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Utilization of Microwave Irradiation and Conventional Methods on Synthesis of Novel Pyridine Derivatives of Expected Anticancer Activity

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ABSTRACT

Novel pyridine derivatives were synthesized by reaction of chalcones 4(a-e) with different acetyls 5(a, b) under microwave irradiations or under reflux conditions. In general, microwave irradiation offered the advantages of high yields, short reaction times, and simplicity compared to the conventional methods. The structures of all the compounds were confirmed by analytical and spectral data. Some of The synthesized compounds were evaluated against HepG-2, and showed significant antitumor activities.

Keywords: Green chemistry; microwave; solventless; grinding; pyridine

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INTRODUCTION

Microwave provides a powerful way in synthesis in light of the green chemistry protocol; in other words, it furnishes many chemical reaction improvements, such as enhanced reaction rates, higher yields of pure products as well as eco-friendly advantages [1]. Thus, procedures employing microwave methodology involving an appropriate green-approach must be welcome.

Chalcones, one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices and soy based foodstuff, have been reported to possess several biological activities such as anti-inflammatory [2], antibacterial [3,4], anti-fungal [5-7], and anti-tumor activities [8-11]. An important feature of chalcones is their ability to act as an intermediate for the synthesis of biologically active heterocyclic compounds such as, pyridine, derivatives [12,13].

Pyridine is the parent ring system of a large number of naturally occurring products and important industrial, pharmaceutical, and agricultural chemicals. Pyridine derivatives exhibit various biological activities such as anticancer [14-16], antibacterial [17,18], antimycobacterial [19,20], antiviral [21-24], antitubercular [25], anticonvulsant [26], anti-inflammatory [27], insecticidal [28], antioxidant [29], antidiabetic [30], and analgesic [31] activities.

EXPERIMENTAL SECTION

Instruments

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT-IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VXR-300 NMR spectrometer. ^{1}H

spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in dimethyl sulphoxide (DMSO-d6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000EX mass spectrometer at 70 e. V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.
Reactions carried out under microwave irradiation were performed in a domestic microwave oven using 50 or 100% power.

Materials, solvents and reagents
All organic solvents were purchased from commercial sources and used as received or dried using standard procedures unless otherwise stated. All chemicals were purchased from Merck, Aldrich or Across and used without further purification, thin layer chromatography (TLC) was performed on precoated Merck 60GF254 silica gel plates with fluorescent indicator, and detection by means of UV light at 254 and 360 nm.

Organic synthesis and reactions

1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)ethanone (2)

Conventional method: *p*-aminoacetophenone (**1**) (100 mmol) was refluxed in 50 ml acetic acid for 6 hours to give buff precipitate which was filtered and recrystalized from acetone to afford 1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)ethanone (**2**) in 88% Yield [32].

Green method: *p*-aminoacetophenone (1) (100 mmol) and one drop of acetic acid was ground in mortar for 1 hour till color change to give buff precipitate which was recrystallized from acetone to afford product identical in all respects (mp, mixed mp and TLC) with 1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)ethanone (**2**) in 95% Yield.
M.p. = 158-160 °C; IR (KBr, cm^{-1}): 1179 (C-N), 1537 (C=C), 1590 (C=N), 1674 (C=O), 3263, 3296 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 2.84 (s, 3H, CH_3C=O), 6.55-7.93 (m, 8H, Ar-H), 10.28 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.65 ($\underline{C}H_3C$=N), 26.87 ($\underline{C}H_3C$=O), 112.91, 118.58, 125.29, 129.94, 131.03, 131.94, 144.11, 154.08, 196.93 (aromatic), 165.40 ($CH_3\underline{C}$=N); MS (*m/z*): 252 (M^+); Anal. For $C_{16}H_{16}N_2O$ (252.13). (Calcd: C, 76.16; H, 6.39; N, 11.10%; Found: C, 76.14; H, 6.38; N, 11.13%)

Reaction of 1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)ethanone (2) with different aldehydes (3a-e)

Conventional method: A mixture of 1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)ethanone (**2**) (50 mmol) and appropriate aldehydes (3a-e) (50 mmol) was stirred at room temperature in 20 ml ethanol in presence of 0.01g potassium hydroxide for appropriate time to afford the corresponding derivatives (4a-e) in 80-85% yield.

Green method: A mixture of 1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)ethanone (2) (50 mmol) and appropriate aldehydes (3a-e) (50 mmol) in presence of 0.01g potassium hydroxide was ground in mortar for appropriate time till color change to afford product identical in all respects (mp, mixed mp and TLC) with (4 a-e) in 93-96% yield.

1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)-3-phenylprop-2-en-1-one (4a)

M.p. = 150-152 °C; IR (KBr, cm^{-1}): 1177 (C-N), 1534 (C=C), 1590 (C=N), 1673 (C=O), 3262, 3299 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.55 (d, 1H, C$\underline{H}$=CH), 6.71-8.66 (m, 13H, Ar-H), 10.29 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.65 ($\underline{C}H_3C$=N), 112.90, 118.98, 129.38, 130.12, 131.03, 131.96, 162.98 (aromatic), 121.96 ($\underline{C}$H=CH), 144.12 (CH=$\underline{C}$H), 169.41 ($CH_3\underline{C}$=N), 196.93 ($\underline{C}$=O); MS (*m/z*): 340 (M^+); Anal. For $C_{23}H_{20}N_2O$ (340.42). (Calcd: C, 81.15; H, 5.92; N, 8.23%; Found: C, 81.19; H, 5.90; N, 8.21%)

1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)-3-(thiophen-2-yl)prop-2-en-1-one (4b)
M.p. = 140-142 °C; IR (KBr, cm^{-1}): 1175 (C-N), 1313 (C-S), 1529 (C=C), 1588 (C=N), 1674 (C=O), 3185, 3299 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 7.21 (d, 1H, CH=CH), 7.55-8.09 (m, 11H, Ar-H), 10.28 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.26 (CH_3C=N), 114.40, 118.99, 120.71, 129.96, 130.23, 130.70, 131.96, 132.44, 136.57, 140.31, 144.11 (aromatic), 129.17 (CH=CH), 133.13 (CH=CH), 169.41 (CH_3C=N),

187.43 (C=O); MS (*m/z*): 346 (M^+); Anal. For $C_{21}H_{18}N_2OS$ (346.45). (Calcd: C, 72.80; H, 5.24; N, 8.09%; Found: C, 72.83; H, 5.23; N, 8.07%)

1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)-3-(furan-2-yl)prop-2-en-1-one (4c)

M.p. = 110-111 °C; IR (KBr, cm^{-1}): 1178 (C-N), 1260 (C-O), 1533 (C=C), 1589 (C=N), 1673 (C=O), 3266, 3297 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.08 (s, 3H, CH_3-C=N-), 6.69 (d, 1H, CH=CH), 7.09-8.07 (m, 11H, Ar-H), 10.31 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 113.96, 117.21, 118.99, 130.14, 130.36, 131.94, 132.47, 144.12, 144.18, 146.52, 151.70, 157.48 (aromatic), 119.10 (CH=CH), 129.94 (CH=CH), 169.46 (CH_3C=N), 187.40 (C=O); MS (*m/z*): 330 (M^+); Anal, For $C_{21}H_{18}N_2O_2$ (330.38). (Calcd: C, 76.34; H, 5.49; N, 8.48%; Found: C, 76.36; H, 5.46; N, 8.49%)

1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)-3-(pyridin-3-yl)prop-2-en-1-one (4d)

M.p. = 200-202 °C; IR (KBr, cm^{-1}): 1179 (C-N), 1529 (C=C), 1589 (C=N), 1676 (C=O), 3268, 3298 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 7.48 (d, 1H, CH=CH), 7.70-8.62 (m, 12H, Ar-H), 10.29 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.79 (CH_3C=N), 114.41, 118.98, 124.39, 129.94, 130.52, 131.09, 132.29, 135.52, 144.40, 150.77, 151.37, 159.26 (aromatic), 124.30 (CH=CH), 140.33 (CH=CH), 169.35 (CH_3C=N), 187.85 (C=O); MS (*m/z*): 341 (M^+); Anal. For $C_{21}H_{18}N_2O_2$ (341.41). (Calcd: C, 77.40; H, 5.61; N, 12.31%; Found: C, 77.42; H, 5.63; N, 12.27%)

1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (4e)

M.p. = 144-145 °C; IR (KBr, cm^{-1}): 1179 (C-N), 1531 (C=C), 1590 (C=N), 1674 (C=O), 3113 (NH), 3268, 3298 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 7.22 (d, 1H, CH=CH),7.24-8.29 (m, 13H, Ar-H), 9.94 (s, 1H, NH), 10.29 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.77 (CH_3C=N), 112.90, 114.73, 118.99, 121.29, 122.99, 123.92, 129.95, 131.95, 137.53, 138.98, 150.86, 158.40 (aromatic), 124.58 (CH=CH), 144.11 (CH=CH), 169.42 (CH_3C=N), 185.43 (C=O); MS (*m/z*): 379 (M^+); Anal. For $C_{25}H_{21}N_3O$ (379.45). (Calcd: C, 79.13; H, 5.58; N, 11.07%; Found: C, 79.10; H, 5.59; N, 11.09%)

Reaction of chalcones (4a-e) with different acetyls (5a, b)

Conventional method: A mixture of chalcones (4a-e) (1 mmol), and 2-acetyl thiophene (5a) or 3-aceyl pyridine (5b) (1 mmol) in the presence of sodium hydroxide (0.1 mmol) was ground in mortar for 20 minutes till color change to obtain diketone then add ammonium acetate (1 mmol) and the mixture was refluxed in glacial acetic acid for 6 hours until completion of the reaction (monitored by TLC) to give precipitates which were filtered and recrystallized from ethanol/DMF (1:1) to afford the corresponding derivatives (6a-j) in 55-71% yield.

Green method: A mixture of chalcones (4a-e) (1mmol) and 2-acetyl thiophene (5a) or 3-aceyl pyridine (5b) (1 mmol) in the presence of sodium hydroxide (0.1 mmol) was ground in mortar for 20 minutes till color change to obtain diketone then add ammonium acetate (1mmol) and one drop of glacial acetic acid in a 10 ml glass vial and subjected to microwave irradiation for 1-2 minutes, the solid formed was purified by recrystallization from ethanol/DMF (1:1), affording product identical in all respects (mp, mixed mp, and TLC) with (6a-j) in 90-96% yield.

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)aniline (6a)**

M.p. = 258-259 °C; IR (KBr, cm^{-1}): 1178 (C-N), 1315 (C-S), 1534 (C=C), 1591 (C=N), 3187, 3297 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.55-8.36 (m, 18H, Ar-H), 10.26 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 114.75, 116.77, 118.48, 122.81, 126.01, 128.04, 129.49, 131.78, 136.43, 139.32, 141.02, 148.24, 150.60, 152.57, 154.34 (aromatic), 169.34 (CH_3C=N); MS (*m/z*): 445 (M^+); Anal. For $C_{29}H_{23}N_3S$ (445.58). (Calcd: C, 78.17; H, 5.20; N, 9.43%; Found: C, 78.19; H, 5.21; N, 9.40%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-phenyl-[2,3'-bipyridin]-6-yl)aniline (6b)**

M.p. = 280-281 °C; IR (KBr, cm^{-1}): 1176 (C-N), 1539 (C=C), 1589 (C=N), 3185, 3295 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.55-9.53 (m, 19H, Ar-H), 10.62 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 113.29, 118.21, 122.54, 124.56, 126.60, 128.04, 129.16, 130.94, 131.77, 136.10, 139.85, 141.36, 148.56, 149.42, 151.45, 153.75 (aromatic), 169.35 (CH_3C=N); MS (*m/z*): 440 (M^+); Anal. For $C_{30}H_{24}N_4$ (440.54). (Calcd: C, 81.79; H, 5.49; N, 12.72%; Found: C, 81.76; H, 5.48; N, 12.76%)

_N_-(1-(4-aminophenyl)ethylidene)-4-(4,6-di(thiophen-2-yl)pyridin-2-yl)aniline (6c)

M.p. = 224-225°C; IR (KBr, cm^{-1}): 1178 (C-N), 1315 (C-S), 1535 (C=C), 1591 (C=N), 3186, 3295 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.55-8.18 (m, 16H, Ar-H), 10.32 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 112.91, 118.62, 122.21, 125.15, 127.45, 128.31, 129.91, 131.03, 131.88, 137.54, 140.43, 144.23, 147.40, 149.16, 151.12, 153.75, 156.61 (aromatic), 169.51 (CH_3C=N); MS (*m/z*): 451 (M^+); Anal. For $C_{27}H_{21}N_3S_2$ (451.61). (Calcd: C, 71.81; H, 4.69; N, 9.30%; Found: C, 71.84; H, 4.65; N, 9.31%)

_N_-(1-(4-aminophenyl)ethylidene)-4-(4-(thiophen-2-yl)-[2,3'-bipyridin]-6-yl)aniline (6d)

M.p. = 245-247°C; IR (KBr, cm^{-1}): 1176 (C-N), 1315 (C-S), 1536 (C=C), 1590 (C=N), 3184, 3293 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.55-9.48 (m, 17H, Ar-H), 10.39 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.53 (CH_3C=N), 113.87, 118.48, 122.22, 124.25, 126.27, 128.03, 129.75, 131.78, 135.25, 138.40, 140.44, 147.13, 149.15, 151.71, 153.48 (aromatic), 169.36 (CH_3C=N); MS (*m/z*): 446 (M^+); Anal. For $C_{28}H_{22}N_4S$ (446.57). (Calcd: C, 75.31; H, 4.97; N, 12.55%; Found: C, 75.33; H, 4.98; N, 12.52%)

_N_-(1-(4-aminophenyl)ethylidene)-4-(4-(furan-2-yl)-6-(thiophen-2-yl)pyridin-2-yl)aniline(6e)

M.p. = 194-196 °C; IR (KBr, cm^{-1}): 1177 (C-N), 1265 (C-O), 1317 (C-S), 1534 (C=C), 1593 (C=N), 3181, 3286 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.11 (s, 3H, CH_3-C=N-), 6.56-8.24 (m, 16H, Ar-H), 10.29 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.53 (CH_3C=N), 108.04, 110.68, 114.34, 118.80, 122.56, 125.42, 126.60, 128.58, 129.49, 130.61, 137.55, 142.47, 147.13, 149.68, 151.13, 154.60 (aromatic), 169.36 (CH_3C=N); MS (*m/z*): 435 (M^+); Anal. For $C_{27}H_{21}N_3OS$ (435.54). (Calcd: C, 74.46; H, 4.86; N, 9.65%; Found: C, 74.48; H, 4.87; N, 9.62%)

_N_-(1-(4-aminophenyl)ethylidene)-4-(4-(furan-2-yl)-[2,3'-bipyridin]-6-yl)aniline (6f)

M.p. = 210-211°C; IR (KBr, cm^{-1}): 1176 (C-N), 1263 (C-O), 1534 (C=C), 1592 (C=N), 3182, 3286 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.77-9.46 (m, 17H, Ar-H), 10.34 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 106.07, 112.70, 115.32, 118.21, 122.53, 124.26, 126.02, 127.72, 129.48, 131.53, 134.67, 138.99, 142.22, 146.54, 148.55, 150.86, 152.29, 155.18 (aromatic), 169.35 (CH_3C=N); MS (*m/z*): 430 (M^+); Anal. For $C_{28}H_{22}N_4O$ (430.50). (Calcd: C, 78.12; H, 5.15; N, 13.01%; Found: C, 78.10; H, 5.13; N, 13.05%)

_N_-(1-(4-aminophenyl)ethylidene)-4-(6'-(thiophen-2-yl)-[3,4'-bipyridin]-2'-yl)aniline (6g)

M.p. = 286-288 °C; IR (KBr, cm^{-1}): 1176 (C-N), 1315 (C-S), 1534 (C=C), 1593 (C=N), 3180, 3289 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 7.22-9.24 (m, 17H, Ar-H), 10.40 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.53 (CH_3C=N), 113.56, 116.18, 118.48, 122.55, 125.16, 128.03, 129.76, 131.20, 133.50, 136.42, 139.58, 141.88, 147.12, 149.42, 151.72, 153.16, 155.18 (aromatic), 169.35 (CH_3C=N); MS (*m/z*): 446 (M^+); Anal. For $C_{28}H_{22}N_4S$ (446.57). (Calcd: C, 75.31; H, 4.97; N, 12.55%; Found: C, 75.33; H, 4.99; N, 12.51%)

4-([3,2':4',3''-terpyridin]-6'-yl)-_N_-(1-(4-aminophenyl)ethylidene)aniline (6h)

M.p. = 272-274°C; IR (KBr, cm^{-1}): 1179 (C-N), 1536 (C=C), 1591 (C=N), 3181, 3290 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 7.50-9.53 (m, 18H, Ar-H), 10.34 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.53 (CH_3C=N), 113.55, 114.40, 122.21, 124.56, 126.61, 128.57, 129.49, 130.62, 133.81, 137.88, 139.31, 147.38, 149.15, 150.59, 152.56, 155.77 (aromatic), 169.35 (CH_3C=N); MS (*m/z*): 441 (M^+); Anal. For $C_{29}H_{23}N_5$ (441.53). (Calcd: C, 78.89; H, 5.25; N, 15.86%; Found: C, 78.88; H, 5.29; N, 15.83%)

4-(4-(1H-indol-3-yl)-6-(thiophen-2-yl)pyridin-2-yl)-_N_-(1-(4-aminophenyl)ethylidene)aniline (6i)

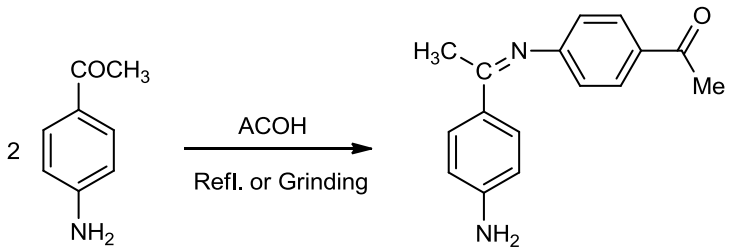
M.p. = 242-243 °C; IR (KBr, cm^{-1}): 1177 (C-N), 1316 (C-S), 1531 (C=C), 1594 (C=N), 3057 (NH), 3185, 3290 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.98-8.26 (m, 18H, Ar-H), 10.30 (s, 1H, NH), 10.58 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.53 (CH_3C=N), 102.60, 110.94, 113.55, 116.16, 122.21, 124.24, 127.13, 129.76, 131.20, 137.29, 139.31, 142.45, 148.24, 150.59, 152.30, 155.77 (aromatic), 169.35 (CH_3C=N); MS (*m/z*): 484 (M^+); Anal. For $C_{31}H_{24}N_4S$ (484.61). (Calcd: C, 76.83; H, 4.99; N, 11.56%; Found: C, 76.85; H, 4.96; N, 11.57%)

4-(4-(1H-indol-3-yl)-[2,3'-bipyridin]-6-yl)-*N*-(1-(4-aminophenyl)ethylidene)aniline (6j)

M.p. = 256-258 °C; IR (KBr, cm^{-1}): 1178 (C-N), 1532 (C=C), 1594 (C=N), 3054 (NH), 3185, 3292 (NH_2); ^1H NMR (DMSO-d_6): δ= 2.09 (s, 3H, CH_3-C=N-), 6.97-9.49 (m, 19H, Ar-H), 10.31 (s, 1H, NH), 10.55 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 100.24, 111.25, 114.74, 118.47, 119.31, 121.68, 123.11, 124.23, 126.01, 127.45, 129.76, 131.51, 134.67, 137.88, 139.33, 147.71, 149.42, 151.13, 153.48, 155.53 (aromatic), 169.35 (CH_3C=N); MS (*m/z*): 479 (M^+); Anal. For $C_{32}H_{25}N_5$ (479.57). (Calcd: C, 80.14; H, 5.25; N, 14.60%; Found: C, 80.11; H, 5.26; N, 14.62%)

RESULTS AND DISCUSSION

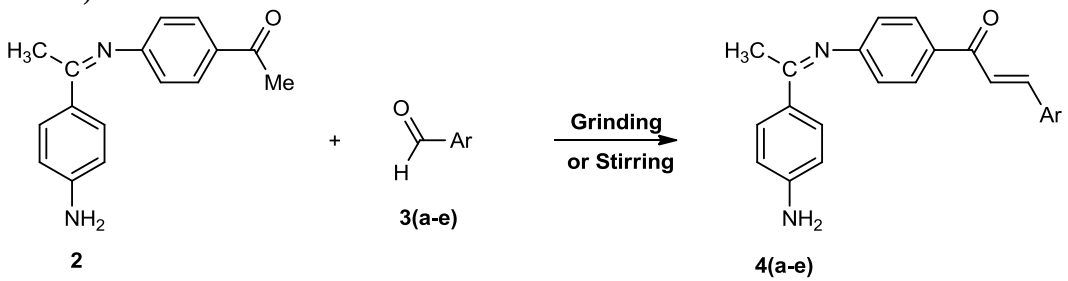
p-aminoacetophenone (1) was ground in presence of one drop of acetic acid to afford 1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl)ethanone (2) in 95% Yield, whereas conventional method occurs for 6 hours with 88% yield (Scheme 1) [32].



1 **2**

Scheme 1

A mixture of 1-(4-((1-(4-aminophenyl)ethylidene)amino)phenyl) ethanone (**2**) and appropriate aldehyde **3(a-e)** was stirred at room temperature in 20 ml ethanol in presence of 0.01g potassium hydroxide for 3-4 hours to afford the corresponding chalcone 4(a-e) in 80-85% yields, whereas grinding method occurs for 0.5-1 hour with (93-96%) yield (Scheme 2).



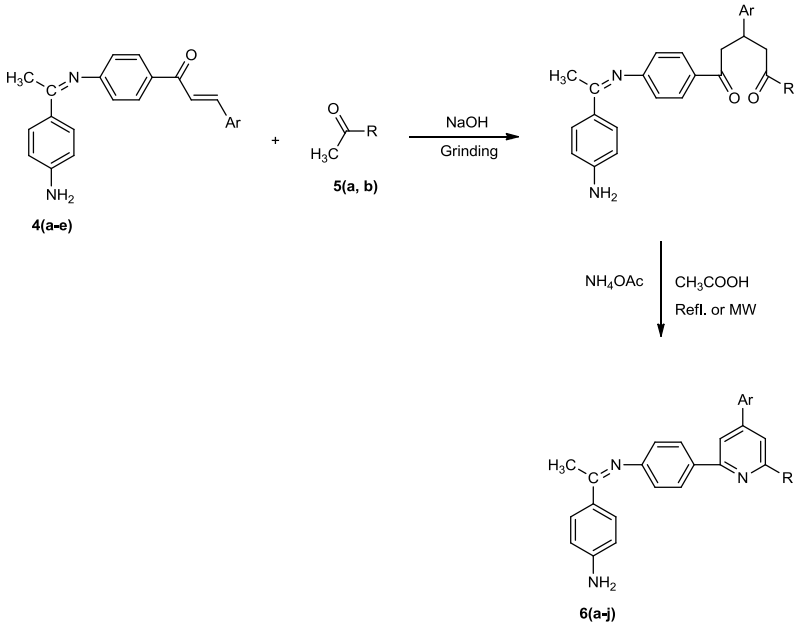
2 **3(a-e)** **4(a-e)**

Scheme 2

The structure of compounds 4(a-e) were confirmed by its elemental analysis and spectral data. For example, its IR spectrum showed C-N bands at 1177-1179 cm^{-1}, C=C bands at 1529-1534 cm^{-1}, C=N bands at 1588-1590 cm^{-1}, C=O bands at 1673-1676 cm^{-1} and two symmetric and asymmetric bands at 3185-3268, 3297-3299 cm^{-1} due to amino group, while compound (4b) appeared C-S band at 1313 cm^{-1}, while compound (4c) appeared C-O band at 1260 cm^{-1} and compound (4e) appeared NH band at 3113 cm^{-1}, its ^1H NMR spectrum displayed a singlet signal at δ 2.09 ppm due to methyl protons (s, 3H, CH_3-C=N-), and a duplet signal at δ 6.55-7.48 ppm due to proton (d, 1H, C<u>H</u>=CH), in addition to an aromatic multiplets in the region δ 6.71-8.66 ppm, The NH_2 protons appeared as a D_2O exchangeable singlet at δ 10.28-10.31 ppm, while compound (4e) showed a singlet signal at δ 9.94 ppm due to NH proton (s, 1H, NH), its ^{13}C NMR spectrum showed a δ 24.26-24.79 (<u>C</u>H_3C=N), 119.10-129.17 (<u>C</u>H=CH), 129.94-144.12 (CH=<u>C</u>H), 169.35-169.46 (CH_3<u>C</u>=N), 185.43-196.93 (<u>C</u>=O).

A mixture of chalcones 4(a-e) (1mmol), and 2-acetyl thiophene or 3-aceyl pyridine 5(a, b) (1mmol) in the presence of sodium hydroxide (0.1mmol) was ground in mortar for 20 minutes till color change to obtain diketone then add ammonium acetate (1mmol) and the mixture was refluxed in acetic acid glacial for 6 hours until completion of the reaction (monitored by TLC) to give precipitates which were filtered and recrystalized from ethanol/DMF (1:1) to

afford the corresponding derivatives 6(a-j) in 55-71% yield, whereas microwave method occurs for 1-2 minutes with 90-96% yield.



Scheme 3

The structure of compounds 6(a-j) were confirmed by its elemental analysis and spectral data. For example, its IR spectrum showed C-N bands at 1176-1179 cm^{-1}, while C-O bands at 1265 and 1263 cm^{-1} for compounds (6e) and (6f),while C-S bands at 1315, 1315, 1315, 1317, 1315and 1316 cm^{-1} for compounds (6a), (6c), (6d), (6e), (6g) and (6i) respectively, C=C bands at 1531-1539 cm^{-1}, C=N bands at 1589-1594 cm^{-1}, while NH bands at 3057 and 354 cm^{-1} for compounds (6i) and (6j), and two symmetric and asymmetric bands at 3180-3187, 3286-3297 cm^{-1} due to amino group, its ^{1}H NMR spectrum displayed a singlet signal at δ 2.09 ppm due to methyl protons (s, 3H, CH_3-C=N-), and disappeared a signal due to proton (CH=CH), in addition to an aromatic multiplets in the region δ 6.55-9.53 ppm, while -NH- proton (s, 1H, NH) showed singlet signals at δ 10.30 and 10.31 ppm for compounds (6i) and (6j), The NH_2 protons appeared as a D_2O exchangeable singlet at δ 10.26-10.62 ppm, its ^{13}C NMR spectrum showed a δ 24.52 (CH_3C=N), 100.24-156.61(aromatics), 169.34 (CH_3C=N) and disappeared (C=O) band.

Table 1: Shows the products of the reaction of compound 2 with aldehydes 3(a-e) under the effect of grinding method and stirring condition

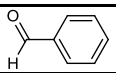
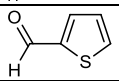
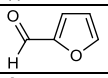
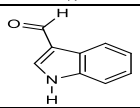
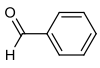
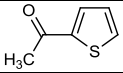
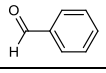
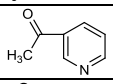
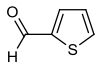
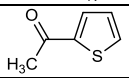
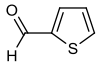
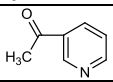
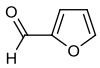
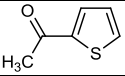
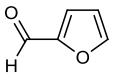
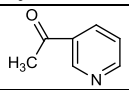
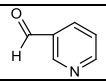
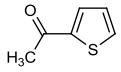
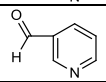
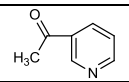
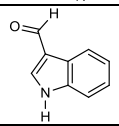
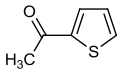
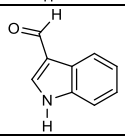
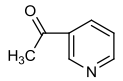
Product	Aldehyde	Stirring		Grinding	
		Time (min.)	Yield (%)	Time (min.)	Yield (%)
4a		180	84	45	95
4b		240	81	60	93
4c		180	83	45	94
4d		180	85	30	96
4e		240	80	60	93

Table 2: Shows the products of the reaction of chalcones 4(a-e) with acetyls 5(a, b) under the effect of microwave irradiation and reflux condition.

Product	Aldehyde	Acetyl	Reflux		Microwave	
			Time (min.)	Yield (%)	Time (min.)	Yield (%)
6a			360	64	1.5	93
6b			360	67	1	94
6c			360	59	1.5	90
6d			360	65	1.5	95
6e			360	61	1	93
6f			360	66	1	94
6g			360	68	1.5	95
6h			360	71	1	96
27i			360	58	2	90
6j			360	55	1.5	92

Anticancer activity

From the screening results **(Table 3),** the result shows that compounds 4a and 6e exhibited good activity on A human liver tumor cell line (HepG2 cells) after 24h. (Figures 1-5)

Table 3: Viability assay of tested samples on HepG2 cells after 24h.

Sample ID	Dilution 1:2 (mg/ml)	O.D			Mean O.D	Viability %	Toxicity %
HepGII		0.213	0.218	0.214	0.215	100	0
4a	10	0.002	0.005	0.004	0.003667	1.705426	98.29457
	5	0.002	0.004	0.004	0.003333	1.550388	98.44961
	2.5	0.003	0.004	0.004	0.003667	1.705426	98.29457
	1.25	0.011	0.012	0.011	0.011333	5.271318	94.72868
	0.625	0.024	0.028	0.027	0.026333	12.24806	87.75194
	0.312	0.047	0.046	0.044	0.045667	21.24031	78.75969
	0.156	0.152	0.157	0.149	0.152667	71.00775	28.99225
	0.078	0.215	0.217	0.219	0.217	100.9302	0
6e	20	0.002	0.004	0.003	0.003	1.395349	98.60465
	10	0.003	0.004	0.007	0.004667	2.170543	97.82946
	5	0.007	0.009	0.003	0.006333	2.945736	97.05426
	2.5	0.007	0.007	0.008	0.007333	3.410853	96.58915
	1.25	0.011	0.012	0.018	0.013667	6.356589	93.64341
	0.625	0.021	0.023	0.027	0.023667	11.00775	88.99225
	0.312	0.022	0.029	0.027	0.026	12.09302	87.90698
	0.156	0.086	0.079	0.089	0.084667	39.37984	60.62016

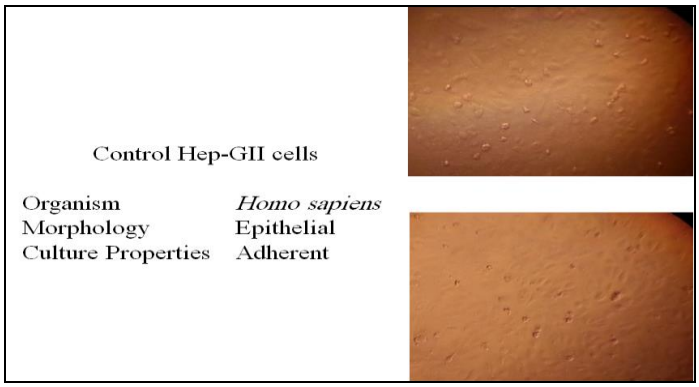


Figure 1: Morphological feature

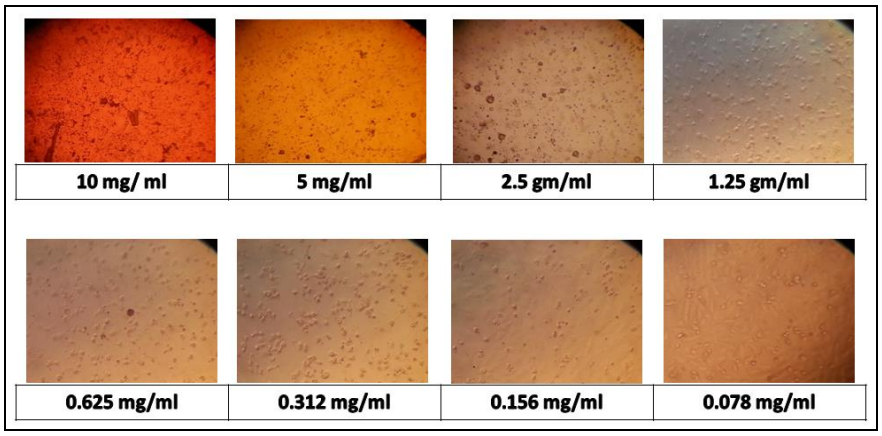


Figure 2: Effect of different concentrations of compound no 4a on HepG2 cells shows partial or complete loss of the dkalkd;alk;alkd;amonolayer, rounding, shrinkage, or cell granulation

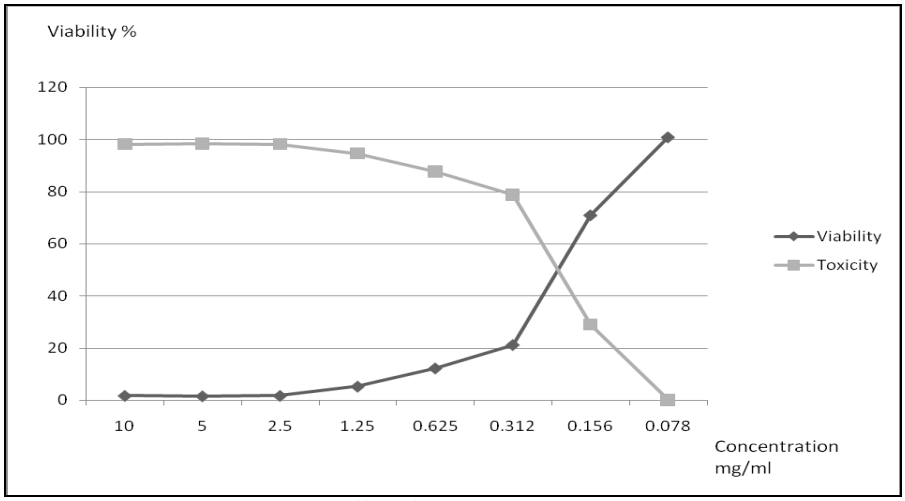


Figure 3: Effect of sample 4a on HepG2 cells

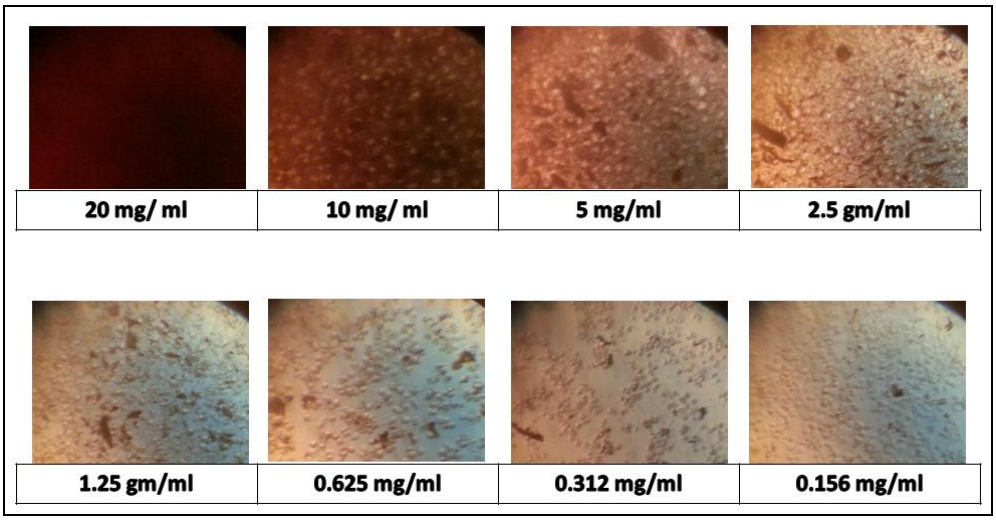


Figure 4: Effect of different concentrations of compound no 6e on HepG2 cells shows partial or complete loss of the monolayer, rounding, shrinkage, or cell granulation

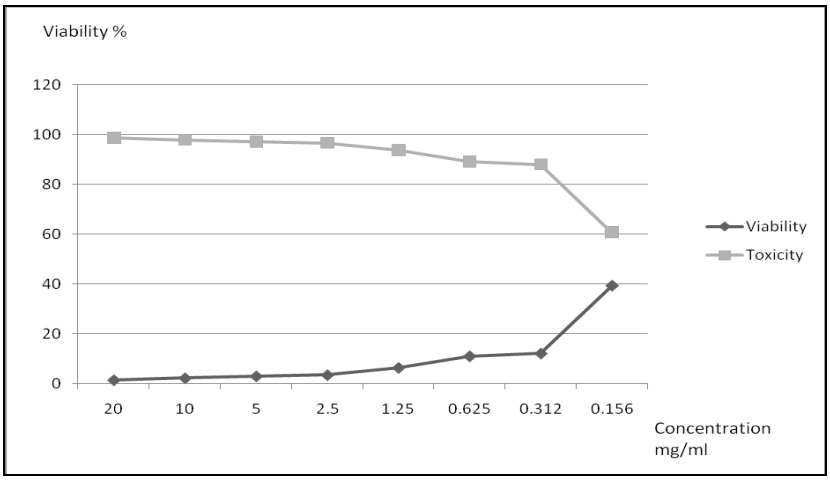


Figure 5: Effect of sample 6e on HepG2 cells

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds in green chemistry such as microwave and grinding methods which increased reaction rates, yields of pure products as well as eco-friendly advantages, and shows significant on HepG2 cells further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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