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

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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 dysenteria”) 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 KBr 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 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...
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-fluorophenol (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-fluorobenzoyl chloride (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) n (cm\(^{-1}\)): 1738 (ester, C=O); \(^1\)H NMR (400 MHz) (DMSO-d\(_6\)) \(\delta\) (ppm): 7.42-7.53 (m, 4H, Ar-H), 8.25-8.28 (m, 3H, Ar-H), MS (EI): m/z (75%): M+ 268.5; Anal. Calcld. for C\(_{13}\)H\(_7\)ClF\(_2\)O\(_2\) (268.5): C, 58.22; H, 2.43; Cl, 13.30; F, 14.29%.

**General procedure for (4-hydroxyarylamethyl 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 × 40 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 (51 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 × 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 compound 4a as pale yellow solid. Yield: 61%; m.p.: 146.3-147.7°C; IR (KBr) \(\text{n (cm}^{-1}\)) : 1671 (C=O); 3545-3635 (OH); \(^1\)H NMR (400 MHz) (DMSO-d\(_6\)) \(\delta\) (ppm): 7.36-7.82 (m, 6H, Ar-H), 11.64 (bs, 1H, OH). MS (EI): m/z (83%): M+ 268.5; Anal. Calcld. for C\(_{17}\)H\(_{13}\)ClF\(_2\)O\(_4\) (268.5): 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%.

**Synthesis of [4-(4-fluorobenzoyl)-2-chloro-6-fluorophenoyl] ethanoic 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-e [8].

**General procedure for 4-aryloylaryloxyacethydrazides (7a-e):**

To a solution of compound 4a (18 g, 0.0532 mol), potassium carbonate (14.14 g, 0.1057 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 × 60 mL), and again with water (3 × 30 mL). The reaction mixture was cooled to 0°C and quenched with 6 N hydrochloric acid (200 mL) and extracted with DCM (3 × 100 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 afford compounds 5a-e as white needle. Yield: 79%; m.p.: 107.5-109.1°C; IR (KBr) \(\text{n (cm}^{-1}\)) : 1610 (C=O), 1645 (amide, C=O), 3100-3205 (NH-NH); \(^1\)H NMR (400 MHz) (DMSO-d\(_6\)) \(\delta\) (ppm): 4.35 (bs, 2H, NH2), 4.69 (s, 2H, OCH2), 7.2-7.86 (m, 6H, Ar-H), 9.32 (bs, 1H, CONH). MS (EI): m/z (42%): M+ 340.5; Anal. Calcld. for C\(_{17}\)H\(_{12}\)ClF\(_2\)O\(_2\) (340.5): C, 52.88; H, 3.25; Cl, 10.41; F, 11.15; N, 8.22. Found: C, 52.75; H, 3.38; Cl, 10.29; F, 11.24; N, 8.11%. Compounds 7b-e were synthesized analogously starting with 6b-e respectively by same method [8].
General procedure for N,N-di[(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[(2-chloro-6-fluoro-4-(4-fluoro-benzoyl)phenoxoy]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, 0.0032 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 (Nujol) nmax (cm⁻¹): 1670 (C=O), 1410 (amide, C=O), 3700-3500 (NH-NH); 1H NMR (400 MHz) (DMSO-d6) d (ppm): 5.6 (s, 4H, 2CH₂), 7.05-7.81 (m, 12H, Ar-H), 10.36 (bs, 2H, NH-NH).

Materials and methods for the antimicrobial activity:

Biology

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-aryloyloxyacetates 5a-e which on treatment with sodium hydroxide in presence of THF gave 4-aryloyloxyethanolic acids 6a-e. Further, compounds 5a-e on treatment with hydrazine hydrate in the presence of ethanol yield 4-aryloyloxyacetyldrazides.
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-arylroylaryloxy) 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 (MRSA) (MTCC 84)), 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 cinerea (MTCC 2880), F. solani, A. flavus, Candida krusei (MTCC 231), Malassaea pachydermatis, F. moniliiforme, C. gloeosporioides, C. parapsilosis were 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-fungal 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 cinerea (MTCC 2880), F. solani, A. flavus, Candida krusei (MTCC 231), Malassaea pachydermatis, F. moniliiforme, 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 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. 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 aryloylxyloxyethyl)-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 fluoro 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 fluoro 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.

| Compounds | Name of the microorganism | MIC in mg/mL |
|-----------|--------------------------|-------------|
|           | A. niger | C. albicans | A. flavus | B. cinerea | C. krusei | F. solani | C. parapsilosis | M. pachydermatis | F. moniliiforme | C. gloeosporioides |
| 9a        | 9.37     | 9.37        | 9.37      | 18.75      | 9.37      | 9.37      | 18.75      | 9.37                  | 18.75              | 9.37                  |
| 9b        | 9.37     | 18.75       | 9.37      | 18.75      | 9.37      | 9.37      | 18.75      | 9.37                  | 18.75              | 18.75                 |
| 9c        | 9.37     | 18.75       | 18.75     | 9.37       | 18.75     | 9.37      | 18.75      | 9.37                  | 18.75              | 9.37                  |
| 9d        | 9.37     | 150         | 18.75     | 9.37       | 18.75     | 9.37      | 18.75      | 9.37                  | 18.75              | 150                   |
| 9e        | 300      | 300         | 150       | 150        | 150       | 150       | 300        | 300                   | 150                | 300                   |
| 9f        | 18.75    | 150         | 9.37      | 18.75      | 9.37      | 9.37      | 18.75      | 9.37                  | 18.75              | 150                   |
| 9g        | 150      | 150         | 300       | 150        | 300       | 300       | 150        | 300                   | 150                | 300                   |
| 9h        | 9.73     | 9.73        | 18.75     | 9.73       | 18.75     | 150       | 9.73       | 150                   | 18.75              | 18.75                 |
| 9i        | 18.75    | 9.37        | 9.37      | 18.75      | 9.37      | 18.75     | 9.37       | 9.37                  | 18.75              | 9.37                  |
| 9j        | 18.75    | 9.37        | 9.37      | 18.75      | 9.37      | 18.75     | 9.37       | 9.37                  | 18.75              | 9.37                  |
| Ketoconazole | 2.4    | 4.6         | 1.2       | 4.7        | 2.33      | 2.34      | 4.68       | 4.68                  | 2.34               | 2.34                  |

Table 1: Antibacterial activity of the compounds: 9a-j; MIC minimum inhibitory concentration MIC in µg/mL.
Further, compounds, 9i with chloro and bromo groups and 9j with bromo group also showed moderate 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 Group on Science and Technology, Bangalore for the financial assistance and Ara Khanum for providing financial assistance under the teacher’s fellowship. Shaukath expresses sincere gratitude to the Government of Karnataka, Vision Group on Science and Technology, Bangalore for the financial assistance and UGC, New Delhi for the financial assistance and UGC, New Delhi for the financial assistance and UGC, New Delhi for the financial assistance.

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