Amination of chloro-substituted heteroarenes with adamantane-containing amines*

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Amination of 3,6-dichloropyridazine, chloropyrazine, 2,3- and 2,6-dichloropyrazines, 2-chloroquinoxaline, 1-chloro- and 1,3-dichloroisoquinolines with various adamantane-containing amines characterized by different steric hindrances at the amino group was studied. The yields of the amination products depended on the structure of starting compounds. In the reactions of all the dichloroheteroarenes, selective substitution of only one chlorine atom took place, with the best yields being observed for 2,6-dichloropyrazine. In the reaction of 1,3-dichloroisoquinoline, the chlorine atom at position 1 was selectively substituted in up to 90% yield.

Key words: amination, heteroarylhalides, adamantane, amines.

Amino derivatives of heteroaromatic compounds are under active studies as pharmaceutical agents, which, depending on the nature of the heteroaromatic core and substituents, demonstrate very wide range of physiological activity. For example, aminopyrazine derivatives act as efficient inhibitors of various kinases, such as tyrosine kinase FLT3 (treatment of acute myeloid leukemia),[1] mitotic kinase Nek2;[2] thiourea derivatives containing 2-aminopyrazine fragments manifested inhibiting activity against tyrosine kinase MK-2.[3] The introduction of aminopyrazine substituents into spiro[indolyl-3,4´-piperidin]-2-one framework led to the synthesis of highly efficient inhibitors of kinases c-Met and ALK.[4] Antimycobacterial activity was found in aminopyridazinecarboxylic acid derivatives such as nitriles,[5], esters,[6] and amides.[7] A series of 3,5-diaryl-2-aminopyrazines demonstrated strong antiplasmoid activity,[8] aminopyrazine derivatives containing benzopyran and piperidine fragments have proved to be efficient agents against African trypanosomiasis.[9] Aminopyrazines were used as a basis for obtaining powerful antagonists of voltage-gated sodium channel Na(v)1.7 in proteins.[10] 3-Amino-6-arylpyridazines are CB(2)-antagonists highly efficient against receptor CB(1), that determines their antiinflammatory action.[11] Similarly, pyrazolone-substituted pyridazines possess antiinflammatory and analgesic activity.[12] Apart from fighting neuroinflammatory processes, some aminopyridazine derivatives can be efficient in treatment of Alzheimer´s disease,[13] whereas diaminopyridazines can act as histamine H4-receptor modulators.[14] 1-Aminoisoquinolines were studied as antidepressants,[15] whereas different 6-substituted 1-aminoisoquinolines were found to exhibit inhibiting activity against Rho-associated protein kinase, that can be used for treatment of cardiovascular diseases.[16] Thus, development of approaches to the preparation of amino-substituted pyrazines, pyridazines, isoquinolines, and other nitrogen heterocycles, undoubtedly, is an important issue.

Since the introduction of adamantane framework in molecules increases their ability to interact with biological membranes containing a lipid layer, as well as with hydrophobic fragments of proteins,[17] in the present work we set a goal to develop a convenient approach to the introduction of heteroaromatic fragments, such as pyrazine, pyridazine, and isoquinoline, to the nitrogen atoms of the adamantane-containing amines in order to prepare a new series of potentially biologically active compounds. Earli-

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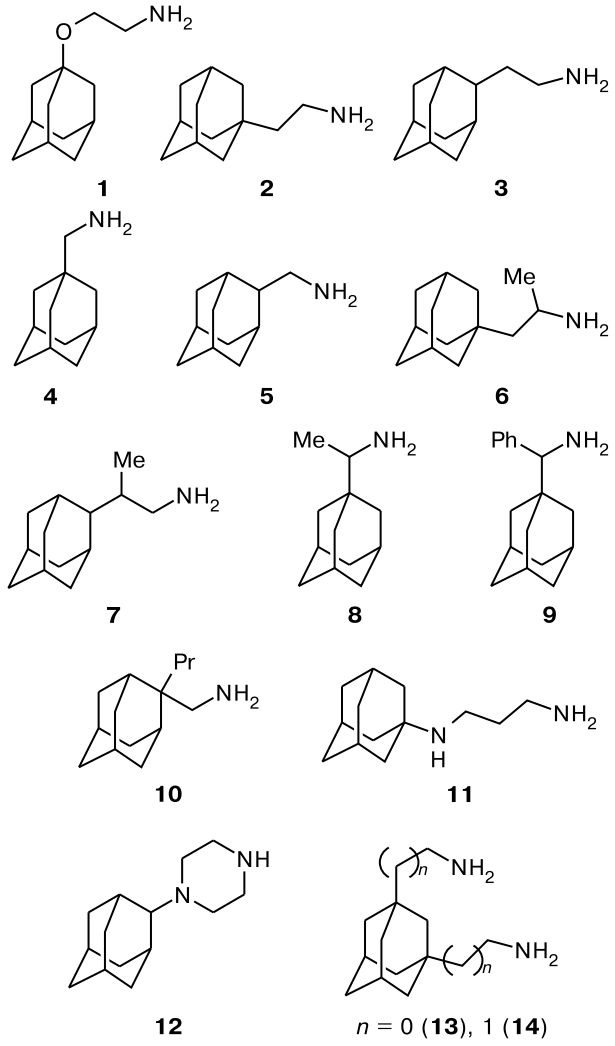
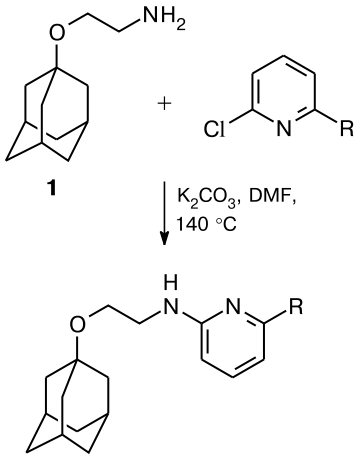
er, we successfully accomplished *N*-heteroarylation of such amines with halopyridines and haloquinolines catalyzed by palladium[18,19] and copper[20] compounds, as well as showed a possibility of noncatalytic reactions involving 2-fluoropyridine and its derivatives.[21]

In the present study, we used chlorine-containing heteroarenes. Compounds **1**—**12** differing in the steric hindrance at the amino group, as well as diamines **13** and **14**, were studied as the amine component.



Earlier, we have shown[20] that 2-bromopyridine exhibits low reactivity in the reaction with amine **1** in the presence of cesium carbonate: even upon prolonged heating in DMF at 140 °C the yield of the product was 11%. We carried out similar reactions with 2-chloropyridine under conditions optimized earlier for 2-fluoropyridines (2.5 equiv. of K_2CO_3, DMF, 140 °C) and showed that the yield of the *N*-heteroarylation product **15** did not exceed 20% (Scheme 1). However, when 2,6-dichloropyridine was introduced in the reaction, the yield of the monoamination product **16** increased to 67%. This was an interesting observation, since the second chlorine atom, being an electron-withdrawing substituent, is at *meta*-position relative to the reaction center and would not have had such a noticeable influence in contrast to the halogen atoms (F, Cl, and Br) in 5-halo-2-fluoropyridines, which, as it was shown earlier,[21] considerably facilitated noncatalytic substitution of a fluorine atom with the amino group in the reactions with adamantane-containing amines.

Scheme 1



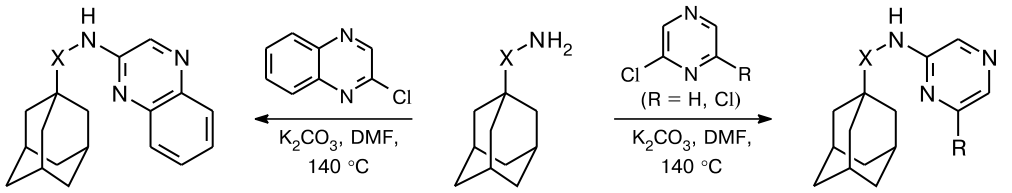
R = H (15), Cl (16)

Similarly, the reactions of amines **1** and **4** with 2-chloropyrazine gave lower yields of heteroarylation products **17** and **18** (31 and 63%) than in the reactions of these amines with 2,6-dichloropyrazine: 82 and 75% for compounds **19** and **20**, respectively (Scheme 2). Apart form that, it was shown that the introduction of the second fused aromatic ring considerably increased the reactivity of the chlorine atom: thus, in the reactions of amines **1** and **4** with 2-chloroquinoxalines, the yields of heteroarylation products **21** and **22** were 81% in each reactions (see Scheme 2).

At the next step, we compared the reactivities of amines **2**, **3**, **5**—**12** under the same conditions in the *N*-heteroarylation reactions with more active 2,6-dichloropyrazine (Scheme 3). The studies showed that in the reactions with all these amines, except the most sterically hindered amine **9**, the corresponding *N*-heteroarylation products were obtained in from 60 to 86% yields. The yield of compound **29** was increased from 28 to 70% when a three-fold excess of 2,6-dichloropyrazine was used. It should be noted that the adamantane-containing diamine **11** reacted selectively at the primary amino group to give product **31** in 82% yield.

The reaction of diamines **13** and **14** with 2,6-dichloropyrazine (2.5 equiv.) led to the preparation of the corresponding *N*,*N*′-diheteroaryl derivatives **33** and **34** in low yields of 25 and 22%, respectively (Scheme 4). The successful accomplishment of these reactions, as well as the amination of 2,6-dichloropyrazine with adamantyl-

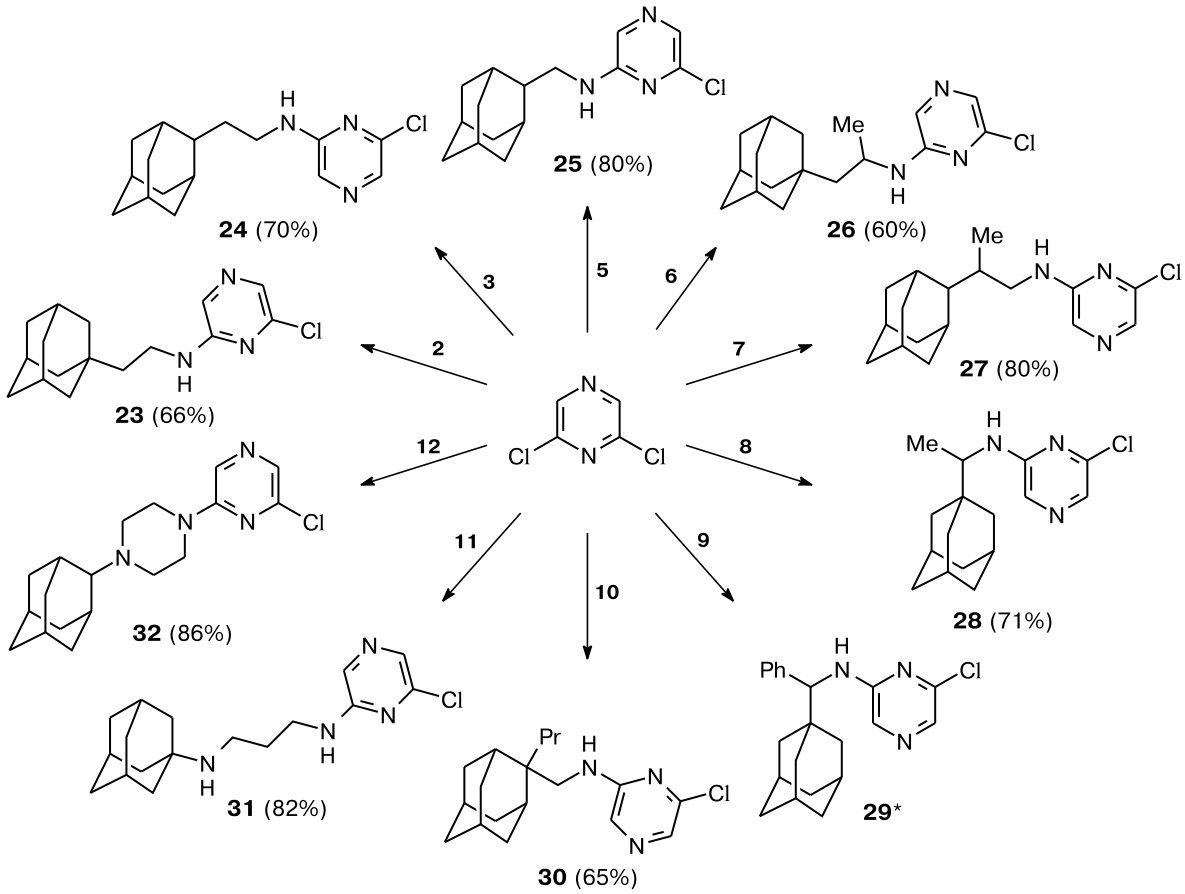
Scheme 2



21, 22 **1, 4** **17—20**

Compound	X	R	Yield (%)	Compound	X	R	Yield (%)
17	OCH_2CH_2	H	31	**20**	CH_2	Cl	75
18	CH_2	H	63	**21**	OCH_2CH_2	—	81
19	OCH_2CH_2	Cl	82	**22**	CH_2	—	81

Scheme 3



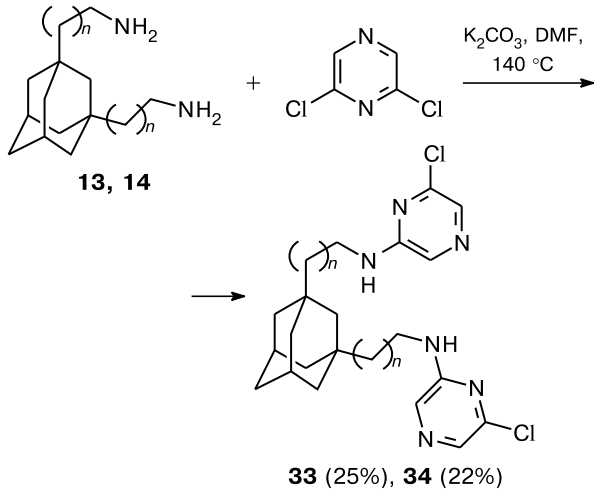
* The yields of compound **29** at the ratio of **9** : 2,6-dichloropyrazine = 1 : 1 and 1 : 3 were 28 and 70%, respectively.

substituted pyperazine **12** (the yield of product **32** was 86%), indicate a rather wide scope of this method for noncatalytic introduction of pyrazine fragment at the nitrogen atom of the adamantane-containing amines.

The reaction of amine **1** with isomeric 2,3-dichloropyrazine gave a lower yield: compound **35** was isolated in 56% yield (Scheme 5), which can be explained by the steric factor, namely, by the presence of the second chlorine atom at *ortho*-position. In this connection, 2,3-dichloropyrazine was not studied in the reactions with other amines.

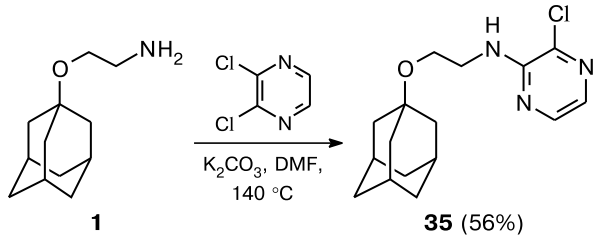
The amination of isomeric 3,6-dichloropyridazine was carried out using amines **1**—**4**, **6**, **7**, and **12** (Scheme 6). The reactions with some sterically unhindered amines such as **1**, **7**, and **12** were successful, giving 74—83% yields of

Scheme 4



n = 0 (**13**, **33**), 1 (**14**, **34**)

Scheme 5

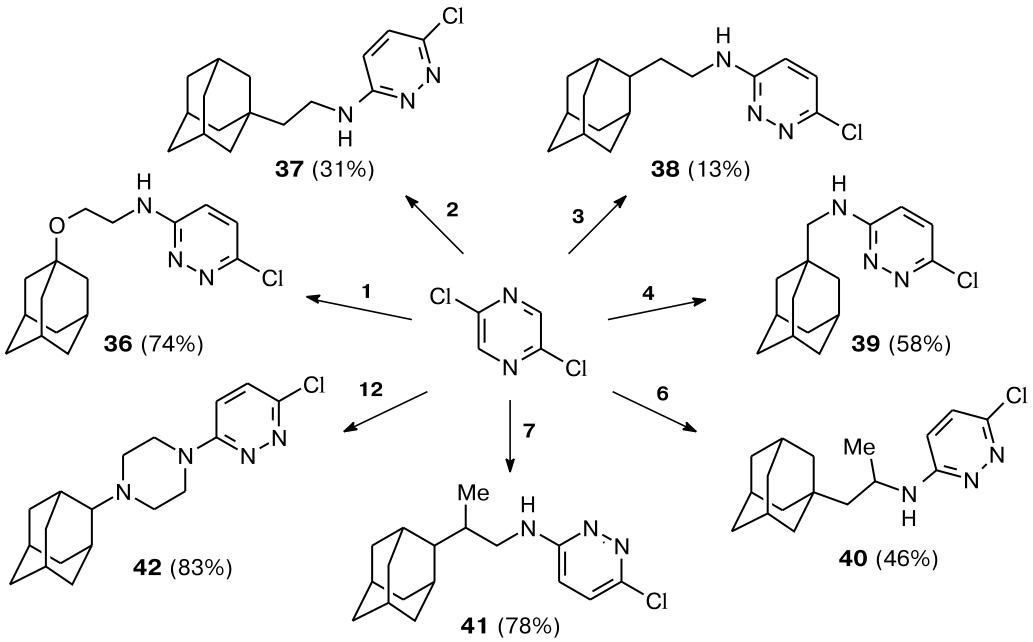


the heteroarylation products. Amines **4** and **6**, in which the steric hindrance at the nitrogen atom was higher, gave lower yields of the corresponding products **39** and **40** (58 and 46%, respectively). It unexpectedly turned out that amines **2** and **3**, whose reactivity in the preceding reactions was comparable with that of amine **1**, in this process gave low yields of *N*-heteroarylation products (31% for **37** and only 13% for **38**). Analysis of the reaction mixture before chromatographic isolation, which was carried out in all the cases, showed that the low yield of the target products, in fact, is a specific feature of these reactions and is not a result of losses in the process of isolation, since the content of the target products in the reaction mixtures was unusually low.

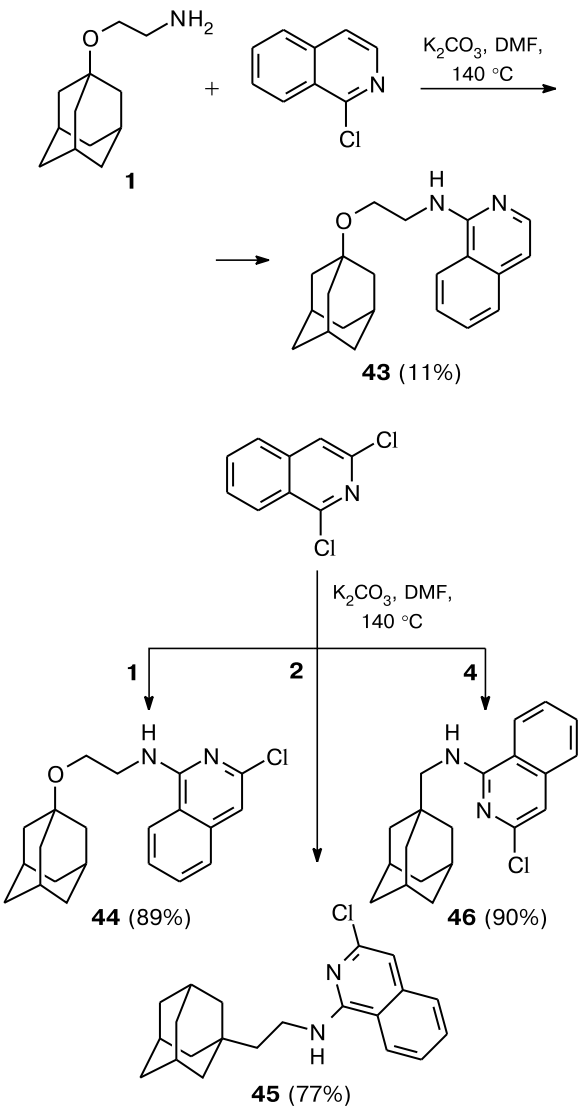
In the final stage of our studies, we carried out the reactions of amines **1**, **2**, and **4** with 1-chloroisoquinoline and 1,3-dichloroisoquinoline in order to reveal a dependence of the product yields on the steric hindrance at the amino group and to determine the selectivity of the substitution of the chlorine atom in 1,3-dichloroisoquinoline (Scheme 7). It turned out that the introduction of the second halogen atom considerably increased the reactivity of the haloheteroarene, since compound **43** was obtained in low yield (11%), whereas the heteroarylation products **44**—**46** were obtained in high yields from 77 to 90%, depending on the steric hindrance at the amino group in the starting amines. It was found that in 1,3-dichloroisoquinoline, the halogen atom at position 1 was selectively substituted, that is substantiated by its considerably higher reactivity.

In conclusion, in the course of the present studies we showed a possibility of noncatalytic substitution of one

Scheme 6



Scheme 7



chlorine atom in dichloroheteroarenes, demonstrated considerably higher reactivity of dichloroheteroarenes as compared to the corresponding monochloro derivatives, found that most of adamantane-containing amines with different steric environment of the amino group can be involved in the *N*-heteroarylation reaction, and only in the case of the most sterically hindered amine **9** the preparation of the reaction product in good yield required the use of a three-fold excess of the haloheteroarene.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz) at 298 K. Chemical shifts in the ^{1}H and ^{13}C NMR spectra are given in the δ scale relative to Me_4Si as an internal standard. MALDI mass spectra of positive pseudomolecular ions $[M + H]^+$ were recorded on a Bruker Autoflex II instrument, using 1,8,9-trihydroxyanthracene as a matrix and polyethylene glycols as internal standards. Preparative column chromatography was performed using Merck silica gel (40/60). The starting halo derivatives of heteroarene and potassium carbonate purchased from Sigma-Aldrich were used without purification.

Amine **1** was obtained according to the method described in the work,[22] amines **2**, **3**, **5**, **7**, **10**, and **12** according to the method indicated in the works,[23,24] amines **4**, **6**, **8**, **9**, **13**, and **14** according to the method described in the works,[18,25] amine **11** according to the earlier published method.[26] Dimethylformamide was purified by distillation *in vacuo* over calcium hydride; light petroleum ether, dichloromethane, and methanol were distilled.

***N*-(Heteroaryl)-substituted adamantane-containing amines 16—46 (general procedure).** A corresponding chloro-substituted heteroarene (0.2—0.5 mmol), finely powdered K_2CO_3 (173 mg, 1.25 mmol), DMF (1 mL), and a corresponding adamantane-containing amine (0.2—0.5 mmol) were placed into a one-neck flask equipped with a magnetic stirrer and reflux condenser and filled with dry argon, and the reaction mixture was stirred for 24 h at 140 °C. When the reaction was carried out with diamines **13** and **14** (0.5 mmol), 2,6-dichloropyrazine (186 mg, 1.25 mmol) and K_2CO_3 (345 mg, 2.5 mmol) were used. On the reaction completion, the mixture was cooled to room temperature, dichloromethane (5 mL) was added, a precipitate was filtered off and additionally washed with dichloromethane (5 mL), the combined organic fractions were concentrated *in vacuo*, the residues were analyzed by NMR spectroscopy. If necessary, the products were purified by chromatography on silica gel, using the following sequence of eluents: light petroleum ether—CH_2Cl_2 (4 : 1 → →1 : 4), CH_2Cl_2, CH_2Cl_2—MeOH (500 : 1 → 3 : 1). The target products were obtained as faintly colored or colorless dense oils or crystalline powders. The spectral data of compound **15** are reported in the work.[20]

***N*-[2-(1-Adamantyloxy)ethyl]-6-chloropyridin-2-amine (16)** was synthesized from 2,6-dichloropyridine (74 mg, 0.5 mmol) and amine **1** (98 mg, 0.5 mmol). Eluent CH_2Cl_2, CH_2Cl_2—MeOH (200 : 1). The yield was 101 mg (67%). A pale yellow crystalline compound, m.p. 109—110 °C. ^{1}H NMR ($CDCl_3$), δ: 1.54—1.65 (m, 6 H, CH_2(Ad)); 1.70—1.72 (m, 6 H, CH_2(Ad)); 2.12 (br.s, 3 H, CH(Ad)); 3.37 (t, 2 H, CH_2N, ^3J = 5.2 Hz); 3.57 (t, 2 H, CH_2O, ^3J = 5.2 Hz); 5.04 (br.s, 1 H, NH); 6.26 (d, 1 H, H3(Pyr), ^3J = 8.1 Hz); 6.53 (d, 1 H, H5(Pyr), ^3J = 7.6 Hz); 7.30 (dd, 1 H, H4(Pyr), ^3J = 8.1 Hz, ^3J = 7.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.4 (3 CH(Ad)), 36.3 (3 CH_2(Ad)), 41.5 (3 CH_2(Ad)), 42.5 (CH_2N), 58.3 (CH_2O), 72.4 (C(Ad)), 104.7 (C3(Pyr)), 111.6 (C5(Pyr)), 139.5 (C4(Pyr)), 149.4 (C6(Pyr)), 158.8 (C2(Pyr)). MS (MALDI), *m/z*: 307.1634 $[M + H]^+$. $C_{17}H_{24}ClN_2O$. Calculated: 307.1577.

***N*-[2-(1-Adamantyloxy)ethyl]pyrazin-2-amine (17)** was synthesized from chloropyrazine (23 mg, 0.2 mmol) and amine **1** (39 mg, 0.2 mmol). The yield was 17 mg (31%). Eluent CH_2Cl_2—MeOH (50 : 1). ^{1}H NMR ($CDCl_3$), δ: 1.52—1.65 (m, 6 H, CH_2(Ad)); 1.69—1.71 (m, 6 H, CH_2(Ad)); 2.12 (br.s, 3 H, CH(Ad)); 3.47 (t, 2 H, CH_2N, ^3J = 5.2 Hz); 3.60 (t, 2 H, CH_2O, ^3J = 5.2 Hz); 5.02 (br.s, 1 H, NH); 7.75 (d, 1 H, H(Pyr), ^3J = 2.8 Hz); 7.78 (d, 1 H, H(Pyr), ^4J = 1.5 Hz); 7.93 (dd, 1 H, H(Pyr), ^3J = 2.8 Hz, ^4J = 1.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.4 (3 CH(Ad)), 36.3 (3 CH_2(Ad)), 41.5 (3 CH_2(Ad)), 41.7 (CH_2N), 58.3 (CH_2O), 72.5 (C(Ad)), 132.6 (2 CH(Pyr)), 141.8 (CH(Pyr)), 154.7 (C(Pyr)). MS (MALDI), *m/z*: 274.21 $[M + H]^+$. $C_{16}H_{24}N_3O$. Calculated: 274.19.

***N*-(1-Adamantylmethyl)pyrazin-2-amine (18)** was synthesized from chloropyrazine (23 mg, 0.2 mmol) and amine **4** (33 mg, 0.2 mmol). The yield was 31 mg (63%). Eluent CH_2Cl_2—MeOH (100 : 1). ^{1}H NMR ($CDCl_3$), δ: 1.53—1.55 (m, 6 H, CH_2(Ad)); 1.59—1.73 (m, 6 H, CH_2(Ad)); 1.98 (br.s, 3 H, CH(Ad)); 3.04 (d, 2 H, CH_2N, ^3J = 6.2 Hz); 4.68 (br.s, 1 H, NH); 7.73 (d, 1 H, H(Pyr), ^3J = 2.7 Hz); 7.88 (d, 1 H, H(Pyr), ^4J = 1.5 Hz); 7.91 (dd, 1 H, H(Pyr), ^3J = 2.7 Hz, ^4J = 1.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.2 (3 CH(Ad)), 34.0 (C(Ad)), 36.9 (3 CH_2(Ad)), 40.4 (3 CH_2(Ad)), 53.1 (CH_2N), 131.9 (CH(Pyr), 132.3 (CH(Pyr)), 141.7 (CH(Pyr)), 155.3 (C(Pyr)). MS (MALDI), *m/z*: 244.16 $[M + H]^+$. $C_{15}H_{22}N_3$. Calculated: 244.18.

***N*-[2-(1-Adamantyloxy)ethyl]-6-chloropyrazin-2-amine (19)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **1** (98 mg, 0.5 mmol). The yield was 126 mg (82%). A light beige crystalline compound, m.p. 83—84 °C. ^{1}H NMR ($CDCl_3$), δ: 1.51—1.62 (m, 6 H, CH_2(Ad)); 1.67—1.69 (m, 6 H, CH_2(Ad)); 2.10 (br.s, 3 H, CH(Ad)); 3.45 (t, 2 H, CH_2N, ^3J = 5.1 Hz); 3.56 (t, 2 H, CH_2O, ^3J = 5.1 Hz); 5.24 (br.s, 1 H, NH); 7.72 (s, 1 H, H(Pyr)); 7.75 (s, 1 H, H(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 30.3 (3 CH(Ad)), 36.2 (3 CH_2(Ad)), 41.4 (3 CH_2(Ad)), 41.8 (CH_2N), 58.0 (CH_2O), 72.5 (C(Ad)), 129.3 (CH(Pyr)), 130.1 (CH(Pyr)), 146.8 (C6(Pyr)), 154.1 (C2(Pyr)). MS (MALDI), *m/z*: 308.1557 $[M + H]^+$. $C_{16}H_{23}ClN_3O$. Calculated: 308.1530.

***N*-(1-Adamantylmethyl)-6-chloropyrazin-2-amine (20)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **4** (83 mg, 0.5 mmol). The yield was 104 mg (75%). ^{1}H NMR ($CDCl_3$), δ: 1.49—1.53 (m, 6 H, CH_2(Ad)); 1.56—1.71 (m, 6 H, CH_2(Ad)); 1.96 (br.s, 3 H, CH(Ad)); 3.01 (d, 2 H, CH_2N, ^3J = 6.2 Hz); 4.95 (br.s, 1 H, NH); 7.69 (s, 1 H, H(Pyr)); 7.74 (s, 1 H, H(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 28.1 (3 CH(Ad)), 34.0 (C(Ad)), 36.8 (3 CH_2(Ad)), 40.2 (3 CH_2(Ad)), 53.2 (CH_2N), 128.6 (CH(Pyr)), 130.0 (CH(Pyr)), 146.7 (C6(Pyr)), 154.8 (C2(Pyr)). MS (MALDI), *m/z*: 278.1381 $[M + H]^+$. $C_{15}H_{21}ClN_3$. Calculated: 278.1424.

***N*-[2-(1-Adamantyloxy)ethyl]quinoxalin-2-amine (21)** was synthesized from 2-chloroquinoxaline (33 mg, 0.2 mmol) and amine **1** (39 mg, 0.2 mmol). The yield was 52 mg (81%). Eluent CH_2Cl_2—MeOH (100 : 1 → 50 : 1). ^{1}H NMR ($CDCl_3$), δ: 1.55—1.66 (m, 6 H, CH_2(Ad)); 1.73—1.75 (m, 6 H, CH_2(Ad)); 2.14 (br.s, 3 H, CH(Ad)); 3.66—3.70 (m, 4 H, CH_2N, CH_2O); 5.39 (br.s, 1 H, NH); 7.32—7.37 (m, 1 H, H(Quin)); 7.51—7.56 (m, 1 H, H(Quin)); 7.65 (d, 1 H, H(Quin), ^3J = 8.3 Hz); 7.84 (d, 1 H, H(Quin), ^3J = 8.2 Hz); 8.20 (s, 1 H, H3(Quin)). ^{13}C NMR ($CDCl_3$), δ: 30.4 (3 CH(Ad)), 36.3 (3 CH_2(Ad)), 41.5 (CH_2N), 41.6 (3 CH_2(Ad)), 58.3 (CH_2O), 72.5 (C(Ad)), 124.1 (CH(Quin)), 126.1 (CH(Quin)), 128.8 (CH(Quin)), 129.9 (CH(Quin)), 137.1 (C(Quin)), 138.8 (CH(Quin)), 141.8 (C(Quin)), 151.8 (C2(Quin)). MS (MALDI), *m/z*: 324.2129 $[M + H]^+$. $C_{20}H_{26}N_3O$. Calculated: 324.2076.

***N*-(1-Adamantylmethyl)quinoxalin-2-amine (22)** was synthesized from 2-chloroquinoxaline (33 mg, 0.2 mmol) and amine **4** (33 mg, 0.2 mmol). The yield was 47 mg (81%). Eluent CH_2Cl_2—MeOH (200 : 1 → 100 : 1). ^{1}H NMR ($CDCl_3$), δ: 1.58—1.60 (m, 6 H, CH_2(Ad)); 1.61—1.75 (m, 6 H, CH_2(Ad)); 1.99 (br.s, 3 H, CH(Ad)); 3.27 (d, 2 H, CH_2N, ^3J = 6.1 Hz); 4.98 (br.s, 1 H, NH); 7.33 (ddd, 1 H, H(Quin), ^3J = 8.3 Hz, ^3J = 7.0 Hz, ^4J = 1.3 Hz); 7.53 (ddd, 1 H, H(Quin), ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.5 Hz); 7.65 (dd, 1 H, H(Quin), ^3J = 8.3 Hz, ^4J = 1.3 Hz); 7.83 (dd, 1 H, H(Quin), ^3J = 8.1 Hz, ^4J = 1.5 Hz); 8.21 (s, 1 H, H3(Quin)). ^{13}C NMR ($CDCl_3$), δ: 28.2 (3 CH(Ad)), 33.9 (C(Ad)), 36.9 (3 CH_2(Ad)), 40.4 (3 CH_2(Ad)), 52.6 (CH_2N), 124.0 (CH(Quin)), 126.1 (CH(Quin)), 128.7 (CH(Quin)), 129.9 (CH(Quin)), 137.1 (C(Quin)), 138.3 (CH(Quin)), 141.8 (C(Quin)), 152.5 (C2(Quin)). MS (MALDI), *m/z*: 294.1928 $[M + H]^+$. $C_{19}H_{24}N_3$. Calculated: 294.1970.

***N*-[2-(1-Adamantyl)ethyl]-6-chloropyrazin-2-amine (23)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **2** (90 mg, 0.5 mmol). The yield was 96 mg (66%). ^{1}H NMR ($CDCl_3$), δ: 1.33—1.37 (m, 2 H, $NCCH_2$Ad); 1.50—1.53 (m, 6 H, CH_2(Ad)); 1.53—1.72 (m, 6 H, CH_2(Ad)); 1.93 (br.s, 3 H, CH(Ad)); 3.26—3.31 (m, 2 H, CH_2N); 4.83 (br.s, 1 H, NH); 7.69 (s, 1 H, H(Pyr)); 7.72 (s, 1 H, H(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 28.5 (3 CH(Ad)), 31.9 (C(Ad)), 36.6 ($AdCH_2$), 36.9 (3 CH_2(Ad)), 42.4 (3 CH_2(Ad)), 43.5 (CH_2N), 128.6 (CH(Pyr)), 130.2 (CH(Pyr)), 146.9 (C6(Pyr)), 154.1 (C2(Pyr)). MS (MALDI), *m/z*: 292.1633 $[M + H]^+$. $C_{16}H_{23}ClN_3$. Calculated: 292.1581.

***N*-[2-(2-Adamantyl)ethyl]-6-chloropyrazin-2-amine (24)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **3** (90 mg, 0.5 mmol). The yield was 102 mg (70%). ^{1}H NMR ($CDCl_3$), δ: 1.53 (d, 2 H, H(Ad), ^3J = 12.1 Hz); 1.68—1.76 (m, 9 H, H(Ad), CH_2Ad); 1.77—1.89 (m, 6 H, H(Ad)); 3.19—3.24 (m, 2 H, CH_2N); 4.77 (br.s, 1 H, NH); 7.73 (s, 1 H, H3(Pyr)); 7.76 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 27.9 (CH(Ad)), 28.1 (CH(Ad)), 31.6 (2 C), 31.8 (2 C), 32.2 (1 C), 38.2 (1 C), 39.0 (2 C), 40.2 (1 C), 41.8 (1 C), 128.6 (C3(Pyr)), 130.5 (C5(Pyr)), 147.0 (C6(Pyr)), 154.0 (C2(Pyr)). MS (MALDI), *m/z*: 292.1613 $[M + H]^+$. $C_{16}H_{23}ClN_3$. Calculated: 292.1581.

***N*-(2-Adamantylmethyl)-6-chloropyrazin-2-amine (25)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **5** (83 mg, 0.5 mmol). The yield was 111 mg (80%). ^{1}H NMR ($CDCl_3$), δ: 1.57 (d, 2 H, H(Ad), ^3J = 12.4 Hz); 1.68—1.75 (m, 4 H, H(Ad)); 1.80—1.94 (m, 9 H, H(Ad)); 3.44 (dd, 2 H, CH_2N, ^3J = 7.5 Hz, ^3J = 5.8 Hz); 4.77 (br.s, 1 H, NH); 7.73 (s, 1 H, H3(Pyr)); 7.74 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 27.8 (CH(Ad)), 28.1 (CH(Ad)), 30.2 (2 C), 31.7 (2 C), 38.0 (1 C), 38.8 (2 C), 44.1 (1 C), 44.4 (1 C), 128.7 (C3(Pyr)), 130.3 (C5(Pyr)), 147.0 (C6(Pyr)), 154.4 (C2(Pyr)). MS (MALDI), *m/z*: 278.1450 $[M + H]^+$. $C_{15}H_{21}ClN_3$. Calculated: 278.1424.

***N*-[2-(1-Adamantyl)-1-methylethyl]-6-chloropyrazin-2-amine (26)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **6** (97 mg, 0.5 mmol). The yield was 92 mg (60%). ^{1}H NMR ($CDCl_3$), δ: 1.18 (d, 3 H, CH_3, ^3J = 6.3 Hz); 1.43—1.53 (m, 8 H, CH_2(Ad), $AdCH_2$); 1.55—1.70 (m, 6 H, CH_2(Ad)); 1.91 (br.s, 3 H, CH(Ad)); 3.94—4.04 (m, 1 H, CHN); 4.53 (d, 1 H, NH, ^3J = 7.7 Hz); 7.67 (s, 1 H, H3(Pyr)); 7.72 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 23.2 (CH_3), 28.6 (3 CH(Ad)), 32.5 (C(Ad)), 36.9 (3 CH_2(Ad)), 42.9 (3 CH_2(Ad)), 43.0 ($AdCH_2$), 52.5 (CHN), 128.6 (C3(Pyr)), 130.1 (C5(Pyr)), 147.1 (C6(Pyr)), 153.1 (C2(Pyr)). MS (MALDI), *m/z*: 306.1689 $[M + H]^+$. $C_{17}H_{25}ClN_3$. Calculated 306.1737.

***N*-[2-(2-Adamantyl)propyl]-6-chloropyrazin-2-amine (27)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **7** (97 mg, 0.5 mmol). The yield was 122 mg (80%). ^{1}H NMR ($CDCl_3$), δ: 0.94 (d, 3 H, CH_3, ^3J = 6.7 Hz); 1.35 (d, 1 H, H(Ad), ^3J = 10.8 Hz); 1.48—1.58 (m, 2 H, H(Ad)); 1.63—1.92 (m, 11 H, H(Ad)); 1.95 (br.s, 1 H, H(Ad)); 2.05 (ddqd, 1 H, AdCH, ^3J = 10.8 Hz, ^3J = 7.8 Hz, ^3J = 6.7 Hz, ^3J = 3.3 Hz); 3.03 (ddd, 1 H, CH_2N, ^2J = 13.0 Hz, ^3J = 7.8 Hz, ^3J = 5.8 Hz); 3.47 (ddd, 1 H, CH_2N, ^2J = 13.0 Hz, ^3J = 5.8 Hz, ^3J = 3.3 Hz); 4.88 (br.s, 1 H, NH); 7.73 (s, 2 H, H3(Pyr), H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 15.9 (CH_3), 27.6 (CH(Ad)), 27.8 (CH(Ad)), 29.0

(CH(Ad)), 29.3 (CH(Ad)), 32.1 (1 C), 32.2 (1 C), 38.1 (1 C), 39.0 (1 C), 39.2 (1 C), 45.6 (1 C), 47.1 (1 C), 128.5 (C3(Pyr)), 130.3 (C5(Pyr)), 146.9 (C6(Pyr)), 154.5 (C2(Pyr)). MS (MALDI), *m/z*: 306.1780 $[M + H]^+$. $C_{17}H_{25}ClN_3$. Calculated: 306.1737.

***N*-[1-(1-Adamantyl)ethyl]-6-chloropyrazin-2-amine (28)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **8** (90 mg, 0.5 mmol). The yield was 103 mg (71%). ^{1}H NMR ($CDCl_3$), δ: 1.05 (d, 3 H, CH_3, ^3J = 6.8 Hz); 1.45—1.68 (m, 12 H, CH_2(Ad)); 1.94 (br.s, 3 H, CH(Ad)); 3.56 (dq, 1 H, CHN, ^3J = 9.9 Hz, ^3J = 6.7 Hz); 4.85 (d, 1 H, NH, ^3J = 9.9 Hz); 7.64 (s, 1 H, H3(Pyr)); 7.70 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 14.3 (CH_3), 28.2 (3 CH(Ad)), 31.3 (C(Ad)), 36.9 (3 CH_2(Ad)), 38.3 (3 CH_2(Ad)), 55.1 (CHN), 128.9 (C3(Pyr)), 129.5 (C5(Pyr)), 146.7 (C6(Pyr)), 154.4 (C2(Pyr)). MS (MALDI), *m/z*: 292.14 $[M + H]^+$. $C_{16}H_{23}ClN_3$. Calculated: 292.16.

***N*-[1-Adamantyl(phenyl)methyl]-6-chloropyrazin-2-amine (29)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **9** (362 mg, 1.5 mmol). The yield was 123 mg (70%). ^{1}H NMR ($CDCl_3$), δ: 1.41—1.55 (m, 6 H, CH_2(Ad)); 1.60—1.67 (m, 6 H, CH_2(Ad)); 1.94 (br.s, 3 H, CH(Ad)); 4.20 (d, 1 H, CHN, ^3J = 6.8 Hz); 5.65 (d, NH, ^3J = 6.8 Hz); 7.15—7.27 (m, 5 H, H(Ph)); 7.53 (s, 1 H, H3(Pyr)); 7.68 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 28.1 (3 CH(Ad)), 36.6 (3 CH_2(Ad)), 37.1 (C(Ad)), 38.7 (3 CH_2(Ad)), 65.7 (CHN), 127.2 (CH(Ph)), 127.7 (2 CH(Ph)), 127.9 (C3(Pyr)), 128.3 (2 CH(Ph)), 130.7 (C5(Pyr)), 140.5 (C(Ph)), 146.4 (C6(Pyr)), 153.6 (C2(Pyr)). MS (MALDI), *m/z*: 354.1691 $[M + H]^+$. $C_{21}H_{25}ClN_3$. Calculated 354.1737.

6-Chloro-*N*-[(2-propyl-2-adamantyl)methyl]pyrazin-2-amine (30) was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **10** (104 mg, 0.5 mmol). The yield was 104 mg (65%). ^{1}H NMR ($CDCl_3$), δ: 0.84 (t, 3 H, CH_3, ^3J = 7.2 Hz); 1.19 (sext, 2 H, $C\underline{H}_2CH_3$, ^3J = 7.7 Hz); 1.46—1.89 (m, 12 H, CH_2(Ad), AdCH_2); 1.99—2.07 (m, 4 H, CH(Ad)); 3.50 (d, 2 H, CH_2N, ^3J = 5.7 Hz); 4.70 (t, 1 H, NH, ^3J = 5.1 Hz); 7.70 (s, 1 H, H3(Pyr)); 7.73 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 14.9 (1 C), 15.4 (1 C), 27.8 (2 C), 32.3 (2 C), 32.5 (2 C), 32.8 (2 C), 34.7 (1 C), 39.4 (1 C), 43.4 (1 C), 128.7 (C3(Pyr)), 130.0 (C5(Pyr)), 146.8 (1 C, C6(Pyr)), 154.7 (C2(Pyr)) (one quaternary carbon atom was not determined). MS (MALDI), *m/z*: 320.1934 $[M + H]^+$. $C_{18}H_{27}ClN_3$. Calculated: 320.1894.

***N*-1-Adamantyl-*N*´-(6-chloropyrazin-2-yl)propane-1,3-diamine (31)** was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **11** (104 mg, 0.5 mmol). The yield was 131 mg (82%). ^{1}H NMR ($CDCl_3$), δ: 1.47—1.60 (m, 12 H, CH_2(Ad)); 1.65 (quint, 2 H, $NCCH_2CN$, ^3J = 6.2 Hz); 1.96 (br.s, 3 H, CH(Ad)); 2.66 (t, 2 H, CH_2NAd, ^3J = 6.2 Hz); 3.33 (br.t, 2 H, CH_2NPyr, $^3J_{obs}$ = 5.8 Hz); 6.91 (br.s, 1 H, NH); 7.58 (s, 1 H, H3(Pyr)); 7.63 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 29.1 ($NC\underline{C}H_2CN$), 29.3 (3 CH(Ad)), 36.3 (CH_2NAd), 36.4 (3 CH_2(Ad)), 42.5 (3 CH_2(Ad)), 50.5 (CH_2NPyr), 129.0 (CH(Pyr)), 129.8 (CH(Pyr)), 146.8 (C6(Pyr)), 154.3 (C2(Pyr)). MS (MALDI), *m/z*: 321.1817 $[M + H]^+$. $C_{17}H_{26}ClN_4$. Calculated: 321.1846.

2-[4-(1-Adamantyl)pyperazin-1-yl]-6-chloropyrazine (32) was synthesized from 2,6-dichloropyrazine (75 mg, 0.5 mmol) and amine **12** (110 mg, 0.5 mmol). The yield was 143 mg (86%). ^{1}H NMR ($CDCl_3$), δ: 1.38 (d, 2 H, H(Ad), ^3J = 12.1 Hz); 1.62 (d, 2 H, H(Ad), ^3J = 11.1 Hz); 1.67 (br.s, 2 H, H(Ad)); 1.73—1.85 (m, 4 H, H(Ad)); 2.00—2.06 (m, 5 H, H(Ad)); 2.46—2.50 (m, 4 H, AdNCH_2); 3.52—3.57 (m, 4 H, CH_2NPyr); 7.72 (s, 1 H, H3(Pyr)); 7.91 (s, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 27.2 (1 CH(Ad)), 27.4 (1 CH(Ad)), 28.9 (2 CH(Ad)), 31.2 (2 CH_2(Ad)), 37.1 (2 CH_2(Ad)), 37.6 (1 CH_2(Ad)), 44.7 (2 AdNCH_2), 48.9 (2 CH_2NPyr), 67.2 (NCH(Ad)), 127.6 (C3(Pyr)), 130.2 (C5(Pyr)), 146.5 (C6(Pyr)), 154.1 (C2(Pyr)). MS (MALDI), *m/z*: 333.1892 $[M + H]^+$. $C_{18}H_{26}ClN_4$. Calculated: 333.1846.

1,3-Bis[(6-chloropyrazin-2-ylamino)methyl]adamantane (33) was synthesized from 2,6-dichloropyrazine (186 mg, 1.25 mmol) and diamine **13** (97 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (100 : 1). The yield was 52 mg (25%). A light beige crystalline compound, m.p. 185—186 °C. ^{1}H NMR ($CDCl_3$), δ: 1.35 (s, 2 H, H(Ad)); 1.43—1.56 (m, 8 H, H(Ad)); 1.62 (s, 2 H, H(Ad)); 2.12 (s, 2 H, CH_2(Ad)); 3.11 (d, 4 H, CH_2N, ^3J = 4.9 Hz); 4.89 (br.s, 2 H, NH); 7.74 (s, 2 H, H3(Pyr)); 7.78 (s, 2 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 28.2 (2 CH(Ad)), 34.8 (2 C(Ad)), 36.1 (CH_2(Ad)), 39.7 (4 CH_2(Ad)), 42.9 (CH_2(Ad)), 52.7 (2 CH_2N), 128.6 (2 C3(Pyr)), 130.2 (2 C5(Pyr)), 146.9 (2 C6(Pyr)), 154.7 (2 C2(Pyr)). MS (MALDI), *m/z*: 419.1635 $[M + H]^+$, 439.1224 $[M - H_2 + Na]^+$. $C_{20}H_{25}Cl_2N_6$. Calculated: 419.1518. $C_{20}H_{22}Cl_2N_6Na$. Calculated: 439.1181.

1,3-Bis[2-(6-chloropyrazin-2-ylamino)ethyl]adamantane (34) was synthesized from 2,6-dichloropyrazine (186 mg, 1.25 mmol) and diamine **14** (111 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (100 : 1). The yield was 50 mg (22%). A light beige crystalline compound, m.p. 158—159 °C. ^{1}H NMR ($CDCl_3$), δ: 1.32 (s, 2 H, H(Ad)); 1.37—1.47 (m, 8 H, H(Ad), AdCH_2); 1.49—1.56 (m, 4 H, H(Ad)); 1.60 (br.s, 2 H, H(Ad)); 2.05 (br.s, 2 H, CH_2(Ad)); 3.28—3.35 (m, 4 H, CH_2N); 4.68 (br.s, 2 H, NH); 7.71 (s, 2 H, H3(Pyr)); 7.75 (s, 2 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 28.7 (2 CH(Ad)), 32.7 (2 C(Ad)), 36.2 (CH_2(Ad)), 36.7 (2 AdCH_2), 41.7 (4 CH_2(Ad), 43.2 (2 CH_2N), 47.4 (CH_2(Ad)), 128.7 (2 C3(Pyr)), 130.5 (2 C5(Pyr)), 147.0 (2 C6(Pyr)), 154.1 (2 C2(Pyr)). MS (MALDI), *m/z*: 447.1888 $[M + H]^+$. $C_{22}H_{29}Cl_2N_6$. Calculated: 447.1831.

***N*-[2-(1-Adamantyloxy)ethyl]-3-chloropyrazin-2-amine (35)** was synthesized from 2,3-dichloropyrazine (75 mg, 0.5 mmol) and amine **1** (98 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (100 : 1). The yield was 86 mg (56%). ^{1}H NMR ($CDCl_3$), δ: 1.53—1.64 (m, 6 H, CH_2(Ad)); 1.70—1.72 (m, 6 H, CH_2(Ad)); 2.12 (br.s, 3 H, CH(Ad)); 3.53—3.61 (m, 4 H, NCH_2CH_2O); 5.63 (br.s, 1 H, NH); 7.52 (d, 1 H, H5(Pyr), ^3J = 2.7 Hz); 7.89 (d, 1 H, H6(Pyr), ^3J = 2.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.4 (3 CH(Ad)), 36.3 (3 CH_2(Ad)), 41.5 (3 CH_2(Ad)), 41.6 (CH_2N), 58.1 (CH_2O), 72.4 (C(Ad)), 130.3 (C5(Pyr)), 134.9 (C3(Pyr)), 140.4 (C6(Pyr)), 151.1 (C2(Pyr)). MS (MALDI), *m/z*: 308.1491 $[M + H]^+$. $C_{16}H_{23}ClN_3O$. Calculated: 308.1530.

***N*-[2-(1-Adamantyloxy)ethyl]-6-chloropyridazin-3-amine (36)** was synthesized from 3,6-dichloropyridazine (75 mg, 0.5 mmol) and amine **1** (98 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (100 : 1). The yield was 114 mg (74%). A colorless crystalline compound, m.p. 201—202 °C (as hydrochloride). ^{1}H NMR ($CDCl_3$), δ: 1.53—1.64 (m, 6 H, CH_2(Ad)); 1.68—1.70 (m, 6 H, CH_2(Ad)); 2.12 (br.s, 3 H, CH(Ad)); 3.54 (q, 2 H, CH_2N, ^3J = 5.0 Hz); 3.62 (t, 2 H, CH_2O, ^3J = 5.0 Hz); 5.47 (br.s, 1 H, NH); 6.75 (d, 1 H, H4(Pyr), ^3J = 9.4 Hz); 7.13 (d, 1 H, H5(Pyr), ^3J = 9.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.4 (3 CH(Ad)), 36.3 (3 CH_2(Ad)), 41.5 (3 CH_2(Ad)), 42.5 (CH_2N), 58.3 (CH_2O), 72.6 (C(Ad)), 117.2 (C4(Pyr)), 129.0 (C5(Pyr)), 146.5 (C6(Pyr)), 158.2 (C3(Pyr)). MS (MALDI), *m/z*: 308.1476 $[M + H]^+$. $C_{16}H_{23}ClN_3O$. Calculated: 308.1530.

***N*-[2-(1-Adamantyl)ethyl]-6-chloropyridazin-3-amine (37)** was synthesized from 3,6-dichloropyridazine (75 mg, 0.5 mmol) and amine **2** (90 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH

(200 : 1 → 100 : 1). The yield was 45 mg (31%). A light beige crystalline compound, m.p. 229—230 °C. ^{1}H NMR ($CDCl_3$), δ: 1.18—1.24 (m, 2 H, $AdCH_2$); 1.34—1.36 (m, 6 H, CH_2(Ad)); 1.41—1.54 (m, 6 H, CH_2(Ad)); 1.75 (br.s, 3 H, CH(Ad)); 3.11—3.17 (m, 2 H, CH_2N); 4.14 (br.s, 1 H, NH); 6.62 (d, 1 H, H4(Pyr), ^3J = 9.4 Hz); 6.98 (d, 1 H, H5(Pyr)). ^{13}C NMR ($CDCl_3$), δ: 28.3 (3 CH(Ad)), 31.5 (C(Ad)), 36.4 ($AdCH_2$), 36.6 (3 CH_2(Ad)), 42.0 (3 CH_2(Ad)), 42.8 (CH_2N), 118.0 (C4(Pyr)), 129.0 (C5(Pyr)), 145.2 (C6(Pyr)), 157.9 (C3(Pyr)). MS (MALDI), *m/z*: 292.1633 $[M + H]^+$. $C_{16}H_{23}ClN_3$. Calculated: 292.1581.

***N*-[2-(2-Adamantyl)ethyl]-6-chloropyridazin-3-amine (38)** was synthesized from 3,6-dichloropyridazine (75 mg, 0.5 mmol) and amine **3** (90 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (200 : 1). The yield was 19 mg (13%). ^{1}H NMR ($CDCl_3$), δ: 1.52 (d, 2 H, H(Ad), ^3J = 12.1 Hz); 1.66—1.90 (m, 15 H, H(Ad), $AdCH_2$); 3.33 (t, 2 H, CH_2N, ^3J = 7.3 Hz); 7.10 (d, 1 H, H4(Pyr), ^3J = 9.4 Hz); 7.31 (d, 1 H, H5(Pyr), ^3J = 9.4 Hz) (the NH proton was not unambiguously determined). MS (MALDI), *m/z*: 292.3 $[M + H]^+$. $C_{16}H_{23}ClN_3$. Calculated: 292.1581.

***N*-(1-Adamantylmethyl)-6-chloropyridazin-3-amine (39)** was synthesized from 3,6-dichloropyridazine (75 mg, 0.5 mmol) and amine **4** (83 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (200 : 1 → 100 : 1). The yield was 80 mg (58%). ^{1}H NMR ($CDCl_3$), δ: 1.54—1.56 (m, 6 H, CH_2(Ad)); 1.59—1.74 (m, 6 H, CH_2(Ad)); 1.98 (br.s, 3 H, CH(Ad)); 3.05 (d, 2 H, CH_2N, ^3J = 6.2 Hz); 5.38 (br.s, 1 H, NH); 6.75 (d, 1 H, H4(Pyr), ^3J = 9.4 Hz); 7.16 (d, 1 H, H5(Pyr), ^3J = 9.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.1 (3 CH(Ad)), 34.2 (C(Ad)), 36.8 (3 CH_2(Ad)), 40.3 (3 CH_2(Ad)), 53.9 (CH_2N), 116.0 (C4(Pyr)), 129.1 (C5(Pyr)), 145.9 (C6(Pyr)), 159.1 (C3(Pyr)). MS (MALDI), *m/z*: 278.12 $[M + H]^+$. $C_{15}H_{21}ClN_3$. Calculated: 278.14.

***N*-[2-(1-Adamantyl)-1-methylethyl]-6-chloropyridazin-3-amine (40)** was synthesized from 3,6-dichloropyridazine (75 mg, 0.5 mmol) and amine **6** (97 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (200 : 1). The yield was 70 mg (46%). ^{1}H NMR ($CDCl_3$), δ: 1.18 (d, 3 H, CH_3, ^3J = 6.3 Hz); 1.28 (dd, 1 H, $AdCH_2$, ^2J = 14.6 Hz, ^3J = 3.9 Hz); 1.33 (dd, 1 H, $AdCH_2$, ^2J = 14.6 Hz, ^3J = 7.6 Hz); 1.49—1.51 (m, 6 H, CH_2(Ad)); 1.52—1.67 (m, 6 H, CH_2(Ad)); 1.89 (br.s, 3 H, CH(Ad)); 4.10 (ddqd, 1 H, CHN, ^3J = 8.1 Hz, ^3J = 7.6 Hz, ^3J = 6.3 Hz, ^3J =3.9 Hz); 4.73 (d, 1 H, NH, ^3J = 8.1 Hz); 6.62 (d, 1 H, H4(Pyr), ^3J = 9.3 Hz); 7.10 (d, 1 H, H5(Pyr), ^3J = 9.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 23.1 (CH_3), 28.5 (3 CH(Ad)), 32.5 (C(Ad)), 36.9 (3 CH_2(Ad)), 42.8 (3 CH_2(Ad)), 43.2 ($AdCH_2$), 52.4 (CHN), 116.3 (C4(Pyr)), 128.8 (C5(Pyr)), 145.9 (C6(Pyr)), 157.3 (C6(Pyr)). MS (MALDI), *m/z*: 306.1762 $[M + H]^+$. $C_{17}H_{25}ClN_3$. Calculated: 306.1737.

***N*-[2-(2-Adamantyl)propyl]-6-chloropyridazin-3-amine (41)** was synthesized from 3,6-dichloropyridazine (75 mg, 0.5 mmol) and amine **7** (97 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (200 : 1 → 400 : 3). The yield was 119 mg (78%). ^{1}H NMR ($CDCl_3$), δ: 0.96 (d, 3 H, CH_3, ^3J = 6.7 Hz); 1.38 (d, 1 H, CH(Ad), ^3J = 10.6 Hz); 1.48—1.57 (m, 2 H, H(Ad)); 1.62—1.73 (m, 4 H, H(Ad)); 1.73—1.95 (m, 8 H, H(Ad)); 2.08 (ddqd, 1 H, AdCH, ^3J = 10.6 Hz, ^3J = 8.0 Hz, ^3J =6.7 Hz, ^3J = 3.4 Hz); 3.06 (ddd, 1 H, CH_2N, ^2J = 13.0 Hz, ^3J = 8.0 Hz, ^3J = 5.8 Hz); 3.51 (ddd, 1 H, CH_2N, ^2J = 13.0 Hz, ^3J = 5.6 Hz, ^3J = 3.4 Hz); 5.06 (br.s, 1 H, NH); 6.67 (d, H4(Pyr), ^3J = 9.4 Hz); 7.14 (d, 1 H, H5(Pyr), ^3J = 9.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 16.0 (CH_3), 27.6 (CH(Ad)), 27.8 (CH(Ad)), 29.0 (CH(Ad)), 29.3 (CH(Ad)), 31.6 (1 CH_2), 32.1 (1 CH_2), 32.2 (1 CH_2), 38.1 (1 CH_2), 39.0 (1 CH_2), 39.2 (1 CH_2), 46.2 (1 CH_2), 47.3 (1 CH_2), 115.7 (C4(Pyr)), 129.0 (C5(Pyr)), 146.2 (C6(Pyr)), 158.8 (C3(Pyr)). MS (MALDI), *m/z*: 306.1688 $[M + H]^+$. $C_{17}H_{25}ClN_3$. Calculated: 306.1737.

3-[4-(2-Adamantyl)pyperazin-1-yl]-6-chloropyridazine (42) was synthesized from 3,6-dichloropyridazine (75 mg, 0.5 mmol) and amine **12** (110 mg, 0.5 mmol). Eluent CH_2Cl_2—MeOH (100 : 1). The yield was 138 mg (83%). A colorless crystalline compound, m.p. >230 °C (decomp., as hydrochloride). ^{1}H NMR ($CDCl_3$), δ: 1.39 (d, 2 H, H(Ad), ^3J = 11.6 Hz); 1.64 (d, 2 H, H(Ad), ^3J = 11.9 Hz); 1.68 (br.s, 2 H, H(Ad)); 1.74—1.88 (m, 4 H, H(Ad)); 2.03—2.09 (m, 5 H, H(Ad)); 2.50—2.54 (m, 4 H, CH_2NAd); 3.56—3.61 (m, 4 H, CH_2NPyr); 6.89 (d, 1 H, H4(Pyr), ^3J = 9.6 Hz); 7.16 (d, 1 H, H5(Pyr), ^3J = 9.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 27.2 (CH(Ad)), 27.4 (CH(Ad)), 28.9 (2 CH(Ad)), 31.3 (2 CH_2(Ad)), 37.1 (2 CH_2(Ad)), 37.6 (CH_2(Ad)), 45.4 (2 $AdNCH_2$), 49.0 (2 CH_2N(Pyr)), 67.3 (CHN), 115.1 (C4(Pyr)), 128.5 (C5(Pyr)), 146.4 (C6(Pyr)), 159.0 (C3(Pyr)). MS (MALDI), *m/z*: 333.1817 $[M + H]^+$. $C_{18}H_{26}ClN_4$. Calculated: 333.1846.

***N*-[2-(1-Adamantyloxy)ethyl]isoquinolin-1-amine (43)** was synthesized from 1-chloroisoquinoline (33 mg, 0.2 mmol) and amine **1** (39 mg, 0.2 mmol). Eluent CH_2Cl_2—MeOH (50 : 1). The yield was 7 mg (11%). ^{1}H NMR ($CDCl_3$), δ: 1.55—1.67 (m, 6 H, CH_2(Ad)); 1.69—1.71 (m, 6 H, CH_2(Ad)); 2.14 (br.s, 3 H, CH(Ad)); 3.37 (q, 2 H, CH_2N, ^3J = 5.2 Hz); 3.48 (t, 2 H, CH_2O, ^3J = 5.0 Hz); 5.91 (br.s, 1 H, NH); 6.54 (d, 1 H, H4(Quin), ^3J = 7.2 Hz); 7.12 (br.d, 1 H, H5(Quin), $^3J_{obs}$ = 6.6 Hz); 7.47—7.52 (m, 1 H, H7(Quin)); 7.64—7.68 (m, 1 H, H6(Quin)); 7.95 (br.d, 1 H, H3(Quin), $^3J_{obs}$ = 6.1 Hz); 8.40 (ddd, 1 H, H8(Quin), ^3J = 8.1 Hz, ^4J = 1.3 Hz, ^5J = 0.6 Hz). MS (MALDI), *m/z*: 323.2149 $[M + H]^+$. $C_{21}H_{27}N_2O$. Calculated: 323.2123.

***N*-[2-(1-Adamantyloxy)ethyl]-3-chloroisoquinolin-1-amine (44)** was synthesized from 1,3-dichloroisoquinoline (99 mg, 0.5 mmol) and amine **1** (98 mg, 0.5 mmol). Eluent CH_2Cl_2. The yield was 159 mg (89%). A pale yellow crystalline compound, m.p. 149—150 °C. ^{1}H NMR ($CDCl_3$), δ: 1.57—1.68 (m, 6 H, CH_2(Ad)); 1.76—1.78 (m, 6 H, CH_2(Ad)); 2.15 (br.s, 3 H, CH(Ad)); 3.65—3.71 (m, 2 H, CH_2O); 3.73—3.78 (m, 2 H, CH_2N); 5.94 (br.s, 1 H, NH); 6.90 (s, 1 H, H4(Quin)); 7.39—7.44 (m, 1 H, H(Quin)); 7.53—7.57 (m, 2 H, H(Quin)); 7.69 (br.d, 1 H, H(Quin), $^3J_{obs}$ = 7.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 30.5 (3 CH(Ad)), 36.4 (3 CH_2(Ad)), 41.7 (3 CH_2(Ad)), 42.0 (CH_2N), 58.5 (CH_2O), 72.5 (C(Ad)), 108.1 (CH(Quin)), 116.6 (C(Quin)), 121.6 (CH(Quin)), 125.7 (CH(Quin)), 126.3 (CH(Quin)), 130.3 (CH(Quin)), 138.8 (C(Quin)), 144.5 (C(Quin)), 155.3 (C1(Quin)). MS (MALDI), *m/z*: 357.1692 $[M + H]^+$. $C_{21}H_{26}ClN_2O$. Calculated: 357.1734.

***N*-[2-(1-Adamantyl)ethyl]-3-chloroisoquinolin-1-amine (45)** was synthesized from 1,3-dichloroisoquinoline (99 mg, 0.5 mmol) and amine **2** (90 mg, 0.5 mmol). The yield was 127 mg (75%). ^{1}H NMR ($CDCl_3$), δ: 1.39—1.45 (m, 2 H, $AdCH_2$); 1.52—1.54 (m, 6 H, CH_2(Ad)); 1.57—1.71 (m, 6 H, CH_2(Ad)); 1.92 (br.s, 3 H, CH(Ad)); 3.51—3.57 (m, 2 H, CH_2N); 5.29 (t, 1 H, NH, ^3J = 4.2 Hz); 6.86 (s, 1 H, H4(Quin)); 7.32—7.36 (m, 1 H, H(Quin)); 7.49—7.52 (m, 2 H, H(Quin)); 7.67 (d, 1 H, H(Quin), ^3J = 8.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.5 (3 CH(Ad)), 32.0 (C(Ad)), 36.8 ($AdCH_2$), 36.9 (3 CH_2(Ad)), 42.4 (3 CH_2(Ad)), 43.7 (CH_2N), 107.8 (C4(Quin)), 116.4 (C(Quin)), 121.5 (CHQuin)), 125.5 (CH(Quin)), 126.2 (CH(Quin)), 130.1 (CH(Quin)), 138.6 (C(Quin)), 144.6 (C(Quin)), 155.2 (C1(Quin)). MS (MALDI), *m/z*: 341.1812 $[M + H]^+$. $C_{21}H_{26}ClN_2$. Calculated: 341.1785.

***N*-(1-Adamantylmethyl)-3-chloroisoquinolin-1-amine (46)** was synthesized from 1,3-dichloroisoquinoline (99 mg, 0.5 mmol) and amine **4** (83 mg, 0.5 mmol). The yield was 146 mg (90%). ^{1}H NMR ($CDCl_3$), δ: 1.58—1.60 (m, 6 H, CH_2(Ad)); 1.61—1.73 (m, 6 H, CH_2(Ad)); 1.97 (br.s, 3 H, CH(Ad)); 3.34 (d, 2 H, CH_2N, ^3J = 5.8 Hz); 5.47 (t, 1 H, NH, ^3J = 5.8 Hz); 6.85 (s, 1 H, H4(Quin)); 7.36—7.40 (m, 1 H, H(Quin)); 7.51—7.53 (m, 2 H, H(Quin)); 7.69 (d, 1 H, H(Quin), ^3J = 8.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 28.2 (3 CH(Ad)), 33.8 (C(Ad)), 36.9 (3 CH_2(Ad)), 40.4 (3 CH_2(Ad)), 52.8 (CH_2N), 107.7 (C4(Quin)), 116.3 (C(Quin)), 121.2 (CH(Quin)), 125.5 (CH(Quin)), 126.3 (CH(Quin)), 130.2 (CH(Quin)), 138.7 (C(Quin)), 144.5 (C(Quin)), 155.6 (C1(Quin)). MS (MALDI), *m/z*: 327.1643 $[M + H]^+$. $C_{20}H_{24}ClN_2$. Calculated: 327.1628.

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