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SYNTHESIS, CHARACTERIZATION AND ANTI-BREAST CANCER ACTIVITY OF SOME PYRROLIDINE-2,5-DIONE DERIVATIVES

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Abstract
In this study, four compounds that are pyrrolidine-2,5-dione derivatives were synthesized. The reaction between N-substituted maleimide and aryl hydrazide (benzohydrazide, N-phenylhydrazine carboxamide or isonazide) produced novel compounds (K1, K2, K3 and K4). The pyrrolidine-2,5-dione derivatives were identified using FT-IR, 1H- and 13C-nuclear magnetic resonance (NMR), mass spectrometry, and the melting point of the prepared compounds. The MTT test was used to investigate four substances with anti-breast cancer (MCF-7) .

Keywords: synthesis, pyrrolidine-2,5-dione, aryl hydrazide and anti-breast cancer.

Introduction

Maleimides, a substantial class of substrates, have been successfully used in asymmetric organocatalytic transformations such as asymmetric cycloadditions, Michael reactions, and asymmetric cascade reactions [1–9]. Asymmetric organocatalysis allows for the chiral substitution of succinimide molecules after maleimide functionalization. The Michael addition [10–13] is one of the strongest and most efficient atom-economical carbon–carbon bond-forming processes. Through the asymmetric Michael addition of maleimide, one technique in particular provides effective direct entrance to substituted succinimides from simple precursors [1–9].

Maleimide derivatives have recently been found to be effective as selective inhibitors of the enzymes monoglyceridelipase, Cdc25B, GSK-3, Bfl-1, and DNMT-1 [14, 15, 16, 17, 18]. Maleimides also belong to the promising group of heterocyclic compounds with the -CO-N(R)-CO chain. They are neutral and hydrophobic, making it easy for them to pass through biological membranes [19]. They are therefore widely employed as antibacterial [20], antimicrobial [21], antiprotozoal [22], analgesics [23], antitiangiogenic [24], and antistress drugs, among other biological applications such as cytotoxicity, DNA binding, and apoptosis causing action. A novel class of heterocyclic compounds known as maleimides has several biological applications. Several studies are driven to produce maleimide derivatives [25, 26].

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EXPERIMENTAL

Chemistry

The melting point was measured using the Gallenkamp apparatus. Deuterated solvents and tetramethylsilane (TMS) as an internal standard were used to record the 1H and 13C-NMR spectra. The chemical shifts were indicated in () ppm using a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz. Infrared spectra were obtained using a Perkin-Elmer FT-IR-1600 spectrophotometer. The spots were visualized in UV and I2 using thin layer chromatography (TLC) with Merck silica gel. The Agilent Technologies 5975C Spectrometer was used to examine mass spectra using EI at 70 eV.

Procedure for synthesis maleimides (M1 and M2):

The same method was used as in literature [27, 28] with some modification, where maleanilic acids (0.01 mol) derivatives were dissolved in acetic anhydride (15 ml) and added anhydrous sodium acetate (10%-20%) by weight, the mixture was refluxed on water bath until the colour was changed, then cooled the solution and poured in ice bath with vigorously stirring. Where the maleimide was precipitated, filtered and dried and recrystallized with suitable solvent.

General procedure the synthesis of compounds (K1, K2, K3 and K4)

A mixture of differently substituted maleimides (0.01mol) and aryl hydrazide (benzohydrazide, N-Phenylhydrazine carboxamide and isonazide) (0.01mol) in ethanol (20 ml) were brought to reflux under magnetic stirring for 4-6 hours. The precipitate formed was filtered and recrystallized in ethanol [29].

3-(3-(2-isonicotinoylhydrazineyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K1)

White solid powder, yield 60%, mp=243-246 °C, FT-IR (KBr, cm-1): 3468-3417 (OH); 3336 (NH amide), 3267 (NH); 3088 (CH-Ar); 1703, 1654, 1610 (C=O); 1537, 1458 (C=C arom.); 1398 (C-N); 1282 (C-O). ^{1}H-NMR (DMSO-d6): δ 13.13 (br.s,1H, OH), 10.54 (d, 1H, J=6.1 Hz, H_a), 8.76-8.73 (m, 3H, H-Ar), 7.98 (dt, 1H, J=7.8, 1.4 Hz, H-Ar), 7.91 (d, 1H, J=1.8 Hz, H-Ar), 7.76-7.7 (m, 3H, H-Ar), 7.64 (d, 1H, J= 7.8 Hz, H-Ar), 7.54 (dt, 1H, J=8 Hz, H-Ar), 6.22 (t, 1H, J=5.9 Hz, H_b), 4.28 (dd, 1H, J=6.5, 2.9 Hz, H_c), 3.11 (dd, 1H, J=17.9, 8.6 Hz, H_d), 2.81 (dd, 1H, J= 17.9, 3.9 Hz, H_e). ^{13}C-NMR (DMSO-d6): δ 175.62 (C1), 175.17 (C2), 167.0 (C3), 164.73 (C4), 150.75, 140.36, 133.04, 132.04, 131.72, 129.73, 129.48, 128.31, 121.66 (C-Ar), 58.04 (C5), 35.04 (C6). MS (z\m): 354 M^+ .

3-(3-(2-benzoylhydrazineyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K2)

White solid powder, yield 72%, mp=226-228 °C, FT-IR (KBr, cm^{-1}): 3469-3419 (OH); 3325 (NH amide), 3228 (NH); 3088 (CH-Ar); 1722, 1701, 1639 (C=O); 1535,1471 (C=C *arom*); 1394 (C-N); 1188 (C-O). ^{1}H-NMR(DMSO-d6): δ 13.29 (br.s, 1H, OH), 10.25 (d, 1H, J=6 Hz, H_a), 7.99-7.83 (m, 4H, H-Ar), 7.64 (t, 1H, J=7.8 Hz, H-Ar), 7.57-7.46 (m, 4H, H-Ar), 6.08 (t, 1H, J=5.6 Hz, H_b), 4.26 (dt, 1H, J=8.4, 4 Hz, H_c), 3.09 (dd, 1H, J=17.9, 8.5 Hz, H_d), 2.83 (dd, 1H, J= 17.9, 3.7 Hz, He). ^{13}C-NMR (DMSO-d6): δ 175.72

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(C1), 175.31 (C2), 167.01 (C3), 166.60 (C4), 133.30, 133.06, 132.06, 132.01, 131.73, 129.73, 129.48, 128.86, 128.32, 127.69, (C-Ar), 58.22 (C5), 35.03 (C6). MS (z\m): 353.1 M^+

3-(2,5-dioxo-3-(2-(phenylcarbamoyl)hydrazineyl)pyrrolidin-1-yl)benzoic acid (K3)

White solid powder**,** yield 60 %, mp=217-219 °C, FT-IR (KBr, cm^{-1}): 3471-3417 (OH); 3360 (NH amide); 3298 (NH); 3084 (CH-Ar); 1716,1687,1676 (C=O); 1535,1450 (C=C *arom*); 1394 (C-N); 1199(C-O).
^{1}H-NMR (DMSO-d6): δ 13.36 (br.s, OH), 8.84 (s, 1H, H_a), 8.73 (d, 1H, J=7.8 Hz, H_b), 7.98 (d, 1H, J=14.7 Hz, H-Ar), 7.53 (t, 1H, J=7.8 Hz, H-Ar), 7.56-7.47 (m, 3H, H-Ar), 7.25 (q, 2H, J=8.0 Hz, H-Ar), 6.94 (t, 1H, J=7.4 Hz, H-Ar), 5.76 (br.s, 1H, H_c), 4.21 (pent, 1H, J=8 Hz, H_d), 3.04 (dd, 1H, J= 17.9, 6.7 Hz, H_e), 2.84 (dd, 1H, J= 17.9, 4.8 Hz, H_f). ^{13}C-NMR (DMSO-d6): δ 176.51 (C1), 175.15 (C2), 166.99 (C3), 157.04 (C4), 140.17, 139.97, 132.99, 132.08, 131.72, 129.72, 129.53, 129.08, 129.32, 128.32, 122.26, 119.01 (C-Ar), 58.67 (C5), 33.99 (C6).
MS (z\m) :368.1 M^+.

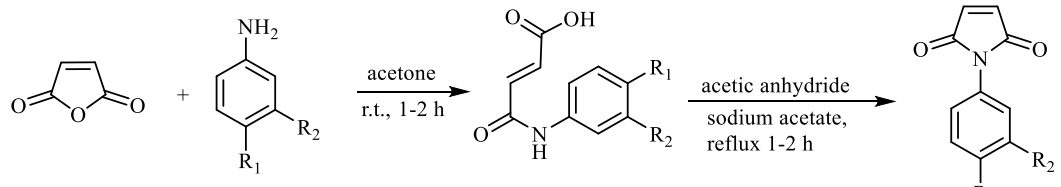
4-(2,5-dioxo-3-(2-(phenylcarbamoyl)hydrazineyl)pyrrolidin-1-yl)benzoic acid (K4)

White solid powder**,** yield 70%, mp=227 °C, FT-IR (KBr, cm^{-1}): 3350 (OH); 3296 (NH amid), 3224 (NH); 1710, 1670, 1600 (C=O); 1535, 1446 (C=C*arom*); 1394 (C-N); 1190 (C-O).
^{1}H-NMR (DMSO-d6): δ 13.14 (br. s, OH), 8.74 (s,1H, H_a), δ8.06-8.01 (m, 2H, H-Ar), 7.88 (s, 1H, H_b), 7.51-7.43 (m, 3H, H-Ar), 7.27-7.23 (m, 2H, H-Ar), 6.97-6.93 (m, 2H, H-Ar), 5.78 (s,1H,H_c), 4.28 (pent., 1H, J=4 Hz, H_d), 3.05 (dd, 1H, J= 17.9, 8.7 Hz, H_e), 2.84 (dd, 1H, J=18.0, 4.7 Hz, H_f). ^{13}C-NMR (DMSO-d6): δ 176.38 (C1),174.94 (C2),167.11(C3), 157.03 (C4), 156.50, 140.16, 139.96, 136.49, 130.88, 130.33, 129.08, 129.04, 127.30,122.27,118.96 (C-Ar), 58.68 (C5), 34.0 (C6). MS (z\m): 368.4 M^+.

Results and Discussion

Following two major routes, the N-substituted maleimides presented here were synthesized: Maleic anhydride and *p*-aminobenzoic acid or *m*-aminobenzoic acid are the building blocks for the first one (scheme 1), whereas aryl hydrazide (benzohydrazide, N-Phenylhydrazine carboxamide and isonazide) and N-substituted maleimides are needed for the second one (scheme 2).

The desired substituted aniline was reacted with maleic anhydride in a solvent like diethyl ether or acetone to produce the corresponding substituted maleanilic acid without the need for any further purification, and this open intermediate was then cycled in acetic anhydride in the presence of sodium acetate to produce the desired N-substituted maleimide (M1 and M2) [30,31].



M1: R_1=COOH, R_2=H
M2: R_1=H, R_2=COOH

Scheme 1: synthesis of N-substituted maleimides (M1 and M2)

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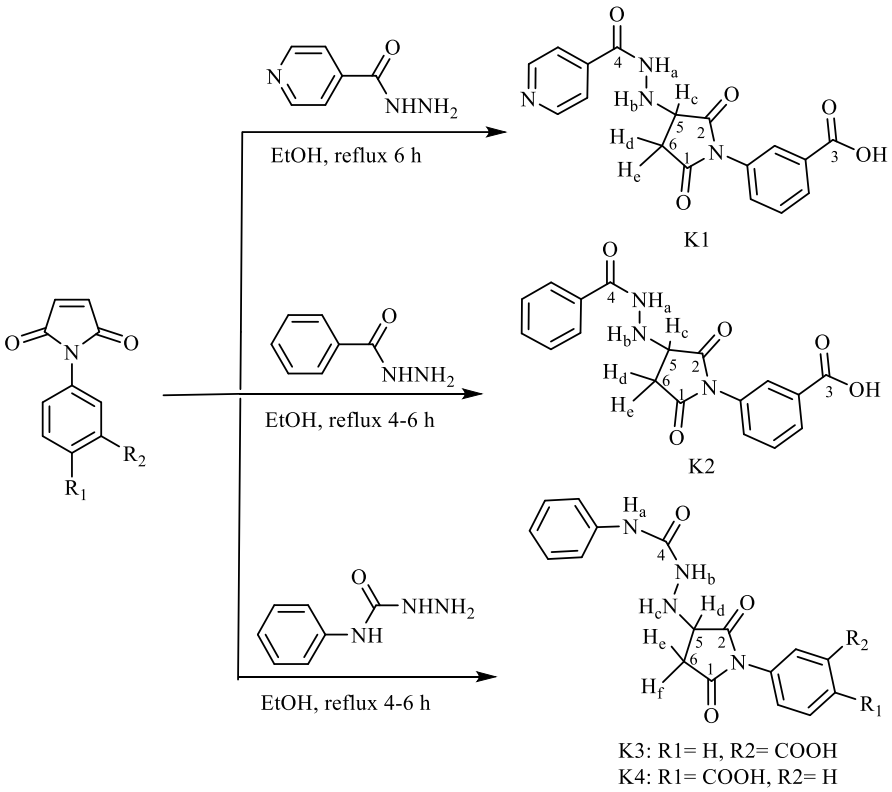
The conversion of N-substituted maleimides into corresponding pyrrolidine-2,5-dione derivatives through Michael addition with an aromatic primary amine is undertaken after the preparation of N-substituted maleimides. The desired pyrrolidine-2,5-dione derivatives were prepared by Michael addition· [32].

Compounds (M1-M2) were reacted with aryl hydrazide in dry ethanol to afford products (K1-K4). (See Scheme 2).



Scheme 2: Synthesis of compounds (K1, K2, K3 and K4)

The chemical structures of all the resulting pyrrolidine-2,5-dione derivatives were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. The KBr disc was used to determine the properties of the IR absorption bands (K1–K4). The IR spectrum was used to identify the functional groups of these compounds. The stretching bands corresponding to OH appeared in the range of 3471–3417 cm^{-1}. The NH amide and NH groups were observed in the range of 3360–3325 and 3298–3228 cm^{-1}, respectively. The absorption bands in the 1722–1604 cm^{-1} area are linked to C=O [33]. The C=C aromatic stretching was assigned a band in the range (1537-1450) cm^{-1} [34, 35].

The maleimide derivatives (K1–K4) were used to generate ^{1}H-NMR spectra. Signals at δ 2.5 and δ 3.3 belong to the solvents DMSO-d6 and water, respectively. In compounds (K1 and K2), the OH proton appears as a broad singlet in the range of δ 13.29–13.13. Because they are attached to carbon adjacent to the chiral center, the doublet of doublets at around δ 3.11-3.09 and 2.83-2.81 belong to H_d and H_e

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protons, respectively. At δ 4.28–4.26, H_c was responsible for the signal of double doublete or double triplete. The proton of H_b was assigned triplet signals between δ 6.22 and 6.08. Doublet signals at around δ 10.54–25.15 were due to H_a. Aromatic protons were given the signals (doublet, triplet, and multiplet) at roughly δ 8.76–7.48 [36].

The ^{13}C- NMR of the compounds K1 and K2 that showed signals at around δ 175.72–164.73 (C_1-C_4) were attributed to carbonyl groups. The signals of the carbon aromatic ring appeared in the range of δ 150.75–121.66. Aliphatic carbons can be found in δ 58.22–58.04 for C_5, and δ 35.04–35.03 for C_6. The mass spectra of the compounds K1 and K2 revealed the presence of a molecular ion (m/z): 354 M^+ and 353.1 M^+.

Other compounds (K3 and K4) were also distinguished by the appearance of signal doublet of doublets at around δ 3.05-3.04 and 2.84-2.82, which belongs to H_e and H_f protons , respectively. Because the hydrogen atoms of the methylene group are adjacent to the chiral center.

At δ 4.25–4.20, H_d was responsible for the signal of multiplet. Singlet signals at δ 5.78-5.76 for H_c. Doublet or singlet signals at around δ 7.98-7.88 were assigned to the proton of H_b. Singlet signal at δ 8.74 was due to H_a. The broad signals corresponding to OH appeared in the range of δ 13.21-13.14. Aromatic protons were given the signals (doublet, triplet and multiplet) at roughly δ 8.06–6.93 [36].

The ^{13}C- NMR of the compounds K3 and K4 that showed signals at around δ 176.53–157.03 (C_1-C_4) were attributed to carbonyl groups. The signals of the carbon aromatic ring appeared in the range of δ 156.5–118.96. Aliphatic carbons can be found in δ 58.69-58.68 for C_5, and δ 34 for C_6. The mass spectra of the compounds K3 and K4 revealed the presence of a molecular ion (m/z): 368.1 M^+ and 368.4 M^+.

The mass spectra indicated that the structures were right. ^{1}H-NMR, ^{13}C-NMR, and MS spectroscopy were established in accordance with the proposed structure.

Cytotoxicity Evaluation

Many studies have shown that heterocyclic derivatives are an important class of compounds that could be used in the development of new anticancer agents [37, 38]. Chemotherapy for breast cancer entails the use of drugs to specifically target and destroy cancer cells. Chemotherapy is frequently combined with other breast cancer treatments, such as surgery, radiation, or hormone therapy. Chemotherapy raises the risk of blood clots such as deep-vein thrombosis because breast cancer patients are predisposed to blood clots. As a result, developing new heterocyclic compounds with fewer side effects to combat breast cancer remains a challenge for researchers [39, 40]. Some reports showed that pyrrolidine-2,5-dione derivatives and succinimide derivatives exhibited promising structures for developing new agents as anticancer agents and merited further investigation [41–44].The prepared compounds were studied against breast cancer using the MTT test. The data indicate, based on the IC50 value, that the compounds in the series do not have anti-breast cancer activity. Table (1) shows the IC_{50} values.

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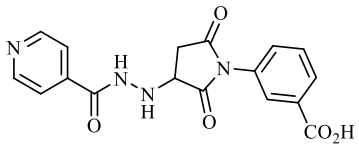
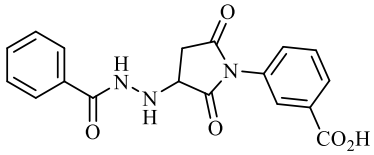
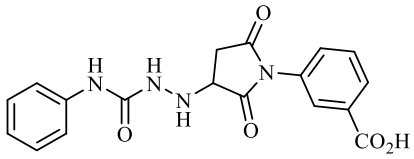
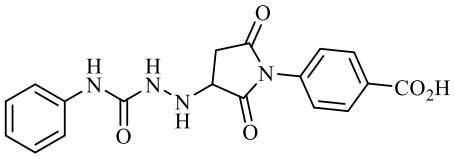
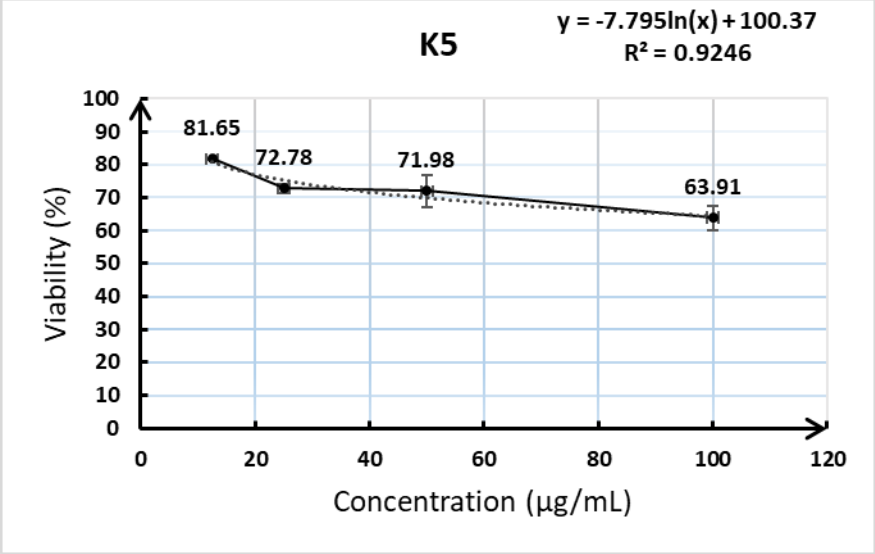
Table 1: shows the IC50 values of (K1, K2, K3 and K4) compounds versus PC3 cells

Symbol	Structure	PC3 cells IC50 in µg/mL	
K1		713.3	Inactive
K2		533.6	Inactive
K3		640.2	Inactive
K4		674.5	Inactive

Below are graphs showing response curves for (K1-K4) vehicles. (See Fig. 1).



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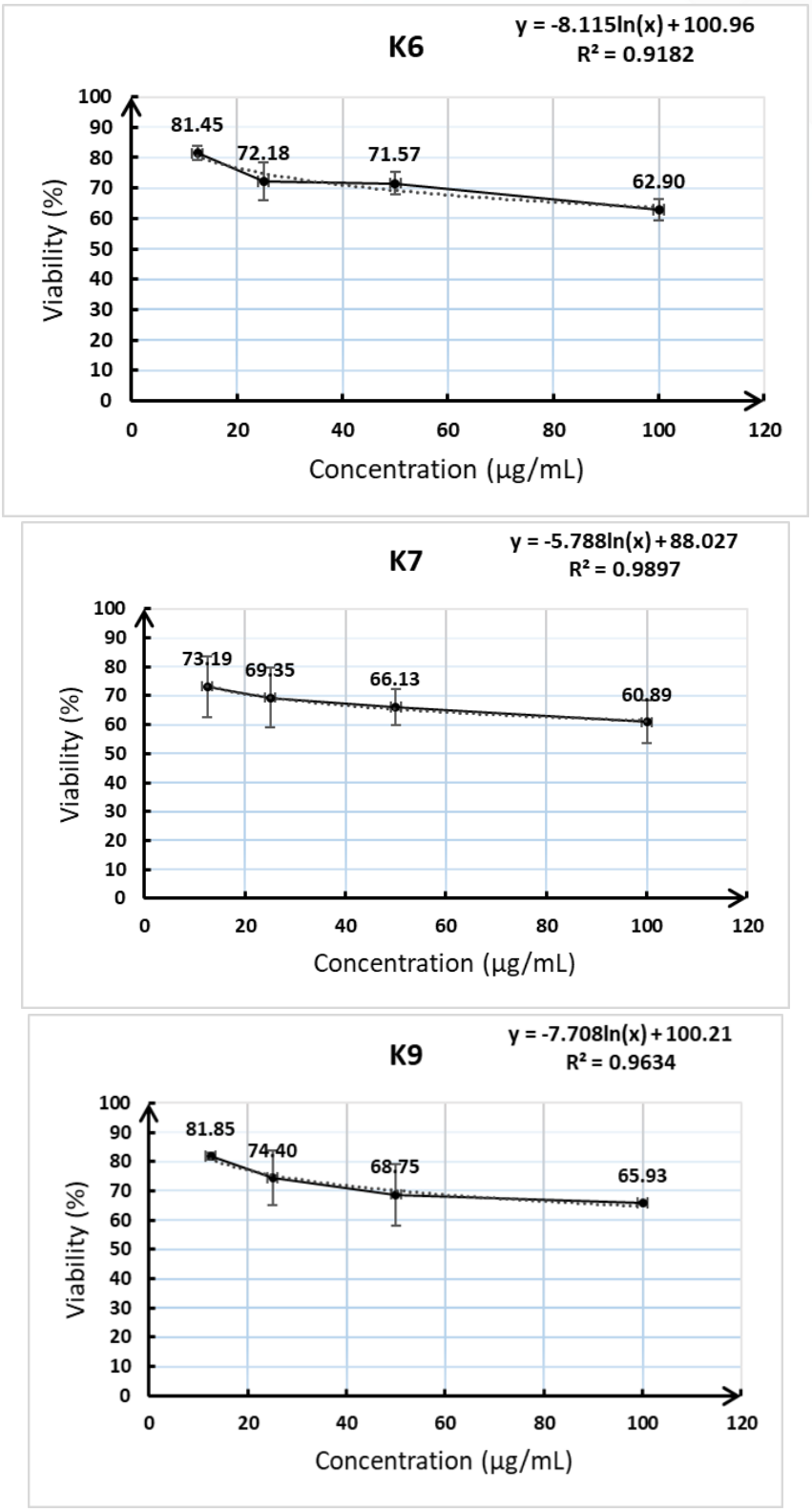

Fig. 1: The graphic curves of the prepared compounds

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Conclusion

In conclusion, a series of pyrrolidine-2,5-dione derivatives were successfully synthesized from N-substituted maleimides with aryl hydrazide (benzohydrazide, N-Phenylhydrazine carboxamide, or isonazide) and characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra. The compounds were studied against breast cancer using the MTT test. The compounds in the series do not have anti-breast cancer activity.

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