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Synthesis and Biological Evaluation of Antifungal Triazolyl Haloaromatic Compounds

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Antifungal triazolyl haloaromatic compounds **5–9, 13, 14, 16, 17, 19, 20** and **21** were synthesized and evaluated for biological activity. These compounds exhibited moderate activity against *Pseudomonas albicans, Aspergillus niger* and *Candida albicans* in comparison with fluconazole *in vitro* studies.

INTRODUCTION

Opportunistic fungal infections represent a significant cause of morbidity and mortality in the immuno-compromised patients, such as those with AIDS, neoplasms and transplants. *Candida albicans* infections occur in 41–79% of AIDS patients[1] and an increased rate of disseminated candidates has been observed. Furthermore, systemic mycoses are being recognized more frequently as serious infections in a diverse and emergent group of patients. In particular, mycotic infections have flourished in response to major medical and surgical achievements, such as potent antibacterial agents and intravascular catheters, which represent the major predisposing factors for opportunistic infections[2]. The widespread incidence of life threatening *Candidiasis, Cryptococcosis* and *Aspergillosis* in immuno-compromised patients has underscored the need for safer and efficacious antifungal reagents[3].

In marked contrast to antibacterials, the pace of discovery of newer antifungals for systemic infections has been rather slow. For the treatment of the above said diseases, orally active antifungal azoles have been developed and are currently used in antifungal chemotherapy. The azole class of antifungals have a potential for a broad antimycotic spectrum which includes almost all forms of human mycoses. They primarily inhibit cytochrome P-450 dependent oxidative 14α-demethylation of lanosterol, causing blockade of ergosterol biosynthesis within the fungal cell. Itraconazole (ITZ), a relatively selective inhibitor of fungal cytochrome P-450, now also in clinical use, offers certain advantages over other agents (*e.g.*, fluconazole and ketoconazole) in terms of spectrum, oral efficacy, and side effects. Saperconazole (SPZ) is an investigational azole reported to have better activity than ITZ against a wide range of *Aspergillus* strains *in vitro* and *in vivo*[4].

The increasing incidence of fungal infection associated with notoriously unsatisfactory therapeutic treatment in debilitated patients and the emergence of azole resistant strains have increased the urgency of new alternative drugs[5–8].

Many of the orally active azole antifungal agents share common characteristic features[9–11] as shown in Fig. 1.

The tertiary 1-phenylazolyl ethanol structure seems to be the pharmocophore for this activity. Furthermore,

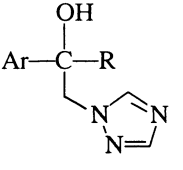
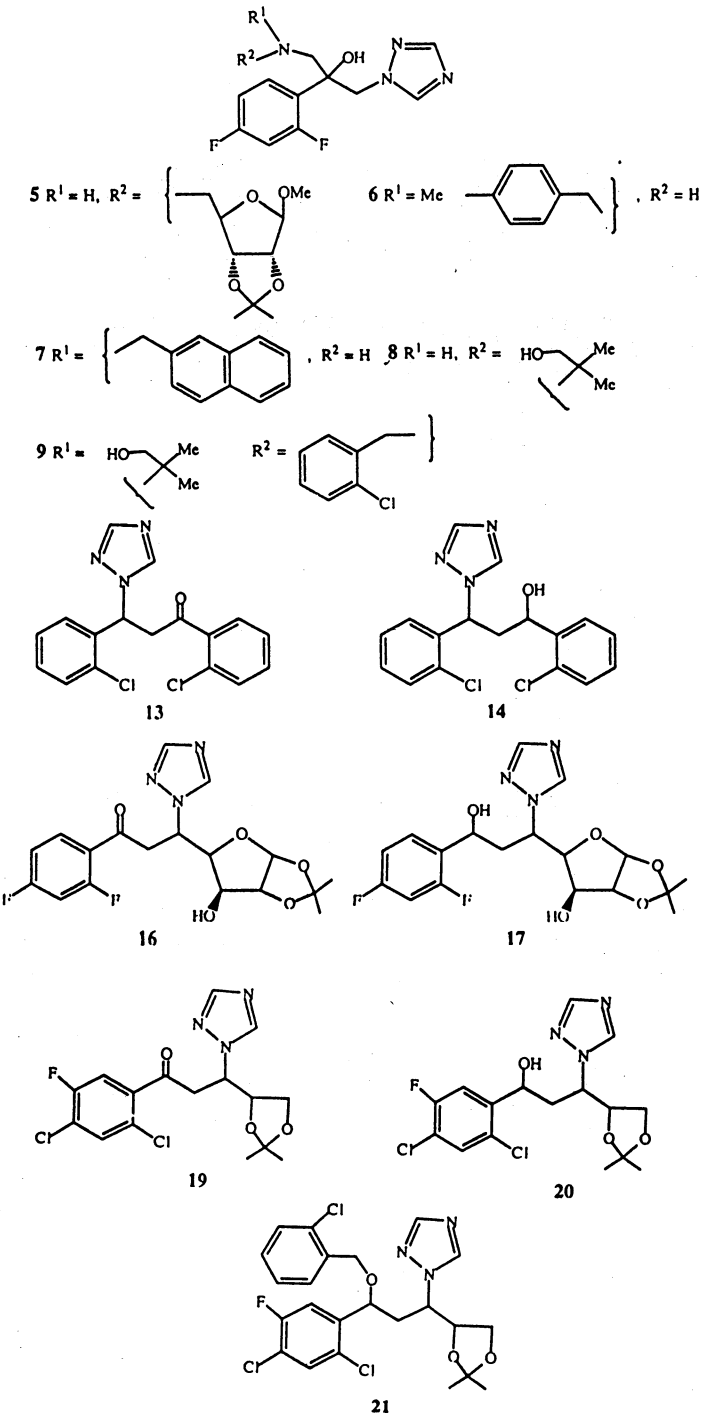


Fig. 1



Scheme-1

numerous ethers of 1-(4-chlorophenyl) or 1-(2,4-dichlorophenyl)-2-(1H-imidazolyl) ethanol have been developed as antifungal agents or show promise for clinical use. With this in mind our interest was directed to triazole derivatives in order to evaluate the effect of substituting the aromatic ring with triazole nucleus that, in itself, shows some antifungal activity like in fluconazole, miconazole, etc. Herein, we report the synthesis and the *in vitro* antifungal activity of a series of azole derivatives **5–9, 13, 14, 16, 17** and **19–21** (Scheme 1).

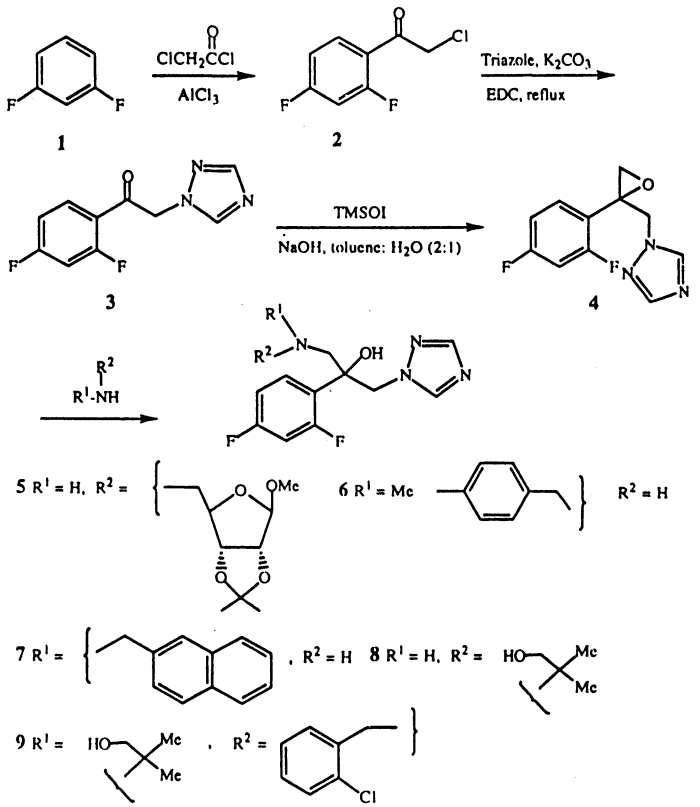
RESULTS AND DISCUSSION

In view of their antifungal activity we have synthesised 2-(2,4-difluorophenyl)-1-[6-methoxy-2,2-dimethyl-(3aR, 6aR)-perhydrofuro [3,4-d][1,3]-dioxol-4-yl methylamino]-3-(1H-1′,2′,4′-triazol-1-yl)-2-propanol **(5)**, 2-(2,4-difluorophenyl)-1-(4-methylbenzylamino)-3-(1H-1′,2′,4′, triazol-1-yl)-2-propanol **(6)**, 2-(2,4-difluorophenyl)-1-(1-naphthylmethylamino)-3-(1H-1′,2′,4′-triazol-1-yl)-2-propanol (7), 2-[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1′,2′,4′-triazol-1-yl) propylamino]-2-methyl-1-propanol **(8)**, 2-[2-chlorobenzyl[2-(2,4-difluorophenyl)-2-hydroxy-3-(1H-1′,2′,4′-triazol-1-yl)propyl]amino]-2-methyl-1-propanol **(9)**, 1,3-di-(2-chlorophenyl)-3-(1H-1′,2,′4′-triazol-1-yl)-1-propanone **(13)**, 1,3-di-(2-chlorophenyl)-3-(1H-1′,2′,4′-triazol-1-yl)-1-propanol **(14)**, 1-(2,4-difluorophenyl)-3-[6-hydroxy-2,2-dimethyl-(6S)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-3-(1H-1′,2′4′-triazol-1-yl)-1-propanone **(16)**, 1-(2,4-difluorophenyl)-3-[6-hydroxy-2,2-dimethyl-(6S)-perhydrofuro[2,3-d][1,3]dioxol-5-yl]-3-(1H-1′,2′,4′-triazol-1 -yl)-1-propanol **(17)**, 1-(2,4-dichloro-5-fluorophenyl)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-(1H-1′,2′,4′-triazol-1-yl)-1-propanone **(19)**, 1-(2,4-dichloro-5-fluoro-phenyl)-3-(2,2-dimethyl-1-3-dioxolan-4-yl)-3-(1H-1′,2′,4′-triazol-1-yl)-1-propanol **(20)**, 1-(2-chlorobenzyloxy)-1-(2,4-di-chlorophenyl)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-(1H-1′,2′,4′-triazol-1-yl)propane **(21)** triazolyl derivatives.

Synthesis of triazolyl pharmacophore containing new chemical entities 5–9

Friedal-crafts acylation of 1,3-difluorobenzene **(1)** with chloroacetyl chloride-$AlCl_3$ gave the chloroacetyl derivative **2** in 82% yield (Scheme 2). **2** on refluxing with triazole in dichloroethane for 12 h gave **3** in 78% yield. ^{1}H NMR spectrum of **3** indicated the presence of triazole protons as two singlets at δ 7.8 and δ 8.05. **3** on treatment with trimethyl sulfoxonium iodide (TMSOI), citrimide and NaOH in toluene: H_2O (2 : 1) gave epoxide **4**. **4** on nucleophilic displacement with various amines gave fluorophenyl triazolyl amino compounds **5–9**. **4** on reaction with 6-methoxy-2,2-dimethyl-(3aR,6aR)-perhydrofuro[3,4-d][1,3]dioxol-4-yl methanamine in methanol for 10 h gave **5** in 69% yield. **5** is a diastereomeric mixture and was characterized from the characteristic OMe protons at δ 3.3 (3H) as a singlet and triazole protons as singlets at δ 7.9 (1H) and δ 8.2 (1H). **4** on reaction with 4-methyl benzylamine in methanol for 12 h gave **6** in 66.6% yield. ^{1}H NMR spectrum of **6** showed methyl protons at δ 2.3 (3H) as singlet, H-1 protons (2H) between δ 2.80–2.98 (m) and H-3 protons (2H) between δ 4.40–4.65 (m). Rest of the protons resonated at expected chemical shifts. **4** on reaction with 2-naphthyl methylamine in methanol for 10 h gave **7** in 72% yield. In the ^{1}H NMR spectrum of **7** H-1 protons (2H) appeared between δ 2.82–3.30 (m), H-3 protons (2H) between δ 4.40–4.70 (m) and rest of the protons resonated at the expected chemical shifts. Similarly, **4** on reaction with 2-amino-2-methyl-1-propanol and 2-[1-(2-chlorophenyl)-(Z)-methylideneamino]-2-methyl-1-propanol respectively gave the corresponding amines **8** and **9**. In the ^{1}H NMR spectrum of **8**, H-1 protons resonated

between δ 2.80–2.95 (m) and H-3 protons between δ 4.55–4.70 (m). **9** was characterized from the appearence of H-1 protons between δ 3.00–3.20 (m), H-3 protons between δ 4.40–4.50 (m), —CH_2OH protons as a triplet at δ 3.45 and —CH_2N protons as a triplet at δ 3.72. These compounds were screened for biological activity against various fungal strains *in vitro*.



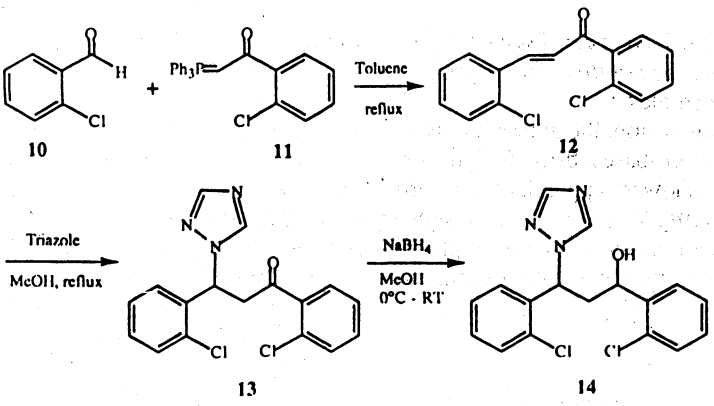
Scheme-2

Synthesis of halophenyl triazolyl derivatives 13 and 14

Wittig olefination of 2-chlorobenzaldehyde **(10)** with phenacyl ylide **11** in toluene for 4 h gave enone **12** in 94% yield (Scheme 3). ^{1}H NMR spectrum of **12** indicated the presence of olefin protons as doublets at δ 6.40 (1H) and δ 6.55 (1H) and aromatic protons (8H) between δ 7.35–7.50 as a multiplet. Reaction of enone **12** with triazole in methanol at reflux temperature gave triazolyl compound **13** in 74% yield. ^{1}H NMR spectrum of **13** showed H-2 protons (2H) as multiplet between δ 3.50–3.65 and δ 4.20–4.40 (m), H-3 proton appeared between δ 6.55–6.70 as a multiplet. **13** on reduction with sodium borohydride in methanol at 0°C gave corresponding alcohol **14** in 92% yield. ^{1}H NMR spectrum of **14** showed the presence of H-2 protons (2H) between δ 3.00–3.25 (m), H-1 proton between δ 6.20–6.50 (m) and rest of the protons resonated at the expected chemical shifts.

Synthesis of chiral triazolyl difluoroaryl derivatives 16 and 17

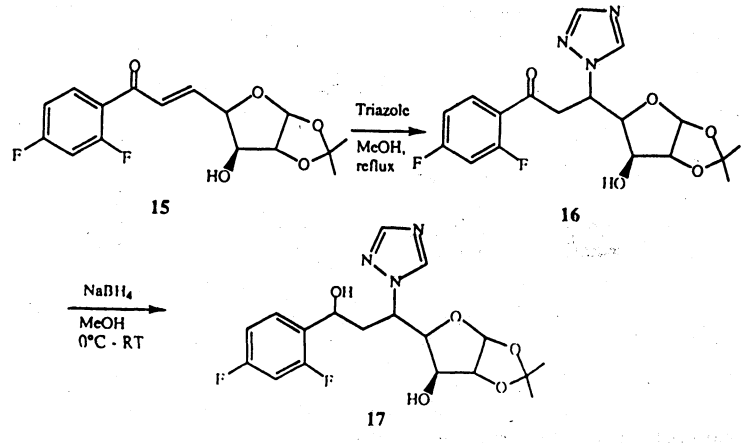
15 which was earlier prepared in our laboratory was refluxed with triazole in methanol to obtain triazolyl compound **16** in 71% yield (Scheme 4). ^{1}H NMR



10 11 12 13 14

Scheme-3

spectrum of **16** showed H-2 protons (2H) between δ 3.20–3.50 (m) and H-3 protons (1H) between δ 6.75–6.90 (m). **16** on reduction with sodium borohydride in methanol at 0°C gave the corresponding alcohol **17** in 90% yield. ^{1}H NMR spectrum of **17** showed H-2 protons between δ 2.30–2.60 (m) and H-1 proton between δ 5.00–5.20 (m).



15 16 17

Scheme-4

Synthesis of chiral haloaryl triazolyl derivatives 19–21

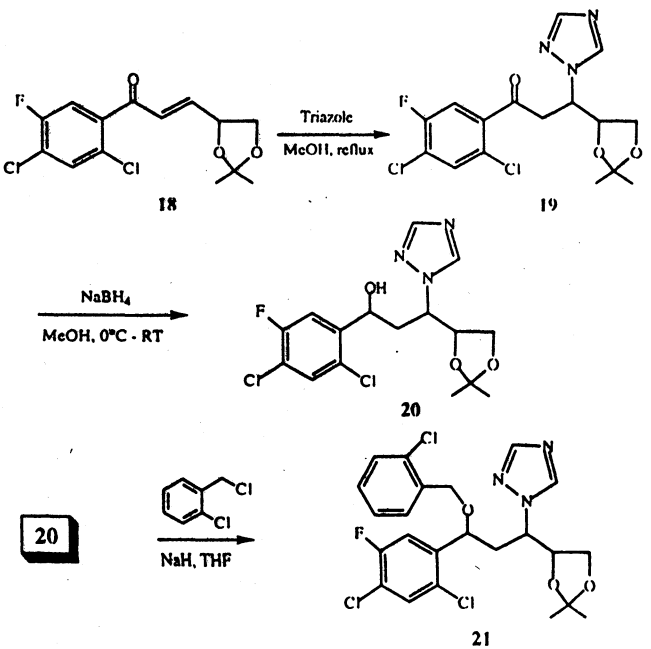
18 on reaction with triazole in methanol at reflux temperature for 12 h gave **19** in 73% yield (Scheme 5). In the ^{1}H NMR spectrum of **19**, H-2 protons (2H) appeared between δ 3.30–3.50 (m) and H-3 proton (1H) between δ 4.90–5.10 (m). **19** on reduction with sodium borohydride in methanol at 0°C to room temperature gave corresponding alcohol **20**. ^{1}H NMR spectrum of **20** showed the presence of H-1, H-3 protons between δ 3.60–5.20 as a multiplet and rest of the protons resonated at expected chemical shifts. **20** on reaction with 2-chlorobenzyl chloride, sodium hydride in THF gave corresponding benzyl ether **21** in 80% yield. In the ^{1}H NMR spectrum of **21**, H-1 and H-3 protons appeared between δ 3.50–4.50 as a multiplet and rest of the protons resonated at expected chemical shifts.

Biological activities of triazolyl derivatives

All the above synthesized triazolyl derivatives **5–9**, **13**, **14**, **16**, **17** and **19–21** were evaluated for antifungal activity at Ranbaxy Research Laboratory, New

Delhi and have been found to exhibit moderate activity against *Pseudomonas albicans*, *Aspergillus niger* and *Candida albicans* in comparison with fluconazole *in vitro* studies.

In conclusion, the author has synthesized a series of triazolyl derivatives based on structure-based drug design and found that secondary amine bearing compounds showed appreciable *in vitro* antifungal activity. Results obtained are encouraging but require to design more molecules with less toxicity. Further investigations are currently in progress to verify the susceptibility of other fungi to these compounds and to outline their pharmaco kinetic profile.



Scheme-5

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