Synthesis of New Pyrazolo[4,3-*c*]quinolin-3-one Derivatives and some Oxazolo[4,5-*c*]quinoline-2,4-diones

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Received December 1, 1998

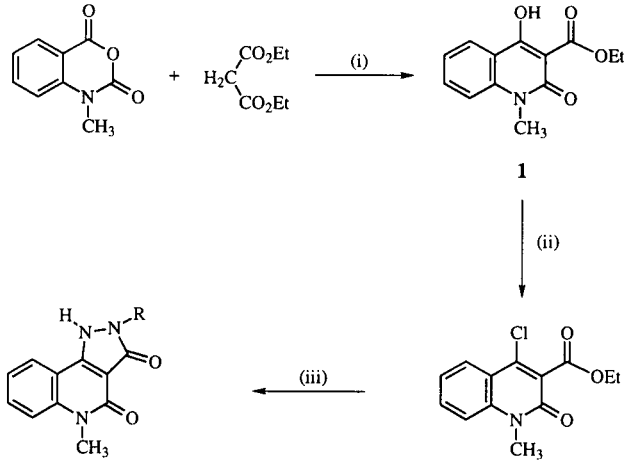
The new pyrazolo[4,3-*c*]quinolin-3-one derivatives **3a-c** and **6a-c** were prepared by the following three steps: first the preparation of ethyl 4-hydroxyquinoline-3-carboxylate derivatives **1** and **4** by reaction of isatoic anhydrides and ethyl malonate and ethyl acetoacetate respectively, then chloration of **1** and **4** with phosphorus oxychloride to give **2** and **5** and finally the condensation of **2** and **5** with hydrazine and its derivatives. In addition, the successful synthesis of oxazolo[4,5-*c*]quinoline-2,4-diones **9a-f** are reported.

J. Heterocyclic Chem., **36**, 719 (1999).

Introduction.

The search for new immunomodulating drugs is an active area of investigation in medicinal chemistry. Recently, the synthesis and immunomodulating effects of quinolins containing a carboxamide group have been discribed [1,2,3,4]. Continuing our research on the synthesis and activity of immunomodulating compounds [5], this paper reports the synthesis of new pyrazolo[4,3-*c*]quinolin-3-one derivatives **3a-c**, **6a-c** (Schemes 1 and 2) and new oxazolo[4,5-*c*]quinoline-2,4-diones **9a-f** (Scheme 3) that can be structurally compared to analogous compounds of known immunomodulatory activity [1,2,3].

Scheme 1

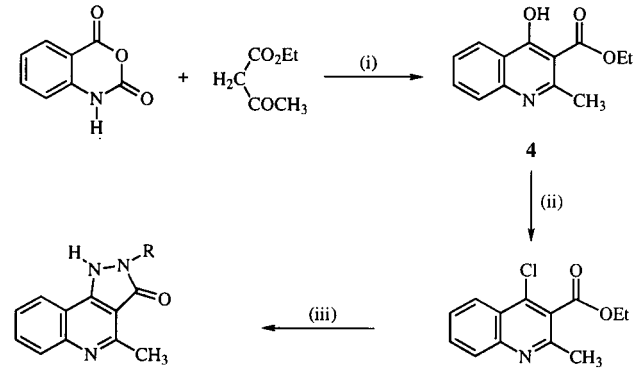


3a R = H
3b R = CH_3
3c R = Phenyl

(i) NaH, *N,N*-dimethylformamide; (ii) $POCl_3$; (iii) $RNH\text{-}NH_2$, ethoxyethanol.

Condensation [6,7] of *N*-methylisatoic anhydride with ethyl malonate gave ethyl *N*-methyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate **1**. Ethyl 4-hydroxy-2-methylquinoline-3-carboxylate **4** was prepared by con-

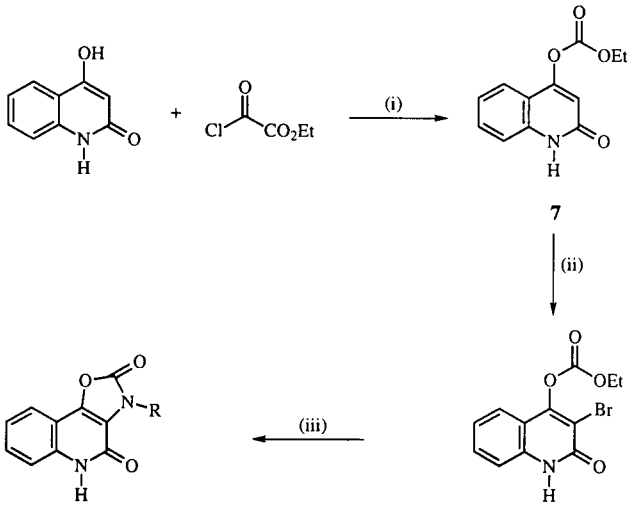
Scheme 2



6a R = H
6b R = CH_3
6c R = Phenyl

(i) NaH, *N,N*-dimethylacetamide; (ii) $POCl_3$; (iii) $RNH\text{-}NH_2$, ethoxyethanol.

Scheme 3



9a R = *p*-$ClCH_2Ph$
9b R = $(CH_2)_2Ph$
9c R = C_6H_{11}
9d R = *i*-Bu
9e R = PhCl
9c R = *i*-Pr

(i) CH_3CN, Et_3NH; (ii) Br_2, glacial acetic acid; (iii) RNH_2, tetrahydrofuran.

densation of isatoic anhydride with ethyl acetoacetate in the presence of sodium hydride. Chlorinating [8] compounds **1** and **4** with phosphorus oxychloride gave products **2** or **5** which were condensed with hydrazine or its derivatives [9,10,11,12] to give respectively compounds **3a-c** and **6a-c** (Schemes 1 and 2). The structure of compounds **3a-c** and **6a-c** were established by ir, nmr, mass spectroscopy and elemental analyses. Thus, the infared spectra of compounds **3a-c** showed two bands for the elongation vibration of C=O lactam groups at 1600 and 1650 cm^{-1} and a band for NH group at 3100 cm^{-1}. The ^1H nmr spectra of compounds **3a-c** showed the signal of the N-CH_3 group at δ 3.85 ppm and multiplet aromatic protons at 7.45-8.32 ppm.

In the infared spectra, compounds **6a-c** showed two bands at 1630 cm^{-1} and 3100 cm^{-1} corresponding respectively to a vibration of C=O lactam and the NH group. The ^1H nmr spectra of these compounds showed the singlet signal of C-CH_3 at δ 2.85 ppm and multiplet aromatic protons at 7.10-8.10 ppm.

The reaction of 2,4-quinolinediols with ethyl chloroformate in acetonitrile using methods [13,14] gave the corresponding compound **6**. Bromination [15,16] of compound **6** with bromine in dry chloroform gave compound **7** which was condensed [17] with a primary amine in tetrahydrofuran to give compounds **9a-f** in 40-50% yields (Scheme 3). These results are summarized in Table 1 and the structure of compounds **9a-f** were established by ir, nmr and elemental analyses. The spectral data proving the suggested stuctures of **9a-f** are listed in Table 2.

Table 1

Physical Constants for Oxazolo[4,5-*c*]quinoline-2,4-diones **9a-f**

Compound No.	R	Yield %	mp °C	Formula (MW)	Calcd. (%)				Found (%)			
					C	H	Cl	N	C	H	Cl	N
9a	Cl-C_6H_4-CH_2-	48	158	$C_{17}H_{11}ClN_2O_3$	62.48	3.37	10.87	8.58	62.56	3.45	11.02	8.41
9b	C_6H_5-$(CH_2)_2$-	52	192	$C_{18}H_{14}N_2O_3$	70.59	4.58		9.15	70.51	4.62		9.22
9c	C_6H_{11}-	45	210	$C_{16}H_{16}N_2O_3$	67.61	5.63		9.86	67.68	5.71		9.77
9d	$(CH_3)_2$-CH-CH_2-	58	171	$C_{14}H_{14}N_2O_3$	65.12	5.43		10.85	65.23	5.52		10.91
9e	Cl-C_6H_4-	38	182	$C_{16}H_9ClN_2O_3$	61.44	2.88	11.36	8.96	61.38	2.82	11.29	9.02
9f	$(CH_3)_2$-CH-	52	125	$C_{13}H_{12}N_2O_3$	63.93	4.92		11.47	63.99	5.01		11.53

Table 2

Spectral Data for Oxazolo[4,5-*c*]quinoline-2,4-diones **9a-f**

Compound No.	IR (potassium bromide) (cm^{-1})		Solvent	^1H NMR δ ppm
	ν (CO Lactam)	ν (CO Carbonate)		
9a	1610	1710	D	4.50 (s, 2H, CH_2), 7.04-7.89 (m, 8H, H6, H7, H8, H9 and Ph), 12.90 (s, 1H, NH)
9b	1630	1740	D	2.84 (t, 2H, CH_2), 3.75 (t, 3H, CH_2), 7.06-7.92 (m, 9H, H6, H7, H8, H9 and Ph), 14.23 (s, 1H, NH)
9c	1680	1790	D	1.21-2.05 (m, 10H, cyclohexyl), 4.50 (m, 1H, cyclohexyl), 7.21-8.12 (m, 4H, H6, H7, H8, H9), 13.43 (s, 1H, NH)
9d	1630	1730	D	1.31 (d, 6H, $2CH_3$), 2.12 (m, 1H, CH), 3.25 (t, 2H, CH_2), 7.18-7.81 (m, 4H, H6, H7, H8, H9), 11.53 (s, 1H, NH)
9e	1640	1710	D	7.08-7.92 (m, 8H, H6, H7, H8, H9 and Ph), 14.13 (s, 1H, NH)
9f	1690	1790	D	1.71 (d, 6H, $2CH_3$), 4.25 (m, 1H, CH), 7.22-7.86 (m, 4H, H6, H7, H8, H9), 11.91 (s, 1H, NH)

The recrystallization solvent for all compounds was methanol; Solvent D is dimethyl-d_6 sulfoxide.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage or on a Buchi No. 510 apparatus and were uncorrected. All compounds were characterized using several methods, *i.e.* elemental analyses, ir and nmr spectroscopy. Infrared spectra were taken in potassium bromide pellets on a Beckman IR 33 spectrometer. The ^1H nmr were recorded on a Bruker AC 200 spectrometer at 200 MHz using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million and signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). The ^{13}C nmr were recorded on a Bruker AC 200 spectrometer at 50 MHz.

Elemental analyses were carried out by the Service Central d'Analyses, Centre National de la Recherche Scientifique, 69390 Vernaison, France. Mass spectra recorded on a Nermag R10-10H spectrometer using electron impact ionization at 70 ev and data are quoted as peak positions (relative intensity %).

Ethyl 4-Hydroxy-2-oxo-*N*-methyl-1,2-dihydroquinoline-3-carboxylate (**1**).

Sodium hydride (1.6 g, 0.04 mole) was added portionwise to a mixture of ethyl malonate (25 ml, 0.16 mole) and *N,N*-dimethylformamide (50 ml) with stirring at room temperature. A mixture of *N*-methylisatoic anhydride (6 g, 0.034 mole) and 50 ml of *N,N*-dimethylformamide was added to this solution followed by stirring at 120° for 2.5 hours. Then, the precipitate which formed was collected by filtration and dissolved in 100 ml of water; 3 ml of hydrochloric acid at 30% was added to the mixture. The precipitated crystals were collected by filtration and dried to give compound **1** as colorless powder, yield 80%, mp 105°; ir (potassium bromide): ν 1670 (CO lactam), 1690 (CO ester) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.61 (t, 3H, CH_3), δ 3.70 (s, 3H, N-CH_3), δ 4.65 (q, 2H, CH_2), δ 7.12-8.41 (m, 4H, H5, H6, H7, H8), δ 14.47 (s, 1H, OH).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.16; H, 5.26; N, 5.66. Found: C, 63.29; H, 5.18; N, 5.73.

Ethyl 4-Chloro-2-oxo-*N*-methyl-1,2-dihydroquinoline-3-carboxylate (**2**).

A solution of (1.75 g, 7 mmoles) of **1** in (1 ml, 10 mmoles) of phosphorus oxychloride was refluxed for 30 minutes. After ice cooling, the solvent was evaporated under reduced presure and water was added to the residue. The mixture was neutralized with 2*N* sodium hydroxide. The resulting precipitate was filtered, washed with water and dried to give white crystals, yield 82%, mp 60°; ir (potassium bromide): ν 1635 (CO lactam), 1730 (CO ester) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (t, 3H, CH_3), δ 3.72 (s, 3H, N-CH_3), δ 4.50 (q, 2H, CH_2), δ 7.35-8.12 (m, 4H, H5, H6, H7, H8).

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.75; H, 4.52; Cl, 13.37; N, 5.27. Found: C, 58.82; H, 4.6; Cl, 13.42; N, 5.02.

5-Methyl-1,2,4,5-tetrahydropyrazolo[4,3-*c*]quinoline-3,4-diones (**3a**).

Ethyl 4-chloro-2-oxo-*N*-methyl-1,2-dihydroquinoline-3-carboxylate **2** (1 g, 0.03 mole) was added with stirring to a solution of 1 ml of 64% hydrazine in 50 ml of ethoxyethanol. The reaction mixture was refluxed for 2 hours. After cooling the precipitate which formed was recovered by filtration, washed with ethyl ether to give white crystals from water, yield 52%, mp ≥300°; ir (potassium bromide): ν 1600 and 1635 (CO lactam) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.57 (s, 3H, N-CH_3), δ 5.50 (s, 2H, 2NH), δ 7.41-8.19 (m, 4H, H6, H7, H8, H9); ms: m/z (relative intensity) (EI) 215 (M^+, 100), 186 (15), 158 (58), 142 (14), 130 (62), 116 (17), 77 (25).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.18; N, 19.53. Found: C, 61.46; H, 4.26; N, 19.47

2,5-Dimethyl-1,2,4,5-tetrahydropyrazolo[4,3-*c*]quinoline-3,4-diones (**3b**).

A solution of (1 g, 0.03 mole) of **2** and 1 ml of methyl hydrazine in 50 ml of ethoxyethanol was heated at reflux for 2 hours. After cooling the solvent was evaporated under reduced pressure, the precipitate was dissolved in chloroform and washed with 3 x 50 ml of water. The organic layer was dried over sodium sulfate, filtered and evaporated. The product obtained was recrystallized from (ethanol-water) (70-30), white crystals, yield 58%, mp ≥300°; ir (potassium bromide): ν 1590 and 1650 (CO lactam) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.73 (s, 3H, N-CH_3), δ 3.82 (s, 3H, N-CH_3), δ 7.18-7.87 (m, 4H, H6, H7, H8, H9), δ 11.92 (s, 1H, NH); ms: m/z (relative intensity) (EI) 229 (M^+, 100), 198 (6), 185 (6), 158 (58), 14 (6), 115 (5), 77 (10).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 63.01; H, 4.73; N, 18.27.

2-Methyl-5-phenyl-1,2,4,5-tetrahydropyrazolo[4,3-*c*]quinoline-3,4-diones (**3c**).

Compound **3c** was prepared with the same procedure as **3b**, yield was 46% of colorless powder from ethanol, mp 180°; ir (potassium bromide): ν 1610 and 1670 (CO lactam) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.85 (s, 3H, N-CH_3), δ 7.45-8.32 (m, 9H, H6, H7, H8, H9 and phenyl), δ 12.33 (s, 1H, NH); ms: m/z (relative intensity) (EI) 291 (M^+, 6), 260 (6), 198 (13), 186 (22), 170 (10), 77 (100).

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.10; H, 4.46; N, 14.43. Found: C, 70.23; H, 4.53; N, 14.30.

Ethyl 4-Hydroxy-2-methylquinoline-3-carboxylate (**4**).

Sodium hydride (0.8 g, 0.02 mole) was added portionwise to a mixture of ethyl acetoacetate (20 ml, 0.2 mole) and *N,N*-dimethylacetoamide (100 ml) with stirring at room temperature. A mixture of isatoic anhydride (2.8 g, 17 mmoles) and *N,N*-dimethylacetoamide (50 ml) was added to this solution followed by stirring at 120° for 10 minutes. Then, the mixture was concentrated under reduced pressure, followed by the addition of water, and then the mixture was subjected to ultrasonic waves. The precipitated crystals were collected by filtration and dried to give **4** as needle crystals, yield 62%, mp 189°; ir (potassium bromide): ν 1720 (CO ester) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.34 (t, 3H, CH_3), δ 2.45 (s, 3H, CH_3), δ 4.32 (q, 2H, CH_2), δ 7.49-8.21 (m, 4H, H5, H6, H7, H8), δ 12.15 (s, 1H, OH).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.62; N, 6.06. Found: C, 67.48; H, 5.72; N, 5.92.

Ethyl 4-Chloro-2-methylquinoline-3-carboxylate (**5**).

A suspension of 1 g, (4 mmoles) of ethyl 4-hydroxy-2-methylquinoline-3-carboxylate **4** in 1 ml of phosphorus oxychloride was refluxed for 30 minutes. After cooling in an ice bath, an aqueous solution of ammonia was slowly added to obtain a *p*H

of **7**. The solution was extracted with 3 x 50 ml of chloroform, dried over sodium sulfate and evaporated to give 0.48 g (48%) of yellow oil; ir (film nujol): ν 1760 (CO ester) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (t, 3H, CH_3), δ 2.61 (s, 3H, CH_3), δ 4.50 (q, 2H, CH_2), δ 7.05-7.89 (m, 4H, H5, H6, H7, H8).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.52; H, 4.81; Cl, 14.23; N, 5.61. Found: C, 62.59; H, 4.76; Cl, 14.31; N, 5.72.

4-Methyl-1,2-dihydropyrazolo[4,3-*c*]quinolin-3-one (**6a**).

Compound **6a** was prepared using the same procedure as for **3a**. The yield was 52% as needle crystals from ethanol, mp ≥300°; ir (potassium bromide): ν 1640 (CO lactam) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.81 (s, 3H, CH_3), δ 5.83 (l, 2H, 2NH), δ 7.10-8.05 (m, 4H, H6, H7, H8, H9); ms: m/z (relative intensity) (EI) 199 (M^+, 100), 185 (4), 169 (10), 143 (24), 114 (14), 77 (12).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.33; H, 4.52; N, 21.11. Found: C, 66.21; H, 4.61; N, 20.98.

2,4-Dimethyl-1,2-dihydropyrazolo[4,3-*c*]quinolin-3-one (**6b**).

Compound **6b** was prepared using the same procedure as **3b**, yield 58% as needle crystals from ethanol, mp ≥300°; ir (potassium bromide): ν 1610 (CO lactam) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.50 (s, 3H, CH_3), δ 3.61 (s, 3H, N-CH_3), δ 7.10-7.79 (m, 4H, H6, H7, H8, H9), δ 11.45 (s, 1H, NH); ms: m/z (relative intensity) (EI) 213 (M^+, 100), 198 (3), 170 (21), 155 (10), 142 (60), 115 (15), 77 (4).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.60; H, 5.16; N, 19.72. Found: C, 67.49; H, 5.31; N, 19.64.

4-Methyl-2-phenyl-1,2-dihydropyrazolo[4,3-*c*]quinolin-3-one (**6c**).

Compound **6c** was prepared using the same procedure as **3b**, yield 42% as white crystals from ethanol, mp 185°; ir (potassium bromide): ν 1635 (CO lactam) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.91 (s, 3H, CH_3), δ 7.43-8.10 (m, 9H, H6, H7, H8, H9 and phenyl), δ 12.35 (s, 1H, NH); ms: m/z (relative intensity) (EI) 275 (M^+,16), 260 (6), 198 (23), 186 (12), 170 (10), 77 (100).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.18; H, 4.73; N, 15.27. Found: C, 73.93; H, 4.82; N, 15.11

4-Ethoxycarbonyloxyquinolin-2(1*H*)-one (**7**).

Ethyl chloroformate (0.015 mole) was slowly added to a solution of quinoline-2,4-diol (0.015 mole, 2.4 g) and triethylamine (0.015 mole, 1.5 g) in acetonitrile. After the addition was complete, the solution was heated at reflux for 48 hours. The reaction mixture was concentrated and the crystals obtained were dissolved in chloroform. The organic layer was washed with 3 x 50 ml of an aqueous solution of 5% sodium carbonate, dried over sodium sulfate, filtered and evaporated. The product obtained was washed with ethyl ether to give a white solid, yield 43%, mp 198°; ir (potassium bromide): ν 1685 (CO lactam), 1740 (CO carbonate) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (t, 3H, CH_3), δ 4.50 (q, 2H, CH_2), δ 6.93 (s, 1H, H_3), δ 7.22-7.95 (m, 4H, H5, H6, H7, H8), δ 13.12 (s, 1H, H_1).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.72; N, 6.01. Found: C, 62.05; H, 4.58; N, 5.96.

3-Bromo-4-ethoxycarbonyloxyquinolin-2(1*H*)-one (**8**).

Bromine (1 ml, 0.02 mole) was added to a stirred mixture of 4-ethoxycarbonyloxyquinolin-2(1*H*)-one **7** (1 g, 0.004 mole) in glacial acetic acid (30 ml), heated to 50° and the reaction mixture was allowed to stand 3 hours at 50° with occasional stirring. The reaction mixture was then poured into 150 ml of ice water with stirring and allowed to stand at room temperature for a few hours. The precipitate was filtered, washed with water and recrystallized from ethyl ether to give white crystals, yield 62%, mp 190°; ir (potassium bromide): ν 1680 (CO lactam), 1710 (CO carbonate) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (t, 3H, CH_3), δ 4.21 (q, 2H, CH_2), δ 7.15-7.83 (m, 4H, H5, H6, H7, H8), δ 13.85 (s, 1H, H_1).

Anal. Calcd. for $C_{12}H_{10}BrNO_4$: C, 46.15; H, 3.21; Br, 25.64; N, 4.45; Found: C, 46.23; Br, 25.72; H, 3.13; N, 4.39.

General Procedure for the Preparation of Oxazolo[4,5-*c*]quinoline-2,4-diones **9a-f**.

A solution (0.5 g, 0.02 mole) of 3-bromo-4-ethoxycarbonyloxyquinolin-2(1*H*)-one **8** in 20 ml of tetrahydrofuran was added slowly to the primary amine (0.03 mole). After the addition was complete, the reaction mixture was stirred and heated at reflux for 2 hours. The reaction mixture was evaporated under reduced pressure. The resulting solid was filtered and washed with water. Recrystallization of the crude product from methanol gave compounds **9a-f**; see Tables 1 and 2 for physical constants and spectral data.

REFERENCES AND NOTES

[1] Z. X. Zhang, L. Y. Yu, F. D. Shi, B. G. Xiao, J. Bjork, G. Hedlund and H. Link, *J. Neuroimmunol.*, **73**, 175 (1997).

[2] S. Hortelano, M. J. M. Diaz Guerra, A. Gonzalez Garcia, E. Leonardo, C. Gamallo, L. Bosca and C. Martineza, *J. Immunol.*, **158**, 1402 (1997).

[3] S. Morecki, C. Nabet, P. Falk, M. Fridkis-Hareli, I. Pecht, J. J. Mond and S. Slavin, *Autoimmunity*, **25**, 223 (1997).

[4] S. Bailly, M. Fay and M. A. Gougerot-Pocidalo, *Pathol.-Biol.*, **41**, 838 (1993).

[5] B. Refouvelet, S. Harraga, L. Nicod, J.-F. Robert, E. Seilles, J. Couquelet and P. Tronche, *Chem. Pharm. Bull.*, **42**, 1076 (1994).

[6] H. Hayashi, Y. Miwa, S. Ichikawa, N. Yoda, I. Miki, A. Ishii, M. Kono, T. Yasuzawa and F. Suzuki, *J. Med. Chem.*, **36**, 617 (1993).

[7] W. Steglich and O. Hollitzer, *Angew. Chem.*, **85**, 505 (1973).

[8] P. Helissey, H. Parrot Lopez, J. Renault and S. Cros, *Eur. J. Med. Chem.*, **22**, 366 (1987).

[9] M. F. Reich, P. F. Fabio, V. J. Lee, N. A. Kuck and R. T. Testa, *J. Med. Chem.*, **32**, 2474 (1989).

[10] R. E. Holmes and R. K. Robins, *J. Am. Chem.* Soc., **87**, 1772 (1965).

[11] S. Bailey, M. R. Harnden, R. L. Jarvest, A. Parkin and M. R. Boyd, *J. Med. Chem.*, **34**, 57 (1991).

[12] B. Refouvelet, *Thèse Pharmaceutique*, Clermont-Ferrand, 1986.

[13] M. P. Sibi and V. Snieckus, *J. Org. Chem.*, **48**, 1935 (1983).

[14] J. Hendralla, E. Cranzer, B.-V. Kerekjarto, R. Krause, U. Schacht, W. Baader, W. Bartman, G. Beck, A. Bergmann, K. Kesseler and G. Wees, *J. Med. Chem.*, **34**, 2962 (1991).

[15] A. M. Maged, B. C. Howard, B. C. Donald, K. R. Roland and D. K. Ganesh, *J. Med. Chem.*, **36**, 3431 (1993).

[16] J. L. Lamatina, P. Mc carty, L. A. Reiter, W. F. Holt and Y. Anych, *J. Med. Chem.*, **33**, 543 (1990).

[17] R. T. Coutts, D. Nobel and D. G. Wibberley, *J. Pharmacol.*, **54**, 773 (1964).