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An efficient synthesis of new lignan scaffolds as antimicrobial inhibition agents

K. R. Raghavendra[1], K. Ajay Kumar[2] and S. Shashikanth*[1]

[1]*Department of Studies in Chemistry, University of Mysore, Manasagangothri, Mysore, India*
[2]*Post Graduate Department of Chemistry, Yuvaraja College, University of Mysore, Mysore, India*

ABSTRACT

The aim of the present study was to synthesize a series of new lignans intermediates as antimicrobial inhibition agents were synthesized by a simple procedure. The cyclocondensation reaction of (Z)-3-(ethoxycarbonyl)-4,4-(diaryl)but-3-enoic acids, ***1(a-d)*** *with acetic anhydride in glacial acetic acid produced Ethyl 4-acetoxy-1-aryl-2-naphthoates* ***2(a-d)*** *and with polyphosphosphoric acid yielded ethyl 1-aryl-4-hydroxy-2-naphthoates* ***4(a-d)*** *in good yields. The synthesized compounds were evaluated for their antimicrobial activity. The new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis. Results of antimicrobial activity reveal that some of the synthesized compounds act as potential antimicrobial agents different fungal and bacterial organisms.*

Key words: Acetic anhydride, antimicrobial, cyclization, inhibition, PPA.

INTRODUCTION

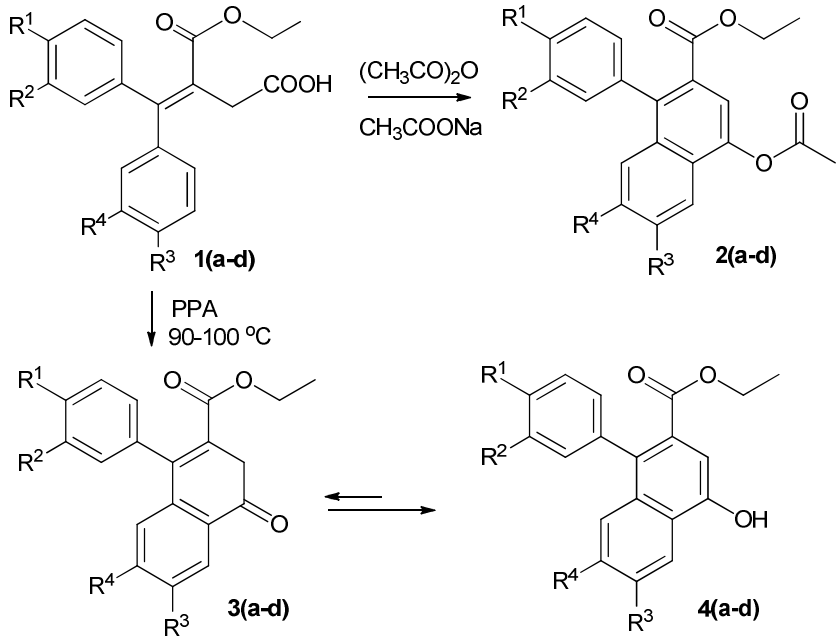
The lignans are a group of secondary metabolites found in plants produced by oxidative dimerization of two phenylpropanoid units. Lignans are known to have anti-tumour, antimitotic and antiviral activity and to specifically inhibit certain enzymes. New lignans continue to be described by natural products chemists at a steady rate and knowledge of their variety is continually expanding [1]. Thiophene-based lignan analogues were synthesized by a selective and high performance synthetic strategy based on the Negishi cross-coupling reaction [2]. An enantiomerically pure α-hydroxylated lactone lignans were synthesized from diisopropyl malate involving stereoselective alkylation followed by saponification and acetalization [3].

1-Phenyl-1H-benzo[b]azepine-2,5-dione prepared by an intramolecular cyclisation of 4-N,N-diphenylamine-4-oxo-2-butenoic acid showed considerable activity against F. Solani and A. Flavus fungal strains [4]. A recent review on lignans describes the different synthetic strategies adopted for the synthesis of lignans [5]. Monica et al [6] reported an asymmetric and regioselective total synthesis approach to 1,4-benzodioxane lignans in which (2R,3R)- and (2S,3S)-3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-1,4-benzodioxan-6-carbaldehydes. l-Aryl-2-methyl-tetrahydronaphthoic acid anhydride reacts with stabilized phosphorus ylide exclusively to the carbonyl remote from the 1-aryl substituent and has been converted into a variety of compounds related in structure to deoxyisopicrophyllotoxin [7].

A series of new lignans ethyl 4-acetoxy-6-ethoxy-1-(4-aryl)-2-naphthoates and ethyl 1-aryl-6-ethoxy-4-hydroxy-2-naphthoates were synthesized by simple and accessible procedure involving cyclocondensation reaction of 3-(ethoxycarbonyl)-4,4-(diaryl)but-3-enoic acids with acetic anhydride in glacial acetic acid and with polyphosphosphoric acid respectively. The synthesized compounds showed antimicrobial inhibitory effect [8]. In view of diverse applications of lignan analogues, we herein report the synthesis of lignan intermediates and their antimicrobial inhibition activity studies.

EXPERIMENTAL SECTION

In a typical procedure, 4-diaryl-3- ethoxycarbonyl-but-3-enoic acids**1**(**a-d**) were subjected to cyclisation reaction with acetic anhydride in the presence of sodium acetate to get Ethyl 4-acetoxy-6-ethoxy-1-(4-aryl)-2-naphthoates, **2**(**a-d**) in good yields. On the other hand, **1**(**a-d**) on cyclisation reaction with PPA at 90-100 ºC afforded ethyl 6-ethoxy-1-(4-aryl)-4-oxo-3,4-dihydronaphthalene-2-carboxylates, **3**(**a-d**) which undergo tautomerization to form **4**(**a-d**) in good yields (Scheme1).

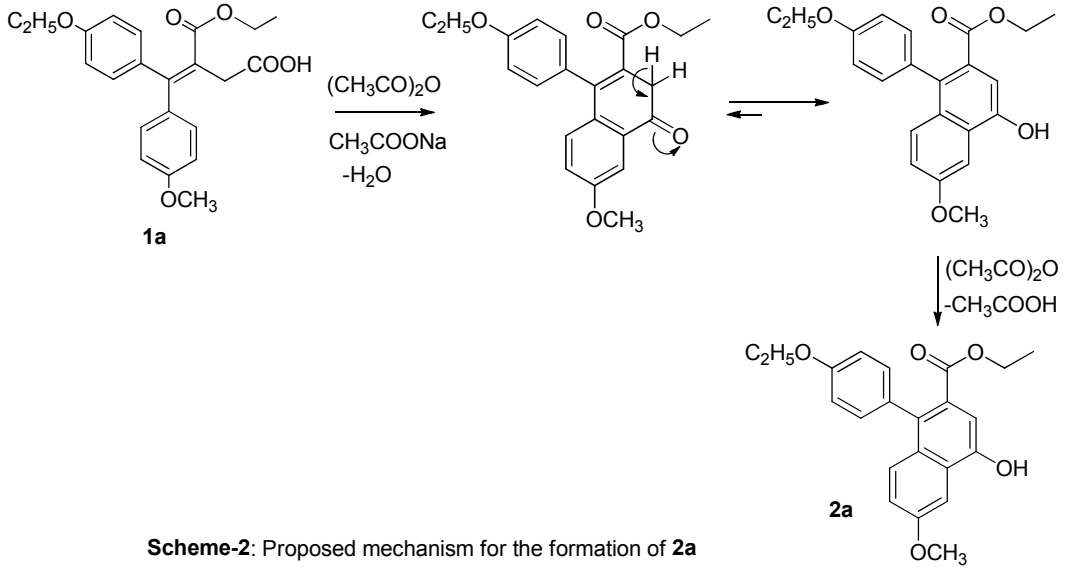


a) $R^1 = OC_2H_5$, $R^2 = H$, $R^3 = OCH_3$, $R^4 = H$; b) $R^1 = OC_2H_5$, $R^2 = H$, $R^3 = OCH_3$, $R^4 = OCH_3$;
c) $R^1 = OCH_3$, $R^2 = H$, $R^3 = OCH_3$, $R^4 = OCH_3$; d) $R^1 = OCH_3$, $R^2 = H$, $R^3 = H$, $R^4 = OCH_3$;

Scheme-1: Synthetic route for lignan scaffolds

(Z)-3-(Ethoxycarbonyl)-4-(4-ethoxyphenyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1a** reacted with acetic anhydride in the presence of a mild base sodium acetate to form a cyclic intermediate ethyl 1-(4-ethoxyphenyl)-6-methoxy-4-oxo-3,4-dihydronaphthalene-2-carboxylate, which rapidly undergo tautomerization to form more stable aromatized ethyl 1-(4-ethoxyphenyl)-4-hydroxy-6-methoxy-2-naphthoate, which reacted with excess of acetic anhydride to form Ethyl 4-acetoxy-1-(4-ethoxyphenyl)-6-methoxy-2-naphthoate, **2a** in good yield (Scheme 2).

On the other hand (Z)-3-(Ethoxycarbonyl)-4-(4-ethoxyphenyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1a** reacted with polyphosphoric acid (PPA) under reflux conditions to form a cyclic intermediate ethyl 1-(4-ethoxyphenyl)-6-methoxy-4-oxo-3,4-dihydronaphthalene-2-carboxylate **3a**, which was not isolated. The compound **3a** rapidly undergo tautomerization to form more stable aromatized ethyl 1-(4-ethoxyphenyl)-4-hydroxy-6-methoxy-2-naphthoate **4a** in good yield. The absence of cyclic C=O str band and a sharp absorption band at γ 3615 cm^{-1} for OH str in the IR spectra of the isolated product confirms the formation of **4a.**



Scheme-2: Proposed mechanism for the formation of **2a**

Materials and methods

Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on a Nujol mull on Shimadzu 8300 spectrometer.^{1}H NMR and ^{13}C NMR spectra were recorded on Agilent-NMR 400 MHz and 100 MHz spectrophotometer respectively in $CDCl_3$ with TMS as an internal standard. The chemical shifts are expressed in δ ppm. Mass spectra were obtained on Mass Lynx SCN781 spectrophotomer TOF mode. Elemental analysis was performed on a Thermo Finnigan Flash EA 1112 CHN analyzer. Chromatographic separations were carried out on silica gel (70-230 mesh, Merck) column using hexane: ethyl acetate (6:2 v/v) as eluent.

4.1. Preparation of polyphosphoric acid (PPA): Initially reagent grade orhopolyphosphoric acid (85 mL) was heated for half an hour to remove traces of water present in it. Phosphorous pentoxide (100g) was taken in a 250 mL three-necked flask and then the flask equipped with a mechanical stirrer, mercury seal tube and guard tube. The hot orhopolyphosphoric acid (75 mL) was added to phosphorous pentoxide and the mixture was vigorously stirred by maintaining the temperature between 170-200 ºC. The whole mixture became a clear viscous liquid. The solid lump left over was removed by means of a spatula and the liquid was stirred for again for 1 hr and cooled to 90-100 ºC.

***4.2. General procedure for the synthesis of Ethyl 4-acetoxy-1-aryl-2-naphthoates, 2(a-d)*:** A solution of (Z)-3-(ethoxycarbonyl)-4,4-(diaryl)but-3-enoic acids, **1**(**a-d**) (0.005 mol) in glacial acetic acid (4 mL) was taken in a two necked RB flask fitted with reflux condenser and guard tube. To this, an acetic anhydride (6 mL) was added slowly through dropping funnel with swirling. The reaction mixture was refluxed on a water bath for 3-4 hr. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was poured to an ice water with stirring. A solid separated was filtered; the residue was washed thoroughly with cold water and dried. The crude solid was recrystallized from ethanol to get the products **2**(**a-d**) in good yields.

RESULTS AND DISCUSSION

Ethyl 4-acetoxy-1-(4-ethoxyphenyl)-6-methoxy-2-naphthoate, **2a**: Obtained from (Z)-3-(ethoxycarbonyl)-4-(4-ethoxyphenyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1a** (1.92g, 0.005 mol) in 80% (1.63g) yield, mp 108-110 ºC.IR (Nujol, γ cm^{-1}): 1746, 1738 (s) (ester C=O str), 1220 (s) (C-O str). ^{1}HNMR ($CDCl_3$): δ 1.232 (t, 3H, CH_3), 1.333 (t, 3H, CH_3), 2.214 (s, 3H, CH_3), 3.855 (s, 3H, OCH_3), 4.101 (q, 2H, OCH_2), 4.236 (q, 2H, OCH_2), 6996 (dd, 2H, Ar-H), 7.690 (dd, 2H, Ar-H), 7.006-7.482 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$): δ14.12 (1C, CH_3), 14.70 (1C, CH_3), 20.14 (1C, CO<u>C</u>H_3), 55.80 (1C, OCH_3), 61.22 (1C, OCH_2), 64.10 (1C, OCH_2), 100.13 (1C, C-8), 114.42 (2C, 3',5'-C), 119.24(1C, C-6), 119.87 (1C, C-2), 123.22 (1C, C-3), 128.09 (1C, C-4a), 128.78 (1C, 1'-C), 129.26 (1C, C-5), 129.72 (2C, 2',6'-C), 131.44 (1C, C-8a), 138.78 (1C, C-4), 142.30 (1C, C-1), 157.36 (1C, 4'-C), 160.08 (1C, C-7), 168.42 (1C, COO), 172.01 (1C, OCO). MS (m/z): 408 (M^+). Anal. Calcd. for $C_{24}H_{24}O_6$: C, 70.57; H, 5.92%; Found: C, 70.38; H, 5.74%.

4.2.2. Ethyl 4-acetoxy-1-(4-ethoxyphenyl)-6,7-dimethoxy-2-naphthoate, **2b**: Obtained from (E)-4-(3,4-dimethoxyphenyl)-3-(ethoxycarbonyl)-4-(4-ethoxyphenyl)but-3-enoic acid, **1b** (2.07g, 0.005 mol) in 78% (1.70g) yield, mp 93-94 ºC. IR (Nujol, γ cm^{-1}): 1748, 1737 (s) (ester C=O str), 1212 (s) (C-O str). ^{1}HNMR ($CDCl_3$): δ 1.290 (t, 3H, CH_3), 1.325 (t, 3H, CH_3), 2.237 (s, 3H, CH_3), 3.852 (s, 6H, OCH_3), 4.116 (q, 2H, OCH_2), 4.272 (q, 2H, OCH_2), 7.016 (dd, 2H, Ar-H), 7.682 (dd, 2H, Ar-H), 7.316-7.389 (m, 3H, Ar-H). ^{13}C NMR ($CDCl_3$): δ14.20 (1C, CH_3), 14.66 (1C, CH_3), 20.36 (1C, CO<u>C</u>H_3), 55.96 (2C, OCH_3), 61.09 (1C, OCH_2), 64.33 (1C, OCH_2), 100.10 (1C, C-8), 106.20(1C, C-5), 114.40 (2C, 3',5'-C), 119.02 (1C, C-2), 123.20 (1C, C-3), 127.40 (1C, C-8a), 128.24 (1C, 1'-C), 129.65 (2C, 2',6'-C), 131.12 (1C, C-4a), 138.63 (1C, C-4), 142.44 (1C, C-1), 149.29 (1C, C-6), 152.18 (1C, C-7), 157.74 (1C, 4'-C), 168.33 (1C, COO), 172.36 (1C, OCO). MS (m/z): 438 (M^+). Anal. Calcd. for $C_{25}H_{26}O_7$: C, 68.48; H, 5.92%; Found: C, 68.26; H, 5.75%.

4.2.3. Ethyl 4-acetoxy-6,7-dimethoxy-1-(4-methoxyphenyl)-2-naphthoate, **2c**: Obtained from (E)-4-(3,4-dimethoxyphenyl)-3-(ethoxycarbonyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1c** (2.00g, 0.005 mol) in 82% (1.73g) yield, mp 101-104 ºC. IR (Nujol, γ cm^{-1}): 1747, 1739 (s) (ester C=O str), 1208 (s) (C-O str). MS (m/z): 424 (M^+). Anal. Calcd. for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70%; Found: C, 67.80; H, 5.56%.

4.2.4. Ethyl 4-acetoxy-7-methoxy-1-(4-methoxyphenyl)-2-naphthoate, **2d**: Obtained from (E)-3-(ethoxycarbonyl)-4-(3-methoxyphenyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1d** (1.85g, 0.005 mol) in 85% (1.67g) yield, mp 109-112 ºC.IR (Nujol, γ cm^{-1}): 1748, 1736 (s) (ester C=O str), 1226 (s) (C-O str). ^{1}HNMR ($CDCl_3$): δ 1.280 (t, 3H, CH_3), 2.271 (s, 3H, CH_3), 3.852 (s, 6H, OCH_3), 4.288 (q, 2H, OCH_2), 7.112 (dd, 2H, Ar-H), 7.656 (dd, 2H, Ar-H), 7.213-7.542 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$): δ14.55 (1C, CH_3), 20.65 (1C, CO<u>C</u>H_3), 55.85 (2C, OCH_3), 60.89 (1C, OCH_2), 106.26(1C, C-5), 114.68 (2C, 3',5'-C), 119.93 (1C, C-2), 121.10 (1C, C-8), 122.10 (1C, C-7), 126.21 (1C, C-3), 127.06 (1C, C-8a), 128.22 (1C, 1'-C), 129.98 (2C, 2',6'-C), 134.10 (1C, C-4a), 138.23 (1C, C-4), 144.40 (1C, C-1), 157.67 (1C, 4'-C), 157.29 (1C, C-6), 168.30 (1C, COO), 171.86 (1C, OCO).MS (m/z): 394 (M^+). Anal. Calcd. for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62%; Found: C, 69.86; H, 5.48%.

***4.3. General procedure for the synthesis of Ethyl 1-aryl-4-hydroxy-2-naphthoates*, *4(a-d)*:**(Z)-3-(Ethoxycarbonyl)-4,4-(diaryl)but-3-enoic acids, **1**(**a-d**) (0.005 mol) was slowly added to the freshly prepared PPA at 80 ºC with swirling, the mixture was stirred for another 15 min. The mixture was vigorously stirred for 3 hr on an oil bath at 90-100 ºC. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature and was poured into ice (250g) with stirring. The dark grey-colored precipitate formed was filtered. The residue is digested with 10% sodium hydroxide (100 mL) for half an hour using mechanical stirrer and filtered again. The solid obtained was repeatedly washed with water to free alkali and then recrystallized from alcohol to get the products **4**(**a-d**) in good yields.

4.3.1. Ethyl 1-(4-ethoxyphenyl)-4-hydroxy-6-methoxy-2-naphthoate, **4a**: Obtained from (Z)-3-(ethoxycarbonyl)-4-(4-ethoxyphenyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1a** (1.92g, 0.005 mol) in 92% (1.68g) yield, mp 121-123 ºC.IR (Nujol, γ cm^{-1}): 3615 (sh) (OH str), 1739 (s) (ester C=O str), 1217 (s) (C-O str). ^{1}HNMR ($CDCl_3$): δ 1.235 (t, 3H, CH_3), 1.318 (t, 3H, CH_3), 3.846 (s, 3H, OCH_3), 4.022 (q, 2H, OCH_2), 4.290 (q, 2H, OCH_2), 5.370 (s, 1H, OH), 6.988-7.751 (m, 8H, Ar-H).^{13}C NMR ($CDCl_3$): δ14.15 (1C, CH_3), 14.82 (1C, CH_3), 55.82 (1C, OCH_3), 61.26 (1C, OCH_2), 63.78 (1C, OCH_2), 100.20 (1C, C-8), 110.12 (1C, C-2), 114.40 (2C, 3',5'-C), 119.34 (1C, C-6), 123.94 (1C, C-3), 127.04 (1C, C-5), 128.48 (1C, C-8a), 128.74 (1C, 1'-C), 129.10 (2C, 2',6'-C), 129.72 (1C, C-4a), 133.22 (1C, C-4), 151.56 (1C, C-1), 157.86 (1C, 4'-C), 159.23 (1C, C-7), 168.50 (1C, COO).MS (m/z): 366 (M^+). Anal. Calcd. for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05%; Found: C, 71.92; H, 5.92%.

4.3.2. Ethyl 1-(4-ethoxyphenyl)-4-hydroxy-6,7-dimethoxy-2-naphthoate, **4b**: Obtained from (E)-4-(3,4-dimethoxyphenyl)-3-(ethoxycarbonyl)-4-(4-ethoxyphenyl)but-3-enoic acid, **1b** (2.07g, 0.005 mol) in 86% (1.70g) yield, mp 113-115 ºC. IR (Nujol, γ cm^{-1}): 3622 (sh) (OH str), 1738 (s) (ester C=O str), 1221 (s) (C-O str). ^{1}HNMR ($CDCl_3$): δ 1.260 (t, 3H, CH_3), 1.321 (t, 3H, CH_3), 3.850 (s, 6H, OCH_3), 4.130 (q, 2H, OCH_2), 4.302 (q, 2H, OCH_2), 5.388 (s, 1H, OH), 6.992-7.760 (m, 7H, Ar-H). ^{13}C NMR ($CDCl_3$): δ14.10 (1C, CH_3), 14.76 (1C, CH_3), 55.45 (2C, OCH_3), 61.08 (1C, OCH_2), 63.87 (1C, OCH_2), 100.34 (1C, C-8), 105.23 (1C, C-5), 110.06 (1C, C-2), 114.45 (2C, 3',5'-C), 124.31 (1C, C-8a), 124.80 (1C, C-3), 128.70 (1C, 1'-C), 129.30 (2C, 2',6'-C), 130.77 (1C, C-4a), 133.20 (1C, C-4), 150.34 (1C, C-6), 151.51 (1C, C-1), 153.20 (1C, C-7), 157.82 (1C, 4'-C), 168.44 (1C, COO).MS (m/z): 396 (M^+). Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10%; Found: C, 69.53; H, 5.93%.

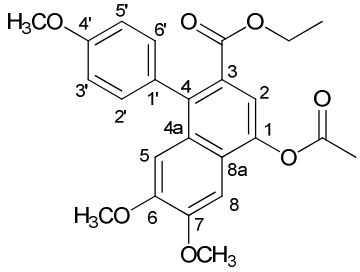
4.3.3. Ethyl 4-hydroxy-6,7-dimethoxy-1-(4-methoxyphenyl)-2-naphthoate, **4c**: Obtained from (E)-4-(3,4-dimethoxyphenyl)-3-(ethoxycarbonyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1c** (2.00g, 0.005 mol) in 90% (1.71g) yield, mp 115-117 ºC.IR (Nujol, γ cm^{-1}): 3630 (sh) (OH str), 1736 (s) (ester C=O str), 1112 (s) (C-O str).MS (m/z): 382 (M^+). Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.01; H, 5.80%; Found: C, 69.10; H, 5.71%.

4.3.4. Ethyl 4-hydroxy-7-methoxy-1-(4-methoxyphenyl)-2-naphthoate, **4d**: Obtained from (E)-3-(ethoxycarbonyl)-4-(3-methoxyphenyl)-4-(4-methoxyphenyl)but-3-enoic acid, **1d** (1.85g, 0.005 mol) in 83% (1.46g) yield, mp 128-129 ºC.IR (Nujol, γ cm^{-1}): 3635 (sh) (OH str), 1748 (s) (ester C=O str), 1226 (s) (C-O str). ^{1}HNMR ($CDCl_3$): δ 1.286 (t, 3H, CH_3), 3.860 (s, 6H, OCH_3), 4.282 (q, 2H, OCH_2), 5.404 (s, 1H, OH), 7.012-7.760 (m, 8H, Ar-H).^{13}C NMR ($CDCl_3$): δ14.33 (1C, CH_3), 55.85 (2C, OCH_3), 60.84 (1C, OCH_2), 106.35 (1C, C-5), 109.02 (1C, C-2), 114.56 (2C, 3',5'-C), 120.20 (1C, C-7), 121.36 (1C, C-8), 124.40 (1C, C-8a), 125.90 (1C, C-3), 128.44 (1C, 1'-C), 129.89 (2C, 2',6'-C), 133.20 (1C, C-4), 135.66 (1C, C-4a), 152.52 (1C, C-1), 158.10 (1C, C-6), 158.46 (1C, 4'-C), 168.22 (1C, COO). MS (m/z): 352 (M^+). Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72%; Found: C, 71.43; H, 5.61%.

Structure proofs of the synthesized new compounds **2**(**a-d**) and **4**(**a-d**) were provided by IR, ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis. In IR spectra, the stretching frequencies for the compounds **2**(**a-d**) showed a strong absorption band in the region 1746-1735 $cm^{-1}$for ester C=O bonds. A strong and intense absorption band is absorbed in the region of 1225-1208 cm^{-1} was assigned to C-O bonds.

The structural analysis of the compounds **2**(**a-d**) were made by ^{1}H NMR and ^{13}C NMR spectral studies by considering ethyl 4-acetoxy-6,7-dimethoxy-1-(4-methoxyphenyl)-2-naphthoate, **2c** as the representative compound. In its ^{1}H NMR spectra, **2c** showed a singlet at δ 2.258,δ 3.860, triplet at δ 1.286, and a quartet at δ 4.290 ppm. were assigned to acetoxy CH_3, OCH_3, ester CH_3 and OCH_2 protons respectively. An array of signals appeared as multiplet in the region δ 7.108-7.674 ppm. for seven protons were assigned to aromatic protons. The compounds **4a**, **4b** and **4c** showed similar consistent pattern signals in their ^{1}H NMR spectra.

In its ^{13}C NMR spectra, the compound **2c** showed the signals at δ 168.55 and δ 172.73 ppm. for ester and acetoxy carbonyl carbons respectively. The signals observed at δ 14.27, 20.53, 55.85 and 61.10 ppm. were assigned to ester CH_3, acetoxy CH_3, OCH_3 and ester OCH_2 carbons. The acetoxy function on C-1 carbon deshielded its signal to a downfield of δ 142.81 ppm. The other carbon chemical shifts of compound **2c** were depicted in fig-1. The compounds **2a**, **2b** and **2d** showed similar consistent pattern signals in their ^{13}C NMR spectra.



^{13}C NMR (CDCl3): d 100.57 (1C, C-8), 107.28 (1C, C-5), 114.43 (2C, 3',5'-C), 119.14 (1C, C-2), 123.98 (1C, C-3), 127.47 (1C, C-8a), 128.30 (1C, 1'-C), 129.12 (2C, 2',6'-C), 131.77 (1C, C-4a), 138.60 (1C, C-4), 149.96 (1C, C-6), 152.02 (1C, C-7), 157.84 (1C, 4'-C).

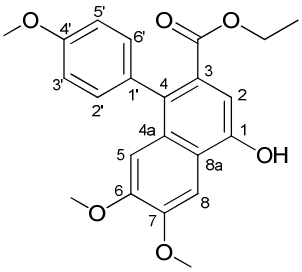
Fig-1: 13C NMR Chemical shifts of Ethyl 4-acetoxy-6,7-dimethoxy-1-(4-methoxyphenyl)-2-naphthoate, **2c**

The stretching frequencies in the IR spectrum of the compounds **4**(**a-d**) showed a sharp absorption band in the region of γ 3635-3618cm^{-1} for phenolic –OH and a strong absorption bands in the region 1748-1736 cm^{-1} for ester C=O bonds. A strong and intense absorption band is absorbed in the region 1226-1112 cm^{-1} was assigned to C-O bonds.

The structural analysis of the compounds **4**(**a-d**) were made by ^{1}H NMR and ^{13}C NMR spectral studies by considering ethyl 4-hydroxy-6,7-dimethoxy-1-(4-methoxyphenyl)-2-naphthoate, **4c** as the representative compound. In its ^{1}H NMR spectra, **4c** showed a signal due to phenolic –OH proton as singlet at δ 5.370 ppm. An array of signals appeared as multiplet in the region δ 6.978-7.526 ppm. for seven protons were assigned to aromatic protons. An intense singlet and a triplet appeared at δ 3.858 ppm. for nine protons and at δ 1.242 ppm. for three protons were assigned to three –OCH_3 protons and ester CH_3 protons respectively. Further, a quartet appeared at δ 4.230 ppm. for

two protons was assigned to ester –OCH_2 protons. The compounds **4a**, **4b** and **4c** showed similar consistent pattern signals in their ^{1}H NMR spectra.

In its ^{13}C NMR spectra, the compound **4c** showed the signal at δ 168.50 ppm. for ester carbonyl carbons. The signals observed at δ 14.15, 55.88 and 61.26 ppm. were assigned to CH_3, OCH_3 and OCH_2 carbons. The –OH function on C-1 carbon deshielded its signal to a downfield at δ 150.56 ppm. The carbon chemical shifts of compound **4c** were depicted in fig-2. The compounds **4a**, **4b** and **4d** showed similar consistent pattern signals in their ^{13}C NMR spectra.



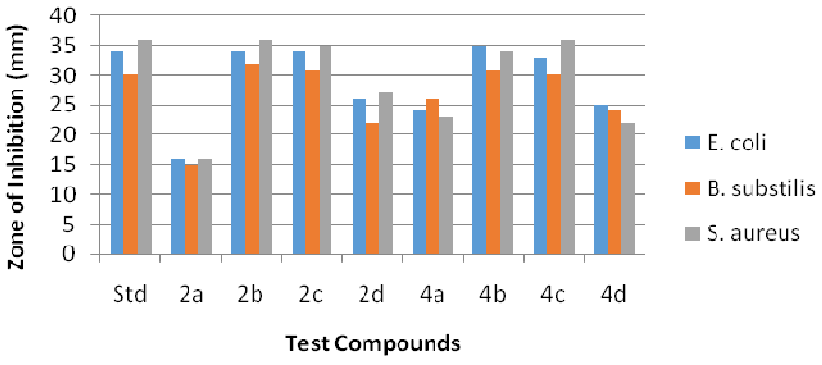
^{13}C NMR, δ ppm: 100.20 (1C, C-8), 105.04 (1C, C-5), 110.10 (1C, C-2), 114.42 (2C, 3',5'-C), 123.94 (1C, C-3), 124.42 (1C, C-8a), 128.74 (1C, 1'-C), 129.10 (2C, 2',6'-C), 130.72 (1C, C-4a), 133.22 (1C, C-4), 151.30 (1C, C-6), 154.23 (1C, C-7), 157.86 (1C, 4'-C).

Fig-2: ^{13}C NMR Chemical shifts of Ethyl 4-hydroxy-6,7-dimethoxy-1-(4-methoxyphenyl)-2-naphthoate **4c**

All the synthesized compounds **2**(**a-d**) and **4**(**a-d**) showed stable molecular mass peaks with their respective M+ ion peak as base peaks. Further their structures were supported by satisfactory elemental analysis.

Antimicrobial activity of the synthesized compounds was done by paper disc diffusion method [9-11]. The test compounds **2**(**a-d**) and **4**(**a-d**) at the concentration of 50 µg/mL in methanol in the nutrient agar media were screened for their antibacterial activity against bacteria species *Escherichia coli*, *Bacillus substilis*, *Staphylococus aureus* and antifungal activity against fungal species *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporium*. The antibiotics ciprofloxacin and nystatin were used as standard drugs against bacteria and fungi species respectively. The screening tests were carried out in triplicate and the results were expressed as a mean of three determinations.
The results of antibacterial activity of the synthesized compounds **2**(**a-d**) and **4**(**a-d**) tested against different bacteria species were summarized in fig 3.

Fig-3: Antibacterial activity of the synthesized compounds **2(a-d)** and **4(a-d)**. [Std = Ciprofloxacin]



The antibacterial activity results of the synthesized compounds **2**(**a-d**) and **4**(**a-d**) revealed that all compounds exerted moderate to excellent activity against the tested organisms, except ethyl 4-acetoxy-1-(4-ethoxyphenyl)-6-methoxy-2-naphthoate **2a**, that contain para substitutions on both the aromatic ring showed poor inhibition against all the tested organisms. The compounds **2b, 2c, 4b** and **4c** which contain 3,4-dimethoxy and 4-ethoxy substitutions showed excellent activity in comparison with the standard. The compounds **2d, 4a** and **4d** showed moderate inhibition against the tested bacterial strains.

The results of antifungal activity of the synthesized compounds **2**(**a-d**) and **4**(**a-d**) tested against different fungi species were summarized in fig 4.

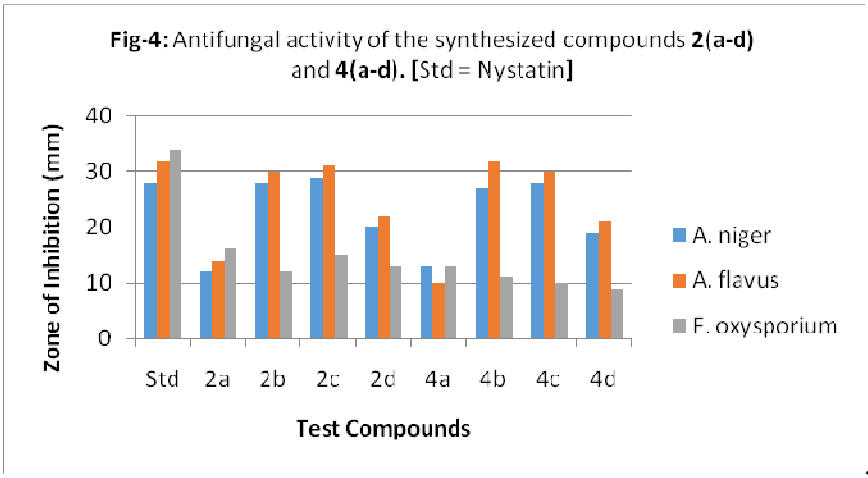


Fig-4: Antifungal activity of the synthesized compounds **2**(a-d) and **4(a-d).** [Std = Nystatin]

From the antifungal activity results, it was observed that compounds **2**(**a-d**) and **4**(**a-d**) showed lesser inhibition effect against *F. oxysporium* organism. The compounds **2b, 2c, 4b** and **4c** having 3,4-dimethoxy and 4-ethoxy substitutions in the aromatic ring showed a greater inhibition against *A. niger* and *A. flavus* organisms. Against the organisms *A. niger* and *A. flavus*, the compounds **2d, 4d** and **2a,4a** showed moderate and lesser inhibition respectively comparison with that of the standard drug.

CONCLUSION

The easy and accessible procedure for the synthesis of ethyl 4-acetoxy-1-aryl-2-naphthoates, **2**(**a-d**) and ethyl 1-aryl-4-hydroxy-2-naphthoates, **4**(**a-d**) from 4,4-diaryl-3-ethoxycarbonyl-but-3-enoic acids was described. The synthesized compounds were screened for their inhibitory effect on bacteria and fungi strains. The efficacy of the synthesized compounds **2b**, **2c**, **4b** and **4d** as potential antifungal and antibacterial agents validates the significance of this study.

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