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ORIGINAL ARTICLE

Synthesis and Study of the Effect New Pyrazoles and Oxadiazole Linked to the 1,4-Dihydropyridine Ring on Breast Cancer

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KEYWORDS

Hantzsch reaction;
Hydrazine;
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ABSTRACT: The Hantzsch reaction created a new series comprising 1,4-dihydropyridine pyrazoles and oxa diazoles (DHP) by initially synthesizing DHP esters, then its carbohydrates, and subsequent treatment with hydrazine. Pyrazole derivatives (Am_1 and Am_2) were obtained via the reaction of hydrazines with acetylacetone or ethyl acetoacetate, whereas the oxadiazole derivative (Am_3) was prepared via reaction with carbon disulfide in an alkaline medium. The prepared compounds were identified using spectroscopic techniques (FTIR, ^{1}H and ^{13}C NMR, and mass spectrometry). The anti-breast cancer activity of new compounds was evaluated. This cytotoxicity activity afforded that compound (AS) was the strongest in this group together with an IC_{50} = 100.24μg mL^{-1}, whereas compound (AT) demonstrated the lowest potency, with an IC_{50} value of 300 µg mL^{-1}. The Hantzsch reaction was used in the synthesis of a new 1,4-dihydropyridine that has pyrazole and oxadiazole moieties. The activity of *in vitro* cytotoxicity (MTT cell viability assay) was determined. *In vitro* MCF7 cells were used in the evaluation of the cytotoxicity activity (MTT cell viability assay) of new compounds. This cytotoxicity activity meant that compound (AS) was the strongest in this group, with an IC_{50} of 100.24 µg mL^{-1}, while compound (AT) had the least potency, with an IC_{50} value of 300 µg mL^{-1}. Based on our findings, we can infer that 1,4-dihydropyridine derivatives (DHPs) are noteworthy heterocyclic compounds with pharmacological potential. This cytotoxicity activity meant that compound (AS) was the strongest in this group, with an IC_{50} of 100.24 µg mL^{-1}, while compound (AT) had the least potency, with an IC_{50} value of 300 µg mL^{-1}.

INTRODUCTION

1,4-dihydropyridine was discovered as a derivative of an important class of heterocyclic compounds, and it is a useful commercial molecule as a calcium channel blockers due to its wide range of pharmacological and biological activities. There are more than 12 commercially valid and clinically important drugs on the market that include nucleophilic 1,4-DHP, such as Nifedipine, Felodipine, and Nicardipine as shown in Figure 1 which are used to treat cardiovascular diseases. 1,4-dihydropyridine (DHP) is a class of organic compounds that contain a pyridine ring with two hydrogen atoms added to the 1 and 4 positions. The general chemical formula for DHP is C_5H_7N. DHP compounds have various applications in chemistry, medicine, and industry [1].

One of the well-known applications of 1,4-dihydropyridine derivatives is in the field of medicine, particularly in cardiovascular pharmacology [2]. Several DHP derivatives are widely employed as calcium channel [3] blockers (CCBs] 4), including nifedipine, nimodipine, and amlodipine. These medications cause blood arteries to widen and relax by blocking calcium

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ion entry into smooth muscle cells. So, they are prescribed for illnesses including hypertension (high blood pressure), angina (chest discomfort), and certain arrhythmias (irregular cardiac rhythms) [5].

The potential of 1,4-dihydropyridines has been investigated for uses outside of the cardiovascular system. Antioxidant capabilities and neuroprotective effects of several DHP derivatives in situations like Parkinson's disease and Alzheimer's have been studied. The possibility of DHP compounds acting as catalysts in organic synthesis reactions has also been investigated [6, 7].

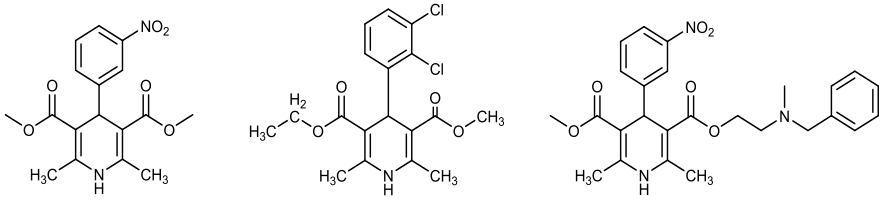


Figure 1. the most well-known 1,4-DHP calcium channel blockers' structures.

The nitrogen atoms in pyrazole are located next to one another in the ring's five-membered structure. $C_3H_2N_2$ is its chemical formula. The pharmaceutical sector frequently employs the utilization of pyrazole, as it is seen as a simple and flexible building block in chemical synthesis. It has several different biological effects, such as reducing inflammation and pain, as well as lowering body temperature [8].

Naproxen and ibuprofen, two examples of NSAIDs, were both synthesized using pyrazole derivatives. Cancer, neurological problems, and infectious diseases have all been studied in relation to pyrazole-based drugs. There are two nitrogen atoms and one oxygen atom in the ring of oxadiazole, making it a heterocyclic molecule with five members. C_2HN_2O is its chemical formula. Due to their wide range of biological activities and medicinal chemistry applications [9-13], oxadiazole derivatives have garnered a lot of interest. Oxadiazoles have been the subject of intense research due to their potential to kill bacteria, fungi, and cancer cells. They've also shown promise as anti-inflammatories, painkillers, and anti-convulsants. For optoelectronic applications, oxadiazole derivatives have also been studied as organic semiconductors and luminous materials [14,15]. Because of their useful pharmacological characteristics and synthetic flexibility, pyrazole and oxadiazole derivatives have played important roles in the drug discovery and development processes[16-24]. The purpose of this study is to create novel DHP derivatives with an oxadiazole or pyrazole group and test their efficacy against breast cancer. All novel derivatives were characterized via IR, ^{1}H NMR, and ^{13}C NMR spectroscopy in addition to mass analysis.

MATERIALS AND METHODS

Chemistry

A digital Stuart SMP-11 device was used to determine the melting point in an open capillary tube. The Perkin-Elmer 293 FTIR spectrophotometer was used to measure the infrared spectra using KBr disks. Using TMS as the internal standard and DMSOd6 as the solvent, the ^{1}H and ^{13}C NMR spectra were calculated using a Bruker DRX 400 spectrometer.

Synthesis of 9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(AT)

(0.122g (0.001 moles) of *p-hydroxybenzaldehyde* and 0.28 g (0.002 moles) of dimedon with 0.308 g (0.004 moles) of ammonium acetate and iodine (15 mol%) in 40 mL of ethanol The reaction mixture was heated under reflux for 4 hours. The reaction was monitored by thin-layer chromatography (TLC). The reaction was cooled, filtered, and recrystallized from methanol to give a yellow solid [25].Yiled 76% M.P.(300-302 . YieldedR (KBr,IR(KBr,cm^{-1}), 3275, 3197, 2954, 1612, 1508, 1222, 114 1, ^{1}H-NMR(DMSO-d_6,δ(ppm)9.22(S,1H,NH),9.02(S,1H,OH OH), 6.9(d, 2H,J=8Hz CH),6.5(d, 2H,J=8Hz CH),4.69(S,1H,CH),2.45(d,_2H,CH2),2.18(d, 2H,CH2), 2.18 (d,2H,C$\underline{H_2}$)1.00-0.86 (s,12H,CH_3),^{13}C-NMR(DMSO-d_6,δ(pp m)193.77, 154 .40,148.27,

137.30127.81, 113. 66,111.23,50.6, 40.59, 31. 32, 31.06, 28.52, 25.83, MS(70 Ev), $C_{23}H_{27}NO_3$, m/z: (M+),Calcd for 365.20 found 366.3.

Synthesis of ethyl 2-4-3,3,6,6-tetramethyl 1,8-dioxo-1,2,3, 4,5,6,7 ,8,9,10 -decahydroacridin-9-ylphenoxyacetate(AS)

Equimolars amount of compound 1 (0.365G, 0.001 mmol) and chloroethyl acetate (0.16 ml, 0.0015 mmol) were mixed, and then K2CO3 (0.276 g, 0.002 mmol) was added in 10 ml of DMSO. The mixture was cooled to room temperature and subsequently poured into ice water.. The product was filtered, dried, and further purified by column chromatography. (DCM: MeOH) (4:6 v/v). Pale yellow crystal. Yield (68%), m.p.174-171^oC [26], IR (KBr,cm^{-1}), 3209, 3066, 2958, 1755, 1627, 1483. ^{1}H-NMR (DMSO-d_6d\ppm), 9.28 (s, 1H, NH), 7.05 (d, 2H, *J* = 6.75Hz, C<u>H</u>), 6.7 (d, 2H, J=8 Hz, CH), 4.75 (s, 1H, CH), 4.66 (s, 2H, OCH_2CO),4.16 (m,2H, OEt),2.45 (d,2H, CH_2),2.18(d,2H, CH_2),1.20 (t, 3H, J=8Hz, CH_3), 1.00-0.86 (s, 12H, CH_3) ^{13}C-NMR(DMSO-d_6/ppm) 194.86, 169.36, 155.91, 140.68, 113.99, 128.9, 149.59, 112.06, 65.02, 61.01,50.71, 40.59, 32.62, 32.38, 29.54, 27.03 14.49, MS(70 Ev), $C_{27}H_{33}NO_5$, *m/z*:(M^+),Calcd for 451.5 found 451.4.

Synthesis of 2,4,3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4, 5,6,7,8 ,9 ,10-decahydroacridin-9-yl-phenoxyacetohydrazid(Am)

A mixture of (0.437 g, 0.001 mole) (2) and (0.14 ml, 0.003 mole) hydrazine hydrate was refluxed in 40 ml of ethanol for 3 hours. After cooling, the reaction mixture was poured over crushed ice. the solid product Filtering was done, as was recrystallization from ethanol.Yellow crystal, Yield 62%, m.p.215-213°C[27], IR(KBr,cm^{-1}),3305,3167 ,3047, 2958 , 1697,1620,1504,1219,1076, ^{1}H-NMR(DMSO-d_6d\ppm) ,9.27 (S,1H,N<u>H</u>), 9.25 (S,1H ,CON<u>H</u>),7.05 (d,2H,J=8.2Hz,C<u>H</u>) ,6.74(d, 2H,J=8Hz, C<u>H</u>), 4.75 (S,1H,C<u>H</u>) ,4.38 (S, 2H ,OC<u>H</u>$_2$CO),4.31(S,2H,N<u>H</u>$_2$),2.45(d,2H,C<u>H</u>$_2$), 2.18(d,2H, C<u>H</u>$_2$), 1.00-0.86(S, 12H, C<u>H</u>$_3$). ^{13}C-NMR(DMSO-d_6d\ppm) ,194.86, 167.29,156.13, 140.62, 128.95, 114.14, 149.57, 112.09, 66.64, 50.73,40.60, 32.62,32.43, 29.54, 27.04.

synthesis of DHP-Pyrazole (Am_1,Am_2) [28]

A mixture of DHP carbohydrazide (3) (0.437.0.001 mol) with acetylacetone or ethyl acetoacetate (0.0012 mol) in MeOH (10 mL) was heated under reflux for 3 hours. The reaction mixture was cooled, filtered, and the chromatography column purified using dichloromethane/methanol.

9,4,2,3,5-dimethyl-1H-pyrazol-1-yl-2-oxoethoxyphenyl-3,3,6,6-tetramethyl -3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(Am_1)

Yellow crystal, Yield 81%, m.p.204-200^oC, IR (KBr,cm^{-1}),3194, 3074, 2958, 1639,1697,1558, 1504,1222,1076,^{1}H-NMR(DMSO-d_6,δ ppm), 9.26(S,1H, N<u>H</u>), 7.03(d,2H, J=8.2Hz, C<u>H</u>),6.8(d,2H, J=8.2Hz, C<u>H</u>), 6.4(S,1H, C<u>H</u>),4.79(S,2H, OC<u>H</u>$_2$CO) 4.75(S,1H, C<u>H</u>), 2.45(d,2H, C<u>H</u>$_2$), 2.18(d,2H, C<u>H</u>$_2$),1.97(S,3H, CH_3), 1.74 (S,3H, CH_3), 1.00-0.86(S,12H, C<u>H</u>$_3$),^{13}C-NMR(DMSO-d_6'δppm), 194.90, 165.48 ,156.56, 155.94 ,149.57,140.20,128.87,113.98,112.13,90.8 66.11, 50.73, 40.62, 32.64, 32.35,29.53 ,27.08,26.30,16.37. MS(70 Ev), $C_{30}H_{35}N_3O_4$, m/z:(M^+),Calcd for 501.26 found 501.4

3,3,6,6-tetramethyl-9,4,2,3-methyl-5-oxo-4,5-dihydro-1Hpyrazol-1-yl-2-methoxyphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dion (Am_2),

Orange crystals, Yield 30% m.p.150-147^oC. , IR(KBr,cm^{-1}),3197,3066, 2954, 1643, 1697, 1620,1558,1485,1222,1080, ^{1}H-NMR (DMSOd_6\ppm) 9.26 (S,1H,NH) ,7.05 (d,2H,J=8Hz),6.71 (d,2H,J=8Hz,C<u>H</u>), 4.6(S,2H,OC<u>H</u>$_2$CO) 4.75 (S,1H,C<u>H</u>), 3.67 (S,3H ,CH_3) 2.45 (,2H,C<u>H</u>$_2$), 2.18(d,2H,CH_2) ,1.97 (d,2H,CH_2),1.75 (S,3H,C <u>H</u>$_3$)1.00-0.86 (S,12H,CH_3) ^{13}C-NMR(DMSO-d_6\ppm), 194.86 ,169.86,155.9 149.60, 140.70 ,128.99 ,113.99,112.05,64.93,52.21.50.72,32.62,32.37,29.51, 27.07.MS(70 Ev), C_{29} H_{33} N_3O_5, m/z:(M^+),Calcd for 503.6 found509.

Synthesis of 3,3,6,6-tetramethyl-9,4,5-methyl-1,3,4 oxadiazol-2-yl-methoxy phenyl -3,4,6,7,9,10 – hexahydroacridine -1,8,2H, 5H-dione(Am_3)

Potassium hydroxide (0.056 g, 0.05 mol) was added to hydrazide solution (0.437 g, 0.001 mol) in methanol (10 mL). (0.1 mL, 0.002 mol) of carbon disulfide was added dropwise to the reaction mixture. The reaction mixture was refluxed for 8 hours, and the product was collected by filtration and then dissolved in water. The solution is acidified by adding 10% HCl with stirring, and the solid product is filtered and recrystallized from methanol [29]. Yellow crystal, the yield of 56%.M.P. 233-230^{o}C, IR(KBr,cm^{-1}), 3286, 3059, 2958 ,1639, ^{1}H-NMR (DMSO-d_6\ppm), 9.27(S,1H,NH), 7.09 (d, 2H, J=8Hz, CH), 6.8 (d,2H,J =8.2Hz,C<u>H</u>),5.12(S,2H,CH_2), 4.76 (S, 1H, C<u>H</u>), 2.45(d, 2H, C<u>H_2</u>), 2.18 (d, 2H, C<u>H_2</u>), 1.00-0.86(s,12H,C<u>H_3</u>),^{13}C-NMR (DMSO-d_6, δ ppm), 194.86, 178.7 160.13, 155.57, 149.66, 141.29, 129.11, 114.31, 111.97, 50.70, 40.60, 32.63, 32.44, 29.52, 27.05. MS(70 Ev), $C_{26}H_{29}N_3O_4S$, m/z:(M^+),Calcd for 479.6 found 479.5.

RESULTS AND DISCUSSION

The synthesis of 1,4-dihydropyridine derivatives as illustrated in Figure 2 from the Hantzsch method by 4-hydroxybenzaldehyde was refluxed with two equivalents of dimedone and NH^{+4}OAC in the presence of iodine in an ethanol medium. The product (AS) was created by alkylating the OH group with ethylchloroacetate in DMSO. Only the phenolic OH group of the DHP ring is alkylated under such mild circumstances; the NH group is not. By refluxing the resultant ester (AS) with hydrazine hydrate in ethanol for roughly 4 hours, it was changed into its hydrazide (Am) through a nucleophilic substitution reaction. It's interesting to note that under these circumstances, the stable ester groups on the DHP ring were unaffected [30]. By condensing hydrazide (Am) with different ethyl aceto acetate or acetylacetone and ketones in a medium of methanol, Figure 3 [28] target pyrazole was produced. By reacting hydrazide (Am) with carbon disulfide in methanolic potassium hydroxide, 1,3,4-oxdiazole was produced [31]. All the synthesized compounds were identified by IR, ^{1}H-NMR , ^{13}C-NMR, DEPT-135, and mass spectra. The IR data of compound AT as shown in Figure 4 showed strong bandings at 3150–3500 cm^{-1} and 17150 cm^{-1} due to vibrational expansion of the NH/OH and ketone carbonyl groups, respectively, and this was further confirmed by the ^{1}H-NMR spectrum in Figure 5, which displays a single signal at 9.22 and 9.02 ppm, which are attributed to the phenolic OH and NH proton of the DHP ring, respectively. As for the ^{13}C-NMR spectrum, it was shown by a signal at 193.77 ppm belonging to the carbonyl ketone group, and other signals at 50.6) ppm belonging to the CH_2 group and the DHP ring, as shown in Figure 6. The mass spectrum of (AT) is shown in Figure 7.

In addition, as can be deduced from Table 1, it reveals that the observed [M^+] is in good agreement with the calculated [M+]. The ^{1}H-NMR spectrum Figure 8 of AS showed two new signals, the first double due to the resonance of the OCH_2 proton and the second triple due to the resonance of the CH_3 protons of the OCH_2CH_3 ester group at the stop groups δ1.20 ppm and 4.15 ppm, respectively. 4.69 ppm belonged to the proton resonance of OCH_2CO, proving that the phenolic hydroxyl group suffered an addition reaction and not the NH amine group in the DHP ring. The ^{13}C-HNMR spectrum is shown in Figure 9. a signal at (169.36) returning to the esterification carbonyl group while preserving the carbonyl structure of the DHP ring, and this was confirmed by DEPT-135 as shown in Figure 10. The mass spectrum of the compound AS is shown in Figure 11. as can be deduced from Table 1, it reveals that the observed [M^+] is in good agreement with the calculated [M^+]. In FTIR, hydrazide (Am) in Figure 12 spectrum, shifting the carbonyl expansion The frequency of 1759 cm^{-1} to a reduced frequency of 1697 cm^{-1} indicates formation of Am. Moreover, its ^{1}H-NMR spectrum displayed two segments at 9.25 and 4.31 ppm confirming the presence of NH and NH_2 hydrazides as shown in Figure 13. The ^{13}C-NMR spectrum showed a signal at 167.29 ppm belonging to the amide carbonyl group, with the capone structure remaining, and this was confirmed by the DEPT-135 spectrum, as shown in the Figure 14, and Figure 15. The FTIR spectra (Am_1) and (Am_2) revealed the elimination of three absorption bands caused by NH_2 and NH groups as well as the emergence of a stretching band at 1558 cm-1 caused by a C=N band and a new absorption band at 1643 cm^{-1} caused by a C=O (endocyclic) group as shown in Figure 16, and Figure 17. The ^{1}H-NMR spectrum of Figure 18 of compound Am_1 showed new signals at a chemical displacement of 6.49

ppm due to C - H proton resonance in the pyrazole ring, The ^{1}HNMR spectrum of compound in Figure 19 while the protons of CH_2-(pyrazole) appeared as a singlet at δ2.45 ppm and another singlet signal appeared at δ3.67 ppm due to three protons of CH_3 group. For compound (Am_3) the infrared spectrum of Figure 20 showed that 2748cm^{-1} belongs to the SH group of the new oxadiazole ring, and the ^{1}H-NMR spectrum in Figure 21 showed a signal at 14.6 ppm as a result of the SH proton resonance.

Table 1. Mass Spectra data for 1,4 Dihydropyridine (DHP) Pyrazoles and oxadiazole derivatives.

Compuond	Structure	Calculate M^+	Found M^+
AT	$C_{23}H_{27}NO_3$	365.20	366.3
AS	$C_{27}H_{33}NO_5$	451.5	451.4
Am_1	$C_{30}H_{35}N_3O_4$	501.26	501.4
Am_2	$C_{29}H_{33}N_3O_5$	503.6	509
Am_3	$C_{26}H_{29}N_3O_4S$	479.6	479.5

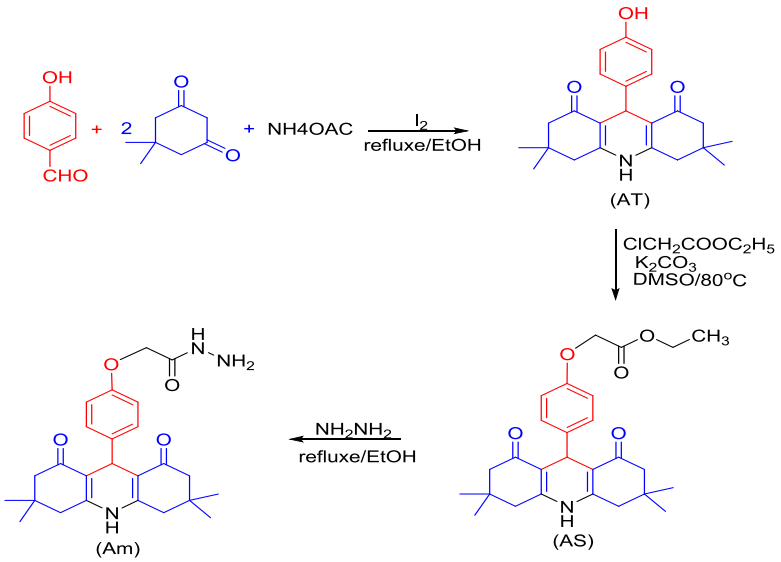


Figure 2. Synthesis pathway of DHPs hydrazide.

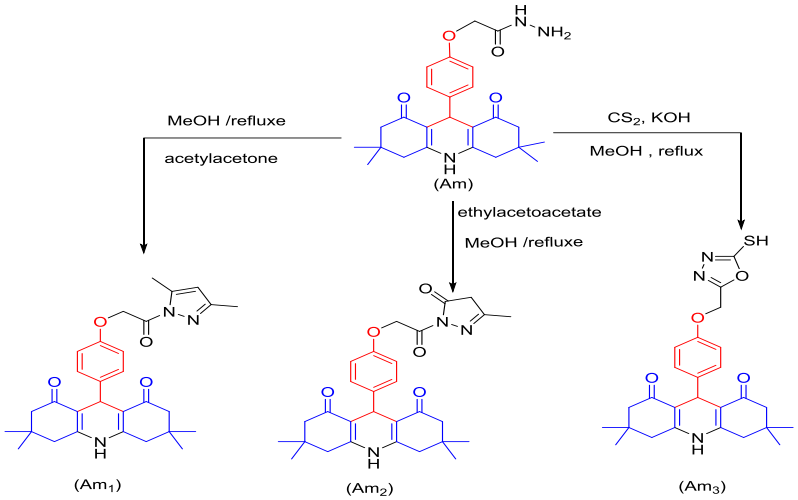


Figure 3. Preparation pathway of DHPs derivatives.

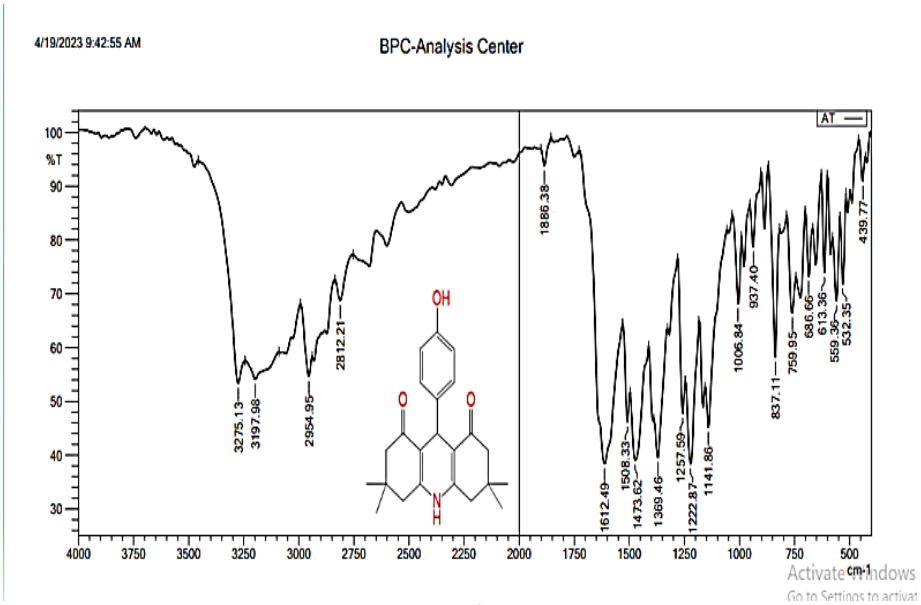


Figure 4 IR spectra of compounds AT .

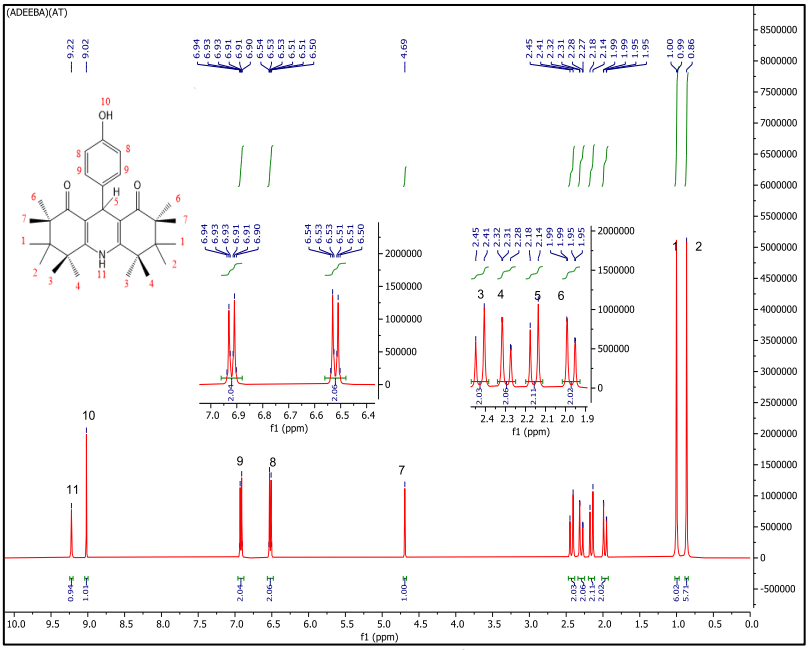


Figure 5. 1H NMR spectra of compound AT

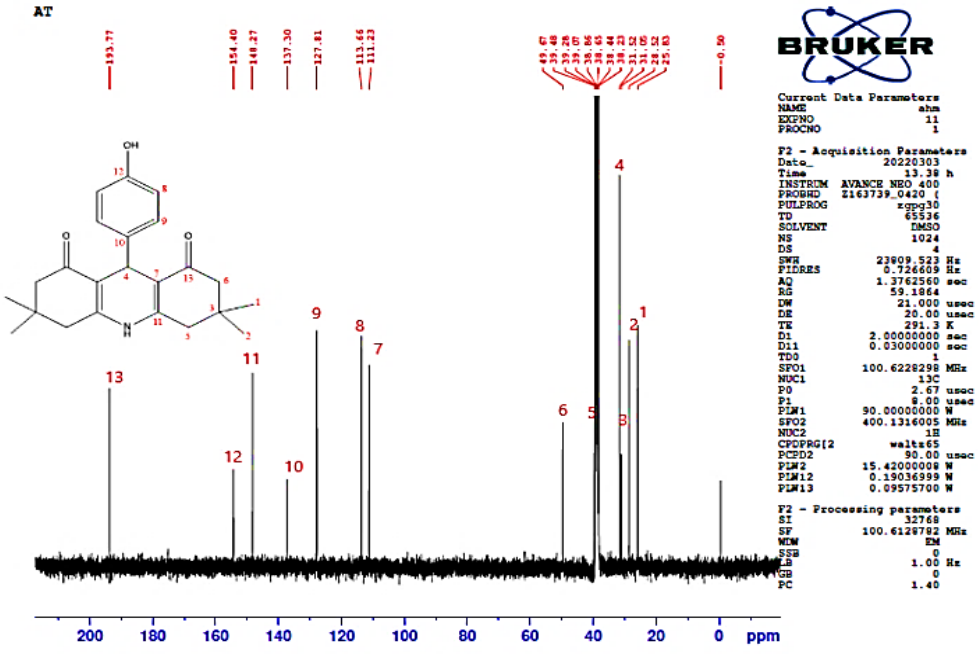


Figure 6. ^{13}C NMR spectrum of compound AT.

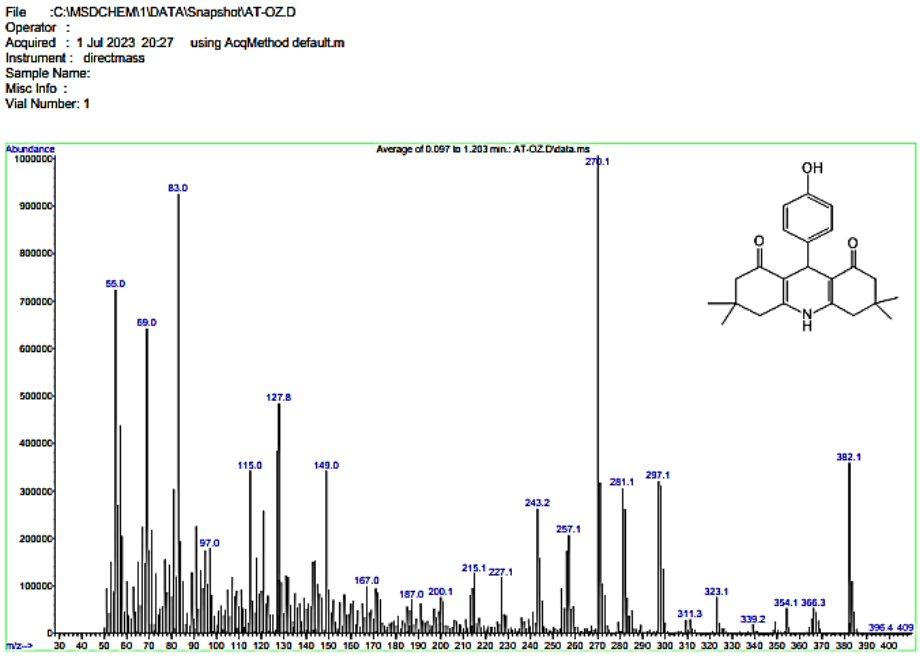


Figure 7. Mass spectrum of compound AT

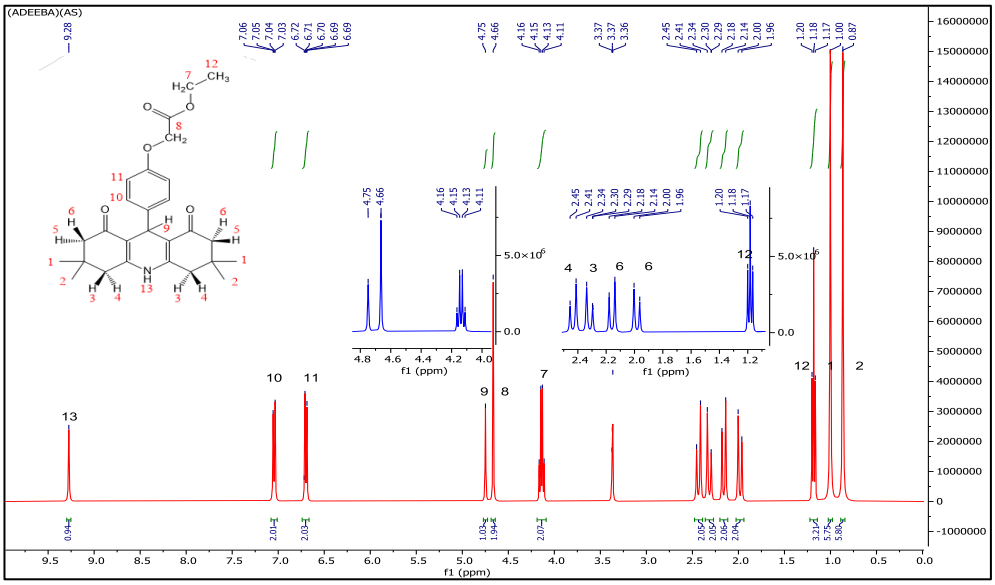


Figure 8. ^{1}H NMR spectra of compound AS

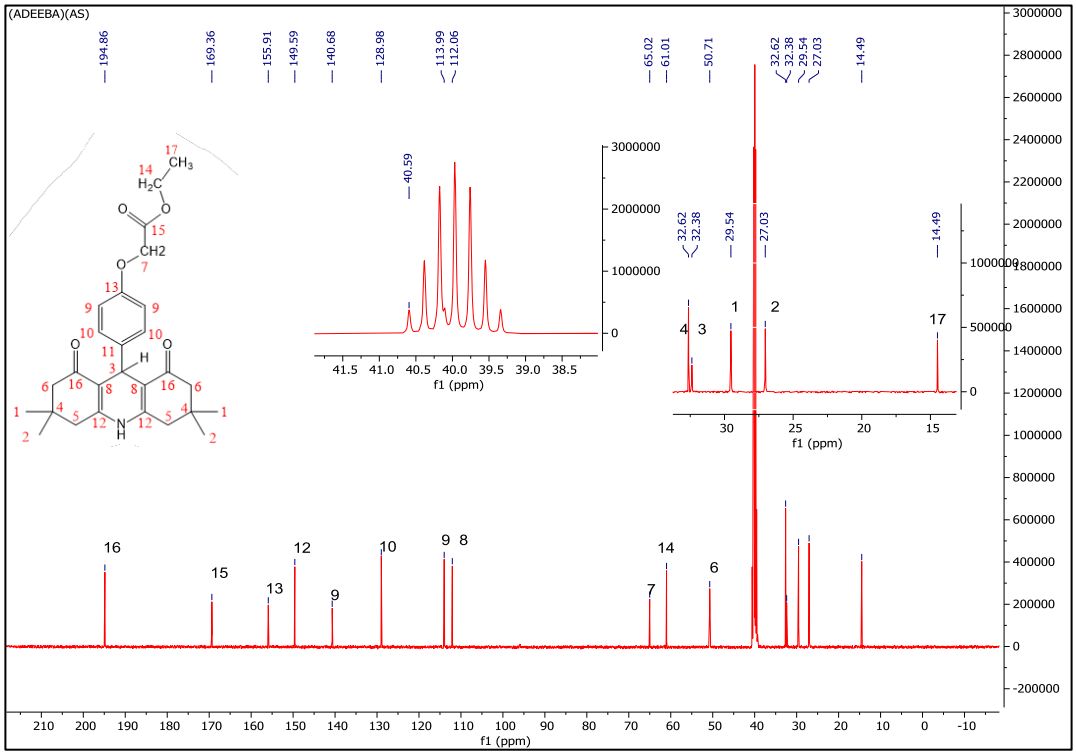


Figure 9. ^{13}C NMR spectrum of compound AS.

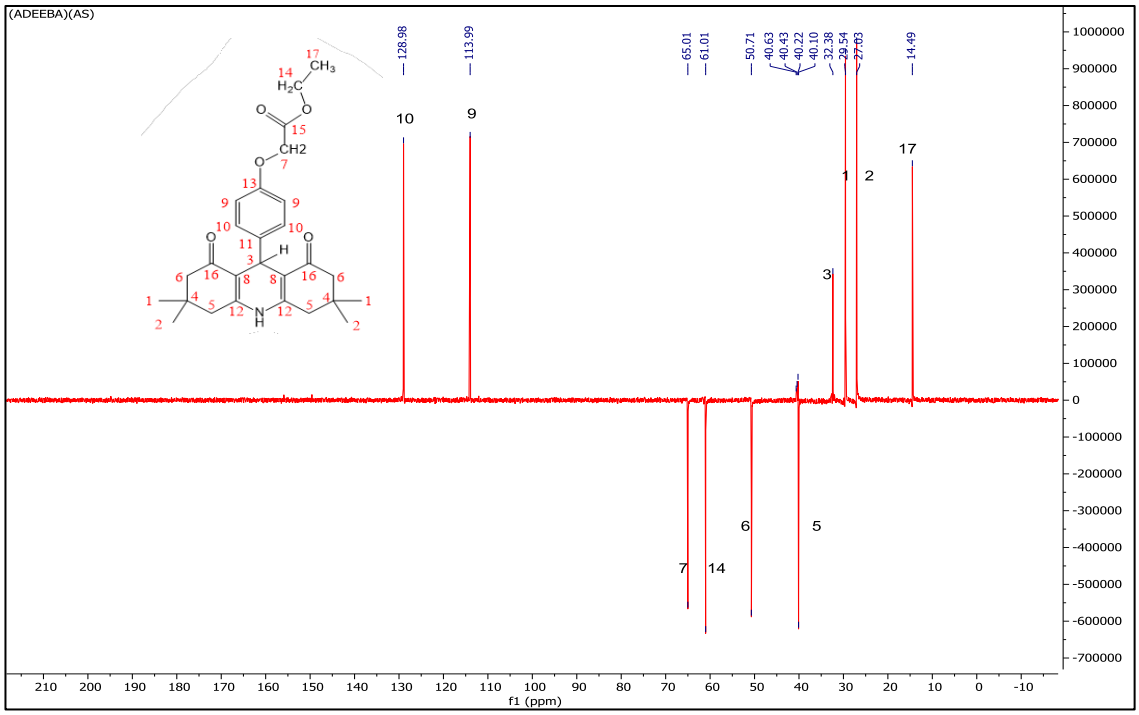


Figure 10. DEPT-135 spectrum of compound AS.

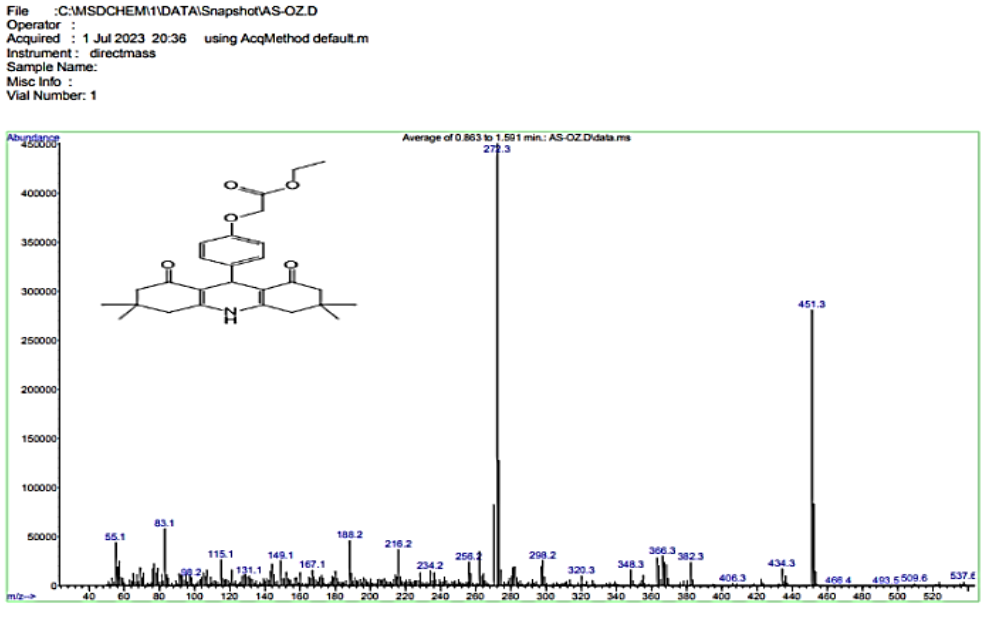


Figure 11. Mass spectrum of compound AS.

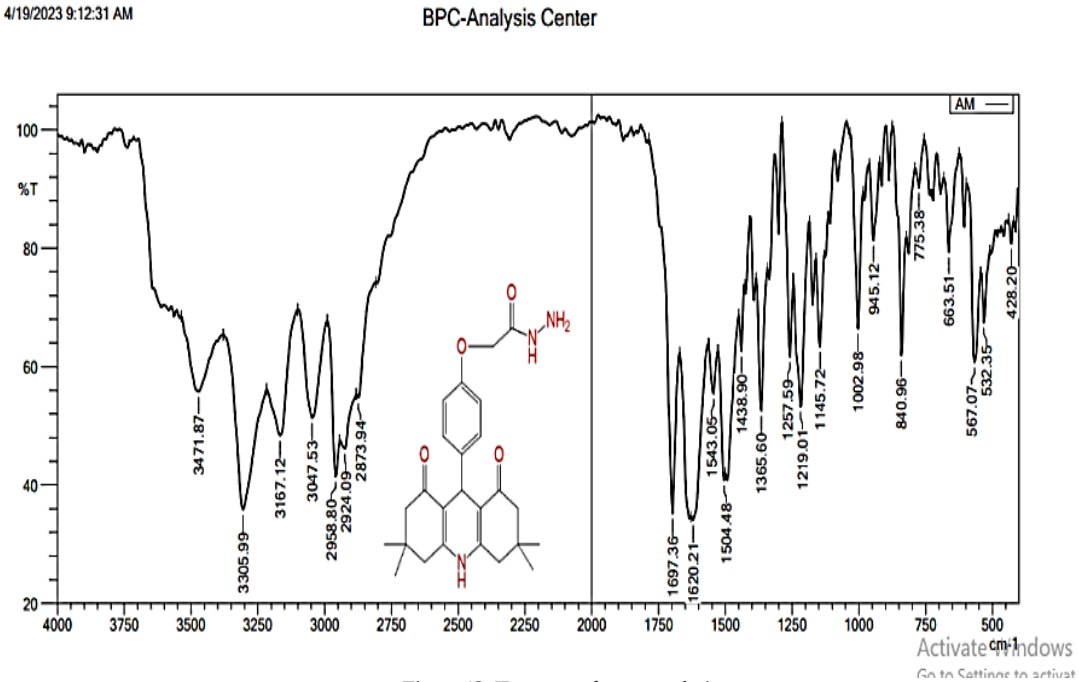


Figure 12. IR spectra of compounds Am.

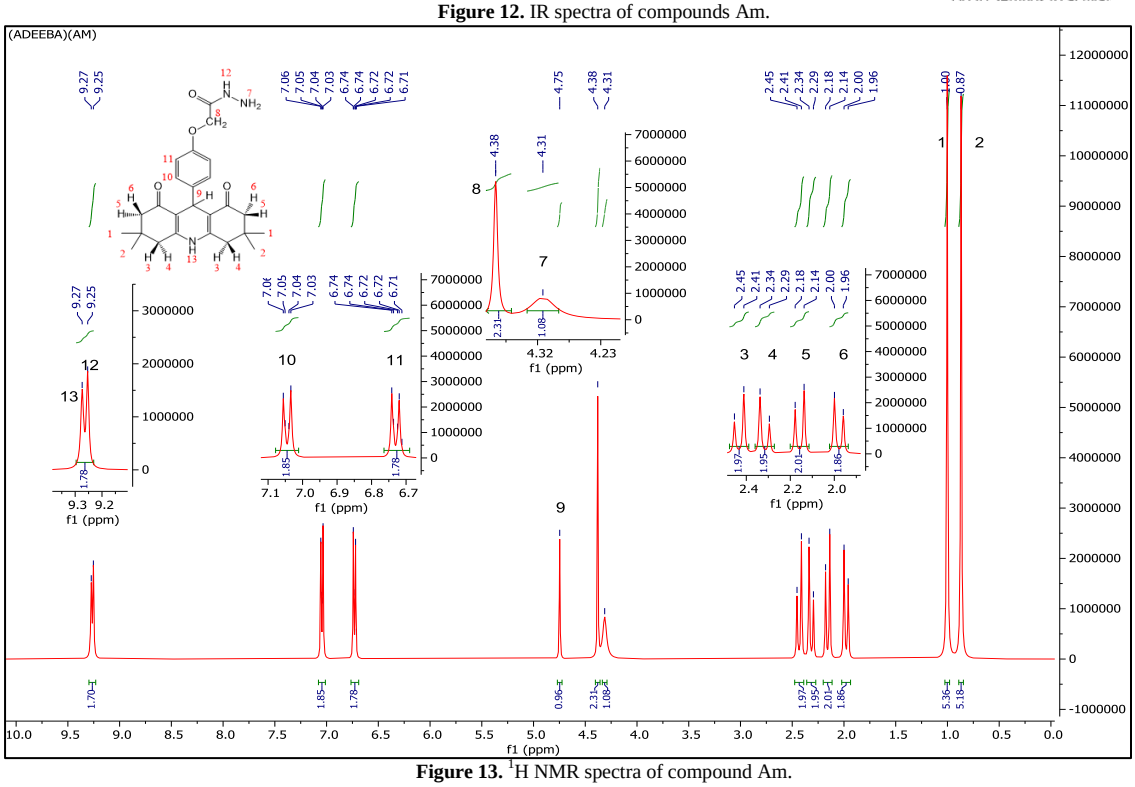


Figure 13. ^{1}H NMR spectra of compound Am.

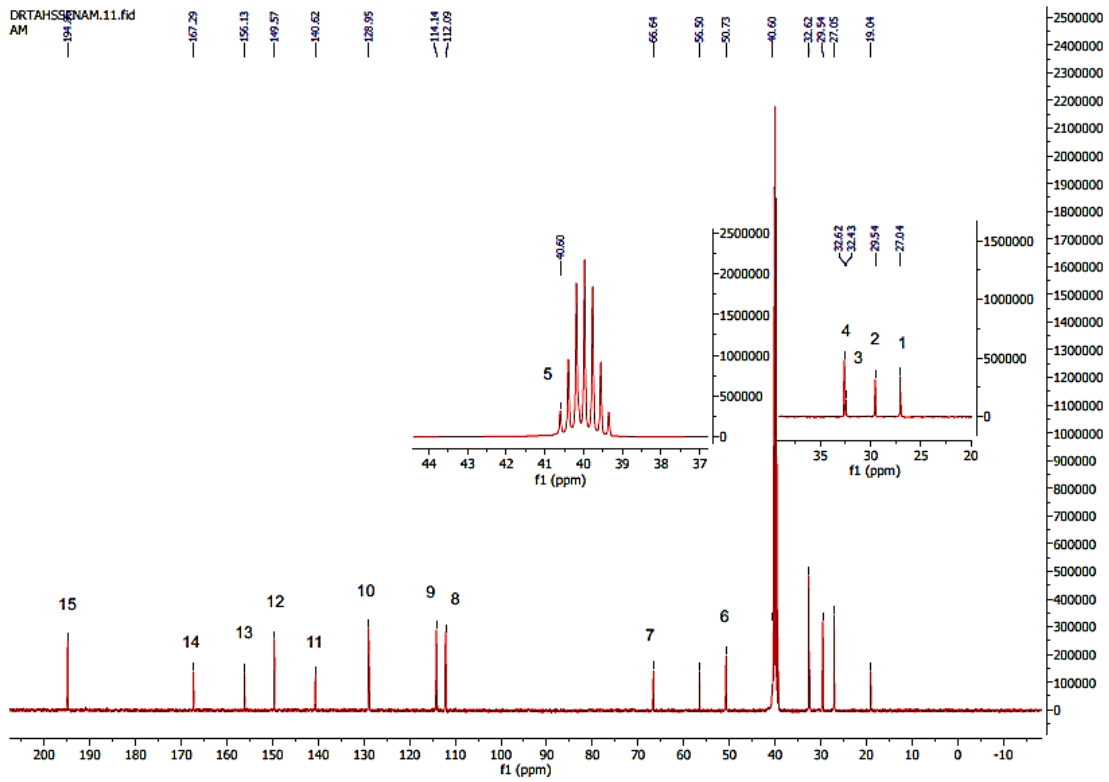


Figure 14. ^{13}C- NMR spectrum of compound Am.

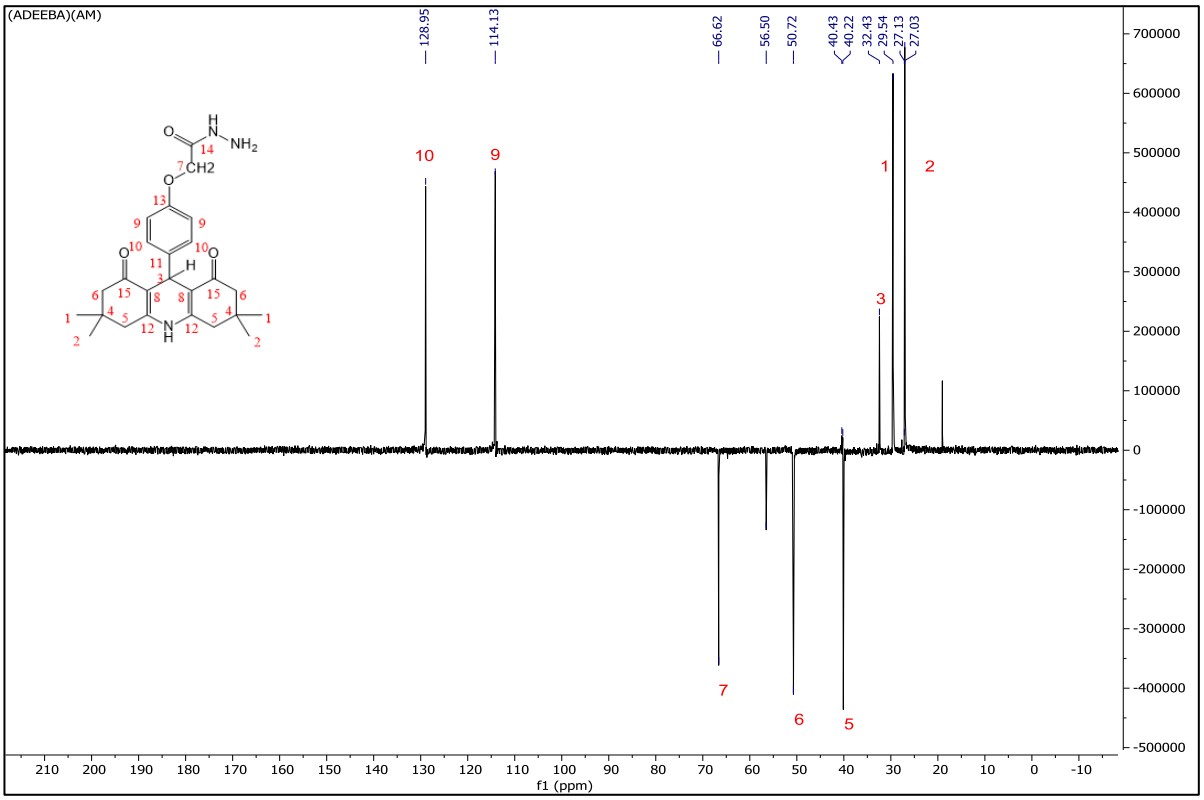


Figure 15. DEPT-135 spectrum of compound Am.

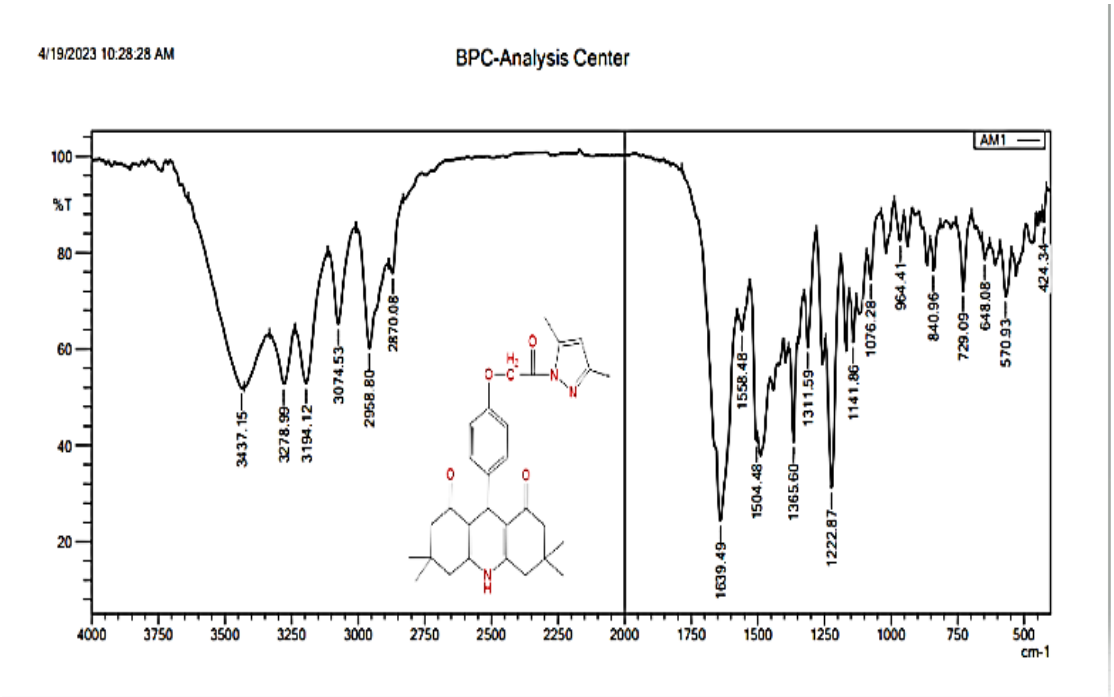


Figure 16. IR spectra of compounds Am_1.

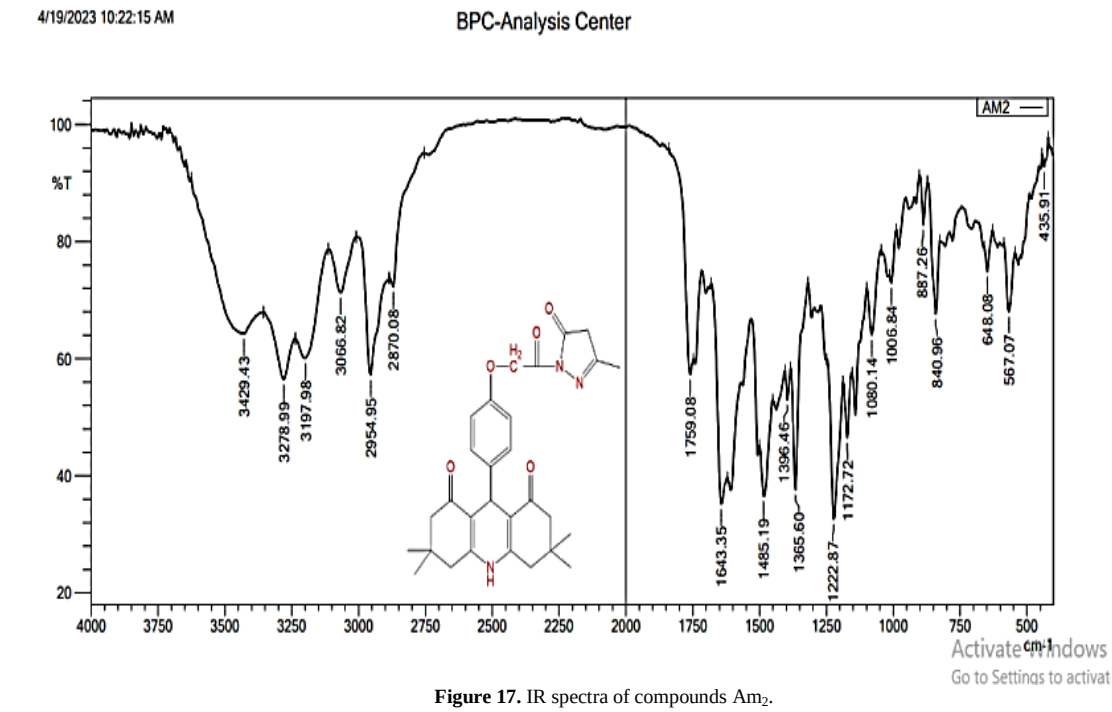


Figure 17. IR spectra of compounds Am_2.

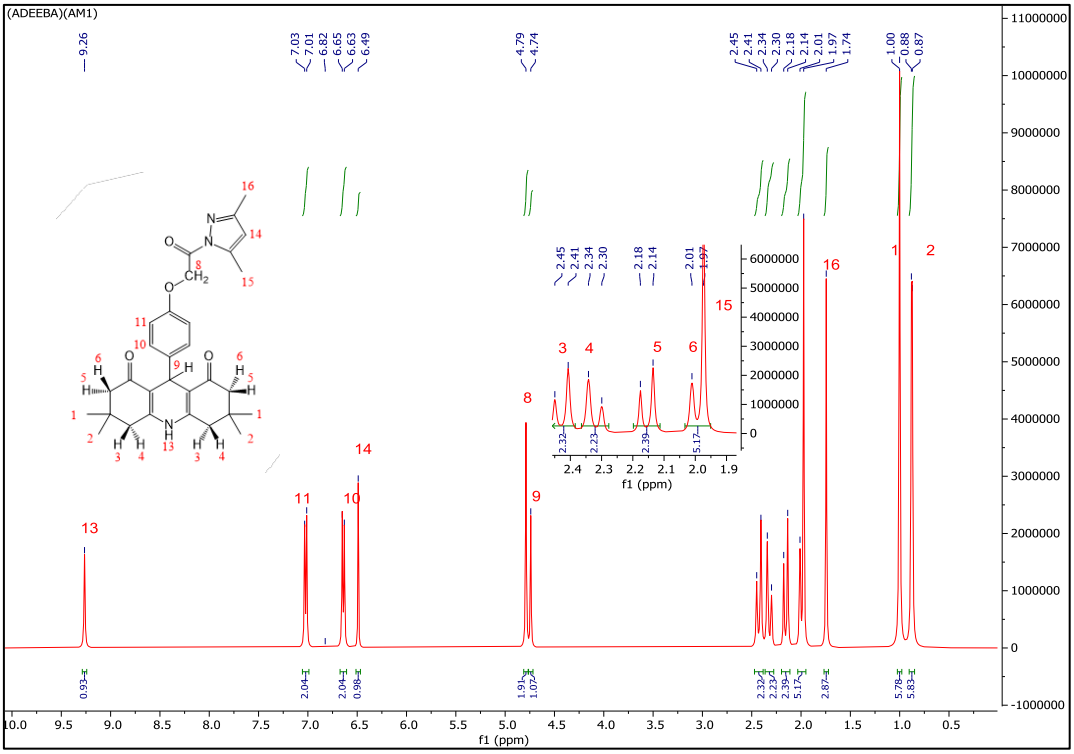


Figure 18. ^{1}H NMR spectra of compound Am_1.

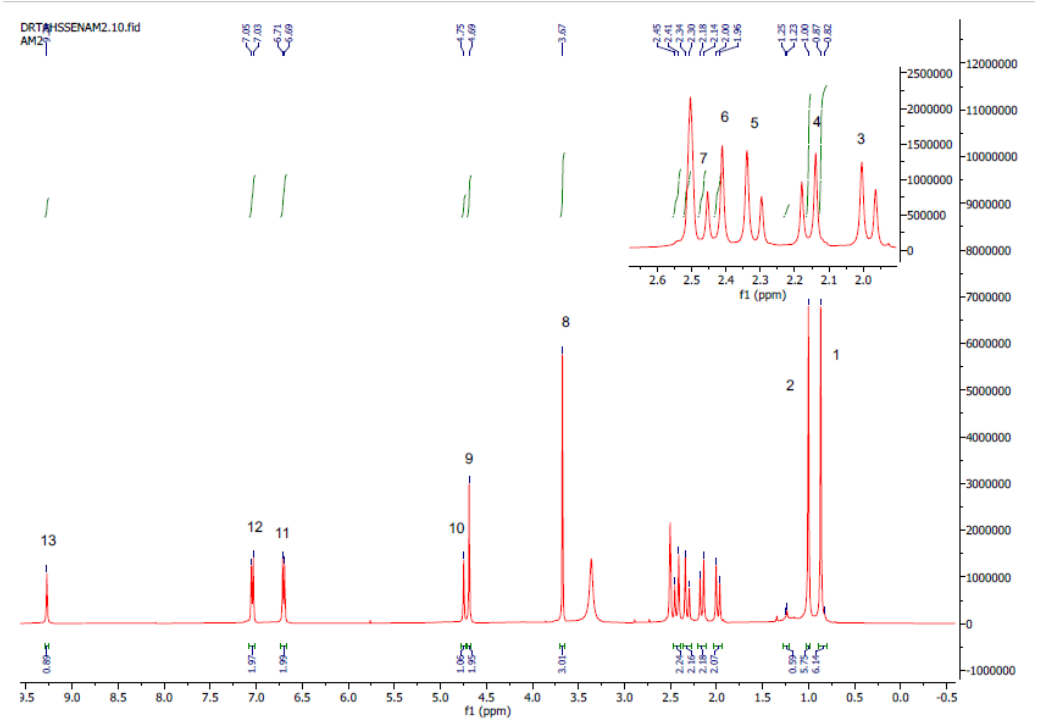


Figure 19. 1H- NMR spectra of compound Am_2

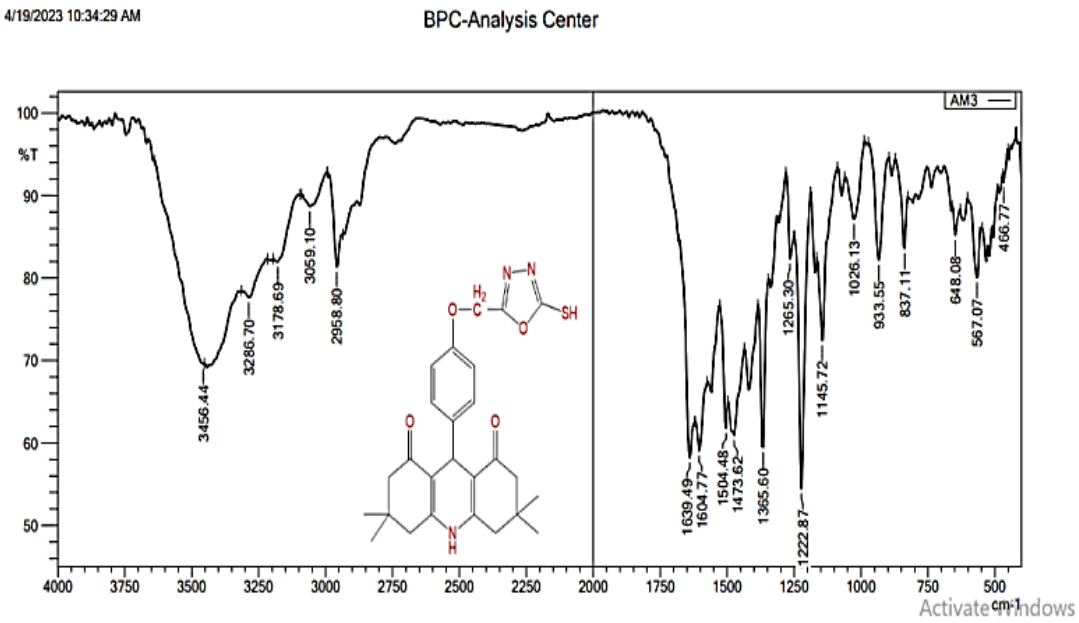


Figure 20. IR spectra of compounds Am_3.

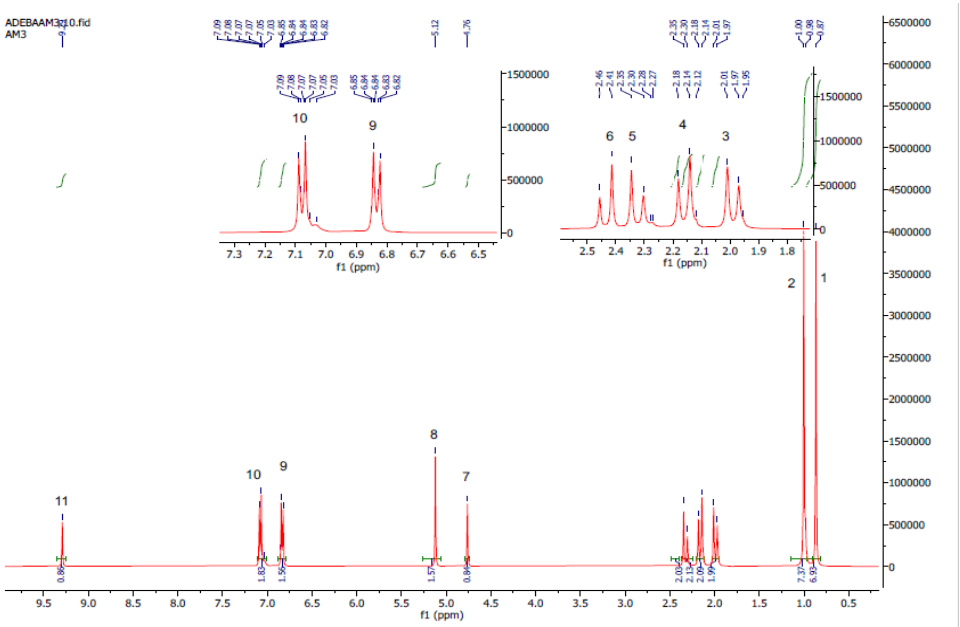


Figure 21. ^{1}H- NMR spectra of compound Am_3

Biological activity

Synthesized substances' cytotoxic effects on a strain of

human breast cancer cells(MCF-7)

The term "IC_{50}" refers to a notion that is frequently employed in the pharmaceutical industry as a measure of the effectiveness of an agent's ability to inhibit a particular biological or biochemical process. Its value reveals the anti-inhibitory level needed to a halving a given biology or biochemistry activity. Higher IC_{50} values compared to compounds with lower IC_{50} values, indicates weaker inhibitory activity of the substance. The MCF-7 cell line was used in this investigation to test the antiproliferative activity of the compounds (AT-AS-Am_1-Am_2-Am_3). As shown in Figure 22, compound (AS) within this group, was the most effective with an IC_{50} value of 100.24µg mL^{-1}, and (AT) was the least potent with an IC_{50} value of 300µg mL^{-1},as displayed in Figure

23. To validate the IC_{50} calculation, a microscopic analysis of the tested compounds in the cell line at a concentration of 300 µg mL^{-1} was conducted, The pharmacological profile of the heterocyclic moiety pyrazole is notable, The pyrazole template is one-of-a-kind and has been linked to a wide range of biological processes [32-34].

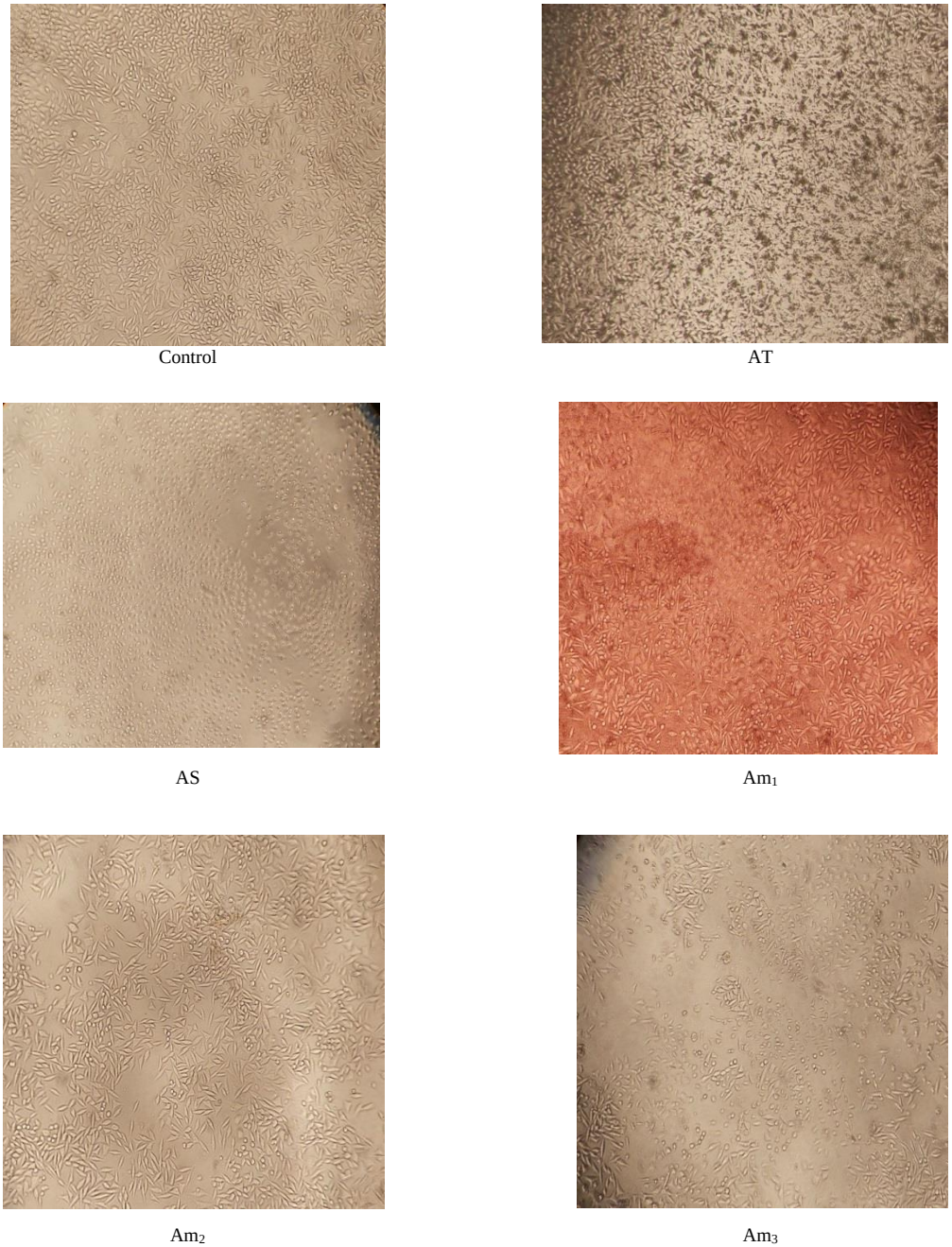
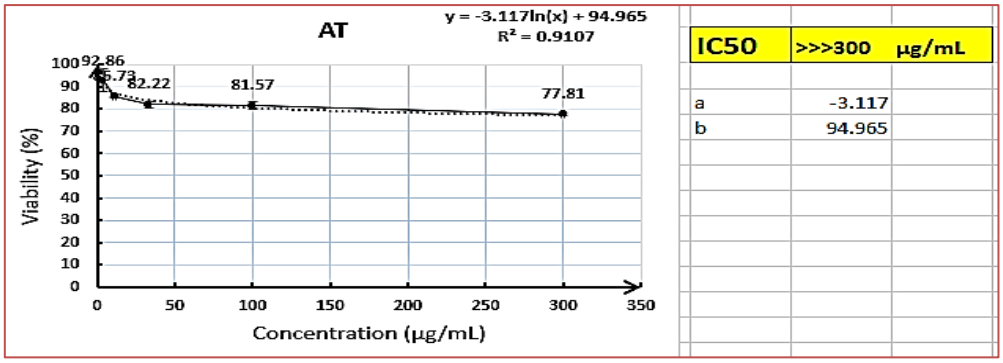
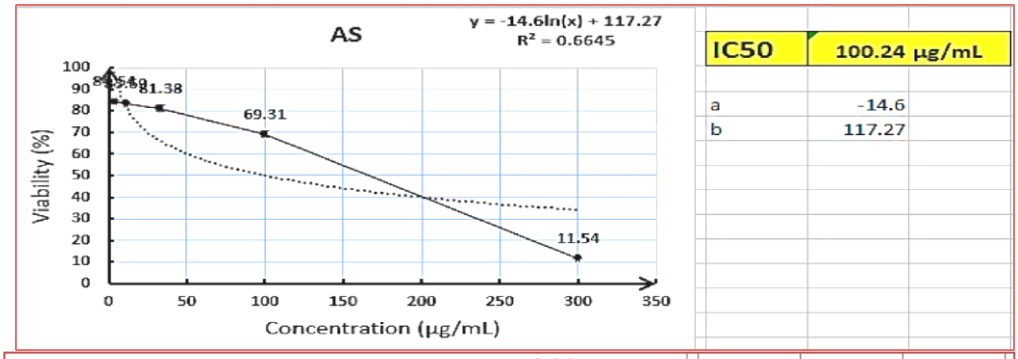
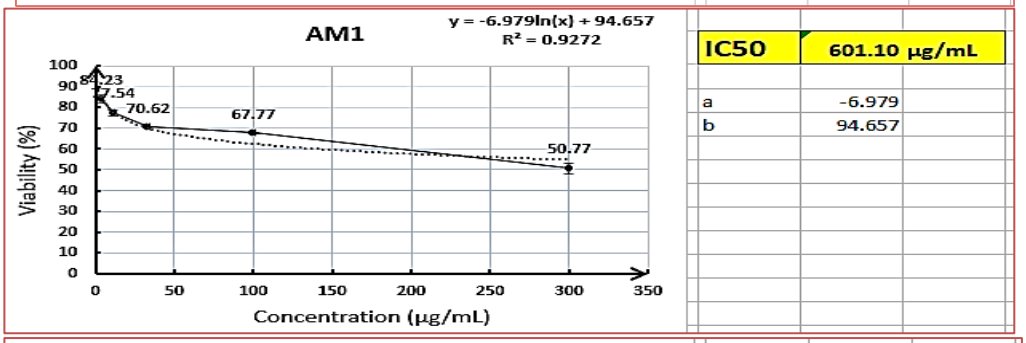
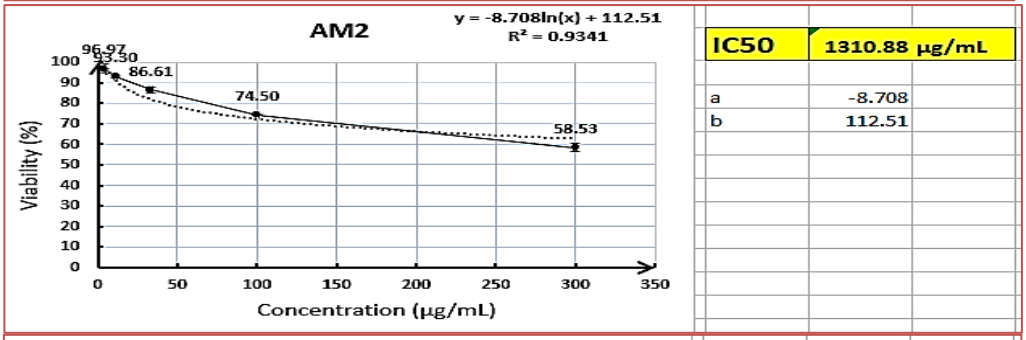


Figure 22. MCF-7 cell line under microscopic examination of control and compounds at 300 µm concentration.









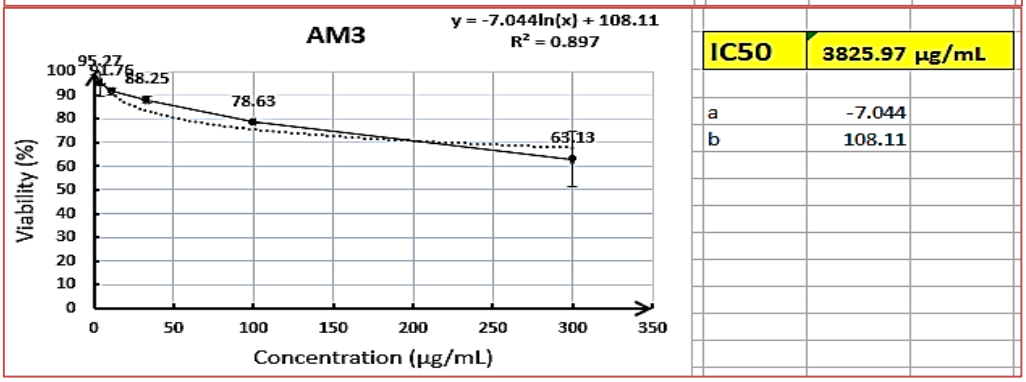


Figure 23. The IC_{50} Values of compounds against MCF-7 Cell line.

CONCLUSIONS

Hansch's condensation process was used to synthesize a new series of 1,4-dihydropyridine derivatives containing 1,3,4-oxadiazole and pyrazole moieties. These compounds were elucidated using spectroscopic techniques such as infrared, ^{1}H, and ^{13}C-NMR, as well as mass analysis. This technique is simple and easy to use to synthesize pyrazole and oxadizaole. The researchers looked at the effectiveness of these substances in the fight against breast cancer.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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