SYNTHESIS OF NEW PHTHALAZINYL COMPOUNDS AS POTENTIAL INHIBITORS OF ALDOSE REDUCTASE AND SORBITOL DEHYDROGENASE

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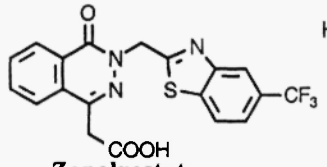
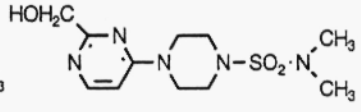
ABSTRACT : Chronic diabetes leads to long term complications which include neuropathy, nephropathy, retinopathy and cataract. The hyperglycemia observed in diabetes results in the intracellular production of sorbitol and fructose due to an increase of the glucose flux to the polyol pathway which is regulated by 2 enzymes : aldose reductase (AR) and sorbitol dehydrogenase (SDH). We envisaged the synthesis of new phthalazinyl derivatives in order to obtain compounds inhibiting both AR and SDH.

INTRODUCTION

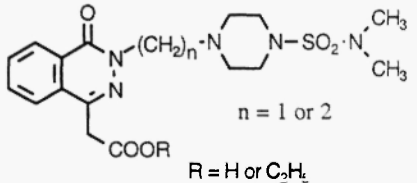
Chronic diabetes leads to long term complication which include neuropathy, nephropathy, retinopathy and cataract. The hyperglycemia observed in diabetes results in the intracellular production of sorbitol and fructose due to an increase of the glucose flux to the polyol pathway. This pathway is regulated by 2 enzymes : aldose reductase (AR) and sorbitol dehydrogenase (SDH) (1, 2). Although there are a number AR inhibitors (3-6), particularly Zopolrestat, only one SDH inhibitor is described (7) : CP 166 572.



Zopolrestat



CP 166 572



R = H or C_2H_5

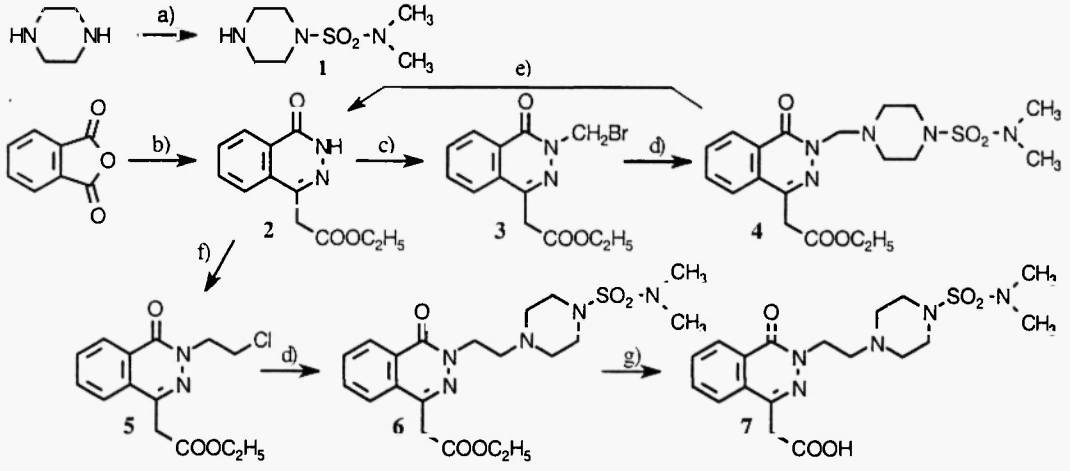
With the aim to obtain compounds inhibiting both AR and SDH, and thus prevent complications, we envisaged the synthesis of ligands having the phthalazinylacetic group of zopolrestat, or the corresponding ester, and the N,N-dimethylsulfamoylpiperazine group of CP 166 572. These 2 groups were separated by 1 or 2 carbones.

RESULTS AND DISCUSSION

1-Synthesis of compounds

Phthalic anhydride, after reacting with (carbetoxymethylene)triphenylphosphorane in refluxing chloroform, gives 3-(ethoxycarbonylmethylene)phthalide which reacts with hydrazine to lead to ethyl (3,4-dihydro-4-oxo-phthalazin-1-yl)acetate **2** (8). Hydroxymethylation of **2** with aqueous formaldehyde leads to an alcohol which was transformed into the corresponding bromo derivative **3** by action of phosphorus tribromide. Bromine atom was then substituted by N,N-dimethylsulfamoylpiperazine **1** (synthesized by treating excess piperazine with N,N-dimethylsulfamoylchloride) in presence of potassium carbonate. Saponification or hydrolysis of the

ester group of **4** failed. In all cases, we observed the formation of phthalazinone **2**. In a second way, phthalazinone **2** is condensed with 2-chlorobromoethane and the chloro derivative **5** substituted by N,N-dimethylsulfamoylpiperazine **1** in presence of potassium carbonate to lead to ester **6** that is then easily saponified in the corresponding acid **7**.



a) $ClSO_2N(CH_3)_2$ b) i) NaH / $(C_6H_5)_3P{=}CHCOOC_2H_5$ ii) $NH_2NH_2 . 6\,H_2O$ c) i) HCHO ii) PBr_3

d) **1**, K_2CO_3 e) saponification or hydrolysis f) $Br\frown\!\!\smile Cl$, K_2CO_3 g) i) NaOH / CH_3OH ii) HCl

2-Enzymatic studies

The 3 compounds present very weak inhibitory effect on the SDH (less than 10 % at 10 µM). It seems that the N,N-dimethylsulfamoylpiperazinyl substituent does not play a role in the inhibition of SDH. Thereby, these compounds were not tested as inhibitors of AR.

EXPERIMENTAL

Melting points were determined on a Buchi 510 capillary and are uncorrected. IR spectra were obtained on a Perkin-Elmer 297 spectrophotometer and are reported in cm^{-1}. ^1H NMR spectra were recorded on a WP 80-54 or a AC 300 Brucker spectrometer. Chemical shifts are reported in δ units (parts per million) relative to $(CH_3)_4Si$. Coupling constant are reported in hertz. Elemental Analyses for final tested compounds were performed by CNRS Laboratories (Vernaison, France). The results were within ± 0,4 of the theoretical values.

*N,N-Dimethylsulfamoylpiperazine (**1**) :*

Piperazine hexahydrate (4.0 g, 20 mmol.) and potassium carbonate (2.7 g, 20 mmol.) are added in 40 mL of absolute ethanol and the mixture cooled into an ice-bath. N,N-Dimethylsulfamoyl chloride (1.4 g, 10 mmol.) is added dropwise, the mixture stirred for 30 minutes and ethanol evaporated under vacuum. The residual solid is dissolved in brine. The aqueous layer is extracted with ethyl acetate. The organic layer is dried (magnesium sulfate) and evaporated under vacuum. The solid obtained is recrystallized from cyclohexane (yield 76 %). M.p. 97-98 °C; IR (KBr, cm^{-1}) 3250

(NH); 1330 and 1130 (SO); ^{1}H NMR (300 MHz, DMSO d_6) δ 2.84 (s, 6H. -CH_3), 2.90 (m, 4H. -CH_2-NH-CH_2-), 3.22 (m, 4H. -CH_2-N-CH_2-), 4.78 (m, 1H, D_2O exchangeable, -NH-).

*Ethyl (3,4-dihydro-4-oxo-phthalazin-1-yl)acetate (**2**) :*

Phthalic anhydride (0.5 g, 3.4 mmol.) is dissolved in 4 mL of chloroform. (Carbetoxymethylene)triphenylphosphorane (1.4 g, 4 mmol.) is then added under stirring and the solution refluxed 24 hours. Chloroform is evaporated under vacuum and the residual oil purified by column chromatography on silicagel (acetone-cyclohexane : 1-9, yield 70 %). The solid obtained (0.5 g, 2.3 mmol.) is dissolved in 4 mL of ethanol. Hydrazine hydrate (0.12 g, 2.4 mmol.) is added and the solution refluxed for 3 hours. Ethanol is evaporated under vacuum and the residue recrystallized from toluene (yield 70 %). M.p. 173-174 °C; IR (KBr, cm^{-1}) 1710 (CO ester); 1640 (CO lactame); ^{1}H NMR (80 MHz, DMSO d_6) δ 1.15 (t, 3H, 8.80 Hz. -O-CH_2-CH_3), 4.00 (m, 4H. -CH_2-CO and -O-CH_2-CH_3), 7.90 (m, 3H. H_6, H_7 and H_8), 8.20 (m, 1H. H_5), 12.60 (s, 1H. *NH*).

*Ethyl [3,4-dihydro-3-(bromomethyl)-4-oxo-phthalazin-1-yl]acetate (**3**) :*

2 (0.5 g, 2.2 mmol.) is dissolved in 4 mL of absolute ethanol and formaldehyde (2 mL, 27 mmol.) is added. The solution is refluxed for 45 hours and then poured into iced water. The solid formed is filtered and recrystallized from cyclohexane (yield 77 %). This solid (0.5 g, 1.9 mmol.) is dissolved in 10 mL of anhydrous ether. Phosphorus tribromide (0.52 g, 1.9 mmol.) is added dropwise and the solution stirred at room temperature for 24 hours. The ether layer is washed with water, dried (magnesium sulfate) and evaporated under vacuum. The residual solid is recrystallized from cyclohexane (yield 69 %). M.p. 92-93 °C; IR (KBr, cm^{-1}) 1710 (CO ester); 1650 (CO lactame); ^{1}H NMR (300 MHz, DMSO d_6) δ 1.20 (t, 3H, 7.13 Hz. -O-CH_2-CH_3), 4.00 (s, 2H. -CH_2-CO), 4.20 (q, 2H, 7.13 Hz. -O-CH_2-CH_3), 6.00 (s, 2H. -CH_2-Br), 7.80 (m, 3H. H_6, H_7 and H_8), 8.50 (dd, 1H, 1.86 and 7.55 Hz. H_5).

*Ethyl [3,4-dihydro-3-[(4-N,N-dimethylsulfamoylpiperazin-1-yl)methyl]-4-oxo-phthalazin-1-yl] acetate (**4**) :*

3 (0.5 g, 1.5 mmol.) is dissolved in 10 mL of acetone. Potassium carbonate (0.4 g, 3 mmol.) and **1** (0.3 g, 1.5 mmol.) are added. The mixture is refluxed for 19 hours and then filtered. The filtrate is evaporated under vacuum and the residual solid recrystallized from cyclohexane (yield 66 %). M.p. 113-114 °C; IR (KBr, cm^{-1}) 1710 (CO ester); 1650 (CO lactame), 1350 and 1150 (SO); ^{1}H NMR (300 MHz, DMSO d_6) δ 1.20 (t, 3H, 7.14 Hz. -O-CH_2-CH_3), 2.80 (s, 6H. -N(CH_3)$_2$), 2.90 (m, 4H. -CH_2-N-CH_2-), 3.22 (m, 4H. -CH_2-N-CH_2-), 3.90 (s, 2H. -CH_2-CO), 4.20 (q, 2H, 7.14 Hz. -O-CH_2-CH_3), 5.10 (s, 2H. -N-CH_2-N-), 7.80 (m, 3H. H_6, H_7 and H_8), 8.50 (dd, 1H, 1.86 and 7.55 Hz. H_5). Analysis calculated for $C_{19}H_{27}N_5O_5S$ (C, H, N).

*Ethyl [3,4-dihydro-3-(2-chloroethyl)-4-oxo-phthalazin-1-yl]acetate (**5**) :*

Sodium hydride, 60 % in dispersion in oil, (0.2 g, 4.3 mmol.) is added in 6 mL of dry DMF. The solution is cooled in an ice-bath and **2** (1 g, 4.3 mmol.) is then added. Stirring is continued untill

the end of the gazeous release. 2-Chlorobromoethane (1,9 g, 13 mmol.) is added, the solution stirred for 1 hour and then poured into water. The precipitate formed is filtered and recrystallized from n-hexane (yield 62 %). M.p. 112-113 °C; IR (KBr, cm^{-1}) 1725 (CO ester); 1655 (CO lactame); ^1H NMR (80 MHz, DMSO d_6) δ 1.20 (t, 3H, 7.10 Hz. -O-CH_2-CH_3), 3.70 (t, 2H, 6.50 Hz. -CH_2-Cl), 3.90 (s, 2H. -CH_2-CO), 4.00 (q, 2H, 7.10 Hz. -O-CH_2-CH_3), 4.60 (t, 2H, 6.50 Hz. N-CH_2-CH_2-Cl), 7.80 (m, 3H. H_6, H_7 and H_8), 8.50 (dd, 1H, 1.80 and 7.50 Hz. H_5).

*Ethyl [3,4-dihydro-3-[(4-N,N-dimethylsulfamoylpiperazin-1-yl)ethyl]-4-oxo-phthalazin-1-yl]acetate (**6**) :*

The synthesis procedure is the same as described for compound **4**. The oil obtained is purified by column chromatography on silicagel (dichloromethane-methanol : 98-2, yield 72 %). IR (KBr, cm^{-1}) 1700 (CO ester); 1650 (CO lactame), 1340 and 1150 (SO); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, 7.03 Hz. -O-CH_2-CH_3), 2.82 (s, 6H. -N(CH_3)$_2$), 3.16 (m, 4H. -CH_2-N-CH_2-), 3.47 (m, 4H. -CH_2-N-CH_2-), 3.97 (s, 2H. -CH_2-CO), 4.19 (q, 2H, 7.03 Hz. -O-CH_2-CH_3), 4.55 (m, 4H. -N-CH_2-CH_2-N-), 7.69 (dd, 1H, 1.48 and 7.77 Hz. H_8), 7.73 (m, 2H. H_6 and H_7), 8.45 (dd, 1H, 1.48 and 7.77 Hz. H_5). Analysis calculated for $C_{20}H_{29}N_5O_5S$ (C, H, N).

*[3,4-dihydro-3-[(4-N,N-dimethylsulfamoylpiperazin-1-yl)ethyl]-4-oxo-phthalazin-1-yl] acetic acid (**7**) :*

Sodium hydroxyde (0.27 g, 6.6 mmol.) is dissolved in 10 mL of ethanol and 3 mL of water. **6** (2.0 g, 4.4 mmol.) is added. The mixture is stirred for 2 hours at room temperature and then evaporated under vacuum. The residual solid is dissolved in water. The aqueous layer is washed with ethylacetate and then acidified with HCl 6N. The precipitate is filtered and recrystallized from water (yield 78 %). IR (KBr, cm^{-1}) 3200-2900 (OH acid), 1700 (CO acid); 1640 (CO lactame), 1340 and 1150 (SO); ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (s, 6H. -N(CH_3)$_2$), 3.06 (m, 4H. -CH_2-N-CH_2-), 3.35 (m, 4H. -CH_2-N-CH_2-), 4.01 (m, 2H. N-CH_2-CH_2-N), 4.38 (m, 4H. -CH_2-CO and N-CH_2-CH_2-N), 7.94 (m, 3H. H_6, H_7 and H_8), 8.32 (dd, 1H, 1.69 and 8.10 Hz. H_5), 12.81 (m, 1H. COO*H*). Analysis calculated for $C_{18}H_{25}N_5O_5S$ (C, H, N).

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