Some new azole type heterocyclic compounds as antifungal agents

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(Received July 2, 2013; Revised December 3, 2014; Accepted December 12, 2014)

Abstract: Schiff’s base 1-[2,4-difluorophenyl]-2-(1H-1,2,4-triazol-1-yl)ethane thiosemicarbazone (compound 1A) was prepared by condensation of 1-(2,4-difluorophenyl)-2-[1 (H)-1,2,4-triazol-1-yl]ethanone (1) with thiosemicarbazide. The compound 1A, on reaction with α-halogenoketones yielded 1-(2, 4-difluorophenyl)-2-[(1H)-1,2,4-triazol-1-yl] ethanone [2-[4-halogenophenyl] thiazoly]hydrazone. Anti-fungal activity of all the compounds has been tested against four fungal organisms: C. albicans, Colletotrichum spp., A. nigarr and Fusarium spp. commonly responsible for fungal infections in Bangladesh.

Keywords: Schiff’s bases; compound 1A; 1-(2,4-difluorophenyl)-2-[1 (H)-1,2,4-triazol-1-yl] ethanone (1); α-halogenoketones; 1-(2,4-difluorophenyl)-2-[(1H)-1,2,4-triazol-1-yl] ethanone [2-[4-halogenophenyl] thiazoly] hydrazone; Anti-fungal activity. © 2014 ACG Publications. All rights reserved.

1. Introduction

Triazole compounds are getting increasing attention because of their extensive medicinal applications as antimicrobial agents particularly in antifungal therapy, and a large number of predominant triazole drugs have been successfully developed and prevalently used for the treatment of various microbial infections for many years1-3. Azoles like fluconazole, itraconazole, voriconazole, and posaconazole are important antifungal drugs for the treatment of IFIs (invasive fungal infections), which continues to be a major cause of morbidity and mortality in immune compromised or in severely ill patients5. However, fluconazole is not effective against invasive aspergillosis and has faced severe drug resistance5-6. The increasing frequency of fungal infections and development of resistance to the current treatment highlight the need for development of new triazole derivatives possessing broader antifungal spectra and higher therapeutic indexes.

Among these, the widespread diffusion of topical and systemic infectious diseases caused by the opportunistic pathogen Candida albicans is often related to the use of broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs7-8. One of the major problems in the treatment of Candida albicans infections is the spread of antifungal drug resistance, mainly in patients chronically subjected to antimycotic therapy such as HIV-infected individuals9-10.

More recently, there has been an expansion in the number of antifungal drugs available. Major classes of antifungal compounds currently in clinical use are: polyenes, azole derivatives, allylamines, thiocarbamates, echinocandins, and fluoropyrimidines11-14. Despite this growing number of antifungal agents, treatment of fungal diseases remains unsatisfactory. In a word, the limitations of current

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The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 12/31/2014 EISSN:1307-6175
antifungal drugs increased the incidence of systemic fungal infections and rapid development of drug resistance has highlighted the need for new antifungal agents with a new structure of compounds and with fewer side effects\textsuperscript{15-19}.

In particular, the azoles are important antifungal agents widely used in clinics\textsuperscript{20}. Azoles exert antifungal activity through the inhibition of cytochrome P450 14α-demethylase (CYP51), which is crucial in the process of ergosterol biosynthesis. The CYP51 enzyme contains an iron protoporphyrin unit located in its active site, which catalyzes the oxidative removal of the 14α-methyl group of lanosterol by typical monooxygenase activity\textsuperscript{21}. Azole antifungal agents bind with the iron of the porphyrin and cause the blockade of the fungal ergosterol biosynthesis pathway by preventing the access of the natural substrate lanosterol to the active site of the enzyme\textsuperscript{22}. The depletion of ergosterol and accumulation of 14α-methylated sterols alter membrane fluidity, with reduction in activity of membrane-associated enzymes and increased permeability. The net effect is to inhibit fungal growth and replication\textsuperscript{23}.

In order to study the SAR (Structure Activity Relationship) of the new compounds, we inserted halogens, alkoxy, and nitro substituted aromatic ring into the side chains.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{synthesis.png}
\caption{Synthesis of the target compounds}
\end{figure}

\section*{2. Materials and Methods}

\subsection*{2.1. Chemicals and Microorganism Material}

All the starting materials and solvents were purchased from Merck chemicals and Sigma-Aldrich companies and were used without further purification. The microorganisms were supplied by Bangladesh Atomic Energy Commissions.

\subsection*{2.2. Experimental General}

Melting points were determined on aStuart SMP-10 melting point apparatus and were uncorrected. Purity of the synthesized compounds was checked by High Performance Liquid
New azole type heterocyclic compounds as antifungal agents

Chromatography (HPLC), SHIMADZU CLASS-VP10 using MeOH:Water (1:1) as mobile phase and spectrum were recorded under ultraviolet (UV) detector at 261 nm. The IR spectra were measured as potassium bromide pellets using a SHIMADZU IR-Prestige-21 series FTIR spectrometer.

\(^1\)H-NMR & \(^{13}\)C-NMR spectra were measured on a Bruker DPX 400 (100) MHz spectrometer. Mass spectra were recorded on LCT Premier TOF MS, KD-146 (Micromass) spectrometer.

3. Experimental Section

3.1. Synthesis of 1-[(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)]ethanone thiosemicarbazone (1A):

To an acidified boiling solution of compound-1 (2.23 g, 10 mmol) in methanol (10 mL), the hot solution of thiosemicarbazide (0.914 g, 10 mmol) in methanol (50 mL) was added drop wise. The reaction mixture was refluxed on water bath for 1.0 hour. Progress of the reaction was monitored by HPLC using methanol: water (1:1) as mobile phase. After completion the resulting mixture was cooled to room temperature. The solvent was removed under vacuum at 40°C. So obtained solid mass was washed with dichloromethane followed by distilled water. The material was dried in desiccator and finally off white crystalline powder 2.6g (87.8%) was obtained. The purity of the compound was checked by HPLC using methanol: water (1:1) as mobile phase and found to be 100% pure with retention time of 5.81 min.

3.2. General procedure for the synthesis of target compounds 1B-5B: 1-[(2,4-difluorophenyl)-2-[(1H)-1,2,4-triazol-1-yl]ethanone [2-[4-(p-bromophenyl)] thiazolyl] hydrazone (1B):

To a hot solution of compound 1A (1 mmol) in methanol (5 mL) in a three necked round bottom flask, the hot solution of 4- bromophenacyl bromide (1 mmol) in methanol (10 mL) was added slowly when the colour of the solution became yellow. The reaction mixture was refluxed on a water bath for three hours. After completion the resulting mixture was cooled to room temperature and kept over night. A yellow coloured precipitate was separated. The precipitate was filtered and re-dissolved in methanol (5 mL), poured into water (5 mL) and the resulting solution was neutralized with 5% sodium carbonate solution. A cream coloured crystal was separated which was filtered and dried in a desiccator and finally an off-white coloured crystals was obtained.

The target compounds 2B-5B were synthesized by the same operation procedure of the compound 1B.

Figure 2. List of synthesized compounds
3.2.1 1-[(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)]ethane thiosemicarbazone (1A):
Melting point 163°-164°C; IR (KBr, v, cm⁻¹): 3394, 3261 cm⁻¹ (NH₂), 3169 cm⁻¹ (NH), 1608 cm⁻¹ (C=N), 1429 cm⁻¹ (C-N), 1300 cm⁻¹ (C=S), 1273 cm⁻¹ (C-F), 1029 cm⁻¹ (N-N); ¹H-NMR (DMSO-d₆, δ ppm): 10.18 (1H, br, s, NH); [8.42 (1H, d, J = 6.9 Hz), 7.89 (1H, d, J = 6.9 Hz) triazole]; 7.31-7.02. (3H, m arH, 2,4-difluorophenyl); 5.57 (2H, s, NH₂); 5.3 (2H, s, -H₂C-);
¹³C-NMR (DMSO-d₆, δ ppm): 179.5 (C = S), 158.22 (C = N); 54.49 (CH₂); [152.01 (HC-3), 145.27 (HC-5) triazole]; [120.5 (C-1), 162.14(C-2), 105.4 (HC-3), 164.6 (C-4), 112.14 (HC-5), 131.5 (HC-6), 2.4-difluorophenyl]; Mass m/z (%): (C₁₅H₁₀N₅F₂S): 297.025 [M+1]⁺ (100%) 280 (38%), 228 (9%).

3.2.2 1-(2,4-difluorophenyl)-2-[(1H)-1, 2, 4-triazol-1-yl]ethane [2-[4-(p-bromophenyl)]thiazolyl]hydrazone (1B): Yield: 524mg (55.0%); Melting point: 168°-169°C;
IR (KBr, v, cm⁻¹): 3446 cm⁻¹ (NH), 1610 cm⁻¹ (C=NH, str.), 1271 cm⁻¹ (C-F), 769 cm⁻¹ (C-Cl); ¹H-NMR (DMSO-d₆, δ ppm): 11.21 (1H, br, s, NH); [8.43 (1H, s) and 7.93 (1H, s) triazole]; [7.79 (2H, d, arH, J=8.0Hz), 7.56 (2H, d, arH, J=8.0Hz) 4-chlorophenyl]; 7.40 (1H, s thiazolyl), 7.32-7.13 (3H, m arH, 2,4-difluorophenyl); 5.31 (2H, s, -CH₂-);Mass m/z (%): (C₁₃H₁₃N₅F₂Br): 474.95/476.96, [M+1, M+2+1] (1:1) (100%).

3.2.3 1-(2,4-difluorophenyl)-2-[(1H)-1,2,4-triazol-1-yl]ethane [2-[4-(p-chlorophenyl)]thiazolyl]hydrazone (2B): White colored crystal; Yield: 265mg (61.5%); Melting point: 169°-170°C; IR (KBr, v, cm⁻¹): 3132 cm⁻¹ (NH), 1616 cm⁻¹ (C=N),1273 cm⁻¹ (C-F), 729cm⁻¹ (C-Cl); ¹¹H-NMR (DMSO-d₆, δ ppm): 11.21 (1H, br, s, NH); [8.42 (1H, s) and 7.93 (1H, s) triazole]; [7.79 (2H, d, arH, J=8.0Hz), 7.41(2H, d, arH, J = 8.40Hz), 7.14(2H, d, arH, J = 8.40 Hz) 4-chlorophenyl]; 7.31 (1H, s, thiazone), 7.29-7.10 (3H, m arH, 2,4-difluorophenyl); 5.31 (2H, s, -CH₂-); ¹¹C-NMR(DMSO-d₆, δ ppm): [152.04 (HC-3) and 145.31 (HC-5) triazole]; 54.42 (-CH₂): 160.94 (C=O); [169.1 (C-2); 158.4 (C-4); 131.47(HC-5); thiazolyl]; [116.1(C-1), 162.18(C-2), 105.21 (HC-3), 164.4 (C-4), 112.53 (HC-5) and 131.6 (HC-6) 2.4-difluorophenyl]; [139.4 (C-1); 129.05 (HC-2/ HC-6), 127.63 (HC-3/HC-5)], 133.4(C-4), 4-chlorophenyl]; Mass m/z (%): (C₁₉H₁₄N₅F₂Cl): 431.03/ 433, [M+1, M+2+1] (ratio: 3:1), 362.04 (10%).

3.2.4 1-(2,4-difluorophenyl)-2-[(1H)-1,2,4-triazol-1-yl]ethane [2-[4-(p-nitro phenyl)]thiazolyl]hydrazone (3B): Yellow colored crystal; Yield:300mg (68.0%); Melting point: 228°~ 230°C; IR (KBr, v, cm⁻¹): 3114, cm⁻¹ (NH),1597 cm⁻¹ (C=N), str.), 1564, 1342 cm⁻¹ (-NO₂), 1273 cm⁻¹ (C-F);¹¹H-NMR (DMSO-d₆, δ ppm): 11.33 (1H, br, s, NH); [8.43 (1H, s) and 7.93 (1H, s) triazole]; [8.21 (2H, d, arH, J=8.80 Hz) and 8.02 (2H, d, arH, J = 8.80 Hz) p-nitrophenyl]; 7.63 (1H, s, thiazolyl), 7.37-7.11 (3H, m arH, 2,4-difluorophenyl); 5.32 (2H, s, -CH₂-); ¹¹C-NMR(DMSO-d₆, δ ppm): [152.05 (C-3) and 145.34 (HC-5) triazole]; 54.38 (-CH₂); 161.1 (C=N); [169.3 (C-2), 158.49 (C-4); 131.57(HC-5) Thiazolyl]; [116.07 (C-1), 162.22 (C-2), 105.2 (HC-3), 164.7 (C-4), 109.53 (HC-5) and 112.57 (HC-6) 2,4-difluorophenyl]; [140.65 (C-1), 126.73 (HC₂/HC-6), 124.5 (HC₃/HC-5), 146.4 (C-4), 4-nitrophenyl];Mass m/z (%): (C₁₉H₁₄N₅F₂SO₂): 442.12, [M+1]⁺ 100%.

3.2.5 1-(2,4-difluorophenyl)-2-[(1H)-1,2,4-triazol-1-yl]ethane [2-[4-(phenyl)thiazolyl] hydrazone (4B):Brown colored crystal; Yield: 200mg (50.5%); Melting point: 78°~ 84°C;
IR (KBr, v, cm⁻¹): 3455 cm⁻¹ (NH), 1616 cm⁻¹ (C-N), 1273 cm⁻¹ (C-F); ¹¹H-NMR (DMSO-d₆, δ ppm): 10.75 (1H, br, s, NH); [8.41 (1H, s) and 7.93 (1H, s) in the triazole); 7.76 (1H, s, thiazolyl), 7.74-7.10 (8H, m, arH, phenyl); 5.29 (2H, s, -CH₂-); ¹¹C-NMR(DMSO-d₆, δ ppm):[151.7 (HC-3) and 145.09 (HC-5) triazole]; 54.23 (-CH₂): 162.0 (C=N); [169.3 (C-2), 150.01 (C-4), 131.35 (HC-5), thiazolyl]; [116.3 (C-1), 163.0 (C-2), 104.29 (HC-3), 165.0 (C-4), 105.0 (HC-5) and 112.45 (HC-6), 2,4-difluorophenyl]; [139.6 (C-1); 125.72 (HC₂/ HC-6), 128.77(HC₃/HC-5) and 127.99 (HC= phenyl); Mass m/z (%): (C₁₉H₁₄N₅F₂S): 397.012 [M+1]⁺ (100%).

3.2.6 1-(2,4-difluorophenyl)-2-[(1H)-1,2,4-triazol-1-yl]ethane [2-[4-(p-methoxyphenyl)] thiazolyl] hydrazone (5B): Yield:283mg (66.2%); Melting point: 79°~ 82°C; IR (KBr, v, cm⁻¹): 3446
cm⁻¹ (NH), 1612 cm⁻¹ (C=N), 1248 cm⁻¹ (C-H of CH₃), 1271 cm⁻¹ (C-F); ¹H-NMR (DMSO-d₆, δ ppm): [8.41 (1H, s) and 7.93 (1H, s) triazol]; [7.69 (2H, d, arH, J= 4.5 Hz) and 6.91 (2H, d, arH, J= 4.5 Hz) 4'-methoxyphenyl]; 7.02 (1H, s, C=H-S, thiazolyl); 7.30-7.09 (3H, m, arH, 2,4-difluorophenyl); 5.30 (2H, s, -CH₂), 3.71 (3H, s, -OCH₃); ¹³C-NMR (DMSO-d₆, δ ppm): [151.9 (HC=3) and 145.2 (HC=5) triazol]; 54.46 (-CH₂-); 161.0 (C=N); [169.18 (C-2), 159.17 (C-4), 131.46 (HC=5) thiazolyl]; [116.4 (C-1), 163.0 (C-2), 102.25 (HC=3), 165.0 (C-4), 105.1 (HC=5) and 112.5 (HC=6) 2,4-difluorophenyl]; [139.5 (C-1), 127.3 (HC=2/HC=6), 114.4 (HC=3/HC=5) and 159.17(C-4); 4-methoxyphenyl]; 55.57 (OCH₃);
Mass m/z (%): (C₂₀H₁₆N₆F₂SO): 427.26, [M+1⁺] (100%) 358.34 (20%) 207.43 (25%).

4. Results and Discussion

4.1. Chemistry

Among the important pharmacophores responsible for antifungal activity, the triazole scaffold is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum antifungal agents²⁸,³¹. It was reported that the primary structural requirement for the antifungal azole class are a difluorophenyl ring and a weakly basic triazole ring bonded by a nitrogen carbon linkage to the rest of the structure. So in our study we kept the basic difluorophenyl ring attached with a triazole ring unchanged.

The sequential steps involved in synthesis of compounds 1B-5B are shown in Figure 1. Formation of 1-{[(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)] ethanone thiosemicarbazide was characterized by the presence of band at 1608 cm⁻¹ due to imine(C-N) group and N-H stretching bands at 3394 and 3261 cm⁻¹ (NH₃), 3169 cm⁻¹ (NH). Further it was also supported by the presence of D₂O ex- changeable broad singlet at δ 10.18 in 1H NMR spectrum due to NH₂ group. The mass spectrum of compound 1A showed peak at m/z 297.025 which ensured the molecular ion peak and formation of 1A.

The structure of 1-{[(2,4-difluorophenyl)-2-{[(1H)-1, 2,4-triazol-1-yl] 2-[4-(p-bromophenyl)] thiazolyl] hydrazonewas assigned by the absence of N–H stretching bands at 3394 and 3261 cm⁻¹ (NH₂) and C=S stretching band at1300cm⁻¹ in IR and the presence of two doublet at δ 7.74 and at 7.56 corresponding to protons of the 4-bromophenyl group and peak around δ 7.40 corresponding to a proton of thiazolyl ring in the ¹H-NMR spectrum, along with the other expected signals. Finally the two molecular ion peaks at m/z 474.95 and m/z 476.96 (1:1) in mass spectrum due to the presence of bromine atom confirmed the formation of 1B.

Formation of 1-{[(2,4-difluorophenyl)-2-{[(1H)-1,2,4-triazol-1-yl]ethanone [2-[4-(p-chlorophenyl)] thiazolyl]hydrazonewas confirmed by the presence of band at 729 cm⁻¹ in IR spectrum, due to C-Cl stretching. In mass spectrum the two molecular ion peaks at m/z 431 and m/z 433 (1:3) due to the presence of chlorine atom confirmed the formation of 2B.

The IR spectrum of 1-{[(2,4-difluorophenyl)-2-{[(1H)-1, 2,4-triazol-1-yl]ethanone [2-[4-(p-nitro phenyl)]thiazolyl]hydrazonewas contained 2 absorption bands originated from –NO₂ groups at 1564 cm⁻¹ and 1342 cm⁻¹. In the ¹H-NMR spectrum, a broad singlet signal belonging to the amino groups appeared at 11.33 ppm integrating for 1 proton (controlled with changing by D₂O) and a singlet at 7.63 ppm integrating for 1 proton in s thiazolyl ring. In addition, mass spectrum containing a peak at m/z 444.15 corresponding to the molecular weight of the molecular formula C₁₉H₁₁₁₃N₆F₂SO₂ of the assigned structure.

In mass spectrum the molecular ion peak appearing at m/z 399.089 consistent with the assigned structures of compound 4B.

In the ¹H-NMR spectrum of compound 1-{[(2,4-difluorophenyl)-2-{[(1H)-1,2,4-triazol-1-yl]ethanone [2-[4-(p-methoxyphenyl)] thiazolyl]hydrazone, the signal derived from –OCH₃ group were recorded at 3.71 ppm. This group resonated at 55.43 ppm in the ¹³C-NMR spectrum. Furthermore, compounds 5B gave molecular ion peak at m/z (%): 427.26, [M+1⁺] (100%) consistent with the assigned structure.
4.2 Antifungal Activity (In vitro)

Fluconazole is a bis-triazole antifungal drug with novel pharmacokinetic properties (metabolic stability, relatively high water solubility) which contribute to its therapeutic activity. Fluconazole has good GIT (gastrointestinal)absorption, and is renally excreted. Fluconazole has no post-antifungal effect. Fluconazole is mainly used for C. albicans infection. Fluconazole is also effective against Cryptococcus neoformans meningitis and Coccidiodomycosis. Itraconazole is most active against Aspergillus spp. and has greater activity than fluconazole against resistant strains of Candida spp. other than C. albicans.

Voriconazole is the newest agent in the armamentarium against fungal infections. It is also a triazole antifungal with a structure related to that of fluconazole and a spectrum of activity comparable to that of itraconazole. Voriconazole was approved by the FDA (Food and Drug Administration) in May 2002 for the treatment of invasive aspergillosis and refractory infections of Scedosporium apiospermum and Fusarium spp. It is also effective against::Histoplasma, Coccidioides, Blastomyces, Paracoccidioides, Cryptococcus, and dermatophytes, Scedosporium apiospermum, Pseudallescheria boydii, Penicillium marneffei, Fusarium spp, Acremonium strictum.

For antifungal screening assay four fungal strains were selected viz. C. albicans, Colletotrichum spp.A. niger and Fusarium spp. Antifungal activity of test compounds were carried out in Sabouraud Dextrose Agar media by diffusion method. Briefly, stock solution (100 µg/mL concentration) of synthesized test compounds and standard (Fluconazole) were prepared in methanol and phosphate buffer. 2.4 gm of Potato-Dextrose broth and 2gm of Agar were dissolved in 100 mL distilled water and then sterilized at 15 lbs pressure and 121°C for 15 min. The sterilized medium was poured in sterile Petri dishes. Medium was then inoculated by streaking of the fungal culture dipped cotton swab over the entire surface of the plate. After the inoculums were dried, wells (bores) were made on the medium using sterile borer. Then 100µL of the test and standard solutions (100µg/mL concentration) were added to the respective bores. Methanol was used as control. Plates were incubated for 18 hr. at 37 °C and the antifungal activity was determined by measuring the zone of inhibition. The data of antifungal activity of the synthesized compounds (1B-5B) at 100 µg/mL concentration, against the micro-organism is shown in Table 1.

<table>
<thead>
<tr>
<th>Test Organism</th>
<th>Conc. in (µg/mL)</th>
<th>Zone of inhibition (mm) of action of the compounds.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
<td>1A</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>100</td>
<td>18.5</td>
</tr>
<tr>
<td>Aspergillus niger</td>
<td>100</td>
<td>22.0</td>
</tr>
<tr>
<td>Colletotrichum spp.</td>
<td>100</td>
<td>22.3</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>100</td>
<td>22.9</td>
</tr>
</tbody>
</table>

Compounds which had a diameter of greater than zero inhibition zones against one or more of the micro-organisms were considered to be active.

The result suggests that of the 5 compound tested against the four fungal isolates: C. albicans, Colletotrichumspp., A. niger and Fusarium spp. Compound 2B and 4B found to be active against all of the micro-organisms tested. Compound 1B, 3B and 5B can be considered to be inactive.

Considering Fluconazole with inhibition zone of diameter 18.5 mm, compound 2B with diameter 20.4mm was found to be more active against C. albicans.

Compound 2B with inhibition zone of diameter 22.4mm found to be more active than Fluconazole with diameter of 22.0mm against A. niger.
Against Colletotrichum spp. compound 4B with inhibition zone of diameter 24.9 mm found to more active than standard Fluconazole with diameter of 22.3 mm.

Compound 2B found to be more effective against C. albicans, A. nigand Fusarium spp.; Compound 4B was more effective than compound 2B against Colletotrichum spp.

**Figure 3.** The comparative zone of inhibition of various compounds

5. Conclusion

Much work has been carried out on triazoles as antifungal agents and many drugs with triazole nucleus having antifungal properties have come into market (e.g. Fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, ravuconazole and posaconazole). This work represents the synthesis of 1,2,4 triazole derivatives and their pharmacological profiles which may contribute in future to synthesize various analogs and to develop new pharmacologically lesstoxic medicines.

Supporting Information

Supporting Information accompanies this paper on [http://www.acgpubs.org/OC](http://www.acgpubs.org/OC)

Acknowledgements

Special thanks to Bangladesh Atomic Energy Commissions for their supply of the microorganisms and support to conduct experiments regarding anti-fungal activities.
References


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