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Synthesis of annulated benzimidazoles via amidine cyclization

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ABSTRACT

Structurally diverse annulated benzimidazoles were synthesized via two copper(I)-catalyzed cyclocondensation reactions. In the first case the title compounds were prepared from lactams and *o*-bromoaniline. An alternative route consisted of an intramolecular cyclization of *o*-bromoarylamidines.

1. Introduction

Annulated benzimidazoles play an important role in drug discovery and can be regarded as key structures in pharmaceutical research. Investigation of biological activity of annulated benzimidazoles started from the middle of the recent century when analgesic activity of numerous pyrido-[1] (**I**) and pyrrolobenzimidazoles[2] (**II**) was found (Fig. 1). In the 1990s Skibo et al. designed a set of pyrrolo[1,2-*c*]benzimidazolequinones (**PBI**s) having high-grade antitumor activity.[3] The most recent studies of the annulated benzimidazoles showed the ring-size influence on their toxicity toward the Fanconi anemia skin cells (**III**).[4] Unfortunately, synthesis of annulated benzimidazoles carried out as multi-step procedures with limited number of starting compounds.[5] Therefore it is of importance to develop methods for the preparation of functionalized annulated benzimidazoles.

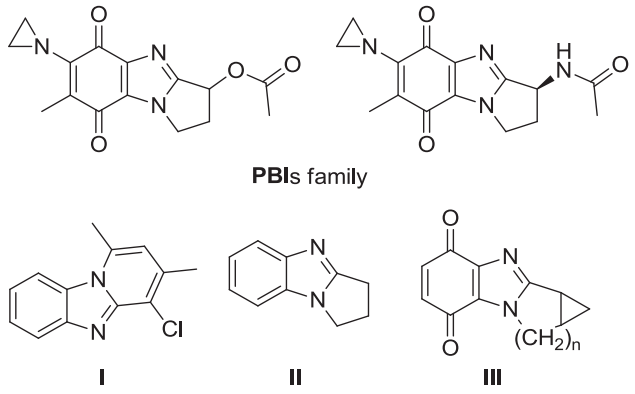
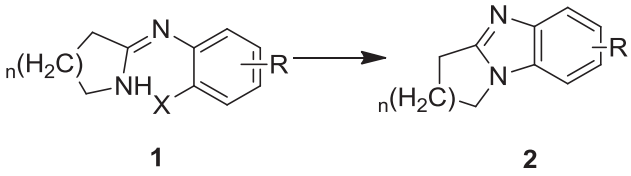


Fig. 1. Biological active benzimidazoles.

We have recently described a novel non-catalytic approach to annulated benzimidazoles of type **2** via an intramolecular arylation of cyclic amidines **1** (Scheme 1).[6] The method combined the ease of a one-pot procedure with the availability of the cyclic amidines. A major obstacle of our published method was a low reactivity of the C–Hal bond requiring quite harsh reaction conditions and activating substituents in the aromatic ring. For instance, amidines **1** (Scheme 1, X=F) undergo cyclocondensation at 150 °C to give **2** only when activated with strong electron-withdrawing groups (R), such as F and NO_2.



Scheme 1. Annulated benzimidazole synthesis.

Nowadays the synthesis of annulated nitrogen heterocycles largely relies on metal-mediated reactions for the C–N bond formation.[7] For example, intramolecular Ullmann-type copper-catalyzed cyclocondensations resulting in the C–N bond formation were employed in the synthesis of many heterocycles, such as indoles[8] and imidazoles.[9] The preparation of 1,2-disubstituted benzimidazoles was carried out in some pathways: (i) a cyclocondensation of *o*-haloanilides;[10] (ii) an arylation of amides with *o*-haloanilines;[11] (iii) a cyclization of arylamidines and related

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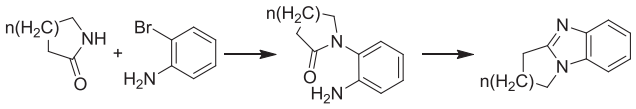
compounds;[12] (iv) an arylation of amidines with 1,2-dihalobenzene derivatives;[13] (v) cascade addition/cyclization amines with *o*-haloarylisocyanides[14] and *o*-haloarylcarbodiimides.[15] Some of these procedures were also employed for the synthesis of annulated benzimidazoles. Thus, a copper/DMEDA-mediated arylation of 2-iminopiperidine with 1,2-diiodobenzene led to compound **2** (*n*=2, R=H) with an isolated yield of 52%.[13] Moreover, a few aminopiperidine-fused benzimidazoles were obtained through a Cu-catalyzed condensation of substituted valerolactams with *o*-bromo- or iodoanilines and 2-aminopyridines.[16]

In this contribution we describe the synthesis of structurally diverse annulated benzimidazoles through two copper(I)-mediated cyclocondensation reactions. In the first case the title compounds were prepared from lactams and *o*-bromoaniline. An alternative route consisted of cyclization of amidines of type **1** (Scheme 1, X=Br).

2. Results and discussion

The reaction of lactams with *o*-bromoaniline was carried out as described by Buchwald et al.[17] in boiling toluene in the presence of 5 mol % CuI, 10 mol % DMEDA, and 2 mol % K_2CO_3 (Table 1). ^{1}H NMR and LC/MS analyses of crude reaction products revealed that in the case of *n*=2–4 the yields of benzimidazoles **2** were in the range 7–19%. At the same time no *N*-arylated intermediates **4** were detected. In the case of n=1 the crude product contained ca. 50% of 1-(2-aminophenyl)pyrrolidine-2-one **4**. All attempts at the cyclization of the latter compound into the corresponding benzimidazole under the given conditions were unsuccessful. Variation of solvents, temperature, and reagents (e.g., the use of *o*-iodoaniline instead of *o*-bromoaniline) did not influence the yields of benzimidazoles **2**.

Table 1
Copper-catalyzed reaction of lactams with *o*-bromoaniline[a]



4 **2**

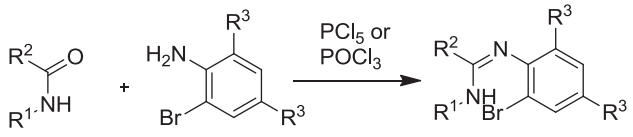
n	Conversion[b] GS/MS, %	
	Product **4**	Product **2**
1	47.1	—
2	—	18.7
3	—	17.0
4	—	7.4

[a] Reaction conditions: 1 mol lactam, 1 mol *o*-bromoaniline, 10 mol % DMEDA, 5 mol % CuI, toluene, stirring and reflux, 16 h.
[b] Conversion given as an average of three independent measurements.

The unsatisfactory yields of bezimidazoles in this reaction prompted us to search for an alternative synthetic approach to the title compounds. As a promising option we suggested an intramolecular cyclization of *o*-bromoarylamidines **1**. The literature analysis showed that a metal-mediated intramolecular N-arylation proceeded under milder conditions and with higher yields compared to an intermolecular N-arylation.[17]

Starting amidines **1a**–**r** were synthesized from *o*-bromoaniline and appropriate amides in the presence of $POCl_3$ (for compounds **1a**–**d**, **k**–**n**) or PCl_5 (for compounds **1e**–**i**, **o**–**r**) (Table 2). In the ^{1}H NMR spectra of cyclic amidines **1a**–**d**, **k**–**n** there are two sets of signals whose ratio depends on the size of the saturated ring, the presence of substituents in the aromatic ring and the solvent.

Table 2
Preparation of amidines **1**



Amidine	R^1, R^2	R^3	Method	Yield, %
1a	$-(CH_2)_3-$	H	A	93
1b	$-(CH_2)_4-$	H	A	80
1c	$-(CH_2)_5-$	H	A	72
1d	$-(CH_2)_6-$	H	A	93
1e	*o*-$C_6H_4-(CH_2)_2-$	H	B	94
1f	*o*-$C_6H_4-(CH_2)_3-$	H	B	71
1g	Me, Me	H	B	83
1h	Et, Me	H	B	80
1i	Ph, Me	H	B	70
1k	$-(CH_2)_3-$	F	A	80
1l	$-(CH_2)_4-$	F	A	54
1m	$-(CH_2)_5-$	F	A	65
1n	$-(CH_2)_6-$	F	A	58
1o	Me, Me	F	B	79
1p	Et, Me	F	B	83
1r	Ph, Me	F	B	83

Reaction conditions: Method A: 2 mol amide, 1 mol *o*-bromoaniline, 1 mol $POCl_3$ in toluene. Method B: 1 mol *o*-bromoaniline, 1.07 mol amide, 1.17 mol PCl_5 in benzene.

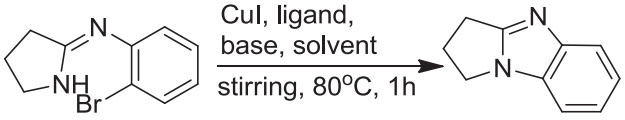
As shown previously, this is due to the presence of reversible *Z*,*E*-isomerization about the exocyclic C=N bond in amidines.[18] The assignment of the signals of the isomers is easily accomplished by the different shielding of the 3-CH_2 group. In the ^{19}F NMR spectra of amidines **1k**–**r** the ratio of *Z*/*E* isomers is rather evident and well correlated with ^{1}H NMR spectra.

To find the most suited procedure for the catalytic cyclocondensation of amidines **1** we have carried out a condition involved solvent, base, and the copper(I) ligand. Our tests were performed on model cyclization amidine **1a** into benzimidazole **2a**. Copper(I) iodide was choused among other copper catalysts (e.g., Cu_2O, CuCl) through its air stability and ample availability. Acetonitrile was found to be a good solvent for the reaction; the reaction rate in toluene or dioxane was considerably slower, whereas the use of DMF complicated the product isolation. In contrast to 1,10-phenanthroline and proline, the use of DMEDA as a chelating ligand resulted in nearly quantitative conversions (Table 3, entries 8, 12, and 13). Potassium carbonate was used as a base to promote the arylation reaction resulting in better yields compared with those obtained with cesium carbonate, sodium hydrogen carbonate, and potassium fluoride on aluminum oxide. High conversions were also observed in the case of sodium hydride in DMF. The latter system was not used further because of the above solvent limitation.

We have found that the CuI-promoted cyclocondensation of **1a** proceeds smoothly in refluxing acetonitrile in the presence of potassium carbonate and 10 mol % of DMEDA as the base and the copper complexing ligand, respectively. Under given conditions the conversion of **1a** to **2a** was complete within 1 h.

The ease of the copper-catalyzed cyclocondensation of **1a** can possibly be explained by the presence of the aliphatic chain in its ring. Further investigation revealed that cyclization of **1b** bearing six-membered saturated ring went identical to the amidine **1a**. Next expansion of the amidine ring slows down the cyclization rate. For example, the conversion of **1c** and **1d** to the corresponding benzimidazoles was complete only after 4 h. Cyclization of six-membered cyclic compound **1b** and its benzannulated analog **1e** did not reveal any differences in their reactivity under the given reaction conditions. However, this was not the case with seven-membered analogous amidines **1c** and **1f**. The latter amidine

Table 3
Optimization of the copper-catalyzed cyclization[a]



Entry	Ligand	Base	Solvent	Conversion[b] (%)
1	No ligand	K_2CO_3	Acetonitrile	16
2	No ligand	NaH	1,4-Dioxane	25
3	DMEDA	KOH	1,4-Dioxane	—
4	DMEDA	K_2CO_3	1,4-Dioxane	12
4	DMEDA	K_2CO_3	Toluene	7
5	DMEDA	K_2CO_3	Toluene	50[c]
6	DMEDA	K_2CO_3	DMF	95
7	DMEDA	NaH	DMF	99
8	DMEDA	K_2CO_3	Acetonitrile	>99
9	DMEDA	Cs_2CO_3	Acetonitrile	72
10	DMEDA	$NaHCO_3$	Acetonitrile	59
11	DMEDA	KF/Al_2O_3	Acetonitrile	79
12	L-Proline	K_2CO_3	Acetonitrile	68
13	1,10-Phenanthroline	K_2CO_3	Acetonitrile	55

[a] Reaction conditions: 1 mol amidine, 0.05 mol CuI, 0.1 mol ligand, 2 mol base, stirring, 80 °C, 1 h.
[b] The conversion was measured by LC/MS analysis of the crude product. The value is an average of three independent measurements.
[c] Heating temperature 110 °C.

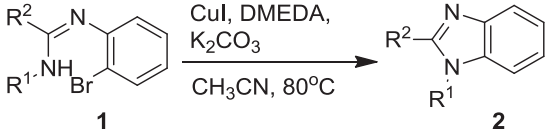
reacted as fast as compounds **1a**,**b**,**e** (Table 4) showing that the presence of the annulated benzene ring enhances the reactivity. Acetamidines **1g**–**i** reacted considerably slower than their cyclic congeners. For example, acetamidines **1g**,**h** bearing alkyl groups at their nitrogen atoms underwent complete conversion to the corresponding benzimidazoles after 6 h of refluxing in acetonitrile. Interestingly, non-cyclic amidine **1i** with two aromatic groups on its nitrogen atoms reacted within 2 h. Most likely, the latter case is similar to that of compound **1f** in which the presence of aromatic substituent at its nitrogen atom increases the reactivity. Finally, the presence of heteroaromatic unit in amidine **1j** make it least reactive compound among **1a**–**j**. Nevertheless, pyrido[1,2-a]benzimidazole **2j** was isolated after 24 h in a yield of 98%. This constitutes a considerable improvement compared with the published preparation of **2j** via Pd-catalyzed cyclization of **1j** (59% after 67 h).[19]

Amidines **1k**–**r** having in their structures aromatic rings with both bromine and fluorine functional groups give an interesting opportunity to investigate the selectivity of the cyclocondensation under different conditions. It was expected that, depending on the reaction conditions, these compounds would undergo either an intramolecular S_NAr substitution reaction (C–F bond) or copper-catalyzed N-arylation (C–Br bond). The data collected in Table 4 show that carrying out the copper-catalyzed reaction (Method A) resulted in a clean substitution of the bromine yielding benzimidazoles **2k**–**r**. LC/MS analysis of the latter benzimidazoles did not reveal any byproducts of the fluorine substitution under given conditions. Refluxing compounds **1k**–**r** in DMF in the presence of potassium carbonate (Table 5, Method B) gave rise to benzimidazoles **3l**–**r**. LC/MS and ^{19}F NMR analysis of the latter compounds showed a selective substitution of the fluorine in the aromatic ring.

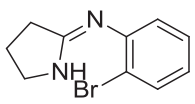
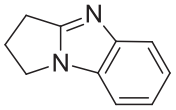
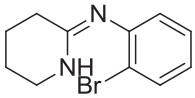
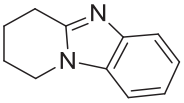
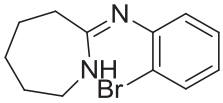
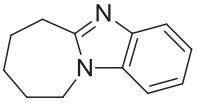
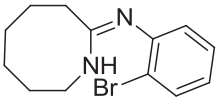
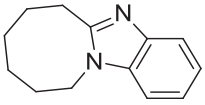
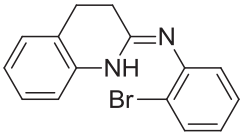
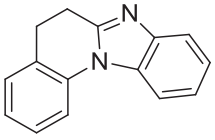
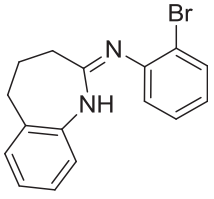
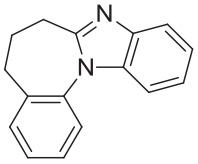
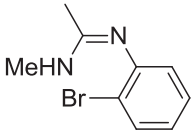
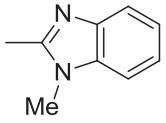
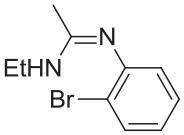
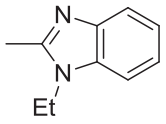
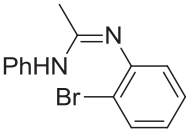
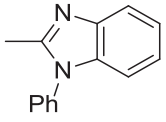
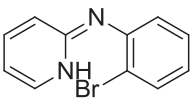
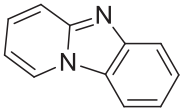
Cyclocondensations of amidines **1o** and **1p** bearing alkyl substituents proceeded similarly to those of **1k**–**r** but required more time to yield benzimidazoles **2o**,**p** and **3o**,**p** under conditions of Method A and Method B, respectively (Table 5).

However, Method B failed in the case of preparation of benzimidazole **3k** from **1k**. This seem to take place due to an excessive steric load in the transition state (Meisenheimer-type sigma complex) of the intramolecular arylation. Given the different reaction

Table 4
Reaction time and yields of cyclocondensations of amidines **1** to benzimidazoles **2**

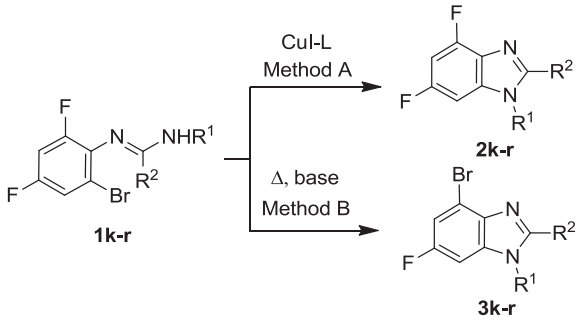


1 **2**

	Amidine	Time[a] h	Benzimidazole	Yield[b] %
a		1		93
b		1		96
c		4		91
d		4		94
e		1		90
f		1		93
g		6		95
h		6		92
i		2		96
j		24		98

[a] Time required for complete conversion. The conversion was estimated by LC/MS analysis of the reaction mixture. The value is an average of three independent measurements.
[b] Isolated yields are given.

Table 5
Synthesis of benzimidazoles **2**,**3** with selective F or Br substitution in amidines **1**[a]



Amidine	R^1, R^2	Method A product **2** yields, %	Method B product **3** yields, %
1k	$-(CH_2)_3-$	87	—
1l	$-(CH_2)_4-$	88	85
1m	$-(CH_2)_5-$	83	87
1n	$-(CH_2)_6-$	95	92
1o	Me, Me	89	91[b]
1p	Et, Me	87	89[b]
1r	Ph, Me	91	95

[a] Method A: CuI, DMEDA, K_2CO_3, CH_3CN, reflux 4 h. Method B: DMF, K_2CO_3, reflux, 4 h.
[b] The reaction time was 24 h.

mechanism, the use of Method A on **1k** successfully affords the cyclization product **2k**.

The present results show that in spite of the high selectivity of the amidine cyclization by either S_NAr-mechanism (Method B) or copper-catalyzed coupling (Method A), there are at least two main factors favoring the ring closure. First, the presence of a saturated ring in amidines seems to stabilize transition states in both cases (with the exception of **1k** in Method B). The second factor is the increased acidity of arylamidines. The deprotonated arylamidines react as efficient *N*-anionic nucleophiles that is reflected in high cyclization rates.

3. Conclusions

We have described an efficient synthetic approach to structurally diverse annulated benzimidazoles. The method consists of intramolecular copper-catalyzed N-arylation of readily available cyclic amidines. The reaction occurs under mild conditions with nearly quantitative yields. The described method can also be employed in the synthesis of 1,2-disubstituted benzimidazoles.

4. Experimental section

4.1. General methods

Commercial reagents of high purity were purchased from either Aldrich or Acros and used without further purification. 1,4-Dioxane, dimethylformamide (DMF), and acetonitrile (CH_3CN) were freshly distilled and dried by standard methods. All solvents for crystallization and flash-column chromatography were used without additional purification. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}) using UV light as a visualizing agent. Merck silica gel 60 (230–400 mesh) was used for flash-column chromatography.

4.2. Instrumentation

Melting points were determined using a Fisher-Jones melting point apparatus. ^{1}H NMR spectra were recorded on the Bruker AVANCE spectrometer at 500 MHz and Varian VXR-300 spectrometer at 300 MHz. ^{13}C NMR spectra were recorded on the Bruker AVANCE spectrometer at 125 MHz. ^{19}F NMR spectra were recorded on Varian VXR-300 spectrometer at 282 MHz. Chemical shifts are reported in parts per million downfield from TMS or C_6F_6 as internal standard. Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph 'Agilent 1100 Series' equipped with diode-matrix and mass-selective detector 'Aligent LC/MSD SL'. The parameters of chromatography–mass analysis: Column: Zorbax SB-C18, 1.8 mm.4.6 mm.15 mm. Solvents: A acetonitrile/water (95:5), 0.1% TFA, B water (0.1% of TFA). Eluent flow: 3 mL/s. The volume of injected sample: 1 mL. UV-detectors operate at 215, 254, and 265 nm. Ionization method: chemical ionization under atmospheric pressure (APCI). Ionization mode: simultaneous scanning of positive and negative ions in the mass range of m/z 80–1000. IR spectra were recorded on Perkin–Elmer FTIR spectrometer. All values are given as cm^{-1}. The Microanalytical Laboratory of Institute of Organic Chemistry of NASU produced quantitative analysis. All values are given as percentages.

4.3. General procedure for amidines 1a–d, 1k–n

Amide (25 mmol) was dissolved in dry toluene (100 mL) and $POCl_3$ (1.93 g, 12.5 mmol) was added dropwise at 0 °C. The reaction solution was kept at the ice-bath with stirring for 2 h. After that aniline (12.5 mmol) was added in one portion and the result mixture was refluxed under stirring for 4 h. The organic layer was removed and the residue was dissolved in 50 mL of water. The mixture was stirred with coal for 30 min and after filtration 2 M NaOH was added to a pH=10. Precipitate was filtered, dried, and crystallized from a mixture of EtOAc/hexane (1:1).

*4.3.1. 2-Bromo-N-[pyrrolidin-2-ylidene]aniline (**1a**).* Crystallized from hexane; yield 2.76 g (93%); mp 143–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J=7.3 Hz, 1H), 7.23–7.00 (m, 2H), 6.89 (t, J=7.1 Hz, 1H), 6.56–5.77 and 4.90–4.26 (br, 1H), 3.71–3.26 (br, 2H), 2.83–2.22 (m, 2H), 2.15–1.95 (m, 2H). IR (KBr) ν_{max}: 2923, 1631, 1578, 1255, 1225. Anal. Calcd for $C_{10}H_{11}BrN_2$: C 50.23; H 4.64; N 11.72. Found C 50.28; H 4.68; N 11.69.

*4.3.2. 2-Bromo-N-[piperidin-2-ylidene]aniline (**1b**).* Yield 1.89 g (60%); mp 75–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J=7.0 Hz, 1H), 7.25–7.14 (m, 1H), 7.03–6.88 (m, 1H), 6.84 (t, J=7.0 Hz, 2H), 5.91–5.00(br, NH(E)) and 4.56–4.30 (br, 1H, NH(Z)), 3.40–3.08 (s, 2H), 2.70–2.01 (m, 2H), 1.92–1.58 (m, 4H). IR (KBr) ν_{max}: 2946, 1633, 1576, 1472, 1218. Anal. Calcd for $C_{11}H_{13}BrN_2$: C 52.19; H 5.18; N 11.07. Found C 52.22; H 5.21; N 11.05.

*4.3.3. N-[-Azepan-2-ylidene]-2-bromoaniline (**1c**).* Yield 2.40 g (72%); mp 106–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J=7.8 Hz, 1H), 7.23 (t, J=7.3 Hz, 1H), 6.95–6.72 (m, 2H), 5.66–5.50 (m, NH(E)) and 4.67–4.50 (m, 1H, NH(Z)), 3.35–3.22 (m, NCH_2(E)) and 3.22–3.05 (m, 2H, NCH_2(Z)), 2.68–2.54 (m, CCH_2(Z)) and 2.32–2.18 (m, 2H, CCH_2(E)), 2.09–1.92 (m) and 1.92–1.80 (m, 2H), 1.80–1.66 (m, 2H), 1.66–1.46 (m, 2H). IR (KBr) ν_{max}: 2932, 1635, 1576, 1218. Anal. Calcd for $C_{12}H_{15}BrN_2$: C 53.95; H 5.66; N 10.49. Found C 53.91; H 5.63; N 10.52.

*4.3.4. N-[2-Azocan-2-ylidene]-2-bromoaniline (**1d**).* Yield 3.26 g (93%); mp 125–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J=8.1 Hz, 1H), 7.23 (t, J=7.8 Hz, 1H), 6.92–6.77 (m, 2H), 5.66–5.19 (br, NH(E)) and 4.38–4.20 (br, 1H, NH (Z)), 3.44–3.32 (m,

$NCH_2(E)$) and 3.32–3.18 (m, 2H, NCH_2 (Z)), 2.62–2.47 (m, $CCH_2(Z)$) and 2.38–2.21 (m, 2H, $CCH_2(E)$), 2.00–1.85 (br, 2H), 1.71–1.54 (m, 4H), 1.54–1.38 (m, 2H). IR (KBr) ν_{max}: 1632, 1577, 1218. Anal. Calcd for $C_{13}H_{17}BrN_2$: C 55.53; H 6.09; N 9.96. Found C 55.52; H 6.08; N 9.96.

*4.3.5. (2-Bromo-4,6-difluorophenyl)-pyrrolidin-2-ylideneamine (**1k**).* Yield 2.75 g (80%); mp 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17–7.03 (m, 1H), 6.87–6.72 (m, 1H), 6.14–6.00 (m, NH(E)) and 4.68–4.54 (m, 1H, NH(Z)), 3.53–3.35 (2H, m, NCH_2), 2.70 (t, J=7.5 Hz, 1H), 2.21–2.00 (m, 3H). ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.5 (d, J=10.1 Hz), −119.4 (m), −119.7 (d, J=8.1 Hz), −120.0 (m). IR (KBr) ν_{max}: 2853, 1650, 1579, 1220. Anal. Calcd for $C_{10}H_9BrF_2N_2$: C 43.66; H 3.30; N 10.18. Found C 43.67; H 3.28; N 10.20.

*4.3.6. (2-Bromo-4,6-difluorophenyl)-piperidin-2-ylideneamine (**1l**).* Yield 1.95 g (54%); mp 109–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21–7.03 (m, 1H), 6.90–6.70 (m, 1H), 6.10–5.71 (m, NH(E)) and 4.67–4.38 (m, 1H, NH(Z)), 3.42–3.27 (m, $NCH_2(E)$) and 3.27–3.10 (m, 2H, NCH_2 (Z)), 2.74–2.49 (m, 1H), 2.30–1.61 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.4 (d, J=8.2 Hz), −119.3, −119.4 (d, J=10.0 Hz), −120.3. IR (KBr) ν_{max}: 2932, 1636, 1576, 1508, 1271, 1211. Anal. Calcd for $C_{11}H_{11}BrF_2N_2$: C 45.70; H 3.83; N 9.69. Found C 45.71; H 3.85; N 9.71.

*4.3.7. N-[-Azepan-2-ylidene]-2-bromo-4,6-difluoroaniline (**1m**).* Yield 2.46 g (65%); mp 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18–7.03 (m, 1H), 6.88–6.70 (m, 1H), 5.87–5.68 (m, NH(E)) and 4.77–4.52 (m, 1H, NH(Z)), 3.29–3.24 (m, $NCH_2(E)$) and 3.24–3.17 (m, 2H, $NCH_2(Z)$), 2.68–2.52 (m, $CCH_2(Z)$) and 2.23–2.12 (m, 2H, $CCH_2(E)$), 1.90–1.59 (m, 6H). ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.64, −119,12, −119.4, −120.12. IR (KBr) ν_{max}: 2853, 1600, 1211. Anal. Calcd for $C_{12}H_{13}BrF_2N_2$: C 47.55; H 4.32; N 9.24. Found C 47.52; H 4.30; N 9.26.

*4.3.8. N-[-Azocan-2-ylidene]-2-bromo-4,6-difluoroaniline (**1n**).* Yield 2.29 g (58%); mp 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.08 (m, 1H), 6.91–6.72 (m, 1H), 5.65–5.50 (br, NH(E)) and 4.44–4.24 (br, 1H, NH(Z)), 3.43–3.25 (m, 2H), 2.66–2.17 (m, 2H), 2.01–1.87 (m, 1H), 1.75–1.42 (m, 7H). ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.3 (d, J=8.1 Hz), −120.4 (m), −119.4 (m). IR (KBr) ν_{max}: 2853, 1633, 1579, 1244, 1200. Anal. Calcd for $C_{13}H_{15}BrF_2N_2$: C 49.23; H 4.77; N 8.83. Found C 49.26; H 4.80; N 8.79.

4.4. General procedure for amidines 1e–i, 1o–r

To solution PCl_5 (0.0165 mol) in 100 mL of dry benzene was added 0.015 mol amide at −5 °C. The solution was stirred for 15 min and 0.014 mol aniline was added at the same temperature. The result mixture was stirred for 20 min at the room temperature and then stirred and refluxed for 4 h. The separation procedure was different in each case: (i) for oily reaction mixture the solvent was removed under reduced pressure. (ii) The precipitate was filtered where it was possible. In any case the residue was dissolved in 75 mL water. Then 5 M NaOH was added to pH=10. The formed oil was solidified during 1–4 h and precipitate was filtered. The product was purified by crystallization from a mixture of EtOAc/hexane (1:1).

*4.4.1. 2-Bromo-N-[3,4-dihydroquinolin-2(1H)-ylidene]aniline (**1e**).* Yield 4.24 g (94%); mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43–7.95 and 6.44–6.32 (br, 1H, NH), 7.63 (d, J=8.3 Hz) and 7.58 (d, J=7.8 Hz 1H), 7.34–7.26 (m, 1H), 7.14 (d, J=7.3 Hz, 1H), 7.08 (d, J=7.1 Hz, 1H), 7.00–6.85 (m, 3H), 6.66 (d, J=6.5 Hz) and 6.54 (d, J=8.1 Hz, 1H), 2.99 (t, J=8.1 Hz, 1H), 2.91–2.80 (m, 2H), 2.46 (t, J=7.3 Hz, 1H). IR (KBr) ν_{max}: 1657, 1384, 1253, 1228, 753. Anal. Calcd for $C_{15}H_{13}BrN_2$: C 59.82; H 4.35; N 9.30. Found C 59.86; H 4.32; N 9.28.

*4.4.2. 2-Bromo-N-[1,3,4,5-tetrahydro-2H-1-benzazepin-2-ylidene] aniline (**1f**).* Yield 3.34 g (71%); mp 124–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J=8.2 Hz) and 7.56 (d, J=8.1 Hz, 1H), 7.35–7.25 (m, 1H), 7.25–7.11 (m, 2H), 7.11–6.85 (m, 3H), 6.76 (d, J=8.1 Hz) and 6.10–5.86 (m, 1H), 2.91 (t, J=7.1 Hz, 1H), 2.84–2.70 (m, 1H), 2.53 (t, J=6.8 Hz, 1H), 2.33–2.09 (m, 3H). IR (KBr) ν_{max}: 1640, 1576, 1383, 1262. Anal. Calcd for $C_{16}H_{15}BrN_2$: C 60.97; H 4.80; N 8.89. Found C 60.96; H 4.82; N. 8.85.

*4.4.3. N′-(2-Bromophenyl)-N-methylethanimidamide (**1g**).* Yield 2.83 g (83%); mp 35–37 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J=7.8 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 6.82 (t, J=8.1 Hz, 2H), 4.51 (s, 1H), 2.95 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2, 150.2, 132.6, 127.9, 123.7, 123.1, 117.6, 28.5, 17.9. IR (KBr) ν_{max}: 1623, 1560, 1466, 1234. Anal. Calcd for $C_9H_{11}BrN_2$: C 47.60; H 4.88; N 12.33. Found C 47.61; H 4.87; N 12.35.

*4.4.4. N′-(2-Bromophenyl)-N-ethylethanimidamide (**1h**).* Yield 2.89 g (80%); mp 38–40 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J=7.8 Hz, 1H), 7.18 (t, J=7.3 Hz, 1H), 6.90–6.73 (m, 2H), 4.51–4.26 (br, NH(E)) and 4.20–3.97 (br, 1H, NH(Z)), 3.48–3.33 (m, (E)) and 3.26–3.08 (m, 2H, $CH_2(Z)$), 1.80–1.65 (s, 3H), 1.26 (t, J=7.3 Hz, (E)) and 1.17–1.04 (m, 3H, (Z)). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 150.3, 132.5, 127.8, 123.6, 123.0, 117.7, 36.2, 18.1, 14.7. IR (KBr) ν_{max}: 1620, 1570. Anal. Calcd for $C_{10}H_{13}BrN_2$: C 49.81; H 5.43; N 11.62. Found C 49.85; H 5.40; N 11.65.

*4.4.5. N′-(2-Bromophenyl)-N-phenylethanimidamide (**1i**).* Yield 3.03 g (70%); mp 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J=8.0 Hz, 2H), 7.41–7.31 (m, 3H), 7.31–7.22 (m, 1H), 7.14–7.03 (m, 1H), 7.03–6.80 (m, 1H), 6.80–6.30 (br, 1H), 2.36–2.10 (s) and 2.10–1.80 (s, 3H, CH_3). IR (KBr) ν_{max}: 2923, 1546, 1218. Anal. Calcd for $C_{14}H_{13}BrN_2$: C 58.15; H 4.53; N 9.69. Found C 58.17; H 4.50; N 9.68.

*4.4.6. N′-(2-Bromo-4,6-difluorophenyl)-N-methylacetimidamide (**1o**).* Yield 3.11 g (79%); mp 83–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (dt, J=2.8, 7.9 Hz, 1H), 6.81 (dt, J=2.7, 9.0 Hz, 1H), 4.69 (br, 1H), 2.97 (d, J=4.4 Hz, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 157.2 (dd, J=12.8, 245.0 Hz), 154.1 (dd, J=12.4, 245.5 Hz), 135.4 (d, J=15.9 Hz), 118.5 (dd, J=3.1, 12.4 Hz), 115.0 (dd, J=3.1, 24.3 Hz), 103.5 (t, J=26.1 Hz), 28.5, 18.3. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −117.8 (m), −118.4 (m), −120.0 (d, J=8.1 Hz), −120.3 (m). IR (KBr) ν_{max}: 1619, 1574, 1472, 1223. Anal. Calcd for $C_9H_9BrF_2N_2$: C 41.09; H 3.45; N 10.65. Found C 41.11; H 3.47; N 10.69.

*4.4.7. N′-(2-Bromo-4,6-difluorophenyl)-N-ethylacetimidamide (**1p**).* Yield 3.44 g (83%); mp 80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (dt, J=2.8, 7.9 Hz, 1H), 6.81 (dt, J=2.8, 8.6 Hz, 1H), 4.61 (br, 1H), 3.44 (m, 2H), 1.71 (s, 3H), 1.26 (t, J=7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.0, 156.8 (dd, J=12.4, 245.0 Hz), 154.1 (dd, J=12.8, 245.9 Hz), 135.4 (dd, J=15.9 Hz), 118.6 (dd, J=3.5, 12.4 Hz), 115.0 (dd, J=3.5, 24.3 Hz), 103.4 (t, J=25.8 Hz), 36.4, 18.5, 14.5. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −120.1 (d, J=8.1 Hz), −120.4. IR (KBr) ν_{max}: 2969, 1616, 1217, 836. Anal. Calcd for $C_{10}H_{11}BrF_2N_2$: C 43.34; H 4.00; N 10.11. Found C 43.35; H 3.98; N 10.13.

*4.4.8. N′-(2-Bromo-4,6-difluorophenyl)-N-phenylacetimidamide (**1r**).* After the general procedure the precipitate was filtered and

75 mL of water was added to it. A large excess of 5 M NaOH was added to the mixture. The resulting mixture was stirred for 4 h and filtered. After crystallization from hexane a white solid was isolated; yield 4.03 g (83%); mp 182–183 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.31 (s, 1H, NH), 7.80 (d, J=8.1 Hz, 2H), 7.46 (d, J=8.8 Hz, 1H), 7.39–7.29 (m, 1H), 7.31 (t, J=7.8 Hz, 2H), 6.99 (t, J=7.6 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 156.9 (dd, J=13.3, 243.2 Hz), 156.8, 153.4 (dd, J=13.7, 245.0 Hz), 152.5, 140.8, 136.5 (dd, J=4.0, 15.5 Hz), 122.7, 120.3, 117.8 (dd, J=4.0, 12.4 Hz), 115.6 (dd, J=4.0, 24.8 Hz), 104.6, 104.4, 104.2, 19.1. ^{19}F NMR (282 MHz, DMSO-d_6, C_6F_6): δ −119.4. IR (KBr) ν_{max}: 1607, 1588, 1468, 1207. Anal. Calcd for $C_{14}H_{11}BrF_2N_2$: C 51.71; H 3.41; N 8.62. Found C 51.71; H 3.42; N 8.61.

*4.4.9. 2-(2-Bromoimino)pyridine (**1j**).* Compound **1j** was obtained from 2-iminopyridine and 1-bromo-2-iodobenzene according to published procedure.[19]

4.5. General procedure for copper-catalyzed amidines cyclization

To a solution 0.84 mmol of amidine in 5 mL dry acetonitrile were added powdered 234 mg (0.84 mmol) K_2CO_3, 0.72 mg (0.084 mmol) DMEDA, and 8 mg (0.042 mmol) powdered CuI. The result mixture was stirred and refluxed for 4 h under Ar atmosphere. After cooling 5 mL of CH_2Cl_2 was added and solution was filtered and solvent was evaporated. The residue was purified by flash-column chromatography (CH_2Cl_2/MeOH=1:9).

*4.5.1. 2,3-Dihydro-1H-pyrrolo[1,2-a]benzimidazole (**2a**).* Yield 123 mg (93%); mp 106–107 °C (lit.[20] 105–107 °C). The spectroscopic data were identical to the reported.[20]

*4.5.2. 1,2,3,4-Tetrahydropyrido[1,2-a]benzimidazole (**2b**).* Yield 138 mg (96%); mp 98–101 °C (lit.[20] 99–100 °C). The spectroscopic data were identical to the reported.[20]

*4.5.3. 7,8,9,10-Tetrahydro-6H-azepino[1,2-a]benzimidazole (**2c**).* Yield 142 mg (91%); mp 123–125 °C (lit.[20] 124–125 °C). The spectroscopic data were identical to the reported.[20]

*4.5.4. 6,7,8,9,10,11-Hexahydroazocino[1,2-a]benzimidazole (**2d**).* Yield 157 mg (94%); mp 76–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (m, 1H), 7.26 (m, 1H), 7.22 (m, 2H), 4.23 (m, 2H), 3.02 (m, 2H), 1.91 (m, 2H), 1.83 (m, 2H), 1.49 (m, 2H), 1.24 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 142.9, 134.5, 121.9, 121.8, 119.2, 109.0, 41.5, 31.1, 29.7, 27.1, 25.6, 24.0. IR (KBr) ν_{max}: 2927, 1507, 1459, 1446, 1255. Anal. Calcd for $C_{13}H_{16}N_2$: C 77.96; H 8.05; N 13.99. Found C 77.97; H 8.00; N 14.03.

*4.5.5. 5,6-Dihydrobenzimidazo[1,2-a]quinoline (**2e**).* Yield 166 mg (90%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95–7.76 (m, 3H), 7.48–7.15 (m, 5H), 3.26 (t, J=7.5 Hz, 2H), 3.05 (t, J=7.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.8, 143.6, 135.7, 131.9, 129.1, 128.6, 127.9, 125.2, 123.2, 122.9, 119.9, 116.6, 111.3, 26.5, 24.6. Anal. Calcd for $C_{15}H_{12}N_2$: C 81.79; H 5.49; N 12.72. Found C 81.78; H 5.52; N 12.70.

*4.5.6. 6,7-Dihydro-5H-benzimidazo[1,2-a][1]benzazepine (**2f**).* Yield 182 mg (93%); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J=6.8 Hz, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.50 (d, J=8.1 Hz, 1H), 7.46 (t, J=7.3 Hz, 1H), 7.42 (d, J=7.3 Hz, 1H), 7.39–7.34 (m, 1H), 7.32–7.23 (m, 2H), 3.28–3.05 (m, 2H), 2.88–2.53 (m, 3H), 2.54–2.38 (m, 1H), 2.38–2.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 143.0, 136.1, 135.4, 130.6, 127.7, 127.6, 123.0, 122.8, 122.6, 119.6, 110.0, 30.2, 30.0, 25.2. IR (KBr) ν_{max}: 1602, 1583, 1452, 1248. Anal. Calcd for $C_{16}H_{14}N_2$: C 82.02; H 6.02; N 11.96. Found C 82.04; H 6.00; N 11.96.

*4.5.7. 1,2-Dimethyl-1H-benzo[d]imidazole (**2g**).* Yield 116 mg (95%); mp 104–105 °C (lit.[21] 101–103 °C). The spectroscopic data were identical to the reported.[21]

*4.5.8. 1-Ethyl-2-methyl-1H-benzo[d]imidazole (**2h**).* Yield 123 mg (92%); oil. The spectroscopic data were identical to the reported.[22]

*4.5.9. 2-Methyl-1-phenyl-1H-benzo[d]imidazole (**2i**).* Yield 167 mg (96%); mp 47–48 °C (lit.[21] 46–48 °C). The spectroscopic data were identical to the reported.[21]

*4.5.10. Pyrido[1,2-a]benzimidazole (**2j**).* For the purification the crude pyrido[1,2-*a*]benzimidazole was dissolved in 5 mL of MeOH and 1 mL of concentrated HCl was added. The solvent was evaporated to dryness and the solid was triturated with acetone. The precipitate was filtered and dissolved in water. 1 N NaOH was added to adjust to pH=10. The mixture was extracted by 50 mL Et_2O twice, dried over Na_2SO_4, and evaporated. Yield 138 mg (98%); mp 179–180 °C (lit.[19] 179–182 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, J=6.8 Hz, 1H), 7.93 (d, J=8.1 Hz, 1H), 7.88 (d, J=8.3 Hz, 1H), 7.68 (d, J=9.4 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.42 (t, J=7.5 Hz, 1H), 7.36 (t, J=7.7 Hz, 1H), 6.84 (t, J=6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 144.5, 129.3, 128.7, 125.7, 121.0, 119.9, 118.0, 110.4, 110.3. Anal. Calcd for $C_{11}H_8N_2$: C 78.55; H 4.79; N 16.66. Found C 78.53; H 4.80; N 16.67.

*4.5.11. 5,7-Difluoro-2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazole (**2k**).* Yield 141 mg (87%); mp 103–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (dd, J=2.2, 8 Hz, 1H), 6.72 (dt, J=2.2, 10.3 Hz, 1H), 4.08 (t, J=7.1 Hz, 2H), 3.06 (t, J=7.6 Hz, 2H), 2.85–2.45 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.01, 158.4 (dd, J=11.0, 240.6 Hz), 152.6 (dd, J=15.0, 253.9 Hz), 134.1, 133.5, 97.2 (dd, J=22.7, 28.7 Hz), 92.7 (dd, J=4.4, 27.4 Hz), 42.9, 26.2, 23.4. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.8 (m), −126.12 (d, J=10.1 Hz). IR (KBr) ν_{max}: 2853, 1745, 1590, 1447. Anal. Calcd for $C_{10}H_8F_2N_2$: C 61.85; H 4.15; N 14.43. Found C 61.83; H 4.13; N 14.42.

*4.5.12. 6,8-Difluoro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**2l**).* Yield 153 mg (88%); mp 111–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79 (dd, J=2.2, 8.2 Hz, 1H), 6.72 (dd, J=2.2, 10.9 Hz, 1H), 4.03 (t, J=6 Hz, 2H), 3.08 (t, J=6.4 Hz, 2H), 2.25–2.10 (m, 2H), 2.10–1.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5 (dd, J=11.1, 240.6 Hz), 152.6 (dd, J=14.2, 253.9 Hz), 152.5, 136.7 (dd, J=10.2, 14.2 Hz), 127.7 (d, J=15.9 Hz), 97.6 (dd, J=22.1, 28.7 Hz), 91.9 (dd, J=4.4, 27.4 Hz), 42.9, 25.4, 22.4, 20.5. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.8 (m), −126.8 (m). IR (KBr) ν_{max}: 1637, 1223, 1118. Anal. Calcd for $C_{11}H_{10}F_2N_2$: C 63.45; H 4.84; N 13.45. Found C 63.46; H 4.82; N 13.46.

*4.5.13. 2,4-Difluoro-7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazole (**2m**).* Yield 154 mg (83%); mp 128–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (dd, J=2.0, 8.6 Hz, 1H), 6.71 (dt, J=2.2, 11.2 Hz, 1H), 4.15–4.00 (m, 2H), 3.15–3.00 (m, 2H), 2.12–1.90 (m, 2H), 1.90–1.70 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7 (dd, J=11.1, 240.2 Hz), 158.3, 152.9 (dd, J=14.6, 254.3 Hz), 137.8 (dd, J=10.6 Hz), 127.4 (d, J=16.8 Hz), 97.0 (dd, J=21.0, 28.7 Hz), 91.9 (dd, J=4.4, 27.4 Hz), 45.2, 30.7, 29.9, 28.6, 25.4. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.6 (m), −126.6 (d, J=8.2 Hz). IR (KBr) ν_{max}: 2853, 1597, 1234, 1220. Anal. Calcd for $C_{12}H_{12}F_2N_2$: C 64.86; H 5.44; N 12.61. Found C 64.81; H 5.48; N 12.66.

*4.5.14. 2,4-Difluoro-6,7,8,9,10,11-hexahydroazocino[1,2-a]benzimidazole (**2n**).* Yield 188 mg (95%); mp 96–97 °C; ^{1}H NMR (500 MHz,

$CDCl_3$): δ 6.80 (d, J=8.3 Hz, 1H), 6.73 (d, J=10.3 Hz, 1H), 4.21 (t, J=5.9 Hz, 2H), 3.06–2.98 (m, 2H), 1.96–1.88 (m, 2H), 1.88–1.80 (m, 2H), 1.57–1.47 (m, 2H), 1.32–1.20 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7 (dd, J=11.1, 240.2 Hz), 157.3 (d, J=2.2 Hz), 153.1 (dd, J=14.6, 254.3 Hz), 136.6 (dd, J=11.5, 14.6 Hz), 128.1 (d, J=18.1 Hz), 97.4 (dd, J=22.1, 28.7 Hz), 92.1 (dd, J=4.4 Hz, 27.9 Hz), 42.0, 31.0, 29.5, 27.1, 25.5, 23.7. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.7, −126.4. IR (KBr) ν_{max}: 2853, 1595, 1221. Anal. Calcd for $C_{13}H_{14}F_2N_2$: C 66.09; H 5.97 N 11.86. Found C 66.11; H 5.93; N 11.82.

*4.5.15. 4,6-Difluoro-1,2-dimethyl-1H-benzimidazole (**2o**).* Yield 136 mg (89%); mp 77–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (d, J=8.5 Hz, 1H), 6.72 (t, J=10.0 Hz, 1H), 3.68 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6 (dd, J=11.1, 240.4 Hz), 152.8 (dd, J=14.6, 254.3 Hz), 152.6, 137.9 (dd, J=11.1, 15.4 Hz), 127.5 (d, J=16.8 Hz), 97.3 (dd, J=21.7, 28.7 Hz), 92.1 (dd, J=4.4, 27.4 Hz), 30.3, 13.8. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.3, −126.6. IR (KBr) ν_{max}: 2853, 1595, 1221. Anal. Calcd for $C_9H_8F_2N_2$: C 59.34; H 4.43; N 15.38. Found C 59.38; H 4.39; N 15.41.

*4.5.16. 1-Ethyl-4,6-difluoro-2-methyl-1H-benzimidazole (**2p**).* Yield 143 mg (87%); mp 81–82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (d, J=8.1 Hz, 1H), 6.72 (t, J=10.0 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 2.61 (s, 3H), 1.40 (t, J=7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6 (dd, J=10.2, 230.4 Hz), 152.8 (dd, J=13.7, 255.6 Hz), 152.0, 136.9 (dd, J=10.6, 15.5 Hz), 127.7 (d, J=16.4 Hz), 97.3 (dd, J=22.6, 29.2 Hz), 92.1 (d, J=27.0 Hz), 39.1, 14.6, 13.7. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.5, −126.5. IR (KBr) ν_{max}: 3034, 1641, 1598, 1495, 1226, 1109. Anal. Calcd for $C_{10}H_{10}F_2N_2$: C 61.22; H 5.14; N 14.28. Found C 61.25; H 5.11; N 14.25.

*4.5.17. 4,6-Difluoro-2-methyl-1-phenyl-1H-benzimidazole (**2r**).* Yield 186 mg (91%); mp 111–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60–7.53 (m, 2H), 7.53–7.46 (m, 1H), 7.29 (d, J=7.1 Hz, 2H), 6.69 (t, J=10.0 Hz, 1H), 6.56 (d, J=7.3 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 (dd, J=10.6, 241.0 Hz), 152.6 (dd, J=14.6, 254.8 Hz), 152.4, 138.5 (dd, J=10.2, 15.0 Hz), 135.3, 130.1, 129.4, 127.7 (d, J=17.2 Hz), 126.8, 97.7 (dd, J=21.7, 28.7 Hz), 93.1 (dd, J=4.9, 27.9 Hz), 14.3; ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −117.7, −126.5. IR (KBr) ν_{max}: 3032, 1499, 1220. Anal. Calcd for $C_{14}H_{10}F_2N_2$: C 68.85; H 4.13; N 11.47. Found C 68.81; H 4.18; N 11.49.

4.6. General procedure for the non-catalytic cyclization amidines

Amidine **3** (0.084 mmol) and 0.168 mol of K_2CO_3 in 5 mL DMF were heated under stirring for 4–24 h. The reaction was monitored by ^{19}F NMR. After that the solvent was evaporated to dryness and the residue was diluted with water and then extracted with 50 mL dichloromethane twice. The crude product was purified by crystallization from a mixture of EtOAc/hexane (1:1).

*4.6.1. 6-Bromo-8-fluoro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (**3l**).* Yield 192 mg (85%); mp 123–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J=2.2 Hz, 1H), 6.95 (d, J=2.2 Hz, 1H), 4.03 (t, J=5.9 Hz, 2H), 3.12 (t, J=6.1 Hz, 2H), 2.19–2.08 (m, 2H), 2.08–1.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5 (d, J=242.2 Hz), 153.1 (d, J=2.2 Hz), 138.2, 134.4 (d, J=13.7 Hz), 113.5 (d, J=27.4 Hz), 112.0 (d, J=12.8 Hz), 95.2 (d, J=27.4 Hz), 43.0, 25.6, 22.5, 20.6. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −119.7 (t, J=8.1 Hz). IR (KBr) ν_{max}: 2853, 1620, 1581, 1473. Anal. Calcd for $C_{11}H_{10}BrFN_2$: C 49.09; H 3.75; N 10.41. Found C 49.13; H 3.76; N 10.44.

*4.6.2. 4-Bromo-2-fluoro-7,8,9,10-tetrahydro-6H-azepino[1,2-a]benzimidazole (**3m**).* Yield 206 mg (87%); mp 141–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, J=1.9 Hz, 9.3 Hz, 1H), 6.92 (d, J=8.6 Hz, 1H), 4.20–4.00 (m, 2H), 3.25–3.00 (m, 2H), 2.07–1.90 (m, 2H), 1.90–1.66 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 158.7 (d, J=242.2 Hz), 137.6, 135.5 (d, J=12.0 Hz), 113.0 (d, J=28.3 Hz), 112.2 (d, J=12.4 Hz), 95.2 (d, J=30.0 Hz), 45.3, 30.7, 29.9, 28.6, 25.3. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −120.0 (t, J=8.1 Hz). IR (KBr) ν_{max}: 2930, 1583, 1470, 1212, 1188. Anal. Calcd for $C_{12}H_{12}BrFN_2$: C 50.90; H 4.27; N 11.72. Found C 50.88; H 4.30; N 11.69.

*4.6.3. 4-Bromo-2-fluoro-6,7,8,9,10,11-hexahydroazocino[1,2-a]benzimidazole (**3n**).* Yield 229 mg (92%); mp 107–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J=9.3 Hz, 1H), 6.93 (d, J=8.3 Hz, 1H), 4.24–4.10 (m, 2H), 3.10–2.94 (m, 2H), 1.98–1.88 (m, 2H), 1.88–1.71 (m, 2H), 1.57–1.45 (m, 2H), 1.33–1.15 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7 (d, J=247.2 Hz), 157.9, 138.3, 134.4 (d, J=13.2 Hz), 113.3 (d, J=27.9 Hz), 112.3 (d, J=11.9 Hz), 96.4 (d, J=27.0 Hz), 45.1, 31.0, 29.5, 27.1, 25.5, 23.9. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −119.9. IR (KBr) ν_{max}: 2857, 1579, 1472, 1251. Anal. Calcd for $C_{13}H_{14}BrFN_2$: C 52.54; H 4.75; N 9.43. Found C 52.52; H 4.81; N 9.41.

*4.6.4. 4-Bromo-6-fluoro-1,2-dimethyl-1H-benzimidazole (**3o**).* The reaction time was 24 h. Yield 208 mg (91%); mp 115–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, J=2.3, 9.4 Hz, 1H), 6.93 (dd, J=2.2, 8.3 Hz, 1H), 3.67 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8 (d, J=243 Hz), 153.27, 153.25; 137.9, 135.6 (d, J=14 Hz), 134.5, 113.2 (d, J=27 Hz), 112.2 (d, J=12 Hz), 95.4 (d, J=27 Hz), 30.4, 13.9; ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −119.0. IR (KBr) ν_{max}: 1381, 1261, 1201, 830. Anal. Calcd for $C_9H_8BrFN_2$: C 44.47; H 3.32; N 11.52. Found: C 44.49; H 3.30; N 11.50.

*4.6.5. 4-Bromo-6-fluoro-2-methyl-1-ethyl-1H-benzimidazole (**3p**).* The reaction time was 24 h. Yield 192 mg (89%); mp 134–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (dd, J=2.2, 9.8 Hz, 1H), 6.98 (dd, J=2.1, 8.6 Hz, 1H), 4.13 (q, J=7.3 Hz, 2H), 2.66 (s, 3H), 1.42 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8 (d, J=241.8 Hz), 152.61, 152.59, 138.0, 134.7, 134.6, 113.2 (d, J=28 Hz), 112.2 (d, J=12 Hz), 95.3 (d, J=27 Hz), 39.1, 14.7, 13.8; ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −118.9. IR (KBr) ν_{max}: 3033, 1598, 1226. Anal. Calcd for $C_{10}H_{10}BrFN_2$: C 46.72; H 3.92; N 10.90. Found: C 46.73; H 3.95; N 10.85.

*4.6.6. 4-Bromo-6-fluoro-2-methyl-1-phenyl-1H-benzimidazole (**3r**).* Yield 243 mg (95%); mp 146–147 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.71–7.50 (m, 5H), 7.43 (dd, J=1.3, 9.5 Hz, 1H), 6.96 (dd, J=1.2, 8.6 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2 (d, J=243.3 Hz), 153.10, 153.08, 137.9, 136.5, 136.4, 135.4, 130.2, 129.5, 126.9, 114.0 (d, J=27.9 Hz), 112.1 (d, J=12.4 Hz), 96.4 (d, J=27.4 Hz), 14.4. ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ −119.9. IR (KBr) ν_{max}: 3034, 1597, 1500, 1232. Anal. Calcd for $C_{14}H_{10}BrFN_2$: C 55.10; H 3.30; N 9.18. Found C 55.13; H 3.27; N 9.16.

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Supplementary data

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.027.

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