Al-Kufa University Journal for Biology / VOL.14 / NO.3 / Year: 2022
Print ISSN: 2073-8854 Online ISSN: 2311-6544

Synthesis, characterization and anti-breast cancer activity of some maleimide derivatives

Saja Jassim Faisal
Dakhil Zughayir Mutlaq
Department of chemistry, College of Education for pure Sciences, University of Basrah, Basrah,

Iraq.

Abstract

This study included the synthesis of four compounds of maleimide derivatives. Novel compounds (K1-K4) resulted from the reaction between N-substituted maleimide and aryl hydrazide (benzohydrazide, *p*-toluic hydrazide or isonazide). The novel maleimide derivatives were identified using infrared spectroscopy (FT-IR), ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry, as well as the melting point of the preparing compounds. The MTT assay were used to examine the anti-breast cancer (MCF-7) activities of four compounds. The compounds K2 and K4 demonstrated anti-cancer activity against breast cancer cells.

Keyword: synthesis, malemides, aryl hydrazide and anti-breast cancer.

Introduction

Asymmetric organocatalytic transformations such asymmetric cycloadditions, Michael reactions, and asymmetric cascade reactions have all been successfully carried out using maleimides, a significant class of substrates [1-9]. Maleimide functionalization by asymmetric organocatalysis makes chiral substituted succinimide compounds accessible. One of the strongest and most effective atom-economical carbon-carbon bond-forming reactions in synthetic chemistry is the Michael addition [10-13]. A potentially appealing method in particular offers up effective direct entry to substituted succinimides from simple precursors via the asymmetric Michael addition of maleimide [1-9].

Recently many researchers reported that maleimide derivatives can be used as selective inhibitors for monoglyceridelipase [14], Cdc25B [15], GSK-3α [16], Bfl-1[17] and DNMT-1[18]. Furthermore, Maleimides are also a member of the promising class of heterocyclic compounds that include the -CO-N(R)-CO chain. It is simple for them to pass across biological membranes because of their hydrophobic and neutral nature [19]. Thus, they are widely used for a variety of biological applications such as cytotoxicity, DNA binding, and apoptosis inducing activity, antibacterial [20], antimicrobial [21], antiprotozoal [22], analgesics [23], antitiangiogenic [24], and antistress agents. Maleimides are a new class of heterocyclic chemicals that have numerous biological uses. In order to create maleimide derivatives, several studies are motivated [25, 26].

EXPERIMENTAL

Chemistry

Gallenkamp apparatus used to measure melting point. The 1H and 13C-NMR spectra were recorded using deuterated solvents and tetramethylsilane (TMS) as

an internal standard. Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, the chemical shifts were indicated in (δ) ppm. Spectrophotometer FT-IR-1600 Perkin-Elmer was obtained from infrared spectra. Thin layer chromatography (TLC) used with Merck silica gel, and the spots were visualized in UV and I_2. Mass spectra were examined using the method using EI at 70 eV with Agilent Technologies 5975C Spectrometer.

Procedure for synthesis maleimides (M1-M2):

The same method was used as in literature [27, 28] with some modification, where maleanilic acids (0.01 mole) 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-K4) [29]**:**

A mixture of differently substituted maleimides (0.01mol) and aryl hydrazide (benzohydrazide, *p*-toluic hydrazide or 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.

4-(3-(2-isonicotinoylhydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K1)

White solid powder, yield 60 %, mp.=254-256 °C, IR (KBr, cm^{-1}): 3547-3477 (OH); 3414 (NH amide); 3329 (NH); 1784, 1714, 1645, 1608 (C=O); 1537, 1471 (C=C); 1396 (C-N); 1292 (C-O).

^{1}H-NMR (DMSO-d6): δ 13.04 (br.s, 1H, OH), 10.54 (d, 1H, J=8Hz, H_a), 8.75 (d, 2H, J=8 Hz, H_b), 8.07 (d, 2H, J=8 Hz, H_c), 7.74 (d, 2H, J=4 Hz, H_d), 7.45 (d, 2H, J=4Hz, H_e), 6.22 (t, 1H, J=8Hz, H_f), 4.29 (pent., 1H, J=4Hz, H_g), 3.12 (dd, 1H, J=8, 16 Hz, H_j), 2.82 (dd, 1H,J=4, 20 Hz, H_n). ^{13}CNMR(DMSO-d6): δ 175.48 (C_1), 175.01 (C_2), 167.16 (C_3), 164.82 (C_4), 150.77 (C_5), 140.35, 136.54, 130.85, 130.36, 127.31, 121.67 (C-Ar), 57.98 (C_6), 35.02 (C_7).

MS (z/m): 354.2 M^+.

3-(3-(2-(4-methylbenzoyl)hydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K2)

White solid powder, yield 75 %, mp.=232-235 °C, FT-IR (KBr, cm^{-1}): 3468-3419 (OH), 3319 (NH amide, 3224 (NH), 3078 (CH-Ar), 1714, 1637, 1612 (C=O), 1539, 1471 (C=C arom.), 1394 (C-N), 1186 (C-O). 1HNMR (DMSO-d6): δ 10.16 (d, 1H, J=4 Hz, H_a), 7.97 (d, 1H, J= 8Hz, H-Ar), 7.89 (t, 1H, J= 4Hz, H-Ar), 7.74 (d, 2H, J= 8 Hz, H-Ar), 7.62 (t, 1H, J= 8 Hz, H-Ar), 7.51 (d, 1H, J= 8Hz, H-Ar), 7.28 (d, 2H, J= 8 Hz, H-Ar), 6.03 (t, 1H, J= 8 Hz, H_b), 4.25 (pent., 1H, J=4 Hz, H_c), 3.08 (dd, 1H, J= 8,16 Hz, H_d), 2.82 (dd, 1H, J= 4, 20 Hz, H_e), 2.35 (s, 3H, CH_3).

13CNMR (DMSO-d6): δ 175.74 (C1), 175.33 (C2), 167.01 (C3), 166.54 (C4), 141.95, 133.05, 132.07, 131.73, 130.45, 129.73, 129.47, 129.38, 128.32, 127.70 (C-Ar), 58.27 (C5), 35.49 (C6), 21.47 (CH_3). MS (z/m): 367.2 M^+

4-(3-(2-benzoylhydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K3)

White solid powder, yield 70 %, mp.=267-268 °C, FT-IR (KBr, cm^{-1}): 3475 (OH), 3417 (NH amide, 3302 (NH), 3064 (CH-Ar), 2997 (CH alph.), 1786, 1714, 1637, 1610 (C=O), 1552, 1471 (C=C arom.), 1400 (C-N), 1184 (C-O).

^{1}HNMR (DMSO-d6): δ 13.21 (br.s, 1H, OH), 10.24 (d, 1H, J=8 Hz, H_a), 8.07 (d, 2H, J= 8Hz, H-Ar), 7.83 (d, 2H, J= 8Hz, H-Ar), 7.65-7.44 (m, 5H, H-Ar), 6.08 (t, 1H, J= 8 Hz, H_b), 4.27 (pent., 1H, J=4 Hz, H_c), 3.11(dd, 1H, J= 8,16 Hz, H_d), 2.84 (dd, 1H, J= 4, 20 Hz, H_e).

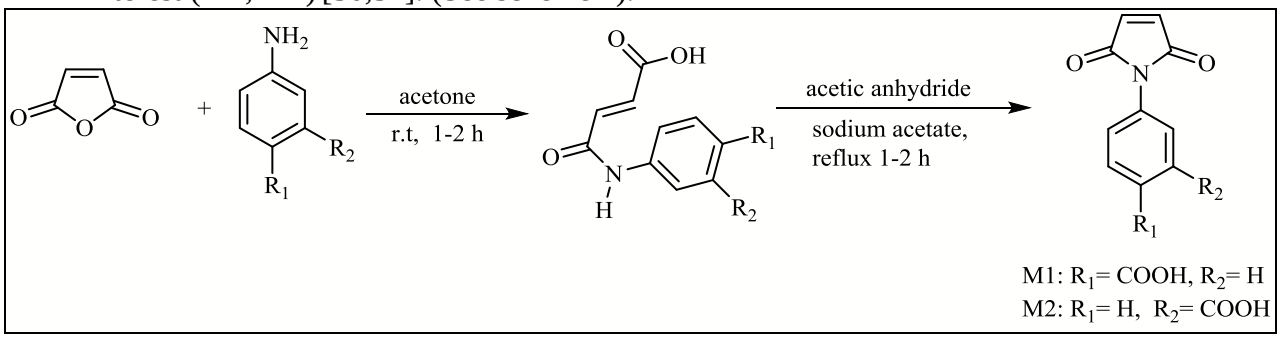
^{13}CNMR (DMSO-d6): δ 175.54 (C1), 175.08 (C2), 167.13 (C3), 166.68 (C4), 136.56, 133.31, 132.01, 130.90, 130.33, 128.86, 127.69, 127.29 (C-Ar), 58.19 (C5), 35.03 (C6).
MS (z/m): 353.1 M^+.

4-(3-(2-(4-methylbenzoyl)hydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K4)
White solid powder, yield 65 %, mp.=262-263 ^{o}C, FT-IR (KBr, cm^{-1}): 3468-3431(OH), 3321 (NH amide, 3261 (NH), 3058 (CH-Ar), 1748, 1710, 1637, 1610 (C=O), 1543, 1471 (C=C arom.), 1398 (C-N), 1182 (C-O).
^{1}HNMR (DMSO-d6): δ 13.18 (br.s, 1H, OH), 10.15 (d, 1H, J=4 Hz, H_a), 8.07-8.05 (m, 2H, H-Ar), 7.75-7.73 (m, 2H, H-Ar), 7.45-7.43 (m, 2H, H-Ar), 7.29 (d, 2H, J=8 Hz, H-Ar), 6.04 (t, 1H, J= 4 Hz, H_b), 4.26 (pent., 1H, J=4 Hz, H_c), 3.09 (dd, 1H, J= 8, 20 Hz, H_d), 2.83 (dd, 1H, J= 4, 16 Hz, H_e), 2.35 (s, 3H, CH_3).
^{13}CNMR (DMSO-d6): δ 175.56 (C1), 175.11 (C2), 167.13 (C3), 166.64 (C4), 141.96, 136.57, 130.86, 130.46, 130.45, 130.33, 129.38, 127.70, 127.29 (C-Ar), 58.24 (C5), 35.02 (C6), 21.45 (CH_3). MS (z/m): 367 M^+.

Results and Discussion

The N-substituted maleimides described herein were synthesized followed two main routs: The first one (scheme1) involves as *p*-aminobenzoic acid or *m*-aminobenzoic acid and maleic anhydride as building blocks, where as the second one requires aryl hydrazide (benzohydrazide, *p*-toluic hydrazide or isonazide) and maleimide (scheme 2).

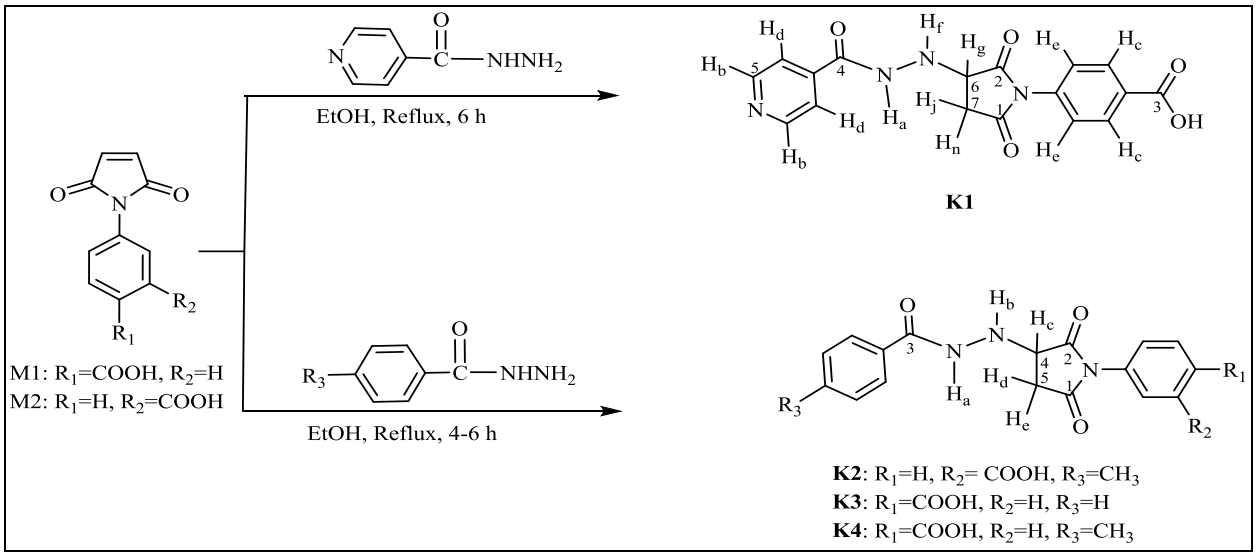
The N-substituted maleimides (M1, M2) were readily obtained using method by reacting the desired substituted aniline with maleic anhydride in solvent such as diethyl ether or acetone leading to the corresponding substituted maleanilic acid without any further purification, this open intermediate was subsequently cyclized in acetic anhydride in the presence of sodium acetate to the N-substituted maleimide of interest (M1, M2) [30,31]. (See scheme 1).



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

Conversion of N-substituted maleimides into corresponding maleimide derivatives through Michael addition with aromatic primary amine. After prepared N-substituted maleimides, synthesis of maleimide derivatives undertaken. The desired maleimide derivatives were prepared by Michael addition [32].

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



Scheme 2: Synthesis of compounds (K1-K4)

The chemical structures of all the resulting maleimide 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 3547-3419 cm^{-1}. The NH amide and NH groups were observed in the range of 3417–3319 and 3329–3224 cm^{-1}, respectively. The absorption bands in the 1786–1608 cm^{-1} area are linked to C=O [33]. The band in range (1552-1471) cm^{-1} was assigned to the C=C aromatic stretching [34,35]. (See Figures 1-4).

The maleimide derivatives (K1-K4) were used to generate ^{1}H-NMR spectra (See Figures 5-8). Signals at δ 2.5 and δ 3.3 belong to the solvent DMSO-d6 and water, respectively. The OH proton in compound (K1) appears at δ 13.04. Because they are attached to carbon adjacent to the chiral center, the doublet of doublets peaks at δ 2.82 and 3.12 belong to H_n and H_j protons, respectively. At δ 4.29, H_g was responsible for the pentent. A triplet signal at δ 6.22 was assigned to the proton of H_f. Doublet signal at δ 10.54 were due to H_a. Aromatic protons (H_b, H_c, H_d, H_e) were given the signals of duplet at roughly 8.75–7.45. The ^{13}C- NMR of the compounds K1 that showed signals at around δ 175.48–164.82 were attributed to carbonyl groups. The signals of the carbon aromatic ring appeared in the range of δ 150.77-121.67. The aliphatic carbons are present in δ 57.98 for C_6 and δ 35.02 for C_7 (See Fig. 9). The mass spectrum of the compound K1 revealed the presence of a molecular ion (*m*/*z*): 354.2 M^{+} (See Fig. 13).

Other compounds (K2-K4) were also distinguished by the appearance of signal doublet of doublets at around δ 3.11-3.08 and 2.84-2.82, which belongs to H_d and H_e protons , respectively. Because the hydrogen atoms of the methylene group are adjacent to the chiral center.

At δ 4.27–4.25, H_c was responsible for the signal of pentent. Triplet signals at around δ 6.08–6.03 were assigned to the proton of H_b. Doublet signals at around δ 10.24–10.15 were due to Ha. The broad signals corresponding to OH appeared in the range of δ 13.21-13.18. Aromatic protons were given the signals (doublet, triplet and

multiplet) at roughly δ 8.07–7.28 [36]. The methyl groups responsible for the singlet are at δ 2.35.

The ^{13}C- NMR of the compounds K2-K4 that showed signals at around δ 175.74–166.54 were attributed to carbonyl groups. The signals of the carbon aromatic ring appeared in the range of δ 141.96-127.29. The aliphatic carbons are present in the range δ 58.27–21.45 (See Fig. 10-12). The mass spectra of the K2–K4 groups revealed the presence of a molecular ion (*m*/*z*): 367.2 (M^+), 353.1 (M^+), and 367 (M^+). (See Fig. 14-16).

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 maleimide derivatives and succinimide derivatives exhibited promising structures for developing new agents as anticancer agents with merit investigation [41–44].

The prepared compounds were studied against anti-breast cancer using the MTT test.

The data indicate, based on the IC_{50} value, that some compounds of the series have anti-breast cancer activity. The compounds (K2 and K4) showed anti-breast cancer activity. The good activity of compound K2 and K4 compared to the rest of the compounds is due to the methyl group. Table (1) shows the IC_{50} values.

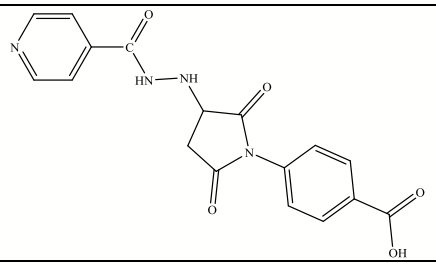
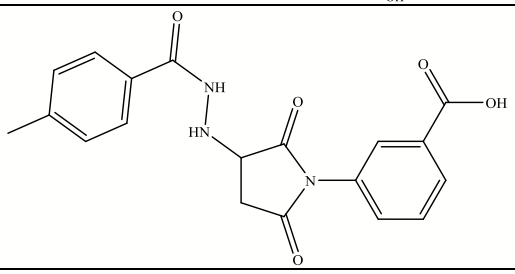
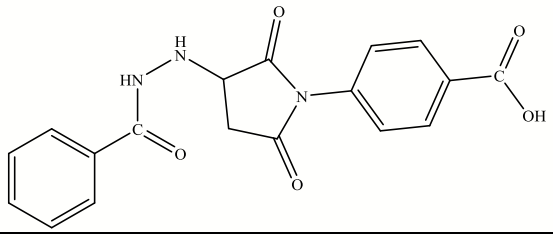
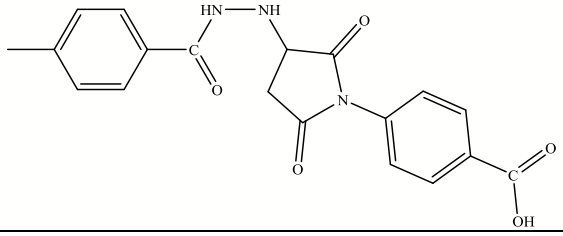
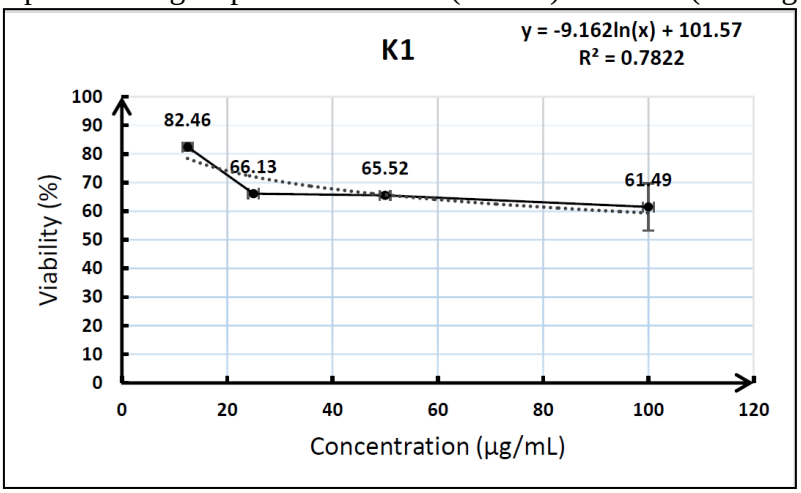
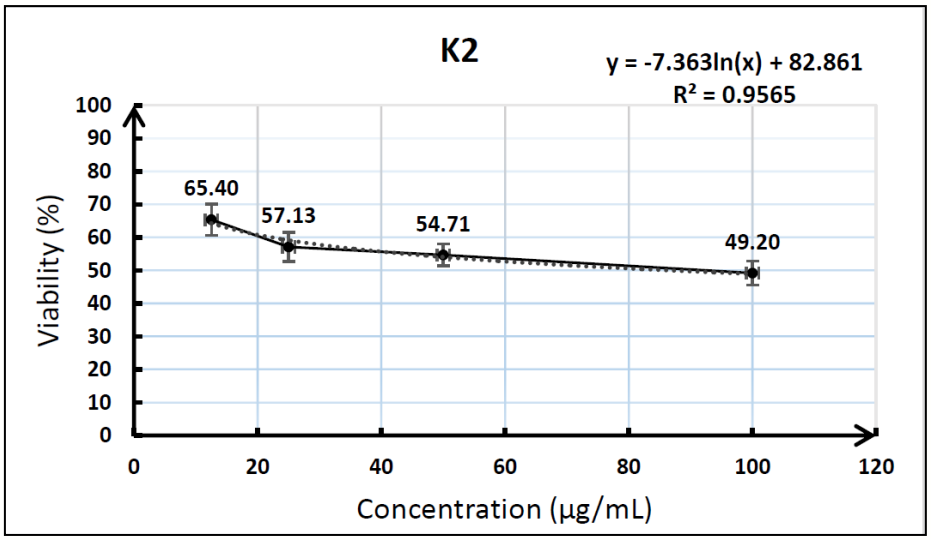
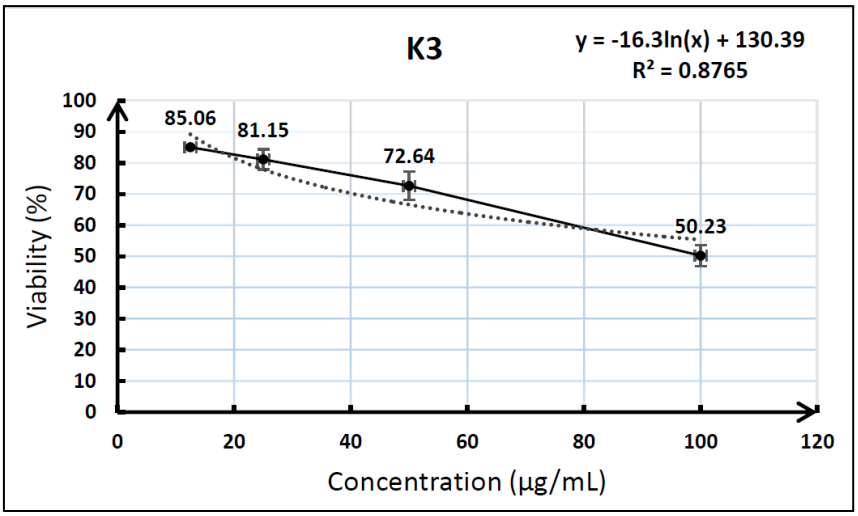
Symbol	Structure	PC3 cells IC50 in µg/mL	
K1		713.3	Inactive
K2		86.7	active
K3		138.6	Inactive
K4		91.2	active

Table 1 shows the IC50 values of (K1-K4) compounds versus PC3 cells

Below are graphs showing response curves for (K1-K4) vehicles. (See Fig. 17).







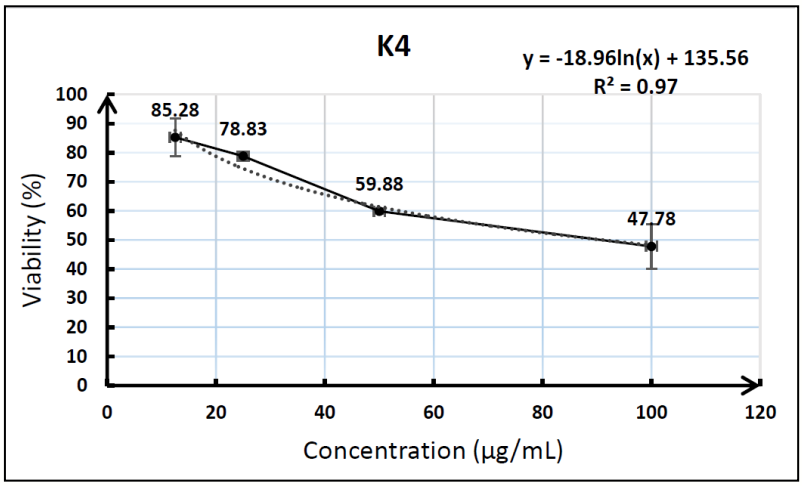


Fig. 17: The graphic curves of the prepared compounds

Conclusion

In conclusion, a series of maleimide derivatives were successfully synthesized from N-substituted maleimides with aryl hydrazide (benzohydrazide, *p*-toluic hydrazide or isonazide) and characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra. The

compounds were tested for anti-breast cancer activities. Anti-breast cancer activity was demonstrated by the compounds 3-(3-(2-(4-methylbenzoyl)hydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K2) and 4-(3-(4-methylbenzoyl)hydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K4).

The compounds 3-(3-(2-(4-methylbenzoyl)hydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K2) and 4-(3-(2-(4-methylbenzoyl)hydrazinyl)-2,5-dioxopyrrolidin-1-yl)benzoic acid (K4) were exhibited anti-breast cancer activity.

References

[1] Bosco M, Carlone A, Cavalli A, Locatelli M, Mazzanti A, Ricci P, Sambri L, Melchiorre P. Organocatalytic asymmetric conjugate addition of 1,3-dicarbonyl compounds to maleimides. *Angew Chem Int Ed* 2006; 45: 4966–4970.

[2]Ye W, Jiang Z, Zhao Y, Goh SLM, Leow D, Soh YT, Tan C-H. Chiral bicyclic guanidine as a versatile Brønsted base catalyst for the enantioselective Michael reactions of dithiomalonates and β-keto thioesters. *Adv Synth Catal* 2007; 349: 2454–2458.

[3] Jiang Z, Ye W, Yang Y, Tan C-H. Rate Acceleration of triethylaminemediated guanidine-catalyzed enantioselective Michael reaction. *Adv Synth Catal* 2008; 350: 2345–2351.

[4] Jiang Z, Pan Y, Zhao Y, Ma T, Lee R, Yang Y, Huang K-W, Wong MW, Tan C-H. Synthesis of a chiral quaternary carbon center bearing a fluorine atom: enantio- and diastereoselective guanidine-catalyzed addition of fluorocarbon nucleophiles. *Angew Chem Int Ed* 2009; 48: 3627–3631.

[5] Bai J-F, Peng L, Wang L-L, Wang L-X, Xu X-Y. Chiral primary amine thiourea promoted highly enantioselective Michael reactions of isobutylaldehyde with maleimides. *Tetrahedron* 2010; 66: 8928–8932.

[6] Miura T, Nishida S, Masuda A, Tada N, Itoh A. Asymmetric Michael additions of aldehydes to maleimides using a recyclable fluorous thiourea organocatalyst. *Tetrahedron Lett* 2011; 52: 4158–4160

[7] Mazzanti A, Calbet T, Font-Bardia M, Moyano A, Rios R. Organocatalytic enantioselective pyrazol-3-one addition to maleimides: Reactivity and stereochemical course. *Org Biomol Chem* 2012;10:1645–1652.

[8] Kokotos CG. An asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides leading to a one-pot enantioselective synthesis of lactones catalyzed by amino acids. *Org Lett* 2013;15:2406–2409.

[9] AbdulJabar, L. A., Al-Shawi, A. A., & Mutlaq, D. Z. Anti-liver and anti-breast cancer activities of 2-thioxo-4-imidazolidinone derivatives. *Medicinal Chemistry Research* 2021; 30(10): 1943-1953.

[10] Berner OM, Tedeschi L, Enders D. Asymmetric Michael additions to nitroalkenes. *Eur J Org Chem* 2002;12:1877–1895.

[11] Christoffers J, Baro A. Construction of quaternary stereocenters: new perspectives through enantioselective Michael reactions. Angew Chem Int Ed 2003;42:1688–1690.

[12] Tsogoeva SB. Recent advances in asymmetric organocatalytic 1,4-conjugate additions. *Eur J Org Chem* 2007;72:1701–1716.

[13] Sulzer-Mosse S, Alexakis A. Chiral amines as organocatalysts for asymmetric conjugate addition to nitroolefins and vinyl sulfones via enamine activation. *Chem Commun* 2007; 43: 3123–3135

[14] Matuszak, N., Muccioli, Laber, G., G., Lambert, D., Synthesis and in Vitro Evaluation of NSubstituted Maleimide Derivatives as Selective Monoglyceride Lipase Inhibitors, *J. Med. Chem.* 2009; 52: 7410-7420. https://doi.org/10.1021/jm900461w

[15] Chen, H., Liu, Y., Wang, I., Shen, Q., Li, J., Nan F., Discovery and structural optimization of pyrazole derivatives as novel inhibitors of Cdc25B, Bioorg. *Med. Chem.* 2010; 20: 2876-2879. https://doi.org/10.1016/j.bmcl.2010.03.040

[16] Sivaprakasam, P., Xie, A., Doerksen, R., Probing the physicochemical and structural
requirements for glycogen synthase kinase-3α inhibition: 2D-QSAR for 3-anilino-4-phenyl maleimides, *Bioorg. Med. Chem*. 2006; 14: 8210-8218.
https://doi.org/10.1016/j.bmc.2006.09.021

[17] Cashman, J.R., MacDonald, M., Ghirmai, S., Okolotowicz, K.J., Serienko, E., Brown, B., Garcio, X., Zhai, D., Dahl, R., Reed, J.C., Inhibition of Bfl-1 with N-aryl maleimides, *Bioorg.*
Med. Chem. 2010; 20: 6560-6564. http://doi.org/10.1016/j.bmcl.2010.09.046

[18] Suzuki, T., Tanaka, R., Hamada, S., Nakagawa, H., Miyata, N., Design, synthesis, inhibitory activity, and binding mode study of novel DNA methyltransferase inhibitors, *Bioorg. Med. Chem.* 2010; 20: 1124-1127. https://doi.org/10.1016/j.bmcl.2009.12.016

[19] Bansode, T.N., Shelke, J.V., Dongre, V.G., Synthesis and antimicrobial activity of some new N-acyl substituted phenothiazines, *Eur. J. Med. Chem.* 2009; 44: 5094-5098.
https://doi.org/10.1016/j.ejmech.2009.07.006

[20] Lopez, S.N., Sortino, M., Escalante, A., Campos, F., Correa, R., Cechinel-Filho, V., Nunes, R.J., Zacchino, S.A., Antifungal properties of novel N- and alpha,beta-substituted succinimides against dermatophytes, Arzneim-Forsch. *Drug. Res.* 2003; 53: 280-288. https://DOI:10.1055/s-0031-1297109

[21] Panov, A.A., Lavrenov, S.N., Imonov, A.Y., Mirchink, E.N., Iakova, E.B., Trenin, A.S.,
Synthesis and antimicrobial activity of 3, 4-bis(arylthio)maleimides, *J. Antibiot* 2018; 72:
122-124. https://doi.org/10.1038/s41429-018-0122-3

[22] Durust, Y., Karakus, H., Kaiser, M., Tasdemir, D., Synthesis and anti-protozoal activity of novel dihydropyrrolo[3,4-d][1,2,3]triazoles, *Eur. J. Med. Chem.* 2012; 48: 296-304.
https://doi.org/10.1016/j.ejmech.2011.12.028

[23] Mahle, F., Guimaraes, T., Meira, A., Correa, R., Cruz, R., Nunes, R., Cechinel_Filho, V., Campo-Buzzi, F., Synthesis and biological evaluation of N-antipyrine-4-substituted amino-3-chloromaleimide derivatives, *Eur. J. Med. Chem.* 2012; 45: 4761-4768.

[24] Acero, N., Brana, M.F., Anorbe, L., Dominguez, G., Munoz-MIngarro, D., Mitjans, F., Piulat, J., Synthesis and biological evaluation of novel indolocarbazoles with anti-angiogenic activity, *Eur. J. Med. Chem.* 2012; 48: 108-113. http://doi.org/10.1016/j.ejmech.2011.11.040

[25] Badru, R., Anand, P., Singh, B., Synthesis, and evaluation of hexahydropyrrolo[3,4-
d]isoxazole-4,6-diones as anti-stress agents, *Eur. J. Med. Chem.* 2012; 48: 81-91. https://doi.org/10.1016/j.ejmech.2011.11.037

[26] Mutlaq, D. Z., & shafiq Abd, M. Synthesis and biological activity of some maleimide derivatives. *Journal of Basrah Researches ((Sciences))*, (2019); 45,88-97.

[27] Matuszak, N.; Muccioli, G. G.; Labar, G. and Lambert, D. M., *J. Med. Chem.*, 2009, 52, 74122-7420.
[28] Yang, C. P.; Wang, S. S., *J. Appl. Polym. Sci*., 1987, 28, 2509.
[29] Salhi, L.; Bouzroura-Aichouche, S.; Benmalek, Y.; Bentarzi, Y.; Poulain-Martini, S.; Cacciuttolo, B.; Dunach, E.; Nedjar-Kolli, B., *Organic Communications*, 2013**,** 6 (2), 87-94.
[30] Matuszak, N., Muccioli, G. G., Labar, G., and Lambert, D. M., *J. Med. Chem.* 2009; 52: 74122-7420.
[31] Yang, C. P., Wang, S. S., *J. Appl. Polym. Sci*. 1987; 28: 2509.
[32] Salhi, L.; Bouzroura-Aichouche, S.; Benmalek, Y.; Bentarzi, Y.; Poulain-Martini, S.; Cacciuttolo, B.; Dunach, E.; Nedjar-Kolli, B., *Organic Communications* 2013**,** 6 (2), 87-94.
[33] Al-Azzawi, A. M.; Yaseen, H. K., *Journal of Chemical and Pharmaceutical Research* 2016**,** *8* (8), 241-247.
[34] A. J. Ashish Kumar and J. K. M. *Heterocyclic Letters* 2012**,** 2 (4), 401-404.
[35] Kumar A, Jakhar A, Makrandi JK. A highly efficient solvent free synthesis of hydrazides using grinding technique. *Heterocyclic Lett* 2012; 2:401–404.
[36] Xia L, Zhai X, Xiong X, Chen P. Synthesis and properties of 1, 3, 4- oxadiazole-containing bismaleimides with asymmetric structure and the copolymerized systems thereof with 4, 4′-bismaleimidodiphenylmethane. *RSC Adv* 2014; 4:4646–4655.
[37] Singh M, Sharma P, Singh PK, Singh TG, Saini B. Medicinal potential of hetero-cyclic compounds from diverse natural sources for the management of cancer. *Mini Rev Med Chem* 2020; 20:942–957.
[38] Khalaf M, Abdulamir A, Al-Shawi AA. Synthesis, characterization and cytotoxicity appraisal of original 1, 2, 3-Triazole derivatives, against breast cancer cell lines (MDA-MB-231). *Mediterr J Chem* 2019; 9:305–310.
[39] Odle TG. Precision medicine in breast cancer. Radiol Technol 2017; 88:401M–421M.
[42] Fisusi FA, Akala EO. Drug combinations in breast cancer therapy. *Pharm Nano Technol* 2019;7:3–23.
[40] Gutierrez-Canon JR, Nahide PD, Ramadoss V, Satkar Y, Ortiz-Alvarado R, Alba-Betancourt C, *et al.* Synthesis and biological evaluation of new 3, 4-diarylmaleimides as enhancers (modulators) of doxorubicin cytotoxic activity on cultured tumor cells from a real case of breast cancer. *J Mex Chem Soc* 2017; 61:41–49.
[41] Lahnsteiner M, Kastner A, Mayr J, Roller A, Keppler BK, Kowol CR. Improving the stability of maleimide-thiol conjugation for drug targeting. *Chemistry* 2020; 26:15867–15870.

[42] Shaikh IN, Rahim A, Faazil S, Adil SF, Assal ME, Hatshan MR. BF3-OEt2 catalyzed C3-alkylation of indole: synthesis of indolylsuccinimidesand their cytotoxicity studies. *Molecules* 2021; 26: 2202.

[43] Imran M, Bisht AS, Asif M. A review on biological and chemical potential of phthalimide and maleimide derivatives. *Acta Sci Pharma Sci* 2019; 3:51–67.

[44] Zhao Z, Yue J, Ji X, Nian M, Kang K, Qiao H, Zheng X. Research progress in biological activities of succinimide derivatives. *Bioorg. Chem.* 2021; 108, 104557.

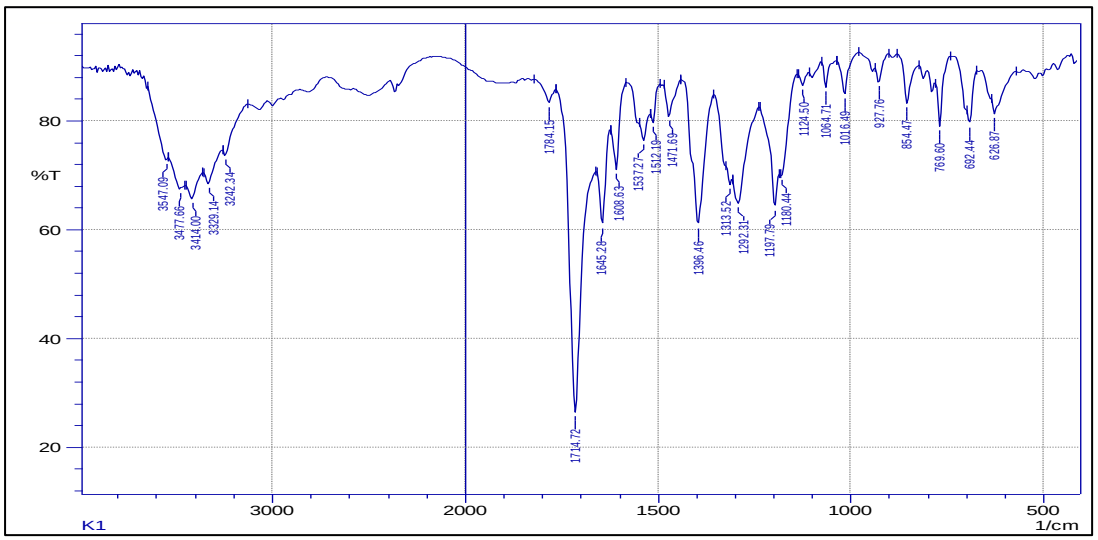


Fig. 1: FT-IR of compound K1

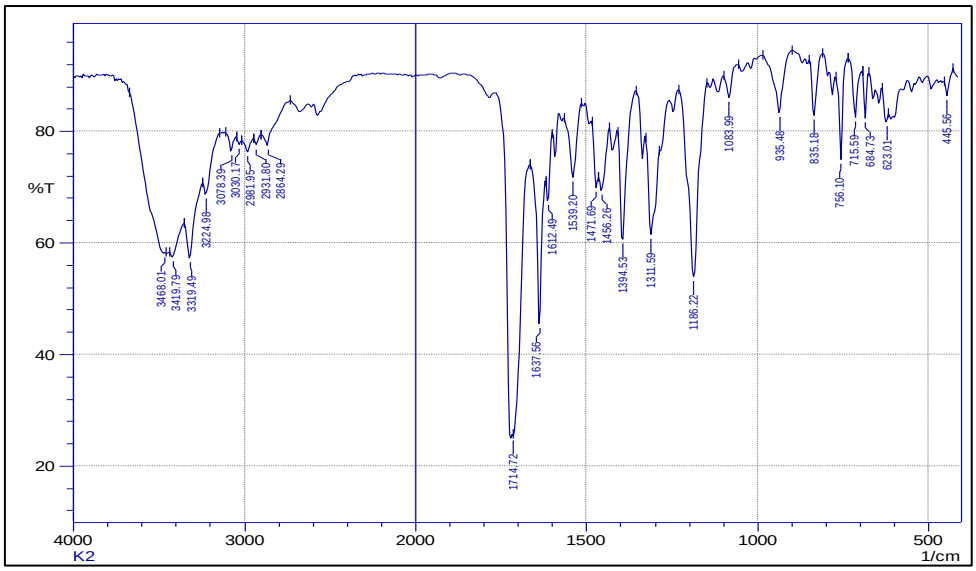


Fig. 2: FT-IR of compound K2

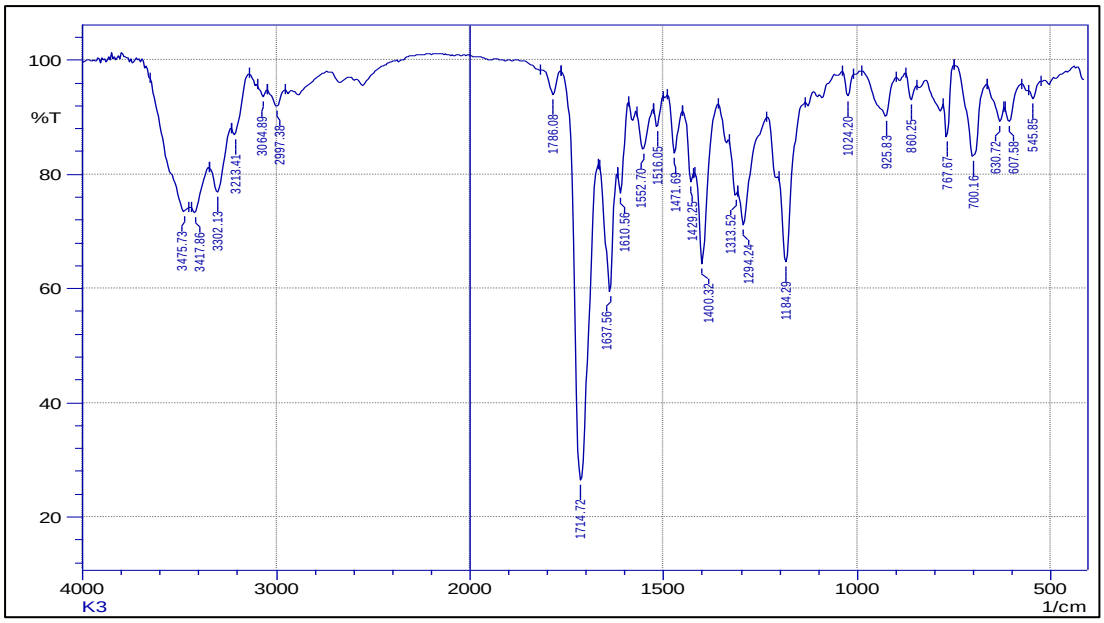


Fig. 3: FT-IR of compound K3

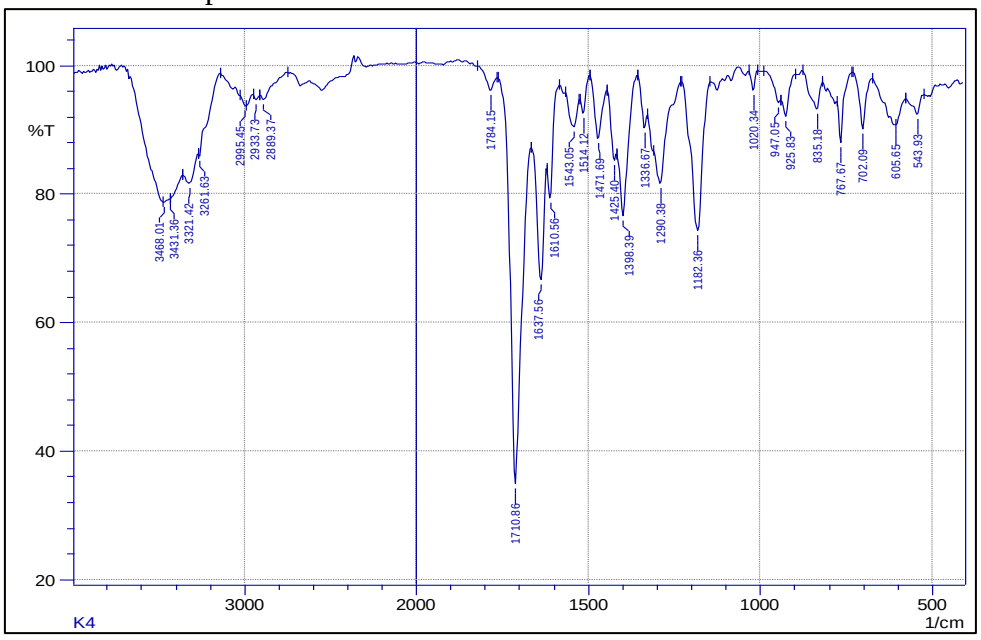


Fig. 4: FT-IR of compound K4

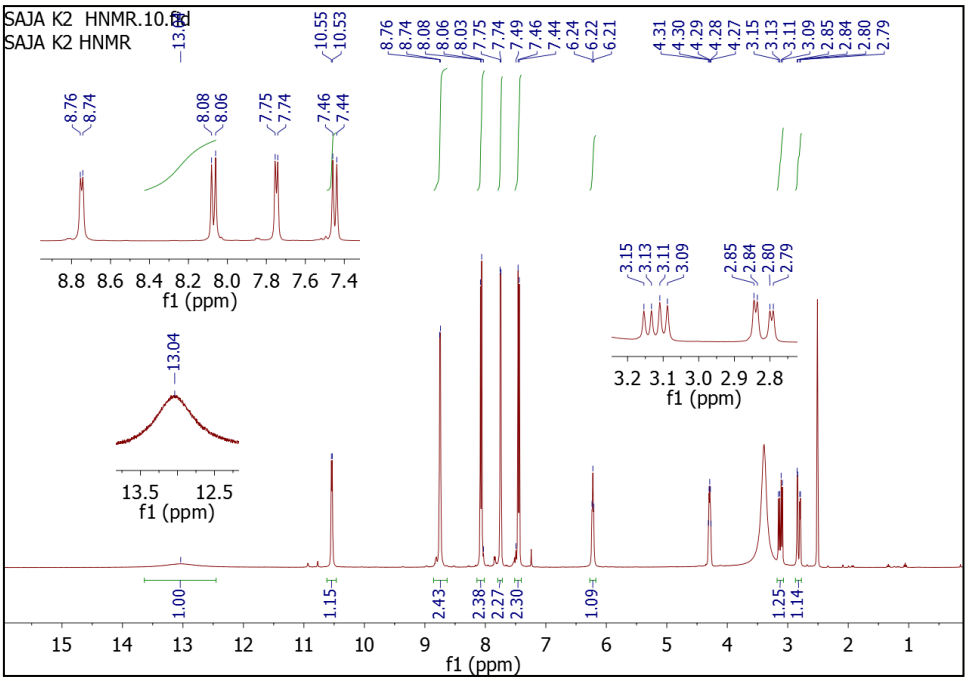


Fig. 5: 1H-NMR of compound K1

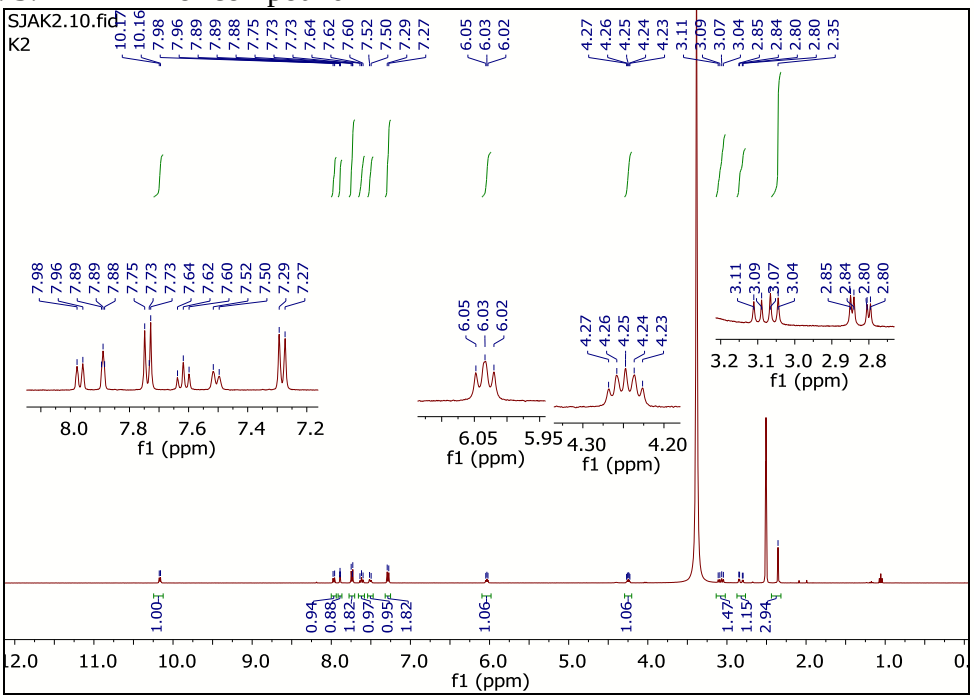


Fig. 6: 1H-NMR of compound K2

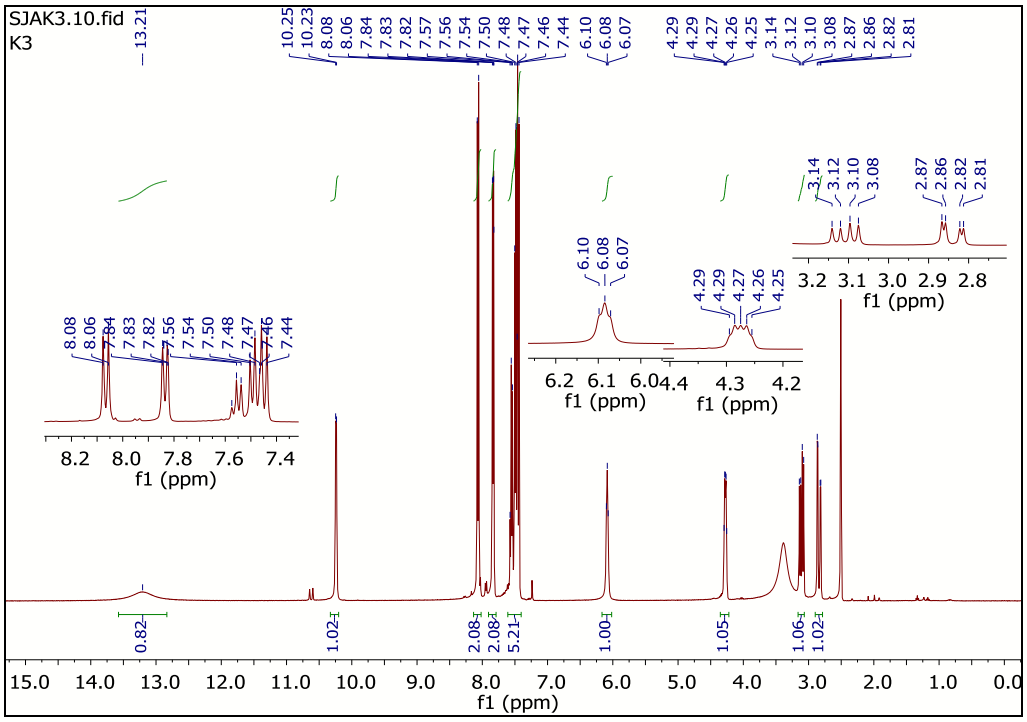


Fig. 7: 1H-NMR of compound K3

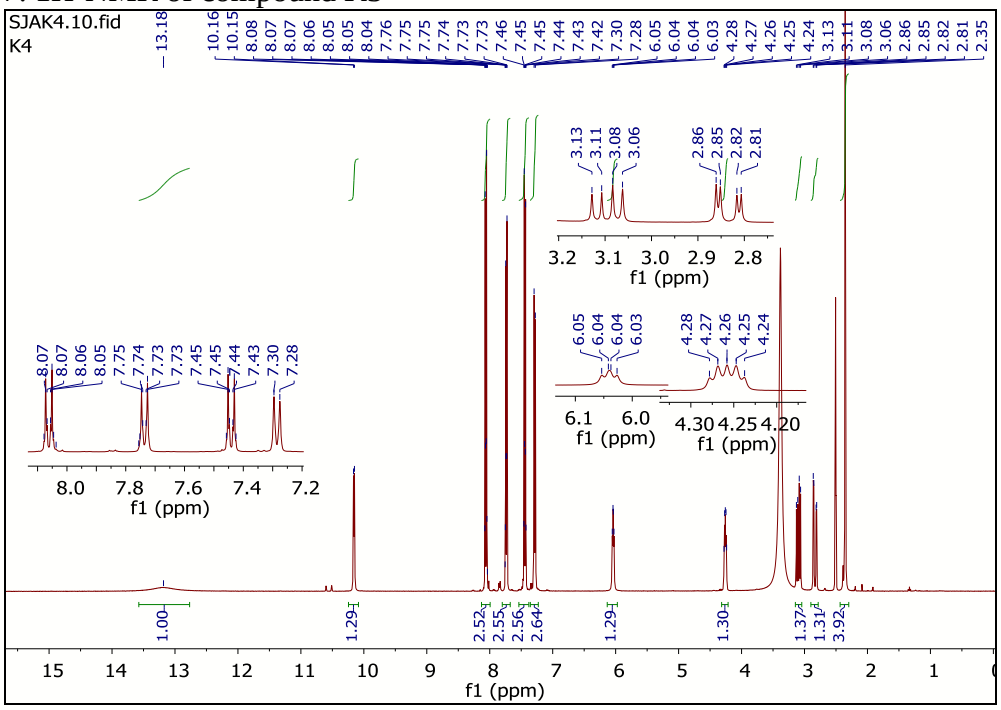


Fig. 8: 1H-NMR of compound K4

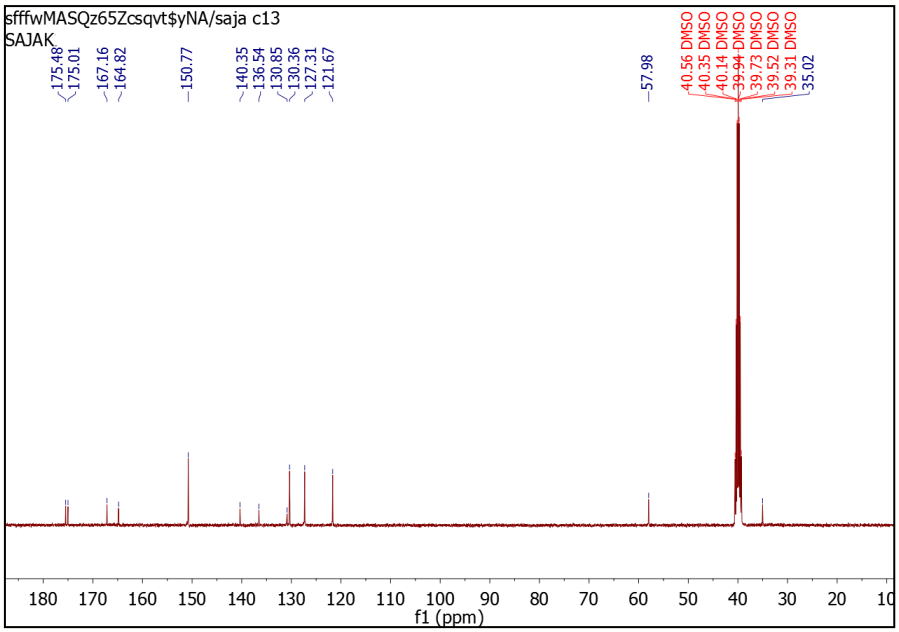


Fig. 9: 13C-NMR of compound K1

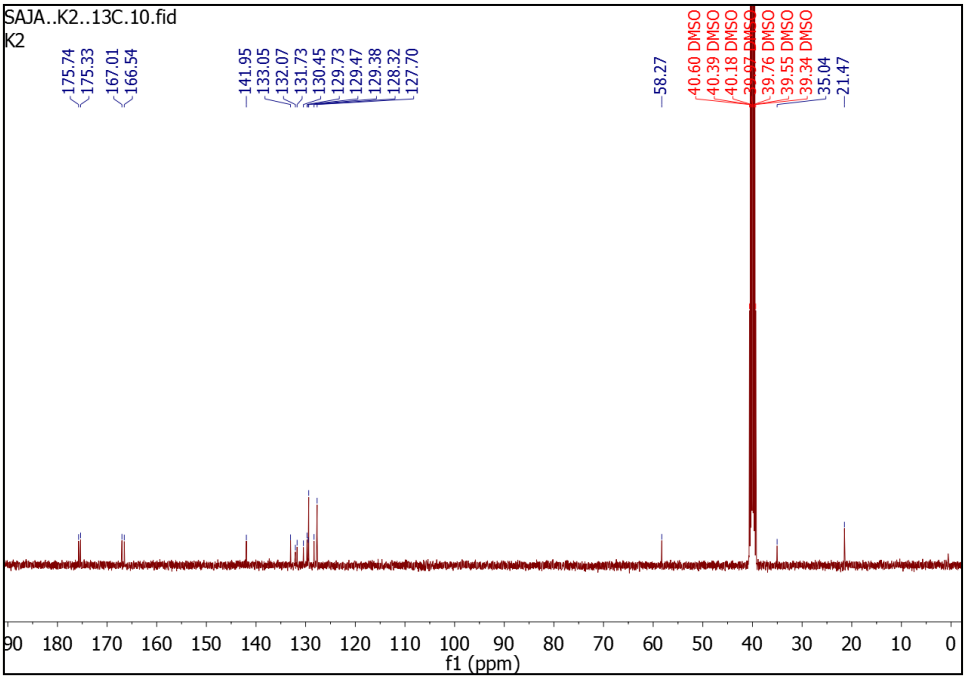


Fig. 10: 13C-NMR of compound K2

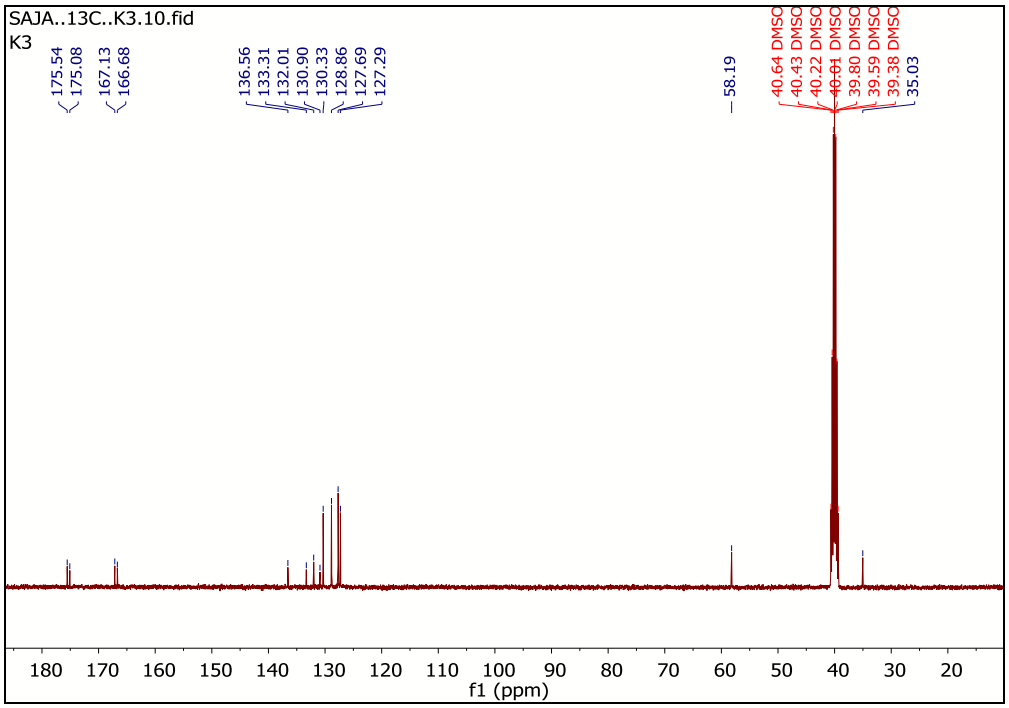


Fig. 11: 13C-NMR of compound K3

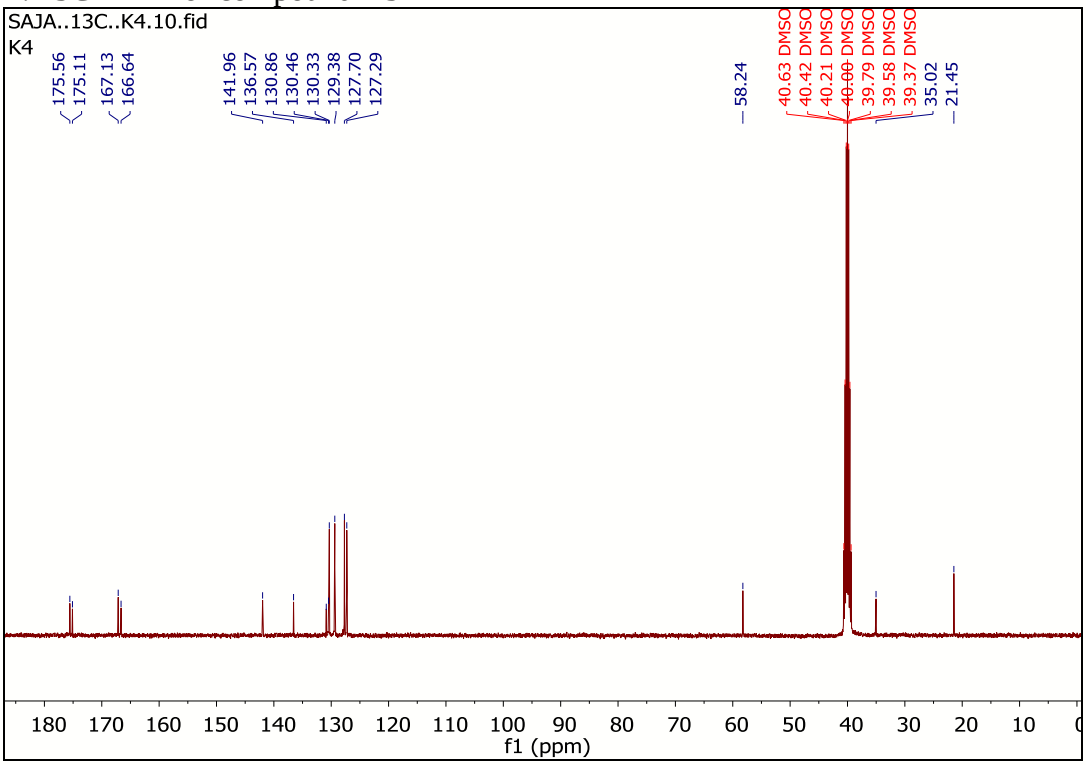


Fig. 12: 13C-NMR of compound K4

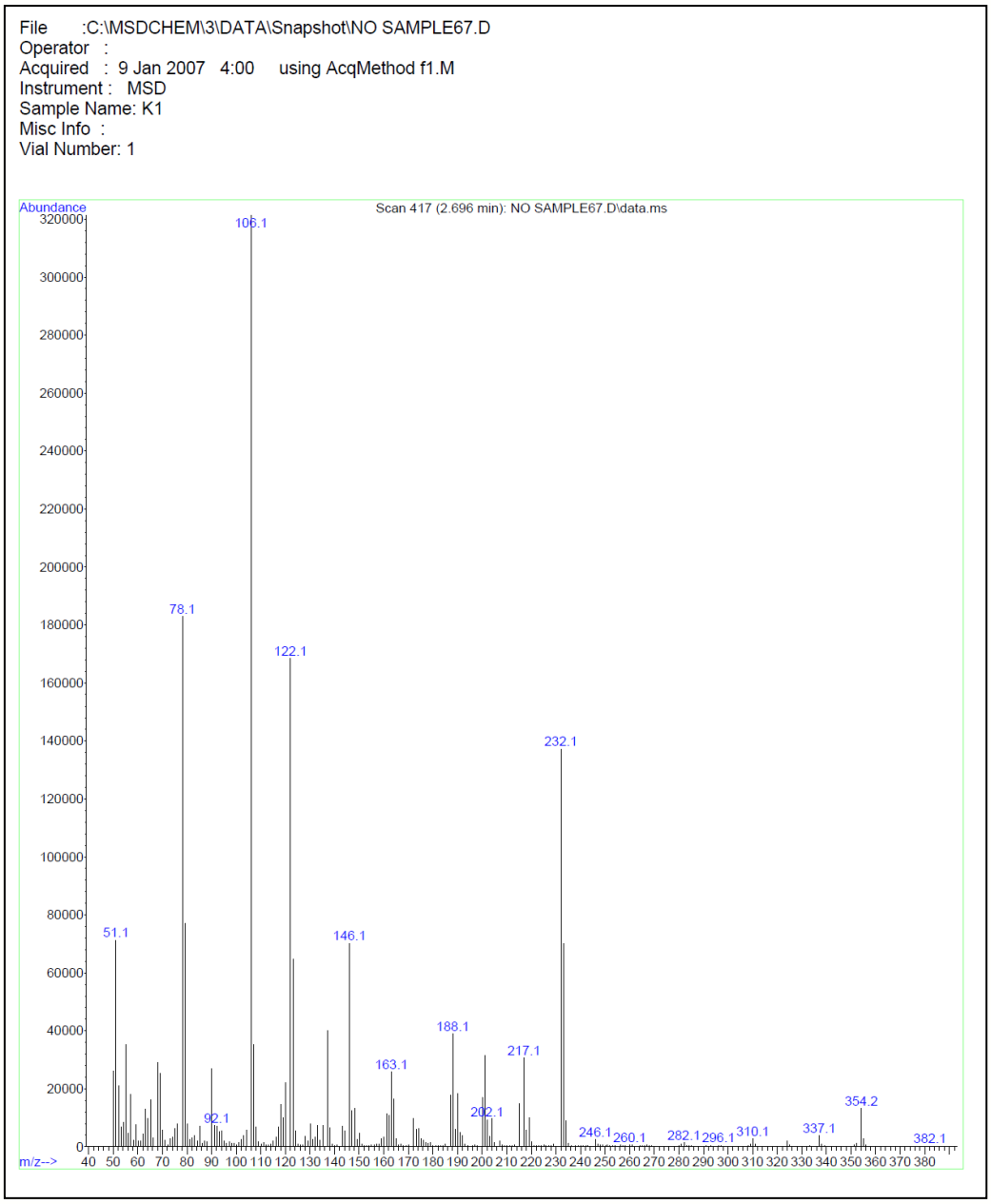


Fig. 13: Mass spectrum of compound K1

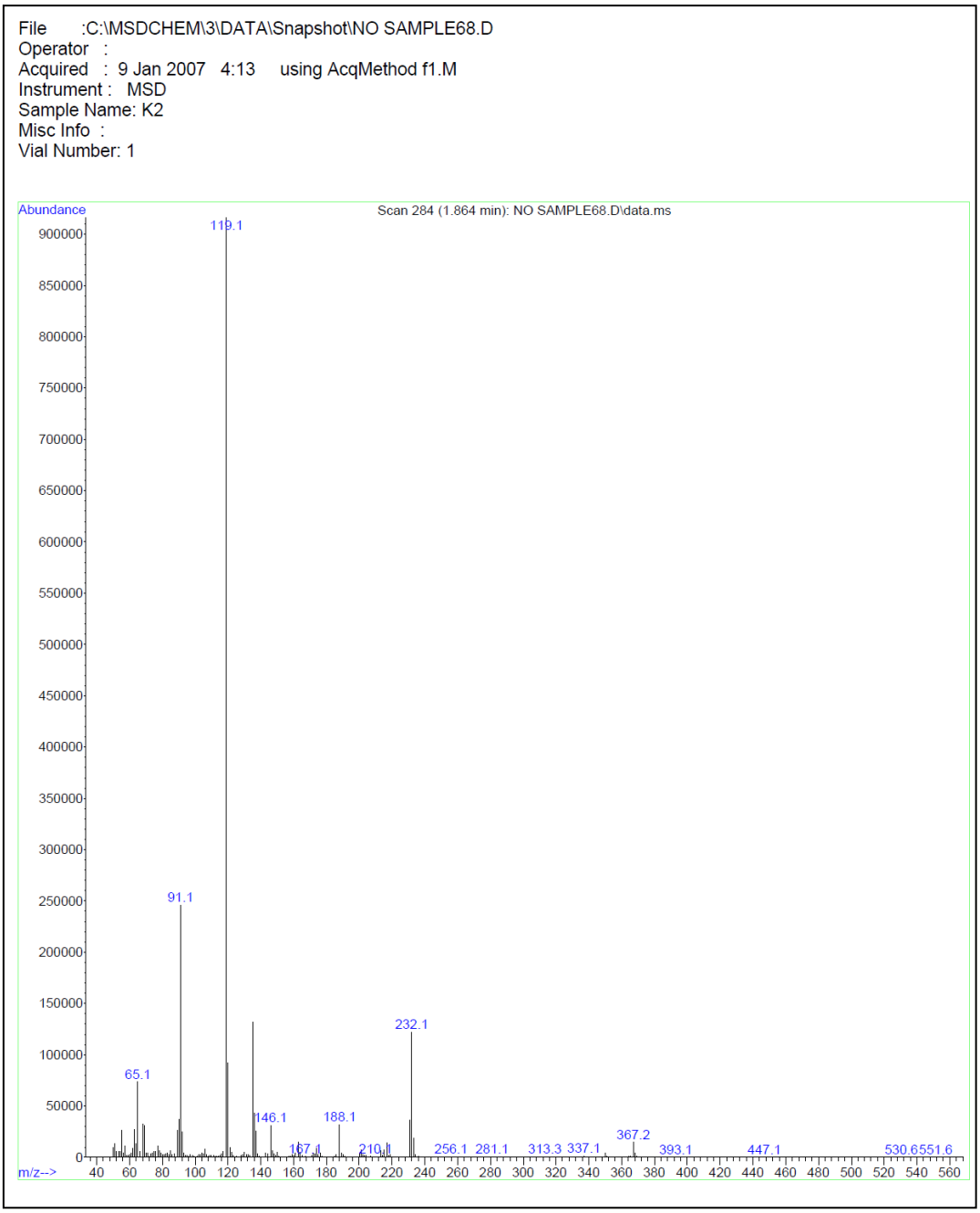


Fig. 14: Mass spectrum of compound K2

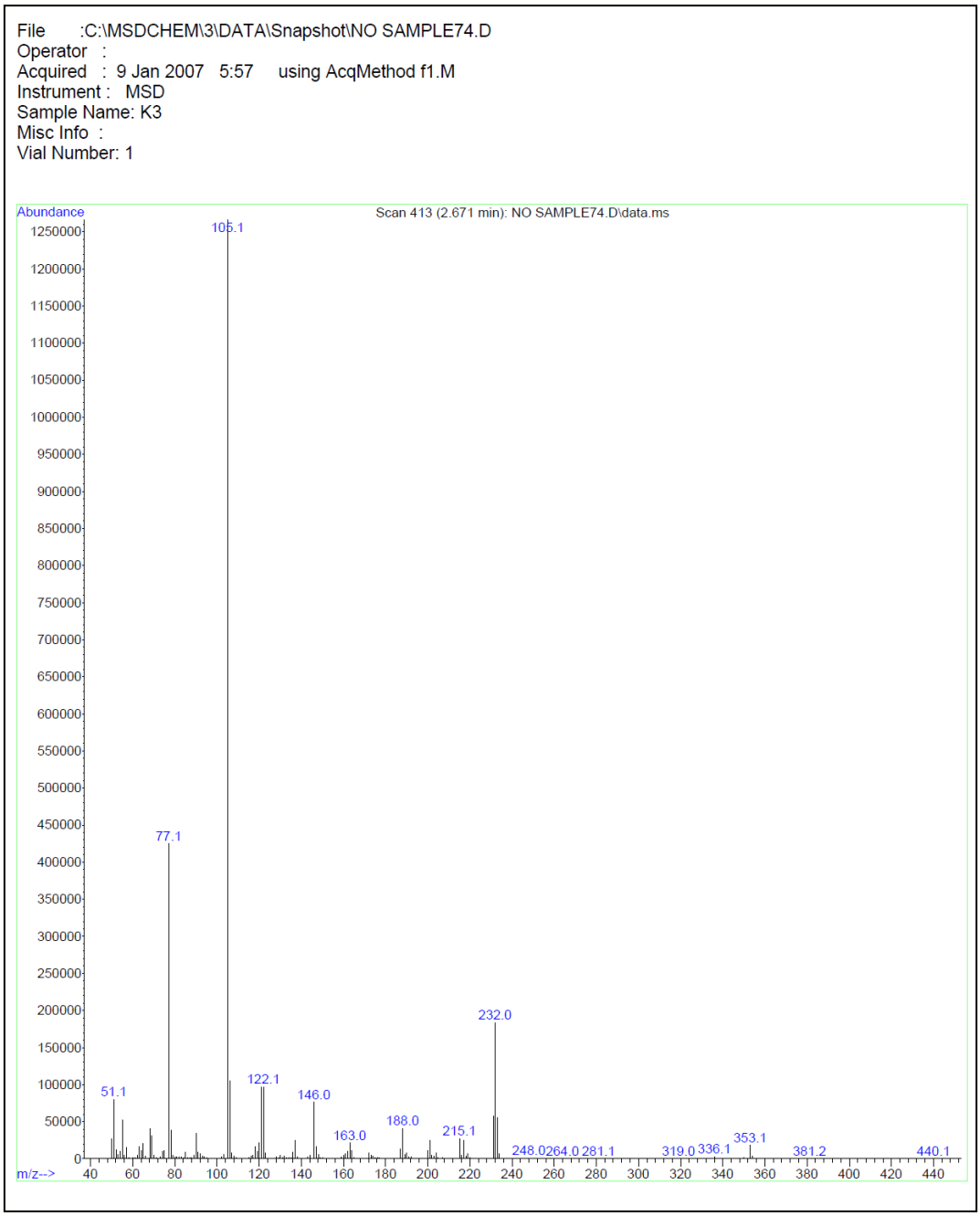


Fig. 15: Mass spectrum of compound K3

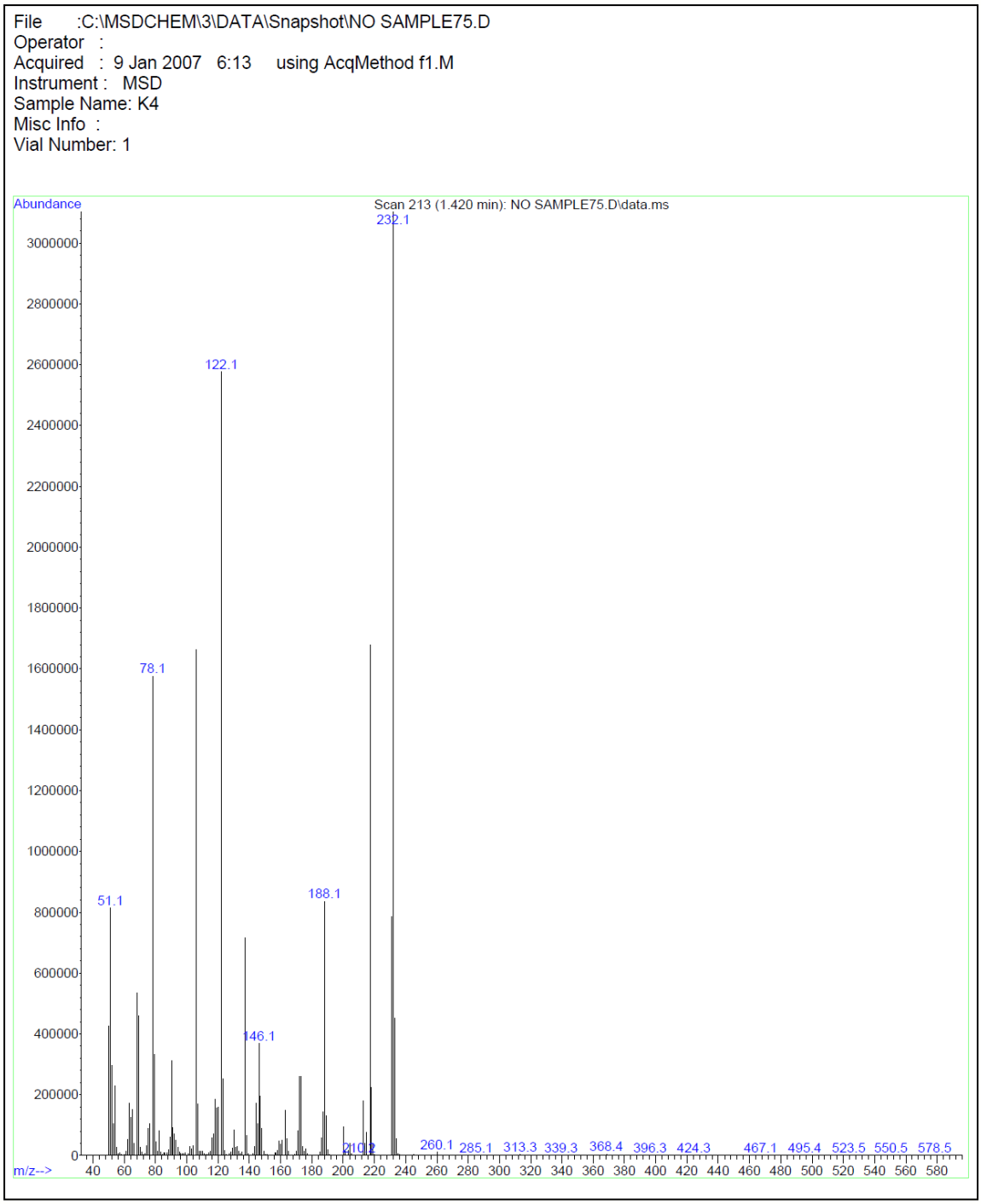


Fig. 16: Mass spectrum of compound K4