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SYNTHESIS OF DIHYDRO-PYRAZOLYL-THIAZOLINONE DERIVATIVES AS ANTICANCER AGENTS

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ABSTRACT

One-pot reaction for the synthesis of arylidene derivatives of 4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one (4a-d) involving reaction of 4, 5-dihydropyrazole-1-carbothioamide derivatives (3a-d) with chloroacetic acid and benzaldehyde in the presence of fused sodium acetate in refluxing acetic acid has been described. The synthesized compounds were characterized by microanalytical and spectral methods (MASS, FT-IR, and ^{1}H NMR) and were assessed for the anticancer activity using Sulfo-Rhodamine-B stain assay.

KEYWORDS

Chalcone, Dihydro-pyrazole, Thiazolinone, HCT-116 and Anticancer Activity.

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INTRODUCTON

Cancer is going to be the leading cause of death worldwide and affects about one third of people during their lives. Despite notable advances have been made in detection, prevention and treatment of cancer diseases, but one-half of cancer patients do not respond to therapy or relapse following initial response[1]. However, chemotherapy is still one of the primary bases for the treatment of cancer diseases. Due to the undesirable side effects of chemotherapeutic agents and emergence of drug resistance, there is an urgent need for developing new chemotherapeutic agents with more potent anti-tumor activity and high therapeutic index[2]. The pyrazoline scaffold represents a common motif in many pharmaceutical actively and remarkable

compounds demonstrating a wide range of interesting biological activities[3-10].

Moreover, literature survey has investigated the worthy of pyrazoline derivatives as anticancer against different human cancer cells[11-23].

Moreover, some of the pyrazoline derivatives had the cytotoxic activities against different human cancer cells.

On the other hand, different literature surveys demonstrated that numerous derivatives carrying thiazolinone moiety produce wide pharmacological activities specially, as anticancer potency[24-29].

In view of these facts, it was rationalized to synthesize and investigate the anticancer activity of the target compounds by combination of pyrazoline and thiazolidine moieties with placing different substituent's at position 4 of the pyrazoline moiety and introduction of arylidene in position 5 of thiazolinone moiety, aiming that these combinations may show enhanced anticancer activity.

MATERIAL AND METHODS

Chemistry

All chemicals and reagents used in the reactions were procured from Sigma-Aldrich and Fisher with purity 98% and used without further purification. The purification of the synthesized compounds was performed by recrystallization with appropriate solvent system. Melting points were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill, UK) and are uncorrected. The IR spectra (KBr, cm^{-1}) were recorded on Shimadzu IR 110 spectrophotometer (Shimadzu, Koyoto, Japan). ^{1}H-NMR spectra were recorded on a Bruker proton NMR-300 (300 MHz) (Bruker, Munuch, Germany), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard (chemical shift in ppm). Mass spectra were determined using a GC/MS Mat 112 S at 70ev spectrometer. Elemental analysis (C, H, N) were performed on Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA) at the microanalytical laboratories of the Faculty of Science, Cairo University. All compounds were within ± 0.4% of the theoretical values. All reactions were monitored by thin layer chomatograph (TLC) using precoated aluminum sheets Silica gel Merck 60 F254 and were visualized by UV lamp (Merck, Damstadt, Germany).

General Procedure for synthesis of 1-(2-hydroxy-4-methylphenyl)-3-(4-substituted-phenyl) prop-2-en-1-one (2a-d)

To a stirred solution of compound 1 (1mmol), appropriate aromatic aldehyde (1.1mmol), ethanol (30ml) and 30% NaOH (4ml) were added and the reaction mixture was stirred at room temperature for 24 hour. The mixture obtained was neutralized using dil HCl to give precipitate that were filtrated and washed carefully with water and dried. The resulting chalcones (2a-d) were purified by crystallization from ethanol.

1-(2-Hydroxy-4-methylphenyl)-3-phenylprop-2-en-1-one (2a)

Yield 67%; m.p. 90-92°C; IR (KBr, cm-1): 3423 (OH), 3088 (CH str), 1635(C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.23 (s, 1H, OH), 8.63-6.45 (m, 10H, 2H, CH=CH, 8H-Ar), 2.34 (s, 3H, CH_3). Mass m/z: 238 (M^+). Anal calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92; Found: C, 80.45; H, 6.09.

3-(4-Chlorophenyl)-1-(2-hydroxy-4-methylphenyl) prop-2-en-1-one (2b)

Yield 73%; m.p. 108-110°C; IR (KBr, cm-1): 3425 (OH), 3095 (CH str), 1640(C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 11.43 (s, 1H, OH), 8.22-6.83 (m, 9H, 2H, CH=CH, 7H-Ar), 2.35 (s, 3H, CH_3). Mass m/z: 272 (M^+). Anal calcd for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80; Found: C, 70.71; H, 4.54.

1-(2-Hydroxy-4-methylphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (2c)

Yield 70%; m.p. 127-129°C; IR (KBr, cm-1): 3444 (OH), 3105 (CH str), 1642(C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 11.98 (s, 1H, OH), 8.74-6.63 (m, 9H, 2H, CH=CH, 7H-Ar), 3.94 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). Mass m/z: 268 (M^+). Anal calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; Found: C, 76.47; H, 6.32.

3-(4-(Dimethylamino) phenyl)-1-(2-hydroxy-4-methylphenyl) prop-2-en-1-one (2d)

Yield 62%; m.p. 115-117°C; IR (KBr, cm-1): 3420(OH), 3080 (CH str), 1641(C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 12.29 (s, 1H, OH), 8.19-6.75 (m, 9H, 2H, CH=CH, 7H-Ar), 3.34 (s, 6H,

$N(CH_3)_2$), 2.34 (s, 3H, CH_3). Mass m/z: 281 (M^+). Anal calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98; Found: C, 76.99; H, 6.63; N, 5.35.

General Procedure for synthesis of 3-(2-hydroxy-4-methylphenyl)-5-(substitutedphenyl-4, 5-dihydro-1H-pyrazole-1-carbothioamide (3a-d)

To mixture of chalcone derivative 2a-d (10mmol), thiosemicarbazide (10mmol), and 10% NaOH (0.025mol, 10ml) and refluxed in ethanol (25ml) for 8-12 hrs. The resulting mixture was cooled and poured into ice-water to obtain precipitate which is filtered, dried and recrystallized from ethanol.

3-(2-Hydroxy-4-methylphenyl)-5-phenyl-4, 5-dihydropyrazole-1-carbothioamide (3a)

Yield 84%; m.p. 162-164°C; IR (KBr, cm-1): 3420(OH), 3220 (NH) 3080 (CH str), 1296(C=S). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 11.45 (s, 1H, OH), 7.85 (s, 2H, NH_2, exch. with D_2O), 7.39-6.60 (m, 10H-Ar), 5.41 (dd, 1H, C5-pyrazoline), 3.22 (dd, 1H, C4-pyrazoline), 3.21 (dd, 1H, C4-pyrazoline), 2.50 (s, 3H, CH_3). Mass m/z: 311 (M^+). Anal calcd for $C_{17}H_{17}N_3O_2S$: C, 65.57; H, 5.50; N, 13.49; Found: C, 65.87; H, 5.81; N, 13.35.

5-(4-Chlorophenyl)-3-(2-hydroxy-4-methylphenyl)-4, 5-dihydropyrazole-1-carbothioamide (3b)

Yield 85%; m.p. 195-197°C; IR (KBr, cm-1): 3430(OH), 3228 (NH) 3089 (CH str), 1295 (C=S). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 12.39 (s, 1H, OH), 7.85 (s, 2H, NH_2, exch. with D_2O), 7.42-6.70 (m, 9H-Ar), 5.43 (dd, 1H, C5-pyrazoline), 3.24 (dd, 1H, C4-pyrazoline), 3.20 (dd, 1H, C4-pyrazoline), 2.51 (s, 3H, CH_3). Mass m/z: 345 (M^+). Anal calcd for $C_{17}H_{16}ClN_3OS$: C, 59.04; H, 4.66; N, 12.15; Found: C, 59.35; H, 4.84; N, 11.97.

3-(2-Hydroxy-4-methylphenyl)-5-(4-methoxyphenyl)-4, 5-dihydropyrazole-1-carbothioamide (3c)

Yield 86%; m.p. 211-213°C; IR (KBr, cm-1): 3445 (OH), 3223 (NH) 3099 (CH str), 1296 (C=S). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 11.30 (s, 1H, OH), 7.85 (s, 2H, NH_2, exch. with D_2O), 7.44-6.66 (m, 9H-Ar), 5.40 (dd, 1H, C5-pyrazoline), 3.73 (s, 3H, OCH_3), 3.24 (dd, 1H, C4-pyrazoline), 3.20 (dd, 1H, C4-pyrazoline), 2.51 (s, 3H, CH_3). Mass m/z: 341 (M^+). Anal calcd for $C_{18}H_{19}N_3O_2S$: C, 63.32; H, 5.61; N, 12.31; Found: C, 63.56; H, 5.54; N, 12.63.

5-(4-(Dimethylamino) phenyl)-3-(2-hydroxy-4-methylphenyl)-4, 5-dihydropyrazole-1-carbothioamide (3d)

Yield 73%; m.p. 183-185°C; IR (KBr, cm-1): 3430 (OH), 3227 (NH) 3090 (CH str), 1296 (C=S). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 10.30 (s, 1H, OH), 7.85 (s, 2H, NH_2, exch. with D_2O), 7.49-6.68 (m, 9H-Ar), 5.40 (dd, 1H, C5-pyrazoline), 3.37 (s, 6H, $N(CH_3)_2$), 3.24 (dd, 1H, C4-pyrazoline), 3.20 (dd, 1H, C4-pyrazoline), 2.51 (s, 3H, CH_3). Mass m/z: 345 (M^+). Anal calcd for $C_{19}H_{22}N_4OS$: C, 64.38; H, 6.26; N, 15.81; Found: C, 64.71; H, 6.43; N, 16.04.

General Procedure for synthesis of 5-benzylidene-2-(5-(4-substitutedphenyl)-3-(2-hydroxy-4-methylphenyl)-4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one (4a-d)

A mixture of the respective 3a-d (2mmol), chloroacetic acid (0.19g, 2mmol), anhydrous sodium acetate (0.17g, 2mmol), and the appropriate aromatic aldehyde (2.4mmol) in glacial acetic acid (10ml) was heated under reflux for 15 hours. The reaction mixture was cooled and poured gradually into crushed ice. The resulting solid product was filtered and recrystallized from a acetic acid-water.

5-benzylidene-2-(3-(2-hydroxy-4-methylphenyl)-5-phenyl-4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one (4a)

Yield 79%; m.p. 251-253°C; IR (KBr, cm-1): 3470(OH), 3224 (NH) 3100 (CH str), 1695 (C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 11.38 (s, 1H, OH), 8.12-6.70 (m, 14H, 13H, Ar-H and 1H, benzylidene), 5.85 (dd, 1H, C5-pyrazoline), 3.77 (dd, 1H, C4-pyrazoline), 3.71 (dd, 1H, C4-pyrazoline), 2.51 (s, 3H, CH_3). Mass m/z: 439 (M^+). Anal calcd for $C_{26}H_{21}N_3O_2S$: C, 71.05; H, 4.82; N, 9.56; Found: C, 71.32; H, 4.62; N, 9.85.

5-benzylidene-2-(5-(4-chlorophenyl)-3-(2-hydroxy-4-methylphenyl)-4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one (4b)

Yield 80%; m.p. 223-225°C; IR (KBr, cm-1): 3476(OH), 3220 (NH) 3996 (CH str), 1695 (C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 12.02 (s, 1H, OH), 8.08-6.65 (m, 13H, 12H, Ar-H and 1H, benzylidene), 5.80 (dd, 1H, C5-pyrazoline), 3.75

(dd, 1H, C4-pyrazoline), 3.70 (dd, 1H, C4-pyrazoline), 2.50 (s, 3H, CH_3). Mass m/z: 473 (M^+). Anal calcd for $C_{26}H_{20}ClN_3O_2S$: C, 65.89; H, 4.25; N, 8.87; Found: C, 65.59; H, 4.47; N, 8.75.

5-benzylidene-2-(3-(2-hydroxy-4-methylphenyl)-5-(4-methoxyphenyl)-4, 5-dihydropyra-zol-1-yl) thiazol-4(5H)-one (4c)

Yield 77%; m.p. 204-206°C; IR (KBr, cm-1): 3456(OH), 3231 (NH) 3991 (CH str), 1693 (C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 12.02 (s, 1H, OH), 8.04-6.60 (m, 13H, 12H, Ar-H and 1H, benzylidene), 5.80 (dd, 1H, C5-pyrazoline), 3.94 (s, 3H, OCH_3), 3.73 (dd, 1H, C4-pyrazoline), 3.69 (dd, 1H, C4-pyrazoline), 2.51 (s, 3H, CH_3). Mass m/z: 469 (M^+). Anal calcd for $C_{26}H_{20}ClN_3O_2S$: C, 69.06; H, 4.94; N, 8.95; Found: C, 69.35; H, 4.67; N, 9.13.

5-benzylidene-2-(5-(4-(dimethylamino) phenyl)-3-(2-hydroxy-4-methylphenyl)-4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one (4d)

Yield 68%; m.p. 168-170°C; IR (KBr, cm-1): 3470 (OH), 3222 (NH) 3989 (CH str), 1694 (C=O). ^{1}H-NMR (DMSO-$_{d6}$) δ (ppm): 11.89 (s, 1H, OH), 8.45-6.79 (m, 13H, 12H, Ar-H and 1H, benzylidene), 5.78 (dd, 1H, C5-pyrazoline), 3.37 (s, 6H, $N(CH_3)_2$), 3.71 (dd, 1H, C4-pyrazoline), 3.84 (dd, 1H, C4-pyrazoline), 3.35 (s, 6H, $N(CH_3)_2$), 2.51 (s, 3H, CH_3). Mass m/z: 482 (M^+). Anal calcd for $C_{26}H_{20}ClN_3O_2S$: C, 69.69; H, 5.43; N, 11.61; Found: C, 69.51; H, 5.71; N, 11.40.

***In vitro* anticancer activity**

The *in vitro* anticancer activity was measured for the synthesized compounds (3a-d) and (4a-d) on human colon cancer cell line (HCT-116) using the Sulfo-Rhodamine-B stain (SRB) assay[30]. The *in vitro* anticancer screening was done by the pharmacological unit at the national cancer institute, Cairo University.

Cells were plated in 96-multiwell microtiter plate (10^4cells/well) for 24hour before treatment with the test compound to allow attachment of cells to the wall of the plate. Test compounds were dissolved in DMSO and diluted with saline to the appropriate volume. Different concentrations of the compound under test (0, 5, 12.5, 25, and 50µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the tested compounds for 48 h at 37ºC and in an atmosphere of 5% CO_2. After 48 hour, cells were fixed, washed, and stained for 30 min with 0.4% (wt/vol) SRB dissolved in 1% acetic acid. Excess unbound dye was removed by four washes with 1% acetic acid and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an ELISA reader at a wavelength of 570nm. The relation between surviving fraction and drug concentration is plotted to get the survival curve for breast tumor cell line after the specified time. The molar concentration required for 50% inhibition of cell viability (IC_{50}) was calculated. Doxorubicin was used as reference drug. The results are listed in (Table No.1).

RESULTS AND DISCUSSION

Chemistry

The synthetic route employed in the synthesis of the targeted compounds is represented in Scheme No.1 and Scheme No.2. 4-Methyl-2-hydroxyacetophenone (1) was obtained according the reported methods[31-33] .

The chalcone derivatives (2a-d) were prepared by Claisen-Schmidt condensation of the 4-methyl-2-hydroxyacetophenone (1) with appropriate aromatic aldehydes in 30% ethanolic NaOH solution[34,35].

The structures of all the synthesized compounds were confirmed by their microanalytical and spectral data. The IR spectra of the compounds (2a-d) showed appearance of bands around 1640 cm^{-1} attributed to the α, β-unsaturated carbonyl group. ^{1}H NMR spectra for compounds (2a-d) showed the appearance of the H-α and H-β protons of chalcones that occur aromatic protons in the ranges 6.45-8.74ppm.

Chalcone derivatives 2a-d allowed to react with thiosemicarbazide in 10% ethanolic NaOH to furnish the corresponding 4, 5-dihydropyrazole-1-carbothioamide derivatives 3a-d[36].

The IR spectra of compounds (3a-d) showed appearance of bands around 3225 1295cm^{-1} attributed to the (NH_2) and (C=S) groups respectively. ^{1}H NMR spectra for compound (3a-d) showed the appearance of three doublet of doublets around 5.40, 3.24 and 3.20ppm for pyrazoline

protons at carbon-5, carbon-4, and carbon-4 respectively. In addition, ^{1}H NMR spectra for compounds (3a-d) showed the appearance of amino protons as singlet at 7.85ppm. The compounds 4a-d were obtained from 4, 5-dihydropyrazole-1-carbothioamide derivatives (3a-d) in two consecutive steps involving cyclization with chloroacetic acid in the presence of and fused sodium acetate in refluxing acetic acid to give the intermediate 4, 5-dihydropyrazol- 1-yl) thiazol-4(5H)-ones followed by condensation with different benzaldehyde[37]. Alternatively, arylidene derivatives of 4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one (4a-d) were prepared by one-pot synthesis involving reaction of 4,5-dihydropyrazole-1-carbothioamide derivatives (3a-d) with chloroacetic acid and benzaldehyde in the presence of fused sodium acetate in refluxing acetic acid[38].

The IR spectra of compounds (4a-d) showed appearance of bands around 1694cm^{-1} attributed to (C=O) group, alongside with disappearance of bands of the (NH_2) and (C=S) groups. ^{1}H NMR spectra for compound (4a-d) showed the appearance of the benzylidene protons at aromatic region and disappearance of singlet of amino protons.

***In vitro* anticancer activity**

The compounds 3a-d and 4a-d were evaluated for their *in vitro* cytotoxic activity against human colon cancer cell line (HCT-116).

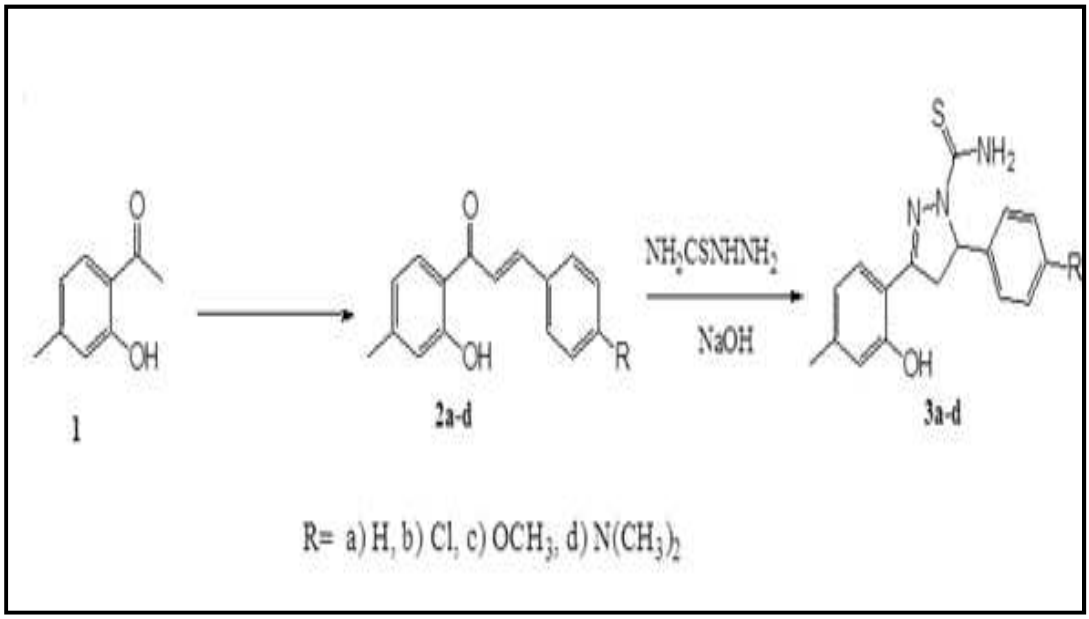
Doxorubicin, which is one of the most effective anti-cancer agents, was used as a reference drug in this study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of human colon cancer cell line (HCT-116). The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. Table No.1 showed the *in vitro* cytotoxic activity of the compounds 3a-3d and 4a-d, where compounds exhibited moderate to good activity compared to the reference drug.

From the results in Table No.1, it was found that the p-chloro derivative 3b (IC_{50} = 0.055µM/ml) and the p-methoxy derivative 3c (IC_{50} = 0.058µM/ml) of the 4, 5-dihydropyrazole-1-carbothioamides exhibited good cytotoxic activities when compared with the reference drug doxorubicin (IC_{50} = 0.010µM/ml). While unsubstituted derivative 3a (IC_{50} = 0.055µM/ml) and dimethylamino derivative 3d (IC_{50} = 0.055µM/ml) showed lower IC_{50} values than that of the reference drug.

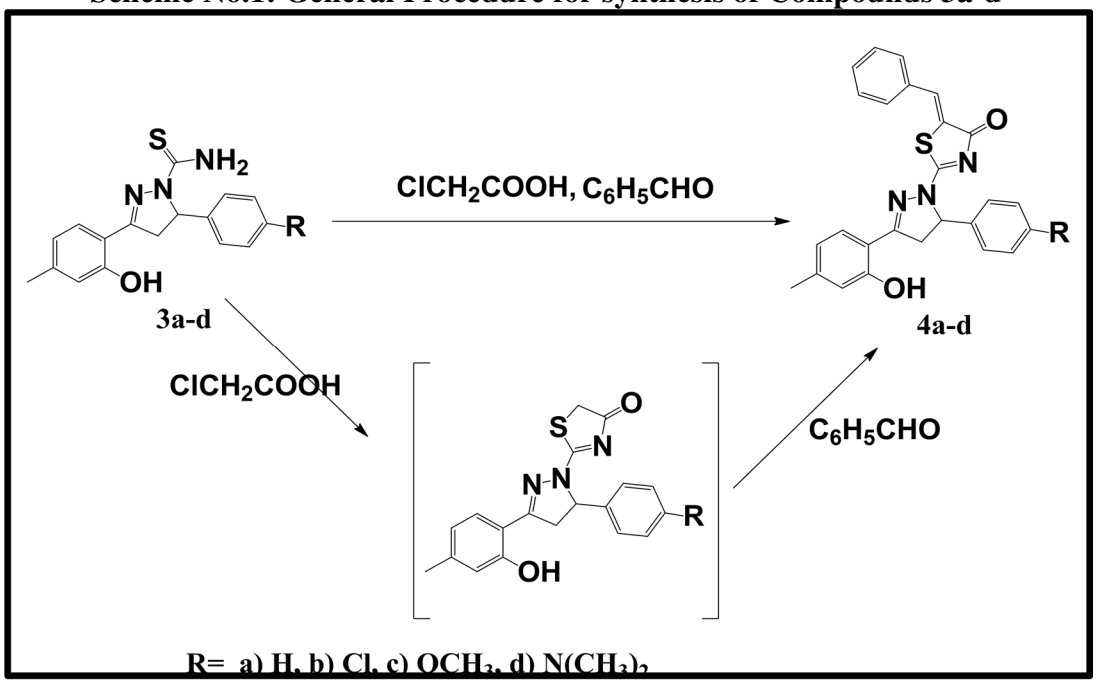
On the other hand, the cyclization of 3a-d into to the corresponding 4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one with introduction of arylidene 4a-d resulted in increasing the cytotoxic activity in all compounds with IC_{50} ranges 0.013-0.127µM/ml. The p-methoxy derivative 4c (IC_{50} = 0.018µM/ml) showed slightly lower IC_{50} values than that of the reference drug. While, the p-chloro derivative 4b (IC_{50} = 0.013µM/ml) is nearly as active as the reference drug doxorubicin (IC_{50} = 0.010µM/ml).

Table No.1: *In vitro* cytotoxic activity of the compounds 3a-d and 4a-d

S.No	Compound No.	IC_{50} (µM/ml)	Compound No.	IC_{50} (µM/ml)
1	3a	0.210	4a	0.127
2	3b	0.055	4b	0.013
3	3c	0.058	4c	0.018
4	3d	0.153	4d	0.045
5	Doxorubicin	0.010	Doxorubicin	0.010



Scheme No.1: General Procedure for synthesis of Compounds 3a-d



Scheme No.2: General Procedure for the synthesis of Compounds 4a-d

CONCLUSION

It can be concluded that the present work for the synthesis of arylidene derivatives of 4, 5-dihydropyrazol-1-yl) thiazol-4(5H)-one (4a-d) via cyclization and condensation is simple and one pot reaction synthesis. The compounds (3a-d) and (4a-d) displayed moderate to good anticancer activity with the best compound 4b which was nearly similar to the reference drug doxorubicin.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

BIBILIOGRAPHY

1. Grant S K. Therapeutic protein kinase inhibitors, *Cellular and Molecular Life Science,* 66 (7), 2009, 1163-1177.
2. Riedl S, Zweytick D, Lohner K. Membrane-active host defense peptides Challenges and perspectives for the development of novel anticancer drugs, *Chemistry and Physics of Lipids,* 164(8), 2009, 766-781.
3. Mohamed A A, Mohammad S, Anees A S. Synthesis, structural activity relationship and anti-tubercular activity of novel pyrazoline derivatives, *Euro Jour of Medic Chemis,* 42(2), 2007, 268-275.
4. Braulio I, Juan R, Diana B, Carlos E, Jairo Q, Rodrigo A, *et al*. An efficient synthesis of new caffeine-based chalcones, pyrazolines and pyrazolo [3, 4-b] [1, 4] diazepines as potential antimalarial, anti-trypanosomal and anti-leishmanial agents, *European Journal of Medicinal Chemistry,* 93C(C), 2015, 401-413.
5. Bhat R A, Fareeda A, Amir A. Bis-pyrazolines: Synthesis, characterization and anti-amoebic activity as inhibitors of growth of Entamoeba histolytica, *European Journal of Medicinal Chemistry,* 44(1), 2009, 426-431.
6. Flora F B, Hanaa M H, Adel S G. Novel bis (1-acyl-2-pyrazolines) of potential anti-inflammatory and molluscicidal properties, *Bioorganic and Medicinal Chemistry,* 14(11), 2006, 3929-3237.
7. Reddy M V R, Vinay K B, Venkat R P, Muralidhar R M, Rengasamy B, Jerome L G, *et al*. Design, synthesis, and biological evaluation of 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) inhibitors, *Bioorganic and Medicinal Chemistry,* 16(7), 2008, 3907-3916.
8. Minmin Y, Hui Y, Kaihua W, Ying J, Lili J, Xiaoyuan L. Novel pyrazoline derivatives as bi-inhibitor of COX-2 and B-Raf in treating cervical carcinoma, *Bioorganic and Medicinal Chemistry,* 22(15), 2014, 4109-4118.
9. Syed O, Pushpalatha H, Reddy G B, Pooja R, Rafia B, Shafiya Y, *et al*. Synthesis and biological evaluation of some new pyrazoline substituted benzenesulfonylurea/thiourea derivatives as anti-hyperglycaemic agents and aldose reductase inhibitors, *European Journal of Medicinal Chemistry,* 80, 2014, 209-217.
10. Zafer A K, Ahmet O, Gulhan T, Mehlika D A, Ozgur D C. New pyrazoline derivatives and their antidepressant activity, *European Journal of Medicinal Chemistry,* 45(9), 2010, 4383-4387.
11. Rafia B, Syed O, Shafiya Y, Hinna H, Alam M S, Mohammad S, *et al*. Synthesis of some new 1, 3, 5-trisubstituted pyrazolines bearing benzene sulfonamide as anticancer and anti-inflammatory agents, *Bioorganic and Medicinal Chemistry Letters,* 21(14), 2011, 4301-4305.
12. Koca I, Ozgur A, Coskun K A, Tutar Y. Synthesis and anticancer activity of acyl thioureas bearing pyrazole moiety, *Bioorganic and Medicinal Chemistry,* 21(13), 2013, 3859-3865.
13. Lv P C, Li H Q, Sun J, Zhou Y, Zhu H L.

Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents, *Bioorganic and Medicinal Chemistry,* 18(13), 2010, 4606-4614.

14. Bhat B A, Dhar K L, Puri S C, Saxena A K, Shanmugavel M, Qazi G N. Synthesis and biological evaluation of chalcones and their derived pyrazoles as potential cytotoxic agents, *Bioorganic and Medicinal Chemistry Letters,* 15(12), 2005, 3177-3180.
15. Fadi M A, Gary A P, Bernard D G, Adam B K, Joshua C C. Synthesis of some dihydropyrimidine-based compounds bearing pyrazoline moiety and evaluation of their antiproliferative activity, *European Journal of Medicinal Chemistry,* 70, 2013, 273-279.
16. Qing-Shan L, Xian-Hai L, Yan-Bin Z, Jing-Jun D, Wen-Ping Z, Yang Y, Hai-Liang Z. Identification of novel 3, 5-diarylpyrazoline derivatives containing salicylamide moiety as potential anti-melanoma agents, *Bioorganic and Medicinal Chemistry Letters,* 22(21), 2012, 6596-6601.
17. Braulio I, Alba M, Diana B, Jairo Q, Rodrigo A, Sara R, *et al*. Synthesis of novel analogs of 2-pyrazoline obtained from [(7-chloroquinolin-4-yl)amino] chalcones and hydrazine as potential antitumor and antimalarial agents, *European Journal of Medicinal Chemistry,* 67(C), 2013, 252-262.
18. Mohammad S, Abdullah M M, Bakht M A, Jaseela M. Pyrazoline bearing benzimidazoles: Search for anticancer agent, *European Journal of Medicinal Chemistry,* 45(1), 2010, 114-119.
19. Pooja R, Shafiya Y, Syed O, Rafia B, Raed Y, Alhamzah D H, *et al.* Synthesis and evaluation of some new pyrazoline substituted benzenesulfonylureas as potential antiproliferative agents, *Bioorganic and Medicinal Chemistry Letters,* 24(7), 2014, 1685-1691.
20. Soon Y S, Hyuk Y, Doseok H, Seunghyun A, Dong-Wook K, Dongsoo K, *et al.* Benzochalcones bearing pyrazoline moieties show anti-colorectal cancer activities and selective inhibitory effects on aurora kinases, *Bioorganic and Medicinal Chemistry,* 21(22), 2013, 7018-7024.
21. Peng-Cheng L, Huan-Qiu L, Juan S, Yang Z, Hai-Liang Z. Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents, *Bioorganic and Medicinal Chemistry,* 18(13), 2010, 4606-4614.
22. Wen Y, Yang H, Yu-Shun Y, Fei Z, Yan-Bin Z, Xiao-Liang W, *et al*. Design, modification and 3D QSAR studies of novel naphthalin-containing pyrazoline derivatives with/without thiourea skeleton as anticancer agents, *Bioorganic and Medicinal Chemistry,* 21(5), 2013, 1050-1063.
23. Kamilia M A, Amal A M E, Sahar M A, Fadi M A, Ghaneya S H. Synthesis and biological evaluation of novel coumarin-pyrazoline hybrids endowed with phenylsulfonyl moiety as antitumor agents, *European Journal of Medicinal Chemistry,* 60, 2013, 187-198.
24. Hai-Hong W, Ke-Ming Q, Hong-En C, Yu-Shun Y, Yin L, Man X, *et al*. Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives containing benzodioxole as potential anticancer agents, *Bioorganic and Medicinal Chemistry,* 21(2), 2013, 448-455.
25. Dmytro H, Borys Z, Olexandr V, Lucjusz Z, Andrzej G, Roman L. Synthesis of novel thiazolone-based compounds containing pyrazoline moiety and evaluation of their anticancer activity, *European Journal of Medicinal Chemistry,* 44(4), 2009, 1396-1404.
26. Yuan J W, Wang S F, Luo Z L, Qiu H Y, Wang P F, Zhang X, *et al*. Synthesis and biological evaluation of compounds which contain pyrazole, thiazole and naphthalene ring as antitumor agents, *Bioorganic and Medicinal Chemistry Letters,* 24(10), 2014, 2324-2328.

27. Lombardo L J, Lee F Y, Chen P, Norris D, Barrish J C, Behnia K, *et al*. Discovery of N-(2-Chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimid-in-4-ylamino) thiazole-5-carboxamide (BMS-354825), a Dual Src/Abl Kinase Inhibitor with potent antitumor activity in preclinical assays, *Journal of Medicinal Chemistry,* 47(27), 2004, 6658-6661.
28. Lu Y, Li C M, Wang Z, Ross C R, Chen J, Dalton J T, *et al*. Discovery of 4-Substituted Methoxybenzoyl-arylthiazole as Novel Anticancer Agents: synthesis, biological evaluation, and structure-activity relationships, *Journal of Medicinal Chemistry,* 52(6), 2009, 1701-1711.
29. Lv P C, Li D D, Li Q S, Lu X, Xiao Z P, Zhu H L. Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives as EGFR TK inhibitors and potential anticancer agents, *Bioorganic and Medicinal Chemistry Letters,* 21(18), 2011, 5374-5377.
30. Skehan P, Storeng R, Scudiero D, *et al*. New colorimetric cytotoxicity assay for anticancer drug screening, *Journal of the National Cancer Institute,* 82(13), 1990, 1107-1112.
31. Burdeska K. Uber 4, 6- disubstituted 2-aminophenol, *Synthesis,* 1982(11), 1982, 940-942.
32. Cullinane N M, Edwards B F R. The Fries rearrangement part V. Effect of the ring substituents and the acyl group, *Journal of Chemical Society,* 1958, 2926-2929.
33. Sandner M R, Hedaya E, Treker D J. Mechanistic studies of the photo-Fries reaction, *Journal of American Chemical Society,* 90(26), 1968, 7249-7254.
34. Seo W D, Kim J H, Kang J E, Ryu H W, Marcus J, Long C, *et al*. Sulfonamide chalcone as a new class of α-glucosidase inhibitors, *Bioorganic and Medicinal Chemistry Letters,* 15(24), 2005, 5514-5516.
35. Dominguez J N, Leon C, Rodrigues J, de Domínguez N G, Gut J, Rosenthal P J. Synthesis and evaluation of new antimalarial phenylurenyl chalcone derivatives, *Journal of Medicinal Chemistry,* 48(10), 2005, 3654-3658.
36. Peng-Cheng L, Huan-Qiu L, Juan S, Yang Z, Hai-Liang Z. Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents, *Bioorganic and Medicinal Chemistry,* 18(13), 2010, 4606-4614.
37. Yu-Shun Y, Qing-Shan L, Shuai S, Yan-Bin Z, Xiao-Liang W, Fei Z. Design, modification and 3D QSAR studies of novel 2,3-dihydrobenzo [b] [1, 4] dioxin-containing 4, 5-dihydro-1H-pyrazole derivatives as inhibitors of B-Raf kinase, *Bioorganic and Medicinal Chemistry,* 20(20), 2012, 6048-6058.
38. Dmytro H, Borys Z, Olexandr V, Lucjusz Z, Andrzej G, Roman L. Synthesis of novel thiazolone-based compounds containing pyrazoline moiety and evaluation of their anticancer activity, *European Journal of Medicinal Chemistry,* 44(4), 2009, 1396-1404.

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