HETEROCYCLES, Vol. 60, No. 2, 2003, pp. 385 - 396
Received, 25th September, 2002, Accepted, 6th December, 2002, Published online, 16th December, 2002

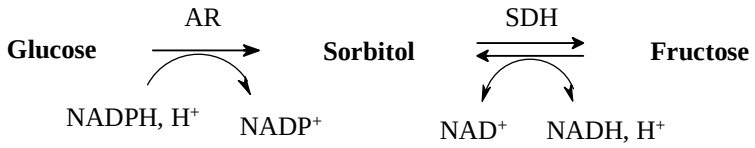
SYNTHESIS OF 4-[4-(*N*,*N*-DIMETHYLSULFAMOYL (PIPERAZIN-1-YL)]-QUINOLINES DERIVATIVES AS SORBITOL DEHYDROGENASE POTENTIAL INHIBITORS

Didier Varlet, Eric Fourmaintraux, Patrick Depreux,* and Daniel Lesieur
*Institut de Chimie Pharmaceutique Albert Lespagnol, University of Lille 2, 3 rue du Professeur Laguesse, 59006 Lille, France

Abstract - Synthesis of various quinolines, substituted in position 4 by [4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl] group and in position 2 by different groups such as hydrogen, methyl, hydroxymethyl, formyl or carboxyl is described. Besides, we have synthesized derivatives of 8-hydroxyquinoline.

INTRODUCTION

Diabetes is characterized by a sustained elevation of blood glucose. Glucose in excess follows the polyol pathway and is reduced in sorbitol by the enzyme Aldose Reductase (AR) with the aid of the cofactor NADPH. This pathway is incriminated in the apparition of long-term diabetic complications[1,2] (neuropathy, nephropathy, retinopathy, cataract, ...) by accumulation of sorbitol in the tissues. The sorbitol may be then oxidized in fructose by Sorbitol Dehydrogenase (SDH), using the cofactor of NAD^+, according to a reversible reaction (Scheme 1).

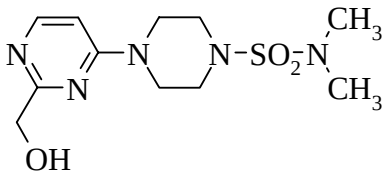


Scheme1

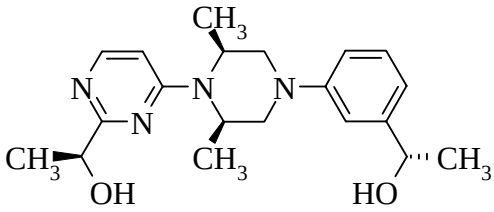
One of the most approaches, to protect vulnerable diabetic tissues from the detrimental elevated blood glucose, has been to block excess glucose metabolism through the first step of polyol pathway via Aldose Reductase Inhibitors (ARIs).[3,4]

Recently, excess glucose flux through the polyol pathway was proposed to create an imbalance in the cytoplasmic redox status (increased free NADH/NAD^+ ratio) because of rapid consumption of NAD^+ during oxidation of sorbitol to fructose by SDH.[5] SDH inhibitors were shown to attenuate the diabetes-induced increase in cytosolic NADPH / NAD^+ ratio.[5] CP-166572 and CP-470711 are reported as strong

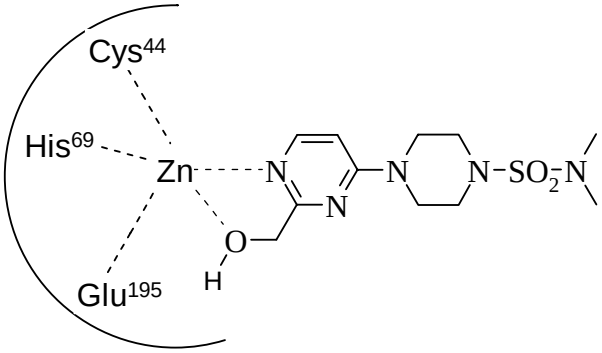
and specific inhibitors of SDH :[6,7] SDH is a zinc-containing enzyme. It has been speculated that the hydroxymethyl group serves as a strong ligand to the zinc atom, mimicking the hydroxymethyl group of sorbitol[8] (Scheme 2).



CP-166572



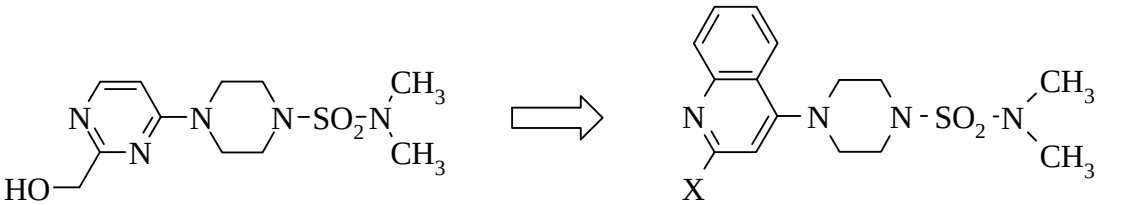
CP-470711



Scheme 2

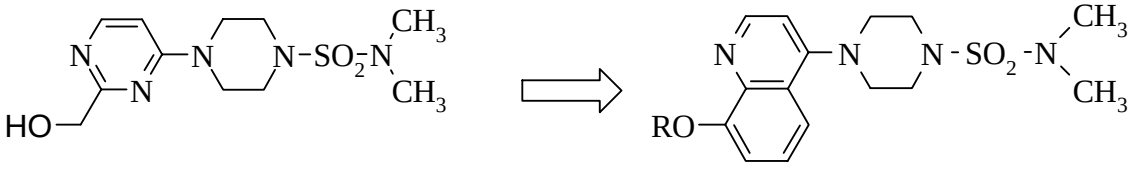
In previous work,[9] in order to obtain new compounds inhibiting SDH and to specify structure activity relationships, we have described the synthesis of pyridinic derivatives potential inhibitors of SDH.

In order to obtain new compounds inhibiting SDH we describe here the synthesis of quinoline derivatives substituted in position 4 by a dimethylsulfamoylpiperazinyl group and in position 2 by various substituents.



X = H, CH_3, CH_2OH, CHO, CO_2H

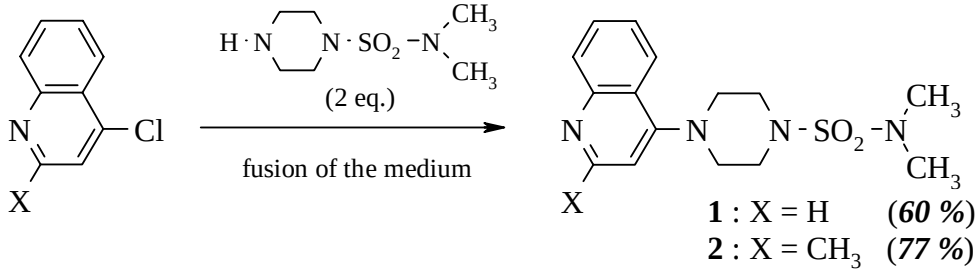
We have also synthesized derivatives of 8-hydroxyquinoline, known to complex metals.



R = H, CH_3

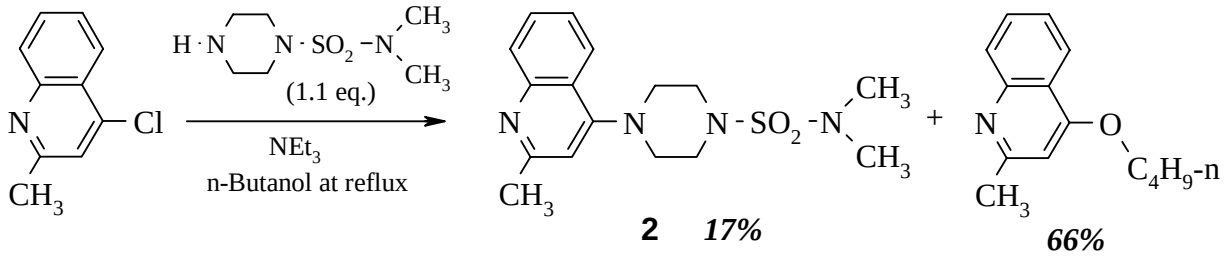
RESULTS AND DISCUSSION

Compounds (**1**) and (**2**) were synthesized by substitution respectively of 4-chloroquinoline and 4-chloroquinaldine with piperazin-1-ylsulfonic acid dimethylamide[9] (Scheme 3). The reaction was carried out without solvent, at the melting point of the medium, with two equivalents of sulfamoylamide (60% yield for **1** and 77% yield for **2**).



Scheme 3

An attempt of substitution of 4-chloroquinaldine in refluxed toluene failed. A second attempt realized in refluxed n-butanol gave (**2**) in only 17% yield while the 4-butoxyquinaldine was obtained with 66% yield (Scheme 4).



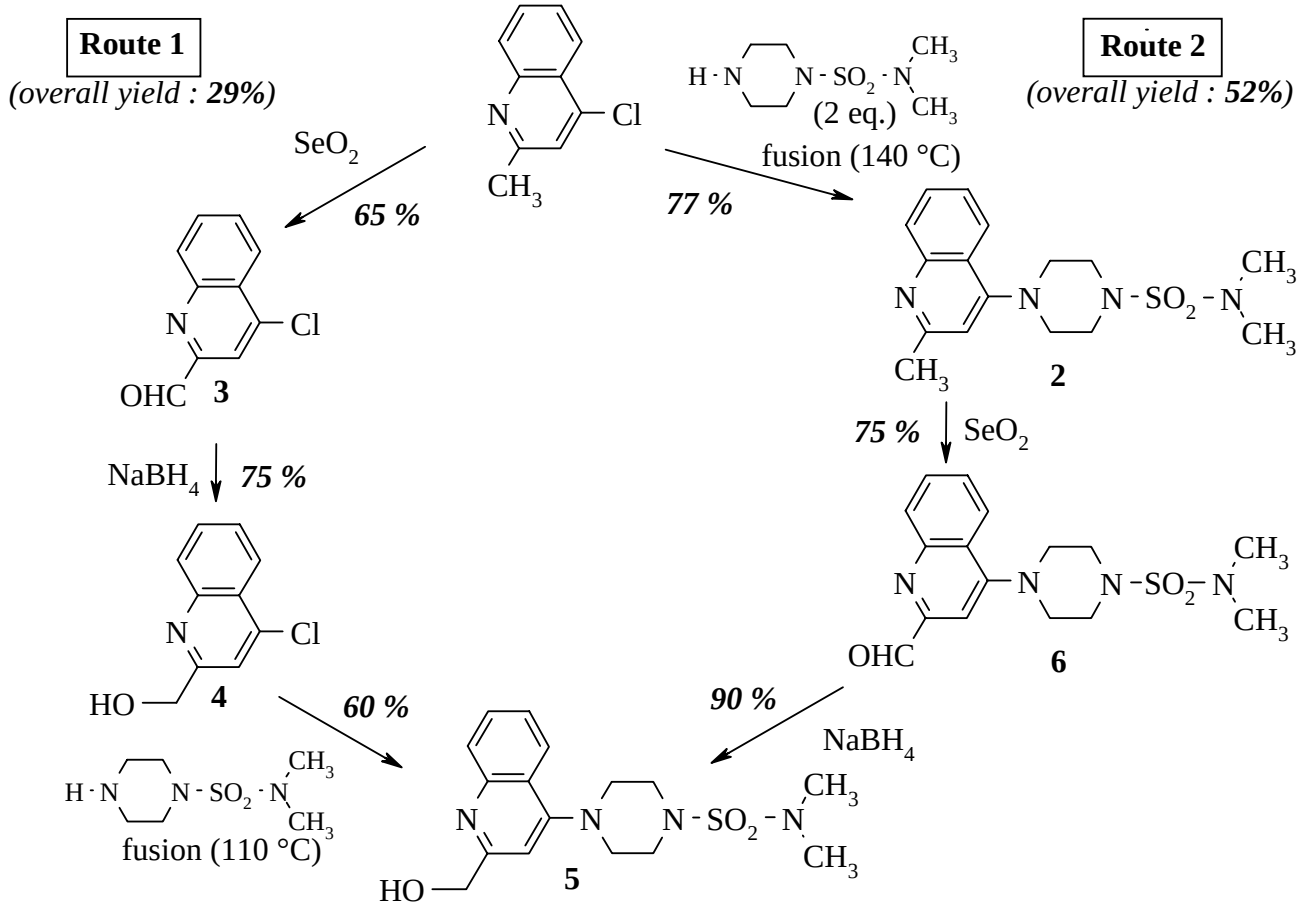
Scheme 4

The alcohol (**5**) was obtained in three steps from 4-chloroquinaldine, according to two ways.

In the first way, the methyl substituent was oxidized by action of selenium dioxide[10] in refluxed dioxanne to afford the aldehyde (**3**) (65% yield) which was reduced in alcohol (**4**) by action of sodium borohydride[11] in refluxed alcohol (75% yield). Substitution of the chlorine atom of compound (**4**) with piperazin-1-ylsulfonic acid dimethylamide was then carried out without solvent, at melting point of the medium, to furnish compound (**5**) (60% yield).

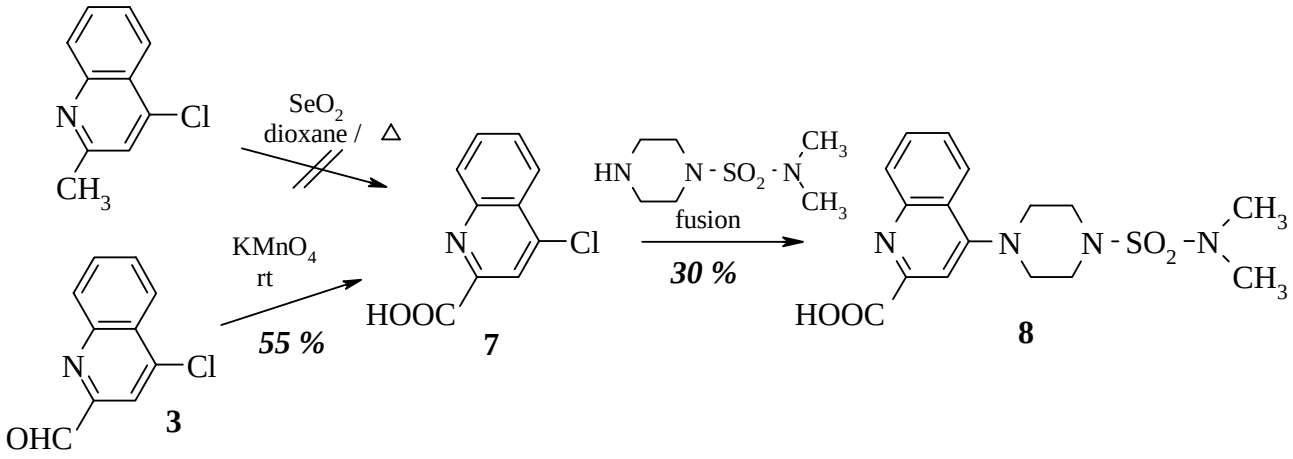
In the second way, the nucleophilic substitution was firstly realized (77% yield). The methyl group was oxidized in aldehyde (**6**) (75% yield) wich was then reduced in alcohol (**5**) (90 % yield) in the same conditions as described above.

Compound (**5**) was obtained with 52% overall yield in the second way versus 29% overall yield in the first way (Scheme 5).



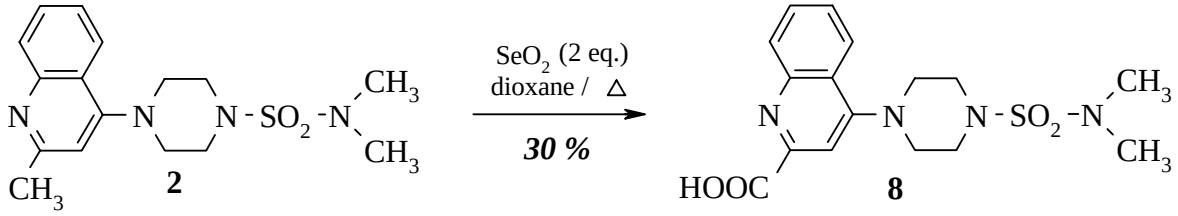
Scheme 5

The carboxylic acid (**8**) was firstly synthesized by substitution of the correspondent chloro acid (**7**) with piperazin-1-ylsulfonic acid dimethylamide (30 % yield). All attempts to obtain compound (**7**) by oxidation of 4-chloro-2-quinaldine with selenium dioxide failed because very numerous products were formed and were difficult to separate. Compound (**7**) was finally obtained by oxidation of 4-chloro-2-formylquinoline (**3**) using potassium permanganate[12] at room temperature (55 % yield) (Scheme 6).



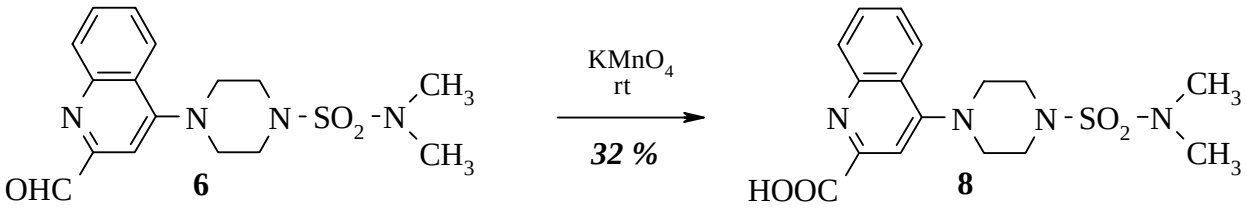
Scheme 6

In a second way (Scheme 7), compound (**8**) was obtained in one step from compound (**2**) by oxidation of the methyl group with two equivalents of selenium dioxide in hot dioxane (30 % yield).



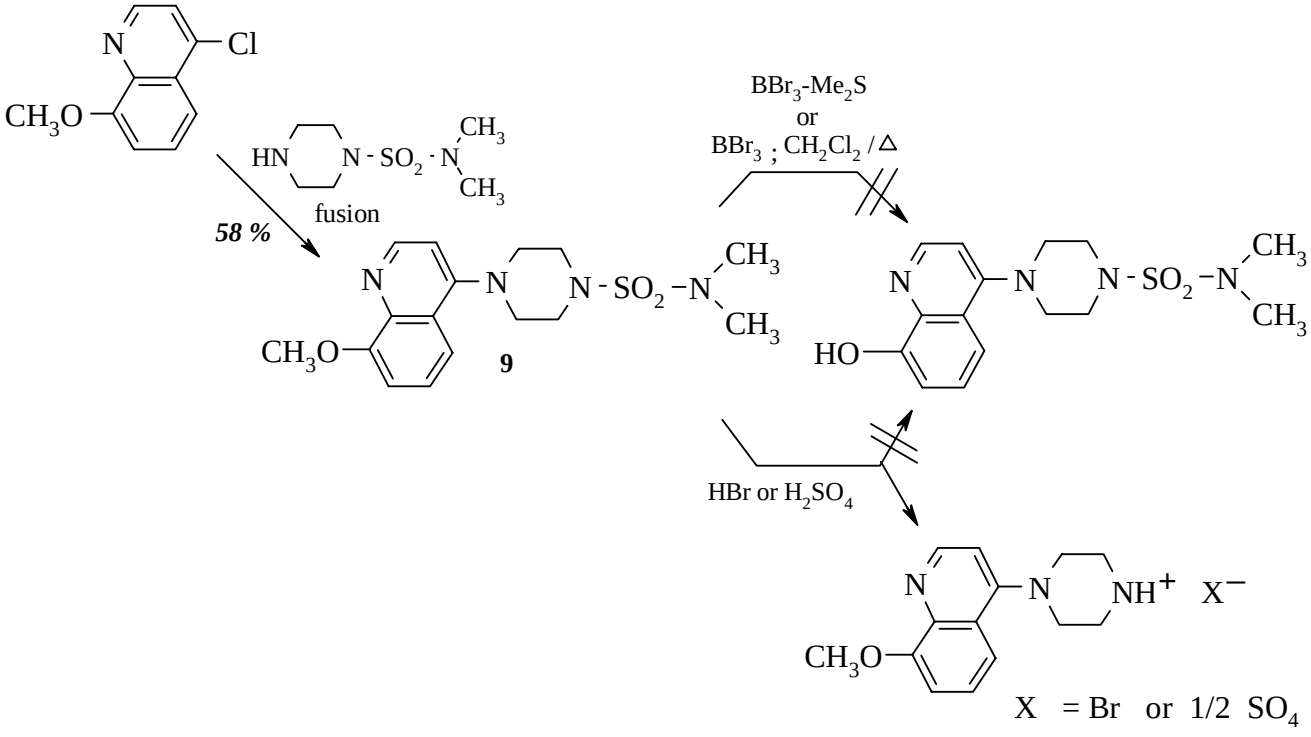
Scheme 7

In order to increase this yield, we finally oxidized the formyl group of compound (**6**) by the mean of potassium permanganate at room temperature (Scheme 8) in the same conditions as previously described (32 % yield).



Scheme 8

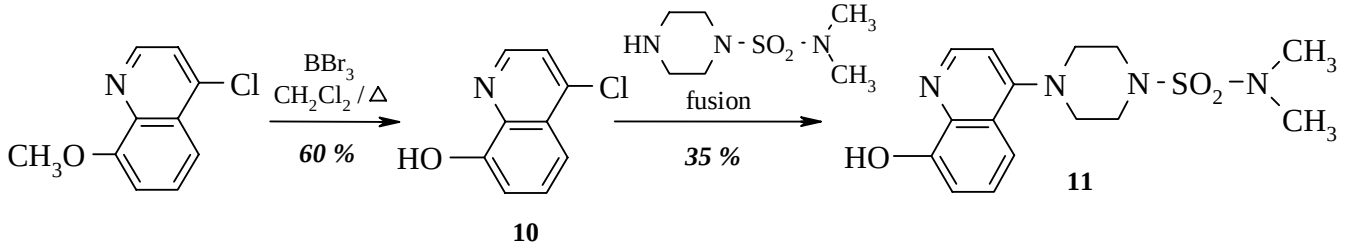
8-Hydroxy- and 8-methoxyquinolines derivatives (compounds (**9**) and (**11**)) were synthesized from 4-chloro-8-methoxyquinoline[13] (Scheme 9).



Scheme 9

The quinoline (**9**) was obtained by substitution of 8-methoxy-4-chloroquinoline with piperazin-1-ylsulfonic acid dimethylamide, without solvent, at the fusion of the medium (58 % yield). We never succeeded in the *O*-demethylation reaction. The use of boron tribromide-methyl sulfide complex or boron tribromide in hot dichloromethane failed.[14] Acid hydrolysis with bromohydric or sulfuric acid in hot concentrated aqueous solution[15] did not give the compound (**11**), but the 8-methoxy-4-piperazinylquinoline due to the hydrolysis of the sulfamoyl group.

Compound (**11**) was finally obtained from 8-methoxy-4-chloroquinoline by first the *O*-demethylation using boron tribromide-methylsulfide complex followed by the substitution of the chlorine atom with piperazin-1-ylsulfonic acid dimethylamide (35 % yield) (Scheme 10).



Scheme 10

CONCLUSION

This paper reports the synthesis of new quinolines derivatives substituted in position 4 by a *N*,*N*-dimethylsulfamoylpiperazin-1-yl group and in position 2 by various substituents such as hydrogen atom, methyl, hydroxymethyl, formyl and hydroxycarbonyl groups (compounds (**1**), (**2**), (**5**), (**6**) and (**8**)). We have also described the synthesis of original quinoline compounds : 8- methoxyquinoline (compound (**9**)) and 8-hydroxyquinoline (compound (**11**)) both substituted in position 4 by a *N*,*N*-dimethylsulfamoyl-piperazin-1-yl group.

These compounds have been tested as sorbitol deshydrogenase potential inhibitors but were less potent than the reference lead compound CP 166572.

All these test results confirm the importance of the two nitrogen atoms in the pyrimidinic cycle to obtain a good interaction with the enzyme.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer, using KBr tablets ; the waves numbers are expressed in cm^{-1}. The ^{1}H-NMR spectra were obtained on a Brücker AC 300P (300 MHz) apparatus, with Me_4Si as the internal standard and with $CDCl_3$ or DMSO-d_6 as solvent ; the chemical

shifts are reported in ppm of Me_4Si in δ units ; coupling constants are expressed in Hz. Melting points were determined using a Büchi SMP-535 apparatus and are uncorrected. Elemental analysis were determined by the CNRS center of analysis in Vernaison (France).

General procedure for nucleophilic substitution (*1, 2, 5, 8, 9 and 11*) :

4-Chloroquinoline derivatives (1 mmol) and *N,N*-dimethylsulfamoylpiperazine (0.289 g, 2 mmol) were heated until the appropriate temperature. The mixture was stirred until the corresponding 4-chloroquinoline derivatives disappeared and then, cooled. Water was added and the mixture was extracted with ethyl acetate. The combined organic layer were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified either by silica gel column chromatography using an appropriate eluent and / or by recrystallization with a suitable solvent (Table 1).

4-[4-(*N,N*-Dimethylsulfamoyl)piperazin-1-yl]quinoline (**1**) : IR 2815, 1590 and 1580, 1330 and 1140 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.85 (s, 6H), 3.13-3.31 (m, 4H), 3.38-3.56 (m, 4H), 7.03 (d, J=5.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H), 7.72 (t, J=8.0 Hz, 1H), 7.98 (d, J=8.0 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 8.72 (d, J=5.0 Hz, 1H). Anal. Calcd for $C_{15}H_{20}N_4O_2S$: C, 56.23; H, 6.29; N, 17.49. Found; C, 56.19; H, 6.39; N, 17.52.

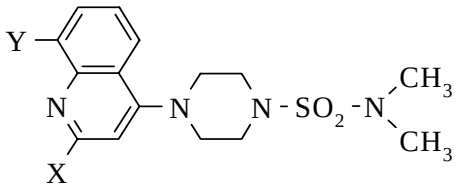
2-Methyl-4-[4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl]quinoline (**2**) : IR 2800, 1570, 1330 and 1140 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.61 (s, 3H), 2.85 (s, 6H), 3.20 (t, J=4.5 Hz, 4H), 3.49 (t, J=4.5 Hz, 4H), 6.90 (s, 1H), 7.51 (t, J=8.2 Hz, 1H), 7.64 (t, J=8.2 Hz, 1H), 7.91 (d, J=8.2 Hz, 1H), 8.02 (d, J=8.2 Hz, 1H). Anal. Calcd for $C_{16}H_{22}N_4O_2S$: C, 57.46; H, 6.63; N, 16.75. Found; C, 57.35; H, 6.80; N, 16.88.

2-Hydroxymethyl-4-[4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl]quinoline (**5**) : IR 3260, 2900, 1590, 1330 and 1150 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.85 (s, 6H), 3.11-3.31 (m, 4H), 3.36-3.57 (m, 4H), 4.65 (s, 2H), 5.60 (s, 1H), 7.21 (s, 1H), 7.49 (t, J=7.8 Hz, 1H), 7.71 (t, J=7.8 Hz, 1H), 7.92 (d, J=7.8 Hz, 1H), 8.05 (d, J=7.8 Hz, 1H). Anal. Calcd for $C_{16}H_{22}N_4O_3S$: C, 54.84; H, 6.33; N, 15.99. Found; C, 54.66; H, 6.42; N, 15.78.

2-Carboxy-4-[4-(*N,N*-dimethylsulfamoyl)piperazin-1-yl]quinoline (**8**) : IR 2960-2800, 1640, 1580, 1330 and 1140 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.83 (s, 6H), 3.24 (m, 4H), 3.45 (m, 4H), 7.37-7.83 (m, 3H), 8.00 (m, 1H), 8.30 (m, 1H), 8.79 (s, 1H). Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.73; H, 5.53; N, 15.37. Found; C, 52.43; H, 5.72; N, 15.29.

8-Methoxy-4-[4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl]quinoline (**9**) : IR 2960-2820, 1600 and 1580, 1330 and 1145 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.84 (s, 6H), 3.15-3.23 (m, 4H), 3.40-3.48 (m, 4H), 3.93 (s, 3H), 7.05 (d, J=5.0 Hz, 1H), 7.15 (d, J=7.5 Hz, 1H), 7.46 (t, J=7.5 Hz, 1H), 7.59 (d, J=7.5 Hz, 1H), 8.65 (d, J=5.0 Hz, 1H). Anal. Calcd for $C_{16}H_{22}N_4O_3S$: C, 54.84; H, 6.33; N, 15.99. Found; C, 54.73; H, 6.39; N, 16.06.

8-Hydroxy-4-[4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl]quinoline (**11**) : IR 3380-3140, 1600, 1340 and 1140 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.85 (s, 6H), 3.17-3.29 (m, 4H), 3.39-3.51 (m, 4H), 6.96-7.12 (m, 2H), 7.33-7.51 (m, 2H), 8.66 (d, J=4.8 Hz, 1H), 9.65 (s, 1H). Anal. Calcd for $C_{15}H_{20}N_4O_3S$: C, 53.56; H, 5.99; N, 16.65. Found; C, 53.22; H, 5.85; N, 16.42.



Compound	X	Y	Yield (%) Recristallization solvent	Mp (°C)	Reaction Temperature (°C)	Reaction Time (h)
1	-H	-H	60 % ethanol-water (1-1)	169-171	140	1
2	- CH_3	-H	77 % ethanol-water (1-1)	147-149	140	1
5	-CH_2OH	-H	60 % ethanol-water (1-1)	190-191	110	0.1
8	-COOH	-H	30 % ethanol-water (95-5)	240-242	110	0.5
9	-H	-OCH_3	83 % Dioxanne	177-179	80	2
11	-H	-OH	35 % Toluene-cyclohexane (1-2)	185-187	130	4

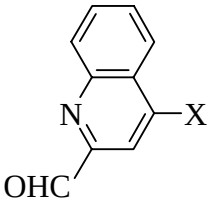
Table 1 : Reactions conditions and physical properties of dimethylaminosulfamoylpiperazinyl quinolines.

General procedure for the oxidation of methyl in aldehyde in quinaldine derivatives (3 and 6) :

Quinaldine derivatives (5.6 mmol) was dissolved in dioxane (60 mL). Selenium dioxide (0.74 g, 6.9 mmol) was added and the mixture refluxed under nitrogen (Table 2). The reaction medium was cooled, filtered on celite and the filtrate evaporated under reduced pressure. The obtained residue was recrystallized.

4-Chloro-2-formylquinoline (**3**) : IR 1710 and 1570 cm^{-1}. ^{1}H-NMR (80 MHz, DMSO-d_6) δ 7.80-8.45 (M, 5H), 10.10 (s, 1H). Anal. Calcd for $C_{10}H_6NOCl$: C, 62.68; H, 3.16; N, 7.31. Found; C, 62.94; H, 3.35; N, 7.08.

2-Formyl-4-[4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl]quinoline (**6**) : IR 2990-2800, 1690, 1560, 1330 and 1150 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.86 (s, 6H), 3.24-3.41 (m, 4H), 3.45-3.63 (m 4H), 7.42 (s, 2H), 7.73 (t, J=7.0 Hz, 1H), 7.87 (t, J=7.0 Hz, 1H), 8.17 (d, J=7.0 Hz, 1H), 8.19 (d, J=7.0 Hz, 1H), 10.07 (s, 1H). Anal. Calcd for $C_{16}H_{20}N_4O_3S$: C, 55.16; H, 5.79; N, 16.08. Found; C, 54.97; H, 5.76; N, 16.04.



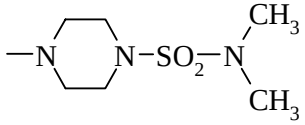
Compound	X	Yield (%) Recrystallization solvent	Mp (°C)	Reaction Time (h)
3	-Cl	65 % cyclohexane	136-139	2.5
6		55 % Toluene-cyclohexane (4-1)	183-186	1

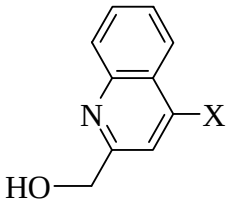
Table 2

General procedure for reduction of aldehyde (*4 *and* 5*) :

To the corresponding 2-formylquinoline derivatives (**3** or **6**) (1.6 mmol) dissolved in ethanol (6 mL), was added sodium borohydride (0.031 g, 0.8 mmol). The reaction medium was refluxed for the appropriate time (Table 3), cooled and alcohol was evaporated under reduced pressure. Water (10 mL) was added and the aqueous layer extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), evaporated and the obtained product recrystallized.

4-Chloro-2-hydroxymethylquinoline (**4**) : IR 3160 and 1580 cm^{-1}. ^{1}H-NMR (80 MHz, DMSO-d_6) δ : 4.70 (s, 2H), 5.75 (s, 1H), 7.75 (t, J=8.0 Hz, 1H), 7.80 (s, 1H), 7.85 (t, J=8.0 Hz, 1H), 8.05 (t, J=8.0 Hz, 1H), 8.20 (d, J=8.0 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 8.72 (d, J=5.0 Hz, 1H). Anal. Calcd for $C_{11}H_{10}NCl$: C, 68.94; H, 5.26; N, 7.31. Found; C, 68.71; H, 5.47; N, 7.01.

2-Hydroxymethyl-4-[4-(*N*,*N*-dimethylsulfamoyl)piperazin-1-yl]quinoline (**5**) : IR 3260, 2900, 1590, 1330 and 1150 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.85 (s, 6H), 3.21 (m, 4H), 3.46 (m, 4H), 4.65 (s, 2H), 5.60 (s, 1H), 7.21 (s, 1H), 7.49 (t, J=7.8 Hz, 1H), 7.71 (t, J=7.8 Hz, 1H), 7.92 (d, J=7.8 Hz, 1H), 8.05 (d, J=7.8 Hz, 1H). Anal. Calcd for $C_{16}H_{22}N_4O_3S$: C, 54.84; H, 6.33; N, 15.99. Found; C, 54.66; H, 6.42; N, 15.78.



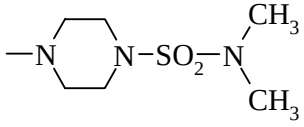
Compound	X	Yield (%) Recrystallization solvent	Mp (°C)	Reaction Time (h)
4	-Cl	75 % cyclohexane	103-106	2
5		90 % ethanol-water (1-1)	190-192	0.5

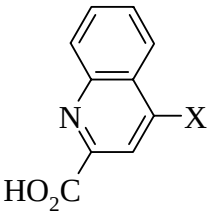
Table 3

General procedure for aldehyde oxidation in carboxylic acid derivatives (7 and 8) :

To the suitable 2-formylquinoline derivative (**3** or **6**) (2.6 mmol) dissolved in acetone (18 mL), was added dropwise a solution of potassium permanganate (0.711 g, 4.5 mmol) in acetone (5 mL). The reaction medium was stirred at rt for 2 h, filtrated and poured in hot water (15 mL). The mixture was then stirred, filtrated and acidified with 0.5 M hydrochloric acid. The formed precipitate was filtrated, dried and recrystallized (Table 4).

2-Carboxy-4-chloroquinoline (**7**) : IR 3300-3020, 1710 and 1580 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.86 (t, J=7.5 Hz, 1H), 8.00 (t, J=7.5 Hz, 1H), 8.22 (m, 3H), 13.69 (s, 1H). Anal. Calcd for $C_{10}H_6NO_2Cl$: C, 57.85; H, 2.91; N, 6.75. Found; C, 57.59; H, 2.98; N, 6.54.

2-Carboxy-4-[4-(*N*,*N*-dimethylsulfamoyl) piperazin-1-yl]quinoline (**8**) : IR 2960-2800, 1640, 1580, 1330 and 1140 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.83 (s, 6H), 3.32 (m, 4H), 3.54 (m, 4H), 7.55 (m, 3H), 8.00 (m, 1H), 8.30 (m, 1H), 8.79 (s, 1H). Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.73; H, 5.53; N, 15.37. Found; C, 52.43; H, 5.72; N, 15.29.



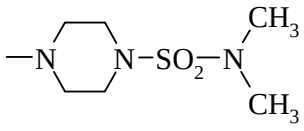
Compound	X	Yield (%) Recrystallization solvent	Mp (°C)	Reaction Time (h)
7	-Cl	55 % acetonitrile	160-162	2
8		32 % ethanol-water (95-5)	240-242	2

Table 4.

REFERENCES

1. D. R. Tomlinson, E. J. Stevens, and L. Diemel, *Trends Pharmacol. Sci.*, 1994, **15**, 293.
2. P. F. Kador, *Med. Res. Rev.*, 1988, **8**, 325.
3. D. T. Fong, F. K. Lee, Z. T. Song, N. A. Calcutta, L. W. Lee, S. S. M. Chung, and S. K. Chung, *Diabetes*, 1998, **47**, 961.
4. P. J. Oates and B. L. Mylari, *Exp. Opin. Invest. Drugs*, 1999, **8**, 2098.
5. J. R. Williamson, K. Chang, M. Frangos, K. S. Hasan, Y. Ido, T. Kawamura, J. R. Nyengaard, M. Van Den Eden, C. Kilo, and R. G. Tilton, *Diabetes*, 1994, **44**, 801.
6. B. L. Mylari, P. J. Oates, D. A. Beebe, N. S. Brackett, J. B. Coutcher, M. S. Dina, and W. J. Zembrowski, *J. Med. Chem.*, 2001, **44**, 2695.
7. M. Y. Chu-Moyer, W. E. Ballinger, D. A. Beebe, R. Berger, J. B. Coutcher, W. W. Day, J. Li, B. L. Mylari, P. J. Oates, and R. M. Weekly, *J. Med. Chem.*, 2002, **45**, 511.
8. N. E. Cameron, M. A. Basso, and T. C. Hohman, *Diabetologia*, 1997, **40**, 271.
9. D. Varlet, E. Fourmaintraux, P. Depreux, and D. Lesieur, *Heterocycles*, 2000, **53**, 797.
10. Krief, Hevesi 'Organoselenium Chemistry', Springer : New York, 776, 1988.
11. S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, 1949, **71**, 122.
12. A. Ashimori, T. Ono, T. Uchida, Y. Ohtaki, C. Fukaya, M. Watanabe, and K. Yokoyama, *Chem. Pharm. Bull.*, 1990, **38**, 2446.
13. 4-Chloro-8-methoxyquinoline was prepared in five steps from ortho-anisidine : C. C. Price and R. Roberts, *J. Am. Chem. Soc.*, 1946, **68**, 1204.

14. R. M. Bartholow and E. J. Walaszek, *J. Med. Chem.*, 1976, **19**, 189.

15. P. Depreux, D. Lesieur, H. Ait Mansour, P. Morgan, H. Edward Howell, P. Renard, D. H. Caignard, B. Pfeiffer, P. Delagrange, B. Guardiola, S. Yous, A. Demarque, G. Adam, and J . Andrieux, *J. Med. Chem.*, 1994, **37**, 3231.