SYNTHESIS OF TWO NEW HETEROCYCLIC RING SYSTEMS: 2-AZA-6-THIA-10-AZASPIRO[4,5]DECANE-1,3,9-TRIONE-7-ENE-7-BENZOYL AND 2-AZA-7-THIA-11-AZASPIRO[5,5]UNDECANE-1,3,10-TRIONE-8-ENE-8-BENZOYL DERIVATIVES

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Abstract: The synthesis of two new type heterocyclic derivatives, 2-aza-6-thia-10-azaspiro[4,5]dccanc-1,3,9-trione-7-ene-7-benzoyl and 2-aza-7-thia-11-azaspiro[5,5]-undecane-1,3,10-trione-8-ene-8-benzoyl, from 2,3-dihydro-1,3-thiazine-4-ones which in turn were obtained via a rearrangement reaction of 3(2H)-isothiazol-3-ones prepared from properly designed 3-benzoylpropionamides, is described.

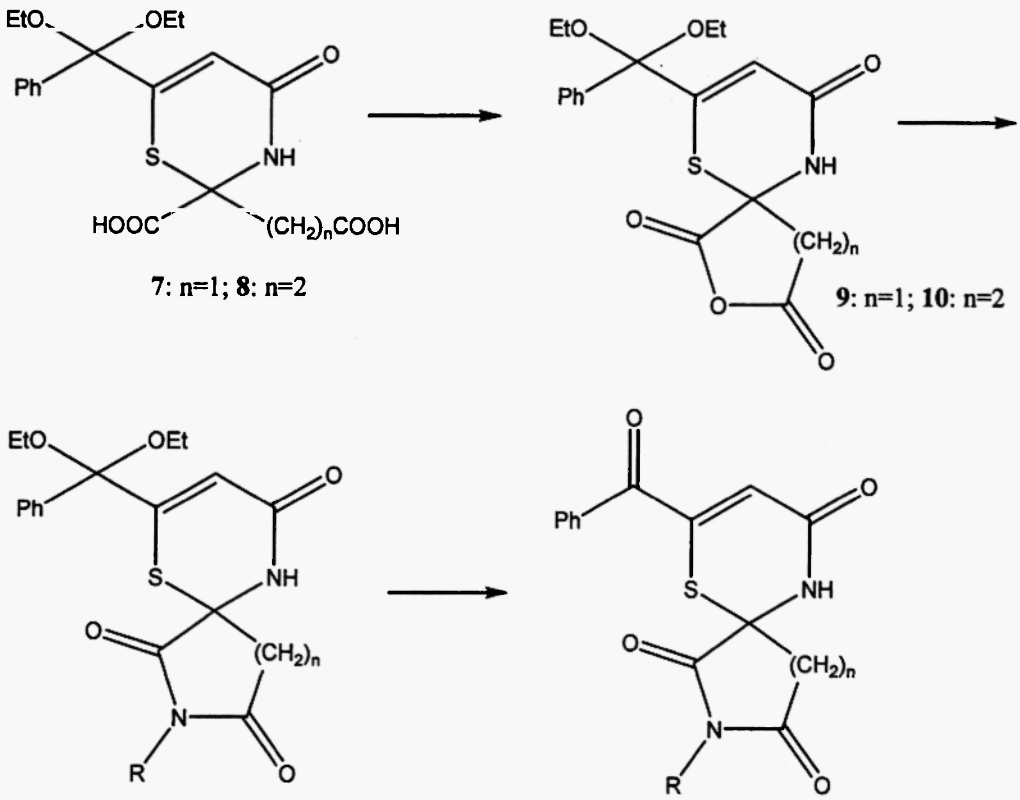
Azabicyclic and azaspiro nuclei, containing a spiro carbon atom had been only cursorily touched in the literature[1,2] until five decades ago, then a large number of azaspirane derivatives were developed[3]. Some of these products have shown inhibitory effects on cancer cells in tissue culture and objective clinical effects in human cancer. At that time, the same research group also reported[4] the synthesis of azaspirodione and azaspirane derivatives with a wide range of useful activities according to biological and pharmacological studies; the most notable was the effect produced on the peripheral and central nervous system.

Later pyrrolidine-2,5-diones containing at the 3-position cycloalkyl moiety connected by a spiro carbon atom showed potent anticonvulsant activity,[5-8] specifically azaspiro[4,5]decane-1,3-diones have been examined, by a maximal electroshock and pentylenetetrazole tests, as antiepileptics. While some of those derivatives were classified to the anticonvulsant screening program 1 class. On the other hand azaspiro[4,5]decane-1,3-dione derivatives were evaluated for antimicrobial activity.[9]

In a previous work[10] we reported the construction of a cephem and a pyrrolo[2,1-b][1,3]thiazine-4,6-dione ring system, following a reaction sequence which includes the preparation of diacids 7 and **8**.

In this communication, we wish to report a new and convenient method for the construction of 2-aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7-ene-7-benzoyl-2-substituted and 2-aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-**8**-ene-8-benzoyl-2-substituted heterocyclic systems, under simple reaction conditions, starting from the diacids 7 and **8** respectively. The diacids 7 and **8** on reaction with acetic anhydride were converted to the corresponding oxaspirotrione derivatives **9** and **10** in good yields. These acid anhydrides on reaction with different amines afforded, through the intermediate oxamic acids, the corresponding azaspiro derivatives **11** and **12**, which after deacetalization were converted to the desired benzoyl derivatives **13** and **14**, (Scheme 1).

Scheme 1



7: n=1; **8**: n=2

9: n=1; **10**: n=2

11: n=1; **12**: n=2

13: n=1; **14**: n=2

R: (a)=Me, (b)=Et, (c)=Ph

Conclusively, here we present the synthesis of two new aza-thia-azaspiro heterocyclic systems the 2-aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7-ene-7-benzoyl and 2-aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8-benzoyl, starting from 2-oxa-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7-ene-7(phenyl-diethoxymethyl) **9** and 2-oxa-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8(phenyldiethoxymethyl) **10**, respectively, which were prepared from the corresponding 2H-1,3-thiazine-2-carboxylic acid-2-acetic acid-6-[benzene-(1,1-diethoxymeth-yl)]-3,4-dihydro-4-oxo, and 2H-1,3-thiazine-2-carboxylic acid-2-propanoic acid-6-[benzene-(1,1-diethoxy-methyl)]-3,4-dihydro-4-oxo which were prepared according to a recent report from us.

Experimental

General. NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer, as potassium bromide pellets, and were calibrated against the polystyrene 1600 cm^{-1} band, and given in reciprocal centimeters.

Synthesis of 2-oxa-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7-ene-7(phenyldiethoxymethyl) **9** and 2-oxa-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8(phenyldiethoxymethyl) **10**. A mixture of 1 mmol of the diacid[10] 7 or **8** and 4 ml of acetic anhydride was warmed on a steam bath under stirring for 1h. The resulting solution was concentrated under vacuum to an oily product which solidified later. After recrystallization from ethyl acetate an analytical product of the desired product was received, in yields 66-74%.

2-Oxa-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7-ene-7(phenyl-diethoxymethyl), 9: yield 2.8 g (74%), mp 187-188 ^{0}C. Anal. Calcd for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71; S, 8.50. Found: C, 57.41; H, 5.21; N, 3.55; S, 8.36. IR: 3236, 1820, 1700. ^{1}H NMR ($CDCl_3$): 1.10-1.37 (m, 6H, two CH_3), 2.87 (s, 2H, CH_2), 3.15-3.51 (m, 4H, two OCH_2Me), 6.42 (s, 1H, =CH-), 7.22-7.43 (m, 5H, arom.), 8.31 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 14.15, 14.31, 26.31, 41.73, 58.38, 58.60, 63.27, 101.30, 116.80, 127.40, 127.83, 128.62, 139.70, 152.40, 165.30, 170.45, 174.23.

2-Oxa-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8(phenyldiethoxymethyl), 10: yield 2.6 g (66%), mp 174-175 ^{0}C. Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58; S, 8.19. Found: C, 58.45; H, 5.27; N, 3.66; S, 7.94. IR: 3210, 1820, 1768. ^{1}H NMR (CDC13): 1.08-1.36 (m, 6H, two CH_3), 2.20-2.58 (m, 4H, anhydride – CH_2CH_2-), 3.11-3.55 (m, 4H, two OCH_2Me), 6.45 (s, 1H, =CH-), 7.18-7.48 (m, 5H, arom.), 8.10 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 14.08, 14.33, 24.43, 29.21, 58.32, 58.61, 64.28, 101.23, 116.34, 127.40, 128.67, 128.60, 138.80, 152.44, 165.47, 168.11, 174.80.

Synthesis of 2-aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7ene-7(phenyldiethoxymethyl)-2-substituted, **11** and 2.aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8(phenyldiethoxymethyl)-2-substituted, **12**. In a solution of the anhydride **9** or **10** 5.5 mmol, in tetrahydrofuran 10 ml, stirred at 5-10 ^{0}C, the desired amine 5.5 mmol was added, (in the case of methylamine and ethylamine aqueous solutions 40 and 70% were used, respectively). The mixture was stirred at this temperature for about 2h and then at room temperature overnight. The resulting mixture was concentrated under vacuum, and the solid residue was assigned, ^{1}H NMR, to be an almost pure succinamic or glutaramic acid derivative. To this crude product 10 ml of dry toluene and 0.6 ml acetic anhydride were added and the mixture was refluxed for 2h. The reaction mixture was concentrated under vacuum and the solid residue recrystallized from ethanol to give an analytical sample of **11** or **12**, in yields 50-64%.

2-Aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7ene-7-(phenyldiethoxymethyl)-2-methyl, 11a: yield 1.33 g (64%), mp 161-162 ^{0}C. Anal. Calcd for $C_{19}H_{22}N_2O_5S$: C, 58.45; H, 5.68; N, 7.17; S, 8.21. Found: C, 58.61; H, 5.51; N, 7.23; S, 7.97. IR: 3220, 1724. ^{1}H NMR ($CDCl_3$): 1.00-1.43 (m, 6H, two CH_3), 2.64 (s, 2H, imide CH_2), 3.11-3.65 (m, 7H, two OCH_2Me and N-Me), 6.37 (s, 1H, =CH-), 7.17-7.54 (m, 5H, arom.), 7.70 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 14.17, 14.33, 26.20, 40.35, 58.37, 58.64, 63.27, 101.31, 116.13, 127.40, 127.83, 128.60, 139.70, 152.40, 165.30, 175.71, 183.20

2-Aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7ene-7(phenyldiethoxymethyl)-2-ethyl, 11b: yield 1.13 g (53%), mp 172-173 ^{0}C. Anal. Calcd for $C_{20}H_{24}N_2O_5S$: C, 59.39; H, 5.98; N, 6.92; S, 7.93. Found: C, 59.47; H, 5.76; N, 6.71; S, 7.75. IR: 3232,

1722. ^{1}H NMR ($CDCl_3$): 1.07-1.41 (m, 9H, three CH_3), 2.73 (s, 2H, imide CH_2), 3.17-3.49 (m, 6H, three CH_2Me), 6.39 (s, 1H, =CH-), 7.15-7.50 (m, 5H, arom.), 7.64 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 12.10, 14.11, 14.27, 31.90, 40.47, 58.30, 58.53, 63.20, 101.40, 116.11, 127.33, 127.70, 128.55, 139.66, 152.33, 165.40, 175.35, 183.45

2-Aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7ene-7(phenyldiethoxymethyl)-2-phenyl, 11c: yield 1.44 g (60%), mp 186-187 ^{0}C. Anal. Calcd for $C_{24}H_{24}N_2O_5S$: C, 63.70; H, 5.34; N, 6.19; S, 7.08. Found: C, 63.42; H, 5.20; N, 6.33; S, 7.17. IR: 3215, 1720. ^{1}H NMR (DMSO-d_6): 1.04-1.37 (m, 6H, two CH_3), 2.76 (s, 2H, imide CH_2), 3.13-3.65 (m, 4H, two OCH_2Me), 6.33 (s, 1H, =CH-), 7.20-7.70 (m, 10H, arom.), 8.35 (br, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.10, 14.23, 40.73, 58.30, 58.47, 63.35, 101.30, 116.09, 127.72, 127.70, 129.10, 135.41, 152.48, 165.50, 175.50, 183.32

2-Aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8(phenyldiethoxymethyl)-2-methyl, 12a: yield 1.3 g (61%), mp 150-151 ^{0}C. Anal. Calcd for $C_{20}H_{24}N_2O_5S$: C, 59.39; H, 5.98; N, 6.92; S, 7.93. Found: C, 59.52; H, 6.13; N, 6.75; S, 7.73. IR: 3180, 1722, 1663. ^{1}H NMR ($CDCl_3$): 1.04-1.39 (m, 6H, two CH_3), 2.20-2.57 (m, 4H, imide CH_2CH_2), 3.08-3.57 (m, 7H, two OCH_2Me and N-Me), 6.40 (s, 1H, =CH-), 7.18-7.74 (m, 5H, arom.), 8.10 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 14.06, 14.30, 23.60, 26.47, 30.33, 58.40, 58.61, 63.35, 101.14, 116.23, 127.38, 127.85, 128.67, 139.40, 152.38, 165.47, 171.75, 177.67.

2-Aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8(phenyldiethoxymethyl)-2-ethyl, 12b: yield 1.4 g (50%), mp 157-158 ^{0}C. Anal. Calcd for $C_{21}H_{26}N_2O_5S$: C, 60.27; H, 6.26; N, 6.69; S, 7.66. Found: C, 60.33; H, 6.18; N, 6.44; S, 7.45. IR: 3195, 1722, 1760. ^{1}H NMR ($CDCl_3$): 1.08-1.33 (m, 9H, three CH_3), 2.17-2.60 (m, 4H, imide CH_2CH_2), 3.11-3.50 (m, 6H, three CH_2Me), 6.40 (s, 1H, =CH-), 7.16-7.70 (m, 5H, arom.), 8.21 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 12.21, 14.13, 14.37, 24.06, 30.47, 33.32, 58.33, 58.57, 63.20, 101.33, 116.30, 127.33, 127.90, 128.62, 139.31, 152.40, 165.30, 171.80, 177.83.

2-Aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8-ene-8(phenyldiethoxymethyl)-2-phenyl, 12c: yield 1.5 g (61%), mp 191-192 ^{0}C. Anal. Calcd for $C_{25}H_{26}N_2O_5S$: C, 64.36; H, 5.62; N, 6.00; S, 6.87. Found: C, 64.51; H, 5.45; N, 6.20; S, 6.65. IR: 3210, 1725, 1660. ^{1}H NMR (DMSO-d_6): 1.11-1.42 (m, 6H, two CH_3), 2.15-2.76 (m, 4H, imide CH_2CH_2), 3.14-3.70 (m, 4H, two OCH_2Me), 6.41 (s, 1H, =CH-), 7.18-7.63 (m, 5H, arom.), 8.35 (br, 1H, NH). ^{13}C NMR (DMSO-d_6): 12.21, 14.17, 14.30, 23.56, 30.63, 58.60, 58.76, 63.32, 101.25, 116.23, 121.60, 127.35, 127.86, 128.62, 129.20, 135.31, 165.40, 171.86, 178.44

Deacetalization of acetalazathiazaspirotriones **11** and **12** to the benzoylazathiazaspirotriones **13** and **14**. A mixture of the acetalazathiazaspirotrione **11** or **12** 1 mmol and a solution of sulfuric acid (50%), 10 ml was stirred at room temperature for one day. The formed solid was filtered off and washed well with water. After recrystallization from ethanol an analytically pure compound **13** or **14** was obtained in yields 59-72%.

2-Aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7ene-7-benzoyl-2-methyl, 13a: yield 0.23 g (72%), mp 149-151 ^{0}C. Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.85; S, 10.14. Found: C, 57.10; H, 3.77; N, 8.68; S, 9.87. IR: 3180, 1720, 1665, 1640. ^{1}H NMR ($CDCl_3$): 3.18 (s, 3H, N-CH_3), 2.78 (s, 2H, imide CH_2), 6.46 (s, 1H, =CH-), 7.35-7.78 (m, 5H, arom.), 8.22 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 26.23, 40.18, 63.25, 125.44, 129.30, 129.83, 134.54, 139.70, 145.44, 164.52, 175.65, 183.80, 192.15.

2-Aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7ene-7-benzoyl-2-ethyl, 13b: yield 0.21 g (63%), mp 163-164 ^{0}C. Anal. Calcd for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48; S, 9.71. Found: C, 58.31; H, 4.44; N, 8.27; S, 9.60. IR: 3210, 1720, 1664, 1640. ^{1}H NMR ($CDCl_3$): 1.17 (t, J=7Hz, 3H, CH_3), 2.74 (s, 2H, imide CH_2), 3.54 (q, J=7Hz, 2H, CH_2Me), 6.47 (s, 1H, =CH-), 7.40-7.87 (m, 5H, arom.), 8.35 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 12.21, 32.08, 40.51, 63.46, 125.28, 129.36, 129.80, 134.80, 139.65, 145.30, 164.48, 175.73, 183.50, 192.15.

2-Aza-6-thia-10-azaspiro[4,5]decane-1,3,9-trione-7ene-7-benzoyl-2-phenyl, 13c: yield 0.25 g (66%), mp 210-211 ^{0}C. Anal. Calcd for $C_{20}H_{14}N_2O_4S$: C, 63.48; H, 3.73; N, 7.40; S, 8.47. Found: C, 63.61; H, 3.50; N, 7.34; S, 8.20. IR: 3230, 1723, 1663, 1640. ^{1}H NMR (DMSO-d_6): 2.81 (s, 2H, imide CH_2), 6.51 (s, 1H, =CH-), 7.33-7.97 (m, 10H, arom.), 8.67 (br, 1H, NH). ^{13}C NMR (DMSO-d_6): 40.86, 63.06, 125.30, 127.20, 128.21, 129.35, 129.87, 134.80, 139.71, 165.22, 175.60, 183.40, 192.27.

2-Aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8ene-8-benzoyl-2-methyl, 14a: yield 0.20 g (59%), mp 153-154 ^{0}C. Anal. Calcd for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48; S, 9.71. Found: C, 58.23; H, 4.40; N, 8.31; S, 9.64. IR: 3195, 1722, 1663, 1640. ^{1}H NMR ($CDCl_3$): 2.18-2.63 (m, 4H, imide CH_2CH_2), 3.18 (s, 3H, N-Me), 6.43 (s, 1H, =CH-), 7.45-7.90 (m, 5H, arom.), 8.33 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 23.65, 26.53, 30.18, 63.10, 125.30, 129.30, 129.85, 134.54, 137.90, 165.47, 171.50, 177.80, 192.30.

2-Aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8ene-8-benzoyl-2-ethyl, 14b: yield 0.22 g (64%), mp 160-161 ^{0}C. Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13; S, 9.31. Found: C, 59.44; H, 4.47; N, 8.28; S, 9.11. IR: 3205, 1720, 1662, 1637. ^{1}H NMR ($CDCl_3$): 1.18 (t, J=7Hz, 3H, CH_3), 1.98-2.74 (m, 4H, imide CH_2CH_2), 3.53 (q, J=7Hz, 2H, CH_2Me), 6.45 (s, 1H, =CH-), 7.37-8.10 (m, 5H, arom.), 8.42 (br, 1H, NH exchangeable). ^{13}C NMR ($CDCl_3$): 12.27, 24.07, 33.43, 62.97, 125.43, 129.20, 129.70, 134.63, 137.90, 165.20, 171.70, 177.70, 192.30.

2-Aza-7-thia-11-azaspiro[5,5]undecane-1,3,10-trione-8ene-8-benzoyl-2-phenyl, 14c: yield 0.27 g (69%), mp 204-206 ^{0}C. Anal. Calcd for $C_{21}H_{16}N_2O_4S$: C, 64.27; H, 4.11; N, 7.14; S, 8.17. Found: C, 64.50; H, 4.00; N, 7.31; S, 8.27. IR: 3220, 1720, 1665, 1642. ^{1}H NMR ($CDCl_3$): 2.06-2.81 (m, 4H, imide CH_2CH_2), 6.46 (s, 1H, =CH), 7.35-8.03 (m, 10H, arom.), 8.60 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): 23.75, 30,35, 63.20, 125.45, 129.00, 129.45, 134.50, 137.90, 165.23, 172.20, 177.86, 192.33.

References

1. J. Boeseken, *Tratte Chim. Org.* **17**, 1787-1793 (1949).
2. K. Thomae, British patent **823**, 338, (1959).
3. L. M. Rice, C. F. Geschickter and C. H. Grogan, *J. Med. Chem.* **6**, 388-402 (1963).
4. C. H. Grogan, C. F. Geschickter and L. M. Rice, *J. Med. Chem.* **7**, 78-87 (1964).
5. K. R. Scott, J. A. Moore, T. B. Zalusky, J. M. Nicholson, J. A. M. Lee and C. N. Chinko, *J. Med. Chem.* **28**, 413-417 (1985).
6. I. O. Edafiogho, K. R. Scott, J. A. Moore, V. A. Farrar and J. M. Nicholson, *J. Med. Chem.* **34**, 387-392 (1991).
7. V. A. Farrar, M. Ciechanowska-Rutsowska, J. Grochowski, P. Serda, T. Pilati, G. Filippini, C. N. Hinko, A. El-Assadi, J. Moore, I. O. Edafiogho, C. A. Andrews, M. Cory, J. M. Cory, J. M. Nicholson and K. R. Scott, *J. Med. Chem.* **36**, 3517-3525 (1993).

8. M. S. Alexander, J. P. Stables, M. Ciechanowska-Rutsowska, M. B. Hursthouse, D. E. Hibbs, I. O. Edafiogho, V. A. Moore and K. R. Scott, *Eur. J. Med. Chem.* **31**, 787-795 (1996).
9. K. R. Scott, P. G. Kennedy, M. Kemp, V. G. Telang and H. W. Matthews, *J. Pharm. Sci.* **72**, 183-186 (1983).
10. G. Tsolomiti, K. Tsolomiti and A. Tsolomitis, *Heterocycl. Commun.* In press.

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