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Synthesis of Novel Michael Adducts and Study of their Antioxidant and Antimicrobial Activities

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ABSTRACT

In the current study, the Michael addition reaction of nitromethane to chalcones was considered. 4-benzeloxy benzaldehyde was synthesized from 4-hydroxybenzaldehyde and benzyl bromide, which was then converted to chalcone derivatives by reaction with substituted acetophenones, and finally nitromethane was added to give Michael adducts. The structures of the synthesized compounds were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. All the products were screened for antioxidant, antimicrobial against *Staphylococcus aureus* G (+*ve*) and *Escherichia coli* G (-*ve*) microorganisms and antifungal activities against *Candida albicans*.

1. Introduction

Ketones with two aromatic groups connected via an enone (Ar–COCH=CH–Ar) are called (Chalcones) [1]. Additionally, there are widespread chalcones, particularly (trans-1,3-diaryl-2-propen-1-ones) in natural products, that are an intermediate in the biosynthesis of flavonoids. Chalcones possess α,β-unsaturated ketone moiety, which leads to several biological activities. Several productive compounds, such as flavonoids and iso-flavonoids, which are usually human diet constituents, are synthesized from chalcones as precursors [2]. The condensation reaction between aryl aldehydes and acetophenone in the presence of a catalyst readily gives chalcones as the product [3]. Aldehydes, substituted aryl, including 5- and 6-membered ring heteroaryl, and acetophenones were selected as constituents for the chaconne array [4]. There is a wide spreading attention toward chalcones due to the simplicity in their structure vital pharmacological influence, and biological activities such as anti-inflammatory [3, 5, 6], antibacterial and antifungal [7], antimalarial [8, 9], antioxidant [10], antitubercular [11], antitumor [12], antiviral [13], antimicrobial [14], antihypertensive [15], antileishmanial [16], antimitotic [10], and anticancer activities [17]. Several protocols and procedures have been documented for the preparation of chalcones. Among them, Aldol condensation and Claisen-Schmidt condensation are considered high-quality and powerful methods still in use.

Claisen-Schmidt condensation reaction is reported to be the best method to synthesize chalcones in the presence of alkaline bases [18] such as $Ba(OH)_2$ [19], LiOH, with ultrasonic irradiation and microwave irradiation [20].

The nitro group ($–NO_2$) is considered one of the most useful functional groups in organic synthesis, biochemistry, and other relevant fields. The crucial point to be noticed regarding this manner is the association of powerful electron attraction (E.A.) character, significantly depending on the moiety type that nitro group is attached. Moreover, the ($–NO_2$) group possess high electronegativity which resulting in the strong inductive electron-accepting property, which influences the electronic and energetic properties of the compounds [21]

The definition of Michael addition reaction stated upon the 1,4- nucleophilic addition (Michael donor) to an unsaturated carbonyl group having an electron-withdrawing group (Michael acceptor) [22]. Generally, it is utilized for the chemical bond formation and synthesizing building block in organic chemistry [23]. This type of reaction is a flexible procedure for the addition of those compounds having conjugated nucleophilic group with an unsaturated electron-withdrawing substituent. The common Michael donor

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mainly contains amine (-NH2), alcohol (-OH.), and thiol (-SH.) [24], and their corresponding reaction name are Aza-Michael addition [25], Oxa-Michael addition [26], and Thiol-Michael addition [24]. The rate of the reaction process depends on the two main factors (1) type of electrophile and nucleophile, and (2) steric hindrance [27]. Michael reaction has a wide spreading application in organic synthesis and is considered one of the most efficient methods to impact the formation of carbon-carbon bond [28, 29]). Commonly, Michael additions are accompanied by a suitable solvent at room temperature and/or elevated temperature when a strong base is present [30]. One of the most powerful economically carbon-carbon bond construction is asymmetric Michael addition of nitro-alkanes to enones, which provides useful adducts to be transformed into several important optical active compounds, for instance, unnatural amino acids and pyrrolidines [31]. Therefore, catalytic asymmetric reaction alternatives, either by using metal catalyst [32] and organic catalyst have developed successfully [33-35]. The asymmetric Addition of nitroalkanes to cyclic enones [36] and chalcones [37] has accomplished an excellent yield (up to 99%). However, few reports about (cinnamons) have been reported [38]. Transformation of nitroalkanes to chalcones which is an asymmetric Michael addition reaction, was first reported in 2001 by Sundararajan and coworkers [39]. Utilization of LiAl and a chiral polymer as a catalyst in the system, following several catalytic systems have developed producing a numerous chiral product with excellent yield [40].

Therefore, the objective of the current study is to investigate the in vitro antimicrobial and DPPH scavenging activity of new synthesized compounds from the Addition of nitroalkane to chalcones, in order to show the consequence of the nitro and ketone groups in the molecule, on the reactivity of the compounds.

2. Experimental

2.1. General

Reagent and materials all chemicals and solvents used of analytical reagent (A.R) grade quality and were used as received. Most of the chemicals were provided by Sigma Aldrich (India). Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by thin-layer chromatography using Merck silica gel 60 F254 coated aluminum plates in ethyl acetate/n-hexane medium. Infrared (I.R.) spectra were recorded on Shimadzu FT-IR 8400S instrument and were calibrated using a polystyrene film. Solid compounds were recorded in potassium bromide disks (KBr). ^{1}H-NMR and ^{13}C-NMR were recorded on a 400MHz Bruker spectrometer instrument using dimethyl sulfoxide (DMSO-d_6), and tetramethyl silane (TMS) as an internal standard. Chemical shifts were quoted in parts per million (ppm) downfield from TMS.

2.2. General method of the synthesis of 4-(benzyloxy) benzaldehyde (3):

4-hydroxybenzaldehyde (1) (1.2212 g, 0.01 mol) was dissolved in 15 mL DMF, then (1.382 g, 0.01mol) of K_2CO_3 was added. The mixture was stirred for 20 minutes at room temperature, benzyl bromide **(2)** (1.8 mL, 0.015 mol) was added dropwise, the mixture was stirred for 3hr., the reaction was monitored by TLC and the reaction was poured into ice water and stirred, the white precipitate was filtrated off and washed with water and ethanol then dried and recrystallized from ethanol. [41]

2.2.1. Spectral data of 4-(benzyloxy) benzaldehyde (3):

Chemical formula= $C_{14}H_{12}O_2$, white color, yield 88%, melting point 70-72 ^{0}C. FTIR (KBr, cm^{-1}): 3035 (C-H Ar. str.), 1829 (C-H alpha. str.), 1685 (C=O str.), 1600, 1452 (C=C ar str.), 1165 (C-O str.), 1508 (C$\underline{H}_2$ bend).^{1}H NMR (400 MHz, DMSO-d_6), δ 5.23 (s, 2H, C$\underline{H}_2$O), 7.212 (d, *J* = 8.4 Hz, 2H, H3', H5'), 7.370- 7.334 (t, *J* = 7.2, 14.4 Hz, H4''), 7.429-7.392 (t, *J* = 7.2, 14.8 Hz, H3'', H5''), 7.478 (d, *J* =7.2 Hz, 2H, H2'', H6''), 7.881 (d, *J* = 8.4 Hz, 2H, H2', H6'), 9.878 (s, 1H, C$\underline{H}$O).^{13}C NMR (400 MHz, DMSO- d_6), δ 70.12 (C$\underline{H}_2$-O), 115.74 (C3', C5'), 128.34 (C2'', C6''), 128.56 (C4''),128.99 (C3'', C5''), 130.24 (C1'), 132.28 (C2', C6'), 136.77 (C1''), 163.75 (C4'), 191.76 (C=O).

2.3. General method for the synthesis of chalcone derivatives (5a-d):

An equimolar quantity of 4-benzyloxy benzaldehyde (3) (2.1224 gm, 0.01 mol) and different substituted aromatic ketones (4a-d) (0.01 mol) were dissolved in 20 mL ethanol stirred for 30 min, then 1mL of 40% NaOH was added. The reaction was stirred for about 24 hr. at room temperature, the reaction was monitored by TLC and then poured into ice water, acidified with 10 % aqueous hydrochloric acid, and kept in the refrigerator for 24 hr. to complete the precipitation, then filtered and washed with water then ethanol, purified twice by recrystallization in ethanol. [42]

2.3.1 Spectral data of 3-(4-(benzyloxy)phenyl)-1-phenylprop-2-en-1-one (5a):

Chemical formula = $C_{22}H_{18}O_2$, yellow color, yield 87%, melting point 116-118 ^{0}C. FTIR (KBr, cm^{-1}): 3034 (C-H ar. str.), 2974 (C-H aliph. str.), 1653 (C=O str.), 1566, 1450 (C=C ar str.), 1589 (C=C aliph. str.), 1172 (C-O str.), 1508 (CH_2 bend). ^{1}H NMR (400 MHz, DMSO-d_6), δ 5.186 (s, 2H, Ar-C$\underline{H}_2$-O), 7.109 (d, *J* = 8.8 Hz, 2H, H3', H5'), 7.328-7.364 (tr, *J* =7.2, 14.4 Hz, H4''), 7.390-7.427 (tr, *J* = 7.6, 14.8 Hz, 2H, H3'', H5''), 7.475 (d, *J* = 7.2 Hz, 2H, H2'', H6''), 7.553-7.590 (tr, *J* = 7.6, 14.8 Hz, 2H, H3, H5), 7.646-7.782 364 (tr, *J* =7.2, 14.4 Hz, H4),7.740 (d, IH, *J* = 15.6, CH=C$\underline{H}$-CO), 7.814-7.883 (m, 3H, H2', H6', CH= C$\underline{H}$-Ar), 8.155 (d, *J* = 7.2 Hz, 2H, H2, H6).^{13}C NMR (400 MHz, DMSO-d_6) δ 69.86 (C$\underline{H}_2$O), 115.7 (C3',C5'), 120.08 (CH=C$\underline{H}$-CO), 127.97 (C2'',C6''), 128.7 (C1'), 128.44 (C4''), 128.90 (C2,C6), 128.95 (C3'',C5''), 129.22 (C3,C5), 131.31 (C2',C6'), 133.42 (C4), 137.15 (C1''), 138.29 (C1), 144.46 (C$\underline{H}$-Ar), 160.93 (C4'), 189.47 (C=O).

2.3.2 Spectral data of 3-(4-(benzyloxy)phenyl)-1-(p-tolyl)prop-2-en-1-one (5b):

Chemical formula = $C_{23}H_{20}O_2$, yellow color, yield 85%, melting point 113-115 ^{0}C. FTIR (KBr, cm^{-1}): 3034 (C-H ar. str.), 2914 (C-H aliph. str.), 1656 (C=O str.), 1565, 1454 (C=C ar str.), 1593 (C=C aliph. str.), 1170 (C-O str.), 1510 (CH_2 bend).^{1}H NMR (400 MHz, DMSO-d_6), δ 2.393 (s, 3H, CH_3), 5.174 (s, 2H, Ar-C$\underline{H}_2$-O), 7.099 (d, *J* = 8.8 Hz, 2H, H3', H5''), 7.424-7.422(m, 5H, H3, H5, H3'', H4'', H5''), 7.472 (d, *J* = 7.6 Hz, 2H, H2'', H6''), 7.722 (d, IH, *J* = 15.6, CH=C$\underline{H}$-CO), 7.800-7.868 (m, 3H, H2', H6', CH=C$\underline{H}$-Ar), 8.071 (d, *J* = 8.4 Hz, 2H, H2, H6).^{13}C NMR (400 MHz, DMSO-d_6) δ 21.65 (-$\underline{C}H_3$), 69.85 ($\underline{C}H_2$O), 115.67 (C3', C5'), 120.08 (CH=$\underline{C}$H-CO), 128.04 (C2'', C6''), 128.26 (C1') 128.42 (C4''), 129.04 (C3,C5), 129.78 (C2,C6), 131.22 (C2', C3'), 135.77 (C1), 137.16 (C1''), 143.79 (C4), 144.04 ($\underline{C}$H-Ar), 160.85 (C4'), 188.89 (C=O).

2.3.3. Spectral data of 3-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)prop-2-en-1-one (5c):

Chemical formula = $C_{22}H_{17}O_2F$, yellow color, yield 88%, melting point 118-120 ^{0}C. FTIR (KBr, cm^{-1}): 3034 (C-H ar. str.), 2870 (C-H alph. str.), 1656 (C=O str.), 1570, 1450 (C=C ar str.), 1600 (C=C aliph. str.), 1170 (C-O str.), 1508 (CH_2 bend), 1033 (C-F). ^{1}H NMR (400 MHz, DMSO-d_6), δ 5.183 (s, 2H, Ar-C$\underline{H}_2$-O), 7.106 (d, *J* = 8.8 Hz, 2H, H3', H5'), 7.325-7.423 (m, 5H, H2'', H3'', H4'', H5'', H6''), 7.473 (d, *J* =7.2 Hz, 2H, H3, H5), 7.737 (d, IH, *J* = 15.6, CH=C$\underline{H}$-CO), 7.819-7.881 (m, 3H, H2', H6', CH=C$\underline{H}$-Ar), 8.232-8.268 (m, 2H, H2, H6).^{13}C NMR (400 MHz, DMSO-d_6) δ 69.86 ($\underline{C}H_2$O), 115.68 (C3', C5'), 116.09 (C3, C5), 119.80 (CH=$\underline{C}$H-CO), 127.93 (C2'', C6''), 128.27 (C1'), 128.43 (C4''), 128.94 (C3'', C5''), 131.35 (C2', C6'), 131.82 (C2, C6), 134.93 (C1''), 137.14 (C1''), 144.61 ($\underline{C}$H-Ar), 160.96 (C4'), 166.67 (C4), 187.96 (C=O).

2.3.4. Spectral data of 3-(4-(benzyloxy)phenyl)-1-(4-chlorophenyl)prop-2-en-1-one (5d):

Chemical formula = $C_{22}H_{17}O_2Cl$, yellow color, yield 83%, melting point 128-130 ^{0}C. FTIR (KBr, cm^{-1}): 3061 (C-H ar. str.), 2976 (C-H aliph. str.), 1791 (C=O str.), 1543, 1454 (C=C ar str.), 1610 (C=C aliph. str.), 1184 (C-O str.), 1514 (CH_2 bend), 688 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6), δ 5.188 (s, 2H, Ar-C$\underline{H}$2-O), 7.108 (d, *J* = 8.8 Hz, 2H, H3', H5'), 7.328-7.364 (tr, *J* =7.2, 14.4 Hz, H4''), 7.390-7.426 (tr, *J* = 6.8, 14.8 Hz, 2H, H3'', H5''), 7.475 (d, *J* = 7.2 Hz, 2H, H2'', H6''), 7.733 (d, *J* = 8.4 Hz, 2H, H3, H5), 7.742 (d, IH, *J* = 15.6, CH=C$\underline{H}$-CO), 7.844-7.886 (m, 3H, H2', H6', CH=C$\underline{H}$-Ar), 8.174 (d, *J* = 8.8 Hz, 2H, H2, H6).^{13}C NMR (400 MHz, DMSO-d_6) δ 69.87 ($\underline{C}H_2$O), 115.70 (C3', C5'), 119.72 (CH=$\underline{C}$H-CO), 127.89 (C2'', C6''), 128.28 (C1'), 128.44 (C4''), 128.95 (C3'', C5''), 129.31 (C3, C5), 130.82 (C2', C6'), 131.42 (C2, C6), 136.92 (C1), 137.13 (C1''), 138.37 (C4), 144.95 $\underline{C}$H-Ar), 161.04 (C4'), 188.33 (C=O).

2.4. General method of Michel addition of nitromethane to chalcone derivatives (7a-d).

Chalcone derivatives (5a-d) (0.001mol) were dissolved with nitromethane (6) (0.001 mol) in 10 mL DMF and stirred for 0.5 hr., then (10 mL, 1M) NaOH was added. The reaction system was stirred at room temperature for 2.0-4.0 hr., monitored by TLC. After the completion of the reaction, the solvent was evaporated in a vacuum and extracted with dichloromethane. The organic phase was dried on (Na_2SO_4), filtrated off, evaporated, and recrystallized from ethanol [43].

2.4.1 Spectral data of 3-(4-(benzyloxy)phenyl)-4-nitro-1-phenylbutan-1-one(7a):

Chemical formula = $C_{23}H_{21}O_4N$, white, yield 91%, melting point 86-88 ^{0}C. FTIR (KBr, cm^{-1}): 3034 (C-H ar. str.), 2900 (C-H aliph. str.), 1678 (C=O str.), 1610, 1452 (C=C str.), 1552-1382 (N-O str.), 1247 (C-N str.), 1182 (C-O str.), 1514 (CH_2 bend). ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.443-3.580 (m, 2H, C$\underline{H}_2$-CHO), 3.962-4.035 (m, 1H, -C$\underline{H}$-CH_2-NO_2), 4.785-4.981 (m, 2H, C$\underline{H}_2$-NO_2), 5.048 (s, 2H, C$\underline{H}_2$O), 6.948 (d, *J* = 8.4 Hz, 2H, H2', H5'), 7.289-7.343 (m, 3H, H4'', H2', H6'), 7.387-7.443 (m, 4H, H2'', H6'', H3'', H5''), 7.501-7.539 (tr, *J* =7.6, 15.2 Hz, 2H, H3,H5), 7.623-7.759 (tr, *J* = 7.2, 14.4 Hz, 1H, H4), 7.938 (d, *J* = 7.2 Hz , 2H, H2, H6).^{13}C NMR (400 MHz, DMSO-d_6) δ 39.04 (-$\underline{C}$H-CH_2-NO_2), 41.70 ($\underline{C}H_2$-CHO), 69.59 ($\underline{C}H_2$O), 80.35 ($\underline{C}H_2$-NO_2), 115.10 (C3', C5'), 128.19 (C2'', C6''), 128.30 (C2', C6'), 128.40 (C4''), 128.89 (C3, C5), 129.21 (C2,C6), 129.36 (C3'',C5''), 132.47 (C1'), 133.87 (C4), 136.87 (C1''), 137.54 (C1), 157.94 (C4'), 197.99 (C=O).

2.4.2. Spectral data of 3-(4-(benzyloxy)phenyl)-4-nitro-1-(p-tolyl)butan-1-one (7b):

Chemical formula = $C_{24}H_{23}O_4N$, white, yield 88%, melting point 95-96 ºC. FTIR (KBr, cm^{-1}): 3034 (C-H ar. str.), 2897 (C-H aliph. str.), 1672 (C=O str.), 1608, 1454 (C=C str.), 1550-1381 (N-O str.), 1247 (C-N str.), 1182 (C-O str.), 1514 (CH_2 bend), 1406 (-CH_3 bend).^{1}H NMR (400 MHz, DMSO-d_6), δ 2.466 (s, 3H, C$\underline{H}_3$), 3.410-3.535 (m, 2H, C$\underline{H}_2$-CHO), 3.952-4.025 (m, 1H, -C$\underline{H}$-CH_2-NO_2), 4.781-4.975(m, 2H, C$\underline{H}_2$-NO_2), 5.044 (s, 2H, C$\underline{H}_2$O), 6.933 (d, *J* = 8.8 Hz, 2H, H3', H5'), 7.282-7.342 (m, 5H, H4'', H2, H6, H3, H5), 7.367-7.403 (tr, *J* =6.8, 14.4 2H, H3'', H5''), 7.433 (d, J =7.2 Hz, 2H, H2',H6'), 7.84 (d, *J* = 8 Hz , 2H, H2'', H6'').^{13}C NMR (400 MHz, DMSO-d_6) δ 21.61 ($\underline{C}H_3$), 39.10 (-$\underline{C}$H-CH_2-NO_2), 41.55 ($\underline{C}H_2$-CHO), 69.59 ($\underline{C}H_2$O), 80.37 ($\underline{C}H_2$-NO_2), 115.08 (C3', C5'), 128.19 (C2'', C6''), 128.30 (C2', C6'), 128.53 (C4''), 128.89 (C2, C6), 129.35 (C3,C5), 129.74 (C3'',C5''), 132.57 (C1'), 134.43 (C1), 137.54 (C1''), 144.27 (C4), 157.93 (C4'), 197.46 (C=O).

2.4.3. Spectral data of 3-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-4-nitrobutan-1-one (7c):

Chemical formula = $C_{23}H_{20}O_4NF$, white, yield 85%, melting point 91-93 ^{0}C. FTIR (KBr, cm^{-1}): 3034 (C-H ar. str.), 2899 (C-H aliph. str.), 1681 (C=O str.), 1595, 1452 (C=C str.), 1550-1382 (N-O str.), 1247 (C-N str.), 1182 (C-O str.), 1514 (CH_2 bend), 1161 (C-F).^{1}H NMR (400 MHz, DMSO-d_6), δ 3.440-3.567 (m, 2H, C$\underline{H}_2$-CHO), 3.949-4.022 (m, 1H, -C$\underline{H}$-CH_2-NO_2), 4.774-4.973 (m, 2H, CH_2-NO_2), 5.049 (s, 2H, C$\underline{H}_2$O), 6.938 (d, *J* = 8.4 Hz, 2H, H3', H5'), 7.285-7.442 (m, 9H, H4'',H3,H5, H2', H6', H3'',H5'', H2'',H6''), 8.005-8.040 (m, 2H, H2, H6).^{13}C NMR (400 MHz, DMSO-d_6) δ 39.03 (-$\underline{C}$H-CH_2-NO2), 41.65 ($\underline{C}H_2$-CHO), 69.59 ($\underline{C}H_2$O), 80.33 ($\underline{C}H_2$-NO_2), 115.10 (C3', C5'), 116.11 (C3, C5), 128.19 (C2'', C6''), 128.30 (C2', C6'), 128.89 (C4''), 129.36 (C3'',C5''), 131.39 (C2,C6), 132.41 (C1'), 133.62 (C1), 137.54 (C1''), 157.94 (C4'),166.82 (C4), 196.62 (C=O).

2.4.4. Spectral data of 3-(4-(benzyloxy)phenyl)-1-(4-chlorophenyl)-4-nitrobutan-1-one (7d):

Chemical formula = $C_{23}H_{20}O_4NCl$, white, yield 83%, melting point 117-118 ^{0}C. FTIR (KBr, cm-1): 3035 (C-H ar. str.), 2900 (C-H aliph. str.), 1681 (C=O str.), 1610, 1452 (C=C str.), 1550-1381 (N-O str.), 1247 (C-N str.), 1180 (C-O str.), 1514 (CH_2 bend), 742 (C-Cl) .^{1}H NMR (400 MHz, DMSO-d_6), δ 3.446-3.567 (m, 2H, C<u>H</u>$_2$-CHO), 3.942-4.015 (m, 1H, -C<u>H</u>-CH$_2$-NO$_2$), 4.769-4.970 (m, 2H, C<u>H</u>$_2$-NO$_2$), 5.049 (s, 2H, C<u>H</u>$_2$O), 6.936 (d, *J* = 8.4 Hz, 2H, H3', H5'), 7.291 (d, *J* = 8.8 Hz, 2H, H2',H6), 7.325-2.442 (m, 5H, H4'', H2'', H6'', H3'', H5''), 7.594 (d, *J* = 8.4 Hz , 2H, H3, H5), 7.948 (d, *J* = 8.4 Hz, 2H, H2,H6).13C NMR (400 MHz, DMSO-d6) δ 38.99 (-<u>C</u>H-CH2-NO2), 41.72 (<u>C</u>H$_2$-CHO), 69.59 (<u>C</u>H$_2$O), 80.31 (<u>C</u>H$_2$-NO$_2$), 128.19 (C2'', C5''), 128.30 (C2', C6'), 128.89 (C4''), 129.33 (C3, C5), 129.35 (C3'', C5''), 130.34 (C2,C6), 132.36 (C1'), 135.53 (C1), 137.53 (C1''), 138.78 (C4), 157.95 (C4), 197.08 (C=O).

2.5. General method of antimicrobial activity:

Two types of bacteria *Staphylococcus aureus* as a Gram-positive bacterial strain, *Escherichia coli* as a Gram-negative bacterial strain, and one type of fungal used to screen synthesized compounds by dilution method. The dilution method was used for the Determination of (MIC). The minimum inhibition concentration (MIC) was measured by using a macro tube dilution, the prepared serial concentration of each synthesized compound (200, 600, and 1000 µg/mL), and for antibacterial ciprofloxacin, HCl was used as standard compared with the results against (*Escherichia coli* (gram-positive), *Staphylococcus aureus* (gram-negative)), for antifungal fluconazole was used as standard compared with results against (*C. albicans*). The MIC was measured for organic materials which inhibited bacterial growth against the control sample which consisted of 2 mL of nutrient broth and 40 µL of the activated culture of bacterial suspension as clarified in (Table 1), and then incubated at 37 °C for 20 h. After incubation, the plates were read using an ELISA reader (BioTek 800TS, USA) at 570 nm. The next day optical density was recorded, as shown in (Table 2). [44-47]

Table 1. Preparation of test sample

Stock solution 4000µg/mL (0.02g in 5mL DMSO				
NO.	Conc. (µg/mL)	Chemical Volume (µl)	Nutrient broth volume (ml)	Bacterial suspension volume (µl)
1	200	50	1.91	40
2	600	150	1.81	40
3	1000	250	1.71	40

Table 2: MIC of the compounds against bacteria strain and fungal strain

	Minimum Inhibitory Concentration (MIC µg/mL)		
	G(+ve) bacteria	G(-ve) bacteria	Fungi
Compound	*S. aureus*	*E. coli*	*C. albicans*
3	1000	600	1000
5a	600	600	600
5b	1000	200	1000
5c	1000	1000	600
5d	600	1000	600
7a	600	1000	600
7b	1000	200	1000
7c	600	600	600
7d	1000	1000	600
CIP 5µg/mL	5		-
FLU 50 µg/mL	-		50

*The MIC is the minimum availability of antibacterial agent that stops the growth of any organism

2.6. General method of antioxidant activity for synthesis compounds:

The antioxidant activity of the synthesized derivatives was observed through the DPPH free radical scavenging assay, and three different concentrations were prepared (25, 50, and 100 µg/ml). An equal amount of sample solution was added to an equal amount of 0.1 mM ethanoic DPPH (2, 2-diphenyl-1- picrylhydrazyl) solution. The mixture was mixed and vortexed thoroughly and kept in a dark place for 30 minutes. After 30 min of incubation, the absorbance was read against a *blank at 517 nm with a UV. /Visible spectrophotometer. [46, 48]*

$$DPPH\ scavenged\ \% = Ac - As/Ac \times 100$$

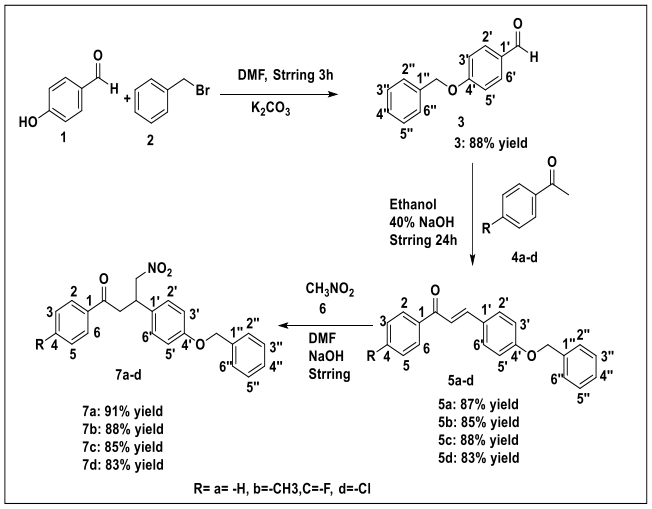
Ac - is the control reaction's absorbance.
As - is synthesized compound's absorbance.

3. Result and Discussion

3.1 Chemistry

All the synthesized compounds were characterized by TLC, melting point, FT-IR, ^{1}H NMR, and ^{13}C NMR; their data are given in the experiment section.

There are three steps for the synthesis of Michael adduct, in the first step the 4-benzyloxy benzaldehyde (3) was synthesized by reacting benzyl bromide with 4-hydroxy benzaldehyde in DMF in the presence of potassium carbonate anhydrous as Catalyst, stirring for 3 hours at room temperature with producing excellent yield (88%) of at a short time. The process is highly advantageous in the comparison with other procedures used for the synthesis of similar products. In other protocols, acetone was used with refluxing process for about 5 hours giving a medium yield of 68% [49]. The amount of the products synthesized via stirring at room temperature has higher than the amount of the products synthesized via reflux, therefore, the present route can be considered a highly efficient and powerful procedure for the preparation of such products.



Scheme 1: Synthesis steps for the formation of Michael adducts from Chalcone derivatives

In the second step, Chalcone derivatives (5a-d) were synthesized by reaction of 4-benzyloxy benzaldehyde with different substituted acetophenone in ethanol in the presence of NaOH as a catalyst, stirring at room temperature for 24 hours gave excellent yield (83-88%) (Scheme 1). Using the Claisen-Schmidt protocol is considered the best and very common procedure for the synthesis of chalcones due to the easy condensation of the reactants and furnishing the products with high yield and the process can be done at room temperature. That is why the Claisen-Schmidt reaction is useful for the synthesis of synthesized chalcones (5a-d) with a *J* value (15.6) which shows the characteristic of E-configuration. The large value of *J* clearly reveals (trans) geometry. Finally, Michael's adducts (7a-d) were synthesized by the reaction between the chalcones with nitromethane in DMF in the presence of NaOH as a catalyst and stirring for 2-4 hours at room temperature (Scheme 1). The Michael conjugate addition is a very useful reaction for the mild formation of C-C bonds in organic synthesis. Therefore, a simple method was implemented for the synthesis of Michael adducts with excellent yield (83-91%). A combination of DMF and aqueous NaOH proved to be the most suitable and effective solvent/base pair among those examined, giving (7a-d) in good yield within a short time. It was worth mentioning that a similar reaction was reported recently which took several hours for complete conversion under reflux conditions [50]. Compound (7a-d) clearly confirmed by FTIR. ^{1}H, and ^{13}C and their data are given in the experimental section.

3.2. Biological activity

3.2.1 Assay of in Vitro Antimicrobial Activity

The biological activity of the compound (3, 5a, 5b, 5c, 5d, 7a, 7b, 7c, and 7d) screened for antibacterial activity against *S. aureus* and *E. coli* for antifungal against *C. albicans* by using broth microdilution method the ciprofloxacin Hcl used as a standard for antibacterial and use fluconazole as standard for antifungal. The MIC result is shown in (table 2) for the compounds (5b, 7b) process the least MIC and inhibit the growth of *E.coli* at 200 µg/ml. while compounds (3,5a,5c,5d,7a,7c,7d) inhibit the growth of *E.coli* ,*S.aureus* , And *C.albicans* at 600 µg/ml. at 1000 µg/ml, the growth of *E.coli* , *C.albicans* and *S.aureus* were inhibited by compound (3,5b,5c,5d,7a,7b,7d).

According to the antibacterial activity screening result, compound (3) possesses effective and selective antibacterial activity against gram-negative Bactria (*E.coli*) with MIC valve 600 µg/ml. On the other hand, compound (3) had moderate antibacterial activity against gram-positive Bactria (*S.aureus*) Compared to the gram-negative Bactria (*E.coli*) with a MIC value of 1000 µg/ml, the antifungal activity of the compound (3) against, *C.albicans*, according to the antifungal studies the compound (3) had an antifungal activity with MIC value 1000 µg/ml

According to the antibacterial activity screening result, the compound (5b) possesses effective and selective antibacterial activity against gram-negative Bactria (*E. coli*) with MIC valve 200 µg/ml. On the other hand, the other compound had moderate antibacterial activity against gram-positive Bactria (*S.aureus*) and gram-negative Bactria (*E.coli*) with MIC value 600-1000, antifungal activity of the compound (5a,5b,5c,5d) against *C.albicans*, according to the antifungal studies the compound (5a,5c,5d) had a high antifungal activity with MIC value 600 µg/ml compared to the compound (5b) with MIC value 1000 µg/ml.

According to the result of the antibacterial activity screening, the compound (7b) possesses effective and selective antibacterial activity against gram-negative Bactria (*E.coli*) with MIC valve 200 µg/ml, on the other hand, the other compound had moderate antibacterial activity, against gram-positive Bactria (*S.aureus*) and gram-negative Bactria (*E.coli*) with MIC value 600-1000, antifungal activity of the compound (7a,7b,7c,7d) against *C.albicans*, according to the antifungal studies the compound (7a,7c,7d) had a high antifungal activity with MIC value 600 µg/ml compared to the compound (5b) with MIC value 1000 µg/ml.

3.2.2 Assay of in Vitro DPPH Radical Scavenging Activity

The antioxidant activity of synthesized compounds are shown in (table 3, 4, and 5) for 4-benzyloxy-benzaldehyde (3), chalcone derivatives (5a-d), and nitro compounds (7a-d), compared to s (ascorbic acid) activity as standard (table 6), the synthesized compound had different antioxidant activity according to the ability of compound to act as free radical scavenger and to evaluated antioxidant.

The antioxidant activity of synthesized 4-benzyloxy benzaldehyde (3) is shown in (table 3). The antioxidant of 4-benzyloxy benzaldehyde (IC50 = 30.81) is higher than ascorbic acid (IC50= 33.09).

Table 3: DPPH scavenging for 4-benzyloxy benzaldehyde (3):

Sample	Concentration µg/ml	%SCV	IC50(µg/ml)
3	25	44.33	30.81
	50	64.98	
	100	91.78	

The antioxidant activity of synthesized chalcone derivatives (5a-d) are shown in (table 4), the antioxidant activity of chalcone derivatives is lower than ascorbic acid except for the compound (5a) IC50, for compound (5a) equal to 29.50, the antioxidant activity of the compound (5a) is greater than ascorbic acid, the strength of antioxidant functions of the chalcone derivatives are in the following order: ascorbic acid› 5c › 5d› 5b.

Table 4: DPPH scavenging for chalcone derivatives (5a-d):

Sample	Concentration µg/ml	%SCV	IC50(µg/ml)
5a	25	45.39	29.50
	50	65.44	
	100	92.78	
5b	25	18.89	96.83
	50	30.9	
	100	51.08	
5c	25	22.34	77.29
	50	35.95	
	100	61.89	
5d	25	20.34	83.45
	50	32.95	
	100	58.43	

The antioxidant activity of synthesized compounds (7a-d) is shown in (table 5). The antioxidant activity is lower than ascorbic acid except for compound (7a) IC50, compound (7a) equal to 23.76, the antioxidant activity of the compound (7a) is greater than ascorbic acid, but the strength of antioxidant functions of the other chalcone derivatives are in the following order: ascorbic acid› 7c › 7d› 7b›

Table 5: DPPH scavenging for nitromethane addition to chalcone (7a-d):

Sample	Concentration µg/ml	%SCV	IC50(µg/ml)
7a	25	49.78	23.76
	50	67.54	
	100	96.22	
7b	25	34.38	55.58
	50	45.54	
	100	74.56	
7c	25	45.78	36.44
	50	54.54	
	100	82.38	
7d	25	38.78	56.17
	50	47.54	
	100	66.05	

3.2.2.4 Antioxidant activity of Ascorbic acid:

Ascorbic acid, also known as vitamin C, is a powerful antioxidant that has an essential part in preventing free radicals as seen in (Table 6). IC50 For ascorbic acid =33.09 µg/ml.

Table 6: *DPPH scavenging for Ascorbic acid:*

	Concentration µg/ml	%SCV	IC50(µg/ml)
Ascorbic acid	25	43.33	33.09
	50	62.98	
	100	90.98	

IC means Inhibition concentration, IC50 is the concentration required to result in 50 % antioxidant activity.

Conclusion

Chalcone derivatives (5a-d) are synthesized with a good yield by a simple method, and Nitro alkane was added by Michael addition reaction to chalcones to obtain compounds (7a-7d) in a respectable yield. Ethanol was used as a suitable solvent for the recrystallization of the products. The nitro compounds (7a-d) showed Moderate antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* except (7b), which have high antibacterial activity compared to the other compounds and showed the compound (7b) moderate antifungal against *Candida albicans* compared to the compound (7a,7c,7d) which had higher antifungal compared to the compound (7b). The result of antioxidant for nitro compound (7a-d) showed that compound (7a) has high antioxidant compared to standard (Ascorbic acid), and compounds (7b-d) have lower antioxidant compared to standard (Ascorbic acid).

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References

[1] Y.K. Rao, S.-H. Fang, and Y.-M. Tzeng, Differential effects of synthesized 2′-oxygenated chalcone derivatives: modulation of human cell cycle phase distribution, *Bioorganic & medicinal chemistry*, 12 (2004) 2679-2686.

[2] H.P. Ávila, E.d.F.A. Smânia, F. Delle Monache, and A.S. Júnior, Structure–activity relationship of antibacterial chalcones, *Bioorganic & medicinal chemistry*, 16 (2008) 9790-9794.

[3] Z. Nowakowska, A review of anti-infective and anti-inflammatory chalcones, *European journal of medicinal chemistry*, 42 (2007) 125-137.

[4] D.G. Powers, D.S. Casebier, D. Fokas, W.J. Ryan, J.R. Troth, and D.L. Coffen, Automated parallel synthesis of chalcone-based screening libraries, *Tetrahedron*, 54 (1998) 4085-4096.

[5] S.H. Lee, G.S. Seo, J.Y. Kim, X.Y. Jin, H.-D. Kim, and D.H. Sohn, Heme oxygenase 1 mediates anti-inflammatory effects of 2′, 4′, 6′-tris (methoxymethoxy) chalcone, European journal of pharmacology, 532 (2006) 178-186.

[6] Y.R. Prasad, A.S. Rao, and R. Rambabu, Synthesis of some 4'-amino chalcones and their antiinflammatory and antimicrobial activity, *Asian J. Chem*, 21 (2009) 907-914.

[7] Z.N. Siddiqui, S. Praveen, T.M. Musthafa, A. Ahmad, and A.U. Khan, Thermal solvent-free synthesis of chromonyl chalcones, pyrazolines and their in vitro antibacterial, antifungal activities, *Journal of enzyme inhibition and medicinal chemistry*, 27 (2012) 84-91.

[8] A. Valla, B. Valla, D. Cartier, R. Le Guillou, R. Labia, L. Florent, S. Charneau, J. Schrevel, and P. Potier, New syntheses and potential antimalarial activities of new

'retinoid-like chalcones', *European Journal of Medicinal Chemistry*, 41 (2006) 142-146.
[9] J.N. Domínguez, C. León, J. Rodrigues, N.G. de Domínguez, J. Gut, and P.J. Rosenthal, Synthesis and antimalarial activity of sulfonamide chalcone derivatives, *Il Farmaco*, 60 (2005) 307-311.
[10] R. Gacche, N. Dhole, S. Kamble, and B. Bandgar, In-vitro evaluation of selected chalcones for antioxidant activity, *Journal of Enzyme Inhibition and Medicinal Chemistry*, 23 (2008) 28-31.
[11] Y.-M. Lin, Y. Zhou, M.T. Flavin, L.-M. Zhou, W. Nie, and F.-C. Chen, Chalcones and flavonoids as anti-tuberculosis agents, *Bioorganic & medicinal chemistry*, 10 (2002) 2795-2802.
[12] W.D. Seo, Y.B. Ryu, M.J. Curtis-Long, C.W. Lee, H.W. Ryu, K.C. Jang, and K.H. Park, Evaluation of anti-pigmentary effect of synthetic sulfonylamino chalcone, *European journal of medicinal chemistry*, 45 (2010).
[13] J.C. Trivedi, J.B. Bariwal, K.D. Upadhyay, Y.T. Naliapara, S.K. Joshi, C.C. Pannecouque, E. De Clercq, and A.K. Shah, Improved and rapid synthesis of new coumarinyl chalcone derivatives and their antiviral activity, *Tetrahedron Letters*, 48 (2007) 8472-8474.
[14] Z. Nowakowska, B. Kędzia, and G. Schroeder, Synthesis, physicochemical properties and antimicrobial evaluation of new (E)-chalcones, *European journal of medicinal chemistry*, 43 (2008) 707-713.
[15] M. Bonesi, M.R. Loizzo, G.A. Statti, S. Michel, F. Tillequin, and F. Menichini, The synthesis and Angiotensin Converting Enzyme (ACE) inhibitory activity of chalcones and their pyrazole derivatives, *Bioorganic & medicinal chemistry letters*, 20 (2010) 1990-1993.
[16] S. Ducki, R. Forrest, J.A. Hadfield, A. Kendall, N.J. Lawrence, A.T. McGown, and D. Rennison, Potent antimitotic and cell growth inhibitory properties of substituted chalcones, *Bioorganic & medicinal chemistry letters*, 8 (1998) 1051-1056.
[17] C. Karthikeyan, N. SH Narayana Moorthy, S. Ramasamy, U. Vanam, E. Manivannan, D. Karunagaran, and P. Trivedi, Advances in chalcones with anticancer activities, *Recent patents on anti-cancer drug discovery*, 10 (2015) 97-115.
[18] Y.R. Prasad, A.L. Rao, R. Rambabu, and P.R. Kumar, Synthesis and biological evaluation of some novel chalcone derivatives, *Oriental Journal of Chemistry*, 23 (2007) 927.
[19] M.S. Rao, J. Kotesh, R. Narukulla, and H. Duddeck, Synthesis and spectroscopic characterization of some chromanochalcones and their dihydro derivatives, *Arkivoc*, (2004) 96-102.
[20] V. Calvino, M. Picallo, A. López-Peinado, R. Martín-Aranda, and C. Durán-Valle, Ultrasound accelerated Claisen–Schmidt condensation: A green route to chalcones, *Applied Surface Science*, 252 (2006) 6071-6074.
[21] A. Jezuita, K. Ejsmont, and H. Szatylowicz, Substituent effects of nitro group in cyclic compounds, S*tructural Chemistry*, 32 (2021) 179-203.
[22] E. Emori, T. Arai, H. Sasai, and M. Shibasaki, A catalytic Michael addition of thiols to α, β-unsaturated carbonyl compounds: asymmetric Michael additions and asymmetric protonations, *Journal of the American Chemical Society*, 120 (1998) 4043-4044.
[23] Y. Zhang, and W. Wang, Recent advances in organocatalytic asymmetric Michael reactions, *Catalysis Science & Technology*, 2 (2012) 42-53.
[24] D.P. Nair, M. Podgorski, S. Chatani, T. Gong, W. Xi, C.R. Fenoli, and C.N. Bowman, The thiol-Michael addition click reaction: a powerful and widely used tool in materials chemistry, *Chemistry of Materials*, 26 (2014) 724-744.
[25] J.L. Vicario, D. Badía, L. Carrillo, J. Etxebarria, E. Reyes, and N. Ruiz, The asymmetric aza-Michael reaction. A review, *Organic preparations and procedures international*, 37 (2005) 513-538.
[26] C.F. Nising, and S. Bräse, The oxa-Michael reaction: from recent developments to applications in natural product synthesis, *Chemical Society Reviews*, 37 (2008) 1218-1228.
[27] H.-W. Chu, B. Sethy, P.-W. Hsieh, and J.-T. Horng, Identification of Potential Drug Targets of Broad-Spectrum Inhibitors with a Michael Acceptor Moiety Using Shotgun Proteomics, *Viruses*, 13 (2021) 1756.
[28] H. Kabashima, H. Tsuji, T. Shibuya, and H. Hattori, Michael addition of nitromethane to α, β-unsaturated carbonyl compounds over solid base catalysts, *Journal of Molecular Catalysis A: Chemical*, 155 (2000) 23-29.
[29] H.O. House, Modern synthetic reactions, (1972).
[30] E.D. Bergmann, D. Ginsburg, and R. Pappo, The M ichael Reaction, *Organic reactions*, 10 (2004) 179-556.
[31] R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, and M. Petrini, Conjugate additions of nitroalkanes to electron-poor alkenes: Recent results, *Chemical reviews*, 105 (2005) 933-972.
[32] L. Wang, Q. Zhang, X. Zhou, X. Liu, L. Lin, B. Qin, and X. Feng, Asymmetric Conjugate Addition of Nitromethane to Enones Catalyzed by Chiral N, N′- Dioxide–Scandium (III) Complexes, *Chemistry–A European Journal*, 16 (2010) 7696-7699.
[33] R. Manzano, J.M. Andres, R. Álvarez, M.D. Muruzabal, A.R. de Lera, and R. Pedrosa, Enantioselective Conjugate Addition of Nitro Compounds to α, β- Unsaturated Ketones: An Experimental and Computational Study, *Chemistry–A European Journal*, 17 (2011) 5931-5938.
[34] P. Kwiatkowski, K. Dudzinski, and D. Łyżwa, Effect of high pressure on the organocatalytic asymmetric Michael reaction: Highly enantioselective synthesis of γ-nitroketones with quaternary stereogenic centers, *Organic Letters*, 13 (2011) 3624-3627.
[35] L.-t. Dong, R.-j. Lu, Q.-s. Du, J.-m. Zhang, S.-p. Liu, Y.-n. Xuan, and M. Yan, Highly enantioselective conjugate addition of 1-bromonitroalkanes to α, β-unsaturated ketones catalyzed by 9-amino-9-deoxyepiquinine, *Tetrahedron*, 65 (2009) 4124-4129.
[36] S. Hanessian, Z. Shao, and J.S. Warrier, Optimization of the Catalytic Asymmetric Addition of Nitroalkanes to Cyclic Enones with Trans-4, 5-methano-l-proline, *Organic Letters*, 8 (2006) 4787-4790.
[37] B. Vakulya, S. Varga, and T. Soos, Epi-cinchona based thiourea organocatalyst family as an efficient asymmetric Michael addition promoter: Enantioselective conjugate addition of nitroalkanes to chalcones and α, β-unsaturated N-acylpyrroles, *The Journal of Organic Chemistry*, 73 (2008) 3475-3480.
[38] G. Szanto, P. Bombicz, A. Gruen, and I. Kadas, Highly enantioselective organocatalytic conjugate addition of nitromethane to benzylidene acetones, Chirality: *The Pharmacological, Biological, and Chemical Consequences of Molecular Asymmetry*, 20 (2008) 1120-1126.

[39] G. Sundararajan, and N. Prabagaran, A new polymer-anchored chiral catalyst for asymmetric Michael addition reactions, *Organic letters*, 3 (2001) 389-392.

[40] B. Vakulya, S. Varga, A. Csámpai, and T. Soós, Highly enantioselective conjugate addition of nitromethane to chalcones using bifunctional cinchona organocatalysts, *Organic letters*, 7 (2005) 1967-1969.

[41] A. Baran, E. Karakilic, F. Özlem, and Ö. Furkan, Synthesis of chalcone-containing zinc and cobalt metallophthalocyanines; investigation of their photochemical, DPPH radical scavenging and metal chelating characters, *Org. Commun*, (2020).

[42] S. Tala, P. Vekariya, R. Ghetiya, B. Dodiya, and H. Joshi, Synthesis and biological study of some new chalcone and pyrazole derivatives,*Indian journal of chemistry*, (2013).

[43] Y. Liang, D. Dong, Y. Lu, Y. Wang, W. Pan, Y. Chai, and Q. Liu, One-pot synthesis of substituted δ1-pyrrolines through the michael addition of nitroalkanes to chalcones and subsequent reductive cyclization in aqueous media, *Synthesis*, 2006 (2006) 3301-3304.

[44] I. Wiegand, K. Hilpert, and R.E. Hancock, Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances, *Nature protocols*, 3 (2008) 163-175.

[45] S.A. Hassan, and D.M. Aziz, Synthesis, in vitro Antimicrobial assay and Molecular Docking Studies of some new Symmetrical Bis-Schiff Bases and their 2-Azetidinones, *Zanco Journal of Pure and Applied Sciences*, 33 (2021) 34-50.

[46] S.A. Hassan, An efficient One-pot three-component synthesis, Molecular docking, ADME and DFT predictions of new series Thiazolidin-4-one derivatives bearing a Sulfonamide moiety as potential Antimicrobial and Antioxidant agents, *Egyptian Journal of Chemistry*, 65 (2022) 1-3.

[47] S.A. Hassan, and D.M. Aziz, Synthesis of New Series Bis-3-Chloro-β-Lactam Derivatives from Symmetrical Bis-Schiff Bases as Effective Antimicrobial Agents with Molecular Docking Studies, *Science Journal of University of Zakho*, 9 (2021) 128-137.

[48] S.A. Hassan, Synthesis, Spectroscopic study and Biological activity of some New Heterocyclic compounds derived from Sulfadiazine, *Zanco Journal of Pure and Applied Sciences*, 31 (2019) 92-109.

[49] A.R. Katritzky, Q. Long, H.-Y. He, G. Qiua, and A.L. Wilcox, Preparation of 2-alkoxy-5-methoxybenzaldehydes and 2-ethoxy-5-alkoxybenzaldehydes, *Arkivoc*, 6 (2006) 868-875.

[50] R. Ballini, P. Marziali, A. Mozzicafreddo, and Amberlyst A-27, an Efficient Heterogeneous Catalyst for the Michael Reaction of Nitroalkanes with β-Substituted Alkene Acceptors, *The Journal of Organic Chemistry*, 61 (1996) 3209-3211.