Synthesis and structural elucidation of new benzylidene imidazolidines and acridinylidene thiazolidines

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Abstract : New benzylidene imidazolidine and acridinylidene thiazolidine derivatives were prepared from substituted imidazolidinones and substituted thio-imidazolidinones either by nucleophilic addition on cyanoacrylates or by condensation with arylaldehydes.

Introduction

It has been shown since a long time that acridines and azolidines are efficient drugs in infectious diseases. Thus we intended to prepare some corresponding condensed derivatives with the aim to obtain new drugs with synergistic activities [1-5].

Results and discussion

3-(4'-Bromo-benzyl)-4-thio-5-benzylidene-imidazolidin-2-ones, **4** and **5**, 1-methyl-3-(4'-chloro-benzyl)-5-benzylidene-imidazolidin-2-ones, **8** and **9**, and 1-methyl-2-thio-5-(4"-bromo-benzylidene) imidazolidin-4-one, **11**, were prepared by two different general routes. The first process used was condensation between 3-(4'-bromo-benzyl)-4-thio-imidazolidin-2-one, **3**, or 1-methyl-2-thio-imidazolidin-4-one, **10**, with substituted benzaldehydes in acetic acid according to Johnson *et al.* [6] while the second one was the nucleophilic addition of 1-methyl-3-(4'-chloro-benzyl)-imidazolin-2,4-dione, **7**, on selected aryl-substituted ethyl-(2-cyano-3-phenyl)-acrylates [7] according to Daboun *et al.* [8].

Imidazolidin-2,4-dione, **1**, 1-methyl-imidazolidin-2,4-dione, **6**, and 1-methyl-2-thio-5-(4"-bromo-benzylidene)-imidazolidin-4-one, **11**, were N(3)-alkylated in the presence of potassium hydroxide which leads to the imidazolidine potassium salt capable to react with benzyl halides in hot alcoholic medium according to Finkbeiner [9]. 3-(4'-Bromo-benzyl)-imidazolidin-2,4-dione, **2**, 1-methyl-3-(4'-chloro-benzyl)-imidazolidin-2,4-dione, **7**, and 1-methyl-2-thio-3-benzyl-5-(4"-bromo-benzylidene)-imidazolidin-4-ones, **12** and **13**, were obtained in this way.

3-(4'-Bromo-benzyl)-4-thio-imidazolidin-2-one, **3**, was obtained from 3-(4'-bromo-benzyl)-imidazolidin-2,4-dione, **2**, using tetraphosphorous decasulfide according to Grishchuk *et al.* [10].

Synthetic pathways are portrayed in figure 1.

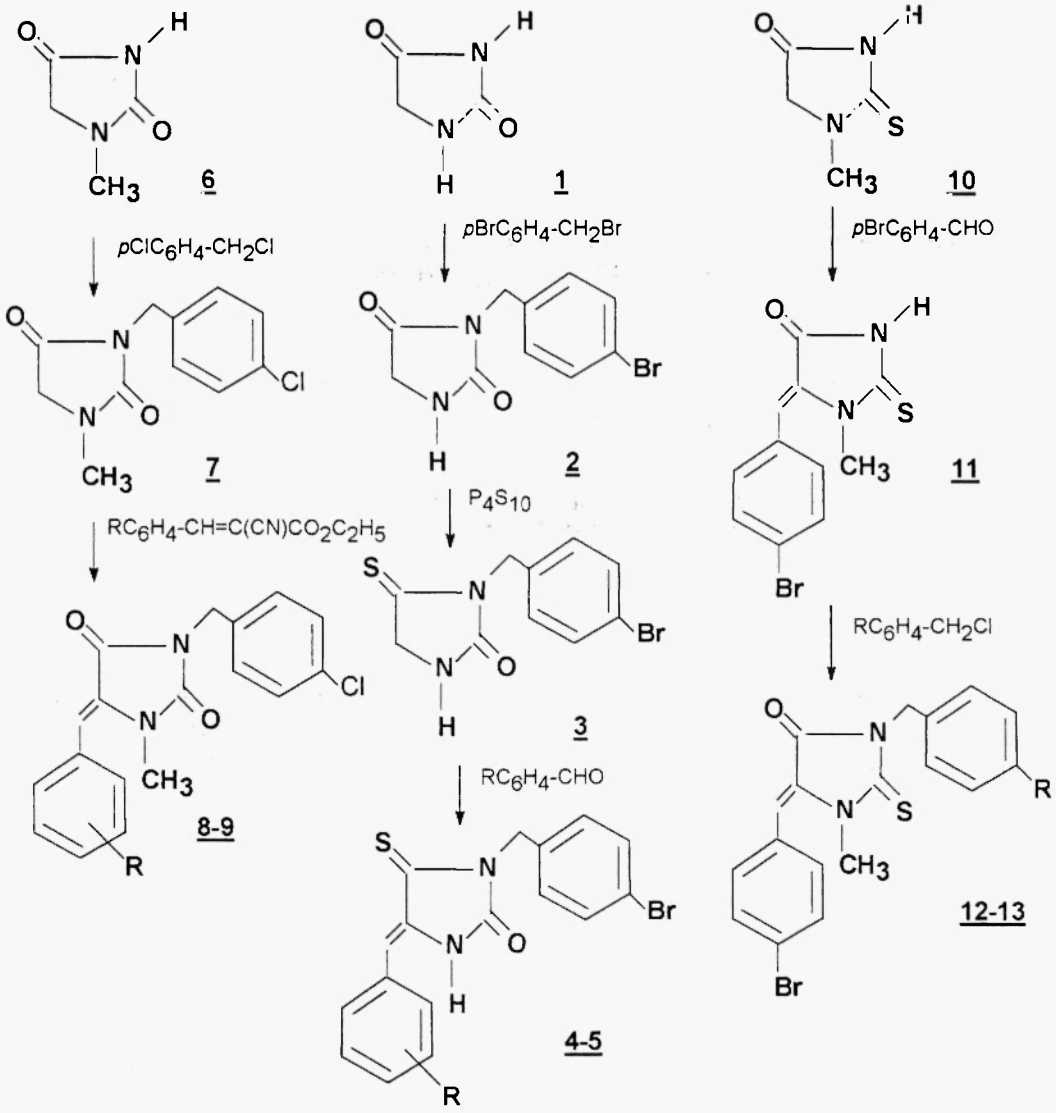

Figure 1.

The thiazolidine-dione derivatives **21-23**, were only synthesized by nucleophilic addition of substituted thiazolidine-diones, **18-20**, on 9-[ethyl-(2'-cyano)-acrylate]-acridine, **16**. Indeed, direct condensation of 9-acridinaldehyde, **15**, with the substituted thiazolidine-diones **18-20**, did not led to the expected 3-benzyl-5-acridinylidene-thiazolidin-2,4-diones, **21-23**, contrarily to that obtained with the imidazolidine reagents.

9-Methyl-acridine, **14**, was prepared from diphenylamine with zinc dichloride in acetic acid medium according to Tsuge *et al.* [11]. Subsequently, oxidation of **14** with pyridinium chlorochromate according to Mosher *et al.* [12] gave the 9-acridinaldehyde, **15**.

Synthetic pathways are portrayed in figure 2.

Benzylidene imidazolidinones were isolated in a single isomer form. X-ray crystallographic studies and ^{13}C NMR have demonstrated the preferred Z configuration for 5-

arylidenethiazolidinones and 5-arylideneimidazolinones [13-15]. $^3J_{CH}$ coupling constant value between the ethylene proton and the carbon atom located at the α position of exocyclic bond is of special interest in this demonstration. Thus, in case of 1-methyl-3-(4'-chloro-benzyl)-5-benzylidene-imidazolidin-2-one, **8**, after the methylene protons of the side chain being irradiated at 4.72 ppm, value of $^3J_{CH}$ is 7.26 Hz. This is in agreement with a Z configuration [16]. In contrast, 1-methyl-3-(4'-chloro-benzyl)-5-benzylidene-imidazolidin-2-one, **9**, and 3-benzyl-5-acridinylidene-thiazolidin-2,4-dione, **22**, were isolated as isomeric mixtures. Isomers were readily identified by ^{1}H NMR. Actually, the ethylene proton is more deshielded in isomer Z than it is in isomer E, owing to the cis-position of exocyclic carbonyl function. Finally, MS data fully agree with the structure proposed.

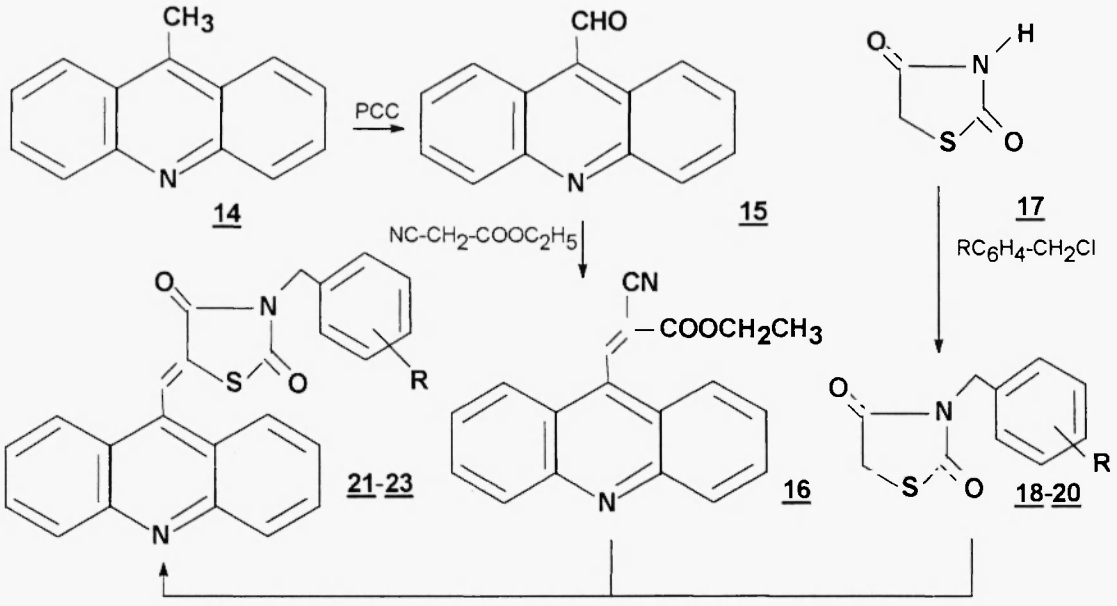

Figure 2.

Experimental

Melting points were measured in capillary tube on Buchi (or Quimis) apparatus. Thin Layer Chromatography was performed on silicagel plates Merck $60F_{254}$. Infrared spectra of 1% KBr pellets were recorded on a Bruker IFS66 spectrometer (or Perkin Elmer 1310 spectrometer for **2**, **9**, **11**, **12** and **13**). ^{1}H NMR spectra were recorded on a Bruker AC 300 P spectrophotometer (or Bruker AC 200 spectrophotometer for **2**, **8**, **9**, **12** and **13**) in DMSO-d_6 or $CDCl_3$ as solvent, with tetramethylsilane as internal standard. Mass spectra were recorded on Delsi-Nermag R 1010 C spectrometer (or HP 5897 for **21**).

The published chemical data on **2** [17], **6**,**7** [3], **10** [18], **19** [19] and **20** [2] have not been reported.

***3-(4'-Bromo-benzyl)-4-thio-imidazolidin-2-one*, 3.**

3-(4'-Bromobenzyl)-imidazolidin-2,4-dione, **2**, (6 g, 21 mmol) and tetraphosphorous decasulfide (2.5 g, 11 mmol) are refluxed in anhydrous dioxane (50 ml) for 40 min before zinc (0.1 g) and coal (0.1 g) be added. Heating is maintained 5 min more. The mixture is filtered and concentrated to the half. Crushed ice is added and the precipitate obtained is filtered. Crude is purified by column chromatography with benzene : methanol (9 : 1) as eluent. $C_{10}H_9N_2OS$. Yield : 88%. Mp : 188-9°C. TLC, benzene : methanol (9:1), R_f : 0.57. IR cm^{-1} (KBr): υ 3240, 1755, 1490, 1450, 1350, 1230, 880, 780. ^{1}H NMR (δ ppm, $CDCl_3$): 4.35 (d, CH_2-5 J = 1Hz); 4.99 (s, CH_2-Ph); 6.05 (s, NH); 7.36 (d, 2H benzyl, J = 8.6Hz); 7.45 (d, 2H benzyl, J = 8.5Hz).

3-(4'-Bromo-benzyl)-4-thio-5-benzylidene-imidazolidin-2-ones, **4**, **5** : general procedure.
A mixture of benzaldehyde (1.2 mmol), 3-(4'-bromo-benzyl)-4-thio-imidazolidin-2-one, **3**, (1.5 mmol) and melt sodium acetate (0.45 g) is heated at 120-140°C in acetic acid (10 ml) for 5-6 h. After cooling, precipitate is washed with water and recrystallized in acetic acid

3-(4'-Bromo-benzyl)-4-thio-5-(2"-chloro-benzylidene)-imidazolidin-4-one, **4**
$C_{17}H_{12}BrClN_2OS$. Yield : 48%. Mp : 218-9°C. TLC, methylene chloride, R_f : 0.58. IR cm^{-1} (KBr): υ 3224, 1736, 1639, 1487, 1305, 1197, 764. ^1H NMR (δ ppm, DMSO-d_6): 5.04 (s, CH_2-Ph); 7.19 (s, CH); 7.31 (d, 2H benzyl, J = 8.7Hz); 7.55 (d, 2H benzyl, J = 8.4Hz); 7.41-7.45 (m, 2H benzylidene) ; 7.56-7.59 (m, 1H benzylidene); 7.74-7.77 (m, 1H benzylidene); 11.5 (NH). Ms, m/z (%) : 371 (M^+ -Cl 71.4), 373(81.5), 169(100), 171(95.2), 90(14.7), 89(14.6).

3-(4'-Bromo-benzyl)- 4-thio-5-(4"-methoxy-benzylidene)-imidazolidin-4-one, **5**
$C_{18}H_{15}BrN_2O_2S$. Yield : 48%. Mp : 225-6°C. TLC, methylene chloride, R_f : 0.50. IR cm^{-1} (KBr): υ 3237, 1733, 1646, 1597, 1347, 1259, 760. ^1H NMR (δ ppm, DMSO-d_6): 3.82 (s, OCH_3); 5.04 (s, CH_2-Ph); 7,04 (s, CH); 7.29 (d, 2H benzyl, J = 8.1Hz); 7.55 (d, 2H benzyl, J = 8.1Hz); 7.02 (d, 2H benzylidene, J = 8.7Hz); 7.7 (d, 2H benzylidene, J = 8.7Hz). Ms, m/z (%) : 402(M^+ 100), 403(79.3), 404(93.8, 290(21.7), 233(15.7), 206(13), 169(38.5), 171(37.3), 89(6.5).

1-Methyl-3-(4'-chloro-benzyl)-5-benzylidene-imidazolidin-2,4-ones, **8**, **9** : general procedure.
A mixture of 1-methyl-3-(4'-chloro-benzyl)-imidazolidin-2,4-dione, **7**, (0.59 g, 2.5 mmol) and ethyl-(2-cyano-3-phenyl)-acrylate (2.7 mmol) is refluxed for 2-6 h in absolute ethanol (20 ml) added with piperidine (0.25 ml). After cooling, precipitates are purified by column chromatography and recrystallized in suitable solvents.

1-Methyl-3-(4'-chloro-benzyl)-5-(4"-chloro-benzylidene)-imidazolidin-2,4-one, **8**.
$C_{18}H_{14}Cl_2N_2O_2$ (purification by column chromatography with chloroform as eluent; recrystallisation in absolute ethanol). Yield : 18%. Mp : 187-8°C. TLC, chloroform : *n*-hexane (1:1), R_f : 0.54. IR cm^{-1} (KBr): υ 1754, 1709, 1629, 1403, 1086, 803. ^1H NMR (δ ppm, $CDCl_3$): 3.21 (s, NCH_3); 4.71 (s, CH_2-Ph); 6.18 (s, CH); 7.28 (d, 2H benzyl, J = 8.2Hz); 7.38 (d, 2H benzyl, J = 8.3Hz); 7.34 (d, 2H benzylidene, J = 8.5Hz); 7.92 (d, 2H benzylidene, J = 8.5Hz). Ms, m/z (%) : 360(M^+ 58), 361(11.3), 362(38.8),166(17.1), 165(21), 150(34.1), 127(32.7), 125(100), 89(15.3).

1-Methyl-3-(4'-chloro-benzyl)-5-(2"-chloro-benzylidene)-imidazolidin-2,4-one, **9**.
$C_{18}H_{14}Cl_2N_2O_2$ (purification by column chromatography with chloroform / n-hexane (8 : 2) as eluent; recrystallization in absolute ethanol). Yield : 15%. Mp : 164-5°C. TLC, chloroform : *n*-hexane (1:1), R_f : 0.47. IR cm^{-1} (KBr): υ 1765, 1715, 1650, 1440, 1405, 1100, 850. ^1H NMR (δ ppm, DMSO-d_6) Z/E 56/44% : 3.16/2.77 (s, NCH_3); 4.68/4.60 (s, CH_2-Ph); 6.67/6.50 (s, CH); 7.32-7.44 (m, arom.) 7.81-7.86 (m, benzylidene). Ms, m/z(%): 360(M^+ 1.8), 361(1), 362(1.1), 325(54), 150(16.9), 127(47.4), 125(100), 99(9.2), 89(27.1). ^{13}C NMR (δ ppm, DMSO-d_6, DEPT) Z/E: 26.4/26.6 (NCH3), 40.9/41.3 (CH2), 107.1/111.1 (CH ethylénique), 126.3/126.7 (CH), 128.4/128.5 (2CH), 128.8/129.1 (CH), 129.5/129.6 (2CH), 129.9/130.1 (CH), 130.6/130.9 (C), 131/131.1 (C), 131.7/131.9 (CH), 132.1/132.2 (C), 132.8/133.2 (C), 135.1/135.2 (C), 152.9/154.7 (CO), 160.8/162.6 (CO). Ms, m/z (%) : 360(M^+ 1.8), 361(1), 362(1.1), 325(54), 327(16.4), 150(16.9), 125(100), 127(47.4), 89(27.1).

1-Methyl-2-thio-5-(4"-bromo-benzylidene)-imidazolidin-4-one, **11**.
A mixture of 1-methyl-2-thio-imidazolidin-4-one, **10**, (1.3 g, 0.01 mmol), 4-bromo-benzaldehyde (2.78 g, 0.015 mmol) and melt sodium acetate (2.5 g) is heated at 140 °C in glacial acetic acid for 3 h. After cooling, the precipitate obtained is washed with water then with chloroform.
$C_{11}H_9BrN_2OS$. Yield : 60%. Mp : 212°C. TLC, chloroform : methanol (94:6), R_f 0.83. IR cm^{-1} (KBr): υ 3130, 1735, 1620, 1580, 1485, 1370, 1160, 1105, 770. ^1H NMR (δ ppm, DMSO-d_6): 3.44 (s, NCH_3); 6.66 (s, CH); 7.56 (d, 2H benzylidene, J = 8.2Hz); 7.96 (d, 2H benzylidene, J = 8.2Hz); 13.42 (s, NH). ^{13}C NMR (δ ppm, DMSO-d_6, DEPT): 29.7(NCH3), 118.4, 122.6, 130.4, 131, 131.7, 132.5, 162.6(CO), 176.1(CS).

1-Methyl-2-thio-3-benzyl-5-(4"-bromo-benzylidene)-imidazolidin-4-ones, **12**, **13** : general procedure.
1-Methyl-2-thio-5-(4"-bromo-benzylidene)-imidazolidin-4-one, **11**, (0.59 g, 2 mmol) is dissolved in methanol (2 ml) before potassium hydroxide (0.12 g) dissolved in methanol (3 ml) be added with stirring. A few time (10 min) later, benzyl halide (2.5 mmol) is added dropwise. The mixture is left at room temperature for 24 h. The precipitate obtained is filtered, before to be washed with water then with ethyl ether. Compounds isolated are of acceptable purity and were analysed without further recrystallization.

***1-Methyl-2-thio-3-benzyl-5-(4"-bromo-benzylidene)-imidazolidin-4-one,* 12.**
$C_{18}H_{15}BrN_2OS$. Yield : 80%. Mp : 209-211°C. TLC, chloroform : methanol (96:4), R_f : 0.9. IR cm^{-1} (KBr): υ 1680, 1620, 1590, 1455, 1435, 1390, 1170, 1020, 720. ^1H NMR (δ ppm, DMSO-d_6): 3.29 (s, NCH_3); 4.57 (s, CH_2); 6.79 (s, CH); 7.31-7.48 (m, 5H benzyl); 7.61 (d, 2H benzylidene, J = 8.4Hz); 8.17 (d, 2H benzylidene, J = 8.4Hz). Ms, m/z (%) : 386(M^+ 18), 388(20), 353(5.2), 274(8.7), 226(7.6), 209(17.9), 194(46.2), 196(51.5), 115(18.7), 91(100), 65(33.8).

***1-Methyl-2-thio-3-(4'-bromo-benzyl)-5-(4"-bromo-benzylidene)-imidazolidin-4-one,* 13.**
$C_{18}H_{14}Br_2N_2OS$. Yield : 85%. Mp : 223-224°C. TLC, chloroform : methanol (96:4), R_f : 0.9. IR cm^{-1} (KBr): υ 1690, 1610, 1580, 1485, 1450, 1435, 1320, 1160, 1010, 890. ^1H NMR (δ ppm, DMSO-d_6): 3.29 (s, NCH_3); 4.55 (s, CH_2); 6.79 (s, CH); 7.43 (d, 2H benzyl, J = 8.5Hz); 7.54 (d, 2H benzyl, J = 8.5Hz); 7.61 (d, 2H benzylidene, J = 8.6Hz); 8.17 (d, 2H benzylidene, J = 8.6Hz). Ms, m/z (%) : 464(M^+ 0.51), 466(0.7), 468(0.65), 352(7.3), 295(6.6), 226(12.9), 209(22.4), 194(39.7), 169(49), 115(26.7), 90(60.6), 89(93.7), 63(100).

***9-Methyl-acridine,* 14.**
A mixture of diphenylamine (2.5 g, 14.7 mmol), zinc dichloride (10 g) and acetic acid (2.5 ml) is heated at 220°C for 6 h. The mixture is acidified with 10% sulfuric acid before to be made alkaline with 30% ammonia. The crude is extracted with toluene and purified by flash chromatography on silica with n-hexane : ethyl acetate (7 : 3) as eluent. $C_{14}H_{11}N$. Yield : 40%. Mp : 115-7°C / 118°C [13]. TLC, *n*-hexan : ethyl acetate (7:3), R_f : 0.59. ^1H NMR (δ ppm, DMSO-d_6): 3.13 (s, CH_3); 7.60-7.66 (m, $2H_{arom}$); 7.81-7.87 (m, $2H_{arom}$); 8.12-8.17 (m, $2H_{arom}$); 8.38-8.42 (m, $2H_{arom}$).

***9-Acridinaldehyde,* 15.**
A mixture of 9-methyl-acridine, **14**, (1.7 g, 8.9 mmol), magnesium sulfate (5.1 g), pyridinium chlorochromate (PCC) (2.04 g, 9.4 mmol) and anhydrous methylene chloride (51 ml) is stirred under nitrogen pressure at room temperature for 18 h. The crude is extracted with ethyl ether. After solvent evaporation, compound is purified by flash chromatography on silica with n-hexane : ethyl acetate (6 : 4) as eluent. $C_{14}H_9NO$. Yield : 55%. Mp : 151-152°C / 147°C [14]. TLC, *n*-hexan : ethyl acetate (6:4), R_f : 0.35. ^1H NMR (δ ppm, DMSO-d_6): 11.67 (s, CHO); 7.22-7.28 (m, $2H_{arom}$); 7.52-7.55 (m, $2H_{arom}$); 7.70-7.75 (m, $2H_{arom}$); 8.22-8.25 (m, $2H_{arom}$).

***9-[Ethyl-(2'-cyano)-acrylate]-acridine,* 16.**
A mixture of 9-acridinaldehyde, **15**, (2.2 g, 10.5 mmol), ethyl cyanoacetate (3 ml), piperidine (250 µl) and anhydrous benzene (50 ml) is refluxed at 110 °C for 8 h. After cooling, the precipitate obtained is purified by flash chromatography on silica with n-hexane : ethyl acetate (6 : 4) as eluent. $C_{19}H_{14}N_2O_2$. Yield : 49%. Mp : 170-171°C. TLC, *n*-hexane :ethyl acetate (7:3), R_f : 0.44. IR cm^{-1} (KBr): υ 3431, 2200, 1727, 1619, 1270, 763. ^1H NMR (δ ppm, DMSO-d_6): 1.40 (t, CH_3, J = 7.2Hz); 4.45 (q, CH_2, J = 7.2Hz); 7.69-7.75 (m, 2H); 7.91-7.97 (m, 2H); 8.11 (d, 2H, J = 8.7Hz); 8.26 (d, 2H, J = 8.4Hz); 9.35 (s, CH). Ms, m/z (%) : 302(M^+ 25.1), 303(5.4), 229(100), 203(19.7), 175(5.3), 101(4.5), 75(5.9), 63(5.1).

***3-(4'-Methyl-benzyl)-thiazolidin-2,4-dione,* 18.**
A solution of sodium hydroxide (1.9 g) in 10 ml of ethanol : water mixture (6 : 4) is added dropwise under stirring to a suspension of thiazolidine-2,4-dione, **17**, in 10 ml of the same ethanol : water mixture. A few time later (10 min), the substituted benzyl chloride (7 ml) is added and the mixture is stirred for 5 min before to be refluxed for 24 h. After cooling at room temperature, the expected compound is precipitated by addition of crushed ice before to be purified by flash chromatography on silica with chloroform : methanol (92 : 8) as eluent. $C_{11}H_{11}NO_2S$. Yield : 21%. Mp : 70-72°C. TLC chloroform : methanol (92:8) R_f : 0.68. IR cm^{-1} (KBr): υ 2996, 1756, 1730, 1676, 1514, 1428, 1378, 1337, 1058, 751. ^1H NMR (δ ppm, DMSO-d_6): 2.27 (s, CH_3); 4.26 (s, CH_2); 4.62 (s, CH_2 phenacyl), 7.14 (s, 4H, arom.).

***3-Benzyl-5-acridinylidene-thiazolidin-2,4-diones,* 21-23** : general procedure.
Benzylthiazolidine, **18-20** (0.9 mmol) and 9-[ethyl-(2'-cyano)-acrylate]-acridine, **16**, (0.9 mmol) are dissolved in absolute ethanol (8 ml). The solution is refluxed for 4 h in the presence of small amount of piperidine as catalyst. The precipitate obtained is filtered and washed with water. Compounds isolated are of acceptable purity and were analysed without further recrystallization.

***3-(4'-Methyl-benzyl)-5-acridinylidene-thiazolidin-2,4-dione*, 21.**
$C_{25}H_{18}N_2O_2S$. Yield : 96%. Mp : 198-199°C. TLC benzene : ethyl acetate (9:1) R_f : 0.45. IR cm^{-1} (KBr): υ 1746, 1697, 1630, 1378, 1339, 1149, 758. ^1H NMR (δ ppm, $CDCl_3$): 2.37 (s, CH_3), 4.92 (s, CH_2); 7.21 (d, 2H benzyl, J = 7.8Hz), 7.42 (d, 2H benzyl, J = 8.1Hz), 7.57-7.62 (m, 2H acridin), 7.8-7.85 (m, 2H acridin), 7.96 (d, 2H acridin, J = 7.8Hz), 8.29 (d, 2H acridin, J = 8.7Hz), 8.69 (s, 1H, CH). Ms, m/z (%) : 410(M^+ 98.1), 411(29.3), 305(24.2), 235(52.9), 190(9), 105(100), 77(8.3).

***3-(4'-Bromo-benzyl)-5-acridinylidene-thiazolidin-2,4-dione*, 22.**
$C_{24}H_{15}BrN_2O_2S$. Yield : 48%. Mp : 258-260°C. TLC ethyl acetate : *n*-hexane (7:3), R_f : 0.53. IR cm^{-1} (KBr): υ 3419, 1745, 1694, 1625, 1378, 1334, 1149, 760. ^1H NMR (δ ppm, DMSO-d_6) Z/E 78/22% : 4.86/4.57 (s, CH_2); 7.39/7.10 (d, 2H benzyl, J = 8.7/8.4Hz); 7.60/7.46 (d, 2H benzyl, J = 8.7Hz); 7.66-7.72 (Z, m, 2H acridin), 7.89-7.95 (Z, m, 2H acridin), 8.14 (Z, d, 2H acridin, J = 8.1Hz), 8.24 (Z, d, 2H acridin, J = 8.4Hz), 8.78/8.37 (s, CH).

***3-(4'-Nitro-benzyl)-5-acridinylidene-thiazolidin-2,4-dione*, 23.**
$C_{24}H_{15}N_3O_4S$. Yield : 60%. Mp : 238-240°C. TLC *n*-hexane : ethyl acetate (6:4) R_f : 0.57. IR cm^{-1} (KBr): υ 3422, 1747, 1694, 1629, 1606, 1530, 1379, 1340, 1149, 760. ^1H NMR (δ ppm, DMSO-d_6) 5.03 (s, CH_2); 7.72 (d, 2H benzyl, J = 8.7Hz); 8.27 (d, 2H benzyl, J = 8.4Hz); 7.68-7.73 (m, 2H acridin), 7.90-7.96 (m, 2H acridin), 8.17 (d, 2H acridin, J = 8.7Hz), 8.25 (d, 2H acridin, J = 8.7Hz), 8.81 (s, 1H, CH).

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References

[1] H.M. SALAMA, I.M. LABOUTA and M. MAA, Alexandria J. Pharm. Sc., **4**, 44-46 (1990).
[2] S.S.F. BRANDÃO, J.A. ROCHA FILHO, J. CHANTEGREL, J.F.C. ALBUQUERQUE, E.A. XIMENES, S.L. GALDINO, I.R. PITTA, M. PERRISSIN and C. LUU-DUC, Ann. Pharm. Fr., **55**, 206-211 (1997).
[3] J.F.C. ALBUQUERQUE, A.J. ROCHA FILHO, S.S.F. BRANDÃO, M.C.A. LIMA, E.A. XIMENES, S.L. GALDINO, I.R. PITTA, J. CHANTEGREL, M. PERRISSIN and C. LUU-DUC, II Farmaco, **54**, 77-82 (1999).
[4] A. ALBERT and R. GOLDACRE, Nature, **162**, 95 (1948)
[5] A. ALBERT, S.D. RUBBO, R.J. GOLDACRE, M.E. DAVEY and J.D. STONE, Brit. J. exptl Pathol., **26**, 160 (1945)
[6] T.B. JOHNSON and W.M. SCOTT, J. amer. chem. Soc., **37**, 1846-1856 (1915).
[7] W.M. PHILLIPS and D.J. CURRIE, Can. J. Chem., **47**, 3137-3146 (1969).
[8] H.A.F. DABOUN, S.E. ABDOU, M.M. HUSSEIN and M.H. ENALGDI, Synthesis, 502-504 (1982).
[9] H. FINKBEINER, J. Org. Chem., **30**, 3414-3419 (1965).
[10] A.P. GRISHCHUK, S.N. BARANOV, T.E. GORIZDRA and I.D. KOMARITSA, Zh. Prikl. Khim., **40**, 1389-1390 (1967) in *Chem. Abstr.* **67**, 116869e (1967).
[11] O. TSUGE, M. NISHINOHARA and M. TASHIRO, Bull. Chem. Soc. Japan, **36**, 1477-1485 (1963).
[12] M.D. MOSHER and N.R. NATALE, J. Heterocycl. Chem., **32**, 779-781 (1995).
[13] S.F. TAN, K.P. ANG and Y.F. FONG, J. Chem. Soc., Perkin Trans. II, 1941-1944 (1986).
[14] J.F.C. ALBUQUERQUE, S.L. GALDINO, J. CHANTEGREL, F. THOMASSON, I.R. PITTA and C. LUU-DUC, Ann. Pharm. Fr., *in press*.
[15] C.A. DE SIMONE, J. ZUKERMAN-SCHPECTOR, M.A. PEREIRA, C. LUU-DUC, I.R. PITTA, S.L. GALDINO and E.L.C. AMORIM, Acta Cryst., **C51**, 2620-2621 (1995).
[16] G.J. KARABATSOS and C.E. ORZECH, J. amer. chem. Soc., **87**, 560-562 (1965).
[17] E.L. AMORIM, S.S.F. BRANDÃO, C.O.M. CAVALCANTI, S.L.GALDINO, I.R. PITTA and C. LUU-DUC, Ann. Pharm. Fr., **50**,103-111 (1992).
[18] S.S.F. BRANDÃO, V.L.M. GUARDA, I.R. PITTA, J. CHANTEGREL, M. PERRISSIN, V.M. SOUZA, S.L. GALDINO, F. THOMASSON, M.C.A.LIMA, L.F.C.C. LEITE and C. LUU-DUC, Boll. Chim. Farm., **139**, 54-58 (2000).
[19] D.L.B. COSTA, J. CHANTEGREL, M.C.A. LIMA, J.F.C. ALBUQUERQUE, R.M.O.C. LIMA, S.L. GALDINO, I.R. PITTA and C. LUU-DUC, J. Pharm. Belg., **50**, 5-10 (1995).

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