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RESEARCH ARTICLE

Synthesis and Characterizations of New Pyrazoles and Study the Toxic Effect of the Compounds in Hella and RD Cancer Cells lines

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Abstract

New Pyrazole Derivatives have been synthesized by reaction of 2-(5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde with hydrazine and substituted phenylhydrazine. The chemical purity of the new synthesized compounds was tested by TLC and the chemical structures were characterized by, FT-IR, ^{1}H, and APT ^{13}C NMR. The biological activity of the new synthesized compounds was conducted to investigate the toxic effect of these compounds on the growth of tumor cells represented by the line of HeLa cell line and the human muscle cancer RD in the laboratory. The study included exposure period 24 and 48 hours, and showed good and different results.

Keywords: *Pyrazole Derivatives, Hydrazine and substituted phenylhydrazine, Hella and RD Cancer Cells lines.*

Introduction

Heterocyclic compounds are the major and important class of organic compound in the nature [1]. Due to their natural occurrence in many natural products such as plant alkaloid, Fungi and marine organisms and significant pharmacological activities, particularly indole and pyrazole rings, have received much attention from synthetic chemists in the recent years [2-3] Literature survey show that these compounds have been exhibit antimicrobial, antifungal, anti-inflammatory, anti-cancer and analgesic properties [4 -6].

In addition, poly functionalized heterocyclic compounds, has found application in the modern drugs synthesis [7] either by present as the core in the structure of the drugs or as building blocks in the organic synthesis for designing pharmaceutical and agrochemicals, and as bi functional ligands for metal catalysis [8].Consequently, a series of new and variety synthesis methods has commenced over the years to established drugs belonging to different categories with diverse therapeutic activities [9] Figure 1.

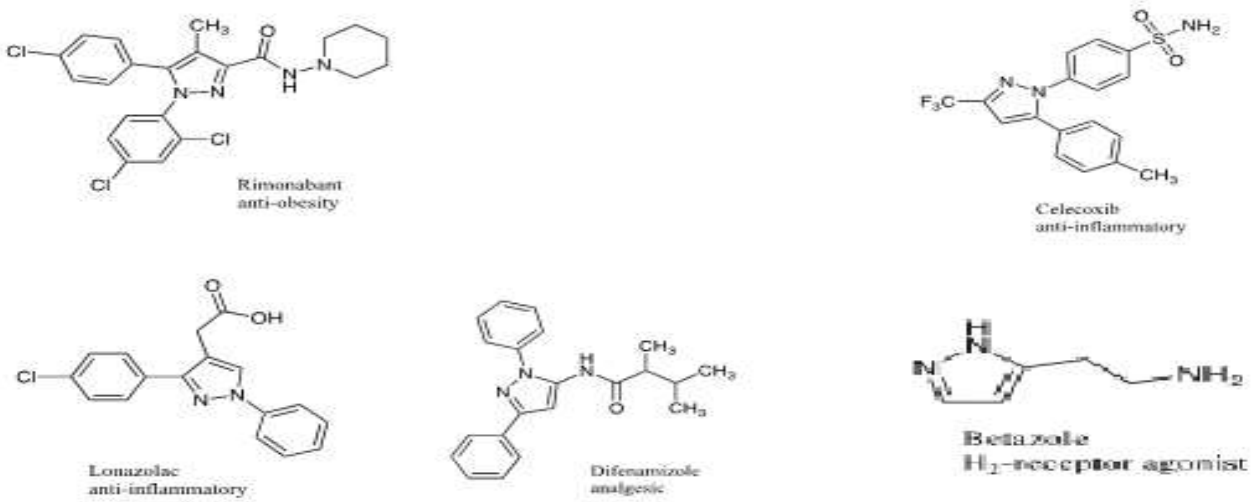
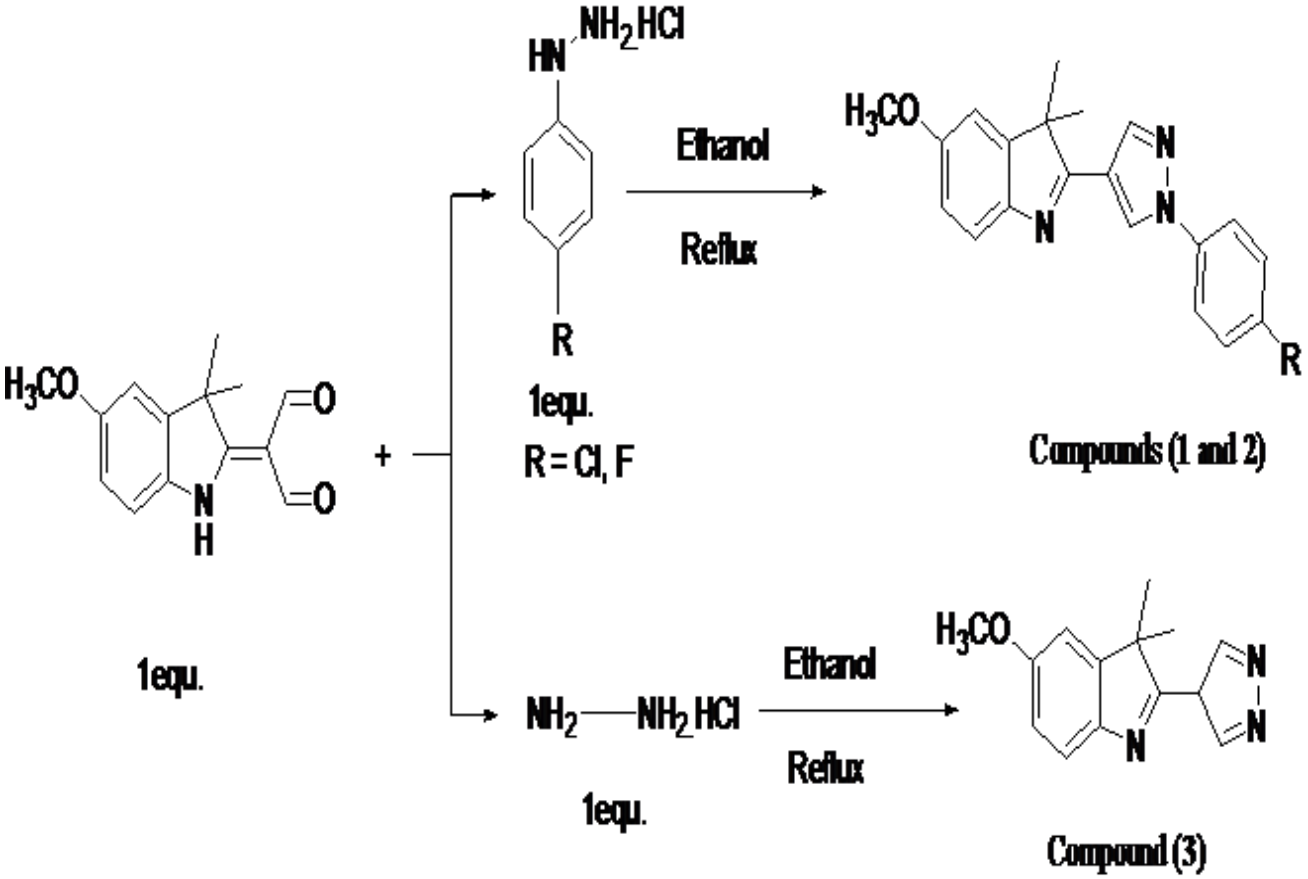


Figure 1: pharmaceutical drugs containing pyrazole unit

Thus, a mild and efficient protocol was used in the synthesis of new heterocyclic poly functional indole derivative systems using 2-(5-Methoxy-3, 3-dimethyl-1, 3-dihydro-indol-2-ylidene)-malonaldehyde as precursors in Scheme 1.



Scheme 1: The synthetic pathway of the new synthesized compounds (1-3)

Experimental Section

Chemistry Part

All chemicals and solvents used in the chemistry part were purchased from a number of different companies such as Merck, BDH, Sigma Aldrich and Fulka. They were used as obtained without further purification. The starting material 2-(5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde was synthesized with modification of a procedure defined by [10]. The purity of the synthesized compounds was checked it by TLC sheet and the melting points were determined by open capillary melting point apparatus.

Synthetic Methods

Synthesis of 2-[1-(4-Chloro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3, 3-dimethyl-3H-indole (**1**) A solution of (0.15g, 6mmol) of 2-(5-methoxy-3, 3-dimethyl-1, 3-dihydro-indol-2-ylidene)-malonaldehyde was dissolved in ethanol 10ml and (0.107g, 6mmol) of 4-choro-phenylhydrazine hydrochloride was dissolved in ethanol 25ml. The mixture was refluxed in water a bath at 78ºC for 16h. Solvent was reduced to one quarter; brown precipitate was formed, filtered off, washed with hexane and dried in an oven at 78ºC. The purity of compound was determined by using TLC (4:1) hexane: ethyl acetate, which gave one spot. Yield: (0,18g, 82%), m.p. 226-227ºC IR data in (cm^{-1}): 3047.3, 2931, 1607.3, 1585.5 and 1440 1352.7, 1280, 1080, 825.45 and 734.45. ^{1}H NMR (400 MHz, DMSO, δ ppm): 9.7 (s, 1H, pyrazole ring), 8.98 (s, 1H, pyrazole ring), 7.03-8.07 (7H, Ar-*H*), 4 (s, 3H, OC*H*$_3$) 1.69 (s, *6H*, 2xC*H*$_3$). APT ^{13}C-NMR (100MHz, DMSO, δ in ppm): shown signals for CH and CH_3 appeared at negative side (below base line of the spectrum) δ = 142.58, 129.53, 121.09, 117.32, 113.99, 108.67 (carbon atoms of the aromatic and pyrazole ring), 55.71 (OCH_3), 24.28 (2x*C*H_3).

Whereas quaternary carbons, CH_2 carbons and carbons deuterated DMSO solvent were observed at positive side (above base line of the spectrum) δ = 178.31, 159.21, 145.97, 137.16, 132.06, 113.08 (carbon atoms of the aromatic and pyrazole ring), and 52.81(CH_3-*C*-CH_3).

Synthesis of 2-[1-(4-Fluoro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3, 3-dimethyl-3H-indole (2)

A solution of (0.2g, 8mmol) of 2-(5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde was dissolved in ethanol 10 ml and (0.13g, 8mmol) of 4-floro-phenylhydazine hydrochloride was dissolved in ethanol 25ml the mixture was refluxed in a water bath at 78ºC for 7h. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, washed with hexane and dried in oven at 78ºC. The purity of this compound was determined by using TLC (4:1) hexane: ethyl acetate, which gave one spot.

Yield: (0,27g, 93%), m.p. 250-251°C IR data in (cm^{-1}): 3076.4, 2981.8, 1614.5, 1585.53 and 1520, 1352.7, 1221.8, 1083.6, 1025.5 and 741.82. ^{1}H NMR (400 MHz, DMSO, δ ppm): 9.59 (s, 1H, pyrazole ring), 8.88 (s, 1H, pyrazole ring), 7.01-8.06 (7H, Ar-*H*), 3.83 (s, 3H, OC*H*$_3$), 1.67 (s, *6H*, 2xC*H*$_3$). APT ^{13}C NMR (100MHz, DMSO, δ in ppm): shown signals for CH and CH_3 appeared at negative side (below base line of the spectrum) δ = 142.16, 117.56, 116.47, 116.24, 113.79, 108.54 (carbon atoms of the aromatic and pyrazole ring), 55.66 (OCH_3), 24.24 (2x*C*H_3).

Whereas quaternary carbons, CH_2 carbons and carbons deuterated DMSO solvent were observed at positive side (above base line of the spectrum) δ= 176.34, 158.97, 162.25, 159.81, 158.97, 146.20, 134.99, 113.44 (carbon atoms of the aromatic and pyrazole ring), and 52.80 (CH_3-*C*-CH_3).

Synthesis of 5-Methoxy-3, 3-dimethyl-2-(4H-pyrazol-4-yl)-3H-indole

A mixture solution of (0.2g, 8mmol) of 2-(5-methoxy-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde and (0.04g, 8mmol) of hydrazine hydrate 80% was dissolved in 10ml, the mixture was left refluxing at 78ºC for 12 h in a water bath. The solvent was concentered under reduced pressure and the yellow residue was filtered off washed with hexane and dried in oven at 78 ºC. The purity of this compound was determined by using TLC (4:1) hexane: ethyl acetate, with pre-coated silica gel, which gave one spot. Yield: (0,19g, 90%), m.p. 289-290ºC.

IR data in (cm-1): 3171, 3098.2, 2967.3, 1611, 1556.4, 1472.7, 1327.3, 1291, 1141.8, 738.18. 1H NMR (400 MHz, DMSO, δ ppm): 8.27 (s, 2H, pyrazole ring), 6.63 -7.53(3H, Ar-H), 4.36 (s, 3H, OCH3), 1.69 (s, H, CH).1.41 (s, 3H, CH3). APT 13C NMR (100MHz, DMSO, δ in ppm): shown signals for CH and CH_3 appeared at negative side (below base line of the spectrum) δ = 119.42, 112.38, 107.66 (carbon atoms of the aromatic and pyrazole ring), 55.36 (OCH_3) and 24.09 (2x*C*H_3). Whereas quaternary carbons, CH_2 carbons and carbons deuterated DMSO solvent were observed at positive side (above base line of the spectrum) δ= 176.68, 157.23, 148.06, 147.14, 114.72 (carbon atoms of the aromatic and pyrazole ring), and 52.72 (CH_3-*C*-CH_3).

Results and Discussion

IR Study

The results of the IR spectra of the new synthesized compounds (**1-2**) displayed absorption bands in range between 400 - 4000 cm^{-1}.Disappeared the absorption bands of NH_2-NH_2 and NH groups at 3200-3300 cm^{-1} which belonged to substituted hydrazine and phenyl hydrazine as well as absorption bands functional groups of aldehydes at 1700 cm^{-1} from a spectrum of the products that is approving of the formation of these new compounds.

NMR Study

^{1}H-NMR and APT ^{13}C-NMR spectra were reported in (dimethyl sulfoxide) DMSO with chemical shifts in ppm and using TMS (tetramethylsilane) as standard. ^{1}H-NMR results of the new synthesized compounds (**1-3**) showed disappearance signals of starting materials and appearance new signals of new synthesized compounds such as, disappearance signals two protons atoms of the carbonyl groups and appearance new signals of two protons atoms of pyrazole ring. As well as disappearance signals protons atoms of substituted phenylhydrazine and hydrazine. This is evidence to form of new synthesized compounds.

^{1}H-NMR and APT ^{13}CNMR results of the Compound

2-[1-(4-Chloro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3, 3-dimethyl-3H-indole **(1)**

The ^{1}H-NMR results for compound (**1**) Figure (**2**) displayed single signals at 9.7 ppm and 8.98 ppm belonged to protons of pyrazole ring.[11]. Signals were appeared in the region between (7.03-8.07) ppm which belonged to

seven protons of an aromatic ring for this compound [12]. Single signal at 4 ppm was attributed to protons of the methoxy group OCH_3 [13].Finally single signal at 1.60 ppm belonged to six protons of two (CH_3) groups [14].

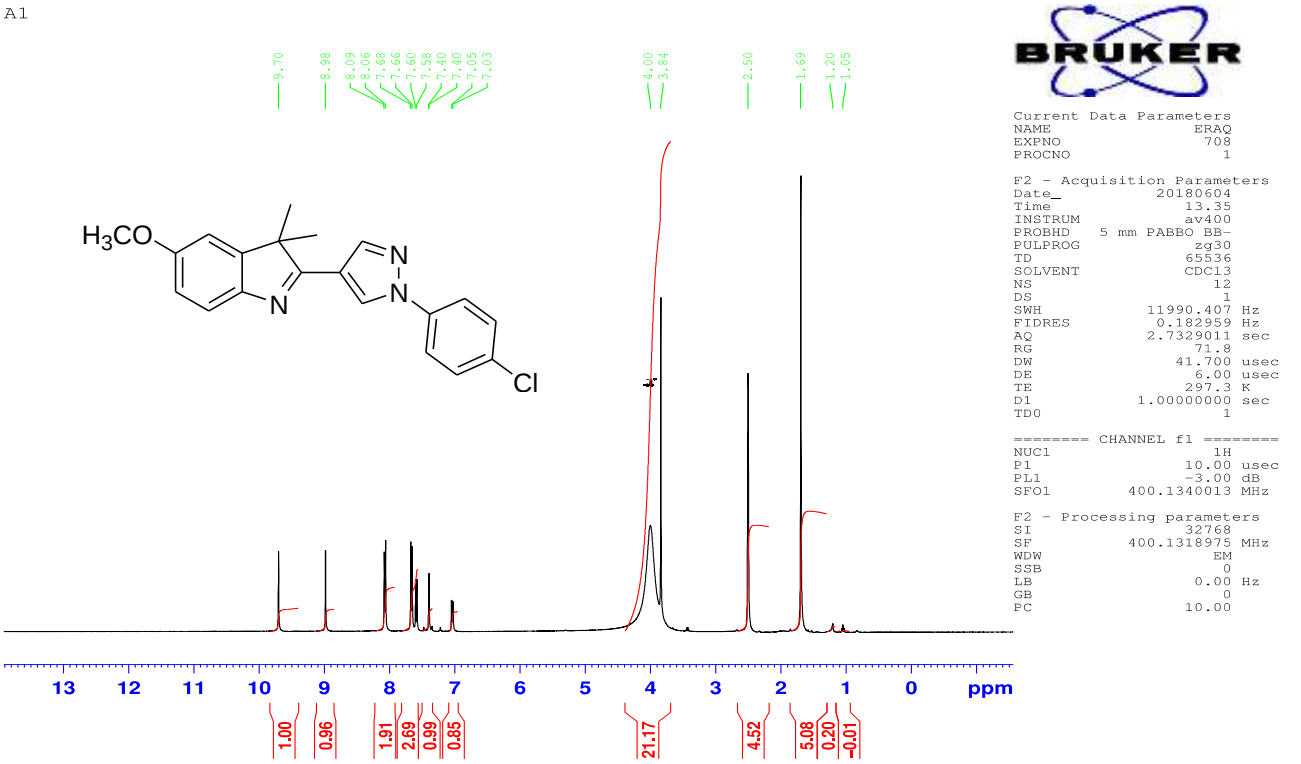


Figure 2: ^{1}H-NMR of 2-[1-(4-Chloro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3,3-dimethyl-3H-indole (1)

APT ^{13}C-NMR results were used to characterize the new synthesized compound, Figure (3) was displayed signals for CH and CH_3 which observed at a negative side (below of the spectrum) (142.58-108.67) for carbon atoms of (pyrazole and *Ar*-<u>C</u>H) [15-16]The signal at 55.71ppm for OCH_3 [17] and the signal at 24.28 for the two groups of CH_3 [18]. While the quaternary carbons, methylene CH_2 and carbons of DMSO solvent which appeared at a positive side (above of the spectrum (178.31-113.08) for carbon atoms of pyrazole and *Ar*-<u>C</u>. [19-20]. The signal at 52.81ppm belonged to CH_3-<u>C</u>-CH_3 [21]. From all these results we founded the ^{1}H-NMR and APT-^{13}C NMR spectrum matched well with the expected signals and are regular with the formation of this new compound.

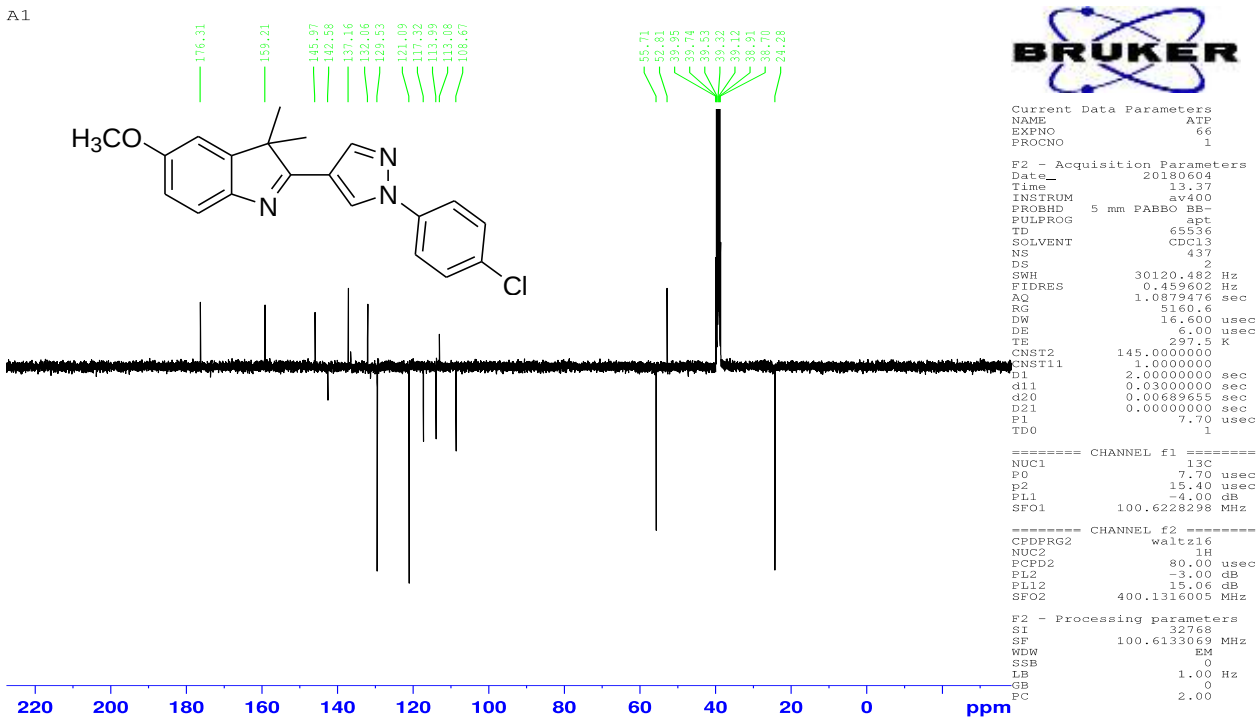


Figure 3: APT 13CNMR of 2-[1-(4-Chloro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3, 3-dimethyl-3H-indole (1)

1H-NMR and APT 13CNMR Results for Compound

2-[1-(4-Fluoro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3, 3-dimethyl-3H-indole) **(2)**

The ^{1}H-NMR results for compound (**2**) Figure (4) displayed single signals at 9.59 ppm and 8.88 ppm belonged to proton atoms of pyrazole ring [22]. Signals appeared in the region between 7.01-8.06 ppm were belonged to seven protons of an aromatic ring [23]. Also single signal at 3.83 ppm was attributed to proton atoms of the methoxy group (OCH_3) [24]. Finally single signal was appeared at 1.67 ppm belonged to six proton atoms of two methyl groups CH_3[25].

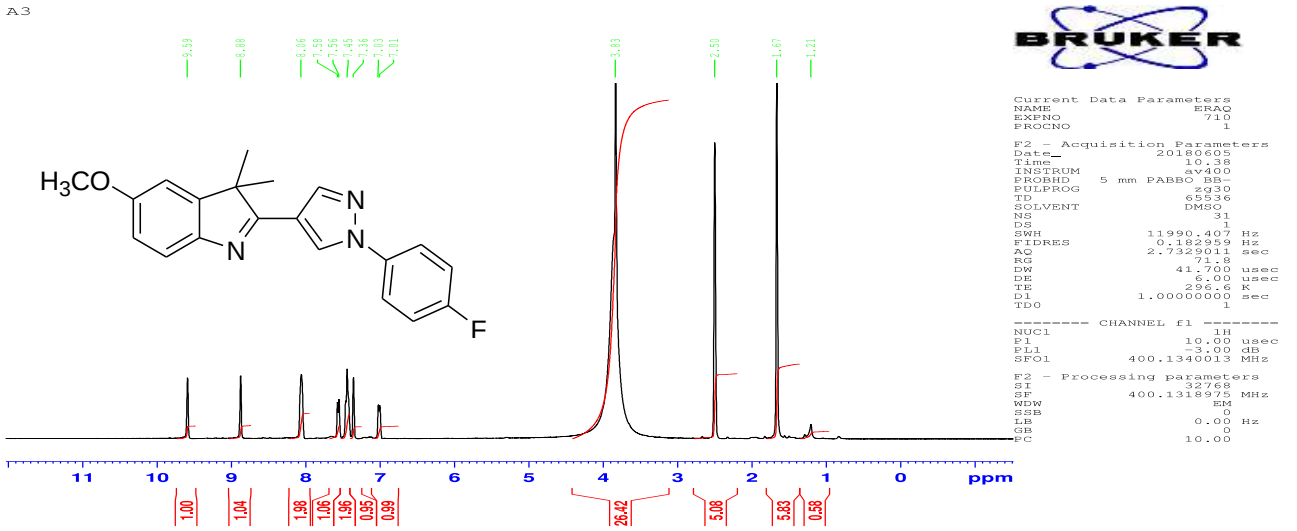


Figure 4: ^{1}H-NMR of 2-[1-(4-Fluoro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3, 3-dimethyl-3H-indole) (2)

APT ^{13}C-NMR results were used to characterize the new synthesized compound. Figure (5) was displayed signals for CH and CH_3 observed at a negative side (below of the spectrum) (142.16-108.54) for (pyrazole and *Ar*-C<u>H</u>) [26-27]. As well as single signal was shown at 55.66 ppm which assigned to OCH_3 group [28]. Signal at 24.24 for the two groups CH_3 [29]. While, the quaternary carbons, methylene CH_2 and carbons of DMSO solvent which appeared at a positive side (above of the spectrum) (176.34-113.44) for (pyrazole and *Ar*-<u>C</u>) [30-31]. Signal at 52.80ppm which belonged to carbon atom bearing two methyl group CH_3-<u>C</u>-CH_3 [32]. All these results founded the ^{1}H-NMR and APT ^{13}C-NMR spectrums matched well with the expected signals and are regular with the formation of this new compound.

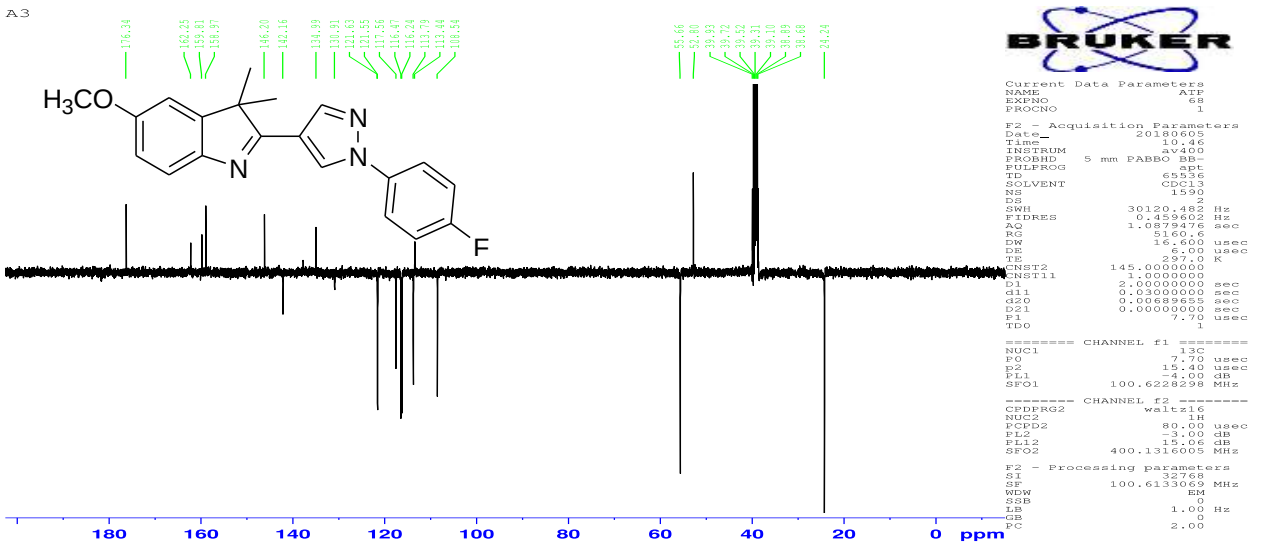


Figure 5: APT ^{13}CNMR of 2-[1-(4-Fluoro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3, 3-dimethyl-3H-indole) (2)

^{1}H-NMR and APT ^{13}CNMR results for compound 5-Methoxy-3, 3-dimethyl-2-(4H-pyrazol-4-yl)-3H-indole (**3**)

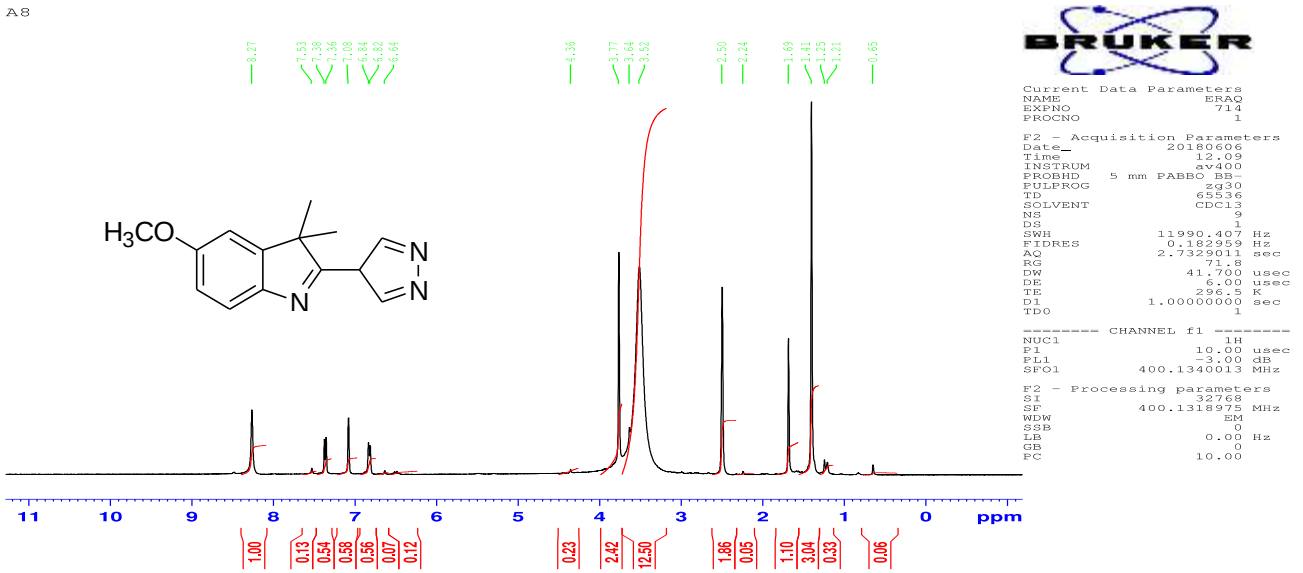


Figure 6: ^{1}H-NMR of 5-Methoxy-3, 3-dimethyl-2-(4H-pyrazol-4-yl)-3H-indole (3)

The ^{1}H-NMR results for compound (**3**) Figure (6) displayed single signal at 8.27 ppm belonged to the two proton atoms of pyrazole ring.[33]. As well as signals were appeared in the region between (6.63 -7.53) ppm which belonged to three proton atoms of an aromatic protons of indole ring for this compound[34]. single signal at 4.36 ppm was attributed to three protons of the methoxy group OCH_3 [35], also single signal at 1.69 ppm which assigned to one proton atom of CH of pyrazole ring. Finally, single signal at 1.41 ppm belonged to six protons of two (CH_3) groups[36].

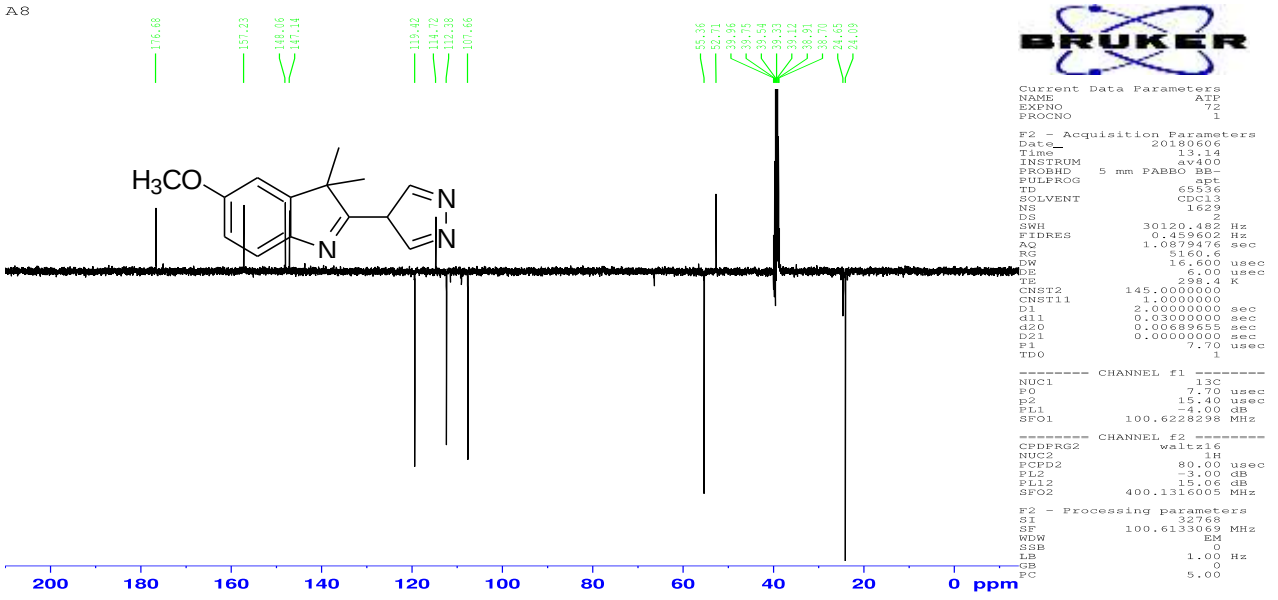


Figure 7: APT ^{13}CNMR of 5-Methoxy-3, 3-dimethyl-2-(4H-pyrazol-4-yl)-3H-indole (3)

APT ^{13}C-NMR results were used to characterize this new compound figure (7) was displayed signals for CH and CH_3 observed at a negative side (below of the spectrum) 119.42, 112.38 and 107.66 for *Ar-C*H [37], 55.36 for OCH_3 [38] 39.33ppm for CH and 24.09 for the two (CH_3) groups [39]. While the quaternary carbons, methylene CH_2 and carbons of DMSO solvent which appeared at a positive side (above of the spectrum)[40]. 176.68-114.72 for (*Ar-C*) [41]and 52.72 for CH_3-*C*-CH_3 [42]. All these results we founded the ^{1}H-NMR and APT ^{13}C-NMR spectrum matched well with the expected signals and are regular with the formation of this new compound.

Biological Part

Hella cell line included exposure 24 hours.

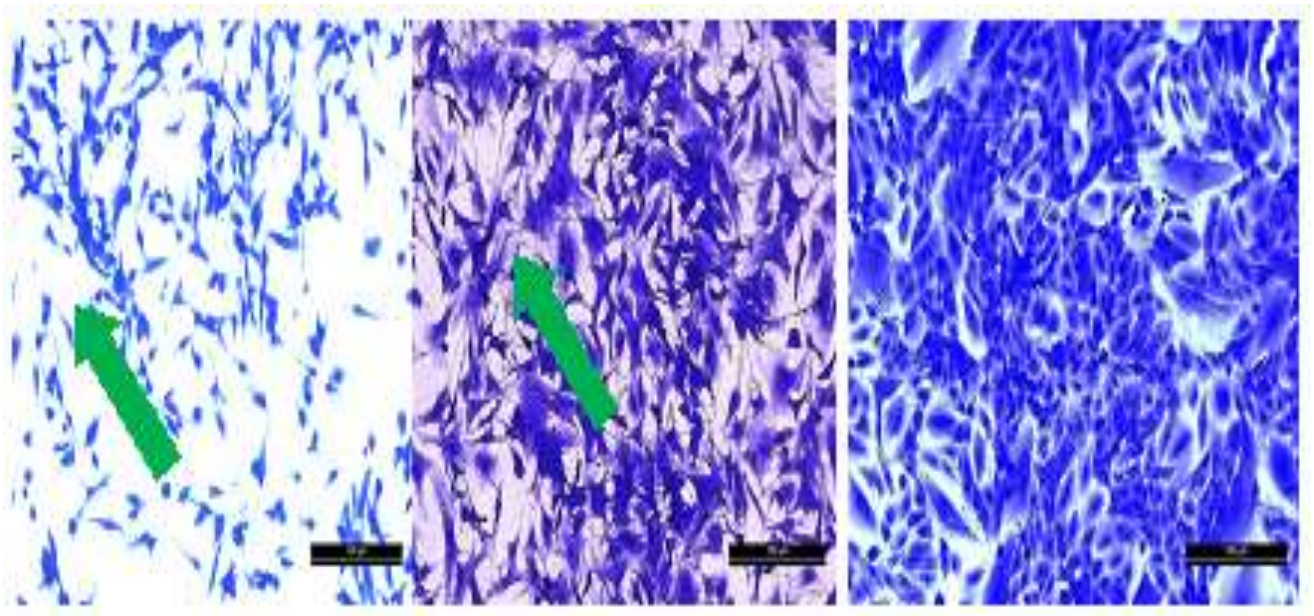
Table 1: Showed that the compound an inhibitory Hella cancer cell line Included exposure 24 hours

48hours	24hours	Mg \ ml (0.2)
% inhibitory	% inhibitory	
0.00+ 1.17	0.00+1.15	A1 Compound (**1**)
0.79+14.70	0.79+4.09	A2 Compound (**2**)
0.33+47.73	0.33+ 31.28	A3 Compound (**3**)

This study showed that hella cell line was begun inhibitory with A1 at a concentration of 0.2. Mg/ml and increased In A2 concentrations became 4.09 % in 24hours then became 31.28% in A3 at 0.2 Mg/ml. There was significant difference at P≤ 0.05 between the compound included exposures 24 hours in Hella cell line.

Hella cell line included exposure 48 hours.

This study showed that hella cell line was begun inhibitory with A1 at a concentration of 0.2. Mg/ml 1.17 % and increased In A2 concentrations became 14.70 % in 24hours then became 47.73% in A3 at 0.2 Mg/ml. There was significant difference at P≤ 0.05 between the compound included exposures 24 hours in Hella cell line.



A **B** **C**

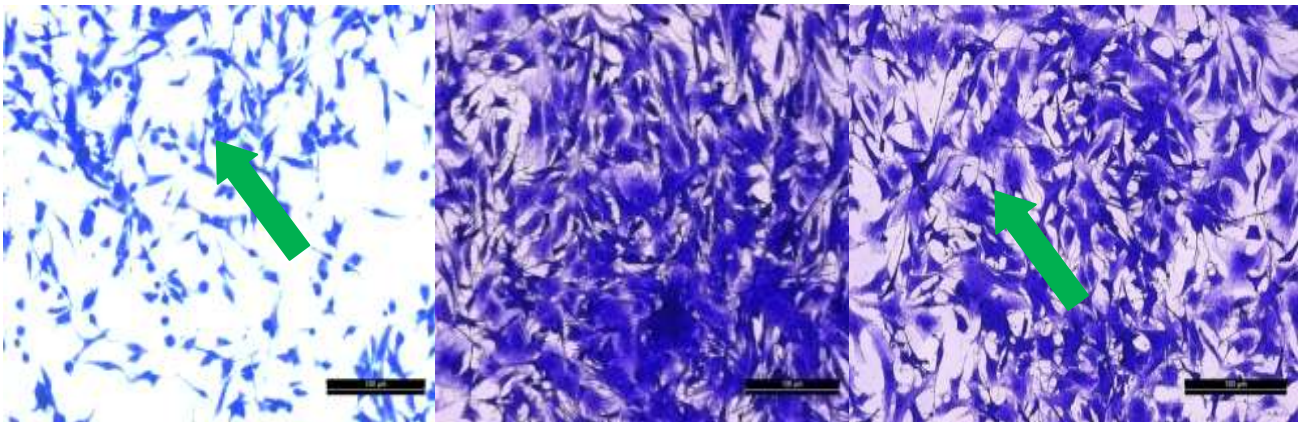
Figure 8: (A) Effect of the compound A1 in hella cancer cell line in exposure for 48h at 37°C using crystal violate dye IN 0.2 Mg\ml. (B). Effect of the compound A1 in hella cancer cell line in exposure for 24h at 37°C using crystal violate dye (C) control Hella cell line

Table 2: Showed that the compound an inhibitory RD cancer cell line Included exposure 24 hours

48hours	24hours	Mg \ ml (0.2)
% inhibitory	% inhibitory	
g 0.00+ 1.15	f 0.00+1.14	A1 Compound (**1**)
e 0.49+6.75	e 0.45+5.41	A2 Compound (**2**)
a 0.33+21.35	a 0.33+ 17.53	A3 Compound (**3**)

This study showed that RD cell line was began inhibitory with A1 at a concentration of 0.2. Mg/ml and increased In A2 concentrations became 5.41 % in 24hours then became 17.53% in A3 at 0.2 Mg/ml. There was significant difference at P≤ 0.05 between the compound included exposures 24 hours in RD cell line.

RD cell line included exposure 48 hours.This study showed that hella cell line was began inhibitory with A1 at a concentration of 0.2. Mg/ml 1.15 % and increased In A2 concentrations became 6.75 % in 24hours then became 21.35% in A3 at 0.2 Mg/ml. There was significant difference at P≤ 0.05 between the compound included exposures 24 hours in RD cell line.



A B C

Figure 9: (A) Effect of the compound A1 in hella cancer cell line in exposure for 48h at 37°C using crystal violate dye IN 0.2 Mg\ml. (B). Effect of the compound A1 in hella cancer cell line in exposure for 24h at 37°C using crystal violate dye (C) control Hella cell line

The results of this study reinforced the findings of many researchers in local studies on the activity of plant extracts on cancer cells. The pharmacological studies on *E. arvense* plant showed that it possessed antioxidant, anticancer, antimicrobial, dermatological immunological, anti-inflammatory, antidiabetic, diuretic, inhibition of platelet aggregation, anti-leishmanial and many other activities. A local study reported that the crude proteins extracted from *E. arvense* inhibited the proliferation of human leukemic U 937 cells.

A cytotoxic study was performed to assess the effect of compounds A1, A2 and A3 on the growth of human cervical carcinoma cells (Hella cells) used 24 and 84 h that show all compound the ability to inhibit the cells growth of Hella cells. This is because these extracts contain compounds that affect the physiological state of these cells and contain compounds that stop the cycle of cancer cells (arrest cell cycle) at a certain stage and prevent of reproduction or contain compounds that stimulate cancer cells to apoptosis.

The tumor cells are unique in their ability to invade cells Proliferation, as well as changes in their proteins and surface antigens, characterized by the permeability of its membranes and this feature facilitates the process of entering the materials into the cell's irregular, which negatively affects those cells and makes it easier to respond to the anticancer to which they are exposed.

Acknowledgments

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Conclusion

New compounds 2-[1-(4-Chloro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3,3-dimethyl-3H-indole **(1),** 2-[1-(4-Fluoro-phenyl)-1H-pyrazol-4-yl]-5-methoxy-3,3-dimethyl-3H-indole) **(2)** and 5-Methoxy-3,3-dimethyl-2-(4H-pyrazol-4-yl)-3H-indole **(3)** have been synthesized by reaction of 2-(5-methoxy-3,3-dimethyl-1, 3-dihydro-indol-2-ylidene)-malonaldehyde with hydrazine and substituted phenylhydrazine.

The chemical structures were characterized by some spectroscopic techniques such as FT-IR, ^{1}H, and APT ^{13}C-NMR. The toxic effect of these compounds on the growth of tumor cells represented by the line of HeLa cell line and the human muscle cancer RD in the laboratory, exposure period 24 and 48 hours, and showed good and different results.

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