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Antifungal activity *in vitro* of some imidazo[1,2-*a*]pyrimidine derivatives

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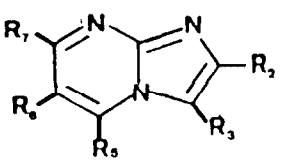
Summary — In regard to fungicidal activity of imidazole ring found in chemical compounds such as econazole, a series of 42 diversely substituted imidazo[1,2-*a*]pyrimidines was synthetized and examined for its antifungal activity in several species.

Résumé — **Activité antifongique *in vitro* de quelques dérivés de l'imidazo[1,2-*a*]pyrimidine.** *Une série de 42 imidazo[1,2-a]-pyrimidines a été synthétisée en vue d'examiner son activité antifongique sur différentes souches de champignons pathogènes pour l'homme.*

imidazo[1,2-*a*]pyrimidines / azaindolizines / antifungal activity

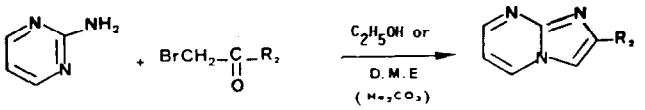
Introduction

Recently we have reported on the variation in the antibacterial activity of diversely substituted imidazo[1,2-*a*]pyrimidines [1]. Moreover, several compounds such as econazole, characterized by the presence of an imidazole ring, show good antifungal properties. This paper deals with the synthesis and the antifungal activity of 42 substituted imidazo[1,2-*a*] pyrimidines.

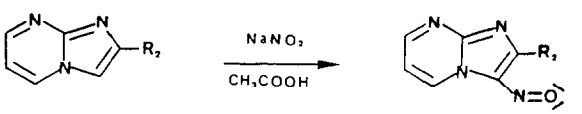


Chemistry

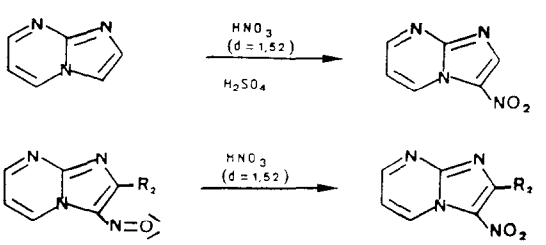
Imidazo[1,2-*a*]pyrimidines were synthetized according to Tschitschibabin [2] by condensation of an aminopyrimidine with the appropriate α-bromoketone [3–17].



The 3-nitroso derivatives were obtained by direct nitrosation of the condensation compound using sodium nitrite in acetic acid [19–24].



The 3-nitro imidazo[1,2-*a*]pyrimidines were prepared either by direct nitration with a mixture of fuming nitric acid and sulfuric acid [25] or by nitric oxidation of the corresponding 3-nitroso compounds [1].



The 3-bromo imidazo[1,2-*a*]pyrimidines were prepared using *N*-bromosuccinimide in CCl_4 solution [1–26].

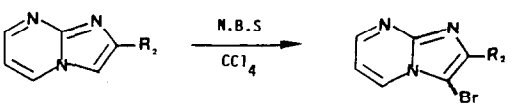
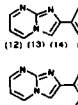


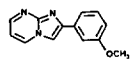
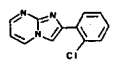
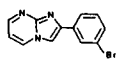
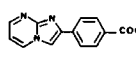
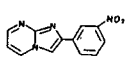
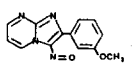
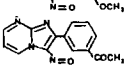
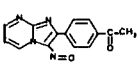
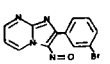
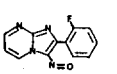
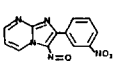
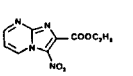
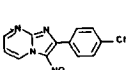
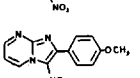
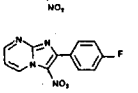
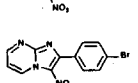
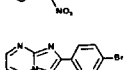
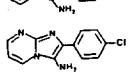
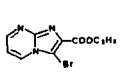
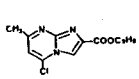
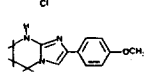
Table I. Imidazo[1,2-*a*]pyrimidines tested. The proton chemical shifts of compounds **1–42** are given. It was found that $J_{5-6} = 4.4$ Hz, $J_{6-7} = 6.6$ Hz and $J_{5-7} = 2$ Hz.

Product	Imidazo[1,2-a] pyrimidines	NMR δ (ppm)	ν (cm⁻¹) IR
1	 (2) (3) (4) (5) (7) (8) (23)	δH6 = 7.16 (m) δH5 = 9.11 (dd) δH7 = 8.06 (dd) δH3 = 7.91 (d) δH2 = 8.06 (d)	νC=N-C:1658 νC=C:1611 νCH imidazole:1072
2	 (5) (6) (8) (18)	δCH3 = 1.36; δCH2 = 4.46; δH3 = 8 (s) δH5 = 8.66 (dd) δH6 = 6.96 (m) δH7 = 8.46 (dd)	νC=N-C:1660; νC=C:1616 νC=O :1720; νC-O: 1251 νCH imidazole: 1097
3	 (5) (6) (8) (18)	δH2 = 8.03 (s) δH5 = 8.60 (dd) δH6 = 6.95 (m) δH7 = 8.46 (dd) δCH3 = 1.41; δCH2 = 8.03.	νC=N-C:1659; νC=O: 1725 νCH imidazole: 1083
4	 (3) (5) (27)	δH3 = 7.81(s) δH5 = 8.5(dd δH6 = 6.83(m) δH7 = 8.43 (dd) δH(phenyl) = 7.42; 7.41; 8.15.	νC=N-C:1690; νC=C:1597 νCH imidazole: 1068
5	 (3) (5) (27)	δH3 = 7.72(s) δH5 = 8.48(dd δH6 = 6.81(m) δH7 = 8.40 (dd) δH(phenyl) = 6.98; 7.96.	νC=N-C:1660; νC=C:1616 νC-O:1289; νC-OCH3:2982 νCH imidazole: 1078
6 (*)		δH(phenyl) = 7.4; 8.25 δOCH3 = 3.7; δH3 = 7.80(s) δH5 = 8.50 (dd) δH6 = 6.80 (m δH7 = 8.40 (dd)	νC=N-C:1677; νC=C:1610 νC-O : 1277 νCH imidazole: 1075
7	 (12) (13) (14) (15) (16) (17) (27)	δH(phenyl) = 7.42; 7.97 δH3 = 7.82 (s) δH5 = 8.56 (dd) δH6 = 6.90(m) δH7 = 8.44(dd)	νC=N-C:1639; νC=C:1611 νC-Cl: 669 νCH imidazole: 1075
8 (*)		δH(phenyl) = 8.1; 7.6 δH3 = 8.5(s) δH5 = 9.05 (dd) δH6 = 7.1(m) δH7 = 8.55 (dd)	νC=N-C:1641; νC=C:1611 νC-Cl : 669-730 νCH imidazole :1080
9	 (12) (13) (14) (15) (16) (17) (21)	δH(phenyl ;= 7.42; 8.3 δH3 = 7.78(s) δH5 = 8.53(dd δH6 = 6.87 (m) δH7 = 8.43(dd)	νC=N-C:1641; νC=C:1612 νC-F :1036-1128 νCH imidazole : 1070
10	 (12) (13) (14) (15) (16) (17) (21) (23)	δH(phenyl) = 7.58; 7.9 δH3 = 7.82(s) δH5 = 8.55(dd) δH6 = 6.88 (m) δH7 = 8.43(dd)	νC=N-C:1645; νC=C:1610 νC-Br : 668-644 νCH imidazole :1067
11(*)		δH(phenyl) = 7.52; 8.15 δH3 = 8.06(s) δH5 = 8.56(dd) δH6 = 6.89(m) δH7 = 8.45(dd)	νC=N-C:1641; νC=C:1616 νC-Br :633 νCH imidazole :1068
12	 (3) (5) (23) (27)	δH(phenyl) = 7.24; 7.91 δH3 = 7.76(s) δH5 = 8.48(dd) δH6 = 6.81(m) δH7 = 8.40(dd)	νC=N-C:1611; νC=C:1549 νC-CH3 :2979-1382 νCH imidazole :1080
13	 (3) (5) (23) (27)	δH(phenyl) = 7.40; 8.15 δH3 = 7.91(s) δH5 = 8.54(dd) δH6 = 6.80(m) δH7 = 8.46(dd) δCH3 = 2.4.	νC=N-C:1646; νC=C:1610 νC-CH3 :2975 νCH imidazole :1091
14(*)		δH(phenyl) = 7.55; 8.1 δH3 = 7.7(s) δH5 = 8.6(dd δH6 = 6.90(m) δH7 = 8.2; δCH3 = 2.15.	νC=N-C:1612; νC=C:1604 νC-CH3:2921; νC=O:1676 νCH imidazole :1067
15	 (23) (27)	δH(phenyl) = 7.4; 8.30 δH3 = 8.06 (s) δH5 = 8.66(dd) δH6 = 6.90(m) δH7 = 8.55(dd)	νC=N-C:1686 νC=C:1617; νC-NO2 :1378-1506 νCH imidazole:1079
16(*)		δH(phenyl) = 7.4; 8.30 δH3 = 7.99 (s) δH5 = 8.6(dd) δH6 = 6.95 (m) δH7 = 8.50(dd)	νC=N-C:1658 νC=C:1616; νC-NO2: 1560 νCH imidazole:1067
17	(19) (20) (21) (22)	δH(phenyl) = 7.6 δH6 = 8.6(m) δH7 = 9.07 (dd) δH5 = 9.95(dd)	νC=N-C:1620; νN=O:1544 νC=C : 1592 νC-C6H5 :692-740-756
18	(19) (20) (22)	δH(phenyl) = 7.10; 8.83 δH5 = 10.07 (dd) δH7 = 8.93 (dd) δH6 = 7.28(m)	νC=N-C:1603 νC=C :1570; νN=O:1532 νC-O : 1242
19	(19) (20) (21) (22)	δH(phenyl) = 7.57; 8.79 δH5 = 10.00 (dd) δH7 = 8.97(dd) δH6 = 7.33(m)	νC=N-C:1659 νC=C :1603 νC-Cl: 735; νN=O:1562
20	(19) (22) (24)	δH(phenyl) = 7.72; 8.7 δH5 = 9.99(dd) δH7 = 8.96(dd) δH6 = 7.32(m)	νC=N-C:1610 νC=C :1595 νC-Br:668; νN=O:1558
21	(19) (21)	δH(phenyl) = 7.6; 8.6 δH5 = 9.99(dd) δH7 = 8.86(dd) δH6 = 7.32(m)	νC=N-C: 1606 νC=C :1592 νC-F :1095; νN=O:1523

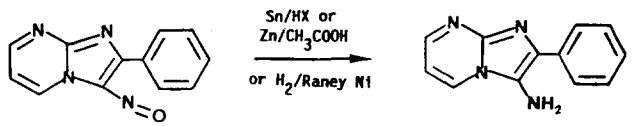
Product	Imidazo[1,2-a] pyrimidines	NMR δ (ppm)	ν (cm⁻¹) IR
22	 (19) (20) (21)	δH(phenyl) = 7.36; 8.78 δH5 = 9.99(dd) δH7 = 8.89(dd) δH6 = 7.25 (m)	νC=N-C :1604 νC=C :1590 νC-CH3 :2948; νN=O:1527
23(*)		δH(phenyl) = 7.52; 9.14 δH5 = 10.00(dd) δH7 = 8.96(dd) δH6 = 7.30(m)	νC=N-C :1686 νC=C :1610 νC-O :1252; νN=O :1599
24(*)		δH(phenyl) = 7.9; 8.9 δH5 = 9.88(dd) δH7 = 8.6(dd) δH6 = 7.16(m)	νC=N-C :1602 νC=C :1590 ; νC=O: 1670 νC-CH3 :2960; νN=O:1548
25(*)		δH(phenyl) = 7.75; 8.65 δH5 = 9.9(dd δH7 = 8.7(dd) δH6 = 7.07 (m)	νC=N-C :1604 νC=C :1596; νC-O:1675 νC-CH3 :2948; νN=O:1550
26(*)		δH(phenyl) = 7.66; 8.95 δH5 = 10.00(dd) δH7 = 8.98(dd) δH6 = 7.32(m)	νC=N-C :1614 νC=C :1592 νC-Br: 633; νN=O:1560
27	 (19) (20) (21) (22)	δH(phenyl) = 7.6 δH6 = 8.67(m) δH7 = 9.06(dd) δH5 = 10.01(dd)	νC=N-C :1665 νC=C :1599 ; νN=O:1554 νC-C6H5:740-756-772
28(*)		δH(phenyl) = 7.6; 8.6 δH5 = 10.46(dd) δH7 = 9.02(dd) δH6 = 7.55(m	νC=N-C :1690 νC=C :1639 νC-F : 1103 ; νN=O:1562
29	 (19) (20) (21) (22) (24)	δH(phenyl) = 7.6; 8.9 δH5 = 10.01(dd) δH7 = 9.06(dd) δH6 = 7.20(m)	νC=N-C :1660 νC=C :1604 νC-NO2 :1475 ; νN=O:1542
30(*)		δH(phenyl) = 7.55; 8.9 δH5 = 10.00(dd) δH7 = 9.00(dd) δH6 = 7.32(m)	νC=N-C :1644 νC=C :1610 νC-NO2:1510; νN=O:1562
31(*)		δCH3 = 1.4; δCH2 = 4.5; δH5 = 9.6(dd) δH7 = 9.15(dd) δH6 = 7.4 (m)	νC=N-C :1670 νC=C :1616; νC=O :1737; νC-O:1292; νC-NO2:1494
32(*)		δH(phenyl) = 8.3; 8.7 δH5 = 9.9(dd) δH6 = 7.7 (m) δH7 = 9.15(dd)	νC=N-C :1695 νC=C :1605 νC-NO2 :1482-1529 νC-Cl :658-719
33(*)		δH(phenyl) = 7.8; 8.8 δH5 = 9.97(dd) δH7 = 9.11(dd) δH6 = 7.65 (m)	νC=N-C :1630 νC=C :1602 νC-O :1263 νC-NO2 :1491-1521
34(*)		δH(phenyl) = 8.3; 8.8 δH5 = 9.89(dd) δH7 = 9.06(dd) δH6 = 7.69 (m)	νC=N-C :1625 νC=C :1612; νC-NO2 :1483-1552 νC-F :1044
35(*)		δH(phenyl) = 8.5; 8.7 δH5 = 9.8(dd δH7 = 9.14(dd) δH6 = 7.69 (m)	νC=N-C :1627 νC=C : 1599 νC-Br :687-731 νC-NO2 :1482-1527
36(*)		δH(phenyl) = 7.34; 7.54 δNH2 = 3.5; δH5 = 8.51(dd) δH6 = 6.93(m) δH7 = 8.23(dd	νC=N-C :1630 νC=C :1585 νC-NH2 :3431 νC-Br : 648
37	(27) (28)	δH(phenyl) = 6.92; 7.92 δNH2 = 5.09; δH5 = 8.44 (dd) δH6 = 6.86(m) δH7 = 8.2(dd)	νC=N-C :1625 νC=C :1590 νC-NH2 :3211
38(*)		δH(phenyl) = 7.36; 7.92 δNH2 = 3.6; δH5 = 8.38(dd) δH6 = 6.7(m) δH7 = 8.24(dd)	νC=N-C :1630 νC=C :1586 νC-NH2 :3271-3418 νC-Cl :658-718
39	(25) (26)	δH2 = 7.9(s) δH5 = 8.65(dd δH6 = 7.1(m) δH7 = 8.56(dd)	νC=N-C :1700 νC=C :1609 νC-Br : 618-633
40 (*)		δCH2 = 4.4; δCH3 = 1.3; δH5 = 8.66 (dd) δH6 = 6.97(m) δH7 = 8.41(dd)	νCH pyrimidine:3067 νC=C:1611 νC=O:1723 νCH imidazole:1041
41(*)		δCH2 = 4.5; δCH3 = 1.4 δH6 = 6.6(s) δH3 = 7.9 (s) δCH3 = 2.7.	νC=N-C: 1645; νC=O: 1730 νC-CH3:2925 ; νC-Cl:725 νCH imidazole: 1065
42(*)		δH(phenyl) = 6.78; 7.3 δOCH3 = 3.9; δNH = 5.2; δH3 = 6.62(s) δH5 = 3.7(m) δH6 = 1.96(m) δH7 = 3.3 (m)	νC=N-C :1672 νC=C : 1606 ; ν C-O:1248 ν NH :3413-3285

*New imidazo[1,2-*a*]pyrimidines synthetized.

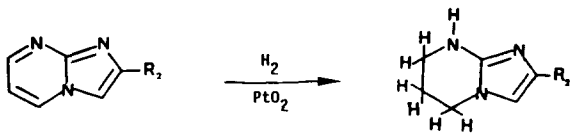
Table II. New imidazo[1,2-*a*]pyrimidines synthetized.

Compound pyrimidines	Imidazo[1,2-a] %	mp °C	Yield	Molec weight	Molecular formula
6		226	75	225	$C_{13}H_{11}N_3O$
8		225	55	229.5	$C_{12}H_8N_3Cl$
11		220	80	274	$C_{12}H_8N_3Br$
14		258	68	237	$C_{14}H_{11}N_3O$
16		260	83	239	$C_{12}H_8N_4O_2$
23		236	80	254	$C_{13}H_{10}N_4O_2$
24		240	80	266	$C_{14}H_{10}N_4O_2$
25		223	85	266	$C_{14}H_{10}N_4O_2$
26		224	70	303	$C_{12}H_7N_4OBr$
28		147	80	242	$C_{12}H_7N_4OF$
30		240	55	269	$C_{12}H_7N_5O_3$
31		96	65	236	$C_9H_8N_4O_4$
32		170	82	274.5	$C_{12}H_7N_4O_2Cl$
33		145	85	270	$C_{13}H_{10}N_4O_3$
34		195	75	258	$C_{12}H_7N_4O_2F$
35		197	80	319	$C_{12}H_7N_4O_2Br$
36		109	80	275	$C_{12}H_9N_4Br$
38		130	64	231	$C_{12}H_9N_4Cl$
40		209	72	270	$C_9H_8N_3O_2Br$
41		230	55	239.5	$C_{10}H_{10}N_3O_2Cl$
42		decomp	85	229	$C_{13}H_{15}N_3O$

The 3-amino derivatives were obtained either by reduction of the 3-nitro imidazo[1,2-*a*] pyrimidines through a mixture Sn/HX [27], either by reduction of the 3-nitroso derivative using Zn/CH_3COOH [28] or Sn/HX [29], or hydrogenation over Raney Ni.



The 5,6,7,8-tetrahydro derivative was prepared by hydrogenation over Adam's catalyst [30].



All the compounds are listed in table I and specially the new compounds in table II.

Biological evaluation

All compounds have been tested *in vitro* for antifungal activity in the strains listed in table III. Tests on fungi were carried out according to the agar dilution method (with serial 2-fold dilution). The compounds were dissolved in DMSO (dimethyl-sulfoxide) at concentrations of 5 mg/ml and subsequently diluted in distilled water. From these solutions, 0.5 ml were transferred into Petri dishes containing 4.5 ml of test medium. The antifungal activity of DMSO towards fungi strains at this concentration is negligible.

The MICs were determined in Casitone Difco medium for *Candida albicans* A, *Aspergillus niger*, *Aspergillus fumigatus* and *Filobasidiella neoformans*. The Sabouraud agar was only used for *Arthroderma benhamiae*.

Table III. Fungi strains.

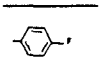
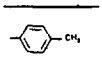
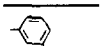
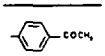
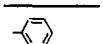
Strain	*Abbreviation*	*Medium*
Candida albicans A	Ca	Casitone
Aspergillus niger	An	Casitone
Aspergillus fumigatus	Af	Casitone
Filobasidiella neoformans	Fn	Casitone
Arthroderma benhamiae	Ab	Sabouraud agar

Each fungus was tested with a dilution of 2–5-d-old broth culture containing approximately 10^5 cells/ml (*ie* 95 10^5 CFU/ml). After 48 h of incubation at 37°C for all fungi except *Arthroderma benhamiae*, the minimum inhibitory concentration (MIC) in µg/ml was determined. An incubation of 7 days is necessary for determining MIC with *Arthroderma benhamiae* (see table IV).

Results and discussion

Of all the compounds synthetized, 16 were inactive, 13 were weakly active and 13 showed antifungal properties.

Table IV. Active compounds (R_6 = R_7 = H) MIC values (µg/ml) in relation to the different strains. See abbreviations in table III.

No	R_2	R_3	MIC Ca	An	Af	Fn	Ab
14		H	121	121	121	121	/
17		NO	14	7	29	29	57
18		NO	65	8	33	65	65
19		NO	2	2	2	17	66
20		NO	5	1	10	19	78
21		NO	15	15	31	62	124
22		NO	30	8	8	61	61
23		NO	8	4	4	130	130
25		NO	9	2	4	34	68
26		NO	5	2	10	19	78
30		NO	9	4	9	138	138
34		NO_2	/	/	132	/	132
31		NO_2	/	121	121	/	121

The activities of these latter compounds against 5 fungi strains (table III) are reported in table IV.

The substituent in position 3 plays a crucial role in that only nitroso substitution in this position led to active compounds. A hydrogen atom (compounds **1**, **2**, **4–13**, **15** and **16** ; table I), a bromine (compounds **39**, **40**), an amino group (compounds **36–38**), a nitro group (compounds **31–35**) in this position systematically induced inactivity. An aryl group in position 2 is favorable (compare **1–12** with **13**). No clear-cut conclusions can be drawn about substituent effects on the aromatic ring in position 2.

The unsubstituted ring, compound **2**, showed comparable activities with *para* or *meta* substituted derivatives (compare **2** with **4**, **5** and **10**). From the only available electrodonating substituent in compound **7**, it seems that electrodonating substituents are rather detrimental.

Concerning the MIC values, potency ranged from 8–64 µmol/l or 2–14 µg/ml for Ca, 4–64 µmol/l or 1–15 µg/ml for An and 8–32 or 2–9 µg/ml for Af. These values are favorably situated in comparison to that found for the reference compounds. Thus, the compounds **19**, **20**, **23**, **25**, **26**, **30** showed antifungal activities towards Ca which were slightly superior to econazole.

Except for compounds **14**, **21**, **34** and **31**, all other compounds showed better antifungal activities than amphotericin B (reference compound) towards An. Compound **19** only showed the same antifungal activity toward Fn as the reference compound flucytosine.

Table V. Reference compounds.

Strain	*Reference compound*	*MIC (µg/ml)*	*MIC (µmol/ml)*	*mw*
Candida albicans A Ca	Econazole	12	31.5	381
	Amphotericine B	1	1	924
Aspergillus niger An	Econazole	6	15.7	381
	Amphotericine B	10	10.8	924
Aspergillus fumigatus Af	Econazole	3	7.8	381
	Amphotericine B	2	2.2	924
Filobasidiella noeformans Fn	Econazole	3	7.8	381
	Flucytosine	10	77.5	129
Arthroderma benhamiae Ab	Econazole	6	15.7	381
	Griseofulvine	25	70.8	252.8

Experimental protocols

Melting points were determined on a Kofler apparatus and were uncorrected. IR spectra were measured on a Perkin–Elmer 983 G spectrometer and NMR ^1H spectra were determined on a Bruker WM 250 (250 MHz). Microanalyses are indicated only by symbols of the elements analyzed ; the results obtained had a maximum deviation of 0.4% from the theoretical value.

Preparation of imidazo[1,2-a]pyrimidines

Unsubstituted in 2-position
2-amino pyrimidine (0.5 mol) was dissolved in 50% hydro-alcoholic solution in presence of sodium hydrogenocarbonate (0.6 mol). To this mixture, a water solution (40%) of chloroacetaldehyde (1 mol) was added slowly under nitrogen with vigorous stirring and was refluxed for 48 h. After this period, the reaction mixture was cooled, concentration *in vacuo*, poured into water and extracted with hot chloroform. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. Pure imidazo[1,2-*a*]pyrimidine was obtained after chromatography on a silica gel column (eluent : ethylacetate).

Substituted in 2-position
A solution of 2-amino pyrimidine (0.02 mol) in dry DME (1,2-dimethoxyethane) was slowly added to a mixture of bromoketone (0.5 mol) in DME. The reaction mixture was refluxed for 48 h. After cooling the solution was filtered. The solid was dissolved in water, alkalinized and added to the alkalinized filtrate. The aqueous phase was extracted with chloroform. The solvent was dried and evaporated *in vacuo*. The compounds were obtained after chromatography on a silica gel column (eluent:ethylacetate).

Preparation of the 3-nitroso imidazo[1,2-a]pyrimidines

A saturated sodium nitrite solution was added under stirring to imidazo[1,2-*a*]pyrimidine or derivative (0.01 mol) in acetic acid (40 ml). A green solid was obtained, which was filtered and recristallized in methanol or purified by chromatography on a silica gel column (eluent : ethylacetate–methanol, 90/10).

Preparation of the 3-nitro imidazo[1,2-a]pyrimidines

Method A
Azaindolizine (0.01 mol) was added to an ice-cooled sulfuric acid (15 cm^3). The solution thus obtained was stirred and cooled. Fuming nitric acid (0.02 mol ; $d = 1.52$) was added slowly. After 30 min, the reaction mixture was allowed to reach room temperature and was stirred for 2 h. The mixture was poured into water and the yellow solid was filtered and dissolved in chloroform. The solid was purified by chromatography on a short silica gel column (eluent: ethylacetate).

Method B
3-Nitroso imidazo[1,2-*a*]pyrimidine (0.02 mol) were dissolved in fuming nitric acid (30 ml). This mixture was slightly heated for 2 h at 60°C. After cooling, the solution was poured into ice-water mixture : the yellow solid obtained was also filtered and the filtrate was alkalinized and extracted with hot chloroform. After removing the solvent, pure compound was obtained by chromatography on silica gel column (eluent: ethylacetate).

Preparation of 3-halogeno imidazo[1,2-a]pyrimidines

An equimolar mixture of azaindolizine and NBS (*N*-bromosuccinimide) was refluxed for 12 h in chloroform. After removing the solvent, the solid was purified by silica gel column chromatography (eluent: ethylacetate–methanol, 75/25).

Preparation of 3-amino imidazo[1,2-a]pyrimidines

Method A
3-Nitroso derivative (1 g) was quickly added to a mixture of tin powder (2 g) and concentrated hydracid (30 ml). The solution was stirred for 2 h at 20°C. The reaction mixture was filtered, alkalinized (pH = 9) and extracted with chloroform. After remov-ing the solvent, the residue was recristallized in absolute ethanol.

Method B
3-Nitroso derivative (1 g) was added to a mixture of granular zinc (2 g) in acetic acid–ethanol (15/15). The reaction mixture was stirred for 2 h at room temperature. After filtering, the solution was alkalinized and extracted with hot chloroform. The solvent was removed and the residue was purified by silica gel column chromatography (eluent: ethanol).

Method C
The 3-nitroso compound (1 g) was dissolved in methanol and Raney Ni (4 g) was added. Hydrogenation under atmospheric pressure was carried out. After filtering, methanol was evaporated under inert gas. Amine was chromatographed on silica gel column with ethanol eluent.

Reduction of the pyrimidine ring

Imidazo[1,2-*a*]pyrimidine (0.025 mol) was dissolved in absolute ethanol (250 ml) and PtO_2 catalyst (1 g) was added so that concentrated hydrochloric acid (20 ml) and then Argon was bubbled. The mixture was hydrogenated under atmospheric pressure with stirring. The solution was filtered, the solvent removed; the residue was dissolved in water and the mixture was alkalinized, then extracted with hot chloroform. A purification by chromatography of silica gel column was used (eluent: ethylacetate).

References

1 Rival Y (1987) Thèse d'État ès Sciences Pharmaceutiques, Toulouse
2 Tschitschibabin AE (1925) *Chem Ber* 58, 1704–1706
3 Petit L, Touratier P (1966) *Bull Soc Chim* 2529–2535
4 Armarego WWF (1966) *J Chem Soc* 2778–2787
5 Abignente E, Arena F, De Caprariis P, Parente L (1977) *Il Farmaco Ed Sci* 32 (10), 735–746
6 Abignente E, Arena F, Luraschi E, Saturnino C, Marmo E, De Rosis A, Filippelli A (1984) *Il Farmaco Ed Sci* 39 (5), 379–388
7 Mosby WL (1961) *In: Heterocyclic Systems with Bridgehead Nitrogen Atoms* (Weissberger A, ed) Interscience Publ Inc, NY
8 Abignente E, Arena F, De Caprariis P, Montagnaro G, Rossi F, Lampa E, Giordano L, Vacca C, Marmo E (1980) *Il Farmaco Ed Sci* 35 (8), 654–673
9 Glennon RA, Rogers ME, El Said MK (1980) *J Heterocycl Chem* 17 (2), 337–340
10 Lombardino JG (1965) *J Org Chem* 30, 2403–2407
11 Heider J, Hauel N, Austel V, Noll K, Bomhard A, Van Meel J, Diederen W (1978) *Ger Offen* DE 3,446,778
12 Buu-Hoi NP, Dat Xuong N (1956) *C R Acad Sci* 243, 2090–2092
13 Patra M, Mahapatra SK, Dask B (1974) *J Indian Chem Soc* 51 (12), 1031–1034
14 Buu-Hoi NP, Dat Xuong N (1961) *Bull Soc Chim* 1344–1346
15 Matsukawa T, Ban S (1951) *J Pharm Soc Jpn* 71, 756–759
16 Matsukawa T, Ban S (1952) *J Pharm Soc Jpn* 72, 610–614
17 Saldabols N, Lando OE (1978) *Khim Geterotsikl Soedin* 2, 258–262

18 Teulade JC, Escale R, Grassy G, Girard JP, Chapat JP (1979) *Bull Soc Chim* II, 9–10, 529–536
19 Pyl T, Baufeld W (1966) *Justus Liebig Ann Chem* 112–127
20 Pentimalli L, Passalacqua V (1966) *Gazz Chim Ital* 100, 110–118
21 Hurst DT, Saldanha JA (1977) *Heterocycles* 6(7), 929–932
22 Thompson BB, Larocca JP, Gibson CA (1971) *J Pharm Sci* 60 (1), 74–76
23 Sundberg RJ, Dahlhausen DJ, Manikumar G, Mavunkel B, Biswas A, Srinivasan V, King FJ, Waid P (1988) *J Heterocycl Chem* 25 (1), 129–137
24 Parkanyi C, Abdelhamid A, Cheng JCS, Shawali AS (1984) *J Heterocycl Chem* 21 (4), 1029–1032
25 Teulade JC (1977) Thèse d'État ès Sciences, Montpellier
26 Paudler WW, Kuder JE (1966) *J Org Chem* 31 (3), 809–812
27 Sarasin J, Wagmann E (1964) *Helv Chim Acta* 7, 713–715
28 Almirante L, Mugnaini A, De Toma N, Murmann W (1971) *Boll Chim Farm* 110 (6), 322–329
29 Teulade JC, Escale R, Viols H, Chapat JP, Grassy G, Carpy A, Léger JM (1983) *J Chem Soc Perkins* 11, 2663–2667
30 Roe AM (1983) *J Chem Soc* 2195–2200