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Synthesis and Evaluation of New Pyrazoline Derivatives as Potential Anti-breast cancer Agents

Mariam Abubaker Salem *
Department of Chemistry, Faculty of Science, University of Sebha, Sebha, Libya

تحضير وتقييم مشتقات جديدة من البيرازولين كعوامل محتملة مضادة لسرطان الثدي

مريم أبوبكر سالم *
قسم الكيمياء، كلية العلوم، جامعة سبها، سبها، ليبيا

*Corresponding author: mariamabubakersalem219@gmail.com

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Abstract:
Using creative, effective anticancer therapeutics, new kinds of heteroaryl pyrazoline compounds were synthesized, designed, and studied based on their anti-proliferative effects against breast cancer cell lines. The following pyrazoline derivatives were designed and synthesized: 5-(naphthalene-2-yl)-3-(phenyl)-1-tosyl-1H-pyrazole (NAPT) and 3-(4-N,N-dimethylamino)-phenyl)-5-(naphthalene-2-yl)-1-tosyl-1H-pyrazole (DMNAPT) Using naphthyl-chalcone derivatives, pyrazoline derivatives were synthesized and were determined using IR and ^{1}H-NMR spectra. Antitumor activity was also evaluated using the MTT assay. It was discovered that the compounds synthesized from 2-naphthyl chalcones (M1 and M2) exhibited relatively better anti-proliferative activity against MCF-7 breast cancer cells. Among the compounds that were evaluated, NAPT and DMNAPT were observed to have significantly moderate anti-proliferative activity on the MCF-7.

Keywords: Synthesis, Pyrazoline derivatives, Chalcone, anti-breast cancer, Cytotoxicity assay.

الملخص
باستخدام علاجات مبتكرة وفعالة لمكافحة السرطان، تم تصنيع وتصميم ودراسة أنواع جديدة من مركبات هيتيروأريل بيرازولين بناءً على تأثيراتها المضادة للتكاثر على سلالات خلايا سرطان الثدي. صُممت ورُكّبت مشتقات بيرازولين التالية: 5-(نفثالين-2-يل)-3-(فينيل)-1-توسيل-H1-بيرازول (NAPT) و3-(N,N-4-ثنائي ميثيل أمينو)-فينيل)-5-(نفثالين-2-يل)-1-توسيل-H1-بيرازول (DMNAPT). باستخدام مشتقات نفثيل-شالكون، تم تصنيع مشتقات بيرازولين وتحديدها باستخدام أطياف الأشعة تحت الحمراء والرنين المغناطيسي النووي. كما تم تقييم النشاط المضاد للأورام باستخدام اختبار MTT. اكتُشف أن المركبات المُصنّعة من 2-نفثيل تشالكونات (M1 وM2) أظهرت نشاطًا مضادًا لتكاثر خلايا سرطان الثدي MCF-7 أفضل نسبيًا. من بين المركبات التي خضعت للتقييم، لوحظ أن NAPT وDMNAPT يتمتعان بنشاط مضاد لتكاثر الخلايا MCF-7 معتدل بشكل ملحوظ.

الكلمات المفتاحية: التحضير، مشتقات البيرازولين ، تشالكونات ، مضاد سرطان الثدي ، أختبار السمية الخلوية.

Introduction

Cancer is considered one of the world's leading global health burdens. With rising incidences every year, it is also considered one of the most serious clinical problems. Cancer leads to the death of about seven million people every year and is thus responsible for approximately 12.5% of deaths worldwide [1]. One of the relatively more general synthetic techniques for the α,β-unsaturated carbonyls (chalcone) involve the preparation by the aryl ketone's convenient Claisen-Schmidt condensation. This occurs in the presence of aryl aldehyde as well as alcoholic alkali [2]. Chalcone is a well-known precursor for the synthesis of various heterocyclic compounds. Cyclic formation of chalcone leads to the production of heterocyclic compounds with nitrogen-containing rings,

such as pyrazoline and pyrimidine [3]. The presence of the α, β-unsaturated carbonyl system allows them to be a part of the reactive addition by attacking the carbonyl group (1,2-addition) or utilizing the β-carbon (1,4-conjugate addition). These mechanisms have turned it into one of the most promising biological compounds [4], [5]. Pyrazolines can be Pyrazolines can be synthesized using a variety of methods, but one of the most common is Fischer and Knoevenagel's. This method is based on α, β-unsaturated ketones reacting with phenyl hydrazine in the presence of acetic acid and in refluxing conditions [6]. Pyrazoline is known as a cyclic hydrazine moiety and has an endocyclic double bond. It exists as a colorless liquid that boils in the 120–150°C range. Furthermore, its electron-rich nitrogen heterocyclics can undergo both reduction and oxidation [7]. In the present work, the synthesis of the pyrazoline derivatives through the cyclization of the 2-naphthyl chalcones in the presence of n-butanol using p-toluene sulfonyl hydrazide. In the present work the synthesis of pyrazoline derivatives 5-(naphthalene-2-yl)-3-(phenyl)-1-tosyl-1H-pyrazole and 3-(4-(N, N-dimethyl-amino)-phenyl)-5-(naphthalene-2-yl)-1-tosyl-1H-pyrazole. Additionally, the synthesis of 3,5-substituted bis-pyrazolines integrated with heterocyclic systems has been explored, highlighting their pharmacological importance and structural diversity, which are crucial for drug discovery [8]. a significant portion of the research in medicinal chemistry in the 21st century has focused on both natural and synthetic chalcones because of their diverse pharmacological potential, including activities and properties [9], such as antibacterial [10], antifungal [11], anti-inflammatory [12], [13], antiparasitic [14], analgesic [15], anticholinergic[16], antiplatelet [17], [18], antiepileptic[19], antiulcer [20], antidiabetic [21], antioxidant [22], [23], antimalarial [24], [25], anticancer [26], [27], [28], [29], [30], [31], [32], [33], antiviral [34], [35], antileishmanial [36], anti-schistosomula [37], [38], antidiabetic [39], [40], immunomodulatory [41], COX-2-inhibiting effects [42], aldose reductase inhibitor [43], [44], estrogen reductase inhibitor [45], acetylcholinesterase inhibitor [46], [47] Pyrazoline's cytotoxicity against the MCF-7 breast cancer cell lineage suggests that it has promising anti-breast cancer properties. pyrazoline derivatives, including this compound, have shown significant antiproliferative activity, Studies have shown that they can induce apoptosis through mechanisms such as BCL-2 inhibition and caspase-3 activation, both of which are important factors in cancer cell death pathways [48]. However, other pyrazoline-based, compounds have exhibited low-micromolar cytotoxicity, affecting multiple signaling pathways and leading to cell cycle arrest and mitochondrial dysfunction [49]. The integration of computational models and preclinical assessments supports the efficacy of pyrazole derivatives in targeting breast cancer cells, highlighting their role in reducing inflammatory cytokines and oxidative stress [50], [51]. Overall, the compound's structural properties are consistent with the known antitumor activities of pyrazoline derivatives, warranting further investigation into its therapeutic applications.

Material and methods

All solvents and starting materials were purchased and procured from commercial sources (Across, Sigma-Aldrich, and Merck). Melting points were determined via an electrothermal melting point in open capillaries. The FT-IR spectra were recorded using the Perkin Elmer 400FT-IR spectrum, model-400, with the KBr disk method. Using a Fourier Transform Nuclear Magnetic Resonance 600 MHz (model Bruker/AVANCE III 600 MHz) spectrometer, 1H and 13C NMR were recorded at 25°C. Tetramethyl silane was used as the internal standard, while DMSO-d6 or $CDCl_3$ served as the solvent. Anti-cancer measurements were done using Microsoft Excel, and GraphPad Prism was used to compute the IC50 value and culture MCF7 (ATCC HTB-22). An estrogen receptor and positive human breast adenocarcinoma cell line was bought from the American Type Culture Collection (ATCC, Manassas, Virginia, USA).

1. Synthesis of chalcone derivatives

1.1 Synthesis of benzal-β-acetylnaphthalene derivatives

To prepare these compounds using Mariam's PhD thesis[52], a β-acetonaphthalene (0.1 mol) solution was mixed with the appropriate aldehydes, benzaldehyde and dimethyl amino benzaldehyde (0.1 mol). This step was carried out using 150 ml ethanol that has been treated with 10% potassium hydroxide (20 ml) at 0°C. The resulting reaction mixture was then stirred for 3 hours. The precipitate (ppt.) produced was then collected and washed with water to give rise to compounds labelled M1 and M2. M1 has a yellow color, a melting point of 110°C, a yield of 98%, and an infrared wavelength of 3052 cm^{-1} ν (CH aromatic), ν (C=O) 1661 cm^{-1}, ν (C=C) 1626 cm^{-1}, ν (CH=CH^{-}) 1602 cm^{-1}, ν (C-O) 1174 cm^{-1}, and ν (C-C) 1049 cm^{-1} 1H NMR (DMSO-d6): δ 7-8 ppm (m, 12H, Ar-H) of H-aromatic and δ 7.45 ppm (d, 2H) of -CH=CH-. For M2, the color of M2 is orange, m.p. 115°C, yield 95%. IR of H3 is 3060 cm^{-1} ν (CH aromatic), ν (CH aliphatic) 2850 cm^{-1}, ν (C=O) 1648 cm^{-1}, ν (C=C) 1622 cm^{-1}, ν (CH=CH^{-}) 1608 cm^{-1}, ν (C-N bending) 1330 cm^{-1}, ν (C-O) 1125 cm^{-1}, and ν (C-C) 1046 cm^{-1}. . 1H NMR (DMSO-d6): δ 7-8 ppm (m, 11H, Ar-H) of H-aromatic and δ 8 ppm (d, 2H) of -CH=CH- and δ 3 ppm of (CH_3). As presented in Scheme 1 .

1. 2 Synthesis of 5-(naphthalene-2-yl)-3-(phenyl)-1-tosyl-1H-pyrazole (NAPT)

In a round bottom with a reflux condenser, a mixture of (M1) (0.01 mol) and p-toluenesulfonyl-hydrazine (0.01 mol) with (20 ml) of sodium hydroxide concentration 10% was refluxed for 5 hours in (30 ml) ethanol. The reaction mixture was allowed to cool; the precipitate was collected and recrystallized from chloroform, yielding white crystals. Yield 88%, m.p. 200°C, IR: 3032 cm^{-1} ν (-CH aromatic), 2920 cm^{-1} ν (-CH aliphatic), 1666-1624 cm^{-1} of ν (C=C), 1583 cm^{-1} ν (C=N), 1321 cm^{-1} of ν (S=O), and 1159 cm^{-1} of ν (S-O). 1H NMR (DMSO-d6): δ 7.30-8.66 ppm (m, 12H, Ar-H), 2.3 ppm (s, 3H, $-CH_3$). As shown in Scheme 1

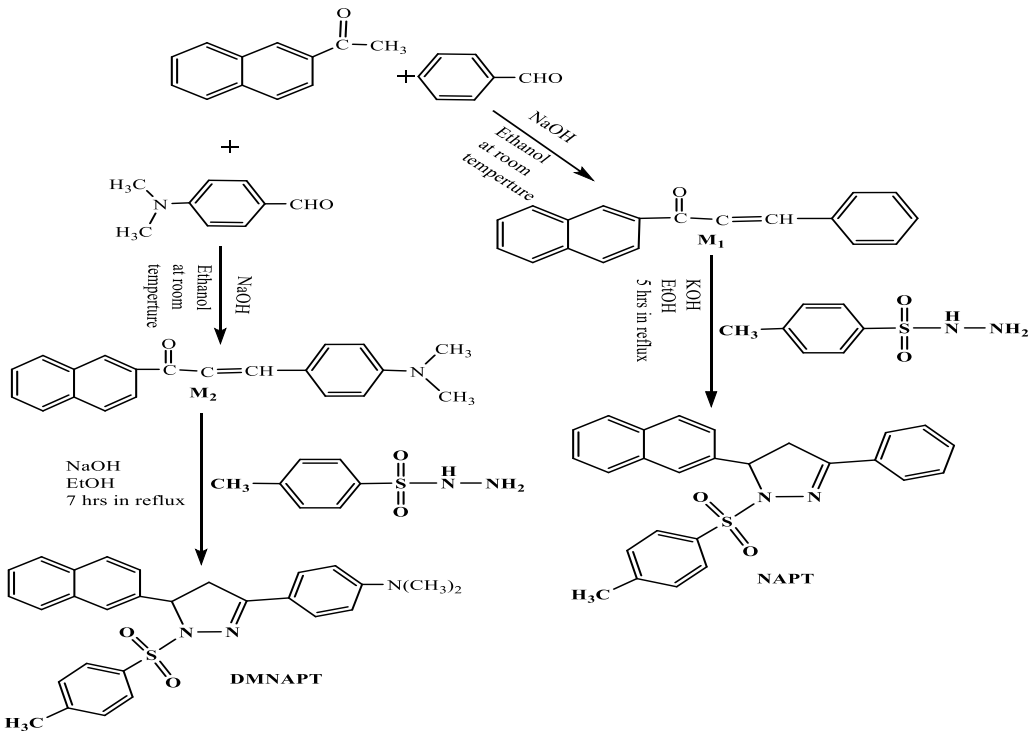
1.3 Synthesis of 3-(4-(N, N-dimethyl-amino)-phenyl) -5-(naphthalene-2-yl) -1-tosyl-1H-pyrazole (DMNAPT)

In a round bottom with a reflux condenser, a mixture of (M2) (0.01 mol), p-toluenesulfonyl-hydrazine (0.01 mol), and (35 ml) of NaOH was refluxed for 7 hours in methanol (30 ml). The reaction mixture was left to cool, and the precipitate was collected and recrystallized from chloroform to give white crystalline. Yield 90%, m.p. 190°C, IR: 3052 cm^{-1} ν (-CH aromatic), 2919 cm^{-1} ν (-CH aliphatic, CH_3), 1670-1611 cm^{-1} of ν (C=C), 1523 cm^{-1} ν (C=N), 1312 cm^{-1} of ν (S=O), and 1130 cm^{-1} of ν (S-O). 1H NMR: (DMSO-d6): δ 7.54- 8.70 ppm (m, 11H, Ar-H), 2.4 ppm (s, 3H, $-CH_3$), and 2.90 ppm ($-N(CH_3)_2$. As shown in Scheme 1

2. Cytotoxicity assay

The cytotoxicity evaluation of chalcones and pyrazoline derivatives on human cancer cell lines, including MCF-7 (human breast cancer cells), was performed by means of MTT (3-(4,5-dimethylthiazole-2yl)-2,5-diphenyl tetrazolium bromide) as a colorimetric reagent. Cell culture with the concentration of 2 x 104 cells/ml was prepared and was plated (100 µl/well) onto 96-well plates. The diluted ranges of sample extracts were added to each well with identified concentrations: 100, 50, 25, 12.5, 6.25, 3.13, and 1.56 µg/mL, incubated for 72 hrs. The MTT solution was added to the cells at the end of the incubation samples and incubated for 3 hours. After the purple formazan crystals were solubilized with DMSO, the optical density (OD) was measured using an ELISA reader at a wavelength of 570 nm. The cytotoxicity was recorded as the drug concentration causing 50% growth inhibition of the tumor cells (IC50 value). After determining the percentage of cell viability, graphs were created plotting the percentage of cell viability against their respective concentrations to calculate IC50 values using absorbance (OD). Cell survival was calculated as the percentage of MTT inhibition as follows:

$$\% \text{ anticancer activity} = 100 - \frac{\text{(mean OD of individual test group)}}{\text{(mean OD each control group)}} \times 100$$



Scheme 1 Synthesis of pyrazoline from chalcone derivatives.

Results and discussion

3. Chemistry

Determination of the structure of benzal-β-acetonaphthalene (M1) and p-dimethylaminobenzal-β-acetonaphthalene (M2) was done using its IR spectrum. This spectrum showed absorption bands at 3052 cm^{-1}. The stretching band was attributed to the ν–CH aromatic, while the strong bands observed at 1661 cm^{-1} were said to be due to the carbonyl group of chalcone ν C=O. On the other hand, at 1626 cm^{-1}, a double bond ν C=C was observed (ν (-CH=CH-) 1606 cm^{-1}, ν (C-O) 1174 cm^{-1}, and ν (C-C) 1049 cm^{-1}). Furthermore, the product H3's structure revealed that the absorption band at 3060 cm^{-1} was due to ν–CH. Additionally, the band at 2852 cm^{-1} was said to be due to the carbonyl group ν (C=O), 1622 cm^{-1} of ν (C=C), 1608 cm^{-1} of ν (-CH=CH-), ν (C-N bending) 1330 cm^{-1}, ν (C-O) 1125 cm^{-1}, and ν (C-C) 1046 cm^{-1}. . Based on the 1H NMR spectra of chalcone, the protons assigned to the chemical shifts (δ, ppm) belonged to the aromatic rings found in the chalcone (M1) at a range of δ 7-8 ppm (12 aromatic protons). Moreover, the value of the chemical shift for -CH=CH- at concentrations near 7.45 ppm was attributed to the conjugation that took place within the aromatic cyclic rings. The 1H NMR of the (M2) spectrum revealed aromatic protons at δ 7-8 ppm (-CH=CH- protons and m,11 aromatic protons moved to the aromatic region from 6.5 ppm due to aromatic ring conjugation). The peak of the methyl group was observed at 3 ppm. The resulting reaction of dimethylaminobenzal-β-acetonaphthalene and benzal-β-acetylnaphthalene with p-toluenesulfonyl-hydrazine in boiling n-butanol gave rise to the pyrazolinederivatives 5-(naphthalene-2-yl)-3-(phenyl)-1-tosyl-1H-pyrazol (NAPT) and 3-(4-N,N-dimethyl-amino)-phenyl) -5-(naphthalene-2-yl)-1-tosyl-1H-pyrazole (DMNAPT). These findings were confirmed using the FT-IR and ^1H NMR spectra. Evaluation of the infrared spectrum of the compound (NAPT) revealed that the absorption bands at 3032 cm^{-1} were due to the ν CH stretching within the aromatic proton. The band at 2920 cm^{-1} corresponded to ν CH_3 aliphatic proton, while the bands at 1666 and 1624 cm^{-1} were due to ν C=C. Absorption peaks were at 1583, 1321, and 1159 cm^{-1} because of ν C=N, ν S=O, and ν S-O, respectively. Consequently, the structure for the (3-(4-N,N-dimethyl-amino)-phenyl)-5-(naphthalene-2-yl)-1-tosyl-1H-pyrazole (DMNAPT) compound within the IR spectrum revealed that there were absorption bands at various attributions (CH) aromatic and ν(CH3) aliphatic of p-toluenesulfonyl-hydrazine. The values were 3052, 2919, respectively. In addition, bands appeared at 1670 and 1611 cm^{-1} because of the ν C=C, and bands were observed at 1523, 1312, and 1130 cm^{-1} because of ν C=N, ν S=O, and ν S-O.

Thus, the 1H NMR spectrum is linked to the chemical shifts of the various types of deuterated DMSO-d6 for the pyrazoline derivatives (NAPT) being observed. At a concentration of 2.3 ppm, three protons were observed as existing in a singlet to the CH_3 group (s, 3H). Aromatic protons, on the other hand, were observed in a number of cases at 7.30-8.66 ppm. In contrast, the 1HNMR of the compound (3-(4-N, N-dimethyl-amino)-phenyl)-5-(naphthalene-2-yl)-1-tosyl-1H-pyrazole (DMNAPT)) at 2.4 ppm concentration revealed three protons in the singlet peak of the methyl group within the toluene ring. The 2.90 ppm was attributed to the methyl found within the aniline ring (-$N(CH_3)_2$). Furthermore, aromatic protons were detected at 7.54 to 8.70 ppm (m and 11H aromatic protons).

Table 1 Physical properties of the prepared compounds

Compound	Molecular Formula	Molecular Weight g/mol	Color	Melting Point ° C	Yield %
M1	$C_{19}H_{14}O_4$	258	Yellow	110	98
M2	$C_{21}H_{19}NO$	301	Orange	115	95
NAPT	$C_{26}H_{20}N_2O_2$	424	White	200	83
DMNAPT	$C_{26}H_{25}N_3O_2S$	467	Brown	190	70

4. In vitro anticancer evaluation

The synthesized compounds were evaluated for their in vitro anticancer activities in the human breast cancer cell line (MCF-7). The MTT assay was used to verify all synthesized compounds. The human breast cancer cell line (MCF-7) was treated with various growing compound concentrations, and the number of viable cells was determined after 72 hours using MTT. Figure 1 and Table 2 show that all compounds had > 80% viability at concentrations ranging from 1.56 to 25 µg/ml. When increasing the concentration range to 100 µg/ml, M1 (viability 24%), M2 (viability 30%), NAPT (viability 26%), and DMNAPT (viability 27%) showed moderate cytotoxicity against the human breast cancer cell line (MCF-7), as shown in Fig. 1 and Table 2. Cytotoxicity IC50 values, as well as standard deviation values for compounds M1, M2, NAPT, and DMNAPT, are 39, 50, 53, and 62 µg/ml, respectively.

Table 2 In vitro anticancer screening of the synthesized compounds against human breast cancer cell line MCF-7

Concentration µgml^{-1}	Cell viability (%) ± SD			
	Compound M1	Compound M2	Compound NATP	Compound DMNAPT
1.56	89.92±0.21	91.79±0.18	94.70±0.04	99.29±0.01
3.125	87.92±0.12	87.23±0.22	91.79±0.05	99.82±0.02
6.5	86.41±0.16	77.76±0.10	89.46±0.02	97.28±0.03
12.5	72.56±0.06	66.88±0.10	79.72±0.03	94.65±0.01
25	57.93±0.09	66.70 ±0.19	69.17±0.03	82.04±0.03
50	52.92±0.07	59.69±0.09	60.74±0.02	63.84±0.01
100	24.46±0.014	30.04±0.053	26.59±0.01	27.51±0.01

*Results are mean values of triplicate determinations± Standard deviation

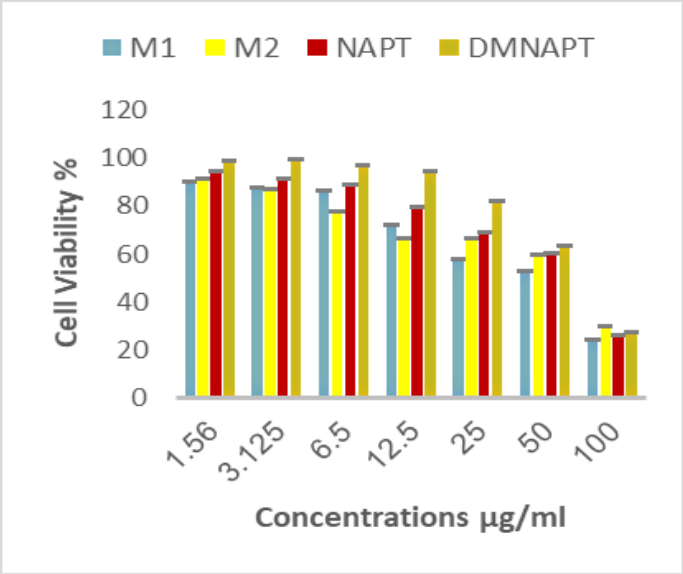


Figure 1 Cytotoxic effect of compounds M1, M2, NAPT, and DMNAPT on human breast cancer MCF-7 cells as assessed by the MTT assay following 72 h treatment. Data represent are mean values of triplicate determinations ± Standard deviation

Conclusion

To summarize, new pyrazoline derivatives were synthesized via the cyclization of chalcones (M1 and M2) within basic conditions. In vitro anti-breast cancer was evaluated using MTT assay and showed that all compounds were nontoxic at a concentration range of 1.56-50 µg/ml. Increasing the concentration range to 100 µg/ml displayed moderate cytotoxicity against the human breast cancer cell line (MCF-7).

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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