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Hetarynic synthesis and chemical transformation of dihydrodipyridopyrazines

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Abstract—Unprecedented dihydrodipyridopyrazines were easily obtained by hetarynic dimerization of 2-alkylamino-3-halogenopyridines in the presence of the complex base $NaNH_2$–*t*BuONa. Derivatizations of the new heterocycles are described. The anticancer activity of these compounds is also mentioned.

1. Introduction

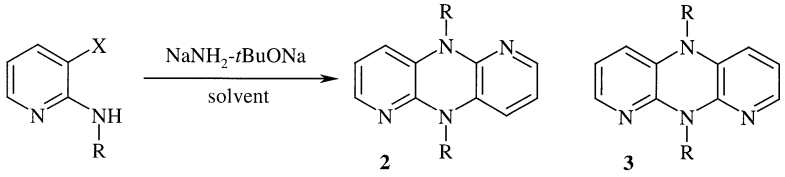
The active current researches for new antitumor agents are due to the unfortunately limited capacity of existing drugs to cure cancers. The huge amount of information gathered during the last 20 years on the mechanism of tumor formation and development led to the identification of several targets to be reached by anticancer drugs.[1] The diversity of these targets explains the structural variety of substrates with antitumor properties. Among them, planar polynuclear nitrogen containing aromatic heterocycles form an important anticancer family.[1a,b,k–v,2]

We have been involved for many years in programs dealing with complex base (CB) initiated arynic reactions[3] and their application in medicinal chemistry.[4] Studying hetarynic reactions, we recently showed that amino pyridines could be obtained by allowing amines to react with dehydropyridines generated from appropriate halogenopyridines and the CB $NaNH_2$–*t*BuONa.[5] We surmised that under analogous conditions, head to tail intermolecular cyclization of 2-amino-3-halogeno pyridines **1** ought to lead to dihydrodipyridopyrazines (DHDPP) for which antitumor activity could be expected. In the present paper, we report the results obtained in this area. A few preliminary experiments have been reported elsewhere.[6]

2. Cyclization of 2-*N*-alkylamino-3-bromopyridines

Exploratory experiments performed with 2-*N*-methylamino-3-bromopyridine **1** (X=Br) unexpectedly led to the formation, in equal amount, of two products possessing the same molecular mass (M=212) as it resulted from a GC/MS analysis.

One of the isomers easily led to single crystals which X-ray diffraction data corresponded to the planar structure **2a** (Scheme 1, R=Me). NMR spectra confirmed this formula. Only single crystals of very poor quality were obtained with the second isomer. X-Ray diffraction analysis also confirmed a planar structure, however, the relative position



Scheme 1.

Keywords: dihydrodipyridopyrazines; formylation; nitration.

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Table 1. Cyclization of **1** (X=Br) with $NaNH_2$–*t*BuONa in THF

Run	R	*t* (h)	Product	**2/3**[a]	Global yield (%)
1	Me	144	**2a**, **3a**	50/50	50
2	Et	120	**2b**, **3b**	54/46	56
3	Bu	72	**2c**, **3c**	50/50	74
4	MeCHPh	72	**2d**	100/0	20
5	$(CH_2)_2NMe_2$	96	**2e**, **3e**[b]	99/1	50
6	$(CH_2)_3NMe_2$	168	**2f**, **3f**	52/48	50
7	$(CH_2)_2OTHP$	96	**2g**	100/0	15[c]

[a] Determined by gas chromatography (GC) (capillary HP1, 6 m).
[b] Not isolated, evidenced by GC/MS.
[c] 10% of monodealkoxyethyl product was also isolated (see Section 6 **2h**).

of nitrogen of the pyridine rings was doubtful. A 2D NMR analysis unambiguously attributed the unexpected structure **3a** (Scheme 1, R=Me) to the second isomer. Note that, for both isomers, the planar formula indicates a strong electron delocalization from the nitrogen of the pyrazine ring which implies an appreciable formal positive charge on these atoms. We will discuss further the formation of this unexpected compound.

A systematic study (data not reported) showed that THF was the most appropriate solvent, that the replacement of the CB by $NaNH_2$ alone was highly unfavorable to the progress of the reaction, and that room temperature was more advisable. Finally, since optimal efficiency of CB in arynic reactions is obtained when $NaNH_2$–*t*BuONa is 2/1,[3] 1 equiv. excess of $NaNH_2$ was necessary to furnish sodium amide **7**. In Table 1 are reported the results obtained under the appropriate conditions thus determined.

The low yield obtained in run 4 was due to a large destruction of the starting material certainly resulting from a proton abstraction on the benzylic position. Replacement of the phenethyl group by a benzyl or triphenylmethyl led only to tar products. In the same way, the alkoxyethyl substituted **1** led to a large amount of by-products (run 7). The monodealkoxylation observed (10%) was attributed to a β-elimination.

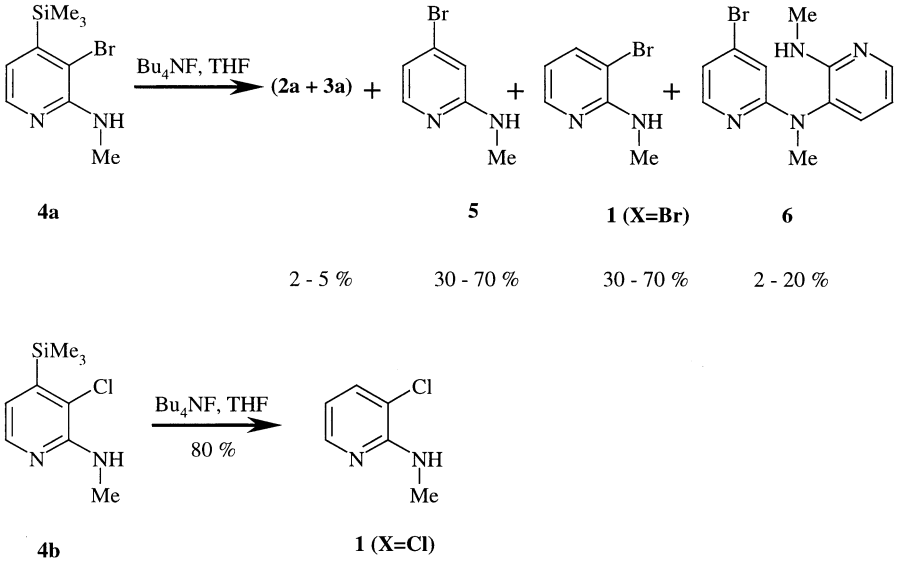
Finally, a few experiments performed with **1** (X=Cl) showed that chloropyridine derivatives may be also used in such reactions. Overall yields were lower (35%) than with bromide but the reaction was very clean and 35% of the starting material was easily recovered. In contrast, iodo derivative **1** (X=I) only led to very low yields due to the large amount formation of tars.

3. Comments about the mechanisms

An arynic mechanism appeared as very likely. Indeed if SN_{Ar} could explain the formation of **2** it cannot justify the formation of **3**. Moreover, the replacement of the complex base by NaH led only to the starting material and in the presence of HMPA, well known as favoring nucleophilic substitution, no cyclization product was observed. In order to obtain some insight into the mechanism, we studied (Scheme 2) the behavior of halogenotrimethylsilyl pyridine derivatives **4a** and **4b** in the presence of fluoride ions. Such generation of arynes is well documented in the literature.[7]

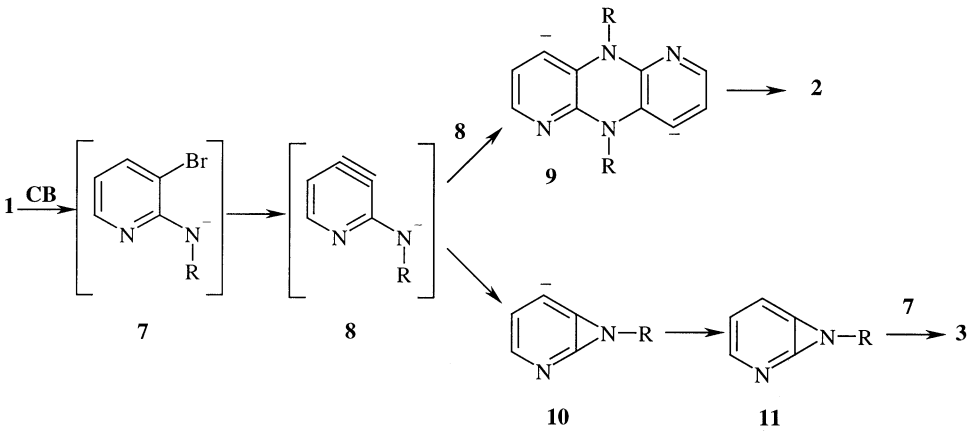
Irrespective of the reaction temperature (−20°C to solvent reflux), the same products were generated from the bromopyridine derivative **4a** and the starting material completely disappeared after 1–3 h. The compounds **2** and **3** were always formed in low but sufficient amounts to be isolated, separated and identified. This result strongly supports the hetarynic mechanism under the conditions of Scheme 1. The formation of **5** and **1** (X=Br) is reminiscent of the halogen dance developed by Bunnett many years ago.[8] Finally, **6** could be due to the reaction of **5** with the hetarynic intermediate. Interestingly, when **6** was submitted to react with the CB $NaNH_2$–*t*BuONa, **2** was formed in 62% yield confirming the structure of this compound and supporting its hetarynic formation. Note that reaction performed with the corresponding chloroderivative **4b** only led to the chloro substrate **1** (X=Cl) in 80% yield. Thus, we tentatively propose the mechanisms A and B reported in Scheme 3.

The possible protonation of anionic intermediates such as **9**

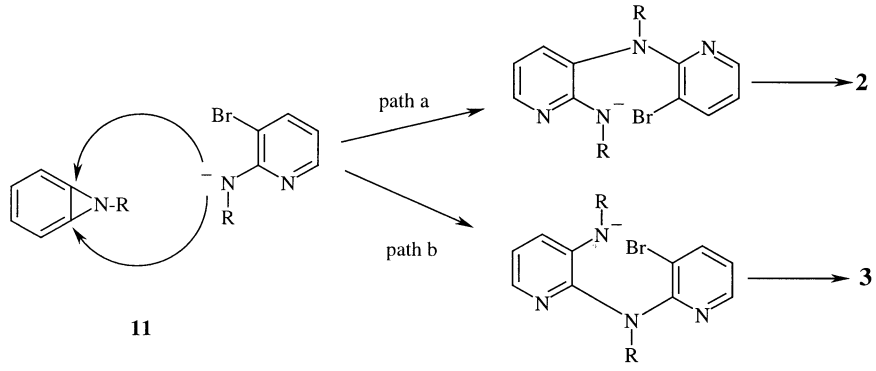


Scheme 2.

Mechanism A



Mechanism B

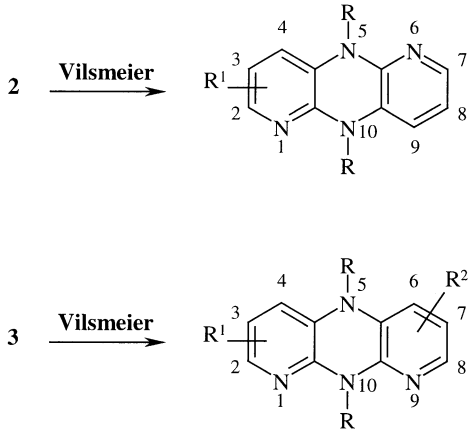


Scheme 3.

or **10** could be due to proton abstraction from the solvent. At present, we are unable to give an explanation for the variations of the **2/3** ratio with the nature of R. Assuming **8→10→11** takes place, both products **2** and **3** could be rationalized as arising from the same intermediate **11** rather than invoking competing mechanisms **8→9** versus **8→10**. This alternative might be offered as a possibility.

4. Chemical reactivity of dihydrodipyridopyrazines

To the best of our knowledge, compounds **3** are unknown and only two DHDPP **2** have been incidentally mentioned in the literature.[9] Therefore, we decided to study the chemical behavior of these substrates keeping in view our medicinal chemistry purpose.



12 R^1 = 2-CHO

13 R^1 = 3-CHO

14 R^1 = 2-CHO, R^2 = H

15 R^1 = 2-CHO, R^2 = 7-CHO

16 R^1 = 2-CHO, R^2 = 8-CHO

Scheme 4.

Table 2. Formylation of **2** and **3**

*Formylation of **2***

Run	Substrate	Solvent	Reaction time (h)	Product						Conv.[a] (%)
				12	R	Yield[b] (%)	**13**	R	Yield[b] (%)	
1	**2a**	DCE[a]	7	**12a**	Me	68	**13a**	Me	25	44
2	**2c**	DCE[a]	18	**12c**	Bu	63	**13c**	Bu	8	95
3	**2f**	CF[c]	14	**12f**	$(CH_2)_3NMe_2$	83[d]	–	–	–	30

*Formylation of **3***

Run	Substrate	Solvent	Reaction time (h)	Product									Conv.[a] (%)
				14	R	Yield[b] (%)	**15**	R	Yield[b] (%)	**16**	R	Yield[b] (%)	
4	**3a**	DCE[a]	18	**14a**	Me	90	–	–	–	–	–	–	89
5	**3c**	DCE[a]	8	**14c**	Bu	70	**15c**	Bu	8	**16c**	Bu	4	100
6	**3f**	CF[c]	14	**14f**	$(CH_2)_3NMe_2$	57[e]	–	–	–	–	–	–	70

$POCl_3$ (10 equiv.)–DMF (23 equiv.) reflux then NaOH 3 M (36 equiv.) reflux 3 h.
[a] This value arises from the following ratio: (initial reacting moles−residual moles)/initial reacting moles.
[b] Based on converted materials.
[c] CF: Chloroform.
[d] Very highly unstable in solution, characterized by GC/MS and IR data.
[e] Unstable characterized only by spectroscopic data.

4.1. Formylation of 2 and 3

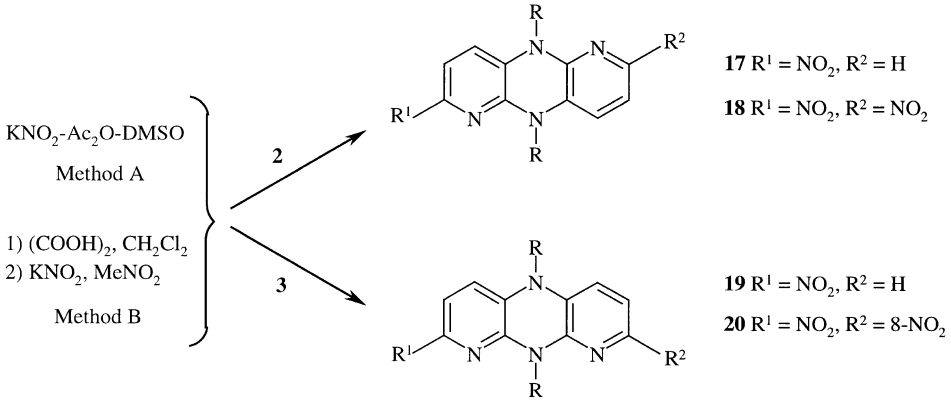
We first examined this electrophilic substitution which may be performed under rather mild conditions and introduce a carboxaldehyde function prone to further transformations. The products which may be formed during this reaction are reported in Scheme 4 and the best results obtained have been gathered in Table 2.

Taking account of the recovered starting material, yields based on converted materials may be considered as good with both series. Irrespective of the starting substrate, selective formylation at the C2 position was observed and substrates **3** were more reactive than **2**. At present, we are unable to rationalize these observations. Finally, it appeared that in a given series the reactivity also depended upon the nature of the substituents R of the pyrazine ring (compare runs 1–3 or 4–6). We attribute this property to a folding of the planar structures due to the nature of the substituents R with, as a consequence, a change in the delocalization of the lone electron pairs of the nitrogens and thus of the π-electron disponibility.

4.2. Nitration of 2 and 3

Nitro group is of interest for further functionalization and in the chemistry of antitumor agents.[1] Our electron rich substrates were very sensitive to usual electrophilic nitration reagents and led only to untractable tars. So, we turned towards nucleophilic nitration using the Ac_2O–DMSO reagent associated to KNO_2[10] (method A). Preliminary experiments showed that nitro compounds could be obtained but some limitations were also observed. So, we reasoned that since the key step of method A was a nucleophilic attack of NO_2^- on a pyridine ring quaternized by a Pummerer's reagent, it ought to be possible to replace this latter by a proton. Exploratory experiments performed using the oxalic salts showed that, as expected, they reacted with KNO_2 in nitromethane to lead to nitro derivatives (method B). The reactions thus performed are summarized in Scheme 5 and the best results obtained gathered in Table 3.

According to the pyridinium nature of the reaction intermediates, the only products obtained were due to the



Scheme 5.

Table 3. Nitration of **2** and **3**

*Nitration of **2***

Run	Substrate	Method[a]	$(HOCO)_2$ (equiv.)	KNO_2 (equiv.)	t (h)	Product						Conv.[b] (%)
						17	R	Yield[c] (%)	**18**	R	Yield[c] (%)	
1	**2a**	A	–	6	2	**17a**	Me	97	–	–	–	100
2	**2a**	B	1	2	2.5	**17a**	Me	60	–	–	–	100
3	**2c**	A	–	6	20	**17c**	Bu	62	**18c**	Bu	15	100
4	**2c**	B	1	2	48	**17c**	Bu	94	–	–	–	55
5	**2e**	B	5	3	6	**17e**	$(CH_2)_2NMe_2$	71	–	–	–	100
6	**2f**	B	5	3	20	**17f**	$(CH_2)_3NMe_2$	67	**18f**	$(CH_2)_3NMe_2$	13	100
7	**2f**	B	5	5	2	**17f**	$(CH_2)_3NMe_2$	97	–	–	–	100

*Nitration of **3***

Run	Substrate	Method[a]	$(HOCO)_2$ (equiv.)	KNO_2 (equiv.)		Product						Conv.[b] (%)
						19	R	Yield[c] (%)	**20**	R	Yield[c] (%)	
8	**3a**	A	–	6	18	**19a**	Me	88	**20a**	Me	8	100
9	**3a**	B	3	3	1.5	**19a**	Me	5	**20a**	Me	72	100
10	**3c**	A	–	6	2.5	–	–	–	**20c**	Bu	90	100
11	**3c**	B	1	2	72	**19c**	Bu	90	–	–	–	100
12	**3f**	B	5	3	20	**19f**	$(CH_2)_3NMe_2$	73	–	–	–	90
13	**3f**	B	5	5	2	**19f**	$(CH_2)_3NMe_2$	71	**20f**	$(CH_2)_3NMe_2$	21	100

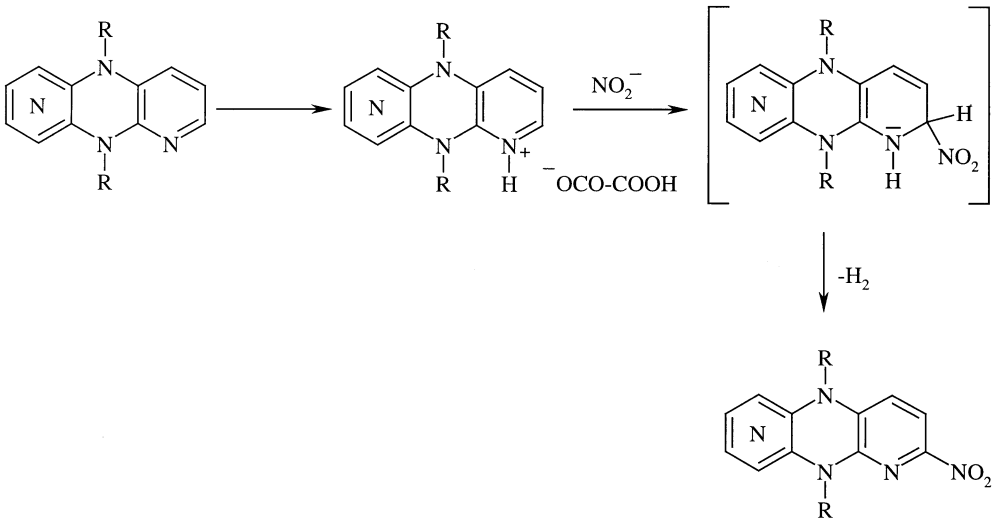
[a] Method A: Ac_2O 6 equiv., DMSO 8 ml for 6 mM of Ac_2O, room temperature; Method B: room temperature, salification in CH_2Cl_2, nitration in CH_3NO_2.
[b] This value arises from the following ratio: (initial reacting moles−residual moles)/initial reacting moles.
[c] Based on converted materials.

nucleophilic attack of the carbon atom bonded to the nitrogen of the pyridine rings. From the data of Table 3, it appears that a large variety of nitro compounds may be obtained. Methods A and B are complementary reactions although method A appeared more limited than method B. Thus, under the conditions of method A, **2e**, **2f** and **3f** led only to intractable mixture of products while method B led to the expected compounds (runs 5–7, 12, 13).

To the best of our knowledge, method B has never been previously described and we propose the mechanism reported in Scheme 6 to account of the reactions observed. Aromatization of the assumed intermediate must instantaneously take place in the reaction medium.

5. Conclusion

In the present paper, we have shown that dihydrodipyridopyrazines may be easily obtained by arynic intermolecular cyclization of 2-aminoalkyl-3-halogenopyridines in the presence of a complex base. These previously unknown heterocycles have interesting chemical properties since they may be functionalized with electrophilic or nucleophilic reagents. On the other hand, exploratory pharmacological investigations performed with L1210 showed that these compounds constitute a new family of antiproliferative agents. Indeed, the IC50 of a number of the products presently described vary from 3 to 7 μM. More interestingly, it was found that they are able to interfere with the cell cycle at 5–25 μM, a good indication



Scheme 6.

for future anticancer agents. Details of the pharmacological properties of the compounds synthesized as well as of a number of their derivatives will be further published in due course.

6. Experimental

6.1. General methods

Mps were determined on a Tottoli melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker AM 400 or a Bruker 250 MHz spectrometer (Attached Proton Test method, APT) or a Bruker instrument Avance DPX250 at 250.131 and 62.9 MHz, respectively. Chemical shifts (δ values) were reported in parts per million and coupling constants (J values) in Hz. Me_4Si was the internal standard. Infrared spectra were recorded using NaCl film or KBr pellets techniques on a Perkin–Elmer spectrometer FT PARAGON 1000PC or on a Perkin Elmer 841 instrument. Elemental analyses were performed by CNRS laboratory (Vernaison). Mass spectra (MS) were recorded on a Perkin–Elmer mass spectrometer SCIEX API 300 by ion spray (IS). Mass HR spectra were recorded by 'peak matching' with a Finnigan MAT 95Q, BEQQ by the Institut de Recherches Servier (Suresnes). TLC were performed with plates coated with Kieselgel G (Merck). The silica gel used for flash chromatography was Kieselgel of 0.04–0.063 mm particle size.

Sodium amide powder was obtained commercially (Merck). Reagent-grade tetrahydrofuran (THF) was first distilled from potassium hydroxide and then from sodium benzophenone ketyl and stored over sodium until used.

6.2. General procedure for the preparation of 2-alkylamino-3-halogenopyridines 1

2-Alkylamino-3-halogenopyridines **1** were prepared according to a literature method[11] using sodium hydride in THF, from 2-amino-3-halogenopyridines. The latters were synthesized by modification of a literature procedure[12] described by Turner. 1,2-Dibromoethane was used as brominating agent to give **1a**, hexachloroethane as chlorinating agent to afford **1b** and iodine as iodinating agent to give **1c**.

6.3. General procedure for the preparation of 2-methylamino-3-halogeno-4-trimethylsilylpyridines 4a,b

6.3.1. *N*-(3-Bromo-4-trimethylsilylpyridin-2-yl)-2,2-dimethylpropanamide. The corresponding *N*-(3-bromo-2-pyridyl)-2,2-dimethylpropanamide (4 g, 0.015 mol) in THF (40 ml) was slowly added to a cold (−75°C) solution of LDA (0.060 mol) and Me_3SiCl (7.89 ml, 0.060 mol) in THF (40 ml). The resulting mixture was stirred for 2 h at −75°C. The reaction was then hydrolyzed at room temperature, extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and the solvent removed under reduced pressure to give a crude product which was purified by chromatography with EtOAc–hexane (15:85) as eluent. Yield: 89%; mp 155°C; MS (IS) 329 (^{79}Br, $M+H^+$), 331 (^{81}Br, $M+H^+$); ^{1}H NMR δ (ppm): 8.40 (d, J=4.7 Hz, 1H, ArH),.11 (s, 1H, NH), 7.09 (d, J=4.7 Hz, 1H, ArH), 1.37 (s, 9H, $C(CH_3)_3$), 0.41 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR δ (ppm): 175.9 (C=O), 153.4, 149.2 (2×arom C), 146.4, 126.6 (2×arom CH), 125.5 (arom C), 40.2 (C), 27.5 (3×CH_3), −1.1 ($Si(CH_3)_3$).

6.3.2. *N*-(3-Chloro-4-trimethylsilylpyridin-2-yl)-2,2-dimethylpropanamide. The previous procedure gave the title compound in 85% yield. Mp 139°C; MS (IS) 285 (^{35}Cl, $M+H^+$), 287 (^{37}Cl, $M+H^+$); ^{1}H NMR δ (ppm): 8.36 (d, J=4.7 Hz, 1H, ArH), 8.05 (s, 1H, NH), 7.13 (d, J=4.7 Hz, 1H, ArH), 1.37 (s, 9H, $C(CH_3)_3$), 0.40 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR δ (ppm): 175.8 (C=O), 150.4, 147.1 (2×arom C), 145.5, 128.8 (2×arom CH), 126.1 (arom C), 39.9 (C), 27.3 (3×CH_3), −1.5 ($Si(CH_3)_3$).

6.3.3. 2-Amino-3-bromo-4-trimethylsilylpyridine. The *N*-(3-bromo-4-(trimethylsilyl)-2-pyridyl)-2,2-dimethylpropanamide (4.5 g, 0.014 mol) in HCl (6N) (50 ml) was refluxed overnight. The mixture was basified to pH 8 (KOH), extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent removed under reduced pressure to give quantitatively the desired product. Mp 88°C; MS (IS) 245 (^{79}Br, $M+H^+$), 247 (^{81}Br, $M+H^+$); ^{1}H NMR δ (ppm): 7.96 (d, J=4.6 Hz, 1H, ArH), 6.95 (d, J=4.7 Hz, 1H, ArH), 5.00 (s, 2H, NH_2), 0.38 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR δ (ppm): 155.1, 151.7 (2×arom C), 145.6, 119.9 (2×arom CH), 112.1 (arom C), −1.1 ($Si(CH_3)_3$).

6.3.4. 2-Amino-3-chloro-4-trimethylsilylpyridine. The previous procedure gave the title compound quantitatively. Mp 92°C; MS (IS) 201 (^{35}Cl, $M+H^+$), 203 (^{37}Cl, $M+H^+$); ^{1}H NMR δ (ppm): 7.93 (d, J=4.6 Hz, 1H, ArH), 6.69 (d, J=4.7 Hz, 1H, ArH), 4.84 (s, 2H, NH_2), 0.36 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR δ (ppm): 154.4, 148.6 (2×arom C), 144.9, 121.1 (2×arom CH), 119.4 (arom C), −1.4 ($Si(CH_3)_3$).

6.3.5. *N*-(3-Bromo-4-trimethylsilylpyridin-2-yl)-*N*-methylamine 4a. To a suspension of 60% sodium hydride (0.56 g, 0.014 mol) in THF (25 ml) was added 2-amino-3-bromo-4-trimethylsilylpyridine (3.3 g, 0.013 mol) in THF (25 ml) under argon. The mixture was heated at 40°C during 30 min, cooled to −40°C and methyl iodide (0.72 ml, 0.014 mol) was added. The mixture was heated to room temperature overnight and hydrolyzed, extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent removed under reduced pressure to give a crude product which was purified by chromatography with EtOAc–hexane (5:95) as eluent. Yield: 80%; mp 57°C; ^{1}H NMR δ (ppm): 8.05 (d, J=4.8 Hz, 1H, ArH), 6.54 (d, J=4.8 Hz, 1H, ArH), 5.18 (br s, 1H, NH), 3.01 (d, J=4.8 Hz, 3H, CH_3), 0.37 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR δ (ppm): 154.6, 150.1 (2×arom C), 145.4, 118.4 (2×arom CH), 113.5 (arom C), 28.8 (CH_3), −1.1 ($Si(CH_3)_3$); (Found: C, 41.53; H, 5.86; N, 10.63. $C_{12}H_{12}N_4$ requires C, 41.70; H, 5.83; N, 10.81%).

6.3.6. *N*-(3-Chloro-4-trimethylsilylpyridin-2-yl)-*N*-methylamine 4b. The previous procedure gave the title compound in 79%. Oil; ^{1}H NMR δ (ppm): 8.03 (d, J=4.7 Hz, 1H, ArH), 6.59 (d, J=4.7 Hz, 1H, ArH), 5.11 (br s, 1H, NH), 3.04 (d, J=4.7 Hz, 3H, CH_3), 0.36 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR δ (ppm): 154.2, 147.1 (2×arom C), 144.7, 121.9 (2×arom CH), 117.3 (arom C), 28.6 (CH_3), −1.1

($Si(CH_3)_3$); (Found: C, 50.32; H, 7.18; N, 12.72. $C_{12}H_{12}N_4$ requires C, 50.33; H, 7.04; N, 13.04%).

6.4. General procedure for arynic cyclization of 2-alkylamino-3-bromopyridines 1 into dihydrodipyridopyrazines 2 and 3

The reactions were performed with the complex base $NaNH_2$–*t*BuONa.

(a) Preparation of the complex base. To a magnetically stirred suspension of 7 mol equiv. of $NaNH_2$ (8.19 g, 210 mmol) in THF (20 ml) was dropwise added at room temperature 2 mol equiv. of *t*BuOH (4.44 g, 60 mmol) in THF (1 ml) under nitrogen flush. After completion of the addition, the mixture was heated at 45°C for 2 h.

(b) Arynic cyclization. To the complex base thus prepared, 1 mol equiv. of 2-alkylamino-3-halogenopyridine (30 mmol) in THF (60 ml) was dropwise added at 0°C. The reaction mixture was allowed to warm to room temperature and was monitored by gas chromatography (GC) (capillary HP1, 6 m). After completion, the reaction mixture was hydrolyzed at 0°C, extracted with CH_2Cl_2, the extract dried over $MgSO_4$, and the solvent removed under reduced pressure.

6.4.1. 5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]-pyrazine 2a. Purified by chromatography with EtOAc–hexane (10:90) as eluent. Mp 152°C; ^{1}H NMR δ (ppm): 7.40 (d, J=4.5 Hz, 2H, ArH), 6.45 (dd, J_1=4.5 Hz, J_2=7 Hz, 2H, ArH), 6.30 (d, J=7 Hz, 2H, ArH), 3.05 (s, 6H, 2×CH_3); ^{1}H NMR δ (ppm): 147.7 (2×arom C), 138.2 (2×arom CH), 132.1 (2×arom C), 116.6, 115.2 (4×arom CH), 28.7 (2×CH_3N); (Found: C, 67.76; H, 5.53; N, 26.32. $C_{12}H_{12}N_4$ requires C, 67.91; H, 5.70; N, 26.40%).

6.4.2. 5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]-pyrazine 3a. Purified by chromatography with EtOAc–hexane (5:95) as eluent. Mp 150°C; ^{1}H NMR δ (ppm): 7.45 (d, J=4.5 Hz, 2H, ArH), 6.45 (dd, J_1=4.5 Hz, J_2=7 Hz, 2H, ArH), 6.30 (d, J=7 Hz, 2H, ArH), 3.25 (s, 3H, CH_3N), 2.80 (s, 3H, CH_3N); ^{13}C NMR δ (ppm): 148.6 (2×arom C), 138.2 (2×arom CH), 132.0 (2×arom C), 116.9, 114.4 (4×arom CH), 30.7, 27.7 (2×CH_3N); (Found: C, 67.60; H, 5.61; N, 26.08. $C_{12}H_{12}N_4$ requires C, 67.91; H, 5.70; N, 26.40%).

6.4.3. 5,10-Diethyl-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]-pyrazine 2b. Purified by chromatography with EtOAc–hexane (3:97) as eluent. Mp 145°C; ^{1}H NMR δ (ppm): 7.33 (d, J=5 Hz, 2H, ArH), 6.37 (m, 2H, ArH), 6.30 (d, J=7.5 Hz, 2H, ArH), 3.69 (q, J=7 Hz, 4H, 2×CH_2), 1.16 (t, J=7 Hz, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 146.9 (2×arom C), 138.0 (2×arom CH), 130.7 (2×arom C), 116.4, 114.5 (4×arom CH), 36.0 (2×CH_2), 10.3 (2×CH_3); (Found: C, 70.04; H, 6.64; N, 23.29. $C_{14}H_{16}N_4$ requires C, 69.97; H, 6.71; N, 23.31%).

6.4.4. 5,10-Diethyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]-pyrazine 3b. Purified by chromatography with EtOAc–hexane (3:97) as eluent. Mp 131°C; ^{1}H NMR δ (ppm): 7.37 (d, J=5 Hz, 2H, ArH), 6.38 (dd, J_1=5 Hz, J_2=7.4 Hz, 2H, ArH), 6.22 (d, J=7.4 Hz, 2H, ArH), 4.00 (q, J=7 Hz, 2H, CH_2), 3.32 (q, J=7 Hz, 2H, CH_2), 1.21–1.13 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 147.4 (2×arom C), 137.8 (2×arom CH), 130.7 (2×arom C), 116.5, 113.4 (4×arom CH), 38.2, 34.8 (2×CH_2), 11.6, 9.2 (2×CH_3); (Found: C, 70.13; H, 6.82; N, 23.57. $C_{14}H_{16}N_4$ requires C, 69.97; H, 6.71; N, 23.31%).

6.4.5. 5,10-Dibutyl-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]-pyrazine 2c. Purified by chromatography with EtOAc–hexane (2:98) as eluent. Mp 94°C; ^{1}H NMR δ (ppm): 7.33 (d, J=4.5 Hz, 2H, ArH), 6.36 (m, 2H, ArH), 6.26 (d, J=7.5 Hz, 2H, ArH), 3.62 (t, J=7 Hz, 4H, 2×CH_2N), 1.60–1.52 (m, 4H, 2×CH_2), 1.47–1.40 (m, 4H, 2×CH_2), 0.99 (t, J=7 Hz, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 145.2 (2×arom C), 137.9 (2×arom CH), 131.0 (2×arom C), 116.3, 114.7 (4×arom CH), 41.0 (2×CH_2N), 26.9, 20.1 (4×CH_2), 13.9 (2×CH_3); (Found: C, 72.92; H, 8.21; N, 18.73. $C_{18}H_{24}N_4$ requires C, 72.94; H, 8.16; N, 18.90%).

6.4.6. 5,10-Dibutyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]-pyrazine 3c. Purified by chromatography with EtOAc–hexane (2:98) as eluent. Mp 115°C; ^{1}H NMR δ (ppm): 7.35 (d, J=5 Hz, 2H, ArH), 6.36 (dd, J_1=5 Hz, J_2=7.6 Hz, 2H, ArH), 6.16 (d, J=7.6 Hz, 2H, ArH), 3.93 (t, J=7.5 Hz, 2H, CH_2N), 3.18 (t, J=8 Hz, 2H, CH_2N), 1.62–1.58 (m, 2H, CH_2), 1.54–1.50 (m, 2H, CH_2), 1.44–1.38 (m, 4H, 2×CH_2), 1.02–0.93 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 147.8 (2×arom C), 137.9 (2×arom CH), 131.2 (2×arom C), 116.5, 113.7 (4×arom CH), 43.8, 39.7 (2×CH_2N), 28.6, 25.8, 20.2, 20.0 (4×CH_2), 14.0 (2×CH_3); (Found: C, 72.97; H, 8.25; N, 18.77. $C_{18}H_{24}N_4$ requires C, 72.94; H, 8.16; N, 18.90%).

6.4.7. 5,10-Bis(1-phenylethyl)-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine 2d. Purified by chromatography with EtOAc–hexane (5:95) as eluent. Mp 153°C; ^{1}H NMR δ (ppm): 7.46–7.25 (m, 12H, ArH), 6.40–6.17 (m, 6H, 4×ArH+2×CH), 1.84 (t, J=6.6 Hz, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 149.4, 149.3, 140.8, 140.7 (4×arom C), 138.3, 138.3 (2×arom CH), 129.4, 129.3 (2×arom C), 128.6, 126.5, 126.1, 119.6, 119.5, 116.3 (14×arom CH), 50.6, 50.5 (2×CH), 14.9 (2×CH_3); (Found: C, 79.48; H, 6.31; N, 14.36. $C_{26}H_{24}N_4$ requires C, 79.56; H, 6.16; N, 14.27%).

6.4.8. *N*,*N*-Dimethyl-2-{10-[2-(dimethylamino)ethyl]-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazin-5-yl}-1-ethanamine 2e. Purified by chromatography with Et_3N–hexane (50:50) as eluent. Mp 144°C; ^{1}H NMR δ (ppm): 7.30 (dd, J_1=1.8 Hz, J_2=4.3 Hz, 2H, ArH), 6.39 (m, 4H, ArH), 3.76 (t, J=7.5 Hz, 4H, 2×CH_2N), 2.45 (t, J=7.5 Hz, 4H, 2×CH_2), 3.32 (s, 12H, 4×CH_3); ^{13}C^{13}C NMR δ (ppm): 146.7 (2×arom C), 138.2 (2×arom CH), 130.7 (2×arom C), 116.5, 114.8 (4×arom CH), 53.8 (2×CH_2N), 45.7 (4×CH_3), 39.8 (2×CH_2N); (Found: C, 66.01; H, 7.95; N, 25.67. $C_{18}H_{26}N_6$ requires C, 66.23; H, 8.03; N, 25.74%).

6.4.9. *N*,*N*-Dimethyl-3-{10-[3-(dimethylamino)propyl]-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazin-5-yl}-1-propanamine 2f. Purified by chromatography with Et_3N as eluent. Mp 100°C; ^{1}H NMR δ (ppm): 7.28 (m, 2H, ArH), 6.34 (m, 4H, ArH), 3.64 (t, J=7 Hz, 4H, 2×CH_2), 2.35 (t, J=7 Hz, 4H, 2×CH_2), 2.25 (s, 12H, 4×CH_3), 1.75 (m, 4H,

2×CH_2); ^{13}C NMR δ (ppm): 147.1 (2×arom C), 138.1 (2×arom CH), 131.1 (2×arom C), 116.5, 114.8 (4×arom CH), 57.0 (2×CH_2N), 45.5 (4×CH_3), 39.6 (2×CH_2N), 23.2 (2×CH_2); (Found: C, 67.64; H, 8.64; N, 23.64. $C_{20}H_{30}N_6$ requires C, 67.76; H, 8.53; N, 23.71%).

6.4.10. *N*,*N*-Dimethyl-3-{10-[3-(dimethylamino)propyl]-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazin-5-yl}-1-propanamine 3f. Purified by chromatography with Et_3N as eluent. Mp 84°C; ^{1}H NMR δ (ppm): 7.33 (d, *J*=5 Hz, 2H, ArH), 6.38–6.33 (dd, J_1=5 Hz, J_2=7 Hz, 2H, ArH), 6.28–6.26 (d, *J*=7 Hz, 2H, ArH), 3.96 (t, *J*=7.5 Hz, 2H, 2×CH_2), 3.28 (t, *J*=7.5 Hz, 2H, CH_2), 2.43–2.28 (m, 4H, 2×CH_2), 2.26 (s, 6H, 2×CH_3), 2.24 (s, 6H, 2×CH_3), 1.84 (m, 2H, CH_2), 1.67 (m, 2H, CH_2); ^{13}C NMR δ (ppm): 147.6 (2×arom C), 138.0 (2×arom CH), 131.2 (2×arom C), 116.6, 113.8 (4×arom CH), 57.3, 56.5 (2×CH_2N), 45.5, 45.4 (4×CH_3), 41.9, 38.2 (2×CH_2N), 24.4, 22.3 (2×CH_2); (Found: C, 67.67; H, 8.45; N, 23.64. $C_{20}H_{30}N_6$ requires C, 67.76; H, 8.53; N, 23.71%).

6.4.11. 5,10-Bis[2-(tetrahydro-2*H*pyran-2-yloxy)ethyl]-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine 2g. Purified by chromatography with EtOAc–hexane (30:70). Mp 110°C; ^{1}H NMR δ (ppm): 7.30 (d, *J*=4.5 Hz, 2H, ArH), 6.60 (d, *J*=8 Hz, 2H, ArH), 6.37 (dd, J_1=4.5 Hz, J_2=8 Hz, 2H, ArH), 4.64 (m, 2H, CHO), 3.91–3.84 (m, 8H, aliph H), 3.72–3.64 (m, 2H, aliph H), 3.53–3.47 (m, 2H, aliph H), 1.80–1.51 (m, 12H, aliph H); ^{13}C NMR δ (ppm): 146.7 (2×arom C), 138.0 (2×arom CH), 131.2 (2×arom C), 116.4, 115.7, 98.8, 98.7 (4×arom CH+2×aliph CH), 63.6, 61.9, 61.9, 41.7, 30.3, 25.2, 19.1 (12×CH_2); (Found: C, 65.03; H, 7.33; N, 12.93. $C_{24}H_{32}N_4O_4$ requires C, 65.43; H, 7.32; N, 12.72%).

6.4.12. 5-[2-(Tetrahydro-2*H*pyran-2-yloxy)ethyl]-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine 2h. Purified by chromatography with EtOAc–hexane (50:50). ^{1}H NMR δ (ppm): 7.31 (d, *J*=4.5 Hz, 1H, ArH), 7.18 (d, *J*=4.5 Hz, 1H, ArH), 6.60 (d, *J*=7.5 Hz, 1H, ArH), 6.39–6.28 (m, 2H, ArH), 6.17 (d, *J*=7.5 Hz, 1H, ArH), 4.65 (t, *J*=1 Hz, 1H, aliph CH), 3.95–3.82 (m, 4H, aliph H), 3.69–3.62 (m, 1H, aliph H), 3.55–3.47 (m, 1H, aliph H), 1.84–1.53 (m, 6H, aliph H); ^{13}C NMR δ (ppm): 147.7, 146.5 (2×arom C), 138.9, 137.3 (2×arom CH), 131.3, 129.3 (2×arom C), 116.7, 116.7, 116.5, 116.2 (4×arom CH), 99.0 (aliph CH), 63.98, 62.17, 41.85, 30.54, 25.38, 19.35 (6×CH_2); (HRMS calcd for $C_{17}H_{20}N_4O_2$ 312.1581, found: 312.1569).

6.5. Reactions of 4a,b with fluoride ions

To a solution of Bu_4NF (1 M in THF) (1.3 or 2.5 equiv.) in THF (6 ml/1 mmol) under molecular sieves 4 Å was added dropwise **4a** or **4b** (1 equiv.) in THF (6 ml/1 mmol). The mixture was stirred 1 h at −20°C, 0°C or room temperature, diluted with ethyl acetate and washed with $NaHCO_3$ (sat). The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure to give a mixture of several products. Compounds **2** and **3** were obtained as traces and identified.

6.5.1. *N*-(4-Bromopyridin-2-yl)-*N*-methylamine 5. Mp 88°C; ^{1}H NMR δ (ppm): 6.87 (d, *J*=5.3 Hz, 1H, ArH), 6.70 (dd, *J*=5.3, 1.2 Hz, 1H, ArH), 6.54 (dd, *J*=1.2 Hz, 1H, ArH), 5.23 (br s, 1H, NH), 2.87 (d, *J*=5.0 Hz, 3H, CH_3); (Found: C, 38.83; H, 3.86; N, 14.74. $C_6H_7BrN_2$ requires C, 38.53; H, 3.77; N, 14.98%).

6.5.2. *N*-(3-Bromopyridin-2-yl)-*N*-methylamine 1a. ^{1}H NMR δ (ppm): 8.09 (dd, *J*=5.0, 1.5 Hz, 1H, ArH), 7.59 (dd, *J*=7.6, 1.5 Hz, 1H, ArH), 6.44 (dd, *J*=7.6, 5.0 Hz, 1H, ArH), 5.03 (br s, 1H, NH), 3.03 (d, *J*=4.7 Hz, 3H, CH_3); ^{1}H NMR δ (ppm): 154.9 (arom C), 146.4, 138.9, 112.6 (3×arom CH), 105.3 (arom C), 28.4 (CH_3); (Found: C, 38.40; H, 3.91; N, 15.11. $C_6H_7BrN_2$ requires C, 38.53; H, 3.77; N, 14.98%).

6.5.3. *N*-(4-Bromopyridin-2-yl)-*N*-methyl-*N*-[2-(methylamino)pyridin-3-yl]amine 6. Oil; ^{1}H NMR δ (ppm): 8.17 (dd, *J*=5.0, 1.5 Hz, 1H, ArH), 8.03 (d, *J*=5.3 Hz, 1H, ArH), 7.27 (dd, *J*=1.3, 1.5 Hz, 1H, ArH), 6.79 (dd, *J*=5.3, 1.3 Hz, 1H, ArH), 6.63 (dd, *J*=7.3, 5.0 Hz, 1H, ArH), 6.37 (d, *J*=1.3 Hz, 1H, ArH), 4.70 (br s, 1H, NH), 3.31 (s, 3H, CH_3), 3.00 (d, *J*=4.7 Hz, 3H, CH_3); ^{13}C NMR δ (ppm): 159.1, 156.0 (2×arom C), 148.6, 147.2, 135.4 (3×arom CH), 133.1, 126.2 (2×arom C), 116.8, 112.7, 110.9 (3×arom CH), 36.9, 28.2 (2×CH_3); (Found: C, 49.54; H, 4.66; N, 18.63. $C_{12}H_{13}BrN_4$ requires C, 49.16; H, 4.47; N, 19.11%).

6.5.4. *N*-(3-Chloropyridin-2-yl)-*N*-methylamine 1b. The previous procedure with **4b** gave only the title compound in 80% yield. Oil; ^{1}H NMR δ (ppm): 8.05 (dd, *J*=5.0, 1.5 Hz, 1H, ArH), 7.41 (dd, *J*=7.5, 1.5 Hz, 1H, ArH), 6.50 (dd, *J*=7.5, 5.0 Hz, 1H, ArH), 5.01 (br s, 1H, NH), 3.04 (d, *J*=4.7 Hz, 3H, CH_3); ^{13}C NMR δ (ppm): 154.6 (arom C),146.0, 137.5, 115.4 (3×arom CH), 112.4 (arom C), 28.4 (CH_3); (Found: C, 50.22; H, 4.67; N, 19.63. $C_6H_7BrN_2$ requires C, 50.54; H, 4.95; N, 19.65%).

6.6. Formylation of 2 and 3

(a) Preparation of the Vilsmeier reagent. $POCl_3$ (9.32 ml, 100 mmol) was added dropwise at 0°C to DMF (17.7 ml, 230 mmol) under magnetic stirring and nitrogen atmosphere. Then, the mixture was allowed to warm quickly to room temperature and stirred for 15 min.

(b) Formylation. The Vilsmeier reagent thus prepared was added to a refluxing solution of dihydrodipyridopyrazine **2** or **3** (10 mmol) in 1,2-dichloroethane or chloroform (100 ml). After completion, the reaction mixture was cooled at 0°C and KOH 3 M (120 ml) was added dropwise. The mixture was heated to reflux for 3 h, then diluted with water (200 ml) and extracted with CH_2Cl_2. The extract was washed with water and the organic layer dried over $MgSO_4$. The solvent was removed under reduced pressure.

6.6.1. 5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]-pyrazine-2-carbaldehyde 12a. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 176°C; IR (KBr), ν_{max}1682 (C=O) cm^{-1}; ^{1}H NMR δ (ppm): 9.61 (s, 1H, CHO), 7.46 (d, *J*=4.5 Hz, 2H, ArH), 7.16 (d, *J*=8.1 Hz, 1H, ArH), 6.56 (dd, J_1=4.5 Hz, J_2=7.6 Hz, 1H, ArH), 6.44 (d, *J*=7.6 Hz, 1H, ArH), 6.36 (d, *J*=8.1 Hz, 1H,

ArH), 3.14 (s, 3H, CH_3N), 3.13 (s, 3H, CH_3N); ^{13}C NMR δ (ppm): 190.8 (CHO), 147.5, 145.9, 143.0 (3×arom C), 138.7 (arom CH), 137.2, 131.7 (2×arom C), 120.5, 118.1, 116.3, 113.9 (4×arom CH), 29.1, 28.7 (2×CH_3); (Found: C, 65.07; H, 5.14; N, 22.91. $C_{13}H_{12}N_4O$ requires C, 64.99; H, 5.03; N, 23.32%).

6.6.2. 5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]-pyrazine-3-carbaldehyde 13a. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 179°C; IR (KBr), ν_{max} 1673 (C=O) cm^{-1}; ^1H NMR δ (ppm): 9.62 (s, 1H, CHO), 7.77 (d, J=1 Hz, 1H, ArH), 7.50 (dd, J_1=2 Hz, J_2=4 Hz, 1H, ArH), 6.62 (s, 1H, ArH), 6.49 (m, 2H, ArH), 3.17 (s, 3H, CH_3), 3.09 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 188.7 (CHO), 151.8 (arom C), 147.7 (arom C), 146.8 (arom C), 140.2 (arom CH), 132.7, 129.9, 127.2 (3×arom C), 117.2, 116.7, 109.6 (3×arom CH), 29.2, 28.7 (2×CH_3); (Found: C, 65.11; H, 5.22; N, 23.20. $C_{13}H_{12}N_4O$ requires C, 64.99; H, 5.03; N, 23.32%).

6.6.3. 5,10-Dibutyl-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]-pyrazine-2-carbaldehyde 12c. Purified by chromatography with EtOAc–hexane (20:80) as eluent. Mp 95°C; IR (KBr), ν_{max} 1690 (C=O) cm^{-1}; ^1H NMR δ (ppm): 9.57 (s, 1H, CHO), 7.38 (d, J=4.5 Hz, 1H, ArH), 7.10 (d, J=7.6 Hz, 1H, ArH), 6.47 (dd, J_1=4.5 Hz, J_2=7.6 Hz, 1H, ArH), 6.36 (d, J=7.6 Hz, 1H, ArH), 6.26 (d, J=7.6 Hz, 1H, ArH), 3.86 (m, 4H, 2×CH_2), 1.56 (m, 4H, 2×CH_2), 1.43 (m, 4H, 2×CH_2), 1.00 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 191.0 (CHO), 147.0, 145.5, 142.7 (3×arom C), 138.4 (arom CH), 136.3, 130.8 (2×arom C), 119.4, 118.0, 115.8, 113.4 (4×arom CH), 41.5, 41.0, 26.9, 26.8, 20.0 (6×CH_2), 13.8 (2×CH_3); (Found: C, 70.78; H, 7.65; N, 17.52. $C_{19}H_{24}N_4O$ requires C, 70.34; H, 7.46; N, 17.27%).

6.6.4. 5,10-Dibutyl-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]-pyrazine-3-carbaldehyde 13c. Purified by chromatography with EtOAc–hexane (20:80) as eluent. Mp 117°C; IR (KBr), ν_{max} 1682 (C=O) cm^{-1}; ^1H NMR δ (ppm): 9.55 (s, 1H, CHO), 7.68 (s, 1H, ArH), 7.43 (m, 1H, ArH), 6.51 (s, 1H, ArH), 6.40 (m, 2H, ArH), 3.67–3.59 (m, 4H, 2×CH_2N), 1.55 (m, 4H, 2×CH_2), 1.42 (m, 4H, 2×CH_2), 0.98 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 188.5 (CHO), 151.6 (arom C), 147.8 (arom CH), 146.6 (arom C), 140.1 (arom CH), 131.7, 128.8, 127.1 (3×arom C), 116.8, 116.5, 109.0 (3 arom CH), 41.8, 41.3 (2×CH_2N), 27.1, 26.6, 20.0 (6×CH_2), 13.8, 13.7 (2×CH_3); (Found: C, 70.32; H, 7.51; N, 17.42. $C_{19}H_{24}N_4O$ requires C, 70.34; H, 7.46; N, 17.27%).

6.6.5. 5,10-Bis[3-(dimethylamino)propyl]-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine-2 carbaldehyde 12f. Purified by chromatography with Et_3N as eluent. Oil; IR (thin film), ν_{max} 1681 (C=O) cm^{-1}; *m/z* (CI, CH_4) 383 (M+1).

6.6.6. 5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]-pyrazine-2-carbaldehyde 14a. Purified by chromatography with EtOAc–hexane (50:50) as eluent. Mp 157°C; IR (KBr), ν_{max} 1684 (C=O) cm^{-1}; ^1H NMR δ (ppm): 9.63 (s, 1H, CHO), 7.53 (d, J=5 Hz, 1H, ArH), 7.17 (d, J=8 Hz, 1H, ArH), 6.49 (dd, J_1=5 Hz, J_2=7.6 Hz, 1H, ArH), 6.39 (d, J=7.6 Hz, 1H, ArH), 6.28 (d, J=8 Hz, 1H, ArH), 3.32 (s, 3H, CH_3N), 2.88 (s, 3H, CH_3N); ^1H NMR δ (ppm): 190.7 (CHO), 148.2, 147.7, 142.7 (3×arom C), 139.7 (arom CH), 136.6, 130.3 (2×arom C), 120.2, 117.1, 115.9, 113.0 (4×arom CH), 31.2, 27.6 (2×CH_3); (Found: C, 65.28; H, 5.00; N, 23.63. $C_{13}H_{12}N_4O$ requires C, 64.99; H, 5.03; N, 23.32%).

6.6.7. 5,10-Dibutyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]-pyrazine-2-carbaldehyde 14c. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 108°C; IR (KBr), ν_{max} 1689 (C=O) cm^{-1}; ^1H NMR δ (ppm): 9.58 (s, 1H, CHO), 7.45 (d, J=4.5 Hz, 1H, ArH), 7.11 (d, J=8.1 Hz, 1H, ArH), 6.41 (dd, J_1=4.5 Hz, J_2=7.6 Hz, 1H, ArH), 6.30 (d, J=7.6 Hz, 1H, ArH), 6.17 (d, J=8.1 Hz, 1H, ArH), 3.99 (t, J=7.6 Hz, 2H, CH_2N), 3.24 (t, J=7.6 Hz, 2H, CH_2N), 1.68–1.39 (m, 8H, 4×CH_2), 1.03–0.95 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 191.2 (CHO), 147.6, 147.3, 142.8 (3×arom C), 139.7 (arom CH), 136.0, 129.6 (2×arom C), 119.2, 116.8, 115.5, 112.5 (4×arom CH), 44.1, 39.7, 28.3, 26.0, 20.1, 19.9 (6×CH_2), 13.9, 13.7 (2×CH_3); (Found: C, 70.51; H, 7.38; N, 17.02. $C_{19}H_{24}N_4O$ requires C, 70.34; H, 7.46; N, 17.27%).

6.6.8. 5,10-Dibutyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]-pyrazine-2,7-dicarbaldehyde 15c. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 159°C; IR (KBr), ν_{max} 1682 (C=O) cm^{-1}; ^1H NMR δ (ppm): 9.63 (s, 1H, CHO), 9.62 (s, 1H, CHO), 7.85 (s, 1H, ArH), 7.25 (d, J=7.9 Hz, 1H, ArH), 6.62 (s, 1H, ArH), 6.36 (d, J=7.9 Hz, 1H, ArH), 4.09 (t, J=7 Hz, 2H, CH_2N), 3.31 (t, J=7 Hz, 2H, CH_2N), 1.67–1.39 (m, 8H, 4×CH_2), 1.06–0.96 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 190.8, 188.5 (CHO), 152.0 (arom C), 148.5 (arom CH), 145.5, 142.9, 135.4, 130.3, 127.1 (5×arom C), 119.9, 114.2, 110.1 (3×arom CH), 44.3, 40.6 (2×CH_2N), 28.2, 25.7, 20.0, 19.8 (4×CH_2), 13.8, 13.6 (2×CH_3); (Found: M, 352.1894. $C_{20}H_{24}N_4O_2$ requires M, 352.1894).

6.6.9. 5,10-Dibutyl-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]-pyrazine-2,8-dicarbaldehyde 16c. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 156°C; IR (KBr), ν_{max} 1686 (C=O) cm^{-1}; ^1H NMR δ (ppm): 9.63 (s, 2H, 2×CHO), 7.16 (d, J=8.1 Hz, 2H, ArH), 6.34 (d, J=8.1 Hz, 2H, ArH), 4.07 (t, J=7.6 Hz, 2H, CH_2N), 3.31 (t, J=7.6 Hz, 2H, CH_2N), 1.67–1.42 (m, 8H, 4×CH_2), 1.05–0.98 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 191.3 (2×CHO), 147.4, 144.0, 134.4 (6×arom CH), 118.5, 114.6 (4×arom CH), 44.6, 39.9, 28.1, 26.1, 20.1, 19.9 (6×CH_2), 13.9, 13.7 (2×CH_3); (Found: C, 67.78; H, 6.94; N, 15.57. $C_{20}H_{24}N_4O_2$ requires C, 68.16; H, 6.86; N, 15.90%).

6.6.10. 5,10-Bis[3-(dimethylamino)propyl]-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazine-2-carbaldehyde 14f. Purified by chromatography with Et_3N as eluent. Oil; IR (thin film), ν_{max} 1688 (C=O) cm^1; ^1H NMR δ (ppm): 9.58 (s, 1H, CHO), 7.44–6.34 (m, 5H, ArH), 4.03 (m, 2H, CH_2), 3.37 (m, 2H, CH_2), 2.44 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.28 (s, 6H, 2×CH_3), 2.22 (s, 6H, 2×CH_3), 1.83 (m, 2H, CH_2), 1.68 (m, 2H, CH_2); ^{13}C NMR δ (ppm): 190.8 (CHO), 143.2, 146.8, 142.5 (3×arom C), 139.6 (arom CH), 136.0, 129.4 (2×arom C), 119.3, 116.8, 115.5, 112.6 (4×arom CH), 57.0, 55.9 (2×CH_2), 45.4, 45.1 (4×CH_3), 41.9, 38.3, 23.8, 22.3 (4×CH_2); *m/z* (CI, CH_4) 383 (M+1).

6.7. Nitration of 2 and 3

Method A. The reactions were performed according to the literature.[10]

Method B. (a) Salt formation. To a solution of 1 mol equiv. of **2** or **3** in CH_2Cl_2 (50 ml for 6 mmol) was added the amount of oxalic acid indicated in Table 3. After stirring during 20 h the salt was either filtered or the solvent removed under vacuum and the solid used without other purification.

(b) Nitration. The salt thus prepared was placed in CH_3NO_2 (50 ml for 6 mmol) and the amount of KNO_2 indicated in Table 3 was added. The reaction was monitored by TLC or gas chromatography. After completion KOH 1 M (150 ml for 6 mmol) was added and the mixture extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure.

6.7.1. 5,10-Dimethyl-2-nitro-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine 17a. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 212°C; IR (KBr), ν_{max} 1545, 1522, 1491 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.49 (d, J=5 Hz, 1H, ArH), 7.47 (d, J=8 Hz, 1H, ArH), 6.58 (dd, J_1=5 Hz, J_2=7.6 Hz, 1H, ArH), 6.48 (d, J=7.6 Hz, 1H, ArH), 6.28 (d, J=8 Hz, 1H, ArH), 3.13 (s, 3H, CH_3N), 3.14 (s, 3H, CH_3N); ^{13}C NMR δ (ppm): 148.6 (C–NO_2), 147.4, 147.1 (2×arom C), 140.3 (arom CH), 137.9, 130.2 (2×arom C), 117.8, 116.7, 114.3, 113.5 (4×arom CH), 31.8, 28.1 (2×CH_3); (Found: C, 55.77; H, 4.44; N, 27.00. $C_{12}H_{11}N_5O_2$ requires C, 56.03; H, 4.31; N, 27.22%).

6.7.2. 5,10-Dibutyl-2-nitro-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine 17c. Purified by chromatography with EtOAc–hexane (20:80) as eluent. Mp 111°C; IR (KBr), ν_{max} 1517, 1485, 1438 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.41–7.38 (m, 2H, ArH), 6.54–6.49 (dd, J_1=4.9 Hz, J_2=7.9 Hz, 1H, ArH), 6.43 (d, J=7.9 Hz, 1H, ArH), 6.20 (d, J=8.6 Hz, 1H, ArH), 3.67 (m, 4H, 2×CH_2N), 1.61–1.38 (m, 8H, 4×CH_2), 1.00 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 148.2 (arom C–NO_2), 145.8, 145.2 (2×arom C), 139.1 (arom CH), 137.3, 129.9 (2×arom C), 118.3, 116.6, 114.0, 113.6 (4×arom CH), 41.8, 41.4 (2×CH_2N), 26.8 (2×CH_2), 20.0 (2×CH_2), 13.8 (2×CH_3); (Found: C, 63.27; H, 6.83; N, 20.39. $C_{18}H_{23}N_5O_2$ requires C, 63.32; H, 6.79; N, 20.51%).

6.7.3. 5,10-Dibutyl-2,7-nitro-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazine 18c. Purified by chromatography with EtOAc–hexane (20:80) as eluent. Mp 221°C; IR (KBr), ν_{max} 1520, 1469, (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.54 (d, J=8.1 Hz, 2H, ArH), 6.47 (d, J=8.1 Hz, 2H, ArH), 3.97 (t, J=7 Hz, 4H, 2×CH_2N), 1.70–1.45 (m, 8H, 4×CH_2), 1.04 (t, J=7 Hz, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 149.2 (2×arom C–NO_2), 144.9, 136.6 (4×arom C), 116.7, 115.4 (4×arom CH), 42.9 (2×CH_2N), 27.2, 20.4 (4×CH_2), 14.1 (2×CH_3); (Found: C, 55.79; H, 5.85; N, 21.45. $C_{18}H_{22}N_6O_4$ requires C, 55.95; H, 5.74; N, 21.75%).

6.7.4. *N*1,*N*1-Dimethyl-2-{10-[2-(dimethylamino)ethyl]-2-nitro-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazin-5-yl}-1-ethanamine 17e. Purified by chromatography with Et_3N as eluent. Mp 110°C; IR (KBr), ν_{max} 1516, 1486, 1441 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.45 (m, 1H, ArH), 7.42 (d, J=8.1 Hz, 1H, ArH), 6.52 (m, 2H, ArH), 6.34 (d, J=8.1 Hz, 1H, ArH), 3.83 (m, 4H, 2×CH_2), 2.42–2.33 (m, 16H, 2×CH_2, 4×CH_3); ^{13}C NMR δ (ppm): 148.4 (arom C–NO_2), 145.6, 145.0 (2×arom C), 139.5 (arom CH), 137.3, 128.9 (2×arom C), 118.6, 116.8, 144.1 (4×arom CH), 53.9, 53.7 (2×CH_2), 45.7 (4×CH_3), 40.8, 40.1 (2×CH_2); (Found: C, 58.03; H, 6.91; N, 26.34. $C_{18}H_{25}N_7O_2$ requires C, 58.21; H, 6.78; N, 26.40%).

6.7.5. *N*1,*N*1-Dimethyl-2-{10-[2-(dimethylamino)propyl]-2-nitro-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazin-5-yl}-1-propanamine 17f. Purified by chromatography with Et_3N as eluent. Mp 95°C; IR (KBr), ν_{max} 1517, 1485, 1440 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.41 (m, 2H, ArH), 6.54–6.39 (m, 3H, ArH), 3.70 (m, 4H, 2×CH_2N), 2.41–2.33 (m, 4H, 2×CH_2N), 2.26 (s, 6H, 2×CH_3), 2.24 (s, 6H, 2×CH_3), 1.74 (m, 4H, 2×CH_2); ^{13}C NMR δ (ppm):148.1 (arom C–NO_2), 145.4, 144.8 (2×arom C), 139.0 (arom CH), 137.3, 129.8 (2×arom C), 118.2, 116.5, 113.9, 113.6 (4×arom CH), 59.5, 56.3 (2×CH_2N), 45.2 (4×CH_3), 40.2 (2×CH_2N), 22.9, 22.6 (2×CH_2); (Found: M, 399.2369. $C_{20}H_{29}N_7O_2$ requires M, 399.2377).

6.7.6. *N*1,*N*1-Dimethyl-2-{10-[2-(dimethylamino)propyl]-2,7-dinitro-5,10-dihydrodipyrido[2,3-*b*:2,3-*e*]pyrazin-5-yl}-1-propanamine 18f. Purified by chromatography with Et_3N–methanol (70:30) as eluent. Oil; IR (thin film), ν_{max} 1513, 1473, 1448 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.52 (d, J=8.1 Hz, 2H, ArH), 6.71 (d, J=8.1 Hz, 2H, ArH), 3.80 (m, 4H, 2×CH_2), 2.43–2.35 (m, 4H, 2×CH_2), 2.26 (s, 12H, 4×CH_3), 1.80 (m, 4H, 2×CH_2); ^{13}C NMR δ (ppm): 148.8 (arom C–NO_2), 145.2 (2×arom C), 136.5 (2×arom CH), 116.6 (2×arom C), 115.0 (4×arom CH), 56.4 (2×CH_2), 45.3 (4×CH_3), 40.4 (2×CH_2), 22.9 (2×CH_2); (Found: C, 53.87; H, 6.58; N, 24.92. $C_{20}H_{28}N_8O_4$ requires C, 54.04; H, 6.35; N, 25.21%).

6.7.7. 5,10-Dimethyl-2-nitro-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazine 19a. Purified by chromatography with EtOAc–hexane (40:60) as eluent. Mp 206°C; IR (KBr), ν_{max} 1513, 1444 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.56 (d, J=5 Hz, 1H, ArH), 7.49 (d, J=8.6 Hz, 1H, ArH), 6.56 (dd, J_1=5 Hz, J_2=8 Hz, 1H, ArH), 6.46 (d, J=8 Hz, 1H, ArH), 6.24 (d, J=8.6 Hz, 1H, ArH), 3.32 (s, 3H, CH_3N), 2.93 (s, 3H, CH_3N); ^{13}C NMR δ (ppm): 140.4 (arom C), 137.9, 130.2 (4×arom CH), 117.9, 116.8, 114.4, 113.5 (4×arom C), 31.8, 28.1 (2×CH_3); (Found: C, 55.72; H, 4.54; N, 26.94. $C_{12}H_{11}N_5O_2$ requires C, 56.03; H, 4.31; N, 27.22%).

6.7.8. 5,10-Dimethyl-2,8-dinitro-5,10-dihydrodipyrido-[2,3-*b*:3,2-*e*]pyrazine 20a. Purified by chromatography with EtOAc–hexane (40:60) as eluent. Mp >270°C; IR (KBr), ν_{max} 1528, 1447 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.58 (d, J=8.3 Hz, 2H, ArH), 6.67 (d, J=8.3 Hz, 2H, ArH), 3.12 (s, 6H, 2×CH_3); (Found: M, 302.0756. $C_{12}H_{10}N_6O_4$ requires M, 302.0758).

6.7.9. 5,10-Dibutyl-2-nitro-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazine 19c. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 128°C; IR (KBr),

ν_{max} 1518, 1493, 1448 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.48 (d, J=4.9 Hz, 1H, ArH), 7.38 (d, J=8.5 Hz, 1H, ArH), 6.46 (m, 1H, ArH), 6.37 (d, J=7.3 Hz, 1H, ArH), 6.12 (d, J=8.5 Hz, 1H, ArH), 3.95 (t, J=6.5 Hz, 2H, CH_2), 3.26 (t, J=6.5 Hz, 2H, CH_2), 1.64–1.38 (m, 8H, 4×CH_2), 1.05–0.94 (m, 6H, 2×CH_3); ^{13}C NMR δ (ppm): 148.0, 146.3, 146.2 (3×arom C), 140.0 (arom CH), 136.9, 129.1 (2×arom C), 117.4, 116.1, 114.1, 112.5 (4×arom CH), 44.3, 40.0, 27.8, 25.8, 19.9, 19.7 (6×CH_2), 13.6, 13.5 (2×CH_3); (Found: C, 63.60; H, 6.67; N, 20.46. $C_{18}H_{23}N_5O_2$ requires C, 63.32; H, 6.79; N, 20.51%).

6.7.10. 5,10-Dibutyl-2,8-dinitro-5,10-dihydrodipyrido-[2,3-*b*:3,2-*e*]pyrazine 20c. Purified by chromatography with EtOAc–hexane (30:70) as eluent. Mp 202°C; IR (KBr), ν_{max} 1521, 1461 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.47 (d, J=8 Hz, 2H, ArH), 6.37 (d, J=8 Hz, 2H, ArH), 4.03 (t, J=7.3 Hz, 2H, CH_2N), 3.35 (t, J=7.3 Hz, 2H, CH_2N), 1.69–0.97 (m, 14H, aliph H); ^{13}C NMR δ (ppm): 149.6 (arom C–NO_2), 146.0, 135.4 (4×arom C), 115.9, 114.2 (4×arom CH), 45.5, 41.2 (2×CH_2N), 27.9, 26.2, 20.1, 20.1 (4×CH_2), 13.9, 13.8 (3×CH_3); (Found: C, 55.81; H, 5.85; N, 21.60. $C_{18}H_{22}N_6O_4$ requires C, 55.95; H, 5.74; N, 21.75%).

6.7.11. *N*1,*N*1-Dimethyl-2-{10-[2-(dimethylamino)propyl]-2-nitro-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazin-5-yl}-1-propanamine 19f. Purified by chromatography with Et_3N as eluent. Mp 123°C; IR (KBr), ν_{max} 1526, 1449 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.46 (d, J=4.5 Hz, 1H, ArH), 7.36 (d, J=8 Hz, 1H, ArH), 6.53 (d, J=7.6 Hz, 1H, ArH), 6.48 (m, 1H, ArH), 6.33 (d, J=8 Hz, 1H, ArH), 3.97 (t, J=7.5 Hz, 2H, CH_2N), 3.38 (t, J=7.5 Hz, 2H, CH_2N), 2.40 (t, J=7 Hz, 2H, CH_2), 2.33 (t, J=7 Hz, 2H, CH_2), 2.26 (s, 6H, 2×CH_3), 2.24 (s, 6H, 2×CH_3), 1.80 (m, 2H, CH_2), 1.69 (m, 2H, CH_2); ^{13}C NMR δ (ppm): 147.9 (arom C–NO_2), 146.1, 145.9 (2×arom C), 139.9 (arom CH), 137.1, 129.1 (2×arom C), 117.4, 116.2, 114.1, 112.7 (4×arom CH), 56.9, 55.7 (2×CH_2N), 45.1, 45.1 (4×CH_3), 42.1, 38.8 (2×CH_2N), 23.5, 22.2 (2×CH_2); (Found: C, 60.41; H, 7.52; N, 24.28. $C_{20}H_{29}N_7O_2$ requires C, 60.13; H, 7.32; N, 24.54%).

6.7.12. *N*1,*N*1-Dimethyl-2-{10-[2-(dimethylamino)propyl]-2,8-dinitro-5,10-dihydrodipyrido[2,3-*b*:3,2-*e*]pyrazin-5-yl}-1-propanamine 20f. Purified by chromatography with Et_3N as eluent. Mp 160–170°C; IR (KBr), ν_{max}1529, 1462 (NO_2) cm^{-1}; ^1H NMR δ (ppm): 7.47 (d, J=8.1 Hz, 2H, ArH), 6.64 (d, J=8.1 Hz, 2H, ArH), 4.05 (t, J=6.1 Hz, 4H, 2×CH_2), 3.51 (t, J=7.1 Hz, 2H, CH_2N), 2.46 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.29 (s, 6H, 2×CH_3), 2.26 (s, 6H, 2×CH_3), 1.85 (m, 2H, CH_2), 1.73 (m, 2H, CH_2); ^{13}C NMR δ (ppm): 148.8 (arom C–NO_2), 144.2, 136.5 (4×arom CH), 116.6 (2×arom C), 115.0 (2×arom C), 56.4 (2×CH_2), 45.3 (4×CH_3), 40.4 (2×CH_2N), 22.9 (2×CH_2); (Found: M, 444.2233. $C_{20}H_{28}N_8O_4$ requires M, 444.2228).

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