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Research Article

Design, Synthesis, Characterization and Biological Evaluation of Novel Depsides as Potential Antibacterials

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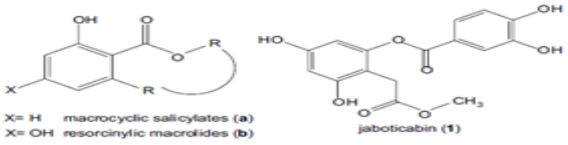
Abstract

Sixteen depsides were synthesized to screen for their antibacterial activity. All of them were reported for the first time. Their chemical structures were clearly determined by FTIR, ^{1}H NMR, ESI mass spectra. All the compounds were assayed for antibacterial and antifungal activities against two Gram-positive bacterial strains (*Bacillus subtilis* ATCC 6633) and (*Staphylococcus aureus* ATCC 29747)and two gram-negative bacterial strains (*Escherichia coli* ATCC 8739) and (*Pseudomonas aeruginosa* ATCC 25619) the MIC and zone of inhibition calculated by cup-plate method and serial dilution method and two fungal strains (*Aspergillus niger* ATCC 90292) and (*Candida albicans* ATCC 24433)by the micro-broth dilution method.Compound2-(2- propoxy -2-oxoethylphenyl (4-methoxyphenyl)acetate(P_6) and 2-(2- propoxy-2-oxoethylphenyl(4-methylphenyl)acetate(P_7) showed powerful antibacterial activities against *E. coli* with MIC of 2.0 40mg/ml while compound 2-(2- propoxy -2-oxoethylphenyl(4-methylphenyl)acetate (P_7) and 2-(2- propoxy -2-oxoethylphenyl and (3-methoxyphenyl)acetate (P_8) exhibited significant antibacterial activities against *B. subtilis* with MIC of 3.12 40mg/ml, which were superior to the positive controls amoxycillin trihydrate and ciprofloxacin HCl, respectively and compound 2-(2-propoxy -2-oxoethyl) phenyl 4-methylbenzoate (P_8) was found to have highest antifungal activity against *Candida albicans* ATCC 24433. On the basis of the biological results, quantitative structure activity relationships were discussed.

Keywords: Depsides, Antibacterials, Antifungal, Quantitative structure activity relationship.

INTRODUCTION

Depsides, in the strict sense, are compounds comprised of two or more aromatic rings bound by a phenolic oxygen ester linkage. They are most often found in lichens, but have also been isolated from higher plants, including species of the Ericaceae, Lamiaceae and Papaveraceae [1,2]. Some depsides isolated from lichens have been reported to have activity against mycobacteria, gram-positive bacteria, insects and nematodes. In addition, several well characterized depsides exhibit antiproliferative, analgesic, antipyretic, anticancer, anti-HIV-1 integrase and antiviral properties[3-11]. As inhibitors of prostaglandin biosynthesis and leukotriene B4 biosynthesis, depsides are potent nonsteroidal anti-inflammatories[12]. Furthermore, it is reported that members of the macrocyclic salicylate family (Fig.1)[13] are potent inhibitors of the mammalian vacuolar ATPase with a potential novel mode-of action[14], whereas resorcinylic macrolides (b, Fig. 1) such as radicicol[15] inhibit the molecular chaperone Hsp90[16]. Recently, a new depside, named jaboticabin (Fig.1), was demonstrated to inhibit chemokine interleukin (IL)-8 production before and after cigarette smoke treatment of cells [17]. Depsides, in the strict sense, are compounds comprised of two or more aromatic rings bound by a phenolic oxygen-ester linkage. They are most often found in lichens, but have also been isolated from higher plants. Depsides isolated from lichens have been reported to have activity against mycobacteria, gram-positive bacteria, insects, and nematodes. In addition, several well-characterized depsides exhibit antiproliferative, analgesic, antipyretic, anticancer, anti-HIV-1 integrase and antiviral properties. Depsides are potent nonsteroidal anti-inflammatory agent. Lichens are a symbiotic association of mostly ascomycetous fungi (mycobiont) and cyanobacterial (photobiont) partners. They occur in a wide variety of habitats and natural environmental conditions such as low temperatures, prolonged darkness, drought, continuous light, etc. It has been suggested that in response to these stresses, natural selection has favoured species producing high concentrations of characteristics phenolic compounds (mainly depsides, depsidones).However, few attentions have focused on the antibacterial activity of depsides up to now, especially gram-negative bacteria. In view of that, we have designed series of novel depsides derivative which are structurally similar to jaboticabin (Fig. 1), and evaluated their antibacterial activities against two gram-positive bacterial strains (*Bacillus subtilis* ATCC 6633),(*Staphylococcus aureus* ATCC29737) and gram-negative bacterial strains (*Escherichia coli* ATCC 8739),(*Pseudomonas aeruginosa* ATCC25619) by cup-plate method and serial dilution method and two fungal strains (*Aspergillus niger* ATCC 90292) and (*Candida albicans* ATCC 24433) by the micro-broth dilution method.



MATERIAL AND METHODS

Chemistry

Chemicals (starting material) used were purchased from Aldrich (U.S.A). Separation of the compounds by and column chromatography was carried out with silica gel 60 (200-300mesh ASTM, E. Merck). The quantity of silica gel used was50-100 times the weight charged on the column. Then, the eluates were monitored using TLC. Melting points (uncorrected) were determined on an open capillary method. ESI mass spectra were obtained on an EI-MS technique on Shimadzu QP 2010 Plus GC-MS mass spectrometer and ^{1}H NMR spectra were recorded on a Bruker advance II 400 NMR spectrometer at25^{0}C with TMS and solvent signals allotted as internal standards. Chemical shifts were reported in parts per million (d).

Experiments

Antibacterial and antifungal activities

The antibacterial activities of the synthesized compounds were tested against (*Bacillus subtilis* ATCC 6633), (*Staphylococcus aureus* ATCC 29747), (*Escherichia coli* ATCC 8739) and (*Pseudomonas aeruginosa* ATCC 25619) the MIC and zone of inhibition calculated by cup-plate method and serial dilution method. The minimum inhibitory concentration of the test compounds were determined by two folds serial dilution technique. The stock solutions of 400µg/ml of each test compounds were prepared. Then 7 sterilized test tubes were taken and numbered. 2ml of stock solution was taken into first test tube and add 1ml of sterile broth to all other test tubes. From the first tube, 1ml of test compound solution was taken and added to the second tube and mixed properly. Again pipette out 1ml from second tube and added to third tube and mixed properly. Same procedure was repeated for all remaining tubes and 1ml was expelled out from last tube to obtain the dilution from 100µg/ml to 3.12µg/ml. Then all tubes were inoculated with a 1ml of corresponding microorganism inoculums suspension and incubated at 37±1°C for 24 hrs. Control tubes (without drug or test compounds) were also incubated similarly. Similar procedure was repeated for all test compounds and standard drugs. The antifungal activities of the synthesized compounds were tested against (*Aspergillus niger* ATCC 90292) and (*Candida albicans* ATCC 24433) by the micro-broth dilution method. 12.80mg of sample was dissolved in 2% DMSO and made up to 100 ml in a volumetric flask to produce a concentration of 128µg/ml. All the sample solution had been prepared in the same manner in Aseptic condition. Amphotericin B was used as a standard drug. The lowest concentration of the test compounds showing no visible microbial growth were considered as minimum inhibitory concentration. The observed MIC values are presented in Table 2.

General procedure for esterification of 2-hydroxy phenyl acetic acid

A solution of 2-hydroxyphenylacetic acid (7.6 g, 50mmol) in methanol or ethanol (50 ml) containing conc. H_2SO_4 (5ml) was refluxed overnight. Water (100 ml) was added, the organic phase was washed with saturated NaCl (100 ml) and was dried over Na_2S0_4, and the solvent was evaporated.

Methyl 2-(2-hydroxyphenyl) acetate (B1): White powder, yield 90%, mp: 61-62^0 C, ^{1}H NMR (300 MHz, d6-DMSO): 3.54 (s, 2H); 3.58 (s, 3H); 6.78 (m, 2H); 7.06 (m, 2H); 9.47 (s,n1H). MS (ESI): 167.1 (**$C_9H_{11}O_3$**, [M+H]$^+$).Anal. Calcd for**$C_9H_{10}O_3$**: C, 65.05; H, 6.07%; Found: C, 65.03; H, 6.10%.

Propyl 2-(2-hydroxyphenyl) acetate (B2): yellow oil, yield 86%, mp: 67-68^{0}C; 1H NMR (300 MHz, d6-DMSO): 1.17 (t, J ¼ 7.1 Hz, 3H); 3.53 (s, 2H); 4.01 (m,2H); 6.75 (m, 2H); 7.07 (m, 2H); 9.46 (s, 1H). MS (ESI): 181.1 (**$C_{11}H_{14}O_3$**,[M + H]$^+$).Anal. Calcd for **$C_{11}H_{14}O_3$**: C, 65.65; H, 6.71%; Found: C, 65.69; H, 6.74%.

Butyl 2-(2-hydroxyphenyl) acetate (B3): yellow oil, yield 85%, mp: 65-70^{0}C; 1H NMR (300 MHz, d6-DMSO): 1.17 (t, J ¼ 7.1 Hz, 3H); 3.53 (s, 2H); 4.01 (m,2H); 6.75 (m, 2H); 7.07 (m, 2H); 9.46 (s, 1H). MS (ESI): 181.1 (**$C_{12}H_{16}O_3$**,[M +H]$^+$).Anal. Calcd for **$C_{12}H_{16}O_3$**: C, 65.65; H, 6.71%; Found: C, 65.69; H, 6.84%.

General procedure for the synthesis of depsides:

To a stirred solution of B (1.04 g, 3.1mmol) in dichloromethane (50 ml) was added 2 (864 mg, 1.96mmol), N, N-dimethyl amino pyridine (248mg, 2.03mmol) and N, N-0-dicyclohexylcarbodiimide (740 mg, 3.6mmol). The mixture was refluxed overnight. Then ethanol (1 ml) and acetic acid (1 ml) was added; the mixture was refluxed for 2 h and concentrated in vacuum.

2-(2-methoxy-2-oxoethyl) phenyl 4-aminobenzoate (P1): Creamy powder, Yield 71.52%, IR spectra (in cm^{-1}) 1573.81 (C=C), 3035.75 (C-H), 1072.34 (C-O), 1724.24 (C=O), 3325.05 (N-H), 1345.9 (C-N),NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 3.41 (m, 3H); 5.54 (s, 2H); 6.56(t, 4H); 7.67 (m, 1H); 7.89 (s, 3H); 8.01 (s, 2H).MS (ESI): 299.116 ($C_{16}H_{15}NO_4$), [M+H]$^+$).

2-(2-methoxy-2-oxoethyl)phenyl4-methoxybenzoate(P2): White powder, Yield 64.2**%,** IR spectra (in cm^{-1}) 1539.09 (C=C), 3031.89 (C-H), 1087.78 (C-O), 1737.74 (C=O)NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 3.73 (s, 2H); 3.52 (s, 3H); 7.31 (m, 1H); 7.43 (m, 3H); 7.94 (m, 1H); 8.58 (m, 1H); 8.76 (m, 1H). MS (ESI): 314.115 ($C_{17}H_{16}O_5$), [M+ H] $^+$).

2-(2-methoxy-2-oxoethyl)phenyl4-methylbenzoate(P3): Red powder, Yield71.0%, IR spectra (in cm^{-1}) 1520.34 (C=C), 3014.53 (C-H), 1072.36 (C-O), 1712.67 (C=O), 1444.53 (CH_3)NMR: ^{1}HNMR (400MHz, DMSO): δ (ppm): 2.46 (s, 3H); 3.47 (s, 3H); 3.68 (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H); 7.98 (d, 2H). MS (ESI): 298.121 ($C_{17}H_{16}O_4$), [M+ H] $^+$).

2-(2-methoxy-2-oxoethyl) phenyl 3-methoxybenzoate(P4): White powder, Yield 65.6**%,** IR spectra (in cm^{-1}) 1573.81 (C=C), 3035.75 (C-H), 1054.99 (C-O), 1774.39 (C=O) NMR: ^{1}HNMR (400 MHz, DMSO): δ (ppm): 3.61(s, 3H); 6.81-7.29 (m, 9H); 8.53 (s, 1H); 7.71(s, 1H). MS (ESI): 314.115 ($C_{17}H_{16}O_5$), [M+ H] $^+$).

2-(2-propoxy-2-oxoethyl) phenyl 4-aminobenzoate (P5): Creamy powder, Yield 71%, IR spectra (in cm^{-1}) 1577.66 (C=C), 3039.60 (C-H), 1047.27 (C-O), 1737.75 (C=O) NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 3.41 (m, 1H); 5.54 (s, 1H); 6.56 (t, 1H,); 7.67 (m, 1H, CH); 7.89 (s, 1H); 8.01 (s, 1H).MS (ESI): 327.147 ($C_{18}H_{19}NO_4$), [M+ H] $^+$).

2-(2- propoxy-2-oxoethyl) phenyl4-methoxybenzoate(P6): Red powder, Yield 68.2%, IR spectra (in cm^{-1}) 1575.20 (C=C), 3030.89 (C-H), 1058.85 (C-O), 1778.25 (C=O), 3386.77 (N-H), 1323.08 (C-N) NMR: ^{1}HNMR (400 MHz, DMSO): δ (ppm): 3.54 (s, 2H); 3.55 (s, 3H); 3.76 (s, 3H); 3.90 (s, 2H); 6.87 (m, 1H); 6.94 (m, 2H); 7.09 (m, 1H); 7.28 (m, 4H). MS (ESI): 305.0 ($C_{19}H_{20}O_5$), [M+ H] $^+$).

2-(2- propoxy-2-oxoethyl) phenyl 4-methylbenzoate (P7): Yellowish powder. Yield64.5%, IR spectra (in cm^{-1}) 1490.75 (C=C), 3124.47 (C-H), 1089.71 (C-O), 1772.46 (C=O), 1440.73 (CH_3) NMR: ^{1}HNMR (400MHz, DMSO): δ (ppm2.46 (s, 3H); 3.47 (s, 3H); 3.68 (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H);): 8.98 (d, 2H). MS (ESI): 297.1 ($C_{19}H_{20}O_4$), [M+ H] $^+$).

2-(2-propoxy-2-oxoethyl) phenyl 3-methoxybenzoate (P8): Reddish brown powder. Yield62.3%, IR spectra (in cm^{-1}) 1589.95 (C=C), 3026.93 (C-H), 1085.85 (C-O), 1728.39 (C=O)NMR:^{1}HNMR (400MHz, DMSO): δ(ppm): 3.49 (s, 2H);

3.51 (s, 3H); 3.72 (s, 3H); 3.73 (s, 3H); 3.82 (s, 2H); 6.84 (m, 1H); 6.90(m, 1H); 6.94 (m, 1H); 7.08 (m, 1H); 7.18 (m, 1H); 7.30 (m, 2H) MS (ESI): 322.147 ($C_{19}H_{20}O_5$), [M+ H] $^+$).

2-(2-butoxy-2-oxoethylphenyl) 4-aminobenzoate (P9): creamy powder. Yield62.7%, IR spectra (in cm^{-1}) 1545.32 (C=C), 3085.51 (C-H), (C-O), 1730.89 (C=O), 3481.41 (NH), 1090.17 (C-N) NMR: ^{1}HNMR (400MHz, DMSO): δ (ppm): 3.41 (m, 4H); 5.54 (s, 2H, NH2); 6.56 (t, 3H); 7.67 (m, 4H); 7.89 (s, 3H); 8.0(s, 2H). MS (ESI): 3241.163 ($C_{19}H_{21}NO_4$), [M+ H] $^+$).

2-(2-butoxy-2-oxoethyl) phenyl 4-methoxybenzoate (P10): White powder, Yield72.6%IR spectra (in cm^{-1}) 1575.75 (C=C), 3035.75 (C-H), 1049.20 (C-O), 1781.81 (C=O) NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 2.46 (s, 3H); 3.47 (s, 3H); 3.68,(s, 2H); 7.27 (m, 2H); 7.39 (m, 4H); 7.98 (d, 2H). MS (ESI): 336.1 ($C_{20}H_{22}O_5$), [M+ H] $^+$).

2-(2-butoxy-2-oxoethyl)phenyl3-methoxyacetate(P11): White powder, Yield 53.3%,IR spectra (in cm^{-1}) 1539.09 (C=C), 3033.82 (C-H), 1047.27 (C-O), 1772.46 (C=O) NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 3.49326.1 (s, 3H); 3.69 (s, 2H); 3.84 (s, 6H); 6.88 (t, 1H); 7.20 (d, 2H); 7.28 (m, 2H); 7.39 (m, 2H). MS (ESI): 319.0($C_{20}H_{22}O_5$), [M+ H] $^+$).

2-(2-butoxy-2-oxoethyl) phenyl 3-methylacetate (P12): Reddish powder, Yield74.8%, IR spectra (in cm^{-1}) 1575.73 (C=C), 3122.54 (C-H), 1014.49 (C-O), 1735.81 (C=O), 1438.80 (CH_3) NMR: ^{1}H NMR (400MHz, DMSO): δ (ppm): 2.46(s, 3H); 3.47 (s, 3H); 3.68 (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H); 8.98 (d, 2H). MS (ESI): 373.1 ($C_{20}H_{22}O_4$), [M+ H] $^+$).

2-(2-methoxy-2-oxoethyl)phenyl 4-iodobenzoate(P13): Creamy powder, Yield73%, IR spectra (in cm^{-1}) 1438.80 (C=C), 2931.60 (C-H), 1026.06 (C-O), 1749.02 (C=O), 489.89 (C-I).NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 2.46 (s, 3H); 3.47 (s, 3H); 3.68 (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H); 8.80 (d, 2H). MS (ESI): 310.0 ($C_{16}H_{13}IO_4$), [M+ H] $^+$).

2-(2-butoxy-2-oxoethyl) phenyl 3,5-dinitrobenzoate(P14): White powder, Yield 55.5%, IR spectra (in cm^{-1}) 1527.52 (C=C), 3041.53 (C-H), 1062.34 (C-O), 1645.17 (C=O), 3481.41 (NH), 1081.99 (C-N), 1346.22 (R-NO_2) NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 3.52 (s, 3H); 3.73 (s, 2H); 7.94 (t, 2H); 7.31 (m, 3H); 7.43 (m, 3H); 8.51 (m, 1H); 8.58 (m, 2H); 8.76 (m, 2H). MS (ESI): 330.105 ($C_{19}H_{18}N_2O_8$), [M+ H] $^+$).

2-(2-propoxy-2-oxoethyl) phenyl 3, 5-dinitrobenzoate (P15): White powder, Yield 61.6%, IR spectra (in cm^{-1}) 1533.30 (C=C), 3105.18 (C-H), 1018.34 (C-O), 1627.81 (C=O), 3326.98 (NH), 1090.17 (C-N), 1450.37 (R-NO_2) NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 3.52 (s, 3H); 3.73 (s, 2H); 7.94 (t, 3H); 8.51 (m, 4H); 8.58 (m, 2H); 8.76 (m, 1H); 7.31 (m, 1H); 7.43 (m, 3H). MS (ESI): 325.00 ($C_{18}H_{16}N_2O_8$), [M+ H] $^+$).

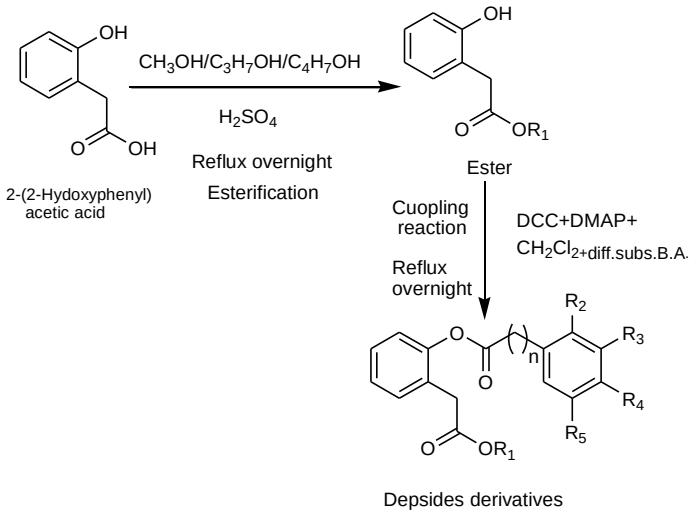
2-(2-methoxy-2-oxoethyl) phenyl 3,5-dinitrobenzoate(P16): White powder, Yield 51.7**%,** IR spectra (in cm^{-1}) 1551.43 (C=C), 3073.62 (C-H), 1062.34 (C-O), 1642.51 (C=O), 3472.3 (NH), 1213.12 (C-N), 1473.91 (R-NO_2) NMR: ^{1}H NMR (400 MHz, DMSO): δ (ppm): 0.99 (t, 3H); 3.71 (s,2H); 3.94 (q, 3H); 7.31 (m, 1H); 7.42 (m, 3H); 7.93 (t, 1H); 8.52 (d, 1H); 8.59 (d, 1H); 8.76 (m, 1H) MS (ESI): 330.10($C_{16}H_{12}N_2O_8$), [M+ H] $^+$).

RESULTS AND DISCUSSION

Sixteen depsides were synthesized to screen for the antibacterial activity. All of them were reported for the first time. The synthesis of compounds P_1-P_{16} followed the general pathway outlined in Scheme 1. They are prepared in two steps. Firstly, a solution of 2-hydroxyphenylacetic acid (compound A) in methanol or ethanol containing concentrated H_2SO_4 was refluxed overnight [18]. This step can yield the corresponding ester. Secondly, the coupling reaction between the obtained esters and the different substituted phenyl acetic acid or benzoic acid was performed through 'step ii' by using N,N-dicyclohexyl- carbodiimide (DCC) and 4-dimethyl amino pyridine (DMAP) in anhydrous CH_2Cl_2[19]. Then, compounds P_1-P_{16} were obtained by subsequent purification. All of the synthetic compounds gave satisfactory analytical and spectroscopic data, which were in full accordance with their depicted structures.

Antibacterial and Antifungal Activity

All the compounds prepared were evaluated for their antibacterial and antifungal activities against two gram-positive bacterial strains (*B. subtilis* ATCC 6633 and *S. aureus* ATCC 29737) and two gram-negative bacterial strains (*E. coli* ATCC 8739 and *P. aeruginosa* ATCC 25619) activities by serial dilution method and two fungal strains (*Aspergillus niger* ATCC 90292) and (*Candida albicans* ATCC 24433) by the micro-broth dilution method. The results are shown in Table1 properties, low toxicity, inertness and chemical stability[22]. Moreover, depsides have been reported to have antibacterial activity[3,4]. Enlightened by the above two factors,2-Hydroxy phenyl acetic acid which has phenolic hydroxyl group in the ortho position was used to synthesize novel depsides with a view to find new antibacterial agents. Then, studies were performed by modification of the parent compounds to determine how the substituents of the subunits affected the antibacterial activities.



Scheme 1 (i) CH_3OH, C_3H_7OH and C_4H_9OH, H_2SO_4, reflux overnight, (ii) DCC, DMAP, CH_2Cl_2, Reflux overnight.

QSAR Analysis

To obtain a significant correlation between structural features and biological activities, QSAR studies were performed using the linear free energy relationship (LFER) model of Hansch and Fujita. Biological activity data were reported as _log MIC on molar basis and used as dependent variable to get the linear relationship in the QSAR model. The physicochemical parameters taken from the list of Skagerberg et al [25] were then correlated with varied molecular descriptors like partition coefficient (log p), lowest unoccupied molecular orbital (LUMO), molar refractivity (MR) and melting point (MP). All the calculations to figure out molecular descriptors were done at SCF level using AM1[26] Hamiltonian incorporated in MOPAC 6.0 package[27]. Geometries were optimized at minimum gradient level using CHEM 3D-6.0 software [28]. In order to perform correlation studies for various descriptors, inter correlated parameters were discarded depending upon their individual correlation with biological activities. Using the

stepwise selection and elimination procedures the resultant parameters were subjected to MLR analysis with the help of Valstat software[29]. The best fit between _log MIC and these explaining parameters were obtained through multiple regression analysis (MRA) using least square. Out of a number of parametric evaluations, the best correlation (r2 > 0.93) was found to exist between molar refractivity and biological activity. The resulting mono-parametric models are displayed in Eqs. (1)-(2) with statistical parameters of regression. No outliers have been detected and these Eqs. (1)-(2) were derived using entire training data set. The overall quality of the models is indicated by coefficient of determination (r2), standard error of estimate (s), and Fisher statistics (F).

QSAR model for activity against *B. subtilis*:

Eqn.1 _log MIC = [3.8516 (± 4.4673)] + mrl [3.3645 (± 1.22073)] + se [26.4534 (± 14.9436)]

n=19, r=0.809503, r^2=0.655296, Variance=0.0960711, std=0.309953, F=17.1093, FIT=136.875

QSAR model for activity against *P. aeruginosa*

Eqn.2 _log MIC= [4.68168 (±0.158409)] +se [-0.0258718 (±0.0152161)] + Lumo [0.0437538 (± 0.0272712)]

n=21, r=0.859191, r^2=0.738209, variance=0.0379778, std =0.194879, F=15.5092, FIT=172.324

CONCLUSIONS

In this paper, we designed a series of novel depsides derivatives and evaluated their antibacterial and antifungal activities against two gram-positive bacterial strains (*B. subtilis* ATCC 6633 and *S. aureus* ATCC 29737) and two gram-negative bacterial strains (*E. coli* ATCC 8739 and *P. aeruginosa* ATCC 25619) by MIC and zone of inhibition method. Compounds (P_7) and (P_8) showed powerful antibacterial activities against *B. subtilis* ATCC 6633 with MIC of 2.0 40mg/ml while compounds p7 and p8 exhibited significant antibacterial activities against E. coli ATCC 8739 with MIC of 3.12 40mg/ml, which were superior to the positive controls amoxycillin trihydrate and ciprofloxacin HCl, respectively. Fungal strains (*Aspergillus niger* ATCC 90292) and (*Candida albicans* ATCC 24433) by the micro-broth dilution method. Compound 2-(2- propoxy -2-oxoethyl) phenyl 4-methylbenzoate (P_8) was found to have highest antifungal activity against *Candida albicans* ATCC 24433 In addition, a comparison of the substitution on E-ring demonstrated that 3-position-substituted derivatives have more potent activity against *B. subtilis* ATCC 6633 than the 4-position-substituted ones. Most significantly, the stronger electron withdrawing substituent the compound.

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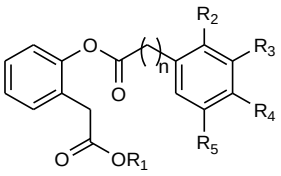
Table1: Structure of proposed compounds



S. NO.	R_1	R_2	R_3	R_4	R_5	n=0,1
1	CH_3	H	H	NH_2	H	0
2	CH_3	H	H	OCH_3	H	0
3	CH_3	H	H	CH_3	H	0
4	CH_3	H	OCH_3	H	H	0
5	C_3H_7	H	H	NH_2	H	0
6	C_3H_7	H	H	OCH_3	H	0
7	C_3H_7	H	H	CH_3	H	0
8	C_3H_7	H	OCH_3	H	H	0
9	C_4H_9	H	H	NH_2	H	0
10	C_4H_9	H	H	OCH_3	H	0
11	C_4H_9	H	H	CH_3	H	0
12	C_4H_9	H	OCH_3	H	H	0
13	C_4H_9	H	H	I	H	0
14	C_4H_9	H	NO_2	H	NO_2	0
15	C_3H_7	H	NO_2	H	NO_2	0
16	CH_3	H	NO_2	H	NO_2	0

Table 2: MICs (minimum inhibitory concentrations) (µg/ml) Zone of inhibition of the synthetic compounds

	Microorganism					
	Gram positive		Gram negative		Fungal strains	
Compounds	S. Aureus ATCC	B. Subtilis ATCC	E. Coli ATCC	P. aeruginosa	Aspergillus	Candida
P_1	Absent (Ab)	Absent(Ab)	3.12(21)	3.12 (24)	14	16
P_2	Absent (Ab)	Absent(Ab)	3.12 (21)	25 (14)	13	12
P_3	Absent (Ab)	Absent(Ab)	3.12 (21)	25 (14)	13	10
P_4	Absent (Ab)	Absent(Ab)	3.12 (21)	25 (14)	14	05
P_5	Absent (Ab)	6.25 (16)	2.0 (21)	12.5 (16)	23	06
P_6	Absent (Ab)	6.25 (18)	2.0 (21)	2.0 (25)	12	12
P_7	Absent (Ab)	3.12 (22)	2.0 (22)	3.12 (24)	12	15
P_8	Absent (Ab)	3.12 (20)	2.0 (22)	25 (14)	14	19
P_9	Absent (Ab)	6.25 (18)	2.0 (21)	25 (14)	15	17
P_{10}	Absent (Ab)	6.25 18)	2.0 (22)	25 (14)	13	12
P_{11}	Absent (Ab)	6.25 (18)	25 (18)	6.25 (18)	23	15
P_{12}	Absent(Ab)	3.12 (21)	25 (18)	6.25 (18)	13	10
P_{13}	Absent (Ab)	3.12 (21)	3.12 (21)	3.12 (18)	12	05
P_{14}	Absent (Ab)	25 (18)	3.12 (21)	25 (14)	12	06
P_{15}	Absent (Ab)	25 (18)	6.25 (16)	25 (14)	12	10
P_{16}	Absent (Ab)	25 (18)	6.25 (16)	6.25 (18)	12	12
Amoxycilin	2.0 (35)	3.12 (21)	3.12 (21)	2.0 (28)		
Ciprofloxacin HCl	2.0 (34)	2.0 (27)	2.0 (27)	2.0 (35)		
Amphotericin B					24	18

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