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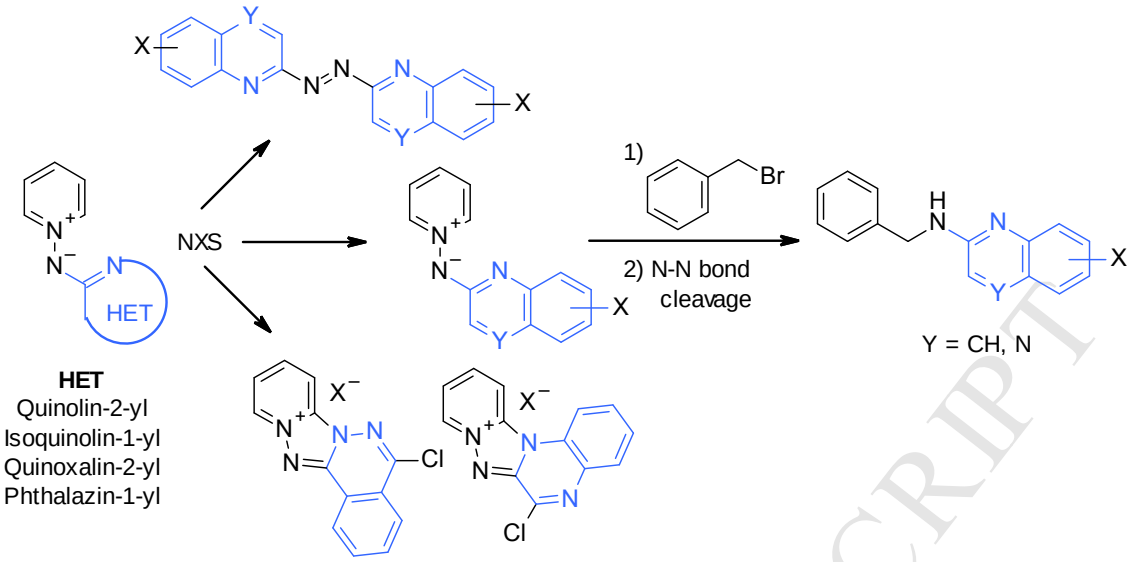

Graphical Abstract

Regioselective halogenation of pyridinium *N*-(benzoazynyl) aminides as a way to produce *N*-benzyl-α-aminobenzoazines

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Dedicated to Professor Miguel Yus on the occasion of his 70th birthday

Keywords: Nitrogen halo-heterocycles, Pyridinium aminides, Ylides, 2-Aminoquinolines, 2-Aminoquinoxalines

Abstract: The halogenation of pyridinium *N*-(benzoazynyl) aminides with *N*-halosuccinimides provides a mild and regioselective method to functionalize the negatively charged diazine moiety in most cases. In some examples, however, formation of other products is explained. Finally, alkylation of the exocyclic nitrogen and reduction of the N–N bond provides a simple and straightforward strategy to obtain functionalized *N*-benzyl-benzoazynyl-α-amines.

1. Introduction

Substituted benzoazines and benzodiazines, such as quinoline, isoquinoline, quinazoline, quinoxaline and phtalazine compounds, are present in natural bioactive compounds but they are also privileged scaffolds in drugs with varied uses.[1] Despite the importance of these structural units, efficient synthetic methods are limited and the development of more direct, efficient and economical approaches for their synthesis would be welcome.[2]

Among the quinoline and quinoxaline derivatives developed to date, 2-aminoquinoline[3] and 2-aminoquinoxaline[4] are interesting moieties due to the biological activities shown by their derivatives. C-3-substituted 2-aminoquinolines have been identified as beta-site amyloid precursor protein cleaving enzyme 1 (BACE 1) inhibitors for Alzheimer's disease therapeutics.[5] In addition, 2-aminoquinoxalines have been used in the construction of complex drug-like scaffolds in multicomponent reactions.[6] Therefore, the synthesis of derivatives of these heterocyclic amines continues to be a topic of interest today.[7]

Pyridinium *N*-pyridin- or pyrazin-2-yl aminides **1** (Figure 1) and related products have been studied by our group as building blocks in the synthesis of heterocyclic derivatives.[8] However, compounds that contain benzoazynyl groups as ylide stabilizers have not been studied, except for two isolated cases.[9] As a continuation of our research, we became interested in studying the reactivity of these betaines containing a benzoazine or diazine moiety (Figure 1).

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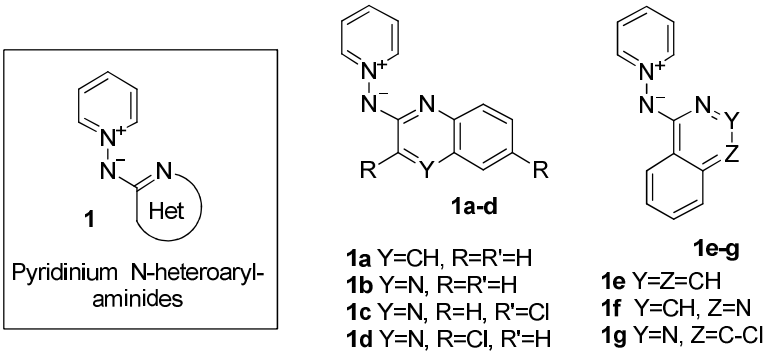


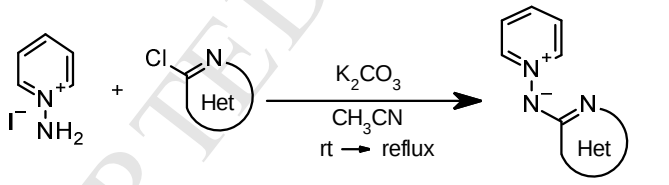
Figure 1

In the present paper, we report the results obtained in a halogenation study (bromination and chlorination) on aminides **1a–g** (Figure 1). Depending on the starting aminide and the halogenating agent, compounds with different structures were obtained. Some of the halogenated aminides were used in the synthesis of the corresponding *N*-benzyl-(quinolin-2-yl)amines and *N*-benzyl-(quinoxalin-2-yl)amines in order to demonstrate the efficiency of the method.

2. Results and discussion

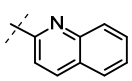
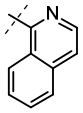
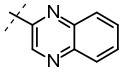
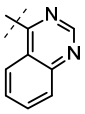
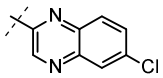
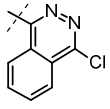
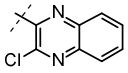
2.1 Synthesis of starting pyridinium N-heteroarylaminides

Compounds **1** are stable heterocyclic betaines that can be easily obtained (Table 1) by a one-step procedure, starting from *N*-aminopyridinium iodide and the corresponding α-chloroheterocycle, using the previously described method (Scheme 1).[10]



Scheme 1: Synthesis of pyridinium *N*-heteroarylaminides **1**

Table 1. Yields for compounds **1**

Compound	Het	Yield (%)	**Compound**	Het	Yield(%)
1a		40	**1e**		55
1b		84	**1f**		75
1c		Quant.	**1g**		95
1d		87			

As a consequence of the delocalization of the nitrogen negative charge over the benzoazine ring, aminides **1** are expected to react readily with electrophiles, such as halogens, to generate substituted aminides.[3a]

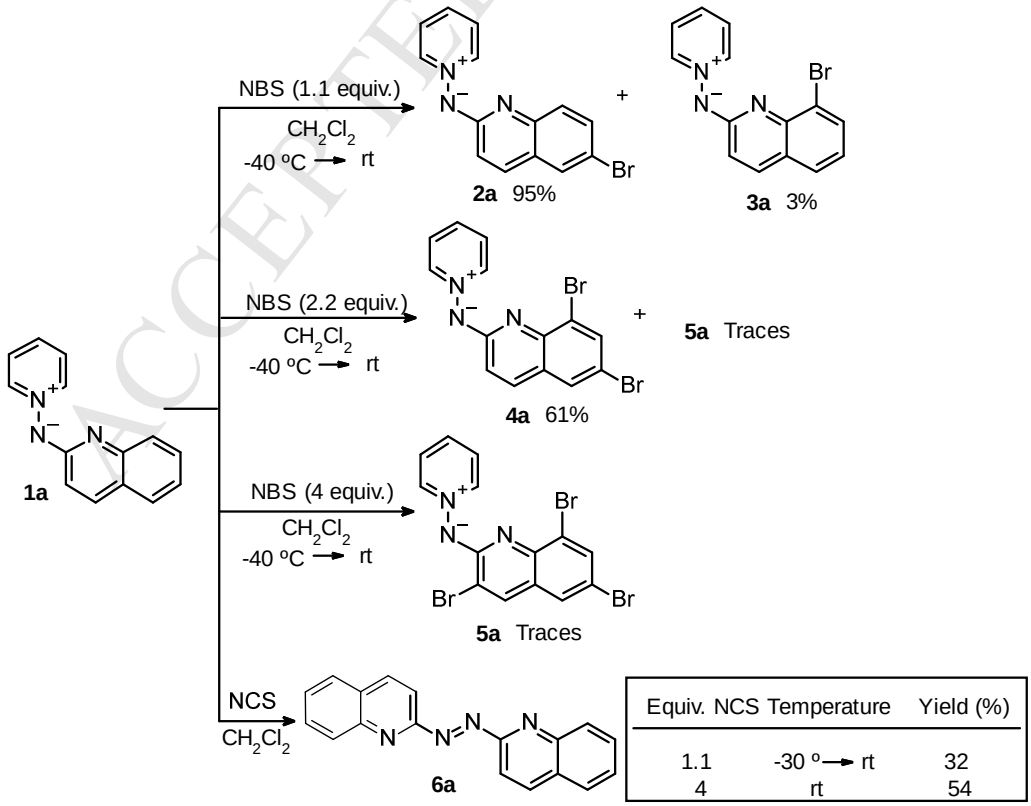
2.2 Treatment of aminides 1 with N-halosuccinimides

Monohalogenation of aminides **1** (Het = pyridine or pyrazine) is a regioselective process that takes place at the 5-position when the NXS is added at –30 ºC. At room temperature, however, dihalogenation occurs at the 3- and 5-positions of the heterocycle.[11]

*2.2.1 Halogenation of pyridinium N-quinolin-2-ylaminide **1a***

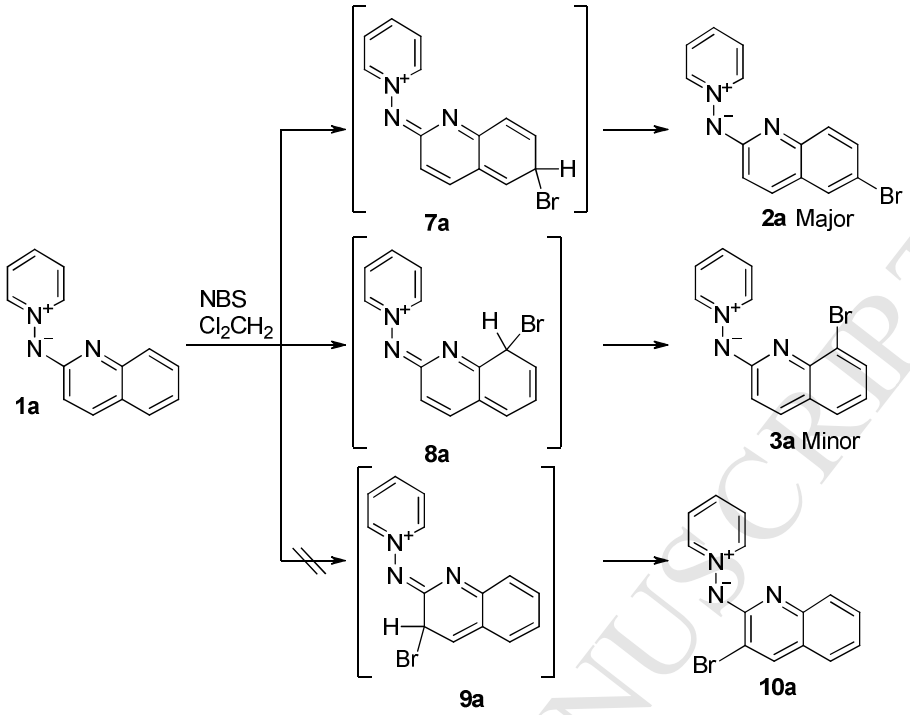
As expected, different brominated aminides were obtained when **1a** was treated with different amounts of NBS. Monobrominated compounds **2a** and **3a** were isolated when **1a** was treated with 1.1 equivalents of NBS at low temperature (–40 ºC). This process yielded **2a** as the main product with high regioselectivity (**see** in scheme 2, yields in isolated pure products). The dibrominated product **4a** was obtained when **1a** was treated with 2.2 equivalents of NBS at the same temperature and, in this case, only traces of the tribrominated compound **5a** were detected. When the process was carried out at room temperature, decomposition of the products took place, and only traces of **4a** were observed. Similar decomposition occurred when the NBS:**1a** ratio was increased to 4:1. In this case, only compound **5a** was again detected in trace amounts (Scheme 2).

Treatment of aminide **1a** with NCS (1.1 equivalents) at low temperature did not yield any halogenated ylide. Surprisingly, azocompound **6a** was the only isolated product in this case. The same result, albeit with a higher yield, was obtained on using a large excess of NCS (4 equivalents) at room temperature (Scheme 2).



Equiv. NCS	Temperature	Yield (%)
1.1	-30 º → rt	32
4	rt	54

Scheme 2: Reaction of aminide **1a** with NBS and NCS

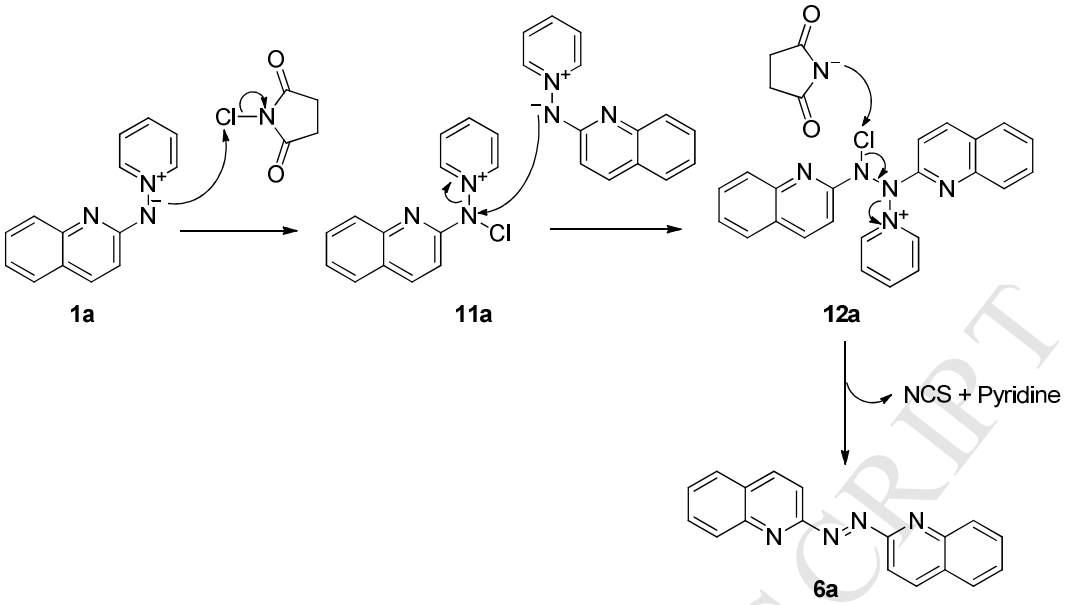


Scheme 3: Halogenation of **1a** with NBS

The possible intermediates through which the process occurs are shown in Scheme 3. Treatment of **1a** with NBS provided the C-6 substituted derivative **2a** as the main product, which was formed via intermediate **7a**, while **3a**, with a substituent in the C-8 position of the quinoline moiety, is always a minor product. The product **10a**, with the substituent in the C-3 position, was not detected in any case. The use of excess NBS (2.2 equivalents) led to substitution in positions C-6 and C-8 and only traces of the trisubstituted compound **5a** were detected. When a larger excess of NBS was used (four equivalents) only **5a** was detected, again in trace amounts.

The 2-aminoquinoline system with a bromo-substituent at the C-6 position has previously been described by Gester et al.,[12] with a tricyclic system bearing a 2-aminoquinoline moiety. This compound was prepared using bromine in conjunction with higher temperatures, and lower yields were obtained.

On using NCS (Scheme 2), N-chlorination appears to be favoured over C-chlorination, since the main product can be explained as being the result of a dimerization process initiated by aminide N-chlorination of **1a**followed by a nucleophilic attack of other aminide molecule. This situation is consistent with a literature precedent.[13] Finally, elimination of NCS and pyridine yielded compound **6a** (Scheme 4).



Scheme 4: Proposed mechanism for the reaction of **1a** with NCS

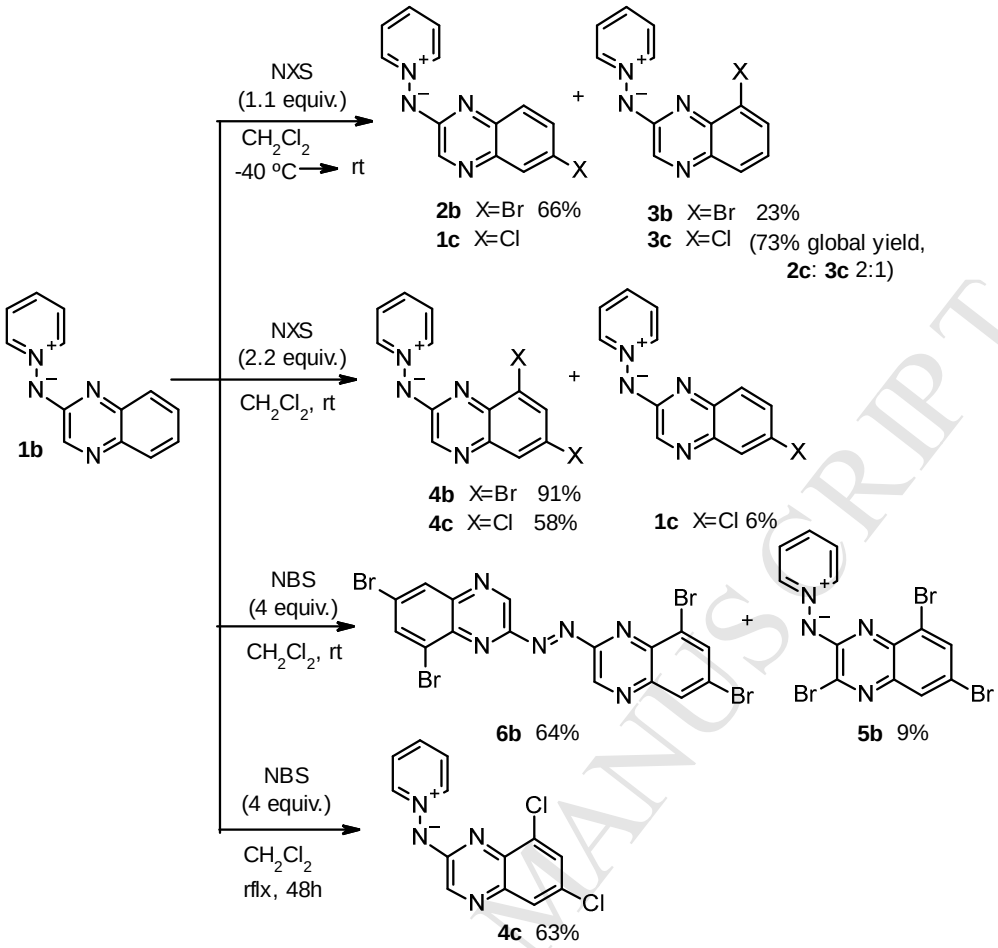
*2.2.2 Halogenation of pyridinium N-quinoxalin-2-ylaminides **1b–d** and **2b***

The results of halogenation of aminides **1b–d** and **2b**, are summarized in Schemes 5, 6 and 7.

Treatment of aminide **1b** (Scheme 5) with 1.1 equivalents of NXS at low temperature (–40 ºC) gave a mixture of the monohalogenated regioisomers at the C-6 and C-8 positions of the quinoxaline ring (compounds **2b**, **1c** and **3**). Monobromination took place with a higher regioselectivity for position C-6 and compounds **2b** and **3b** were separated. However, different behaviour was observed with monochlorination, where the ratio of the mixture **1c**: **3c** was determined by NMR spectroscopy (Scheme 5). When monobromination was carried out at –78 ºC, in an effort to improve regioselectivity, similar results were obtained. On the other hand, a 1:1 mixture of **2b:3b** was obtained on carrying out the monobromination of **1b** at room temperature.

Dihalogenation of compound **1b** by using 2.2 equivalents of the corresponding *N*-halosuccinimide afforded products **4**. In the dichlorination reaction, only a small amount (6%) of aminide **1c** was also identified.

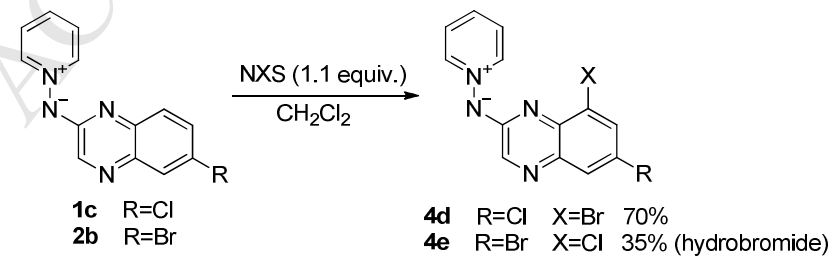
Treatment of aminide **1b** with a large excess (4 equivalents) of halosuccinimide gave different results depending on the halogen. The use of NBS gave the azocompound **6b** as the main product (64%) along with the tribrominated compound **5b** (9%) (Scheme 5). However, the dichlorinated product **4c** was the only compound obtained, in 63% yield, after 48 hours of reaction with NCS. All of the C-substitution processes in quinoxaline can be explained as indicated for quinoline in Scheme 3, with the quantitative differences attributed to the additional nitrogen in the heterocyclic system.



Scheme 5: Halogenation of pyridinium quinoxalin-2-ylaminide **1b**

The proposed mechanism for the formation of **6b** could be the same as that discussed previously for **6a** (Scheme 4). This process would take place after the dibromination steps.

Monohalogenation also occurred when the C-6 position was occupied. In this case a regioselective attack at on the C-8 position of the pyridinium 6-haloquinoxalin-2-ylaminides **1c** and **2b** (Scheme 6) was observed. While **4d** was produced in good yield, chlorination of aminide **2b** was incomplete (56% conversion) and a proportion of the starting material was recovered after 36 hours under reflux. In addition, **4e** was isolated as the hydrobromide from the reaction mixture with NCS.



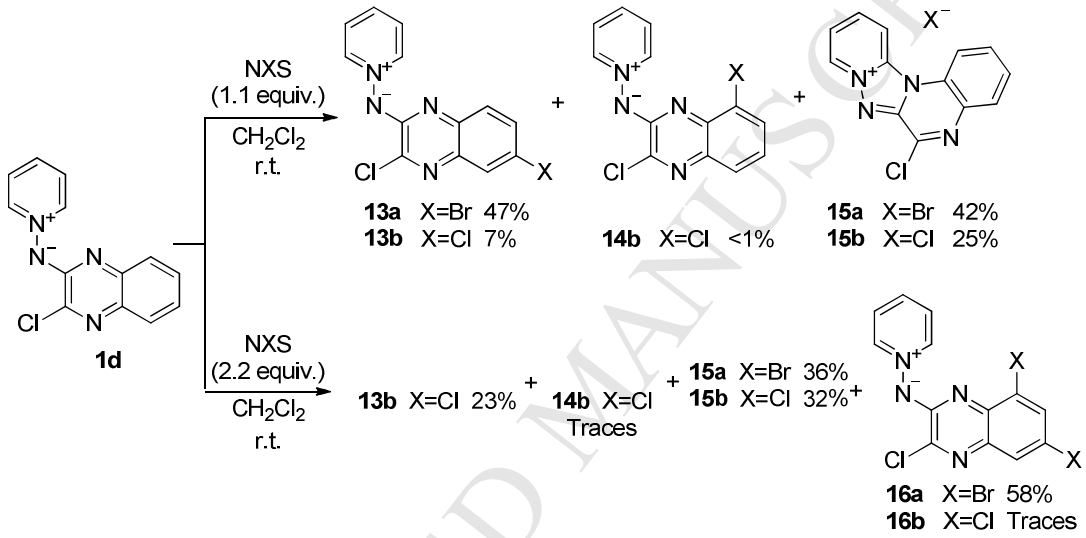
Scheme 6: Halogenation of pyridinium 6-haloquinoxalin-2-ylaminides **1c** and **2b**

Treatment of aminide **1d** with 1.1 equivalents of NBS (Scheme 7) led to a mixture of the monobrominated product **13a** (47%) and the tetracyclic product **15a** (42%). On using 2.2

equivalents of NBS the dibrominated aminide **16a** was the main product (58%) along with **15a** (36%).

The conversion was lower with NCS, and gave the tetracyclic salt **15b** on using 1.1 equivalents of NCS, with small amounts of mono- and dihalogenated compounds **13b** and **14b** also formed. The use of 2.2 equivalents of NCS led to an increase in the yield of **13b** (23%) as well as the yield of tetracyclic salt **15b** (32%), with traces of the mono-and dichlorinated compounds **14b** and **16b** also detected (Scheme 7). In both processes some of the starting material **1d** was also recovered.

When formed, compounds **15** precipitated quickly under different addition conditions (rate and temperature) and the formation of the corresponding mono- or dihalogenated aminides was much slower.

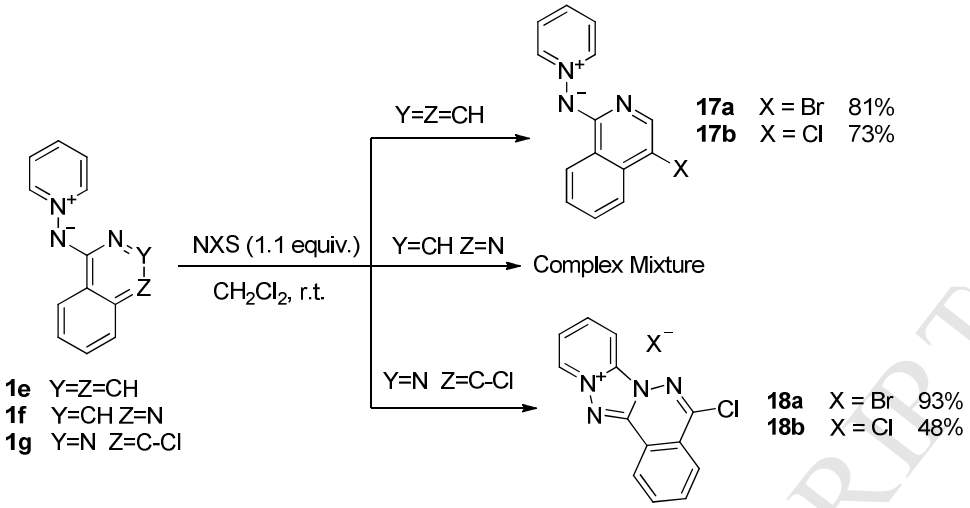


Scheme 7: Halogenation of pyridinium 3-chloroquinoxalin-2-yl aminide **1d**

*2.2.3. Treatment of pyridinium N-isoquinolin-1-yl aminide **1e**, pyridinium N-quinazolin-2-yl aminide **1f** and pyridinium N-4-chlorophthalazin-1-yl aminide **1g** with N-halosuccinimides*

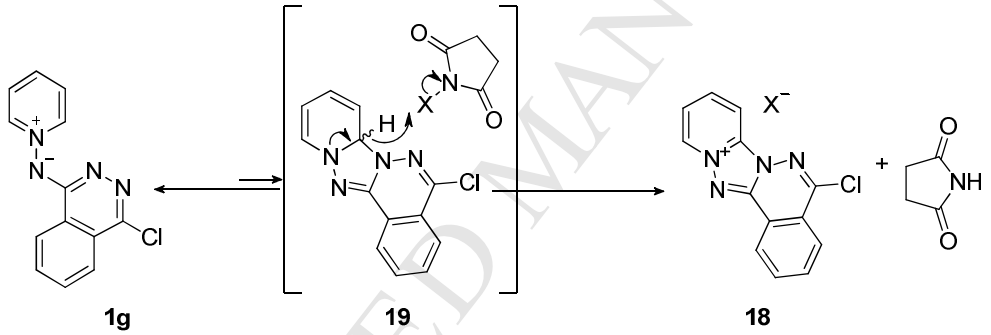
The aminides **1e–g** were highly reactive towards NXS (1.1 equivalents) at room temperature, but they exhibited very different behaviour. Pyridinium *N*-(isoquinolin-1-yl) aminide **1e** yielded either bromo- or chloro-substituted products **17** in good yield. A related halogenation has been described on 1-aminoisoquinoline using bromine,[14a] and bromination on substrates of substituted 1-aminoisoquinoline with NBS have also been described[14b] in several patents,[14c-e] but in these cases higher temperatures and/or longer times were employed. The same can be said for a related chlorination with NCS described in a patent.[14f] An attempt to dihalogenate **1e** using 2.2 equivalents of NXS produced decomposition products, even at low temperature (–40°C).

Pyridinium *N*-(quinazolin-1-yl)aminide **1f**, upon treatment with either with NBS or NCS, produced decomposition mixtures under all conditions tested. Pyridinium *N*-(4-chlorophthalazin-1-yl)aminide **1g**, however, yielded tetracyclic derivatives **18** (Scheme 8).



Scheme 8: Reaction of aminides **1e–g** with NBS and NCS

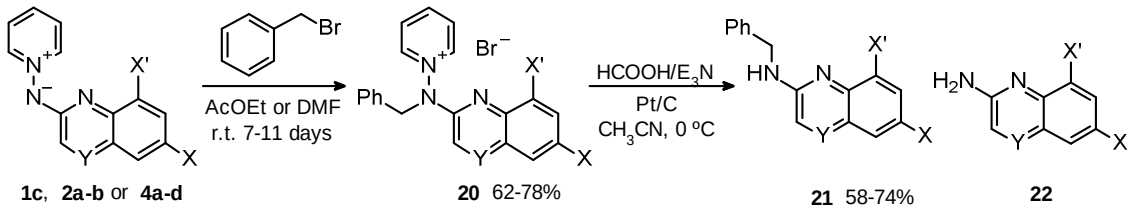
The formation of the cyclized products **15** and **18** can be explained by the existence, in CH_2Cl_2 solution, of a small proportion of the cyclic tautomer **19** of the aminides **1d** and **1g**, which would allow oxidation with NXS to the tetracyclic salts (see Scheme 9).[9b]



Scheme 9: Proposed mechanism for the reaction of **1g** with NXS

*2.3. Synthesis of N-benzyl-N-haloquinolin(or quinoxalin)-2-yl amines **21***

Given the opportunities to use the halo and dihalo pyridinium *N*-heteroaryl aminides in organometallic procedures such as the Suzuki[15a] or Sonogashira[15b] couplings, the possibility of alkylating the aminide nitrogen and reducing the N–N bond to eliminate the pyridine moiety was tested on some of the products. Thus, pyridinium *N*-heteroaryl aminides **1c**, **2a–b** and **4a–d** were regioselectively alkylated to obtain the salts **20**. Subsequent reduction of the N–N bond (Scheme 10, Table 1) yielded the functionalized benzoazines **21**. Only in the reduction process of **20b,** 6,8-dibromoquinolin-2-ylamine **22** was formed in 6% yield, in addition with the expected amine **21b**. Other debenzylation products were not observed in the other examples.



Scheme 10: Synthesis of *N*-benzyl-*N*-haloquinolin(or quinoxalin)-2-yl amines **21**

Table 2.

Y	X	X'	Compound	Yield (%)	Compound	Yield (%)
CH	Br	H	**20a**	78	**21a**	69
CH	Br	Br	**20b**	72	**21b**	59
N	Br	H	**20c**	71	**21c**	61
N	Cl	H	**20d**	76	**21d**	67
N	Br	Br	**20e**	66	**21e**	61
N	Cl	Cl	**20f**	62	**21f**	74
N	Cl	Br	**20g**	93	**21g**	58

3. Conclusions

A method to functionalize, with good regioselectivity in most cases, α-aminobenzoazine systems via pyridinium *N*-(benzoazynyl) aminides, halogenation with *N*-halosuccinimides, nitrogen alkylation and reduction has been described. The negative charge stabilised by the *N*-aminide facilitates halogenation at low temperature. In some cases, however, this has the drawback that products like (*E*)-bis(2-heteroaryl)diazenes are obtained–especially with *N*-chlorosuccinimide. Furthermore, oxidation of two *N*-aminides with the *N*-halosuccinimide predominated to produce the tetracyclic [1,2,4]triazolo[1,5-a]pyridin-4-ium salts. In most cases, however, the method provides a simple and straightforward strategy to obtain functionalized α-benzylaminobenzoazines.

4. Experimental section

4.1. General Experimental Details

Melting points were determined in open capillary tubes on a Stuart Scientific SMP3 melting point apparatus. IR spectra were obtained on a Perkin-Elmer FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Unity 300/500 MHz or Varian Mercury VX-300 systems at room temperature. Chemical shifts are given in ppm (δ) downfield from TMS. Coupling constants (*J*) are in Hertz (Hz) and signals are described as follows: s, singlet; d, doublet; t, triplet; m, multiplet; ap, apparent; br, broad. Low resolution mass spectra (MS) were recorded on a Thermo Scientific ITQ900 system using Electronic Impact (EI) and high resolution analysis (TOF) was performed on an Agilent 6210 time-of-flight LC-MS system using Electro Spray Ionization (ESI). All reagents were obtained from commercial sources and were used without further purification, except for both the NXS samples, which were recrystallized from water. TLC analyses were performed on silica gel (DC-Fertigfolien ALUGRAM Xtra Sil G/UV$_{254}$, Macherey-Nagel) and spots were visualised under UV light. Column chromatography was carried out on silica gel 60 (40–63 μm, Silicycle) columns using the eluent reported in each case.

*4.2. Preparation of pyridinium N-(heteroaryl) aminides **1***[10]

Potassium carbonate (1.86 g, 13.5 mmol) was added to a solution of *N*-aminopyridinium iodide (1 g, 4.5 mmol) in acetonitrile (20 mL) and the reaction mixture was vigorously stirred for 90 min at room temperature to give a dark purple solution. To the reaction mixture was added a solution of the corresponding haloheterocycle (4.7 mmol) in acetonitrile (5 mL). The mixture was stirred and heated under reflux until all starting material had been consumed (detected by TLC). The inorganic salts were filtered off on Celite and the filtrate was evaporated *in vacuo*. The product was purified by chromatography on silica gel using ethanol as eluent.

***N*-(Quinolin-2-yl)pyridinium aminide (1a):**[9b] After 5 h of reaction, product **1a** was obtained as an orange solid (398 mg, 40%, 1.8 mmol).

***N*-(Quinoxalin-2-yl)pyridinium aminide (1b):**[10] After 16 h of reaction, product **1b** was obtained as a yellow solid (839 mg, 84%, 3.8 mmol).

***N*-(6-Chloroquinoxalin-2-yl)pyridinium aminide (1c):** After 3 h of reaction, product **1c** was obtained as a yellow solid (1.15 g, quantitative, 4.5 mmol), m.p. 197–199 °C, IR (KBr): $\tilde{\upsilon}$ = 1717, 1537, 1414, 1306, 1153, 934, 817, 649. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.32 (dd, J = 7.3 and 1.3 Hz, 2 H, 2-H, 6-H), 8.28 (s, 1 H, 3'-H), 7.73 (d, J = 2.4 Hz, 1 H, 5'-H), 7.73 (tt, J = 7.8 and 1.3 Hz, 1 H, 4-H) (overlapped signals), 7.61 (ap t, J = 7.4 Hz, 2 H, 3-H, 5-H), 7.35 (dd, J = 8.8 and 2.4 Hz, 1 H, 7'-H), 7.31 (d, J = 8.8 Hz, 1 H, 8'-H). ^{13}C-NMR (125 MHz, $CDCl_3$), δ: 159.1 (2'-C), 149.0 (3'-C), 143.6 (2-C, 6-C), 142.7 (8a'-C), 139.7 (4a'-C), 136.3 (4-C), 132.2 (7'-C), 130.2 (5'-C), 130.1 (6'-C), 128.7 (3-C, 5-C), 128.6 (8'-C). MS (EI, *m*/*z*): 258/256 (14/43, $M^{+\bullet}$), 257/255 (37/100), 177 (18), 150 (27), 115 (15). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_{10}{}^{35}ClN_4$ $[M + H]^+$ 257.0589; found 257.0580.

***N*-(3-Chloroquinoxalin-2-yl)pyridinium aminide (1d):** After 1 h of reaction, product **1d** was obtained as a yellow solid (1.00 g, 87%, 3.9 mmol), m.p. 192–195 °C, IR (KBr): $\tilde{\upsilon}$ = 3060, 1531, 1485, 1431, 1155, 1053, 943, 742, 675 cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD), δ: 8.81 (dd, J = 6.8 and 1.5 Hz, 2 H, 2-H, 6-H), 8.30 (tt, J = 7.8 and 1.2 Hz, 1 H, 4-H), 7.98 (dd, J = 7.8 and 6.8 Hz, 2 H, 3-H, 5-H), 7.57 (dd, J = 8.3 and 1.5 Hz, 1 H, 5'-H), 7.37 (ddd, J = 8.9, 6.9 and 1.5 Hz, 1 H, 7'-H), 7.20 (dd, J = 8.9 and 1.5 Hz, 1 H, 8'-H), 7.17 (ddd, J = 8.3, 6.9 and 1.5 Hz, 1 H, 6'-H). ^{13}C-NMR (125 MHz, CD_3OD), δ: 157.9 (2'-C), 147.2 (2-C, 6-C), 144.0 (8a'-C), 142.2 (3'-C), 142.2 (4-C), 138.1 (4a'-C), 131.9 (7'-C), 130.2 (3-C, 5-C), 129.3 (5'-C), 126.4 (8'-C), 125.1 (6'-C). MS (EI, *m*/*z*): 258/256 (16/48, $M^{+\bullet}$), 257/255 (39/100). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_{10}{}^{35}ClN_4$ $[M + H]^+$ 257.0589; found 257.0591.

***N*-(Isoquinolin-1-yl)pyridinium aminide (1e):**[10] After 16 h of reaction, product **1e** was obtained as a yellow solid (546 mg, 55%, 2.5 mmol).

***N*-(Quinazolin-4-yl)pyridinium aminide (1f):** After 5 h of reaction, product **1f** was obtained as a brown solid (749 mg, 75%, 3.4 mmol), m.p. 178–180 °C, IR (KBr): $\tilde{\upsilon}$ = 3102, 3015, 1616, 1571, 1490, 1434, 1349, 1560, 915, 783, 750, 678. ^{1}H-NMR (500 MHz, CD_3OD), δ: 8.74 (dd, J = 6.9 and 1.4 Hz, 2 H, 2-H, 6-H), 8.31 (tt, J = 7.7 and 1.4 Hz, 1 H, 4-H), 8.25 (dd, J = 8.2 and 1.4 Hz, 1 H, 5'-H), 7.99 (m, 3 H, 3-H, 5-H and 2'-H), 7.63 (ddd, J = 8.2, 6.9 and 1.3 Hz, 1 H, 6'-H), 7.49 (br d, J = 8.3 Hz, 1 H, 8'-H), 7.41 (ddd, J = 8.3, 6.9 and 1.1 Hz, 1 H, 7'-H). ^{13}C-NMR (75 MHz, CD_3OD), δ: 164.6 (4'-C), 154.4 (2'-C), 146.3 (4a'-C), 145.9 (2-C, 6-C), 141.5 (4-C), 133.7 (6'-C), 128.8 (3-C, 5-C), 126.7 (7'-C), 125.4 (5'-C), 124.0 (8'-C), 117.7 (8a'-C). MS (EI, *m*/*z*): 222 (28, $M^{+\bullet}$), 221 (100), 78 (16). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_{11}N_4$ $[M + H]^+$ 223.0978; found 223.0980.

***N*-(4-Chlorophthalazin-1-yl)pyridinium aminide (1g):** After 4 h of reaction, product **1g** was obtained as a brown solid (1.09 g, 95%, 4.3 mmol), m.p. 148–150 °C, IR (KBr): $\tilde{\upsilon}$ = 3065, 1513, 1487, 1404, 1139, 1105, 978, 785, 750, 661. ^{1}H-NMR (500 MHz, CD_3OD), δ: 8.83 (dd, J = 6.8 and 1.0 Hz, 2 H, 2-H, 6-H), 8.29 (dd, J = 7.3 and 2.0 Hz, 1 H, 8'-H), 8.23 (tt, J = 7.8 and 1.0 Hz, 1 H, 4-H), 7.93 (dd, J = 7.8 and 6.8 Hz, 2 H, 3-H, 5-H), 7.85 (dd, J = 6.9 and 2.4 Hz, 1 H, 5'-H), 7.78 (ap td, J = 7.3 and 1.5 Hz, 1 H, 7'-H or 6'-H), 7.75 (ap td, J = 7.3 and 1.9 Hz, 1 H, 6'-H or 7'-H). ^{13}C-NMR (125 MHz, CD_3OD), δ: 162.2 (1'-C), 147.1 (2-C, 6-C), 144.7 (4'-C), 142.1 (4-C), 134.7 and 134.4 (6'-C and 7'-C), 130.4 (3-C, 5-C), 128.9 (8a'-C), 126.7 (8'-C), 126.6 (5'-C), 125.7 (4a'-C). MS (EI, *m*/*z*): 258/256 (7/22, $M^{+\bullet}$), 257/255 (35/100), 220 (11), 114 (35), 52 (11). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_{10}{}^{35}ClN_4$ $[M + H]^+$ 257.0589; found 257.0588.

*4.3. Treatment of aminides **1** with N-halosuccinimides*

General procedures

Method A: To a stirred solution of the corresponding aminide **1** (2 mmol) in CH_2Cl_2 (10 mL) at the indicated temperature, a solution of the corresponding *N*-halosuccinimide (2.2 mmol) in CH_2Cl_2 (40 mL) was added dropwise. Once the addition was finished, the mixture was allowed to react at the indicated temperature in each case until aminide **1** was not observed by TLC.

The purification was carried out according to the procedures indicated below:

- Compounds **2a**, **2b**, **4d**, **4e** and mixture **1c**/**3c**. Once the starting material was consumed, the product/s was/were purified by flash chromatography (CH_2Cl_2/CH_3OH, 95:5).
- Compounds **17**. After 10 min of reaction, the crude mixture was treated with commercial HBr. The excess acid was evaporated and the residue was treated with ethyl acetate in an ultrasonic bath for 30 min to give the corresponding salt as a solid. The product was vigorously stirred in acetone (20 mL) in the presence of potassium carbonate (10 equiv.) overnight. The inorganic salts were filtered off on Celite and the filtrate was evaporated *in vacuo* to obtain the desired aminides **17**.
- Compounds **13**, **14**, **15** and **16**. The solid formed in the reaction (salt **15**) was isolated by filtration and washed with cold dichloromethane. The products dissolved in the filtrate were purified by flash chromatography (CH_2Cl_2/CH_3OH, 95:5).
- Compounds **6a** and **18**. The reaction products precipitated in the reaction media. The solid was filtered off and washed with cold CH_2Cl_2.

Method B: To a stirred solution of the pyridinium *N*-[quinoline- or quinoxalin-2-yl]aminide **1a** or **1b** (2 mmol) in CH_2Cl_2 (10 mL) at the indicated temperature, a solution of *N*-halosuccinimide (4.4 mmol) in CH_2Cl_2 (80 mL) was added dropwise. Once the addition was complete, the mixture was allowed to react at room temperature until aminide **1** was not observed by TLC. Once the starting material was consumed, the product was purified by flash chromatography (CH_2Cl_2/CH_3OH, 95:5).

Method C: To a stirred solution of aminide **1** (2 mmol) in CH_2Cl_2 (10 mL) at room temperature, a solution of *N*-bromosuccinimide (1.42 g, 8 mmol) in CH_2Cl_2 (100 mL) was added. Once the starting material was consumed, the products were isolated as follows: diazene **6b** precipitated in the reaction medium and it was isolated by filtration. Aminide **5b**, dissolved in the filtrate, was purified by flash chromatography (CH_2Cl_2/CH_3OH, 95:5).

*4.3.1. Reaction of pyridinium N-quinolin-2-yl aminide **1a** with NXS*

***N*-(6-Bromoquinolin-2-yl)pyridinium aminide (2a):** Following method A, by addition of NBS (391.6 mg) to a solution of **1a** (442 mg) at –40 ºC and after 16 h of reaction at room temperature, product **2a** was obtained as an orange solid (570 mg, 95%, 1.9 mmol), m.p. 213–215 °C, IR (KBr): $\tilde{\upsilon}$ = 1646, 1591, 1472, 1449, 1400, 814, 802, 666. ^{1}H-NMR (500 MHz, DMSO), δ: 9.07 (dd, J = 6.9 and 1.0 Hz, 2 H, 2-H, 6-H), 8.16 (br t, J = 7.3 Hz, 1 H, 4-H), 7.94 (ap t, J = 7.1 Hz, 2 H, 3-H, 5-H), 7.78 (d, J = 2.0 Hz, 1 H, 5'-H), 7.75 (d, J = 9.3 Hz, 1 H, 4'-H), 7.47 (dd, J = 8.8 and 2.0 Hz, 1 H, 7'-H), 7.21 (d, J = 8.8 Hz, 1 H, 8'-H), 6.66 (d, J = 9.3 Hz, 1 H, 3'-H). ^{13}C-NMR (75 MHz, DMSO), δ: 159.7 (2'-C), 142.1 (two overlapped signals) (2-C, 6-C and 8a'-C), 137.6 (4-C), 135.4 (4'-C), 131.5 (7'-C), 128.8 (5'-C), 127.1 (two overlapped signals) (3-C, 5-C and 4a'-C), 123.2 (8'-C), 116.3 (3'-C), 111.9 (6'-C). MS (EI, *m*/*z*): 301/299 (35/35, $M^{+\bullet}$), 300/298 (100/99), 219 (38), 141 (18), 114 (32). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_{11}{}^{79}BrN_3$ $[M + H]^+$ 300.0131; found 300.0107.

As a secondary product, ***N*-(8-bromoquinolin-2-yl)pyridinium aminide (3a)** was obtained: Orange solid (18 mg, 3%, 0.06 mmol), m.p. 116–118 °C, IR (KBr): $\tilde{\upsilon}$ = 1532, 1460, 1301, 989, 771, 751. ^{1}H-NMR (300 MHz, DMSO), δ: 9.52 (dd, J = 7.0 and 1.2 Hz, 2 H, 2-H, 6-H), 7.93 (tt, J = 7.8 and 1.2 Hz, 1 H. 4-H), 7.81 (dd, J = 7.8 and 7.0 Hz, 2 H, 3-H, 5-H), 7.73 (d, J = 9.1 Hz, 1 H, 4'-H), 7.67 (dd, J = 7.8 and 1.6 Hz, 1 H, 7'-H), 7.50 (dd, J = 7.8 and 1.6 Hz, 1 H, 5'-H), 6.91 (ap t, J = 7.8 Hz, 1 H, 6'-H), 6.72 (d, J = 9.1 Hz, 1 H, 3'-H). ^{13}C-NMR (75 MHz, DMSO), δ: 160.7 (2'-C), 143.8 (8a'-C), 140.8 (2-C, 6-C), 134.9 and 134.1 (4-C and 4'-C), 131.1 (7'-C), 126.3 (5'-C), 125.8 (3-C, 5-C), 123.8 (4a'-C), 120.1 (6-C'), 118.7 (8'-C), 117.7 (3'-C). MS (EI, *m*/*z*): 301/299 (60/62, $M^{+\bullet}$), 300/298 (100/92), 219 (47), 218 (26), 141 (24), 114 (37). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_{11}{}^{79}BrN_3$ $[M + H]^+$ 300.0131; found 300.0130.

***N*-(6,8-Dibromoquinolin-2-yl)pyridinium aminide (4a):** Following method B, by addition of NBS (783.2 mg) to a solution of **1a** (442 mg) at –40 ºC and after 21 h of reaction at room temperature, product **4a** was obtained as an orange solid (467 mg, 61%, 1.22 mmol), m.p. 206–208 °C, IR (KBr): $\tilde{\upsilon}$ = 1600, 1524, 1462, 1447, 1394, 1327, 1283, 1141, 940, 758, 664. ^{1}H-NMR (500 MHz, DMSO), δ: 9.37 (dd, J = 6.9 and 1.5 Hz, 2 H, 2-H, 6-H), 8.00 (tt, J = 7.9 and 1.5 Hz, 1 H, 4-H), 7.84 (ap t, J = 7.4 Hz, 2 H, 3-H, 5-H), 7.77 (d, J = 2.4 Hz, 1 H, 7'-H or 5'-H), 7.73 (d, J = 2.4 Hz, 1 H, 5'-H or 7'-H), 7.68 (d, J = 8.8 Hz, 1 H. 4'-H), 6.72 (d, J = 8.8 Hz, 1 H, 3'-H). ^{13}C-NMR (125 MHz, DMSO), δ: 164.9 (2'-C), 146.8 (8a'-C), 145.0 (2-C, 6-C), 138.7, 137.6 and 136.3 (4-C, 4'-C and 7'-C), 131.8 (5'-C), 129.5 (3-C, 5-C), 128.2 (4a'-C), 122.9 (8'-C), 122.3 (3'-C), 113.3 (6'-C). MS (EI, *m*/*z*): 381/379/377 (39/74/39, $M^{+\bullet}$), 380/378/376 (57/100/50), 304/302/300 (33/69/41), 219 (38). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_{10}{}^{79}Br_2N_3$ $[M + H]^+$ 377.9236; found 377.9232.

As a secondary product, ***N*-(3,6,8-bromoquinolin-2-yl)pyridinium aminide (5a)** was detected along with traces of succinimide as an impurity. ^{1}H-NMR (500 MHz, DMSO), δ: 8.99 (dd, J = 6.8 and 1.5 Hz, 2 H, 2-H, 6-H), 8.19 (tt, J = 7.8 and 1.5 Hz, 1 H, 4-H), 8.17 (s, 1 H, 4'-H), 7.91 (ap t, J = 7.3 Hz, 2 H, 3-H, 5-H), 7.73 (d, J = 2.0 Hz, 1 H, 7'-H or 5'-H), 7.72 (d, J = 2.4 Hz, 1 H, 5'-H or 7'-H). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_9{}^{79}Br_3N_3$ $[M + H]^+$ 455.8341; found 455.8340. This compound was also detected as traces following method 2C.

1,2-Bis(quinolin-2-yl)diazene (6a): Following method A, by addition of NCS (293.7 mg) to a solution of **1a** (442 mg) at –40 ºC and after 10 min of reaction at room temperature, compound **6a** was obtained as an orange solid (181.8 mg, 32%, 0.64 mmol), m.p. 228–230 °C, IR (KBr): $\tilde{\upsilon}$

= 1592, 1500, 1426, 874, 842, 766, 752. ^{1}H-NMR (500 MHz, DMSO), δ: 8.37 (m, 4H, 4-H and 8-H), 8.22 (d, J = 8.3 Hz, 2 H, 3-H), 7.92 (dd, J = 8.0 and 1.4 Hz, 2 H, 5-H), 7.82 (ddd, J = 8.3, 6.9 and 1.4, 2 H, 7-H), 7.66 (ddd, J = 8.0, 6.9 and 1.4 Hz, 2 H, 6-H). ^{13}C-NMR (75 MHz, DMSO), δ: 164.4 (2-C), 150.3 (8a-C), 141.5 (4-C), 133.1 and 133.0 (7-C and 8-C), 132.1 (4a-C), 131.2 (6-C), 130.3 (5-C), 113.3 (3-C). MS (EI, *m*/*z*): 256 (72), 255 (100), 128 (61), 77 (23). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{18}H_{13}N_4$ $[M + H]^+$ 285.1135; found 285.1129. When the reaction was carried out using 8 mmol of NCS, **6a** was obtained with a yield of 54%.

*4.3.2. Reaction of pyridinium N-quinoxalin-2-ylaminides **1b**, **1c**, **1d** and **2b** with NXS*

***N*-(6-Bromoquinoxalin-2-yl)pyridinium aminide (2b):** Following method A, by addition of NBS (391.6 mg) to a solution of **1b** (444 mg) at –40 ºC and after 4 h of reaction at room temperature, product **2b** was obtained as a yellow solid (397 mg, 66%, 1.32 mmol), m.p. 244–246 °C, IR (KBr): $\tilde{\upsilon}$ = 1532, 1436, 1411, 1305, 816, 672. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 9.36 (d, J = 7.2 Hz, 2 H, 2-H, 6-H),8.31 (s, 1 H 3'-H), 7.92 (d, J = 2.3 Hz, 1 H, 5'-H), 7.76 (t, J = 7.9 Hz, 1 H, 4-H), 7.64 (ap t, J = 7.4 Hz, 2 H, 3-H, 5-H), 7.50 (dd, J = 8.8 and 2.3 Hz, 1 H, 7'-H), 7.28 (d, J = 8.8 Hz, 1 H, 8'-H). ^{13}C-NMR (125 MHz, $CDCl_3$), δ: 156.2 (2'-C, deduced by gHMBC), 149.1 (3'-C), 143.5 (two overlapped signals) (2-C, 6-C and 8a'-C), 137.6 (4a'-C), 136.2 (4-C), 134.8(7'-C), 133.5 (5'-C), 128.9 (8'-C), 128.6 (3-C, 5-C), 117.7 (6'-C). MS(EI, *m*/*z*): 302/300 (46/46, $M^{+\bullet}$), 301/299 (100/97), 223/221 (21/18), 142 (18), 115 (34). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_{10}{}^{79}BrN_4$ $[M + H]^+$ 301.0083; found 301.0076.

As a secondary product, ***N*-(8-bromoquinoxalin-2-yl)pyridinium aminide (3b)** was obtained: Yellow solid (138 mg, 23%, 0.46 mmol), m.p. 214–215 °C, IR (KBr): $\tilde{\upsilon}$ = 1533, 1492, 1460, 1409, 752. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.73 (d, J = 5.8 Hz, 2 H, 2-H, 6-H), 8.28 (s, 1 H, 3'-H), 7.71 (m, 2 H, 5'-H and 7'-H), 7.65 (br t, J = 7.3 Hz, 1 H, 4-H), 7.58 (ap t, J = 7.1 Hz, 2 H, 3-H, 5-H), 7.07 (t, J = 7.9 Hz, 1 H, 6'-H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 155.9 (2'-C), 146.2 (3'-C), 140.5 (2-C, 6-C), 139.1 (8a'-C), 137.5 (4a'-C), 133.0 (4-C), 132.2 (7'-C), 128.0 (5'-C), 125.7 (3-C, 5-C), 122.9 (6'-C), 119.6 (8'-C). MS (EI, *m*/*z*): 302/300 (76/77, $M^{+\bullet}$), 301/299 (100/91), 142 (35), 115 (56). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_{10}{}^{79}BrN_4$ $[M + H]^+$ 301.0083; found 301.0074.

***N*-(6-Chloroquinoxalin-2-yl)pyridinium aminide (1c)** and ***N*-(8-chloroquinoxalin-2-yl)pyridinium aminide (3c)**: Following method A, by addition of NCS (293.7 mg) to a solution of **1b** (444 mg) at –40 ºC and after 4 h of reaction at room temperature, a mixture of aminides **1c** and **3c** in a 2:1 ratio (deduced by ^{1}H NMR) was isolated as a yellow solid (73% overall yield, 375 mg, 1.46 mmol).

***N*-(6-Chloroquinoxalin-2-yl)pyridinium aminide (1c):** Characterization details of this compound have already been reported in section 1.

***N*-(8-Chloroquinoxalin-2-yl)pyridinium aminide (3c):** ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.73 (dd, J = 6.8 and 1.5 Hz, 2 H. 2-H, 6-H), 8.34 (s,1 H, 3'-H), 7.55 (dd, J = 7.9 and 1.5 Hz, 1 H, 7'-H), 7.15 (ap t, J = 8.0 Hz, 1 H, 6'-H). Signals of 4-H, 3-H, 5-H and 5'-H appear overlapped with the signals of compound **1c**.

***N*-(6,8-Dibromoquinoxalin-2-yl)pyridinium aminide (4b):**[9a] Following method B, by addition of NBS (783.2 mg) to a solution of **1b** (444 mg) at room temperature and after 3 h of reaction, product **4b** was obtained as a yellow solid (692 mg, 91%, 1.82 mmol).

***N*-(6,8-Dichloroquinoxalin-2-yl)pyridinium aminide (4c):** Following method B, by addition of NCS (587 mg) to a solution of **1b** (444 mg) at room temperature and after 3 h of reaction, product **4c** was obtained as an orange solid (355 mg, 61%, 1.22 mmol), m.p. 221–223 °C, IR (KBr): $\tilde{\upsilon}$ = 1654, 1597, 1533, 1462, 1408, 1319, 951. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.64 (dd, J = 7.2 and 1.2 Hz, 2 H, 2-H, 6-H), 8.32 (s, 1 H, 3'-H), 7.74 (tt, J = 7.5 and 1.2 Hz, 1 H, 4-H), 7.66 (d, J = 2.5 Hz, 1 H, 5'-H), 7.63 (ap t, J = 7.3 Hz, 2 H, 3-H, 5-H), 7.51 (d, J = 2.5 Hz, 1 H, 7'-H). ^{13}C-NMR (125 MHz, $CDCl_3$), δ: 155.6 (2'-C), 147.0 (3'-C), 140.8 (2-C, 6-C), 137.5 (4a'-C), 137.1 (8a'-C), 133.8 (4-C), 129.2 (7'-C), 128.8 (6'-C), 126.7 (two overlapped signals) (5'-C and 8'-C), 125.9 (3-C, 5-C). MS(EI, *m*/*z*): 293/291 (31/87, $M^{+\bullet}$), 292/290 (66/100), 213 (32), 211 (31), 149 (60), 80 (35). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_{10}{}^{79}Br_2N_3$ $[M + H]^+$ 291.0199; found 291.0195.

1,2-Bis(6,8-Dibromoquinoxalin-2-yl)diazene (6b): Following method C, and after 16 h of reaction of **1b** (444 mg) with NBS, product **6b** was obtained as a brown solid (722 mg, 64%, 1.28 mmol), m.p. > 185 °C (dec.), IR (KBr): $\tilde{\upsilon}$ = 1585, 1450, 1405, 1333, 1178, 1076, 1006, 866, 773. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.55 (s, 2 H, 3-H), 8.40 (d, J = 1.9 Hz, 2 H, 7-H or 5-H), 8.40 (d, J = 1.9 Hz, 2 H, 5-H or 7-H). MS (EI, *m*/*z*): 288 (56), 287 (52), 208 (67), 179 (51), 100 (100), 99 (59), 87 (53). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{16}H_7{}^{79}Br_4N_6$ $[M + H]^+$ 598.7430; found 598.7422.

As secondary product, ***N*-(3,6,8-tribromoquinoxalin-2-yl)pyridinium aminide (5b)** was obtained: Yellow solid (82.6 mg, 9%, 0.18 mmol), m.p. 129–130 °C, IR (KBr): $\tilde{\upsilon}$ = 1515, 1460, 1402, 1118, 1051. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.16 (dd, J = 7.0 and 1.3 Hz, 2 H, 2-H, 6-H), 7.97 (tt, J = 7.7 and 1.3 Hz, 1 H, 4-H), 7.81 (d, J = 2.0 Hz, 1 H, 5'-H), 7.78 (d, J = 2.0 Hz, 1 H, 7'-H), 7.75 (dd, J = 7.7 and 7.0 Hz, 2 H, 3-H, 5-H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 156.9 (2'-C), 143.2 (2-C, 6-C), 137.7 (8a'-C), 137.2 (three overlapped signals) (4-C, 4a'-C and 7'-C), 135.0 (3'-C), 129.7 (5'-C), 123.6 (3-C, 5-C), 119.2 (8'-C), 114.7 (6'-C). MS (EI, *m*/*z*): 462/460/458/456 (34/99/100/34, $M^{+\bullet}$), 381/379/377 (28/53/17), 300/298 (39/21), 219 (11), 79 (16), 52 (12). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_9{}^{79}Br_3N_3$ $[M + H]^+$ 456.8299; found 456.8282.

***N*-(8-Bromo-6-chloroquinoxalin-2-yl)pyridinium aminide (4d):** Following method A, by addition of NBS (391.6 mg) to a solution of **1c** (513.4 mg) at room temperature and after 22 h of reaction at the same temperature, product **4d** was obtained as a brown solid (470 mg, 70%, 1.4 mmol), m.p. 218–220 °C, IR (KBr): $\tilde{\upsilon}$ = 1595, 1526, 1456, 1406, 1316, 1295, 1145, 991, 791, 764. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.70 (dd, J = 7.1 and 1.2 Hz, 2 H, 2-H, 6-H), 8.29 (s, 1 H, 3'-H), 7.74 (tt, J = 7.4 and 1.2 Hz, 1 H, 4-H), 7.72 (ap s, 2 H, 5'-H and 7'-H), 7.64 (ap t, J = 7.2 Hz, 2 H, 3-H, 5-H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 159.0 (2'-C, deduced by gHMBC), 149.9 (3'-C), 143.4 (2-C, 6-C), 139.9 (8a'-C), 137.7 (4a'-C), 136.1 (4-C), 134.8 (7'-C), 130.0 (5'-C), 129.8 (6'-C), 128.5 (3-C, 5-C), 122.4 (8'-C). MS (EI, *m*/*z*): 338/336/334 (25/100/78, $M^{+\bullet}$), 337/335/333 (33/97/65), 259/257/255 (16/37/30), 149 (38), 79 (20), 52 (23). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_9{}^{79}Br^{35}ClN_4$ $[M + H]^+$ 334.9694; found 334.9673.

***N*-(6-Bromo-8-chloroquinoxalin-2-yl)pyridinium aminide(4e):** Following method A, by addition of NCS (293.7 mg) to a solution of **2b** (602.2 mg) at room temperature and after 36 h of reaction at reflux, product **4d** was obtained as a solid along with succinimide as an impurity. The mixture was treated with commercial HBr, the excess acid was evaporated and the residue was treated with ethyl acetate in an ultrasonic bath for 30 min to give **1-[(6-bromo-8-chloroquinoxalin-2-yl)amino]pyridin-1-ium bromide** as a yellow solid (235.6 mg, 35%, 0.7

mmol), m.p. > 234 °C (dec.), IR (KBr): $\tilde{\upsilon}$ = 1596, 1534, 1471, 1294, 1194, 1026, 770, 699. ^{1}H-NMR (500 MHz, CD_3OD), δ: 9.28 (dd, J = 6.9 and 1.5 Hz, 2 H, 2-H, 6-H), 8.87 (tt, J = 7.8 and 1.5 Hz, 1 H, 4-H), 8.83 (s, 1 H, 3'-H), 8.39 (dd, J = 7.8 and 6.9 Hz, 2 H, 3-H, 5-H), 8.15 (d, J = 2.2 Hz, 1 H, 5'-H), 7.94 (d, J = 2.2 Hz, 1 H, 7'-H). ^{13}C-NMR (75 MHz, CD_3OD), δ: 151.3 (2'-C), 148.3 (2-C, 6-C), 148.2 (4-C), 141.6 (4a'-C, deduced by gHMBC), 139.8 (3'-C, deduced by gHMBC), 137.4 (8a'-C), 134.6 (7'-C), 132.2 (8'-C, deduced by gHMBC), 131.6 (5'-C), 130.3 (3-C, 5-C), 120.5 (6'-C). MS (EI, *m*/*z*): 339/337/335 (4/35/100, $[M - Br]^+$), 338/336/334, (23/91/70). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_9{}^{79}Br\,{}^{35}ClN_4$ $[M - Br]^+$ 334.9694; found 334.9688.

***N*-(6-Bromo-3-chloroquinoxalin-2-yl)pyridinium aminide (13a):** Following method A, by addition of NBS (391.6 mg) to a solution of **1d** (513.4 mg) at –40 ºC and after 24 h of reaction at room temperature, product **13a** was obtained as a yellow solid (315 mg, 47%, 0.94 mmol), m.p. 192–194 °C, IR (KBr): $\tilde{\upsilon}$ = 1523, 1457, 1407, 1069, 755. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 8.86 (dd, J = 6.8 and 1.1 Hz, 2 H, 2-H, 6-H), 7.93 (tt, J = 7.6 and 1.1 Hz, 1 H, 4-H), 7.76 (d, J = 2.1 Hz, 1 H, 5'-H), 7.70 (dd, J = 7.6 and 6.8 Hz, 2 H, 3-H, 5-H), 7.38 (dd, J = 8.8 and 2.1 Hz, 1 H, 7'-H), 7.07 (d, J = 8.8 Hz, 1 H, 8'-H). ^{13}C-NMR (125 MHz, $CDCl_3$), δ: 154.3 (2'-C), 143.4 (2-C, 6-C), 142.8 (3'-C), 140.1 (8a'-C), 136.8 (4-C), 136.6 (4a'-C), 132.1 (7'-C), 129.6 (5'-C), 126.3 (3-C, 5-C), 125.5 (8'-C), 114.7 (6'-C). MS (EI, *m*/*z*): 338/336/334 (25/93/73, $M^{+\bullet}$), 337/335/333 (42/100/64), 257 (46), 220 (99), 141 (44), 115 (40), 79 (69). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_9{}^{79}Br{}^{35}ClN_4$ $[M + H]^+$ 334.9694; found 334.9697.

As secondary product, **6-chloropyrido[1',2':1,5][1,2,4]triazolo[4,3-*a*]quinoxalin-8-ium bromide (15a)** was formed as a brown solid (280.6 mg, 42%, 0.84 mmol), m.p. > 135 °C (dec.), IR (KBr): $\tilde{\upsilon}$ = 1636, 1100, 982, 906, 758. ^{1}H-NMR (500 MHz, DMSO), δ: 9.99 (br d, J = 7.8 Hz, 1 H, 9-H), 9.66 (d, J = 8.8 Hz, 1 H, 12-H), 9.03 (d, J = 7.9 Hz, 1 H, 4-H), 8.78 (ddd, J = 8.8, 7.8 and 1.0 Hz, 1 H, 11-H), 8.33 (m, 2 H, 1-H and 10-H), 8.12 (ap td, J = 8.4 and 1.5 Hz, 1 H, 3-H), 7.98 (ap t, J = 7.8 Hz, 1 H, 2-H).^{13}C-NMR (125 MHz, DMSO), δ: 141.6, 140.1 and 140.0 (6-C, 6a-Cand 12a-C), 140.8 (11-C), 135.2 (13a-C), 134.2 (9-C), 133.4 (3-C), 131.2 (1-C), 130.5 (2-C), 125.4 (4a-C), 123.7 (10-C), 117.6 (4-C), 115.7 (12-C). MS (EI, *m*/*z*): 254 (100), 149 (23), 128 (19), 127 (37). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_8{}^{35}ClN_4$ $[M - Br]^+$ 255.0432; found 255.0431.

6-Chloropyrido[1',2':1,5][1,2,4]triazolo[4,3-*a*]quinoxalin-8-ium chloride (15b): Following method A, by addition of NCS (293.7 mg) to a solution of **1d** (513.4 mg) at –40 ºC and after 3 days of reaction at room temperature, product **15b** was obtained as a brown solid (145 mg, 25%, 0.50 mmol).

As secondary products, ***N*-(3,6-dichloroquinoxalin-2-yl)pyridinium aminide (13b)** and ***N*-(3,8-dichloroquinoxalin-2-yl)pyridinium aminide (14b)** were obtained. ***N*-(3,6-Dichloroquinoxalin-2-yl)pyridinium aminide (13b):** Yellow solid (40.7 mg, 7%, 0.14 mmol), m.p. 167–169 °C, IR (KBr): $\tilde{\upsilon}$ = 1526, 1483, 1422, 1319, 1056, 815. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 8.92 (dd, J = 6.8 and 1.5 Hz, 2 H, 2-H, 6-H), 7.93 (tt, J = 7.9 and 1.5 Hz, 1 H, 4-H), 7.71 (ap t, J = 7.4 Hz, 2 H, 3-H, 5-H), 7.64 (d, J = 2.4 Hz, 1 H, 5'-H), 7.29 (dd, J = 8.8 and 2.4 Hz, 1 H, 7'-H), 7.19 (d, J = 8.8 Hz, 1 H, 8'-H). ^{13}C-NMR (125 MHz, $CDCl_3$), δ: 153.9 (2'-C), 143.2 (3'-C), 143.1 (2-C, 6-C), 139.6 (8a'-C), 136.5 (4-C), 136.3 (4a'-C), 129.5 (7'-C), 127.5 (6'-C), 126.6 (5'-C), 126.3 (3-C, 5-C), 125.1 (8'-C). MS (EI, *m*/*z*): 294/292/290 (6/33/53, $M^{+\bullet}$), 293/291/289 (15/71/100), 257/255 (6/18), 213 (18), 176 (19). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_9{}^{35}Cl_2N_4$ $[M + H]^+$ 291.0199; found 291.0189. ***N*-(3,8-Dichloroquinoxalin-2-**

yl)pyridinium aminide (14b): This product was isolated impure with succinimide. The mixture was treated with commercial HBr, the excess acid was evaporated and the residue was treated with ethyl acetate in an ultrasonic bath for 30 min to give **1-[(3,8-dichloroquinoxalin-2-yl)amino]pyridin-1-ium bromide** as an orange solid (5.8 mg, <1%). ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.30 (dd, J = 6.9 and 1.5 Hz, 2 H, 2-H, 6-H), 8.92 (tt, J = 7.8 and 1.5 Hz, 1 H, 4-H), 8.42 (dd, J = 7.8 and 6.8 Hz, 2 H, 3-H, 5-H), 7.94 (dd, J = 7.3 and 1.0 Hz, 1 H, 5'-H or 7'-H), 7.83 (dd, J = 7.3 and 1.0 Hz, 1 H, 5'-H or 7'-H), 7.65 (ap t, J = 7.3 Hz, 1 H, 6'-H). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_9{}^{35}Cl_2N_4$ [M – Br]$^+$ 291.0199; found 291.0198.

***N*-(6,8-Dibromo-3-chloroquinoxalin-2-yl)pyridinium aminide (16a):** Following method B, by addition of NBS (783 mg) to a solution of **1d** (513.4 mg) at room temperature and after 24 h of reaction, product **16a** was obtained as a yellow solid (481 mg, 58%, 1.16 mmol). m.p. 220–222 °C, IR (KBr): $\tilde{\upsilon}$ = 1516, 1458, 1404, 1327, 1068, 763. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 9.19 (dd, J = 7.2 and 1.4 Hz, 2 H, 2-H, 6-H), 7.92 (tt, J = 7.7 and 1.4 Hz, 1 H, 4-H), 7.76 (m, 2 H, 5'-H and 7'-H), 7.72 (ap t, J = 7.4 Hz, 2 H, 3-H, 5-H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 153.8 (2'-C), 142.8 (2-C, 6-C), 142.0 (8a'-C or 4a'-C), 136.3 (4-C), 134.9 (4a'-C or 8a'-C), 134.7 (5'-C), 129.6 (3'-C), 129.5 (7'-C), 126.3 (3-C, 5-C), 119.0 (8'-C), 114.1 (6'-C). MS (EI, *m*/*z*): 418/416/414/412 (14/69/100/44, $M^{+\bullet}$), 417/415/413/411 (19/57/68/27), 300 (66), 219 (29). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_3{}^{79}Br_2{}^{35}ClN_4$ [M + H]$^+$ 412.8799; found 412.8799.

As secondary product, **6-chloropyrido[1',2':1,5][1,2,4]triazolo[4,3-*a*]quinoxalin-8-ium bromide (15a)**, was obtained (241.6 mg, 36%, 0.72 mmol).

6-Chloropyrido[1',2':1,5][1,2,4]triazolo[4,3-*a*]quinoxalin-8-ium chloride (15b): Following method C, after 11 days of reaction of **1d** (513.4 mg) with NCS (587 mg), product **15b** was obtained as the main product (186 mg, 32%, 0.64 mmol).

As secondary product, ***N*-(3,6-dichloroquinoxalin-2-yl)pyridinium aminide (13b)** (134 mg, 23%, 0.26 mmol), was obtained.

*4.3.3. Reaction of pyridinium N-(isoquinolin-1-yl) aminide **1e** and pyridinium N-(4-chlorophthalazin-1-yl) aminide **1g** with NXS*

***N*-(4-Bromoisoquinolin-1-yl)pyridinium aminide (17a):** Following method A, by addition of NBS (391.6 mg) to a solution of **1e** (442 mg) at r.t. and after 10 min of the reaction at the same temperature, product **17a** was obtained as a red oil (366 mg, 61%, 1.22 mmol), IR (NaCl): $\tilde{\upsilon}$ = 1536, 1494, 1403, 1288, 1159, 760, 664. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 8.90 (dd, J = 7.1 and 1.2 Hz, 2 H, 2-H, 6-H), 8.44 (dd, J = 8.3 and 1.9 Hz, 1 H, 8'-H), 7.85 (m, 2 H, 4-H and 5'-H), 7.75 (s, 1 H, 3'-H), 7.67 (m, 1 H, 3-H, 5-H and 6'-H), 7.47 (ddd, J = 8.3, 6.9 and 1.1 Hz, 1 H, 7'-H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 158.8 (1'-C), 142.3 (2-C, 6-C), 138.8 (3'-C), 135.4 and 135.3 (4a'-C and 4-C), 131.0 (6'-C), 126.9 (3-C, 5-C), 126.4, 125.2 and 125.0 (5'-C, 7'-C and 8'-C), 122.4 (8a'-C), 103.9 (4'-C). MS (EI, *m*/*z*): 301/299 (60/62, $M^{+\bullet}$), 300/298 (100/92), 219 (47), 218 (26), 141 (24), 114 (37). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_{11}{}^{79}BrN_3$ [M + H]$^+$ 300.0131; found 300.0123.

***N*-(4-Chloroisoquinolin-1-yl)pyridinium aminide (17b):** Following method A, by addition of NCS (293.7 mg) to a solution of **1e** (442 mg) at r.t. and after 10 min of reaction at the same temperature, product **17b** was obtained as a red solid (373 mg, 73%, 1.46 mmol), m.p. 92–94 °C, IR (KBr): $\tilde{\upsilon}$ = 1590, 1536, 1490, 1398, 1286, 1159, 785, 761. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 9.03 (dd, J = 6.9 and 1.0 Hz, 2 H, 2-H, 6-H), 8.48 (dd, J = 8.4 and 1.5 Hz, 1 H, 8'-H), 7.91 (br

d, *J* = 8.3 Hz, 1 H, 5'-H), 7.69 (s, 1 H, 3'-H), 7.64 (ddd, *J* = 8.3, 6.9 and 1.5 Hz, 1 H, 6'-H), 7.59 (tt, *J* = 7.5 and 1.0 Hz, 1 H, 4-H), 7.47 (ap t, *J* = 7.3 Hz, 2 H, 3-H, 5-H), 7.45 (ddd, *J* = 8.4, 6.9 and 1.5 Hz, 1 H, 7'-H). ^{13}C-NMR (125 MHz, $CDCl_3$), *δ*: 162.3 (1'-C), 144.6 (2-C, 6-C), 141.6 (3'-C), 137.3 (4a'-C), 135.7 (4-C), 132.8 (6'-C), 128.6 (3-C, 5-C), 128.4 (7'-C), 127.6 (8'-C), 125.1 (5'-C), 125.0 (8a'-C), 116.9 (4'-C). MS (EI, *m*/*z*): 257/255 (18/54, $M^{+\bullet}$), 256/254 (44/100), 114 (36). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{14}H_{11}{}^{35}ClN_3$ $[M + H]^+$ 256.0636; found 256.0627.

5-Chloropyrido[1',2':1,5][1,2,4]triazolo[3,4-*a*]phthalazin-12-ium bromide (18a): Following method A, by addition of NBS (391.6 mg) to a solution of **1g** (513.4 mg) at –40 ºC and after 10 min of reaction at room temperature, product **18a** was obtained as a yellow solid (654 mg, 93%, 1.83 mmol), m.p. 275–276 °C, IR (KBr): $\tilde{\upsilon}$ = 1604, 1447, 1413, 1389, 1135, 767, 741. ^{1}H-NMR (500 MHz, DMSO), *δ*: 9.75 (ap dt, *J* = 6.9 and 1.0 Hz, 1 H, 11-H), 8.89 (ap dt, *J* = 8.8 and 1.0 Hz, 1 H, 8-H), 8.83 (dd, *J* = 7.8 and 1.6 Hz, 1 H, 1-H), 8.60 (m, 2 H, 4-H and 9-H), 8.38 (m, 2 H, 2-H and 3-H), 8.13 (ddd, *J* = 8.4, 6.9 and 1.5 Hz, 1 H, 10-H). ^{13}C-NMR (125 MHz, DMSO), *δ*: 155.9 (7a-C), 147.3 (13a-C), 142.3 (5-C), 142.0 (9-C), 140.0 (2-C), 139.0 (3-C), 135.3 (11-C), 131.7 (4-C), 128.2 (1-C), 127.6 (4a-C), 125.3 (10-C), 123.6 (13b-C), 114.8 (8-C). MS (EI, *m*/*z*): 157 (14), 79 (100), 78 (26). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{13}H_8{}^{35}ClN_4$ $[M – Br]^+$ 255.0432; found 255.0440.

5-Chloropyrido[1',2':1,5][1,2,4]triazolo[3,4-*a*]phthalazin-12-ium chloride (18b): Following method A, after 16 h of reaction of **1g** (513.4 mg) with NCS (293.7 mg), product **18b** was obtained as brown solid (243.6 mg, 42%, 0.84 mmol).

*4.4. Synthesis of N-benzyl-N-haloquinolin(or quinoxalin)-2-yl amines **21***

*4.4.1. Synthesis of pyridinium salts **20***

General procedure: The corresponding aminide **1c**, **2a–b** or **4a–d** (1 mmol) was dissolved in anhydrous solvent in a dry round-bottomed flask. The benzyl bromide (3.5 mmol) was added and the mixture was stirred at room temperature under argon until the starting aminide was no longer detected by TLC (ethanol as eluent). Once the reaction was complete, the solid was filtered off and washed with cold ethyl acetate. When the salt was soluble in the reaction solvent, the latter was removed and the residue was treated with ethyl acetate in an ultrasonic bath for 30 min to give the corresponding salt as a solid. The salts **20** were used in the next step without further purification.

1-[*N*-Benzyl-*N*-(6-bromoquinolin-2-yl)amino]pyridinium bromide (20a): After 7 days of reaction in DMF, **20a** was obtained as a beige solid (368 mg, 78%, 0.78 mmol), m.p. > 185 °C (dec.), IR (KBr): $\tilde{\upsilon}$ = 1641, 1616, 1468, 1123, 1116, 1095, 950, 806. ^{1}H-NMR (500 MHz, CD_3OD), *δ*: 9.21 (dd, *J* = 6.6 and 1.3 Hz, 2 H, 2-H, 6-H), 8.79 (tt, *J* = 7.8 and 1.3 Hz, 1 H, 4-H), 8.39 (d, *J* = 9.2 Hz, 1 H, 4'-H), 8.25 (dd, *J* = 7.8 and 6.6 Hz, 2 H, 3-H, 5-H), 8.13 (d, *J* = 2.2 Hz, 1 H, 5'-H), 7.74 (dd, *J* = 8.8 and 2.2 Hz, 1 H, 7'-H), 7.49 (m, 2 H, 3'-H and 8'-H), 7.42 (m, 2 H, 2"-H, 6"-H), 7.34 (m, 3 H, 3"-H, 5"-H and 4"-H), 5.55 (s, 2 H, CH_2). ^{13}C-NMR (75 MHz, CD_3OD), *δ*: 155.7 (2'-C), 148.5 (2-C, 6-C), 148.0 (4-C), 144.6 (8a'-C), 139.0 (4'-C), 133.6 (7'-C), 134.0 (1"-C), 129.5 (5'-C), 129.2, 129.1, 129.0, 128.9 and 128.7 (3-C, 5-C, 8'-C, 2"-C, 6"-C, 3"-C, 5"-C and 4"-C), 126.7 (4a'-C), 118.5 (6'-C), 110.7 (3'-C), 57.5 (CH_2). MS (EI, *m*/*z*): 300/298 (27/26), 224/222 (60/60), 91 (100). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{21}H_{17}{}^{79}BrN_3$ $[M – Br]^+$ 390.0600; found 390.0608.

1-[*N*-Benzyl-*N*-(6,8-dibromoquinolin-2-yl)amino]pyridinium bromide (20b): After 6 days of reaction in ethyl acetate, **20b** was obtained as a white solid (396 mg, 72%, 0.72 mmol), m.p. 219–220 °C, IR (KBr): $\tilde{\upsilon}$ = 3020, 1607, 1587, 1478, 1455, 1325, 1191, 866, 780, 724, 674. ^{1}H-NMR (500 MHz, CD_3OD), δ: 9.21 (dd, J = 6.8 and 1.5 Hz, 2 H, 2-H, 6-H), 8.79 (tt, J = 7.8 and 1.5 Hz, 1 H, 4-H), 8.39 (d, J = 9.3 Hz, 1 H, 4'-H), 8.26 (dd, J = 7.8 and 6.8 Hz, 2 H, 3-H, 5-H), 8.09 (d, J = 2.0 Hz, 1 H, 5'-H), 8.04 (d, J = 2.0 Hz, 1 H, 7'-H), 7.64 (d, J = 9.3 Hz, 1 H, 3'-H), 7.48 (dd, J = 7.4 and 1.8 Hz, 2 H, 2"-H, 6"-H), 7.36 (m, 3 H, 3"-H, 5"-H and 4"-H), 5.62 (s, 2 H, CH_2). ^{13}C-NMR (125 MHz, CD_3OD), δ: 158.6 (2'-C), 151.2 (2-C, 6-C), 150.7 (4-C), 144.4 (8a'-C), 142.4 (4'-C), 138.7 (7'-C), 135.9 (1"-C), 132.1 (5'-C), 131.9 (3-C, 5-C), 131.7 and 131.6 (2"-C, 6"-C and 3"-C, 5"-C), 131.5 (4"-C), 129.8 (4a'-C), 125.8 (8'-C), 120.3 (6'-C), 114.0 (3'-C), 60.0 (CH_2). MS (EI, *m*/*z*): 391 (29), 381 (34), 380 (59), 379 (69), 378 (100), 377 (36), 376 (48), 287 (51), 91 (58). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{21}H_{16}{}^{79}Br_2N_3$ $[M - Br]^+$ 467.9705; found 467.9700.

1-[*N*-Benzyl-*N*-(6-bromoquinoxalin-2-yl)amino]pyridinium bromide (20c): After 8 days of reaction in DMF, **20c** was obtained as a brown solid (335 mg, 71%, 0.71 mmol), m.p.162–163 °C, IR (KBr): $\tilde{\upsilon}$ = 1659, 1620, 1599, 1557, 1476, 1338, 1177, 710, 680. ^{1}H-NMR (500 MHz, CD_3OD), δ: 9.32 (dd, J = 6.9 and 1.5 Hz, 2 H, 2-H, 6-H), 9.10 (s, 1 H, 3'-H), 8.84 (tt, J = 7.8 and 1.5 Hz, 1 H, 4-H), 8.30 (dd, J = 7.8 and 6.9 Hz, 2 H, 3-H, 5-H), 8.20 (d, J = 2.4 Hz, 1 H, 5'-H), 7.83 (dd, J = 8.8 and 2.4 Hz, 1 H, 7'-H), 7.56 (d, J = 8.8 Hz, 1 H, 8'-H), 7.52 (m, 2 H, 2"-H, 6"-H), 7.37 (m, 3 H, 3"-H, 5"-H and 4"-H), 5.74 (s, 2 H, CH_2). ^{13}C-NMR (75 MHz, CD_3OD), δ: 152.0 (2'-C), 149.5 (4-C), 149.4 (2-C, 6-C), 140.6 and 139.4 (4a'-C and 8a'-C), 137.6 (3'-C), 135.3 (7'-C), 133.8 (1"-C), 131.7 (5'-C), 130.7 (3-C, 5-C), 130.4 and 130.2 (2"-C, 6"-C and 3"-C, 5"-C), 130.1 and 130.0 (8'-C and 4"-C), 122.2 (6'-C), 58.7 (CH_2). MS (EI, *m*/*z*): 313 (71), 301 (52), 299 (47), 223 (27), 106 (60), 91 (100), 79 (30). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{20}H_{16}{}^{79}BrN_4$ $[M - Br]^+$ 391.0553; found 391.0542.

1-[*N*-Benzyl-*N*-(6-chloroquinoxalin-2-yl)amino]pyridinium bromide (20d): After 7 days of reaction in DMF, **20d** was obtained as an orange solid (323 mg, 76%, 0.76 mmol), m.p. 156–158 °C, IR (KBr): $\tilde{\upsilon}$ = 1614, 1484, 1454, 1175, 714. ^{1}H-NMR (500 MHz, CD_3OD), δ: 9.24 (dd, J = 6.8 and 1.5 Hz, 2 H, 2-H, 6-H), 9.06 (s, 1 H, 3'-H), 8.80 (tt, J = 7.9 and 1.5 Hz, 1 H, 4-H), 8.26 (dd, J = 7.9 and 6.8 Hz, 2 H, 3-H, 5-H), 8.07 (d, J = 2.4 Hz, 1 H, 5'-H), 7.72 (dd, J = 8.8 and 2.4 Hz, 1 H, 7'-H), 7.63 (d, J = 8.8 Hz, 1 H, 8'-H), 7.46 (m, 2 H, 2"-H, 6"-H), 7.37 (m, 3 H, 3"-H, 5"-H and 4"-H), 5.67 (s, 2 H, CH_2). ^{13}C-NMR (75 MHz, CD_3OD), δ: 152.1 (2'-C), 149.6 (4-C), 149.5 (2-C, 6-C), 140.6 (4a'-C), 139.2 (8a'-C), 137.7 (3'-C), 134.6 (6'-C), 133.9 (1"-C), 132.9 (7'-C), 130.7 (3-C, 5-C), 130.4 and 130.3 (2"-C, 6"-C and 3"-C, 5"-C), 130.2 (4"-C), 130.0 (8'-C), 128.6 (5'-C), 58.9 (CH_2). MS (EI, *m*/*z*): 257 (47), 256 (58), 255 (100), 91 (48). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{20}H_{16}{}^{35}ClN_4$ $[M - Br]^+$ 347.1058; found 347.1052.

1-[*N*-Benzyl-*N*-(6,8-dibromoquinoxalin-2-yl)amino]pyridinium bromide (20e): After 5 days of reaction in DMF, **20e** was obtained as a pale yellow solid (364 mg, 66%, 0.66 mmol), m.p. 185–187 °C, IR (KBr): $\tilde{\upsilon}$ = 1616, 1589, 1568, 1474, 1174, 980, 726, 701. ^{1}H-NMR (500 MHz, CD_3OD), δ: 9.27 (dd, J = 6.6 and 1.4 Hz, 2 H, 2-H, 6-H), 9.15 (s, 1 H, 3'-H), 8.85 (tt, J = 7.8 and 1.4 Hz, 1 H, 4-H), 8.32 (dd, J = 7.8 and 6.6 Hz, 2 H, 3-H, 5-H), 8.29 (d, J = 2.0 Hz, 1 H, 5'-H), 8.21 (d, J = 2.0 Hz, 1 H, 7'-H), 7.52 (m, 2 H, 2"-H, 6"-H), 7.41 (m, 3 H, 3"-H, 5"-H and 4"-H), 5.74 (s, 2 H, CH_2). ^{13}C-NMR (125 MHz, CD_3OD), δ: 152.5 (2'-C), 150.0 (4-C), 149.8 (2-C, 6-C), 141.4 (4a'-C), 138.4 (3'-C), 138.1 (7'-C), 137.7 (8a'-C), 134.0 (1"-C), 132.0 (5'-C), 130.9 (3-C, 5-C), 130.5 (three overlapped signals) (2"-C, 6"-C, 3"-C, 5"-C and 4"-C), 123.7 (8'-C), 121.9 (6'-C), 58.6 (CH_2). MS (EI, *m*/*z*): 380 (53), 379 (100), 378 (85), 303 (64), 301 (51), 106

(71), 91 (69), 79 (49). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{20}H_{15}{}^{79}Br_2N_4$ $[M - Br]^+$ 468.9658; found 468.9670.

1-[*N*-Benzyl-*N*-(6,8-dichloroquinoxalin-2-yl)amino]pyridinium bromide (20f): After 11 days of reaction in DMF, **20f** was obtained as a brown solid (287 mg, 62%, 0.62 mmol), m.p. 189–191 °C, IR (KBr): $\tilde{\upsilon}$ = 1617, 1571, 1470, 1177, 995, 705, 670. ^{1}H-NMR (500 MHz, CD_3OD), δ: 9.30 (dd, J = 6.4 and 1.5 Hz, 2 H, 2-H, 6-H), 9.17 (s, 1 H, 3'-H), 9.09 (tt, J = 7.8 and 1.5 Hz, 1 H, 4-H), 8.33 (dd, J = 7.8 and 6.4 Hz, 2 H, 3-H, 5-H), 8.07 (d, J = 2.5 Hz, 1 H, 5'-H), 7.91 (d, J = 2.5 Hz, 1 H, 7'-H), 7.53 (m, 2 H, 2''-H, 6''-H), 7.40 (m, 3 H, 3''-H, 5''-H and 4''-H), 5.76 (s, 2 H, CH_2). ^{13}C-NMR (75 MHz, CD_3OD), δ: 152.2 (2'-C), 150.0 (4-C), 149.8 (2-C, 6-C), 141.1 (4a'-C), 138.6 (3'-C), 136.5 (8a'-C), 134.0 (two overlapped signals) (6'-C and 1''-C), 133.2 (8'-C), 132.4 (7'-C), 130.9 (3-C, 5-C), 130.4 and 130.2 (two overlapped signals) (2''-C, 6''-C, 3''-C, 5''-C and 4''-C), 128.1 (5'-C), 58.7 (CH_2). MS (EI, *m*/*z*): 292 (57), 291 (74), 290 (82), 289 (66), 91 (100), 80 (23). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{20}H_{15}{}^{35}Cl_2N_4$ $[M - Br]^+$ 381.0668; found 381.0671.

1-[*N*-Benzyl-*N*-(8-bromo-6-chloroquinoxalin-2-yl)amino]pyridinium bromide (20g): After 7 days of reaction in DMF, **20g** was obtained as a brown solid (471 mg, 93%, 0.93 mmol), m.p.> 140 °C (dec.), IR (KBr): $\tilde{\upsilon}$ = 1616, 1595, 1568, 1470, 1229, 1176, 983, 764, 704, 669. ^{1}H-NMR (500 MHz, CD_3OD), δ: 9.34 (dd, J = 6.4 and 1.4 Hz, 2 H, 2-H, 6-H), 9.18 (s, 1 H, 3'-H), 8.88 (tt, J = 8.0 and 1.4 Hz, 1 H, 4-H), 8.35 (dd, J = 8.0 and 6.4 Hz, 2 H, 3-H, 5-H), 8.05 (d, J = 2.5 Hz, 1 H, 5'-H or 7'-H), 8.03 (d, J = 2.5 Hz, 1 H, 7'-H or 5'-H), 7.57 (m, 2 H, 2''-H, 6''-H), 7.40 (m, 3 H, 3''-H, 5''-H and 4''-H), 5.80 (s, 2 H, CH_2). ^{13}C-NMR (75 MHz, CD_3OD), δ: 152.5 (2'-C), 149.9 (4-C), 149.7 (2-C, 6-C), 140.9 (4a'-C), 138.5 (3'-C), 137.4 (8a'-C), 135.6 (7'-C), 134.4 and 134.0 (1''-C and 6'-C), 130.9 (3-C, 5-C), 130.6 and 130.4 (two overlapped signals) (2''-C, 6''-C, 3''-C, 5''-C and 4''-C), 128.7 (5'-C), 123.6 (8'-C), 58.6 (CH_2). MS (EI, *m*/*z*): 338/336/334 (26/100/83, M^+ – Br), 91 (72). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{20}H_{15}{}^{35}Br^{35}ClN_4$ $[M - Br]^+$ 425.0163; found 425.0171.

*4.4.2. Synthesis of N-benzyl-N-haloquinolin(or quinoxalin)-2-yl amines **21***

General procedure: Platinum on charcoal (5%) (87 mg) was added to a stirred solution of the corresponding pyridinium salt **20** (0.4 mmol) in CH_3CN (6 mL), cooled in an ice bath. Formic acid (98%, 1.7 mL) in CH_3CN (3 mL) and then triethylamine (4.1 mL) in the same solvent (6 mL) were added dropwise. The reaction mixture was stirred at room temperature for the time indicated in each case and the resulting suspension was filtered through Celite. The filtrate was evaporated, made basic with saturated aqueous potassium carbonate and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated to dryness. The residue was purified by flash chromatography (hexane/ethyl acetate, 7:3) and identified.

***N*-Benzyl-*N*-(6-bromoquinolin-2-yl)amine (21a):** After 15 minutes of reaction, **21a** was obtained as a colourless oil (86.6 mg, 69%, 0.276 mmol), IR (NaCl): $\tilde{\upsilon}$ = 3426, 1617, 1601, 1518, 1401, 1341, 824, 698. ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 7.69 (m, 2 H, 4-H and 5-H), 7.56 (m, 2 H, 7-H and 8-H), 7.32 (m, 5 H, 2'-H, 6'-H, 3'-H, 5'-H and 4'-H), 6.61 (d, J = 8.8 Hz, 1 H, 3-H), 5.14 (br s, 1 H, NH), 4.71 (d, J = 5.5 Hz, 2 H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 156.6 (2-C), 146.5 (8a-C), 138.9 (1'-C), 136.2 (4-C), 132.5 (7-C), 129.3 (5-C), 128.6 (3'-C, 5'-C), 127.8 (8-C), 127.7 (2'-C, 6'-C), 127.3 (4'-C), 124.6 (4a-C), 114.8 (6-C), 112.2 (3-C), 45.8 (CH_2).

MS (EI, *m*/*z*): 314/312 (65/100), 313 (28). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{16}H_{14}{}^{79}BrN_2$ $[M + H]^+$ 313.0335; found 313.0333.

***N*-Benzyl-*N*-(6,8-dibromoquinolin-2-yl)amine (21b):** After 1 hour of reaction, **21b** was obtained as a white solid (92.5 mg, 59%, 0.236 mmol), m.p. 91–93 °C, IR (KBr): $\tilde{\upsilon}$ = 3422, 1611, 1505, 1464, 1186, 861, 816, 707. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 7.96 (d, J = 2.4 Hz, 1 H, 7-H), 7.66 (d, J = 2.4 Hz, 1 H, 5-H), 7.65 (d, J = 8.7 Hz, 1 H, 4-H), 7.47 (br d, J = 7.3 Hz, 2 H, 2'-H, 6'-H), 7.35 (ap t, J = 7.3 Hz, 2 H, 3'-H, 5'-H), 7.29 (tt, J = 7.3 and 1.5 Hz, 1 H, 4'-H), 6.61 (d, J = 8.7 Hz, 1 H, 3-H), 5.23 (br s, 1 H, NH), 4.77 (d, J = 5.4 Hz, 2 H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 156.9 (2-C), 144.0 (8a-C), 139.0 (1'-C), 136.7 (4-C), 135.4 (7-C), 129.2 (5-C), 128.7 (2'-C, 6'-C), 128.2 (3'-C, 5'-C), 127.5 (4'-C), 125.2 (4a-C), 122.4 (8-C), 113.9 (3-C), 113.1 (6-C), 45.8 (CH_2). MS (EI, *m*/*z*): 393/391/389 (50/100/50), 106 (97), 91 (31). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{16}H_{13}{}^{79}Br_2N_2$ $[M + H]^+$ 390.9440; found 390.9443.

As a secondary product***N*-(6,8-dibromoquinolin-2-yl)amine (22)** was obtained: white solid (7.2 mg, 6%, 0.06 mmol), m.p. 176–178 °C, IR (KBr): $\tilde{\upsilon}$ = 3479, 3334, 1643, 1490, 1398, 864. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 7.97 (d, J = 2.2 Hz, 1 H, 7-H), 7.77 (d, J = 8.7 Hz, 1 H, 4-H), 7.72 (d, J = 2.2 Hz, 1 H, 5-H), 6.75 (d, J = 8.7 Hz, 1 H, 3-H), 5.03 (s, 2 H, NH_2). ^{13}C-NMR (75 MHz, $CDCl_3$), δ: 159.7 (2-C), 143.9 (8a-C), 137.5 (4-C), 135.7 (7-C), 129.3 (5-C), 125.4 (4a-C), 121.8 (8-C), 114.6 (6-C), 113.2 (3-C). MS (EI, *m*/*z*): 303/301/299 (52/100/46, $M^{+\bullet}$), 276/274/272 (10/19/10), 142 (24), 115 (17). HRMS (ESI-TOF, CH_3OH) calcd. for $C_9H_7{}^{79}Br_2N_2$ $[M + H]^+$ 300. 8971; found 300.8971.

***N*-Benzyl-*N*-(6-bromoquinoxalin-2-yl)amine (21c):** After 10 minutes of reaction, **21c** was obtained as a brown oil (94.3 mg, 61%, 0.30 mmol), IR (NaCl): $\tilde{\upsilon}$ = 3414, 1607, 1582, 1526, 1407, 1298, 1174, 915, 824, 737. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 8.18 (s, 1 H, 3-H), 8.02 (d, J = 2.5 Hz, 1 H, 5-H), 7.65 (dd, J = 9.0 and 2.5 Hz, 1 H, 7-H), 7.58 (d, J = 9.0 Hz, 1 H, 8-H), 7.36 (m, 5 H, 2'-H, 6'-H, 3'-H, 5'-H and 4'-H), 5.27 (br t, J = 5.2 Hz, 1 H, NH), 4.73 (d, J = 5.2 Hz, 2 H, CH_2). ^{13}C-NMR (125 MHz, $CDCl_3$), δ: 151.5 (2-C), 140.8 (1'-C), 139.1 (3-C), 138.2 and 138.0 (8a-C and 4a-C), 133.2 (7-C), 131.1 (5-C), 128.8 (3'-C, 5'-C), 128.0 (2'-C, 6'-C), 127.8 (8-C), 127.7 (4'-C), 117.1 (6-C), 45.3 (CH_2). MS (EI, *m*/*z*): 315/313 (48/50, $M^{+\bullet}$), 314/312 (27/19), 225 (10), 106 (100), 91 (47), 79 (12), 65 (14). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{15}H_{13}{}^{79}BrN_3$ $[M + H]^+$ 314.0287; found 314.0285.

***N*-Benzyl-*N*-(6-chloroquinoxalin-2-yl)amine (21d):** After 1 hour of reaction, **21d** was obtained as a brown oil (107.9 mg, 67%, 0.27 mmol), IR (NaCl): $\tilde{\upsilon}$ = 3421, 2919, 1610, 1587, 1538, 1532, 1409, 826, 699. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 8.16 (s, 1 H, 3-H), 7.85 (d, J = 2.4 Hz, 1 H, 5-H), 7.63 (d, J = 8.8 Hz, 1 H, 8-H), 7.51 (dd, J = 8.8 and 2.4 Hz, 1 H, 7-H), 7.40 (dd, J = 7.3 and 1.7 Hz, 2 H, 2'-H, 6'-H), 7.36 (m, 2 H, 3'-H, 5'-H), 7.30 (tt, J = 7.1 and 1.7, 1 H, 4'-H), 5.37 (br s, 1 H, NH), 4.72 (d, J = 5.6 Hz, 2 H, CH_2). ^{13}C-NMR (125 MHz, $CDCl_3$), δ: 151.6 (2-C), 140.4 (8a-C), 139.1 (3-C), 138.2 (1'-C), 137.5 (4a-C), 130.6 (7-C), 129.4 (6-C), 128.7 (3'-C, 5'-C), 128.0 (2'-C, 6'-C), 127.8 (5-C), 127.6 (4'-C), 127.5 (8-C), 45.2 (CH_2). MS (EI, *m*/*z*): 271/269 (32/95, $M^{+\bullet}$), 106 (100), 91 (69), 65 (26). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{15}H_{13}{}^{35}ClN_3$ $[M + H]^+$ 270.0793; found 270.0789.

***N*-Benzyl-*N*-(6,8-dibromoquinoxalin-2-yl)amine (21e):** After 1 hour of reaction, **21e** was obtained as a beige solid (95.9 mg, 61%, 0.244 mmol), m.p. 137–139 °C, IR (KBr): $\tilde{\upsilon}$ = 1604, 1572, 1537, 1524, 1399, 864, 740, 695. ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 8.13 (s,1 H, 3-H), 7.96 (s (AB system), 2 H, 5-H and 7-H), 7.45 (br d, J = 7.4 Hz, 2 H, 2'-H, 6'-H), 7.34 (br t, J = 7.3

Hz, 2 H, 3'-H, 5'-H), 7.29 (br t, *J* = 7.3 Hz, 1 H, 4'-H), 5.42 (br s, 1 H, NH), 4.75 (d, *J* = 5.4 Hz, 2 H, CH_2). ^{13}C-NMR (125 MHz, $CDCl_3$), *δ*: 151.7 (2-C), 139.5 (3-C), 138.8, 138.2 and 138.0 (1'-C, 8a-C and 4a-C), 135.9 (7-C), 130.8 (5-C), 128.8 (3'-C, 5'-C), 128.4 (2'-C, 6'-C), 127.8 (4'-C), 121.6 (8-C), 116.3 (6-C), 46.7 (CH_2). MS (EI, *m*/*z*): 395/393/391 (50/100/53, $M^{+\bullet}$), 394/392/390 (19/38/20). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{15}H_{12}{}^{79}Br_2N_3$ $[M + H]^+$ 391.9394; found 391.9392.

***N*-Benzyl-*N*-(6,8-dichloroquinoxalin-2-yl)amine (21f):** After 10 minutes of reaction,**21f**was obtained as a yellow oil (90.0 mg, 74%, 0.296 mmol), IR (NaCl): $\tilde{\upsilon}$ = 3419, 1605, 1580, 1527, 1403, 1182, 1028, 700. ^{1}H-NMR (500 MHz, $CDCl_3$), *δ*: 8.19 (s, 1 H, 3-H), 7.75 (d, *J* = 2.4 Hz, 1 H, 5-H), 7.64 (d, *J* = 2.4 Hz, 1 H, 7-H), 7.43 (br d, *J* = 7.4 Hz, 2 H, 2'-H, 6'-H), 7.34 (ap t, *J* = 7.3 Hz, 2 H, 3'-H, 5'-H), 7.28 (tt, *J* = 7.4 and 1.4 Hz, 1 H, 4'-H), 5.64 (br s, 1 H, NH), 4.75 (d, *J* = 5.5 Hz, 2 H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$), *δ*: 151.2 (2-C), 139.5 (3-C), 137.7 and 137.6 (two overlapped signals) (8a-C, 4a-C and 1'-C), 130.3 (two overlapped signals) (7-C and 8-C), 128.7 (3'-C, 5'-C), 128.6 (6-C), 128.2 (2'-C, 6'-C), 127.7 (4'-C), 126.8 (5-C), 45.5 (CH_2). MS (EI, *m*/*z*): 305/303 (9/17, $M^{+\bullet}$), 304/302 (21/29), 106 (100). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{15}H_{12}{}^{35}Cl_2N_3$ $[M + H]^+$ 304.0403; found 304.0399.

***N*-Benzyl-*N*-(8-bromo-6-chloroquinoxalin-2-yl)amine (21g):** After 1 hour of reaction, **21g** was obtained as a yellow solid (80.9 mg, 58%, 0.232 mmol), m.p. 122–124 °C, IR (KBr):$\tilde{\upsilon}$ = 1604, 1578, 1351, 1293, 1175, 794, 754, 700. ^{1}H-NMR (500 MHz, $CDCl_3$), *δ*: 8.13 (s, 1 H, 3-H), 7.85 (br s, 1 H, 7-H), 7.81 (br s, 1 H, 5-H), 7.47 (br d, *J* = 6.8 Hz, 2 H, 2'-H, 6'-H), 7.37 (ap t, *J* = 7.3 Hz, 2 H, 3'-H, 5'-H), 7.31 (t, *J* = 7.3 Hz, 1 H, 4'-H), 5.48 (br s, 1 H, NH), 4.76 (d, *J* = 5.6 Hz, 2 H, CH_2). ^{13}C-NMR (125 MHz, $CDCl_3$), *δ*: 154.4 (2-C), 142.2 (3-C), 141.8 (8a-C), 140.7 (1'-C), 140.3 (4a-C), 136.2 (7-C), 131.8 (6-C), 131.4 (3'-C, 5'-C), 131.1 (2'-C, 6'-C), 130.5 (4'-C), 130.3 (5-C), 124.1 (8-C), 48.2 (CH_2). MS (EI, *m*/*z*): 351/349/347 (10/37/29, $M^{+\bullet}$), 269 (19), 149 (14), 106 (100), 91 (58), 65 (23). HRMS (ESI-TOF, CH_3OH) calcd. for $C_{15}H_{12}{}^{79}Br^{35}Cl$ N_3 $[M + H]^+$ 347.9902; found 347.9898.

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References and notes

1. Alajarín, R.; Burgos, C. In *Modern Heterocyclic Chemistry*; Alvarez-Buílla, J., Vaquero J.J., Barluenga, J., Ed.; Wiley-VCH Verlag. GmbH & Co. KGaA: Weinheim, Germany, 2011; Vol. 3, pp 1527–1629.

2. a) Narwal S, Kumar S, Verma PK. *Res. Chem. Intermed.* 2017; 43:2765; b) Khan I, Zaib S, Batool S, Abbas N, Ashraf Z, Iqbal J, Saeed A. *Bioorg. Med. Chem.* 2016, 24:2361; c) Babu KS, Prabhakar V, Ravindranath LK, Kishore NVK, Latha J. *World J. Pharm. Pharmac. Sci.* 2016; 5:905; d) El-Azm FSMA, Mahmoud MR, Hekal MH. *Org. Chem. Curr. Res.* 2015; 4:132; e) Laskina OB, Mel'nikova SF, Tselinskii IV. *Russ. J. Org. Chem.* 2012, 48:278; f) Saari R, Törmä J-C, Nevalainen T. *Bioorg. Med. Chem.* 2011; 19:939.

3. a) Kokatla HP, Sil D, Malladi SS, Balakrishna R, Hermanson AR, Fox LM, Wang X, Dixit A, David SA. *J. Med. Chem.* 2013; 56:6871; b) Inglis SR, Jones RK, Booker GW, Pyke SM. *Bioorg. Med. Chem.Lett.* 2006; 16:387; c) Inglis S, Jones R, Fritz D, Booker G, Pyke

S. *Org. Biomol. Chem.* 2005; 3:2543; d) Inglis SR, Stojkoski C, Branson KM, Cawthray JF, Fritz D, Wiadrowski E, Pyke SM, Booker GW. *J. Med. Chem.* 2004; 47:5405.

4. González M, Cerecetto H. *Expert Opin. Ther. Pat*. 2012; 22:1289.

5. Cheng Y, Judd TC, Bartberger MD, Brown J, Chen K, Fremeau Jr. RT, Hickman D, Hitchcock SA, Jordan B, Li V, Lopez P, Louie SW, Luo Y, Michelsen K, Nixey T, Powers TS, Rattan C, Sickmier EA, St. Jean Jr. DJ, Wahl RC, Wen PH, Wood S. *J. Med. Chem.* 2011; 54:5836.

6. a) Dömling A. *Chem. Rev*. 2006; 106:17; b) Blackburn C, Guan B, Fleming P, Shiosaki K, Tsai S. *Tetrahedron Lett.* 1998; 39:3635; c) Groebke K, Weber L, Mehlin F. *Synlett* 1998:661.

7. a) Guchhait SK, Priyadarshani G, Gulghane NM. *RSC Advances* 2016; 6:56056; b) Zheng Q, Ding Q, Wang C, Chen W, Peng Y. *Tetrahedron* 2016; 72:952; c) Jin H, Tian B, Song X, Xie J, Rudolph M, Rominger F, Hashmi ASK. *Angew. Chem. Int. Ed.* 2016; 55:12688; d) Dou G, Wang D, Shi D. *Heterocycles* 2016; 92:521; e) Zhang L, Zheng L, Guo B, Hua R. *J. Org. Chem.* 2014; 79:11541; f) Cho Y-H, Kim K-H, Cheon C-H. *J. Org. Chem.* 2014; 79:901; g) Shi, S, Wang, T, Yang, W, Rudolph M, Hashmi, SK. *Chem. Eur. J*., 2013, 19:6576.

8. a) Gala E, Reyes MJ, Alvarez-Builla J, Izquierdo ML. *Eur. J. Org. Chem.* 2016; 12:2145; b) Gala E, Córdoba M, Izquierdo ML, Alvarez-Builla J. *Arkivoc* 2014; v:319; c) Filace F, Sucunza D, Izquierdo ML, Burgos C, Alvarez-Builla J. *Tetrahedron* 2013; 69:6088; d) Córdoba M, Galájov M, Izquierdo ML, Alvarez-Builla J. *Tetrahedron* 2013; 69:2484.

9. a) Córdoba M, Abet V, Morón M, Castillo R, Burgos C, Izquierdo ML. *Arkivoc* 2011; iii:156; b) Carceller R, García-Navío JL, Izquierdo ML, Alvarez-Builla J, Fajardo M, Gómez-Sal P, Gago F. *Tetrahedron* 1994; 50:4995.

10. Córdoba M, Izquierdo ML, Alvarez-Builla J. *Tetrahedron* 2008; 64:7914.

11. Burgos C, Delgado F, García-Navío JL, Izquierdo ML, Alvarez-Builla J. *Tetrahedron* 1995; 51:8649.

12. Gerster JF, Lindstrom KJ, Miller RL, Tomai MA, Birmachu W, Bomersine SN, Gibson SJ, Imbertson LM, Jacobson JR, Knafla RT, Maye PV, Nikolaides N, Oneyemi FY, Parkhurst GJ, Pecore SE, Reiter MJ, Scribner LS, Testerman TL; Thompson NJ, Wagner TL, Weeks CE, Andre JD, Lagain D, Bastard Y, Lupu M. *J. Med. Chem.* 2005; 48:3481.

13. Itoh T, Kato S, Nonoyama N, Wada T, Maeda K, Mase T. *Org. Process Res. Dev.* 2006, 10:822.

14. a) Huang KS, Haddadin MJ, Olmstead MM, Kurth MJ. *J. Org. Chem.* 2001; 66:1310; b) Ndubaku CO, Crawford TD, Chen H, Jason JW, Drobnick J, Harris SF, Jesudason R, McNamara E, Nonomiya J, Sambrone A, Schmidt S, Smyczek T, Vitorino P, Wang L, Wu P, Yeung S, Chen J, Chen K, Ding CZ, Wang T, Xu Z, Gould SE, Murray LJ, Ye W. *ACS Med. Chem. Lett.* 2015; 6:913; c) Huang, K. H., Veal, J., Barta, T., Smith, E. D., Ma, W. , Ommen, A. Patent WO 2008024977 A2 20080228, 2008; d) Stoessel, P., Jatsch, A., Breuning, E. Patent WO 2013000531 A1 20130103, 2013; e) Chen, H., Crawford, T., Magnuson, S. R., Ndubaku, C., Wang, L. Patent WO 2013113669 A1 20130808, 2013; f) Schiemann, K., Blagg, J., Mallinger, A., Rink, C., Sejberg, J., Honey M. Patent WO 2016009076 A1 20160121, 2016.

15. a) Castillo R, Reyes MJ, Izquierdo ML, Alvarez-Builla J. *Tetrahedron* 2008, 64:1351; b) Córdoba M, Galájov M, Izquierdo ML, Alvarez-Builla J. *Tetrahedron* 2013, 69:2484.