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# SYNTHESIS OF SOME CHALCONES AND PYRAZOLINES CONTAINING B-NAPHTHOL AS ANTICANCER AGENTS

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**ABSTRACT**

A series of pyrazolines **(5a-d)** were synthesized by reaction of chalcones **(4a-d)** with thiosemicarbazide. The pyrazoline **(5b)** ($IC_{50,}$ 8.02) showed moderate anticancer activity (IC50= 8.02 µM) when compared to standard drug doxorubicin (IC50= 5.04 µM).

**KEYWORDS:** Chalcone, pyrazoline, thioamide, β-naphthol, anticancer.

## INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer among women.[1] The development of resistance against the existing anticancer drugs[2] in addition to the general toxicity chemotherapeutics which can severely limit the therapeutic value of these drugs[3] Therefore, the identification of novel structures with potent, selective, and less toxic anticancer agents is still a major challenge to medicinal chemistry researchers.

Some chalcones manifested potent selective cytotoxicity against human breast cancer cell lines MCF-7[4-6] Many pyrazoline derivatives have been reported to possess antitumor and anti-proliferative potential.[7-28] From the above findings, it seemed of interest to synthesize naphthyl nucleus carrying a biologically active chalcone and pyrazoline moieties to be evaluated as potential anticancer agents against human cancer cell line (MCF-7).

## RESULTS AND DISCUSSION

### Chemistry

The targeted compounds were synthesized vai the routes illustrated in scheme 1. Naphthalen-2-yl acetate**[2]** by heating of β-naphthol with acetic anhydride in sodium hydroxide solution[29] which upon heating at 165-170°C in an oil bath in the presence of anhydrous aluminium chloride (fries rearrangement) produced **1-(1-hydroxynaphthalen-2-yl)ethanone.[3]**

chalcones 4**(a-d)** were prepared by condensation of the compound**[3]** with the required benzaldehyde. Cyclization of chalcones 4**(a-d)** with thiosemicarbazide in alkaline medium furnished the corresponding dihydropyrazole-1-carbothioamide 5**(a-d) scheme.1**.

### Anticancer Activity

It was obvious that the nature of pharmacophores at positions 4 of phenyl moeity of chalcones and pyrazolines have clear effect on the cytotoxic activity as shown in table.2.

It was noticed that the series of chalcones **4a**, **4b, 4c** and **4d** showed moderate cytotoxic activity ($IC_{50}$ 19.12, 12.06, 16.40 and 15.32 µM respectively) in compared to the reference standard doxorubicin ($IC_{50,}$ 5.04 µM). The derivative **4b** with p-chlorophenyl substituent showed the best activity within the series of chalcones.

Cyclization of chalcones **4a-d** into to the corresponding pyrazoline thioamide moieties **5a-d** resulted in an improved in activity in all compound specially the compound **5b** which has p-chlorophenyl substituent ($IC_{50,}$ 8.02 µM).

## EXPERIMENTAL

### Chemistry

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 Aluminium sheets Silica gel Merck 60 F254 and were visualized by UV lamp (Merck, Damstadt, Germany).

**Naphthalen-2-yl acetate (2)**
The naphthalen-2-yl acetate (2) was synthesized according to the previously reported method (m.p. 123°C).[29]

**1-(1-Hydroxynaphthalen-2-yl)ethanone (3)**
Naphthalen-2-yl acetate **(2)** (1 mmol) was added dropwise to anhydrous $AlCl_3$ slowly (4 mmol) and the mixture was heated at 165-170°C for 3 hrs in oil bath. The cooled reaction mixture was decomposed with crushed ice and diluted hydrochloric acid. The resulting solution was extracted with ethylacetate (3×20ml). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to obtain solid which was filtered, dried and crystallized from an ethanol to give compounds **3.**

Compound **3**; M.p: 49 °C; Yield: 90 %; I.R (**KBr,** $cm^{-1}$): 3431 (OH), 3050 (CH, aromatic), 2927 (CH, aliphatic), 1755 (C=O); 1H NMR (300 MHz, DMSO-d) ppm: 3.03 (s, 3H, $CH_3$), 5.04 (s, 1H, OH, $D_2O$ exchangeable), 7.41-8.44 (m, 6H, naphtyl-H).

**General procedure for synthesis of: 1-(2-hydroxynaphthalen-1-yl)-3-substituted phenylprop-2-en-1-one. 4(a-d)**
**The titled compounds were synthesized according to scheme. 1**
To Compound **(3)** (1.86 g, 10 mmol), benzaldehyde derivative (12 mmol), ethanol (40 ml) and 30% aqueous NaOH solution (20 ml) were added. The reaction mixture stirred for 24 hrs at room temperature and neutralized with diluted HCl and ice water with stirring to obtain precipitate, which was filtrated, dried and recrystallized from ethanol to give **compounds 4a-d** as shown in (table 1).

Compound **4a**; IR (KBr, $cm^{-1}$): 3420 (OH), 3041 (CH, aromatic), 2933 (CH, aliphatic), 1633 (C=O). $^1$HNMR (300 MHz, DMSO-d) ppm: 5.04 (s, 1H, OH, $D_2O$ exchangeable), 6.70-6.75 (dd, 2H, *J*=15.3 Hz, α-olefinic proton and phenyl H-6), 7.30-7.45 (dd, 2H, *J*=15.3 Hz, β-olefinic proton and phenyl H-4), 7.76-8.29 (m, 11H, phenyl-H, naphtyl-H); MS: m/z (%) = 274 (20.40).

Compound **4b**; IR (KBr, $cm^{-1}$): 3423 (OH), 3044 (CH, aromatic), 2935 (CH, aliphatic), 1636 (C=O). $^1$HNMR (300 MHz, DMSO-d) ppm: 5.03 (s, 1H, OH, $D_2O$ exchangeable), 6.69-6.77 (dd, 2H, *J*=15.3 Hz, α-olefinic proton and phenyl H-6), 7.31-7.42 (dd, 2H, *J*=15.3 Hz, β-olefinic proton and phenyl H-4), 7.78-8.21 (m, 10H, phenyl-H, naphtyl-H); MS: m/z (%) = 308 (16.70).

Compound **4c**; IR (KBr, $cm^{-1}$): 3424 (OH), 3040 (CH, aromatic), 2930 (CH, aliphatic), 1640 (C=O). $^1$HNMR (300 MHz, DMSO-d) ppm: 3.90 (s, 3H, $OCH_3$), 5.02 (s, 1H, OH, $D_2O$ exchangeable), 6.67-6.73 (dd, 2H, *J*=15.3 Hz, α-olefinic proton and phenyl H-6), 7.20-7.36 (dd, 2H, *J*=15.3 Hz, β-olefinic proton and phenyl H-4), 7.74-8.17 (m, 10H, phenyl-H, naphtyl-H); MS: m/z (%) = 304 (12.16).

Compound **4d**; IR (KBr, $cm^{-1}$): 3422 (OH), 3038 (CH, aromatic), 2930 (CH, aliphatic), 1638 (C=O). $^1$HNMR (300 MHz, DMSO-d) ppm: 2.85 (s, 6H, $N(CH_3)_2$), 5.01 (s, 1H, OH, $D_2O$ exchangeable), 6.57-6.65 (dd, 2H, *J*=15.3 Hz, α-olefinic proton and phenyl H-6), 7.17-7.29 (dd, 2H, *J*=15.3 Hz, β-olefinic proton and phenyl H-4), 7.65-8.12 (m, 10H, phenyl-H, naphtyl-H); MS: m/z (%) = 317 (30.13).

**General procedure for synthesis of: 3-(2-hydroxynaphthalen-1-yl)-5-phenyl-4,5-dihydropyrazole-1-carbothioamide. 5(a-d)**
**The titled compounds were synthesized according to scheme. 1**
Chalcone derivative **4a-d** (1 mmol), thiosemicarbazide (1.2 mmol) and 10 % NaOH (0.025 mole, 10 ml) were refluxed in ethanol (25 ml) for 6-8 hrs. The resulting mixture was cooled and poured into ice-water to produce precipitate, which was filtrated, dried and recrystallized from ethanol to obtain compounds **5(a-d)** as shown in (table 1).

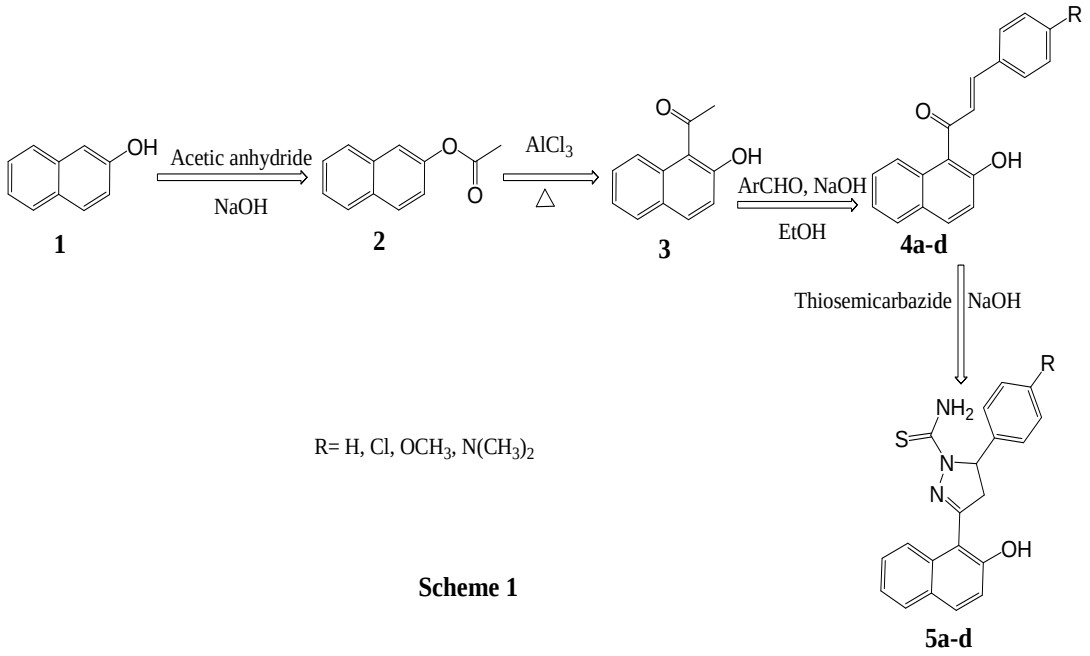
Compound **5a**; IR (KBr, $cm^{-1}$): 3483 (OH), 3223 (NH), 3039 (CH, aromatic), 2934 (CH, aliphatic), 1620 (NH), 1296 (C=S); $^1$HNMR (300 MHz, DMSO-d) ppm: 3.03 (dd, 1H, C4-$H_a$ pyrazoline), 4.02 (dd, 1H, C4-$H_b$pyrazoline), 5.02 (s, 1H, OH, $D_2O$ exchangeable), 5.88 (dd, 1H, C5-$H_x$pyrazoline), 7.62-8.22 (m, 11H, phenyl-H, naphtyl-H); MS: m/z (%) = 347 (41.50).

Compound **5b**; IR (KBr, $cm^{-1}$): 3480 (OH), 3220 (NH), 3037 (CH, aromatic), 2933 (CH, aliphatic), 1620 (NH), 1294 (C=S); $^1$HNMR (300 MHz, DMSO-d) ppm: 3.04 (dd, 1H, C4-$H_a$ pyrazoline), 4.03 (dd, 1H, C4-$H_b$pyrazoline), 5.04 (s, 1H, OH, $D_2O$ exchangeable), 5.89 (dd, 1H, C5-$H_x$pyrazoline), 7.64-8.25 (m, 10H, phenyl-H, naphtyl-H); MS: m/z (%) = 381 (32.30).

Compound **5c**; IR (KBr, $cm^{-1}$): 3482 (OH), 3221 (NH), 3036 (CH, aromatic), 2934 (CH, aliphatic), 1622 (NH), 1295 (C=S); $^1$HNMR (300 MHz, DMSO-d) ppm: 3.02 (dd, 1H, C4-$H_a$ pyrazoline), 4.03 (dd, 1H, C4-$H_b$pyrazoline), 3.94 (s, 3H, $OCH_3$), 5.03 (s, 1H, OH, $D_2O$ exchangeable), 5.86 (dd, 1H, C5-$H_x$pyrazoline), 7.60-8.21 (m, 10H, phenyl-H, naphtyl-H); MS: m/z (%) = 377 (20.23).

Compound **5d**; IR (KBr, $cm^{-1}$): 3484 (OH), 3222 (NH), 3037 (CH, aromatic), 2936 (CH, aliphatic), 1621 (NH), 1296 (C=S); $^1$HNMR (300 MHz, DMSO-d) ppm: 2.84 (s, 6H, $N(CH_3)_2$), 3.02 (dd, 1H, C4-$H_a$ pyrazoline), 4.01

(dd, 1H, C4-$H_b$pyrazoline), 5.02 (s, 1H, OH, $D_2O$ exchangeable), 5.85 (dd, 1H, C5-$H_x$pyrazoline), 7.60-8.18 (m, 10H, phenyl-H, naphtyl-H).; MS: m/z (%) = 390 (42.21).




**Scheme 1**

**Table 1: 1-(2-Hydroxynaphthalen-1-yl)-3-Substituted Phenylprop-2-en-1-One. 4(a-d) and 3-(2-Hydroxynaphthalen-1-yl)-5-Phenyl-4,5-Dihydropyrazole-1-Carbothioamide. 5(a-d).**

| Comp. No. | R | M.F. (M.W.) | M.p. (°C) | Yield (%) | % analysis of C, H, N (Calcd./ found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| 4a | H | $C_{19}H_{14}O_2$ (274) | 76 | 83 | 83.19<br>83.49 | 5.14<br>5.45 | - |
| 4b | Cl | $C_{19}H_{13}ClO_2$ (308) | 133 | 86 | 73.91<br>74.31 | 4.24<br>4.35 | - |
| 4c | $OCH_3$ | $C_{20}H_{16}O_3$ (304) | 130 | 80 | 78.93<br>78.64 | 5.30<br>4.97 | - |
| 4d | $N(CH_3)_2$ | $C_{21}H_{19}NO_2$ (317) | 113 | 70 | 79.47<br>79.94 | 6.03<br>6.37 | 4.41<br>4.76 |
| 5a | H | $C_{20}H_{17}N_3OS$ (347) | 248 | 34 | 69.14<br>69.44 | 4.93<br>4.67 | 12.09<br>12.36 |
| 5b | Cl | $C_{20}H_{16}ClN_3OS$ (381) | 267 | 45 | 62.90<br>62.54 | 4.22<br>4.62 | 11.00<br>11.32 |
| 5c | $OCH_3$ | $C_{21}H_{19}N_3O_2S$ (377) | 263 | 48 | 66.82<br>66.53 | 5.07<br>4.91 | 11.13<br>11.22 |
| 5d | $N(CH_3)_2$ | $C_{22}H_{22}N_4OS$ (390) | 251 | 41 | 67.67<br>67.55 | 5.68<br>5.93 | 14.35<br>14.29 |

**The anticancer activities**

The synthesized compounds **(4a-d)** and **(5a-d)** were tested for their anticancer activity against MCF-7 breast cancer cell line in National Cancer Institute (Cairo, Egypt). The newly synthesized screened compounds are listed in table (2).

**Measurement of potential cytotoxicity by SRB assay in NCI (Cairo, Egypt)**

The in vitro anticancer screening was done by the pharmacology unit at the National Cancer Institute, Cairo University.

The cytotoxic activity of the synthesized compounds was measured in vitro using the Sulfo-Rhodamine-B stain (SRB) assay by the method of Skehan et al.[30]

Cells were plated in 96-multiwell microtiter plate (104 cells/ well) for 24 h before treatment with the compound (s) to allow attachment of cell 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, 1, 2.5, 5, and 10 µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose.

Monolayer cells were incubated with the compound(s) for 48 h at 37 ºC and in atmosphere of 5% $CO_2$. After 48 h, cells were fixed, washed, and stained for 30 min with 0.4% (wt/vol) with 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 at λ (570 nm) in an ELISA reader. 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 (IC50) was calculated. Doxorubicin was used as reference drug. The results are listed in table (2).

**Table. 2: Cytotoxic Activity of The Synthesized Compounds Against Mcf-7 Breast Cancer Cell Line.**

| Compound No. | $IC_{50}$ (µM) |
|---|---|
| 4a | 19.12 |
| 4b | 12.06 |
| 4c | 16.40 |
| 4d | 15.32 |
| 5a | 13.28 |
| 5b | 8.02 |
| 5c | 14.2 |
| 5d | 13.41 |
| Doxorubicin | 5.04 |

## CONCLUSION

On the basis of biological screening against the MCF7 Cell Line, the synthesized pyrazoline derivative **(5b)** showed moderate anticancer activity when compared to standard drug doxorubicin.

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