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Synthesis and Cytotoxicity Evaluation of Some Novel Tetrahydronaphthalene-Pyrazole Derivatives

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1-(1,2,3,4-Tetrahydronaphthalen-6-yl)-3- (1,3-diphenyl-*1H*-pyrazol-4-yl)prop-2-en-1-one (3) was synthesized and then treated with various hydrazine hydrate derivatives to afford the corresponding dihydropyrazoles 4-9, respectively. Condensation of pyrazole carbothioamide 9 with α-haloketones yielded the corresponding thiazole derivatives 10a,b. Also, the reaction of the chalcone 3 with various sulphonyl hydrazide derivatives produced the corresponding sulphonyl pyrazole derivatives 11a,b, while its reaction with hydroxylamine hydrochloride yielded the isoxazole derivative 12. Treatment of the chalcone 3 with thiourea or guanidine sulfate gave the pyrimidine derivatives 13 and 14 respectively. Furthermore, the pyrane derivatives 15-17 were obtained by cyclization of the chalcone 3 with malononitrile, ethyl cyanoacetate and/or ethyl acetoacetate respectively. In addition, 2-oxopyridine 18 was allowed to react with different alkyl halides to yield the corresponding 2-substituted pyridine derivatives 19-21. Schiff base 23 was obtained by the reaction of carbohydrzide derivative 22 with anisaldehyde. Some of synthesized compounds were evaluated for cytotoxicity activity against HepG2 (liver carcinoma cell line) and MCF-7 (brest carcinoma cell line) using Doxorubicin as a reference drug.

Keywords: Tetrahydronaphthalene, Pyrazole, Pyrazoline, Pyrane, Pyridine, Cytotoxic screening, HepG2 and MCF-7.

The burden of cancer is increasing across the world and thus it is the leading cause of deaths in economically developed countries and the second leading cause of deaths in developing countries [(1)].

Cancer is a disease characterized by a shift in the controlled mechanisms that govern cell proliferation and differentiation. Malignancy is caused by abnormalities in cells, which might be due to inherited genes or caused by outside exposure of the body to chemicals, radiation, or even infectious agents. Several techniques were adopted for the treatment and eradication of cancerous cells. These techniques involved surgery, radiation, immunotherapy, chemotherapy and chemoprevention [(2)].

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Tetrahydronaphthalene derivatives have attracted significant attention in the field of drug discovery because of their wide array of pharmacological activities, including action as non-steroidal glucocorticoid receptor modulators[3], anticancer [4,5], antimicrobial [6], antifungal [7] and anti-HIV effects [8].

Pyrazole derivatives have been the subject of medical research due to their various biological and pharmacological properties such as antitumor[9,10], antimicrobial [11,12], anti-inflammatory [13] and anticonvulsant [14] activities.

Chalcones have attracted much attention due to their diverse biological activities, such as anti-cancer, anti-oxidant, anti-inflammatory, and/or anti-infective activities [15,16]. The chalcones which possess α,β-unsaturated carbonyl group are the convenient intermediates for the synthesis five, six and seven members [17] heterocycles, often have exhibited diverse biological activity.

Molecular hybridization is one of the many strategies, which have been successfully applied for the design and development of new and efficient chemotherapeutic agents [18]. Molecular hybridization involves the combination of two or more chemical entities by either linking or fusing each other to form new hybrid moieties [19]. The selection of the chemical moieties is based upon their known bio-profiles and it is expected that the hybrid molecules might exhibit additive pharmacological activities [20,21] .

In the light of the above findings, we report herein the synthesis of some new tetrahydronaphthalene derivatives bearing pyrazoline, pyrimidine, pyrane, pyrdine and pyrazole moieties and some of the newly synthesized derivatives were tested for anticancer agents against human hepatocelluar carcinoma HepG2 and human breast cancer MCF-7.

Results and Discussion

Chemistry

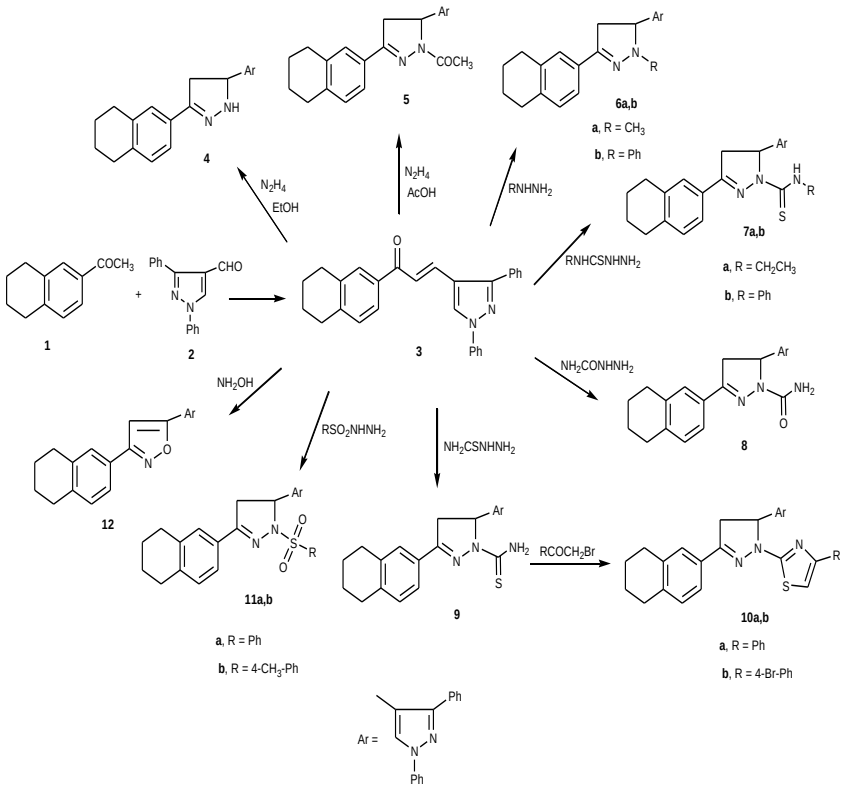
The synthetic strategies adopted for the synthesis of the intermediate and target compounds are depicted in Schemes 1-3. The synthesis of the key intermediate compound 1-(1,2,3,4-tetrahoursydronaphthalen-6-yl)-3-(1,3-diphenyl-*1H*-pyrazol-4-yl) prop-2-en-1-one (3) was achieved according to Claisen-Schmidt condensation, by reacting of 6-acetyl-1,2,3,4-tetrahydronaphthalene (1) with 1,3-diphenyl-*1H*-pyrazole-4-carboxaldehyde (2) in ethanolic sodium hydroxide. IR spectrum of compound 3 showed a band at 1650 cm^{-1} due to α,β unsaturated ketone. Cyclocondensation of the chalcones with hydrazine hydrate derivatives afforded the corresponding pyrazolines. Thus the treatment of the chalcone 3 with hydrazine hydrate in ethanol led to the formation of the pyrazoline derivative 4, while in acetic acid yielded the corresponding N-acetyl pyrazoline derivative 5. IR spectrum of pyrazoline derivative 4 revealed the appearance of the absorption band at 3310 cm^{-1} corresponding to (NH) and the

disappearance of any band corresponding to α,β unsaturated ketone. ^{1}H-NMR spectrum of pyrazoline derivative 4 showed the signals of Ha, Hb, Hx of pyrazoline ring as doublet of doublet in the regions 3.12-3.20, 3.45-3.55 and 5.13-5.23 ppm, respectively and ^{1}H-NMR spectrum of pyrazoline derivative 5 showed a singlet signal at δ 2.30 ppm referring to ($COCH_3$) group.

Also, the chalcone 3 was functionalized by a classical condensation reaction with substituted hydrazines in refluxed ethanol to give the corresponding *N*-methyl/phenyl pyrazoline derivatives 6a,b. ^{1}H NMR spectrum of 6a showed the appearance of a singlet signal at δ 2.90 ppm corresponding to the methyl protons. Furthermore, the reaction of the chalcone 3 with ethyl and/or phenylthiosemicarbazide in ethanol afforded the corresponding substituted thioamide pyrazoline derivatives 7a,b. IR spectra of compounds 7a,b showed absorption bands at 3189, 3205 cm^{-1} referring to (NH) groups, while ^{1}H NMR spectrum of 7a showed quartet and triplet signals at δ 3.33, 0.94 ppm referring to ethyl protons. In addition the reaction of the chalcone 3 with semicarbazide hydrochloride in ethanol in the presence of sodium acetate afforded amido-pyrazoline derivative 8. IR spectrum of compounds 8 showed absorption bands at 3201, 3124 cm^{-1} referring to (NH_2) group and at 1651 cm^{-1} referring to (C=O) group.

Several authors have reported that the synthesis of 1-(thiazol-2-yl)pyrazolines from the corresponding chalcones. In the same sense, the reaction of the chalcone 3 with thiosemicarbazide in refluxing ethanol afforded 4,5-dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-5-(1,3-diphenyl-*1H*-pyrazol-4-yl)pyrazole-1-carbothioamide (9). IR spectrum of compound 9 showed absorption bands at 3265, 3177 cm^{-1} referring to (NH_2) group. The reaction of thioamido-pyrazoline 9 with phenacyl bromide and/or 4-bromophenacyl bromide in refluxing ethanol gave the corresponding thiazolyl-pyrazolines 10a,b.

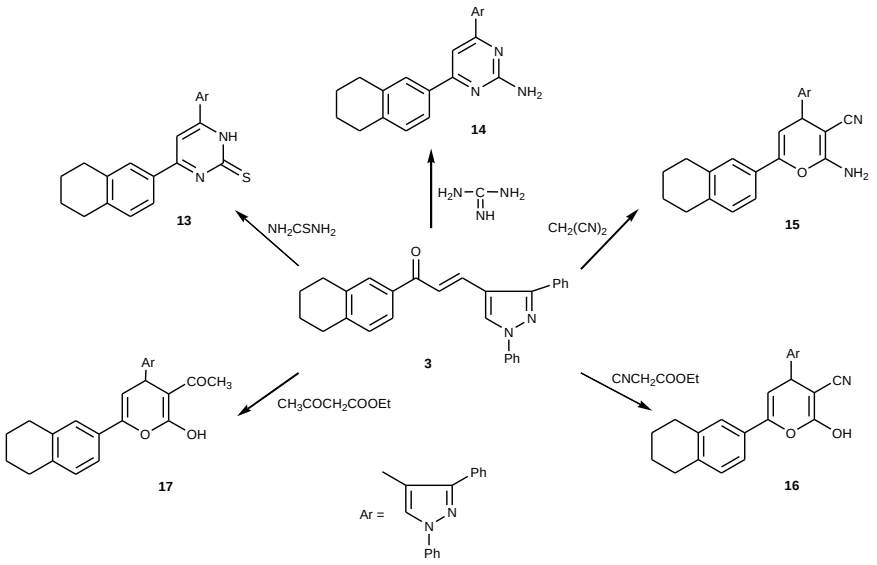
On the other hand, sulphonyl pyrazoline derivatives 11a,b were obtained from the refluxing of the chalcone 3 with benzene and/or tolyl sulphonylhydrazide in ethanol. IR spectra of compounds 11a showed absorption bands at 1357, 1173 cm^{1} referring to (SO_2) group. ^{1}H NMR spectrum of 11b showed a singlet signal at δ 2.41 ppm referring to the methyl group. Finally, cyclization of the chalcone 3 with hydroxylamine hydrochloride in ethanolic sodium hydroxide produced 4-(2,3-dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)isoxazol-5-yl)-1,3-diphenyl-*1H*-pyrazole (12). Its IR spectrum revealed the disappearance of any absorption band attributed to α,β unsaturated ketone and the mass spectrum showed a peak at 419 referring to the molecular ion peak (Scheme 1).



Scheme 1

Moreover, cyclocondensation of the chalcones with different reagents such as thiourea and guanidine afforded the corresponding pyrimidine derivatives. Thus the synthesis of the thiopyrimidine derivative 13 and aminopyrimidine derivative 14 could be successfully achieved by heating a mixture of chalcone 3 with either thiourea or guanidine sulphate in sodium ethoxide, respectively. IR spectrum of compound 13 showed an absorption band at 1159 cm^{-1} referring to (C=S) group while IR spectrum of compound 14 showed an absorption band at 3326, 3189 cm^{-1} referring to (NH_2) group. Also, the mass spectra of compounds 13 and 14 revealed the molecular ion peaks at 460 and 443 corresponding to the correct molecular formulae of compounds. Also, heating the chalcone 3 with active methylene derivatives namely; malononitrile, ethyl cyanoacetate and/or ethyl acetoacetate in sodium ethoxide solution yielded the targeted pyrane derivatives 15-17, respectively. IR spectrum of pyrane derivative 15 showed absorption bands at 2219 cm^{-1} referring to (CN) and at 3222, 3124 cm^{-1} referring to (NH_2) group. Also, IR spectrum of the pyrane derivative 16 showed absorption bands at 2212 cm^{-1} referring to (CN) and at 3428 cm^{-1} referring to (OH) group and IR spectrum of the pyrane derivative 17 showed absorption bands at 3423 cm^{-1}

referring to (OH) and at 1724 cm^{-1} referring to ($COCH_3$) group. The mass spectra of compounds 15-17 revealed the molecular ion peaks at 470, 471 and 488 corresponding to their correct molecular formulae (Scheme 2).



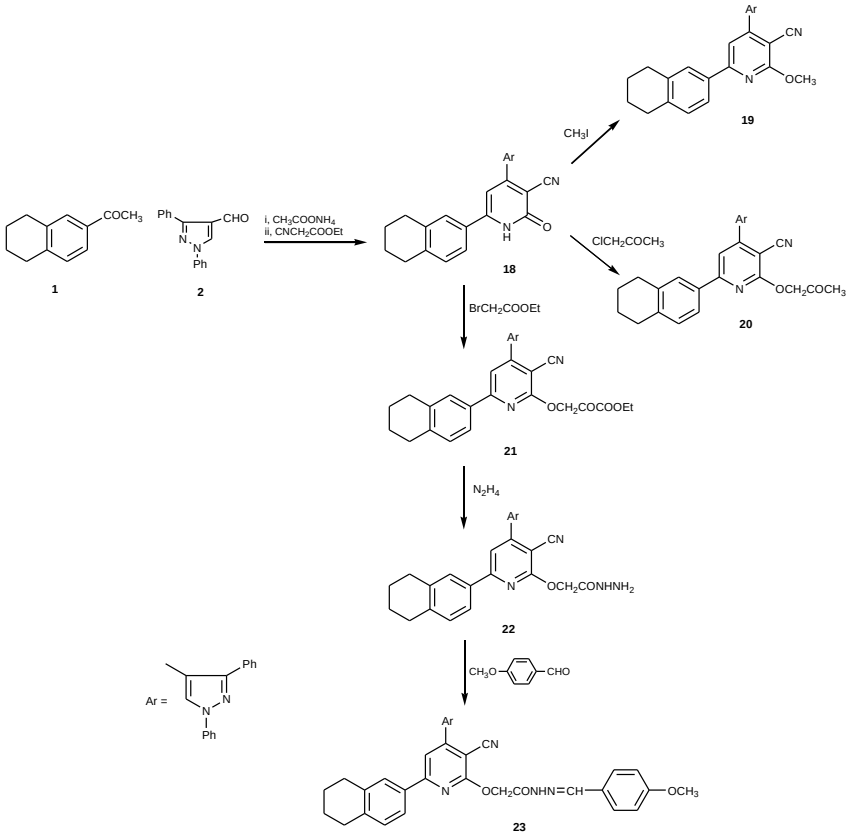
Scheme 2

On the other hand, 1,2-dihydro-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-2-oxo-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)pyridine-3-carbonitrile (18) was synthesized via one-pot multicomponent reaction of 6-acetyl-1,2,3,4-tetrahydronaphthalene (1), 1,3-diphenyl-*1H*-pyrazole-4-carboxaldehyde (2), ethyl cyanoacetate and excess of ammonium acetate in ethanolic medium. IR spectrum of the pyridone derivative 18 showed absorption bands at 3134, 2220 and 1658 cm^{-1} referring to NH_2, CN and CO groups, respectively. Also, the mass spectrum revealed the molecular ion peak at m/e 468 which is in agreement with its molecular formula.

Different pyridine derivatives could be successfully achieved by the reaction of the pyridone derivative 18 with different reagents. Thus, refluxing of pyridone derivative 18 with methyl iodide and/or chloroacetone in dry dimethylformamide containing anhydrous K_2CO_3 yielded the corresponding 2-alkyloxy-pyridine derivatives 19 and 20, respectively. ^{1}H NMR spectrum of compound 19 showed a singlet signal at δ 3.71 ppm referring to the methyl group while ^{1}H NMR spectrum of compound 20 showed two singlet signals at δ 2.95 and 2.88 ppm referring to (-CH_2-) and (CH_3) groups, respectively. Also, ethyl 2-(3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-(1,3-diphenyl-*1H*-pyrazol-4-yl)pyridin-2-yloxy)acetate (21) was prepared by the treatment of the pyridone derivative 18 with ethyl bromoacetate in dry dimethylformamide containing anhydrous K_2CO_3. IR spectrum of the pyridine derivative 21 showed an absorption band at 2219,

1736 cm^{-1} referring to (CN) and ester groups, while ^1H NMR spectrum exhibited the ester group signals at δ 1.41 and 4.38 ppm, respectively and the ($-CH_2-$) protons appeared as a singlet signal at δ 5.13 ppm.

Condensation of the pyridine ester derivative 21 with hydrazine hydrate in absolute ethanol afforded the corresponding the pyridine hydrazide derivative 22. Its IR spectrum showed an absorption band at 3407, 3124 cm^{-1} referring to ($NHNH_2$) group. Reaction of the pyridine hydrazide derivative 22 with p-anisaldehyde in ethanol yielded the corresponding Schiff base 2-(3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-(1,3-diphenyl-*1H*-pyrazol-4-yl)pyridin-2-yloxy)-*N'*-(4-methoxybenzylidene) acetohydrazide (23) (Scheme 3).



Scheme 3

Cytotoxicity evaluation

The target of this work is to study the cytotoxic activity of the newly synthesized compounds against different carcinoma cell lines and to find the relationship between their chemical structures and their cytotoxic activities. For this reason, fifteen compounds were chosen as examples to examine their *in vitro*

potency as cytotoxic agents against human liver carcinoma cell lines (HepG2) and human breast carcinoma cell lines (MCF-7). The cytotoxic activity was expressed as IC_{50} values measured in µM (the dose that reduces the survival cells to 50%), using Doxorubicin as a reference standard.

Regarding to the obtained results in Table 1& Fig. 1. It has been observed that the combination between tetrahydronaphthalene and pyrazole rings can develop a remarkable cytotoxic activity depending upon the type of the nuclei they attach to. Thus, it can be noticed that the conjugate tetrahydronaphthalene-pyridine-pyrazole as derivative 22 produced the highest cytotoxic activity exceeds that gained by the reference drug Doxorubicin against both types of the examined cell lines ($IC_{50;}$ 11, 6.5, 29 µM, respectively), while the attachment of the hydrazide ethereal linkage of the latter compound to an azomethine side chain as compound 23 greatly reduced the activity against HepG2 cell lines ($IC_{50;}$ 63 µM), but the decrease of the activity was slightly less than that of Doxorubicin ($IC_{50;}$ 33 µM). On the other hand, the conjugation of tetrahydronaphthalene moiety with pyrazolo-2-aminopyrimidine core as compound 14 produced equipotent cytotoxicity to that of Doxorubicin against breast carcinoma cell lines (MCF-7) ($IC_{50;}$ 29 µM), but the activity was 1.5 times less than that of Doxorubicin against liver carcinoma cell lines (HepG2). Remarkable decrease in the cytotoxic activity against both carcinoma cell lines to be twice times less than that of reference drug was obtained upon conversion of the amino group of the latter derivative to the mercapto group as compound 13 ($IC_{50;}$ 60, 53µM). Unfortunately, the rest of the tested derivatives produced weak potency which requires more structural modifications to improve their cytotoxic activity.

TABLE 1. The effect of the selected compounds on liver carcinoma cell line (HepG2) and Breast carcinoma cell line (MCF-7) compared with Doxorubicin.

Compound Number	Cell Line	
	HepG2 IC_{50} (µM)	MCF-7 IC_{50} (µM)
Doxorubicin	29	0.24
3	287	182
4	218	448
5	198	346
8	198	1000
9	156	113
10a	305	136
11a	105	60
13	60	53
14	46	29
16	239	488
17	167	142
22	11	6.5
23	63	33

IC_{50}: the dose of the compound which reduces survival to 50 %.

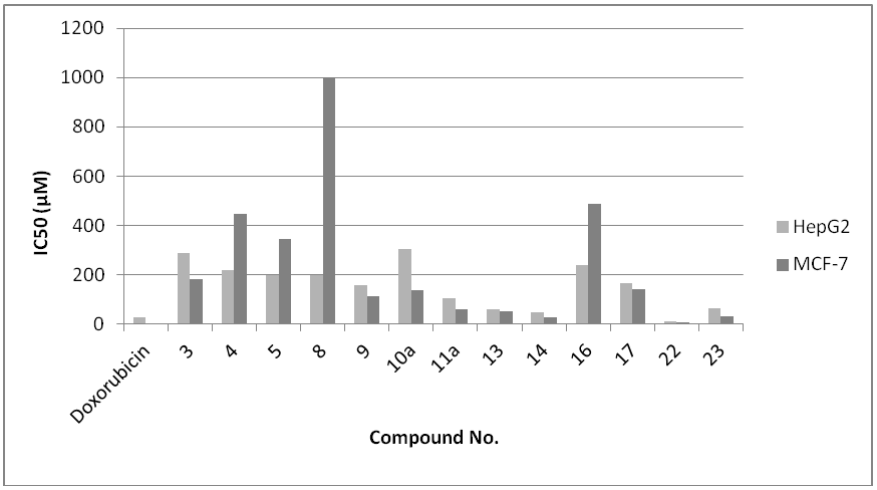


Fig. 1. The effect of the selected compounds on (HepG2) and (MCF-7) compared with Doxorubicin.

Experimental

All melting points are uncorrected and were taken in open capillary tubes using Electrothermal apparatus 9100. Elemental microanalyses were carried out at Microanalytical Unit, Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt, using Vario Elementar and were found within ±0.4% of the theoretical values. Infrared spectra were recorded on a FT/IR-4100 Jasco-Japan, Fourier transform, Infrared spectrometer at cm^{-1} scale using KBr disc technique at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. ^1H NMR spectra were determined by using a Varian Gemini-200 MHZ NMR spectrometer at Central Services Laboratory, Cairo University, Cairo, Egypt, chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard. The mass spectra were measured with a GC MS-Qp1000EX Shimadzu, Cairo University, Cairo, Egypt. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminium sheets (Type 60, F 254, Merck, Darmstadt, Germany) using chloroform/ methanol (5:1, v/v) and the spots were detected by exposure to UV lamp at λ_{254} nanometer for few seconds and by iodine vapor.

The chemical names given for the prepared compounds are according to the IUPAC system. 1,3-diphenyl-*1H*-pyrazole-4-carboxaldehyde (2) was prepared according the reported method [22] .

1-(1,2,3,4-Tetrahydronaphthalen-6-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (3)

A mixture of 6-acetyl-1,2,3,4-tetrahydronaphthalene (1) (8.7 ml, 0.05 mol) and 1, 3-diphenyl-*1H*-pyrazole-4-carboxaldehyde (2) (12.4 g, 0.05 mol) in alcoholic sodium hydroxide (10%, 200 ml) was stirred overnight at room temperature. The formed precipitate was filtered, washed several times with water, dried and recrystallized from ethanol to give the title compound 3.

Yield 90%, mp. 164-165^{o}C; IR (KBr, cm^{-1}): 3057 (CH-aromatic), 2928, 2864 (CH_2-tetrahydronaphthalene), 1650 (C=O, α,β unsaturated ketone), 1582 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.83 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.83 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 7.15-7.90 (m, 15H, CH=CH, Ar-H), 8.35 (s, 1H, pyrazole proton); MS, m/z (%): 405 [M^++1] (14), 404 [M^+] (15), 403 [M^+-1] (8), 77 [C_6H_5] (68), 57 [C_4H_9] (100); Anal. For $C_{28}H_{24}N_2O$ (404.50): Calcd. C, 83.14; H, 5.98; N, 6.93; Found: C, 83.31; H, 6.13; N, 6.71.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1H-pyrazol-5-yl)-1,3-diphenyl -1H-pyrazole (4)

A mixture of compound 3 (0.4 g, 0.001 mol) and hydrazine hydrate 98% (0.10 ml, 0.002 mol) in absolute ethanol (10 ml) was refluxed for 4 hr. The formed precipitate was filtered, dried and recrystallized from ethanol to give the title compound 4.

Yield 72%, mp. 179-180^{o}C; IR (KBr, cm^{-1}): 3310 (NH), 3057 (CH-aromatic), 2924, 2860 (CH_2-tetrahydronaphthalene), 1596 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.82 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.80 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.12, 3.45 (2dd, 2H, CH_2-pyrazoline protons), 5.13 (dd, 1H, CH-pyrazoline proton), 7.10-8.05 (m, 13H, Ar-H), 8.38 (s, 1H, pyrazole proton), 9.51 (s, 1H, NH, exchangeable by D_2O); MS, m/z (%): 419 [M^++1] (19), 418 [M^+] (71), 417 [M^{-1}] (65), 77 [C_6H_5] (100); Anal. For $C_{26}H_{26}N_4$ (418.53): Calcd. C, 80.35; H, 6.21; N, 13.39; Found: C, 80.52; H, 6.37; N, 13.17.

1-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-5-(1,3-diphenyl-1H-pyrazol-4-yl) pyrazol-1-yl) ethanone (5).

A mixture of compound 3 (0.4 g, 0.001 mol) and hydrazine hydrate 98% (0.10 ml, 0.002 mol) in glacial acetic acid (10 ml) was refluxed for 4 hr. The formed precipitate was filtered, dried and recrystallized from acetic acid to give the title compound 5.

Yield 98%, mp. 220-221^{o}C; IR (KBr, cm^{-1}): 3046 (CH-aromatic), 2933, 2860 (CH_2-tetrahydronaphthalene), 1657 (C=O), 1591 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.75 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.30 (s, 3H, -$COCH_3$), 2.73 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.16, 3.87 (2dd, 2H, CH_2-pyrazoline protons), 5.68 (dd, 1H, CH-pyrazoline proton), 7.10-7.89 (m, 13H, Ar-H), 8.30 (s, 1H, pyrazole proton); MS, m/z (%): 461 [M^++1] (24), 460 [M^+]

(67), 459 [M^+-1] (31), 77 [C_6H_5] (100); Anal. For $C_{30}H_{28}N_4O$ (460.57): Calcd. C, 78.23; H, 6.13; N, 12.16; Found: C, 78.54; H, 6.28; N, 12.38.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1-substituted-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (6a,b)

A mixture of compound 3 (0.4 g, 0.001 mol), methyl hydrazine and/or phenyl hydrazine (0.002 mol) in absolute ethanol (10 ml) was refluxed for 3 hr. After cooling the formed precipitate was filtered, dried and recrystallized from ethanol to give the title compounds 6a,b.

4-(4,5-Dihydro-3- (1,2,3,4-tetrahydronaphthalen-6-yl) -1-methyl-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (6a)

Yield 58%, mp. 120-121°C; IR (KBr, cm^{-1}): 3057 (CH-aromatic), 2926, 2855 (CH_2-tetrahydronaphthalene), 1597 (C=N); ^{1}H NMR ($CDCl_3$): δ 1.82 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.78 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.90 (s, 3H, CH_3), 3.57, 3.97 (2dd, 2H, CH_2-pyrazoline protons), 6.12 (dd, 1H, CH-pyrazoline proton), 7.06-8.07 (m, 13H, Ar-H), 8.30 (s, 1H, pyrazole proton); MS, m/z (%): 433 [M^++1] (8), 432 [M^+] (10), 431 [M^+-1] (33), 430 [M^+-2] (100); Anal. For $C_{29}H_{28}N_4$ (432.56): Calcd. C, 80.52; H, 6.52; N, 12.95; Found: C, 80.34; H, 6.22; N, 13.13.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1-phenyl-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (6b)

Yield 72%, mp. 150-151°C; IR (KBr, cm^{-1}): 3060 (CH-aromatic), 2922, 2855 (CH_2-tetrahydronaphthalene), 1594 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.74 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.72 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.96, 3.40 (2dd, 2H, CH_2-pyrazoline protons), 5.00 (dd, 1H, CH-pyrazoline proton), 7.04-7.91 (m, 18H, Ar-H), 8.54 (s, 1H, pyrazole proton); MS, m/z (%): 417 [M-C_6H_5]$^+$ (29), 416 [M-C_6H_6]$^+$ (100); Anal. For $C_{34}H_{30}N_4$ (494.63): Calcd. C, 82.56; H, 6.11; N, 11.33; Found: C, 82.29; H, 6.31; N, 11.02.

N-substituted-4,5-dihydro-3-(1,2,3,4- tetrahydronaphthalen -6- yl)-5-(1, 3- diphenyl-1H-pyrazol-4-yl)pyrazole-1-carbothioamide (7a,b)

A mixture of compound 3 (0.4 g, 0.001 mol), ethyl thiosemicarbazide and/or phenyl thiosemicarbazide (0.001 mol) in absolute ethanol (15 ml) was refluxed for 6 hr. After cooling the formed precipitate was filtered, dried and recrystallized from the methanol to give the title compounds 7a,b

N-ethyl-4,5-dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-5-(1,3-diphenyl-1H-pyrazol-4-yl)pyrazole-1-carbothioamide (7a)

Yield 43%, mp. 196-197°C; IR (KBr, cm^{-1}): 3189 (NH), 3056 (CH-aromatic), 2927, 2867 (CH_2-tetrahydronaphthalene), 1598 (C=N); ^{1}H NMR (DMSO-d_6): δ 0.94 (t, 3H, -$NHCH_2\underline{CH_3}$), 1.76 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.80 (m, 4H, $2CH_2$ - tetrahydronaphthalene protons), 3.40, 3.83 (2m, 4H,-$NHCH_2CH_3$, CH_2-pyrazoline protons), 5.42 (dd, 1H, CH-pyrazoline proton), 7.15-7.97 (m, 13H, Ar-H), 8.65 (s, 1H, pyrazole proton), 9.42 (s, 1H, NH,

exchangeable with D_2O); MS, m/z (%): 505 [M^+] (3), 504 [M^+ -1] (3), 159 [$C_{12}H_{15}$] (100); Anal. For $C_{31}H_{31}N_5S$ (505.68): Calcd. C, 73.63; H, 6.18; N, 13.85; Found: C, 73.41; H, 6.29; N, 13.54.

4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-N-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)pyrazole-1-carbothioamide (7b)

Yield 57%, mp. 200-201°C; IR (KBr, cm^{-1}): 3205 (NH), 3063 (CH-aromatic), 2929, 2864 (CH_2-tetrahydronaphthalene), 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.79 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.85 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.12, 3.56 (2dd, 2H, CH_2-pyrazoline protons), 5.16 (dd, 1H, CH-pyrazoline proton), 7.04-7.91 (m, 18H, Ar-H), 8.46 (s, 1H, pyrazole proton), 9.20 (s, 1H, NH, exchangeable with D_2O); MS, m/z (%): 554 [M^+ +1] (11), 553 [M^+] (11), 552 [M^{-1}] (13), 77 [C_6H_5] (15), 55 [C_4H_7] (100); Anal. For $C_{35}H_{31}N_5S$ (553.72): Calcd. C, 75.92; H, 5.64; N, 12.65; Found: C, 75.62; H, 5.81; N, 12.39.

4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-5-(1,3-diphenyl-1H-pyrazol-4-yl)pyrazole-1-carboxamide (8)

A mixture of compound 3 (0.4 g, 0.001 mol), semicarbazide hydrochloride (0.11 g, 0.001 mol) and sodium acetate (0.082 g, 0.001 mol) in absolute ethanol (15 ml) was refluxed for 6 hr. Then the reaction mixture was poured onto ice/cold water. The formed precipitate was filtered, dried and recrystallized from ethanol to give the title compound 8.

Yield 70%, mp. 248-249°C; IR (KBr, cm^{-1}): 3201, 3124 (NH_2), 3061 (CH-aromatic), 2931, 2870 (CH_2-tetrahydronaphthalene), 1651 (C=O), 1597 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.76 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.71 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.19, 3.42 (2dd, 2H, CH_2-pyrazoline protons), 5.10 (dd, 1H, CH-pyrazoline proton), 7.04-7.91 (m, 13H, Ar-H), 8.46 (s, 1H, pyrazole proton), 9.30 (s, 2H, NH_2, exchangeable with D_2O); MS, m/z (%): 417 [M^+-$CONH_2$] (2), 245 [$C_{14}H_{19}N_3O$] (100), 77 [C_6H_5] (64); Anal. For $C_{29}H_{27}N_5O$ (461.56): Calcd. C, 75.46; H, 5.90; N, 15.17; Found: C, 75.21; H, 5.76; N, 15.29.

4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-5-(1,3-diphenyl-1H-pyrazol-4-yl)pyrazole-1-carbothioamide (9)

A mixture of compound 3 (1.6 g, 0.004 mol) and thiosemicarbazide (0.36 g, 0.004 mol) in absolute ethanol (20 ml) was refluxed for 10 hr. The formed precipitate after cooling was filtered, dried and recrystallized from ethanol to give the title compound 9.

Yield 78%, mp. 181-182°C; IR (KBr, cm^{-1}): 3265, 3177 (NH_2), 3050 (CH-aromatic), 2933, 2870 (CH_2-tetrahydronaphthalene), 1610 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.76 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.81 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.11, 3.40 (2dd, 2H, CH_2-pyrazoline protons), 4.50 (dd, 1H, CH-pyrazoline proton), 7.22-7.96 (m, 14H, Ar-H,

pyrazole proton), 9.41 (s, 2H, NH_2, exchangeable with D_2O); MS, m/z (%): 477 [M^+] (3), 476 [M^+-1] (2), 159 [$C_{12}H_{15}$] (100); Anal. For $C_{29}H_{27}N_5S$ (477.62): Calcd. C, 72.93; H, 5.70; N, 14.66; Found: C, 72.74; H, 5.23; N, 14.83.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1-(4-substituted thiazol-2-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (10a,b)

A mixture of compound 9 (0.55 g, 0.001 mol), phencyl bromide and/or 4-bromophencyl bromide (0.001 mol) in absolute ethanol (15 ml) was refluxed for 5 hr. Then the reaction mixture was cooled, poured onto ice/cold water. The formed precipitate was filtered, washed several times by diluted ammonia solution, filtered, dried and recrystallized from ethanol to give the title compounds 10a,b.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (10a)

Yield 71%, mp. 206-207°C; IR (KBr, cm^{-1}): 3047 (CH-aromatic), 2926, 2858 (CH_2-tetrahydronaphthalene), 1607 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.78 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.80 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.01, 3.45 (2dd, 2H, CH_2-pyrazoline protons), 4.19 (dd, 1H, CH-pyrazoline proton), 6.74-7.95 (m, 20H, Ar-H, thiazole proton, pyrazole proton); MS, m/z (%): 578 [M^+ +1] (36), 577 [M^+] (76), 576 [M^+-1] (76), 77 [C_6H_5] (100); Anal. For $C_{37}H_{31}N_5S$ (577.74): Calcd. C, 76.92; H, 5.41; N, 12.12; Found: C, 76.61; H, 5.23; N, 12.39.

4-(1-(4-(4-Bromophenyl)thiazol-2-yl)-4,5-dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (10b)

Yield 78%, mp. 155-156°C; IR (KBr, cm^{-1}): 3057 (CH-aromatic), 2925, 2857 (CH_2-tetrahydronaphthalene), 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.76 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.79 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.18, 3.52 (2dd, 2H, CH_2-pyrazoline protons), 4.24 (dd, 1H, CH-pyrazoline proton), 6.71-8.01 (m, 19H, Ar-H, thiazole proton, pyrazole proton); MS, m/z (%): 654, 656 [M^+ -1] (63, 51), 577, 575 [M^+ - C_6H_6] (54, 38), 65 [C_5H_5] (100); Anal. For $C_{37}H_{30}BrN_5S$ (656.64): Calcd. C, 67.68; H, 4.61; N, 10.67; Found: C, 67.45; H, 4.29; N, 10.81.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1-(substituted sulphonyl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (11a,b)

A mixture of compound 3 (0.4 g, 0.001 mol), benzene sulphonyl hydrazide and/or tolyl sulphonyl hydrazide (0.001 mol) in absolute ethanol (20 ml) was refluxed for 5 hr. After cooling the formed precipitate was filtered, dried and recrystallized from methanol to give the title compound 11a,b.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1-(benzenesulphonyl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (11a)

Yield 32%, mp. 187-188°C; IR (KBr, cm^{-1}): 3059 (CH-aromatic), 2928, 2858 (CH_2-tetrahydronaphthalene), 1595 (C=N), 1357, 1173 (SO_2); ^1H NMR (DMSO-d_6): δ 1.79 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.81 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.13, 3.42 (2dd, 2H, CH_2-pyrazoline protons), 5.16 (dd, 1H, CH-pyrazoline proton), 7.07-7.99 (m, 18H, Ar-H), 8.36 (s, 1H, pyrazole proton); MS, m/z (%): 559 [M^+ +1] (27), 558 [M^+] (39), 557 [M^+ -1] (27), 55 [C_4H_7] (100); Anal. For $C_{34}H_{30}N_4O_2S$ (558.69): Calcd. C, 73.09; H, 5.41; N, 10.03; Found: C, 73.32; H, 5.27; N, 10.42.

4-(4,5-Dihydro-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-1-(tolylsulphonyl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (11b)

Yield 57%, mp. 190-191°C; IR (KBr, cm^{-1}): 3056 (CH-aromatic), 2926, 2863 (CH_2-tetrahydronaphthalene), 1597 (C=N), 1307, 1158 (SO_2); ^1H NMR (DMSO-d_6): δ 1.75 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.37 (s, 3H, CH_3), 2.77 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.03, 3.39 (2dd, 2H, CH_2-pyrazoline protons), 5.12 (dd, 1H, CH-pyrazoline proton), 7.04-7.98 (m, 17H, Ar-H), 8.48 (s, 1H, pyrazole proton); MS, m/z (%): 572 [M^+] (3), 416 [M^+-$C_7H_8O_2S$] (70), 159 [$C_{12}H_{15}$] (100); Anal. For $C_{35}H_{32}N_4O_2S$ (572.72): Calcd. C, 73.40; H, 5.63; N, 9.78; Found: C, 73.62; H, 5.81; N, 9.49.

4-(3-(1,2,3,4-Tetrahydronaphthalen-6-yl) isoxazol-5-yl) -1,3-diphenyl-1H-pyrazole (12)

A mixture of compound 3 (0.8 g, 0.002 mol) and hydroxylamine hydrochloride (0.14 g, 0.002 mol) in alcoholic sodium hydroxide (5%, 20 ml) was refluxed for 10 hr. The reaction mixture was cooled, poured onto ice/cold water and acidified by diluted hydrochloric acid. The formed precipitate was filtered, dried and recrystallized from ethanol to give the title compound 12.

Yield 85%, mp. 150-151°C; IR (KBr, cm^{-1}): 3053 (CH-aromatic), 2925, 2858 (CH_2-tetrahydronaphthalene), 1597 (C=N); ^1H NMR ($CDCl_3$): δ 1.81 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.80 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 7.08-8.06 (m, 14H, isoxazole proton, Ar-H), 8.43 (s, 1H, pyrazole proton); MS, m/z (%): 419 [M^++2] (25), 418 [M^+ +1] (20), 417 [M^+] (9), 77 [C_6H_5] (100); Anal. For $C_{28}H_{23}N_3O$ (417.50): Calcd. C, 80.55; H, 5.55; N, 10.06; Found: C, 80.34; H, 5.26; N, 10.36.

6-(1,2,3,4-Tetrahydronaphthalen-6-yl) -4-(1,3-diphenyl-1H-pyrazol-4-yl) pyrimidine-2(1H)-thione (13)

A mixture of compound 2 (0.8 g, 0.002 mol) and thiourea (0.23 g, 0.002 mol) in sodium ethoxide solution (5%, 15 ml) was refluxed for 24 hr. The reaction mixture was cooled, poured onto ice/cold water and acidified by diluted hydrochloric acid. The formed precipitate was filtered, dried and recrystallized from ethanol to give the title compound 13.

Yield 83%, mp. 133-134°C; IR (KBr, cm^{-1}): 3417 (NH), 3057 (CH-aromatic), 2925, 2856 (CH_2-tetrahydronaphthalene), 1602 (C=N), 1159 (C=S); ^1H NMR (DMSO-d_6): δ 1.78 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.81 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 5.03 (d, 1H, pyrimidine proton), 7.16-7.93 (m, 14H, pyrimidine proton, Ar-H), 8.52 (s, 1H, pyrazole proton), 9.21 (s, 1H, NH, exchangeable with D_2O); MS, m/z (%): 461 [M^+ +1] (50), 460 [M^+] (70), 459 [M^+ -1] (51), 82 [C_6H_{10}] (100); Anal. For $C_{29}H_{24}N_4S$ (460.59): Calcd. C, 75.62; H, 5.25; N, 12.16; Found: C, 75.73; H, 5.43; N, 12.31.

4-(1,2,3,4-Tetrahydronaphthalen-6-yl)-6- (1,3-diphenyl-1H-pyrazol-4-yl) pyrimidin-2-amine (14)

A mixture of compound 3 (1.6 g, 0.004 mol) and guanidine sulfate (0.43 g, 0.004 mol) in sodium ethoxide solution (5%, 30 ml) was refluxed for 24 hr. The reaction mixture was cooled, poured onto ice/cold water and acidified by diluted hydrochloric acid. The formed precipitate was filtered, dried and recrystallized from ethanol to give the title compound 14.

Yield 83%, mp. 240-241°C; IR (KBr, cm^{-1}): 3326, 3189 (NH_2), 3057 (CH-aromatic), 2925, 2862 (CH_2-tetrahydronaphthalene), 1574 (C=N); ^1H NMR (DMSO-d_6): δ 1.80 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.82 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 6.93-7.97 (m, 14H, pyrimidine proton, Ar-H), 8.36 (s, 1H, pyrazole proton), 9.23 (s, 2H, NH_2, exchangeable with D_2O); MS, m/z (%): 444 [M^+ +1] (15), 443 [M^+] (38), 442 [M^+ -1] (44), 77 [C_6H_5] (100), 57 [C_4H_9] (100); Anal. For $C_{29}H_{25}N_5$ (443.54): Calcd. C, 78.53; H, 5.68; N, 15.79; Found: C, 78.29; H, 5.42; N, 15.58.

2-Amino-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-(1,3-diphenyl-1H-pyrazol -4-yl)-4H-pyran-3-carbonitrile (15), 6-(1,2,3,4-tetrahydronaphthalen -6-yl) -2-hydroxy-4-(1,3-diphenyl -1H-pyrazol-4-yl) -4H-pyran-3- carbonitrile (16) and 1-(6-(1,2,3,4-tetrahydronaphthalen-6-yl) -2-hydroxy-4- (1,3-diphenyl-1H-pyrazol-4-yl)-4H-pyran -3-yl) ethanone (17)

A mixture of compound 3 (0.8g, 0.002 mol) and active methylene compounds namely; malononitrile, ethyl cyanoacetate and/or ethyl acetoacetate (0.002 mol) in sodium ethoxide solution (5%, 15 ml) was refluxed for 6 hr. Then the reaction mixture was cooled, poured onto ice/cold water and acidified by diluted hydrochloric acid. The formed precipitate was filtered, dried and recrystallized from ethanol to give the title compounds 15-17.

2-Amino-6- (1,2,3,4-tetrahydronaphthalen -6-yl)-4- (1,3-diphenyl-1H- pyrazol-4-yl)- 4H-pyran-3-carbonitrile (15)

Yield 85%, mp. 208-209°C; IR (KBr, cm^{-1}): 3422, 3124 (NH_2), 3059 (CH-aromatic), 2924, 2855 (CH_2-tetrahydronaphthalene), 2219 (C≡N), 1594 (C=N); ^1H NMR ($CDCl_3$): δ 1.81 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.78 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.90, 4.92 (2d, 2H, pyrane protons), 7.11-7.84 (m, 13H, Ar-H), 8.55 (s, 1H, pyrazole proton); MS, m/z (%): 471 [M^+ +1] (2), 470 [M^+] (3), 444 [M^+ -CN] (7), 442 [444-2] (100); Anal. For

$C_{31}H_{26}N_4O$ (470.56): Calcd. C, 79.12; H, 5.57; N, 11.91; Found: C, 79.28; H, 5.31; N, 11.76.

6-(1,2,3,4-Tetrahydronaphthalen-6-yl)-2-hydroxy-4-(1,3-diphenyl-1H-pyrazol-4-yl)-4H-pyran-3-carbonitrile (16)

Yield 85%, mp. 104-105^{o}C; IR (KBr, cm^{-1}): Broad band centered at 3428 (OH), 3056 (CH-aromatic), 2925, 2857 (CH_2-tetrahydronaphthalene), 2212 (C≡N), 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.76 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.77 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.80, 5.54 (2d, 2H, pyrane protons) 7.02-7.96 (m, 13H, Ar-H), 8.33 (s, 1H, pyrazole proton), 12.10 (br. s, 1H, OH, exchangeable with D_2O); MS, m/z (%): 470 [M^+ -1] (51), 469 [M^+ -2] (70), 77 [C_6H_5] (100); Anal. For $C_{31}H_{25}N_3O_2$ (471.55): Calcd. C, 78.96; H, 5.34; N, 8.91; Found: C, 78.68; H, 5.08; N, 8.73.

1-(6-(1,2,3,4-Tetrahydronaphthalen-6-yl)-2-hydroxy-4-(1,3-diphenyl-1H-pyrazol-4-yl)-4H-pyran-3-yl)ethanone (17)

Yield 95%, mp. 143-144^{o}C; IR (KBr, cm^{-1}): Broad band centered at 3423 (OH), 3058 (CH-aromatic), 2924, 2856 (CH_2-tetrahydronaphthalene), 1728 (C=O), 1600 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.81 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.34 (s, 3H, $COCH_3$), 2.79 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.80, 5.70 (2d, 2H, pyrane protons) 7.02-7.96 (m, 13H, Ar-H), 8.33 (s, 1H, pyrazole proton), 12.10 (br. s, 1H, OH, exchangeable with D_2O); MS, m/z (%): 487 [M^+ -1] (12), 91 [C_6H_5N] (100); Anal. For $C_{32}H_{28}N_2O_3$ (488.58): Calcd. C, 78.67; H, 5.78; N, 5.73; Found: C, 78.49; H, 5.61; N, 5.89.

1,2-Dihydro-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-2-oxo-4-(1,3-diphenyl-1H-pyrazol -4-yl)pyridine-3-carbonitrile (18)

A mixture of compound 1 (3.48 g, 0.02 mol), 1,3-diphenyl-*1H*-pyrazole-4-carboxaldehyde (4.96 g, 0.02 mol) , ethyl cyanoacetate (2.26 ml, 0.02 mol) and ammonium acetate (12.32 g, 0.16 mol) in absolute ethanol (50 ml) was refluxed for 10 hr. The formed precipitate was filtered, washed with ethanol, dried and recrystallized from acetic acid to give the title compound 18.

Yield 71%, mp. >300^{o}C; IR (KBr, cm^{-1}): 3414 (NH), 3061 (CH-aromatic), 2929, 2866 (CH_2-tetrahydronaphthalene), 2220 (C≡N), 1658 (C=O), 1593 (C=N) ; ^{1}H NMR ($CDCl_3$): δ 1.81 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.80 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 7.15-7.86 (m, 14H, pyridine proton, Ar-H), 8.32 (s, 1H, pyrazole proton), 9.15 (s, 1H, NH, exchangeable with D_2O); MS, m/z (%): 469 [M^+ +1] (17), 468 [M^+] (45), 467 [M^+ -1] (16), 77 [C_6H_5] (100); Anal. For $C_{31}H_{24}N_4O$ (468.55): Calcd. C, 79.46; H, 5.16; N, 11.96; Found: C, 79.28; H, 5.31; N, 11.78.

6-(1,2,3,4-Tetrahydronaphthalen-6-yl)-2-substituted-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carbonitrile (19-21)

A mixture of compound 18 (1.88 g, 0.004 mol), different alkyl halide namely; methyl iodide, chloroacetone and/or ethyl bromoacetate (0.004 mol) and potassium carbonate (0.56 g, 0.004 mol) in DMF (10 ml) was refluxed for 8-10hr. Then, the reaction mixture was cooled and poured onto ice/cold water. The formed precipitate was filtered, dried and recrystallized from methanol to give the title compounds 19-21, respectively.

6-(1,2,3,4-Tetrahydronaphthalen-6-yl)-2-methoxy-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carbonitrile (19)

Yield 50%, mp. 187-188°C; IR (KBr, cm^{-1}): 3059 (CH-aromatic), 2926, 2859 (CH_2-tetrahydronaphthalene), 2216 (C≡N), 1590 (C=N); ^1H NMR ($CDCl_3$): δ 2.09 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.96 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.71 (s, 3H, $-OCH_3$), 7.28-8.07 (m, 14H, pyridine proton, Ar-H), 8.46 (s, 1H, pyrazole proton; MS, m/z (%): 482 [M^+] (68), 481 [M^+ -1] (69), 451 [M^+- OCH_3] (79), 77 [C_6H_5] (100); Anal. For $C_{32}H_{26}N_2O$ (482.58): Calcd. C, 79.64; H, 5.43; N, 11.61; Found: C, 79.30; H, 5.71; N, 11.29.

2-(2-Oxopropoxy)-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carbonitrile (20)

Yield 75%, mp. 127-128°C; IR (KBr, cm^{-1}): 3054 (CH-aromatic), 2925, 2863 (CH_2-tetrahydronaphthalene), 2217 (C≡N), 1710 (C=O), 1602 (C=N); ^1H NMR ($CDCl_3$): δ 1.80 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.77 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.88 (s, 3H, $-COCH_3$), 2.95 (s, 2H, $-OCH_2CO$), 7.11-7.85 (m, 14H, pyridine proton, Ar-H), 8.22 (s, 1H, pyrazole proton); MS, m/z (%): 525 [M^+ +1] (81), 524 [M^+] (100); Anal. For $C_{34}H_{28}N_4O_2$ (524.61): Calcd. C, 77.84; H, 5.38; N, 10.68; Found: C, 77.61; H, 5.45; N, 10.50.

Ethyl 2-(3-cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-(1,3-diphenyl-1H-pyrazol -4-yl)pyridin-2-yloxy)acetate (21)

Yield 74%, mp. 145-146°C; IR (KBr, cm^{-1}): 3055 (CH-aromatic), 2926, 2859 (CH_2-tetrahydronaphthalene), 2219 (C≡N), 1736 (C=O, ester), 1595 (C=N); ^1H NMR ($CDCl_3$): δ 1.41 (t, 3H, $-CH_2CH_3$), 1.81 (m, 4H, $2CH_2$-tetrahy dronaphthalene protons), 2.70 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 4.38 (q, 2H, $-CH_2CH_3$), 5.13 (s, 2H, $-OCH_2$), 7.00-7.87 (m, 14H, pyridine proton, Ar-H), 8.24 (s, 1H, pyrazole proton); MS, m/z (%): 555 [M^+ +1] (50), 554 [M^+] (19), 553 [M^+ -1] (15), 77 [C_6H_5] (100), 57 [C_4H_9] (100); Anal. For $C_{35}H_{30}N_4O_3$ (554.64): Calcd. C, 75.79; H, 5.45; N, 10.10%; Found: C, 75.92; H, 5.32; N, 10.26.

2-(3-Cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridin-2-yloxy)acetohydrazide (22)

A mixture of compound 20 (2.2 g, 0.004 mol) and hydrazine hydrate (0.4 ml, 0.008 mol) in absolute ethanol (20 ml) was refluxed for 5 hr. The formed

precipitate was filtered, dried and recrystallized from ethanol to give the title compound 22.

Yield 90%, mp. 193-194°C; IR (KBr, cm^{-1}): 3407, 3124 (NH_2, NH), 3056 (CH-aromatic), 2927, 2861 (CH_2-tetrahydronaphthalene), 2219 (C≡N); ^1H NMR ($CDCl_3$): δ 1.82 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.74 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 5.16 (s, 2H, -OCH_2CO), 7.13-7.84 (m, 14H, pyridine proton, Ar-H), 8.60 (s, 1H, pyrazole proton); MS, m/z (%): 540 [M^+] (73), 539 [M^+ -1] (44), 109 [$C_6H_9N_2$] (100); Anal. For $C_{33}H_{28}N_6O_2$ (540.61): Calcd. C, 73.32; H, 5.22; N, 15.55; Found: C, 73.45; H, 5.39; N, 15.23.

2-(3-Cyano-6-(1,2,3,4-tetrahydronaphthalen-6-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridin-2-yloxy)-N'-(4-methoxybenzylidene)acetohydrazide (23)

A mixture of compound 22 (0.54 g, 0.001 mol) and anisaldehyde (0.14 ml, 0.001 mol) in absolute ethanol (10 ml) was refluxed for 8 hr. After cooling, the formed precipitate was filtered, dried and recrystallized from ethanol to give the title compound 23.

Yield 67%, mp. 277-278°C; IR (KBr, cm^{-1}): 3429 (NH), 3058 (CH-aromatic), 2929, 2857 (CH_2-tetrahydronaphthalene), 2220 (C≡N), 1600 (C=N); ^1H NMR ($CDCl_3$): δ 1.79 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 2.76 (m, 4H, $2CH_2$-tetrahydronaphthalene protons), 3.73 (s, 3H, -OCH_3), 5.03 (s, 2H, -OCH_2CO), 7.13-7.84 (m, 19H, pyridine proton, -N=CH, Ar-H), 8.39 (s, 1H, pyrazole proton); MS, m/z (%): 659 [M^+ +1] (28), 658 [M^+] (52), 77 [C_6H_5] (100); Anal. For $C_{41}H_{34}N_6O_3$ (658.75): Calcd. C, 74.75; H, 5.20; N, 12.76; Found: C, 74.56; H, 5.42; N, 12.49.

Biological assay

Cytotoxicity assessment

Chemicals: Sulforhodamine-B (SRB) and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (St. Louis, MO). RPMI-1640 medium, fetal bovine serum and other cell culture materials were purchased from Lonza (Basel, Switzerland).

Cell culture: MCF-7 human breast cancer cell line and HepG2 human hepatocellular carcinoma cancer cells was purchased from VACCERA (Cairo, Egypt) and grown in RPMI-1640 medium and supplemented with 10% heat inactivated FBS, 100 units/ml of penicillin and 100 mg/ml of streptomycin and maintained at 37° in a humidified atmosphere containing 5% CO_2.

SRB cytotoxicity assay: Cytotoxicity was determined using SRB method as previously described by Skehan *et al* [23]. Exponentially growing cells were collected using 0.25% Trypsin-EDTA and seeded in 96-well plates at 2500 cells/well in RPMI-1640 supplemented medium. The cells were allowed for attachment for 24 hr. Then, cells were incubated for 72 hr with six different concentrations (0: 10^3µM) of the tested compounds. After 72 hr exposure, the

cells were fixed with 10% trichloroacetic acid for 1 hr at 4 ºC. The plates were stained for 10 min at room temperature with 0.4% sulforhodamine b (SRB) dissolved in 1% acetic acid. The plates were air dried for 24 hr and the protein-dye complex was solubilized with Tris-HCl (10mM, pH 7.4) for 5 min on a shaker at 1500 rpm. The optical density (OD) was measured spectrophotometrically at 564 nm using a microplate reader (ChroMate-4300, FL, USA). Half-maximal inhibitory concentration (IC50), the drug concentration at which 50% growth inhibition is achieved, was calculated using Sigma Plot software, version 9.0 (Systat Software, San Jose, CA).

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تشييد وتقييم السمية ضد الخلايا السرطانية لبعض مشتقات رباعى هيدرونفثالين- بيرازول الجديدة

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تناول هذا البحث تشييد المركب 1- (1,2,3,4-رباعى هيدرونفثالين-6-يل)-3-(1,3-ثنائى فينيل-1 ه- بيرازول-4-يل) بروب-2-ين-1-ين (3) والذى بدوره تم تفاعله مع مجموعة من مشتقات الهيدرازين هيدرات للحصول على مركبات ثنائى البيرازول المقابلة 4-9. عند تكاثف مركب البيرازول كاربوثيواميد 9 مع عدد من مشتقات الالفا هالوكيتون ادى الى تكوين مشتقات الثيازول المقابلة 10a,b . ايضا عند تفاعل الشالكون 3 مع مجموعة من مشتقات السلفونيل هيدرازيد ادى ذلك للحصول على مركبات السلفونيل بيرازول المقابلة 11a,b , فى حين ان تفاعلها مع هيدروكسيل امين هيدروكلورايد تكون مشتق الايزواوكسازول المقابل 12 . عند معالجة الشالكون 3 بالثيويوريا وسلفات الجوانيدين ادى الى تكوين مشتقات البيريميدين المقابلة 13, 14. بالاضافة الى ذلك فان مشتقات البيران 15-17 تم الحصول عليها بحولقة الشالكون 3 بالمالونونيتريل, ايثيل سيانواسيتات, ايثيل اسيتو اسيتات. بالاضافة لما سبق تفاعل المركب 2-اوكسوبيريدين 18 مع مجموعة من هاليدات الالكيل المختلفة للحصول على مشتقات البيريدين المقابلة 19-21. عند تفاعل مشتق الكاربوهيدرازيد 22 مع الديهيد الانيسالديهيد تكون مركب الشيف القاعدى المقابل 23 . تناولت هذه الدراسة ايضا تقييم سمية بعض المركبات التى تم تشييدها ضد خلايا الكبد وخلايا الثدى السرطانية باستخدام الدوكسوروبيسين كدواء مرجعى.