One-Pot Synthesis of New Pyrazolo [3, 4, -d] Pyrimidine Derivatives and Study of their Antioxidant and Anticancer Activities

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Abstract

An effort was made to synthesize a new series of pyrazolo [3,4-d] pyrimidine derivatives (2-5). The synthesis of these compounds was achieved via reaction of 3-methyl-1,4-dihydropyrazol-5-one (1) with a substituted aromatic aldehyde and urea or thiourea in mild reaction conditions, giving satisfactory yields. FT-IR and ^{1}H-NMR spectroscopies were used to characterize the structure of the newly synthesized compounds (2-5), where the spectral data confirmed the formation of these compounds. The antioxidant activity of these compounds (2-5) was examined in this study the synthesized compounds showed a moderate-high antioxidant effect, which was examined by using 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assays. The cellular toxicity of the compounds (2-5) was studied on MCF-7 cell lines using MTT assay. Compound (5) showed the highest toxicitytowards MCF-7 cell lines.

Keywords: *Pyrazole, Pyrimidine, anticancer, antioxidant DPPH; MCF-7*

Introduction

Chemists and biologists in recent years were motivated tofocus their attention to study these compounds. The pyrazole derivatives havea wide spectrum of biological activities such asanticancer[1], antimicrobial, antitubercular[2], antidepressant, analgesic, anti-inflammatory[3], antidiabetic[4], anticonvulsant, antiulcer[5], and antipyretic[6], activities. Further, the pyrazole ring is not only significantasa biologically active moiety, but it's also an important and synthetically versatile substrate which can be utilized as a starting material for the building of other fused heterocycles[7]. On the other hand, Pyrimidines are very well known for their pharmacological properties, and it was demonstrated that pyrimidine derivatives constitute an interesting class of heterocycles in drug design[8], where some of them actingas anticancer[9], bactericide, fungicide,vermicide, and antiviral agents[10]. Pyrazolo [3,4-*d*] pyrimidine is a fused heterocyclic scaffold which is analogous for purines and has gained an interest in the drug discovery[11].

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Procedures:

Synthesis of 3-methyl-1, 4-dihydropyrazol-5-one (1): To a round bottom flask containing ethyl acetoacetate (1 mol), 3 drops of glacial acetic acid were added with stirring, then hydrazine hydrate (1.2 mol) was slowly added. The reaction mixture was stirred at room temperature for 10 min, and then solid was precipitated. The separated solid was filtered by gravity filtration, washed twice with water and air dried[12].Yield 81%. FT-IR (KBr, cm^{-1}, stretching), 3439 (N-H), 2959 (CH_3), 1686 (C=O), 1606 (C=N); ^{1}H-NMR (300MHz,

DMSO-d_6): 10.59 (br, 1H, NH-Pyrazole), 2.11 ppm(s, 3H, CH_3), 5.27 ppm(s, 2H, CH_2- ring).

General procedure for the synthesis of pyrazolo[3, 4-d]pyrimidine derivatives(2-5): To three component mixture of compound **(1)**(0.01 mol), substituted aromatic aldehyde(0.01mol) and urea or thiourea(0.01 mol)that dissolved in acetonitrile(20 mL), 3-4 drops of concentrated HCl was added. The resulted clear solution was refluxedfor 4-6 h. The reaction mixture was then cooled to room temperature. The resulted precipitate was then obtained by filtration, washed several times with acetonitrile and air dried[13].

Synthesis of 4-[4-(dimethylamino)phenyl]-3-methyl-1, 4, 5, 7-tetrahydro-6H-pyrazolo[3, 4-d] pyrimidin-6-one(2): Yield 74%. FT-IR (KBr, cm^{-1}, stretching), 3259(-NH), 3034(Ar-H), 2933(C-H, aliphatic), 1620(C=O), 1550(C=N), 1519(Ar, C=C); ^{1}H-NMR (300MHz, DMSO-d_6): δ 7.91 (s, 1H, NH-Pyrimidine), 7.45 (s, 1H, NH-Pyrimidine), 6.66-6.99 (dd, 4H, Ar-H), 7.21 (br, 1H, NH-Pyrazole), 4.77 (s, 1H, CH-Pyrimidine), 2.82 (s, 6H, CH_3-N), 2.20 (s, 3H, CH_3).

Synthesis of 4-[4-(dimethylamino)phenyl]-3-methyl-1, 4, 5, 7-tetrahydro-6H-pyrazolo[3, 4-d] pyrimidine-6-thione(3): Yield 77%. FT-IR (KBr, cm^{-1}, stretching), 3184(-NH), 3044(Ar-H), 2929(C-H, aliphatic), 1610(C=N), 1491(Ar, C=C), 1271(C=S); ^{1}H-NMR (300MHz, DMSO-d_6):δ9.53 (br, 1H, NH-Pyrimidine), 8.13 (s, 1H, NH-Pyrimidine), 6.79-7.17 (dd, 4H, Ar-H), 7.56 (s, 1H, NH-Pyrazole), 5.07 (s, 1H, CH-Pyrimidine), 2.26 (s, 6H, CH_3-N), 2.07 (s, 3H, CH_3).

Synthesis of 4-(5-bromo-2-hydroxyphenyl)-3-methyl-1, 4, 5, 7-tetrahydro-6H-pyrazolo[3, 4-d] pyrimidine-6-thione(4): Yield 68%. FT-IR (KBr, cm^{-1}, stretching), 2400-3500(Ar-OH), 3167(-NH), 3049(Ar-H), 2953(C-H, aliphatic), 1599(C=N), 1516(Ar, C=C), 1143(C=S), 756(Ar-Br); ^{1}H-NMR (300MHz, DMSO-d_6): δ 8.12 (s, 1H, NH Pyrimidine), 7.90 (s, 1H, NH-Pyrimidine), 7.54 (s, 1H, NH-Pyrazole), 6.97-7.27 (m, 3H, Ar-H), 5.83 (s, 1H, Ar-OH), 5.52 (s, 1H, CH-Pyrimidine), 2.18 (s, 3H, CH_3).

4-(2-hydroxynaphthalen-1-yl)-3-methyl - 1, 4, 5, 7-tetrahydro-6H-pyrazolo [3, 4-d] pyrimidine-6-thione (5): Yield 71%. FT-IR (KBr, cm^{-1}, stretching), 2400-3500(Ar-OH), 3126(-NH), 3047(Ar-H), 2997(C-H, aliphatic), 1622(C=N), 1545(Ar, C=C), 1236(C=S); ^{1}H-NMR (300MHz, DMSO-d_6): 8.71 (s, 1H, NH-Pyrimidine), 7.2 (s, 1H, NH-Pyrimidine), 6.33 (s, 1H, NH-Pyrazole), 7.35-7.77 (m, 6H, Ar-H), 6.00 (s, 1H, CH-Pyrimidine), 5.75 (s, 1H, Ar-OH), 2.16 (s, 3H, CH_3).

Antioxidant activity[14]:

DPPH radical scavenging activity: Methanolic solutions of 1, 000 ppm concentration of synthesized of pyrazolo [3, 4-*d*] pyrimidine derivatives **(2-5)** were prepared. Different amounts (5, 10, 15, 20 and 25 µL) of the methanolic solution of pyrazolo [3, 4-*d*] pyrimidine derivatives **(2-5)**were transferred into separate test tubes having 5 mL of 0.004% methanolic solution of DPPH. All the test solution was prepared in triplicate. The mixtures were shaken vigorously and left in the dark for 2 hours, or until obtaining stable values.

Reducing Power Activity: Different amounts of methanolic solutions of pyrazolo [3, 4-*d*] pyrimidine derivatives **(2-5)** (0.1, 0.2, 0.3, 0.4 and 0.5) mg/mL was mixed with 2.5 mL of the phosphate buffer (200 mmol and pH 6.6) and 2.5 mL of 1% potassium ferricyanide. The mixtures were incubated at 50 °C. After the incubation, 2.5 mL of 10% trichloroacetic acid was added to the mixture. This was followed by centrifugation at 650 rpm for 10 minutes. The upper layer was separated. 5.0 mL of this was mixed with 5.0 mL of distilled water and 1.0 mL of 0.1% ferric chloride. The absorbance of the resulting solution was measured at 700 nm.

Determination of Cytotoxicity: Human Erythrocytes was treated with different amounts of pyrazolo [3, 4-*d*] pyrimidine derivatives **(2-5)**solutions of 0.1, 0.2, 0.3, 0.4 and 0.5 mg/mL. A serial dilution of the compounds **(2-5)**was made up in phosphate-buffered saline solution. A total volume of 0.8 mL for every dilution was prepared in an Eppendorf tube. A negative control tube (having saline only) and a positive control tube (having tap water) were also prepared for the analysis. Human erythrocytes were added to every tube, to make-up a final volume of 1.0 mL. The prepared solutions were incubated at 37°C for 30 minutes. The tubes were then examined for red blood cell decomposition.The experiment was repeated in duplicate.

Anticancer Activity:

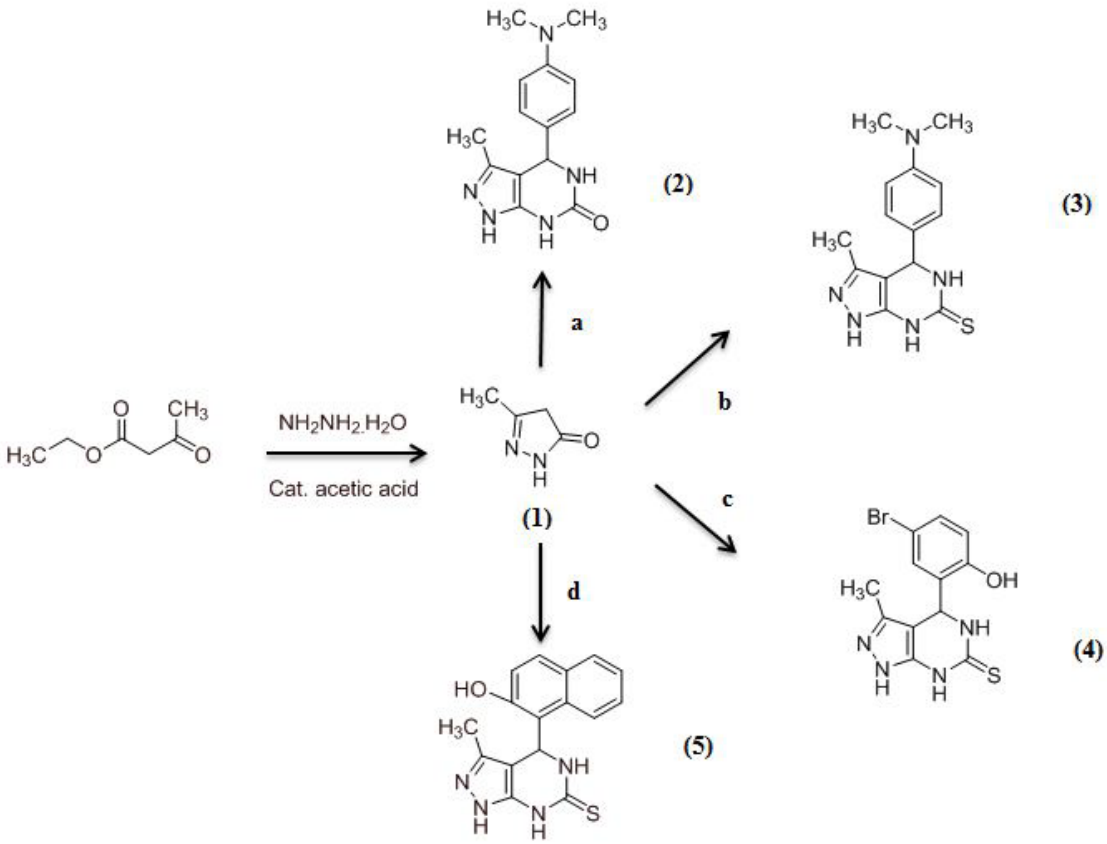
Maintenance Of Cell Cultures[15]: These human cell line has been maintained in RPMI-1640, supplemented with 10% fetal bovine, 100units/mL penicillin, and 100 µg/mL streptomycin. The cells were passed through the Trypsin-EDTA reseeded at 50% confluence two times

per-week and incubated at 37 °C.

Cytotoxicity Assays (MTT assay)[16]: MTT cell viability was carried out on 96-well plates. Cell lines were seeded at 1 x 10^4 cells/well. After 24h or a confluent monolayer was accomplished. Cells were treated with the test compounds **(2-5)**.The cell viability was calculated after 72h of treatment. The medium was removed and 28 µL of 2 mg/mL solution of MTT was added. This was followed by incubation of the cells for 1.5 h at 37 °C. After removing the MTT solution, the crystals that remained in the wells were solubilized by adding 130 µL of DMSO followed by incubation at 37 °C for 15 minutes with shaking. The absorbance was measuredand identified on a microplate reader at 492 nm (test wavelength).The assay was performed in triplicate.

Result and Discussion

The structures of the synthesized compounds were confirmed depending on the obtained spectral data ofFT-IR, and ^{1}H-NMR spectroscopies. The FT-IR spectrum of compound (**1**), displays an absorption bandat 3439 cm^{-1},which is attributed to stretching vibration of NH group, a week absorption band at 2959 cm^{-1} corresponding to stretching vibration of CH_3 group, in addition to strong absorption bands at 1686 $cm^{-1}$and 1606 cm^{-1} corresponding to stretching vibration of C=O and C=N, respectively.On the other hand, theFT-IR spectra of the title compounds **(2-5)** were showed absorption bandsassigned to NH functionranged at 3259-31126 cm^{-1}, absorption bandsof C=N ranged at 1622-1550cm^{-1} and absorption bands corresponding to C=S group in the region 1271- 1143 cm^{-1}. In addition, compound (**4**) and compound (**5**)wereshown a broad absorption band attributed to aromatic hydroxyl group ranged at 3500-2400 cm^{-1}.Moreover, the ^{1}H-NMR spectra of compound (1) revealed singlet signal assigned tothe one proton NH of ring at 10.59 ppm, singletsignal assigned to the three protons of CH_3at 2.11 ppm and singlet signal to the two protons CH_2 of ring at 5.27 ppm.the ^{1}H-NMR spectra of compounds (**2**) revealed singlet signals assigned to the two NH of pyrimidine ring at 7.91 and 7.45 ppm, singlet signals assigned to the NH of pyrazole ring at 7.21 ppm and singlet signals assigned to the three protons of CH_3 (olefinic) at 2.20 ppm. In addition, the ^{1}H-NMR spectra of compound **(2)**revealed singlet signals belong to six protons of CH_3-N at 2.82 ppm andthe aromatic region of double doublet signals at 6.66-6.99ppm for four protons.



Scheme 1. (a) 4-(dimethylamino) benzaldehyde, urea, acetonitrile, Conc.HCl (b) 4-(dimethylamino) benzaldehyde, thiourea, acetonitrile, Conc.HCl (c) 5-bromo-2-hydroxybenzaldehyde, thiourea, acetonitrile, Conc. HCl (d) 2-hydroxynaphthalene-1-carbaldehyde, thiourea, acetonitrile, Conc. HCl.

Antioxidant activity:

DPPH radical scavenging activity[17]: Antioxidant activity of the prepared compounds was established by using DPPH assay. The antioxidant could reduce the alcoholic solution of DPPH to the non-radical form, i.e. DPPH-H in the reaction. In addition, the dark-color of the DPPH solution is transformed into a yellow colored solution in the presence of an antioxidant, resulting in a decrease in the absorbance.

The DPPH assay is often used to measure the free radical scavenging activities of antioxidants. Table 1 illustrates the scavenging capability of the test compounds. The variation in the absorbance was evaluated at 517 nm. The percentages inhibition of the samplesranges from 82% to 69%. Vitamin C exhibited inhibition of 94% at 25 µL in 1000 ppm concentration. On the other hand, compound **(5)**showed the maximum inhibition at 82% compared with all the test compounds at 25 µL in 1000 ppm. In addition, lower inhibition was recorded for all samples lower than 25 µL in 1000 ppm. The least inhibition was recorded for compound(2) (69%) at 25 µL in 1000 ppm. Overall, all the compounds tested exhibited various antioxidant activities when compared with vitamin C.

Table 1. The values of inhibition shown by the test compound

Comp.	Concentration of 1000 ppm														
	5 µL			10 µL			15 µL			20 µL			25 µL		
	A_a	A_o	(I%)	A_a	A_o	(I%)	A_a	A_o	(I%)	A_a	A_o	(I%)	A_a	A_o	(I%)
2	0.45	0.752	40.15	0.39	0.752	48.13	0.31	0.752	58.77	0.26	0.752	65.42	0.23	0.752	69.41
3	0.401	0.752	46.67	0.347	0.752	53.85	0.306	0.752	59.30	0.255	0.752	66.09	0.218	0.752	71.01
4	0.362	0.752	51.86	0.311	0.752	58.64	0.249	0.752	66.88	0.218	0.752	71.01	0.188	0.752	75
5	0.31	0.752	58.77	0.24	0.752	68.08	0.184	0.752	75.53	0.152	0.752	79.78	0.134	0.752	82.18
Vit. C	0.15	0.752	78.98	0.122	0.752	83.77	0.098	0.752	86.96	0.066	0.752	91.22	0.041	0.752	94.54

Reducing power assay[18]: Table 2. illustrates the decreasing power of compounds **(2-5)** as a function of their concentration. For each assay, the yellow color of the test solution transformed into different shades of blue and green, according to the decreasing power of the compound. The presence of the antioxidants results in the decrease of the Fe^{3+}/ferri-cyanide complex and transform into the ferrous forms. Thus, measuring the formations of Perl's Prussian blue at 700 nm can be used to monitor the Fe^{2+} concentration. The decreasing power of every compound was found to increase with concentration. The decreasing power of compound (5) at 0.5 mg/mL was more than 0.64. At 0.1 mg/mL, the decreasing power of compound (5) was 0.28, and at 0.3 mg/mL was 0.45. As for compound 2, it had the least decreasing power of 0.21 at 0.1 mg/mL, 0.36 at 0.3 mg/mL and 0.47 at 0.5 mg/mL.

Table 2. The absorption values of the compounds (2-5) and vitamin C

Comp	Concentration (mg/ml)																			
	0.1				0.2				0.3				0.4				0.5			
	A_1	A_2	A_3	A_a	A_1	A_2	A_3	A_a	A_1	A_2	A_3	A_a	A_1	A_2	A_3	A_a	A_1	A_2	A_3	A_a
2	0.2	0.21	0.22	0.21	0.29	0.29	0.3	0.29	0.35	0.36	0.36	0.36	0.41	0.42	0.4	0.41	0.48	0.48	0.47	0.48
3	0.22	0.23	0.24	0.23	0.29	0.28	0.28	0.28	0.35	0.35	0.35	0.35	0.43	0.43	0.44	0.43	0.48	0.48	0.49	0.49
4	0.25	0.25	0.26	0.25	0.31	0.31	0.31	0.31	0.38	0.39	0.39	0.39	0.46	0.46	0.46	0.46	0.52	0.52	0.53	0.52
5	0.28	0.28	0.29	0.28	0.39	0.4	0.39	0.39	0.46	0.45	0.44	0.45	0.52	0.51	0.52	0.52	0.65	0.64	0.64	0.64
Vit.C	0.32	0.32	0.32	0.32	0.45	0.44	0.45	0.45	0.57	0.57	0.57	0.57	0.69	0.68	0.7	0.69	0.84	0.83	0.84	0.84

Cytotoxicity Testing[19]: The results of cytotoxicity towards human red blood cells showed that the compounds **(2-5)**did not have any toxicity at the concentrations of 0.1, 0.2, 0.3, 0.4 and 0.5 mg/mL. Red blood cells have been used to detect the toxicity of prepared compounds because this method is inexpensive, easy to apply and the results can be obtained quickly. Red blood cell decomposition depends on the concentration of the material, incubation period and temperature.

Anticancer Profiles: The percentage cytotoxicity of the compounds **(2-5)** on MCF-7 at varying concentrations of 6.25, 12.5, 25, 50 and 100 µg/mL (Table 3)were determined and are shown in Table 3. It can be seen that the compound (5) shows the highest inhibition rate of 84% at a concentration of 100 µg/mL as shown in table 3. Thus, MCF-7 cells showed low viability on treatment with (5) which indicated good anticancer activities of this compound. Compound (2) was least effective on the MCF-7 cells at only 60% at a concentration of 100 µg/mL which indicated the moderate anticancer potential of this compound.

Table 3. In hibitionrate of cell growth for compounds

Comp.	Concentration i iµg/mL				
	6.25 i	**12.5 i**	**25**	**50 i**	**100**
2	21.55	25.34	44.87	52.38	60.12
3	25.66	34.89	54.87	60.57	73.94
4	29.23	38.85	56.78	62.19	77.36
5	32.06	41	69	77	84

Conclusion

Our findings indicate that all the newly synthesized pyrimidines had moderate-highantioxidant and anticancer activities. Finally, further biological investigations are needed to evaluate the potential pharmacological properties.

Conflict of Interests: Nil.

Ethical Clearance: Take from cancer Centre in Baghdad by approval ethical committee.

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