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SYNTHESIS AND STRUCTURAL FEATURES OF NEW CYCLOFUNCTIONALIZED BENZIMIDAZOLES

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Abstract - The synthesis of new tricyclic derivatives having sulfur-containing six or seven-membered rings fused to the «a» edge of benzimidazole system, is reported. The stereochemical characteristics of thiazino- and thiazepinobenzimidazoles (**4-7**) are described and comparative NMR data are discussed. The synthetic approach to new benzo- or pyridothiazinobenzimidazole tetracyclic systems (**8**) is also reported.

INTRODUCTION

The benzimidazole system is present in numerous compounds of biological interest and plays an important role in medicinal chemistry research.[1]

Over the past years, the introduction of an additional ring on the benzimidazole system has been increasing attention in the expectation that such changes could potentially affect the interaction of the molecules with biological targets.[2,3] In particular, in our research, the introduction of a thiazole nucleus on the «a» edge of benzimidazole has been investigated as an approach to the discovery of anti-HIV (human immunodeficiency virus) agents. This effort has resulted in the preparation of several 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles (TBZs), some of which were found to be potent inhibitors of HIV-1 induced cytopathicity and virus replication.[4-12]

Moreover, in our previous papers,[13-15] the introduction of a pyrrole nucleus on benzimidazole system resulted in generally active compounds endowed with anticonvulsant properties better than that of valproate and comparable to that of phenytoin.

In connection with these studies on the chemistry of cyclofunctionalized benzimidazoles as potential pharmacological agents, we have extended the research to the study of new tricyclic and tetracyclic systems in which sulfur-containing six or seven-membered rings are fused at the «a» edge of the benzimidazole moiety.

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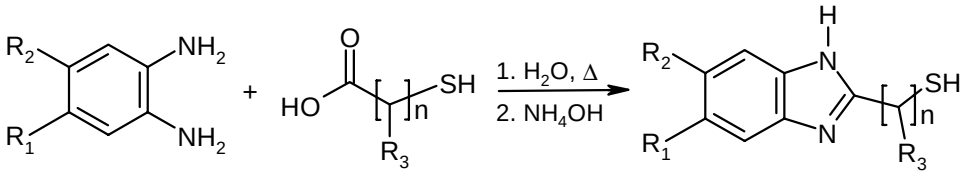
As far as we know very limited data on thiazino- or thiazepinobenzimidazole derivatives as well as on benzo- or pyridothiazinobenzimidazole ones have appeared in literature.[16-17] The structural features of the newly synthesized compounds have been unambiguously assigned by means of spectroscopic measurements.

RESULTS AND DISCUSSION

A multi-step procedure (Schemes 1-3) was employed for the synthesis of thiazinobenzimidazoles (**4** and **6**) and thiazepinobenzimidazoles (**5** and **7**).

The appropriate 1,2-phenylenediamine hydrochloride (**1a-c**) was alternatively treated with mercaptoacetic acid (**2a**) or with 2- or 3-mercaptopropionic acid (**2b** or **2c**) to afford, after treatment with NH_4OH, mercaptoalkylbenzimidazoles (**3a-f**)[18-20] as intermediate compounds (Scheme 1).



1a-c

	R^1	R^2
1a	H	H
1b	Cl	H
1c	Me	Me

2a-c

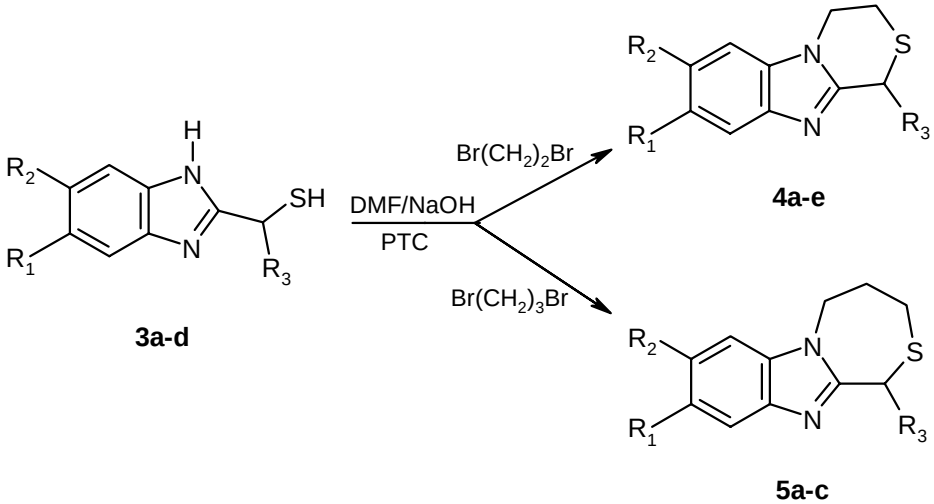
	R^3	n
2a	H	1
2b	Me	1
2c	H	2

3a-f

	R^1	R^2	R^3	n
3a	H	H	H	1
3b	H	H	Me	1
3c	Cl	H	H	1
3d	Me	Me	H	1
3e	H	H	H	2
3f	Me	Me	H	2

Scheme 1

The subsequent reaction of **3a-d** with a suitable dibromoalkane in phase-transfer catalysis (PTC) conditions afforded, after conventional work-up, 3,4-dihydro-1*H*-[1,4]thiazino[4,3-*a*]benzimidazoles (**4a-e**) and 4,5-dihydro-1*H*,3*H*-[1,4]thiazepino[4,3-*a*]benzimidazoles (**5a-c**) (Scheme 2).

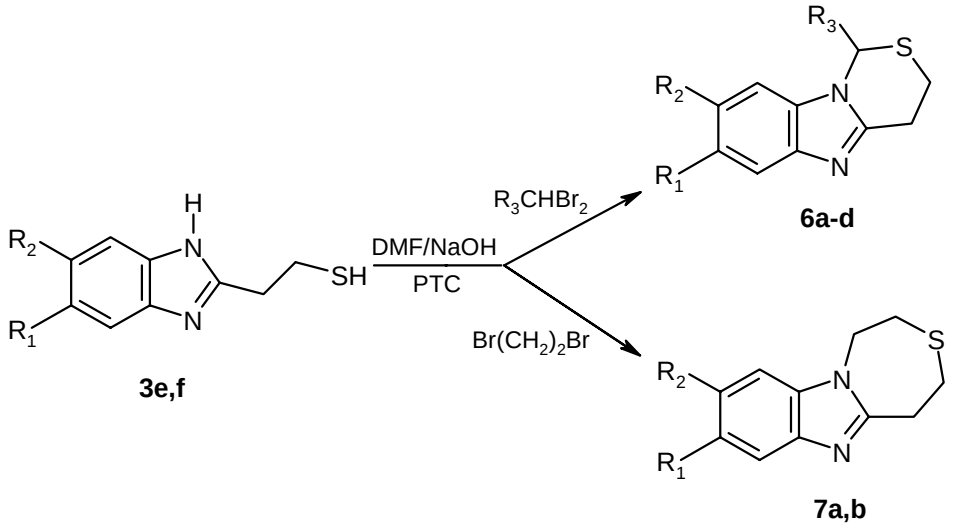


3a-d

	R^1	R^2	R^3
4a	H	H	H
4b	H	H	Me
4c	Cl	H	H
4d	H	Cl	H
4e	Me	Me	H
5a	H	H	H
5b	H	H	Me
5c	Me	Me	H

Scheme 2

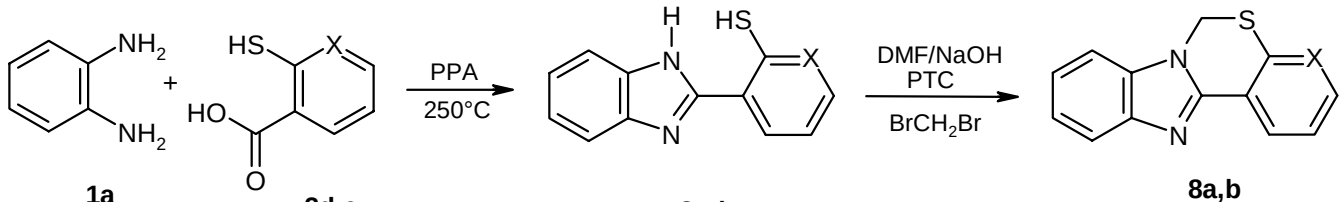
Similarly, the reactions in which derivatives (**3e,f**) were used as substrates, gave 3,4-dihydro-1*H*-[1,3]thiazino[3,4-*a*]benzimidazoles (**6a-d**) and 1,2,4,5-tetrahydro[1,4]thiazepino[4,5-*a*]benzimidazoles (**7a,b**) (Scheme 3).



	R^1	R^2	R^3
6a	H	H	H
6b	Me	Me	H
6c	H	H	Ph
6d	H	H	3-FC_6H_4
7a	H	H	
7b	Me	Me	

Scheme 3

The synthesis of tetracyclic derivatives 6*H*-benzo[*e*][1,3]thiazino[3,4-*a*]benzimidazole (**8a**) and 11*H*-pyrido[2',3':6,5][1,3]thiazino[3,4-*a*]benzimidazole (**8b**) (Scheme 4) was derived from reaction of dibromomethane with 2-(2'-mercaptoaryl)benzimidazoles (**3g,h**) previously obtained by condensation of 1,2-phenylenediamine (**1a**) with 2-mercaptobenzoic acid (**2d**) or 2-mercaptonicotinic acid (**2e**), respectively.



	X
2d, **3g**, **8a**	CH
2e, **3h**, **8b**	N

Scheme 4

The structures of the synthesized compounds were deduced from spectral data and supported by satisfactory elemental analysis (Table 1).

The ^{1}H-NMR spectra (Table 2) are characterized for the aliphatic region by resonance patterns, such as A_2 or A_2B_2 systems, that are indicative of a conformational mobility of the heterocycle fused on the «a» edge of the benzimidazole system in solution at room temperature. In derivatives (**4b**, **5b**, **6c** and **6d**), in which a substituent is present on the thiazino or thiazepino nucleus, the alicyclic bridge gives rise to a more complex resonance pattern, which can be explained on the basis both of a reduced conformational mobility and of the presence of a chiral center.

Table 1. Tricyclic and tetracyclic benzimidazoles

Compound	Yield (%)	mp (°C)[a]	Solvent[b]	Formula	Analysis Calculated/Found (%)		
					C	H	N
4a	24	145-148	-	$C_{10}H_{10}N_2S$	63.13 63.21	5.30 5.42	14.72 14.63
4b	60	127-130	C	$C_{11}H_{12}N_2S$	64.67 64.98	5.92 5.63	13.71 13.55
4c	47	214 (dec)	D	$C_{10}H_9N_2SCl$	53.45 53.59	4.04 4.16	12.47 12.21
4d	45	202 (dec)	D	$C_{10}H_9N_2SCl$	53.45 53.22	4.04 4.14	12.47 12.68
4e	60	218 (dec)	-	$C_{12}H_{14}N_2S$	66.02 66.37	6.46 6.32	12.83 12.77
5a	25	158-160	A	$C_{11}H_{12}N_2S$	64.67 64.35	5.92 5.61	13.71 13.95
5b	38	177-179	-	$C_{12}H_{14}N_2S$	66.02 66.21	6.46 6.15	12.83 12.74
5c	88	215-218	-	$C_{13}H_{16}N_2S$	67.20 67.54	6.94 7.07	12.06 12.32
6a	55	204-207	-	$C_{10}H_{10}N_2S$	63.13 63.47	5.30 5.55	14.72 14.52
6b	30	200-202	C	$C_{12}H_{14}N_2S$	66.02 66.09	6.46 6.59	12.83 12.66
6c	12	165-168	C	$C_{16}H_{14}N_2S$	72.15 72.45	5.30 5.49	10.52 10.29
6d	16	146-149	C	$C_{16}H_{13}N_2SF$	67.58 67.42	4.61 4.86	9.85 9.64
7a	15	132-135	A	$C_{11}H_{12}N_2S$	64.67 64.73	5.92 5.72	13.71 13.90
7b	32	229-232	A	$C_{13}H_{16}N_2S$	67.20 67.31	6.94 6.85	12.06 12.22
8a	20	123-125	B	$C_{14}H_{10}N_2S$	70.56 70.22	4.23 4.48	11.75 11.33
8b	22	170-173	B	$C_{13}H_9N_2S$	65.62 65.28	3.79 3.95	17.56 17.49

[a]Crystallization solvents were: EtOAc for **4a** and **6a**; EtOH for **4b-e**, **5a**, **6b-d**, **7a,b** and **8a,b**; Et_2O/EtOH for **5b,c**

[b]Solvent for column chromatography: $CHCl_3$/MeOH 97:3 (A), 96:4 (B), 95:5 (C), $CHCl_3$/EtOAc 6:4 (D).

The characterization of the position isomers (**4c**) and (**4d**) was obtained by a careful examination of the resonance pattern of the aromatic moiety, considering that the imine nitrogen exerts a deshielding effect on the proximal aromatic proton.

MS spectra and ^{13}C-NMR data of selected compounds are reported in Table 3. MS spectra show correct molecular ion and fragmentations that are in agreement with the proposed structures. ^{13}C-NMR spectra give conclusive evidence for the structural assignment of the synthesized compounds.

In conclusion, by reacting 1,2-phenylenediamine with easily available synthones, we have developed a simple strategy for the synthesis of a variety of cyclofunctionalized benzimidazole derivatives of potential pharmacological interest.

Table 2. ^{1}H NMR spectral data of tricyclic and tetracyclic benzimidazole derivatives

Compound	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
4a	3.17 (t, 2H, J=5.7, H-3), 4.10 (s, 2H, H-1), 4.34 (t, 2H, J=5.7, H-4), 7.27-7.72 (m, 4H, ArH)
4b	1.85 (d, 3H, J=6.9, Me-1), 3.19-3.25 (m, 2H, H-3), 4.29-4.38 (m, 3H, H-4 and H-1), 7.27-7.76 (m, 4H, ArH)
4c	3.19 (t, 2H, J=5.8, H-3), 4.10 (s, 2H, H-1), 4.34 (t, 2H, J=5.8, H-4), 7.23 (m, 2H, H-6 e H-7), 7.69 (d, 1H, J=1.8, H-9)
4d	3.19 (t, 2H, J=5.7, H-3), 4.10 (s, 2H, H-1), 4.32 (t, 2H, J=5.7, H-4), 7.25 (dd, 1H, J=1.9 and 8.5, H-8), 7.31 (d, 1H, J=1.9, H-6), 7.61 (d, 1H, J=8.5, H-9)
4e	2.37 and 2.39 (2s, 6H, Me), 3.16 (t, 2H, J=5.8, H-3), 4.10 (s, 2H, H-1), 4.30 (t, 2H, J=5.8, H-4), 7.07 (s, 1H, H-6), 7.46 (s, 1H, H-9).
5a	2.15 (quintet, 2H, H-4), 3.02 (t, 2H, J=5.4, H-3), 4.04 (s, 2H, H-1), 4.27 (t, 2H, J=5.0, H-5), 7.23-7.74 (m, 4H, ArH)
5b	1.84 (m, 1H, H_A-4), 1.89 (d, 3H, J=7.2, Me), 2.32 (m, 1H, H_B-4), 2,93 (m, 1H, H_A-3), 3.15 (m, 1H, H_B-3), 4,08 (m, 1H, H_A-5), 4.26 (q, 1H, J=7.2, H-1), 4.52 (m, 1H, H_B-5), 7.22-7.79 (m, 4H, ArH).
5c	2.12 (quintet, 2H, H-4), 2.37 and 2.39 (2s, 6H, Me), 2.99 (t, 2H, J=5.0, H-3), 4.01 (s, 2H, H-1), 4.22 (t, 2H, J=5.0, H-5), 7.05 (s, 1H, H-7), 7.46 (s, 1H, H-10).
6a	3.12 (t, 2H, J=6.1, H-3), 3.47 (t, 2H, J=6.1, H-4), 5.10 (s, 2H, H-1), 7.27-7.72 (m, 4H, ArH).
6b	2.37 and 2.39 (2s, 6H, Me), 3.10 (t, 2H, J=6.05, H-3), 3.43 (t, 2H, J=6.05, H-4), 5.03 (s, 2H, H-1), 7.07 (s, 1H, H-9), 7.46 (s, 1H, H-6).
6c	2.92-3.10 (m, 2H, H-3), 3.47-3.63 (m, 2H, H-4), 6.46 (s, 1H, H-1), 6.81-7.74 (m, 9H, ArH).
6d	2.93-3.09 (m, 2H, H-3), 3.46-3.63 (m, 2H, H-4), 6.43 (s, 1H, H-1), 6.75-7.75 (m, 8H, ArH).
7a	2.86 (t, 2H, J=5.7, H-4), 2.88 (t, 2H, J=4.4, H-2), 3.59 (t, 2H, J=5.7, H-5), 4.60 (t, 2H, J=4.4, H-1), 7.27-7.73 (m, 4H, ArH).
7b	2.37 and 2.39 (2s, 6H, Me), 2.83 (t, 2H, J=5.3, H-4), 2.85 (t, 2H, J=4.7, H-2), 3.55 (t, 2H, J=5.3, H-5), 4.54 (t, 2H, J=4.7, H-1), 7.04 (s, 1H, H-10), 7.46 (s, 1H, H-7).
8a	5.33 (s, 2H, CH_2), 7.27-8.38 (m, 8H, ArH).
8b	5.41 (s, 2H, CH_2), 7.22-8.54 (m, 7H, ArH).

Table 3. MS and ^{13}C NMR spectral data of selected tricyclic and tetracyclic benzimidazole derivatives

Compound	MS *m/z (%)*	^{13}C NMR ($CDCl_3$/TMS) δ
4a	190 (M^+, 100), 157 (13), 144 (53), 117 (12), 77 (10).	26.43 (C-3), 26.691 (C-1), 45.22 (C-4) 109.31 (C-6), 119.48 (C-9), 123.11 (C-7), 123.46 (C-8), 135.05 (C-5a), 141.22 (C-9a), 147.10 (C-10a).
4b	204 (M^+, 68), 189 (100), 157 (15), 144 (9), 102 (9), 77 (11).	20.15 (Me-1), 25.31 (C-3), 34.84 (C-1) 45.48 (C-4), 109.53 (C-6), 119.53 (C-9), 123.26 (C-7), 123.51 (C-8), 135.02 (C-5a), 140.10 (C-9a), 151.93 (C-10a).
4c	224 (M^+, 100), 189 (46), 178 (46), 152 (14), 151 (14), 112 (6), 89 (5), 75 (11).	25.86 (C-3), 26.59 (C-1) 44.83 (C-4), 109.44 (C-6), 119.08 (C-9), 122.77 (C-7), 128.16 (C-8), 133.50 (C-5a), 142.35 (C-9a), 147.93 (C-10a).
4d	224 (M^+, 100), 189 (60), 178 (59), 152 (30), 151 (24), 112 (14), 89 (19), 75 (35).	25.91 (C-3), 26.56 (C-1) 44.87 (C-4), 108.98 (C-6), 120.08 (C-9), 123.27 (C-8), 128.14 (C-7), 135.54 (C-5a), 140.04 (C-9a), 147.53 (C-10a).
5a	204 (M^+, 100), 175 (11), 171 (39), 157 (27), 131 (13), 118 (10), 77 (14).	30.09 (C-4), 30.15 (C-1), 34.74 (C-3), 44.52 (C-5), 109.33 (C-7), 119.85 (C-10), 122.77 (C-8), 123.33 (C-9), 135.92 (C-6a), 141.53 (C-10a), 155.72 (C-11a).
5b	218 (M^+, 100), 203 (58), 185 (36), 171 (35), 157 (37), 131 (14), 118 (15), 90 (15), 77 (80), 65 (16).	18.20 (Me-1), 29.48 (C-4), 33.98 (C-3) 37.37 (C-1), 44.06 (C-5), 109.10 (C-7), 120.10 (C-10), 122.55 (C-8), 123.19 (C-9), 135.84 (C-6a), 141.82 (C-10a), 158.63 (C-11a).
6a	190 (M^+, 100), 157 (14), 144 (91), 118 (15), 77 (19).	25.61 (C-3), 28.73 (C-4), 43.93 (C-1), 109.09 (C-9), 119.39 (C-6), 122.99 (C-8), 123.33 (C-7), 134.29 (C-9a), 141.15 (C-6a), 150.20 (C-5a).
7a	204 (M^+, 63), 171 (18), 158 (25), 102 (100), 90 (52), 77 (54), 63 (18).	27.86 (C-4), 30.85 (C-2) 34.70 (C-5), 48.72 (C-1), 109.30 (C-10), 119.57 (C-7), 122.98 (C-9), 123.39 (C-8), 135.76 (C-10a), 141.29 (C-6a), 155.82 (C-5a).
8a	238 (M^+, 100), 237 (73), 119 (11), 77 (16).	42.47 (C-6), 109.48 (C-8), 120.22 (C-11), 123.72 (C-9), 123.72 (C-9), 123.94 (C-10), 126.51 (C-4a), 127.15, 127.65, 127.91, 130.34 (C-1, C-2, C-3, C-4), 131.40 (C-12b), 133.77 (C-7a), 143.28 (C-11a), 148.11 (C-12a).
8b	239 (M^+, 100), 238 (80), 120 (10), 77 (9).	42.47 (C-11), 109.76 (C-9), 120.27 (C-6), 122.35 (C-8), 123.07 (C-4a), 124.17 (C-7), 124.65 (C-3), 133.87 (C-9a), 135.24 (C-4), 143.95 (C-5a), 147.26 (C-4b), 151.48 (C-2), 155.20 (C-12a).

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out on a C. Erba Model 1106 Elemental Analyzer. Column chromatography was performed with Merck silica gel (63-200 μm). The following mixtures of solvents were used as eluents: $CHCl_3$/MeOH 97:3 (A), 96:4 (B), 95:5 (C), $CHCl_3$/EtOAc 6:4 (D). ^1H- and ^{13}C-NMR spectra were measured with a Varian Gemini-300 instrument in $CDCl_3$ as solvent. Chemical shifts are expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in Hz. MS spectra were recorded with a QP5050A Shimadzu mass spectrometer.

General procedure for the synthesis of mercaptoalkylbenzimidazoles (3a-f)

To a solution of the suitable 1,2-phenylenediamine hydrochloride (0.01 mol) in H_2O (7 mL) was added mercaptoacetic, 2-mercaptopropionic or 3-mercaptopropionic acid (0.03 mol). The reaction mixture was refluxed for 1-2 h then cooled and treated with concd NH_4OH to afford a crude product which was purified by recrystallization from EtOH.

General procedure for the synthesis of 2-(2'-mercaptoaryl)benzimidazoles (3g-h)

A mixture of 1,2-phenylenediamine (0.01 mol) and 2-mercaptosalicylic or 2-mercaptonicotinic acid (0.01 mol) in 20 g of PPA was heated until 250°C under stirring and then maintained at this temperature for 4 h. The mixture was allowed to cool to 100°C and then poured into H_2O (60 mL) and neutralized with a solution of 50% aq. NaOH. The precipitate obtained was filtered and recrystallized from EtOH.

General procedure for the synthesis of cyclofunctionalized benzimidazoles (4a-e, 5a-c, 6a-d, 7a-b and 8a-b)

The suitable mercaptoalkylbenzimidazole (0.005 mol) and a catalytic amount of benzyltriethylammonium chloride were added to a solution of 50% aq. NaOH (10 mL). The resulting mixture was treated with a solution of the appropriate dibromoalkane (0.01 mol) in 80 mL of DMF and stirred at rt until completion of the reaction. After separation of inorganic salts, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The combined organic solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The oily residue was recrystallized to afford compounds (**4a**, **4e**, **5b-c** and **6a**) or purified by column chromatography as reported in Table 1.

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REFERENCES

1. S. Sharma and S. Abuzar, *Prog. Drug Res*., 1983, **27**, 85.
2. A. Chimirri, S. Grasso, G. Romeo, and M. Zappalà, *Heterocycles*, 1988, **27**, 1975.
3. E. Badawey and T. Kappe, *Eur. J. Med. Chem*., 1995, **30**, 327.
4. A. Chimirri, S. Grasso, P. Monforte, G. Romeo, and M. Zappalà, *Synthesis*, 1988, 244.
5. A. Chimirri, S. Grasso, A.M. Monforte, P. Monforte, and M. Zappalà, *Il Farmaco*, 1991, **46**, 817.
6. A. Chimirri, S. Grasso, A.M. Monforte, P. Monforte, and M. Zappalà, *Il Farmaco*, 1991, **46**, 925.
7. P. Monforte, A. M. Monforte, M. Zappalà, G. Romeo, S. Grasso, and A. Chimirri, *EP* 471991, 1992, (*Chem. Abstr.* 1992, **116**, P 214503d).
8. A. Chimirri, S. Grasso, C. Molica, A.M. Monforte, P. Monforte, and M. Zappalà, *Il Farmaco*, 1996, **51**, 279.
9. A. Chimirri, S. Grasso, A.M. Monforte, P. Monforte, A. Rao, M. Zappalà, G. Bruno, F. Nicolò, and R. Scopelliti, *Il Farmaco*, 1997, **52**, 673.

10. A. Chimirri, S. Grasso, C Molica, A.M. Monforte, P. Monforte, M. Zappalà, G. Bruno, F. Nicolò, M. Witvrouw, H. Jonckeere, J. Balzarini, and E. De Clercq, *Antiviral Chem. Chemother*. , 1997, **8**, 363.
11. A. Chimirri, S. Grasso, A.M. Monforte, P. Monforte, A. Rao, M. Zappalà, G. Bruno, F. Nicolò, C. Pannecouque, M. Witvrouw, and E. De Clercq, *Antiviral Chem. Chemother*., 1998, **9**, 431.
12. A. Chimirri, S. Grasso, P. Monforte, A. Rao, M. Zappalà, A.M. Monforte, C. Pannecouque, M. Witvrouw, J. Balzarini, and E. De Clercq, *Antiviral Chem. Chemother*., 1999, **10**, 211.
13. A. Chimirri, A. De Sarro, G.B. De Sarro, S. Grasso, G.R. Trimarchi, and M. Zappalà, *J. Med. Chem*., 1989, **32**, 93.
14. A. Chimirri, S. Grasso, P. Monforte, M. Zappalà, and G. Genchi, *Il Farmaco*, 1993, **48**, 1261.
15. A. De Sarro, G.B. De Sarro, A. Chimirri, S. Grasso, A.M. Monforte, and M. Zappalà, *Gen. Pharmacol.*, 1994, **25**, 1027.
16. S. Singh, H. Singh, M. Singh, and K.S. Narang, *Indian J. Chem.*, 1970, 232.
17. S. Singh and H. Singh, *Indian J. Chem.*, 1975, 323.
18. E.S. Milner, S. Snyder, and M.M. Jouillié, *J. Chem. Soc*., 1964, 4151.
19. A. Brembilla, D. Roizard, and P. Lochon, *J. Chem. Phys. Phys.-Chem*. *Biol.*, 1986, **83**, 577.
20. J.F. Constansa, A.C. Pinol, and J.P. Corominas, Fr. Demande FR 2,593,178, 1987 (*Chem. Abstr.*, 1988, **109**, 6513).