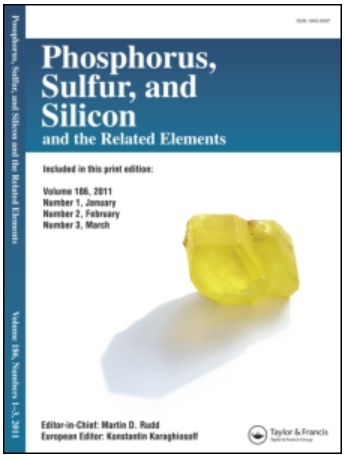

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SYNTHESIS OF SOME NEW PROPANOL DERIVATIVES ANALOGOUS TO FLUCONAZOLE

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A series of 2-(2,4-difluorophenyl)-1-(1H-1,2,4 triazol-1-yl-methyl)-3-(substituted heterocycl)-propan-2-ol, which are analogous to fluconazole, were synthesized via the reaction of 2-(2,4-difluorophenyl)-2-[1-(1,2,4-triazolmethide)]oxiran with various heterocyclic systems.

Keywords: Fluconazole; propanol; triazine; triazole

Fluconazole, α(2,4-difluorophenyl)-α-(1H-1,2,4 triazol-1-yl-methyl)-1H-1,2,4 triazol-1-ethanol **4** is a potent inhibitor of the cytochrome P450 (CYP)-mediated metabolism of the antiepileptic agent phenytion, a well-known human and animal tetragon.[1] Fluconazole was introduced in 1990 as one of the most effective water-soluble oral antifungal agent.[2,3]

In continuation of our interest in the synthesis of heterocycles[4] containing sulphur and nitrogen, in this communication we wish to report the synthesis of some new propanol derivatives analogous to fluconazole.

Due to its biological importance, several routes have been developed for the synthesis of fluconazole **4**.[5] The applicable method at the industrial level involves a one-pot, three-component reaction of 2,4 difluoro-2-(1H-1,2,4 triazole-1-yl)acetophenone **1**, triazole **2** and trimethylsulfoxonium iodide **3** (Scheme 1).[6]

In order to synthesize compounds analogous to fluconazole, we applied a similar strategy using other heterocyclic containing thio and amino groups such as 3-thio-1,2,4 triazoles, 2-thiopyrimidines, 3-thio-1,2,4 triazines and 3-amino-1,2,4 triazines. These attempts were unsuccessful. In 1992 Yajing et al.[7] reported the reaction of cyclic

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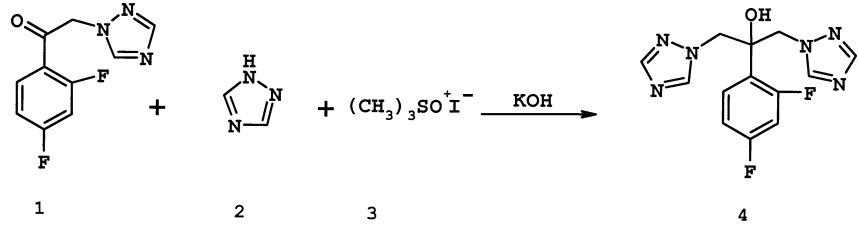
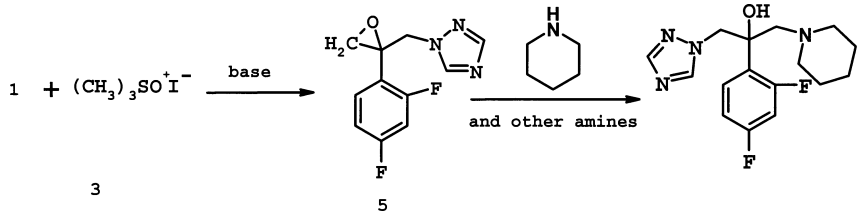


SCHEME 1

amines with**1** in a two-step reaction via the oxirane intermediate **5** (Scheme 2).[7]

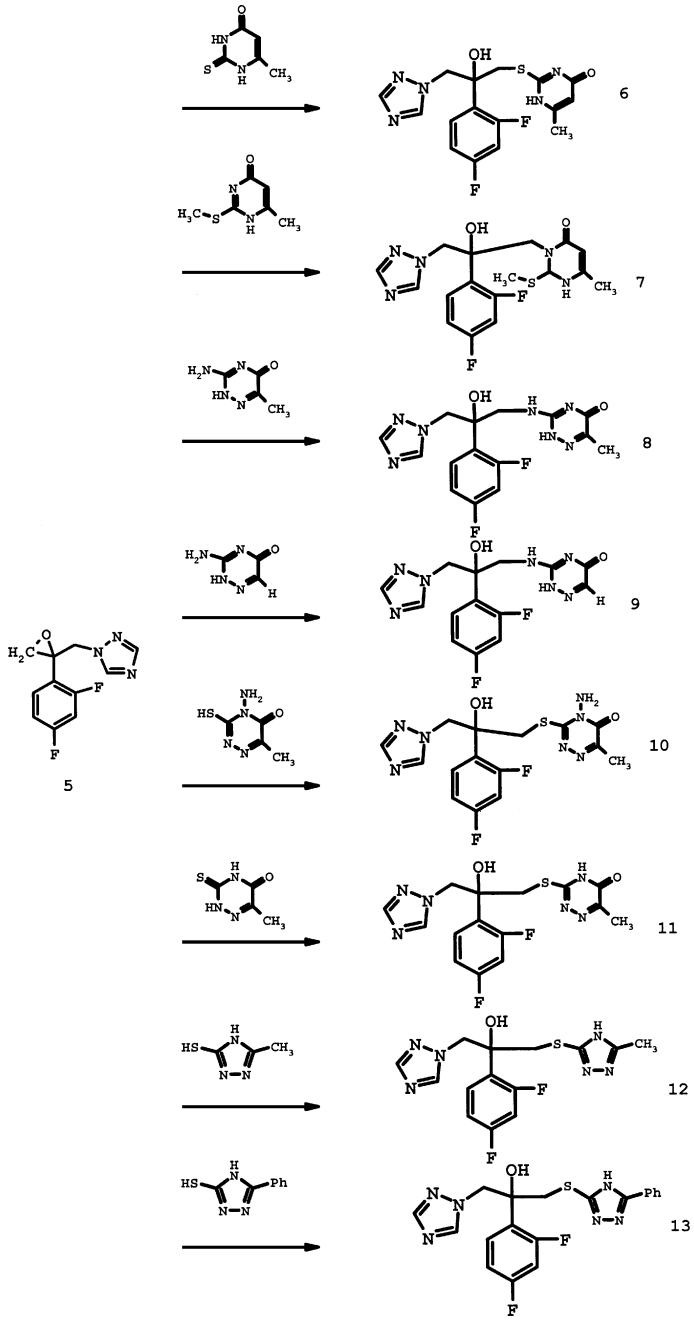


SCHEME 2

We applied this two-step strategy and found that the ring opening of the intermediate epoxide gives bis unsymmetrical heterocyclic derivatives of propanol (Scheme 3). As expected, the intermediate epoxide **5** opens regioselectively to give only one alcohol. It is also notable that in the presence of an amino group aminoalkylation (formulas 8 and 9) occurred, and in the presence of a thio group thioalkylation (formulas 11–13) occurred predominantly over ring nitrogen alkylation with epoxide **5**. It is also worthwhile to mention that in the presence of an amino group and a thio group on the heterocyclic system s-alkylation occurs predominantly (Scheme 3, formula 10).

EXPERIMENTAL

Melting points were determined on an electrothermal IA-9100 digital melting point apparatus and are uncorrected. IR spectra were recorded with a Nicolet Magna spectrometer 750-1992-1997. ^{1}H NMR Spectra were recorded on a Brucker spectrometer at 500 MHz using tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on a GC-Mass HP, GC 689 network GC system, mass 5973 at 70 ev. Thin layer chromatography (TLC) was developed on Merck silica gel-coated



SCHEME 3

polyester plates containing a 254 mm fluorescent indicator. Triazoles, pyrimidines, and 1,2,4 triazoles were prepared according to literature.

1-[2-(2,4 Diflurophenyl)-2,3-epoxypropyl]-1H-1,2,4 triazole Methansulphonate (5)

2,4 difluoro-2-(1H-1,2,4 triazol-1-yl)acetophenone hydrochloride (59.6 g, 0.23 mol), trimethylsulfoxonium iodide (50.6 g, 0.23 mol), and cetrimide (2.1 g) were stirred in a mixture of toluene (370 ml) and 20% w/w aqueous sodium hydroxide at 60°C for 3 h. The toluene layer was separated and concentrated to 110 ml, then ethyl acetate was added (150 ml). To this mixture a solution of methansulphonic acid (16.6 g, 0.172 mol) in ethyl acetate (20 ml) was added. More ethyl acetate (100 ml) was added, and the mixture was stirred at 0°C for 1 h. Filtration of the mixture gave the title compound (43 g, 56%). The crude product was dissolved in hot petroleum ether (60–80°C, 140 ml), and charcoal (2 g) was added. The mixture was filtered, the filtrate was concentrated to 100 ml, and then the mixture was stirred at 0°C for 1 h. Filtration of this mixture gave the title compound (7.8 g, 39%), m.p. 128–129°C. ^{1}H NMR-δ (d_4-MeOH): 2.7 (s, 3H), 2.9 (d, $J = 4.57$ Hz, 1H), 3.1 (d, $J = 4.57$ Hz, 1H), 4.7 (d, $J = 14.83$ Hz, 1H), 5.1 (d, $J = 14.83$ Hz, 1H), 6.93 (m, 1H), 7.0 (m, 1H), 7.3 (m, 1H), 8.7 (s, 1H), 9.8 (s, 1H). IR(KBr): 3120 cm^{-1} (CH aromatic), Anal.% Calc. for C12H13F2N3O4S: C, 43.2; H, 3.9; N, 12.6. Found: C, 42.83; H, 3.92; N, 12.96.

Synthesis of Triazolylpropanol Derivatives 6–13

The appropriate heterocyclic compound (0.001 mol) was dissolved in NaOMe/MeOH(Na, 0.15 g, 0.002 mol in MeOH 20 ml). The epoxide **5** (0.3 g, 0.001 mol) was added, the mixture was refluxed for 6–12 h (the progress of reaction was controlled by TLC analysis). After completion of the reaction, the solvent was evaporated off under reduced pressure. To the crude, water was added and extracted with $CHCl_3$ (50 ml). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude was subjected to column chromatography using $CHCl_3$:MeOH (1:60–1: 20) as the eluent to afford the pure product.

Selected Data for 6

Yield: 78%, m.p. 165°C. ^{1}H NMR-δ (d_6-DMSO): 2.03 (s, 3H), 2.5 (d, $J = 12$ Hz, 1H), 2.7 (d, $J = 12$ Hz, 1H), 4.71 (d, $J = 14.1$ Hz, 1H), 4.78 (d, $J = 14.1$ Hz, 1H), 5.6 (s, 1H), 6.2 (s, 1H), 6.8 (m, 1H), 6.9 (m, 1H), 7.4 (m, 1H), 7.78 (s, 1H), 8.3 (s, 1H), 10.2 (br s,1H). IR(KBr): 3436.70 cm^{-1}(OH),

Ms, m/z, 379(M^+), 239 (14%), 224 (100%), 173 (70%), 155 (28%), 141 (39%), 83 (66%).

Selected Data for 7

Yield: 72%, m.p. 140–142°C. ^{1}H NMR-δ(d_3-MeOD): 2.03 (s, 3H), 2.5 (s, 3H), 3.9 (d, $J = 13.5$ Hz, 1H), 4.0 (d, $J = 13.5$ Hz, 1H), 4.7 (d, $J = 14.4$ Hz, 1H), 4.8 (d, $J = 14.4$ Hz, 1H), 5.9 (s, 1H), 6.81–6.91 (m, 2H), 7.0 (s, 1H), 7.4 (m, 1H), 8.3 (s, 1H), 8.5 (s, 1H). IR (KBr): 3480 cm^{-1} (OH), Ms, m/z, 393 (M^+), 281 (21%), 238 (27%), 224 (100%), 169 (16%), 155 (28%), 82 (8.2%), 63(16%).

Selected Data for 8

Yield: 68%, m.p. 181–183°C. ^{1}H NMR-(d_6_DMSO): 2.2 (s,3H), 3.4–3.6 (m, 2H), 4.5 (br s, 1H), 4.6 (d, $J = 14.2$ Hz, 1H), 4.7 (d, $J = 14.2$ Hz, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.1 (m, 1H), 7.3 (m, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 11.5 (br s,1H). IR(KBr): 3450.22 cm^{-1} (OH), Ms, m/z: 363 (M^+), 298 (%6.4), 282 (18%), 238 (%19%), 224 (100%), 173 (72%), 127 (73%), 125 (27%), 68 (20%).

Selected Data for 9

Yield: 70%, m.p. 173–175°C. ^{1}H NMR-(d_6_DMSO): 3.48–3.54 (m, 2H), 4.39 (d, $J = 14.4$ Hz, 1H), 4.43 (d, $J = 14.4$ Hz, 1H), 4.8 (br s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.1 (m, 1H), 7.3 (m, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 12.0 (br s, 1H). IR(KBr): 3541.38 cm^{-1}(OH), Ms, m/z: 349 (M^+), 332 (9.3%), 267 (30%), 238 (22%), 224 (100%), 125 (32%), 111 (15%), 82 (40%).

Selected Data for 10

Yield: 66%, m.p. 155°C. ^{1}H NMR-(d_6_DMSO): 2.2 (s, 3H), 2.8 (d, $J = 12.8$ Hz, 1H), 2.9 (d, $J = 12.8$ Hz, 1H) , 4.6 (d, $J = 14.1$ Hz, 1H), 4.7 (d, $J = 14.1$ Hz, 1H), 5.8 (br s, 1H), 6.4 (s, 2H), 7.0 (m, 1H), 7.2 (m, 1H), 7.4 (m, 1H), 7.7 (s, 1H), 8.3 (s, 1H). IR(KBr): 3550.84 cm^{-1}(OH), Ms, m/z: 395(M^+), 327 (27.6%), 282 (23%), 238 (39.5%), 224 (100%), 171 (71%), 157 (26%), 127 (17%), 82 (8%).

Selected Data for 11

Yield: 64%, m.p. 179°C. ^{1}H NMR-δ(d_3-MeOD): 2.0 (s, 3H), 2.6 (d, $J = 11.5$ Hz, 1H), 2.7 (d, $J = 11.5$ Hz, 1H), 4.6 (d, $J = 14.2$ Hz, 1H), 4.7 (d, $J = 14.2$ Hz, 1H), 5.9 (s, 1H), 6.8 (m, 1H), 6.9 (m, 1H), 7.8 (m, 1H), 8.2 (s, 1H), 8.5 (s, 1H), 11.0 (br s, 1H). IR (KBr): 3467.76 cm^{-1} (OH), Ms, m/z: 381 (M + 1), 312 (12%), 238 (38%), 224 (100%), 155 (11%), 142 (78%), 86 (39%), 68 (15%), 42 (38%).

Selected Data for 12

Yield: 58%, m.p. 128°C. ^{1}H NMR-δ(d_3-MeOD): 2.1 (s, 3H), 2.5 (d, $J = 12$ Hz, 1H), 2.6 (d, $J = 12$ Hz, 1H), 4.6 (d, $J = 14$ Hz, 1H), 4.7 (d, $J = 14$ Hz , 1H), 5.9 (s, 1H), 6.82–6.89 (m, 2H),7.5 (m, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 8.6 (br s, 1H). IR(KBr): 3400.12 cm^{-1} (OH). Ms, m/z: 352 (M^+), 282 (34%), 270 (60%), 238 (29%), 224 (100%), 128 (21%), 125 (34%), 113 (22%), 82 (48%), 42 (38%).

Selected Data for 13

Yield: 56%, m.p. 149°C. ^{1}H NMR-δ(d_3-MeOD) : 2.6 (d, $J = 12.3$ Hz, 1H), 2.7 (d, $J = 12.3$ Hz, 1H), 4.6 (d, $J = 14.2$ Hz, 1H), 4.7 (d, $J = 14.2$ Hz, 1H), 6.1 (s, 1H), 6.82–6.89 (m, 2H), 7.4–7.5 (m, 4H), 7.7 (s, 1H) 7.8–7.83 (m, 2H), 8.31 (s, 1H), 8.42 (s, 1H), 8.9 (br s, 1H). IR (KBr): 3325.36 cm^{-1} (OH), Ms, m/z: 414 (M^+), 396 (9.4%), 345 (40%), 238 (29%), 224 (100%), 190 (24%), 176 (39%), 82 (57%).

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