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속 보

우수한 항균 활성을 나타내는 aryl phenyl ether pyrazole 계 화합물의 합성

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Synthesis of Novel Pyrazole Derivative Containing Aryl Phenyl Ether as Potential Antifungal Agent

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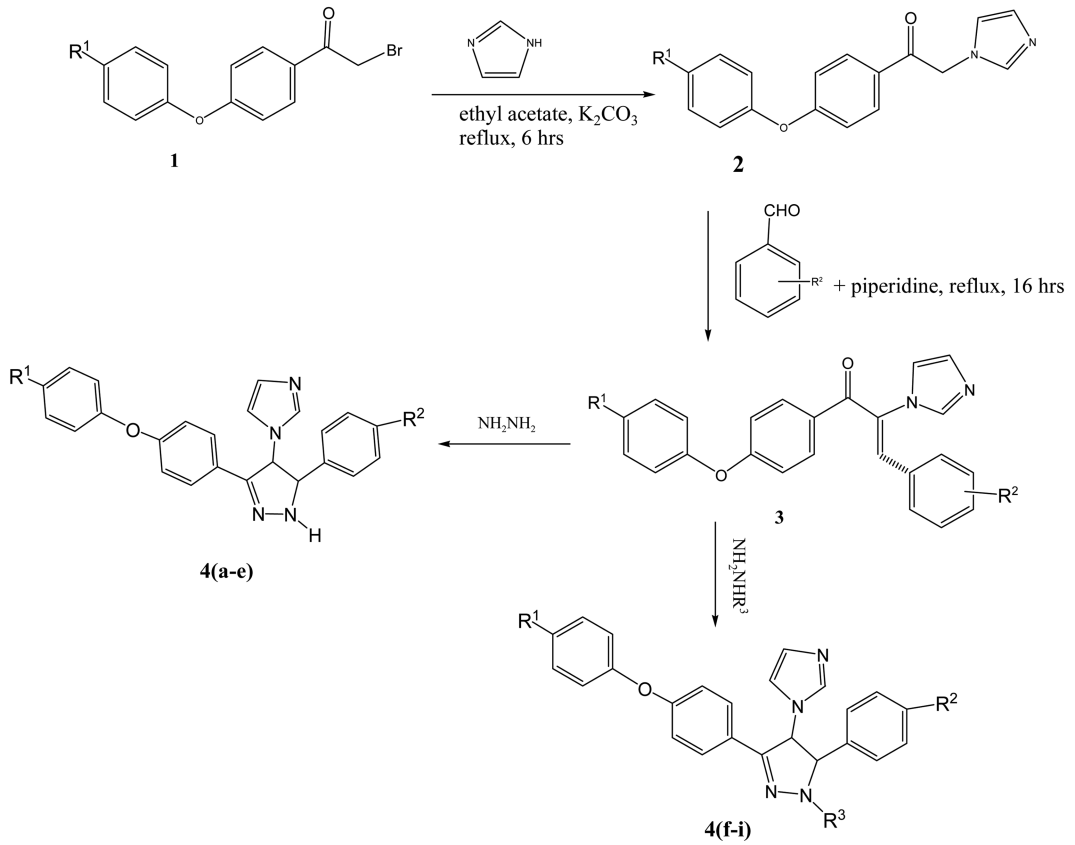
The incidence of invasive fungal infections caused by opportunistic pathogens, often characterized by high mortality rates, has been increasing over the past two decades. Patients that become severely immunocompromised because of underlying diseases such as leukemia or, recently, acquired immunodeficiency syndrome or patients who undergo cancer chemotherapy or organ transplantation are particularly susceptible to opportunistic fungal infections.[1] A matter of concern in the treatment of fungal infections is the limited number of efficacious antifungal drugs. Many of the currently available drugs are toxic, produce recurrence because they are fungistatic and not fungicides or lead to the development of resistance due in part to the prolonged periods of administration of the available antifungal drugs. There is, therefore, a clear need for the discovery of new structures with antifungal properties, which could lead to the development of new drugs for the management of fungal infections and treatment of systemic mycoses.[2]

Up to only 30 years ago the choice of systemically available antimycotics was between two drugs, amphotericin B and flucytosine, neither of which was satisfactory. Then a series of inhibitors of the biosynthesis of ergosterol, the major sterol of the fungal cell membrane, were found to have excellent antifungal activity, improved safety, and some were also active after oral or parenteral application. Starting with miconazole and ketoconazole, and improving through fluconazole and itraconazole, the imidazole and triazole inhibitors of lanosterol l4α-ademethylation have been the most successful. Although the use of a new generation of triazoles, the available polyenes in lipid formulations, the use of echinocandins or the combination therapy have been introduced as alternatives in the last 10 years, the number of available preparations to treat systemic fungal infections is still limited and more alternatives are needed, particularly with improved efficacy against emerging pathogens with limited susceptibility to the available preparations.[3]

We find out that the imidazole derivatives have shown potent antifungal activity associated with good antimycobacterial activity.[4] In addition, aryl phenyl ether group is a widely used in pesticide and drug molecular design.[5] With the reference to above information and help of bioisoterism, we have synthesized a series of compounds in which the imidazole moiety is directly linked at position 4 and aryl phenyl ether at the position 3 of pyrazole ring to improve antifungal activity.

RESULTS AND DISCUSSION

The synthesis of compound **4 (a-i)** was carried out via a three step reaction which involves an *N*-alkylation of imidazole with the substituted bromoacetopheone **1 (a-i)**. This affords the corresponding 1-[4-(4-Chloro-phenoxy)-phenyl]-2-imidazol-1-yl-ethanone, **2 (a-i)**, in accordance with literature[6] procedure. Compound **2 (a-i)** on condensation with substituted benzaldehyde gave α,β-unsaturated ketones **3 (a-i)**. These compounds, when treated with



***Scheme* 1.**

hydrazine or substituted hydrazine, gave titled compounds **4 (a-i)** (*Scheme* 1).

In vitro antifungal activity was measured by means of the minimal inhibitory concentrations (MIC) using the serial dilution method in 96-well micro test plates. Fungal strains used in test were obtained from the ATCC or clinical isolates. The MIC determination was performed according to the national committee for clinical laboratory standards (NCLCC) recommendations. The results of antifungal activities of the target compounds in vitro are listed in *Table* 1.

The antifungal activity of compounds **4c**, **4d**, **4h**, and **4i** were remarkable reaching MIC values of 0.06 μg/mL even at 48 hrs for *C. albicans*. and 1.00 μg/mL even at 48 hrs

***Table* 1.** Activity of compound **4 (a-i)** against *A. Niger* and *C. Albicans*

Compounds	R^1	R^2	R^3	*A. niger* (MIC μg/mL)		*C.albicans* (MIC μg/mL)	
				24 hrs	48 hrs	24 hrs	48 hrs
Miconazole	-	-	-	1.00	2.00	0.06	0.12
Amphotericin B	-	-	-	4.00	6.00	1.00	1.00
4a	Cl	OCH_3	H	8.00	32.00	4.00	20
4b	Cl	$NHCH_3$	H	20	64	16	>64
4c	Cl	Br	H	1.00	3.00	0.06	0.06
4d	Cl	Cl	H	1.00	1.00	0.06	0.06
4e	Cl	CH_3	H	10	20	8	16
4f	Cl	OCH_3	CH_3	14	64	8	64
4g	Cl	$NHCH_3$	CH_3	20	64	2	64
4h	Cl	Br	CH_3	1.00	3.00	0.06	0.06
4i	Cl	Cl	CH_3	1.00	1.00	0.06	0.06

for *A. niger*. Their activities were superior to that of the reference drug Amphotericin B and Miconazole. From the obtained data it seems that the presence of the electron-withdrawing group chloro or bromo groups at the *para* position in the phenyl residue enhances the activity. Moreover, synthesized compounds show better activity for *C. albicans*. Finally, concluded that by introduction of aryl phenyl ether group in imidazole derivatives, a new type of fungicidal candidate was synthesized and activity is enhanced.

EXPERIMENTAL

To a solution of 2-Bromo-1-[4-(4-chloro-phenoxy)-phenyl]-ethanone (0.1 mol) and imidazole (0.12 mol) in ethyl acetate (70 mL) was added potassium carbonate (0.12 mol), the resulting mixture was refluxed for 6 hours and the filterate was condensed. The residue was recrystallized with ethyl acetate to give compound **2**.

To a solution of compound **2** (10 mmol), 80 mL of toluene, 4-substituted benzaldehyde (13 mmol) and piperidine were added. The reaction mixture was stirred under reflux for 16 hrs. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$ (300 mL) and the organic phase was washed with distilled water. The collected organic phase were dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was crystallised from diethyl ether.

To an ethanolic solution of compound **3** (5 mmol), hydrazine (6 mmol) or methyl hydrazine sulphate (6 mmol) was added with stirring. The reaction was allowed to stirring at room temperature and monitored by T.L.C. The solvent was evaporated under reduced pressure and solid obtained was recrystallized from diethyl ether.

4a: mp 173-175 ºC; yield 54%, ^{1}H NMR ($CDCl_3$, TMS): δ 3.73 (s, 3H, OCH_3), 4.80 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} = 6.10 Hz), 5.54 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 6.10 Hz), 6.41 (s, broad signal, 1H, NH, disappearing on deuteration), 6.86-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 56.0, 70.0, 73.2, 117.4, 118.7, 126.4, 126.9, 127.2, 128.6, 129.2, 129.5, 129.7, 130.7, 131.8, 134.4, 136.8, 139.4, 145.7, 154.2.

4b: mp 177-178 ºC; yield 61%, ^{1}H NMR ($CDCl_3$, TMS): δ 2.78 (d, 3H, NCH_3), 4.0 (q, $NHCH_3$), 4.80 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} = 6.10 Hz), 5.54 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 6.10 Hz), 6.41 (s, broad signal, 1H, NH, disappearing on deuteration), 6.86-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 35.3, 70.0, 73.2, 117.4, 118.7, 126.4, 126.9, 127.2, 128.6, 129.2, 129.5, 129.7, 130.7, 131.8, 134.4, 136.8, 139.4, 145.7, 154.2.

4c: mp 159-161 ºC; yield 59%, ^{1}H NMR ($CDCl_3$, TMS): δ 4.79 (dd, 1H, CH, H_5 pyrazole, J_{H5-H4} = 5.86 Hz; J_{H5-NH} = 2.20 Hz), 5.54 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 5.86 Hz), 6.46 (d, 1H, NH, disappearing on deuteration; J_{NH-H5} = 2.20Hz), 6.94-7.61 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 70.0, 73.2, 116.9, 118.7, 125.8, 126.4, 126.9, 127.8, 128.6, 129.5, 129.7, 130.7, 131.8, 136.8, 139.4, 145.7, 154.2.

4d: mp 170-171 ºC; yield 49%, ^{1}H NMR ($CDCl_3$, TMS): δ 4.80 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} = 6.10 Hz), 5.54 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 6.10 Hz), 6.41 (s, broad signal, 1H, NH, disappearing on deuteration), 6.86-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 70.0, 73.2, 117.4, 118.7, 126.4, 126.9, 127.2, 128.6, 129.2, 129.5, 129.7, 130.7, 131.8, 134.4, 136.8, 139.4, 145.7, 154.2.

4e: mp 175-177 ºC; yield 56%, ^{1}H NMR ($CDCl_3$, TMS): δ 2.35 (s, 3H, CH_3), 4.80 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} = 6.10 Hz), 5.54 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 6.10 Hz), 6.41 (s, broad signal, 1H, NH, disappearing on deuteration), 6.86-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 20.0, 70.0, 73.2, 117.4, 118.7, 126.4, 126.9, 127.2, 128.6, 129.2, 129.5, 129.7, 130.7, 131.8, 134.4, 136.8, 139.4, 145.7, 154.2.

4f: mp 149-151 ºC; yield 58%, ^{1}H NMR ($CDCl_3$, TMS): δ 2.96 (s,3H, CH_3), 3.73 (s, 3H, OCH_3), 4.16 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} = 10.98Hz), 5.55 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 10.98Hz), 6.92-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 41.5, 56.0, 71.3, 80.7, 117.3, 118.7, 125.8, 126.3, 126.9, 127.7, 128.6, 128.7, 129.5, 130.9, 131.9, 136.7, 139.4, 145.9, 154.2.

4g: mp 143-145 ºC; yield 69%, ^{1}H NMR ($CDCl_3$, TMS): δ 2.78 (d, 3H, $NHCH_3$), 2.96 (s,3H, CH_3), 4.0 (q,1H, NH), 4.16 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} = 10.98Hz), 5.55 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 10.98Hz), 6.92-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 35.3, 41.5, 71.3, 80.7, 117.3, 118.7, 125.8, 126.3, 126.9, 127.7, 128.6, 128.7, 129.5, 130.9, 131.9, 136.7, 139.4, 145.9, 154.2.

4h: mp 148-150 ºC; yield 73%, ^{1}H NMR ($CDCl_3$, TMS): δ 2.96 (s, 3H, CH_3), 4.16 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} = 10.98 Hz), 5.55 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 10.98 Hz), 6.92-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 41.5, 71.3, 80.7, 117.3, 118.7, 125.8, 126.3, 126.9, 127.7, 128.6, 128.7, 129.5, 130.9, 131.9, 136.7, 139.4, 145.9, 154.2.

4i: mp 136 ºC; yield 51%, ^{1}H NMR ($CDCl_3$, TMS): δ 2.95 (s, 3H, CH_3), 4.17 (d, 1H, CH, H_5 pyrazole, J_{H5-H4} =

10.98 Hz), 5.54 (d, 1H, CH, H_4 pyrazole, J_{H5-H4} = 10.98 Hz), 6.84-7.60 (m, 15H, 12H arom. and 3H imidazole). ^{13}C NMR ($CDCl_3$, TMS): δ 41.5, 71.6, 80.7, 117.4, 118.7, 126.4, 126.9, 127.0, 128.6, 129.3, 129.5, 129.7, 130.7, 121.9, 134.5, 136.8, 139.9, 145.8, 154.2.

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