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"Heteroaromatic Rings of the Future": Exploration of Unconquered Chemical Space

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Abstract William Pitt and co-workers have created a virtual exploratory heterocyclic library "VEHICLe" containing over 200 unconquered bicyclic heteroaromatic rings, synthetically feasible with potential medicinal interest. Since the publication of the 22 "heteroaromatic rings of the future" by Pitt in 2009, 15 of them have been successfully synthesized as bicyclic or polycyclic forms and evaluated for applications in both biology and material science. This short review presents the critical synthesis associated with innovative synthetic methodologies of the synthetically conquered rings scaffolds from the list of 22 with a spotlight of the scientific contribution of this fascinating article for the expansion of the chemical diversity.

Key words : Heteroaromatic rings, chemical space, medicinal chemistry, virtual exploratory heterocycle library

1 Introduction

The development of new and original scaffolds is a perpetual quest in medicinal chemistry. Among all the required The development of new and original scaffolds is a perpetual quest in medicinal chemistry. Among all the required criteria for the elaboration of novel hit or lead

compounds (*in vitro* & *in vivo* activity, metabolic stability, solubility etc.), originality of the chemical structure is crucial for patentability reasons in a very competitive economical context and for the expansion of chemical diversity. Until the end of 2012, there were only 351 ring systems and 1197 frameworks contained in the drug space describing rings and molecular scaffolds.[1] Each year a small number of 6 ring systems compared of those predicted by calculation studies enter the drug space limiting thereof the number of new drug containing original ring system.[2] In 2009, William Pitt and co-workers within UCB Celltech have reported a calculation study describing the systematic generation of heteroaromatic bicyclic structures.[3] More than 24000 rings have been generated with a set of rules such as not more than 5 heteroatoms limited to N,O and S, only mono or bicyclic ring obeying to the Huckel's aromaticity. The authors listed them in a virtual exploratory heterocyclic library called "VEHICLe". After refinement following several chemical feasibility filters such as chemical tractability, motif bibliographic occurrence, they finally extracted a list of 232 heteroaromatic bicyclic systems with a p good > 0.95 (p = predicted tractability), unreported before and chemically reachable. 22 of these bicyclic rings have been selected as representative examples (**P1** to **P22**, Figure 1) and showed by the authors as synthetically challenging scaffolds for the chemist community, thus providing the opportunity to generate new and original chemical series of potential medicinal interest. This fascinating publication with a catchy title "heteroaromatic rings of the future" has been cited 151 times since 2009 in the Sci-finder database and 188 times in google scholar citations[4] showing how it has become a must-see article in the search of the renewal of the structures for the scientific community.

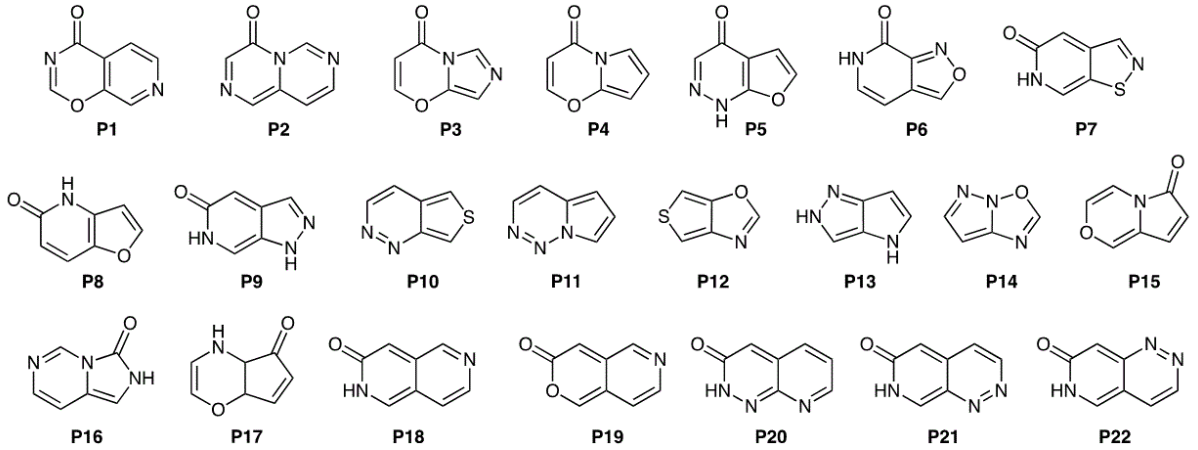


Figure 1 The unconquered 22 "heteroaromatic rings of the future" reported by Pitt in 2009.

In essence, Pitt's publication addresses specifically to the medicinal chemists community needing clues for the development of potent biologically active molecules. The production of original heterocyclic scaffolds used as fragments in medicinal program is limited by synthetic accessibility. Medicinal chemists are more focused on heterocycles whose syntheses are known leaving the more complicated ones, most-at-risk, even though some of them are promising. Besides, Pitt and Coll. noticed that among the all possible ring systems included both in VEHICLe and in real compounds database (1701 rings), only few of them are exploited by medicinal chemists those with the simplest structures with fewer heteroatoms easier to find and synthesize. In addition, other authors pointed out that known ring systems part of bioactive molecules are relied all together by structural analogy as small islands in a restricted area of chemical space.

Having made these observations, Pitt and Coll. aim at providing simple and original ring systems that medicinal chemists wouldn't have imagine by conventional way while highlighting the fact that these rings are biologically compatible and synthetically feasible as those already reported and incorporated into drug molecules.

In this review, we would like to show the organic chemists point of view through the synthetic description of some original heteroaromatic rings virtually generated and to demonstrate the benefits of calculation studies showing an innovative way to predict synthetic tractability on experimental organic chemistry.

We have examined each of the 22 heteroaromatic structures showed by Pitt in his article and found that to date, 9 of them have been synthesized whereas 7 are not yet described in the literature under any forms. The others 6 bicyclic rings may appear within polycyclic systems or with a very limited panel of substituents. In this review, we report an analysis of all published syntheses of the 9 original heteroaromatic rings of the future (**P1**, **P5-P9**, **P12-P13**, **P18**, Figure 1) and those appearing under polycyclic system. We wish to show how uncommon but synthetically feasible molecular scaffolds may stimulate the development of innovative synthetic methodologies and further provide new molecular scaffolds to expand diversity and novelty of compound libraries for medicinal uses or for materials. In addition, we will expose promising applications of these original heterocycles as potent enzymes inhibitors, herbicides but also as organic semiconductors materials.

Since 2009, two major publications concerning theoretical studies of the 22 heteroaromatic rings of Pitt have appeared in the literature showing the high potential of these heteroaromatic ring in drug design. In 2011, a team from Astra-Zeneca described a computational protocol based on quantum mechanical calculation binding energies for the 22 heteroaromatic ring of Pitt to heme iron in cytochrome P450 affording direct link between the heterocyclic structure and the biochemical inhibition observed. Five Pitt 's heterocycles mostly with nitrogen in five membered ring and with adjacent donor showed enhance inhibition.[5] Later, Graton and co-workers reported the prediction by calculation studies of H-bond accepting abilities for acceptors involved in the original structure of Pitt which is important for criteria in drug recognition processes.[6]

2 Heteroaromatic rings of the future: the synthetic challenge?

We were pleased to see that a number of synthetic organic chemists have met the challenge proposed by Pitt for the synthesis of heteroaromatic rings from the list of the 22. Driven by medicinal research program restriction such as time, efficiency and simplicity, they succeeded to develop original and straightforward synthetic methodologies to these structures. When we looked in detail to the related publications, we noticed that most of the "rings of the future" containing a pyridine ring have been designed as aza-analogs of reported structures which led the authors to develop innovative synthetic route on pyridine ring. In addition, some of the heteroaromatic bicyclic rings from the list have been synthesized as substructures of benzo-fused systems for synthetic accessibility reasons. Finally, rare examples of the unsubstituted exact rings predicted by Pitt, have been prepared. Presumably, most of the heterocycles from the list have been synthesized with specific substituents to ensure stability and biological activities.

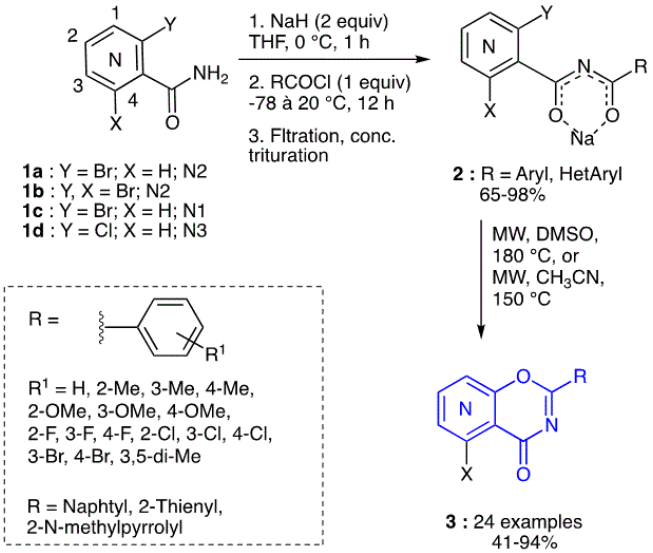
In the following part, we present the critical synthesis of the conquered 15 rings of the list, either in their exact bicyclic form or included in polycyclic structures followed in some cases by their biological evaluation.

2.1 4*H*-pyrido[1,3]oxazin-4-one-P1

4*H*-pyrido[1,3]oxazin-4-one **P1** is the first heterobicyclic compound listed in the 22 "heteroaromatic rings of the future" by Pitt. This bicyclic ring could be considered as an aza-analog of 4*H*-benzo[1,3]oxazin-4-one which has emerged in the past two decades as a promising medicinal compound. For example, benzo- and thieno[1,3]oxazin-4-ones have been used as SCCE inhibitors for the treatment of skin conditions[7a] or as fragment in fragment-based design of selective GSK-3 inhibitors.[7b] In addition, a 2-(2'-hydroxyphenyl)-1,3-benzoxazin-4-one has been designed as fluorescent sensors for Zn^{2+} cations.[7c] Some 4*H*-benzo[1,3]oxazin-4-ones have also been used as key intermediates for the preparation of various small heterocycles of interest such as 1,2,4-triazoles[8], trisubstituted-1,3,5-triazines[9] and 1,2,4-oxadiazoles[10] for medicinal uses.

Synthesis of hydroxyl substituted **P1** functionalized at the C2 position was first reported as its tautomeric form 2*H*-pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione in 1966 and later in 1995. In the synthetic procedure, the desired pyridoxazinediones were obtained in good yields from condensation of substituted 3-hydroxyisonicotinamides with ethylchlorocarbonate or 1,1'-carbonyldiimidazole.[11]

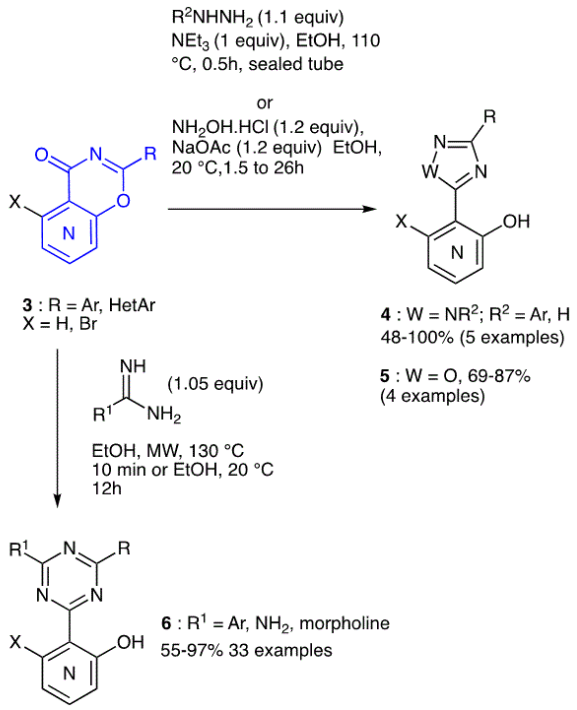
For our part, we have developed through a collaborative work with Slowinski and co-workers from Sanofi a rapid and efficient access to diverse 2-substituted 4*H*-pyrido[1,3]oxazin-4-ones **3** *via* an unprecedented intramolecular microwave assisted O-arylation of *N*-aroyl and *N*-heteroaroyl-(iso-)nicotinamides **2**.[12] The reaction was performed starting with the deprotonation of bromo(iso)nicotinamides **1** with 2 equivalents of NaH in THF at 0 °C. Addition of 1 equivalent of various substituted aroyl chlorides or heteroaroyl chlorides to the anions afforded the imide sodium salts **2** as stable precursors for the intramolecular O-arylation step with yield up to 97%. The cyclization reaction proceeded only under microwave irradiation in polar solvent. (Scheme 1)



Scheme 1 First synthesis of 4*H*-pyrido[1,3]oxazin-4-ones via an intramolecular o-arylation reaction

This strategy was successfully extended to the synthesis of 24 examples of 2-substituted 4H-pyrido[1,3]oxazin-4-ones with a broad variety of substituent at the C2 position and 3 possible positions for the nitrogen atom of the pyridine ring. Interestingly, no reaction or degradation of the starting material occurred with alkyl substituent at the C2 position on the oxazinone ring suggesting

that the pyridoxazinone stability is ensured by only aryl or heteroaryl substituent through a planar conjugated system. Best yields were obtained with those possessing para-substituted phenyl ring at the C2 position on the oxazinone thus stabilizing electronic resonance between the bicyclic core and the phenyl substituent. We further explored the chemical potential of 4*H*-pyrido[1,3]oxazin-4-ones **3** by reacting them with various nucleophiles. Exposure of 4*H*-pyrido[1,3]oxazin-4-ones **3** to phenylhydrazine or hydroxylamine led respectively to the corresponding hydroxypyridine substituted 1,2,4-triazoles **4** and 1,2,4-oxadiazoles **5** in good yield *via* an ANRORC type mechanism (Scheme 2).[13] Efficient access to 2-hydroxy-pyridyl substituted 1,3,5-triazines **6** was also developed from a wide panel of pyridoxazinones and the corresponding amidines in one step under microwave assisted reaction conditions in good to excellent yields.[14] In the meantime, we have developed Pd(II)-catalyzed cross-coupling reactions on 2-substituted-4*H*-pyrido[*e*][1,3]oxazin-4-ones **3** to access polyfunctionalized precursors with extended π-conjugation for further applications as fluorescent material.[15]



Scheme 2 Transformation of 4*H*-pyrido[1,3]oxazin-4-ones into 2-hydroxypyridyl-1,2,4-oxadiazoles, -1,2,4-triazoles and -1,3,5-triazines.

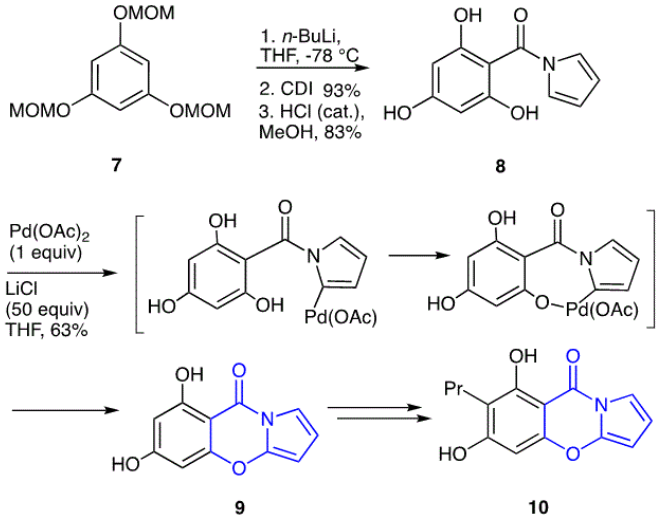
2.2 Pyrrolo[2,1-b][1,3]oxazin-4-one-P4

No report for the synthesis of pyrrolo[2,1-b][1,3]oxazin-4-one was found in the literature. The pyrrolooxazin-4-one ring system exists only as substructure within polycyclic or as tautomeric forms. Kollenz and co-workers have reported in 1977 the synthesis of pyrrolo[2,3-b]chinoxalin-4-one *via* two cyclocondensation reactions from N-(phenylacetyl)acrylamide.[16]

Later in 1999, Simpson and co-workers reported the biosynthesis of streptopyrrole XR587.[17] This benzopyranopyrrole containing metabolite was isolated from streptomyces strain identified during a screening program for antibacterial agents as *Streptomyces rimosus.* In the meantime, Ellsworth and co-workers published the total synthesis of the 6,8-dihydroxy-7-propyl-9*H*-pyrrolo[1,2-b][1,3]-benzoxazin-9-one **10**, the dechlorinated form of natural product XR587 by using an O-

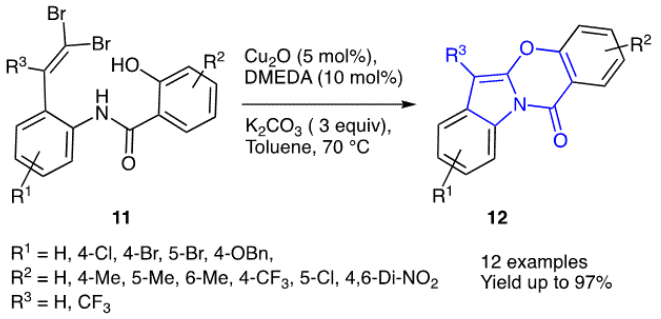
arylation reaction as a key step (Scheme 3).[18] The synthetic strategy began with the *ortho*-lithiation of MOM-protected phloroglucinol **7** followed by treatment with carbonyldiimidazole and an acidic deprotection step to furnish the benzoylpyrrole **8** in 77% overall yield. The key transformation was achieved via palladation of the electron rich pyrrole ring at the C2 position using 1 equivalent of $Pd(OAc)_2$ and 50 equivalents of LiCl followed by subsequent attack of the phenol. Using this methodology, compound **9** was isolated in 63% yield. Attempts to run this reaction with a catalytic amount of palladium and air as oxidant were unsuccessful. Next, the *n*-propyl side chain was introduced to provide the pyrrolobenzoxazine **10** (Scheme 3).

The streptopyrrole XR587 has been further evaluated by computational studies as a potential inhibitor on histidine kinase protein BAeS to target multidrug-resistant salmonella.[19]



Scheme 3 Total synthesis of the dechlorinated form of streptopyrrole XR587

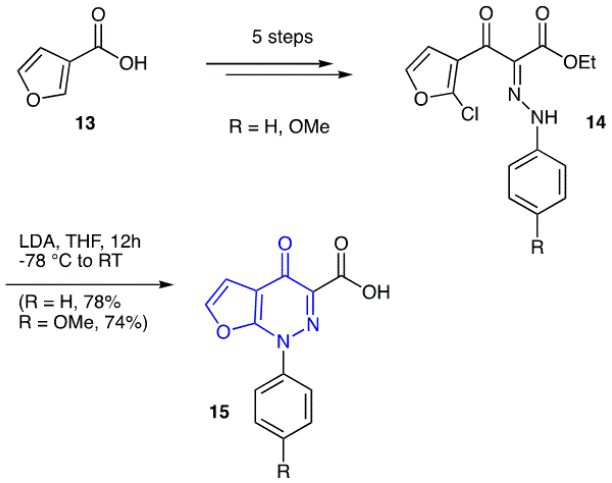
Finally in 2012, Lv and co-workers have reported an efficient approach to a variety of benzoxazino[3,2-a]indol-12-ones **12** with potential biological activities from corresponding *o*-gem-dibromovinyl salicylanilide substrates **11** by using a Cu_2O-catalyzed domino intramolecular C-N coupling /C-O bond formation process as a key step (Scheme 4).[20]



Scheme 4 Copper-catalysed synthesis of benzoxazino[3,2-a]indol-12-ones

2.3 Furo[2,3-c]pyridazin-4(1*H*)-one-P5

The 1,2-pyridazine-4-one substructure is represented in some medicinal ring systems such as the cinnolin-4(1*H*)-one in the antibacterial drug cinoxacin.[21] However, only few examples of furan-fused pyridazinone with potent pharmaceutical properties are reported in the literature.[22] The bicyclic system furo[2,3-c]pyridazin-4(1*H*)-one **15** has been synthesized for the first time in 2015 by Keserü and co-workers. In the synthetic strategy, the authors used a LDA mediated cyclization reaction on aryl-hydrazones derivatives **14** synthesized in five steps from furan-3-carboxylic acid **13**.[23] The cyclization step was performed using LDA as lithiated reagent providing furo[2,3-c]pyridazin-4(1*H*)-ones **15** in good yield albeit with limited range of substituent (Scheme 5). No exploitation of this new ring system in drug discovery projects has been reported so far.

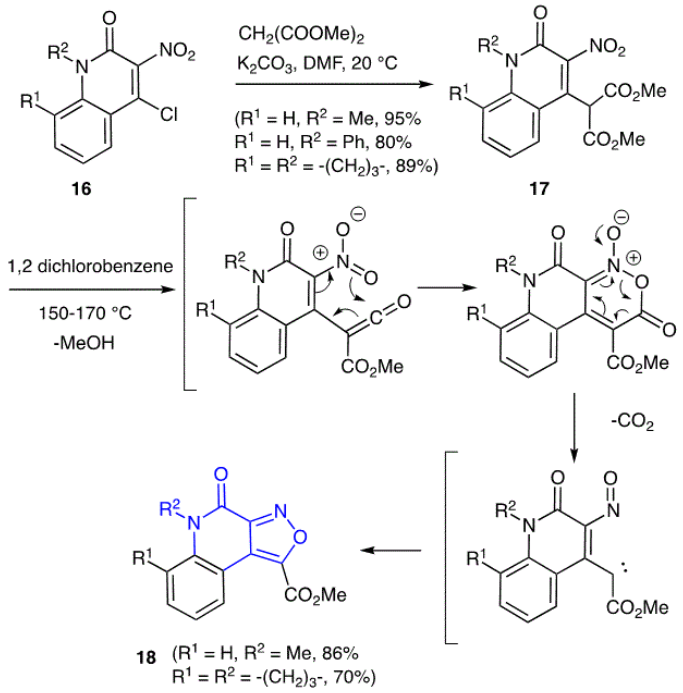


Scheme 5 Synthesis of furo[2,3-c]pyridazin-4(1H)-one via LDA mediated cyclization reaction

2.4 Isoxazolo [3,4-c]pyridine-7-ones-P6

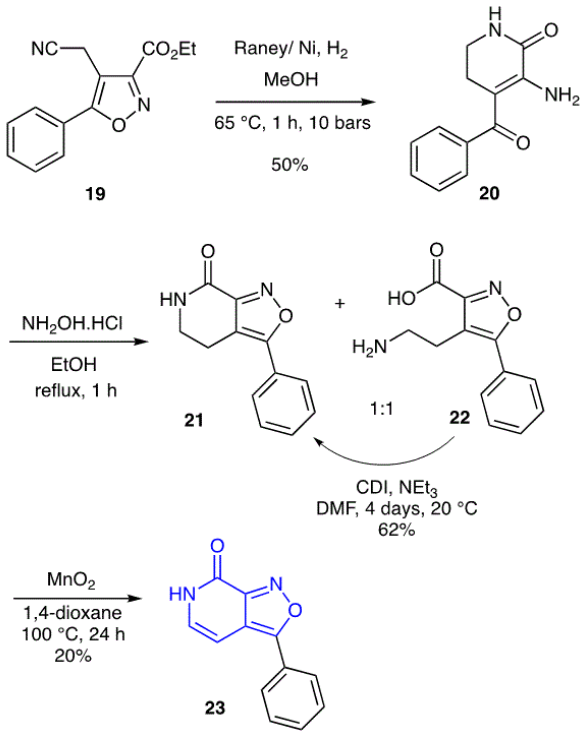
Before being synthesized in 2016 by Keserü and co-workers, this heterobicycle was first reported in 1997 as benzo- fused isoxazolo-pyridinones by Stadlbauer and co-workers.[24] This scaffold was selected by the authors to develop thermoanalytic methods for synthetic organic chemistry, more specifically for ring closure and rearrangement experiments.

Starting from different substituted 4-chloro-3-nitro-2-quinolones **16** as synthetic precursors and dimethylmalonates, the authors developed a route in which different substituted 2-(oxo-3-nitro-4-quinolinyl)malonates **17** underwent a thermal cyclization at 150-170°C to give the corresponding 1-methoxycarbonylisoxazolo[3,4-c]quinol-4(*5H*)-ones **18** in good yield (86% for R^1 = H, R^2 = Me) (Scheme 6). Surprisingly, the thermolysis of quinolinone dimethylmalonates **17** with an *ortho*-nitro group occurred via a ring closure reaction and the extrusion of methanol and carbone dioxide.



Scheme 6 Synthesis of 1-methoxycarbonylisoxazolo[3,4-c]quinol-4(5H)-ones

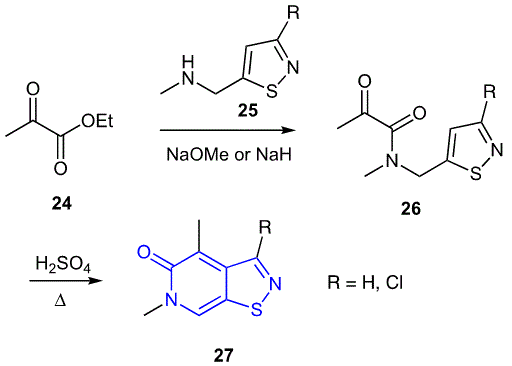
Later in 2016, Keserü and co-workers reported the first synthesis of isoxazolo[3,4-c]pyridin-7-ones **23**[25] included in the list of the 22 "heteroromatic rings of the future". This scaffold has been selected by the authors for their potential lead-like properties and for their similarity with compounds showing widespread biological activities including glutamate transporters,[26] aldose reductase inhibitors,[27] antibacterial or antifungic agents.[28] The synthesis of 3-phenylisoxazolo[3,4-c]pyridin-7(6*H*)-one **23** was achieved in eight steps from commercially available propiophenone which could allowed an easy access to further functionalized derivatives (Scheme 7). Notably, 3-amino-4-benzoyl-5,6-dihydropyridin-2(1*H*)-one **20** was obtained in moderate yield from the key intermediate ethyl 4-(cyanomethyl)-phenylisoxazole-3-carboxylate **19** by reduction of the nitrile function and isoxazole ring opening with Raney Nickel under 10 bars of hydrogen. Treatment of **20** with an excess hydroxylamine hydrochloride in ethanol gave a mixture containing 5,6-dihydroisoxazolo[3,4-c]pyridin-7(4*H*)one **21** and side product **22** in 1 :1 proportion. Addition of CDI and triethylamine to the mixture yielded **21** as a single product. Finally the targeted molecule **23** was successfully obtained by dehydrogenation of 5,6-dihydroisoxazolo[3,4-c]pyridin-7(4*H*)one **21** with activated MnO_2. The authors demonstrated that properties of **23** fitted well with lead like criteria (size, 16 non-hydrogen atoms, aromatic content, log P = 1.64) opening the way for a further development in drug discovery projects (Scheme 7).



Scheme 7 A ring opening-ring closure sequence for the synthesis of isoxazolo[3,4-c]pyridin-7-one

2.5 5*H*,6*H*-[1,2]thiazolo[5,4-c]pyridin-5-one-P7

5*H*,6*H*-[1,2]thiazolo[5,4-c]pyridin-5-one was first synthesized as its *N*-methylated form **27** in 2010 by DuPont de Nemours.[29] In a two-steps strategy, the bicycle **27** was formed from the condensation of α-keto ester **24** with amine **25** in the presence of the appropriate base and solvent affording -ketamine **26**. A subsequent intramolecular dehydrative cyclization in boiling concentrated sulfuric acid gave the thiazolopyridinone **27** (Scheme 8).[29] Despite the lack of information about yields and scope of the reaction, this strategy seems quite concise and easily generalizable to other substrates containing electron rich five-membered heteroaromatic rings.



Scheme 8 Synthesis of 5H,6H[1,2]thiazolo[5,4-c]pyridine-5-ones using an intramolecular dehydrative cyclization

A library of these original heterocyclic scaffold substituted with an isooxazoline moiety (**28-31**) found efficient applications as herbicides. (Figure 2).

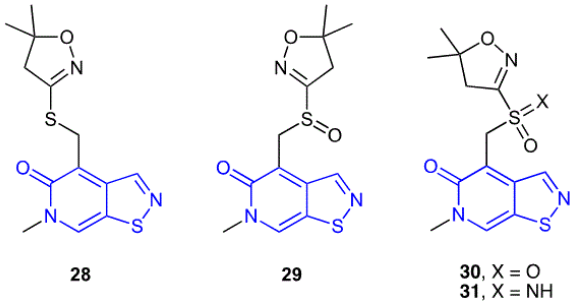
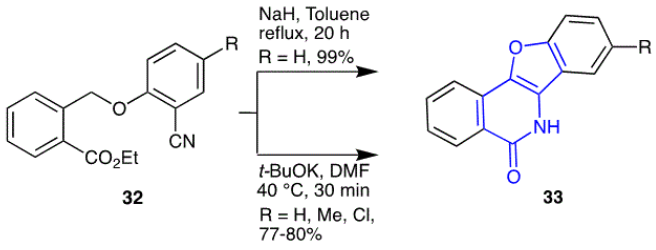


Figure 2 Substituted thiazolo[5,4-c]pyridin-5-ones as herbicides

2.6 Synthesis of 4*H*,5*H*-furo[3,2-b]pyridin-5-one-P8

Syntheses of various examples of 4*H*,5*H*-furo[3,2-b]pyridin-5-one were reported mainly as their benzo-fused version. In 1981, Vaidya and co-workers used the Friedländer's method for their synthetic approach starting from 2-hydroxybenzonitrile and α-bromoketone.[30]

In 1995, the synthesis of this heterocycle was further described by Yamaguchi and co-workers by using a new strategy involving a Dieckmann condensation followed by a thermolysis step and subsequent treatment with gaseous ammonia under high pressure to get benzofuroisoquinolinones.[31] In 2011, Kalugin and co-workers reported synthesis of benzofuro[3,2-b]pyridinones **33** with several improvements and structural diversity (Scheme 9).[32] Cyanoester **32** cyclized under mild basic conditions using potassium *tert*-butoxide in DMF or NaH in toluene and shorter reaction time leading to the desired substituted heterocycles **33** in good yields (Scheme 9).

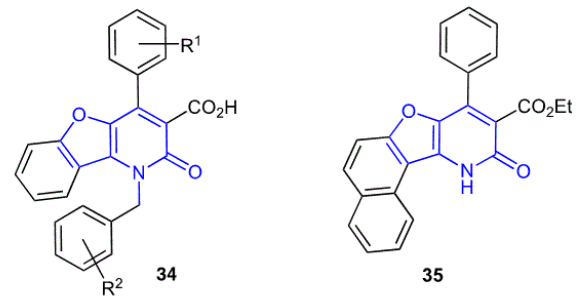


Scheme 9 The key step in the synthesis of benzofuro[3,2-b]pyridinones

Beyond chemical studies, these original structures were also reported to be of great biological interest. Mederski and co-workers from Merck conducted SAR studies on a library of heterocycles containing the discussed scaffold (Figure 3).[33]

Some of the substituted benzofuro[3,2-b]pyridinones **34** exhibited nanomolar binding affinities with the endothelin receptor (ET_A/ET_B), which makes them useful for the treatment of pulmonary hypertension. Moreover, the naphtofuro[3,2-b]pyridinones **35** turned out to have

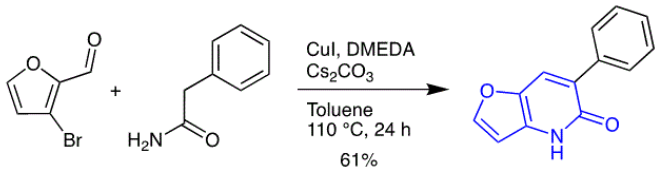
promising antibacterial and antifungal properties, as reported by Ramesh and co-workers (Figure 3).[34]



R^1 = H, 4-OMe, 3-OMe, 2-OMe
2,5-di-OMe, 2,4-di-OMe, 3,4,5-tri-OMe
3,4-OCH_2O-
R^2 = H, 4-OMe, 3-OMe, 2-OMe,
2-Me, 2-OEt, 2-*i*Pr, 2-SMe
2-Cl, 2,5-di-OMe, 2,3-di-OMe,
2,6-di-OMe, 2,4,5-tri-OMe.

Figure 3 Benzofuro[3,2-b]pyridinones exhibiting binding affinities for endothelin receptors

In 2011, Fu and co-workers successfully synthesized the first example of 4*H*,5*H*-furo[3,2-b]pyridin-5-one as its bicyclic form with phenyl group as substituent on the pyridone ring. The heterocycle **38** was obtained with good yield among other quinolinones by reacting 3-bromo-2-furaldehyde **36** with 2-phenylacetamide **37** in the presence of copper iodide, DMEDA and cesium carbonate (Scheme 10).[35] The authors reported that this reaction did not work for alkylacetamides. This bicyclic structure was not further used and evaluated as its benzo-fused analogs in any medicinal domain.



36 **37** **38**

Scheme 10 Copper-mediated synthesis of 4H,5H-furo[3,2-b]pyridine-5-one

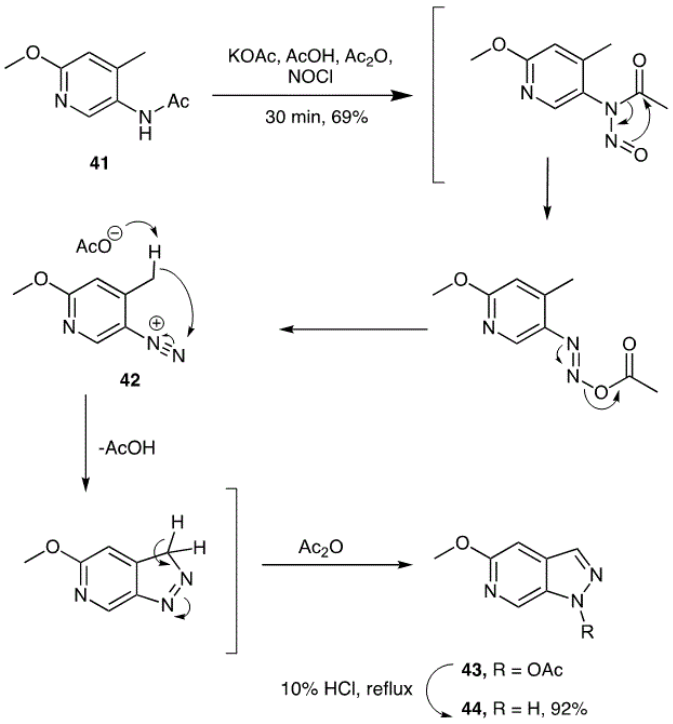
2.7 1*H*,5*H*,6*H*-pyrazolo[3,4-c]pyridin-5-one-P9

The pyrazolo[3,4-c]pyridin -5-one ring system can be described as two different tautomers **39** and **40** (Figure 4). Although 5-substituted pyrazolo[3,4-c]pyridines are known to be potent inhibitors of phosphodiesterases and cyclin-dependent kinases,[36] no biological applications were reported for their pyridinone analogs.

39 40

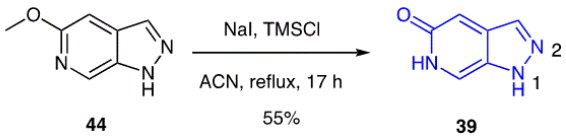
Figure 4 Tautomeric forms of pyrazolo[3,4-c]pyridin-5-one

Historically, pyrazolo[3,4-c]pyridin-5-one was first synthesized as its tautomeric form in 1980 by Chapman and Hurst.[37] The 5-methoxy-pyrazolo[3,4-c]pyridine **44** was prepared regioselectively in good yield by *N*-nitrosylation of 3-acetamido-4-methylpyridine **41** with nitrosyl chloride followed by thermal rearrangement in acidic conditions leading to the diazonium intermediate **42**. (Scheme 11).



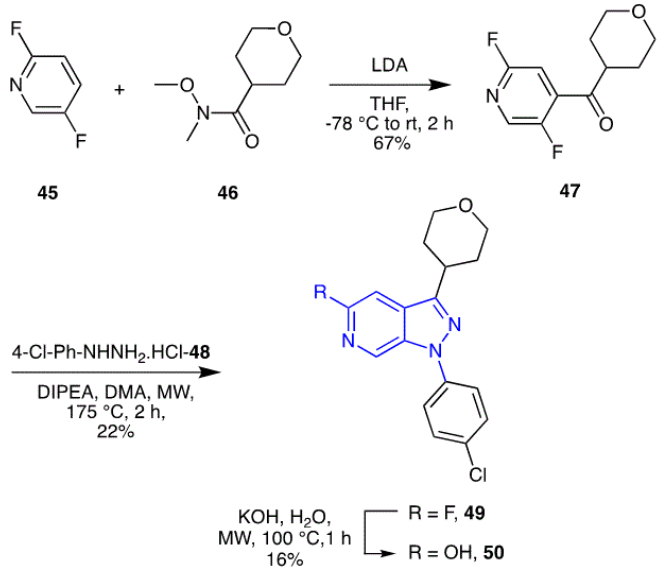
Scheme 11 Synthesis of 5-methoxy-pyrazolo[3,4-c]pyridine using thermal rearrangement

Later in 2008, this synthetic strategy was employed by Tsikouris and co-workers to synthesize 5-substituted pyrazolo[3,4-c]pyridin-5-ones to investigate the possible N1-H and N2-H tautomerism by NMR studies.[38] The pyridinone **39** was obtained from 2-methoxypyridine **44** by a subsequent demethylation step using sodium iodide and TMSCl in boiling acetonitrile (Scheme 12). Thanks to ^{1}H, ^{13}C and ^{15}N NMR experiments at ambient and low temperatures, all of the studied compounds were shown to exist predominantly in the N1-H tautomeric form. This conclusion was also supported by DFT calculations.



Scheme 12 Demethylation of 5-methoxy-pyrazolo[3,4-c]pyridine

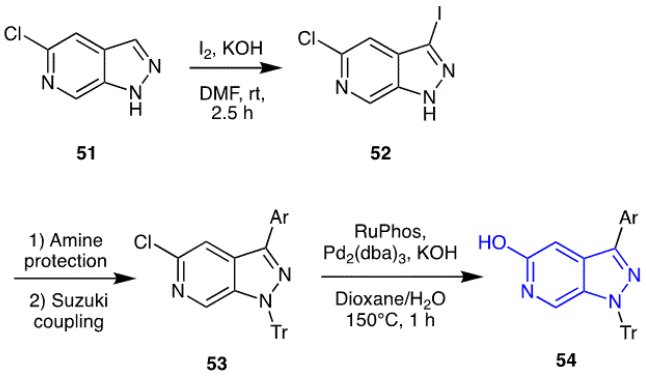
In 2011, researchers from Proximagen patented pyrazolo[3,4-c]pyridin-5-ol compounds as inhibitors of semicarbazide-sensitive amine oxidase (SSAO) involved in the treatment of inflammatory diseases and immune disorders.[39] The 2,5-difluoro-pyridine **45** was regioselectively lithiated at the C4 position of the pyridine ring by LDA (Scheme 13). Electrophilic quenching of the resulting lithiated species with Weinreb amide **46** afforded ketone **47**. Reaction of 4-chlorophenylhydrazinium chloride **48** with ketone **47** and a base gave the corresponding hydrazine which underwent an intramolecular S_NAr and a subsequent nucleophilic substitution of the fluorine atom with hydroxide ions to furnish the expected 5-hydroxy-pyrazolo[3,4-c]pyridine **50** (Scheme 13).



Scheme 13 Synthesis of 5-hydroxypyrazolo[3,4-c]pyridine via an intramolecular SNAr

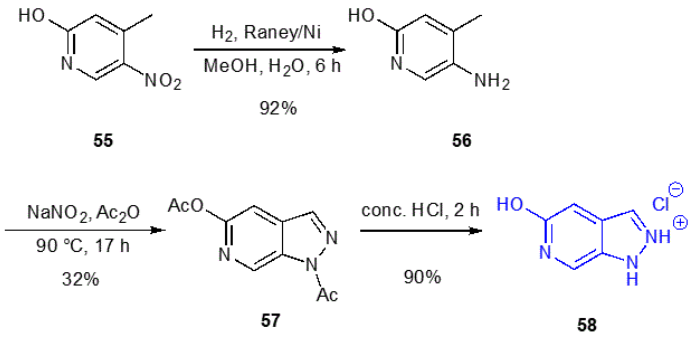
Despite some low yields, this synthetic pathway shows some advantages such as very short reaction times and a potentially easy exemplification with different alkyl or aryl substituents at position 3 and different aryl group at position 1.

More recently, MSD laboratories used the pyrazolo[3,4-c]pyridin-5-ol scaffold as a synthetic intermediate for the development of compounds inhibiting Leucine-Rich Repeat Kinase enzyme activity, which can be used for treatment of Parkinson's Disease.[40] To prepare 3-substituted pyrazolo[3,4-c]pyridin-5-ol **54**, the authors used a synthetic strategy starting from 5-chloro-1*H*-pyrazolo[3,4-c]pyridine **51.** Regioselective iodination at C3 position of the pyridine ring followed by a classical trityl amine protection and a Suzuki coupling afforded aryl-functionalized heterocycles **53**. Finally, 5-hydroxy-pyrazolo[3,4-c]pyridines **54** were obtained using a palladium-assisted nucleophilic substitution-hydroxylation sequence.



Scheme 14 Synthesis of 5-hydroxy-pyrazolo[3,4-c]pyridines by a Pd-mediated nucleophilic substitution-hydroxylation sequence

The latest attempt to synthesize of pyrazolo[3,4-c]pyridin-5-ol was conducted by Silva Júnior and co-workers in 2016.[41] In this paper, they used the same synthetic strategy developed by Chapman and Hurst (Scheme 11) to successfully get the pyrazolo[3,4-c]pyridin-5-ol **58** in 3 steps from 3-nitro-pyridine **55** (Scheme 15).



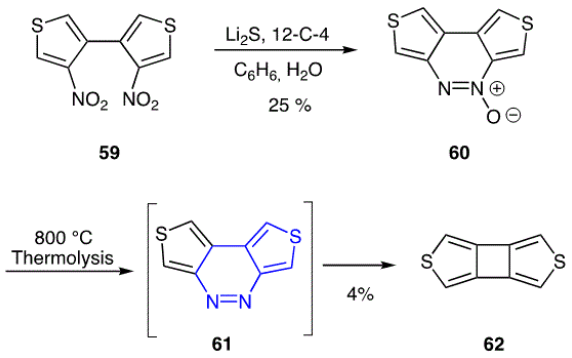
Scheme 15 A three-steps synthesis of pyrazolo[3,4-c]pyridine-5-ol

Furthermore, this three-step sequence was greatly improved using a one-pot methodology. This way, all chromatographic purifications were avoided, and the overall yield jumped from 26% to 82%. However, this strategy is limited by the availability of the starting pyridols which may be a major drawback for an easy access to substituted pyrazolo[3,4-c]pyridine-5-ols. Therefore, post-functionalization on compound **58** could be considered for further applications in the synthesis of original bioactive molecules.

2.8 Thieno[3,4-c]pyridazine-P10

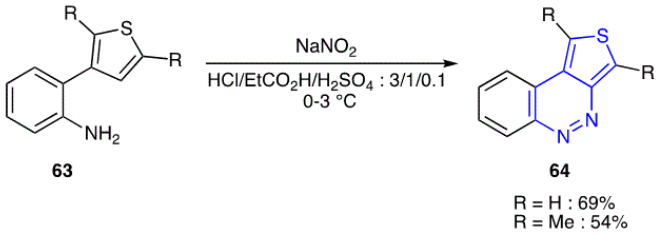
The synthesis of thieno[3,4-c]pyridazine ring system has not been described yet. However, more elaborated tricyclic compounds were prepared before 2009. Interestingly, the dithienopyridazine **61** was observed as an air sensitive intermediate during the synthesis of

cyclobuta[1,2-c:3,4-c']dithiophenes **62** from 4,4'-dinitro-3,3'-bithienyl **59** by Shepherd and co-workers in 1985.[42] (Scheme 16).



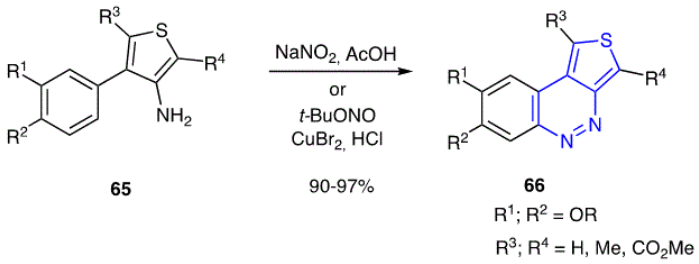
Scheme 16 Dithienopyridazine as intermediate for the synthesis of cyclobuta[1,2-c:3,4-c'] dithiophenes

In the meantime, Barton and co-workers prepared the thieno[3,4-c]cinnolines **64** by an intramolecular diazo coupling reaction on 2-(*o*-aminophenyl)thiophenes **63** (Scheme 17).[43]



Scheme 17 Synthesis of thieno[3,4-c]cinnolines *via* an intramolecular diazo coupling reaction on 2-(*o*-aminophenyl)thiophenes

Fifteen years later, the synthetic strategy to obtain thieno[3,4-c]cinnolines has been improved by a slight modification of the thienyl precursors (Scheme 18). Indeed, moving the amino group from the phenyl ring to the thienyl ring allowed the groups of Rault[44] and Bogza[45] to report the preparation of thieno[3,4-c]cinnolines **66** by diazo coupling reaction on 3-aminothiophenes **65** with good yields. It should be pointed out that the phenyl ring required electron-donating substituents to attack the diazonium moiety. Moreover, when R^1 = H, the cyclization step does not proceed with the same efficiency.

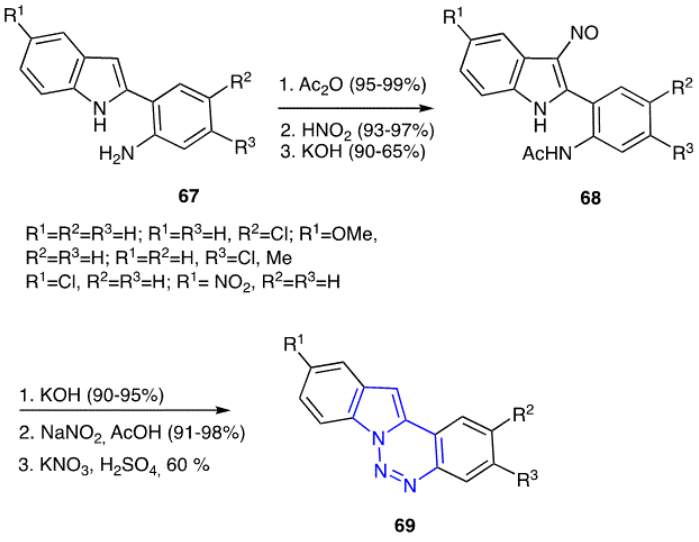


Scheme 18 Synthesis of thieno[3,4-c]cinnolines *via* an intramolecular diazo coupling reaction on 3-aminothiophenes

2.9 Pyrrolo[1,2-c][1,2,3]triazine-P11

The pyrrolotriazine core as its bicyclic form has not been reported yet. However, more elaborated structures have been described and synthesized such as the corresponding indolo- or benzo-triazines.

In 1999, Cirrincione and La Colla reported the potential antimicrobial and antitumor effect of various Indolo[1,2-c]benzo[1,2,3]triazines **69**.[46] The preparation of **69** started from atropoisomeric indoloanilines **67** which were acetylated and nitrosated to give 3-nitrosoindoles **68** in excellent yields (Scheme 19). The removal of the amino protecting group followed by diazotation in the presence of sodium nitrite and acetic acid gave the expecting indolo[1,2-c]benzo[1,2,3]triazines **69** in good yields. It has been proved that in such reaction the C3 position of the indole ring should be substituted to avoid any undesired cyclization. Some years later, the same group reported the preparation of pyrido-pyrrolo benzotriazines exhibiting antitumor activities.[47]



Scheme 19 Synthesis of indolo[1,2-c]benzo[1,2,3]triazines exhibiting antitumor activities

2.10. Thieno[3,4-a]oxazole-P12

The thienyl moiety is well known for its electronic properties and is often used in devices requiring good conduction of electrons. Substituted thienyl[3,4-a]oxazoles have been prepared as

monomers to be incorporated into more elaborated oligomeric structures, conjugated polymers and organic semiconductors **70**[48], **71**[49] and electrochromic material **72** (Figure 5).[50]

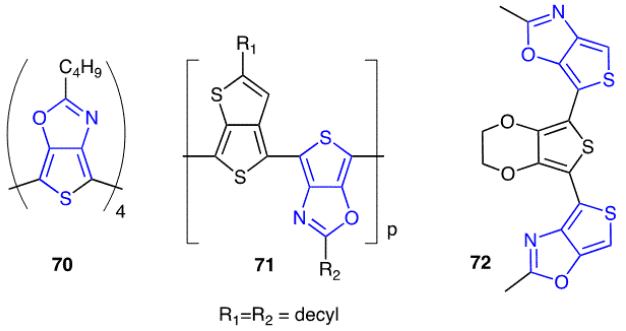
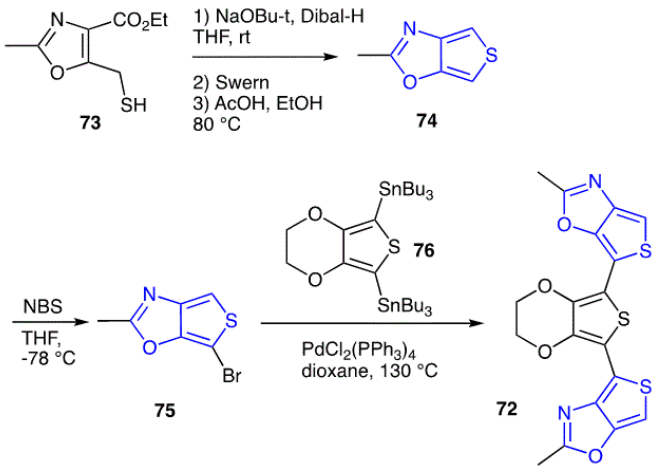


Figure 5 Thieno[3,4-a]oxazoles as organic semiconductors

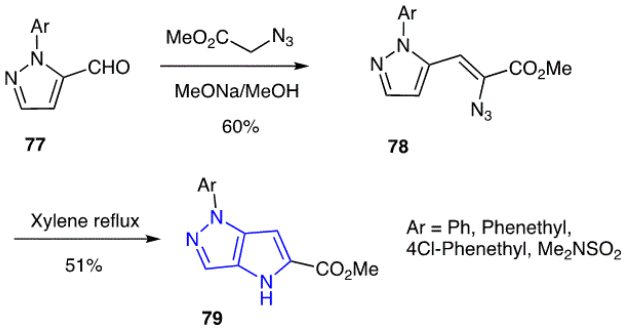
Three patents have reported the use of 6-bromo-2-methylthieno[3,4-d][1,3]oxazole **75** in Stille cross-coupling polymerization to produce coupling product **72**. However, only Otake ad co-workers have described the preparation of bromo thienoxazole **75** in 3 steps from oxazole **73** (Scheme 20).[50] Next monobromation or dibromation of the thienyl system was performed using NBS at low temperature.



Scheme 20 Synthesis of mono bromo-thienoxazole for Stille coupling

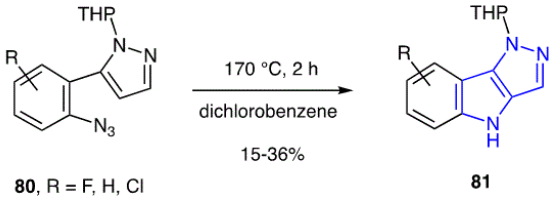
2.11 2,4-dihydropyrrolo[3,2-c]pyrazole-P13

The first synthesis of this heterocycle was published by Merck in 2008 during the reviewing process of Pitt's publication. This heterocycle was identified during an HTS campaign among other fused pyrrole heterocycles to possess potent activity as D-amino acid oxidase (DAO) inhibitors.[51] An efficient two-steps process was used to synthesize various heterobicycles fused pyrrole by a condensation-thermal cyclization sequence. The strategy was adapted to the synthesis of pyrrolo-fused pyrazole **79** by using the appropriate *N*-substituted pyrazole-2-carboxaldehyde **77.** (Scheme 21). Thanks to the good availability of many starting *N*-substituted pyrazole aldehydes, this methodology allowed to generate various *N*-substituted pyrrolo-fused pyrazoles for the further screening as DAO inhibitors.



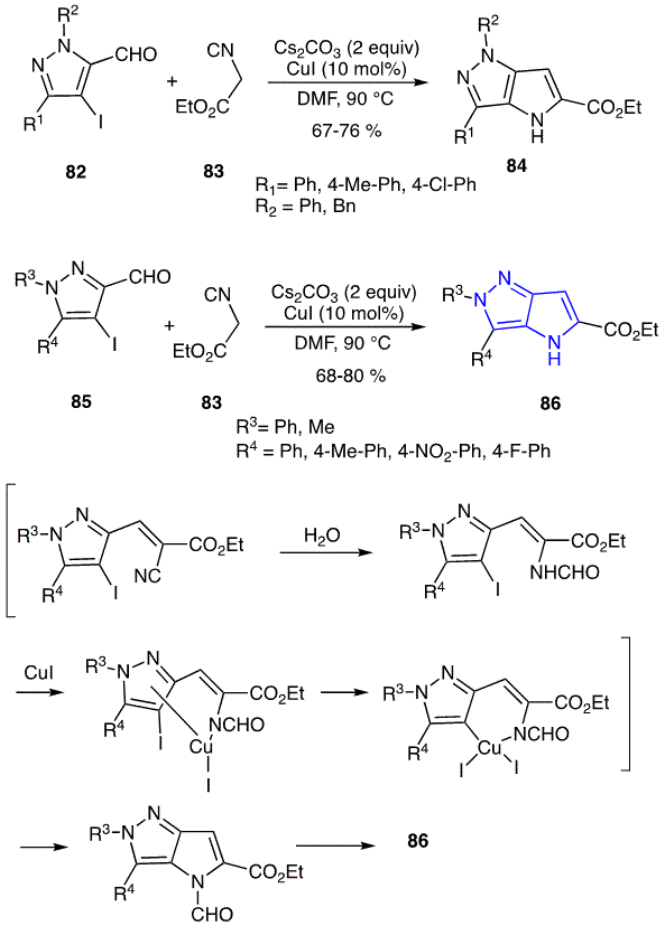
Scheme 21 A two-steps synthesis of 2,4-dihydropyrrolo[3,2-c]pyrazole using a thermal cyclization sequence

A similar thermal cyclization of substituted 2-azidophenyl pyrazole **80** was employed to prepare the indole-fused pyrazole **81** with potent reversible methionine amino-peptidase 2 (MetAP2) inhibition activities, promising for the treatment of obesity (Scheme 22).[52, 53]



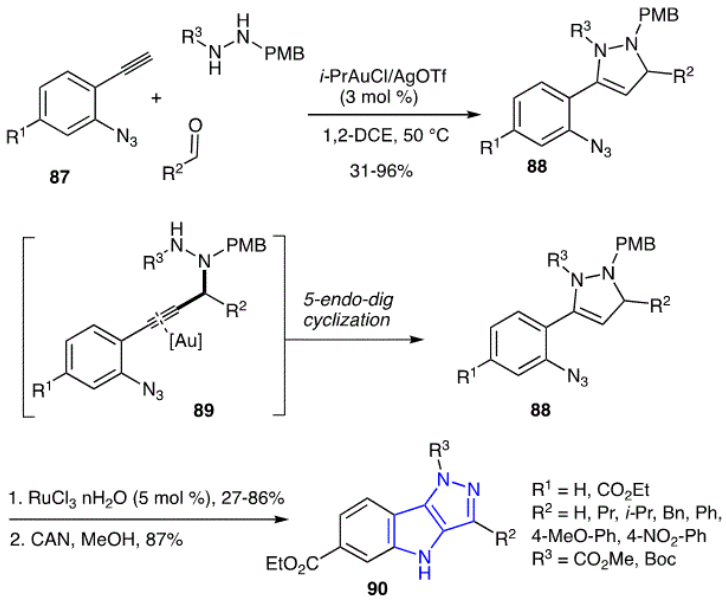
Scheme 22 Synthesis of indole fused pyrazole with potent reversible MetAP2 inhibition activities

In 2012, Batra and co-workers optimized the cyclisation step by using a domino reaction between halogenated pyrazole carbaldehydes and ethylisocyanoacetate in the presence of copper iodide as catalyst (Scheme 23). One should notice that the authors used both tautomeric halogeno pyrazolecarbaldehyde **82** and **85** to get the corresponding pyrrolopyrazoles **84** and **86**.[54] A plausible mechanism for the formation of pyrrolopyrazole involving a condensation reaction -Cu-mediated C-N cross coupling and deformylation sequence was proposed by the authors (Scheme 23). In addition, even less substituted pyrazoles could react under such conditions and gave pyrrole-fused heterocycle with similar yields.



Scheme 23 Preparation of pyrrolopyrazoles isomers using domino reactions

Other pyrazolo[4,3-b]indoles have been reported to act as protein kinase CK2 inhibitors used as therapeutics for cancer treatment. A series of pyrazolo[4,3-b]indoles scaffolds has been prepared *via* a diversity-oriented synthesis. In the synthetic strategy, a gold-catalyzed three-component annulation afforded various dihydropyrazoles **88** with a good control of the diversity of the substituents (Scheme 24). The mechanism involved a Mannich-type coupling reaction followed by a *5-endo-dig* cyclization step from the (alkynyl) gold (I) complex **89**. The desired indole-fused heterocycles **90** were next obtained *via* an intramolecular C-H amination and oxidative aromatization in moderate yield.[55] The standard protocol was extended to the synthesis of other polysubstituted scaffolds by using both electron-withdrawing and electron-donating substituent on ethynylbenzene, other protected hydrazines and aldehydes with good tolerance.



Scheme 24 Synthesis of pyrazolo[4,3-b]indoles, potent protein kinases CK2 inhibitors.

2.12 Pyrazolo[1,5-b]isoxazole-P14

This heterocycle has been used in 2016 by Konica Minolta as a substructure of tetracyclic pyrido- and benzo-fused ligands to construct blue phosphorescent iridium (III) **91** and platinum (II) **92** complexes (Figure 6).[56]

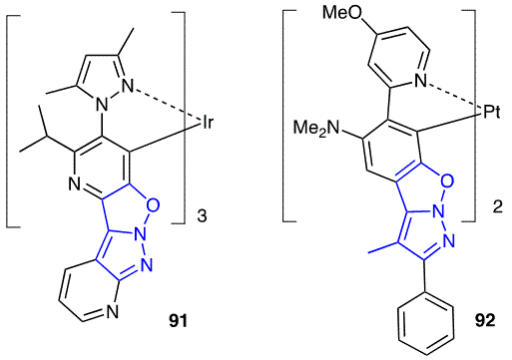
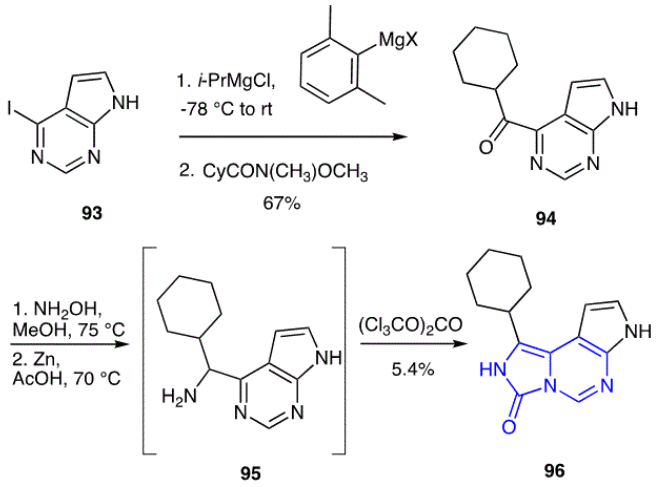


Figure 6 Phosphorescent iridium(III) and platinium (II) complexes based on benzofused pyrazoloisoxazoles

2.13 Imidazo[1,5-c]pyrimidin-3(2*H*)-one-P16

A tricyclic version of these heterocycles has only been reported so far. Imidazo-fused pyrrolo-pyrimidin-3-ones including the bicyclic ring have been described as Janus kinase (JAK) inhibitors for the prevention or treatment of organ transplant rejection.[57] The synthesis of imidazopyrimidone core **96** began with the condensation of an *in-situ* generated pyrimidine Grignard from iodo pyrimidine **93**, with the desired Weinreb amide. It afforded ketone **94** which was converted into amine **95** by reductive amination. A final addition of triphosgene allowed the formation of imidazopyrimidone **96** albeit in low yield (Scheme 25).

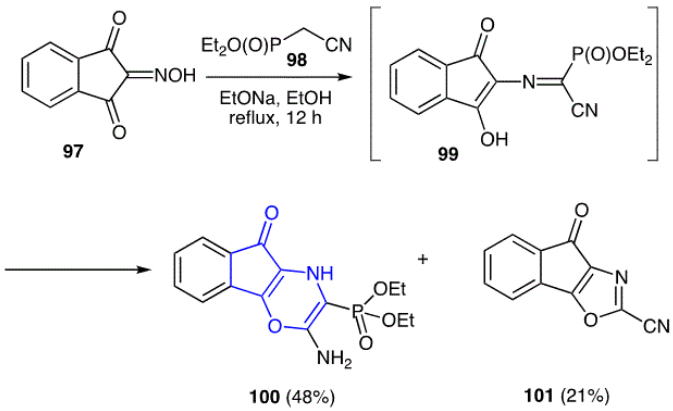


Scheme 25 Synthesis of imidazo-fused pyrrolo pyrimidin-3-one, a potent Janus kinase inhibitor

2.14 Cyclopenta[b][1,4]oxazin-5(4*H*)-one-P17

Nothing is known about this heterobicycle yet. However, benzofused cyclopenta[b][1,4]oxazin-5(4*H*)-one phosphoresters have been reported in the literature in 2008 by Abdou and co-workers and screened against bacteria and fungi.[58] Compound **100** showed a good fungicidal activity when it was tested against *D. specifera*.

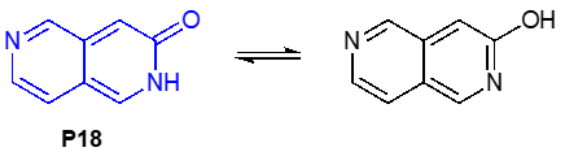
Fused oxazinephosphonate **100** was synthesized from oxime **97** (Scheme 26). The reaction of the sodium anion of diethylcyanomethylphosphonate **98** with oxime **97** gave after dehydration the adduct **99** which cyclized under basic condition to give the oxazine **100** in 48% yield together with oxazole **101** in 21% yield (Scheme 26).



Scheme 26 Synthesis of benzo-fused cyclopenta[b][1,4]oxazin-5(4*H*)-one with fungicidal activities

2.15 2,3-dihydro-2,6-naphthyridin-3-one-P18

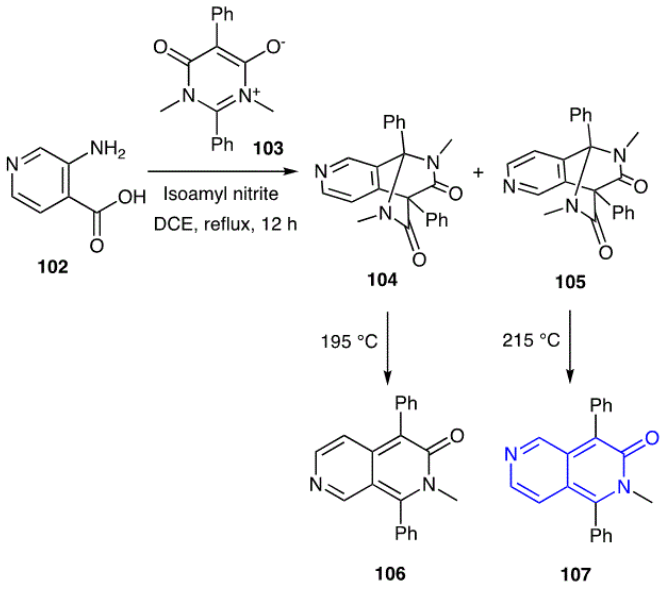
Heterocycle **P18** could be considered as the aza-analog of 3-hydroxyisoquinoline (HIQ) exhibiting lactim–lactam tautomerization and used as organic blue emitters[59] or as inhibitors of hepatitis C Virus ribonucleic acid (RNA) polymerase (Scheme 27).[60]



P18

Scheme 27 Tautomeric forms of 2,3-dihydro-2,6-naphthyridin-3-one

The first synthesis of substituted azaisoquinolinones was reported in 2013 by Li and co-workers using a two-steps strategy (Scheme 28).[61] The [4+2] cycloaddition reaction between mesoionic pyrimidine **103** and 3,4-pyridyne intermediate *in-situ* generated from 3-amino-pyridine-4-carboxylic acid **102** afforded a mixture of two separable isomers **104** and **105.** Each of the two isomers **104** and **105** decomposed at high temperatures via a retro Diels-Alder reaction to give respectively **106** and **107**. Despite a relatively straightforward strategy, this method only provides diphenylated heterocycles with *N*-methylated lactam.

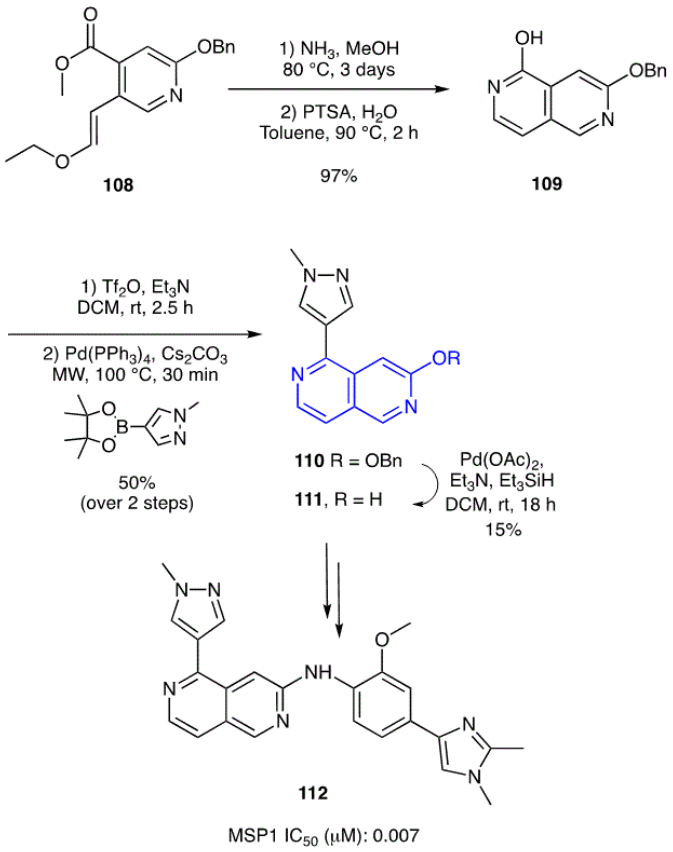


Scheme 28 Synthesis of 2,3-dihydro-2,6-naphthyridin-3-ones *via* a [4+2] cycloaddition reaction

During their work, Li and co-workers found that the position of the nitrogen atom in azaisoquinolinones plays a key role in the optical properties of these novel compounds. Differences in emission wavelengths and intensities in fluorescence were noticed between the two isomers allowing 6-azaisoquinolinone **107** to be used as a more efficient colorimetric probe for Fe^{3+} ions compared to its isomers 7-azaisoquinolinone **106**.

In 2014, the Cancer Research Technology patented the preparation of some isoquinolines-based heterocycles and their use as monopolar spindle 1 (Mps-1) inhibitors for the treatment of cancer.[62]

Among them, the general scaffold 6-azaisoquinolinone proposed by Pitt was described as its tautomeric form with a methyl pyrazole substituent at the 5-position (Scheme 29). Ethoxyvinylisonicotinate **108** was reacted with methanolic ammonia followed by acidic treatment with PTSA to afford naphthyridine ring **109** in high yield**.** After activation of the resulting hydroxyl group into triflate, the methyl pyrazole substituent was then introduced at the 5-position from the corresponding aryl boronic ester *via* a classical Suzuki coupling. Finally, the benzyl protecting group was removed using catalytic palladium acetate and triethylsilane to restore the azaisoquinolinol core of compound **111.** This one was next transformed into naphthyridine amine **112** and tested as Mps-1 inhibitors showing promising micromolar activities to target cancer (Scheme 29).

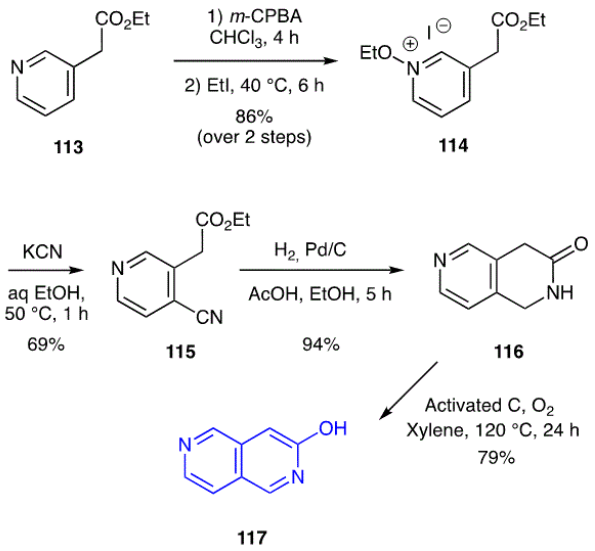


Scheme 29 Synthesis of 2,6-naphthyridin-3-ol as intermediate of efficient Mps1 inhibitor

Despite numerous drawbacks, such as long reaction times and a low yield in the final step, this strategy gives access to differently substituted original heterocycles.

More recently, Silva Júnior and co-workers have reported a straightforward and efficient synthesis of two molecules selected from Pitt's list. Ethyl 2-(pyridin-3-yl) acetate **113** easily underwent N-oxidation followed by O-alkylation to afford compound **114** in high yield (Scheme 30).[41] Thanks to this modification on the pyridine ring, nucleophilic addition of cyanide was made possible and furnished intermediate **115** after rearomatization. The cyano group was further hydrogenated to give the amine intermediate which spontaneously cyclized into lactam **116**. At this stage, the final step involved the oxidation of **116** into the desired heterocycle **117**. Yet, this reaction turned out to be the most challenging as classical dehydrogenation methods (Pd/C, DDQ, and MnO_2) did not succeed.

Finally, by using activated charcoal under an oxygen-rich atmosphere, they obtained the desired "ring of the future" **117** in good yield (Scheme 30).[41]



Scheme 30 A recent strategy to access 2,6-naphthyridin-3-ol

3 Conclusion

In this review, we have highlighted the contribution of the publication "heteroaromatic rings of the future" in the quest of renewal of rings scaffolds for medicinal uses. We hope to have demonstrated that the study of Pitt has challenged the creativity of synthetic organic chemists giving some clues to medicinal chemistry program. Colin Groom, one of the co-authors of heteroaromatic rings of the future article said in 2009: "I would love people to try and make some of these molecules because that will show whether or not our predictions are right about which ones can and can't be made".[63] From the twenty-two heteroaromatic rings selected by Pitt, nine bicyclic systems have been synthesized and functionalized confirming the prediction of their synthetic feasibility from calculation studies. Five of them (**P6**, **P7**, **P9**, **P13** and **P18**) have been evaluated in medicinal programs and showed promising biological activities. Only one (**P12**) found application as organic semiconductor. Despite a good synthetic feasibility few of the twenty-two have not been synthesized yet and remain a synthetic challenge for the chemist community. Interestingly, in his article, Pitt chose to show a small set of twenty-two simple rings systems among a complete list of thousands of original structures still unconquered that have been entirely reported in the virtual exploratory heterocyclic library "VEHICle" database available on the European bioinformatics institute website (www.ebi.ac.uk).

The files contain over 3,000 of heteroaromatic rings considered as viable, still waiting creative medicinal organic chemists to be synthesized and evaluated in programs.

Pitt focused on heteroaromatic ring systems as a model set for his virtual exploring work since these 2D flat rings systems are common in bioactive compounds and pivotal in series developed by medicinal chemists' community. However, the use of 2D flat systems as main medicinal scaffolds has been recently controverted. Hydrophobic nature, flat shape and the lack of flexibility seem to limit the success of heteroaromatic core to explore the 3D nature of biological systems. In the meantime,

of Pitt's publication, Lovering and co-workers demonstrated in their publication "Escape from flatland" an approach to improve clinical success by increasing saturation and by incorporating chiral center in molecules.[64] They demonstrated that in 3D- molecules the presence of saturation allows to access wider area of chemical space and to increase both solubility and selectivity. Interestingly, even if this movement is critical about 2D-flat systems for drug discovery, both authors of these two articles are searching in the same direction and are complementary in the exploration of chemical space.

Acknowledgment

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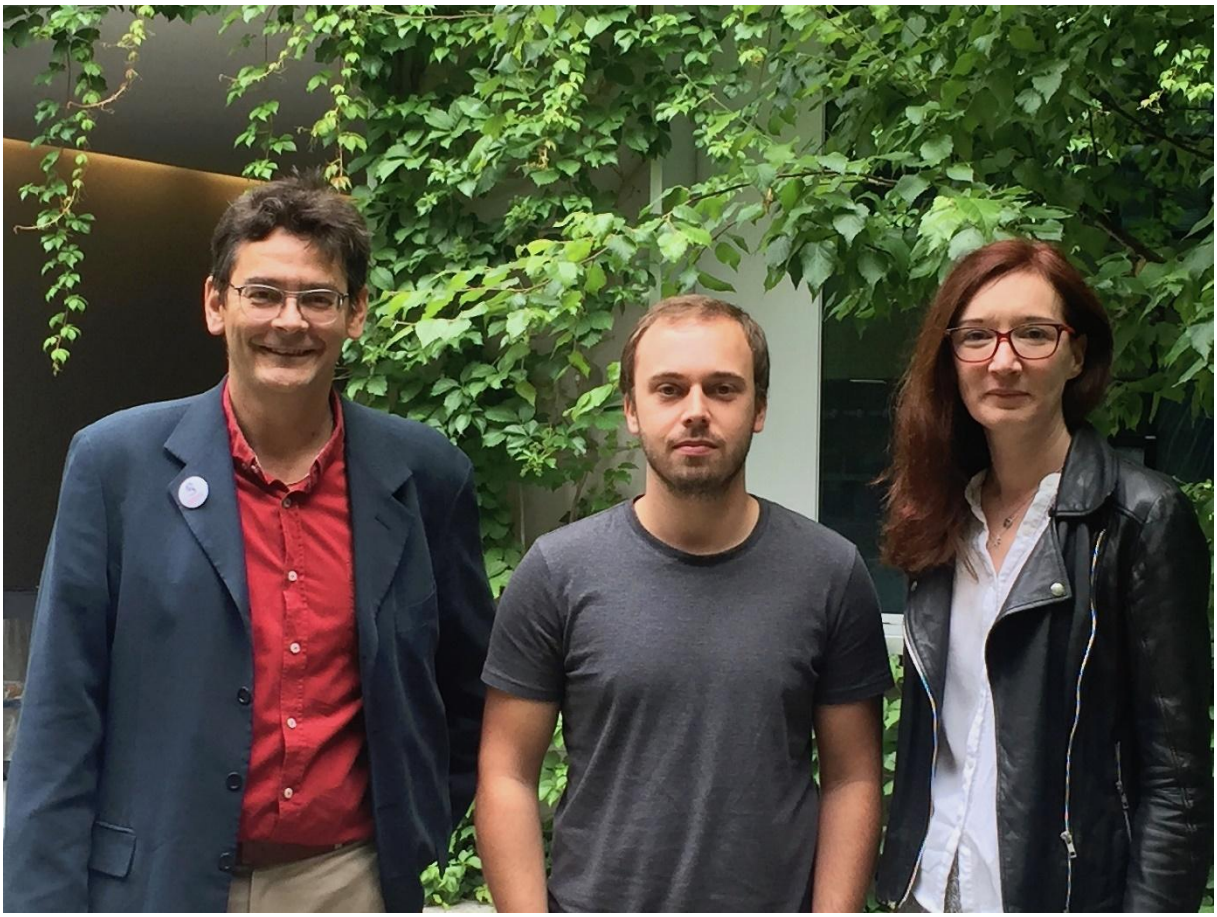
Biosketches



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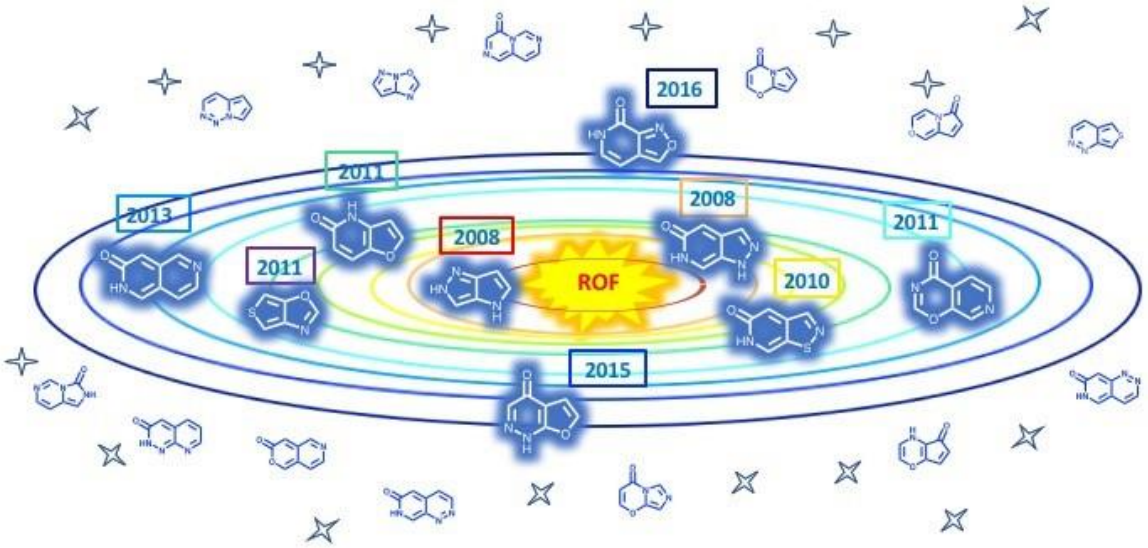

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