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Microwave-Assisted One-Pot Synthesis of Novel Polyarylpyrrole Derivatives of Expected Anticancer Activity

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ABSTRACT

An efficient synthesis of Novel pyrrolederivatives was achieved via solventless reaction of chalcones 1(a-e) with different aldehydes 2(a-e) and ammonium acetate in the presence of sodium cyanide in one-pot under microwave irradiation. The notable features are short reaction time, high yield and purification of product by non-chromatographic methods, i.e., by simple recrystalization compared to the classical condition. Some of the synthesized compounds were evaluated against HepG-2, and showed significant antitumor activities.

Keywords: Green chemistry, Microwave, Solventless, One-pot reactions

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INTRODUCTION

One-pot reactions are one of the good green chemistry methods due to the reduction of work-up procedures and purification steps required compared to a more stepwise approach in addition to effect of microwave irradiation on the yield improvement and reduction of reaction time so. The chemistry is greener [1-3]. In reactions that require a catalyst it is possible to combine several catalytic processes in the same reaction vessel [4].

Chalcones are valuable intermediates in organic synthesis and exhibit a multimode of biological activities. The most important feature of chalcones from a chemical point of view, its ability to act as activated α, β-unsaturated carbonyl systems [5-7].

Pyrrole derivatives are considered from one of the most important classes of heterocyclic compounds. They exhibit extensive biological and pharmacological properties [8] such as antimicrobial [9-16] antifungal [17], anti-inflammatory [18-20], antiviral [21], anti-cancer [22,23], anti-hyperglycemic [24,25], anticonvulsant [26], antioxidant [27] and immune suppressant activities [28]. Highly functionalized pyrroles are subunits of heme, chlorophyll, bile pigments, vitamin B12 and pyrrole alkaloids isolated from marine source [29].

A new chemical class of 5-heteroaryl-3-carboxamido-2-substituted pyrrole derivative A was evaluated in vivo and in vitro for antitumor activity and showed promised results. The compound B represented a novel prototype Cdc7 kinase inhibitor [30]. Two compounds C and D exhibited potential cytotoxicity against human non-small cell lung carcinoma cell lines A549 (Figure 1) [31].

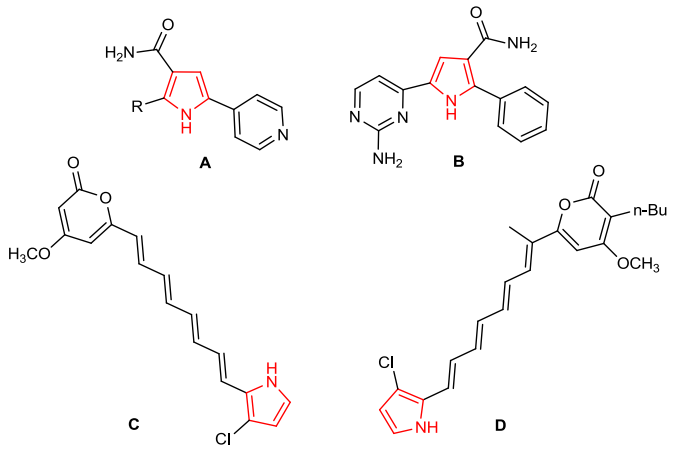


Figure 1: Examples of antitumor compounds containing pyrrole groups

Motivated by the fore-mentioned findings, and in continuation of our interest in synthesis of a wide range of heterocyclic systems for biological screening programme using green chemistry tools [32]. We describe here a facile synthesis of polysubstituted pyrroles under microwave irradiation. The structure of the products was confirmed on different analytical and spectroscopic data.

MATERIALS AND METHODS

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. 1H 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 Micro analytical Center of Cairo University, Giza, Egypt. Reactions carried out under microwave irradiation were performed in 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

Reaction of chalcones 1(a-e) with different aldehydes 2(a-e)

Conventional method

A mixture of chalcones 1(a-e) (1mmol) [33], and appropriate aldehyde 2(a-e) (1 mmol) in the presence of sodium cyanide (0.18 mmol) and ammonium acetate (1 mmol) was refluxed in DMF for 10 hrs 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 3(a-y) in 56-72% yield.

Green method

A mixture of chalcones 1(a-e) (1 mmol), and appropriate aldehyde 2(a-e) (1 mmol) in the presence of sodium cyanide (0.18 mmol), ammonium acetate (1 mmol) and 3 ml DMF are mixed in a 10 ml glass vial and subjected to microwave irradiation for 1-2 mins, the solid formed was purified by recrystallization from ethanol/DMF (1:1) affording product identical in all respects (mp, mixed mp and TLC) with 3(a-y) in 92-97% yield.

***N*-(1-(4-aminophenyl)ethylidene)-4-(4,5-diphenyl-1H-pyrrol-2-yl)aniline (3a)**

M.p.=176-178ºC; IR (KBr, cm^{-1}): 1175 (C-N), 1533 (C=C), 1590 (C=N), 3114 (NH), 3260, 3294 (NH_2); ^{1}H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 4.92 (s, 1H, NH), 6.55-7.97 (m, 19H, Ar-H), 10.41 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 107.19, 112.91, 118.60, 122.22, 127.58, 129.92, 131.03, 131.91, 137.88, 144.17, 152.30, 154.09 (aromatic), 169.45 (CH_3C=N); MS (m/z): 427 (M^+); Anal. For $C_{30}H_{25}N_3$ (427.54). (Calcd: C, 84.28; H, 5.89; N, 9.83%; Found: C, 84.32; H, 5.87; N, 9.81%).

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-phenyl-5-(thiophen-2-yl)-1H-pyrrol-2-yl)aniline (3b)**

M.p.=160-161ºC; IR (KBr, cm^{-1}): 1178 (C-N), 1317 (C-S), 1513 (C=C), 1597 (C=N), 3055 (NH), 3112, 3186 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 6.04 (s, 1H, NH), 6.55-7.93 (m, 17H, Ar-H), 10.36 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 107.53, 112.91, 118.99, 122.53, 125.28, 127.45, 129.93, 131.03, 131.93, 135.52, 141.36, 144.15, 151.71, 154.09 (aromatic), 169.43 (CH_3C=N); MS (m/z): 433 (M^+); Anal. For $C_{28}H_{23}N_3S$ (433.57). (Calcd: C, 77.57; H, 5.35; N, 9.69%; Found: C, 77.59; H, 5.36; N, 9.66%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(5-(furan-2-yl)-4-phenyl-1H-pyrrol-2-yl)aniline (3c)**

M.p.=160-161ºC; IR (KBr, cm^{-1}): 1175 (C-N), 1263 (C-O), 1532 (C=C), 1590 (C=N), 3115 (NH), 3266, 3296 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.53 (s, 1H, NH), 6.55-7.93 (m, 17H, Ar-H), 10.40 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.50 (CH_3C=N), 106.35, 108.05, 112.90, 114.14, 118.60, 122.54, 125.27, 127.46, 128.31, 129.93, 131.03, 131.92, 136.70, 141.03, 144.17, 150.86, 153.50, 159.52 (aromatic), 169.35 (CH_3C=N); MS (m/z): 417 (M^+); Anal. For $C_{28}H_{23}N_3O$ (417.50). Calcd: C, 80.55; H, 5.55; N, 10.06%; Found: C, 80.59; H, 5.53; N, 10.04%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-phenyl-5-(pyridin-3-yl)-1H-pyrrol-2-yl)aniline (3d)**

M.p.=170-171ºC; IR (KBr, cm^{-1}): 1178 (C-N), 1532 (C=C), 1591 (C=N), 3110 (NH), 3267, 3297 (NH_2); ^1H NMR (DMSO-d_6):δ=2.09 (s, 3H, CH_3-C=N-), 5.53 (s, 1H, NH), 6.55-8.34 (m, 18H, Ar-H), 10.37 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 107.78, 112.91, 118.60, 122.54, 124.57, 126.62, 128.04, 129.93, 131.03, 131.93, 135.26, 144.15, 148.56, 152.55, 154.94 (aromatic), 169.35 (CH_3C=N); MS (m/z): 428(M^+); Anal. For $C_{29}H_{24}N_4$ (428.53). (Calcd: C, 81.28; H, 5.65; N, 13.07%; Found: C, 81.25; H, 5.66; N, 13.09%)

4-(5-(1H-indol-3-yl)-4-phenyl-1H-pyrrol-2-yl)-*N*-(1-(4-aminophenyl)ethylidene)aniline (3e)

M.p.=176-178ºC; IR (KBr, cm^{-1}): 1178 (C-N), 1528 (C=C), 1591 (C=N), 3110 (NH), 3265, 3296 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.14 (s, 1H, NH), 6.55-8.34 (m, 19H, Ar-H), 9.93 (s, 1H, NH), 10.40 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 105.49, 111.27, 113.07, 116.19, 118.60, 121.23, 122.47, 123.78, 126.02, 128. 30, 129.93, 131.03, 131.92, 134.07, 144.17, 150.01, 152.29 (aromatic), 169.45 (CH_3C=N); MS (m/z): 466(M^+); Anal. For $C_{32}H_{26}N_4$ (466.58). (Calcd: C, 82.38; H, 5.62; N, 12.01%; Found: C, 82.39; H, 5.60; N, 12.02%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(5-phenyl-4-(thiophen-2-yl)-1H-pyrrol-2-yl)aniline (3f)**

M.p.=165-166ºC; IR (KBr, cm^{-1}): 1175 (C-N), 1314 (C-S), 1532 (C=C), 1590 (C=N), 3113 (NH), 3185, 3296 (NH_2); ^1H NMR (DMSO-d_6):δ=2.09 (s, 3H, CH_3-C=N-), 5.10 (s, 1H, NH), 7.19-8.09 (m, 17H, Ar-H), 10.41 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.24 (CH_3C=N), 100.00, 106.08, 112.91, 118.60, 118.79, 120.72, 122.80, 127.58, 129.15, 129.92, 130.20, 131.91, 132.42, 133.10, 136.54, 140.32, 152.57, 154.60 (aromatic), 169.45 (CH_3C=N); MS (m/z): 433 (M^+); Anal. For $C_{28}H_{23}N_3S$ (433.57). (Calcd: C, 77.57; H, 5.35; N, 9.69%; Found: C, 77.59; H, 5.37; N, 9.65%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4,5-di(thiophen-2-yl)-1H-pyrrol-2-yl)aniline (3g)**

M.p.=158-160ºC; IR (KBr, cm^{-1}): 1176 (C-N), 1318 (C-S), 1527 (C=C), 1592 (C=N), 3106 (NH), 3264, 3295 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.30 (s, 1H, NH), 6.55-8.09 (m, 15H, Ar-H), 10.24 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.39 (CH_3C=N), 100.58, 109.24, 113.88, 118.60, 120.72, 129.16, 129.93, 130.21, 131.92, 132.42, 133.12, 136.55, 140.32, 144.16, 151.12, 153.49 (aromatic), 169.36 (CH_3C=N); MS (m/z): 439 (M^+); Anal. For $C_{26}H_{21}N_3S_2$ (439.60). (Calcd: C, 71.04; H, 4.82; N, 9.56%; Found: C, 71.01; H, 4.84; N, 9.57%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(5-(furan-2-yl)-4-(thiophen-2-yl)-1H-pyrrol-2-yl)aniline (3h)**

M.p.=154-156ºC; IR (KBr, cm^{-1}): 1175 (C-N), 1263 (C-O), 1315 (C-S), 1530 (C=C), 1591 (C=N), 3111 (NH), 3273, 3295 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 4.90 (s, 1H, NH), 7.18-8.09 (m, 15H, Ar-H), 10.38 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 101.42, 106.09, 108.64, 118.60, 118.79, 120.72, 124.24, 128.32, 129.15, 129.92, 130.20, 131.92, 132.42, 133.09, 136.54, 140.32, 144.16, 152.30, 154.99, 159.52 (aromatic), 169.35 (CH_3C=N); MS (m/z): 423 (M^+); Analysis For $C_{26}H_{21}N_3OS$ (423.53). (Calcd: C, 73.73; H, 5.00; N, 9.92%; Found: C, 73.76; H, 5.01; N, 9.88%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(5-(pyridin-3-yl)-4-(thiophen-2-yl)-1H-pyrrol-2-yl)aniline (3i)**

M.p.=155-156ºC; IR (KBr, cm^{-1}): 1178 (C-N), 1315 (C-S), 1531 (C=C), 1591 (C=N), 3109 (NH), 3267, 3297 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.27 (s, 1H, NH), 6.55-8.09 (m, 16H, Ar-H), 10.36 (s, 2H, NH_2 D_2O exchangeable) ; ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 100.24, 108.37, 113.57, 118.22, 123.97, 125.68, 128.31, 129.74, 130.09, 131.52, 133.23, 136.11, 139.58, 148.23, 151.45, 153.49 (aromatic), 169.35 (CH_3C=N); MS (m/z): 434 (M^+); Anal. For $C_{27}H_{22}N_4S$ (434.56). (Calcd: C, 74.63; H, 5.10; N, 12.89%; Found: C, 74.60; H, 5.09; N, 12.93%)

4-(5-(1H-indol-3-yl)-4-(thiophen-2-yl)-1H-pyrrol-2-yl)-*N*-(1-(4-aminophenyl)ethylidene)aniline (3j)

M.p.=120-122ºC; IR (KBr, cm^{-1}): 1175 (C-N), 1314 (C-S), 1528 (C=C), 1592 (C=N), 3109 (NH), 3182, 3261 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.33 (s, 1H, NH), 6.55-8.28 (m, 17H, Ar-H), 9.93 (s, 1H, NH), 10.38 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.50 (CH_3C=N), 100.26, 109.23, 111.26, 113.01, 116.18, 118.60, 121.25, 122.51, 123.83, 124.66, 126.27, 128.33, 129.93, 131.93, 136.70, 137.73, 139.17, 151.45, 153.48 (aromatic), 169.35 (CH_3C=N); MS (m/z): 472 (M^+); Anal. For $C_{30}H_{24}N_4S$ (472.60). (Calcd: C, 76.24; H, 5.12; N, 11.85%; Found: C, 76.22; H, 5.10; N, 11.89%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-(furan-2-yl)-5-phenyl-1H-pyrrol-2-yl)aniline (3k)**

M.p.=120-122ºC; IR (KBr, cm^{-1}): 1175 (C-N), 1262 (C-O), 1527 (C=C), 1595 (C=N), 3113 (NH), 3189, 3261 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 4.82 (s, 1H, NH), 6.68-8.06 (m, 17H, Ar-H), 10.45 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.26 (CH_3C=N), 100.57, 107.18, 109.90, 113.55, 117.19, 118.61, 119.11, 125.15, 127.13, 129.92, 130.12, 131.91, 132.44, 135.26, 144.17, 146.51, 151.69, 153.75 (aromatic), 169.35 (CH_3C=N); MS (m/z): 417 (M^+); Anal. For $C_{28}H_{23}N_3O$ (417.50). (Calcd: C, 80.55; H, 5.55; N, 10.06%; Found: C, 80.59; H, 5.52; N, 10.05%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-(furan-2-yl)-5-(thiophen-2-yl)-1H-pyrrol-2-yl)aniline (3l)**

M.p.=126-128ºC; IR (KBr, cm^{-1}): 1174 (C-N), 1261 (C-O), 1327 (C-S), 1526 (C=C), 1595 (C=N), 3112 (NH), 3189, 3260 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.10 (s, 1H, NH), 6.68-8.14 (m, 15H, Ar-H), 10.45 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 99.71, 106.35, 108.04, 113.55, 117.19, 118.83, 119.11, 122.81, 129.91, 130.12, 131.90, 132.43, 135.85, 144.20, 146.51, 151.70, 154.60 (aromatic), 169.36 (CH_3C=N); MS (m/z): 423 (M^+); Anal. For $C_{26}H_{21}N_3OS$ (423.53). (Calcd: C, 73.73; H, 5.00; N, 9.92%; Found: C, 73.70; H, 5.01; N,9.94%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4,5-di(furan-2-yl)-1H-pyrrol-2-yl)aniline (3m)**

M.p.=120-122ºC; IR (KBr, cm^{-1}): 1172 (C-N), 1260 (C-O), 1527 (C=C), 1592 (C=N), 3110 (NH), 3187, 3262 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 4.77 (s, 1H, NH), 6.69-8.07 (m, 15H, Ar-H), 10.39 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 100.99, 106.09, 108.37, 113.56, 117.20, 118.82, 119.11, 123.40, 126.28, 128.31, 129.93, 130.35, 131.92, 132.44, 144.17, 146.52, 151.70, 153.47, 156.96, 159.25 (aromatic), 169.35 (CH_3C=N); MS (m/z): 407 (M^+); Anal. For $C_{26}H_{21}N_3O_2$ (407.46). (Calcd: C, 76.64; H, 5.19; N, 10.31%; Found: C, 76.68; H, 5.17; N, 10.29%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-(furan-2-yl)-5-(pyridin-3-yl)-1H-pyrrol-2-yl)aniline (3n)**

M.p.=156-158ºC; IR (KBr, cm^{-1}): 1174 (C-N), 1262 (C-O), 1527 (C=C), 1594 (C=N), 3112 (NH), 3189, 3259 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.12 (s, 1H, NH), 6.57-8.99 (m, 16H, Ar-H), 10.41 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 101.42, 106.62, 108.96, 113.56, 117.20, 118.61, 119.11, 123.14, 125.68, 128.57, 129.92, 130.13, 131.92, 132.44, 144.23, 146.52, 151.69, 155.51 (aromatic), 169.50 (CH_3C=N); MS (m/z): 418 (M^+); Anal. For $C_{27}H_{22}N_4O$ (418.49). (Calcd: C, 77.49; H, 5.30; N, 13.39%; Found: C, 77.50; H, 5.32; N, 13.36%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-(furan-2-yl)-5-(1H-indol-3-yl)-1H-pyrrol-2-yl)aniline (3o)**

M.p.=124-125ºC; IR (KBr, cm^{-1}): 1172 (C-N), 1257 (C-O), 1525 (C=C), 1591 (C=N), 3109 (NH), 3179, 3259 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.14 (s, 1H, NH), 6.68-8.28 (m, 17H, Ar-H), 9.94 (s, 1H, NH), 10.40 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 100.25, 105.16, 108.03, 112.95, 113.56, 117.20, 118.60, 119.11, 121.27, 122.54, 123.87, 124.61, 126.02, 129.93, 130.14, 131.93, 132.45, 137.61, 139.05, 144.15, 146.51, 151.70, 154.08 (aromatic), 169.35 (CH_3C=N); MS (m/z): 456 (M^+); Anal. For $C_{30}H_{24}N_4O$ (456.54). (Calcd: C, 78.92; H, 5.30; N, 12.27%; Found: C, 78.88; H, 5.32; N, 12.29%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(5-phenyl-4-(pyridin-3-yl)-1H-pyrrol-2-yl)aniline (3p)**

M.p.=280-282 ºC; IR (KBr, cm^{-1}): 1181 (C-N), 1533 (C=C), 1592 (C=N), 3100 (NH), 3178, 3249 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.14 (s, 1H, NH), 7.29-9.02 (m, 18H, Ar-H), 10.43 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 99.12, 109.23, 114.73, 118.60, 122.55, 124.31, 124.38, 129.92, 130.50, 131.10, 132.26, 135.51, 140.31, 144.18, 144.48, 150.77, 151.36 (aromatic), 169.67 (CH_3C=N); MS (m/z): 428 (M^+); Anal. For $C_{29}H_{24}N_4$ (428.53). (Calcd: C, 81.28; H, 5.65; N, 13.07%; Found: C, 81.30; H, 5.66; N, 13.04%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4-(pyridin-3-yl)-5-(thiophen-2-yl)-1H-pyrrol-2-yl)aniline (3q)**

M.p.=210-211ºC; IR (KBr, cm^{-1}): 1183 (C-N), 1314 (C-S), 1536 (C=C), 1591 (C=N), 3099 (NH), 3247, 3296 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 4.70 (s, 1H, NH), 7.48-9.03 (m, 16H, Ar-H), 10.44 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.51 (CH_3C=N), 101.43, 108.37, 114.15, 118.99, 122.22, 124.31, 124.38, 129.93, 130.51, 131.92, 132.27, 135.52, 140.32, 144.45, 148.57, 150.78, 151.36 (aromatic), 169.36 (CH_3C=N); MS (m/z): 434 (M^+); Anal. For $C_{27}H_{22}N_4S$ (434.56). (Calcd: C, 74.63; H, 5.10; N, 12.89%; Found: C, 74.61; H, 5.08; N, 12.93%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(5-(furan-2-yl)-4-(pyridin-3-yl)-1H-pyrrol-2-yl)aniline (3r)**

M.p.=220-222ºC; IR (KBr, cm^{-1}): 1183 (C-N), 1235 (C-O), 1536 (C=C), 1599 (C=N), 3099 (NH), 3245, 3298 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 4.92 (s, 1H, NH), 7.49-9.03 (m, 16H, Ar-H), 10.37 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 101.43, 107.52, 109.49, 112.43, 114.14, 118.58, 122.80, 124.31, 124.39, 126.27, 129.96, 130.53, 131.10, 132.29, 135.53, 140.34, 144.41, 148.57, 150.78, 151.37, 157.82 (aromatic), 169.35 (CH_3C=N); MS (m/z): 418 (M^+); Anal. For $C_{27}H_{22}N_4O$ (418.49). (Calcd: C, 77.49; H, 5.30; N, 13.39%; Found: C, 77.48; H, 5.33; N, 13.37%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4,5-di(pyridin-3-yl)-1H-pyrrol-2-yl)aniline (3s)**

M.p.=210-212ºC; IR (KBr, cm^{-1}): 1184 (C-N), 1538 (C=C), 1588 (C=N), 3098 (NH), 3245, 3299 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.43 (s, 1H, NH), 7.48-9.03 (m, 17H, Ar-H), 10.44 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 102.01, 109.23, 114.41, 118.60, 122.54, 124.30, 127.72, 129.93, 130.51, 131.10, 132.27, 135.52, 139.59, 146.79, 148.24, 150.60, 151.46 (aromatic), 169.36 (CH_3C=N); MS (m/z): 429 (M^+); Anal. For $C_{28}H_{23}N_5$ (429.52). (Calcd: C, 78.30; H, 5.40; N, 16.31%; Found: C, 78.34; H, 5.37; N, 16.30%)

4-(5-(1H-indol-3-yl)-4-(pyridin-3-yl)-1H-pyrrol-2-yl)-*N*-(1-(4-aminophenyl)ethylidene)aniline (3t)

M.p.=180-181ºC; IR (KBr, cm^{-1}): 1184 (C-N), 1537 (C=C), 1587 (C=N), 3102 (NH), 3244, 3296 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.50 (s, 1H, NH), 7.23-8.62 (m, 18H, Ar-H), 9.95 (s, 1H, NH), 10.42 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.52 (CH_3C=N), 100.25, 109.49, 112.98, 115.32, 118.76, 120.76, 122.21, 123.73, 124.83, 126.86, 128.57, 129.75, 130.62, 131.78, 135.85, 138.99, 146.80, 148.82, 150.27, 151.44 (aromatic), 169.36 (CH_3C=N); MS (m/z): 467 (M^+); Anal. For $C_{31}H_{25}N_5$ (467.56). (Calcd: C, 79.63; H, 5.39; N, 14.98%; Found: C, 79.66; H, 5.35; N, 14.99%)

4-(4-(1H-indol-3-yl)-5-phenyl-1H-pyrrol-2-yl)-*N*-(1-(4-aminophenyl)ethylidene)aniline (3u)

M.p.=150-152ºC; IR (KBr, cm^{-1}): 1175 (C-N), 1529 (C=C), 1590 (C=N), 3112 (NH), 3182, 3259 (NH_2); ^1H NMR (DMSO-d_6): δ=2.11 (s, 3H, CH_3-C=N-), 5.24 (s, 1H, NH), 7.20-8.29 (m, 19H, Ar-H), 9.94 (s, 1H, NH), 10.32 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.26 (CH_3C=N), 95.34, 108.36, 112.90, 114.15, 118.99, 121.28, 122.57, 123.91, 124.98, 129.93, 131.94, 134.66, 137.53, 138.96, 144.12, 150.60, 152.96 (aromatic), 169.66 (CH_3C=N); MS (m/z): 466 (M^+); Anal. For $C_{32}H_{26}N_4$ (466.58). (Calcd: C, 82.38; H, 5.62; N, 12.01%; Found: C, 82.37; H, 5.60; N, 12.04%)

4-(4-(1H-indol-3-yl)-5-(thiophen-2-yl)-1H-pyrrol-2-yl)-*N*-(1-(4-aminophenyl)ethylidene)aniline (3v)

M.p.=138-140ºC; IR (KBr, cm^{-1}): 1179 (C-N), 1316 (C-S), 1527 (C=C), 1590 (C=N), 3111 (NH), 3260, 3293 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.22 (s, 1H, NH), 7.20-8.63 (m, 17H, Ar-H), 9.94 (s, 1H, NH), 10.33 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.77 (CH_3C=N), 95.32, 100.57, 107.19, 111.27, 112.92, 118.99, 121.28, 122.57, 123.90, 124.99, 129.94, 131.94, 135.84, 137.55, 139.00, 144.14, 150.60, 152.57 (aromatic), 169.09 (CH_3C=N); MS (m/z): 472 (M^+); Anal. For $C_{30}H_{24}N_4S$ (472.60). (Calcd: C, 76.24; H, 5.12; N, 11.85%; Found: C, 76.25; H, 5.13; N, 11.83%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(5-(furan-2-yl)-4-(1H-indol-3-yl)-1H-pyrrol-2-yl)aniline (3w)**

M.p.=150-152ºC; IR (KBr, cm^{-1}): 1178 (C-N), 1262 (C-O), 1528 (C=C), 1590 (C=N), 3111 (NH), 3262, 3294 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.20 (s, 1H, NH), 7.20-8.57 (m, 17H, Ar-H), 9.94 (s, 1H, NH), 10.32 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.26 (CH_3C=N), 95.33, 100.25, 106.08, 108.96, 112.91, 115.33, 118.99, 121.28, 122.58, 123.91, 124.58, 127.71, 129.94, 131.94, 137.54, 138.98, 144.13, 151.46, 153.75, 158.99 (aromatic), 169.09 (CH_3C=N); MS (m/z): 456 (M^+); Anal. For $C_{30}H_{24}N_4O$ (456.54). (Calcd: C, 78.92; H, 5.30; N, 12.27%; Found: C, 78.96; H, 5.28; N, 12.25%)

4-(4-(1H-indol-3-yl)-5-(pyridin-3-yl)-1H-pyrrol-2-yl)-*N*-(1-(4-aminophenyl)ethylidene)aniline (3x)

M.p.=162-164ºC; IR (KBr, cm^{-1}): 1177 (C-N), 1531 (C=C), 1588 (C=N), 3111 (NH), 3260, 3309 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.50 (s, 1H, NH), 7.20-9.01 (m, 18H, Ar-H), 9.94 (s, 1H, NH), 10.35 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.53 (CH_3C=N), 95.08, 99.40, 108.05, 112.93, 115.32, 118.60, 121.27, 122.56, 123.89, 124.59, 126.01, 128.31, 129.94, 131.93, 135.26, 137.57, 139.02, 147.39, 149.41, 150.01, 153.15 (aromatic), 169.35 (CH_3C=N); MS (m/z): 467 (M^+); Anal. For $C_{31}H_{25}N_5$ (467.56). (Calcd: C, 79.63; H, 5.39; N, 14.98%; Found: C, 79.67; H, 5.36; N, 14.97%)

***N*-(1-(4-aminophenyl)ethylidene)-4-(4,5-di(1H-indol-3-yl)-1H-pyrrol-2-yl)aniline (3y)**

M.p.=152-154ºC; IR (KBr, cm^{-1}): 1179 (C-N), 1525 (C=C), 1589 (C=N), 3110 (NH), 3172, 3260 (NH_2); ^1H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3-C=N-), 5.42 (s, 1H, NH), 7.20-8.63 (m, 19H, Ar-H), 10.11 (s, 1H, NH), 10.44 (s, 2H, NH_2 D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 24.53 (CH_3C=N), 11.54, 16.13, 101.69, 107.52, 109.48, 114.25, 118.22, 122.57, 123.98, 124.83, 126.61, 128.56, 130.07, 131.77, 137.55, 139.00, 150.27, 152.04 (aromatic), 169.35 (CH_3C=N); MS (m/z): 505 (M^+); Anal. For $C_{34}H_{27}N_5$ (505.61). (Calcd: C, 80.77; H, 5.38; N, 13.85%; Found: C, 80.79; H, 5.39; N, 13.82%)

The MTT protocol

(1) The 96 well tissue culture plate was inoculated with 1×10^5 cells/ml (100 ul/well) and incubated at 37ºC for 24 hrs to develop a complete monolayer sheet.

(2) Growth medium was decanted from 96 well microtiter plates after confluent sheet of cells were formed, the cell monolayer was washed twice with wash media.

(3) Two-fold dilutions of tested sample were made in Roswell Park Memorial Institute (RPMI) medium (CAISSON RPMI 1640 Medium) with 2% serum (maintenance medium).

(4) 0.1 ml of each dilution was tested in different wells leaving 3 wells as control, receiving only maintenance medium.

(5) The plate was incubated at 37ºC and examined. Cells were checked for any physical signs of toxicity, e.g. partial or complete loss of the monolayer, rounding, shrinkage, or cell granulation.

(6) MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole) solution was prepared (5 mg/ml in PBS (phosphate buffered saline)) (BIO BASIC CANADA INC).

(7) 25 ul MTT solution was added to each well. Place on a shaking table, 150 rpm for 5 minutes, to thoroughly mix the MTT into the media.

(8) Incubate (37ºC, 5% CO_2) for 1-5 hrs to allow the MTT to be metabolized.

(9) Dump off the media. (Dry plate on paper towels to remove residue if necessary).

(10) Resuspend formazan (MTT metabolic product) in 200 ul DMSO. Place on a shaking table, 150 rpm for 5 min, to thoroughly mix the formazan into the solvent.

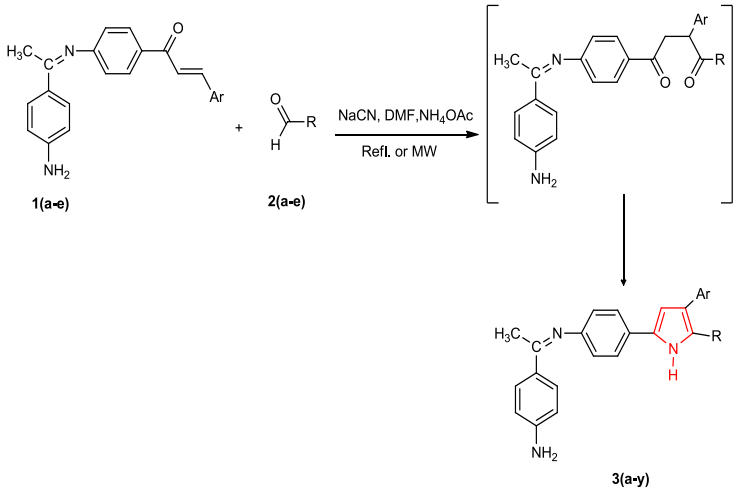
(11) Read optical density at 545 nm and subtract background at 620 nm. Optical density should be directly correlated with cell quantity.

RESULTS AND DISCUSSION

Chemistry

Classical Paal-Knorr method is involved for synthesis of polysubstituted pyrroles via the reaction of 1, 4-butanediones with amines [34,35]. Although a wide variety of pyrrole derivatives can be synthesized by this versatile and applicable procedure, it is limited to the availability of 1,4-diketons in addition to long reaction time and unsatisfied yield.

Thus, the author interested in modification a versatile synthesis of pyrrole derivatives via Paal-Knorr method from readily available starting materials, a facile and efficient one-pot synthesis of new polyarylpyrrole derivatives under microwave irradiation was introduced in which chalcones 1(a-e) and aldehydes 2(a-e) were mixed in DMF in presence of sodium cyanide as catalyst and smoothly converted into pyrrole derivatives 3(a-y) in presence of ammonium acetate under microwave irradiations in good yield and small reaction time (Scheme 1).

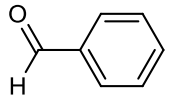
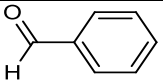
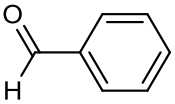
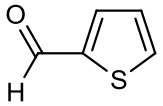
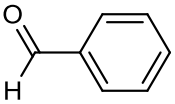
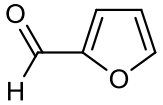
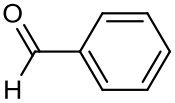
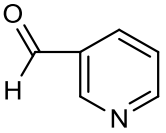
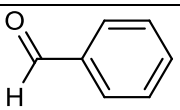
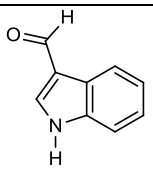


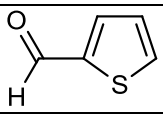
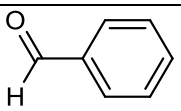
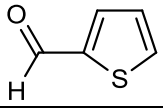
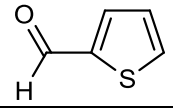
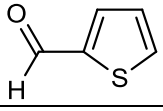
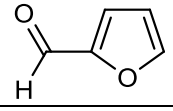
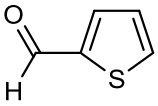
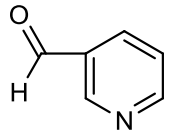
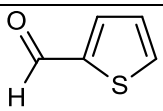
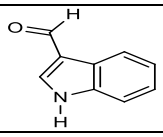
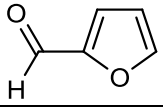
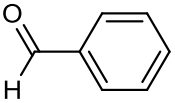
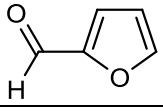
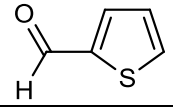
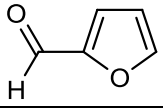
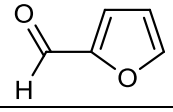
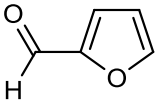
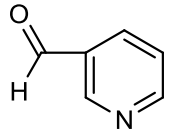
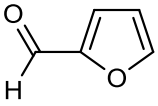
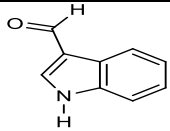
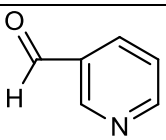
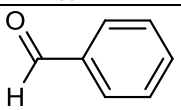
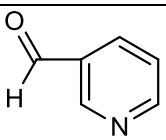
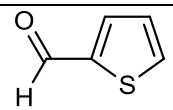
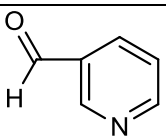
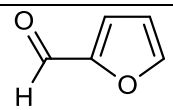
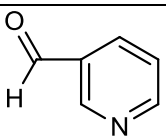
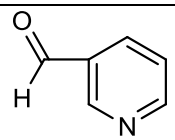
Scheme 1: Synthesis of pyrrole derivatives

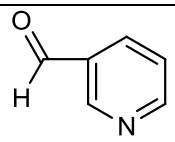
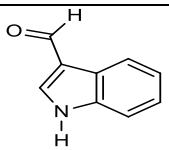
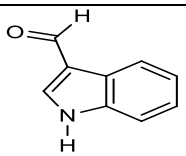
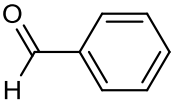
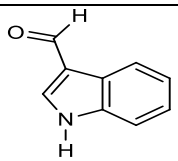
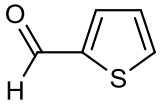
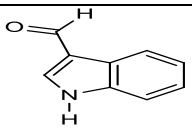
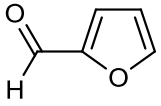
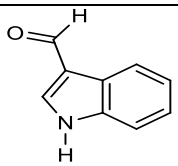
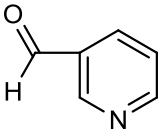
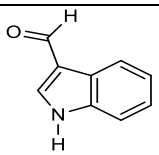
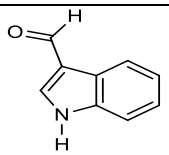
The formation of compounds 3(a-y) are assumed to take place via an initial Micheal-type addition of aldehydes 2(a-e) with chalcones 1(a-e) to form non-isolable intermediate 1,4-diketons followed by ring closure of the resulting intermediate using ammonium acetate to afford pyrrole derivatives 3(a-e) So the above method which used in synthesis of poly substituted pyrrole overcame the disadvantage of Paal-Knorr method since the reaction product obtained in a very good yield more than 90%, also the reaction rate was accelerated under microwave irradiation greatly and reaction completed after only 1-2 min, as examined by TLC.

The structures of compounds 3(a-y) were elucidated by its elemental analysis and spectroscopic data. where, its IR spectrum showed C-N bands in the region from 1172 to1184 cm^{-1}, C-O bands at 1235 and 1263 cm^{-1} for compounds 3(c, h, k, l, m, n, o, r, w), C-S bands in the region from 1314 to1327cm^{-1} for compounds 3(b, f, g, h, i, j, l, q, v), C=C bands in the region from 1513 to 1538cm^{-1}, C=N bands in the region from 1587 to 1599 cm^{-1}, NH bands in the region from 3055 to 3115 cm^{-1} and two symmetric and asymmetric bands due to amino group in the region from 3112 to 3309 cm^{-1}, the ^{1}H NMR spectrum of these compounds displayed a characteristic singlet signal in all compounds at δ 2.09 ppm due to methyl protons (s, 3H, CH_3-C=N-), and disappeared a signal due to proton (CH=CH), while a signal due to proton (-NH-Pyrrole) appeared at 4.70-6.04, in addition to singlet signals due to -NH-proton (s, 1H, NH) at δ 9.93 and 10.11 ppm for compounds (3e), (3j),(3o) and 3(t-y), The common amino protons appeared around δ 10.24-10.45 ppm as a D_2O exchangeable singlet signal, its ^{13}C NMR spectrum showed a δ 24.26-24.77 ppm (CH_3C=N), 169.09-169.67ppm (CH_3C=N) while (C=O) signal disappeared (Table 1).

Table 1: Shows the products of the reaction of chalcones 1(a-e) with aldehydes 2(a-e) under the effect of microwave irradiation and reflux condition

Product	Aldehyde Ar	Aldehyde R	Reflux		Microwave	
			Time (min)	Yield (%)	Time (min)	Yield (%)
3a			600	70	1.5	94
3b			600	67	1.5	92
3c			600	66	1	93
3d			600	71	1	95
3e			600	62	1.5	92

Product	Aldehyde Ar	Aldehyde R	Reflux		Microwave	
			Time (min)	Yield (%)	Time (min)	Yield (%)
3f			600	63	1	93
3g			600	68	1.5	95
3h			600	60	2	92
3i			600	67	1.5	95
3j			600	58	2	92
3k			600	64	1	94
3l			600	66	2	92
3m			600	61	1	94
3n			600	68	1	96
3o			600	59	1.5	93
3p			600	68	1	94
3q			600	66	1	95
3r			600	69	1.5	96
3s			600	72	1	97

Product	Aldehyde Ar	Aldehyde R	Reflux		Microwave	
			Time (min)	Yield (%)	Time (min)	Yield (%)
3t			600	63	2	95
3u			600	66	1.5	93
3v			600	62	2	92
3w			600	65	1.5	94
3x			600	61	1	93
3y			600	56	2	92

Biological activity

Anticancer activity

Cell viability and cytotoxicity assays are used for drug screening and cytotoxicity tests of chemicals. In this work, we have used the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide)tetrazolium reduction assay for determination the cytotoxicity of some synthesized samples on HepG2 cells.

All of the tested compounds 3b, 3i, 3l, 3t and 3v showed in-vitro cytotoxic activity against (HepG2) and give good results (Table 2 and Figures 2-7).

Table 2: Viability assay of tested samples on HepG2 cells after 24 h

Sample ID HepGII	Dilution (mg/ml)	O.D			Mean O.D	Viability %	Toxicity %
		0.213	**0.218**	**0.214**	**0.215**	**100**	**0**
3b	20	0.005	0.002	0.002	0.003	1.395349	98.60465
	10	0.003	0.004	0.005	0.004	1.860465	98.13953
	5	0.004	0.007	0.008	0.006333	2.945736	97.05426
	2.5	0.009	0.009	0.013	0.010333	4.806202	95.1938
	1.25	0.027	0.026	0.027	0.026667	12.4031	87.5969
	0.625	0.021	0.024	0.028	0.024333	11.31783	88.68217
	0.312	0.026	0.024	0.029	0.026333	12.24806	87.75194
	0.156	0.134	0.123	0.010	0.089267	41.51938	58.48062
3i	20	0.007	0.003	0.004	0.004667	2.170543	97.82946
	10	0.005	0.006	0.004	0.005	2.325581	97.67442
	5	0.003	0.002	0.007	0.004	1.860465	98.13953
	2.5	0.006	0.007	0.009	0.007333	3.410853	96.58915

Sample ID	Dilution	O.D			Mean O.D	Viability %	Toxicity %
HepGII	**(mg/ml)**	**0.213**	**0.218**	**0.214**	**0.215**	**100**	**0**
	1.25	0.008	0.009	0.012	0.009667	4.496124	95.50388
	0.625	0.006	0.004	0.009	0.006333	2.945736	97.05426
	0.312	0.009	0.09	0.014	0.037667	17.51938	82.48062
	0.156	0.012	0.009	0.014	0.011667	5.426357	94.57364
3l	10	0.003	0.002	0.004	0.003	1.395349	98.60465
	5	0.002	0.004	0.003	0.003	1.395349	98.60465
	2.5	0.004	0.005	0.004	0.004333	2.015504	97.9845
	1.25	0.004	0.004	0.004	0.004	1.860465	98.13953
	0.625	0.006	0.004	0.005	0.005	2.325581	97.67442
	0.312	0.006	0.008	0.007	0.007	3.255814	96.74419
	0.156	0.009	0.008	0.009	0.008667	4.031008	95.96899
	0.078	0.011	0.012	0.017	0.013333	6.20155	93.79845
3t	10	0.008	0.003	0.005	0.005333	2.48062	97.51938
	5	0.003	0.003	0.002	0.002667	1.24031	98.75969
	2.5	0.003	0.008	0.009	0.006667	3.100775	96.89922
	1.25	0.006	0.006	0.009	0.007	3.255814	96.74419
	0.625	0.008	0.006	0.008	0.007333	3.410853	96.58915
	0.312	0.009	0.006	0.007	0.007333	3.410853	96.58915
	0.156	0.006	0.008	0.01	0.008	3.72093	96.27907
	0.078	0.011	0.012	0.014	0.012333	5.736434	94.26357
3v	10	0.003	0.004	0.003	0.003333	1.550388	98.44961
	5	0.004	0.006	0.004	0.004667	2.170543	97.82946
	2.5	0.006	0.007	0.007	0.006667	3.100775	96.89922
	1.25	0.039	0.056	0.059	0.051333	23.87597	76.12403
	0.625	0.049	0.079	0.077	0.068333	31.78295	68.21705
	0.312	0.089	0.087	0.088	0.088	40.93023	59.06977
	0.156	0.092	0.099	0.089	0.093333	43.41085	56.58915
	0.078	0.109	0.11	0.107	0.108667	50.54264	49.45736

Figure 2: Morphological feature

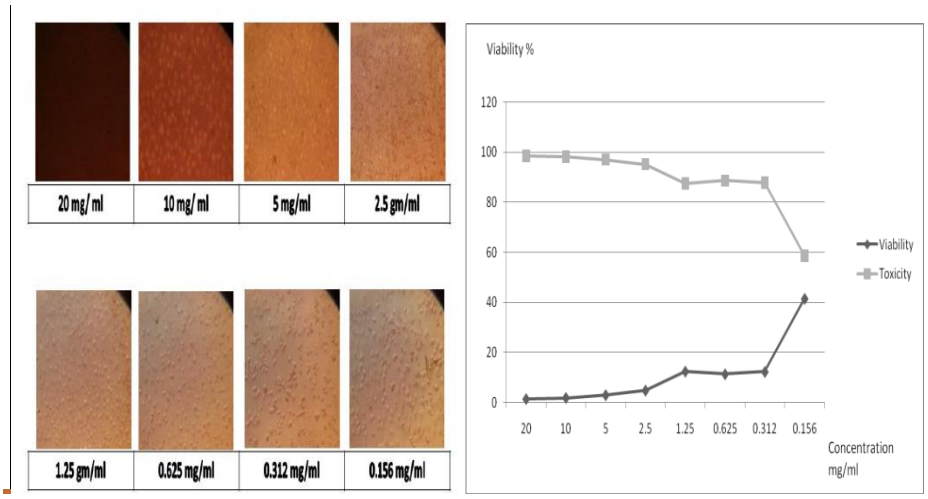


Figure 3: Effect of different concentration of compound 3b on HepG2 cells shows rounding, shrinkage, or cell granulation

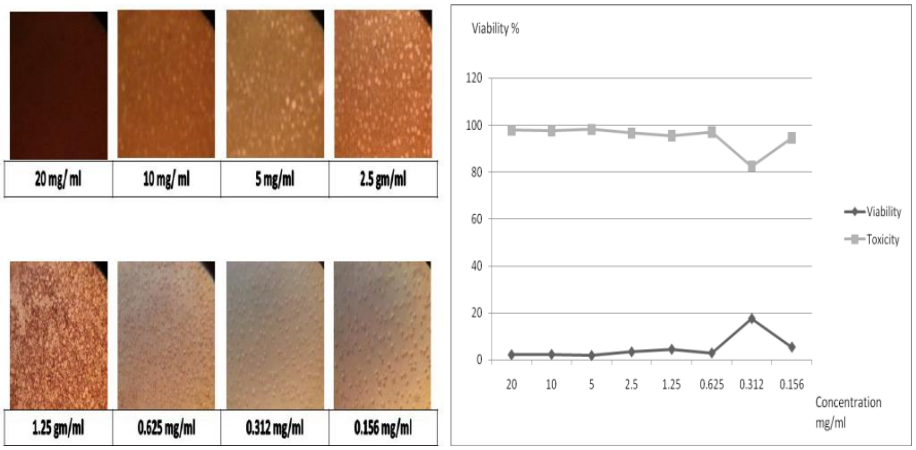


Figure 4: Effect of different concentration of compound 3i on HepG2 cells shows rounding, shrinkage, or cell granulation

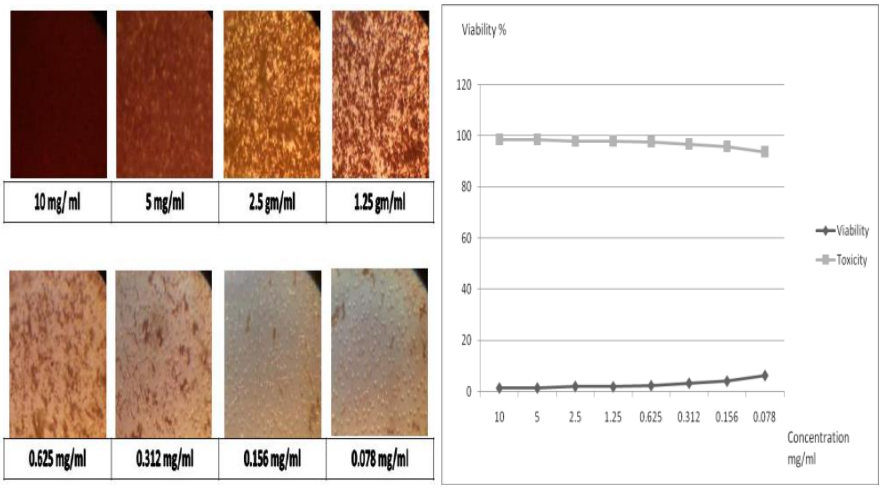


Figure 5: Effect of different concentration of compound 3l on HepG2 cells shows partial or complete loss of the monolayer, rounding, shrinkage, or cell granulatio

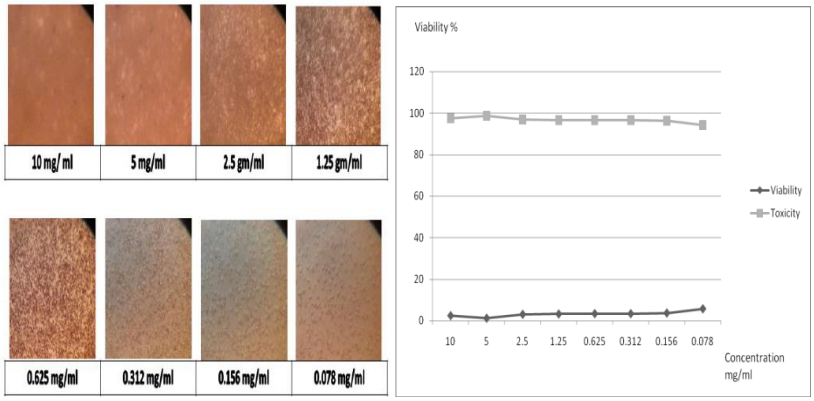


Figure 6: Effect of different concentration of compound 3t on HepG2 cells shows partial or complete loss of the monolayer, rounding, shrinkage, or cell granulation

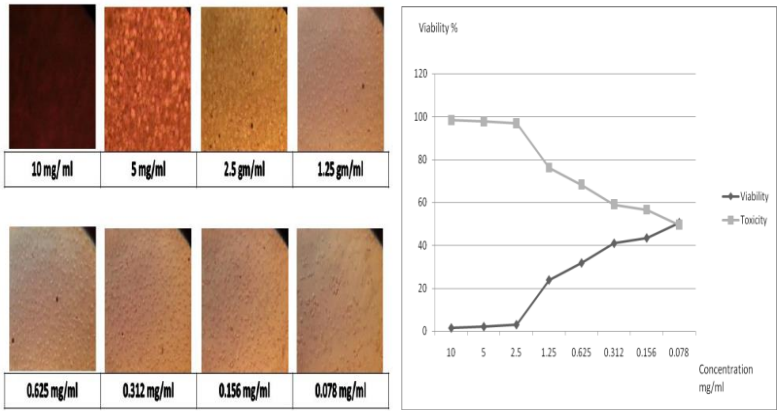


Figure 7: Effect of different concentration of compound 3v on HepG2 cells shows rounding, shrinkage, or cell granulation

CONCLUSION

Conclusively, polyarylpyrrole derivatives were synthesized from readily available starting materialsvia a facile and efficientone-potPaal-Knorr method under both traditional and microwave methods. Microwave reactions increased reaction rates, yields of pure products as well as eco-friendly advantagesMost of the newly synthesized compoundsshow good results on HepG2as anticancer

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