Biological Evaluation of 2, 5-Di (4 Aryloylaryloxy Methyl) - 1, 3, 4-Oxadiazoles Derivatives as Antimicrobial Agents

Yasser Hussein Eissa Mohammed1,2, Gurupadaswamy HD1 and Shaukath Ara Khanum1

1Department of Chemistry, Yuvaraja’s College, University of Mysore, Mysore, Karnataka, India
2Department of Biochemistry, Applied Science College, University of Hajja, Yemen

Abstract

A series of potential biologically active substituted 2,5-di(4 aryloylaryloxy methyl)-1,3,4-oxadiazoles 9a-j were evaluated for its potential antimicrobial activity comparing with the standard drugs Streptomycin and Ketoconazole respectively. Compound 9a with fluoro group exhibited highest activity against both gram-positive and gram-negative bacteria. Compounds 9a with fluoro group and 9c with fluoro and bromo showed good activity against antifungal activities.

Keywords: 1,3,4-Oxadiazoles; Synthesis; Antibacterial; Antimicrobial

Introduction

Infection of microbes is a serious problem in modern medicine. Among the most purchased drugs, antimicrobials drugs are usually used worldwide. Such a necessary treatment is needed especially in the upcoming world where infectious diseases are a common cause of death. An alarming level has been reached by the new emerging drug resistant micro-organisms around the world causing life-threatening infectious diseases. Recently, the wound infections, blood stream infections are caused by the Staphylococcus aureus and that of Diarrhoea (“bacillary dysentery”) by the Shigella species [1]. An increasing number of immuno-compromised patients as a result of HIV infection, cancer chemotherapy and organ transplantation is also one of the major factors contributing to the increasing use of antimicrobial drugs. Also, the smart arising claim for the material protection from microbial infection has paved the way for the pharmacological research [2,3]. The above-mentioned fact is the cause for a great concern creating a insistent need for new anti-microbial agents. Despite of great effort from the pharmaceutical industry to manage the resistance problem, the discovery and development of new mechanistic classes of antibiotics has found very little success [4]. The difficulty of this task has been demonstrated by the fact that only two antibiotics of new classes, linezolid (an oxazolidinone) and daptomycin (a cyclic lipopeptide), have been successfully developed in the past three decades [5,6]. In the past 20 years, the incidence of microbial infection has reached a peak level over the world as a result of resistance against the drugs. The health problems pose to explore and synthesize a novel class of antimicrobial species effective against pathogenic microorganisms that has developed resistance to the antibiotics in the current regimen [3,7]. However, additional mutations may compensate for this fitness cost and aids the survival of these bacteria. Hence, the search for a new and potent antimicrobial agents is gaining interest. When the era of synthetic drugs began, it opened up thousand doors for the development of various synthetic molecules with a potential action. The compounds with the backbone of benzophenones have been reported to possess various biological activities such as anticancer [8] antimicrobial [9] antioxidant [10].1,3,4-Oxadiazole ring is associated with many types of biological properties such as anti-inflammatory [11-13], hypoglycemic [14], antifungal and antibacterial [15-19] activities. 1,3,4-Oxadiazoles and its derivatives have a broad range of biological and pharmacological properties and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and substrates for the drug synthesis. Some of its derivatives show a wide range of biological and pharmacological activity, such as anticancer [8,20] antiviral activities [21]. Prompted by these, the present paper emphasizes on the synthesis, characterization and antimicrobial evaluation of 2,5-di(4 aryloylaryloxy methyl)-1,3,4-oxadiazoles derivatives. All the synthesized compounds were characterized on the basis of their physical properties IR, 1H and 13C NMR spectral data and elemental analysis. The physical data of titled compounds are summarized and present in the result and discussion part.

Materials and Methods

Experimental section

All solvents and reagents were purchased from Sigma Aldrich chemicals Pvt ltd. TLC was performed on aluminum-backed silica plates and visualized by UV-light. Melting points (M.P) were determined on an electrically heated VMP-III melting point apparatus. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 elemental analyzer. The results of elemental analyses were within ± 0.4% of the theoretical values. The FT-IR spectra were recorded using KBrs discs and Nujol on FT-IR Jasco 4100 infrared spectrophotometer. 1H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer in CDCl3 or DMSO and the chemical shifts were recorded in parts per million downfi ld from tetramethylsilane. Mass spectra were recorded on LC-MS (API-4000) mass spectrometer. MTT was purchased from Sigma Aldrich, USA and CD31 antibodies were procured from Santa Cruz, USA.

Synthesis

General procedure for substituted arylbenzoates (3a-e): 2-Chloro-6-fluoro phenol (1, 0.2054 mol) was dissolved in DCM, triethylamine (TEA, 0.4519 mol) was added and the reaction mixture was cooled to 0°C. A solution of benzoyl chloride derivatives (2a-e, 0.2157 mol) in DCM was added slowly to the above mixture and

*Corresponding author: Shaukath Ara Khanum, Department of chemistry, Yuvaraja’s College, University of Mysore, Mysore, Karnataka, India, Tel: +919901888755; E-mail: shaukatara@yahoo.co.in

Received March 03, 2017; Accepted April 06, 2017; Published April 10, 2017

Citation: Eissa Mohammed YH, Gurupadaswamy HD, Khanum SA (2017) Biological Evaluation of 2, 5-Di (4 Aryloylaryloxy Methyl) - 1, 3, 4-Oxadiazoles Derivatives as Antimicrobial Agents. Med Chem (Los Angeles) 7: 837-843. doi: 10.4172/2161-0444.1000438

Copyright: © 2017 Eissa Mohammed YH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
stirred for 3 h. Then the reaction mass was diluted with DCM (200 mL), washed with 10% sodium hydroxide solution (3 × 30 mL), water (3 × 30 mL), brine (2 × 60 mL), and again with water (3 × 30 mL). The organic layer was dried over sodium sulfate and the solvent was evaporated to achieve compounds 3a-e [8].

Synthesis of 2-chloro-6-fluorophenyl-4-fluorobenzoate (3a): 2-Chloro-6-fluoro phenol (1, 30 g, 0.2054 mol) was dissolved in DCM, triethylamine (TEA, 45.73 g, 0.4519 mol) was added and the reaction mixture was cooled to 0°C. A solution of 4-fluorobenzyl chloroide (2a, 33.9 g, 0.2157 mol) in DCM was added slowly to the above mixture and internal temperature was maintained to 0-10°C. Finally the reaction mixture was stirred at ambient temperature for 3 h. Then the reaction mass was diluted with DCM (200 mL), washed with 10% sodium hydroxide solution (3 × 30 mL), water (3 × 30 mL), brine (2 × 60 mL), and again with water (3 × 30 mL). The organic layer was dried over sodium sulfate and the solvent was evaporated to achieve compound 3a as white solid. Yield: 94%; m.p.: 52.6-54.1°C; IR (KBr) nmax (cm⁻¹): 1738 (ester, C=O); 1H NMR (400 MHz) (DMSO-d₆) d (ppm): 7.42-7.53 (m, 4H, Ar-H), 8.25-8.28 (m, 3H, Ar=H); MS (EI): m/z (75%) M⁺ 281.5; Anal. Calcd. for C₁₃H₇ClF₂O₂ (281.5): C, 58.12; H, 2.63; Cl, 13.20; F, 14.14. Found: C, 58.21; H, 2.52; Cl, 13.20; F, 14.29%. Compounds 3b-e were synthesized analogously starting with 2b-e respectively by same method [8].

General procedure for (4-hydroxyaryl)aryl methanones (4a-e): Compound 3a (0.1903 mol) and aluminum chloride (0.5388 mol) were blended and the mixture was heated to 150°C and this temperature was maintained for 1 h. Then the reaction mixture was cooled to 0°C and quenched with 6 N hydrochloric acid (200 mL) and extracted with DCM (3 × 100 mL). The organic layer was washed with water (3 × 40 mL), brine (3 × 30 mL) and again with water (3 × 40 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated to afford compounds 4a-e.

Synthesis of (3-chloro-5-fluoro-4-hydroxyphenyl)-4-fluorophenyl methanone (4a): Compound 3a (5 g, 0.1903 mol) and aluminum chloride (71.05 g, 0.5388 mol) were blended and the mixture was heated to 150°C and this temperature was maintained for 1 h. Then the reaction mixture was cooled to 0°C and quenched with 6 N hydrochloric acid (200 mL) and extracted with DCM (3 × 100 mL). The combined organic layer was washed with water (3 × 30 mL), brine (3 × 30 mL) and again with water (3 × 40 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated to afford compound 4a as pale yellow solid. Yield: 61%; m.p.: 146.3-147.7°C; IR (KBr) nmax (cm⁻¹): 1761 (C=O); 3545-3635 (OH); 1H NMR (400 MHz) (DMSO-d₆) d (ppm): 7.36-7.82 (m, 6H, Ar=H), 11.64 (bs, 1H, OH). MS (EI): m/z (83%): M⁺ + 268.5; Anal. Calcd. for C₁₃H₁₁ClF₂O₂ (268.5): C, 58.12; H, 2.63; Cl, 13.20; F, 14.14. Found: C, 58.21; H, 2.52; Cl, 13.20; F, 14.25%. Compounds 4b-e were synthesized analogously starting with 2b-e respectively by same method [8].

General procedure for ethyl 4-aryloylaryloxyacetates (5a-e): To a solution of compounds 4a-e (0.01156 mol) in dry DMF (175 mL), potassium carbonate (0.3468 mol) and ethyl bromoacetate (0.1273 mol) were added and the reaction mass was heated to 60°C for 3 h. The reaction mass was diluted with ethyl acetate (200 mL), potassium carbonate was filtered off and the bed was washed with ethyl acetate (100 mL). The organic layer was washed with water (3 × 30 mL), brine (2 × 40 mL), dried over sodium sulfate and concentrated to yield compounds 5a-e.

Synthesis of ethyl [2-(4-fluorobenzoyl)-2-chlоро-6-fluorophenoyl] acetate (5a): To a solution of compound 4a (31 g, 0.1156 mol) in dry DMF (175 mL), potassium carbonate (47.83 g, 0.3468 mol) and ethyl bromoacetate (21.11 g, 0.1273 mol) were added and the reaction mass was heated to 60°C and maintained for 3 h. The reaction mass was diluted with ethyl acetate (200 mL), potassium carbonate was filtered off and the bed was washed with ethyl acetate (100 mL). The organic layer was washed with water (3 × 30 mL), brine (2 × 40 mL), dried over sodium sulfate and concentrated to yield compound 5a as brown pasty mass. Yield: 97%; IR (KBr) nmax (cm⁻¹): 1660 (C=O), 1730 (ester, C=O); 1H NMR (400 MHz) (DMSO-d₆) d (ppm): 1.16-1.22 (t, 3H, CH₃), 4.14-4.21 (q, 2H, CH₂), 5.02 (s, 2H, OCH₂), 7.64-7.8 (m, 6H, Ar=H). MS (EI): m/z (59%): M⁺ + 340.5; Anal. Calcd. for C₁₃H₁₁ClF₂O₂ (340.5): C, 57.56; H, 3.69; Cl, 9.99; F, 10.71. Found: C, 57.41; H, 3.52; Cl, 9.79; F, 10.88%. Compounds 5b-e were synthesized analogously starting with 4b-e respectively by same method [8].

General procedure for 4-aryloxy-aryloxyethanoloic acids (6a-e): A mixture of compounds 5a-e (0.0532 mol), 10% aqueous sodium hydroxide solution (100 mL) and THF (100 mL) was stirred at room temperature for 1 h. The reaction mass was acidified with 6 N hydrochloric acid (150 mL) and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with brine (3 × 60 mL), dried over anhydrous sodium sulfate and concentrated to achieve compounds 6a-e.

Synthesis of [4-(4-fluorobenzoyl)-2-chloro-6-fluorophenoyethyl] acid (6a): A mixture of compound 5a (18 g, 0.0532 mol), 10% aqueous sodium hydroxide solution (100 mL) and THF (100 mL) was stirred at room temperature for 1 h. The reaction mass was acidified with 6 N hydrochloric acid (150 mL) and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with brine (3 × 60 mL), dried over anhydrous sodium sulfate and concentrated to achieve compounds 6a.

General procedure for 4-aryloxyaryloxyacethydrazides (7a-e): To a solution of compound 5a (16.90 g, 0.3372 mol) in ethanol (100 mL) at 0°C and stirred the reaction mixture at the same temperature for 1 h. A white solid was separated out, which was quenched with water (100 mL), filtered and washed with water (50 mL). Finally, solid was dried under vacuum to obtain compounds 7a-e.

Synthesis of 2-[4-(4-fluorobenzoyl)-2-chloro-6-fluorophenoyl] acethyldrazide (7a): Hydrazine hydrate (0.3372 mol) was added to a solution of compounds 6a (0.0562 mol) in ethanol (100 mL) at 0°C and stirred the reaction mixture at the same temperature for 1 h. A white solid was separated out, which was quenched with water (100 mL), filtered and washed with water (50 mL). Finally, solid was dried under vacuum to obtain compounds 7a-e.
General procedure for N,N-di[2-(4-aryloylaryloxy)acetyl] hydrazines (8a-j): To a solution of compounds 6a-e (0.0032 mol) in DCM (20 mL), 2,6-dimethylpyridine (0.0107 mol) and TBTU (0.00323 mol) were added at room temperature. Finally, compounds 7a-e (0.00294 mol) were added to the reaction mixture and stirred at room temperature for 12 h. The reaction mixture was quenched with 10% sodium bicarbonate solution (20 mL) and stirred for 30 min. The solid precipitate was filtered, washed with water (20 mL) and dried to yield compounds 8a-j.

Synthesis of N,N-di[di(2-chloro-6-fluoro-4-(4-fluoro-benzoyl) phenoxyl)acetyl] hydrazide (8a): To a solution of compound 6a (1.05 g, 0.0032 mol) in DCM (20 mL), 2,6-dimethylpyridine (1 g, 0.0107 mol) and TBTU (1.04 g, 0.00323 mol) were added at room temperature. Finally, compound 7a (1 g, 0.00294 mol) was added to the reaction mixture and stirred at room temperature for 12 h. The reaction mixture was quenched with 10% sodium bicarbonate solution (20 mL) and stirred for 30 min. The solid precipitate was filtered, washed with water (20 mL) and dried to yield compound 8a as white solid. Yield: 81%; m.p.: 194.8-196.2°C; IR (KBr) nmax (cm⁻¹): 3299 (N-H), 1690 (C=O), 1610 (amide, C=O), 3700-3500 (NH-NH); ¹H NMR (400 MHz) (DMSO-d₆) δ (ppm): 4.90 (s, 4H, 2CH₂), 7.1-7.87 (m, 12H, Ar-H), 10.36 (bs, 2H, NH). MS (EI): m/z (61%): M+1 649; Anal. Calcd. For C₃₀H₁₈Cl₂F₄N₂O₆: C, 57.07; H, 2.55; N, 4.44. Found: C, 57.17; H, 2.47; N, 4.36%.

Similarly compounds 8b-j were synthesized starting from compounds 6b-e and 7a-e by same method [8].

General procedure for 2,5-di-(4-aryloyl oxy methyl)-1,3,4-oxadiazoles (9a-j): To a solution of compounds 8a-j (0.0023 mol) in DCM (20 mL), pyridine (0.0069 mol) and triflic anhydride (0.0051 mol) were added at 0°C and the reaction mixture was stirred at 0°C for 3 h. The reaction mass was diluted with DCM (20 mL), the organic layer was washed with 10% sodium bicarbonate (3 × 10 mL), water (3 × 10 mL) and brine (3 × 10 mL). Finally, the organic layer was dried over sodium sulfate and concentrated to yield compounds 9a-j.

Synthesis of 2,5-di[2-fluoro-4-(4-fluoro) benzoyl-6-chlorophenoxymethyl]1,3,4-oxadiazole (9a): To a solution of compound 8a (1.5 g, 0.0023 mol) in DCM (20 mL), pyridine (0.0069 mol) and triflic anhydride (0.0051 mol) were added at 0°C and the reaction mixture was stirred at 0°C for 3 h. After the completion of the reaction monitored by TLC, the reaction mass was allowed to dry for 10 mins. The tests were conducted at 1000 µg/disc. The loaded discs were placed on the surface of the medium and left for 30 min at room temperature for compound diffusion. Negative control was prepared using respective solvent. Streptomycin (10 µg/disc) was used as positive control. The plates were incubated for 24 h at 37°C for bacteria and for 48 h at 27°C for fungi. Zone of inhibition was recorded in millimeters and the experiment was repeated twice.

Results and Discussion

Chemistry

The synthesis of the hitherto unreported title compounds is as outlined in Scheme 1. (4 Hydroxyaryl)aryl methanes commonly known as hydroxybenzophenones 4a-e were achieved in excellent yield using benzoylation of compound 1 with benzoyl chloride derivatives 2a-e followed by Fries rearrangement of substituted arylbenzoates 3a-e. Compounds 4a-e on reaction with ethyl bromoacetate afforded ethyl 4-aryloxyoxacycates 5a-e which on treatment with sodium hydroxide in presence of THF gave 4- aryloxyoxacytonic acids 6a-e. Further, compounds 5a-e on treatment with hydradine hydrate in the presence of ethanol yield 4-aryloxyoxacyethylhydrazides.
7a-e. Condensation of 6a-e with 7a-e in the presence of 2,6-lutidine, O-(benzotriazol-1-yl)-N,N,N0,N0-tetramethyluronium tetrafluoroborate (TBTU) and dichloromethane (DCM) afforded N,N-di(2-(4-aryloylaryloxy) acetyl)hydrazines 8a-j. Finally, title compounds 9a-j were achieved by intramolecular cyclization of 8a-j in the presence of triflic anhydride, pyridine and DCM.
In vitro anti-microbial activity

**Anti-bacterial activity assay:** The anti-bacterial screenings of the synthesized compounds were undertaken using disc diffusion method. The screening results of the tested compounds against the gram positive bacteria (Staphylococcus aureus (MTCC 7443), B. cereus, Staphylococcus aureus (MRS)), B. subtilis, M. luteus, Enterobacter aerogenes (MTCC 111), gram negative bacteria (Escherichia coli, P. aeruginosa, P. vulgaris, Salmonella typhimurium (MTCC 2488), Klebsiella pneumoniae (MTCC 109), Salmonella paratyphi-B (MTCC 733), in addition to the pathogenic fungi A. niger, Candida albicans (MTCC 227), Botrytis cinereal (MTCC 2880), F. solani, A. flavus, Candida krusei (MTCC 231), Malassezia pachydermatis, F. moniliforme, C. gloeosporioides, C. parapsilosis are summarized in Figure 1 and Table 1.

In antibacterial activity the obtained data revealed that most of the compounds showed moderate to excellent activities against the tested microorganisms. Among all the synthesized substituted 2,5-di(4 aryloylaryloxy methyl)-1,3,4-oxadiazoles compounds 9a-j, compounds 9a with fluoro group exhibited highest activity compared with the standard drug Streptomycin. Compounds 9c with fluoro and bromo groups has shown second highest activity. Further, compounds 9b with fluoro and chloro groups, 9d with fluoro and iodo groups, 9f with chloro group and 9j with bromo group also exhibited moderate activity.

**Anti-fungi activity assay:** The anti-bacterial screenings of the synthesized compounds were undertaken using disc diffusion method. The screening results of the tested compounds against the pathogenic fungi A. niger, Candida albicans (MTCC 227), Botrytis cinereal (MTCC 227), F. solani, A. flavus, Candida krusei (MTCC 231), Malassezia pachydermatis, F. moniliforme, C. gloeosporioides, C. parapsilosis are summarized in Figure 2 and Table 2.

In anti-fungi activity assay the obtained data shown that most of the compounds showed moderate to excellent activities against the tested microorganisms. Among all the synthesized substituted 2,5-di(4 aryloylaryloxy methyl)-1,3,4-oxadiazoles compounds 9a-j, compounds 9a with fluoro group exhibited highest activity compared with the standard drug Ketoconazole. Compounds 9b with floro and chloro groups, 9c with fluoro and bromo groups, 9d with floro and iodo groups and 9h with chloro and iodo groups has shown good activity. Further, compounds, 9i with chloro and bromo groups and 9j with bromo group also showed moderate activity.

**Conclusion**

From the results of the present study, it is concluded that, a series of novel biologically active substituted 2,5-di(4 aryloylaryloxy methyl)-1,3,4-oxadiazoles 9a-j were synthesized and screened for antimicrobial activity and were compared with standard drugs-Streptomycin and Ketoconazole respectively. The antibacterial activity result shows that compound 9a with fluoro group exhibited highest activity. Compounds 9c with fluoro and bromo groups has shown second highest activity. Further, compounds 9b with fluoro and chloro groups, 9d with floro and iodo groups, 9f with chloro group and 9j with bromo group also exhibited moderate activity. Further, The Antifungal activity of the compounds 9a-j result shows that compound 9a with floro group exhibited highest activity. Compounds 9b with fluoro and chloro groups, 9c with fluoro and bromo groups, 9d with fluoro and iodo groups and 9b with chloro and iodo groups has shown good activity.
Acknowledgements

Yasser Hussein Eissa Mohammed is thankful to the University of Hajja, Yemen, for providing financial assistance under the Teacher’s fellowship. Shaukath Ara Khanum expresses sincere gratitude to the Government of Karnataka, Vision Wing, for providing financial assistance under the teacher’s fellowship. Shaukath and Ara Khanum also showed moderate activity.

References


Further, compounds, 9i with chloro and bromo groups and 9j with bromo group also showed moderate activity.

Table 2: Antifungal activity of the compounds: 9a-j MIC in µg/mL.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>9a</th>
<th>9b</th>
<th>9c</th>
<th>9d</th>
<th>9e</th>
<th>9f</th>
<th>9g</th>
<th>9h</th>
<th>9i</th>
<th>9j</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive bacteria</td>
<td>B. subtilis</td>
<td>B. cereus</td>
<td>S. aureus (MRSA)</td>
<td>M. luteus</td>
<td>E. aerogens</td>
<td>S. typhimurium</td>
<td>K. pneumonia</td>
<td>P. aeruginosa</td>
<td>E. coli</td>
<td>P. vulgaris</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>MIC in µg/mL</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
</tbody>
</table>

Table 2: Antifungal activity of the compounds: 9a-j MIC in µg/mL.

Figure 2: The inhibitory effects of compounds 9a-j on different fungal strain.


