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Chalcone Analogues as Substrates in the Synthesis of Some *N*-acyl Pyrazolines †

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Abstract: Heterocyclic compounds are one of the most important organic compounds, that frequently present as active pharmaceuticals products. Among them, nitrogen-containing heterocycles have attracted much interest from various researchers due to their wide range of biological activities. Considering the importance of all these characteristics and the very pronounced application, and as a continuation of our work on pyrazolines, this paper shows the synthesis of some new *N*-acyl pyrazolines in very good yields. These products were obtained by reacting chalcone analogues with hydrazine in the presence of boiling formic or acetic acid.

Keywords: chalcone analogues; heterocyclic; pyrazolines

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1. Introduction

The large increase in various diseases in recent times has led to a huge demand for new drugs that would be more effective than the existing ones and less toxic to humans. For these purposes, many natural compounds are used, as well as products obtained by their further transformations. Among them, the most famous are the chalcones. Chalcones are natural products belonging to the flavonoid family. They can be found in larger quantities in fruits, vegetables, spices, tea, and soy-based foods [1].

Chalcones have attracted considerable attention from various researchers due to their simple chemistry, ease of synthesis, diversity of substituents, and enormous and unique biological and pharmacological activities [2]. These compounds show various activities such as antimicrobial [3], antitumor [4], antioxidant [5], anti-inflammatory [6], antimalarial [7], antituberculosis [8], antimycotic [9], analgesic [10], anti-HIV [11] and antiprotozoal [12].

Although the mechanism of the biological actions of chalcones is still not entirely revealed, the presence of an α,β-unsaturated ketone system (enone system) is believed to be responsible for the various bioactivities. This enone system is also very reactive and provides an opportunity for the synthesis of different biologically interesting molecules starting from chalcones and their analogues. They are useful intermediates for obtaining a variety of heterocyclic compounds [13,14]. The most important among them are *N*-based heterocycles; bearing in mind that 60% of unique small molecule drugs contain this fragment which shows their big significance in drug design and drug discovery (according to the FDA databases) [15].

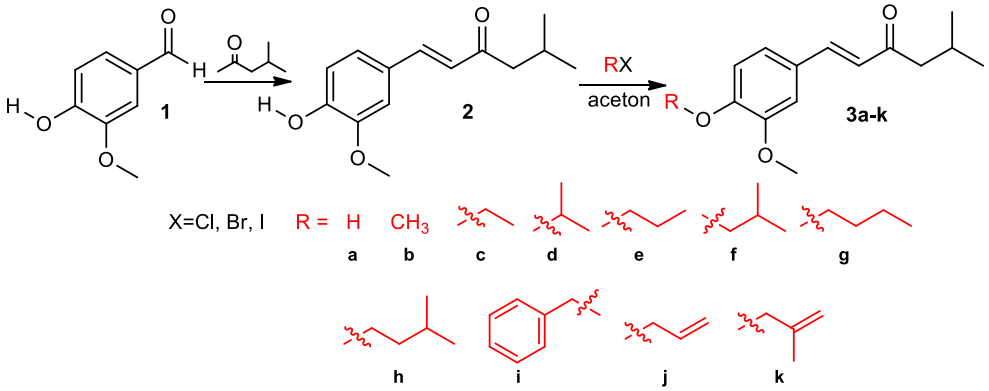
Encouraged by these observations, we decided to synthesize some new *N*-acyl pyrazolines starting from corresponding vanillin chalcone analogues [16]. Our previous experience with this type of chalcone analogues and their very good activity [16,17], led

us to use them as substrates in this synthesis. Considering our results related to various pyrazolines [18–20], we supposed that the incorporation of different pharmacophores into one molecule would be a good solution for the synthesis of some biologically active compounds.

2. Results and Discussion

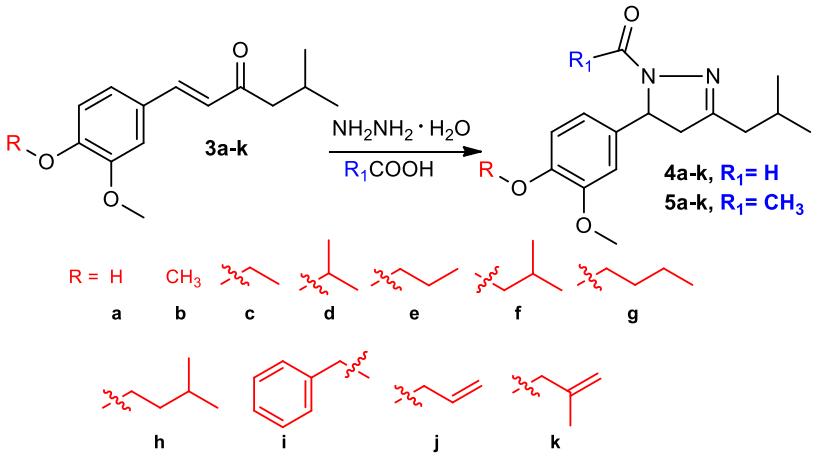
Chemistry Synthesis

In a reaction, Claisen-Schmidt condensation of vanillin and 4-methylpentan-2-one, (*E*)-1-(4-hydroxy-3-methoxyphenyl)-5-methylhex-1-en-3-one **(2)** was prepared. Keeping in mind the reactivity of the phenolic functional group, a set of *O*-alkyl derivatives **(3a-k)**, was prepared by alkylation of a free phenolic group with corresponding alkyl halides, according to the described literature procedures [16], Scheme 1.



Scheme 1. Synthesis of (*E*)-1-(4-alkoxy-3-methoxyphenyl)-5-methylhex-1-en-3-ones.

Synthesized products, **3a-k** possess a conjugated enone system, which is suitable for further transformations. A series of novel *N*-acyl pyrazolines (**4a-k** and **5a-k**) was prepared in a reaction of compounds **3a-k** with hydrazine hydrate in boiling formic or acetic acid (Scheme 2). All new products were well characterized by ^{1}H, ^{13}C NMR, and physical data.

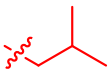
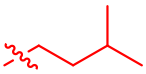
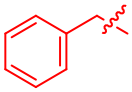
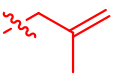


Scheme 2. Synthesis of *N*-acyl pyrazolines **4a-k** and **5a-k.**

The new 22 compounds were synthesized in very good yields which are shown in Table 1. Screening of the new products in vitro against human cervical cancer cells (HeLa), human colon cancer cells (HCT-116), and human fibroblast (MRC-5, as control cells) by the MTT method were performed. The results showed very strong cytotoxic activity

toward cancer cells and very low cytotoxic activity toward MRC-5, non-cancerous cells. These investigations are still in progress.

Table 1. The yields of synthesized *N*-acyl pyrazolines.

R	$R_1 = H$ (%)	$R_1 = CH_3$ (%)
H	**83.7**	**54.8**
CH_3	**92.7**	**84.9**
	**77.3**	**76.1**
	**89.6**	**77.4**
	**80.8**	**78.6**
	**90.1**	**59.8**
	**85.2**	**85.5**
	**72.2**	**78.6**
	**93.2**	**84.2**
	**71.8**	**66.4**
	**92.4**	**80.8**

3. Materials and Methods

Chemistry

All starting chemicals were commercially available and used as received, except that the solvents were purified by distillation.

NMR spectra: Varian Gemini 200 MHz spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C), using $CDCl_3$ as the solvent and TMS as the internal standard. ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million (ppm) and were referenced to the solvent peak; $CDCl_3$ (7.26 ppm for ^{1}H and 76.90 for ^{13}C). Multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplet), and m (multiplet). Coupling constants (*J*) are in Hertz (Hz). The melting point of products was determined with the MelTemp1000 apparatus.

General Procedure for the Synthesis of N-formyl and N-acetyl Pyrazolines

To a stirred solution of **3a-k** (1 mmol) in formic or acetic acid (4 mL) hydrazine monohydrate (0.8 mL, 16 mmol) was added and the reaction mixture was heated to reflux for 5 h. The mixture was poured out into crushed ice and water and neutralized by $NaHCO_3$ (solid). The organic layer was extracted with dichloromethane and washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried. After the removal of the main part of the solvent, the residue was filtered over a SiO_2 pad using dichloromethane. The products are mostly obtained as solid substances, except for compounds **4a**, **4f,** and **5a** which are oily substances.

- **5-(4-hydroxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4a):** Light pink powder, yield: 83.7%; mp 101–102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96–1.01 (m, 6H, $2CH_3$), 1.88–2.02 (m, 1H, CH), 2.28 (d, *J* = 7.6 Hz, 2H, CH_2), 2.73 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.2, 11.6 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 5.32 (dd, *J* = 11.8, 4.6 Hz, 1H, CH), 5.79 (s, 1H, OH), 6.66–6.71 (m, 2H, Ar-H), 6.84 (d, *J* = 8.6 Hz, 1H, Ar-H), 8.83 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz,

$CDCl_3$): δ 22.4, 22.7, 26.4, 39.1, 45.5, 55.9, 58.1, 108.2, 114.8, 118.2, 132.7, 145.3, 146.8, 159.6, 160.1.

- **5-(3,4-dimethoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4b):** Light-orange oil; yield: 92.7%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96–1.01 (m, 6H, $2CH_3$), 1.86–2.06 (m, 1H, CH), 2.28 (d, *J* = 7.0 Hz, 2H, CH_2), 2.74 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.36 (dd, *J* = 18.2, 11.6 Hz, 1H, CH_2), 3.85 (s, 6H, $2OCH_3$), 5.34 (dd, *J* = 11.4, 4.4 Hz, 1H, CH), 6.68–6.85 (m, 3H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 22.6, 26.4, 39.1, 45.4, 55.8, 55.9, 58, 108.8, 111.6, 117.6, 133.4, 148.7, 149.4, 159.6, 159.9.
- **5-(4-ethoxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4c):** Light orange oil; yield: 77.3%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96–1.01 (m, 6H, $2CH_3$), 1.44 (t, *J* = 7.0 Hz, 2H, CH_2), 1.85–2.05 (m, 1H, CH), 2.26–2.29 (m, 2H, CH_2), 2.74 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.2, 11.4 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 4.07 (q, *J* = 7.0 Hz, 2H, CH_2), 5.33 (dd, *J* = 11.2, 4.2 Hz, 1H, CH), 6.68–6.75 (m, 2H, Ar-H), 6.82 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.8, 22.4, 22.6, 26.4, 39.1, 45.4, 55.9, 58, 64.5, 109.1, 113.2, 117.6, 133.4, 147.9, 149.8, 159.6, 160.
- **3-isobutyl-5-(4-isopropoxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4d):** Light orange oil; yield: 89.6%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95–1.01 (m, 6H, $2CH_3$), 1.34 (d, *J* = 6.2 Hz, 6H, $2CH_3$), 1.85–2.02 (m, 1H, CH), 2.28 (d, *J* = 7.2 Hz, 2H, CH_2), 2.74 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.2, 11.6 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 4.42–4.54 (m, 1H, CH), 5.34 (dd, *J* = 11.4, 4.2 Hz, 1H, CH), 6.69–6.73 (m, 2H, Ar-H), 6.83 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.84 (d, *J* = 0.8 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.2, 22.4, 22.7, 26.4, 39.1, 45.4, 56, 58, 71.6, 109.6, 116.1, 117.6, 133.8, 147, 150.8, 159.6, 160.1.
- **3-isobutyl-5-(3-methoxy-4-propoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4e):** Light orange oil; yield: 80.8%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96–1.05 (m, 9H, $3CH_3$), 1.79–2.02 (m, 3H, CH_2, CH), 2.28 (d, *J* = 7.0 Hz, 2H, CH_2), 2.68–2.79 (m, 1H, CH), 3.36 (dd, *J* = 18.0, 11.4 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 3.95 (t, *J* = 6.8 Hz, 2H, CH_2), 5.33 (dd, *J* = 11.2, 4.4 Hz, 1H, CH), 6.68–6.75 (m, 2H, Ar-H), 6.82 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.4, 22.4, 22.5, 22.6, 26.4, 39.1, 45.4, 56, 58, 70.6, 109.3, 113.3, 117.6, 133.3, 148.2, 149.8, 159.6, 160.
- **5-(4-isobutoxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4f):** Orange oil; yield: 90.1%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96–1.03 (m, 12H, $4CH_3$), 1.85–2.02 (m, 1H, CH), 2.07–2.20 (m, 1H, CH), 2.28 (d, *J* = 7.0 Hz, 2H, CH_2), 2.73 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.2, 11.4 Hz, 1H, CH_2), 3.73 (d, *J* = 6.8 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 5.33 (dd, *J* = 11.4, 4.4 Hz, 1H, CH), 6.68–6.74 (m, 2H, Ar-H), 6.81 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 22.4, 22.7, 26.4, 28.2, 39.1, 45.4, 56.2, 58, 75.7, 109.7, 113.6, 117.8, 133.4, 148.6, 149.9, 159.6, 160.
- **5-(4-butoxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4g):** Light yellow powder; yield: 85.2%; mp 53–54°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96–1.01 (m, 9H, $3CH_3$), 1.38–1.57 (m, 2H, CH_2), 1.73–1.84 (m, 2H, CH_2), 1.88–2.05 (m, 1H, CH), 2.28 (d, *J* = 7.6 Hz, 2H, CH_2), 2.74 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.2, 11.6 Hz, 1H, CH_2), 3.83 (s, 3H, OCH_3), 3.99 (t, *J* = 6.8 Hz, 2H, CH_2), 5.33 (dd, *J* = 11.4, 4.4 Hz, 1H, CH), 6.68–6.69 (m, 2H, Ar-H), 6.74 (d, *J* = 2.2 Hz, 1H, Ar-H), 6.83 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 19.2, 22.4, 22.7, 26.4, 31.3, 39.1, 45.4, 56.1, 58, 68.9, 109.4, 113.4, 117.7, 133.3, 148.3, 149.9, 159.6, 160.
- **3-isobutyl-5-(4-(isopentyloxy)-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4h):** Orange oil; yield: 72.2%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.94–1.01 (m, 12H, $4CH_3$), 1.66–2.05 (m, 4H, CH_2, 2CH), 2.28 (d, *J* = 7.2 Hz, 2H, CH_2), 2.74 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.0, 11.4 Hz, 1H, CH_2), 3.83 (s, 3H, OCH_3), 4.01

(t, *J* = 6.6 Hz, 2H, OCH_2), 5.33 (dd, *J* = 11.4, 4.4 Hz, 1H, CH), 6.68–6.75 (m, 2H, Ar-H), 6.83 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.3, 22.5, 25.1, 26.3, 37.9, 39, 45.3, 56, 57.9, 67.5, 109.3, 113.3, 117.6, 133.3, 148.2, 149.8, 159.5, 159.9.

- **5-(4-(benzyloxy)-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1H-pyrazole-1-carbaldehyde (4i):** Light orange oil; yield: 93.2%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95–1.00 (m, 6H, $2CH_3$), 1.87–2.01 (m, 1H, CH), 2.27 (d, *J* = 7.0 Hz, 2H, CH_2), 2.72 (dd, *J* = 18.2, 4.8 Hz, 1H, CH_2), 3.34 (dd, *J* = 18.2, 11.6 Hz, 1H, CH_2), 3.86 (s, 3H, OCH_3), 5.12 (s, 2H, OCH_2), 5.32 (dd, *J* = 11.2, 4.4 Hz, 1H, CH), 6.65–6.71 (m, 2H, Ar-H), 6.83 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.28–7.45 (m, 5H, Ar-H), 8.83 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 22.7, 26.4, 39.1, 45.4, 56.1, 58, 71.2, 109.4, 114.5, 117.6, 127.2, 127.7, 128.4, 134, 137.1, 147.9, 159.6, 160.
- **5-(4-(allyloxy)-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4j):** Light orange oil; yield: 71.8%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.96–1.01 (m, 6H, $2CH_3$), 1.85–2.06 (m, 1H, CH), 2.28 (d, *J* = 7.2 Hz, 2H, CH_2), 2.74 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.36 (dd, *J* = 18.2, 11.4 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 4.58 (dt, *J* = 5.4, 1.4 Hz, 2H, OCH_2), 5.23–5.44 (m, 3H, CH_2, CH), 5.96–6.16 (m, 1H, CH), 6.69–6.85 (m, 3H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.3, 22.6, 26.3, 39, 45.3, 55.9, 57.9, 69.9, 109.1, 113.8, 117.5, 117.7, 133.2, 133.7, 147.6, 149.8, 159.5, 159.9.
- **3-isobutyl-5-(3-methoxy-4-((2-methylallyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbaldehyde (4k):** Light orange oil; yield: 92.4%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95–1.01 (m, 6H, $2CH_3$), 1.81 (d, *J* = 0.4 Hz, 3H, CH_3), 1.88–2.05 (m, 1H, CH), 2.28 (d, *J* = 7.4 Hz, 2H, CH_2), 2.74 (dd, *J* = 18.2, 4.6 Hz, 1H, CH_2), 3.35 (dd, *J* = 18.0, 11.4 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 4.48 (s, 2H, OCH_2), 4.95–4.98 (m, 1H, CH_2), 5.06–5.07 (m, 1H, CH_2), 5.33 (dd, *J* = 11.2, 4.2 Hz, 1H, CH), 6.67–6.73 (m, 2H, Ar-H), 6.82 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.84 (d, *J* = 1.0 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 22.4, 22.6, 26.4, 39.1, 45.4, 56, 57.9, 72.9, 109.3, 112.6, 113.9, 117.6, 133.7, 140.7, 147.9, 149.9, 159.6, 160.
- **1-(5-(4-hydroxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5a)**: Beige powder; yield: 54.8%; mp 114–115°C; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95–0.99 (m, 6H, $2CH_3$), 1.84–2.04 (m, 1H, CH), 2.26 (d, *J* = 7.2 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3CO), 2.67 (dd, *J* = 17.6, 3.8 Hz, 1H, CH_2), 3.28 (dd, *J* = 17.6, 11.0 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 5.36 (dd, *J* = 11.8, 4.4 Hz, 1H, CH), 6.01 (br. s, 1H, OH), 6.59–6.65 (m, 2H, Ar-H), 6.77 (d, *J* = 8.0 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8, 22.3, 22.6, 26.3, 39.2, 45.1, 55.8, 58.9, 108.4, 114.8, 117.9, 133.9, 145, 146.7, 158.5, 168.4.
- **1-(5-(3,4-dimethoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5b)**: Light orange oil; yield: 84.9%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95–1.00 (m, 6H, $2CH_3$), 1.84–2.05 (m, 1H, CH), 2.26 (d, *J* = 7.0 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3CO), 2.51–2.73 (m, 1H, CH), 3.29 (dd, *J* = 18.0, 11.6 Hz, 1H, CH_2), 3.84 (d, *J* = 1.2 Hz, 3H, OCH_3), 5.38 (dd, *J* = 11.6, 4.4 Hz, 1H, CH), 6.68–6.91 (m, 3H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 22.4, 22.7, 26.4, 28.9, 39.3, 45.2, 55.8, 55.9, 58.9, 93.3, 108.9, 111.6, 117.4, 134.8, 158.1, 168.3.
- **1-(5-(4-ethoxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5c)**: Orange oil; yield: 76.1%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95–0.99 (m, 6H, $2CH_3$), 1.43 (t, *J* = 7.0 Hz, 3H, CH_3), 1.84–2.04 (m, 1H, CH), 2.26 (d, *J* = 7.4 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.2, 4.4 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.0, 11.6 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 4.06 (q, *J* = 7.0 Hz, 2H, OCH_2), 5.38 (dd, *J* = 11.6, 4.4 Hz, 1H, CH), 6.68–6.71 (m, 2H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.8, 21.9, 22.4, 22.6, 26.4, 39.2, 45.1, 55.9, 58.9, 64.4, 109.2, 113.2, 117.4, 134.7, 147.6, 149.6, 158.1, 168.3.
- **1-(3-isobutyl-5-(4-isopropoxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5d)** Dark orange oil; yield: 77.4%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.94–0.99 (m, 6H, $2CH_3$), 1.34, (d, *J* = 6.2 Hz, 6H, $2CH_3$), 1.94–2.07 (m, 1H, CH), 2.26 (d, *J* =

7.4 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.0, 4.4 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.0, 11.4 Hz, 1H, CH_2), 3.81 (s, 3H, OCH_3), 4.40–4.55 (m, 1H, CH), 5.38 (dd, *J* = 11.6, 4.2 Hz, 1H, CH), 6.64–6.69 (m, 2H, Ar-H), 6.81 (d, *J* = 8.8 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 22.2, 22.4, 22.7, 26.4, 39.2, 45.2, 55.9, 58.9, 71.5, 109.6, 116.1, 117.4, 135.1, 150.6, 158.3, 168.3.

- **1-(3-isobutyl-5-(3-methoxy-4-propoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5e)**: Light orange oil; yield: 78.6%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95–1.01 (m, 9H, $3CH_3$), 1.74–1.98 (m, 3H, CH_2, CH), 2.26 (d, *J* = 7.6 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.0, 4.4 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.0, 11.4 Hz, 1H, CH_2), 3.83 (s, 3H, OCH_3), 3,93 (t, *J* = 6.8 Hz, 2H, OCH_2), 5,37 (dd, *J* = 11.6, 4.4 Hz, 1H, CH), 6.67–6.71 (m, 2H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.4, 21.9, 22.4, 22.5, 22.6, 26.4, 39.2, 45.2, 56, 58.9, 70.7, 109.5, 113.4, 117.5, 134.8, 147.9, 149.7, 158.1, 168.3.
- **1-(5-(4-isobutoxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5f):** Light orange oil; yield: 59.8%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95–1.02 (m, 12H, $4CH_3$), 1.87–2.01 (m, 1H, CH), 2.07–2.19 (m, 1H, CH), 2.26 (d, *J* = 7.2 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.2, 4.4 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.0, 11.6 Hz, 1H, CH_2), 3.72 (d, *J* = 6.8 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 5.37 (dd, *J* = 11.6, 4.4 Hz, 1H, CH), 6.66–6.71 (m, 2H, Ar-H), 6.79 (d, *J* = 8.8 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 21.9, 22.4, 22.7, 26.4, 28.2, 39.3, 45.1, 56.2, 58.9, 75.7, 109.8, 113.6, 117.5, 134.7, 148.2, 149.8, 158.1, 168.2.
- **1-(5-(4-butoxy-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5g)**: Dark yellow oil; yield: 85.5%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92–1.00 (m, 9H, $3CH_3$), 1.38–1.56 (m, 2H, CH_2), 1.73–1.84 (m, 2H, CH_2), 1.91–2.01 (m, 1H, CH), 2.26 (d, *J* = 7.0 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.0, 4.2 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.0, 11.4 Hz, 1H, CH), 3.83 (s, 3H, OCH_3), 3.98 (t, *J* = 6.6 Hz, 2H, OCH_2), 5.38 (dd, *J* = 11.6, 4.4 Hz, 1H, CH_2), 6.67–6.71 (m, 2H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 19.2, 21.9, 22.6, 22.7, 26.4, 31.3, 39.2, 45.1, 56, 58.9, 68.8, 109.4, 113.3, 117.4, 117.6, 134.7, 147.9, 149.7, 158.2, 168.3.
- **1-(3-isobutyl-5-(4-(isopentyloxy)-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5h)**: Light orange oil; yield: 78.6%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93–0.99 (m, 12H, $4CH_3$), 1.65–2.01 (m, 4H, CH_2, 2CH), 2.26 (d, *J* = 7.2 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.2, 4.2 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.2, 11.6 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.99 (t, *J* = 6.8 Hz, 2H, OCH_2), 5.38 (dd, *J* = 11.6, 4.2 Hz, 1H, CH), 6.67–6.71 (m, 2H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 22.4, 22.6, 22.7, 25.2, 26.4, 28.9, 38, 39.3, 45.2, 56.1, 58.9, 67.6, 109.5, 113.4, 117.5, 134.7, 148, 149.7, 158.2, 168.3.
- **1-(5-(4-(benzyloxy)-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5i):** Light orange oil; yield: 84.2%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95–0.99 (m, 6H, $2CH_3$), 1.87–2.01 (m, 1H, CH), 2.25 (d, *J* = 7.0 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3CO), 2.66 (dd, *J* =18.0, 4.2 Hz, 1H, CH_2), 3.28 (dd, *J* = 18.0, 11.6 Hz, 1H, CH_2), 3.86 (s, 3H, OCH_3), 5.11 (s, 2H, OCH_2), 5.37 (dd, *J* = 11.6, 4.4 Hz, 1H, CH), 6.62–6.71 (m, 2H, Ar-H), 6.81 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.28–7.45 (m, 5H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 22.4, 22.7, 26.4, 39.3, 45.1, 56.1, 58.9, 71.2, 109.6, 114.5, 117.4, 127.2, 127.7, 128.4, 135.4, 137.2, 145, 147.6, 149.9, 158.1, 168.3.
- **1-(5-(4-(allyloxy)-3-methoxyphenyl)-3-isobutyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5j):** Yellow oil; yield: 66.4%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95–1.01 (m, 6H, $2CH_3$), 1.78–2.07 (m, 1H, CH), 2.26 (d, *J* = 7.0 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.0, 4.4 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.0, 11.6 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 4.57 (dt, *J* = 5.4, 1.4 Hz, 2H, CH_2), 5.23–5.42 (m, 3H, CH_2, CH), 5.96–6.16 (m, 1H, CH_2, CH), 6.66–6.83 (m, 3H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.4, 21.9, 22.4, 22.6, 26.4, 39.2, 45.1, 55.9, 58.8, 69.9, 109.3, 113.8, 117.3, 117.7, 133.3, 135.1, 149.6, 158.2, 168.2.

- **1-(3-isobutyl-5-(3-methoxy-4-((2-methylallyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (5k):** Yellow oil; yield: 80.8%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95–0.99 (m, 6H, $2CH_3$), 1.80 (d, *J* = 0.4 Hz, 3H, CH_3), 1.87–2.01 (m, 1H, CH), 2.26 (d, *J* = 7.6 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3CO), 2.67 (dd, *J* = 18.0, 4.2 Hz, 1H, CH_2), 3.29 (dd, *J* = 18.0, 11.4 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 4.47 (s, 2H, CH_2), 4.94–4.97 (m, 1H, CH_2), 5.05–5.07 (m, 1H, CH_2), 5.37 (dd, *J* = 11.4, 4.2 Hz, 1H, CH), 6.37–6.68 (m, 2H, Ar-H), 6.80 (d, *J* = 8.4 Hz, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.3, 21.9, 22.4, 22.7, 26.4, 39.3, 45.1, 56, 58.9, 72.9, 109.5, 112.5, 114, 117.4, 135.1, 140.8, 147.7, 149.7, 158.1, 168.3.

4. Conclusions

In this paper, the syntheses of twenty-two *N*-acyl pyrazolines (*N*-formyl, **4a-k,** and *N*-acetyl, **5a-k**) containing vanillin core are described. These compounds were prepared by reaction of the (*E*)-1-(4-alkoxy-3-methoxyphenyl)-5-methylhex-1-en-3-ones, **3a-k** with hydrazine hydrate in the presence of corresponding carboxylic acid. The new products were obtained with very good yields. The preliminary investigations of antitumor activity against some cancer cell lines (HeLa, HCT-116) and non-cancerous cell lines (MRC-5) have shown very good results, but these examinations are still in progress.

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