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SYNTHESIS OF 4-[4'-(*N,N*-DIMETHYLSULFAMOYL)PIPERAZIN-1-YL]PYRIDINE DERIVATIVES AS SORBITOL DEHYROGENASE POTENTIAL INHIBITORS

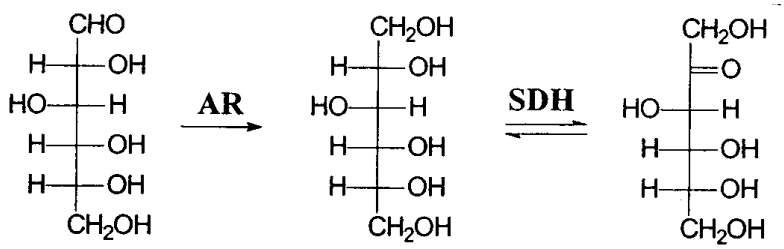
Didier Varlet, Eric Fourmaintraux, Patrick Depreux, and Daniel Lesieur*

Institut de Chimie Pharmaceutique, Université de Lille 2, rue du Professeur Laguesse, 59006 Lille, France

Abstract - A synthesis of various pyridines disubstituted in position 4 by a [4'-(*N,N*-dimethylsulfamoyl)piperazin-1-yl] group and in position 2 by different functionalities such as hydrogen, hydroxymethyl, formyl, carboxamido or cyano, is described.

INTRODUCTION

Under normal conditions, blood glucose is transformed in glucose-6-phosphate by hexokinase.[1] In diabetic patients, hexokinase is rapidly saturated and glucose in excess follows the polyol pathway being reduced in sorbitol by aldose reductase (AR). Sorbitol may then be oxidized in fructose by sorbitol dehydrogenase (SDH) according to a reversible reaction (Scheme 1). This pathway is responsible for the apparition of long-term diabetic complications (neuropathy, nephropathy, retinopathy, cataract...). [1,2]

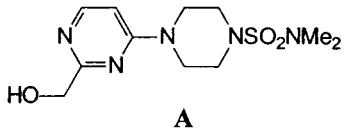


Glucose **Sorbitol** **Fructose**

Scheme 1

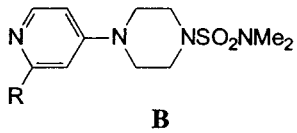
With the aim to prevent these complications by an enzyme inhibition mechanism, a great number of AR inhibitors have been described[3] while only one strong and specific inhibitor of SDH (CP 166572) (A) has been reported.

In order to specify structure activity relationships in this series and to obtain compounds inhibiting SDH, we have synthesized pyridine derivatives (**B**) bearing a dimethylsulfamoylpiperazinyl group in position 4 and various substituents in position 2.



A

CP 166572



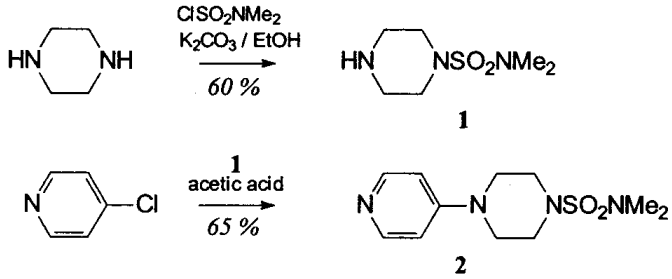
B

R : -H, -CH_2OH, -CHO, -$CONH_2$, -CN

RESULTS AND DISCUSSION

Monosubstitute dpyridine (compound **2**) :

Monosubstituted pyridine (**2**) (Scheme 2) was synthesized according to an aromatic nucleophilic substitution of 4-chloropyridine by piperazine-1-sulfonic acid dimethylamide (**1**) (previously obtained by reaction in ethanol of *N,N*-dimethylsulfamoyl chloride with piperazine). In a first time, the synthesis of compound (**2**) in refluxing toluene was unsuccessful. Use of refluxing n-butanol as solvent[5] afforded compound (**2**) but its purification was difficult and the reaction time too long (2 days). In acetic acid howewer, compound (**2**) was easily obtained in good yield (65% after heating during 6 hours).

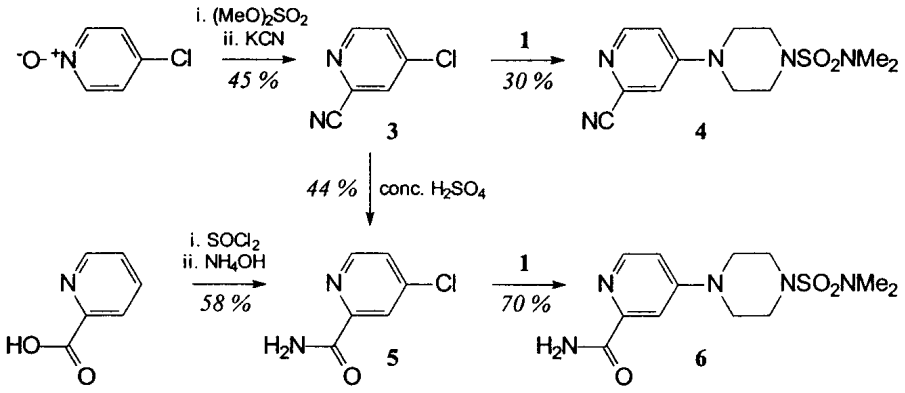


Scheme 2

Disubstituted pyridines : 2-cyano- and 2-carbamoylpyridines (compounds (**4**) and (**6**)) :

Disubstituted compounds (**4**) and (**6**) (Scheme 3) were respectively prepared in 2 and 3 steps. Cyanation in position 2 of 4-chloropyridine *N*-oxide, according to a Reissert-Kaufmann type reaction,[6] by successive action of dimethyl sulfate and potassium cyanide, gave nitrile (**3**) (45 % yield) whose chlorine atom was then substituted by compound (**1**) to afford **4** . This substitution reaction using different solvents (toluene, n-butanol, acetic acid) was unavailing and was carried without solvent at the melting point of the medium (bath temperature : 80 ° C, 30 % yield).

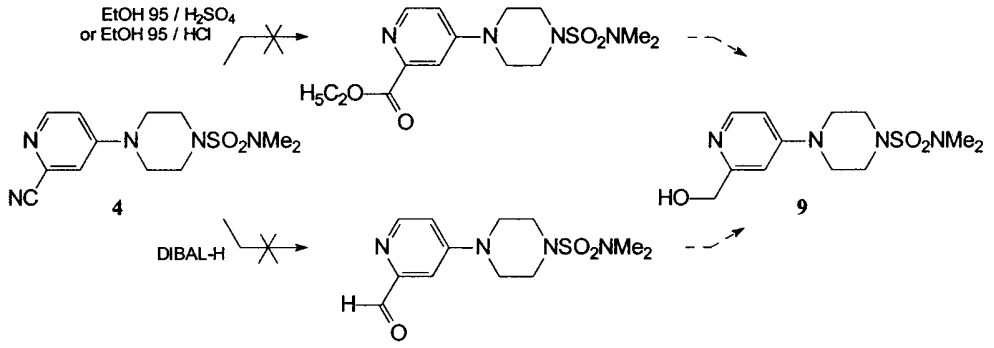
Acid hydrolysis of nitrile (**3**) led to the 4-chloropicolinamide (**5**) (44 % yield). This compound was also obtained from picolinic acid by successive action of refluxing thionyl chloride during 3 days and 28 % ammona solution with a better yield (58 %). Nucleophilic substitution of the amide (**5**) with compound (**1**) was realized according to two methods. In the first one, the reaction was carried out in refluxing DMF during 3 days in the presence of potassium carbonate. In the second, the reaction was realized without solvent at 80 °C (fusion of the mixture) and was faster (3 hours). In these two cases, yields were the same (70 %).



Scheme 3

2-Hydroxymethyl- and 2-formylpyridines *(compounds* (**9**) *and* (**10**)*)* :

Firstly, we tried to obtain the hydroxymethyl derivative (**9**) from nitrile (**4**) (Scheme 4). Transformation of the cyano function either in ester by acid ethanolysis or in formyl group by action of diisobutylaluminum hydride (DIBAL-H) failed. The reduction of these 2 functions would have given compound (**9**).

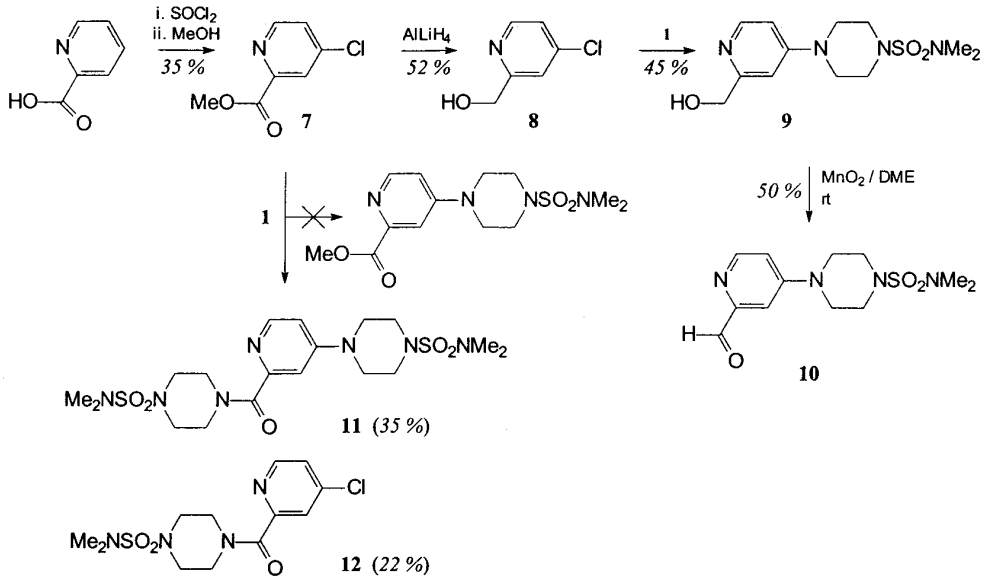


Scheme 4

Compound (**9**) was finally obtained in 3 steps from picolinic acid (Scheme 5). This acid was chlorinated[7] in position 4 and esterified by action of refluxing thionyl chloride during 3 days followed by action of methanol leading the ester (**7**) (35% yield). Reduction of compound (**7**) by lithium aluminum hydride[8] gave alcohol (**8**) (52% yield) whose chlorine atom was substituted by piperazine (**1**) in refluxing xylene to afford the alcohol (**9**) (45% yield). This solvent was finally chosen because preliminary assays (refluxing toluene, melting point of the medium) were unsuccessful.

Attemps to substitute the chloroester (**7**) by piperazine (**1**) did not afford the desired ester but amides (**11**) and (**12**) (respectively 35% and 22% yields). Aminolysis of the ester function by compound (**1**) was accomplished more easily than the chlorine substitution.

Ester (**7**) was then reduced by action of lithium aluminum hydride and the chlorine atom substituted by compound (**1**) to afford **9** . Aldehyde (**10**) was obtained by oxidation of alcohol (**9**) with manganese(IV) oxide in dimethoxyethane (DME) at room temperature (50 % yield).



Scheme 5

CONCLUSION

This paper reports the synthesis of original pyridines substituted in position 4 by a *N,N*-dimethyl-sulfamoylpiperazin-1-yl group and in position 2 by various functionalities such as hydrogen atom, cyano, carboxamido, hydroxymethyl and formyl group to give respectively compounds (**2, 4, 6, 9** and **10**). All these compounds have been tested as sorbitol dehydrogenase potential inhibitors but were less potent than the reference lead compound CP 166572 described by Pfizer laboratories. These results show the importance of the pyrimidinic cycle in the interaction with the activity site of the enzyme.

EXPERIMENTAL PART

Melting points were determined using a Büchi SMP-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer, using KBr tablets : wave numbers are expressed in cm^{-1}. ^{1}H-NMR spectra were measured with a Brücker WP 80 SY (80 MHz) or AC 300P (300 MHz) apparatus, with Me_4Si as the internal standard and $CDC1_3$ or DMSO-d_6 as solvent : chemical shifts (δ) are reported in ppm; coupling constants J are expressed in Hz. Tested compounds were characterized by elemental analysis which was determined by the CNRS center of analysis in Vernaison (France).

Piperazine-1-sulfonic acid dimethylamide (1) .

Potassium carbonate (6.91 g, 50 mmol) was added to a stirred solution of piperazine (4.31 g, 50 mmol) dissolved in absolute ethanol (100 mL). The mixture was cooled in an ice bath and *N,N*-dimethyl-

sulfamoyl chloride (4.31 g, 30 mmol) was added dropwise. Stirring was continued for 30 min and the medium filtered. The filtrate was evaporated under reduced pressure. The residue was washed with brine and extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), evaporated under reduced pressure and the residue recrystallised. mp 97-99℃ (cyclohexane) (1it.,[9]: 97-99 ℃); yield 7.05 g (73 %). IR (KBr) : 3250, 1330 and 1130 cm^{-1}. ^{1}H-NMR (300 MHz. $CDC1_3$) δ 2.84 (s, 6H ; N(CH_3)$_2$); 2.88-2.95 (m, 4H ; CH_2 piperazine); 3.18-3.27 (m, 4H ; CH_2 piperazine); 4.78 (m, IH; N*H*).

4-[4'-(*N,N*-Dimethylsulfamoyl)piperazin-1-yl]pyridine (2).

Method A **:** 4-Chloropyridine (0.38 g, 3.3 mmol) and **1** (1.54 g, 7.9 mmol) in acetic acid (10 mL) were heated at 110℃ for 6 h. Acetic acid was evaporated and the residue taken up in acetone. The precipitate was filtered, the filtrate evaporated under reduced pressure and the resulting residue recrystallised. mp 118-119 ℃ (cyclohexane); yield 0.58 g (65 %).

Method B **:** Potassium carbonate (1 g, 7.2 mmol) was added to a solution of 4-chloropyridine hydrochloride (0.5 g, 3.3 mmol) and **1** (0.77 g, 4.0 mmol) in butan-1-o1 (10 mL). The reaction medium was refluxed for 48 h and filtered hot. The filtrate was evaporated under reduced pressure and the residue taken up in acetone. The precipitate was filtered, the filtrate evaporated under reduced pressure, and the resulting residue recrystallised, mp 118-119 ℃(cyclohexane); yield 0.58 g (65 %). IR (KBr) : 1560, 1320 and 1130 cm^{-1}. ^{1}H-NMR (300 MHz, $CDC1_3$) δ 2.83 (s, 6H; N(CH_3)$_2$); 3.22-3.43 (m, 8H; CH_2 piperazine); 6.65 (d, 2H, J= 6.5 Hz; H_3 and H_5); 8.28 (d, 2H, J= 6.5 Hz; H_2 and H_6). *Anal*. Calcd for $C_{11}H_{18}N_4O_2S$: C, 48.87; H, 6.71; N, 20.72. Found : C, 48.69; H, 6.63; N, 20.33.

4-Chloro-2-cyanopyridine (3).

4-Chloropyridine *N*-oxide (0.5 g, 4.0 mmol) was dissolved in dimethyl sulfate (0.5 g, 4.0 mmol). The mixture was heated at 65^{0}C for 4 h, cooled to rt and a solution ofpotassium cyanide (0.4 g, 6.0 mmol) in water (3.5 mL) was added. The resulting precipitate was filtered and recrystallised. mp 84-85℃ (n-hexane) (lit.,[10] : 85-86^{0}C); yield 0.25 g (45 %). IR (KBr) : 3080, 2230, 1570 cm^{-1}. ^{1}H-NMR (300 MHz, $CDC1_3$) δ 7.56 (dd, 1H, J= 5.4 Hz and 1.7 Hz; H_5); 7.73 (d, 1H, J= 1.7 Hz; H_3); 8.64 (d, 1H. J= 5.4 Hz; H_6).

2-Cyano-4-[4'-(*N,N*-dimethylsulfamoyl)piperazin-1-yl] pyridine (4).

3 (1 g, 7.2 mmol) and **1** (4.17 g, 21.6 mmol) were stirred at melting point of the mixture (bath temperature : 80℃) for 3 h. The reaction mixture was cooled to rt and poured into water. The aqueous layer was extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), evaporated under reduced pressure, and the resulting residue recrystallised. mp 119-121℃ (cyclohexane-toluene : 3-1); yield 0.64 g (30 %). IR (KBr) : 2220, 1590, 1320 and 1140 cm^{-1}. ^{1}H-NMR (300MHz,DMSO-d_6) δ 2.79 (s, 6H; N(CH_3)$_2$); 3.20-3.30 (m, 4H; CH_2 piperazine), 3.47-3.57 (m, 4H; CH_2 piperazine); 7.09(dd,

1H, J=6.0 Hz and 2.5 Hz, H_5); 7.59 (d ,1H, J=2.5 Hz, H_3); 8.27 (d, 1H, J= 6.0 Hz, H_6). *Anal*. Calcd for $C_{12}H_{17}N_5O_2S$: C 48.80; H, 5.80; N, 23.71. Found : C, 48.62; H, 5.84; N, 23.61.

4-Chloropicolinamide (5).

***Method A* : 3** (1 g, 7.2 mmol) and 98 % sulfuric acid (2 g, 11.0 mmol) were heated at 100℃ for 30 min. The mixture was poured into water and the resulting precipitate filtered and recrystallised, mp 162-163℃ (cyclohexane) (lit.,[10] : 160-162 ℃); yield 0.50 g (44 %).

***Method B* :** Picolinic acid (1 g, 8. 1 mmol) in thionyl chloride (4 mL, 55.0 mmol) was refluxed for 3 days. Excess of thionyl chloride was evaporated under reduced pressure. The residue was dissolved in ether and the solution cooled in an ice bath. Aqueous 28 % ammoniac (10 mL, 165.0 mmol) was added in once. The resulting precipitate was filtered and recrystallised. mp 162-163℃ (cyclohexane); yield 0.73 g (58 %). IR (KBr) : 3260, 3080 and 1660 cm^{-1}. ^{1}H-NMR (300 MHz, CDC1$_3$) δ 7.77 (dd, 1H, J= 5.1 Hz and l.9 Hz; H_5); 7.86 (d, 1H, J= 1.9 Hz; H_3); 8.05 (m, 1H; N*H*); 8.24 (m, 1H; N*H*); 8.63 (d, 1H, J= 5.1 Hz; H_6).

4-[4'-(*N,N*-Dimethylsulfamoyl)piperazin-1-yl]picolinamide (6).

***Method A* : 5** (1 g, 6.4 mmol), **1** (1.85 g, 9.6 mmol) and potassium carbonate (1.77 g, 12.8 mmol) were added to dimethylformamide (10 mL), and the mixture refluxed for 3 days. The mixture was cooled at rt, poured into ice water, and the aqueous layer extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), evaporated under reduced pressure, and the resulting residue recrystallised, mp 193-195 ℃ (isopropanol); yield 1 .4 g (70 %).

***Method B* : 5** (1 g, 6.4 mmol) and **1** (2.4 g, 12.8 mmol) were heated at the melting point of the medium (bath temperature : 80℃) for 3 h. The mixture was poured into water and the aqueous layer extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), evaporated under reduced pressure, and the residue recystallised. mp 193-195℃ (isopropanol); yield 1.4 g (70%). IR (KBr) : 3270, 3110, 1640, 1320 and 1140 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 2.81 (s, 6H; N(CH_3)$_2$); 3.21-3.38 (m, 4H; CH_2 piperazine); 3.40-3.53 (m, 4H; CH_2 piperazine); 7.01 (m, 1H; N*H*); 7.50 (m, 1H; H_5); 7.57 (m, 1H; H_3), 8 03 (m, 1H; N*H*); 8.24 (m, 1H; H_6). *Anal*. Calcd for $C_{12}H_{19}N_5O_3S$: C, 45.99; H, 6,11; N, 22.35. Found : C, 45.94; H, 6.09; N, 22.45.

Methyl 4-chloropicolinate (7).

Picolinic acid (1 g, 8.1 mmol) in thionyl chloride (4 mL, 55.0 mmol) was refluxed for 3 days. Excess of thionyl chloride was evaporated under reduced pressure. The residue was dissolved in ether and the solution cooled in an ice bath. Methanol (2 mL, 50.0 mmol) was added dropwise under stirring. The solution was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using dichloromethane-methanol (9-1) as eluent and then recrystallised, mp 56-58℃ (n-

hexane) (litt.,[10] : 57-58^{0}C); yield 0.86 g (62 %). IR (KBr) : 1720, 1570 and 1550 cm^{-1}. ^{1}H-NMR (80 MHz. $CDC1_3$) δ 4.05 (s, 3H; CH_3); 7.50 (m, 1H; H_5); 7.85 (m, 1H; H_3); 8.80 (m, 1H; H_6).

4-Chloro-2-hydroxymethylpyridine (8).

Lithium aluminum hydride (0.18 g, 4.7 mmol) was added into anhydrous ether (5 mL), and the solution cooled in an ice bath. A solution of **7** (0.8 g, 4.7 mmol) in ether (5 mL) was added dropwise under stirring. The reaction medium was stirred for 3 h at rt. Water (0.2 mL), 15 % sodium hydroxide aqueous solution (0.2 mL) and then water (0.6 mL) were added dropwise. The reaction medium was filtered, the filtrate evaporated, and the resulting solid recrystallised. mp 68-69 ℃ (cyclohexane-toluene : 1 - 1); yield 0.35 g (52 %). IR (KBr) : 3250, 1580 cm^{-1}. ^{1}H-NMR (300 MHZ DMSO-d_6) δ 4.57 (d, 2H, J=5.7 Hz; CH_2-OH); 5.59 (t, 1H, J= 5.7 Hz; CH_2-O*H*); 7.40 (dd, 1H, J= 5.3 Hz and 2.3 Hz; H_5); 7.51 (d, 1H, J= 2.3 Hz; H_3); 8.46 (d, 1H, J= 5.3 Hz; H_6)

2-Hydroxymethyl-4-[4'-(*N,N*-dimethylsulfamoyl)piperazin-1-yl]pyridine (9).

A solution of **8** (0.7 g, 4.9 mmol) and **1** (2.1 g, l0.8 mmol) in xylene (15 mL) was refluxed for 4 h. The solvent was evaporated under reduced pressure and the residue recrystallised. mp 147-149 ℃ (cyclohexane-toluene : 1-9); yield 0.68 g (45 %). IR (KBr) : 3250, 1600, 1340 and 1150 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.80 (s, 6H; n(CH_3)$_2$); 3.21-3.44 (m, 8H; CH_2 piperazine); 4.44 (m, 2H; CH_2-OH); 5.31 (m, 1H; CH_2-O*H*); 6.73 (dd, 1H, J= 6.0 Hz and 2.5 Hz; H_5); 6.92 (d, 1H, J= 2.5 Hz; H_3); 8.11 (d, 1H, J= 6.0 Hz; H_6). *Anal*. Calcd for $C_{12}H_{20}N_4O_3S$: C, 47.98; H, 6.71; N, 18.65. Found : C, 47.63; H, 6.86; N, 18.80.

2-Formyl-4-[4'-(*N,N*-dimethylsulfamoyl)piperazin-1-yl]pyridine (10).

9 (0.5 g, 1.7 mmol) was dissolved in 1,2-dimethoxyethane (5mL). Manganese(IV) oxide (1.4 g, 16.0 mmol) was added and the reaction medium stirred at rt for 24 h. The black precipitate was filtered, washed with 1,2-dimethoxyethane, and then with ethyl acetate. The filtrate was evaporated under reduced pressure and the resulting residue dissolved in 0.5N HCl. The aqueous layer was washed with ethyl acetate and then neutralized by addition of sodium hydrogencarbonate until pH 7-8. The resulting precipitate was filtered, and recrystallised. mp 93-95 ℃ (cyclohexane-toluene : 2-1); yield 0.24 g (50 %). IR (KBr) : 1700, 1590, 1330 and 1130 cm^{-1}. ^{1}H-NMR (300 MHz, $CDC1_3$) δ 2.88 (s, 6H; N(CH_3)$_2$);3.38 (m, 4H; CH_2piperazine); 3.50 (m, 4H; CH_2 piperazine); 6.86 (dd, 1H, J= 6.1 Hz and 2.7 Hz; H_5); 7.36(d, 1H, J= 2.7 Hz; H_3); 8.47 (d, 1H, J= 6.1 Hz; H_6); l0.01 (s, IH; C*HO*). *Anal*. Calcd for $C_{12}H_{18}N_4O_3S$: C, 48.31; H, 6.08; N, 18.78. Found : C, 48.12; H, 5.98; N, 18.92.

2-[4'-(*N,N*-Dimethylsulfamoyl)piperazin-1-ylcarbonyl]-4-[4'-(*N,N*-dimethylsulfamoyl)piperazin-1-

yl]pyridine (11) and 2-[4-(*N,N*-dimethylsulfamoyl) piperazin-1-ylcarbonyl]-4-chloropyridine (12). **7** (2 g, 11.7 mmol) and **1**(4.5 g, 23.2 mmol) were mixed at the melting point of the medium (bath temperature : 100℃) for 5 h. The mixture was cooled and water was added. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with water, dried (magnesium sulfate), and evaporated under reduced pressure. The residue was purified on silica gel column using dichloromethane-methanol (95-5) as eluent and the 2 separated compounds recrystallised.

2-[4'-(*N,N*-Dimethylsulfamoyl)piperazin-1 -ylcarbonyl]-4-[4'-(*N,N* –dimethylsulfamoyl) piperazin-1-yl]pyridine (11). mp 182-183 ℃ (ethanol); yield 2 g (35 %). IR (KBr) : 1640, 1590 1450, 1365 and 1140 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.76-2.81 (m, 12H; N(CH_3)$_2$); 3.09-3.29 (m, 8H; CH_2 piperazine); 3.40-3.72 (m, 8H; CH_2 piperazine); 6.92 (dd, 1H, J= 6.1 Hz and 2.5 Hz; *H5*); 7.01 (d, 1H, J= 2.5 Hz; H_3); 8. 19 (d, 1H, J= 6. I Hz; H_6). *Anal*. Calcd for $C_{18}H_{31}N_7O_5S_2$: C, 44.16; H, 6.38; N, 20.03. Found : C,43.92; H, 6.50; N, 19.68.

2-[4-(*N,N* -Dimethylsulfamoyl)piperazin-1-ylcarbonyl]-4-chloropyridine (12). mp 120- 122 ℃ (isopropanol); yield 0.82 g (21 %). IR (KBr) : 3390, 1630, 1340 and 1150 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.80 (s, 6H; N(CH_3)$_2$); 3.24-3.36 (m, 4H; CH_2 piperazine); 3.60-3.72 (m, 4H; CH_2 piperazine); 7.12 (dd, 1H, J= 6.0 Hz and 2.4 Hz; H_5); 7.48 (d, 1H, J= 2.4 Hz; H_3); 8.28 (d, 1H, J= 6.0 Hz; H_5). Anal. Calcd for $C_{12}H_{17}N_4O_3ClS$: C, 43.31; H, 5.15; N, 16.84. Found : C, 43.20; H, 5.32; N, 17.01.

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