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An effective contribution to functionalized pyridines synthesis by way of an unusual rearrangement of amidines

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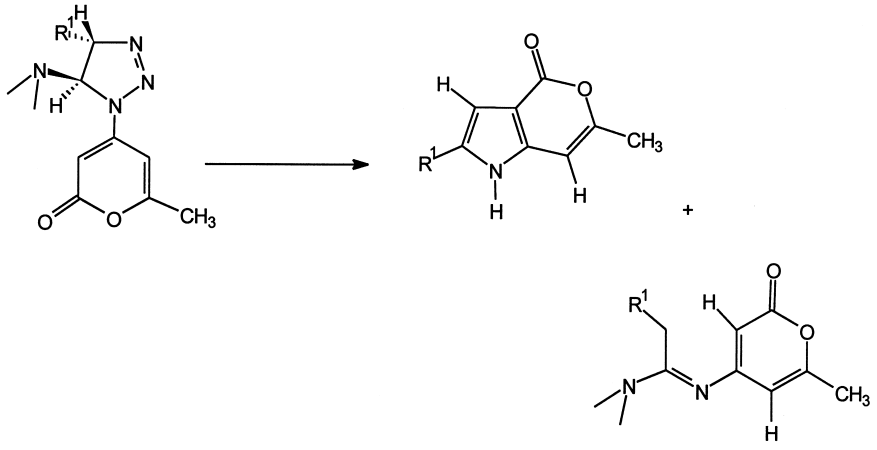
Abstract—A new synthesis of 2-pyridineacetamides was developed starting from pyran-2-one *N*-functionalized amidines **4**. Secondary amines reacted in a sealed tube with amidines **4** and, by nucleophilic attack on pyran-2-one nucleus and thermal rearrangement, afforded exclusively the 2-pyridineacetamide derivatives **6** or a mixture of amide compounds **6** and **7** depending on the substituents linked to C-α of the starting amidine **4**.

Amidines find widespread applications in organic chemistry as starting materials for preparation of many different nitrogen-containing heterocycles.[1]

For some years we have been interested in developing syntheses of nitrogen heterocycles through intramolecular rearrangements and/or condensations involving functionalized acetamidines. We recently reported that the thermal rearrangement of the 5-amino-4,5-dihydro-ν-triazoles bearing a 2-*H*-pyran-2-one group at N-1 gave a mixture of nitrogen functionalized tertiary amidines and 1*H*-pyrano[4,3-*b*]pyrrol-4-ones. The amidine yield depends strongly on selected reaction conditions and on C-4 substitution of dihydro-ν-triazoles[2] (Scheme 1).

In particular we decided to synthesize some 4,5-dihydro-ν-triazoles bearing on C-4 an useful substituent which shifted the reaction to achieve the amidines with the purpose to study in detail the reactivity of these substrates. We furthermore point out the presence of the pyran-2-one nucleus on the N-1 position.

It is well known that several kinds of nucleophiles can react with pyran-2-one at C-2 and C-6 causing initial ring opening, followed by a recyclization into a new heterocyclic system.[3] As well, the methylene group linked to amidine tertiary function is easily transformed into carbanion able to react in intramolecular nucleophilic condensations.[4]



Scheme 1. *Reagents and conditions*: toluene, reflux; or *n*.PrOH, reflux, or toluene, $BF_3.Et_2O$, reflux

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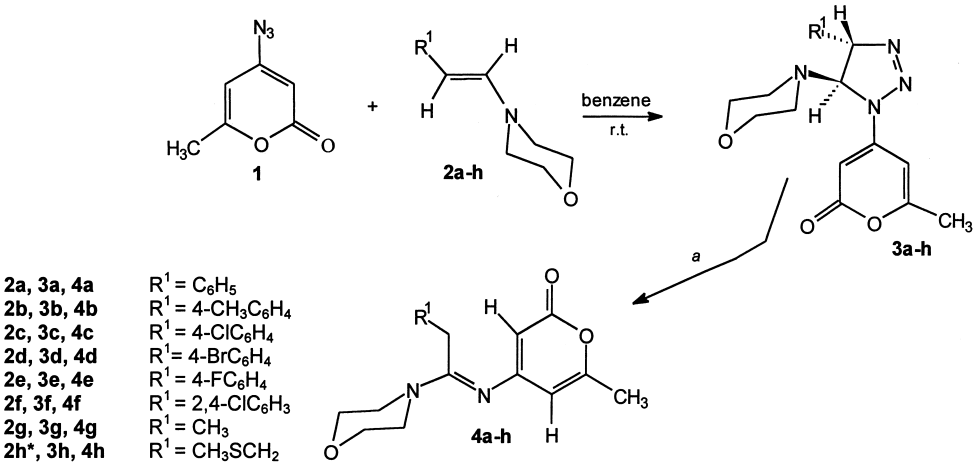


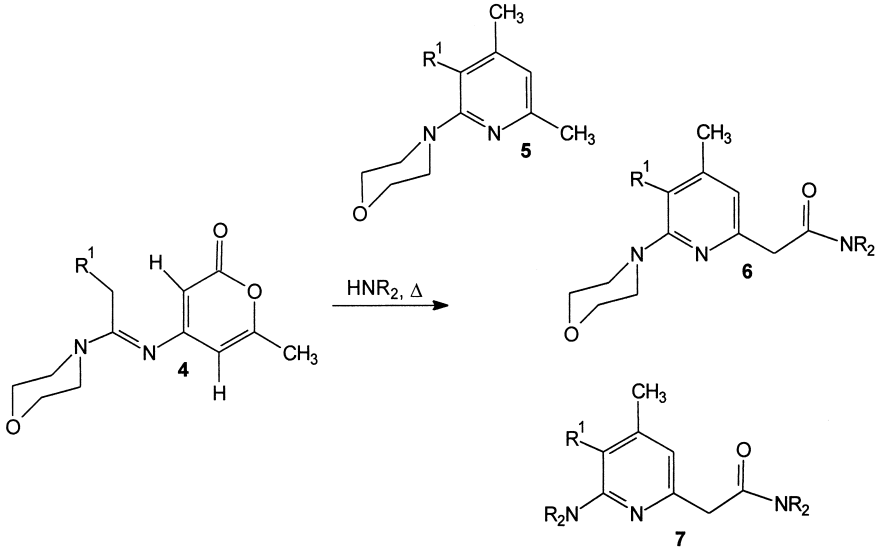
Scheme 2. [a]*Reagents and conditions*: toluene, reflux or *n*.propanol, reflux. [*]**2h** not isolated, but obtained *in situ*: see Experimental.

For this reason we decided to exploit either pyran-2-one nucleus reactivity and nucleophilic carbon atom on C-α to amidine group, with the purpose to find a satisfactory route to synthesize 2-pyridineacetamides. These substituted pyridines are of general interest owing to the presence of similar structures in several compounds with antiarrhytmic,[5] anti HIV[6] and enzymatic inhibitory activity.[7]

We now report that the reaction between secondary amines and pyran-2-one nitrogen-functionalized amidines offers a new effective route to highly substituted 2-pyridine-acetamides with the advantage to avoid a multi-step synthesis, through an unusual rearrangement.

1. Results and discussion

The preparation of 4,5-dihydro-ν-triazoles **3a–h** from



5 $R^1 = C_6H_5$

6a $R^1 = C_6H_5$, NR_2 = piperidine
6b $R^1 = C_6H_5$, NR_2 = N-methylpiperazine
6c $R^1 = C_6H_5$, NR_2 = morpholine
6d $R^1 = 4\text{-}CH_3C_6H_4$, NR_2 = piperidine
6e $R^1 = 4\text{-}ClC_6H_4$, NR_2 = piperidine
6f $R^1 = 4\text{-}ClC_6H_4$, NR_2 = N-methylpiperazine
6g $R^1 = 4\text{-}BrC_6H_4$, NR_2 = piperidine
6h $R^1 = 4\text{-}BrC_6H_4$, NR_2 = N-methylpiperazine
6i $R^1 = 4\text{-}BrC_6H_4$, NR_2 = N-carbethoxypiperazine
6j $R^1 = 4\text{-}FC_6H_4$, NR_2 = piperidine
6k $R^1 = 4\text{-}FC_6H_4$, NR_2 = N-methylpiperazine
6l $R^1 = 2,4\text{-}ClC_6H_3$, NR_2 = N-methylpiperazine
6m $R^1 = CH_3$, NR_2 = piperidine
6n $R^1 = CH_3$, NR_2 = N-methylpiperazine
6o $R^1 = C_6H_5$, NR_2 = diethylamine
6p $R^1 = CH_3SCH_2$, NR_2 = N-methylpiperazine

7a $R^1 = CH_3$, NR_2 = piperidine
7b $R^1 = CH_3$, NR_2 = N-methylpiperazine
7c $R^1 = CH_3SCH_2$, NR_2 = N-methylpiperazine

Scheme 3.

cycloaddition of azide **1** and appropriate enamines **2a–h** in benzene solution has already been described.[2] Compounds **3a–e**, **g** are known and have *trans* configuration. The same configuration was also assigned to new products **3f** and **3h** which show a NMR coupling constant of about 3 Hz.

Compounds **3a–h** when heated in boiling *n*-propanol or in toluene gave the corresponding amidines **4a–h** (Scheme 2). It is well known the cleavage of the N(1)–N(2) bond in the 4,5-dihydro-*v*-triazole nucleus is made easier by electron-withdrawing groups on N-1.[8]

During our preliminary experiment the 6-methyl-4-(1-morpholino-2-phenylethylideneamino)-2*H*-pyran-2-one **4a** was refluxed in piperidine as solvent and after 17 h turned into a mixture of substituted pyridines **5** and **6a** in the ratio of 1:2 (Scheme 3).

Their spectral data were in agreement with the proposed structures and with available data in literature for similar substitution pattern.[9] ^{13}C NMR spectrum of 2-pyridine-acetamide **6a** showed the signals related to CH-3 at about 119 ppm and to amide carbonyl group at 169 ppm, the latter was validated also by IR stretching at 1630 cm^{-1}. ^{1}H NMR was characterized by three singlets (2.06, 3.80 and 6.87 δ) associated with CH_3 on C-4, CH_2 linked to amide carbonyl group on C-2 and H-3 on C-3, respectively.

In ^{1}H NMR spectrum of 4,6-dimethylpyridine derivative **5** three singlets at 2.05, 2.44 and 6.70 δ associated, respectively, with the methyl groups linked to C-4 and C-2 and H-3 of the pyridine ring appeared diagnostic.

It can be quite reasonable to assume that **5** and **6a** come from two different pathways, which seem competitive in these reaction conditions (Scheme 4).

According to *path a* the pyridine amide derivative **6a** resulted from the nucleophilic attack of the amino group on the C-2 position of 2-pyranone nucleus followed by ring opening and intramolecular cyclization, by way of the C-α amidinic carbanion intermediate.

According to *path b* the formation of 4,6-dimethylpyridine derivative **5** is rationalized as follows: addition of the amino group on the C-6 position of the pyran-2-one nucleus, ring opening, followed by ring closure of the C-α amidinic carbanion intermediate. The final product **5** was achieved after decarboxylation step, as it is well known on the pyridine nucleus,[10] and amino group elimination favored by aromatization to give pyridine ring.

To confirm the proposed mechanism and to determine the best conditions to enhance the yield of amide derivatives **6** we decided to investigate the reaction closely.

The reaction of the amidine **4a** in piperidine as solvent at 60°C for 35 h afforded a reaction mixture containing 15% of amide **6a** and pyridine **5** in 85% yield. During subsequent experiments the piperidine and the amidine **4a** were mixed in a sealed tube and put in a preheated oil bath at 170 and then at 200°C. Significant improvements in yields were achieved by these reaction conditions. Just in 5 h at 170°C the major isomer was shown to be the 2-pyridineacetamide **6a** (88%) beside the 4,6-dimethylpyridine **5** in 12% yield. The ratio of **5** and **6a** in the mixture was determined by ^{1}H NMR analysis. In fact the different hydrogen shift on C-3 for **5** and **6a** (6.70 and 6.87 δ, respectively) allowed a clear difference between the two pyridines obtained. Performing the reaction at 200°C, the amide derivative **6a** was only obtained.

These results point out that under mild conditions the nucleophylic addition on the C-6 (*path b*) prevails, but at higher temperatures the addition product to C-2 position (*path a*) is favored.[11]

In order to verify that **5** does not arise from hydrolysis of amide **6a**, this product was reacted 35 h at 60°C under the most favorable conditions to **5** formation. The ^{1}H NMR spectrum of the crude mixture showed only the signals of amide derivative **6a**, thus confirming the independence of paths leading to **5** and **6**, respectively.

We thought therefore to extend the reaction to amidines **4b–h** and perform the reaction at 200°C. Amidines **4b–h** were mixed with an excess of secondary amines in a sealed tube and put in preheated oil bath at 200°C. The transformation required a reaction time within 2–4 h. The expected amides **6** are listed in Table 1.

Moreover the high temperature of the reaction mixture was responsible in some cases of low yields besides the formation of polymerised material.

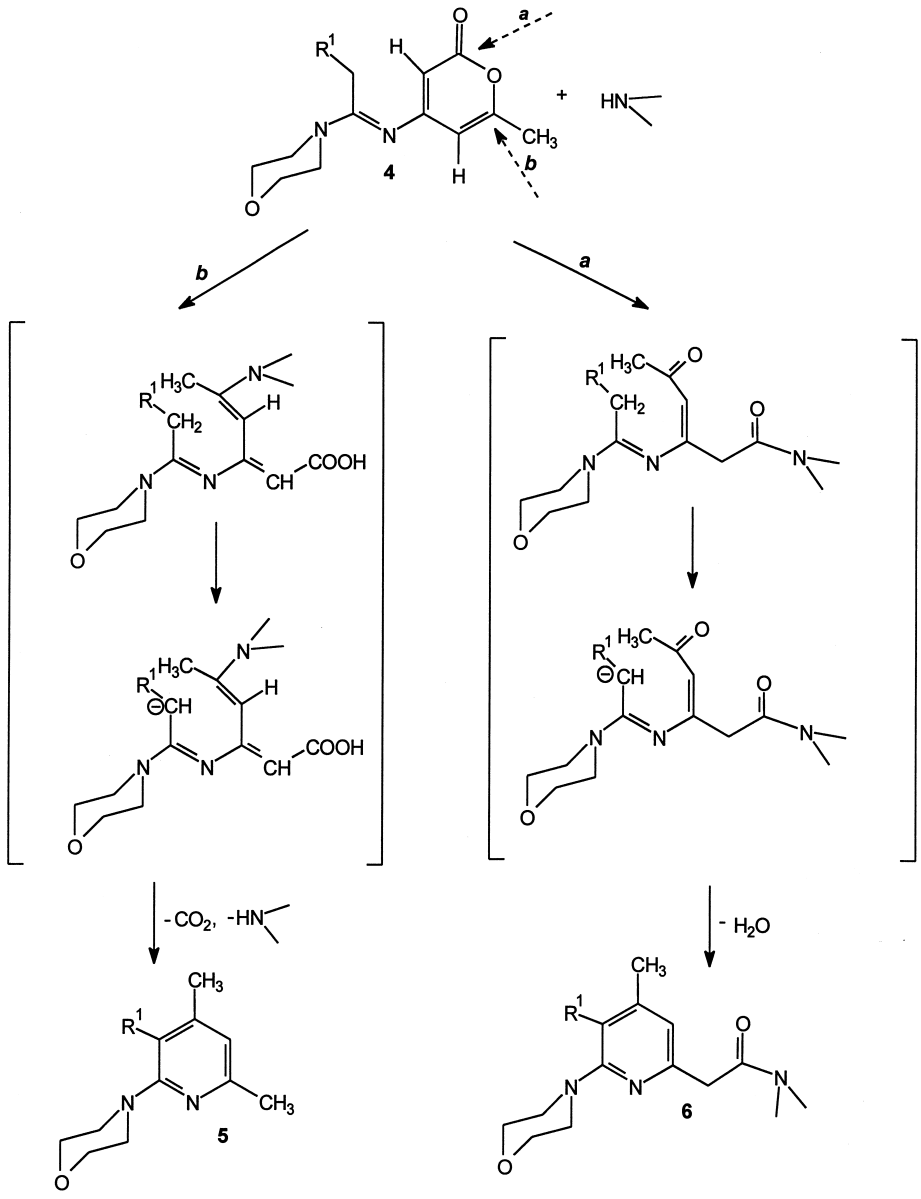
The best results were achieved from the amidines **4a–f** and suggest that the yields of the amide derivatives **6a–l**, **o** are depending on easy deprotonation of methylene group bound to aryl substituents.

Under these reaction conditions the amidines **4b–f** were converted into the expected pyridineacetamides **6a–l** and **6o**, whereas the compounds **4g**, **h** gave a mixture of two amide derivatives **6m** and **7a**, **6n** and **7b**, **6p** and **7c**, respectively. Confirmation of the structures was obtained from both ^{1}H and ^{13}C NMR of the purified materials obtained in a ratio of about 2:1, respectively.

It can be reasonably assumed that **7a–c** arise from a trans-amidation reaction of the amidines **4g**, **h** or of their intermediate compounds (Scheme 4). Amine exchange reaction has already been studied[12] on formamidines.

Considering that the key synthetic step in the formation of pyridine nucleus was the final cyclization of the C-α amidinic carbanion intermediate, the difficult formation of ethyl or methylsulfanylethyl carbanion could explain the low yield of the desired amides **6m**, **6n** and **6p** and the concomitant formation of the amides **7a–c**.

In order to verify that the amides **7a–c** do not arise from nucleophilic attack on C-α of the pyridine nucleus,[13] the amide **6m** was treated with a large amount of piperidine and heated in a sealed tube for 4 h, under the same previously adopted conditions. ^{1}H NMR analysis of the



Scheme 4.

Table 1. Preparation of 2-pyridineacetamides **6** and **7** from amidines **4**

Starting compounds	Amine	Reaction time (h)	Amide **6** yield (%)	Amide **7** yield (%)
4a	Piperidine	4	**6a** (70)	
4a	*N*-Methylpiperazine	3	**6b** (72)	
4a	Morpholine	2.5	**6c** (75)	
4b	Piperidine	4	**6d** (67)	
4c	Piperidine	2.5	**6e** (70)	
4c	*N*-Methylpiperazine	2.5	**6f** (73)	
4d	piperidine	2.5	**6g** (60)	
4d	*N*-Methylpiperazine	2.5	**6h** (60)	
4d	*N*-Carbethoxypiperazine	4	**6i** (53)	
4e	Piperidine	2.5	**6j** (70)	
4e	*N*-Methylpiperazine	2.5	**6k** (65)	
4f	*N*-Methylpiperazine	4	**6l** (65)	
4g	Piperidine	4	**6m** (40)	**7a** (20)
4g	*N*-Methylpiperazine	3	**6n** (57)	**7b** (26)
4a	Diethylamine	2	**6o** (65)	
4h	*N*-Methylpiperazine	2	**6p** (42)	**7c** (23)

crude reaction mixture showed only the amide **6m** peaks and confirmed transamidation hypothesis.

2. Conclusion

These results demonstrated the double reactivity of the amidines functionalized at iminic nitrogen with pyran-2-one nucleus and the synthetic potentiality of the substrate. In this case the amidines became part of a wide chapter of the synthetic methodology to obtain functionalized pyridines.

3. Experimental

3.1. General

Melting points were determined using a Buchi 510 (capillary) or an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured using a JASCO IR Report 100 instrument. ^{1}H and ^{13}C NMR spectra (tetramethylsilane as internal standard) were recorded with EM Varian Gemini 200, Bruker AC 200 and Bruker Avance 300 Spectrometers. *J* values are given in Hz for solutions in $CDCl_3$. Column chromatography was performed on Kieselgel 60 (Merck) 0.063–0.200 mm with eluents and ratios indicated.

Materials. 2,4-Dichlorophenylacetaldehyde,[14] azide **1**[15] and enamines **2a**, **b**, **d**,[16] **2c**,[17] **2e**[18] have already been described. 4,5-Dihydrotriazoles **3a**–**e** and **3g** and amidines **4a**–**e** and **4g** are known compounds.[2]

3.1.1. (*E*) 4-[2-(2,4-Dichlorophenyl)-ethenyl]-morpholine 2f. 2,4-Dichlorophenylacetaldehyde (5.9 g, 30 mmol) and morpholine (2.7 ml, 30 mmol) were dissolved in anhydrous toluene (60 ml) and heated at reflux with azeotropic removal of water. The reaction progress was checked by IR spectroscopy until aldehyde absorption disappeared. The toluene solution was dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. After IR and ^{1}H NMR analysis and without further purification, the pale yellow oily residue (7 g, 90%) was reacted with azide. IR (liquid film) ν_{max} 1633 cm^{-1}; ^{1}H NMR δ 3.05–3.15 (4H, m, CH_2NCH_2), 3.72–3.80 (4H, m, CH_2OCH_2), 5.63 (1H, d, *J*=13.9 Hz, vinylic H), 6.60 (1H, d, *J*=13.9 Hz, vinylic H), 7.07–7.34 (3H, m, ArH). Anal. calcd for $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08; N, 5.43; found: C, 55.64; H, 4.96; N, 5.31.

3.1.2. 4-[4-(2,4-Dichlorophenyl)-4,5-dihydro-5-morpholino-1*H*-1,2,3-triazol-1-yl]-6-methyl-2*H*-pyran-2-one 3f. Azide **1** (3.0 g, 20 mmol) was dissolved in benzene (20 ml) and an equimolar amount of enamine **2f**, dissolved in benzene (20 ml), was added dropwise. The mixture was stirred overnight at room temperature. (TLC cyclohexane/EtOAc, 1:9) The white precipitate was filtered off and recrystallized from benzene to give pure **3f** as white crystals (5.97 g, 73%); mp 154°C (decomp.); IR (Nujol) ν_{max} 1716 (C=O) cm^{-1}; ^{1}H NMR δ 2.33 (3H, s, CH_3); 2.43–2.52 (4H, m, CH_2NCH_2); 3.65–3.75 (4H, m, CH_2OCH_2); 4.57 (1H, d, *J*=3.3 Hz, H-5); 5.98 (1H, d, *J*=3.3 Hz, H-4); 5.73 (1H, s, H-3 pyranone); 6.77 (1H, s, H-5 pyranone); 6.57 (1H, d, *J*=8.4 Hz, ArH-6′); 7.25 (1H, dd, *J*=8.4 and 2.2 Hz, ArH-5′); 7.52 (1H, d, *J*=2.2 Hz, ArH-3′). Anal. calcd for $C_{18}H_{18}Cl_2N_4O_3$: C, 52.83; H, 4.43; N, 13.69; found: C, 52.94; H, 4.51; N, 13.42.

3.1.3. 4-(4,5-Dihydro-4-methylsulfanylmethyl-5-morpholino-1*H*-1,2,3-triazol-1-yl)-6-methyl-2*H*-pyran-2-one 3h. A benzene solution (20 ml) of morpholine (1.74 g, 20 mmol) was added dropwise to a stirred solution of azide **1** (3 g, 20 mmol) and 3-methylsulfanylpropionaldehyde (2.08 g, 20 mmol) in benzene (30 ml). The mixture was stirred at rt until the starting azide disappeared (about 3 h) (TLC cyclohexane/EtOAc, 1:9). The solution was dried with Na_2SO_4, filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and by adding iPr$_2$O afforded pure **3h** (4.8 g, 74%) as cream needles; mp 99°C (decomp.); IR (Nujol) ν_{max} 1727 (C=O) cm^{-1}; ^{1}H NMR δ 2.20 (3H, s, CH_3S), 2.29 (3H, s, CH_3), 2.21–2.45 (5H, m, CH_2NCH_2 and 1H of CH_2S linked to C-4), 2.99 (1H, dd, *J*=4.3 Hz and J_{gem}=13.8 Hz, H of CH_2S linked to C-4), 3.60–3.70 (4H, m, CH_2OCH_2), 4.65 (1H, d, J_{trans}=3.0 Hz, H-5), 4.75 (1H, ddd, J_{trans}=3.0 Hz, *J*=4.3 and 7.3 Hz, H-4), 5.77 (1H, s, H-3 pyranone), 6.71 (1H, s, H-5 pyranone). Anal. calcd for $C_{14}H_{20}N_4O_3S$: C, 51.84; H, 6.21; N, 17.27; found C, 51.89; H, 6.27; N, 16.98.

3.1.4. 4-[2-(2,4-Dichlorophenyl)-1-morpholino-ethylideneamino]-6-methyl-2*H*-pyran-2-one 4f. Dihydrotriazole **3f** (4.1 g, 10 mmol) was dissolved in *n*-propanol (70 ml) and heated under reflux until the starting compound disappeared (2 h), progress of the reaction being followed by TLC (cyclohexane/EtOAc 4:6). The solvent was removed in vacuo. The crude residue was taken up with CH_2Cl_2 and insoluble precipitate was filtered off. The filtrate was evaporated under reduced pressure to give a residue, which was crystallized from *n*-PrOH to afford the amidine **4f** (2.67 g, 70%) as orange plates; mp 137°C; IR (Nujol) ν_{max} 1715 (C=O) cm^{-1}; ^{1}H NMR δ 2.18 (3H, s, CH_3); 3.41–3.65 (8H, m, morpholine); 3.78 (2H, s, CH_2); 5.23 (1H, s, H–3), 5.63 (1H, s, H-5); 7.10 (1H, d, *J*=8.4 Hz, ArH-6′), 7.29 (1H, dd, *J*=8.4 and 1.8 Hz, ArH-5′), 7.44 (1H, d, *J*=1.8 Hz, ArH-3′). Anal. calcd for $C_{18}H_{18}Cl_2N_2O_3$: C, 56.71; H, 4.76; N, 7.35. Found: C, 56.68; H, 4.74; N, 7.41.

3.1.5. 6-Methyl-4-(3-methylsulfanyl-1-morpholino-propylideneamino)-2*H*-pyran-2-one 4h. A solution of dihydrotriazole **3h** (3.2 g, 10 mmol) was refluxed in toluene (60 ml), progress of the reaction being followed by TLC (cyclohexane/EtOAc, 1:9). After disappearance of the starting material (3 h) the solvent was removed in vacuo and the oily residue crystallized by adding of Et_2O to give **4h** (2.46 g, 83%) as cream needles; mp 111°C; IR (Nujol) ν_{max} 1690 (C=O) cm^{-1}; ^{1}H NMR δ 2.08 (3H, s, CH_3); 2.22 (3H, s, SCH_3), 2.56–2.70 (4H, m, 2×CH_2), 3.45–3.53 (4H, m, CH_2NCH_2); 3.70–3.78 (4H, m, CH_2OCH_2); 5.28 (1H, s, H-3), 5.67 (1H, s, H-5). Anal. calcd for $C_{14}H_{20}N_2O_3S$: C, 56.74; H, 6.80; N, 9.45; found: C, 56.65; H, 6.73; N, 9.30.

3.1.6. Reaction of the amidine 4a with piperidine at reflux. Synthesis of 4-(4,6-dimethyl-3-phenyl-pyridin-2-yl)-morpholine 5 and 2-(4-methyl-6-morpholino-5-phenyl-pyridin-2-yl)-1-piperidin-1-yl-ethanone 6a. Amidine

4a (1.56 g, 5 mmol) was suspended in piperidine (15 ml). The reaction mixture was refluxed until disappearance (TLC monitoring) of the starting compound (17 h). The amine excess was removed in vacuo and the crude residue chromatographed on a silica gel column, eluent EtOAc/cyclohexane (4:6). Two fractions were collected: a first minor fraction containing the pyridine derivative **5** and a second fraction containing the pyridine amide **6a**

Compound **5**: White crystals from *i*Pr_2O, 0.39 g, yield 29%, mp 87°C; ^{1}H NMR δ 2.05 (3H, s, *p*-CH_3); 2.44 (3H, s, *o*-CH_3); 2.92–3.02 (4H, m, CH_2NCH_2); 3.43–3.50 (4H, m, CH_2OCH_2); 6.70 (1H, s, H-3); 7.2–7.44 (5H, m, ArH); ^{13}C NMR δ 20.8 (*p*-CH_3); 24.5 (*o*-CH_3); 50.1 (CH_2NCH_2); 67.4 (CH_2OCH_2); 119.1 (*m*-CH); 127.3, 128.8, 130.6, (ArCH); 125.0, 138.8, 147.2 (ArCqu); 155.2 (C bound to *o*-CH_3); 160.0 (C bound to morpholino group). Anal. calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44; found: C,76.01; H, 7.62; N, 10.33.

Compound **6a**: cream crystals from petroleum ether, 1.14 g, yield 60%, mp 112°C; IR (Nujol) ν_{max} 1630 (C═O) cm^{-1}; ^{1}H NMR δ 1.45–1.70 (6H, m, $CH_2CH_2CH_2$); 2.06 (3H, s, *p*-CH_3); 2.90–3.00 (4H, m, CH_2NCH_2); 3.42–3.50 (4H, m, CH_2OCH_2); 3.54–3.69 (4H, m, O═C–N(CH_2)$_2$); 3.80 (2H, s, CH_2); 6.87 (1H, s, H-3); 7.29–7.47 (5H, m, ArH); ^{13}C NMR δ 20.6 (*p*-CH_3); 24.6, 25.6, 26.5 ($CH_2CH_2CH_2$); 43.0, 43.6 (O═C–N(CH_2)$_2$); 47.7 (CH_2–C═O); 49.7 (CH_2NCH_2); 66.9 (CH_2OCH_2), 118.9 (C-3); 127.1, 128.5, 130.1 (ArCH); 125.6, 138.0, 147.4 (ArCqu), 152.2 (C-2); 159.6 (C-6); 169.0 (C═O). Anal. calcd for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07; found: C, 72.67; H, 7.63; N, 11.09.

3.2. General procedure for the preparation of amide derivatives 6 and 7

Amidines **4a**–**h** (5 mmol) mixed with a large amount of the appropriate amine (100 mmol) in a sealed tube were put in a preheated oil bath at 200°C and heated for at least 2 h. Afterwards, the progress of the reaction was monitored by TLC every 30 min, until disappearance of the starting amidine **4**.

The amine excess was removed in vacuo and the residue was chromatographed on silica gel affording compound **6** and in some cases minor amounts of compound **7** (eluent described later). The yields of isolated and purified products **6** and **7** are listed in Table 1.

3.2.1. 2-(4-Methyl-6-morpholino-5-phenyl-pyridin-2-yl)-1-piperidin-1-yl-ethanone 6a. (EtOAc/cyclohexane, 4:6). Analytical data are described earlier.

3.2.2. 2-(4-Methyl-6-morpholino-5-phenyl-pyridin-2-yl)-1-(4-methyl-pyperazin-1-yl)-ethanone 6b. (MeOH/EtOAc, 7:3); cream plates from *i*Pr_2O; mp 110°C; IR (Nujol) ν_{max} 1620 (C═O) cm^{-1}; ^{1}H NMR δ 2.05 (3H, s, *p*-CH_3); 2.33 (3H, s, H_3C–N); 2.35–2.47 (4H, m, H_3C–N(CH_2)$_2$); 2.87–2.96 (4H, m, CH_2NCH_2); 3.38–3.48 (4H, m, CH_2OCH_2); 3.67–3.82 (4H, m, O═CN(CH_2)$_2$); 3.80 (2H, s, CH_2); 6.85 (1H, s, H-3); 7.20–7.42 (5H, m, ArH).^{13}C NMR δ 20.9 (*p*-CH_3); 42.0 and 43.8 (H_3C–N(CH_2)$_2$); 46.3 (H_3C–N); 46.6 (CH_2–C═O); 50.1 (CH_2NCH_2); 55.0 and 55.6 (O═C–N(CH_2)$_2$); 67.2 (CH_2OCH_2); 119.3 (C-3); 127.5, 128.9, 130.4 (ArCH); 126.2, 138.3, 147.9 (ArCqu); 152.3 (C-2); 160.1 (C-6); 169.5 (C═O). Anal. calcd for $C_{23}H_{30}N_4O_2$: C, 70.02; H, 7.66; N, 14.20; found: C, 69.87; H, 7.54; N, 13.99.

3.2.3. 2-(4-Methyl-6-morpholino-5-phenyl-pyridin-2-yl)-1-morpholin-4-yl-ethanone 6c. (EtOAc); orange plates from *i*Pr_2O; mp 134°C; IR (Nujol) ν_{max} 1634 (C═O) cm^{-1}; ^{1}H NMR δ 2.06 (3H, s, *p*-CH_3); 2.90–2.98 (4H, m, CH_2NCH_2); 3.42–3.50 (4H, m, CH_2OCH_2); 3.60–3.77 (8H, m, O═CN(CH_2)$_2$ and CH_2OCH_2); 3.80 (2H, s, CH_2); 6.87 (1H, s, H-3); 7.26–7.45 (5H, m, ArH). ^{13}C NMR δ 20.6 (*p*-CH_3) 42.3 and 43.3 (O═C–N(CH_2)$_2$); 47.0 (CH_2–C═O); 49.7 (CH_2NCH_2); 66.9 (2×CH_2OCH_2), 119.0 (C-3); 127.2, 128.5, 130.0 (ArCH); 125.9, 137.8, 147.6 (ArCqu), 151.7 (C-2); 159.7 (C-6); 169.4 (C═O). Anal. calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02; found: C, 69.02; H, 7.16; N, 10.81.

3.2.4. 2-(4-Methyl-6-morpholino-5-*p*-tolyl-pyridin-2-yl)-1-piperidin-1-yl-ethanone 6d. (EtOAc/cyclohexane, 7:3); cream needles from *i*Pr_2O; mp 90°C; IR (Nujol) ν_{max} 1644 (C═O) cm^{-1}; ^{1}H NMR δ 1.42–1.65 (6H, m, $CH_2CH_2CH_2$); 2.05 (3H, s, *p*-CH_3); 2.39 (3H, s, CH_3-tolyl); 2.84–2.98 (4H, m, CH_2NCH_2); 3.43–3.50 (4H, m, CH_2OCH_2); 3.56–3.68 (4H, m, O═CN(CH_2)$_2$); 3.79 (2H, s, CH_2); 6.85 (1H, s, H-3); 7.11–7.24 (4H, m, ArH); ^{13}C NMR δ 20.6 (*p*-CH_3); 21.3 (CH_3-tolyl); 24.6, 25.6, 26.5 ($CH_2CH_2CH_2$); 43.0 and 43.7 (O═C–N(CH_2)$_2$); 47.6 (CH_2–C═O); 49.6 (CH_2NCH_2); 66.9 (CH_2OCH_2), 118.8 (C-3); 129.2, 129.9, (ArCH); 125.5, 134.9, 136.6, 147.4 (ArCqu); 152.0 (C-2); 159.6 (C-6); 168.9 (C═O). Anal. calcd for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.94; N, 10.68; found: C, 73.17; H, 7.85; N, 10.89.

3.2.5. 2-[5-(4-Chlorophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-1-piperidin-1-yl-ethanone 6e. (EtOAc/cyclohexane, 6:4); cream plates from *i*Pr_2O; mp 86°C; IR (Nujol) ν_{max} 1620 (C═O) cm^{-1}; ^{1}H NMR δ 1.38–1.70 (6H, m, $CH_2CH_2CH_2$); 2.04 (3H, s, *p*-CH_3); 2.90–3.00 (4H, m, CH_2NCH_2); 3.43–3.54 (4H, m, CH_2OCH_2); 3.53–3.68 (4H, m, O═C–N(CH_2)$_2$); 3.79 (2H, s, CH_2); 6.87 (1H, s, H-3); 7.23 and 7.40 (4H, 2 x d, AB system, *J*=8.5 Hz, ArH); ^{13}C NMR δ 20.9 (*p*-CH_3); 25.0, 26.0, 26.9 ($CH_2CH_2CH_2$); 43.4 and 43.9 (O═C–N(CH_2)$_2$); 48.0 (CH_2–C═O); 50.2 (CH_2NCH_2); 67.2 (CH_2OCH_2); 119.5 (C-3); 129.2, 131.9 (ArCH); 124.9, 133.3, 136.9, 147.7 (ArCqu); 153.1 (C-2); 160.0 (C-6); 169.1 (C═O). Anal. calcd for $C_{23}H_{28}ClN_3O_2$: C, 66.74, H, 6.82, N, 10.15; found: C, 66.63; H, 6.77; N, 10.21.

3.2.6. 2-[5-(4-Chlorophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-1-(4-methyl-piperazin-1-yl)-ethanone 6f. (MeOH/EtOAc, 7:3); cream plates from *i*Pr_2O; mp 115°C; IR (Nujol) ν_{max} 1630 (C═O) cm^{-1}; ^{1}H NMR δ 2.06 (3H, s, *p*-CH_3); 2.31 (3H, s, CH_3–N); 2.30–2.50 (4H, m, (CH_2)$_2$NCH$_3$); 2.93–3.00 (4H, m, CH_2NCH_2); 3.45–3.57 (4H, m, CH_2OCH_2); 3.65–3.80 (4H, m, O═C–N(CH_2)$_2$); 3.81 (2H, s, CH_2); 6.88 (1H, s, H-3); 7.25 and 7.41 (4H, 2 x d, AB system, *J*=8.4 Hz, ArH); ^{13}C NMR δ 20.4 (*p*-CH_3); 41.8 and 43.3 (H_3C–N(CH_2)$_2$); 46.1 (H_3C–N); 46.5 (CH_2–C═O); 49.8 (CH_2NCH_2); 54.7 and 55.3 (O═CN(CH_2)$_2$); 66.8 (CH_2OCH_2); 119.2 (C-3); 128.8, 131.5 (ArCH); 124.6, 133.0, 136.4, 147.5 (ArCqu); 152.4 (C-2,); 159.6

(C-6); 169.0 (C═O). Anal. calcd for $C_{23}H_{29}ClN_4O_2$: C, 66.46; H, 6.83; N, 13.08; found: C, 66.39; H, 6.81; N, 13.09.

3.2.7. 2-[5-(4-Bromophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-1-piperidin-1-yl-ethanone 6g. (EtOAc/cyclohexane, 7:3); orange plates from *i*Pr_2O; mp 93°C; IR (Nujol) ν_{max} 1633 (C═O) cm^{-1}; ^1H NMR (200 MHz,) δ 1.40–1.78 (6H, m, $CH_2CH_2CH_2$), 2.06 (3H, s, *p*-CH_3), 2.92–3.00 (4H, m, CH_2NCH_2), 3.48–3.56 (4H, m, CH_2OCH_2); 3.58–3.71 (4H, m, O═C–N(CH_2)$_2$); 3.81 (2H, s, CH_2); 6.89 (1H, s, H-3) 7.20 and 7.56 (4H, 2×d, AB system, *J*=8.4 Hz, ArH); ^{13}C NMR δ 20.5 (*p*-CH_3); 24.6, 25.6, 26.6 ($CH_2CH_2CH_2$); 43.0 and 43.6 (O═C–N(CH_2)$_2$); 47.6 (CH_2–C═O); 49.8 (CH_2NCH_2); 66.9 (CH_2OCH_2); 119.2 (C-3); 121.5 (C-5);131.7 and 131.8 (ArCH) 124.5 and 137 (2 ArCqu) 147.3 (C-4); 152.8 (C-2); 159.5 (C-6); 168.8 (C═O). Anal. calcd for $C_{23}H_{28}BrN_3O_2$: C, 60.26; H, 6.16; N, 9.17; found: C, 59.94; H, 6.15; N, 8.98.

3.2.8. 2-[5-(4-Bromophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-1-(4-methyl-piperazin-1-yl)-ethanone 6h. (MeOH/EtOAc, 7:3); ochre plates from *i*Pr_2O; mp 112°C; IR (Nujol) ν_{max} 1650 (C═O) cm^{-1}; ^1H NMR δ 2.06 (3H, s, 3H, *p*-CH_3); 2.32 (3H, s, N–CH_3); 2.36–2.44 (4H, m, (CH_2)$_2$NCH$_3$); 2.92–2.97 (4H, m, CH_2NCH_2); 3.47–3.52 (4H, m, CH_2OCH_2); 3.68–3.79 (4H, m, O═C–N(CH_2)$_2$); 3.81 (2H, s, CH_2); 6.88 (1H, s, H-3); 7.19 and 7.57 (4H, 2×d, AB system, *J*=8.1 Hz, ArH); ^{13}C NMR δ 20.5 (*p*-CH_3); 41.8 and 43.3 (H_3C–N(CH_2)$_2$); 46.1 (H_3C–N); 46.5 (CH_2–C═O); 49.8 (CH_2NCH_2); 54.7 and 55.3 (O═C–N(CH_2)$_2$); 66.8 (CH_2OCH_2); 119.2 (C-3); 131.8 (ArCH); 121.1, 124.6, 136.9, 147.4 (ArCqu); 152.4 (C-2); 159.6 (C-6); 169.0 (C═O). Anal. calcd for $C_{23}H_{29}BrN_4O_2$: C, 58.35, H, 6.17, N, 11.83; found: C, 58.50; H, 6.17; N, 11.71.

3.2.9. 4-{2-[5-(4-Bromophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-acetyl}-piperazine-1-carboxylic acid ethyl ester 6i. (EtOAc/cyclohexane, 9:1); white crystals from *i*Pr_2O; mp 142°C; IR (Nujol) ν_{max} 1632 (C═O), 1680 (N–C–OO) cm^{-1}; ^1H NMR δ 1.29 (3H, t, *J*=7 Hz, CH_3–CH_2); 2.07 (3H, s, *p*-CH_3), 2.92–2.97 (4H, m, CH_2NCH_2); 3.40–3.60 (8H, m, CH_2OCH_2 and (CH_2)$_2$NCOOEt); 3.64–3.77 (4H, m, O═C–N(CH_2)$_2$); 3.83 (2H, s, CH_2); 4.17 (2H, dd, *J*=7 Hz, CH_2–CH_3); 6.89 (1H, s, H-3); 7.19 and 7.58 (4H, 2×d, AB system, *J*=8.4 Hz, ArH); ^{13}C NMR δ 14.7 (CH_3–CH_2); 20.5 (*p*-CH_3); 41.7 (C_2H_5OCO–N(CH_2)$_2$); 43.5 and 43.9 (O═C–N(CH_2)$_2$); 46.3 (CH_2–C═O); 49.8 (CH_2NCH_2); 61.8 (CH_2OC═O); 66.8 (CH_2OCH_2); 119.2 (C-3); 132.0 and 132.1 (ArCH); 121.2, 124.8, 136.7, 147.6 (ArCqu); 152.1 (C-2); 155.8 ($COOC_2H_5$); 160.0 (C-6); 169.2 (C═O). Anal. calcd for $C_{25}H_{31}BrN_4O_4$: C, 56.59; H, 5.89; N, 10.57; found: C, 56.36; H, 5.72; N, 10.34.

3.2.10. 2-[5-(4-Fluorophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-1-piperidin-1-yl-ethanone 6j. (EtOAc/cyclohexane, 7:3); pale yellow oil; IR (liquid film) ν_{max} 1640 (C═O) cm^{-1}; ^1H NMR δ 1.42–1.63 (6H, m, $CH_2CH_2CH_2$); 2.04 (3H, s, *p*-CH_3); 2.95–2.99 (4H, m, CH_2NCH_2); 3.45–3.51 (4H, m, CH_2OCH_2); 3.54–3.67 (4H, m, O═C–N(CH_2)$_2$); 3.79 (2H, s, CH_2); 6.87 (1H, s, H-3); 7.10 and 7.29 (4H, 2×d, AB system, *J*=8.8 Hz, ArH); ^{13}C NMR δ 20.4 (*p*-CH_3); 24.5, 25.6, 26.5 ($CH_2CH_2CH_2$); 42.9 and 43.5 (O═C–N–(CH_2)$_2$); 47.6 (CH_2–C═O); 49.7 (CH_2NCH_2); 66.8 (CH_2OCH_2); 115.3 and 115.7 (ArCH. *ortho* to F, *J*=21.5 Hz); 119.0 (C-3); 124.7 (C-5); 131.6 and 131.8 (ArCH *meta* to F, *J*=7.7 Hz); 133.7 and 133.8 (ArCqu *para* to F, *J*=3 Hz); 147.4 (C-4); 152.5 (C-2); 159.7 (C-6); 159.3 and 164.2 (*C* linked to F, J_{CF}=247.0 Hz); 168.8 (C═O). Anal. calcd for $C_{23}H_{28}FN_3O_2$: C, 69.48; H, 7.10; N, 10.58; found: C, 69.39; H, 7.03; N, 10.46.

3.2.11. 2-[5-(4-Fluorophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-1-(4-methyl-piperazin-1-yl)-ethanone 6k. (MeOH/EtOAc, 7:3); cream plates from *i*Pr_2O; mp 50°C; IR (Nujol) ν_{max} 1632 (C═O) cm^{-1}; ^1H NMR δ 2.04 (3H, s, *p*-CH_3), 2.27 (3H, s, CH_3–N); 2.30–2.43 (4H, m, (CH_2)$_2$NCH$_3$); 2.85–2.97 (4H, m, CH_2NCH_2); 3.35–3.47 (4H, m, CH_2OCH_2); 3.60–3.75 (4H, m, O═C–N(CH_2)$_2$); 3.78 (2H, s, CH_2); 6.87 (1H, s, H-3); 7.10 and 7.29 (4H, 2×d, AB system *J*=8.8 Hz, ArH). ^{13}C NMR δ 20.4 (*p*-CH_3); 41.8 and 43.3 (H_3C–N(CH_2)$_2$); 46.1 (H_3C–N); 46.4 (CH_2–C═O); 49.8 (CH_2NCH_2); 54.7 and 55.3 (O═C–N(CH_2)$_2$); 66.8 (CH_2OCH_2); 115.3 and 115.8 (ArCH *ortho* to F, *J*=21.5 Hz); 119.1 (C-3); 124.8 (C-5); 131.6 and 131.8 (ArCH *meta* to F *J*=7.8 Hz); 133.7 and 133.8 (ArCqu *para* to F, *J*=2.9 Hz); 147.5 (C-4); 152.2 (C-2); 159.80 (C-6); 159.4 and 164.3 (*C* linked to F, J_{CF}= 247.0 Hz); 169.1 (C═O). Anal. calcd for $C_{23}H_{29}FN_4O_2$: C, 66.95; H, 7.09; N, 13.59; found: C, 66.75; H, 6.99; N, 13.51.

3.2.12. 2-[5-(2,4-Dichlorophenyl)-4-methyl-6-morpholino-pyridin-2-yl]-1-(4-methyl-piperazin-1-yl)-ethanone 6l. (MeOH/EtOAc, 7:3); yellow oil; IR (liquid film) ν_{max} 1643 (C═O) cm^{-1}; ^1H NMR δ 2.00 (3H, s, *p*-CH_3); 2.30 (3H, s, CH_3–N); 2.32–2.40 (4H, m, (CH_2)$_2$NCH$_3$); 2.95–3.00 (4H, m, CH_2NCH_2); 3.47–3.55 (4H, m, CH_2OCH_2); 3.66–3.78 (4H, m, O═C–N (CH_2)$_2$); 3.83 (2H, s, CH_2); 6.90 (1H, s, H-3); 7.18 (1H, d, *J*=8.1 Hz, H-6′); 7.34 (1H, dd, *J*=8.1 and 2.2 Hz, H-5′), 7.53 (1H, d, *J*=2.2 Hz, H-3′); ^{13}C NMR δ 19.6 (*p*-CH_3); 41.8 and 43.5 (H_3C–N(CH_2)$_2$); 46.0 (H_3C–N); 46.4 (CH_2–C═O); 49.73 (CH_2NCH_2); 54.7 and 55.2 (O═C–N(CH_2)$_2$); 66.8 (CH_2OCH_2); 118.9 (C-3); 127.5, 129.7, 132.8 (ArCH); 122.9, 134.0, 135.1, 135.7, 148.5 (ArCqu); 153.3 (C-2); 159.7 (C-6); 169.0 (C═O). Anal. calcd for $C_{23}H_{28}Cl_2N_4O_2$: C, 59.72; H, 6.11; N, 12.12; found: C, 59.57; H, 6.04; N, 11.96.

3.2.13. 2-(4,5-Dimethyl-6-morpholino-pyridin-2-yl)-1-piperidin-1-yl-ethanone 6m. (EtOAc/cyclohexane, 7:3); white needles from *i*Pr_2O; mp 81°C; IR (Nujol) ν_{max} 1630 (C═O) cm^{-1}; ^1H NMR δ 1.30–1.65 (6H, m, $CH_2CH_2CH_2$); 2.17 (3H, s, *m*-CH_3); 2.23 (3H, s, *p*-CH_3); 2.98–3.10 (4H, m, CH_2NCH_2); 3.50–3.68 (4H, m, O═C–N(CH_2)$_2$); 3.78 (2H, s, CH_2); 3.80–3.87 (4H, m, CH_2OCH_2); 6.87 (1H, s, H-3); ^{13}C NMR δ 14.2 (*m*-CH_3); 20.2 (*p*-CH_3); 24.9, 25.9, 26.9 ($CH_2CH_2CH_2$); 43.3 and 44.1 (O═C–N–(CH_2)$_2$); 47.9 (CH_2–C═O); 51.1 (CH_2NCH_2); 67.6 (CH_2OCH_2); 120.1 (C-3); 121.7 (C-5); 148.4 (C-4); 151.1 (C-2); 161.4 (C-6); 169.3 (C═O). Anal. calcd for $C_{18}H_{27}N_3O_2$: C, 68.09; H, 8.58; N, 13.24; found: C, 68.36; H, 8.65; N, 13.19.

3.2.14. 2-(4,5-Dimethyl-6-piperidino-pyridin-2-yl)-1-piperidin-1-yl-ethanone 7a. White needles from *i*Pr_2O; mp 72°C; IR (Nujol) ν_{max} 1630 (C═O) cm^{-1}; ^1H NMR δ

1.30–1.80 (12H, m, 2×$CH_2CH_2CH_2$); 2.15 (3H, s, *m*-CH_3); 2.19 (3H, s, *p*-CH_3); 2.92–3.06 (4H, m, CH_2NCH_2); 3.50–3.68 (4H, m, O=C–N(CH_2)$_2$); 3.76 (2H, s, CH_2); 6.80 (1H, s, 1H, H-3); ^{13}C NMR δ 14.3 (*m*-CH_3); 20.3 (*p*-CH_3); 25.0, 25.1, 26.0, 26.7, 26.8 (CH_2 of piperidines); 43.3, 44.4 (O=C–N–(CH_2)$_2$); 47.9 (CH_2–C=O); 52.0 (CH_2NCH_2); 119.3 (C-3); 121.9 (C-5); 148.0 (C-4); 150.8 (C-2); 162.9 (C-6); 169.6 (C=O). Anal. calcd for $C_{19}H_{29}N_3O$: C, 72.33, H, 9.27, N, 13.33; found: C, 72.28; H, 9.19; N, 13.25.

3.2.15. 2-(4,5-Dimethyl-6-morpholino-pyridin-2-yl)-1-(4-methyl-piperazin-1-yl)-ethanone 6n. (MeOH/EtOAc, 7:3); pale yellow oil; IR (liquid film) ν_{max} 1644 (C=O) cm^{-1}; ^{1}H NMR δ 2.18 (3H, s, *m*-CH_3); 2.23 (3H, s, *p*-CH_3) 2.31 (3H, s, CH_3–N); 2.33–2.43 (4H, m, (CH_2)$_2$NCH$_3$); 3.02–3.10 (4H, m, CH_2NCH_2); 3.62–3.76 (4H, m, O=C–N(CH_2)$_2$); 3.77 (2H, s, CH_2); 3.82–3.88 (4H, m, CH_2OCH_2); 6.85 (1H, s, H-3); ^{13}C NMR δ 14.0 (*m*-CH_3); 20.0 (*p*-CH_3); 41.7 and 43.5 ((CH_2)$_2$NCH$_3$); 46.1 (NCH$_3$); 46.3 (CH_2C=O); 50.8 (CH_2NCH_2); 54.7 and 55.3 (O=C–N(CH_2)$_2$); 67.2 (CH_2OCH_2); 119.9 (C-3); 121.6 (C-5); 148.3 (C-4); 150.4 (C-2); 161.1 (C-6); 169.3 (C=O). Anal. calcd for $C_{18}H_{28}N_4O_2$: C, 65.02, H, 8.48, N, 16.86; found: C, 64.83; H, 8.42; N, 16.68.

3.2.16. 2-[4,5-Dimethyl-6-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-1-(4-methyl-piperazin-1-yl)-ethanone 7b. Pale yellow oil; IR (liquid film) ν_{max} 1643 (C=O) cm^{-1}; ^{1}H NMR δ 2.15 (3H, s, *m*-CH_3); 2.21 (3H, s, *p*-CH_3); 2.27 (3H, s, CH_3–N); 2.33–2.38 (4H, m, (CH_2)$_2$NCH$_3$); 2.44 (3H, s, CH_3–N); 2.64–2.74 (4H, m, (CH_2)$_2$NCH$_3$); 3.12–3.22 (4H, m, CH_2NCH_2); 3.61–3.73 (4H, m, O=C–N–(CH_2)$_2$); 3.76 (2H, s, CH_2); 6.83 (1H, s, H-3); ^{13}C NMR δ 14.1 (*m*-CH_3); 20.0 (*p*-CH_3); 41.7 and 43.6 ((CH_2)$_2$NCH$_3$); 46.0 (NCH$_3$); 46.2 (NCH$_3$); 46.4 (CH_2C=O); 50.0 (CH_2NCH_2); 54.7 and 55.3 (O=C–N(CH_2)$_2$ and CH_2NCH_2); 119.5 (C-3); 121.5 (C-5); 148.1 (C-4); 150.2 (C-2); 161.1 (C-6); 169.4 (C=O). Anal. calcd for $C_{19}H_{31}N_5O$: C, 66.04, H, 9.05, N, 20.28; found: C, 66.31; H, 9.13; N, 20.07.

3.2.17. *N*,*N*-Diethyl-2-(4-methyl-6-morpholino-5-phenyl-pyridin-2-yl)-acetamide 6o. (EtOAc/cyclohexane, 7:3); chestnut plates from *i*Pr$_2$O; mp 77°C; IR (Nujol) ν_{max} 1631 (C=O) cm^{-1}; ^{1}H NMR δ 1.13–1.25 (6H, m, 2×CH_3CH_2); 2.08 (3H, s, *p*-CH_3); 2.93–3.01 (4H, m, CH_2NCH_2); 3.43–3.50 (4H, m, CH_2OCH_2); 3.52–3.63 (4H, m, 2×CH_2CH_3); 3.79 (2H, s, CH_2C=O); 6.88 (s; 1H, H-3); 7.27–7.43 (5H, m, ArH); ^{13}C NMR δ 13.1 (CH_3); 14.4 (CH_3); 20.5 (*p*-CH_3); 40.3 (CH_2); 42.6 (CH_2); 43.2 (CH_2C=O); 49.7 (CH_2NCH_2); 66.9 (CH_2OCH_2); 119.0 (C-3); 127.0, 128.5, 130.1 (ArCH); 125.6, 138.1, 147.3 (ArCqu); 152.5 (C-2); 159.6 (C-6.); 169.9 (C=O). Anal. calcd for $C_{22}H_{29}N_3O_2$: C, 71.89; H, 7.96; N, 11.44; found: C, 71.75; H, 7.83; N, 11.29.

3.2.18. 2-(4-Methyl-5-methylsulfanylmethyl-6-morpholino-pyridin-2-yl)-1-(4-methyl-piperazin-1-yl)-ethanone 6p. (MeOH/EtOAc, 7:3); chestnut plates from *i*Pr$_2$O; mp 72°C; IR (Nujol) ν_{max} 1643 (C=O) cm^{-1}; ^{1}H NMR δ 2.11 (3H, s, CH_3S); 2.25 (3H, s, *p*-CH_3); 2.20–2.34 (4H, m, (CH_2)$_2$NCH$_3$); 2.37 (3H, s, CH_3–N); 3.08–3.14 (4H, m, CH_2NCH_2); 3.40–3.72 (4H, m, O=C–N(CH_2)$_2$); 3.75 (2H, s, CH_2S); 3.77 (2H, s, CH_2CO); 3.80–3.86 (4H, m, CH_2OCH_2); 6.87 (1H, s, H-3); ^{13}C NMR δ 16.3 (CH_3S); 19.2 (*p*-CH_3); 31.3 (CH_2S); 41.8 and 43.5 ((CH_2)$_2$NCH$_3$); 46.0 (NCH$_3$); 46.3 (CH_2C=O); 51.8 (CH_2NCH_2); 54.7 and 55.2 (O=C–N(CH_2)$_2$); 67.3 (CH_2OCH_2); 121.3 (C-3); 123.0 (C-5); 149.5 (C-4); 152.2 (C-2); 161.9 (C-6); 168.9 (C=O). Anal. calcd for $C_{19}H_{30}N_4O_2S$: C, 60.28; H, 7.99; N, 14.81; found: C, 60.35; H, 8.13; N, 14.76.

3.2.19. 2-[4-Methyl-6-(4-methyl-piperazin-1-yl)-5-methylsulfanylmethyl-pyridin-2-yl]-1-(4-methyl-piperazin-1-yl)-ethanone 7c. Yellow oil; IR (liquid film) ν_{max} 1644 (C=O) cm^{-1}; ^{1}H NMR δ 2.13 (3H, s, CH_3S); 2.27 (3H, s, *p*-CH_3); 2.30–2.42 (4H, m, (CH_2)$_2$NCH$_3$); 2.39 (3H, s, CH_3–N); 2.41 (3H, s, CH_3–N); 2.58–2.67 (4H, m, (CH_2)$_2$NCH$_3$); 3.18–3.24 (4H, m, CH_2NCH_2); 3.58–3.72 (4H, m, O=C–N(CH_2)$_2$); 3.77 (2H, s, CH_2S); 3.78 (2H, s, CH_2CO); 6.89 (1H, s, H-3); ^{13}C NMR δ 16.3 (CH_3S); 19.3 (*p*-CH_3); 31.3 (CH_2S); 41.8 and 43.6 (CH_2)$_2$NCH$_3$); 46.1 (NCH$_3$); 46.3 (NCH$_3$); 46.4 (CH_2C=O); 51.3 (CH_2NCH_2); 54.7 and 55.0 (O=C–N(CH_2)$_2$); 55.2 and 55.5 ((CH_2)$_2$NCH$_3$); 121.0 (C-3); 122.9 (C-5); 149.3 (C-4); 152.0 (C-2); 161.9 (C-6); 169.1 (C=O). Anal. calcd for $C_{20}H_{33}N_5OS$: C, 61.34; H, 8.50; N, 17.90; found: C, 61.39; H, 8.65; N, 17.81.

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