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Synthesis and anti-breast cancer activity of some succinimide derivatives via Michael addition reaction: arylhydrazide to maleimides

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ABSTRACT

In this study five compounds were synthesized that includedsuccinimidederivatives. New compounds (S_1-S_5) were produced by the reaction of hydrazide derivatives with N-substituted maleimide and were diagnosed by mass spectrometry, NMR spectra of 1H and 13C, infrared spectroscopy, and the melting point of the generated compounds. Five substances wereexaminedfor their ability to inhibit breast cancer (MCF-7) using the MTT assay. When tested on breast cancer cells, the substances S_3, S_4, and S_5 showed anti-cancer activity.

1. Introduction

Succinimides, also known as pyrrolidine-2,5-diones, are a fascinating group of heterocyclic chemicals that are frequently used in biochemistry and organic synthesis. For instance, compounds of succinimide have anticonvulsant and protease [1] and esterase [2] inhibitory properties [3, 4].
For numerous physiologically significant medications, including phensuuximide, ethosuximide, methsuximide, and andrimias, the succinimide molecule is frequently employed as a precursor [5, 6]. A few of the compounds exhibited intriguing biological properties, including muscle relaxant [7], anticancer [8], antisplasmodic [9], analgesic [10], and antibacterial [11,12].
Thus, synthetic methods that yield new succinimide compounds are very desirable. For the purpose of producing derivatives of substituted succinimide [13], one method is to add nucleophiles to the maleimide double bond via the Michael addition. Because maleimide derivatives are widely used and are known to respond with thiols, they are often utilized in bioconjugation processes [14]. Other hetero-Michael additions [15] that maleimides experience include phospha-Michael [16], aza-Michael [17, 18], and the less thoroughly researched oxa-Michael responses [19]. The latter produces derivatives of O-alkylated succinimide and happens under simple circumstances. Previous literature reports on the oxa-Michael reaction's ability to generate N-substituted alkoxysuccinimides [14, 15]. Five succinimide derivatives were created in this work, and 1H, 13C-NMR, mass spectroscopy, and FTIR were used to confirm the compounds' structures.

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2. Materials and Instruments

Equipment for measuring the Gallenkamp melting point. Tetramethylsilane (TMS) was employed as the internal standard, and the 1H and 13C-NMR spectra were registered utilize deuterated solvents. A Bruker DRX-400 spectrometer was used to measure chemical shifts at 400 and 100 MHz in (δ) ppm. By examining infrared spectra, the FT-IR-1600 Perkin-Elmer spectrophotometer was acquired. In addition to UV and I2 imaging, Merck silica gel thin layer chromatography (TLC) was employed to find the points. An Agilent Technologies 5975C Spectrometer was employed to analyze cluster spectra utilize the EI method at 70 eV.

3. Synthesis

3.1. Procedure for synthesis maleimides (M_1-M_3):

With minor modifications, the procedure followed the literature [20, 21]: Maleanilic acid derivatives (0.01 mole) were fixed in 15 milliliters of acetic anhydride, and then anhydrous sodium acetate (10%–20% by weight) was added. After refluxing the mixture on a water bath until it changed color, it was cooled and then put into an ice bath while being agitated ferociously. where the maleimide was filtered, precipitated, dried, and recrystallized using an appropriate solvent.

3.2. The general method of creating compounds (2a, 2b, and 5c)

A mixture of dry acetone (300 ml), anhydrous K2CO3 (100 mmole), phenol or p-methoxy phenol or 1-nephthol (100 mmole), and ethyl chloroacetate (100 mmole) was heated under reflux for 10 hours using thin-layer chromatography (TLC). The resultant solvent was then allowed to evaporate at a lower pressure following filtration. White powder was obtained in a 75–80% yield by recrystallizing the resultant precipitate from absolute ethanol.

3.3. General procedure the synthesis of hydrazide derivatives (3a, 3b and 6c)

For five hours, under reflux, a combination of ester (2a, 2b, and 5c) (10 mmole), ethanol (50 ml), and hydrazine hydrate (30 mmole) was heated. After being filtered out, the final chemical was recrystallized from pure ethanol, yielding 65–70% white powder.

3.4. General procedure the synthesis of compounds (S_1-S_5) [22]:

For seventy-two hours, a combination of hydrazide derivatives (3a, 3b, and 6c) (0.01mol) and variously substituted maleimides (0.01mol) in 20 milliliters of ethanol were refluxed while being stirred magnetically. After filtering, the white precipitate that had developed recrystallized in ethanol.

3.5. N'-(1-(4-methyl-3-nitrophenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenoxyacetohydrazide (S_1):

A mixture of 4-methyl-3-nitrophenylmaleimide (0.001mol) and 2-Phenoxyacetohydrazide (0.001mol) in (25ml) ethanol gave a white solid (79% yield), m.p=195-197 °C**.** FT-IR (KBr, cm^{-1}): 3364 (NH amid, 3214 (NH), 3080 (C-H Ar), 1700 (C=O),1533, 1490 (C=C Ar),1346 (C-N), ,1174 (C-O).^{1}H NMR (DMSO-d6):δ 9.83 (d, 1H, J=8 Hz, NHa_{amide}), 7.98 (s, 1H, H_{Ar}), 7.65 (d, 1H, J=8 Hz, H_{Ar}), 7.56 (d, 1H, J=8 Hz, H_{Ar}), 7.30-7.24 (m, 2H, H_{Ar}), 6.95 (d, 3H, J=8Hz, H_{Ar}), 5.92 (t, 1H, J=4 Hz, NH_b), 4.55 (s, 2H, CH_2O), 4.19 (pent., 1H, J=4 Hz,H_c), 3.00 (dd, 1H, J=12, 20 Hz, H_d), 2.74 (dd, 1H, J=4, 16 Hz, H_e), 2.58 (s, 3H, CH_3).^{13}C-NMR(DMSO-d6): δ 175.53 (C1), 174.89 (C2), 167.68 (C3), [158.20, 149.03, 133.81, 133.62, 132.17, 131.42, 129.94, 123.22, 121.65, 115.09] C-Ar, 66.54 (O-CH_2), 58.25 (C4), 34.81 (C5), 19.96 (CH_3);MS (z/m): 398.2 M^+.

3.6. 2-(4-methoxyphenoxy)-N'-(1-(4-methyl-3-nitrophenyl)-2,5-dioxopyrrolidin-3-yl) acetohydrazide(S_2):

A mixture of 4-methyl-3-nitrophenyl maleimide (0.001mol) And 2-(4-methoxyphenoxy) acetohydrazide (0.001mol) in (25ml)ethanol gave a white solid (60% yield), m.p=207-209 °C. FT-IR (KBr, cm^{-1}):3358 (NH amid, 3209 (NH), 3073 (C-H Ar), 1697 (C=O),1536,1500 (C=C Ar), 1346 (C-N), 1174 (C-O).^{1}H NMR (DMSO-d6):δ 9.78 (d, 1H, J=8 Hz, NH_a), 7.98 (s, 1H, H_{Ar}), 7.65 (d, 1H, J=8 Hz, H_{Ar}),7.57 (d, 1H, J=8 Hz, H_{Ar}), 6.90-6.79 (m, 4H, H_{Ar}), 5.90 (t, 1H, J=4 Hz, NH_b), 4.48 (s, 2H, CH_2O), 4.18 (pent., 1H, J=4 Hz, H_c), 3.67 (s, 3H, OCH_3), 3.00 (dd, 1H, J=12, 20 Hz, H_d), 2.74 (dd, 1H, J=4, 16 Hz, H_e), 2.58 (s, 3H, CH_3).^{13}C-NMR (DMSO-d6): δ 175.53 (C1), 174.90 (C2), 167.86 (C3), [154.26, 152.21, 149.01, 133.80, 133.61, 132.15, 131.41, 123.20, 116.10, 115.00] C-Ar, 67.31 (O-CH_2), 58.25 (C4), 55.78 (O-CH_3), 34.79 (C5), 19.97 (CH_3); MS (z/m): 428.3 M^+.

3.7. N'-(1-(4-methyl-3-nitrophenyl)-2,5-dioxopyrrolidin-3-yl)-2-(naphthalen-2-yloxy) acetohydrazide (S_3):

A mixture of 4-methyl-3-nitrophenyl maleimide (0.001mol) and 2-(Naphthalene-2-loxy) acetohydrazide (0.001mol) in (25ml) ethanol gave a white solid (80% yield), m.p=225-227°C. FT-IR (KBr, cm^{-1}): 3311 (NH amid, 3203 (NH), 3031 (C-H Ar), 1659, 1623 (C=O),1522,1469 (C=C Ar), 1390 (C-N), 1184 (C-O).^{1}H NMR (DMSO-d6): δ 9.92 (d, 1H, J=4 Hz, 1H,NH_a), 7.99 (s, 1H, H_{Ar}), 7.68-7.26 (m, 9H, H_{Ar}),5.97 (t, 1H, J=4 Hz, NH_b), 4.86 (s, 2H,CH_2O), 4.12 (pent., 1H, J=4 Hz, H_c),3.01 (dd, 1H, J=8, 20 Hz, H_d), 2.77 (dd, 1H, J=4, 16 Hz,H_e), 2.56 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d6): δ 175.56 (C1), 174.92 (C2), 167.55 (C3), [156.09, 148.97, 134.49, 133.78, 133.61, 132.13, 131.39, 129.83, 129.21, 127.98, 127.22, 126.91, 124.33, 123.19, 119.09, 107.58] C-Ar, 66.62 (O-CH_2), 58.21 (C4), 34.85 (C5), 19.99 (CH_3); MS (z/m): 448.3 M^+.

3.8. N'-(1-(4-bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenoxyacetohydrazide (S_4):

A mixture of 4-bromophenyl maleimide (0.001mol)and 2- Phenoxyacetohydrazide (0.001mol) in (20ml) ethanol gave a white stiff (93% output), m.p=263-265°C. FT-IR (KBr, cm^{-1}): 3347 (NH amid, 3215 (NH), 3074 (C-H Ar), , 1777, 1698 (C=O), , 1592, 1485 (C=C Ar), 1399 (C-N), 1176 (C-O). ^{1}H NMR (DMSO-d6): δ 9.81 (d, 1H, J=8 Hz, NH_a), 7.72-6.94 (m, 9H, H_{Ar}), 5.88 (t, 1H, J=8 Hz, NH_b), 4.54 (s, 2H,CH_2O), 4.17 (pent., 1H, J=4 Hz, H_c), 2.97 (dd, 1H, J=8, 20 Hz, H_d), 2.71 (dd, 1H, J=4, 16 Hz, H_e).^{13}C-NMR (DMSO-d6): δ 175.64 (C1), 174.99 (C2), 167.68 (C3), [158.19, 132.36, 132.04, 129.96, 129.49, 121.71, 121.67, 115.08] C-Ar, 66.51 (O-CH_2), 58.13 (C4), 34.77 (C5); MS (z/m): 419.1 M^+.

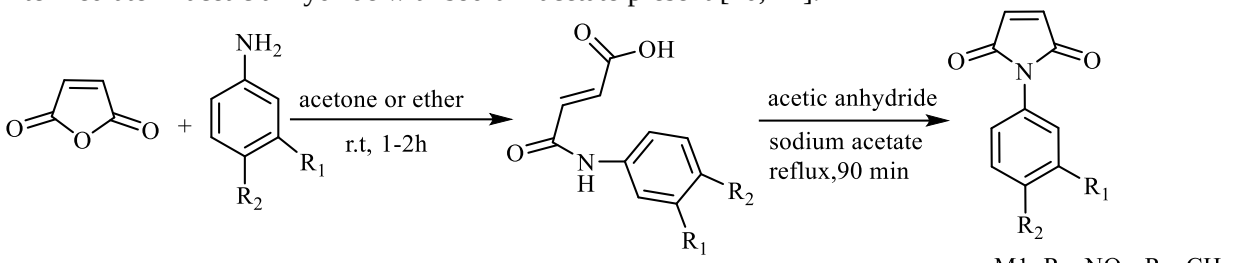
3.9.N'-(2,5-dioxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)-2-phenoxyacetohydrazide (S_5):

A mixture of phenyl maleimide (0.001mol)and 2- Phenoxyacetohydrazide (0.001mol) in (20ml) ethanol gave a white solid (95% yield), m.p=240-243°C.FT-IR (KBr, cm^{-1}): 3346 (NH amid, 3218 (NH), (C-H Ar), 1776, 1698 (C=O), 1591, 1487 (C=C Ar), 1398 (C-N), 1176 (C-O). ^{1}H NMR (DMSO-d6): δ 9.81 (d, 1H, J=4 Hz, NH_a), 7.59-6.94 (m, 10H, H_{Ar}), 5.89 (t, 1H, J=4 Hz, NH_b), 4.55 (s, 2H, CH_2O), 4.21-4.15 (m, 1H, H_c), 2.98 (dd, 1H, J=8, 16 Hz, H_d), 2.75-2.70 (m, 1H, He). ^{13}C-NMR(DMSO-d6): δ 175.69 (C1), 175.04 (C2), 167.69 (C3), [158.19, 133.22, 132.77, 131.61, 129.97, 129.73, 129.41, 129.33, 129.19, 121.67, 115.09] C-Ar, 66.51 (O-CH2), 58.12 (C4), 34.77 (C5); MS (z/m): 339.1 M^+.

4. Results and Discussion

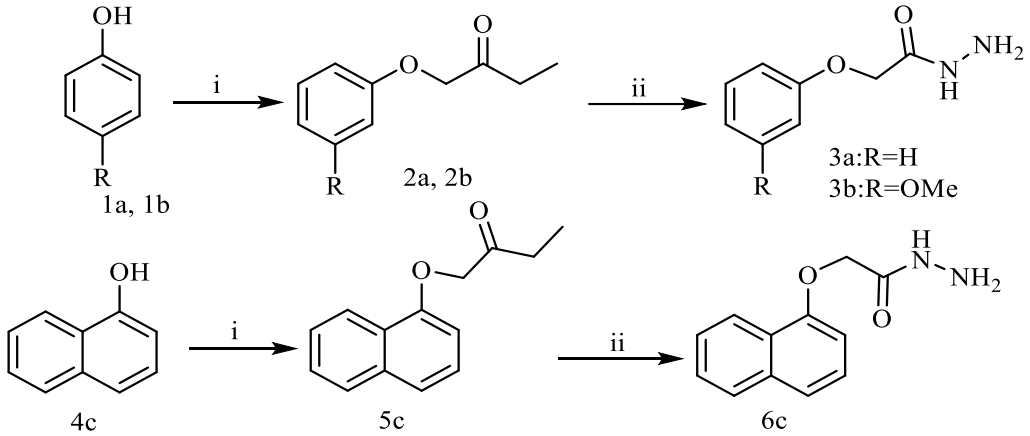
Two fundamental techniques were used to synthesize the N-substituted maleimides displayed here: scheme 1, which required N-substituted maleimides and aryl hydrazide, and scheme 2, which required replaced aniline and maleic anhydride as building blocks. To create the desired N-substituted maleimides (M1–M3), the corresponding substituted maleanilic acid was produced by responsive the required replaced aniline with maleic anhydride in a dissolvent like acetone or diethyl ether.The desired N-substituted maleimides (M1–M3) were then produced by cycling this open

intermediate in acetic anhydride with sodium acetate present [20, 21].



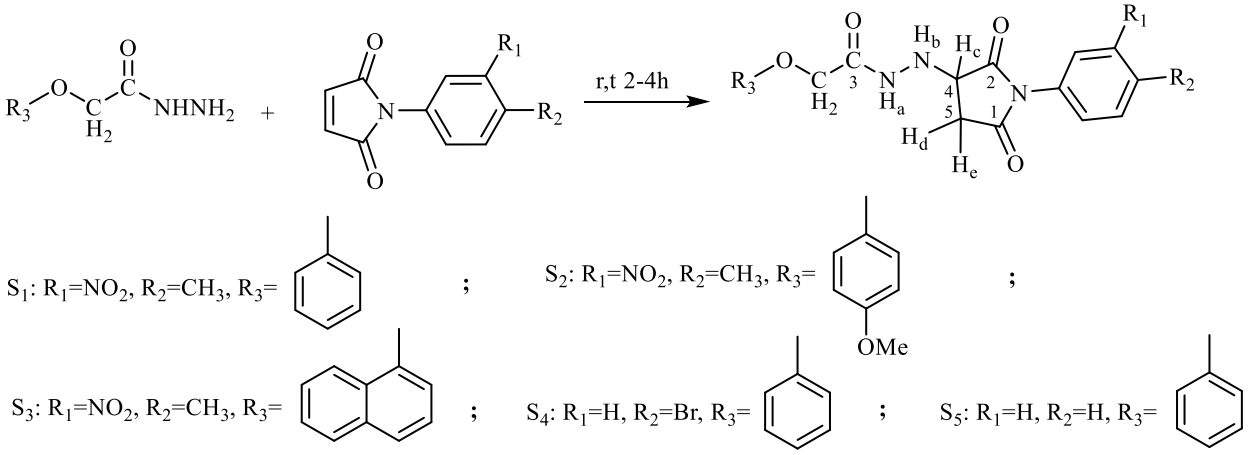
Scheme 1: Synthesis of maleimide derivatives (M_1-M_3)

The process [32–26] yields the ester derivative (2a, 2b, and 5c) when phenol, p-methoxy phenol, or 1-nephthol reacts with ethyl chloroacetate in the presence of potassium carbonate. This ester derivative then reacts with hydrazine hydrate to yield the hydrazide derivatives (3a, 3b, and 6c).



Scheme 2: (i) $ClCH_2COOEt$, K_2CO_3, acetone, reflux; (ii) $NH_2NH_2.H_2O$, EtOH, reflux

conversion of N-substituted maleimides by Michael addition using an aromatic primary amine to the corresponding succinimide derivatives. Maleimides with N-substituents were developed first, followed by succinimide derivatives.Michael addition was utilized to prepare the necessary succinimide derivatives [22]. Substances (M_1-M_3) were mixed with hydrazide derivatives in dry ethanol or acetonitrile to yield a output (S_1-S_5). (See Scheme 3).



Scheme 3: Synthesis of succinimide derivatives (S_1-S_5)

FT-IR, 1H-NMR, 13C-NMR, and cluster spectrometry were utilized to emphasize the chemical structure of all succinimide compounds. The characteristics of the IR assimilation bands (S1-S5) were specified utilize the KBr disc. The infrared spectra were used to identify these compounds'

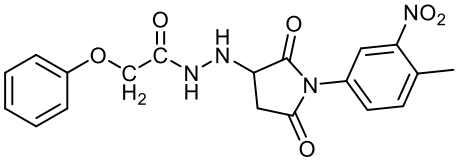
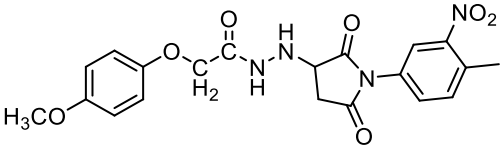
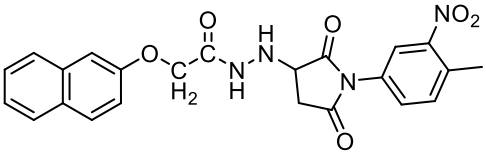
functional groups. The range of 3364-3311 and 3218-3203 cm^{-1}, respectively, was where the stretching bands corresponding to NH groups and NH amide were observed. The 1777–1623 cm^{-1} range was where the C=O groups were observed [27]. Assigned to the C=C aromatic stretching was the band in scope (1592-1485) cm^{-1} [28, 29]. (See figures 6-10).Succinimide derivatives (S_1-S_5) were characterized by ^{1}H-NMR spectra. The combinations were characterized by the manifestation of double and triplet signals ranging from δ 9.92-9.78 and 5.97-5.89, which belong to H_a and H_b protons, respectively. The H_d and $H_e$protons are responsible for the doublet of doublets peaks at δ 3.01-2.97 and 2.77-2.70, respectively, in order that they are bonded to carbon next to the chiral center.Hc was accountable for the pentent at δ 4.19-4.12. Multiple signals were applied to aromatic protons at approximately δ 7.99-6.79. The singlet is caused by the methyl groups at δ 2.58-2.56. The proton of the -OCH_3 group was the cause of the singlet signal at δ 3.67. (See fig. 11-15).
The ^{13}C-NMR of compounds (S_1-S_5) that showed signals at δ175.69-167.55 were attributed to carbonyl groups. Signals appeared in the range δ 158.20-107.58 belonging to the carbon aromatic ring. Aliphatic carbons appear in the scope δ 67.31-19.96. (See fig. 16-20).
A molecular ion (m/z) was detected in the cluster spectra of the S1–S5 groups, which were 398.2 (M+), 428.3 (M+), 448.3 (M+), 419.1 (M+), and 3399.1 (M+). (See fig. 21-25).
The accuracy of the structures was validated by the mass spectra. MS, ^{13}C-NMR, and 1H-NMR spectroscopy were determined to be consistent with the proposed structure.

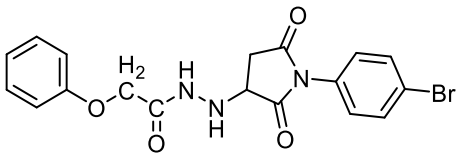
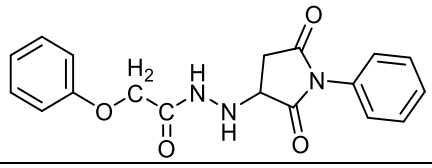
5. Cytotoxicity evaluation

Heterocyclic derivatives are a significant class of chemicals that may be applied to create novel anticancer medications, according to numerous studies [30, 31]. Drugs that specifically target and destroy cancer cells are used in chemotherapy for breast cancer. For the treatment of breast cancer, chemotherapy is frequently combined with hormone therapy, radiation, or surgery. Chemotherapy increases the danger of blood curdssuch as profound vein thrombosis in order that breast cancer patients are more likely to experience blood curds. As a result, improve novel heterocyclic combinations with fewer side impactsto treat breast cancer keeps difficult[32, 33]. Several reports suggest that studying the structures of maleimide and succinimide derivatives could be beneficial for the creation of new anticancer medications [34–37].

The MTT test was used to investigate the produced compounds' ability to prevent breast cancer. According to the IC50 value, the data suggest that a few of the series' compounds have anti-breast cancer properties. combinations (S_1-S_5) shown anti-breast cancer properties. The methyl, methoxy, and nitro groups of substances S_3, S_4 and S_5 are what give them their superior activity over the other compounds. IC_{50} values are displayed in Table (1). (See fig. 1-5).

Table 1: Express the IC50 values of (S_1-S_5) combinations versus MDA-MB-231 cells

Symbol	Structure	MDA-MB-231 cell IC_{50} in µg/mL
S_1		1729.03
S_2		4992.61
S_3		210.80

S_4		256.95
S_5		454.22

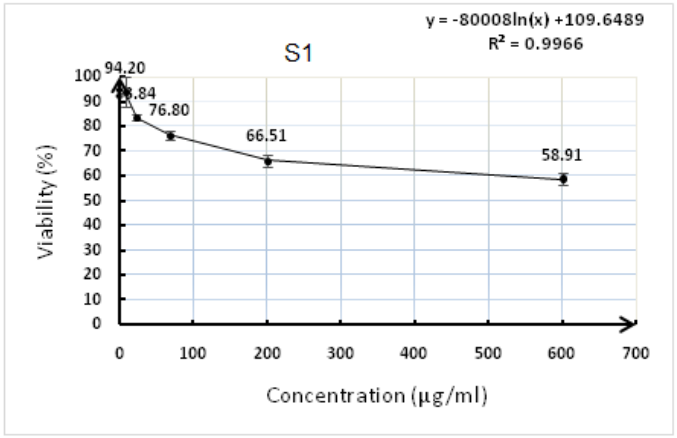


Fig. 1: Compound S1

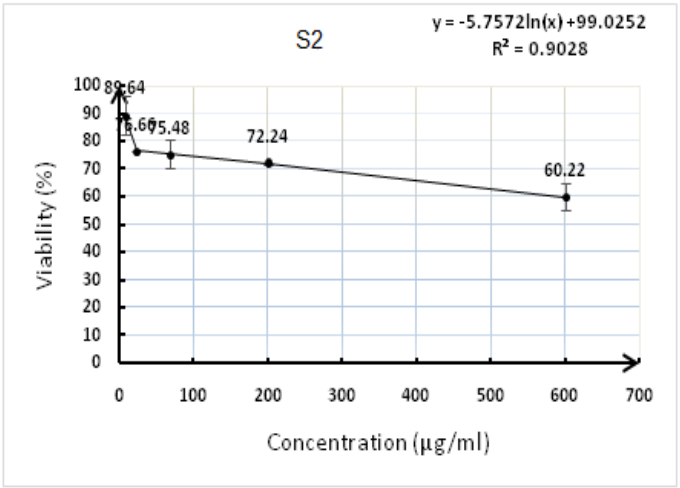


Fig. 2: Compound S2

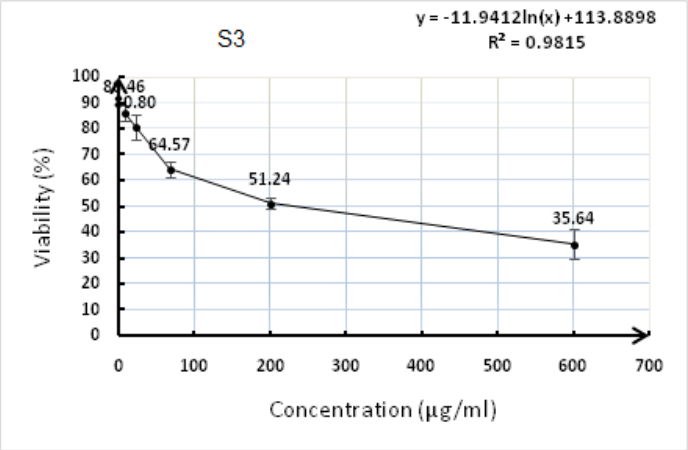


Fig. 3: Compound S3

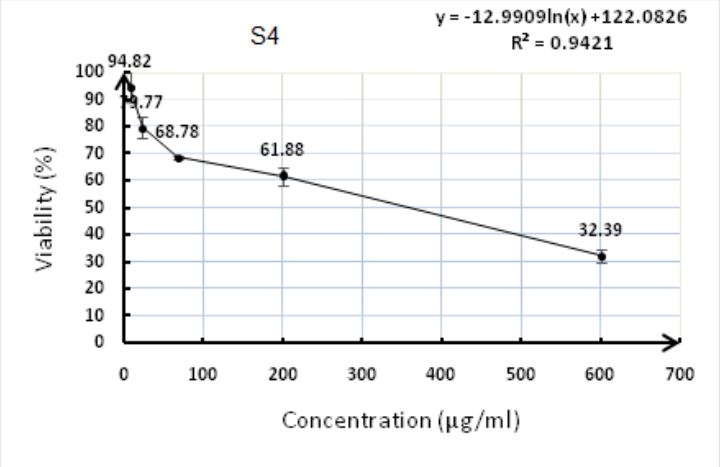


Fig. 4: Compound S4

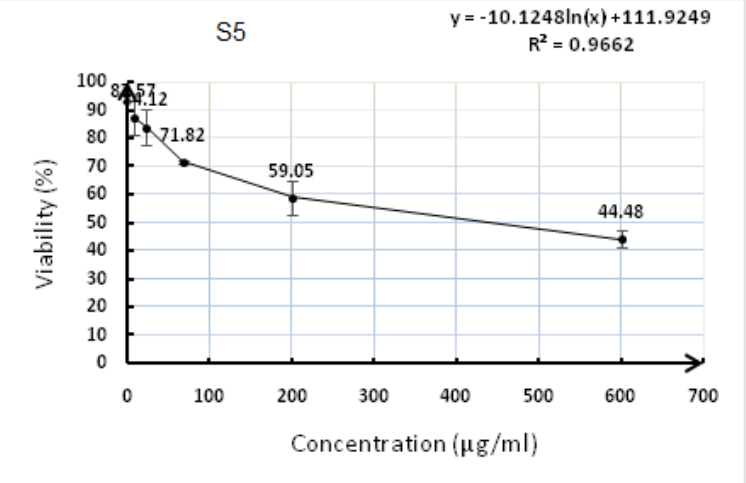


Fig. 5: Compound S5

6. Conclusion

In conclusion, N-substituted maleimides with hydrazide derivatives were successfully used to create a variety of succinimide derivatives, which were then characterized by mass spectra, 1H-NMR, 13C-NMR, and FT-IR. The substances' potential to prevent breast cancer was investigated. The substances (S1-S4) exhibited anti-breast cancer action. Compounds S3, S4, and S5 demonstrated anti-breast cancer properties.

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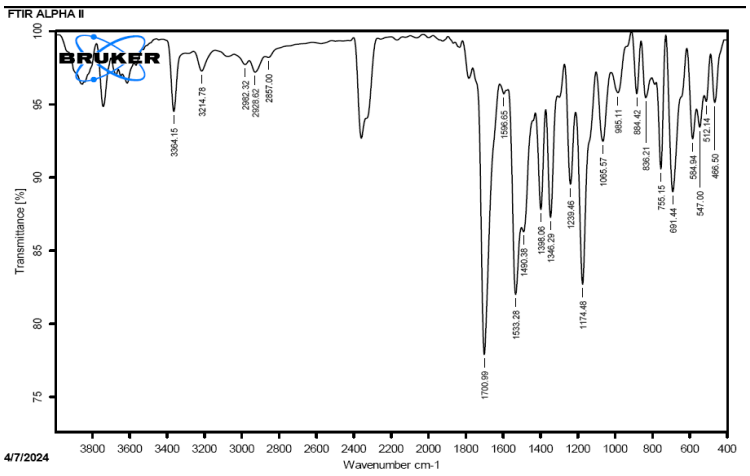

Fig. 6: FT-IR of S_1

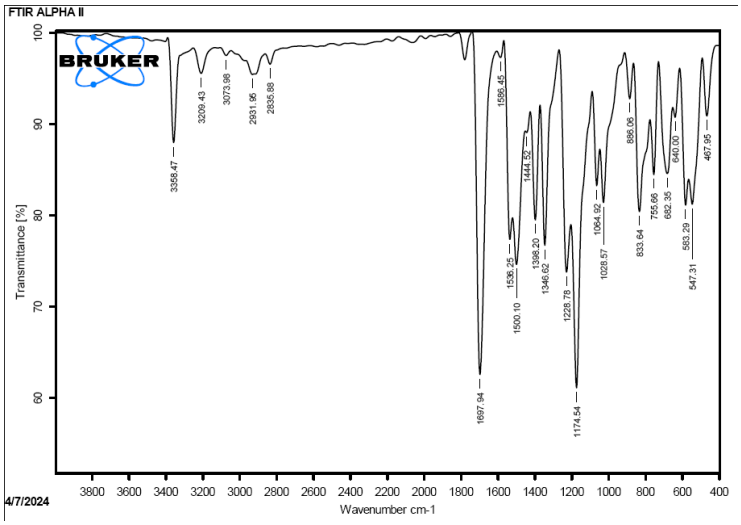

Fig. 7: FT-IR of S_2

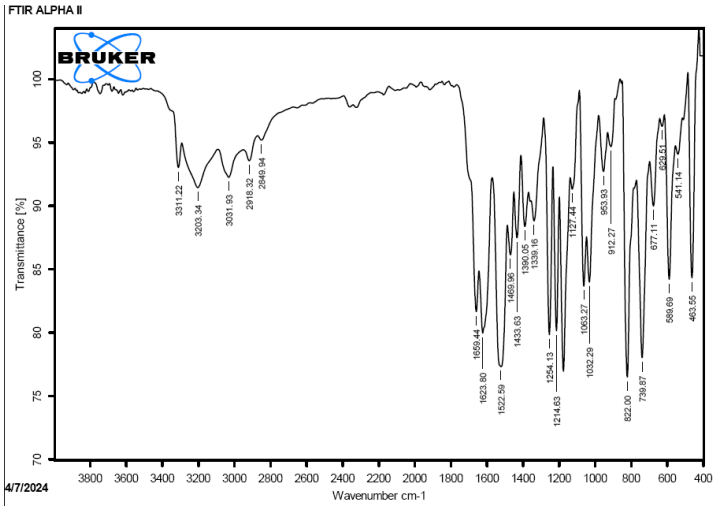

Fig. 8: FT-IR of S_3

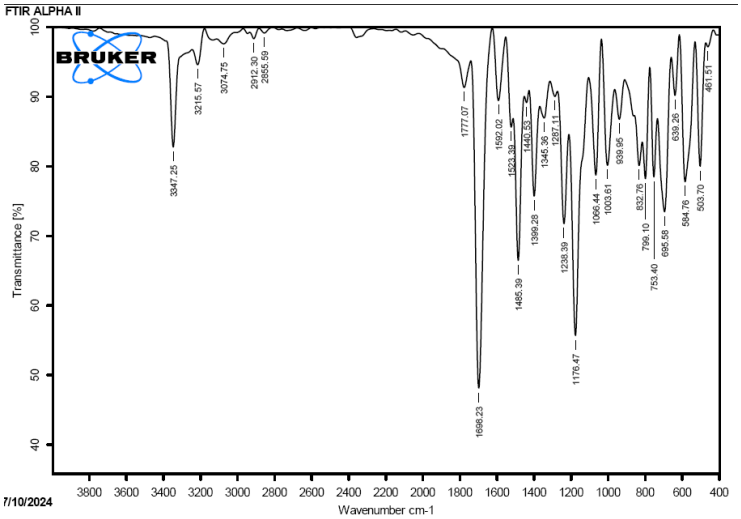

Fig 9: FT-IR of S_4

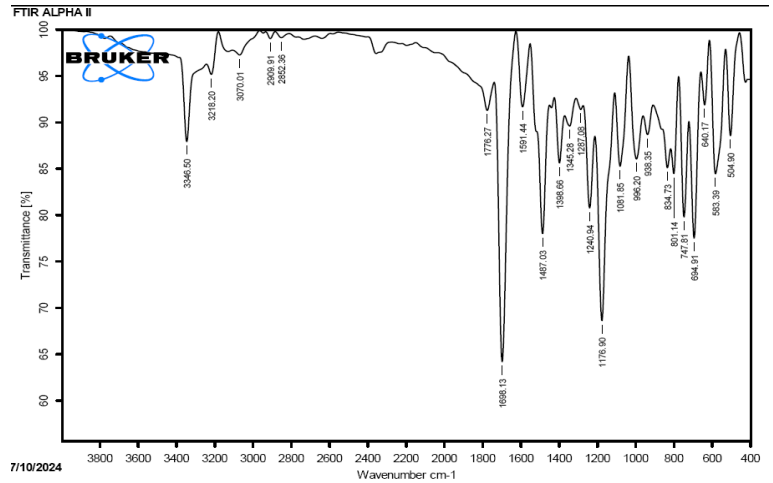

Fig. 10: FT-IR of S_5

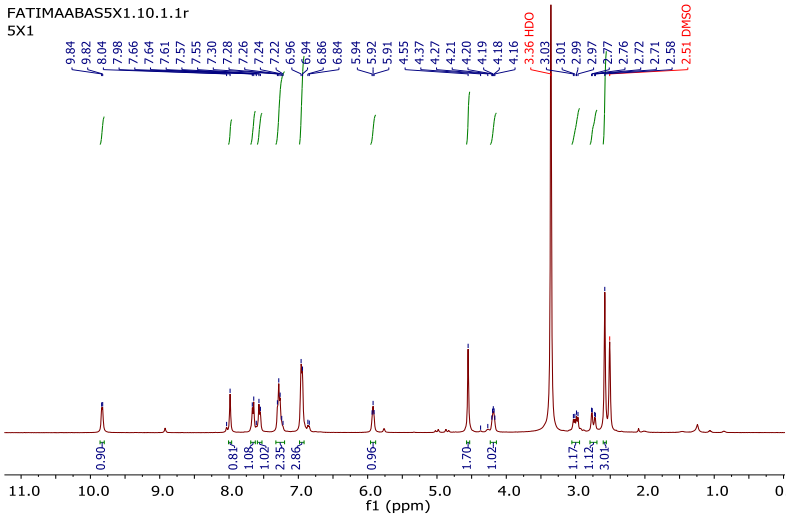

Fig. 11: 1HNMR of S_1

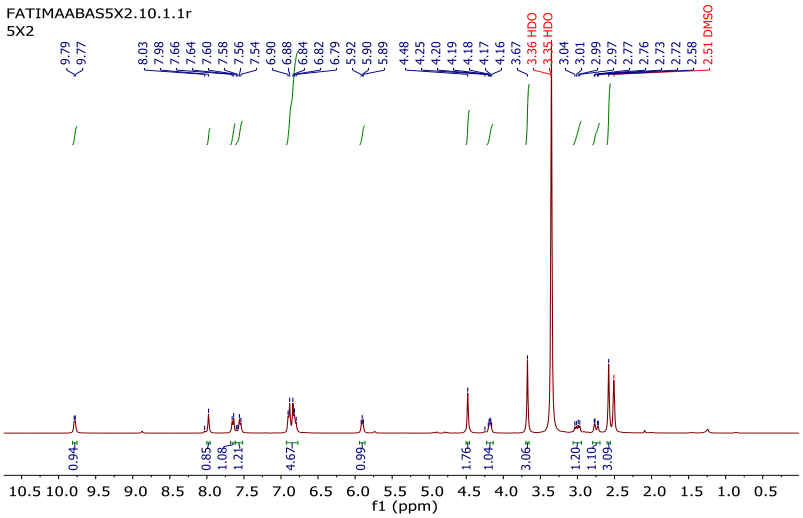

Fig.12: 1HNMR of S_2

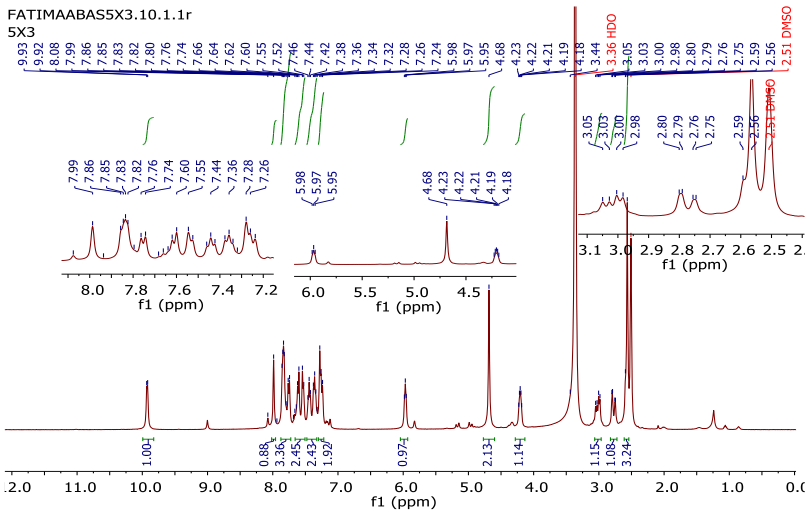

Fig. 13: 1HNMR of S_3

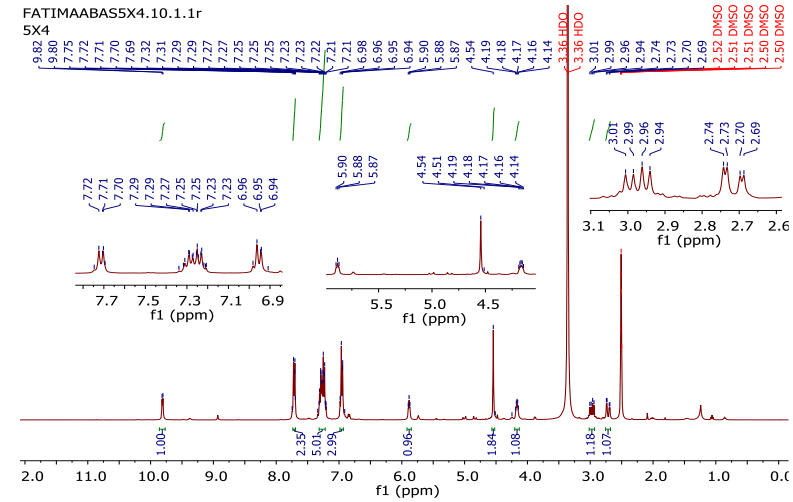

Fig. 14: 1HNMR of S_4

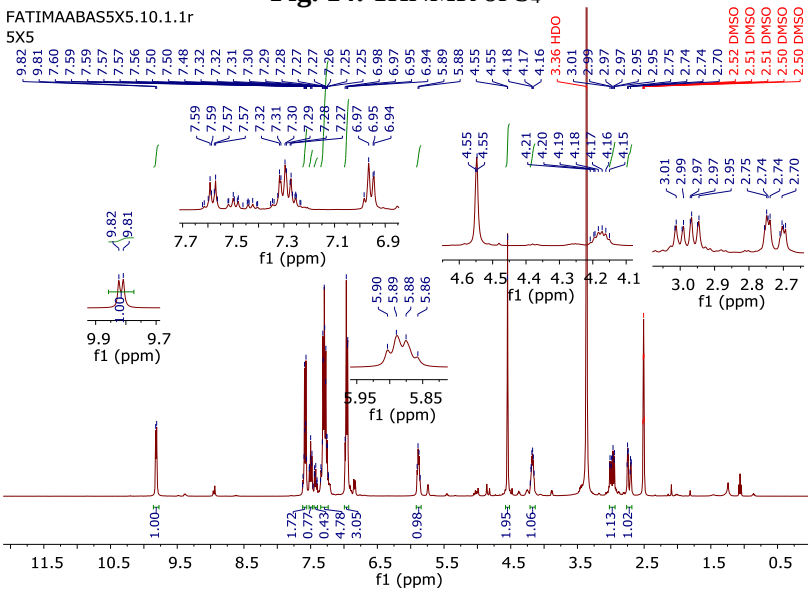

Fig. 15: 1HNMR of S_5

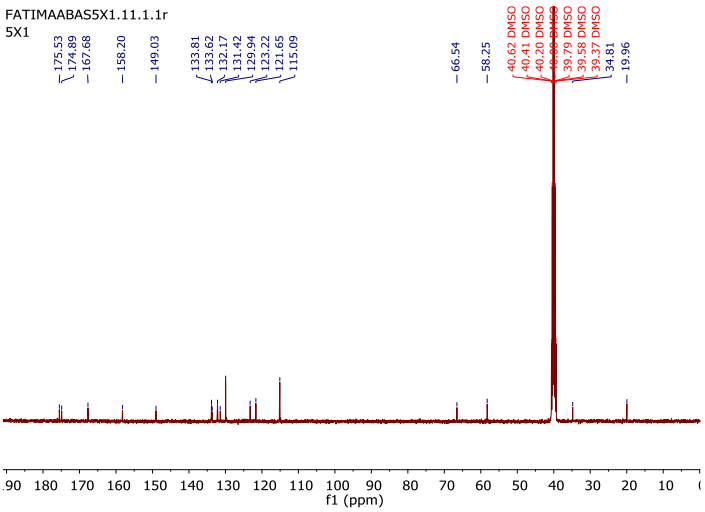

Fig. 16: 13C-NMR of S_1

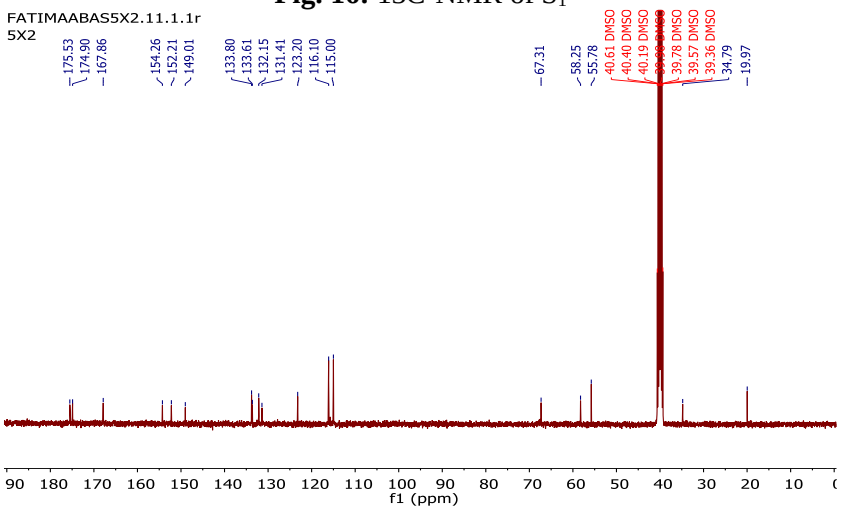

Fig. 17: 13C-NMR of S_2

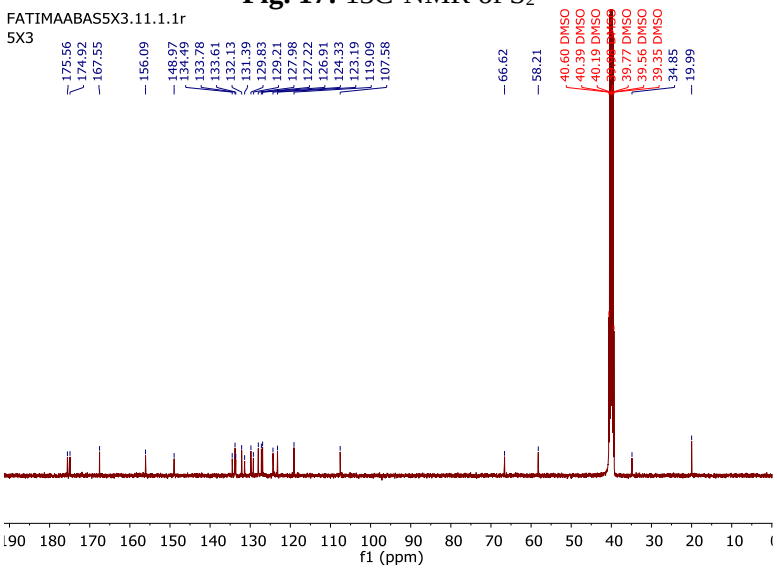

Fig. 18: 13C-NMR of S_3

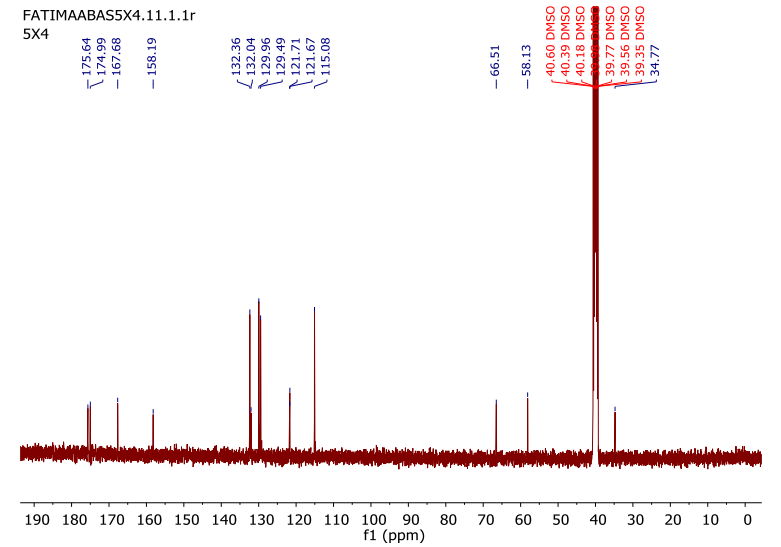

Fig.19: 13C-NMR of S_4

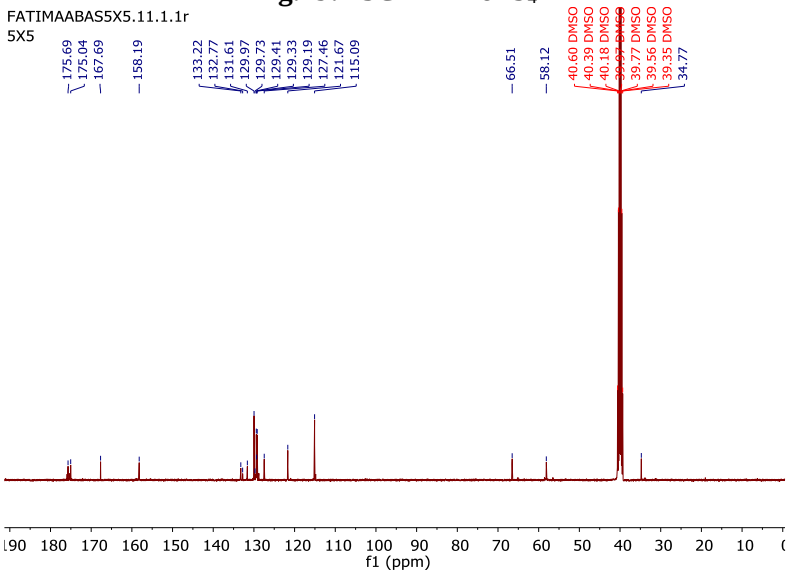

Fig. 20: 13C-NMR of S_5

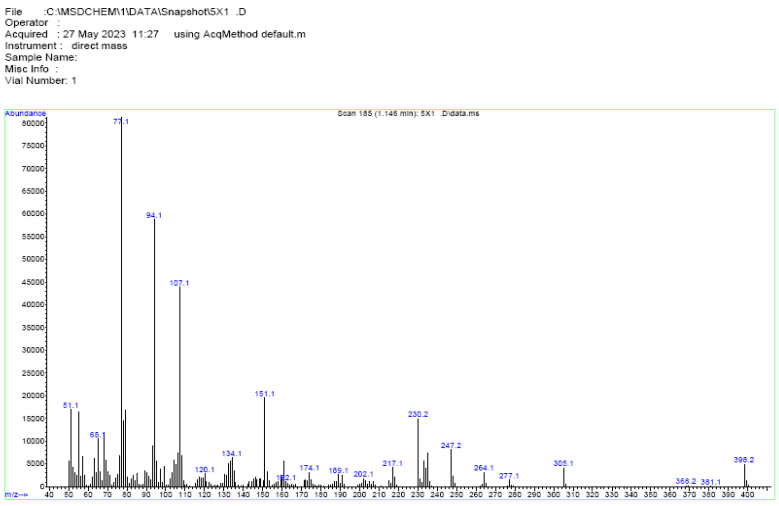

Fig. 21: Mass spectrum of S_1

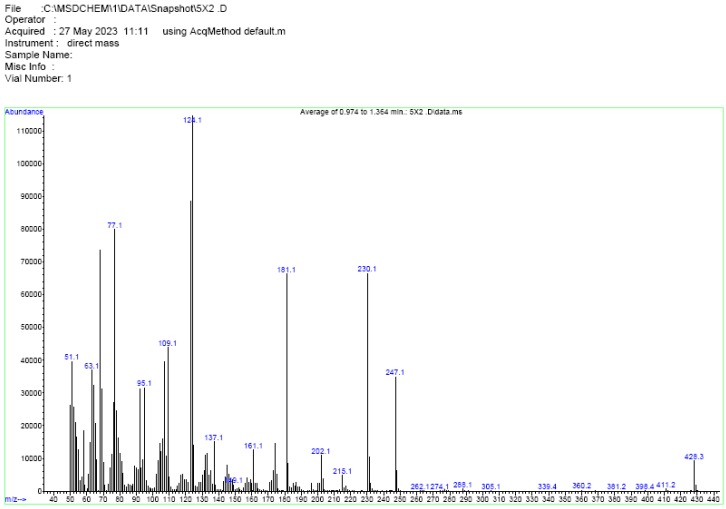

Fig.22: Mass spectrum of S_2

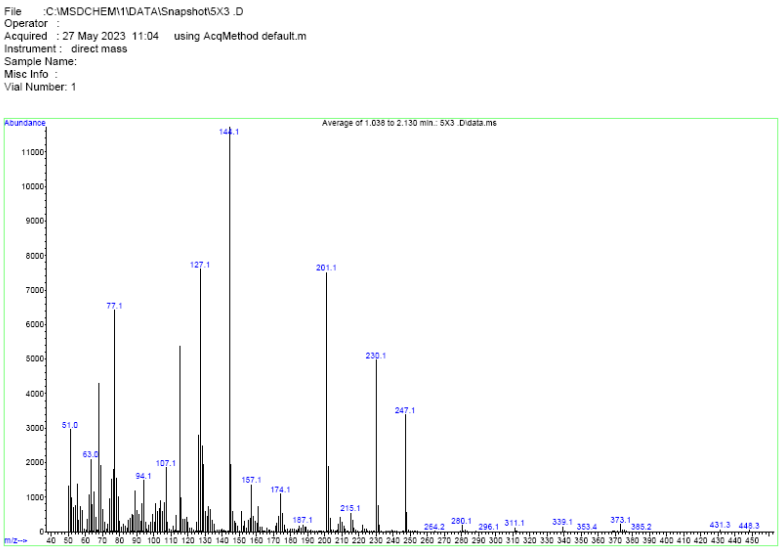

Fig.23: Mass spectrum of S_3

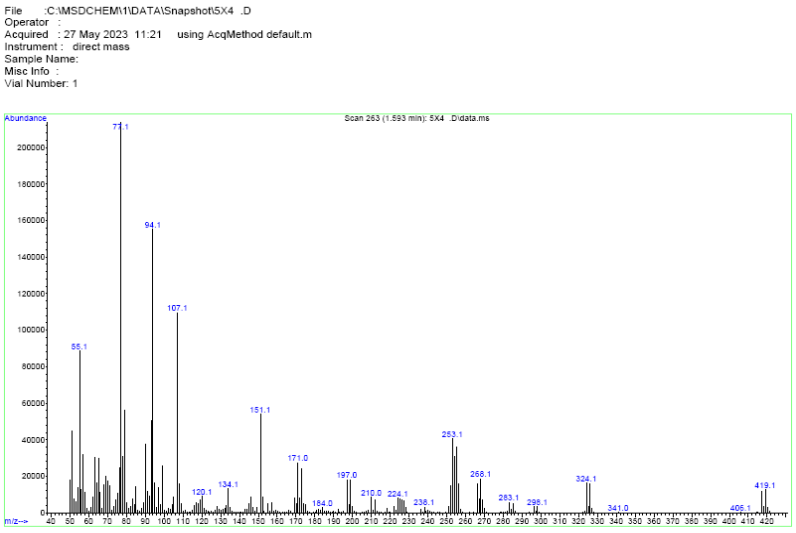

Fig.24: Mass spectrum of S_4

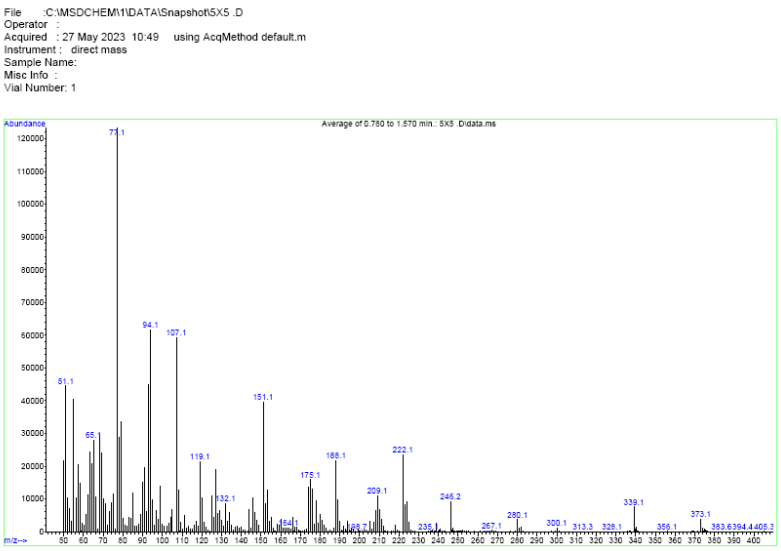

Fig.25: Mass spectrum of S_5

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تحضيروفعالية بعض مشتقات السكسينيمايد في مقاومة سرطان الثدي من خلال تفاعل اضافة مايكل: الاريل هيدرازايد الى الماليمايدات

فاطمة عباس احمد و داخل زغير مطلق

قسم الكيمياء,كلية التربية للعلوم الصرفة, جامعة البصرة, البصرة, العراق.

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معلومات البحث

الاستلام 6 أيلول 2024
المراجعة 10 كانون الأول 2024
القبول 16 كانون الأول 2024
النشر 31 كانون الأول 2024

الكلمات المفتاحية

التخليق , ن-الماليمايد المعوض , مشتقات الهيدرازايد و مضاد سرطان الثدي.

الملخص

في هذه الدراسة تم تخليق خمسة مركبات تضمنت مشتقات السكسينيمايد. تم تحضير مركبات جديدة (S_1-S_5) عن طريق تفاعل مشتقات الهيدرازيد مع ن-معوضات الماليمايد وتم تشخيصها بواسطة مطيافية الكتلة وبروتون وكاربون-13 للرنين النووي المغناطيسي ومطيافية الاشعة تحت الحمراء ونقطة انصهار المركبات المحضرة . تم اختبار خمسة مركبات لقدرتها على تثبيط سرطان الثدي باستخدام فحص MTT. عند اختبارها على خلايا سرطان الثدي اضهرت المركبات S_3 و S_4 و S_5 نشاطا مضادا للسرطان.

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