

Synthesis and activities of tricyclic pyrido[3,4-*g*]quinazolines, pyrazolo[3,4-*g*]quinoxalines and pyrroloindazole regioisomers

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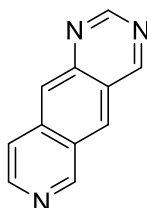
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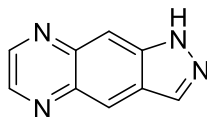
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Abstract

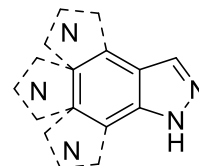
Heteroaromatics constitute an important class of organic compounds with wide-ranging applications. This account, including patent literature, describes reported synthetic methods leading to tricyclic nitrogen-containing heterocyclic systems (pyrido[3,4-*g*]quinazolines, pyrazolo[3,4-*g*]quinoxalines and pyrroloindazoles) which are found in many biologically active compounds.



Pyrido[3,4-*g*]quinazolines



Pyrazolo[3,4-*g*]quinoxalines



Pyrroloindazole regioisomers

Keywords: Nitrogen-containing heterocyclic systems, pyrido[3,4-*g*]quinazolines, pyrazolo[3,4-*g*]quinoxalines; pyrroloindazoles

Table of Contents

1. Introduction
 2. Synthesis and Biological Activities of Pyrido[3,4-*g*]quinazolines
 3. Synthesis and Biological Activities of Pyrazolo[3,4-*g*]quinoxalines
 4. Synthesis and Biological Activities of Pyrroloindazole Regioisomers
 - 4.1. Pyrrolo[2,3-*e*]indazoles
 - 4.2. Pyrrolo[3,2-*e*]indazoles
 - 4.3. Pyrrolo[3,2-*f*]indazoles
 - 4.4. Pyrrolo[2,3-*g*]indazoles
 - 4.5. Pyrrolo[3,4-*g*]indazoles
 - 4.6. Pyrrolo[3,2-*g*]indazoles
 5. Conclusions
- References

1. Introduction

Heteroaromatics containing systems such as indole, indazole or pyrazole constitute a large family of organic compounds with a wide range of applications in biology¹⁻⁴ as active ingredients or molecular probes due to their biological and physicochemical properties. Some heteroaromatic derivatives are also of high interest due to their application in organic optoelectronic materials.⁵ Therefore, the development of new synthetic methodologies allowing access to these classes of compounds has given rise to numerous studies.⁶ As part of our work aiming at identifying new biologically active skeletons, we are particularly interested in the design and synthesis of novel structural series with protein kinase inhibitory potencies.

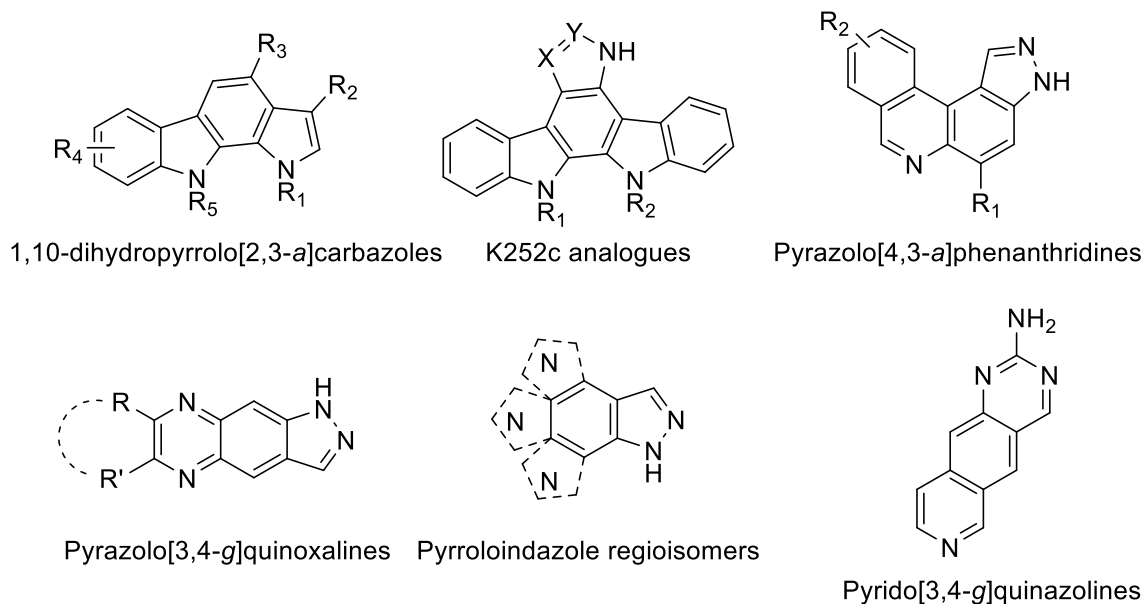


Figure 1. Nitrogen-containing heteroaromatic scaffolds found in protein kinase inhibitors developed by our group.

The scaffolds presented Figure 1 are found in potent protein kinase inhibitors (targeting Pim kinases, except for the pyrido[3,4-*g*]quinazoline series which exhibited activities toward DYRK1A/CLK1). Synthesis and properties of various series such as dihydropyrrolocarbazoles⁴ and indolocarbazoles⁷ have already been reviewed while very few examples of pyrazolo[4,3-*a*]phenanthridines can be found in the literature. Therefore, due to our interest in these tricyclic systems we decided to focus this account on pyrido[3,4-*g*]quinazolines, pyrazolo[3,4-*g*]quinoxalines and pyrroloindazole regioisomers (Figure 2). To the best of our knowledge, none of these fully aromatic systems has been reported so far, the majority of syntheses concerning dihydropyrroloindazole derivatives. Moreover, the synthesis of some series was never or rarely reported, such as pyrrolo[3,4-*e*]-, pyrrolo[2,3-*f*]- and pyrrolo[3,4-*f*]indazoles.

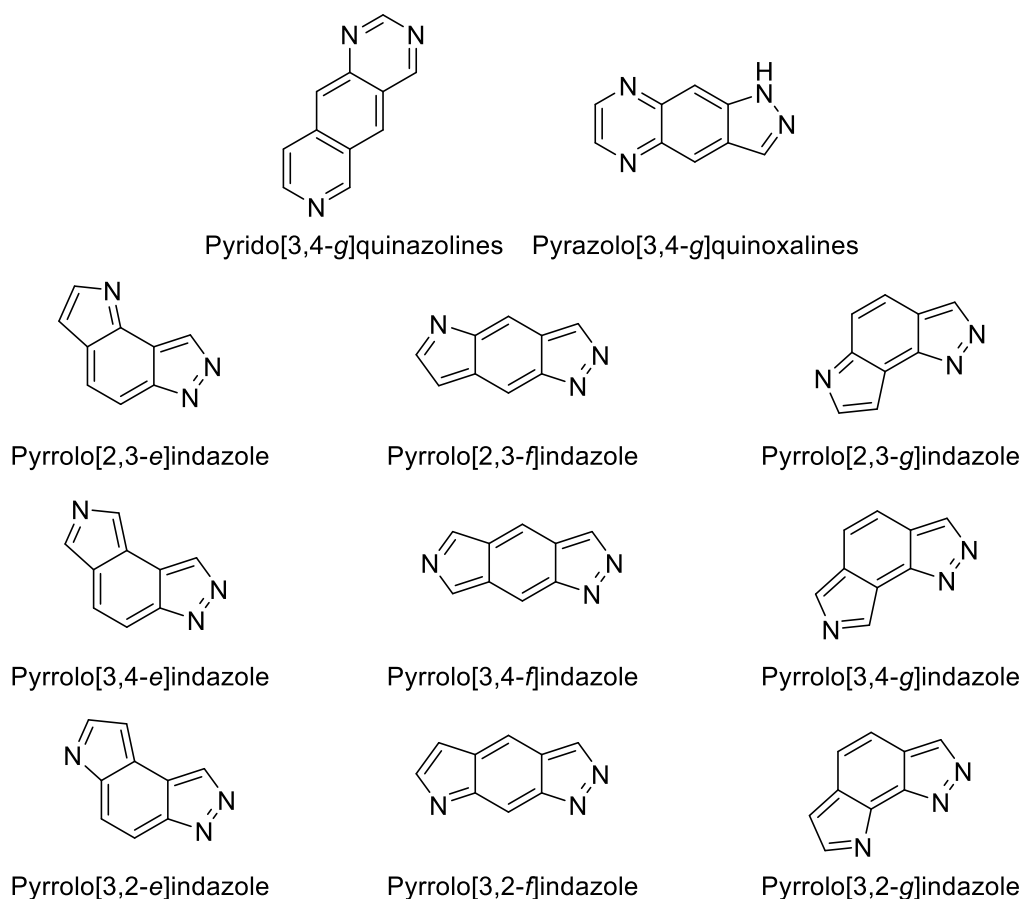
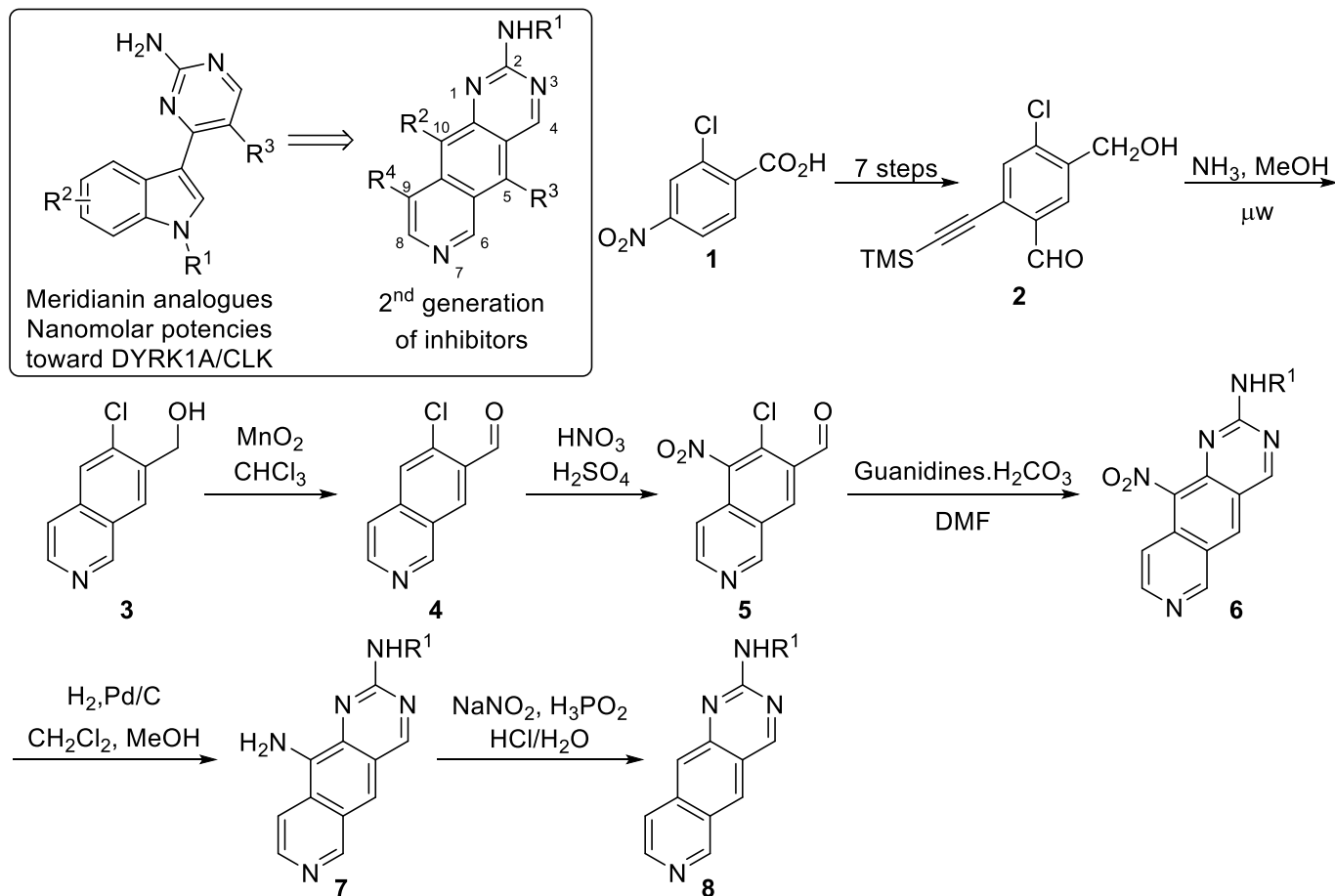


Figure 2. Structure of pyrido[3,4-*g*]quinazolines, pyrazolo[3,4-*g*]quinoxalines and regioisomeric series of pyrroloindazoles.

2. Synthesis and biological activities of pyrido[3,4-*g*]quinazolines

The pyrido[3,4-*g*]quinazoline scaffold was designed in our group on the basis of a structure-activity relationship study performed around meridianins, marine alkaloids isolated from the ascidian *Aplidium meridianum*, possessing an indole moiety substituted in the 3-position by a 2-aminopyrimidine ring. The best activities were found for CLK1 and DYRK1A kinases where nanomolar potencies were encountered. After molecular modelling studies, the design of a second generation of inhibitors ended up with this new pyridoquinazoline series (Scheme 1).⁸

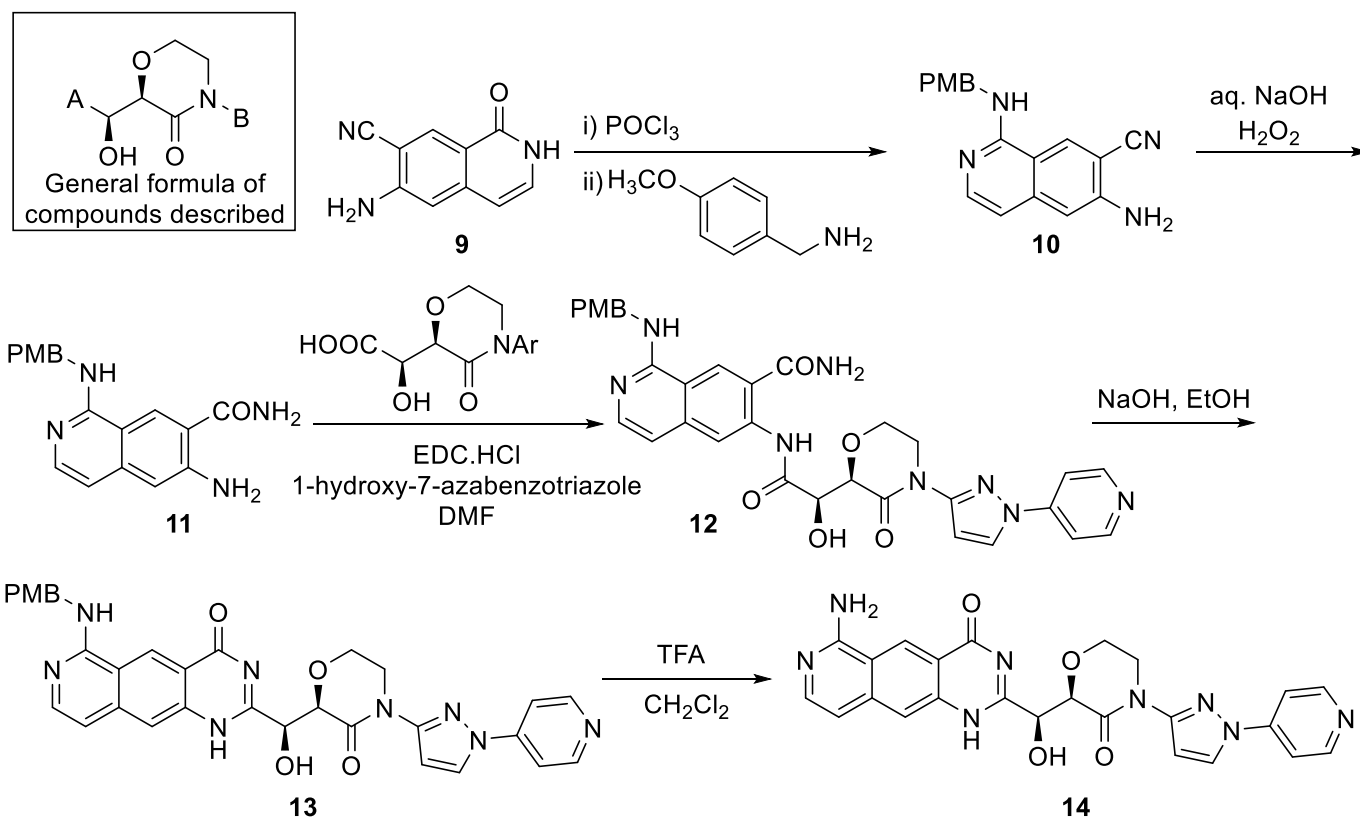


Scheme 1. Design and synthesis of pyrido[3,4-g]quinazolines.⁸⁻¹⁰

The synthesis of this pyridoquinazoline scaffold was achieved *via* intermediate **2**, a tetrasubstituted benzene derivative obtained in seven steps from benzoic acid derivative **1** using trivial aromatic chemistry (Scheme 1). The upper substituents are necessary to establish the aminopyrimidine moiety and the lowers to form the pyridine part. The isoquinoline ring system was first formed under microwave irradiation in the presence of ammonia in methanol. Next, oxidation of **3** using MnO_2 led to the isoquinoline **4**. Then, the regioselective introduction of a nitro group at the ortho position to the chlorine atom was necessary to ensure a suitable reactivity of the system, with respect to amidine or guanidinium salts, in order to obtain the tricyclic system **6**. Catalytic hydrogenation of **6** led to the corresponding amino derivatives. The amino group could be removed from **7** ($\text{R}^1 = \text{H}$) after diazotation/reduction.⁸⁻¹⁰ The reaction of compound **6** ($\text{R}^1 = \text{H}$) with organolithium or Grignard reagents allowed the introduction of alkyl/aryl substituents at the 5-position (R^3) while electrophilic aromatic substitution led to the functionalization of the 9-position ($\text{R}^4 = \text{Br}$).¹¹ All compounds were evaluated towards CDK5/p25, CK1 δ/ϵ , GSK-3 α/β , DYRK1A and CLK1. Nanomolar activities were observed toward DYRK1A/CLK1. Nitro derivatives were generally more active towards CLK1 in comparison to DYRK1A whereas amino analogues could exert potent activities towards both CLK1 and DYRK1A or, in some cases were more active towards DYRK1A. Therefore, this series affords interesting research tools to study DYRK1A/CLK1 protein kinases.

An example of a related compound (**14**, Scheme 2) is reported in a patent dealing with the identification of factor IXa inhibitors.¹² In this case, the formation of the pyridoquinazoline derivative scaffold (compound **13**)

was achieved by cyclization under basic conditions of the corresponding 6-acylamino-7-carboxamidoquinazoline **12** prepared in 3 steps from 6-amino-7-cyano-2*H*-isoquinoline-1-one **9**.

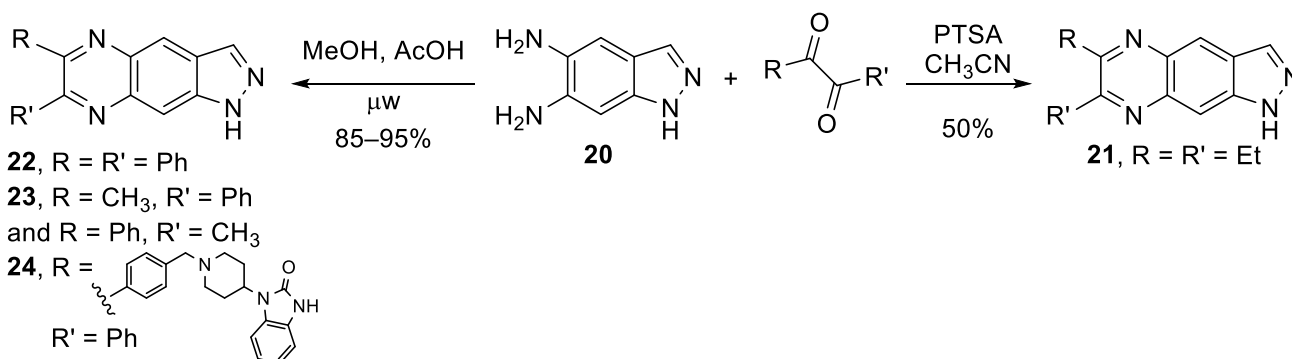
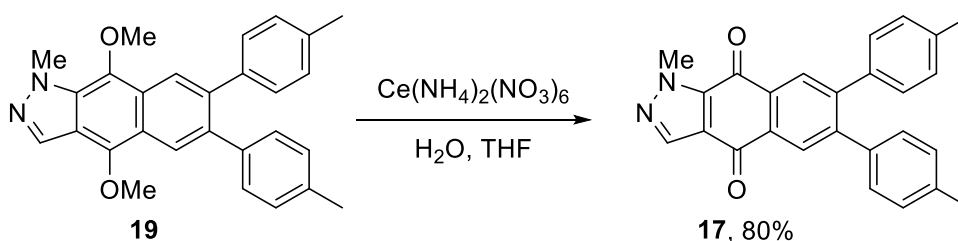
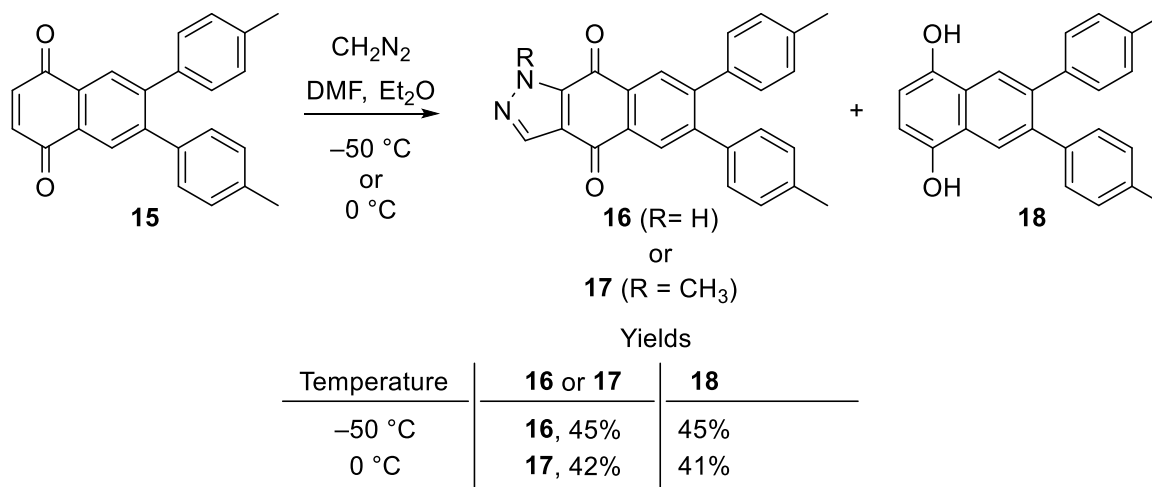


Scheme 2. Structure and synthesis of factor IXa inhibitors containing a pyridoquinazoline moiety.¹²

3. Synthesis and biological activities of pyrazolo[3,4-*g*]quinoxalines

Pyrazolo[3,4-*g*]quinoxaline is another scaffold that has attracted great interest for its biological potential. Compounds **16** or its methylated analogue **17** were prepared at $-50\text{ }^{\circ}\text{C}$ or $0\text{ }^{\circ}\text{C}$, respectively, in moderate yields by dipolar cycloaddition reactions using quinoxalinequinone **15** and diazomethane (Scheme 3).¹³ **17** was also prepared from the corresponding methoxy analogue **19** using ceric ammonium nitrate (Scheme 3).¹⁴

As part of our work aiming at the identification of Pim kinase inhibitors, we prepared diversely substituted tetra- and tricyclic analogues.^{15,16} These compounds (*e.g.* **21**) were obtained in moderate yields by reacting 1*H*-indazole-5,6-diamine **20** and suitable 1,2-dicarbonyl compounds (Scheme 3).¹⁶



Scheme 3. Synthesis of tricyclic pyrazolo[3,4-g]quinoxalines **16,17**,^{13,14} **21**¹⁶ and **22–24**.^{17,18}

High yielding access to diversely substituted analogues (**22–24**) was described by Linsley's group using microwave irradiation. Compound **24** was reported as a submicromolar allosteric inhibitor of Akt (protein kinase B/PKB) (Scheme 3).^{17,18} Related compounds (general formula, Figure 3), similarly prepared from **20** and diversely substituted 1,2-dicarbonyls were also pointed out by the same group in patents presenting the use of Akt inhibitors in cancer therapy alone or in combination with inhibitor(s) of other protein kinase(s).^{19–21}

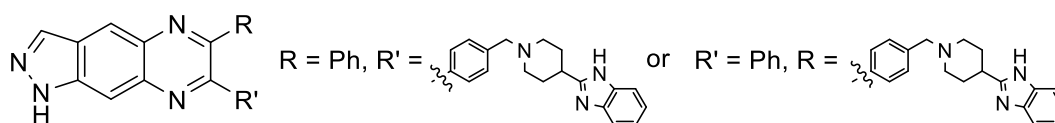
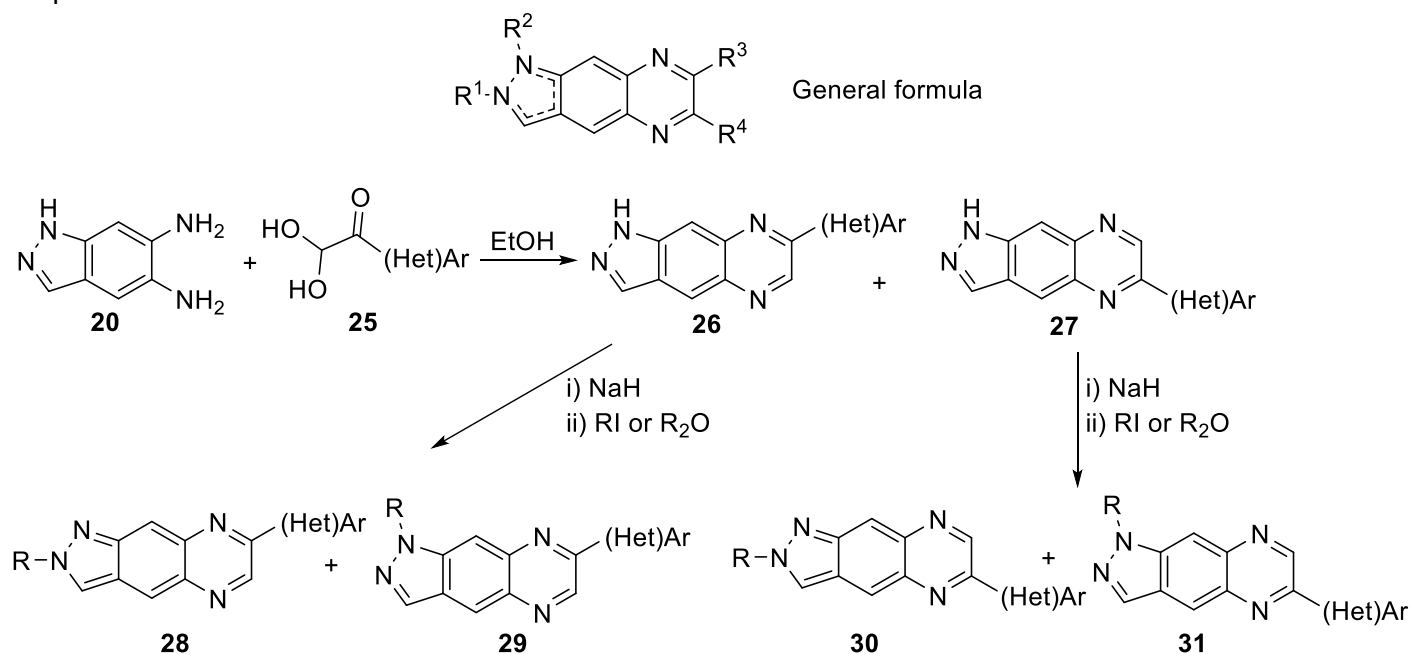


Figure 3. Examples of Akt inhibitors reported in patents.^{19–21}

Other pyrazolo[3,4-*g*]quinoxalines were also synthesized similarly by reacting 5,6-diaminoindazole **20** and glyoxylyl(Het)Ar **25**. Pairs of separable regioisomers were obtained in all steps (compounds **26–31**, Scheme 4). Evaluation of their PDGFR-inhibitory potency demonstrated nanomolar activities for the most active compounds.²²

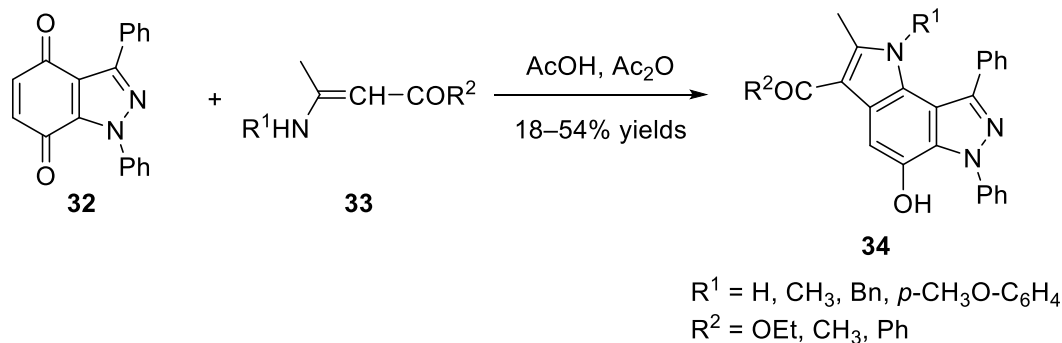


Scheme 4. General formula and synthesis of pyrazolo[3,4-*g*]quinoxalines with potential PDGFR-inhibitory potency **26–31**.²²

4. Synthesis and biological activities of pyrroloindazole regioisomers

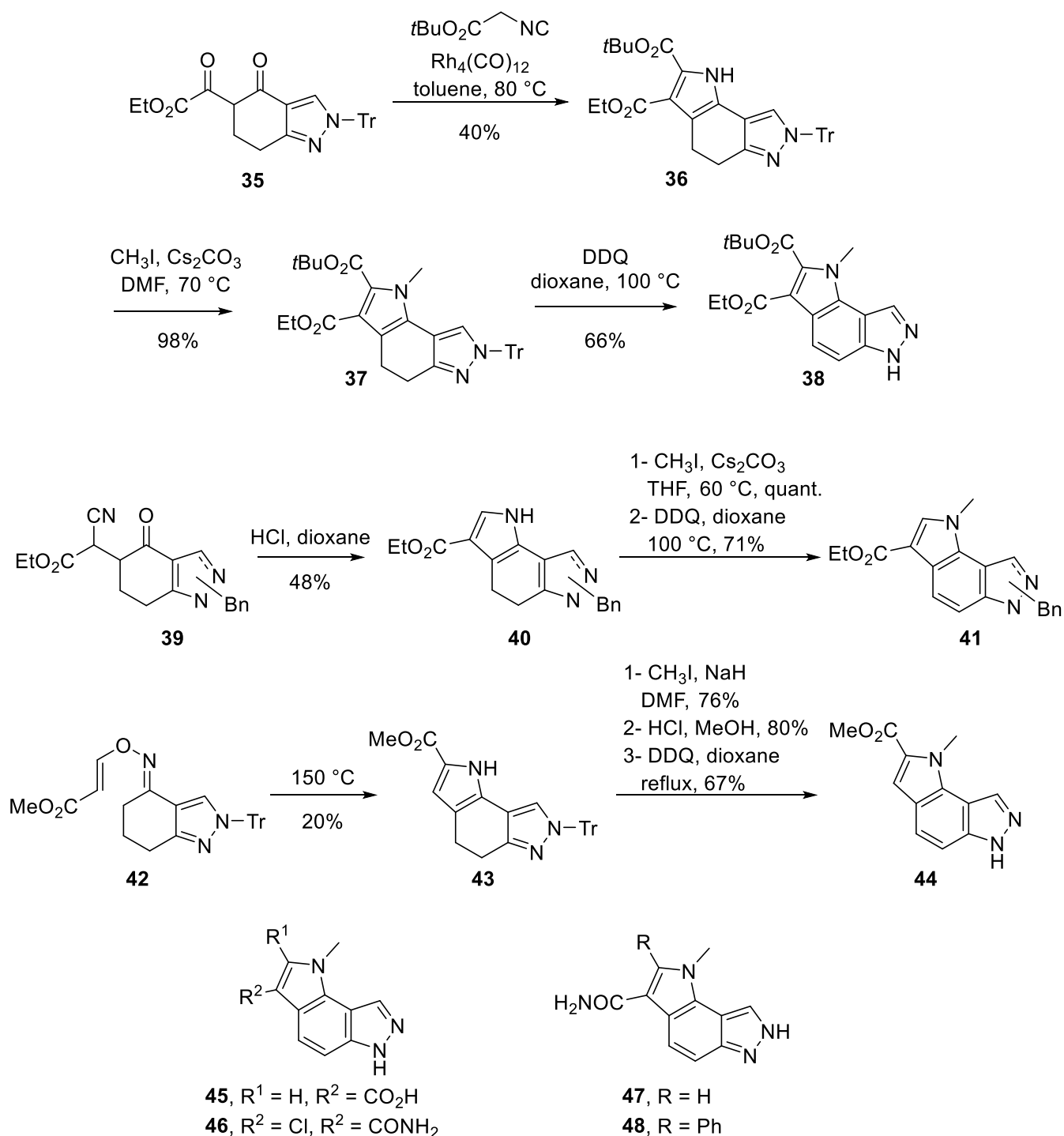
4.1. Pyrrolo[2,3-*e*]indazoles

In 2000, V. M. Lyubchanskaya *et al.* reported the synthesis of 1,4-dihydropyrrolo[2,3-*e*]indazoles *via* a Nenitzescu indole synthesis from quinone derivatives **32** and enamines **33** (Scheme 5).²³ Cyclization to the corresponding furo[2,3-*e*]indazoles was also observed, but was reduced when enamino esters (**33**, R² = OEt) substituted at the nitrogen atom with a methyl or a benzyl group (R¹ = CH₃ or Bn) were used.



Scheme 5. Nenitzescu indole synthesis applied to the preparation of compounds **34**.²³

Pyrrole ring formation from indazole derivatives was also the strategy adopted by Nerviano Medical Sciences to obtain the pyrrolo[2,3-*e*]indazole scaffold.²⁴ In their PCT patent application, three different processes were reported, starting from 4-oxo-4,5,6,7-tetrahydroindazoles (Scheme 6). For example, from

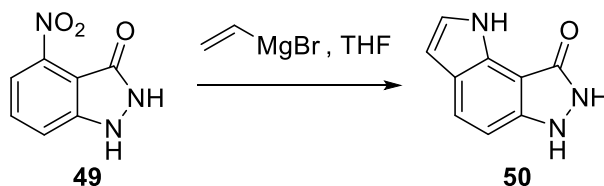


Scheme 6. Synthesis of dihydropyrrolo[2,3-*e*]indazoles from 4-oxo-4,5,6,7-tetrahydroindazole derivatives.²⁴

compound **35**, a cyclocondensation using low-valent rhodium and *tert*-butyl isocyanoacetate²⁵ was performed before alkylation of the pyrrole nitrogen, aromatization and indazole deprotection. In another process, ketonitrile **39** (mixture of *N*-benzylated regioisomers) was cyclized under acidic conditions to give

tetrahydropyrroloindazole **40**. Finally, a third process described the rearrangement and cyclization of *O*-vinyloxime **42** to produce **43**. Nevertheless, these selected examples afforded tetrahydropyrrolo[2,3-*e*]indazoles in low to modest yields. However, some interesting biological activities were found towards protein kinase Cdc7/Dbf4 with IC₅₀ values lower than 100 nM for compounds **45–48**.

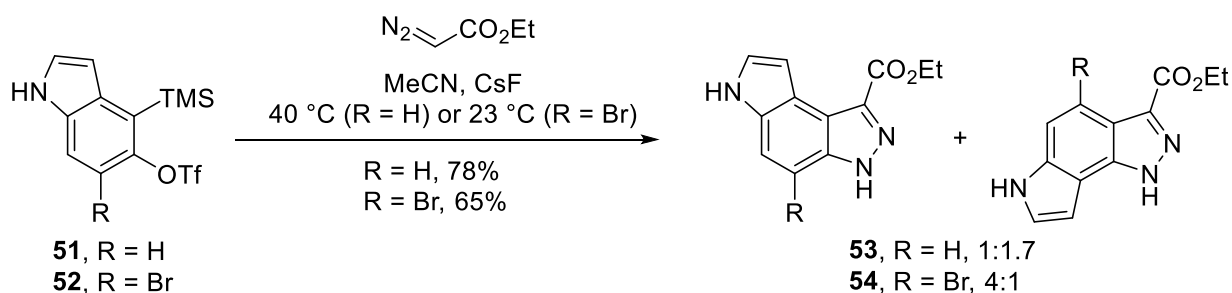
Finally, a recent patent application showed that the pyrroloindazolone scaffold can be obtained *via* Bartoli indole synthesis from 4-nitroindazolone **49**. Compound **50** is expected to be developed as a drug to treat atherosclerosis.²⁶



Scheme 7. Synthesis of pyrrolo[2,3-*e*]indazole-3-one **50**.²⁶

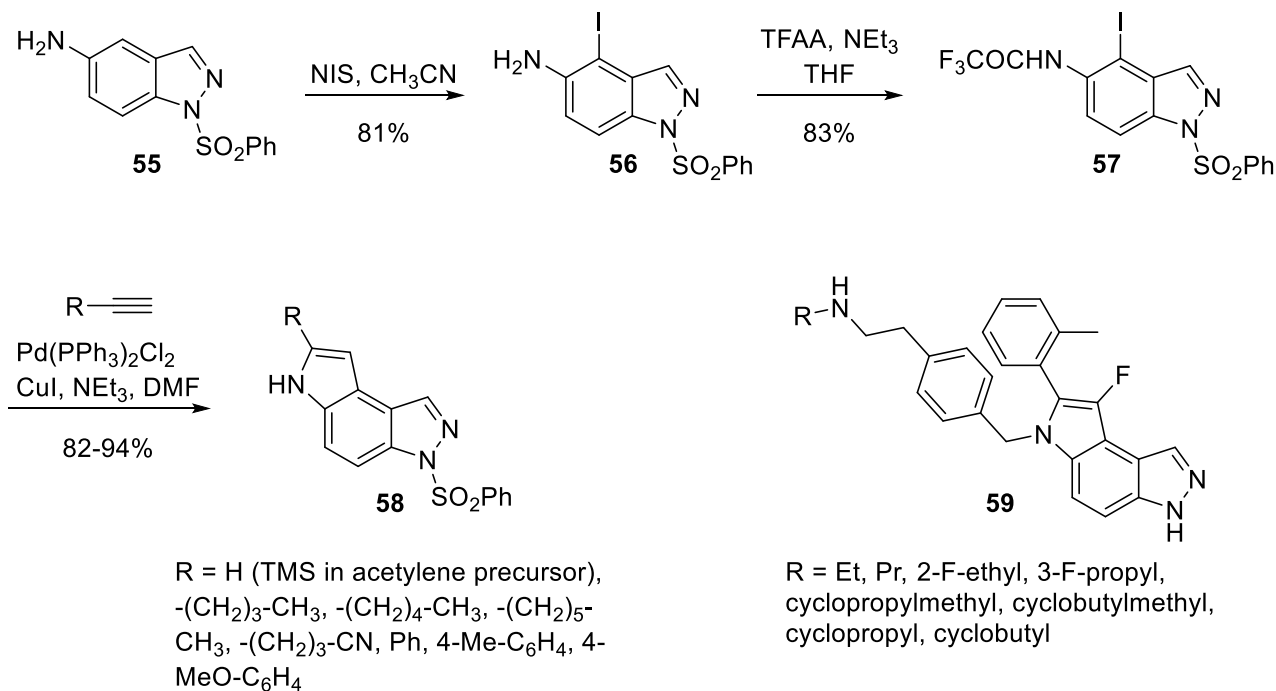
4.2. Pyrrolo[3,2-*e*]indazoles

The regioisomeric 1,6-dihydropyrrolo[3,2-*e*]indazole synthesis has been reported by S. M. Bronner starting from the indolynes generated from indole derivatives **51** and **52** (Scheme 8).²⁷ These reactive intermediates were trapped with ethyl diazoacetate to give the [3,2-*e*]- and the [2,3-*g*]-regioisomers in varying proportion depending on the substitution at the 6-position of the starting indole derivative. The 1,6-dihydropyrrolo[3,2-*e*]indazole was favored in the case of a bromine substitution, and this preference was reversed in the case of R = H.



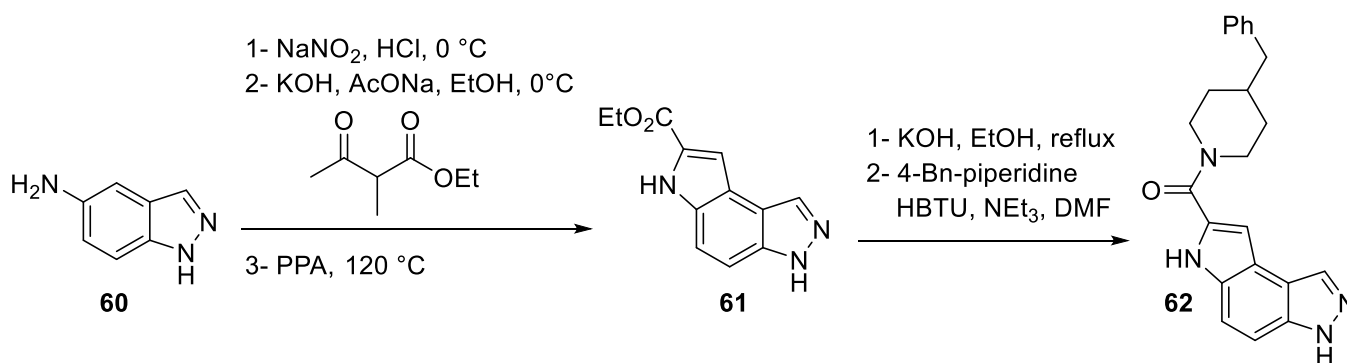
Scheme 8. Indolyne trapping with ethyldiazoacetate leading to **53** or **54**.²⁷

Another strategy was reported in 2014 by M. Chakrabarty and collaborators,²⁸ starting from 5-aminoindazole **55**, which was iodinated/acylated to give **57**. Using a Sonogashira/Cacchi procedure from **57** involving consecutive palladium-catalyzed Sonogashira coupling, aminopalladation and reductive elimination, the 1,6-dihydropyrrolo[3,2-*e*]indazoles **58** were obtained in good yields (Scheme 9). Contrarily to the preceding example, the regioselectivity of the reaction was controlled by the appropriate functionalization at the 4- and 5-positions of compound **57**. This strategy appeared recently in a PCT patent application of Radius Pharmaceuticals, focused on the preparation of substituted indoles as estrogen receptor-modulating compounds.²⁹ Compounds **59** were reported (Scheme 9), showing high activity towards the MCF7 cell line, with IC₅₀ values lower than 1 nM in proliferation inhibition assays in the presence of estradiol at a concentration of 10 pM.



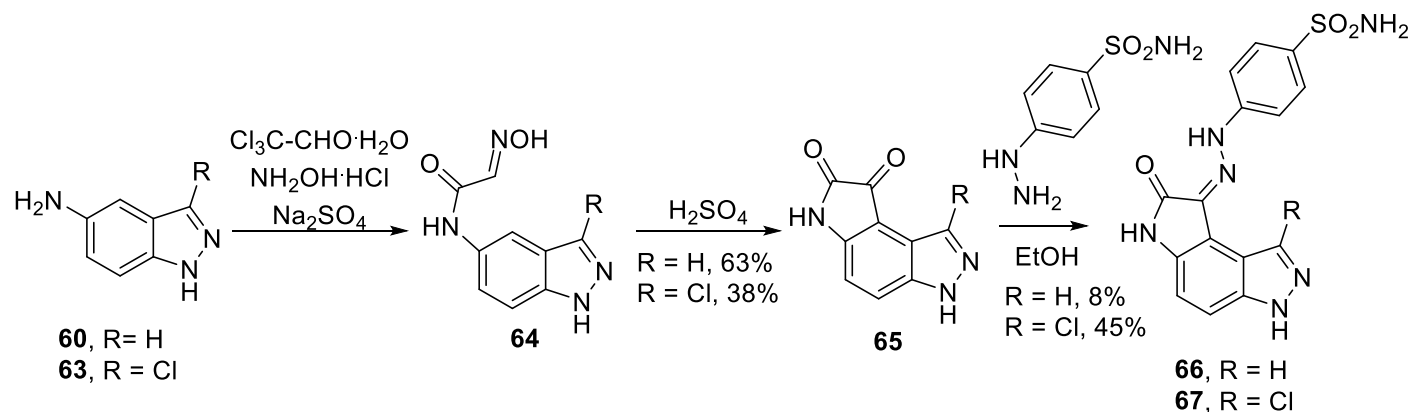
Scheme 9. Preparation of 1,6-dihydropyrrolo[3,2-*e*]indazoles **58** via a Sonogashira/Cacchi procedure.²⁹ Structure of compounds **59**.

Fischer indolization is another reaction that could be used for the preparation of 1,6-dihydropyrrolo[3,2-*e*]indazole. Starting from 5-aminoindazole **60**, I. Borza *et al.* reported the preparation of **61**, as well as of its [2,3-*g*]-isomer from 6-aminoindazole.³⁰ An hydrazone was first produced from **60** using the Japp-Klingemann procedure, and indolization in PPA led to compound **61** (Scheme 10). Compound **62** inhibited *N*-methyl-D-aspartate (NMDA)-evoked elevation of cytoplasmic calcium concentration in primary rat neocortical cell cultures (IC₅₀ = 20 nM) and was active in an NR2B-selective binding assay (IC₅₀ = 5 nM).



Scheme 10. Japp-Klingemann /Fischer strategy for the preparation of 1,6-dihydropyrrolo[3,2-*e*]indazole **61**.³⁰

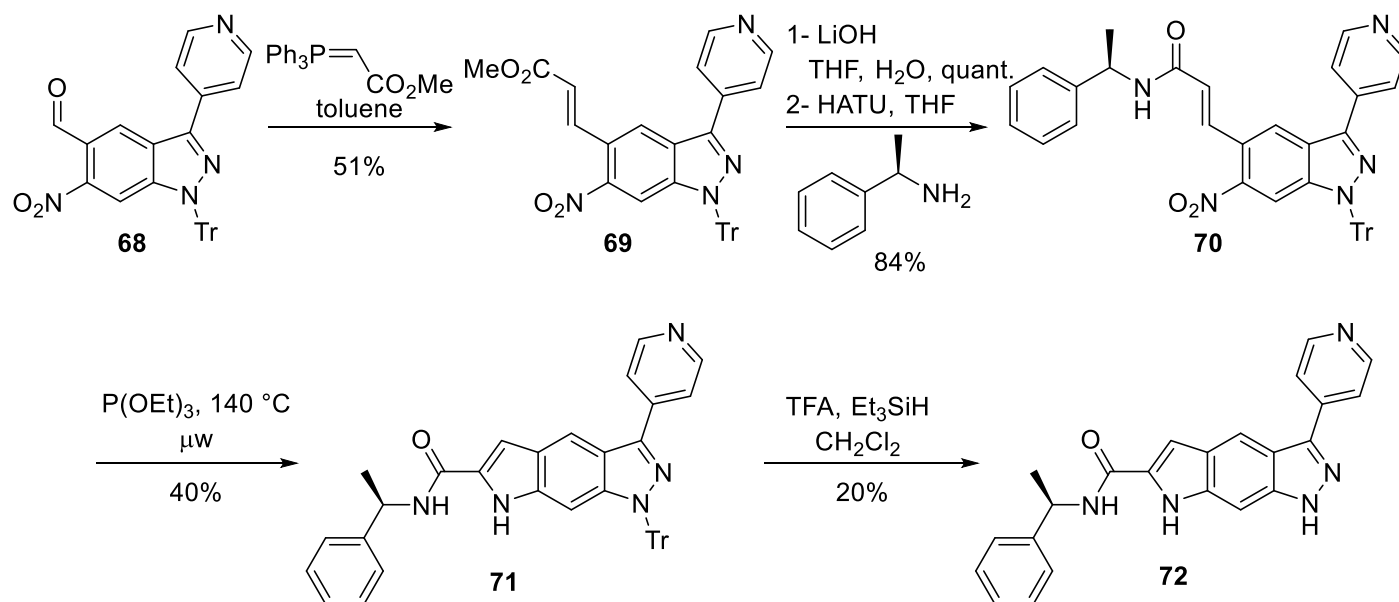
Isatine derivatives fused to a pyrazole system have also been reported (Scheme 11).^{31,32} The pyrrole ring was formed from 5-aminoindazoles **60** or **63** using chloral hydrate and hydroxylamine to give oxime **64** that can be cyclized under acidic treatment to give **65**. Compounds **66** and **67** are CDK1 and CDK2 inhibitors. In particular, **67** inhibited CDK2/cyclinA with an IC₅₀ of 2.2 nM.³²



Scheme 11. Preparation of isatine derivatives **65–67**.^{31,32}

4.3. Pyrrolo[3,2-*f*]indazoles

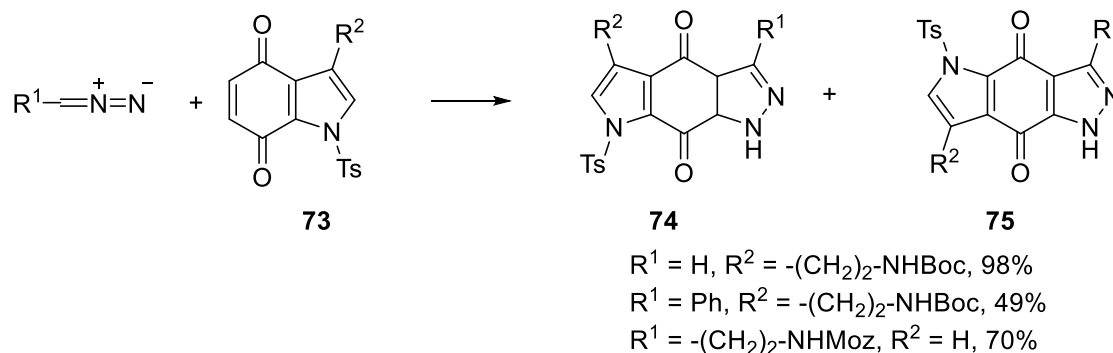
The preparation of pyrrolo[3,2-*f*]indazoles has been recently reported in a patent application by Jiangsu Hansoh Pharmaceutical group and the Shanghai Hansoh Biomedical company, relative to the preparation of pyrazolyl-containing tricyclic derivatives and their application as anticancer agents.³³ A selected example is presented in Scheme 12. The pyrroloindazole scaffold was constructed by Cadogan-Sundberg cyclization of compound **70**, promoted by triethyl phosphite, with a yield of 40%. Compound **72** showed high protein kinase inhibitory potency of ERK-1 and ERK-2 ($IC_{50} = 0.29$ and 0.17 nM, respectively), antiproliferative activity towards human pancreatic MiaPaCa-2 cells ($IC_{50} = 122.9$ nM), and it inhibited the growth of MiaPaCa-2 xenografts in nude mice.



Scheme 12. Synthesis of pyrrolo[3,2-*f*]indazole **71** via a Cadogan-Sundberg indole synthesis.³³

The synthesis of quinonic derivatives of the pyrrolo[3,2-*f*]indazole scaffold has also been reported by E. Delfourne and collaborators, in a work dedicated to the synthesis of pyrazolic analogues of the marine alkaloids Wakayin and Tsitsikammamines.^{34,35} Selected examples are presented Scheme 13. The [3 + 2]

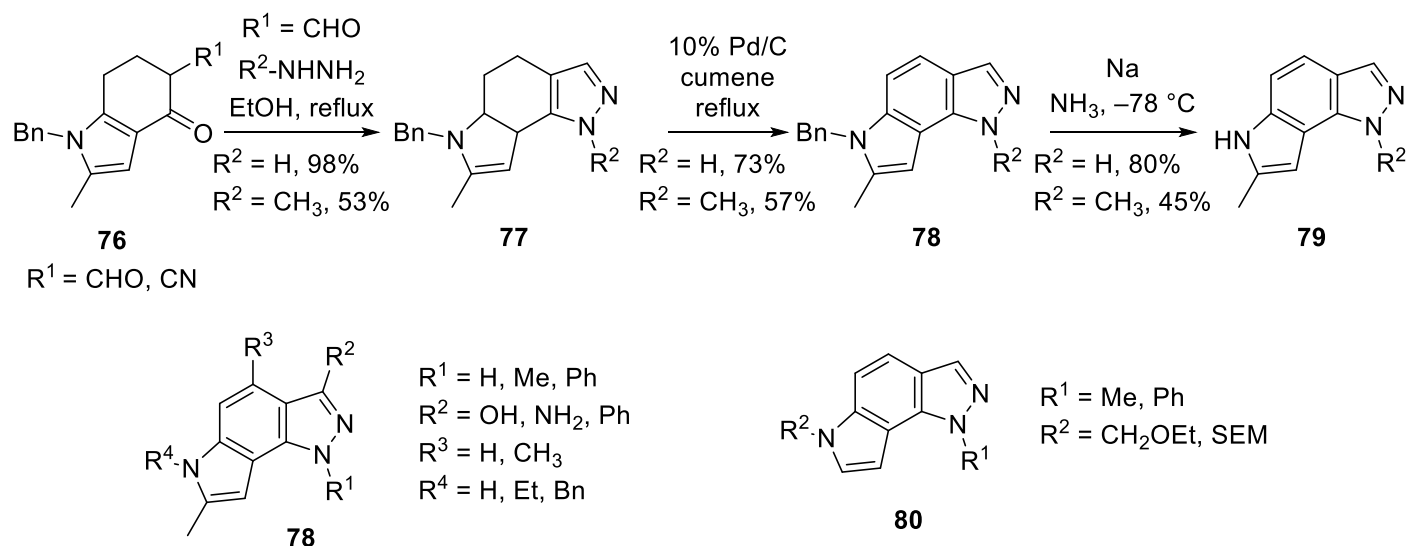
cycloaddition of quinone **73** with diazomethane or diazomethane derivatives led to the pyrrolo[3,2-*f*]indazole **74** in mixture with its pyrrolo[2,3-*f*]indazole regioisomer **75**.



Scheme 13. Cycloaddition of quinone **73** with diazomethane or diazomethane derivatives.^{34,35}

4.4. Pyrrolo[2,3-*g*]indazoles

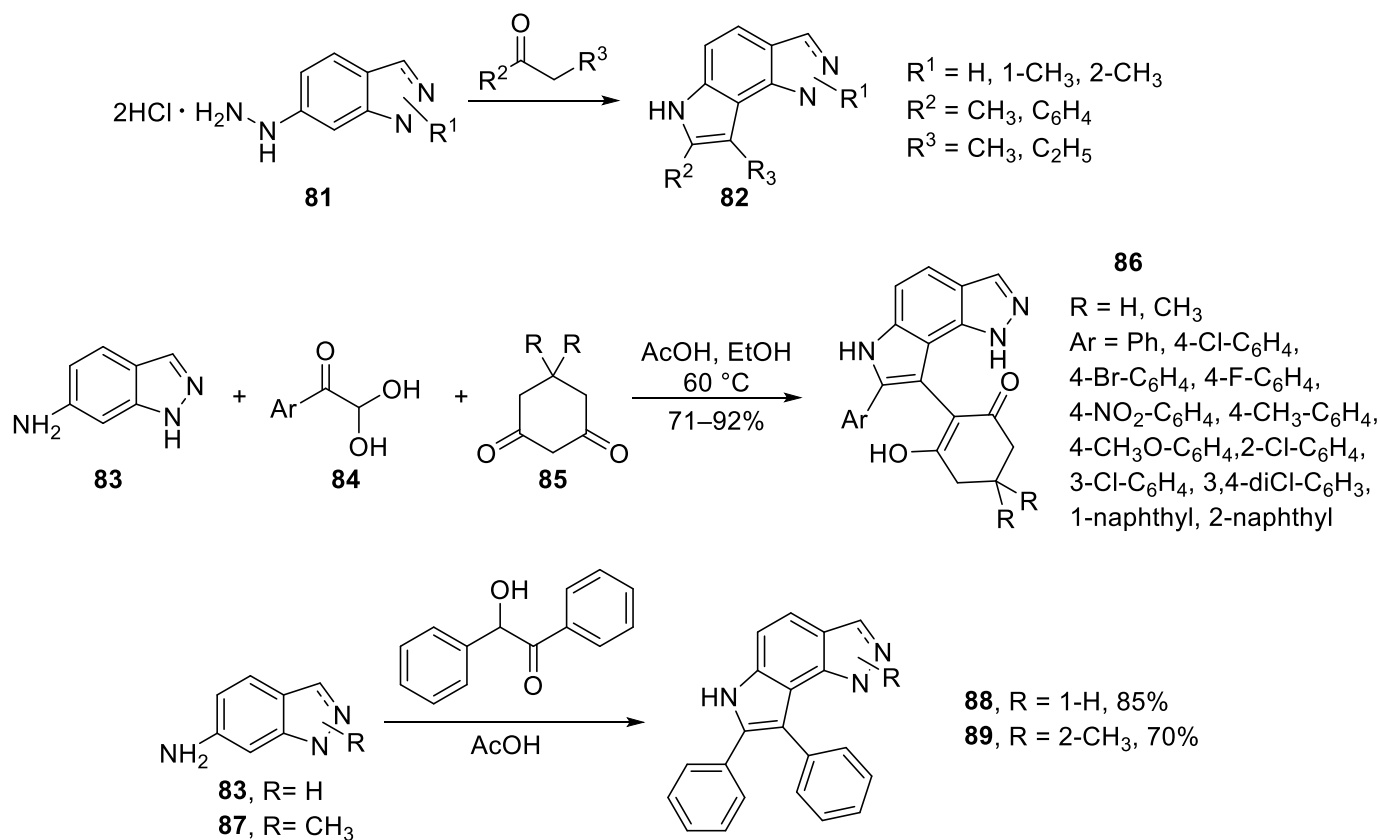
The first references of pyrrolo[2,4-*g*]indazole preparation dates from the 1960's in patent applications by American Cyanamide^{36,37}, reporting compounds with analgesic and anti-inflammatory activity.³⁶ Reaction of **76** with hydrazines and subsequent aromatization using Pd/C in refluxing cumene led to a series of differently substituted compounds **78** (Scheme 14). This strategy has also been used for the synthesis of compounds **80** in a work dedicated to the preparation of potential inhibitors of soluble guanylate cyclase.³⁸ In this work, DDQ was used instead of Pd/C for the dehydrogenation, and the protecting group of the pyrrole moiety was changed to ethoxymethyl or the SEM group. The same approach was used for the preparation of pyrroloindazoles in the [3,4-*g*] (see below) or [3,2-*g*]³⁹ series.



Scheme 14. General structure of compounds **78**^{36,37} or **80**³⁸. Preparation of compounds **79** from **76**.³⁶

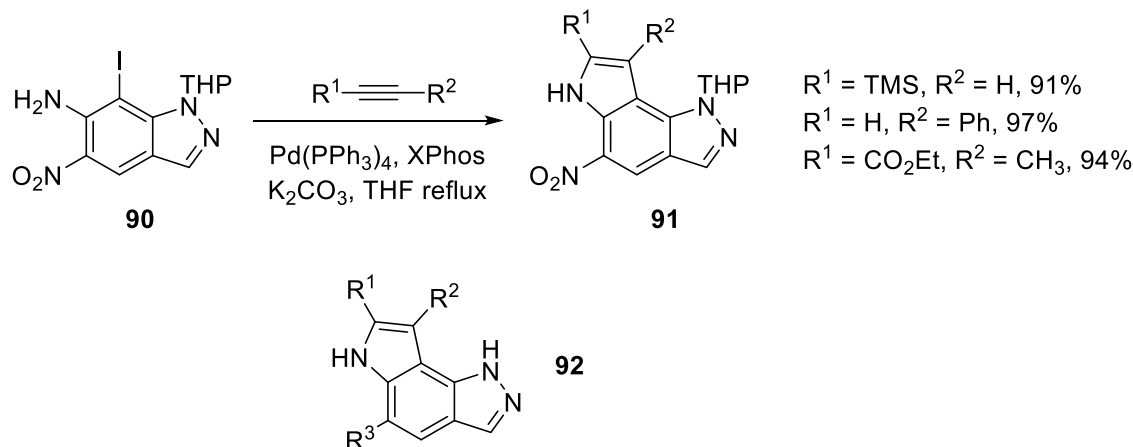
As presented above for the preparation of pyrrolo[2,3-*e*]indazoles (Scheme 10), the work by Borza *et al.* was also carried out from 6-aminoindazole to get the [2,3-*g*]-regioisomers.³⁰ Previously, Fischer indolization was also reported in the [2,3-*g*]-series, from 6-hydrazinoindazoles **81** (Scheme 15).⁴⁰ Formation of the pyrrole

nucleus could also be achieved by reaction of 6-aminoindazoles **83** with arylglyoxal hydrates and cyclic 1,3-dicarbonyl compounds to give **86**⁴¹, or by condensation of **83** or **87** with benzoin, to give 7,8-diphenyl derivatives **85** and **86**⁴², (Scheme 15). The pyrrolo[3,2-*f*]indazole scaffold could also be formed using this reaction, starting from 6-amino-7-chloroindazole.⁴²



Scheme 15. Fischer indolization from 6-hydrazinoindazole **81**.⁴⁰ Three-component reaction using 6-aminoindazole **83**, arylglyoxal hydrates and cyclic 1,3-dicarbonyl compounds.⁴¹ Condensation of indazoles **83** and **87** with benzoin.⁴²

In 2011, we reported the preparation of diversely substituted pyrrolo[2,3-*g*]indazoles.^{43,44} The method involved a palladium-catalyzed annulation from 6-amino-7-iodoindazole **90** and terminal or internal alkynes using $Pd(PPh_3)_4$ as a palladium source and XPhos as a ligand (Scheme 16). High yields were attained, and a single regioisomer could be obtained as in the cases of examples presented Scheme 16. This synthetic method was used to prepare a series of potential Pim kinase inhibitors of general structure **92**. In particular, high inhibitory potency was observed towards Pim-1 and Pim-3 protein kinases, with IC_{50} values in the submicromolar range (**92**, $R_1 = R_2 = H$, $R^3 = NH_2$, IC_{50} Pim-3 = 33 nM).

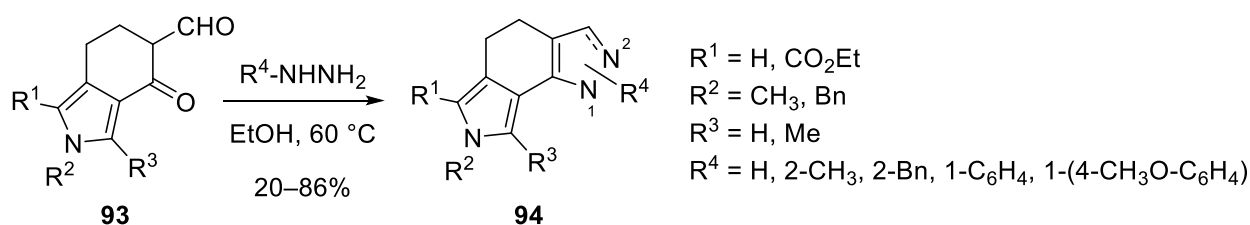


Scheme 16. Palladium-catalyzed synthesis of pyrrolo[2,3-*g*]indazole derivatives **91**.⁴³ General structure **92** of potential Pim kinase inhibitors.⁴⁴

Similarly to the [3,2-*e*]-series (see Scheme 11), fused pyrazole derivatives of isatin have been prepared from 6-aminoindazole⁴⁵ or 6-amino-5-methylindazole.⁴⁶ The synthetic method is similar, with the use of chloral hydrate and hydroxylamine hydrochloride to give a 2-(hydroxyimino)acetamide intermediate which was cyclized under acidic conditions.

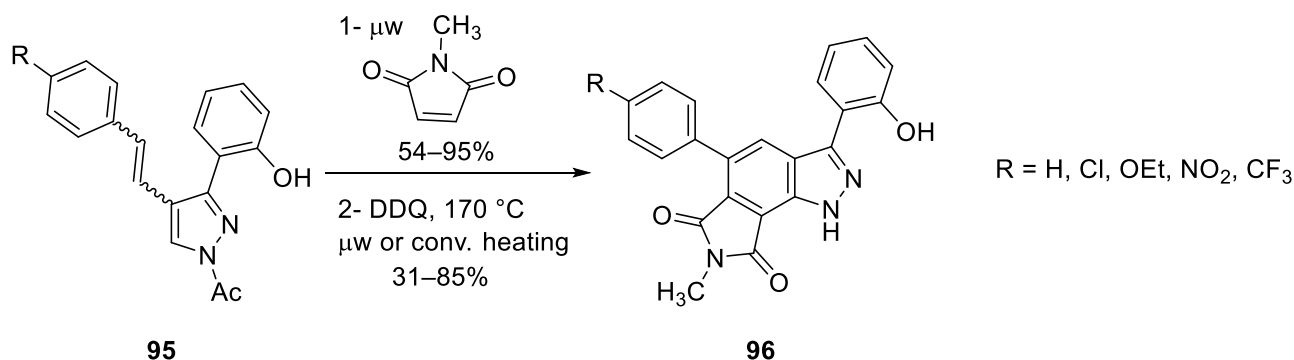
4.5. Pyrrolo[3,4-*g*]indazoles

A single article on the preparation of 1,7-dihydropyrrolo[3,4-*g*]indazoles has been published by P. Barraja and collaborators.⁴⁷ The strategy is the same as reported above for the preparation of pyrrolo[2,3-*g*]indazoles (see Scheme 14), involving isoindoles **93** to afford pyrazole derivatives **94** (Scheme 17). Reaction with alkyl- or arylhydrazine was rather regioselective (N1 for aryl, N2 for alkyl). Derivatives benzylated at the N1 instead of the N2 position could be obtained in an additional step of N-alkylation from the non-substituted pyrazole (**94**, $R^4 = H$). Oxidation using DDQ in benzene led to the 1,7-dihydropyrrolo[3,4-*g*]indazoles in 42–74% yields.



Scheme 17. Synthesis of pyrazole derivatives **94**.⁴⁷

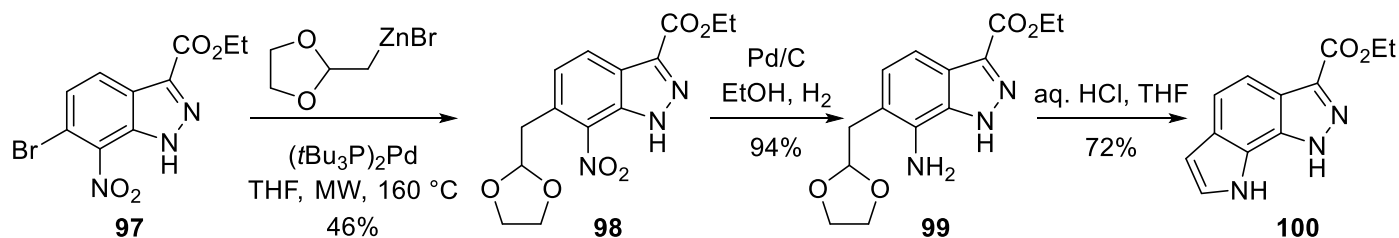
Diels-Alder reaction has been frequently used in the synthesis of heterocyclic systems containing a phthalimide moiety. This strategy has also been applied to the preparation of pyrrolo[3,4-*g*]indazole-6,8-diones **96**, from styrylpyrazoles **95** and *N*-methylmaleimide (Scheme 18).⁴⁸



Scheme 18. Diels-Alder/dehydrogenation sequence leading to pyrrolo[3,4-*g*]indazole-6,8-diones **96**.⁴⁸

4.6. Pyrrolo[3,2-*g*]indazoles

This last example has been reported in a patent application deposited by the Memory Pharmaceuticals Corporation, in a work related to the preparation of ligands for the $\alpha 7$ nicotinic acetylcholine receptor.⁴⁹ The synthesis started from the adequately functionalized indazole **97** (Scheme 19). A Negishi cross-coupling was first carried out to introduce the 2-carbon atom chain necessary for pyrrole formation. Reduction of the nitro group and acetal hydrolysis/cyclization led to compound **100** in 72% yield.



Scheme 19. Synthesis of 1,8-dihydropyrrolo[3,2-*g*]indazole **100**.⁴⁹

Conclusions

Nitrogen-containing heteroaromatic derivatives are particularly interesting due to their various areas of application, especially in biology. The development of efficient methods allowing access to these scaffolds has sparked many efforts, and synthetic approaches using either multi-step synthesis, multi-component or metal-catalyzed reactions enabled the preparation of heterocyclic rings and the expansion of the chemical space in this domain. Nevertheless, the synthesis of many heterocyclic systems remains challenging in order to enlarge the scope of synthetic methodologies, control the regioselectivity or overcome reactivity and stability issues. This account, focused on pyrido[3,4-*g*]quinazolines, pyrazolo[3,4-*g*]quinoxalines and pyrroloindazoles, explored the existing synthetic methods to obtain these structures, some of them demonstrating potential biological activities, particularly protein kinase inhibitory potencies. The literature analysis showed that some series have not or sparsely been reported (*e.g.* pyrrolo[2,3-*f*]indazoles, pyrrolo[3,4-*e*]indazoles, pyrrolo[3,4-*f*]indazoles), or that the existing synthetic methods can limit the choice of substitution and functionalization, highlighting that the development of new methodologies for the preparation of simple but challenging heteroaromatic moieties is still needed.

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Authors' Biographies



After a Master Degree in biophysicochemistry and cellular and molecular biology (1989), **Pascale Moreau** received her Ph.D (University of Orléans, France) in 1993 working on the synthesis and reactivity of 1,4-benzodioxine derivatives. Then she joined Prof. Victor A. Snieckus' group at Waterloo University (Canada), as a postdoctoral fellow in 1994-1995, working on macrocycles synthesis and directed ortho-metalation. During a second post-doctoral position at Bristol-Myers-Squibb (Marne-la-Vallée, France) she focused on asymmetric synthesis. In 1996, she moved to Blaise Pascal University (Clermont-Ferrand, France) as a lecturer in the group of Prof. Michelle Prudhomme working on hemisynthesis of rebeccamycin derivatives. She was appointed as a Professor in 2007. She is currently the leader of "Enzyme and receptor inhibitors" group within the Institute of Chemistry of Clermont-Ferrand. Her current research is devoted to the development of new bioactive heteroaromatic compounds.



Fabrice Anizon obtained a Master in Chemistry in 1996 from Blaise Pascal University (Clermont-Ferrand, France), after carrying out research in the groups of Prof. G. Jeminet (Clermont-Fd) and Daniel T. Glatzhofer (Oklahoma University, United States). In 1999, he received his PhD in organic and biological chemistry at Blaise Pascal University, under the supervision of Prof. Michelle Prudhomme, working on the synthesis of rebeccamycin derivatives as topoisomerase I or protein kinase inhibitors. He joined the group of Prof. Philip J. Kocienski at the Universities of Glasgow (Scotland) and Leeds (England) as a post-doctoral fellow focusing on targeting peptides in drug delivery. He carried on in the same group as a Lecturer at the University of Leeds (2001), working in the fields of organometallic chemistry and asymmetric synthesis, and from September 2001 at Blaise Pascal University in the group of Prof. Michelle Prudhomme. He was appointed Professor in the same University in 2008. His research interests focus on the design and synthesis of biologically active hetero-aromatic compounds.

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