Egypt. J. Chem. **Vol. 63**, No. 11, pp. 4409 - 4421 (2020)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis of Novel 2, 3'-Bipyrrole Derivatives from Chalcone and Amino Acids as Antitumor Agents

Atef Kalmouch, [1] Mohamed A. A. Radwan, [2, 3] Mervat M. Omran, [4]

Marwa Sharaky, [4] Gaber O. Moustafa, [1, 5]*

[1] *Peptide Chemistry Department, Chemical Industries Research Division, National Research Centre, 12622-Dokki, Cairo, Egypt.*

[2] *Department of Applied Organic Chemistry, National Research Centre, Dokki, 12622, Egypt.*

[3] *Department of Chemistry, College of Science, Qassim University, Buraydah, Kingdom of Saudi Arabia.*

[4] *Pharmacology Unit, Cancer Biology Department, National Cancer Institute, Cairo University.*

[5] *Nahda University, New Benisuef City, Postal code (62521), Beni sueif, Egypt.*

Abstract

A series of a novel 2, 3'-bipyrrole derivatives was synthesized via the reaction of chalcone, (E)-1-(furan-2-*yl*)-3-(1*H*-pyrrol-2-*yl*) prop-2-en-one, with different amino acids in an alkaline medium. The reaction proceeds throughout the condensation of the amino acids with chalcone to give imine intermediate consequent by decarboxylation, and then intramolecular cyclization to yield 2, 3'-bipyrrole derivatives. Antitumor activities of the newly synthesized bipyrrole were evaluated against different six cancer cell lines, and compounds (**3d, 3e, 3c** and **3h**) derivatives showed the strongest anticancer activity amongst the studied compounds. Compound (**3h**) showed the broadest spectrum of anticancer activity against all cell lines tested. The results of this work offer a basis for further study of selected 2, 3'-bipyrrole derivatives as antitumor agents.

Keywords: amino acids, pyrrole, bipyrrole, furan, antitumor, chalcone.

1. Introduction

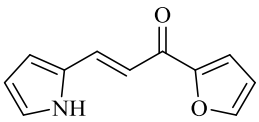
The pyrrole moiety is one of the most vital heterocycles. Pyrrole ring and their derivatives normally exist in various natural products [1, 2] and pharmaceuticals [3]. They are key intermediates for the synthesis of a variety of biologically active molecules [4-7] and act as functional materials [8]. Compounds that bearing a pyrrole ring [9] show several biological and pharmacological activities such as antitumor [10], antibacterial [11], antioxidative [12], anti-inflammatory [13], and antifungal properties [14]. Bipyrroles are an appreciated pioneer for the synthesis of several marine natural products [15]. Marinopyrroles A (1) and B (2) (Figure 1) with a unique 1,3'-bipyrrole structure display anti-bacterial results towards methicillin-resistant Staphylococcus aureus (MRSA) and cytotoxicity contrary to specific human cancer cells [16-18]. Also, bipyrroles and their derivatives are the basic components in several natural products and medicines (e.g., prodigiosin) [19-23]. Due to the promising of bipyrroles, they have of the interest of several researchers. Some approaches to the bipyrrole

*Corresponding author e-mail: gosman79@gmail.com, Tel: 00201003123355.
Receive Date: 02 April 2020, Revise Date: 05 April 2020, Accept Date: 13 April 2020
DOI: 10.21608/EJCHEM.2020.27117.2560

and its derivatives have been reported, as well as the Paal-Knorr condensation reaction [24, 25], catalytic dehydrogenation reactions [26], coupling reactions [26-28], and a double Michael addition reaction [29], and the metal-catalyzed 1, 3-dipolar cycloaddition of azomethine ylides [30]. However, the literature covers limited information for the synthesis bipyrroles, suggesting that methods to their synthesis are limiting. Hua and Wu [31] synthesized some of the bis-pyrrole-3, 4-dicarboxylate derivatives by the condensation of diethyl 2, 3-diacetyl succinate with diamines catalyzed by organic acids. Banik et al. [32] presented that 1, 1'-ethylene-bis (2, 5-dimethyl-1H-pyrrole) synthesized by the use of either an iodine-catalyzed, or a montmorillonite KSF clay-induced improved Paal-Knorr reaction. In contrast to the syntheses of 2, 2'-bipyrroles, rarer approaches for the synthesis of 2, 3'-bipyrroles, regularly in small yields, are known up to date [33-40]. In this manuscript, we report quick one-step access into novel 2, 3'-bipyrrole derivatives from chalcone. The key point in this technique is the addition of amino acids to (furanyl-pyrrolyl) prop-2-enone, chalcone. This reaction proceeds in pyridine; firstly, by condensation to give the corresponding imine then, decarboxylation generates carbanion and followed by cyclization to the 2, 3'-bipyrrole derivatives. Current effort originated as an extension our investigation program directing to the synthesis of a variety of heterocyclic candidates for biological evaluation [41-53].

2. Experimental

Synthesis of Chalcone; 1-(furan-2-yl)-3-(1H-pyrrol-2-yl) prop-2-en-1-one **1,** [54].

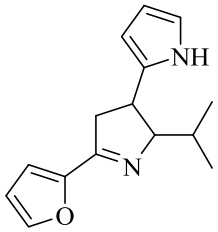


To obtain the required chalcone, 2-acetyl furan (10 mmol), and 2-pyrrole-carboxyaldehyde (10 mmol) are dissolved in ethanol and stirred under an ice bath for 5 min. The reaction was initiated by dropwise addition of 10 ml of 60 % sodium hydroxide solution in 30 min interval. To ensure the end of the reaction, the mixture was allowed for continuous stirring for another 2-3 h at room temperature. The reaction mixture was kept in a refrigerator for overnight and diluted with ice-cold distilled water (40 mL). The precipitated chalcone was filtered, washed well with cold water and air dried. The chalcone was recrystallized from methanol, yield 93% mp = 169-171^{0}C [54].

General procedure for synthesis of the 2- 5'-(furan-2-yl)-2', 3', 4'-trihydro-2, 3'-bipyrrole derivatives **3a-i.**

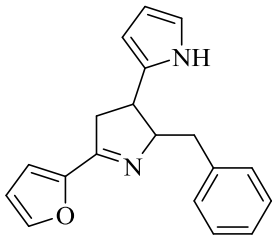
Chalcone (1.0 mmol) **1** was dissolved in pyridine (4 mL), and the appropriate amino acids **2** (3.0 mmol) were added. The reaction mixture was stirring at room temperature for 5 min. Then, the reaction was heated at 120 °C for 50 min. The reaction was controlled by TLC analysis. Next, the reaction was cooled and concentrated in vacuo, and the resulting product was purified by column chromatography using hexane/EtOAc (90/10) to obtain the bipyrrole derivatives **3a-i**.

5'-(Furan-2-yl)-2'-isopropyl-3',4'-dihydro-1H,2'H-2,3'-bipyrrole ***3a*.**



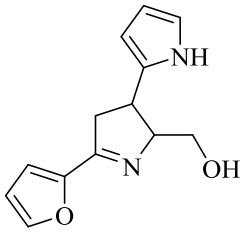
Yield: 85 %; m.p.= 94^{0}C oil; Rf x100 (solvent system): 68 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3433 (NH-stretching), 2997 (CH-aromatic), 2912 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 11.70 (s, 1H, NH), 8.02 (d, 1H, furan, H-5), 7.57-7.60 (d, 1H, furan, H-3), 7.44 (d, 1H, pyrrole, H-5), 7.30-7.32 (d, 1H, furan, H-3), 6.73-6.74 (d, 2H, pyrrole, H-3, H-4), 3.90 (t, 1H, trihydropyrrole, H-2'), 1.90-1.93 (m, 1H, trihydropyrrole, H-3'), 1.85-1.87 (d, 2H, CH_2, trihydropyrrole, H-4'), 1.80 (m, 1H, CH of valine moiety), 0.75-0.55 (d, 6H, $2CH_3$). MS (70-eV;-*EI*):-m/z-(%) =242 (M^+, 0.28%), 240 (0.79%), 72 (69.45%), **59 (100%)**, 51(0.51%). Molecular formula (M.wt.), $C_{15}H_{18}N_2O$ (242.1), calculated-analysis; C, 74.35; H, 7.49; N, 11.56; found; C, 74.25; H, 7.40; N, 11.55.

2'-Benzyl-5'-(furan-2-yl)-3',4'-dihydro-1H,2'H-2,3'-bipyrrole ***3b*.**



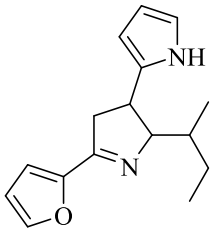
Yield: 8٠ %; m.p.= 99 ^{0}C.; Rf x100: (solvent system): 78 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3429 (NH-stretching), 2998 (CH-aromatic), 2913 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 11.71 (s, 1H, NH), 7.98-8.10 (d, 1H, furan, H-5), 7.56-7.60 (m, 5H, 5CH, Ph), 7.43 (d, 1H, furan, H-3), 734, 731 (d, 1H, pyrrole, H-5), 7.13 (d, 1H, furan, H-4), 6.22-6.66 (d, 2H, pyrrole, H-3, H-4), 2.5 (t, 2H, CH_2 of benzyl), 3.95 (t, 1H, trihydropyrrole, H-2'), 1.96-1.98 (m, 1H, trihydropyrrole, H-3'), 1.86-1.88 (d, 2H, CH_2, trihydropyrrole, H-4'). MS (70-eV;-*EI*):-m/z-(%) =291 (M^++1, 0.16%), 290 (M^+, 0.34%), 114 (2.77%), 72 (64.09%), **59 (100%)**, 55 (30.57%), 50(0.50%). Molecular formula (M.wt.), $C_{19}H_{18}N_2O$ (290.4), calculated-analysis; C, 78.59; H, 6.25; N, 9.65; found; C, 78.48; H, 6.21; N, 9.60.

(5'-(Furan-2-yl)-3',4'-dihydro-1H,2'H-[2,3'-bipyrrol]-2'-yl)methanol ***3c***.



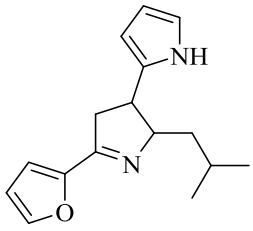
Yield: ٧5 %; m.p.=86^{0}C; Rf x100 (solvent system): 58 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3431 (NH-stretching), 2998 (CH-aromatic), 2913 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 12.77 (s, 1H, OH), 11.73 (s, 1H, NH), 8.02-8.04 (d, 1H, furan, H-5), 7.61 (d, 1H, furan, H-3), 7.55-7.57 (d, 1H, pyrrole, H-5), 7.44-7.45 (d, 1H, furan, H-4), 7.27-7.34 (d, 2H, pyrrole, H-3, H-4), 4.12-4.2 (d, 2H, CH_2-OH), 3.98 (t, 1H, trihydropyrrole, H-2'), 1.99-2.10 (m, 1H, trihydropyrrole, H-3'), 1.92-1.94 (d, 2H, CH_2, trihydropyrrole, H-4'). MS (70-eV;-*EI*):-m/z-(%) =230 (M^+, 0.44%), 126 (2.29%), 97 (7.19%), 72 (66.29%), **59 (100%)**, 55 (42.46%), 50(0.57%). Molecular formula (M.wt.), $C_{13}H_{14}N_2O_2$ (230.3), calculated-analysis; C, 67.81; H, 6.13; N, 12.17; found; C, 67.77; H, 6.10; N, 02.10.

2'-(sec-Butyl)-5'-(furan-2-yl)-3',4'-dihydro-1H,2'H-2,3'-bipyrrole ***3d.***



Yield: ٧٧ %; 81^{0}C.; Rf x100 (solvent system): 69 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3432 (NH-stretching), 2998 (CH-aromatic), 2913 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 11.72 (s, 1H, NH), 8.01(d, 1H, furan, H-5), 7.53-7.63 (d, 1H, furan, H-3), 7.45 (d, 1H, pyrrole, H-5), 7.36 (d, 1H, furan, H-3), 6.70-6.76 (d, 2H, pyrrole, H-3, H-4), 3.88 (t, 1H, trihydropyrrole, H-2'), 1.91-1.93 (m, 1H, trihydropyrrole, H-3'), 1.81-1.84 (d, 2H, CH_2, trihydropyrrole, H-4'), 1.70 (m, 1H, CH of isoleucine moiety), 1.60 (m, 2H, CH_2 of isoleucine moiety), 0.94-0.87 (d, 6H, 2CH_3, of isoleucine moiety). MS (70-eV;-*EI*):-m/z-(%) =256 (M^+, 3.08%), 255 (M^+-1, 4.91%), 115 (6.06%), 82 (46.49%), 69 (69.05%), 59 (76.62%), 57 (99.53%), **55 (100%)**, 50 (4.16%). Molecular formula (M.wt.), $C_{16}H_{20}N_2O$ (256.3), calculated-analysis; C, 74.97; H, 7.86; N, 10.93; found; C, 74.91; H, 7.75; N, 10.90.

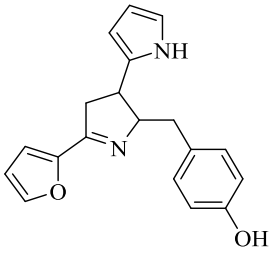
5'-(Furan-2-yl)-2'-isobutyl-3',4'-dihydro-1H,2'H-2,3'-bipyrrole ***3e***.



Yield: 8١ %; m.p.=87 ^{0}C; Rf x100 (solvent system): 55 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3426 (NH-stretching), 3001 (CH-aromatic), 2915 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 11.70 (s, 1H, NH), 8.02 (d, 1H, furan, H-5), 7.54-7.57 (d, 1H, furan, H-3), 7.41 (d, 1H, pyrrole, H-5), 7.24-7.26 (d, 1H, furan, H-3), 6.72-6.73 (d, 2H, pyrrole, H-3, H-4), 3.92 (t, 1H, trihydropyrrole, H-2'),

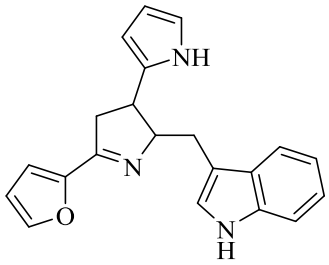
1.90-1.92 (m, 1H, trihydropyrrole, H-3'), 1.87-1.89 (d, 2H, CH_2, trihydropyrrole, H-4'), 1.75 (m, 1H, CH of leucine moiety), 1.60 (m, 2H, CH_2 of leucine moiety), 0.93-0.86 (d, 6H, $2CH_3$, of leucine moiety). MS (70-eV;-*EI*):-m/z-(%) =257 (M^++1, 0.41%), 256 (M^+, 1.38%), 255 (M^+-1, 0.76%), 114 (4.25%), 72 (66.02%), **59 (100%)**, 50 (0.32%). Molecular formula (M.wt.), $C_{16}H_{20}N_2O$ (256.3), calculated-analysis; C, 74.97; H, 7.86; N, 10.93; found; C, 74.92; H, 7.76; N, 10.82.

4-((5'-(Furan-2-yl)-3',4'-dihydro-1H,2'H-[2,3'-bipyrrol]-2'-yl)methyl)phenol ***3f***.



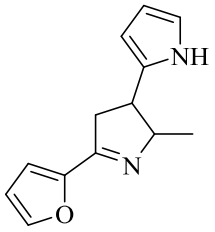
Yield: ٧٣ %; m.p.=89^{0}C; Rf x100 (solvent system): 74 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3435 (NH, OH, broad band), 2996 (CH-aromatic), 2912 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ: 12.78 (s, 1H, OH), 11.70 (s, 1H, NH), 8.01-8.04 (d, 1H, furan, H-5), 7.67-7.70 (d, 2H, Ph), 7.48 (d, 1H, furan, H-3), 7.44-7.45 (d, 2H, Ph), 7.34 (d, 1H, pyrrole, H-5), 7.12 (d, 1H, furan, H-4), 6.24-6.36 (d, 2H, pyrrole, H-3, H-4), 2.8 (t, 2H, CH_2-benzyl), 3.92 (t, 1H, trihydropyrrole, H-2'), 1.96-1.97 (m, 1H, trihydropyrrole, H-3'), 1.86-1.87 (d, 2H, CH_2, trihydropyrrole, H-4'). MS (70-eV;-*EI*):-m/z-(%) =306 (M^+, 1.2%), 264 (1.36%), 156 (1.00%), 126 (3.72%), 72 (72.38%), **59 (100%)**, 55(37.80%), 50 (0.28%). Molecular formula (M.wt.), $C_{19}H_{18}N_2O_2$ (306.4), calculated-analysis; C, 74.49; H, 5.92; N, 9.14; found; C, 74.41; H, 5.90; N, 9.04.

3-((5'-(Furan-2-yl)-3',4'-dihydro-1H,2'H-[2,3'-bipyrrol]-2'-yl)methyl)-1H-indole ***3g***.



Yield: ٦5 %; m.p. = 97 ^{0}C.; Rf x100 (solvent system): 73 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3431 (NH-stretching), 2998 (CH-aromatic), 2913 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 12.75 (s, 1H, NH), 11.70 (s, 1H, NH), 8.02-8.04 (d, 1H, furan, H-5), 7.75 (s,1H, indole-H-2), 7.56 (d,1H, indole-H-4), 7.52 (d, 1H, furan, H-3), 7.44-7.46 (m, 2H, indole-H-5,H-6), 7.40 (d,1H, indole-H-7), 7.34-7.35 (d, 1H, pyrrole, H-5), 7.31-7.32 (d, 1H, furan, H-4), 7.22-7.24 (d, 2H, pyrrole, H-3, H-4), 3.98 (t, 1H, trihydropyrrole, H-2'), 2.5 (d, 2H, CH_2), 1.99-2.10 (m, 1H, trihydropyrrole, H-3'), 1.92-1.94 (d, 2H, CH_2, trihydropyrrole, H-4'). MS (70-eV;-*EI*):-m/z-(%) =329 (M^+, 0.12%), 238 (1.94%), 128 (3.56%), 72 (72.86%), 59 **(100%)**, 55 (39.06%), 50 (0.27%). Molecular formula (M.wt.), $C_{21}H_{19}N_3O$ (329.4), calculated-analysis; C, 76.57; H, 5.81; N, 12.76; found; C, 76.52; H, 5.70; N, 12.72.

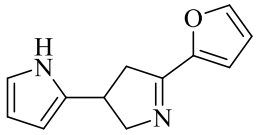
5'-(Furan-2-yl)-2'-methyl-3',4'-dihydro-1H,2'H-2,3'-bipyrrole ***3h***.



Yield: 79 %; m.p. = 91 ^{0}C.; Rf x100 (solvent system): 60 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3435 (NH-stretching), 2996 (CH-aromatic), 2912 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 11.70 (s, 1H, NH), 8.03 (d, 1H, furan, H-5), 7.61 (d, 1H, furan, H-3), 7.44 (d, 1H, pyrrole, H-5), 7.34-7.35 (d, 1H, furan, H-3), 6.78-6.80 (d, 2H, pyrrole, H-3, H-4), 3.90 (t, 1H, trihydropyrrole, H-2'), 1.90-1.93 (m, 1H, trihydropyrrole, H-3'), 1.85-1.87 (d, 2H, CH_2, trihydropyrrole, H-4'), 0.98 (3H, CH_3). MS (70-eV;-

EI):-m/z-(%) =214 (M^+, 0.45%), 149 (2.07%), 72 (61.76%), **59 (100%)**, 55 (30.30%), 50 (0.25%). Molecular formula (M.wt.), $C_{13}H_{14}N_2O$ (214.3), calculated-analysis; C, 72.87; H, 6.59; N, 13.07; found; C, 72.77; H, 6.48; N, 13.01.

5'-(Furan-2-yl)-3',4'-dihydro-1H,2'H-2,3'-bipyrrole ***3i***.



Yield: ٦٦ %; m.p. 93 ^{0}C.; Rf x100 (solvent system): 63 (N-hexane: ethyl acetate 7:3). IR in (cm^{-1}; KBr): 3427 (NH-stretching), 3000 (CH-aromatic), 2915 (CH-aliphatic). ^{1}H-NMR (500 MHz, DMSO-*d6*) δ : 11.70 (s, 1H, NH of pyrrole ring), 8.23 (d, 1H, furan, H-5), 7.55 (d, 1H, furan, H-3), 7.44 (d, 1H, pyrrole, H-5), 7.31-7.33 (d, 1H, furan, H-3), 6.76-6.80 (d, 2H, pyrrole, H-3, H-4), 4.12 (d, 2H, CH_2, trihydropyrrole, H-2'), 1.90-1.93 (m, 1H, trihydropyrrole, H-3'), 1.85-1.87 (d, 2H, CH_2, trihydropyrrole, H-4'). MS (70-eV;-*EI*):-m/z-(%) =200 (M^+, 0.49%), 187 (92.44%), 158 (55.49%), 130 (51.83%), 92 (51.53%), 72 (57.72%), **58 (100%)**, 55 (39.87%), 50 (16.21%). Molecular formula (M.wt.), $C_{12}H_{12}N_2O$ (200.2), calculated-analysis; C, 71.98; H, 6.04; N, 13.99; found; C, 71.90; H, 6.96; N, 13.97.

2.1. Human cancer cell line

In this study, a panel of human cancer cell lines was tested for their chemosensitivity to 2, 3'-bipyrrole derivatives: Human Breast carcinoma cell line (MCF7), Human Colon carcinoma cell line (HCT_{116}), Human Lung carcinoma cell line (A549), Human Pharyngeal carcinoma cell line (FADU), Human Liver carcinoma cell line (HEPG2), were obtained frozen in liquid nitrogen (-180^{o}C) from American Type Culture Collection (ATCC; Washington, DC, USA). Human Tamoxifen Resistant MCF7 Breast carcinoma cell line (TMR_{10}), prepared in pharmacology Unit Lab, National Cancer Institute to be resistant to 10μM Tamoxifen. and were maintained at National Cancer Institute as monolayer cultures in RPMI-1640 supplemented with 10% FBS and 1% penicillin- streptomycin.

2.1.1. Cytotoxicity assay

Cytotoxicity was determined using sulforhodamine-B (SRB) method [55]. Cells were seeded in 96-well microtiter plates at a concentration of 3×10^3 cells/well. They were left to attach for 24 h before incubation with drugs. The cells were treated for 48 h with single dose (100 ug/ml) of compound and for IC_{50} the cells were treated by different concentrations (0, 5, 12.5, 25 and 50 ug/ml) of compounds. The optical density (O.D) of each well was measured spectrophotometrically at 570 nm using ELISA microplate reader (TECAN Sunrise TM, Germany).The mean values were estimated as percentage of cell viability as follows: O.D (treated cells) / O.D (control cells) × 100. The IC50 value (the concentration that produces 50% inhibition of cell growth) of each drug was calculated using dose response curve-fitting models (Graph-Pad Prism software, version 5).

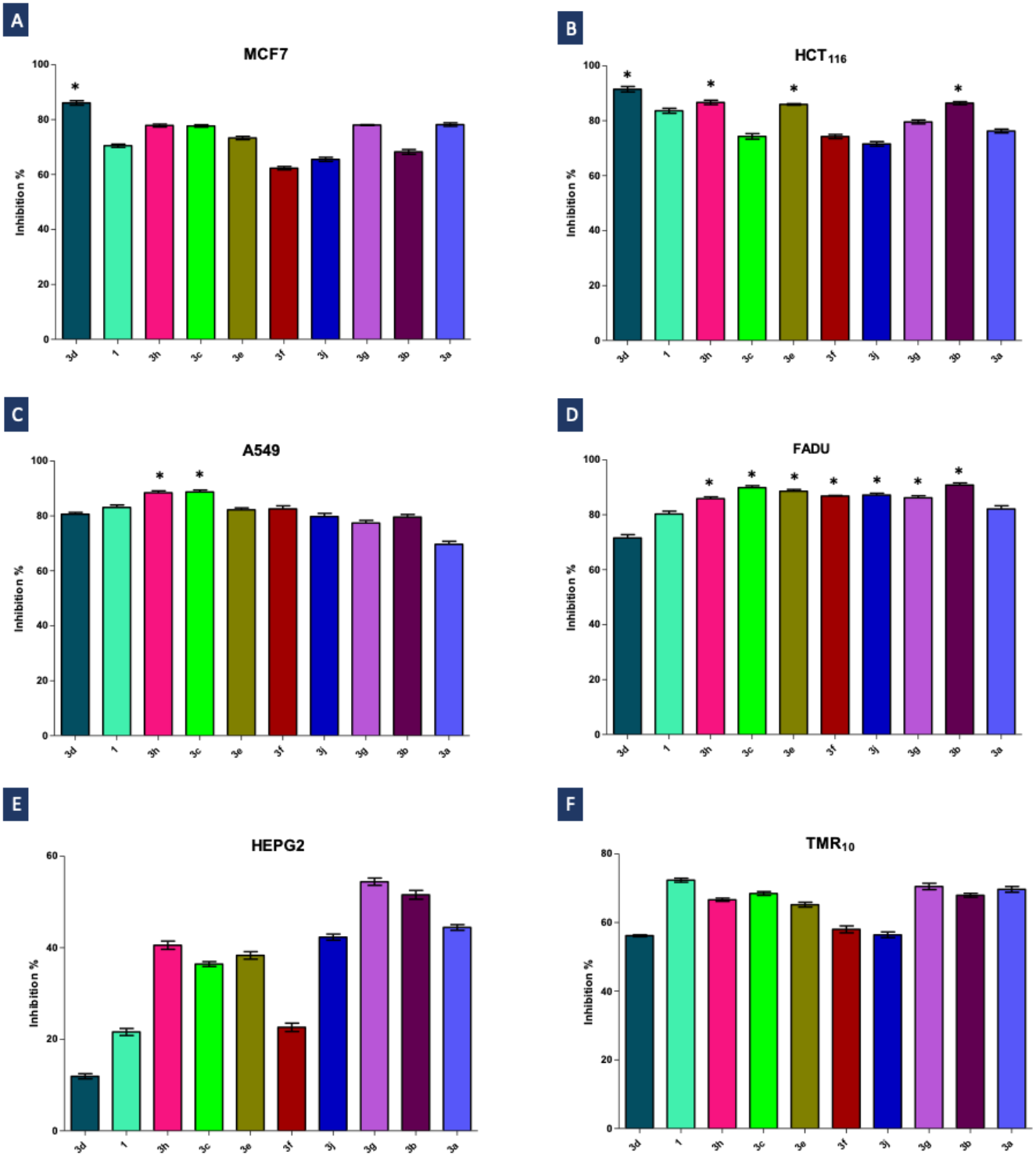


Figure (1): % inhibition in Surviving fractions in different cancer cell lines after treatment with single dose (100ug/ml) of 2, 3'-bipyrrole derivatives. MCF7 Human breast carcinoma cell line (A), HCT_{116} Human colon carcinoma cell line (B), A549 Human lung carcinoma cell line (C), FADU Human Pharyngeal carcinoma cell line (D), HEPG2 Human Liver carcinoma cell line (E), TMR_{10} Human Tamoxifen Resistant Breast carcinoma cell line (F). Values are the means ± SD of three independent experiments performed in triplicates.

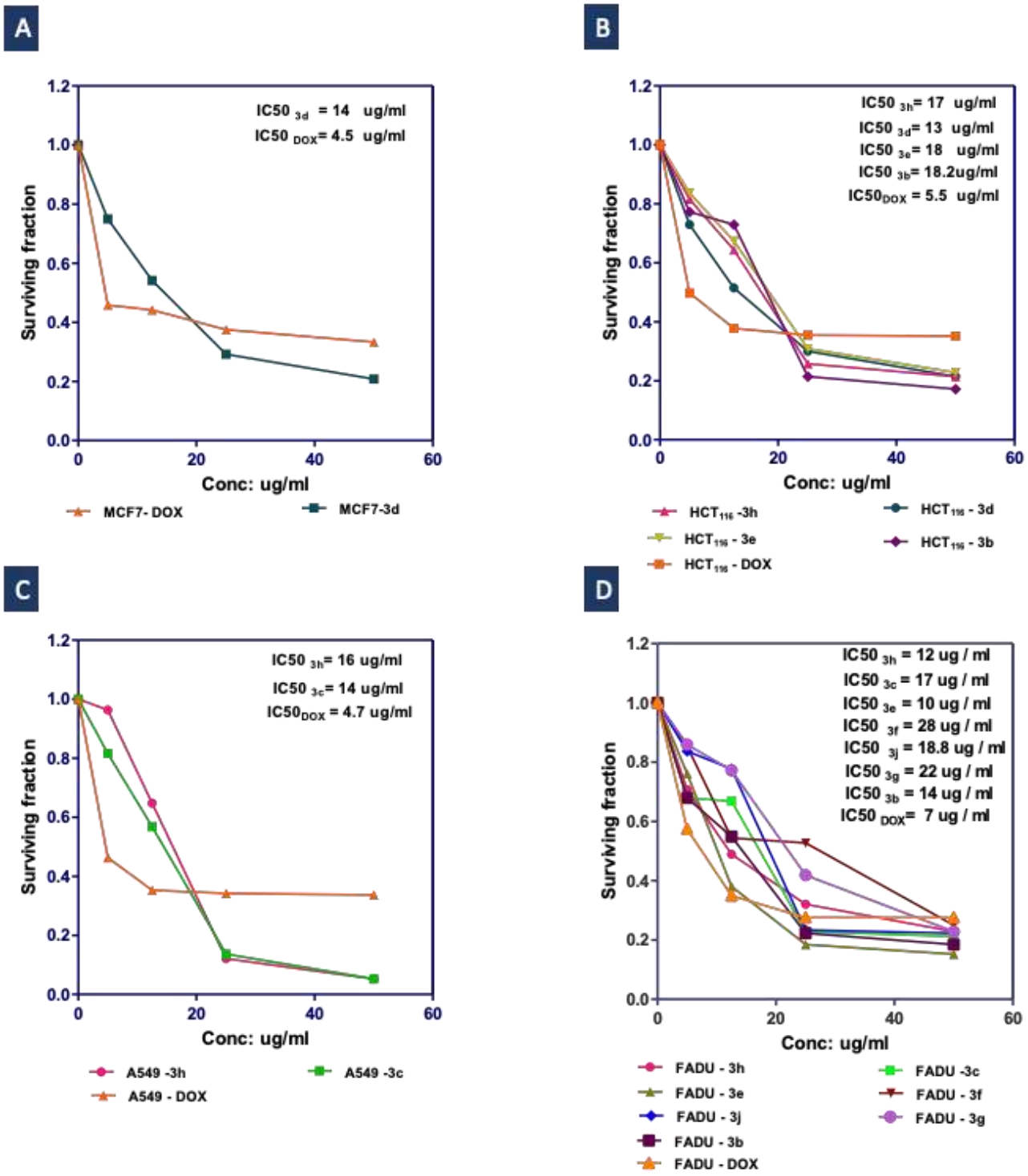
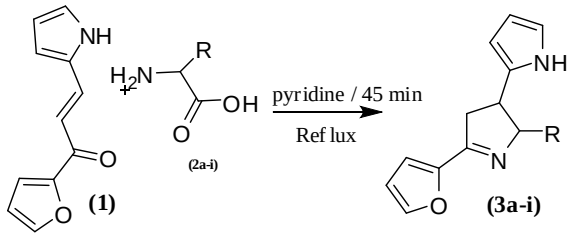


FIGURE (2): Cytotoxicity of 2, 3'-bipyrrole derivatives on cancer cell lines after 48h. Surviving fraction of: (A) MCF7 treated with (**3d**). (B) HCT_{116} treated with (**3b, 3d, 3e** and **3h**). (C) A549 treated with (**3c** and **3h**). (D) FADU treated with (**3b, 3c, 3e, 3f, 3g, 3h** and **3i**).

3. Results and Discussion

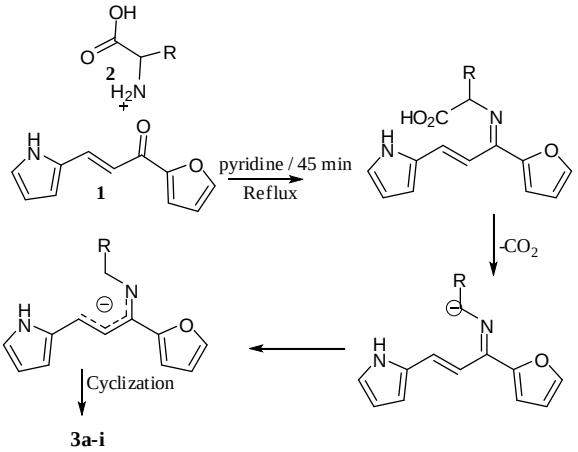
3.1. Chemistry

Throughout our investigation program, we found that the chemistry of amino acids is promising in the synthesis of biologically active compounds [56-76]. Herein, we describe a convenient strategy for the synthesis of a series of novel 2, 3'-bipyrrole derivatives via the reaction of chalcone **1**, with different amino acids in an alkaline medium. The reaction proceeds in pyridine, which initiates a successive immunization, decarboxylation, and subsequently cyclization, leading to an efficient synthesis of novel 2, 3'-bipyrrole derivatives **3a-i**, Scheme 1. Decarboxylation would give carbanion and followed by the electrocyclization to give 2, 3'-bipyrrole derivatives in one step, Scheme 2. To test this anticipated method, the study starting using chalcone **1** and glycine **2a** in pyridine at 120 ºC for 50 minutes yields 2, 3'-bipyrrole **3a**. Structure elucidation of the final product was established on the basis of its spectral data and elemental analysis. The IR (KBr, cm^{-1}) spectra of this compound released a distinct NH group between 3121-3355 cm^{-1} and the absence of a carbonyl group. Also, ^{1}H-NMR data of compound **3a** displayed abroad signal at δ: 8.57 ppm for NH proton and aliphatic signals at δ: 2.3-3.73 ppm in addition to aromatic signals at δ: 7.32–8.02 ppm (see experimental section).



2a = D-Val; **2b** = L-Phe; **2c** = L-Ser; **2d** = L-IIe; **2e** = L-Leu; **2f** = L-Tyr; **2g** = L-Trp; **2h** = L-ala; **2i** = Gly

Scheme 1. Synthetic route for 5'-(furan-2-yl)-2', 3', 4'-trihydro-2, 3'-bipyrrole derivatives 3a-i.



Scheme 2. Suggested reaction mechanism for 2, 3'-bipyrrole derivatives 3a-i.

3.2. Anticancer activity

After performing single dose (100ug/ml) testing for all 2, 3'-bipyrrole derivatives on different 6 cancer cell lines. **Figure (1)** showing the inhibition % of the 2, 3'-bipyrrole derivatives on the used 6 cancer cell lines. All the compounds exert mild effect (< 85% inhibition) on both HEPG-2 and TMR_{10}. On the other hand, 2, 3'-bipyrrole derivatives exert moderate to severe effect on MCF7, HCT_{116}, A549, and FADU. (**3d**) showing ≥85% inhibition on MCF7 cell line with IC50=17, 14 µg/ml, respectively **(Figure 2A)**. (**3d**) exert the better effect on MCF7 cell line. (**3h**, **3d**, **3e**, and **3b**) showing ≥85% inhibition on HCT_{116} cell line with IC50=17, 13, 18, 18.2µg/ml, respectively **(Figure 2B)**. (**3h**, and **3c**) showing ≥85% inhibition on A549cell line with IC50=16, 14µg/ml, respectively **(Figure 2C)**. Compound (**3c**) exert the better effect on A549 cell line. (**3d**) derivative exert the better effect on HCT_{116} cell line. (**3h**, **3c**, **3e**, **3f**, **3j**, **3g**, and **3b**) showing ≥85% inhibition on FADU cell line with IC50=12, 17, 10, 28, 18.8, 22, and 14 µg/ml, respectively **(Figure 2D)**. L- Leu (**3e**) derivative exert the better effect on FADU cell line.

Structure-Activity Relationship

Generally, bipyrrole derivatives represent promising building blocks as candidates for biological activity. Antitumor activities of the newly synthesized bipyrrole derivatives were evaluated against different six cancer cell lines, and (**3d, 3e, 3c** and **3h**) derivatives showed the strongest anticancer activity amongst the studied compounds. Compound **3d** with 2'- *sec-butyl*-bipyrrole derivative showed the

strongest anticancer activity against both HCT_{116} & MCF7 cell lines. While compound **3e** with 2'-*isobutyl*-bipyrrole derivative showed the strongest anticancer activity against FADU cell line. Compound **3c** with 2'- hydroxy methyl-bipyrrole derivative showed the strongest anticancer activity against A549cell line. On the other hand, Compound **3h** with 2'- methyl-bipyrrole derivative showed the broadest spectrum anticancer activity all over most of the tested cell lines. Farther investigations are required for studying the mechanism of action and toxicity of bipyrrole derivatives especially bipyrrole substituted with aliphatic groups at 2'-position.

4. Conclusion

In this article, we report fast one-step access into novel 2, 3'-bipyrrole derivatives from chalcone and amino acids. The key point in this technique is the addition of amino acids to chalcone. This reaction proceeds in pyridine; firstly, by condensation to give the corresponding imine then, decarboxylation generates carbanion and followed by cyclization to the 2, 3'-bipyrrole derivatives. Antitumor activities of the newly synthesized bipyrrole were evaluated against different six cancer cell lines, and compounds (**3d, 3e, 3c** and **3h**) derivatives showed the strongest anticancer activity amongst the studied compounds. Compound (**3h**) showed the broadest spectrum of anticancer activity against all cell lines tested. Further investigations are required for studying the mechanism of action and toxicity of these compounds.

5. References

1. Gholap S.S. Pyrrole: An emerging scaffold for construction of valuable therapeutic agents. *European journal of medicinal chemistry*, **110**, 13-31 (2016).
2. Qiu F., Wu J., Zhang Y., Hu M. and Yu Y. One-pot cascade approach to 1, 3′-bipyrrole derivatives from trisubstituted olefins with tosylmethyl-isocyanide (TosMIC). *Tetrahedron Letters*, **53**(4), 446-448 (2012).
3. Murineddu G., Loriga G., Gavini E., Peana A.T., Mulè A.C. and Pinna G.A. Synthesis and analgesic- antiinflammatory activities of novel acylarylhydrazones with a 5- phenyl- 4- R- 3- pyrrolyl- acyl moiety. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, **334**(12), 393-398 (2001).
4. Liu H., Ueta S., Yagishita F., Nishiuchi M. and Kawamura Y. One-pot synthesis of novel polysubstituted 1, 1′-phenylene-bipyrrole via the double [3+ 2] cycloaddition reaction. *Tetrahedron*, **71**(22), 3614-3618 (2015).
5. Sydor P.K., Barry S.M., Odulate O.M., Barona-Gomez F., Haynes S.W., Corre C., Song, L. and Challis, G.L. Regio-and stereo divergent antibiotic oxidative carbocyclizations catalysed by Rieske oxygenase-like enzymes. *Nature chemistry*, **3**(5), 388 (2011).
6. Sessler J.L., An D., Cho W.S., Lynch V. and Calix [n] bipyrroles: Synthesis, Characterization, and Anion Binding Studies. *Angewandte Chemie International Edition*, 42(20), 2278-2281 (2003).
7. Manderville, R. Synthesis, proton-affinity and anti-cancer properties of the prodigiosin-group natural products. *Current Medicinal Chemistry-Anti-Cancer Agents*, **1**(2), 195-218 (2001).
8. Liu H., Ueta S., Yagishita F., Nishiuchi M. and Kawamura Y. One-pot synthesis of novel polysubstituted 1, 1′-phenylene-bipyrrole via the double [3+ 2] cycloaddition reaction. *Tetrahedron*, **71**, 3614-3618 (2015).
9. Michael J.P. Indolizidine and quinolizidine alkaloids. *Natural product reports*, **15**, 571-594 (1998).
10. Jonas R., Klockow M., Lues I., Pruecher H., Schliep H. and Wurziger H. Synthesis and biological activities of meribendan and related heterocyclic benzimidazolo-pyridazinones. *European journal of medicinal chemistry*, **28**, 129-140 (1993).
11. Daidone G., Maggio B. and Schillaci D. Salicylanilide and its heterocyclic analogues. A comparative study of their antimicrobial activity. *Pharmazie*, **45**, 441-452 (1990).
12. Meshram H., Prasad B. and Kumar D.A. A green approach for efficient synthesis of N-substituted pyrroles in ionic liquid under microwave irradiation. *Tetrahedron Letters*, **51**, 3477-3480 (2010).
13. Battilocchio C., Poce G., Alfonso S., Porretta G.C., Consalvi S., Sautebin L., Pace S., Rossi A., Ghelardini C., Di Cesare Mannelli L., Schenone S., Giordani A., Di Francesco L., Patrignani P. and Biava M. A class of pyrrole derivatives endowed with analgesic/anti-inflammatory activity. *Bioorganic & medicinal chemistry*, **21**, 3695-3701 (2013).
14. Bhosale J.D., Dabur R., Jadhav G.P. and Bendre R. Facile syntheses and molecular-docking of novel substituted 3, 4-dimethyl-1H-pyrrole-2-carboxamide/carbohydrazide analogues with

antimicrobial and antifungal properties. *Molecules,* **23**, 875 (2018).

15. Fu L. and Gribble G.W. Synthesis of 1, 2′-and 1, 3′-bipyrroles from 2-and 3-nitropyrroles. *Tetrahedron Letters,* **49**, 3545-3548 (2008).

16. Hughes C.C., Prieto-Davo A., Jensen P.R. and Fenical W. The marinopyrroles, antibiotics of an unprecedented structure class from a marine Streptomyces sp. *Organic letters,* **10**, 629-631 (2008).

17. Hughes C.C., Yang Y.L., Liu W.T., Dorrestein P.C., Clair J.J.L. and Fenical W. Marinopyrrole A target elucidation by acyl dye transfer. *Journal of the American Chemical Society,* **131**, 12094-12096 (2009).

18. Nicolaou K., Simmons N.L., Chen J.S., Haste N.M. and Nizet V. Total synthesis and biological evaluation of marinopyrrole A and analogs. *Tetrahedron letters,* **52**, 2041-2043 (2011).

19. Chang C. and Adams R.. Stereochemistry Of N, N′-Dipyrryls. Resolution Of N, N′, 2, 5, 2′, 5′-Tetramethyl-3, 3′-Dicarboxydipyrryl. XVI. *Journal of the American Chemical Society,* **53**, 2353-2357 (1931).

20. Webb J.L. The Chemistry of Bipyrryls. II. The Preparation and Resolution of A 1, 1'-Disubstituted 2, 2'-Bipyrryl Exhibiting Restricted Rotation. *The Journal of Organic Chemistry,* **18**, 1413-1417 (1953).

21. Rapoport H. and Holden K.G. The synthesis of prodigiosin. *Journal of the American Chemical Society,* **84**, 635-642 (1962).

22. Hughes C.C., Kauffman C.A., Jensen P.R. and Fenical W. Structures, reactivities, and antibiotic properties of the marinopyrroles A− F. *The Journal of organic chemistry,* **75**, 3240-3250 (2010).

23. Hu D.X., Clift M.D., Lazarski K.E. and Thomson R.J. Enantioselective total synthesis and confirmation of the absolute and relative stereochemistry of streptorubin B. *Journal of the American Chemical Society,* **133**, 1799-1804 (2011).

24. Sessler J.L., An D., Cho W.S. and Lynch V. Calix [n] bipyrroles: Synthesis, Characterization, and Anion-Binding Studies. *Angewandte Chemie International Edition,* **42**, 2278-2281 (2003).

25. Webb J.L. and Threlkeld R.R. The Chemistry of Bipyrryls. I. The Preparation of a 1, 1'-Unsubstituted 2, 2'-Bipyrryl. *The Journal of Organic Chemistry,* **18,** 1406-1412 (1953).

26. Merz A., Kronberger J., Dunsch L., Neudeck A., Petr A. and Parkanyi L. Radical Dimerization of 5, 5′-Diphenyl-3, 3′, 4, 4′-tetramethoxy-2, 2′-bipyrrole: π Dimer in the Crystal, σ Dimer in Solution. *Angewandte Chemie International Edition,* **38**, 1442-1446 (1999).

27. Merz A., Anikin S., Lieser B., Heinze J. and John H. 3, 3′-and 4, 4′-Dimethoxy-2, 2′-bipyrroles: Highly Electron-Rich Model Compounds for Polypyrrole Formation. *Chemistry–A European Journal,* **9**, 449-455 (2003).

28. Dey S., Pal C., Nandi D., Giri V.S., Zaidlewicz M., Krzeminski M., Smentek L., Hess, B.A., Gawronski J., Kwit M., Babu N.J., Nangia A. and Jaisankar P. Lewis Acid-Catalyzed One-Pot, Three-Component Route to Chiral 3, 3 ‘-Bipyrroles. *Organic letters,* **10**, 1373-1376 (2008).

29. López-Pérez A., Robles-Machín R., Adrio J. and Carretero J.C. Oligopyrrole Synthesis by 1, 3-Dipolar Cycloaddition of Azomethine Ylides with Bissulfonyl Ethylenes. *Angewandte Chemie International Edition,* **46**, 9261-9264 (2007).

30. Manderville R. Synthesis, proton-affinity and anti-cancer properties of the prodigiosin-group natural products. *Current Medicinal Chemistry-Anti-Cancer Agents,* **1**, 195-218 (2001).

31. Fürstner A. Chemistry and biology of roseophilin and the prodigiosin alkaloids: a survey of the last 2500 years. *Angewandte Chemie International Edition,* **42**, 3582-3603 (2003).

32. Kancharla P., Kelly J.X. and Reynolds K.A. Synthesis and structure–activity relationships of tambjamines and B-ring functionalized prodiginines as potent antimalarials. *Journal of medicinal chemistry*, **58**, 7286-7309 (2015).

33. Dohi T., Morimoto K., Maruyama A. and Kita Y. Direct synthesis of bipyrroles using phenyliodine bis (trifluoroacetate) with bromotrimethylsilane. *Organic letters,* **8**, 2007-2010 (2006).

34. Dohi T., Morimoto K., Ogawa C., Fujioka H. and Kita Y. Clean and Direct Synthesis of α, α′-Bithiophenes and Bipyrroles by Metal-Free Oxidative Coupling Using Recyclable Hypervalent Iodine (III) Reagents. *Chemical and Pharmaceutical Bulletin,* **57**, 710-713 (2009).

35. Castro A.J., Giannini D.D. and Greenlee W.F. Synthesis of a 2, 3'-bipyrrole. Denitrosation in the Knorr pyrrole synthesis. *The Journal of Organic Chemistry,* **35**(8), 2815-2816 (1970).

36. Silvestri G., Gambino S., Filardo G., Petruso S.,

Caronna S. and Sprio V. Electrochemical oxidation of 2, 4, 5-triaryl-substituted pyrroles. II. Oxidative dimerization of 4, 5-diphenyl-2-mesitylylpyrrole. *Journal of heterocyclic chemistry*, **26**(2), 489-492 (1989).

37. Zaitsev A.B., Schmidt E.Y., Mikhaleva A.M., Afonin A.V. and Ushakov I. A. Dioximes of 1, 3-diketones in the trofimov reaction: New 3-substituted pyrroles. *Chemistry of Heterocyclic Compounds*, **41**(6), 722-729 (2005).

38. Lopchuk J.M., Song M., Butler B. and Gribble G.W. Synthesis of heteroaryl-substituted pyrroles via the 1, 3-dipolar cycloaddition of unsymmetrical Münchnones and nitrovinylheterocycles. *Synthesis*, **47**(18), 2776-2780 (2015).

39. Brandsma L., Nedolya N.A., Verkruijsse H.D. and Trofimov B.A. Synthesis of 5-alkoxy-2-alkylthio-3-pyrrol-2-ylpyrroles. *Chemistry of Heterocyclic Compounds*, **36**(7), 876-877 (2000).

40. Dasari S.R., Tondepu S., Vadali L.R., Ganivada M.N. and Seelam, N. Synthesis, Molecular Properties, and Biological Evaluation of Hybrid 1, 2, 3- Triazolylpolyaza Heterocyclic Compounds. *Journal of Heterocyclic Chemistry*, **56**(1), 195-208(2019).

41. Radwan, M. A., El-Sherbiny, M. Synthesis and antitumor activity of indolylpyrimidines: marine natural product meridianin D analogues. *Bioorg Med Chem.*, **15**(3), 1206-1211 (2007).

42. Radwan, M. A., Ragab, E. A., Sabry, N. M., El-Shenawy, S. M. Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents. *Bioorg Med Chem*, **15** (11), 3832-41 (2007).

43. Radwan, M.A.A., Ragab, E.A., Shaaban, M.R., El-Nezhawy, A.O.H. Application of (2Z)-3-dimethylamino-2-(1H-indole-3-carbonyl) acrylonitrile in the synthesis of novel 3-heteroarylindoles: condensed meridianine analogs, *ARKIVOC*, (***vii***), 281-293 (2009).

44. El-Nezhawy, A. O., Eweas, A. F., Radwan, M. A. El-Naggar, T. B. Synthesis and Molecular Docking Studies of Novel 2-Phenyl-4-Substituted Oxazole Derivatives as Potential Anti-cancer Agents. *Journal of Heterocyclic Chemistry*, **53**(1), 271-279 (2016).

45. Fakhr, I. M., Radwan, M. A., el-Batran, S., Abd el-Salam, O. M., el-Shenawy, S. M. Synthesis and pharmacological evaluation of 2-substituted benzo[b]thiophenes as anti-inflammatory and analgesic agents. *Eur J Med Chem*, **44** (4), 1718-25 (2009).

46. Radwan, M. A., Shehab, M. A., El-Shenawy, S. M. Synthesis and biological evaluation of 5-substituted benzo [b] thiophene derivatives as anti-inflammatory agents. *Monatshefte für Chemie*, **140**(4), 445-50 (2009).

47. Radwan, M. A. A., Alminderej, F. M., Awad, H. M. One-Pot Multicomponent Synthesis and Cytotoxic Evaluation of Novel 7-Substituted-5-(*1H*-Indol-3-*yl*)Tetrazolo[1,5-a] Pyrimidine-6-Carbonitrile. *Molecules*, **25**, 255 (2020).

48. Muhammad, Z., Radwan, M. A. A., Farghaly, T., Gaber, H., Elaasser, M. Synthesis and antitumor activity of novel [1, 2, 4, 5]-tetrazepino[6,7-b] indole derivatives: Marine natural product hyrtioreticuline C and D analogues. *Mini-Reviews in Medicinal Chemistry*, **19,** 79-86 ***(2019).***

49. El Nezhawy, A., Gaballah, S., Radwan, M. A. A. Studying the reactivity of (phthalazin-1(2H)-on-2-yl)methyl trichloroacetimidate towards different C- and O-nucleophiles. *Tetrahedron Letters*, **50,** 6646-6650 (2009).

50. El Nezhawy A., Radwan M. A. A., Gaballah S., Synthesis of chiral N-(2-(1-oxophthalazin-2(1H)-yl) ethanoyl)-α-amino acid derivatives as antitumor agents. *Arkivoc, 12* ***119-130 (2009).***

51. Radwan M. A. A., Abbas E., Synthesis of some pyridine, thiopyrimidine, and isoxazoline derivatives based on the pyrrole moiety. *Monatshefte fur Chemie*, **140,** 229-233 (2009).

52. Ghorab M., Radwan M. A. A., Taha N., Amin N., Shehab M., Faker I., Dapson in heterocyclic chemistry, part II: Antimicrobial and antitumor activities of some novel sulfone biscompounds containing biologically active thioureido, carbamothioate, quinazoline, imidazolidine, and thiazole moieties. *Phosphorus, Sulfur and Silicon and the Related Elements*, **183,** 2906-2917 (2008).

53. Fakhr I., Hamdy N., Radwan M. A. A., Ahmed Y., Synthesis of new bioactive benzothiophene derivatives. *Egyptian Journal of Chemistry*, **47,** 201-215 (2004).

54. Mohammed, O. J., Radi, M. F., Abdula, A. M., Al-Ahdami, B. W.; Rodhan, W. F., Sha'aban, H. G. Synthesis of four chalcone derivatives bearing heterocylic moieties as new AChE inhibitors by docking simulation. *International Journal of Chemical Sciences*. **13**(1), 157-166 (2015).

55. Skehan P., Storeng R., Scudiero D., A. Monks A., McMahon J., Vistica D., Bokesch H., New colorimetric cytotoxicity assay for anticancer drug screening, J. Natl .Cancer Inst.,82, 1107–1112

(1990).

56. Moustafa G.O., El-Sawy A.A. and Abo-Ghalia M.H., Synthesis of Novel Cyclopeptide Candidates: I-Cyclo-[N^{α}-isophthaloyl-bis-(Glycine-Amino Acid)-L-Lysine] Derivatives with Expected Anticancer Activity., *Egyptian Journal of Chemistry*, **56**(5), 473-494 (2013).

57. Abo-Ghalia M.H., Moustafa G.O., Alwasidi A.S. and Naglah A.M., Cytotoxic investigation of isophthaloyl cyclopentapeptides., *Lat. Am. J. Pharm.*, **36**(10), 1957-1962 (2017).

58. Amr A.E.E., Abo-Ghalia M.H., Moustafa G.O., Al-Omar M.A., Nossier E.S. and Elsayed E.A., Design, synthesis and docking studies of novel macrocyclic pentapeptides as anticancer multi-targeted kinase inhibitors., *Molecules*, **23**, 2416 (2018).

59. Moustafa G.O., Younis A., Al-Yousef S.A. and Mahmoud S.Y., Design, synthesis of novel cyclic pentapeptide derivatives based on 1, 2-benzenedicarbonyl chloride with expected anticancer activity., *J. Comput. Theor. Nanosci.*, **16**(5-6), 1733-1739 (2019).

60. Kassem A.F., Moustafa G.O., Nossier E.S., Khalaf H.S., Mounier M.M., Al-Yousef S.A. and Mahmoud S.Y., In vitro anticancer potentiality and molecular modelling study of novel amino acid derivatives based on N^1, N^3-bis-(1-hydrazinyl-1-oxopropan-2-yl) isophthalamide., *J. Enzyme Inhib. Med. Chem.*, **34**(1), 1247-1258 (2019).

61. Elhenawy A.A., Al-Harbi L.M., Moustafa G.O., El-Gazzar M.A., Abdel-Rahman R.F. and Salim A.E., Synthesis, comparative docking, and pharmacological activity of naproxen amino acid derivatives as possible anti-inflammatory and analgesic agents., *Drug Des. Devel. Ther.*, **13**, 1773-1790 (2019).

62. Naglah A.M., Moustafa G.O., Al-Omar M.A., Al-Salem H.S.A. and Hozzein W.N., Synthesis, characterization and in vitro antimicrobial investigation of novel amino acids and dipeptides based on dibenzofuran-2-sulfonyl-chloride., *J. Comput. Theor. Nanosci.*, **14**(7), 3183-3190 (2017).

63. Al-Salem H.S.A., Naglah A.M., Moustafa G.O., Mahmoud A.Z. and Al-Omar M.A., Synthesis of novel tripeptides based on dibenzofuran-2-sulfonyl-[aromatic and hydroxy aromatic residues]: Towards antimicrobial and antifungal agents., *J. Comput. Theor. Nanosci.*, **14**(8), 3958-3966 (2017).

64. Moustafa G.O., Khalaf H., Naglah A., Al-Wasidi A., Al-Jafshar N. and Awad H., The Synthesis of Molecular Docking Studies, In Vitro Antimicrobial and Antifungal Activities of Novel Dipeptide Derivatives Based on N-(2-(2-Hydrazinyl-2-oxoethylamino)-2-oxoethyl)-nicotinamide., *Molecules*, **23**(4), 761, (2018).

65. Hasanin, M.S., Moustafa, G.O. New potential green, bioactive and antimicrobial nanocomposites based on cellulose and amino acid. *International Journal of Biological Macromolecules*, **144**, 441-448 (2019).

66. Elsherif, M.A., Hassan, AS., Moustafa, G.O., Awad, H.M., Morsy, N.M. Antimicrobial Evaluation and Molecular Properties Prediction of Pyrazolines Incorporating Benzofuran and Pyrazole Moieties. *Bulletin of the Chemical Society of Ethiopia*, **10** (02), 037-043 (2020).

67. Al-Wasidi, A.S., Wafeek, M. Abd El-Ghaffar, H.A., Naglah, A.M., Kalmouch, A., Hamed, M., Moustafa, G.O. Effect of Density on Growth Hormone and Some Physiological Parameters and its Relation to Growth Performance. *Egyptian Journal of Chemistry*, **63** (4), 1575-1584, (2020).

68. Al-Wasidi, A.S., Naglah, A.M., Refat, M.S., El-Megharbel, S.M., Kalmouch, A., Moustafa, G.O. Synthesis, spectroscopic characterization and antimicrobial studies of Mn(II), Co(II), Ni(II), Cr(III) and Fe(III) melatonin drug complexes. *Egyptian Journal of Chemistry*, **63** (4), 1469-1481, (2020).

69. Moustafa, G.O., Al-Wasidi, A.S., Naglah, A.M., Refat, M.S. Isolation and Synthesis of Dibenzofuran Derivatives Possessing Anticancer Activities: A Review. *Egyptian Journal of Chemistry*, **63** (6), 2355-2367, (2020).

70. Abo-Ghalia, M.H., Moustafa, G.O., Amr, A.E., Naglah, A.M., Elsayed, E.A., Bakheit, A.H. Anticancer activities and 3D-QSAR studies of some new synthesized macrocyclic heptapeptide derivatives. *Molecules*, **25** (5), 1253 (2020).

71. Al-Wasidi, A.S., Naglah, A.M., Kalmouch, A., Adam, A.M.A., Refat, M.S., Moustafa, G.O. Preparation of Cr_2O_3, MnO_2, Fe_2O_3, NiO, CuO, and ZnO oxides using their glycine complexes as precursors for in situ thermal decomposition. *Egyptian Journal of Chemistry*, **63** (3), 1109-1118, (2020).

72. Mohamed F.H., Shalaby A.M., Soliman H.A., Abdelazem A.Z., Mounier M.M., Nossier E.S. and Moustafa G.O., Design, Synthesis and Molecular Docking Studies of Novel Cyclic Pentapeptides Based on Phthaloyl Chloride with Expected Anticancer Activity. *Egyptian Journal of Chemistry*, **63** (5), 1723-1736, (2020).

73. Khalaf, H.S., Naglah, A.M., Al-Omar, M.A., Awad, H.M., Bakheit, A.H. Synthesis, docking, computational studies, and antimicrobial evaluations of new dipeptide derivatives based on nicotinoylglycylglycine hydrazide. *Molecules*, 25 (16), 3589, (2020).

74. Hassan, A.S., Askar, A.A., Nossier, E.S., Moustafa, G.O., Al-Omar, M.A. Antibacterial Evaluation, in Silico Characters and Molecular Docking of Schiff Bases Derived from 5-aminopyrazoles. *Molecules*, **24** (17), 3130, (2019).

75. Hassan, A.S., Moustafa, G.O., Askar, A.A., Naglah, A.M., Al-Omar, M.A. Synthesis and antibacterial evaluation of fused pyrazoles and Schiff bases. *Synthetic Communications*, **48** (21), 2761-2772, (2018).

76. Hassan, A.S., Moustafa, G.O., Awad, H.M. Synthesis and in vitro anticancer activity of pyrazolo[1,5-a]pyrimidines and pyrazolo[3,4-d][1,2,3]triazines. *Synthetic Communications*, **47** (21), 1963-1972, (2017).