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Chemistry of Heterocyclic Compounds **2017**, *53*(3), 240–255

REVIEWS

N-(Hetero)aryl-2-imidazolines: an emerging privileged motif for contemporary drug design

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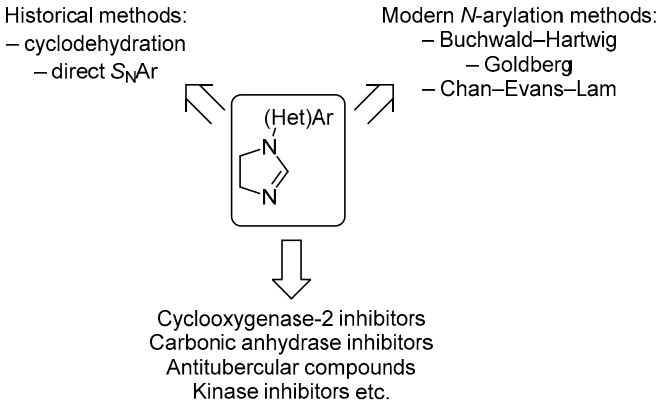

The diverse biological activities of compounds containing *N*-(hetero)aryl-2-imidazoline moiety and methods to construct them are comprehensively reviewed for the first time. This intriguing non-flat, cyclic amidine motif clearly represents an emerging privileged structure.

Keywords: cyclodehydration, imidazoline *N*-arylation, lead-like compounds, privileged structures.

2-Imidazolines represent a distinctly important case of cyclic *N,N'*-dialkylamidines, as they act as primary modulators of an entire family of cell surface receptors which are expressed in the central nervous system and, notably, were designated imidazoline receptors due to the high affinity to 4,5-dihydro-1*H*-imidazole-containing compounds.[1] 2-Imidazoline scaffold is central to numerous biologically active compounds whose targets are vastly different from imidazoline receptors, as was reviewed recently.[2] Prominent examples include estrogen receptor modulator **1** for oncology applications,[3] proteasome inhibitor **2** for multiple myeloma,[4] P_2X_7 ion channel blocker **3** useful in the treatment of inflammatory conditions,[5] and Nutlin-3 (**4**)[6] known to disrupt the oncogenic p53-mdm2 protein–protein interactions (Fig. 1). Thus, one can confidently regard the 2-imidazoline core as a privileged scaffold for drug design, as defined by Evans et al.[7]

Acyclic *N*-(hetero)aryl amidines have been richly exemplified in the synthetic chemistry literature[8,9] and can be accessed *via* a number of arylation protocols from the parent amidine substrates. *N*-Arylation of substrates containing a nucleophilic (basic) nitrogen atom is an important modification in the practice of medicinal chemistry the consequences of which are generally

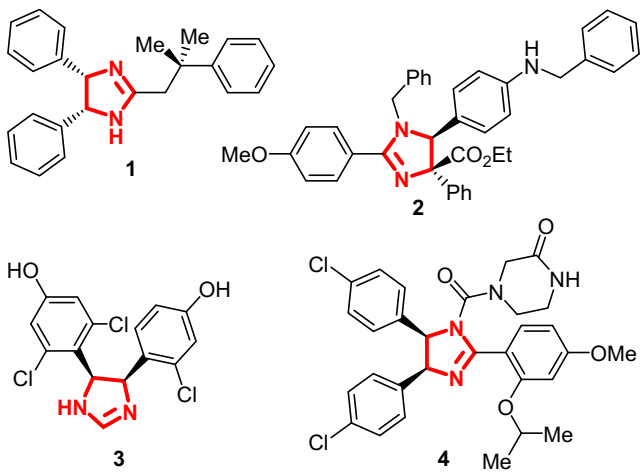

Figure 1. Examples of biologically active 2-imidazolines.

Here and further the corresponding author is marked with *.

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twofold. On the one hand, introduction of an aryl (or heteroaryl) substituent at a nitrogen atom attenuates its basicity. On the other, addition of an aromatic group increases compound's lipophilicity and creates new opportunities of building specific contacts with a protein target *via* hydrophobic and π-stacking interactions.[10] Hence, various acyclic *N*-(hetero)arylamidines have found utility in the medicinal chemistry design.[11] The same, however, could not be said about *N*-(hetero)aryl-2-imidazolines even five years ago when only a handful of examples had been reported in the literature.

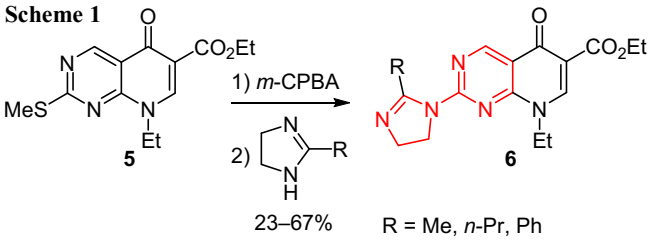
In 2012, we became puzzled by the absence of dedicated methodology studies on the *N*-(hetero)arylation of 2-imidazolines and developed[12] a Buchwald–Hartwig-type method to prepare lead-like[13] and even fragment-like[14] *N*-(hetero)aryl-2-imidazolines as discussed below. Capitalizing on this methodology, we have now identified a number of bioactive chemical series that employ the said *N*-(hetero)arylation as a primary scaffold-generating event. Considering the range of diverse biological activities identified for these compounds based on this scaffold in relatively short period of time, we would like to designate *N*-(hetero)aryl-2-imidazolines as an emerging privileged motif useful for the drug design and aim to summarize the chemistries and the biological data substantiating this motion in present review.

Early (pre-2012) examples of 2-imidazoline *N*-(hetero)arylation

Until dedicated methodological efforts on metal-catalyzed *N*-(hetero)arylation of 2-imidazolines commenced in 2012,[12] the literature reports amounted to a handful of isolated examples, primarily in the patent literature, which included either direct S_NAr-type *N*-(hetero)-arylation or a few cases of the same reaction brought about under Pd- or Cu-catalyzed conditions.

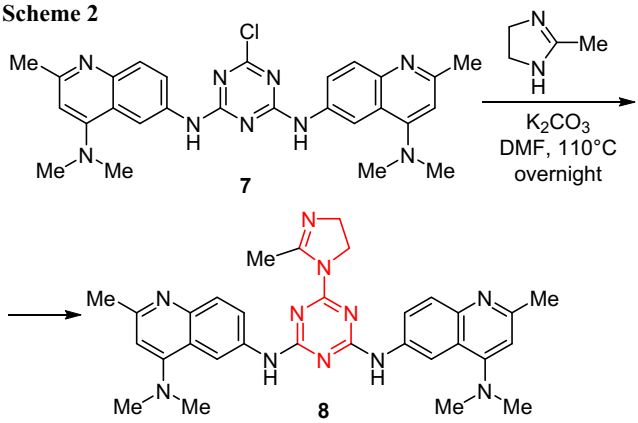
Examples of direct S_NAr using 2-imidazoline as a nucleophile are limited to very active aromatic electrophilic partner. The first example ever encountered was a part of a 1975 study, reported by Servier researchers, directed toward development of antibacterials. In this work, a series of 2-imidazoline-substituted 6,8-diazaquinolonic acid esters **6** was produced by reacting their sulfone precursor (generated *in situ* from compound **5**) with appropriate 2-imidazolines (Scheme 1).[15]

Scheme 1



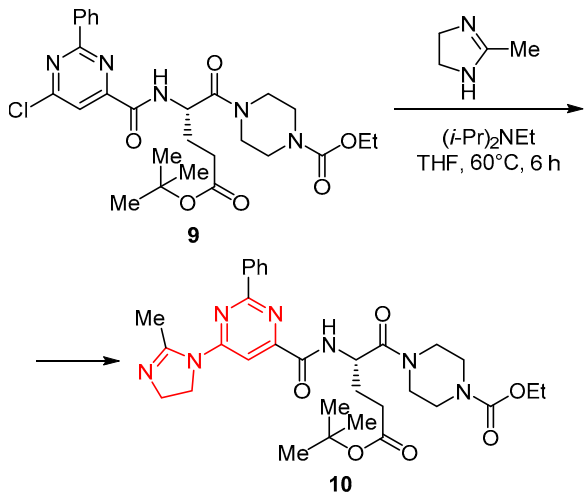
The interest to *N*-(hetero)aryl-2-imidazoline moieties for medicinal chemistry design seemed to have been dormant for over 25 years, i.e., until 2002 when Aventis scientists used 2-methylimidazoline to displace chlorine in precursor **7** *en route* to telomerase inhibitor **8** *via* a base-promoted S_NAr reaction (Scheme 2, yield not reported).[16]

Scheme 2



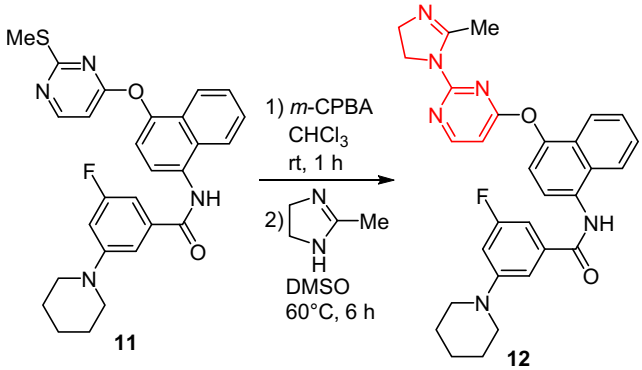
A similar reaction with 4-chloropyrimidine **9** reported by Actelion Pharmaceuticals required much less forcing conditions and delivered P2Y12 receptor antagonist **10**, representative of a useful class of antithrombotic agents (Scheme 3, yield not reported).[17]

Scheme 3



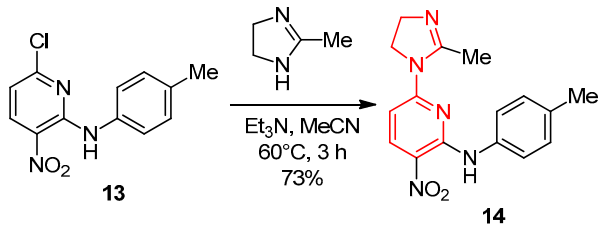
N-Heteroarylation of 2-methylimidazoline with 2-chloropyrimidine **11** reported in the preparation of p38 MAP kinase inhibitor **12** by Glaxo required that the methylsulfanyl group be oxidized to a more labile methyl sulfone prior to the displacement (Scheme 4, yield not reported).[18]

Scheme 4



The previous three examples included S_NAr events at the pyrimidine or 1,3,5-triazine nucleus. Korean scientists described a similar chlorine displacement at 6-anilino-5-nitropyridine **13** to produce compound **14** (Scheme 5) investigated for inhibition of osteoblast differentiation, a promising approach for the treatment of osteoporosis.[19]

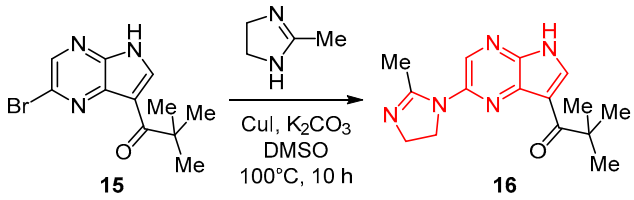
Scheme 5



13 **14**

The only example of Cu-catalyzed *N*-arylation of 2-imidazolines encountered in the literature prior to 2012 is the preparation, by the Roche scientists, of JAK and SYK kinase inhibitors *via* intermediate **16** synthesized, in turn, *via* *N*-heteroarylation of 2-methylimidazoline with pyrrolopyrazine bromide **15** (Scheme 6, yield not reported).[20]

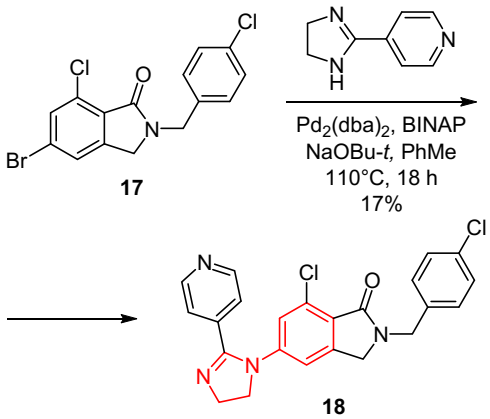
Scheme 6



15 **16**

Reports on Pd-catalyzed reactions are similarly scarce prior to 2012. Only one such example, $Pd_2(dba)_3$–BINAP-catalyzed and somewhat low-yielding *N*-arylation of 2-(4-pyridyl)imidazoline with 5-bromoisoindolinone **17**, was disclosed by AstraZeneca as a part of a large set of metabolotropic glutamate receptor potentiators exemplified by compound **18** (Scheme 7).[21]

Scheme 7

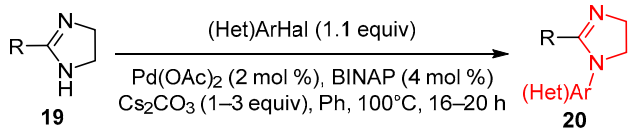


17 **18**

Dedicated methodology studies toward 2-imidazoline *N*-(hetero)arylation

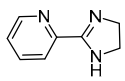
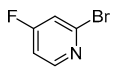
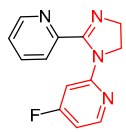
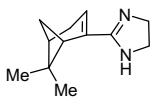
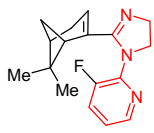
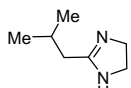
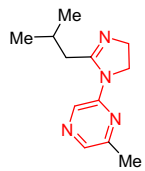
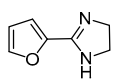
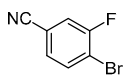
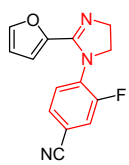
Lead-[13] and fragment-like[14] compounds are scarce in the world's modern arsenal of screening libraries. Aiming to fill that void, we paid a particular attention to *N*-(hetero)-aryl-2-imidazolines as a rich source of such compounds. The absence of robust, amply exemplified methodology studies toward these compounds in the literature (*vide supra*) prompted us to investigate and develop a Pd-catalyzed Buchwald–Hartwig-type arylation protocol (Scheme 8) that was found applicable to a range of 2-imidazolines **19** and various electron-deficient (hetero) aromatic halides (the scope of the reaction is concisely captured by selected products **20** shown in Table 1).[12] The molecular metrics presented (molecular weight (MW) and partition coefficient (cLogP)[22]) clearly attests to these compounds' being well within the limits of lead-likeness and fragment-likeness (defined by the 'rule-of-three', i.e., MW < 300 and cLogP < 3.0).[23]

Scheme 8



19 **20**

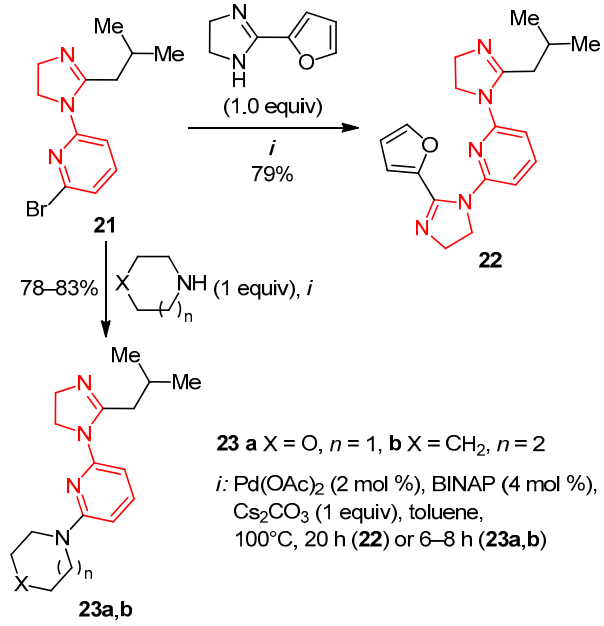
Table 1. The scope of Buchwald–Hartwig-type *N*-(hetero)arylation of 2-imidazolines

Starting materials		Product			
19	(Het)ArHal	**20**	Isolated yield, %	MW	cLogP
			78	242.3	0.79
			66	285.4	2.66
			78	218.3	2.12
			24	255.3	1.85

The Buchwald–Hartwig *N*-arylation protocol, despite the somewhat forcing conditions required to achieve good conversions in this reaction, was found to be compatible with a 2-imidazoline moiety already present in the

heteroaryl halide partner (like in compound **21**). This finding allowed us to bring about a second Pd-catalyzed coupling without the disruption of the 2-imidazoline linkage – either with another 2-imidazoline moiety or with a secondary amine – to produce compounds **22** and **23a**,**b**, respectively (Scheme 9).[12] The possibility to perform sequential "imidazolination" of dihalo(hetero)aromatic substrates found a particular utility in the design of bioactive compounds discussed below.

Scheme 9



The Pd-catalyzed Buchwald–Hartwig arylation displayed an obvious limitation of scope, namely, being workable only for highly reactive, electron-deficient halo(hetero)aromatics. In 2013, the Bull team from Imperial College London described a ligand-free, CuBr-catalyzed approach to *N*-(hetero)aryl-2-imidazolines (Scheme 10), which employed a wider range of iodo(hetero)aromatic reagents, including electron-neutral and even electron-rich ones, as illustrated in Figure 2.[24]

Scheme 10

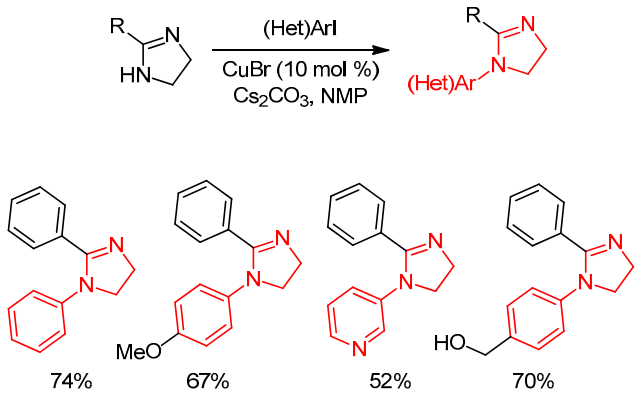
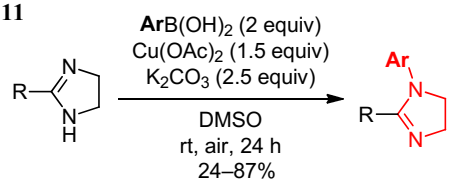


Figure 2. Examples of *N*-(hetero)aryl-2-imidazolines obtained by CuBr-catalyzed protocol.

Both methods described above suffer from the same drawback, namely, requiring elevated temperatures to achieve conversion to the product. This makes the methods inapplicable to thermally-unstable substrates. To circumvent this obstacle, we developed a Chan–Evans–Lam copper(II)-promoted *N*-(hetero)arylation of 2-imidazolines (Scheme 11) using a collection of boronic acids. This finding allowed not only tapping into the vast reagent space of aromatic boronic acids (commercially available or ad hoc synthesized), but also conducting the (hetero)arylation reaction at ambient temperature while achieving full conversions and excellent product yields (Scheme 11, Fig. 3).[25]

Scheme 11



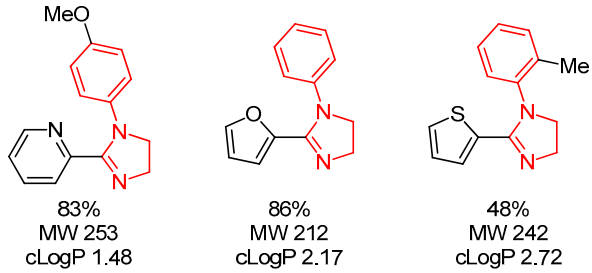
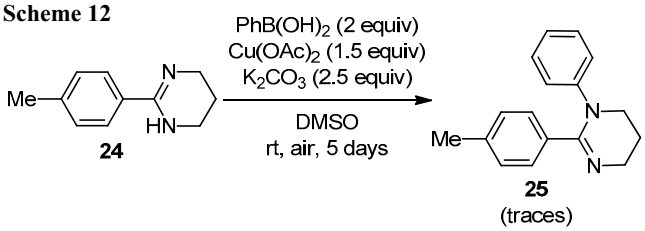


Figure 3. Examples of *N*-(hetero)aryl 2-imidazolines obtained by the Chan–Evans–Lam protocol.

Interestingly, the same protocol was found inapplicable to the *N*-arylation of 1,4,5,6-tetrahydropyrimidine **24** as it yielded only a trace amount of the anticipated product **25** (Scheme 12). This was in line with the previous report[26] where Pd-catalyzed *N*-(hetero)arylation of 1,4,5,6-tetrahydropyrimidine was only marginally effective, which attests to 2-imidazoline scaffold's being a stand-alone class of heterocycles rather than a mere version of a cyclic amidine.

Scheme 12



Isoform-selective inhibitors of human cyclooxygenase-2 and carbonic anhydrase

Vicinal diaryl heterocycles **26** in which one of the aromatic rings is substituted with an amino- or methylsulfonyl group represent an important class of non-steroidal anti-inflammatory agents, selective cyclooxygenase-2 (COX-2) inhibitors, useful in treatment of such debilitating

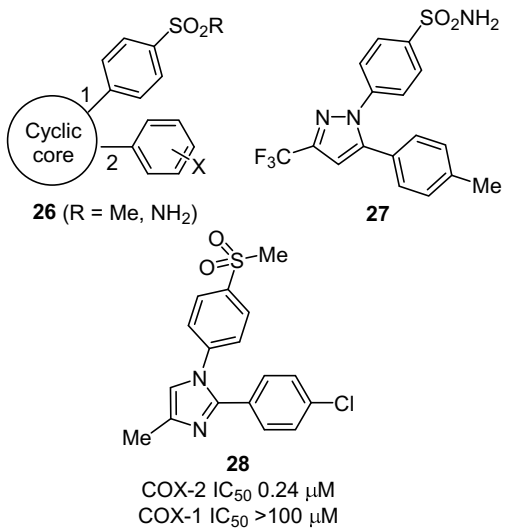
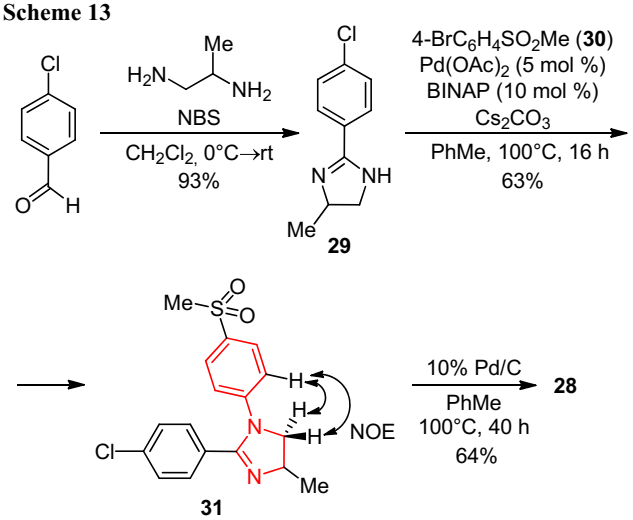


Figure 4. General structure of selective COX-2 inhibitors (compound **26**), celecoxib (**27**), and an advanced imidazole-based inhibitor from Searle (compound **28**).

chronic condition as rheumatoid arthritis. This class of drugs is represented, among others, by the blockbuster drug celecoxib (Celebrex®) (**27**).[27] The latter drug was originally developed by G. D. Searle & Co. (now a fully-owned subsidiary of Pfizer) as part of a large-scale project exploring various heterocyclic chemotypes besides pyrazole present in compound **27**. One of the advanced compounds displaying a marked COX-2 potency (and selectivity *vs* COX-1) was imidazole derivative **28**[28] (Fig. 4).

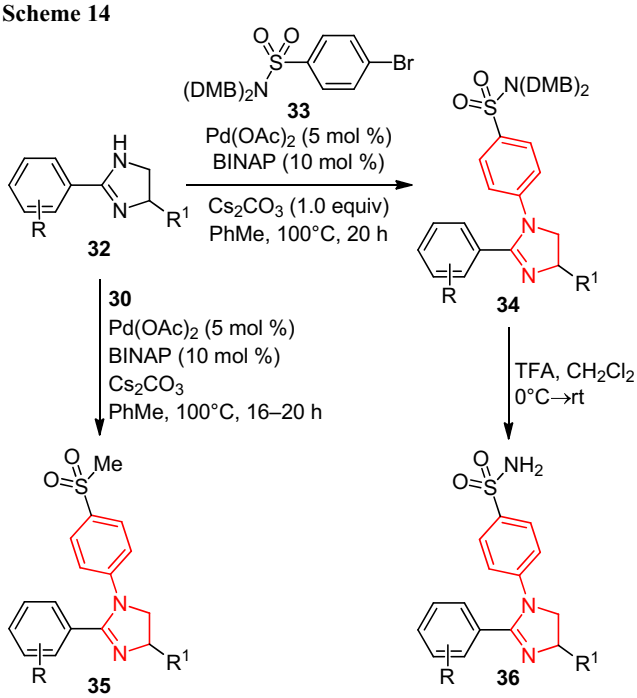
Considering the structure **28**, we reasoned that the published synthesis of this compound[28] can be altered to include an *N*-arylation step of 2-imidazoline developed by us earlier.[12] This turned out to be true, as *N*-arylation of 4-methylimidazoline **29** with 1-bromo-4-methylsulfonylbenzene (**30**) proceeded with a high yield (likely due to the electron-deficient character of sulfone **30**) and regiospecifically at the less hindered nitrogen atom (ratio of isomers >10:1, identity confirmed by NOESY spectrum of product **31**). The latter was aromatized into imidazoline **28** by dehydrogenation on Pd/C (Scheme 13).[29]

Scheme 13



While being short and high-yielding, the above synthetic route included a cumbersome aromatization step. This gave us an idea to consider *N*-arylimidazolines (like compound **31**) as potential COX-2 inhibitors. At the onset, it was considered a risky move due to the popular dogma articulated in the literature[30] that potent and selective COX-2 inhibitors could be designed only around flat, aromatic, and relatively lipophilic cores (of which 2-imidazoline is neither). To verify this bold hypothesis, we performed a Pd-catalyzed *N*-arylation of a set of 15 2-imidazolines **32** (selected on the basis of the SAR information for imidazole inhibitors[28]) with either sulfone **30** or with 2,4-dimethoxybenzyl-protected (DMB-protected) sulfonamide **33** er (Scheme 14). This resulted in the set of 15 methylsulfone compounds **35** and 15 primary sulfonamides **36** (obtained after removal of the DMB groups in the initial *N*-arylation products **34**).[31]

Scheme 14



While methylsulfone derivatives **35** turned out completely inactive against COX-1 and COX-2, one of primary sulfonamides (compound **36n**) displayed a COX-2 inhibitory potency comparable to that of celecoxib (**27**) and also a better COX-2 selectivity (Fig. 5).[32]

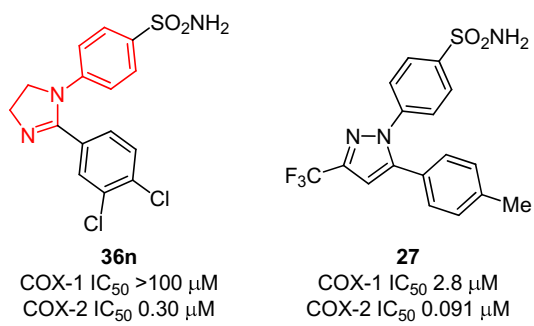
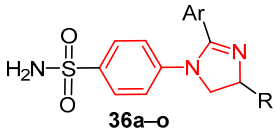


Figure 5. Comparison of the *in vitro* pharmacological profile of compounds **36n** and **27**.

Table 2. Inhibitory activity data for compounds **36a–o** obtained against *h*CA isoforms I, II, IV, and VII



36a–o

Compound	Ar	R	K_i, nM				SI (*h*CAIV/*h*CAII)
			*h*CAI	*h*CAII	*h*CAIV	*h*CAVII	
36a	4-FC_6H_4	H	2,343.0	76.1	9,726.0	303.5	127.8
36b	4-FC_6H_4	Me	816.5	52.4	8,705.0	86.6	166.1
36c	4-ClC_6H_4	H	960.5	46.7	8,142.0	269.0	174.3
36d	4-ClC_6H_4	Me	897.9	54.1	6,785.0	69.6	125.4
36e	3-BrC_6H_4	H	1,844.0	53.0	5,010.0	204.7	94.5
36f	3-BrC_6H_4	Me	1,281.0	55.3	5,272.0	45.8	95.3
36g	3-FC_6H_4	H	3,230.0	75.9	>10,000	311.6	131.8
36h	3-ClC_6H_4	H	1,668.0	185.1	5,701.0	204.2	30.8
36i	3-MeC_6H_4	H	3,943.0	111.9	9,778.0	906.7	87.4
36j	3-F,4-$MeOC_6H_3$	H	1,231.0	80.7	8,266.0	709.4	102.4
36k	4-F,3-$MeOC_6H_3$	H	2,166.0	61.6	4,228.0	258.6	68.6
36l	3-Cl,4-$MeOC_6H_3$	H	3,987.0	227.1	>10,000	1039	44.0
36m	3,4-diFC_6H_3	H	746.8	34.6	5,381.0	71.3	155.5
36n	3,4-diClC_6H_3	H	787.7	30.2	932.0	35.5	30.9
36o	4-Cl,3-$CF_3C_6H_3$	H	3,685.0	84.3	3,845.0	32.6	45.6
Acetazolamide			250.0	12.0	74.0	2.5	6.2

The presence of the primary sulfonamide moiety in compound **36** prompted us to investigate the above series of 15 compounds as inhibitors of various isoforms of human carbonic anhydrase (*h*CA).[33] This ubiquitous enzyme superfamily is known to be inhibited by primary sulfonamides due to the latter group binding to the enzyme prosthetic zinc ion.[34] As shown in Table 2, compounds **36a–o** displayed an excellent (pK_i 7–8) inhibitory profile against *h*CAII (a cytosolic anti-glaucoma and anti-edema biological target) and *h*CAVII (also a cytosolic target believed to be involved in epilepsy and neuropathic pain) and a marked (1–2 orders of magnitude) selectivity (SI) against cytosolic isoform *h*CAI and membrane-bound isoform *h*CAIV.

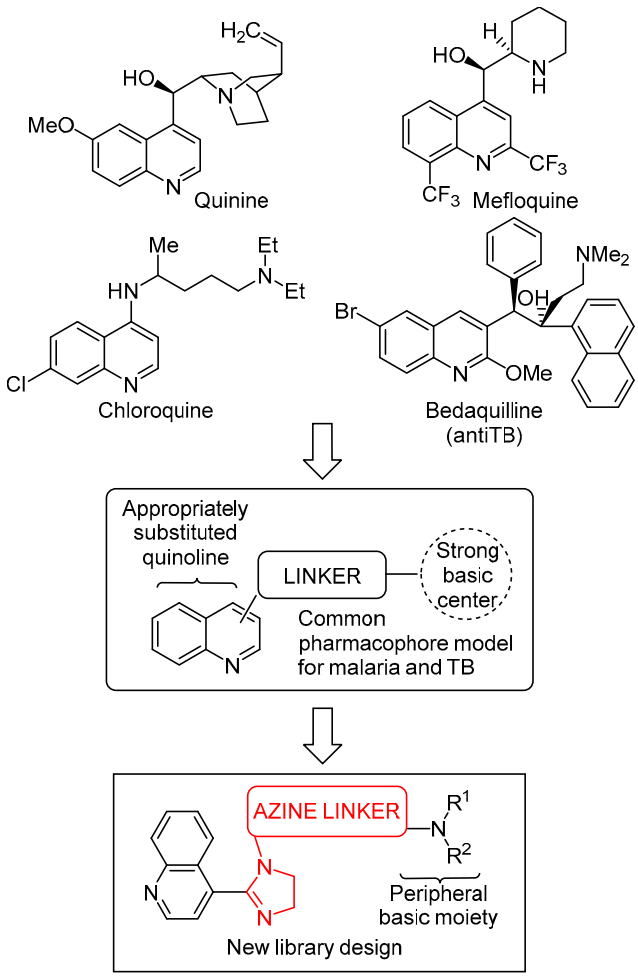


Figure 6. Focused 2-(quinolin-4-yl)imidazoline library design.

Antitubercular 2-imidazoline-based compounds

N-Heteroaryl-2-imidazoline moiety has been explored[35] as a scaffold for the design of a 2-(quinolin-4-yl)-imidazoline library focused to display antimalarial and/or antitubercular activity as shown in Figure 6.

Compounds exemplifying the library design were synthesized according to the sequential Buchwald–Hartwig protocol (Scheme 15) employing 2-(quinolin-4-yl)imidazoline (**37**) and a range of dihaloazines **38** in combination with primary and secondary amines. The first Pd-catalyzed arylation proceeded with good yield and gave core *N*-(hetero)aryl-2-imidazoline building blocks **39a–e**. The latter were aminated in a combinatorial fashion, and the resulting compounds **40–75** were obtained in good to excellent yields as well (Table 3).

Scheme 15

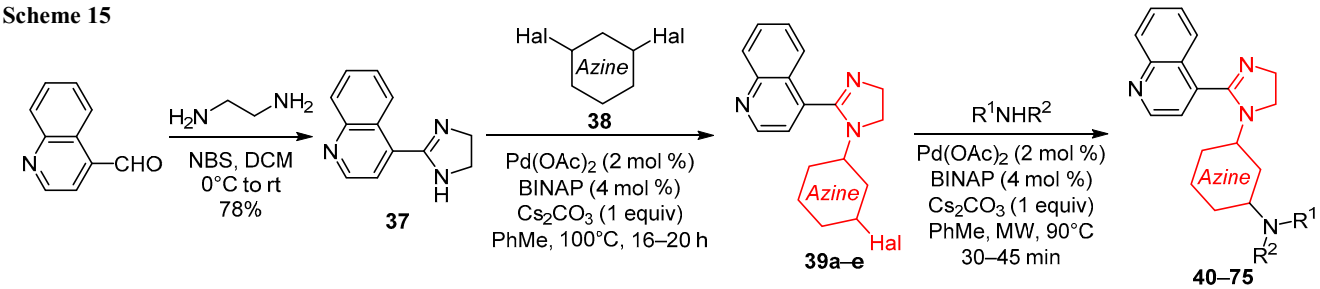
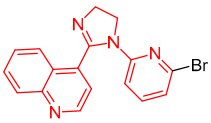
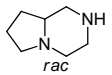
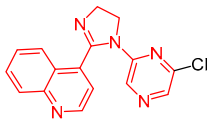
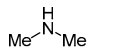
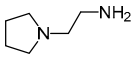
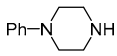
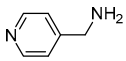
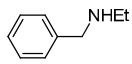
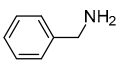
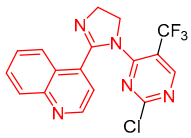
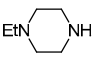
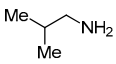
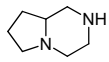
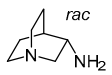
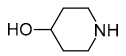
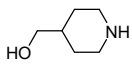
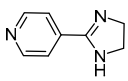
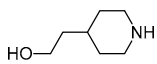
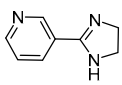
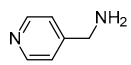
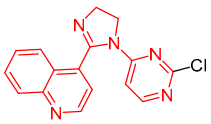
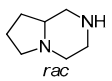
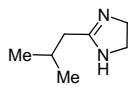
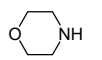
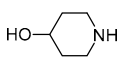
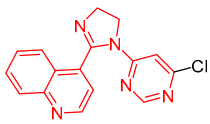
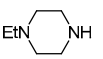
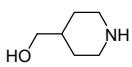
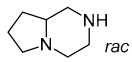
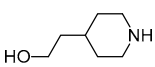
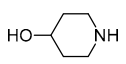
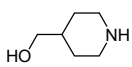
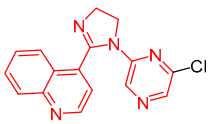
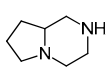
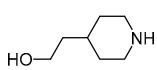


Table 3. Compounds **40**–**75** synthesized according to Scheme 15

Imidazoline–azine coupling product **39** (yield)	R^1NHR^2	Amination product	Yield, %	Imidazoline–azine coupling product **39** (yield)	R^1NHR^2	Amination product	Yield, %
 **39a** (73%)	 *rac*	**40**	47	 **39c** (81%)		**58**	78
		**41**	37			**59**	81
		**42**	65			**60**	66
		**43**	78			**61**	65
		**44**	43	 **39d** (56%)		**62**	77
		**45**	45		 *rac*	**63**	63
	 *rac*	**46**	39			**64**	77
		**47**	83			**65**	64
		**48**	65			**66**	66
		**49**	72			**67**	36
 **39b** (68%)	 *rac*	**50**	52			**68**	71
		**51**	78			**69**	84
		**52**	73	 **39e** (79%)		**70**	65
		**53**	67		 *rac*	**71**	38
		**54**	56			**72**	66
		**55**	78			**73**	37
 **39c** (81%)	 *rac*		44			**74**	39
			83			**75**	83

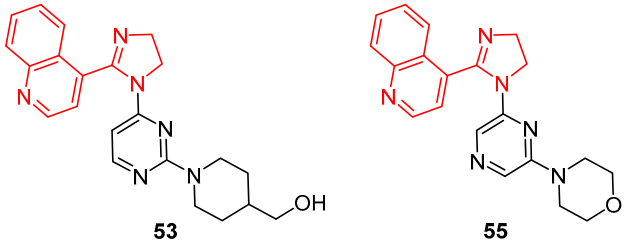


Figure 7. Compounds **53** and **55** endowed with specific antimycobacterial activity.

Despite the initial expectations, none of compounds **40**–**75** displayed a specific antimalarial activity in a 3-day SYBR green I growth and proliferation assay.[36] However, compounds **53** and **55** displayed a moderate activity against *Mycobacterium tuberculosis* H37Rv and no noticeable cytotoxicity, thus manifesting themselves as specific antimycobacterial agents (Fig. 7).[35]

Selective kinase inhibitors

N-Azine-substituted 2-imidazoline moiety was envisioned as a nonclassical binder to the so-called "hinge region" in the ATP-binding pocket of protein tyrosine kinases.[37] Due to the high basicity (pK_a ~4–5) such a moiety is likely to be protonated and is likely to participate in the hydrogen-bonding interaction with the hinge region of the protein backbone. The additional appendages on the azine moiety can be viewed as the basis for providing additional interactions within the ATP-binding pocket, such as additional hydrogen-bonding and hydrophobic interactions (Fig. 8).

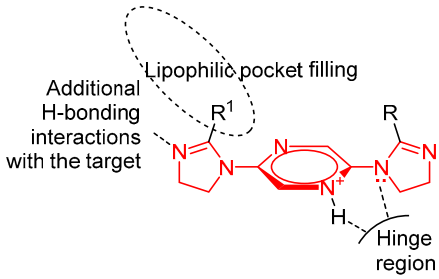
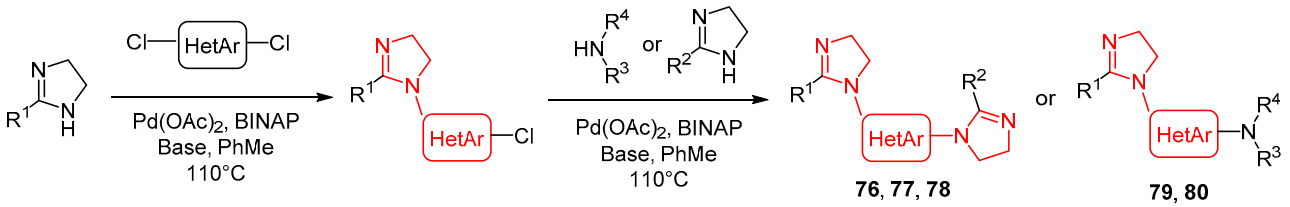


Figure 8. Kinase-focused library design rationale.

The number of possible compounds within this chemotype is enormous, and in order to reduce it to a small number of promising candidates, we generated a structurally diverse virtual library of 1,235 compounds and screened it *in silico* against a panel of 48 therapeutically relevant human kinases. The virtual screening delivered five top-scoring candidate molecules **76**–**80** (Fig. 9).[38] Compounds **76**–**80** were synthesized using the sequential Buchwald–Hartwig coupling approach described above (Scheme 16).[39] These compounds were screened against a panel of 48 human kinases, and the data revealed that three of the five compounds tested exhibited >30% inhibition of only a few therapeutically relevant kinases: IRK (compound **76**), TRKA (compound **78**), Src (compound **78**), CDK1/2 (compound **80**), TAOK2 (compound **80**). Concentration–response retesting of the same compound–kinase pairs confirmed compound **78** as a ~10 μM inhibitor of TRKA and Src, compound **80** – as a ~10 μM inhibitor of CDK1/2, TAOK2. While the inhibitory activity of compounds **78** and **80** appears to be low compared to clinically used kinase inhibitors, the two compounds represent valuable starting points for further development, in a similar fashion to the new 4–470 μM kinase inhibitory cores present in the commercial domain.[40]

Scheme 16



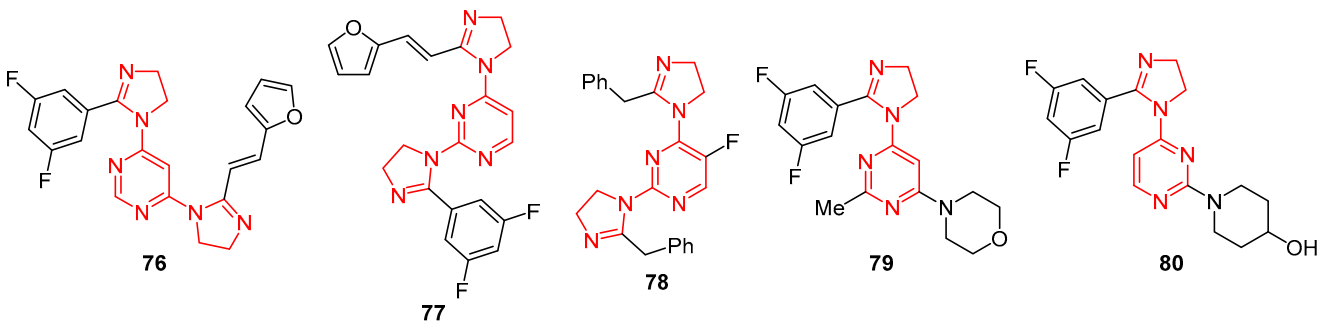
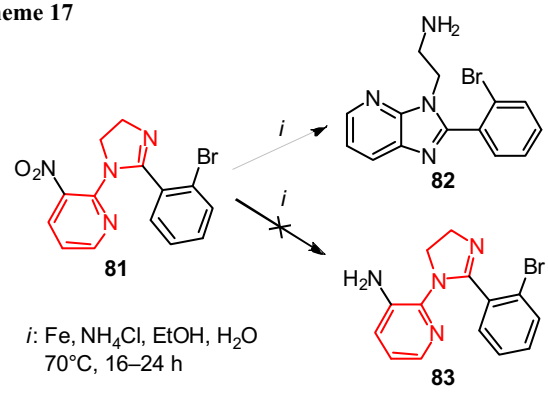


Figure 9. Top five potential kinase inhibitors identified by *in silico* screening approach.

N-(Hetero)arylation of 2-imidazolines en route to other novel and privileged scaffolds

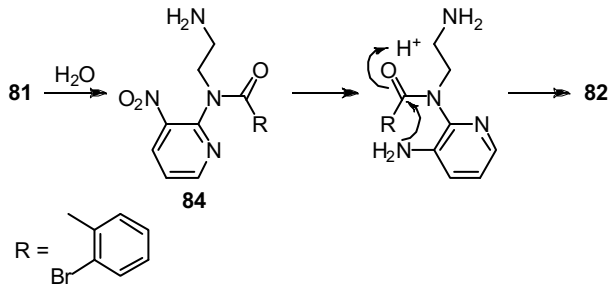
In 2013, when attempting to reduce the nitro group in compound **81** using the so-called Bechamp conditions (Fe, NH_4Cl, EtOH, H_2O, heating), we observed an unexpected formation of imidazo[4,5-*b*]pyridine derivative **82**, and not the expected *N*-heteroaryl-2-imidazoline **83** (Scheme 17).[41]

Scheme 17



Imidazo[4,5-*b*]pyridines containing 2-aminoethyl side chain such as compound **82** are bioisosteres of privileged benzimidazoles[42] and can be regarded as privileged structures on their own, as they have been reported as histamine H3 receptor inverse agonists,[43] histone deacetylase inhibitors,[44] and cannabinoid CB2 receptor modulators.[45] The formation of compound **82** (instead of compound **83**) can be rationalized by the hydrolytic instability[46] of the 2-imidazoline linkage which can lead to expulsion of the 2-aminoethyl side chain, resulting in intermediate **84** (isolated in a control experiment performed in the absence of Fe), followed by the nitro group reduction and cyclodehydration to form compound **82** (Scheme 18).

Scheme 18



This serendipitous discovery essentially led to a fundamentally new method (Scheme 19) to prepare a range of 2-aminoethyl-containing imidazo[4,5-*b*]pyridines and benzimidazoles, some examples of which are shown in Figure 10.[41]

Compound **82** can be viewed as a substrate for the second, intramolecular Buchwald–Hartwig *N*-arylation process. Indeed, under the Pd-catalyzed conditions it furnished rare tetracyclic compound **85** (Scheme 20) the structure of which was confirmed by X-ray crystallography.[47]

Scheme 19

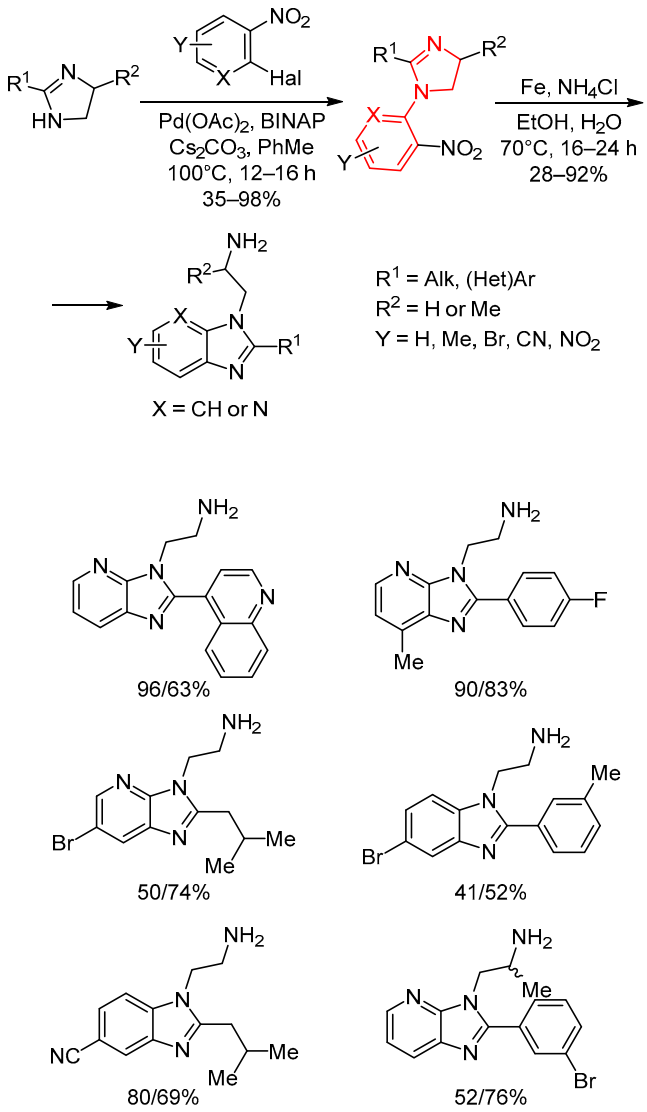
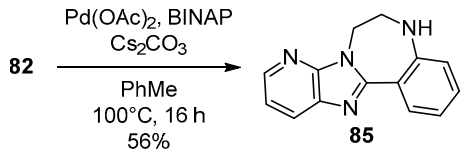


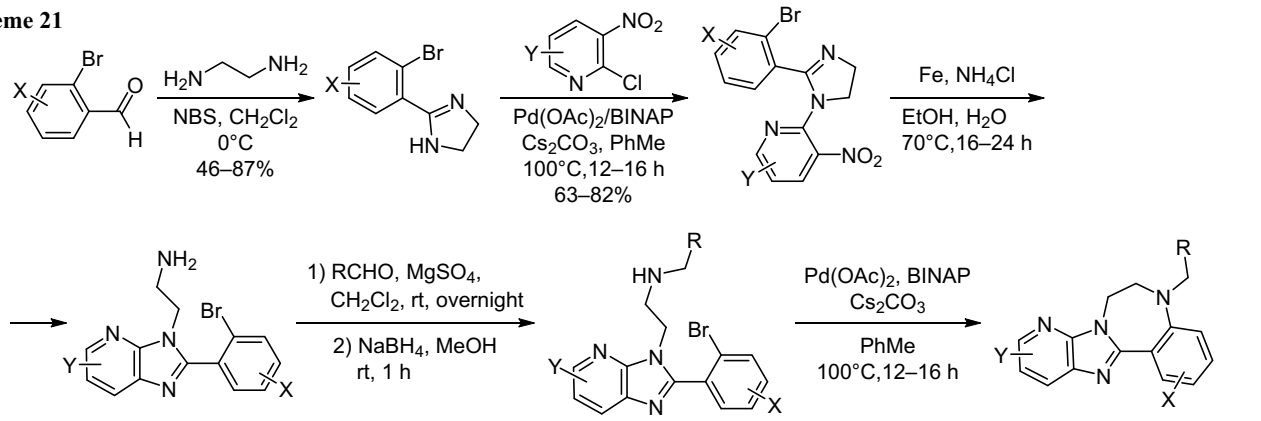
Figure 10. Examples of imidazo[4,5-*b*]pyridines and benzimidazoles accessible as shown in Scheme 19 (yields given are for the first/second step).

Scheme 20



This novel core can be further diversified on the basis of on the following considerations. Firstly, the aminoethyl side chain can be reductively alkylated prior to the intramolecular *N*-arylation step, thus introducing alkyl groups at the nitrogen atom of the seven-membered (diazepine) ring. Secondly, considering the generality of the approach to 2-aminoethyl-substituted imidazo[4,5-*b*]pyridines and benzimidazoles presented above, the phenyl and pyridine

Scheme 21



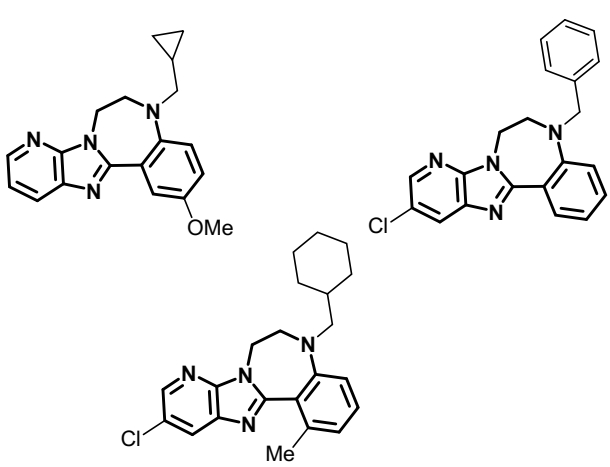


Figure 11. "Decorated" versions of tetracyclic compound **85** accessed as shown in Scheme 20.

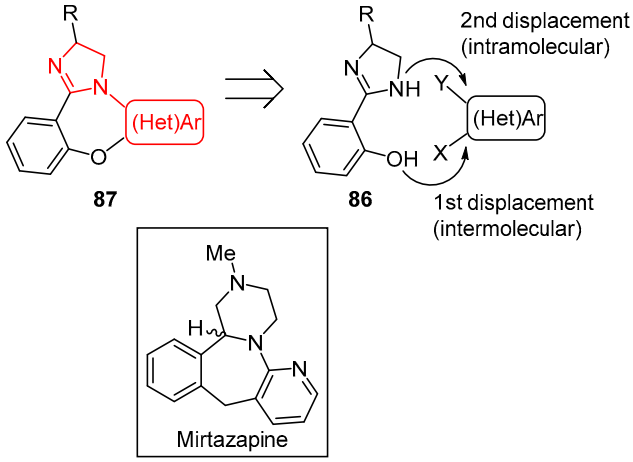


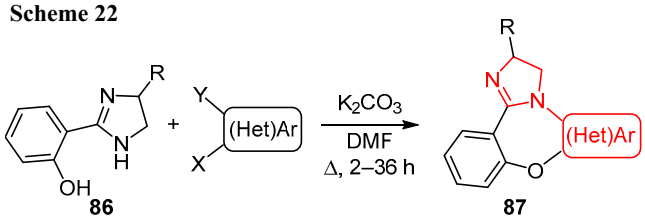
Figure 12. Double S_NAr ("2 × S_NAr") approach to tetracyclic 2-imidazoline-containing [1,4]oxazepines **87**.

rings can perhaps contain independently variable substituents. This was indeed realized in the general approach presented in Scheme 21.[47] The range of tetracyclic compounds akin to structure **85** resulting therefrom is illustrated by the examples shown in Figure 11.

An interesting opportunity to achieve 2-imidazoline *N*-arylation in the absence of any transition metal catalyst was identified last year when 2-(2-hydroxyphenyl)imidazolines **86**, envisioned as a bis-nucleophiles, were introduced into the reaction with reactivity-matched bis-electrophilic aromatic substrates.[48] The compounds expected to result therefrom were tetracyclic [1,4]oxazepines **87** which are analogs of mirtazapine, a selective noradrenaline reuptake inhibitor (Fig. 12).

The strategy was indeed realized in practice and resulted in the general method to access compounds **87** in a practically convenient and atom-economical fashion (Scheme 22).[48]

Scheme 22



The fact that in order to achieve the challenging *N*-arylation of the 2-imidazoline moiety no metal-based catalysis was required can be rationalized in this case by the intramolecular character of this S_NAr event. Indeed, as it has been shown previously[49] for analogous "2 × S_NAr" reactions, the reaction begins by phenoxide anion displacing the most labile leaving group in the aromatic partner. A Smiles rearrangement (which in this case is essentially an intramolecular 2-imidazoline *N*-arylation step!) then follows, and the cyclization is completed by yet another intramolecular displacement by the phenoxide (as shown for the reaction between 2-(2-hydroxyphenyl)-imidazoline and 2,3-dichloro-5-trifluoromethylpyridine in Scheme 23).[48] The range of tetracyclic products **87** that can be accessed by this remarkably simple yet efficient methodology is illustrated by the examples shown in Figure 13. Notably, here, too, the *N*-arylation of the methyl-substituted imidazoline takes place at the less sterically hindered nitrogen atom. However, the regiospecificity in this case appear lower compared to the isomeric ratio observed earlier for compound **31** (Scheme 13). This is unsurprising, as the selectivity can be expected to be lower between two intramolecular events which proceed with lower activation barriers in comparison to intermolecular reactions.

Scheme 23

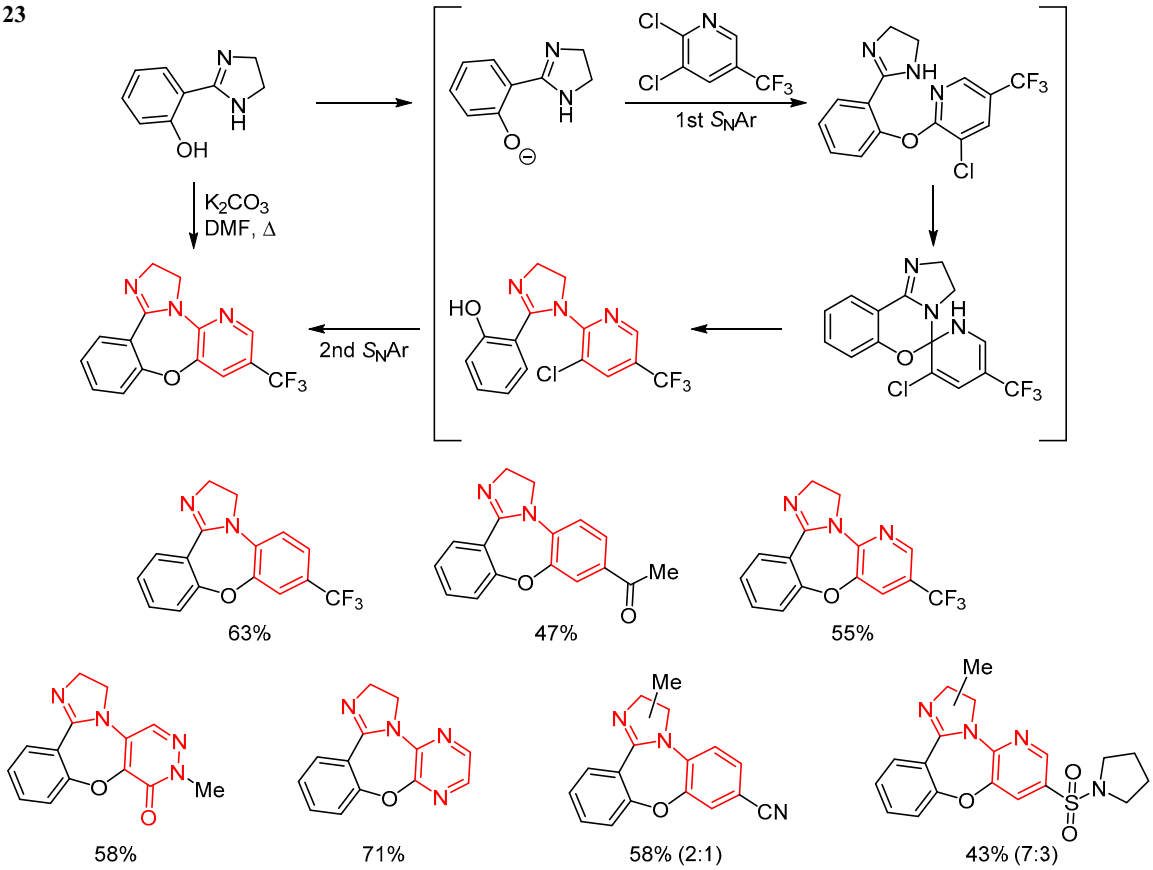
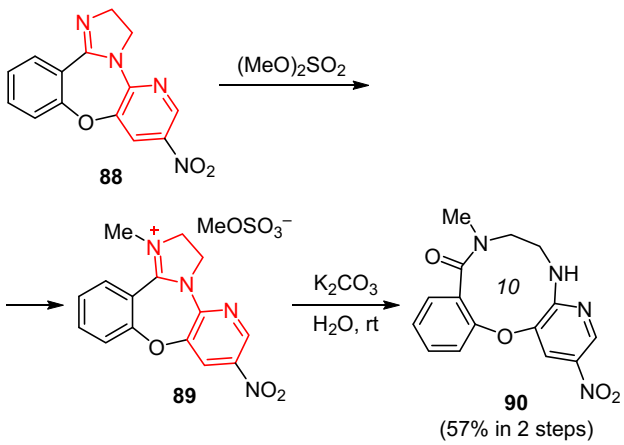


Figure 13. Examples of tetracyclic 2-imidazoline-containing products **87** accessed as shown in Scheme 23.

Recently, we have identified[50] an intriguing reactivity aspect of tetracyclic 2-imidazoline-containing [1,4]oxazepines **87** which is a corollary of the hydrolytic instability of the 2-imidazoline (and especially, 2-imidazolinium) moiety, the synthetic utility of which we have already described above. Representative compound of this class (compound **88**) can be regiospecifically methylated at the 2-imidazoline moiety furnishing the reactive imidazolinium salt **89**. The latter reacts further in 0.1% aqueous potassium carbonate solution at room temperature. However, the result is not a 2-aminoethyl side chain-containing compound (*vide supra*), but rather a ring-expanded 8-methyl-2-nitro-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]-oxadiazecin-9-one (**90**) obtained in a good overall yield (Scheme 24). The structure of compound **90** was confirmed by single-crystal X-ray analysis. In light of the general scarcity of medium-sized ring compounds in contemporary screening collections,[51] compounds like compound **90** represent a rather fortunate trophy from our quest into 2-imidazoline *N*-arylation.

Scheme 24



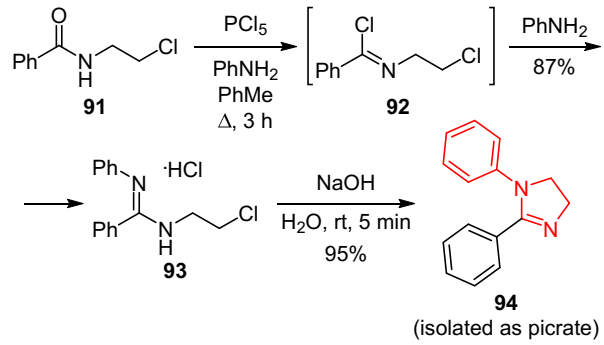
Non-arylation methods to construct *N*-(hetero)aryl-2-imidazolines

There is a number of reports in the literature describing the synthesis of *N*-(hetero)aryl-2-imidazolines by routes other than direct *N*-(hetero)arylation of an NH-imidazoline (mostly involving cyclodehydration of an appropriately substituted ethylenediamine precursor). Some of these studies were conducted in the context of developing 2-imidazoline derivatives endowed with specific biological activity. Therefore, we find it appropriate to present a summary of these reports in present review. We also would like to briefly review dedicated methodology studies aimed at 2-imidazoline formation where *N*-(hetero)aryl versions of this heterocycle have been exemplified.

An early report on the synthesis of *N*-aryl-2-imidazolines (termed "1-aryl-4:5-dihydroglyoxalines") was published in 1949 by the Partridge group from University of Nottingham[52] (although the first preparation of *N*-aryl-5-methyl-

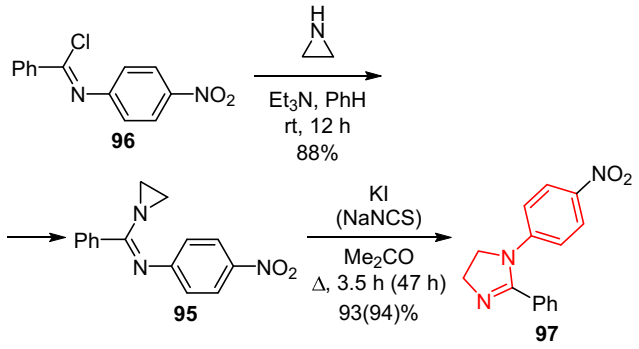
imidazolines from *N*-allylamides and arylamine hydrochlorides or from anilides and allylamine hydrochlorides was published as far back as 1895,[53] see also Scheme 29). They described a reaction between *N*-(2-chloroethyl)-enzamide (**91**) and PCl_5 conducted in presence of aniline. The initially formed imidoyl chloride **92** is trapped by aniline to form amidinium salt **93**. The latter was extremely prone to cyclization and afforded in an excellent yield the desired *N*-phenyl-2-imidazoline **94** which was isolated as a picrate salt (Scheme 25).[52]

Scheme 25

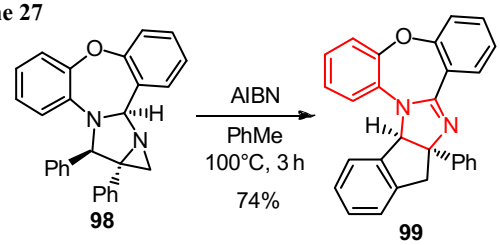


N-(Imidoyl)aziridines **95** (obtained by the reaction of imidoyl chloride **96** with aziridines) were found to rearrange into respective *N*-aryl-2-imidazolines **97** on treatment with sodium iodide or potassium thiocyanate (Scheme 26).[54] This curious entry into the heterocycle in question is vaguely reminiscent of (though mechanistically quite different from) a recently described radical rearrangement of aziridine precursor **98** into compound **99** which contains an *N*-aryl-2-imidazolines moiety (Scheme 27).[55]

Scheme 26

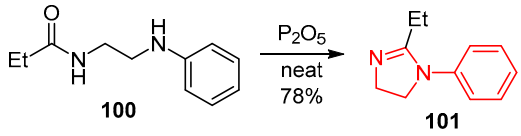


Scheme 27



The cyclodehydration of *N*-aryl-*N*'-acylethylenediamine precursor **100** into respective *N*-aryl-2-imidazoline **101** (Scheme 28) was described in 1966[56] and, later, various versions of essentially this particular powerful approach

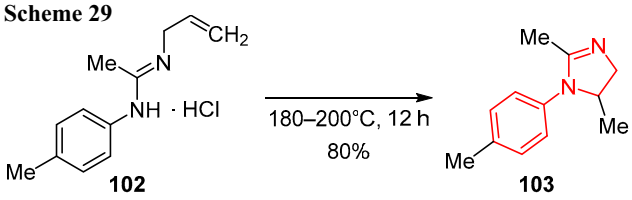
Scheme 28



have been employed in preparation of many medicinally relevant *N*-aryl-2-imidazolines (*vide infra*).

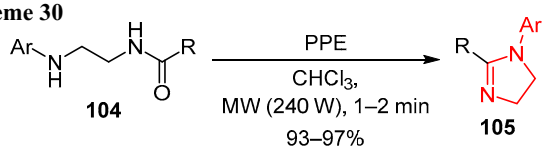
In 1973, Partridge and Smith re-visited[57] the cyclo-condensation of *N*-allyl-*N*'-arylamidines (which had been alleged[53] to be intermediates in the transformation of *N*-allyl amides and arylamine hydrochlorides or from anilides and allylamine hydrochlorides into *N*-aryl-5-methyl-imidazolines) and confirmed that isolated acetamidine hydrochlorides **102** indeed produce 1-aryl-2,5-dimethyl-imidazolines **103** on heating (Scheme 29).

Scheme 29



In 2006, Orelli and coworkers employed a microwave-assisted cyclodehydration of *N*-acyl-*N*'-arylethylene-diamines **104** into *N*-aryl-2-imidazolines **105** using ethyl polyphosphate (PPE) as dehydrating agent (Scheme 30).[58] The main advantage of the microwave-promoted reaction over conventional heating was the markedly shorter reaction time (1–2 min *vs* 5 h). However, the yields obtained in both protocols were comparable. Curiously, in 2012, a different team from the same institution applied microwave radiation to promote cyclization of precursor **104** into imidazoline **105** using trimethylsilyl polyphosphate.[59]

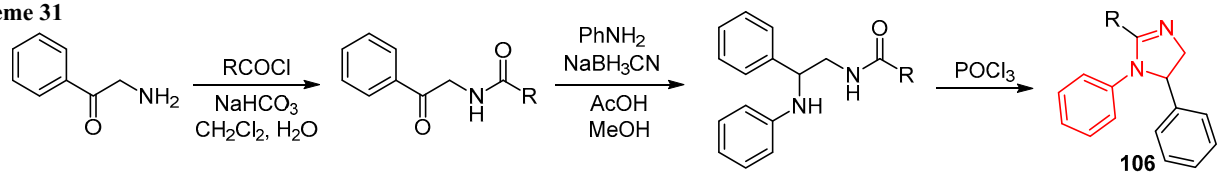
Scheme 30



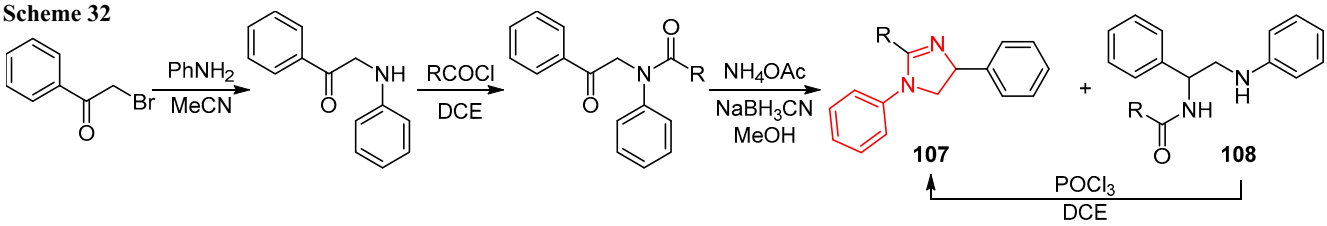
Ar = 2-$O_2NC_6H_4$, R = Ph, *t*-Bu; Ar = 1-Naphth, R = Ph

In 2009, Khvat and coworkers described two practical synthetic routes toward *N*-phenyl-2-imidazolines **106** (Scheme 31) and **107** (Scheme 32) varying only in the position of the second phenyl substituent in the 2-imidazoline ring.[60] Since cyclodehydration was the key step in both approaches, the preparation of the two regioisomers, in principle, only mandated judicious crafting of the cyclodehydration precursors. Interestingly, compound **107** was only one of the two products in the last step of the second sequence which involved reductive amination with ammonium acetate and spontaneous cyclodehydration of the intermediate primary aliphatic amine. The latter, however, represented an "easy target" for the *N*→*N* acyl migration that resulted in compound **108** which did not cyclize into **107** spontaneously (due to the reduced nucleo-

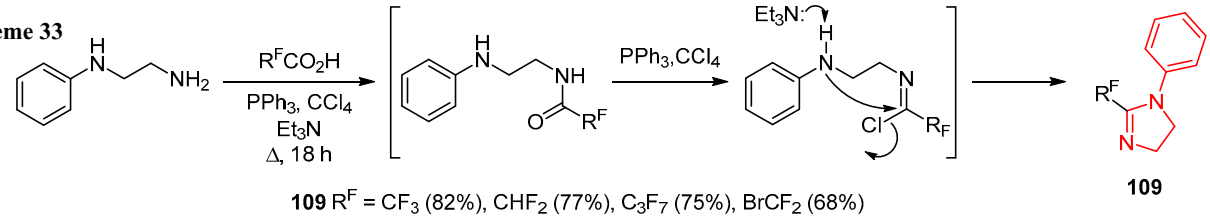
Scheme 31



Scheme 32



Scheme 33



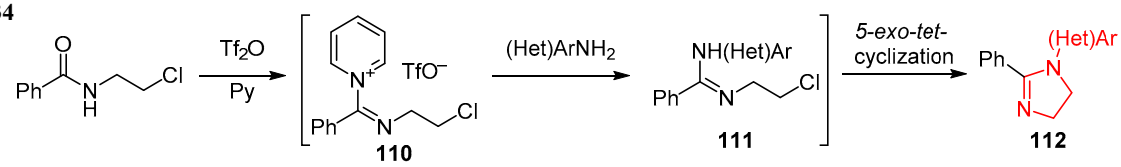
109 R^F = CF_3 (82%), CHF_2 (77%), C_3F_7 (75%), $BrCF_2$ (68%)

philicity of the aniline nitrogen) and required more forcing dehydration conditions to achieve full conversion (Scheme 32).

In 2012, Jiang and coworkers synthesized a small set of *N*-phenyl-2-imidazolines **109** containing various fluoroalkyl substituents.[61] This approach represented essentially the following sequence of events realized in a one-pot format (in which both triethylamine and the PPh_3–CCl_4 system played a masterfully orchestrated dual role): 1) acylation of *N*-phenylethylenediamine with polyfluorinated carboxylic acid requiring all three reagents, 2) conversion of the resulting polyfluorinated carboxamide into the respective imidoyl chloride promoted by the PPh_3–CCl_4 dyad, and 3) spontaneous cyclization into imidazoline **109** requiring only triethylamine (Scheme 33).

Last year, Mosey and coworkers published[62] a modern version of the cyclization of 2-chloroethylamidines into the respective 2-imidazolines described by Partridge in 1949.[52] *N*-(2-Chloroethyl)benzamide was treated with triflic anhydride in pyridine which led to the formation of the *N*-imidoylpyridinium triflate intermediate **110**. The latter could then be treated with various aromatic amines to form amidine **111** which cyclized spontaneously to give the target 2-imidazolines **112** (Scheme 34). The scope of (hetero)aromatic groups that can be conveniently accommodated at the nitrogen atom of 2-imidazoline nucleus is remarkable and so are the yields (Fig. 14). Therefore, it is likely that this approach will nicely complement the metal-catalyzed versions[12, 24–25] to access compounds **112**, particularly when

Scheme 34



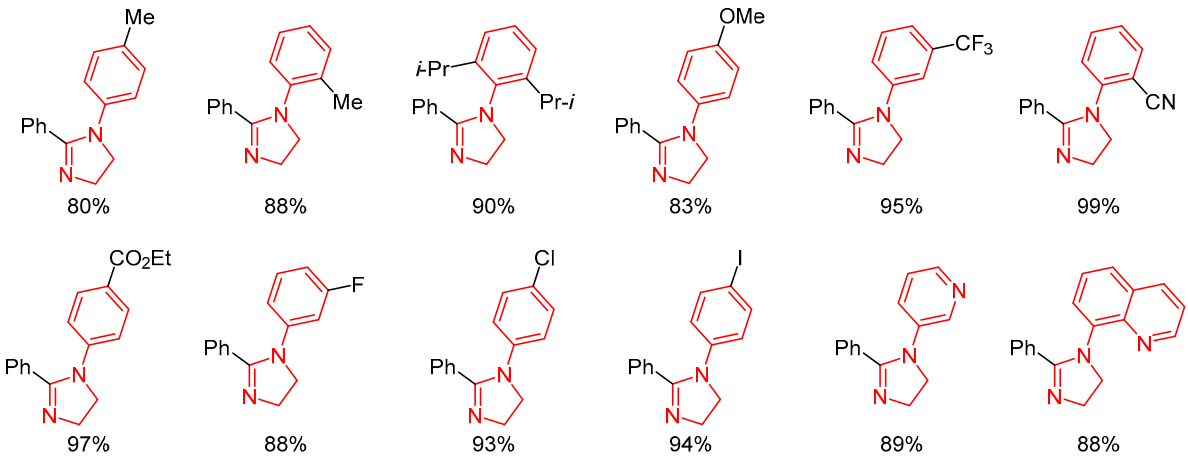


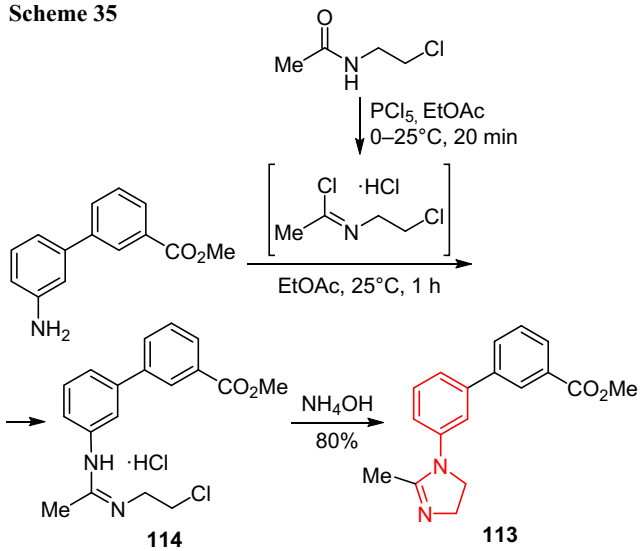
Figure 14. Scope of *N*-(hetero)aryl-2-imidazolines **112** accessed as shown in Scheme 33.

it comes to the preparation of the most sterically congested analogs where using the Mosey protocol appears to be particularly advantageous.

In 2002, Glaxo scientists reported agonists of beta-3 adrenoreceptor (of particular utility as anti-obesity and anti-diabetes agents) exemplified by compound **113** which was prepared according to the synthetic route shown in Scheme 35[63,64] It involves the preparation of amidinium hydrochloride **114** which underwent spontaneous cyclization into imidazoline **113** when converted to free base.

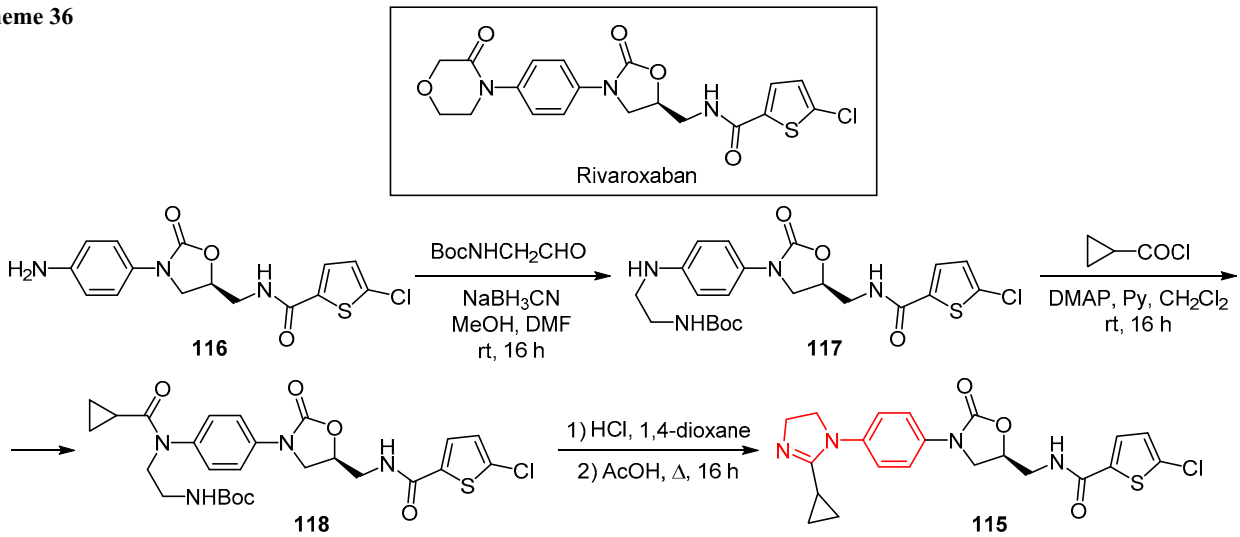
In 2008, Korean scientists from Legochem Bioscience reported factor Xa inhibitors (exemplified by compound **115**), potentially useful as anticoagulant drugs devoid of bleeding risk effects, which are related to marketed drug rivaroxaban (the latter belongs to the same class of anticlotting agents).[65] The *N*-aryl-2-imidazoline moiety in compound **115** (serving as a biosteric replacement of morpholinone in rivaroxaban) was installed in a somewhat elaborate fashion starting from aniline **116**. The latter was reductively alkylated with Boc-aminoacetaldehyde. Acylation of the resulting compound **117** afforded intermediate **118**. The latter was treated with HCl to remove the Boc group and refluxing AcOH to form the 2-imidazoline cycle in the structure **115** (Scheme 36). Clearly, a single 2-imidazoline *N*-arylation step would significantly shorten this route.

Scheme 35

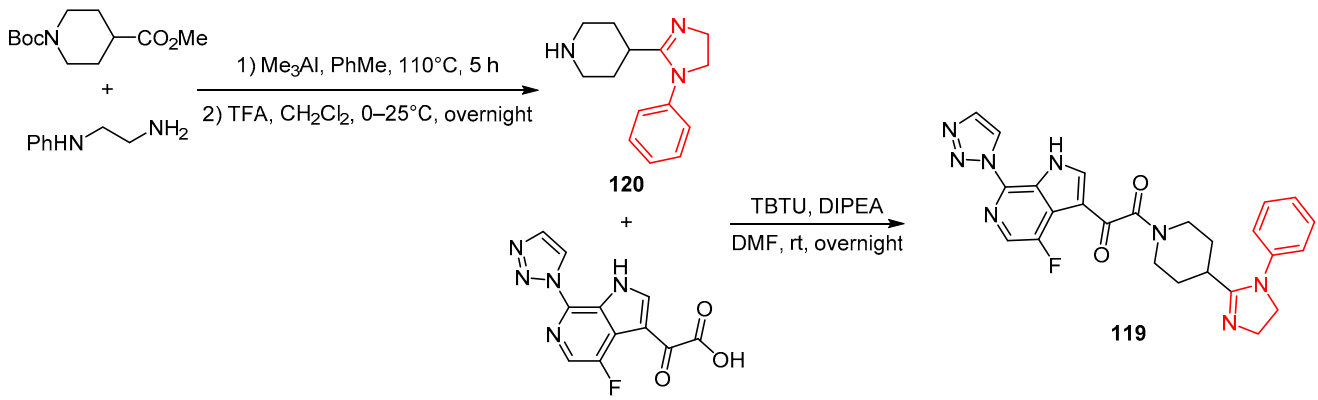


Bristol-Myers Squibb scientists described antiviral activity of 1*H*-pyrrolo[2,3-*c*]pyridine compounds containing imidazoline periphery (such as compound **119**).[66] The latter was synthesized as shown in Scheme 37. The route involves rather standard linear construction of the 2-imidazoline nucleus in the amide coupling partner **120**. Again, this attests to the advantages of the recently reported convergent 2-imidazoline *N*-(hetero)arylation approaches.[12,24,25]

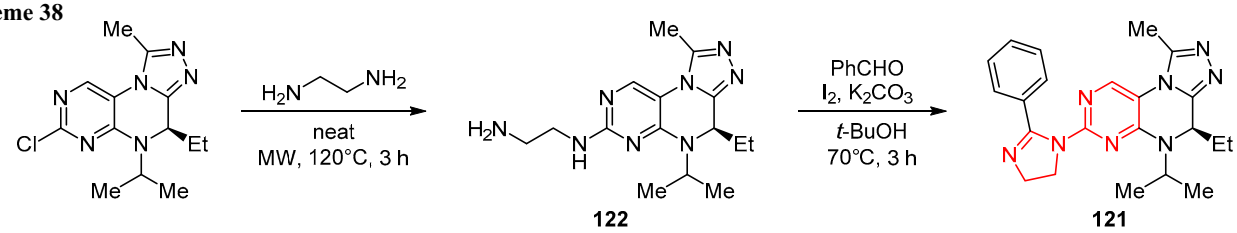
Scheme 36



Scheme 37



Scheme 38



Interesting pteridine-based inhibitors of polo-like kinases containing *N*-aryl-2-imidazoline periphery were described by Elan Pharmaceuticals.[67,68] The installation of the 2-imidazoline nucleus (shown for one of the examples, compound **121**) involved a rare example of oxidative condensation of an *N*-(hetero)arylethylenediamine (in this case, compound **122**) with benzaldehyde, a transformation widely used[69] to prepare NH-imidazolines (Scheme 38).

The *N*-(hetero)aryl-2-imidazoline moiety was present in the synthetic and medicinal chemistry literature since the middle of the 20th century in the form of rather sporadic reports. Quite often the heterocycle in question was constructed using linear sequences. Until 2012, no dedicated methodological studies were undertaken to allow for independent variation of the periphery element around the *N*-(hetero)aryl-2-imidazoline core. The recently described metal-catalyzed and cyclocondensation methodologies attest to the resurgence of interest toward this heterocycle. Moreover, its privileged character in medicinal chemistry continues to be substantiated by emerging reports in the literature.

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