New Triazole Antifungal Agents Derived from Mercaptomethylisoxazoles

M. Moreno-Mañas*, Y. Arredondo, R. Pleixats and M. Teixidó

Department of Chemistry,
Universitat Autònoma de Barcelona,
Bellaterra, 08193-Barcelona, Spain

M. M. Raga, C. Palacín, J. M. Castelló and J. A. Ortiz*

Centro de Investigación Grupo Ferrer,
Juan de Sada, 32,
08028-Barcelona, Spain

Received April 9, 1992

Several new triazole antifungal agents derived from mercaptomethylisoxazoles of general structure 2-(2,4-dihalogenophenyl)-3-((X-isoxazolyl)methylthio)-1-(1,2,4-triazol-1-yl)-2-propanol, as well as some selected sulfoxides and sulfones derived thereof, have been synthesized and tested for antifungal activity. Some of these compounds showed good activity against yeasts and dermatophytes.

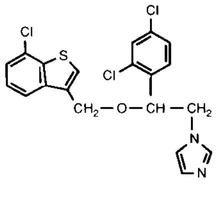
J. Heterocyclic Chem., **29**, 1557 (1992).

Introduction.

In the last 20 years a great variety of antifungal agents bearing an imidazole or a 1,2,4-triazole ring, substituted at N-1 with a complex and highly lipophylic moiety, has been successfully used. Excellent reviews on this subject are available [1-3].

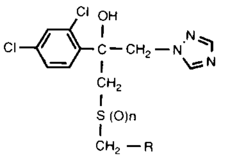
However, side effects observed on some of these products such as contact allergies upon topical administration [4-6], and also an important increase in the number of mycoses during the past few years, prompted us to begin the search of new improved azole antifungal agents. Thus, the synthesis and pharmacological testing of some imidazole antifungal compounds have been published by our group [7,8]. One of them, sertaconazole, **1**, has been patented [9] and will be commercialized in the near future.

Then, our attention was directed towards the development of systemic antifungal agents. Two families of compounds reported in the literature are represented by general formulae **2** and **3** [10,11].



1 SERTACONAZOLE

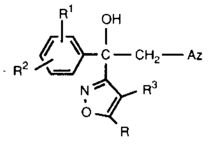
Formulae 1



2 R = heterocycles (not isoxazole)

n = 0, 1

Formulae 2



3 Az = imidazolyl or triazolyl

Formulae 3

We considered the possibility of combining the structural features of both types of compounds in order to improve their pharmacological properties. Thus, we wish to describe herein the preparation and biological testing of new antifungal agents **14-21** (Scheme 1).

Results.

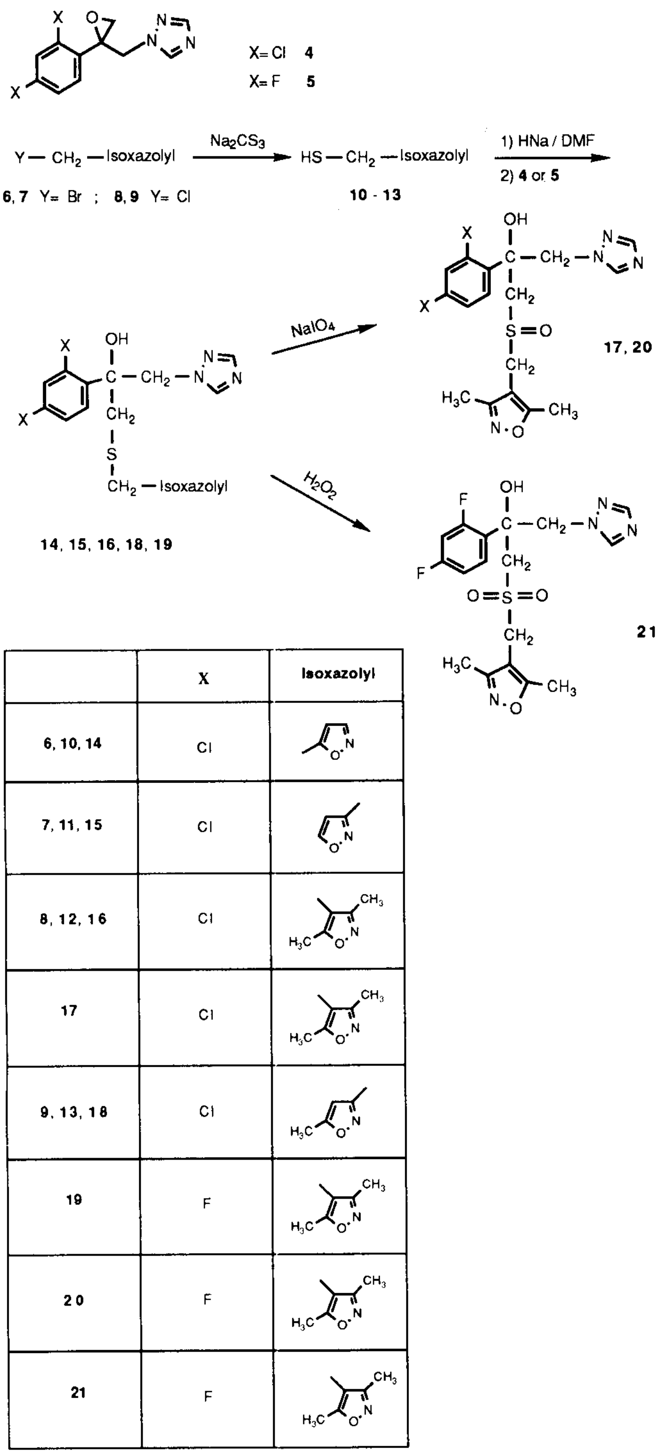
Compounds **14**, **15**, **16**, **18** and **19** were obtained by opening the oxiranes **4** and **5** with mercaptomethylisoxazoles **10-13** (Scheme 1). Preliminary *in vivo* pharmacological tests of those compounds showed that **16** was the best of this series. Therefore, the related difluorinated product **19** was also synthesized.

Oxidation of **16** and **19** with sodium metaperiodate gave **17** and **20**, respectively. Finally, compound **19** was converted into the sulfone **21** by oxidation with hydrogen peroxide in acetic acid (Scheme 1).

The required oxiranes **4** and **5** were prepared as reported [10,12]. The mercaptomethylisoxazoles **10-13** were prepared by treating the corresponding halogeno derivatives **6** [13], **7** [14], **8** [15] and **9** [16] with sodium trithiocarbonate according to a reported general method [17]. Elemental analysis of these thiols could not be secured because they were readily oxidized to their corresponding disulfides.

The antifungal activities towards a series of yeasts and fungi have been evaluated as the minimal inhibitory concentration (MIC), according to the method of progressive double dilutions in solid media [18]. The results are collected in Table 1.

Scheme 1



	X	Isoxazolyl
6, 10, 14	Cl	
7, 11, 15	Cl	
8, 12, 16	Cl	
17	Cl	
9, 13, 18	Cl	
19	F	
20	F	
21	F	

EXPERIMENTAL

The pmr and cmr spectra were determined at 80 and 20 MHz respectively using TMS as internal standard. Chemical shifts are given in δ (ppm). Mass spectra were determined under electron impact (70 eV).

The following compounds were prepared according to the literature: **4** [10], **5** [12], **6** [13], **7** [14], **8** [15], and **9** [16].

5-Mercaptomethylisoxazole (**10**) (General Procedure).

A solution of 5.00 g (0.031 mole) of **6** in 150 ml of deoxygenated methanol was added dropwise at 0°, under argon atmosphere and magnetic stirring, to a mixture of 31 ml of $2M$ sodium trithiocarbonate (0.062 mole) [17] and 160 ml of deoxygenated water. The mixture was kept at this temperature for one hour after the addition, then acidified with diluted hydrochloric acid until *p*H 5 and extracted with dichloromethane. The organic phase was dried and evaporated to yield 3.40 g (95%) of a brown-red liquid identified as **10**. This compound was kept in the freezer under an inert atmosphere to prevent oxidation; ir (film): 1595, 1470, 1246, 1184, 992, 915, 895, 802 cm^{-1}; pmr (deuteriochloroform): 8.22 (d, J *ca* 2 Hz, 1H), 6.22 (d, J *ca* 2 Hz, 1H), 3.87 (d, J *ca* 9 Hz, 2H), 2.09 (t, J *ca* 9 Hz, 1H); cmr (deuteriochloroform): 170.6, 150.4, 101.1, 18.9.

3-Mercaptomethylisoxazole (**11**).

Triphenylphosphine (23.30 g, 0.0889 mole) was added in portions with stirring to a mixture of 3-hydroxymethylisoxazole [16] (5.87 g, 0.0593 mole), tetrabromomethane (24.60 g, 0.0741 mole) and dichloromethane (125 ml) kept at 25-30°. After one hour at room temperature, the mixture was refluxed for two hours and the solvent evaporated. The resulting orange oil was washed repeatedly with diethyl ether. The ether extracts were evaporated and the residue was distilled under reduced pressure, to afford 3-bromomethylisoxazole, **7** (4.51 g, 47%) , bp 79-82°/15 mm Hg; ir (film): 1562, 1424, 1220, 1134, 1112, 1050, 897, 860, 782, 682, 656 cm^{-1}; pmr (deuteriochloroform): 8.30 (d, J = 2 Hz, 1H), 6.39 (d, J = 2 Hz, 1H), 4.36 (s, 2H).

3-Mercaptomethylisoxazole, **11**, was obtained from **7** in 69% yield as for **10**; ir (potassium bromide): 2931, 2558, 1552, 1422, 1114, 1050, 888, 783 cm^{-1}; pmr (deuteriochloroform): 8.33 (d, J = 2 Hz, 1H), 6.33 (d, J = 2 Hz, 1H), 3.71 (d, J *ca* 7 Hz, 2H), 1.86 (t, J *ca* 7 Hz, 1H); cmr (deuteriochloroform): 159.2, 158.5, 103.6, 18.6.

4-Chloromethyl-3,5-dimethylisoxazole (**8**) (Improved Procedure).

Hydrogen chloride was passed for 12 hours through a mixture of 3,5-dimethylisoxazole (40.40 g, 0.42 mole), aqueous formaldehyde (40%) (75.18 g, 2.51 mole) and concentrated hydrochloric acid (35%) (51.60 g, 1.41 moles) at a temperature of 65-70°. The solution was extracted with chloroform and washed with sodium hydrogen carbonate. The organic layer was dried and evaporated to afford 32.2 g of 4-hydroxymethyl-3,5-dimethylisoxazole; ir (film): 3231, 1639, 1457, 1422, 1010 cm^{-1}; pmr (deuteriochloroform): 4.34 (s, 2H), 2.37 (s, 3H), 2.25 (s, 3H). Thionyl chloride (17.12 g, 0.140 mole) was added at room temperature with stirring to a solution of this compound (18.30 g, 0.144 mole) in dichloromethane (50 ml). The mixture was left 1.5 hours at this temperature after the addition, excess thionyl chloride was evaporated and the residue distilled under reduced pressure to yield 8.72 g (42%) of **8** as a colorless liquid, bp 120-122°/25 mm Hg, (Lit [15] bp 88-90°/7 mm Hg); ir (film): 2969, 2931, 1638, 1426, 1284, 1211, 709 cm^{-1}; pmr (deuteriochloroform): 4.43 (s, 2H), 2.44 (s, 3H), 2.34 (s, 3H).

4-Mercaptomethyl-3,5-dimethylisoxazole (**12**).

Table 1

Activity of Compounds 14-21 [a]

	Canida albicans (8 strains)	*Canida no albicans* (4 strains)	*Cryptococcus* (3 strains)	*Aspergillus* (5 strains)	*Trichophyton mentagrophytes* (6 strains)
14	0.12	0.39	0.25	55.7	18.3
15	0.16	0.39	0.50	>128	>128
16	0.23	0.49	0.79	24.2	10.5
18	0.27	0.31	0.50	128	128
19	0.61	3.17	8	32	8
20	>128	>128	>128	>128	>128
21	86	64	>128	>128	>128
Fluconazole	3.08	16	4	>128	32

[a] Antifungal activity in MIC (µg/ml).

This compound was obtained from **8** in 96% yield as for **10**; ir (film): 2965, 2925, 2540, 1635, 1452, 1424, 1270, 1250, 1197, 1040, 1010, 880, 735 cm^{-1}; pmr (deuteriochloroform): 3.52 (d, J = 7 Hz, 2H), 2.39 (s, 3H), 2.30 (s, 3H), 1.70 (t, J = 7 Hz, 1H); cmr (deuteriochloroform): 164.6, 158.4, 112.9, 15.5, 10.4, 9.5.

3-Mercaptomethyl-5-methylisoxazole (**13**).

This compound was obtained from **9** in 73% yield as for **10**; ir (film): 2979, 2928, 2551, 1605, 1475, 1450, 1429, 1259, 1226, 1151, 1124, 1039, 1009, 903, 799, 753, 621 cm^{-1}; pmr (deuteriochloroform): 6.06 (s, 1H), 3.73 (d, J = 8.4 Hz, 2H), 2.42 (s, 3H), 1.87 (t, J = 8.4 Hz, 1H).

2-(2,4-Dichlorophenyl)-3-(5-isoxazolylmethylthio)-1-(1,2,4-triazol-1-yl)-2-propanol (**14**) (General Procedure).

A solution of 2.70 g (0.0236 mole) of 5-mercaptomethylisoxazole, **10**, in 30 ml of anhydrous dimethylformamide is added dropwise at room temperature, under stirring and inert atmosphere, to a suspension of 0.84 g (0.0193 mole) of sodium hydride (55% in oil) (previously washed three times with hexane) in 10 ml of anhydrous dimethylformamide. The mixture was kept under stirring at room temperature about 30 minutes and then a solution of 5.85 g (0.0216 mole) of 1-(2,4-dichlorophenyl)-1-(1*H*-1,2,4-triazolylmethyl)oxirane, **4** in 25 ml of anhydrous dimethylformamide was added dropwise. The resulting clear red solution was left 48 hours at room temperature, under stirring and inert atmosphere, then poured into ice-water (150 ml) and extracted several times with ethyl acetate. The organic layer was washed with water, dried and evaporated. The residue was purified through a silica gel column (ethyl acetate-dichloromethane 7:3 as eluent) to afford 2.00 g (27% yield) of **14** as an oil; ir (film): 3375-3083 (broad), 1590, 1509, 1469, 1275, 1138, 805, 733 cm^{-1}; pmr (deuteriochloroform): 8.17 (d, J = 1.7 Hz, 1H), 7.96 (s, 1H), 7.83 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.48-7.13 (m, 2H), 6.17 (d, J = 1.7 Hz, 1H), 5.21 (d, J = 14 Hz, 1H), 5.0 (broad s, 1H, OH), 4.78 (d, J = 14 Hz, 1H), 3.87 (s, 2H), 3.54 (d, J = 14 Hz, 1H), 3.15 (d, J = 14 Hz, 1H); cmr (deuteriochloroform): 168.5, 151.4, 150.0, 144.1, 136.5, 134.7, 130.5, 130.2, 127.4, 101.6, 77.3, 54.7, 38.4, 27.1; ms: (m/e) 386 (1), 385 (M+1, 3), 351 (2), 350 (1), 349 (3), 304 (3), 302 (5), 272 (3), 270 (6), 260 (11), 259 (8), 258 (64), 257 (13), 256 (100), 254 (10), 175 (10), 173 (16), 161 (15), 159 (23), 114 (13), 83 (25), 82 (62), 70 (14).

Compounds **15**, **16**, **18** and **19** were prepared as for **14**.

2-(2,4-Dichlorophenyl)-3-(3-isoxazolylmethylthio)-1-(1,2,4-triazol-1-yl)-2-propanol (**15**).

This compound was obtained in 38% yield by column chromatography as an oil that crystallized upon treatment with diethyl ether, mp 103-105°; ir (potassium bromide): 3150, 3112, 1581, 1559, 1512, 1456, 1419, 1369, 1277, 1132, 1093, 874, 801, 771, 680, 588 cm^{-1}; pmr (deuteriochloroform): 8.33 (d, J = 1.7 Hz, 1H), 8.0 (s, 1H), 7.83 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.40-7.13 (m, 2H), 6.30 (d, J = 1.7 Hz, 1H), 5.15 (d, J = 15.6 Hz, 1H), 4.76 (d, J = 15.6 Hz, 1H), 3.78 (s, 2H), 3.54 (d, J = 14 Hz, 1H), 3.04 (d, J = 14 Hz, 1H); cmr (deuteriochloroform): 160.2, 158.7, 151.6, 137.0, 134.8, 130.6, 130.5, 130.4, 127.4, 104.0, 77.2, 55.0, 38.4, 27.1.

Anal. Calcd. for $C_{15}H_{14}Cl_2N_4O_2S$: C, 46.76; H, 3.66; N, 14.54. Found: C, 46.66; H, 3.63; N, 14.44.

2-(2,4-Dichlorophenyl)-3-((3,5-dimethylisoxazol-4-yl)methylthio)-1-(1,2,4-triazol-1-yl)-2-propanol (**16**).

The crude mixture was an oil from which a solid crystallized upon treatment with diethyl ether (43% yield), mp 134-136° (ethanol-pentane); ir (potassium bromide): 3363-3293 (broad), 1634, 1584, 1503, 1453, 1427, 1375, 1272, 1200, 1137, 1055, 1011, 802, 737, 678 cm^{-1}; pmr (deuteriochloroform): 8.06 (s, 1H), 7.87 (s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.37-7.15 (m, 2H), 5.22 (d, J = 15.0 Hz, 1H), 4.81 (d, J = 15.0 Hz, 1H), 3.62 (d, J = 12.5 Hz, 1H), 3.41 (d, J = 12.5 Hz, 1H), 3.37 (d, J = 15 Hz, 1H), 3.06 (d, J = 15 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H); cmr (deuteriochloroform): 166.1, 159.2, 151.5, 144.0, 137.2, 134.7, 130.5, 130.4, 130.2, 127.3, 109.8, 77.4, 54.7, 38.1, 24.8, 10.7, 9.7.

Anal. Calcd. for $C_{17}H_{18}Cl_2N_4O_2S$: C, 49.40; H, 4.39; N, 13.55. Found: C, 49.31; H, 4.29; N, 13.43.

2-(2,4-Dichlorophenyl)-3-((5-methylisoxazol-3-yl)methylthio)-1-(1,2,4-triazol-1-yl)-2-propanol (**18**).

From the crude mixture a solid was obtained upon treatment with diethyl ether (73% yield), mp 114-115° (ethanol-pentane); ir (potassium bromide): 3139, 3125, 3062, 1601, 1583, 1510, 1465, 1425, 1376, 1280, 1207, 1134, 1099, 1053, 1016, 902, 807, 770, 675 cm^{-1}; pmr (deuteriochloroform): 8.04 (s, 1H), 7.83 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.43-7.13 (m, 2H), 5.91 (s, 1H), 5.15 (d, J = 15.6 Hz, 1H), 4.76 (d, J = 15.6 Hz, 1H), 3.65 (s, 2H), 3.61 (d, J = 14 Hz, 1H), 3.09 (d, J = 14 Hz, 1H), 2.39 (s, 3H); cmr (deuteriochloroform): 169.7, 161.1, 151.2, 144.0, 137.0, 134.5, 130.6, 130.4, 127.2, 101.0, 78.9, 55.0, 38.3, 27.2, 12.0.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_4O_2S$: C, 48.13; H, 4.04; N, 14.03. Found: C, 47.98; H, 4.13; N, 13.82.

2-(2,4-Difluorophenyl)-3-((3,5-dimethylisoxazol-4-yl)methylthio)-1-(1,2,4-triazol-1-yl)-2-propanol (**19**).

A solid was obtained from the crude mixture upon treatment with diethyl ether (57% yield), mp 128-132° (diethyl ether); ir (potassium bromide): 3174, 3139, 2931, 1616, 1503, 1423, 1272, 1200, 1139, 1104, 962, 845, 736, 675 cm^{-1}; pmr (deuteriochloroform): 8.06 (s, 1H), 7.88 (s, 1H), 7.69-7.38 (m, 1H), 6.94-6.72 (m, 2H), 4.78 (s, 2H), 3.66 (d, J = 15 Hz, 1H), 3.44 (d, J = 15 Hz, 1H), 3.13 (d, J = 15 Hz, 1H), 2.87 (d, J = 15 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H); ms: (m/e) 381 (M + 1, 1), 270 (22), 225 (12), 224 (100), 220 (12), 141 (12), 127 (15), 110 (22), 82 (12), 68 (19), 43 (18).

Anal. Calcd. for $C_{17}H_{18}F_2N_4O_2S$: C, 53.68; H, 4.74; N, 14.74; S, 8.42. Found: C, 53.78; H, 4.94; N, 14.58; S, 8.35.

2-(2,4-Dichlorophenyl)-3-((3,5-dimethylisoxazol-4-yl)methylsulfinyl)-1-(1,2,4-triazol-1-yl)-2-propanol (**17**).

An aqueous solution (10 ml) of sodium metaperiodate (0.269 g, 1.3 mmoles) was added dropwise at 0° to a solution of 0.400 g (0.97 mmole) of **16** in methanol (15 ml). The mixture was kept overnight at room temperature under stirring. The formed white solid was filtered off, the filtrate was evaporated and the aqueous residue extracted with dichloromethane. The organic layer was dried and evaporated and the residue was chromatographed through silica-gel (ethyl acetate-ethanol 4:1 as eluent) affording 0.097 g (23% yield) of **17**, mp 123-128° (diethyl ether); ir (potassium bromide): 3314, 3142, 2966, 2924, 1634, 1585, 1505, 1458, 1425, 1374, 1272, 1203, 1137, 1045, 1008, 807, 678 cm^{-1}; pmr (deuteriochloroform): 8.19 (s, 1H), 7.88 (s, 1H), 7.75 (s, 1H), 7.41-7.23 (m, 2H), 5.00 (d, J = 15 Hz, 1H), 4.44 (d, J = 15 Hz, 1H), 4.00 (d, J = 14 Hz, 1H), 3.72 (s, 2H), 2.78 (d, J = 14 Hz, 1H), 2.37 (s, 3H), 2.22 (s, 3H); ms: (m/e) 430 (M, 2), 428 (3), 393 (1), 321 (1), 319 (2), 258 (3), 256 (4), 175 (12), 173 (18), 110 (100), 83 (15), 82 (16), 68 (55).

Anal. Calcd. for $C_{17}H_{18}Cl_2N_4O_3S$: C, 47.56; H, 4.22; N, 13.05; S, 7.45. Found: C, 46.61; H, 4.23; N, 12.22; S, 7.24.

2-(2,4-Difluorophenyl)-3-((3,5-dimethylisoxazol-4-yl)methylsulfinyl)-1-(1,2,4-triazol-1-yl)-2-propanol (**20**).

This compound was obtained as for **17** from **19** in 24% yield, mp 154-156° (ethyl acetate); ir (potassium bromide): 3311, 3142, 2987, 2931, 1615, 1500, 1423, 1273, 1139, 1097, 1007, 857 cm^{-1}; pmr (deuteriochloroform): 8.31 (s, 1H), 7.97 (s, 1H), 7.87-7.56 (m, 1H), 7.13-6.73 (m, 2H), 4.73 (d, J = 14 Hz, 1H), 4.37 (d, J = 14 Hz, 1H), 3.72 (s, 2H), 3.48 (d, J = 14 Hz, 1H), 2.83 (d, J = 14 Hz, 1H), 2.37 (s, 3H), 2.23 (s, 3H); ms: (m/e) 396 (M, 13), 287 (10), 224 (8), 179 (6), 141 (26), 127 (14), 110 (100), 82 (13), 69 (10), 68 (59), 43 (38), 42 (14), 41 (12).

Anal. Calcd. for $C_{17}H_{18}F_2N_4O_3S$: C, 51.51; H, 4.58; N, 14.13; S, 8.09. Found: C, 51.19; H, 4.78; N, 13.58; S, 7.66.

2-(2,4-Difluorophenyl)-3-((3,5-dimethylisoxazol-4-yl)methylsulfonyl)-1-(1,2,4-triazol-1-yl)-2-propanol (**21**).

Aqueous hydrogen peroxide (36%) (2.45 g, 26.30 mmoles) was slowly added at room temperature with stirring to a solution of 1.00 g (2.63 mmoles) of **19** in glacial acetic acid (6 ml). After 48 hours the mixture was neutralized with sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was washed, dried and evaporated to afford 0.91 g (84% yield) of **21**, mp 158-161° (diethyl ether); ir (potassium bromide): 3394, 3114, 2924, 1619, 1501, 1427, 1316, 1277, 1256, 1129, 851 cm^{-1}; pmr (deuteriochloroform): 8.05 (s, 1H), 7.90 (s, 1H), 7.66-7.34 (m, 1H), 7.03-6.75 (m, 2H), 5.06 (d, J = 14 Hz, 1H), 4.69 (d, J = 14 Hz, 1H), 4.22 (d, J = 15 Hz, 1H), 4.00 (d, J = 15 Hz, 1H), 3.81 (d, J = 15 Hz, 1H), 3.47 (d, J = 15 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H); ms: (m/e) 413 (M + 1, 1), 330 (6), 238 (5), 179 (26), 141 (44), 110 (100), 68 (62), 55 (10), 43 (45), 42 (15).

Anal. Calcd. for $C_{17}H_{18}F_2N_4O_4S$: C, 49.51; H, 4.37; N, 13.59; S, 7.77. Found: C, 49.41; H, 4.58; N, 13.30; S, 7.72.

Acknowledgements.

Financial support from DGICYT (Ministry of Education and Science of Spain) through project PTR90-0017 is gratefully acknowledged.

REFERENCES AND NOTES

[1] L. Zirngibl, *Prog. Drug Res.*, **27**, 253 (1983).

[2] R. A. Fromtling, *Drugs Today*, **20**, 325 (1984).

[3] A. K. Saksena, V. M. Girijavallabhan, A. B. Cooper and D. Loebenberg, *Annu. Rep. Med. Chem.*, **24**, 111 (1989).

[4] J. P. Nater and A. C. De Groot, in Side Effects of Drugs, 8th Annual, Elsevier, Amsterdam, 1984, p 151.

[5] A. V. Astahova, in Side Effects of Drugs, 9th Annual, Elsevier, Amsterdam, 1985, p 247.

[6] R. E. Kalb and M. E. Grossman, *Cutis*, **36**, 240 (1985).

[7] M. Raga, C. Palacín, J. M. Castelló, J. A. Ortiz, M. R. Cuberes and M. Moreno-Mañas, *Eur. J. Med. Chem.*, **21**, 329 (1986).

[8] M. Moreno-Mañas, M. R. Cuberes, C. Palacín, M. Raga, J. M. Castelló and J. A. Ortiz, *Eur. J. Med. Chem.*, **23**, 477 (1988).

[9] R. Foguet, M. Moreno-Mañas, M. Raga, R. M. Cuberes, J. M. Castelló and J. A. Ortiz, Ferrer Int. S.A., European Patent 151,477 (1985).

[10] K. Cooper, P. J. Whittie and K. Richardson, Pfizer Ltd., European Patent 107,392 (1983).

[11] Y. Makisumi, A. Murabayashi, K. Tawara and T. Hatta, Shionogi Seiyaku Kabushiki Kaisha, European Patent 241,232 (1987).

[12] K. Richardson, Pfizer Ltd., British Patent 2,099,818 (1982).

[13] P. DeShong, J. A. Cipollina and N. K. Lowmaster, *J. Org. Chem.*, **53**, 1356 (1988).

[14] P. J. Kocienski, G. Cernigliaro and G. Feldstein, *J. Org. Chem.*, **42**, 353 (1977).

[15] N. K. Kochetkov, E. D. Khomutova and M. V. Bazilevskii, *Zh. Obshch. Khim.*, **28**, 2736 (1958); *Chem. Abstr.*, **53**, 9187e (1959).

[16] N. H. Rogers, P. J. O'Hanlon, G. Walker and M. J. Crimmin, Beecham Group Plc., European Patent 87,953 (1983).

[17] D. J. Martin and C. C. Greco, *J. Org. Chem.*, **33**, 1275 (1968).

[18] S. Shadomy S and A. Espinel, in Manual of Clinical Microbiology, 3rd Ed, American Society of Microbiology, Washington, D.C., 1977, p 647.