *142*, 355158.
138. Jiang, J. Z.; Koehl, J. R.; Mehdi, S.; Moorcroft, N. D.; Musick, K. Y.; Weintraub, P. M.; Eastwood, P. R. U.S. Patent 0,54,631, 2005; *Chem. Abstr.* **2005**, *142*, 297989.
139. Beswick, P.; Gleave, R.; Swarbrick, M. Appl. Int. WO 016924, 2005; *Chem. Abstr.* **2005**, *142*, 261524.
140. Salituro, F.; Farmer, L.; Bethiel, R.; Harrington, E.; Green, J.; Court, J.; Come, J.; Lauffer, D.; Aronov, A.; Binch, H.; Boyall, D.; Charrier, J.-D.; Everitt, S.; Fraysse, D.; Mortimore, M.; Pierard, F.; Robinson, D. Appl. Int. WO 095400, 2005; *Chem. Abstr.* **2005**, *143*, 387011.
141. Koenig, M.; Cui, J.; Wei, C. C.; Do, S. H.; Zhang, F.-J.; Vojkovsky, T.; Ramphal, J.; Yang, G.; Mattson, M.; Nelson, C.; Tang, P. C. Appl. Int. WO 005378, 2005; *Chem. Abstr.* **2005**, *142*, 155814.
142. Arnold, J.; Artis, D. R.; Hurt, C.; Ibrahim, P. N.; Krupka, H.; Lin, J.; Milburn, M. V.; Wang, W.; Zhang, C. Appl. Int. WO 009958, 2005; *Chem. Abstr* **2005**, *142*, 197873.

143. Bloxham, J.; Crew, A. P.; Honda, A.; Li, A.-H.; Panicker, B.; Tardibono, L.; Wynne, G. M. U.S. Patent 154,014, 2005; *Chem. Abstr.* **2005**, *143*, 133292.
144. Oikawa, N.; Mizuguchi, E.; Morikami, K.; Shimma, N.; Ishii, N.; Tsukaguchi, T.; Ozawa, S. Appl. Int. WO 080330, 2005; *Chem. Abstr.* **2005**, *143*, 266944.
145. Bright, G. M.; Coffman, K. J. Appl. Int. WO 067703, 2004; *Chem. Abstr.* **2004**, *141*, 174192.
146. Bernotas, R. C.; Lenicek, S. E.; Elokdah, H. M.; Li, D. Z. Appl. Int. WO 009600, 2004; *Chem. Abstr.* **2004**, *140*, 146118.
147. Carry, J. C.; Mignani, S.; Evers, M.; Doerflinger, G.; Genevois, B. A.; Le Brun, A.; Martin, J. P.; Desmazeau, P.; Kleemann, H. W. French Patent Appl. FR 2856062, 2004; *Chem. Abstr.* **2004**, *142*, 56277.
148. Graczyk, P.; Numata, H.; Bhatia, G.; Medland, D. P. Appl. Int. WO 082869, 2003; *Chem. Abstr.* **2003**, *139*, 307750.
149. Graczyk, P.; Numata, H.; Khan, A.; Palmer, V. Appl. Int. WO 082868, 2003; *Chem. Abstr* **2003**, *139*, 307749.
150. (a) Smith, N. D.; Cosford, N. D. P.; Reger, T. R.; Roppe, J. R.; Poon, S. F.; Huang, D.; Chen, C.; Eastman, B. W. Int. Appl. WO 077918, 2003; *Chem. Abstr.* **2003**, *139*, 276903; (b) Huang, D.; Poon, S. F.; Chapman, D. F.; Chung, J.; Cramer, M.; Reger, T. S.; Roppe, J. R.; Tehrani, L.; Cosford, N. D. P.; Smith, N. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5473–5476.
151. Ibrahim, P. N.; Hurt, C. R.; Zhang, C.; Zhang, J. Appl. Int. WO 009797, 2006; *Chem. Abstr* **2006**, *144*, 170974.
152. Joseph, B.; Meijer, L.; Liger, F. French Patent Appl. FR 2876377, 2006; *Chem. Abstr.* **2006**, *144*, 390900.

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 of 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 Professsor 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.

Sylvain Routier was born in Montreuil sur Mer (France) in 1969. He achieved his Ph.D. under the supervision of Professors J. L. Bernier and J. P. Catteau in 1996. His research work was dedicated to the design of new anticancer agents. After a post-doctoral position of 1 year in medicinal chemistry research for UCB Pharma SA (Belgium), he joined the groups of Professor G. Guillaumet and Professor J.-Y. Merour at the Institut de Chimie Organique et Analytique atin the Université d'Orléans (France) as an assistant professor in 1998. Since his research areas focus on the development of new tools in heterocyclic chemistry and their application in medicinal chemistry.

Benoît Joseph was born in Vendôme (France) in 1965. He completed his Ph.D. under the supervision of Professor P. Rollin at the Université d'Orléans in the fields of carbohydrate chemistry and thiochemistry. In 1994, he joined the group of Professor J. B. Bremner at the University of Wollongong (Australia) as a post-doctoral fellow to work on the design of new α-adrenergic antagonists. At the end of 1994, he became assistant professor at the Université d'Orléans and worked on nitrogen heterocyclic chemistry at the Institut de Chimie Organique et Analytique under the supervision of Professors J.-Y. Mérour and G. Guillaumet. In 2000, he received his habilitation and was promoted to full professor in 2001 at the Université Claude Bernard, Lyon 1. His current main research interests are the design of heterocyclic scaffolds through palladium-catalyzed reactions and the synthesis of bioactive molecules.

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.