**Electronic Supplementary Information**

# An Efficient Protocol for Novel Hybrid Pyrimidines Synthesis: Anti-proliferative Activity, DFT Analyses, and Molecular Docking Studies

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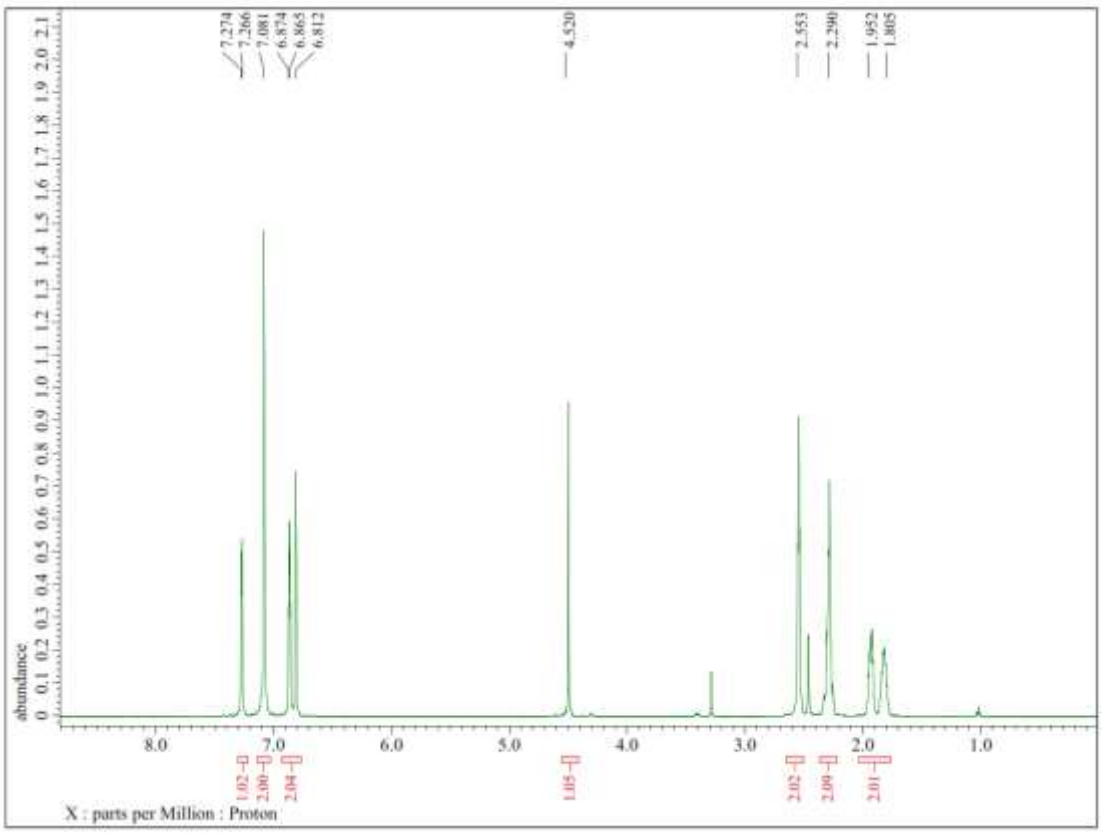



**Figure S1:** $^{1}$H NMR (DMSO-*d6*) of **1**

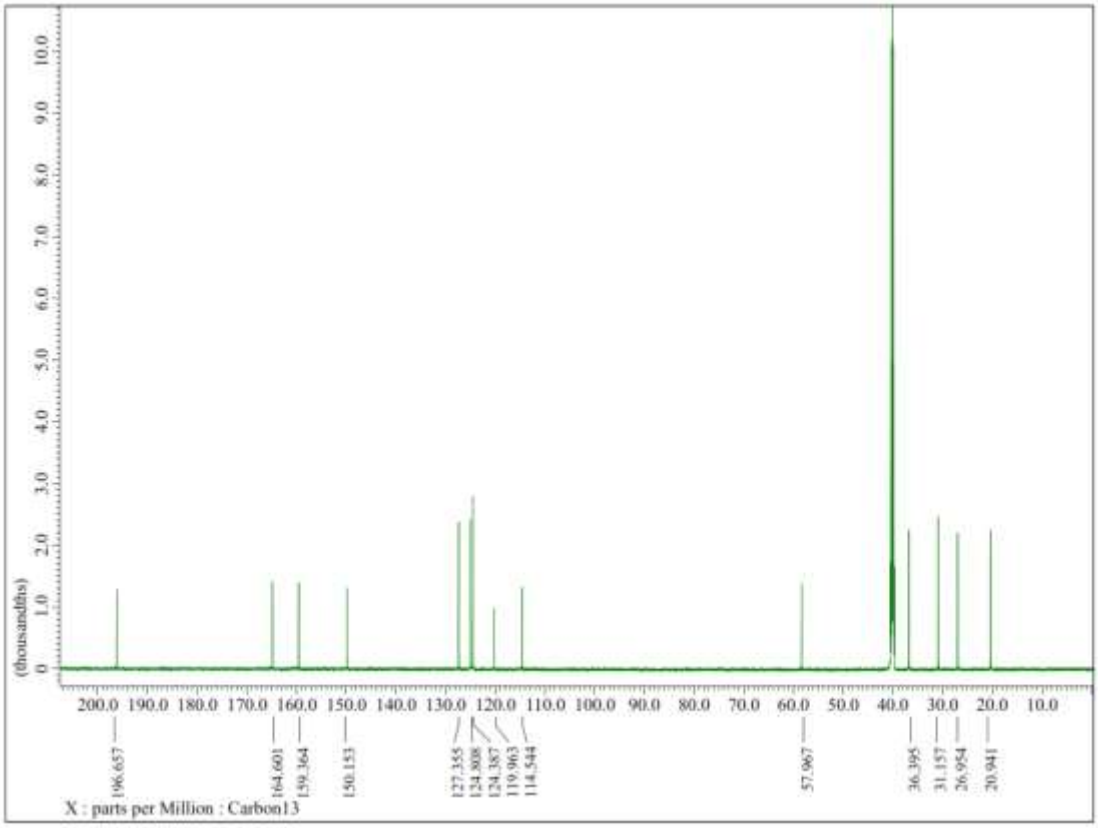



**Figure S2:** $^{13}$C NMR (DMSO-*d6*) of **1**

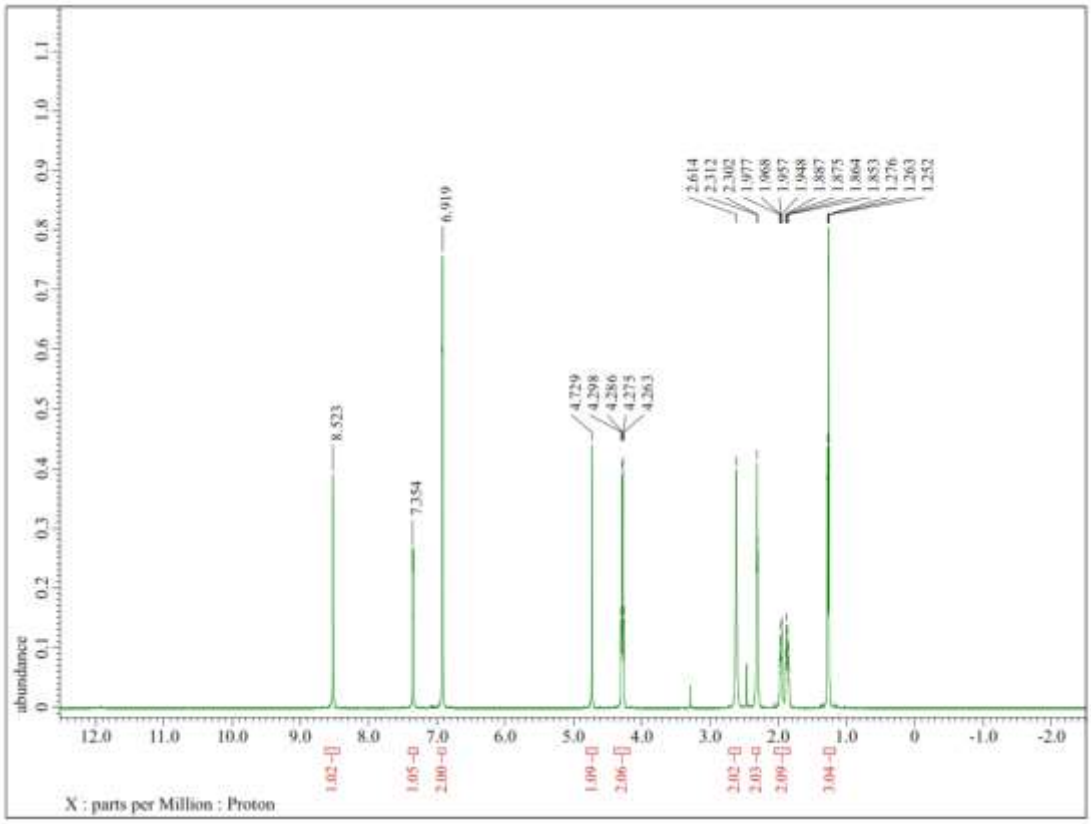



**Figure S3:** $^{1}$H NMR (DMSO-*d6*) of **2**

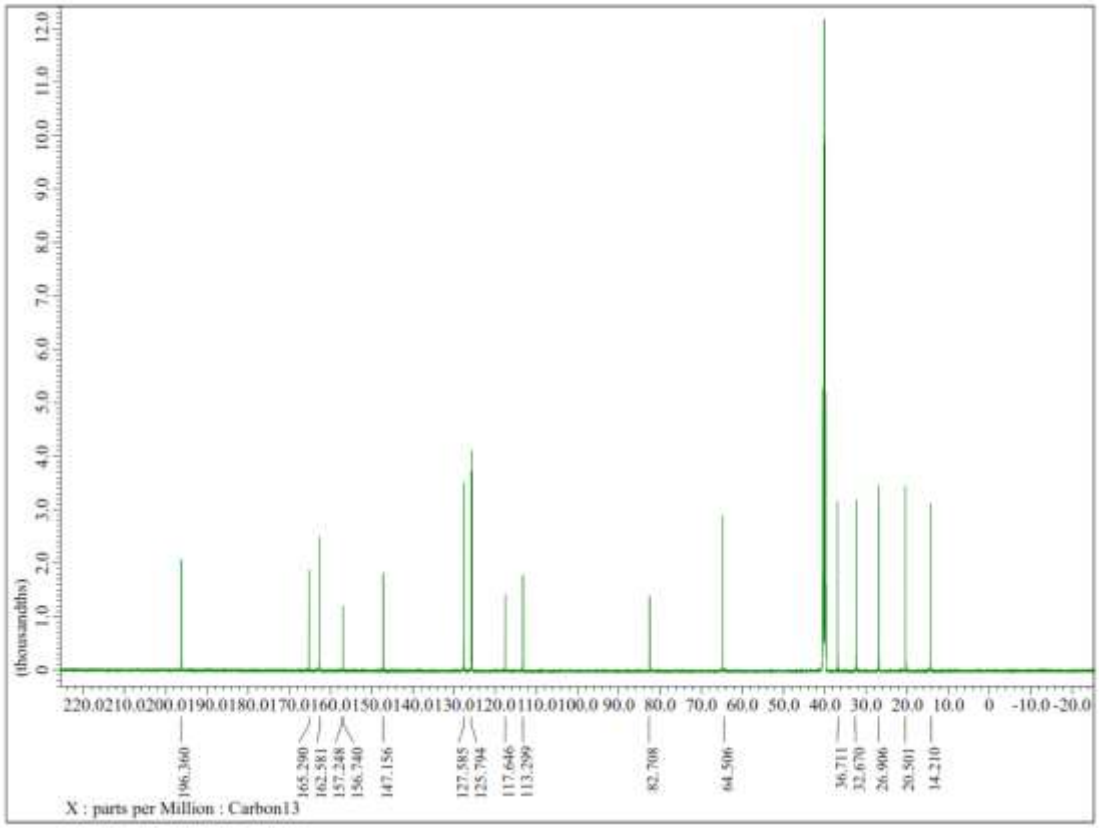



**Figure S4:** $^{13}$C NMR (DMSO-*d6*) of **2**

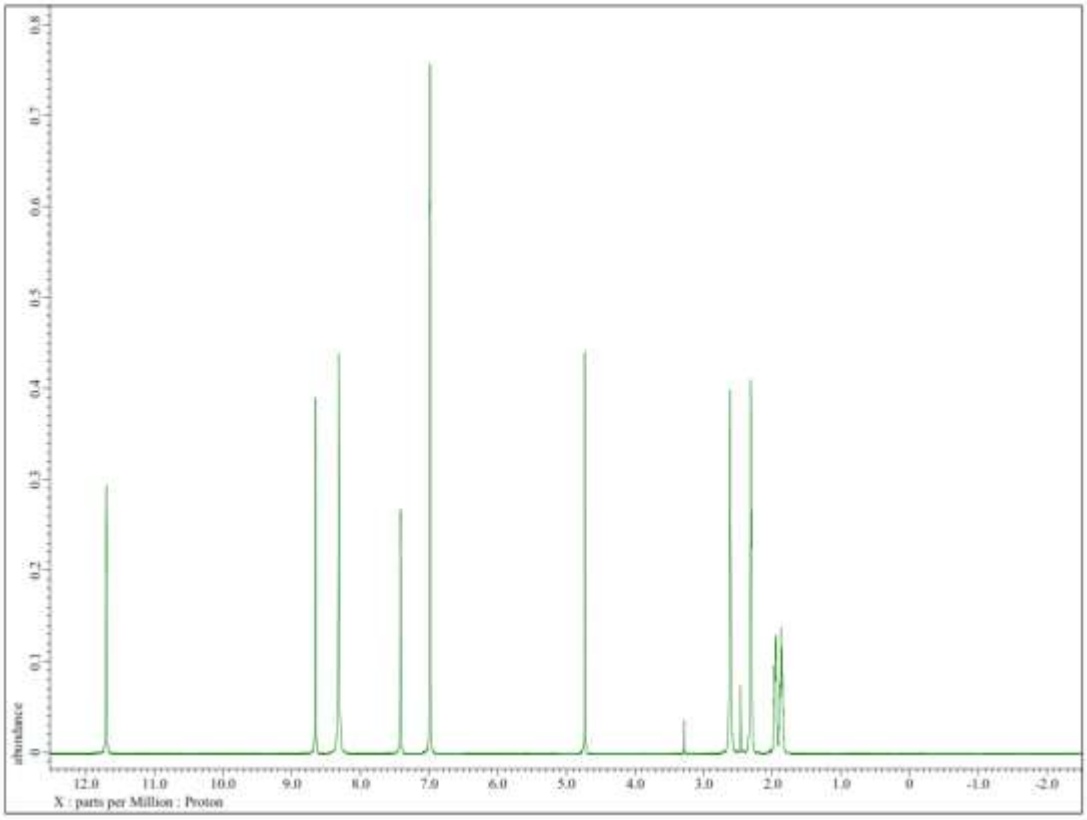



**Figure S5:** $^{1}$H NMR (DMSO-*d6*) of **3**

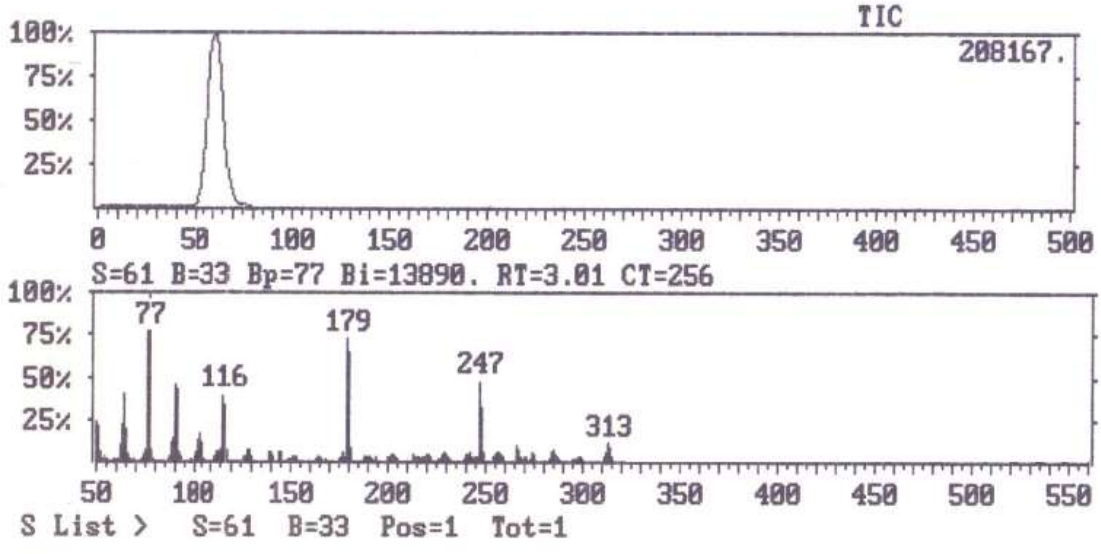



**Figure S6:** MS of **3**

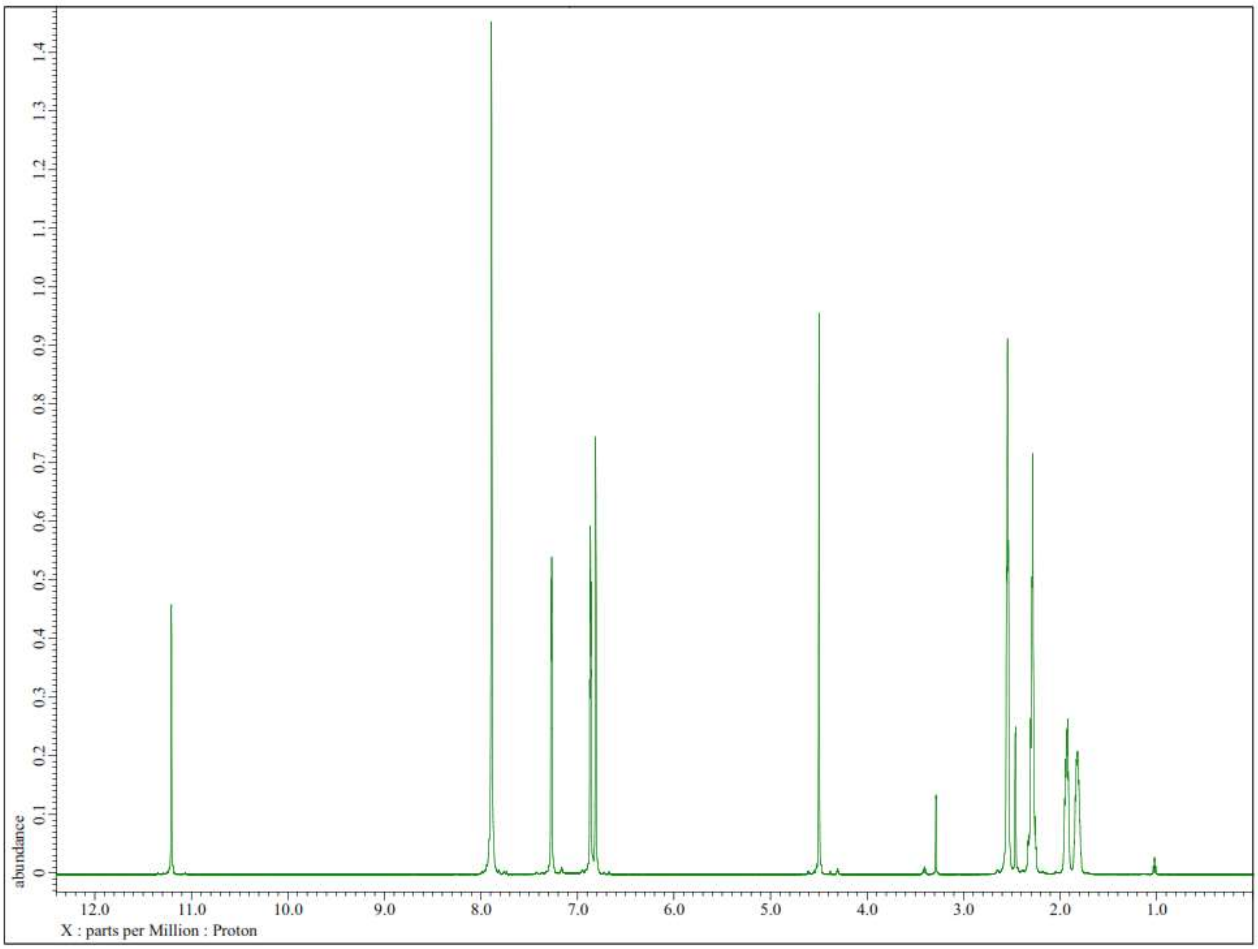



**Figure S7:** $^{1}$H NMR of **4a**

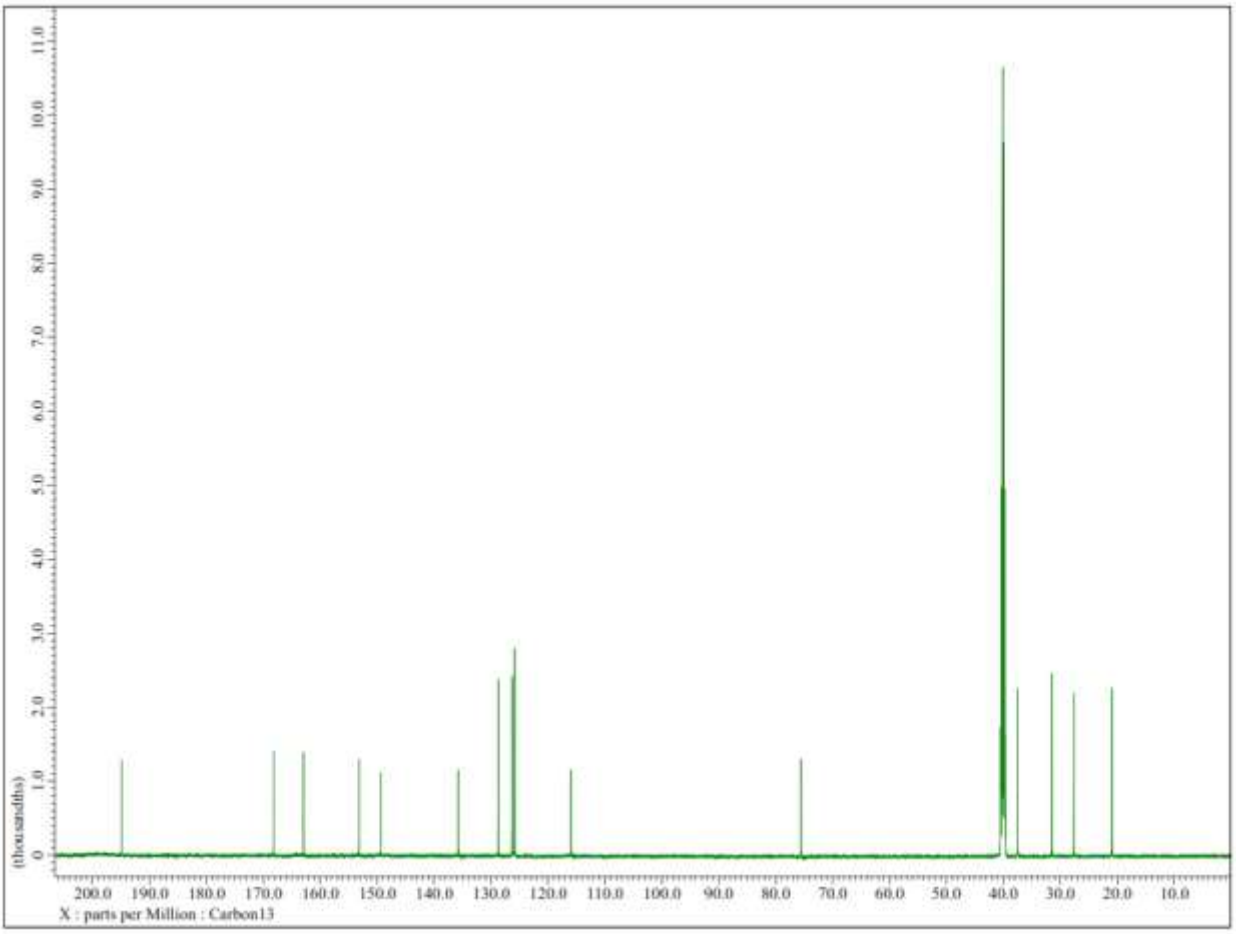



**Figure S8:** $^{13}$C NMR of **4a**

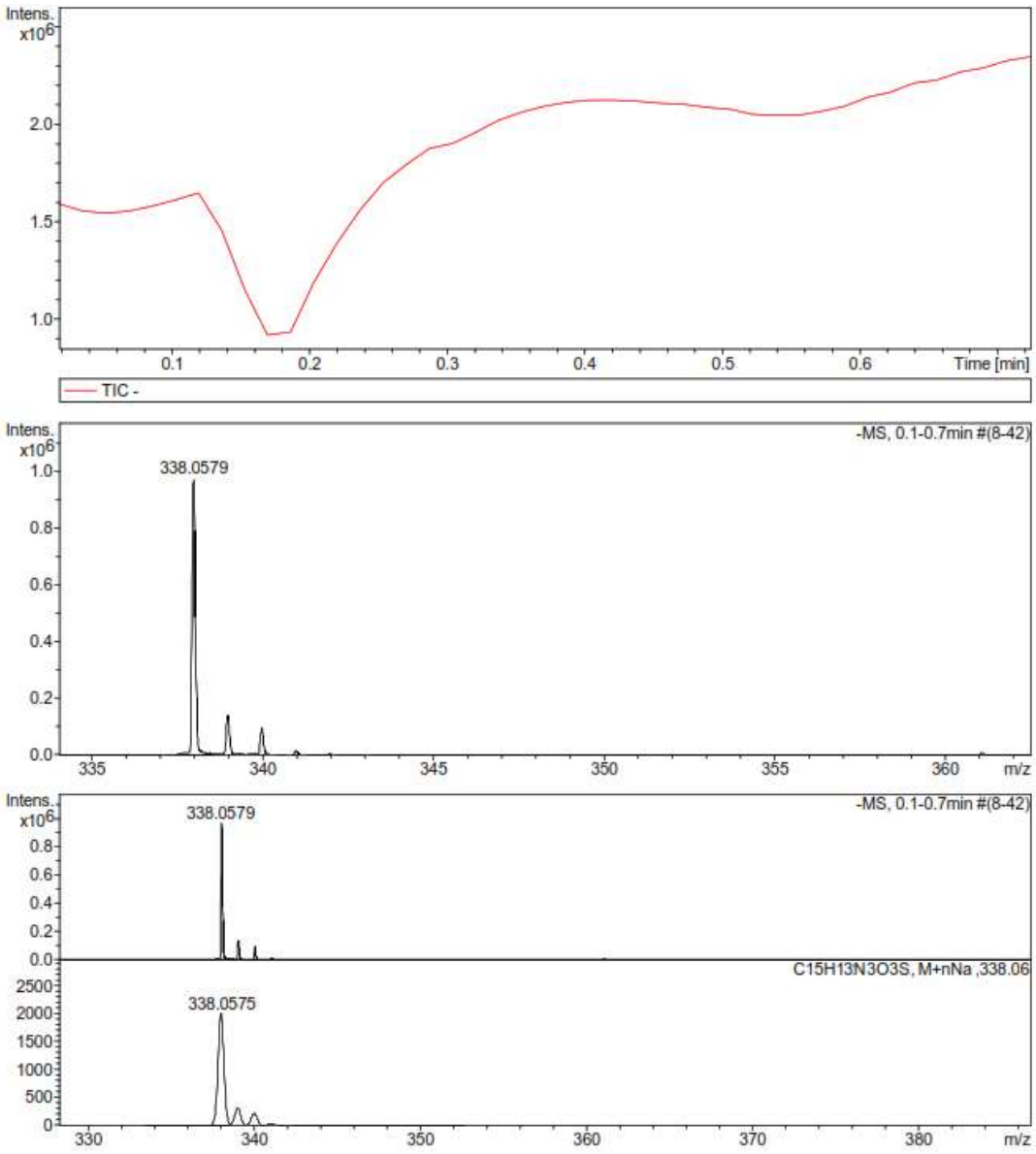



**Figure S9:** HRMS of **4a**

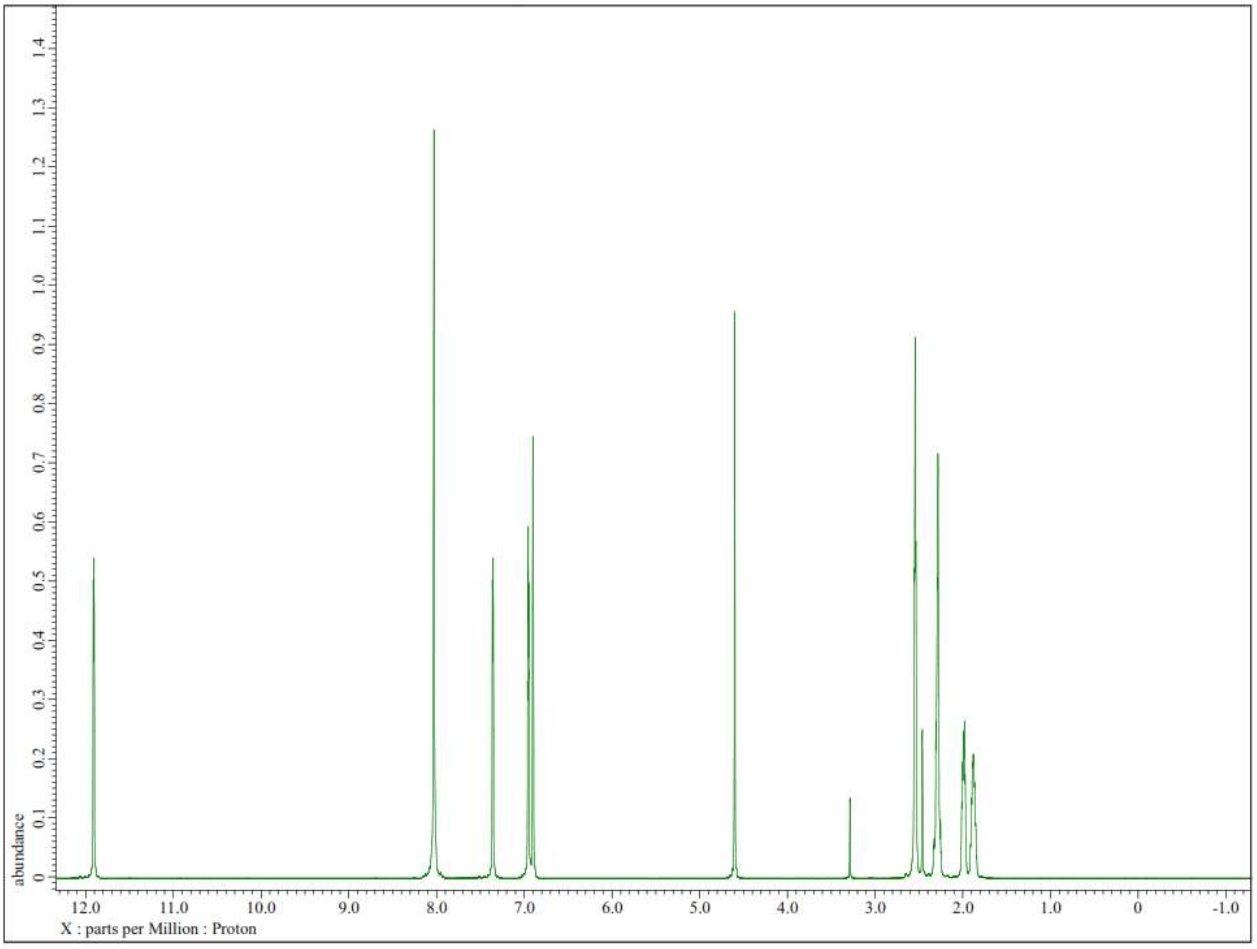



**Figure S10:** $^{1}$H NMR of **4b**

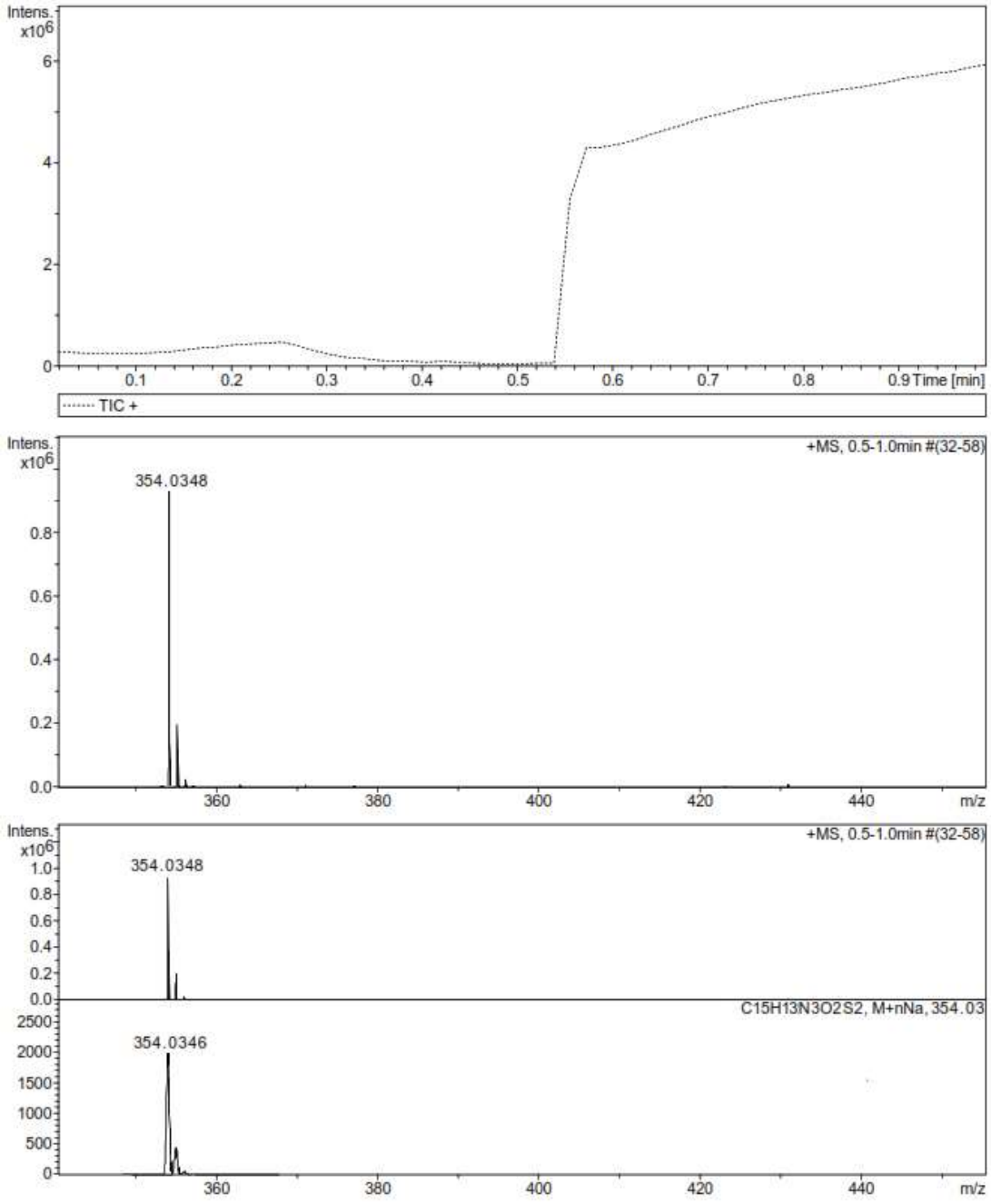



**Figure S11:** HRMS of **4b**

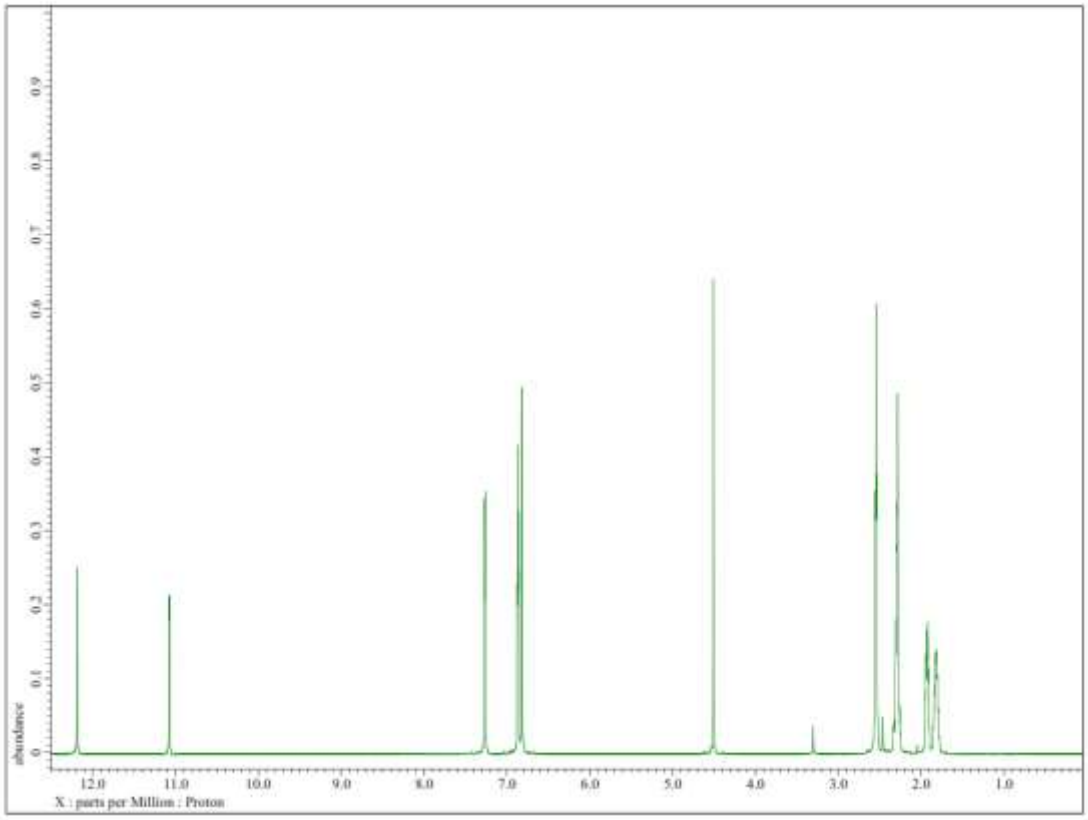



**Figure S12:** $^{1}$H NMR of **6**

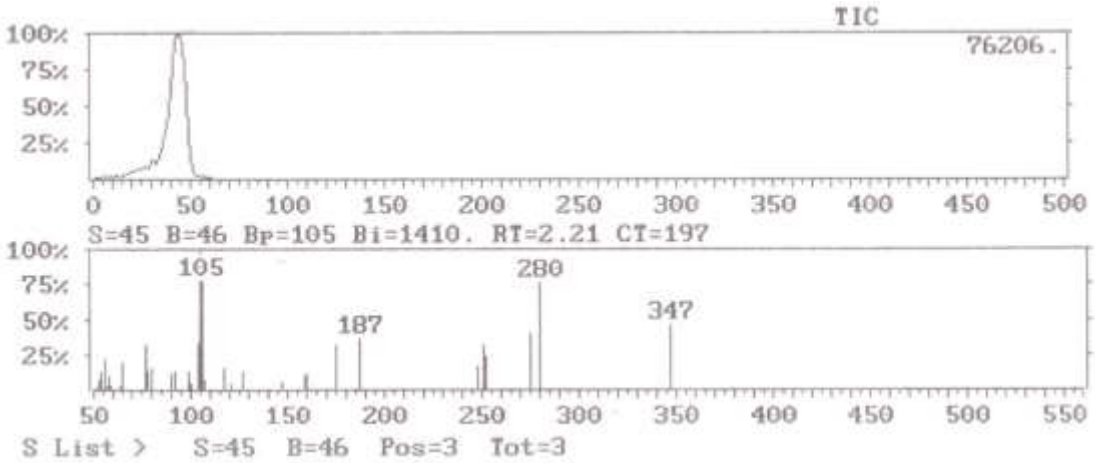



**Figure S13:** MS of **6**

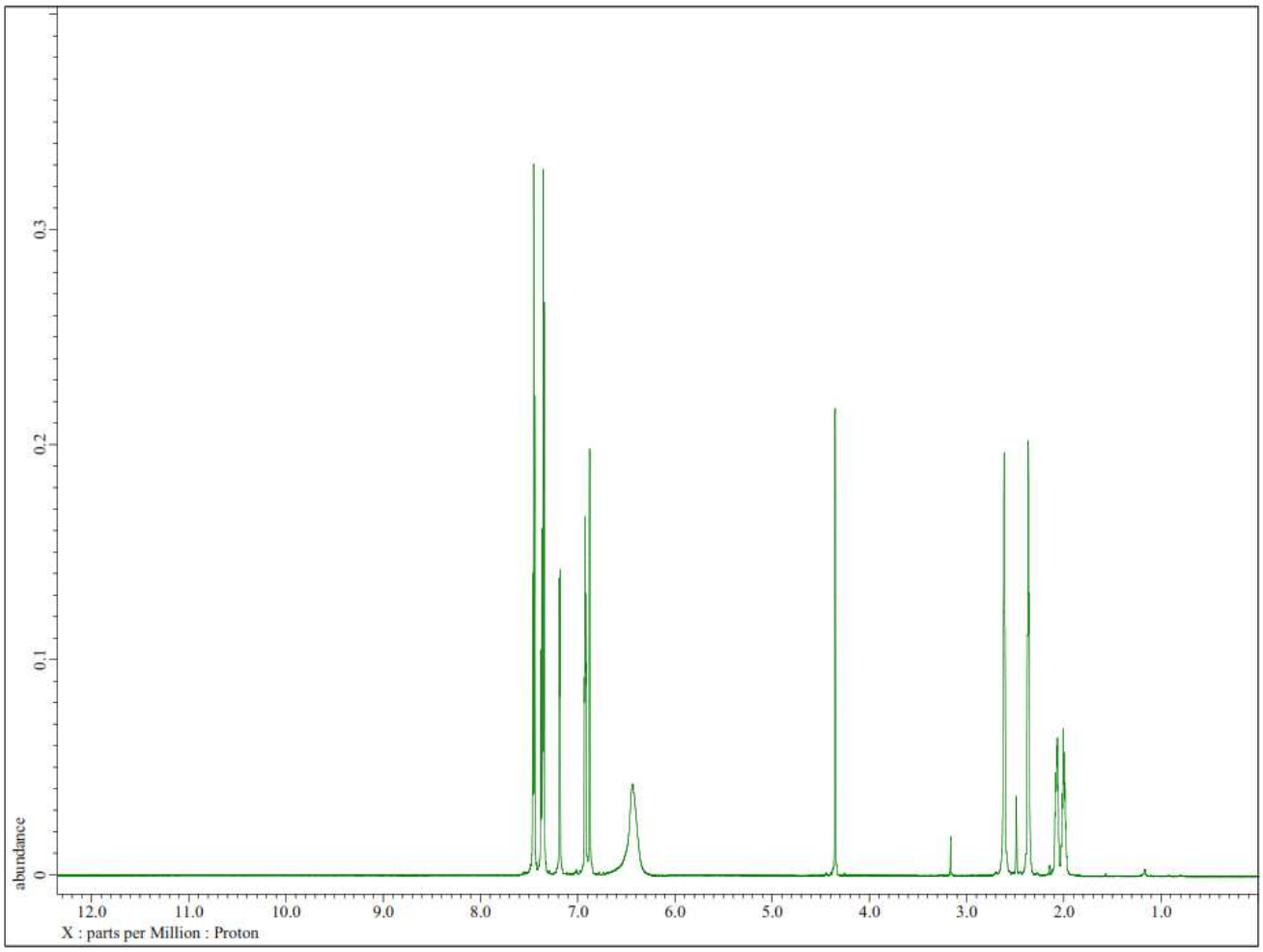
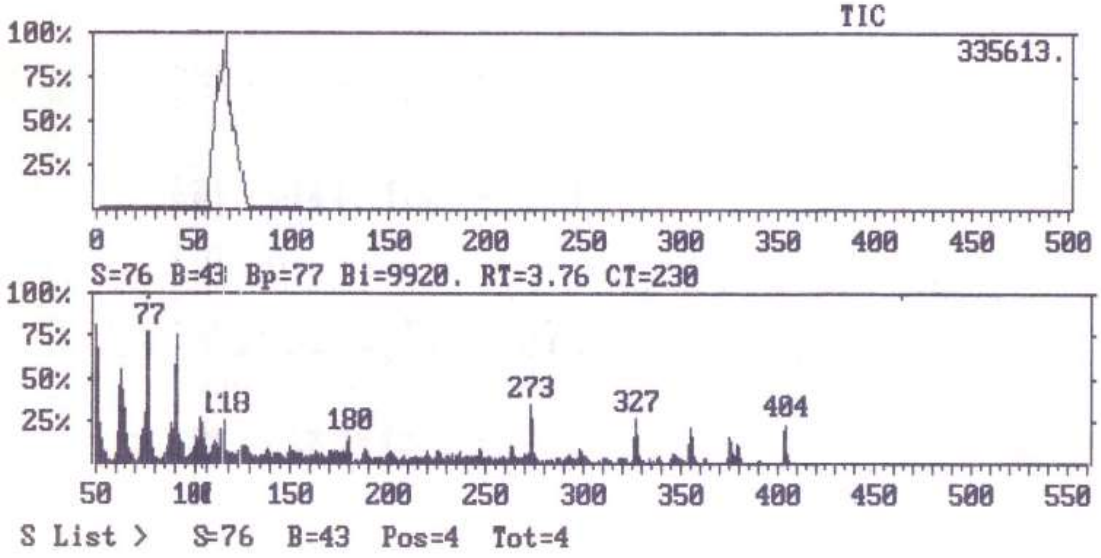



**Figure S14:** $^{1}$H NMR of **7**

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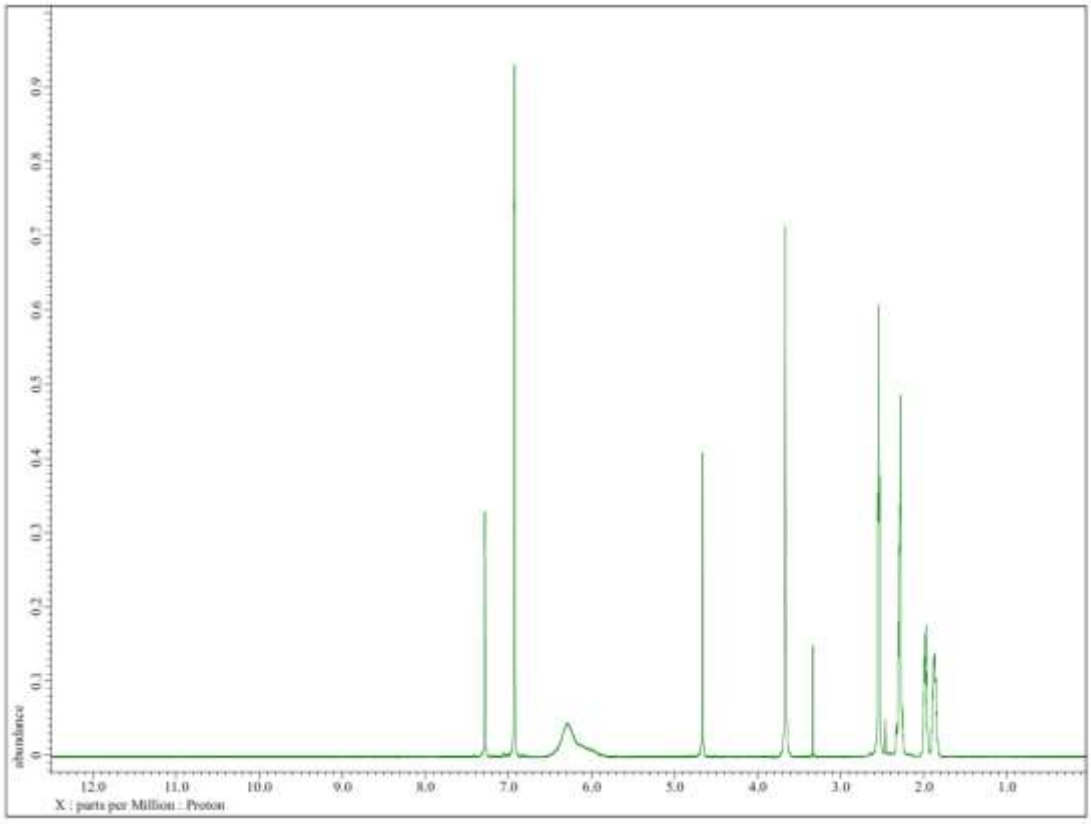



**Figure S16:** $^{1}$H NMR of **11**

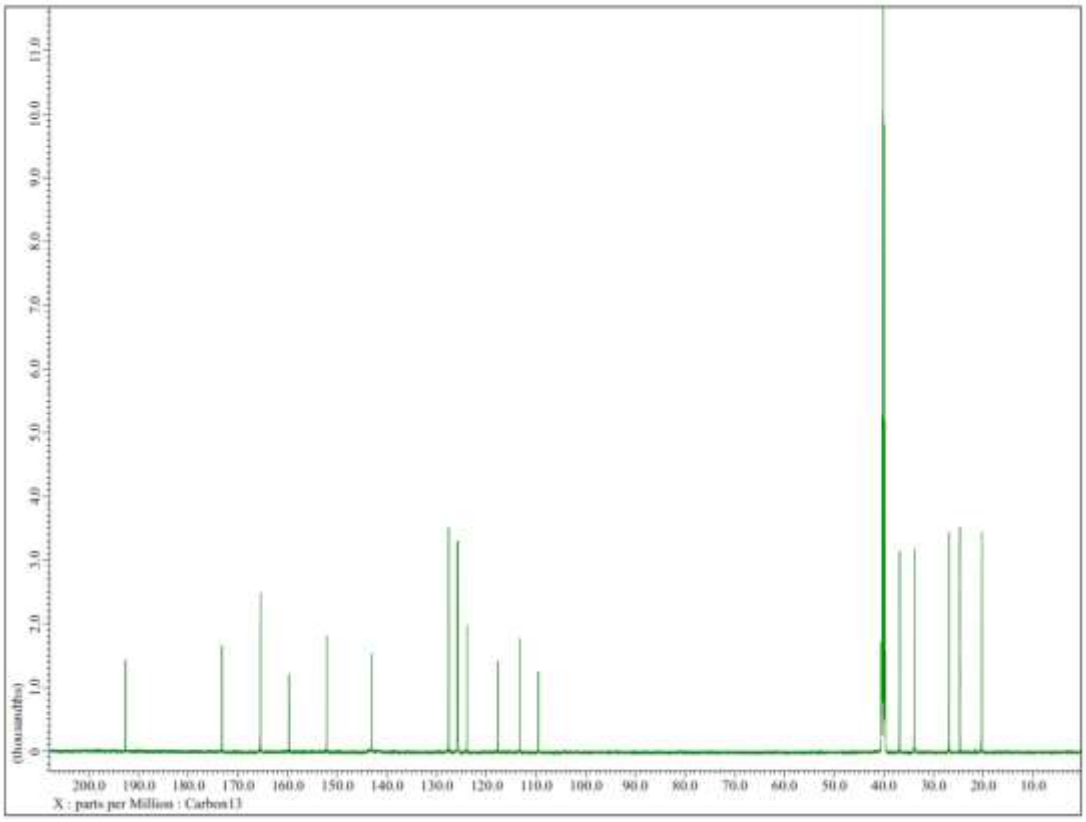
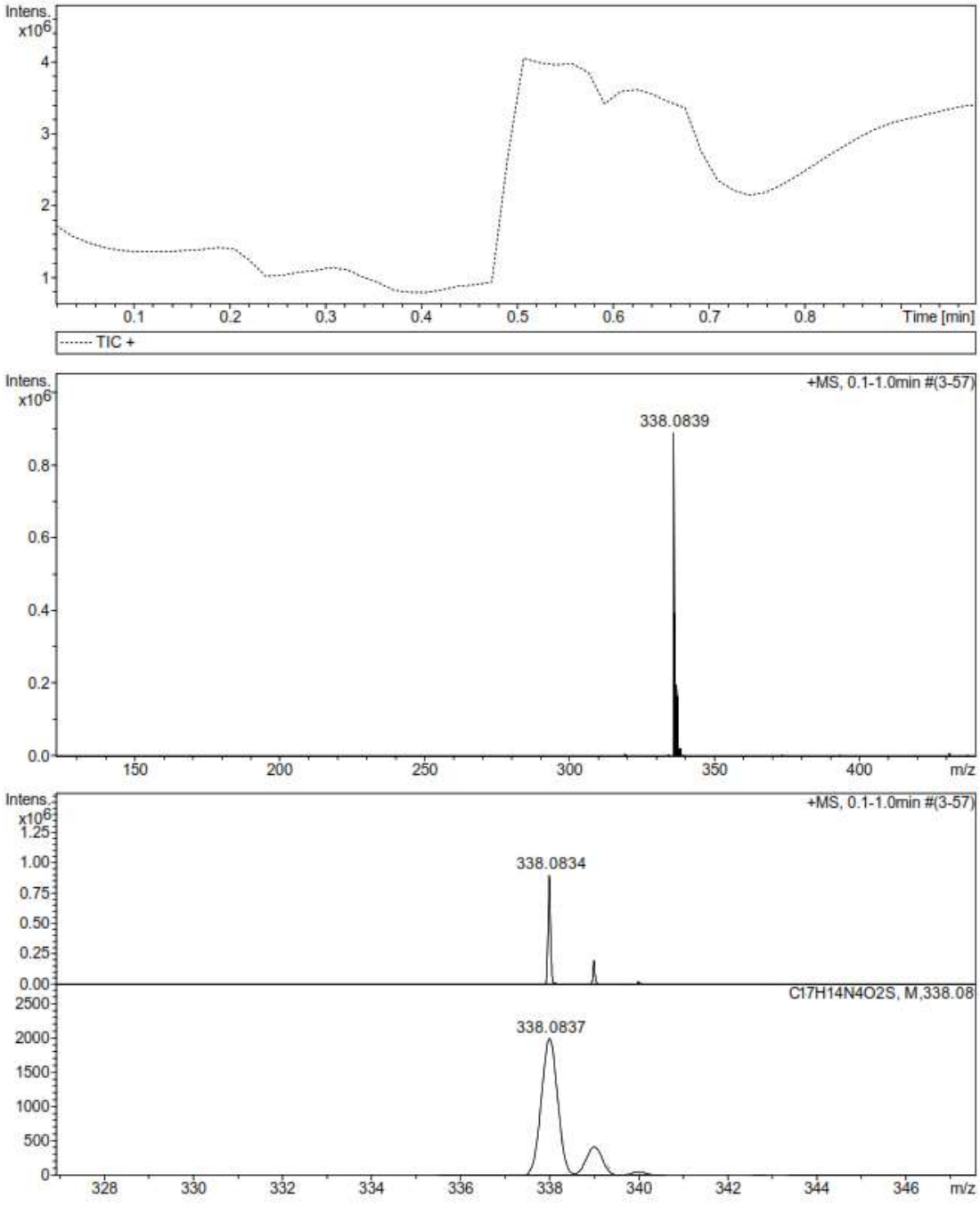



**Figure S17:** $^{13}$C NMR of **11**

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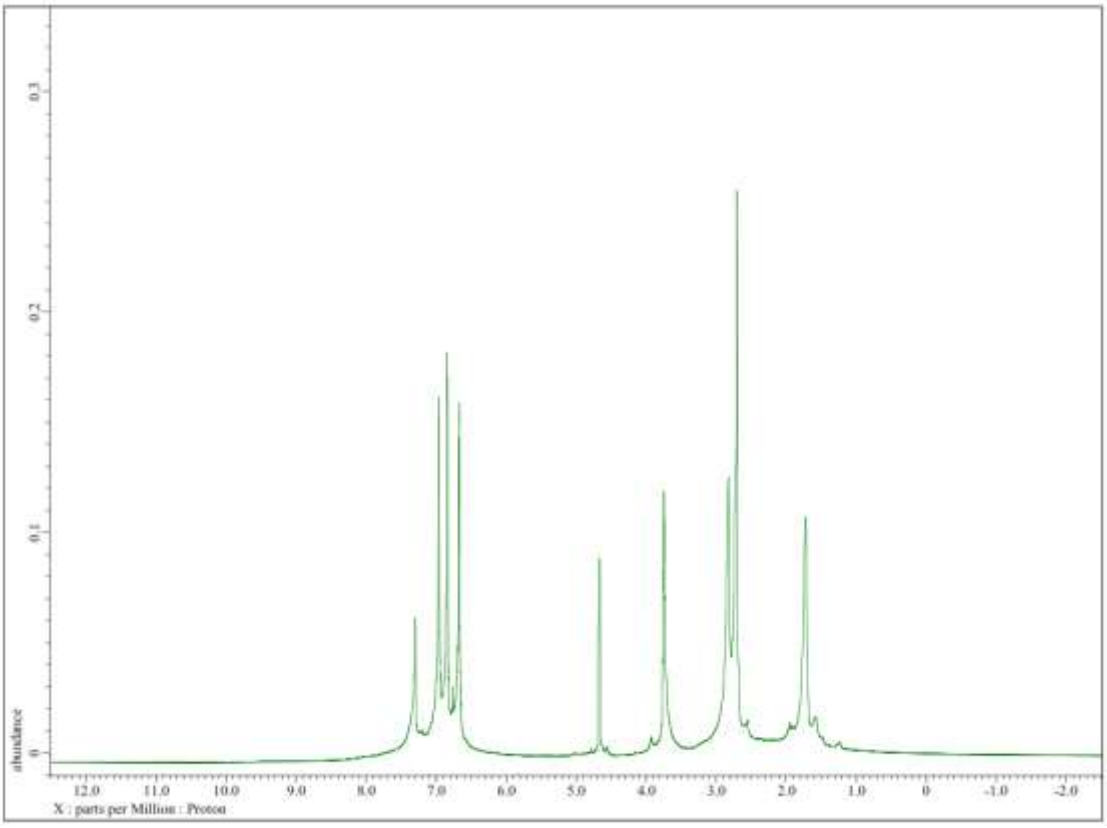



**Figure S19:** $^{1}$H NMR of **13**

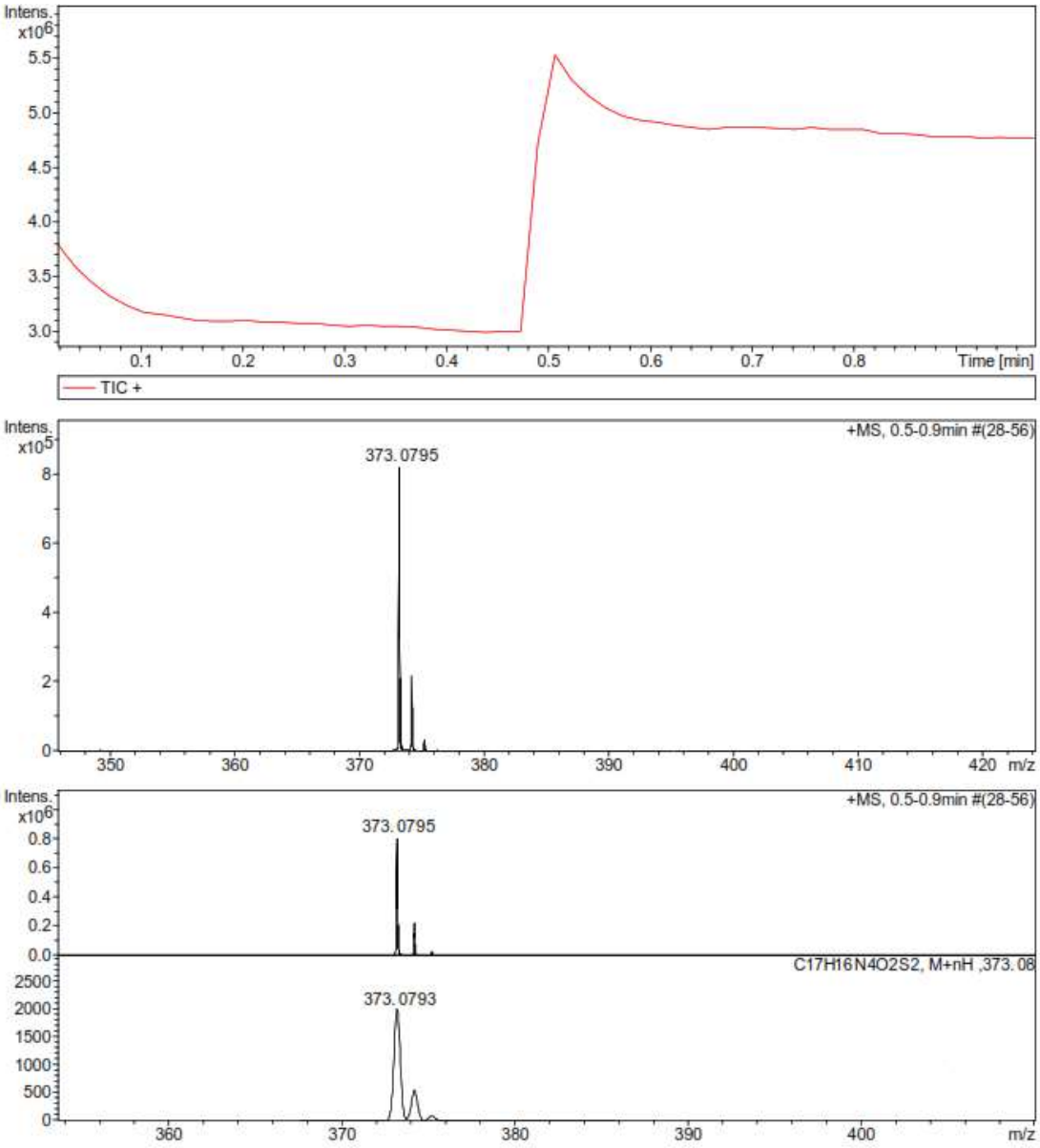



**Figure S20:** HRMS of **13**

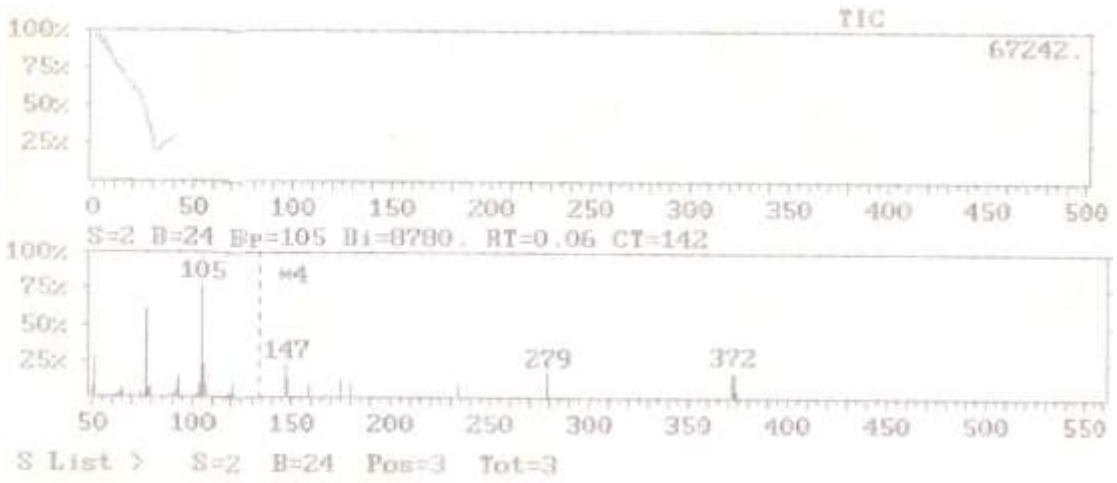
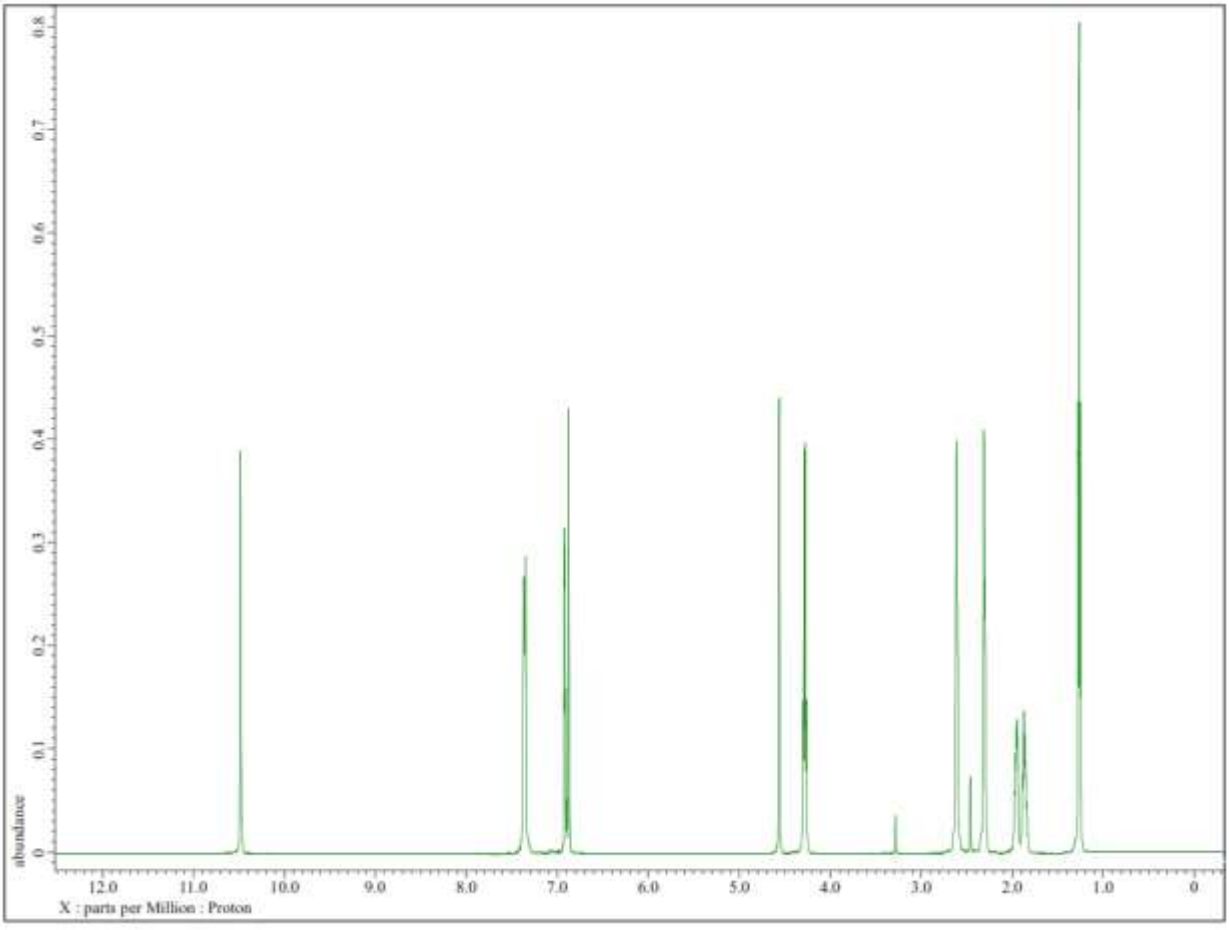



**Figure S21:** MS of **13**

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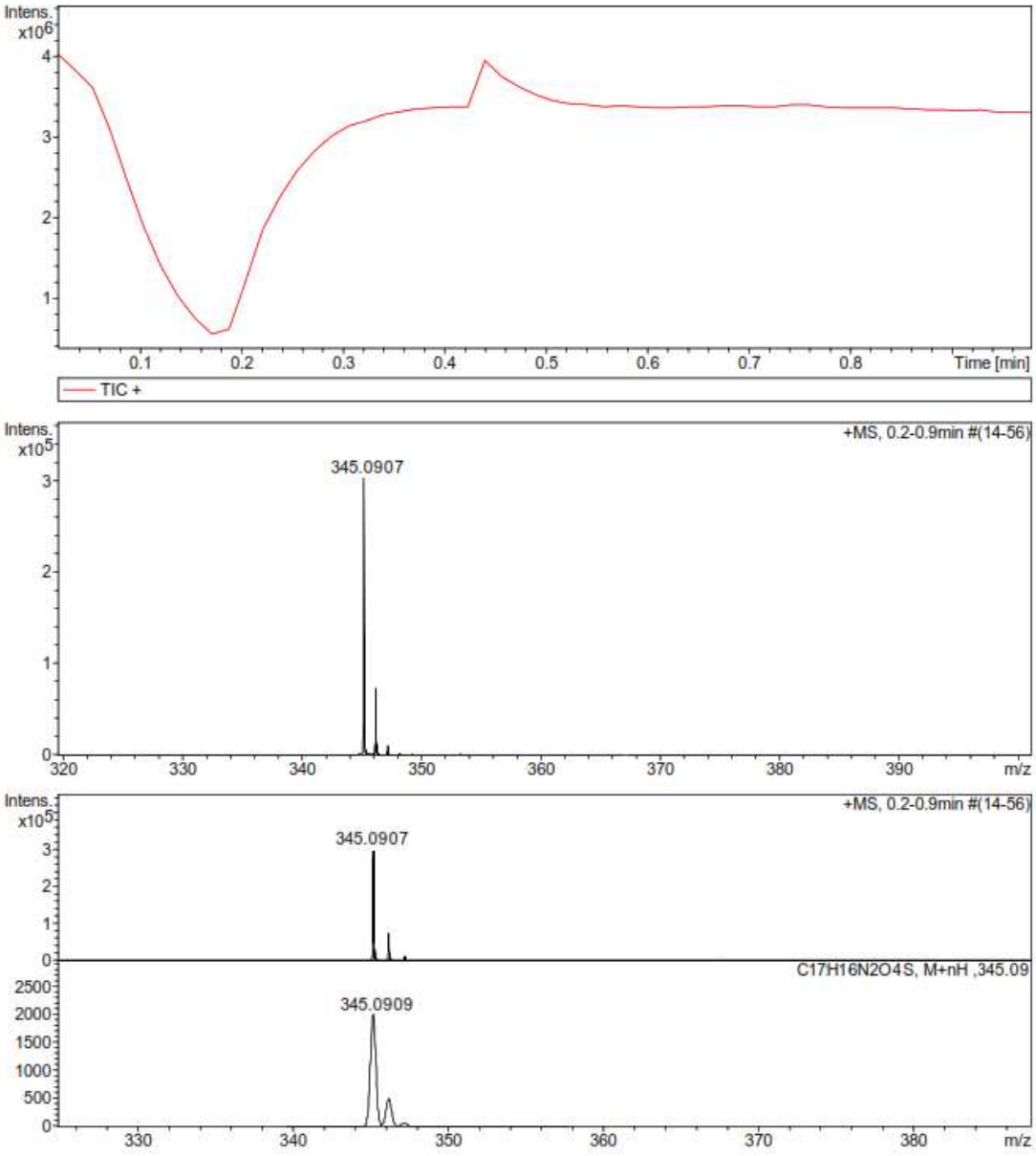


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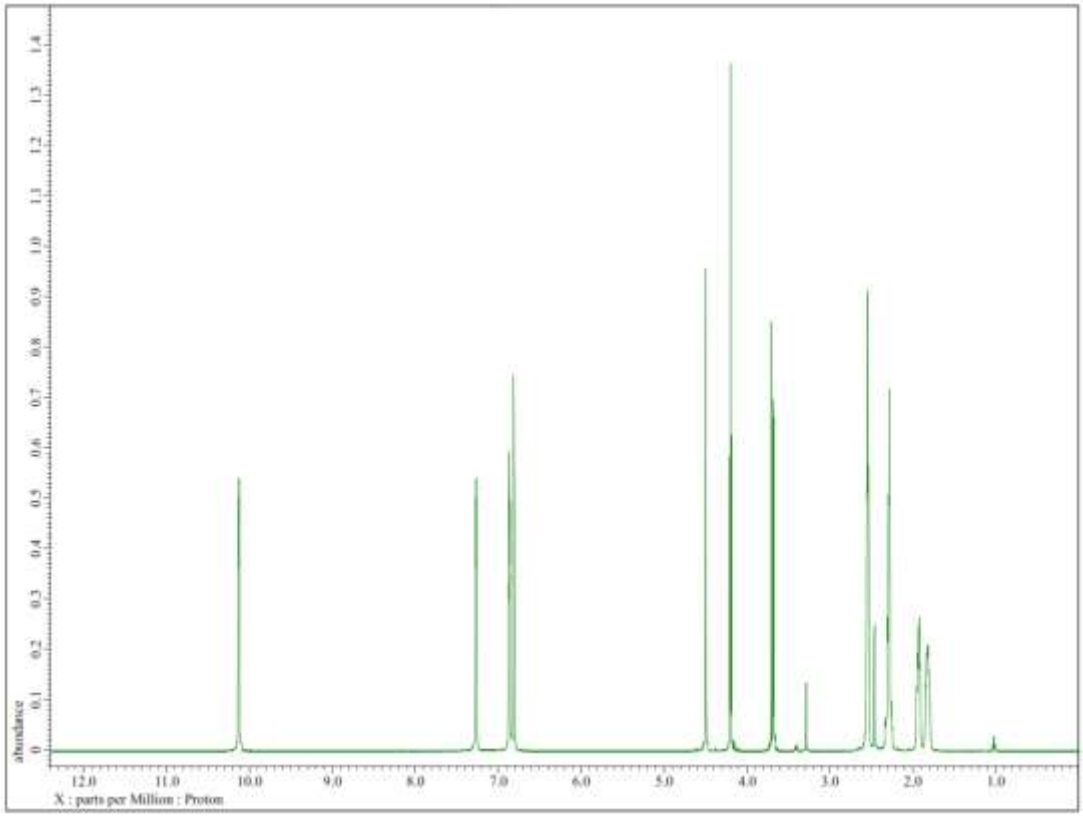
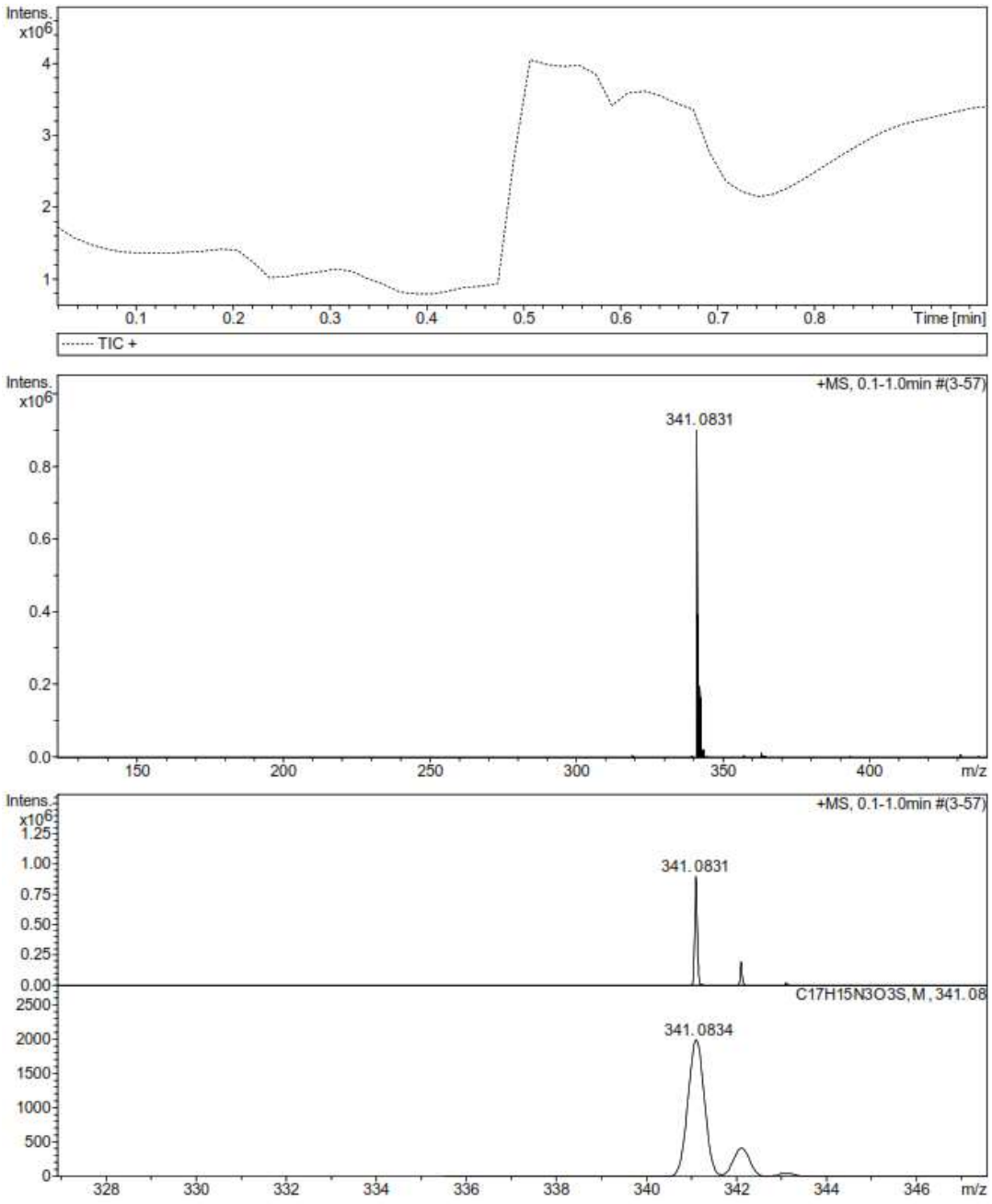



**Figure S24:** $^{1}$H NMR of **15**

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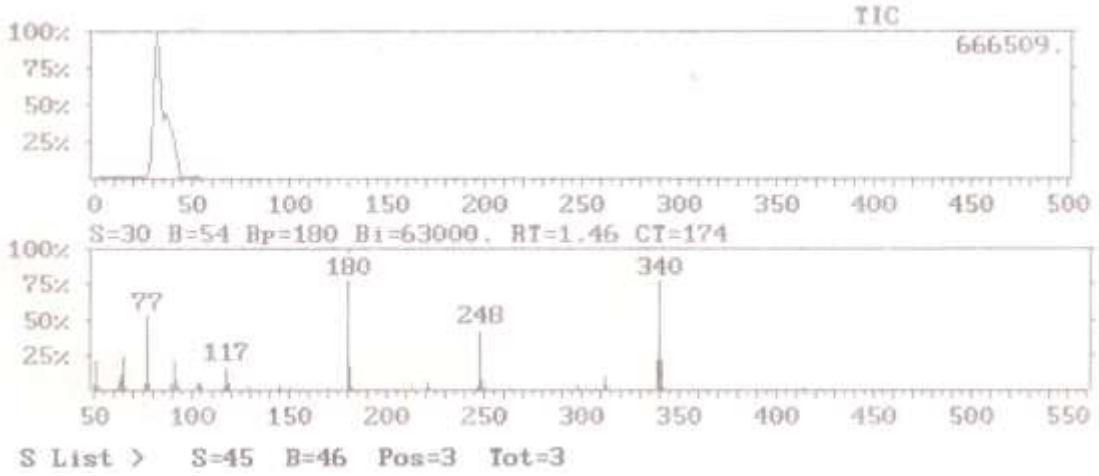


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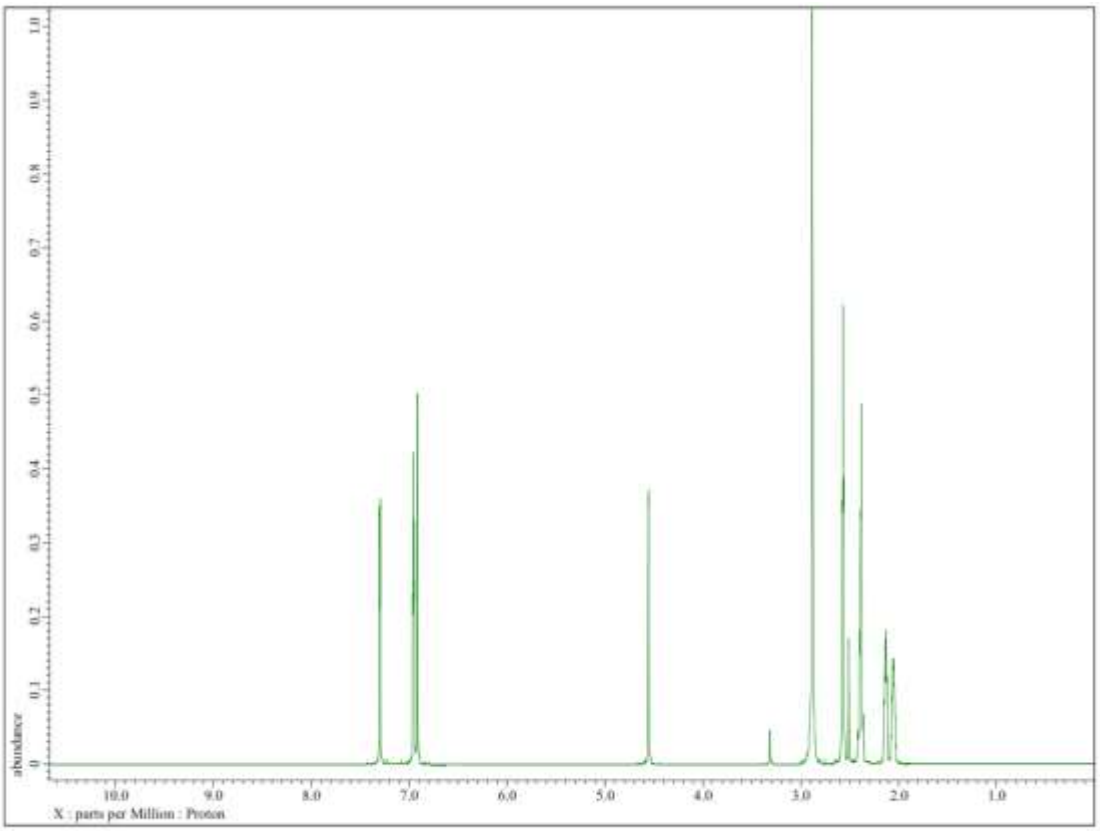
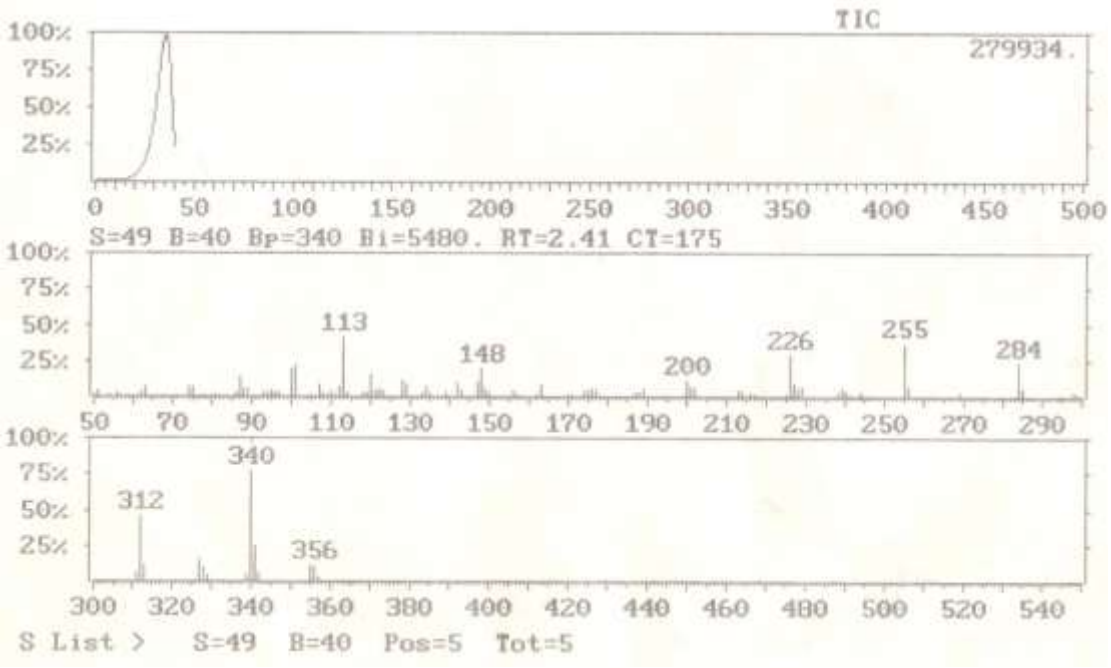



**Figure S27:** $^{1}$H NMR of **17**

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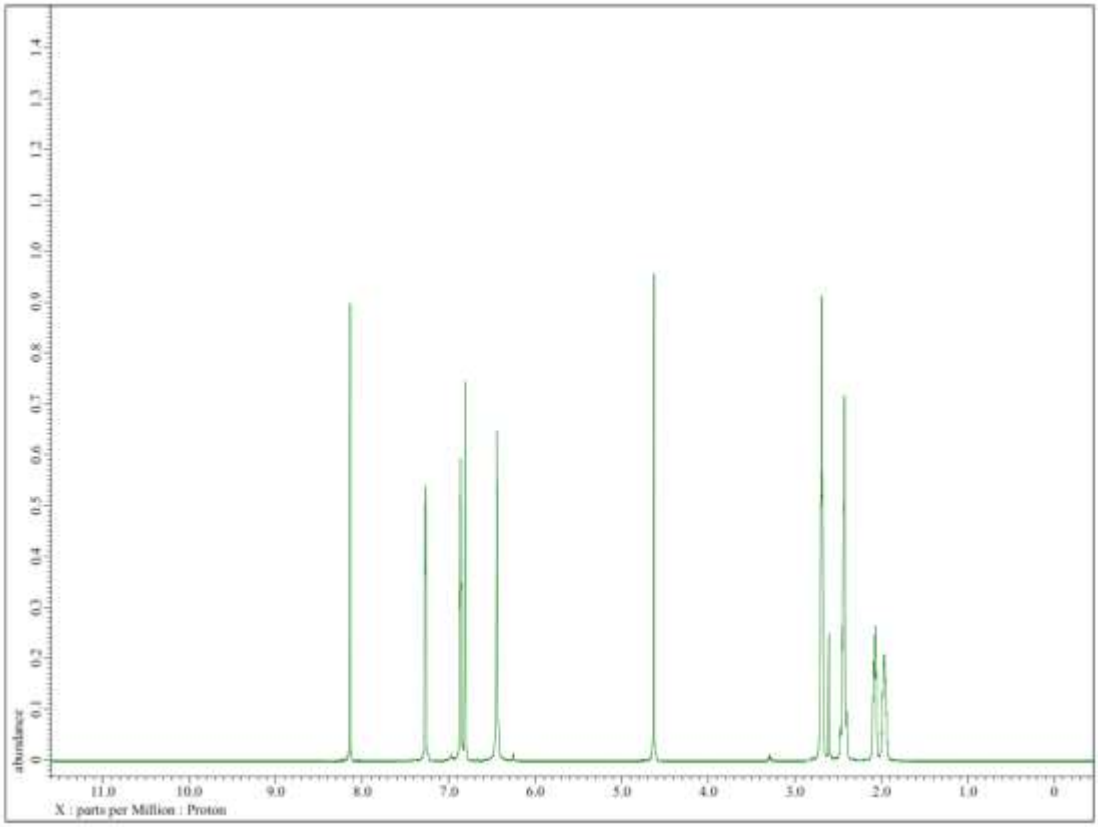



**Figure S29:** $^{1}$H NMR of **18**

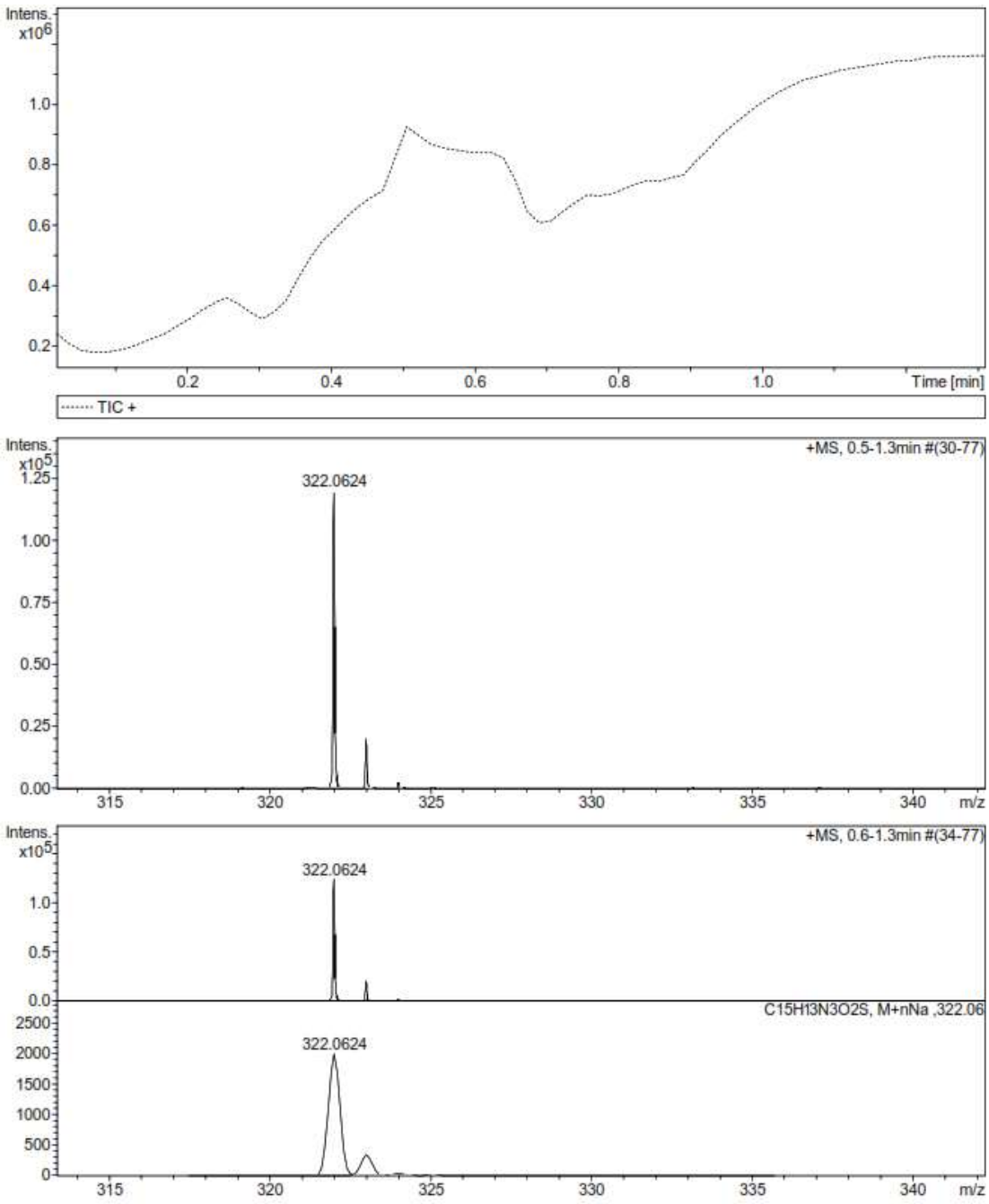



**Figure S30:** HRMS of **18**

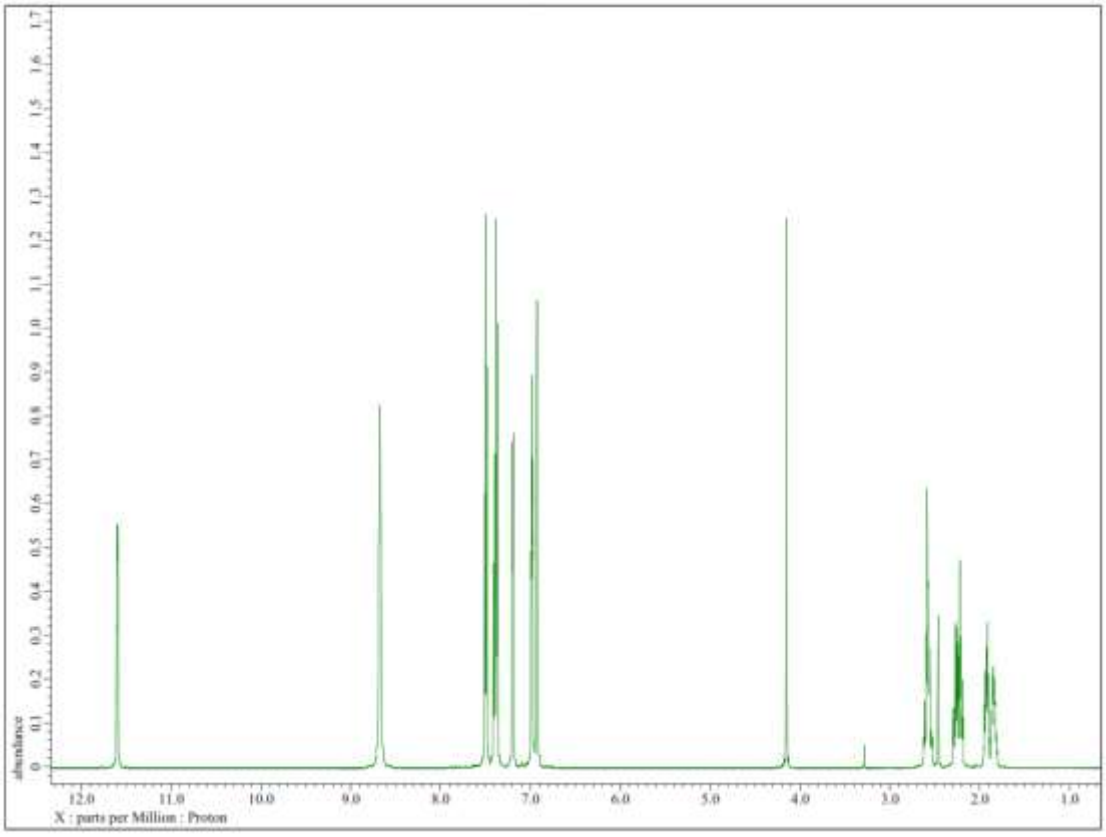



**Figure S31:** $^{1}$H NMR of **19**

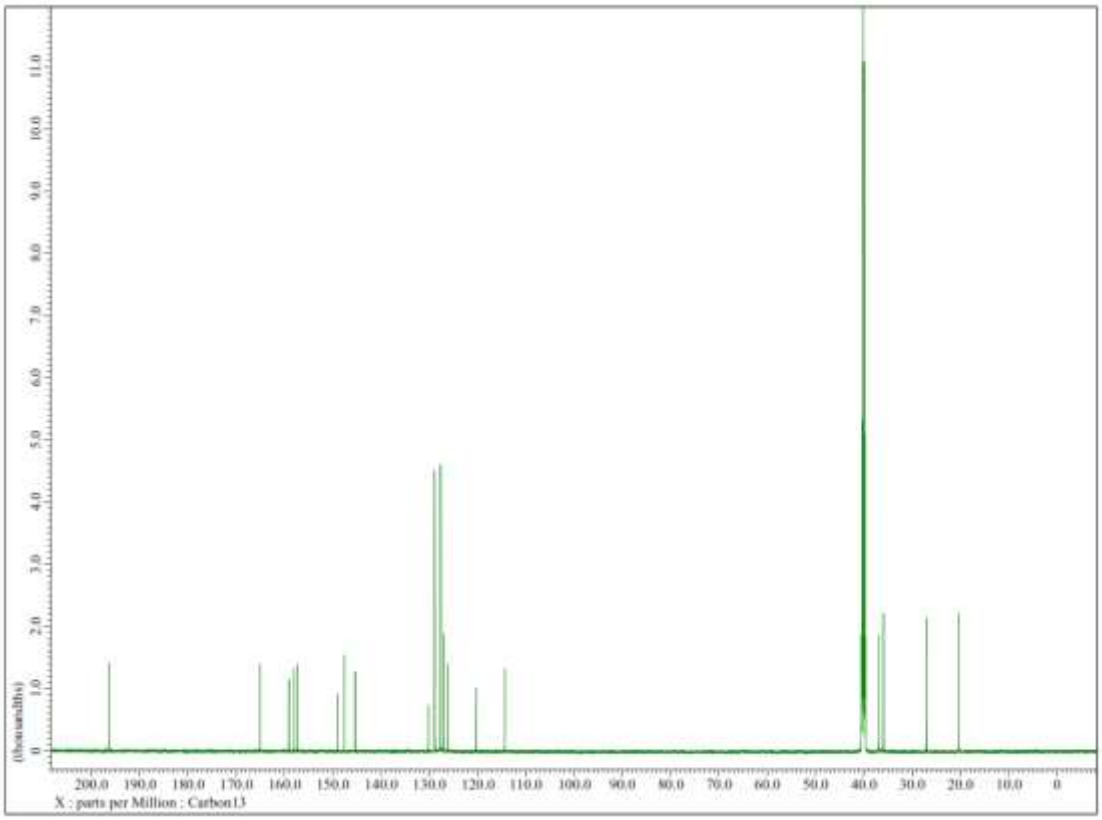



**Figure S32:** $^{13}$C NMR of **19**

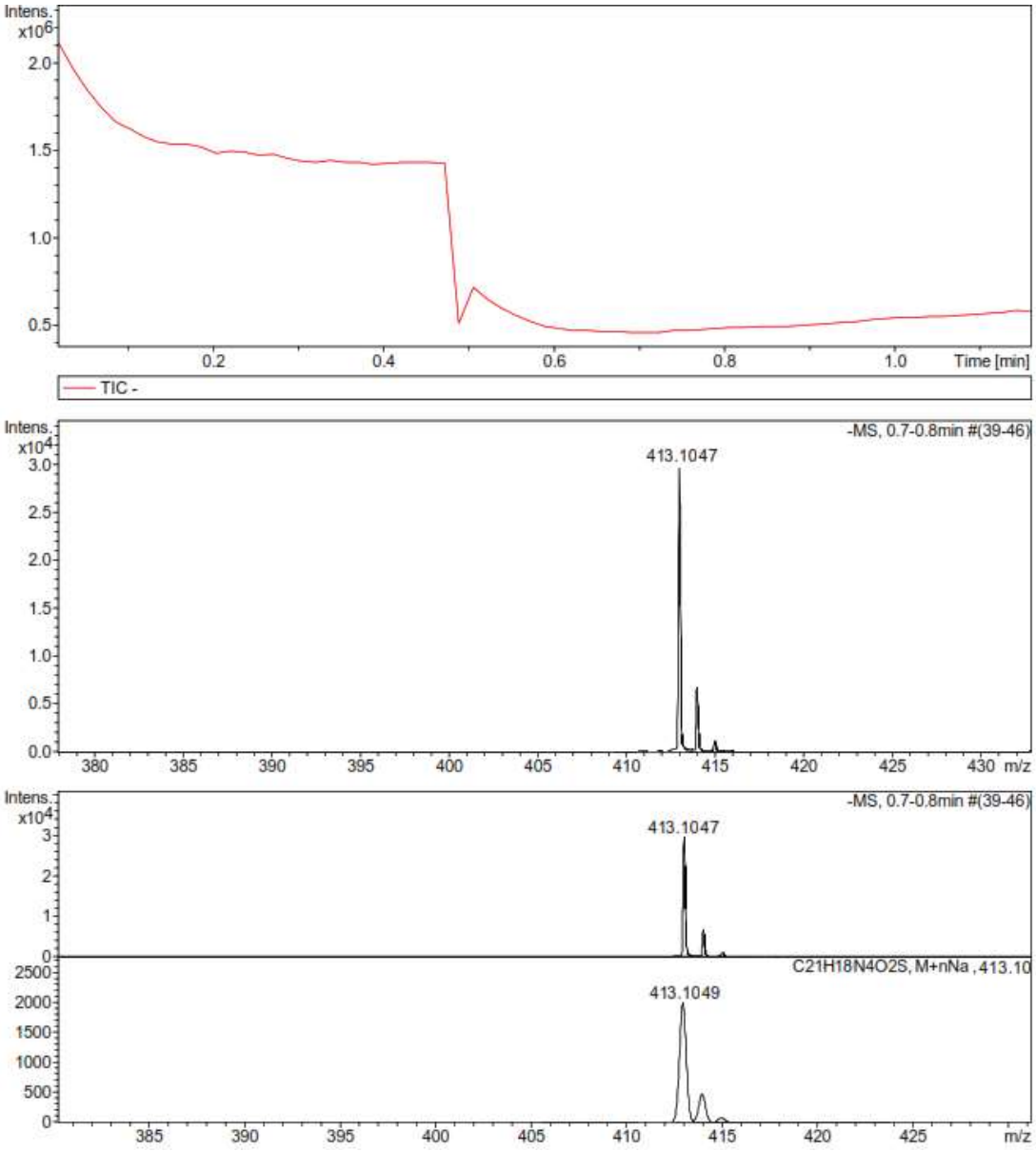
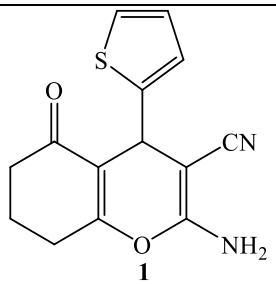
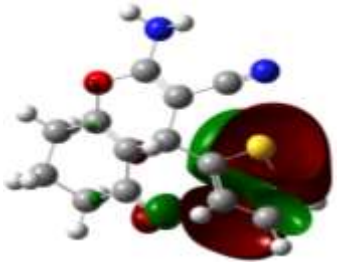
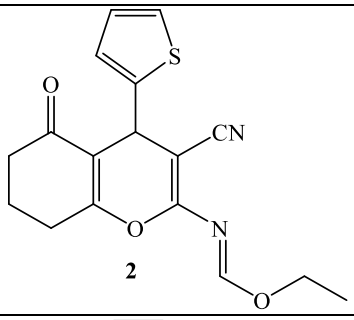
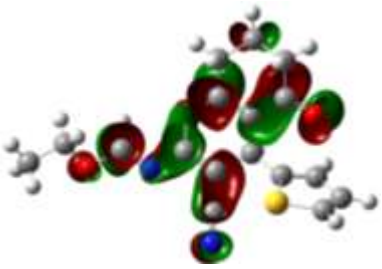
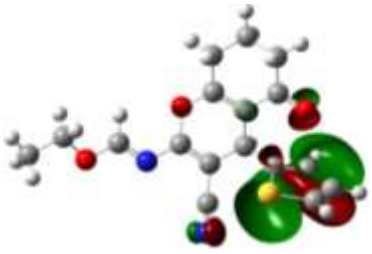
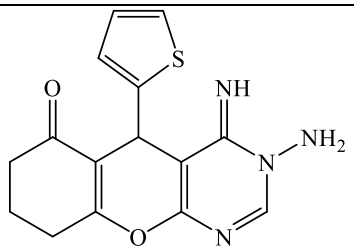
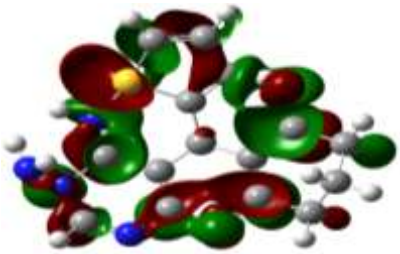
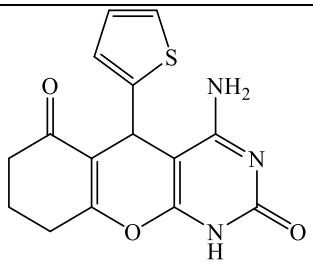
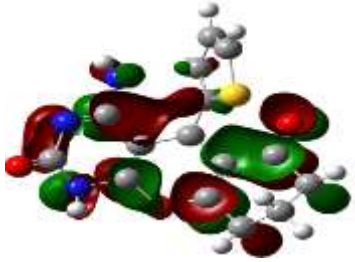
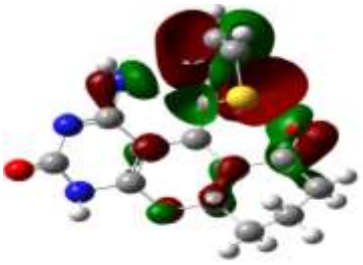
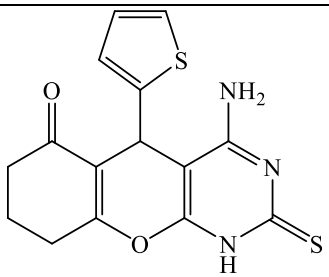
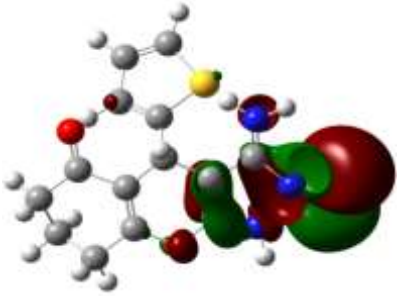



**Figure S33:** HRMS of **19**

**Table S1.** HOMO and LUMO of the assembled molecules and Doxorubicin.

| Comp. | LUMO | HOMO |
|---|---|---|
|  **1** |  |  |
|  **2** |  |  |
|  **3** |  |  |
|  **4a** |  |  |
|  **4b** |  |  |

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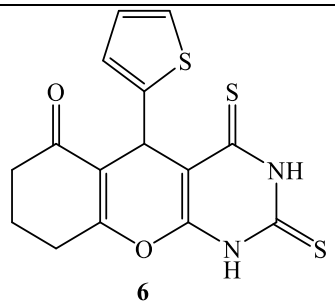
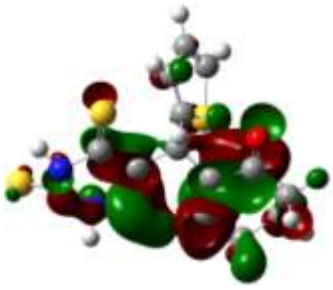
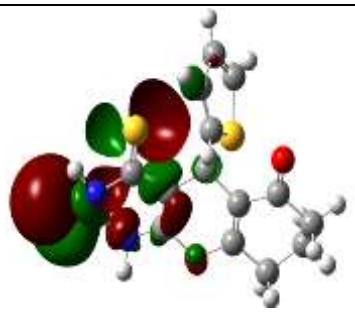
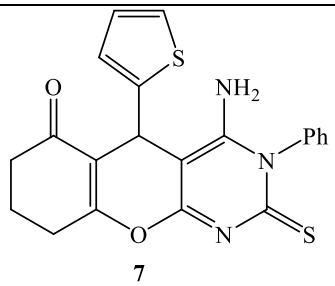
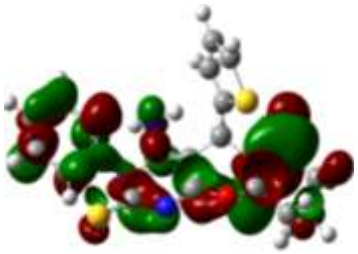
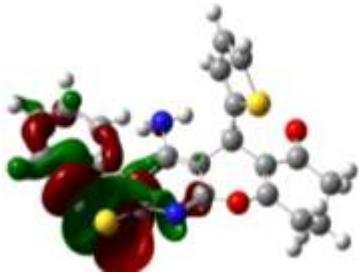
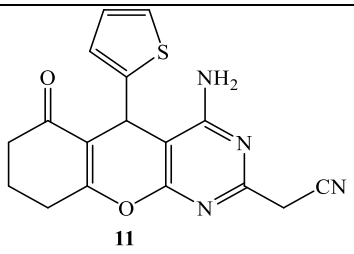
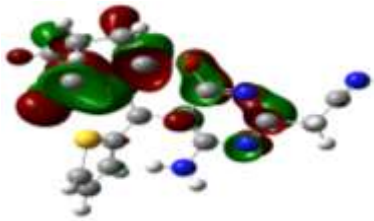
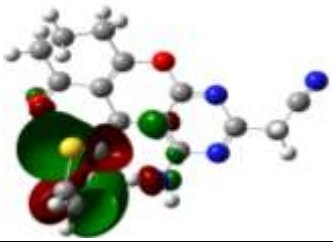
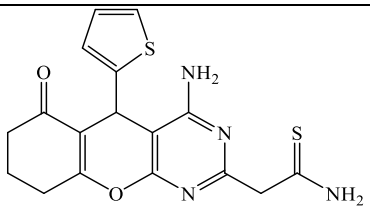
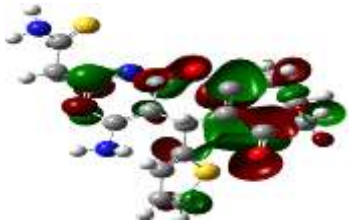
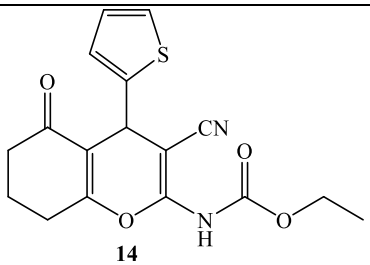
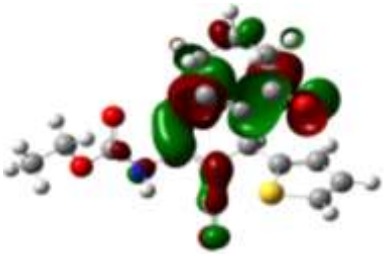
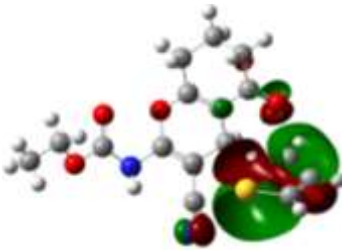
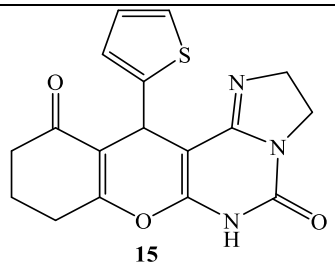
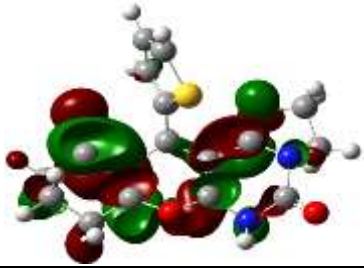
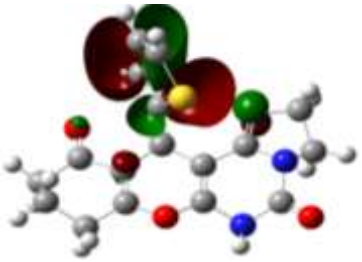
|  **6** |  |  |
|  **7** |  |  |
|  **11** |  |  |
|  **13** |  |  |
|  **14** |  |  |
|  **15** |  |  |

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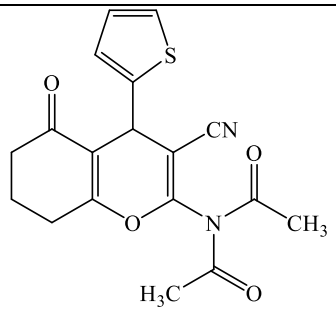
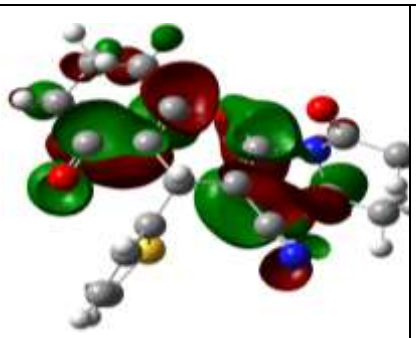
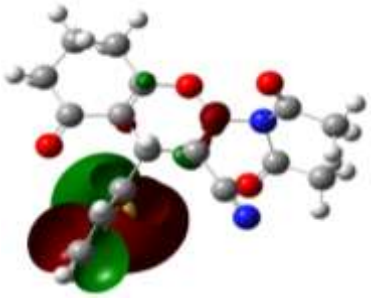
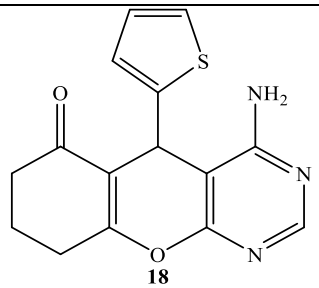
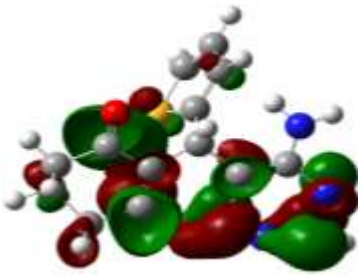
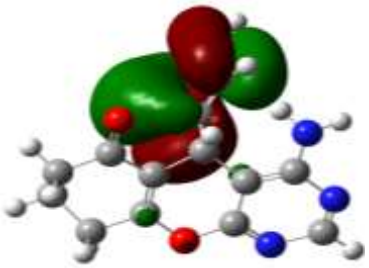
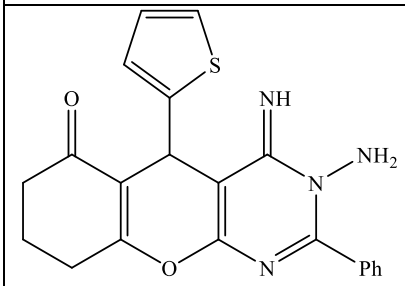
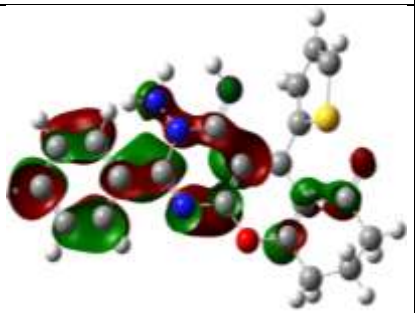
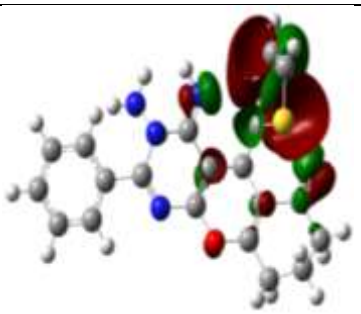
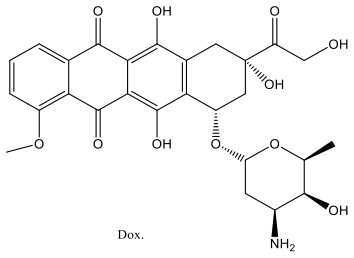
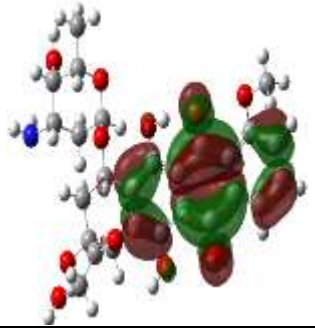
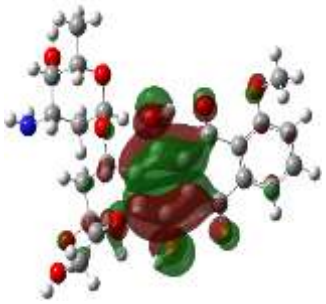
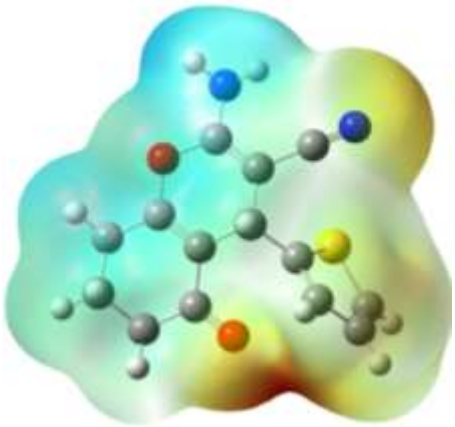
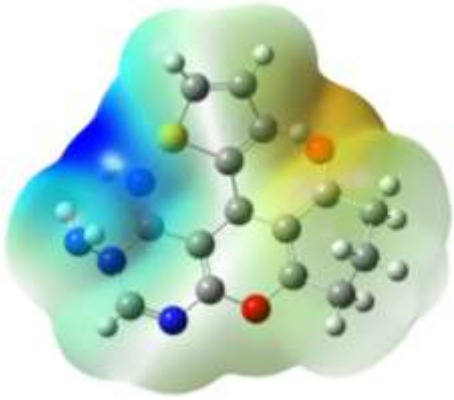
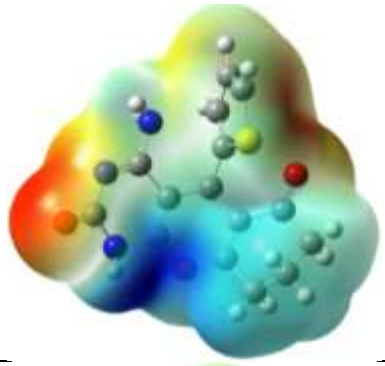
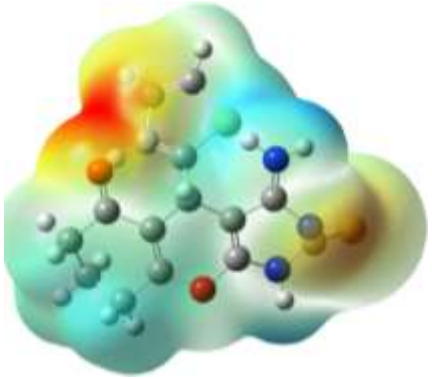
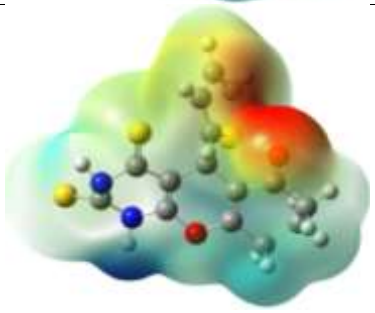
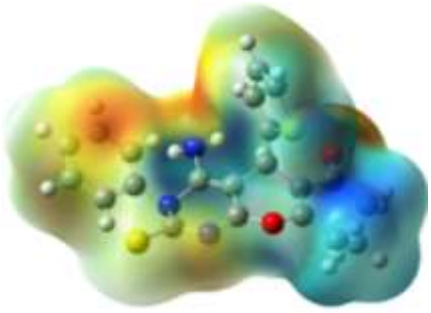
|---|---|---|
|  **17** |  |  |
|  **18** |  |  |
|  **19** |  |  |
|  Dox. |  |  |

**Table S2.** Computed electrostatic potential (ESP) surface for the assembled molecules and Doxorubicin.

| Comp. | ESP | Comp. | ESP |
|---|---|---|---|
| **1** |  | **3** |  |
| **4a** |  | **4b** |  |
| **6** |  | **7** |  |

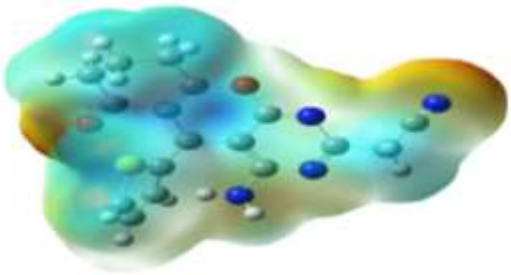
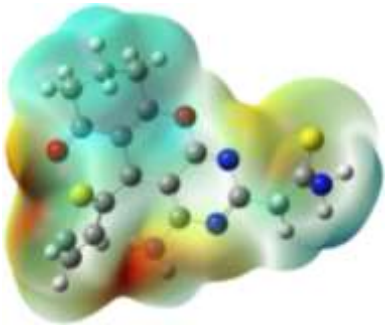
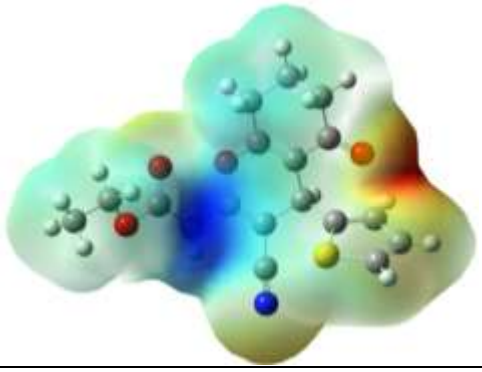
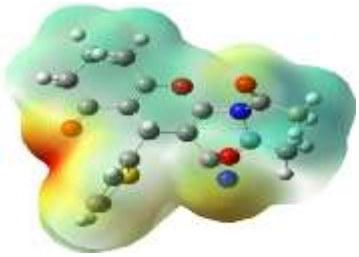
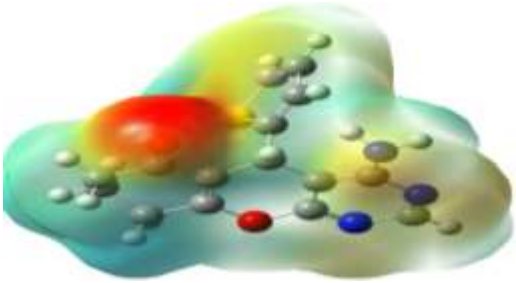
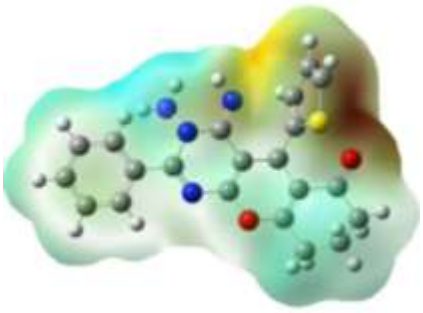
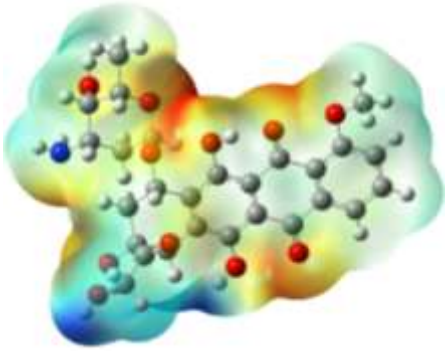
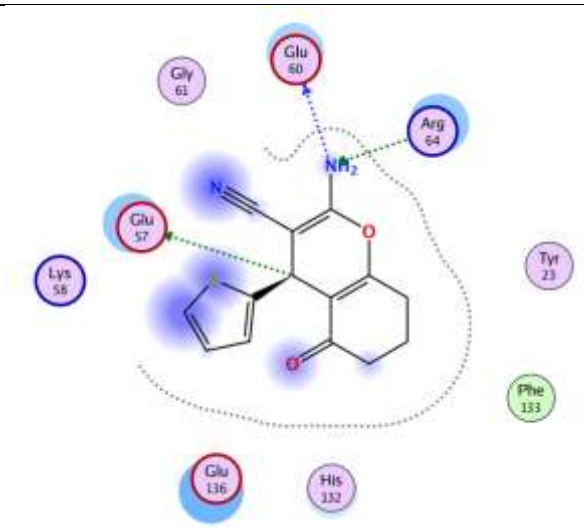
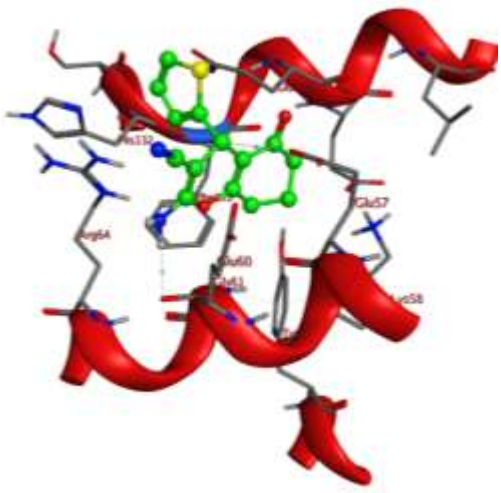
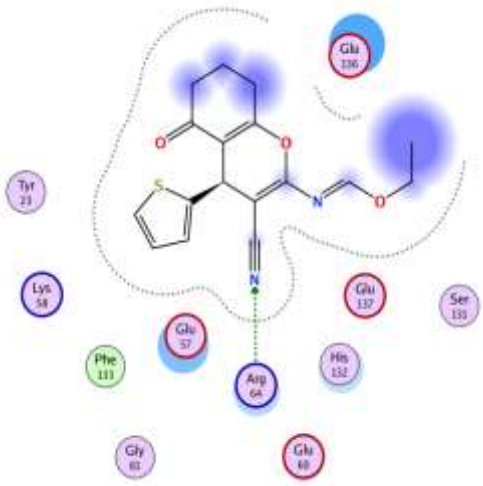
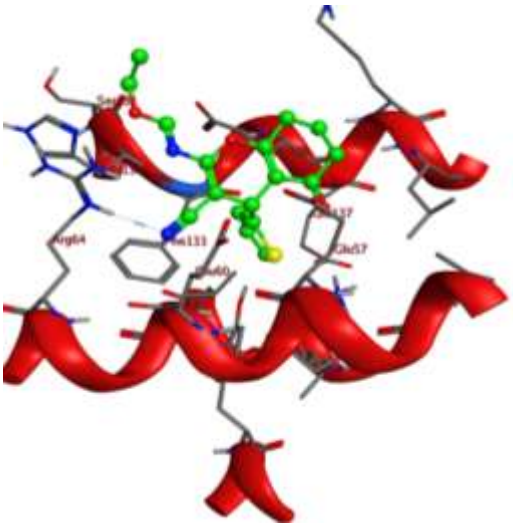
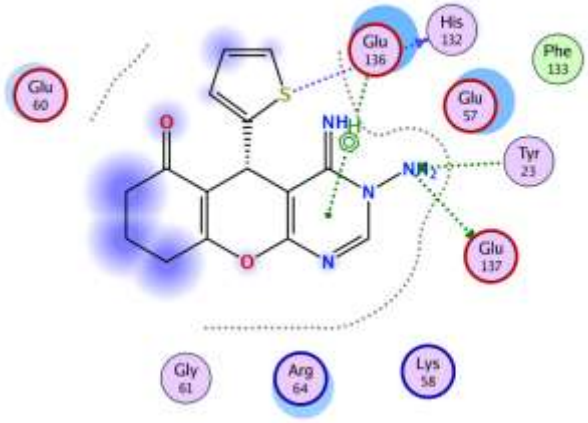
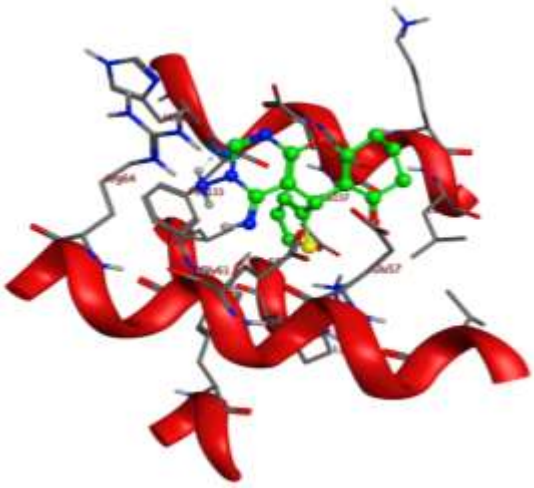
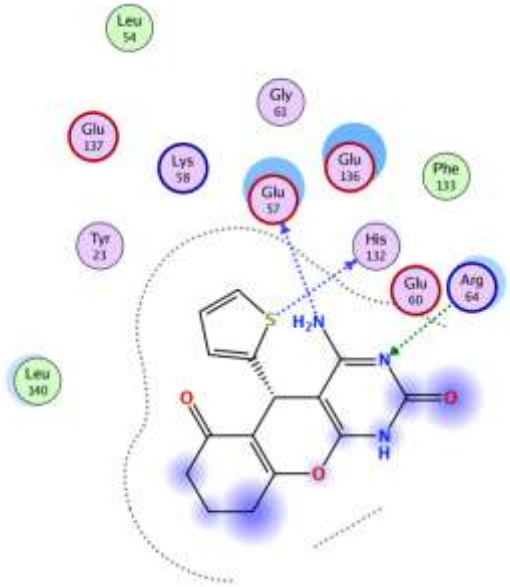
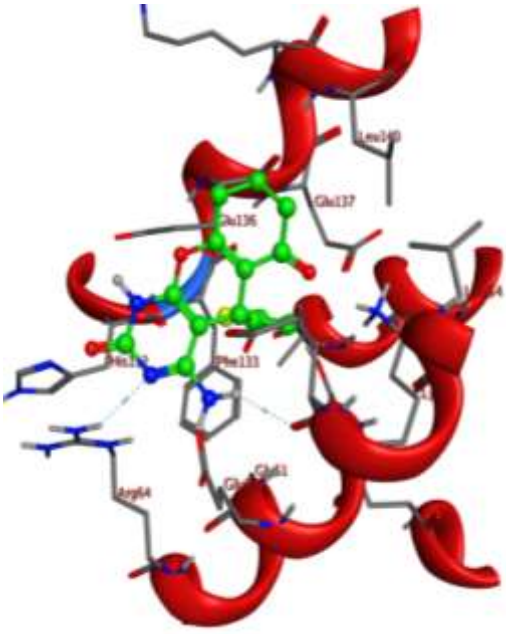
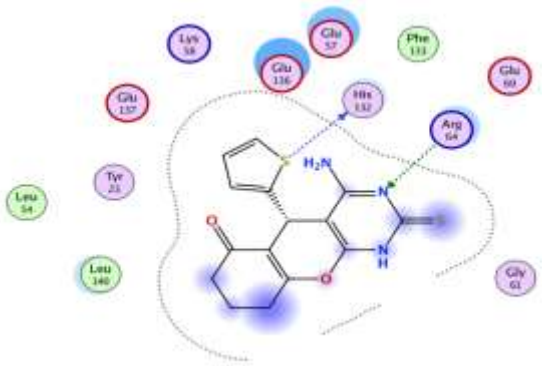
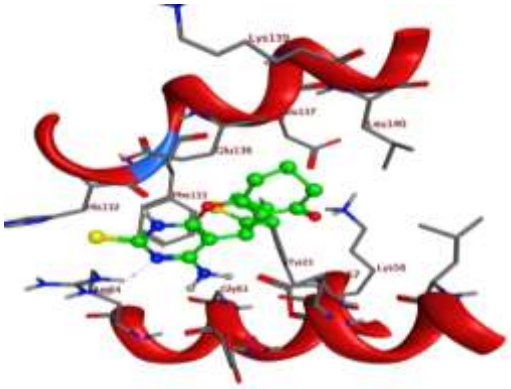
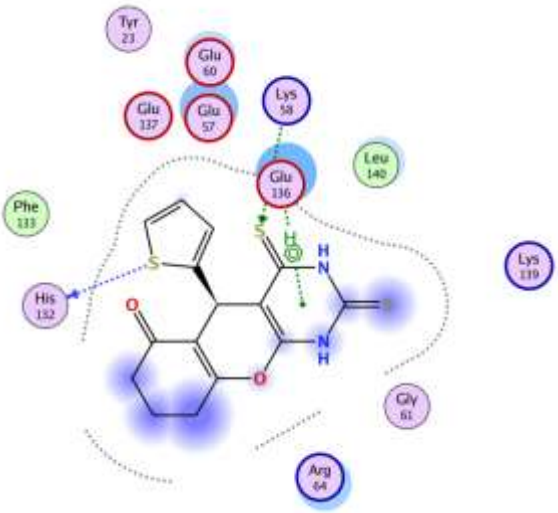
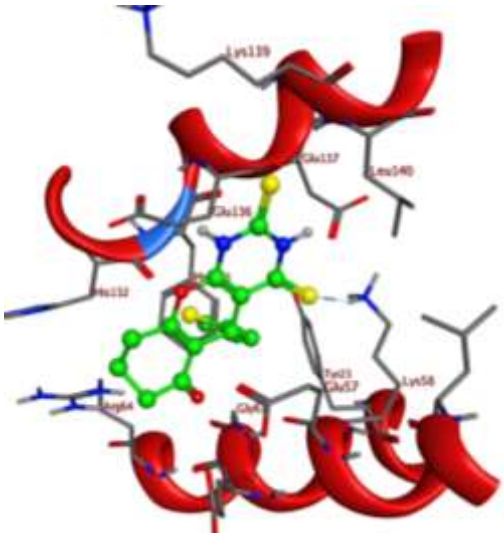
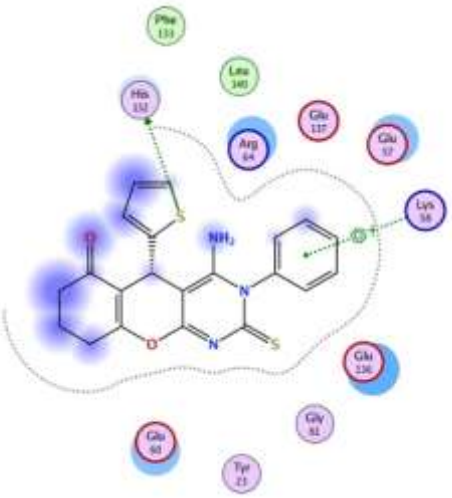
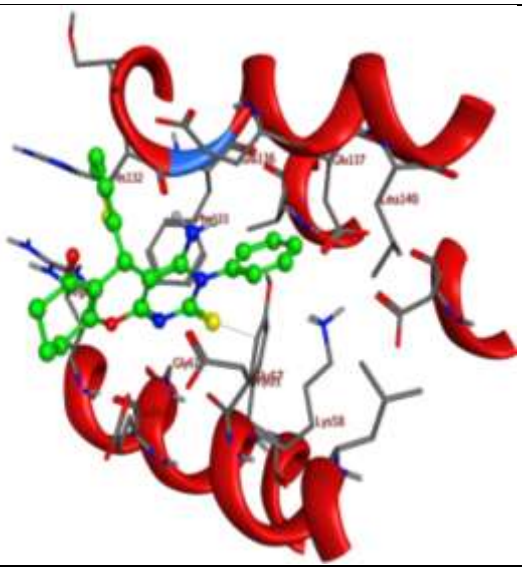
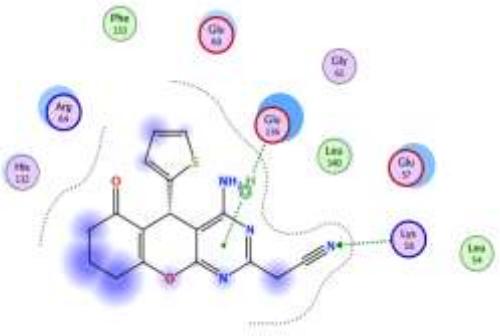
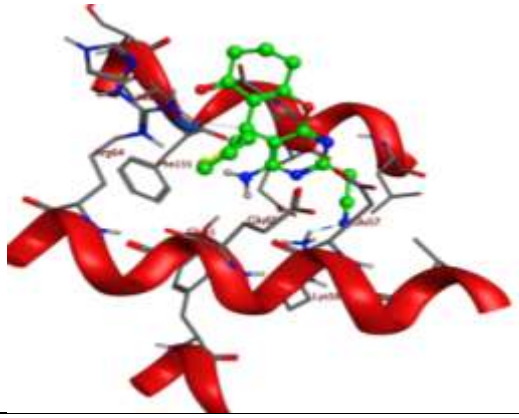
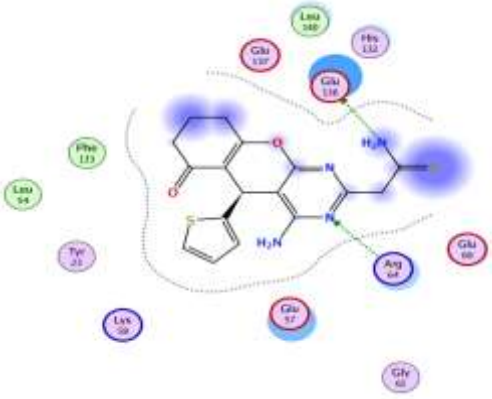
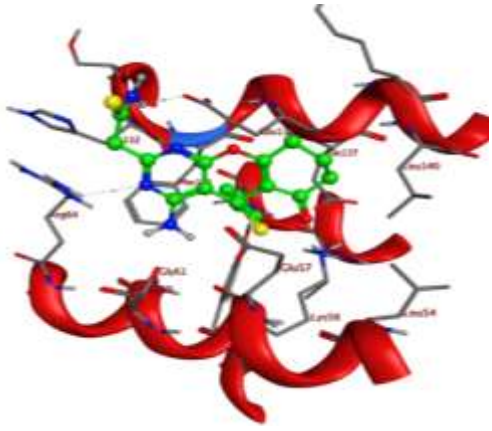
| | | | |
|---|---|---|---|
| **11** |  | **13** |  |
| **14** |  | **17** |  |
| **18** |  | **19** |  |
| **Dox.** |  | | |

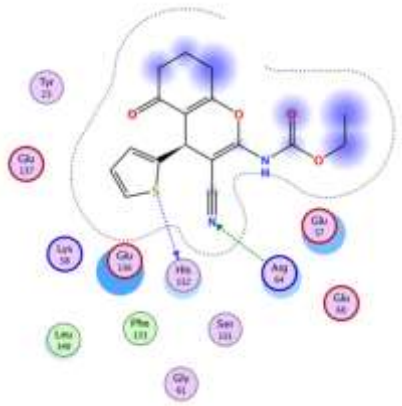
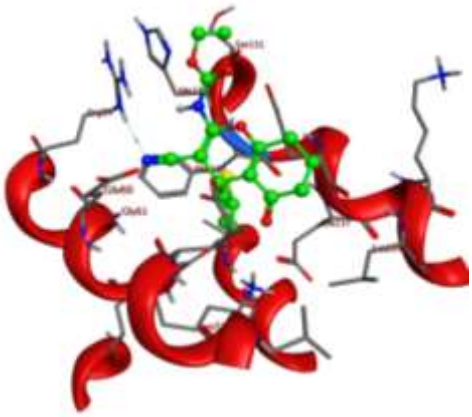
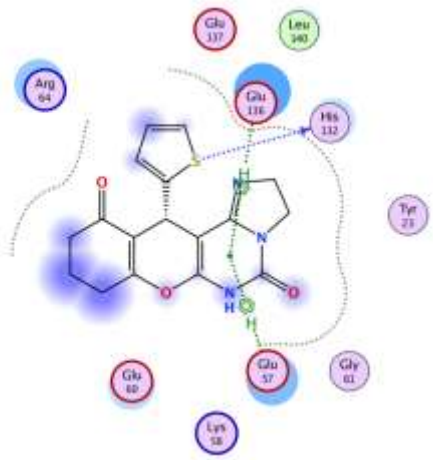
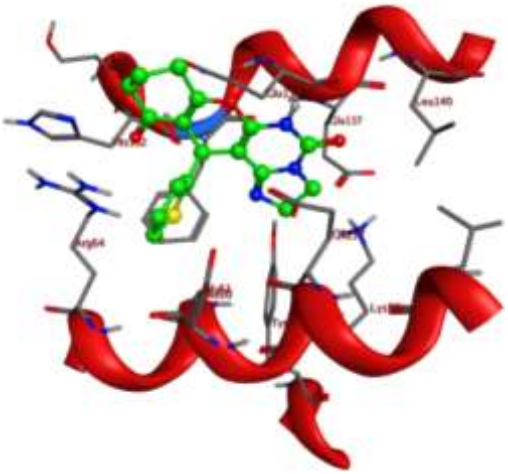
**Table S3.** 2D and 3D docking of the newly prepared compounds to 6ENV-MCV-7.

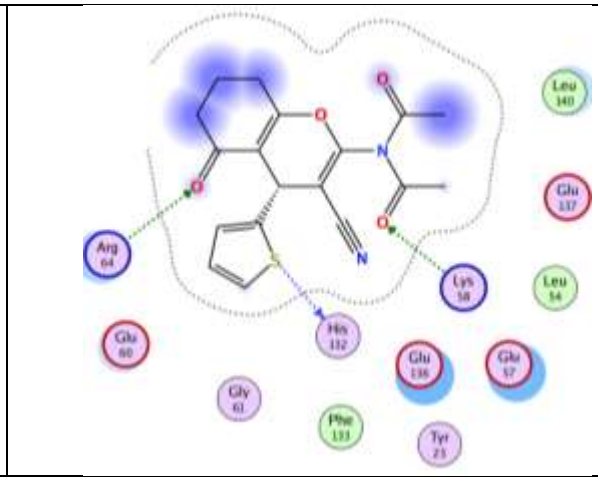
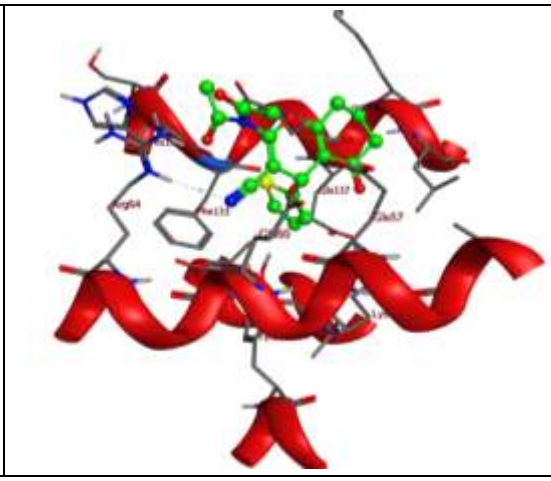
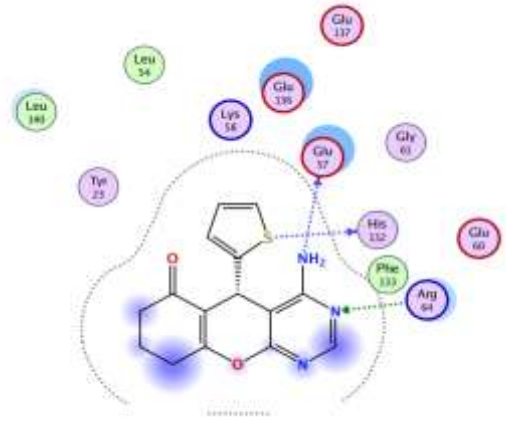
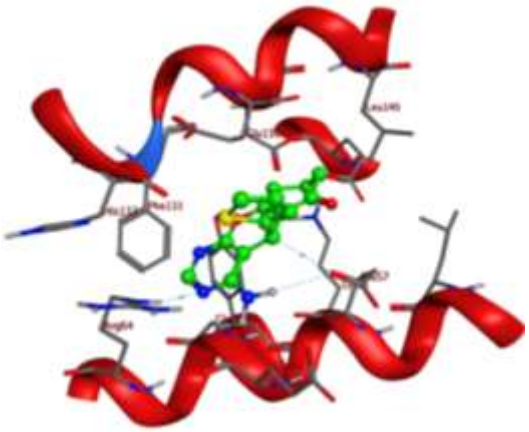
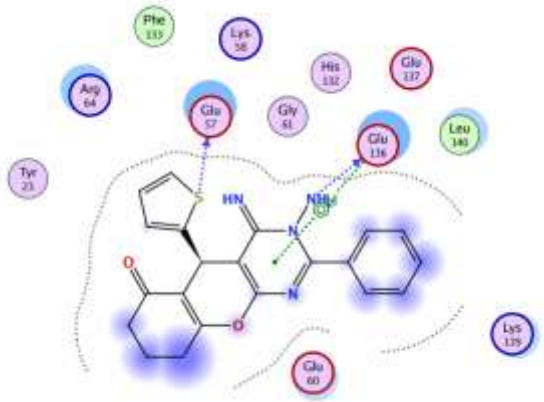
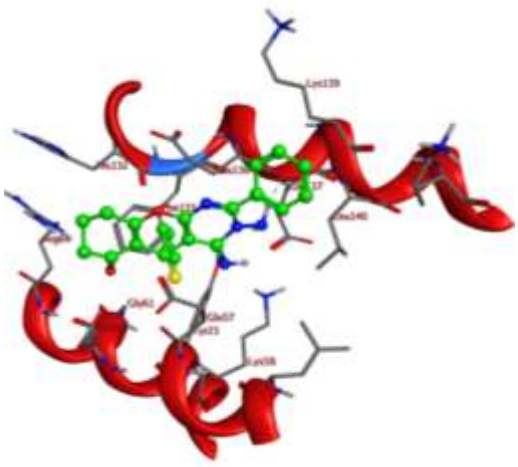
| Comp. | 2D | 3D |
|---|---|---|
| **1** |  |  |
| Docking data for compound **1** with 6ENV-MCV-7 showed that the amino group formed two hydrogen bonds with both Glu60 and Arg64. Besides, a hydrogen bonding interaction with Glu57 was also observed. A binding energy of -5.47951 kcal/mol was recorded for this derivative. | | |
| **2** |  |  |
| Compound **2** formed one binding interaction *via* hydrogen bonds: the nitrile motif bended with Arg64 with binding score equal to -6.25608 kcal/mol | | |

| | | |
|---|---|---|
| **3** |  |  |
| Compound **3** modeling configuration with 6ENV-MCV-7 protein shows hydrogen bonding interactions with Glu137, Tyr23 and His132. Besides, it formed hydrophobic interaction with Glu136 with a binding energy score of -5.8625 kcal/mol. | | |
| **4a** |  |  |
| Compound **4a** modeling configuration with 6ENV-MCV-7 shows three hydrogen bonding interteractions with His132, Glu57, and Arg64 with binding energy score of -5.83893 kcal/mol. | | |

| | | |
|---|---|---|
| **4b** |  |  |
| Compound **4b** modeling configuration with 6ENV-MCV-7 shows hydrogen bonding interteractions with both His132 and Arg64 with binding energy score of -5.77245 kcal/mol. | | |
| **6** |  |  |
| Compound **6** modeling configuration with 6ENV-MCV-7 shows hydrogen bonding interteractions with both His132 and Lys58 and one hydrophobic interaction with Glu136 with binding energy score of -5.82066 kcal/mol. | | |

| | | |
|---|---|---|
| **7** |  |  |
| Compound **7** (binding energy score = -5.94382 kcal/mol) formed one hydrogen bond with His132 aminoacid residue. Also, the phenyl moiety bended with Lys58 aminoacid residue *via* hydrophobic interaction. | | |
| **11** |  |  |
| The pyrimidine ring of compound **11** made hydrophobic interaction with Glu136, besides, the C≡N group formed hydrogen bonds with Lys58 with binding energy score = -6.13866 kcal/mol. | | |
| **13** |  |  |

| | | |
|---|---|---|
| In compound **13**, two hydrogen bonds were formed as follows: i) Arg64 and pyrimidine-N and ii) Glu136 and $NH_2$ group with binding energy score = -6.0665 kcal/mol. | | |
| **14** |  |  |
| Compound **14** formed two hydrogen bonds through the interaction of C≡N group with Arg64 and thiophene–S with His132. This compound recorded binding energy score of -6.22066 kcal/mol. | | |
| **15** |  |  |
| Compound **15** modeling configuration with 6ENV-MCV-7 shows one hydrogen bonding interteraction with His132. Besides, two hydrophobic interactions with Glu57 and Glu136. This compound recorded binding energy score of -5.69644 kcal/mol. | | |

| | | |
|---|---|---|
| **17** |  |  |
| Compound **17** modelling configuration with 6ENV-MCV-7 protein possessed the greatest activity with the lower binding value (-6.5531 kcal/mol). This derivative (**17**) formed three binding interactions *via* hydrogen bonds: carbonyl oxygen bended with Arg64, amide carbonyl oxygen bended with Lys58, and thiophene-S bended with His132. | | |
| **18** |  |  |
| Compound **18** modeling configuration with 6ENV-MCV-7 shows three hydrogen bonding interteractions with His132, Glu57, and Arg64 with binding energy score of -5.72812 kcal/mol. | | |
| **19** |  |  |

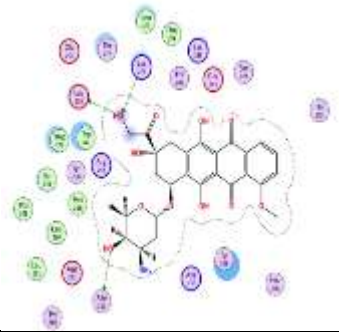
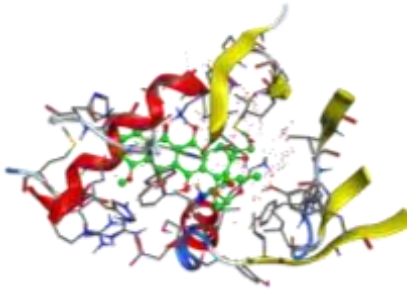
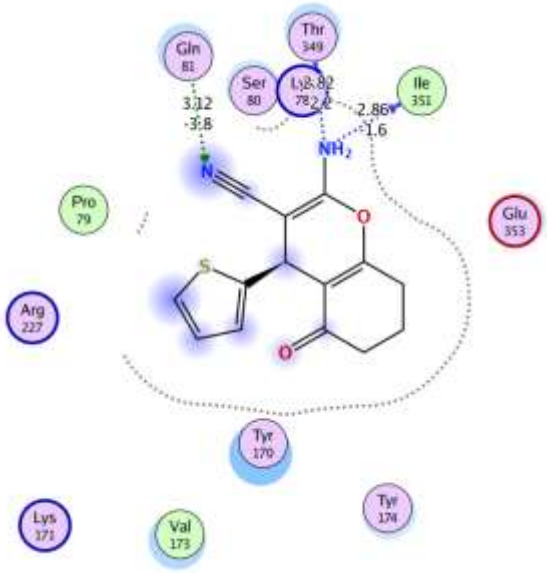
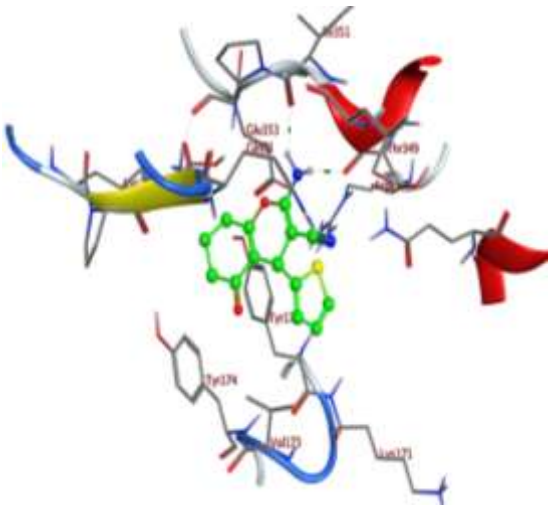
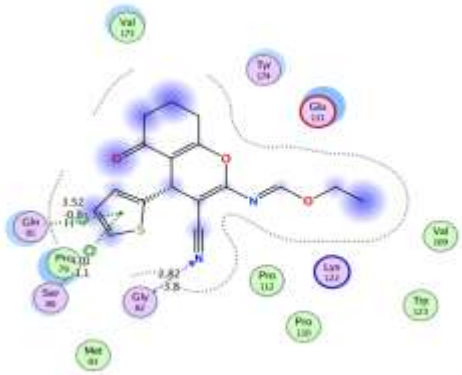
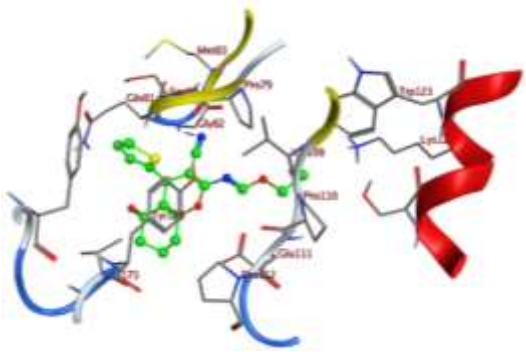
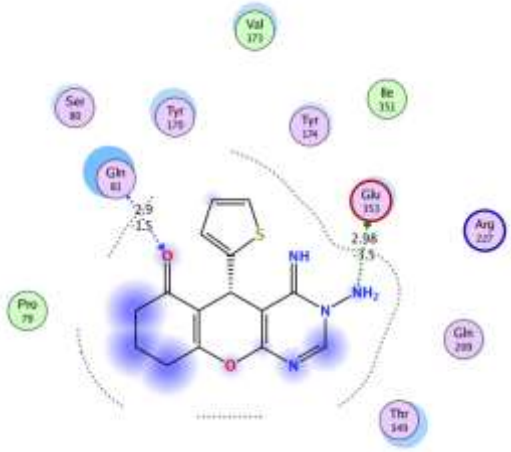
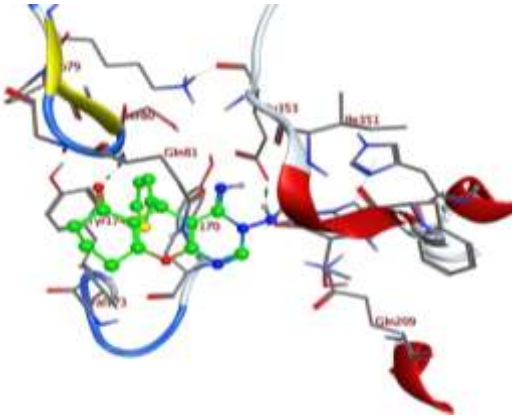
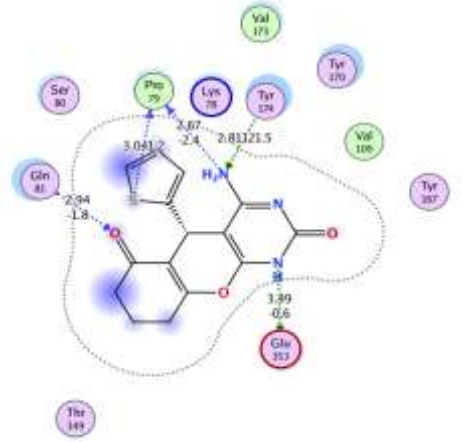
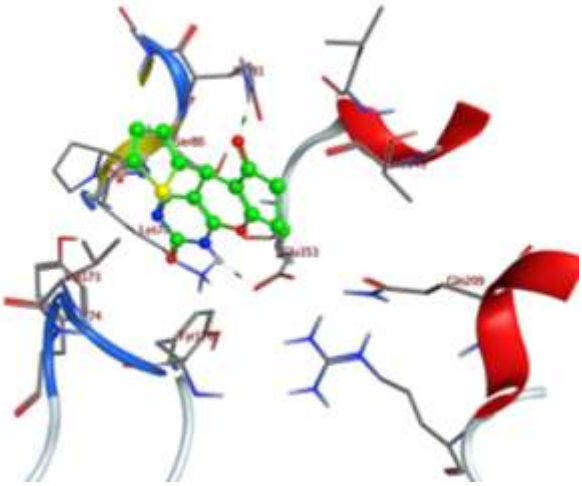
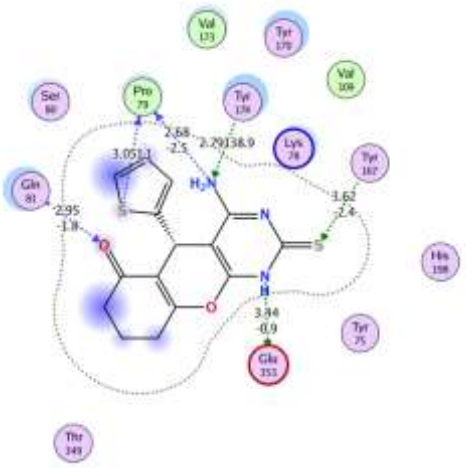
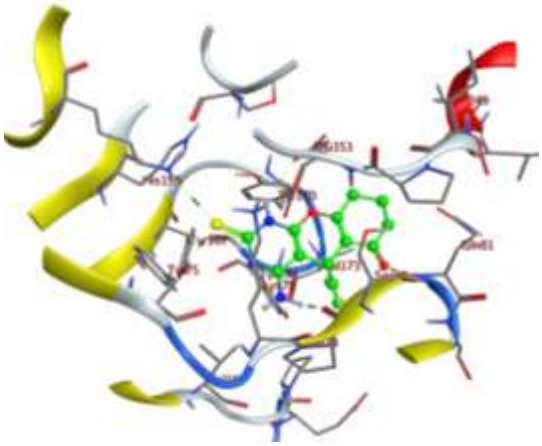
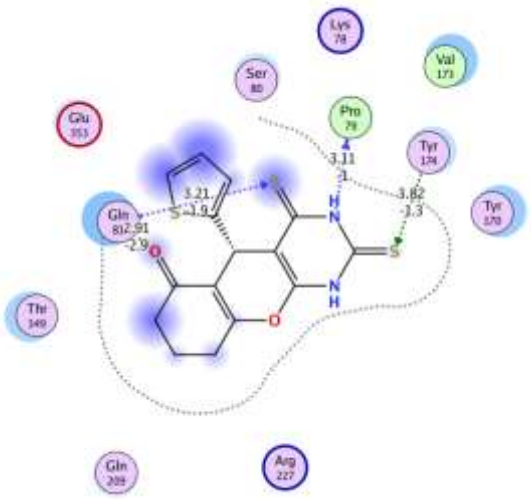
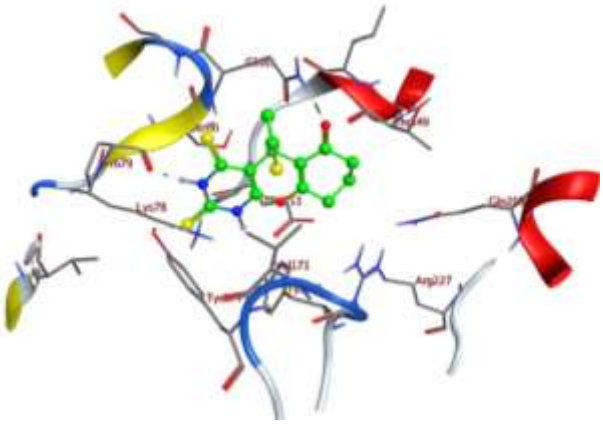
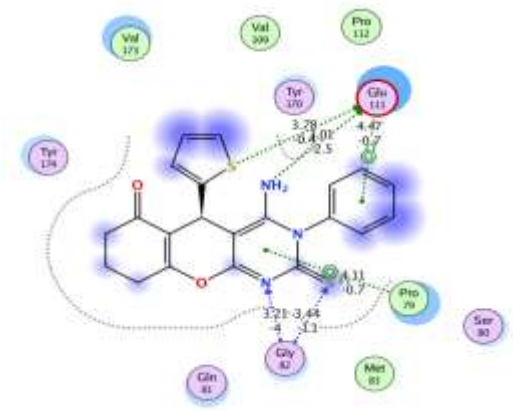
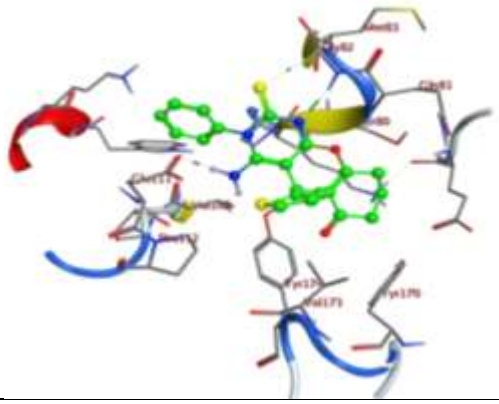
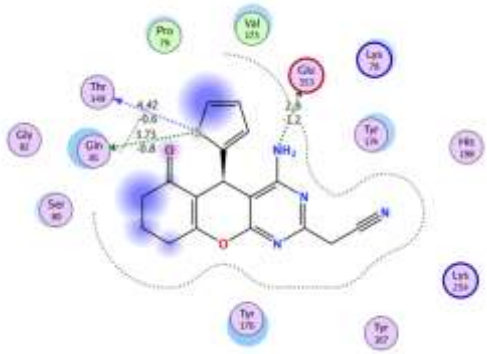
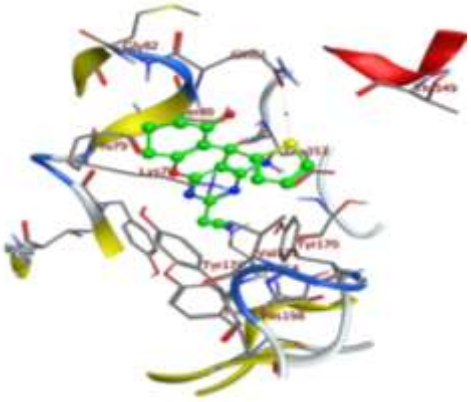
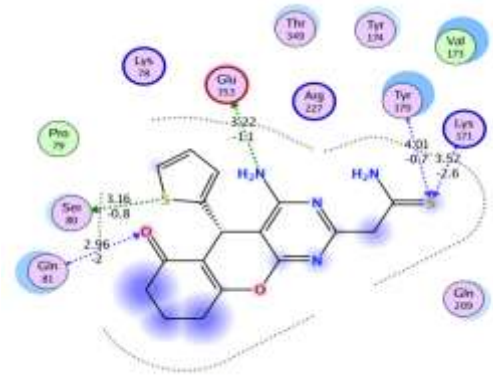
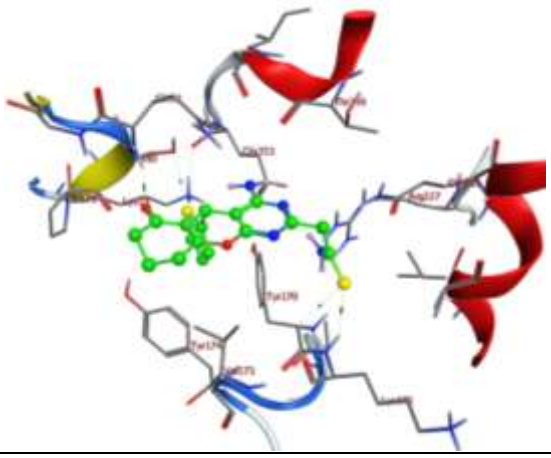
| | | |
|---|---|---|
| Compound **19** revealed Ar-H interaction *via* its pyrimidine motif with Glu136, besides one hydrogen bond with Glu57 through thiophene-S with a binding energy of -6.11341 kcal/mol. | | |
| **Dox.** |  |  |
| Dox. Formed three hydrogen bonding interactions *vis* Glu253, Lys273, and Asn282 with binding energy of -8.1865 kcal/mol. | | |

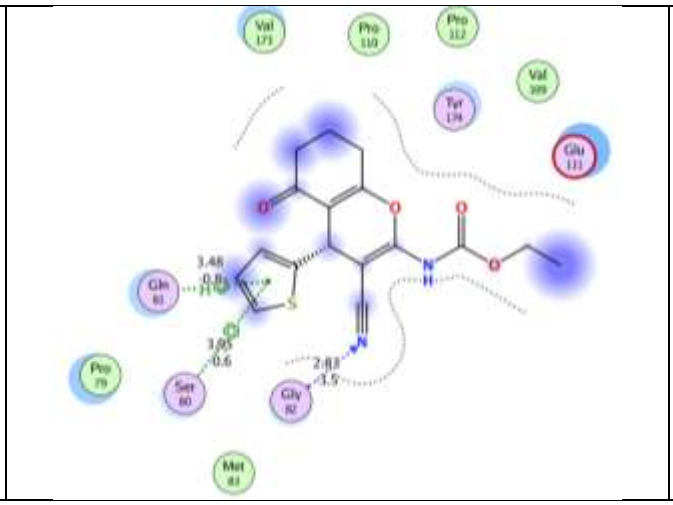
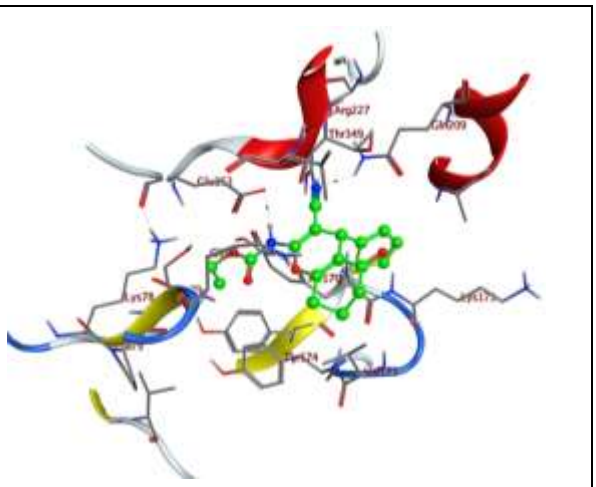
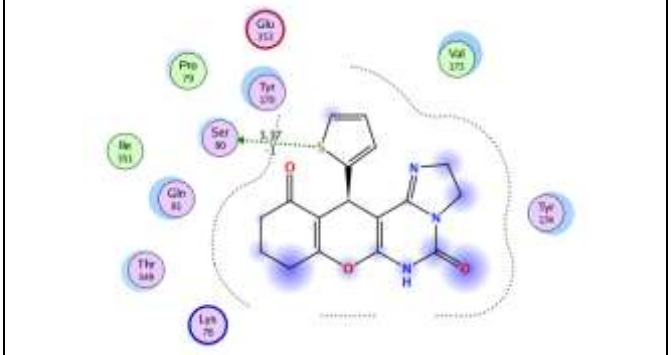
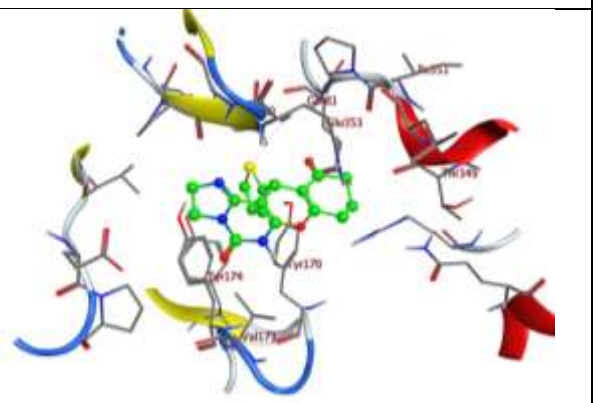
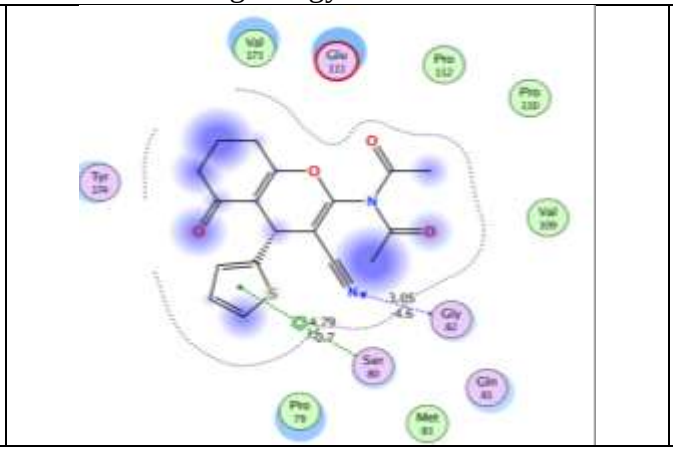
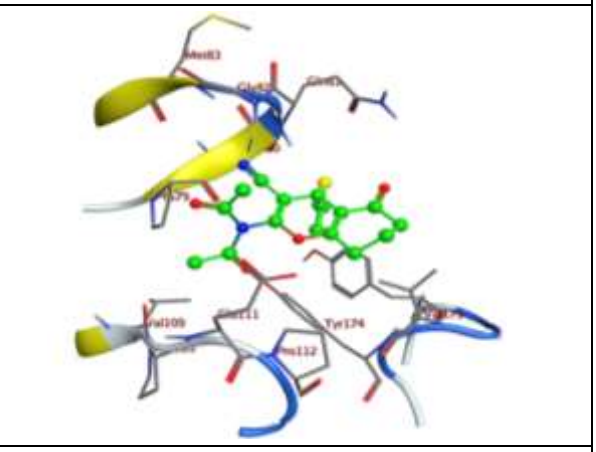
**Table S4.** Binding score of the newly prepared compounds to 4b3z-Lung.

| Comp. | 2D | 3D |
|---|---|---|
| **1** |  |  |
| Docking data for compound **1** with 4b3z-Lung showed that the amino group formed two hydrogen bonds with Il2351 and Lys78. Besides, a hydrogen bonding interaction with Gln81 was also observed the the nitrile group. A binding energy of -5.19771 kcal/mol was recorded for this derivative. | | |

| | | |
|---|---|---|
| **2** |  |  |
| Compound **2** formed one binding interaction *via* hydrogen bonding of cyano group with Gly82. Besides two hydrophobic interactions of thiophene motif with both Gln81 and Ser80. This derivatives recorded a binding score equal to -5.88317 kcal/mol. | | |
| **3** |  |  |
| Compound **3** modeling configuration with 4b3z-Lung protein shows hydrogen bonding interaction of Glu353 and Gln81 with amino and carbonyl groups, respectvely. The recorded binding energy score is -5.50277 kcal/mol. | | |
| **4a** |  |  |

| | | |
|---|---|---|
| Compound **4a** modeling configuration with 4b3z-Lung shows five hydrogen bonding interteractions with Gln81, Glu353, 2Pro79, and Tyr174 and recorded a binding energy score of -5.40306 kcal/mol. | | |
| **4b** |  |  |
| Compound **4b** modeling configuration with 4b3z-Lung shows six hydrogen bonding interteractions with Gln81, Glu353, 2Pro79, Tyr168, and Tyr174 and recorded a binding energy score of -5.42736 kcal/mol. | | |
| **6** |  |  |
| Compound **6** modeling configuration with 4b3z-Lung shows four hydrogen bonding interteractions with 2Gln81, Pro79, and Tyr174, and recorded a binding energy score of -5.69825 kcal/mol. | | |

| | | |
|---|---|---|
| **7** |  |  |
| Compound **7** formed four hydrogen bonds with 2Gly82, 2Glu111 aminoacid residue. Also, the phenyl and pyrimidine moieties bended with Glu111 and Pro79 aminoacid residues, respectively *via* hydrophobic interactions. The binding energy score = -6.17619 kcal/mol. | | |
| **11** |  |  |
| Compound **11** formed three hydrogen bonds with Glu353, Thr349, and Gln81 with binding energy score of -5.80001 kcal/mol. | | |
| **13** |  |  |
| In compound **13**, five hydrogen bonds were formed as follows: i) Tyr170 and Lys171 with thione moiety, Glu353 with the amino group, Ser80 with thiophene-S, and ii) Gln81 with carbonyl group. The binding energy score = -6.03983 kcal/mol. | | |

| | | |
|---|---|---|
| **14** |  |  |
| Compound **14** formed one hydrogen bond through the interaction of C≡N group with Gly82 and two hydrophobic interactions of thiophene ring with Sr80 and Gln81. This compound recorded binding energy score -6.21129 kcal/mol. | | |
| **15** |  |  |
| Compound **15** modeling configuration with 4b3z-Lung shows one hydrophobic interaction with Ser80. This compound recorded binding energy score of -5.6829 kcal/mol. | | |
| **17** |  |  |
| Compound **17** modelling configuration with 4b3z-Lung protein possessed binding value of -6.12329 kcal/mol. This derivative formed one binding interaction *via* hydrogen bond of the cyano group bended with Gly82, and hydrophobic interaction of thiophene ring with Ser80. | | |

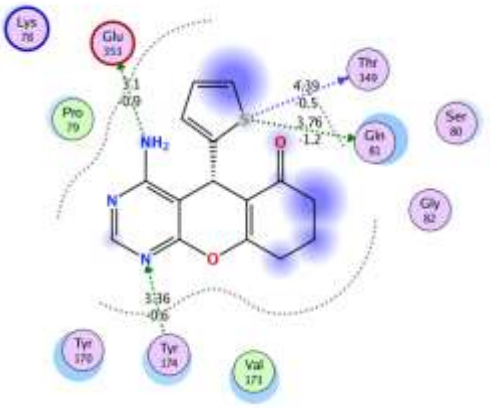
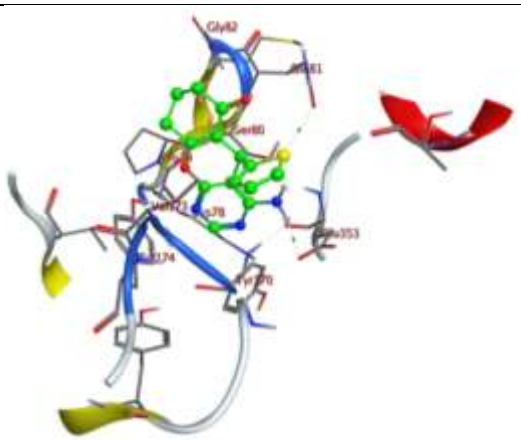
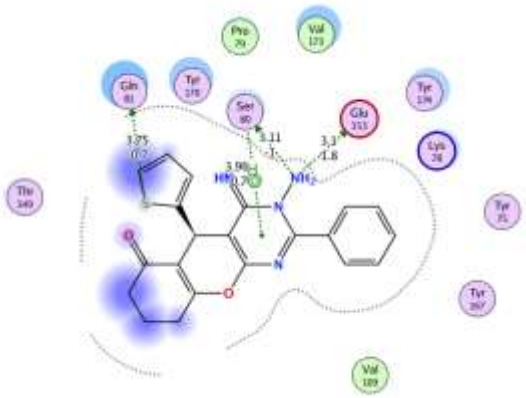
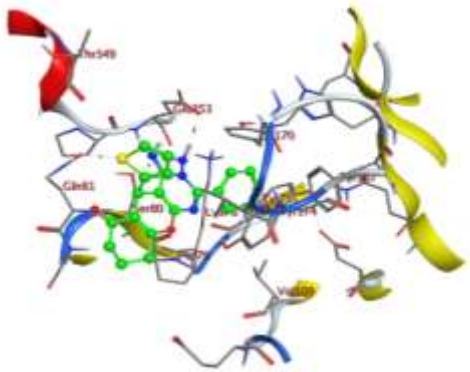
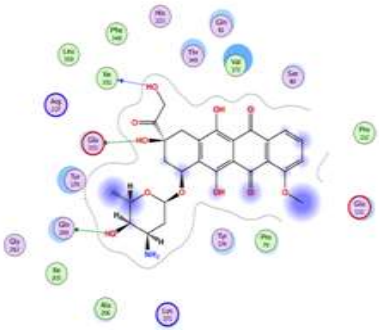
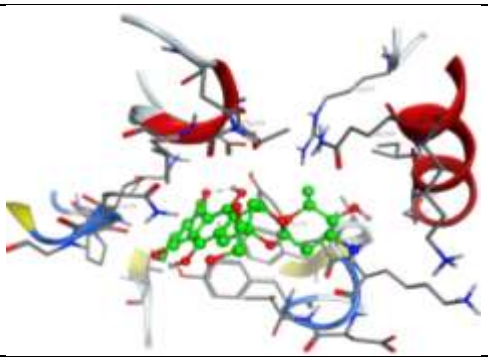
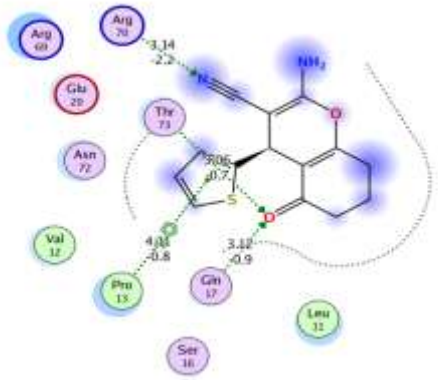
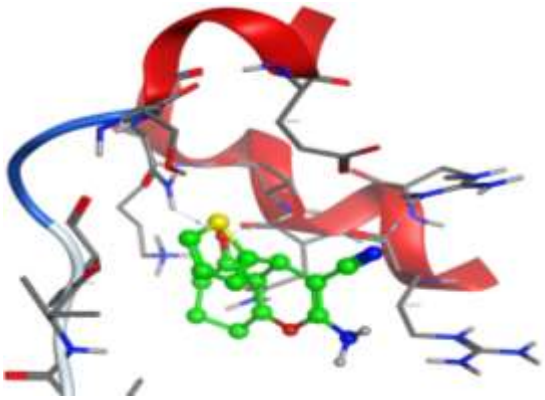
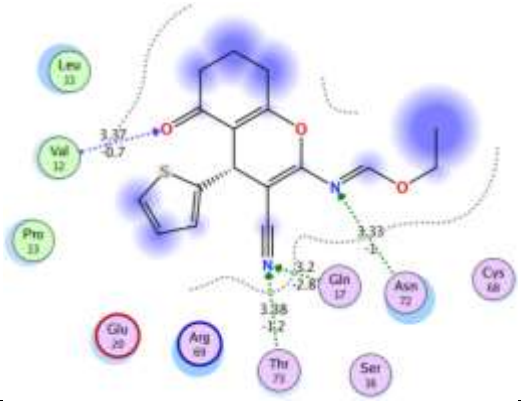
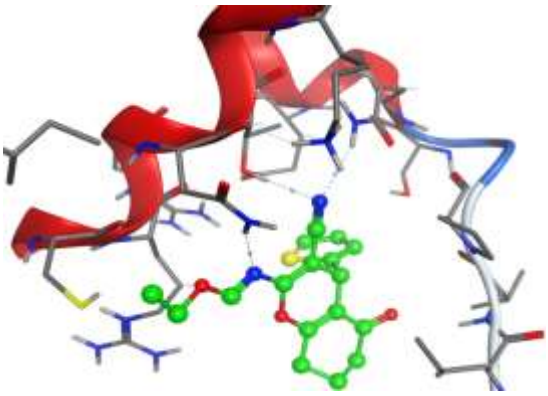
| | | |
|---|---|---|
| **18** |  |  |
| Compound **18** modeling configuration with 4b3z-Lung shows four hydrogen bonding interteractions with Thr349, Gln81, Glu353, and Tyr174 with binding energy score of -5.17581 kcal/mol. | | |
| **19** |  |  |
| Compound **19** modelling configuration with 4b3z-Lung protein possessed the greatest activity with the lowest binding value (-6.33115 kcal/mol). This derivative formed three binding interactions *via* hydrogen bonds: amino group bended with both Glu353 and Ser80, and thiophene-S bended with Gln81. Besides, one hydrophobic interaction of pyrinmidine motif with Sr80. | | |
| **Dox.** |  |  |
| Dox. formed three hydrogen bonds with Glu289, Gla353, and Le351 that afforded a binding energy of -7.2391 kcal/mol**.** | | |

**Table S5.** Binding score of the newly prepared compounds to HepG2-2JW2

| Comp. | 2D | 3D |
|---|---|---|
| **1** |  |  |
| Docking data for compound **1** with HepG2-2JW2 showed that the amino groups formed three hydrogen bonds with Arg70, Thr73 and Gln17. Besides, a hydrophobic interaction with Pro13 was also observed the thiophene ring. A binding energy of -4.89862 kcal/mol was recorded for this derivative. | | |
| **2** |  |  |
| Compound **2** formed four binding interaction *via* hydrogen bonding with Val12, Thr73, Gln17 and Asn72. This derivatives recorded a binding score equal to -5.5669 kcal/mol. | | |

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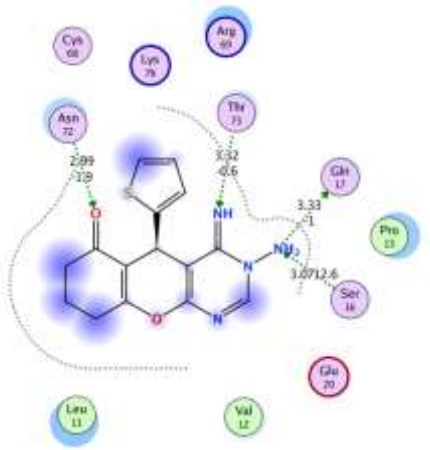
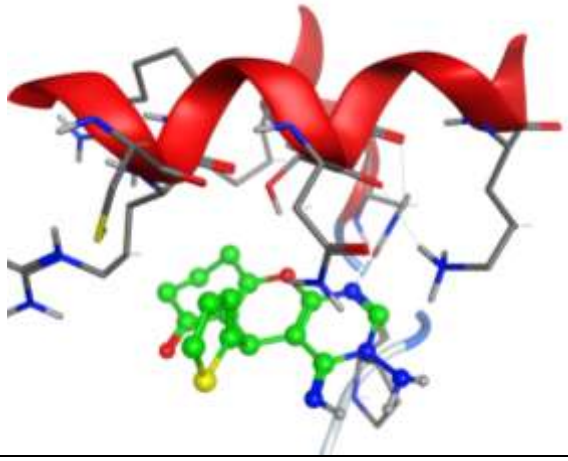
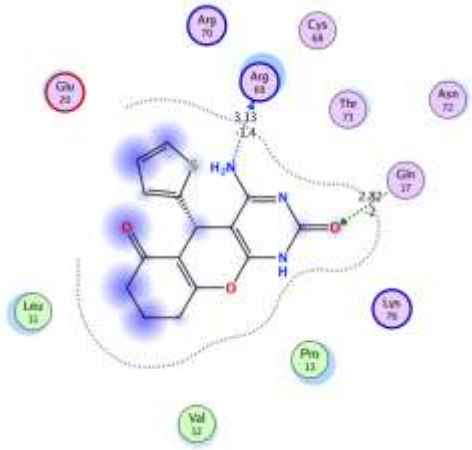
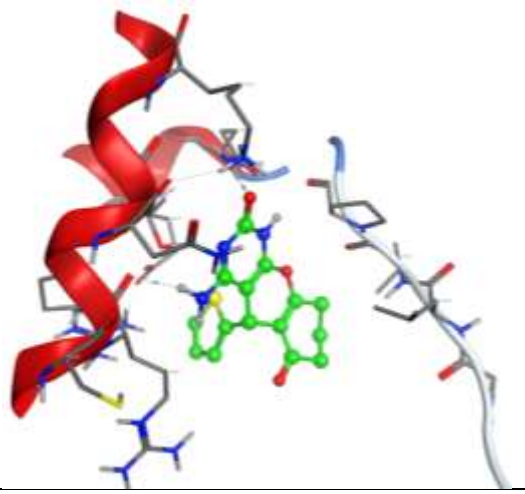
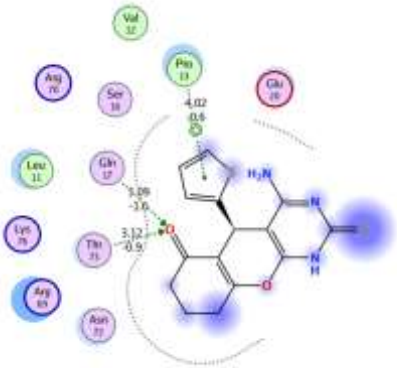
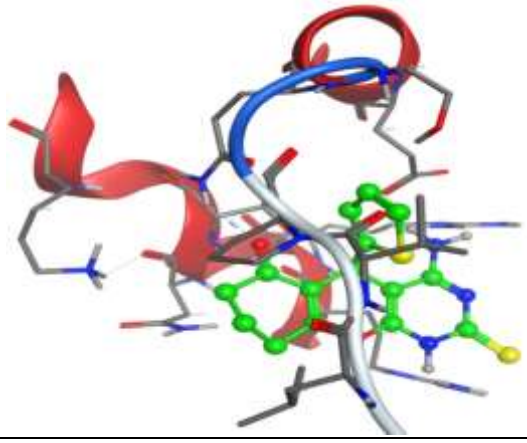
| **3** |  |  |
| Compound **3** modeling configuration with HepG2-2JW2 protein shows hydrogen bonding interactions of Thr73, Gln17, Ser16 and Asn72 with NH, $NH_2$ and C=O groups, respectvely. The recorded binding energy score is -5.5669 kcal/mol. | | |
| **4a** |  |  |
| Compound **4a** modeling configuration with HepG2-2JW2 shows two hydrogen bonding interteractions with Arg69 and Gln and recorded a binding energy score of -5.16215 kcal/mol. | | |
| **4b** |  |  |

Compound **4b** modeling configuration with HepG2-2JW2 shows two hydrogen bonding interteractions with Gln17 and Thr73. Besdies, on hydrophobic interaction with Pro13. It recorded a binding energy score of -5.11563 kcal/mol.

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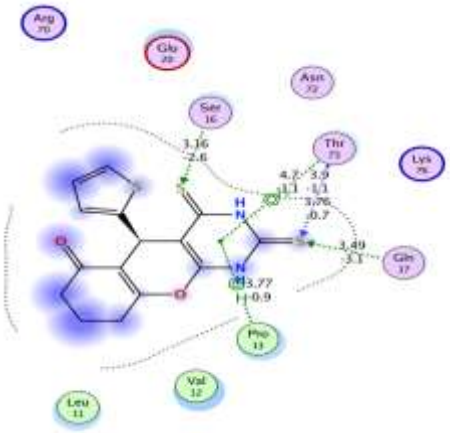
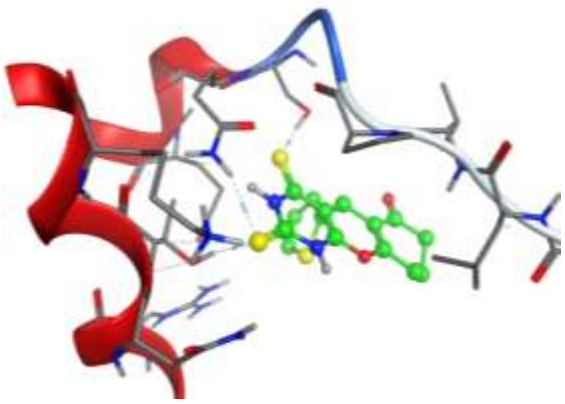
| **6** |  |  |

Compound **6** modeling configuration with HepG2-2JW2 shows three hydrogen bonding interteractions with Thr73, Gln17, and Sr16. In addition, it exhibited two hydrophobic interactions with Thr73 and Pro13 and recorded a binding energy score of -5.14694 kcal/mol.

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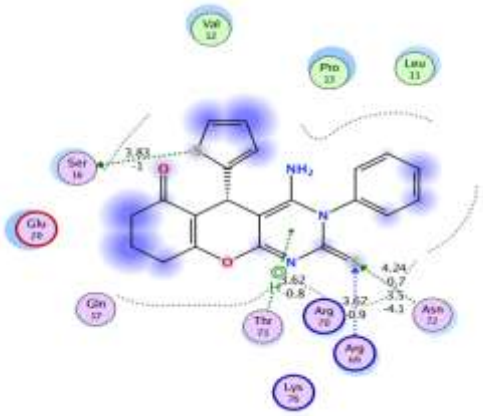
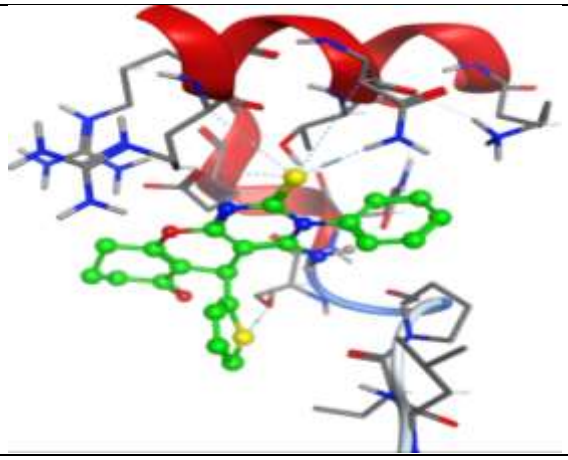
| **7** |  |  |

Compound **7** formed four hydrogen bonds with Ser16, Asn72, Arg69 aminoacid residue. Also, the pyrimidine moiety bended with Thr73 aminoacid residue *via* hydrophobic interactions. The binding energy score = -5.43515 kcal/mol.

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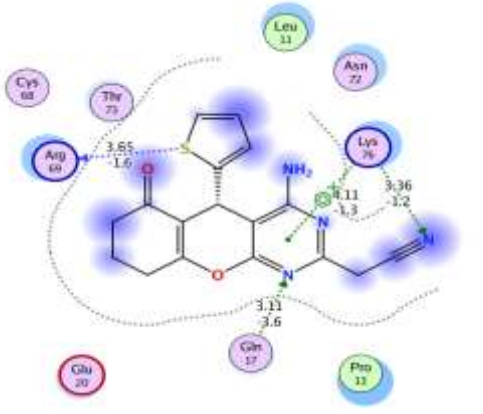
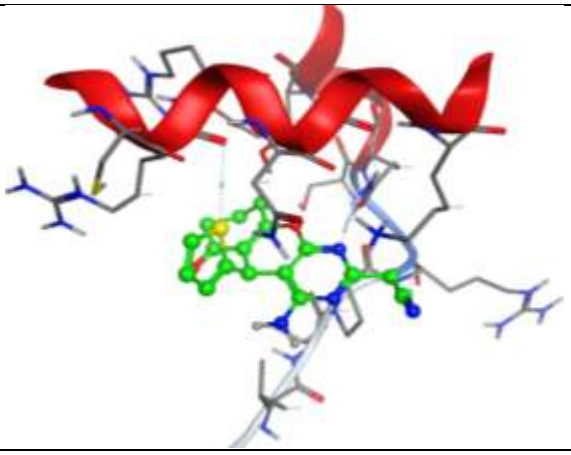
| **11** |  |  |

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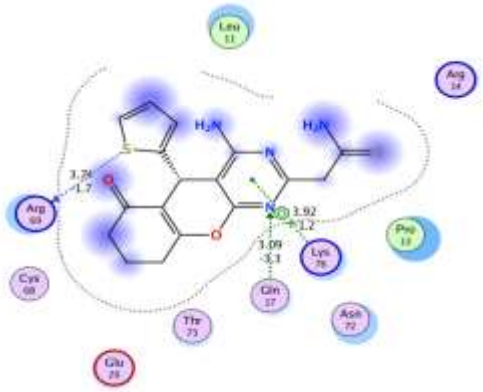
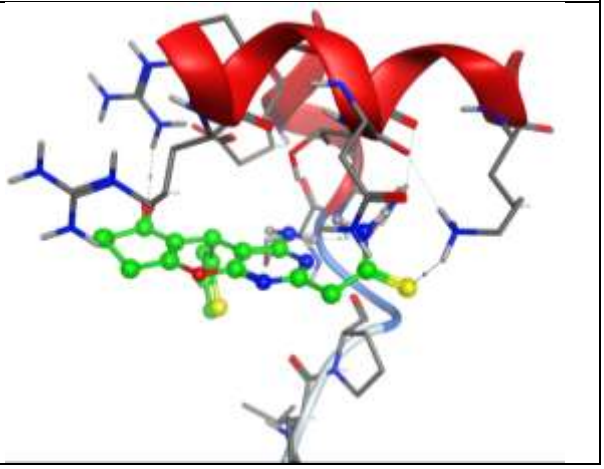
| Compound **11** formed three hydrogen bonds with Arg69, Gln17, and Lys76, as well as on hydrophobic interaction with Lys76 and recorded a binding energy score of 5.29499 kcal/mol. | | |
| **13** |  |  |

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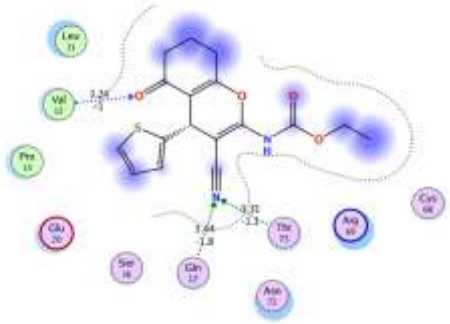
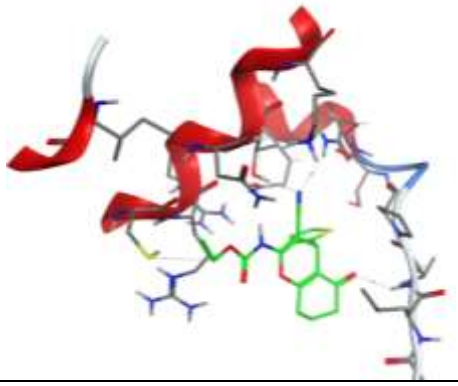
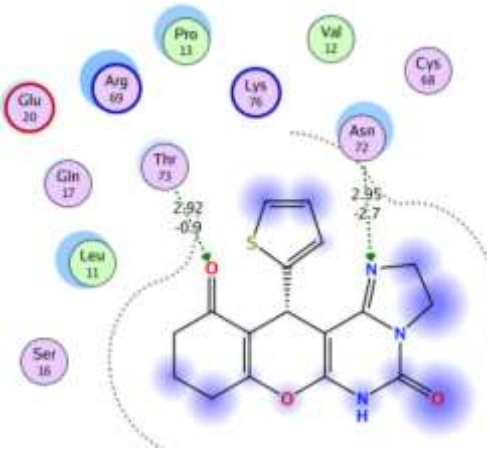
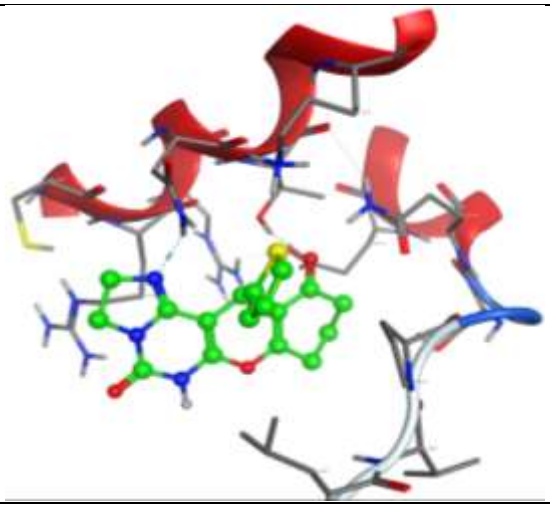
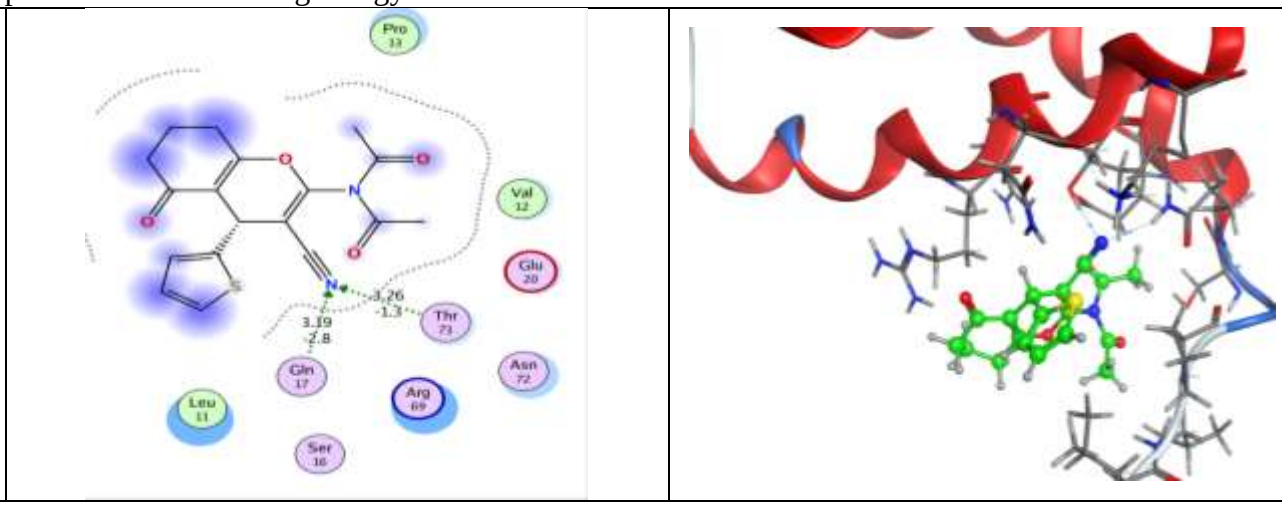
| In compound **13**, two hydrogen bonds were formed as follows: Arg69 with thiophene-S and Glu17 with pyrimidine-N. Also, compound **13** formed one hydrophobic interaction with Lys76 *via* its pyrimidine ring. The binding energy score = -5.4955kcal/mol. | | |
| **14** |  |  |
| Compound **14** formed three hydrogen bonds through the interaction of C≡N and C=O groups with Gln17, Thr73, and Val12. This compound recorded binding energy score -5.43210 kcal/mol. | | |
| **15** |  |  |

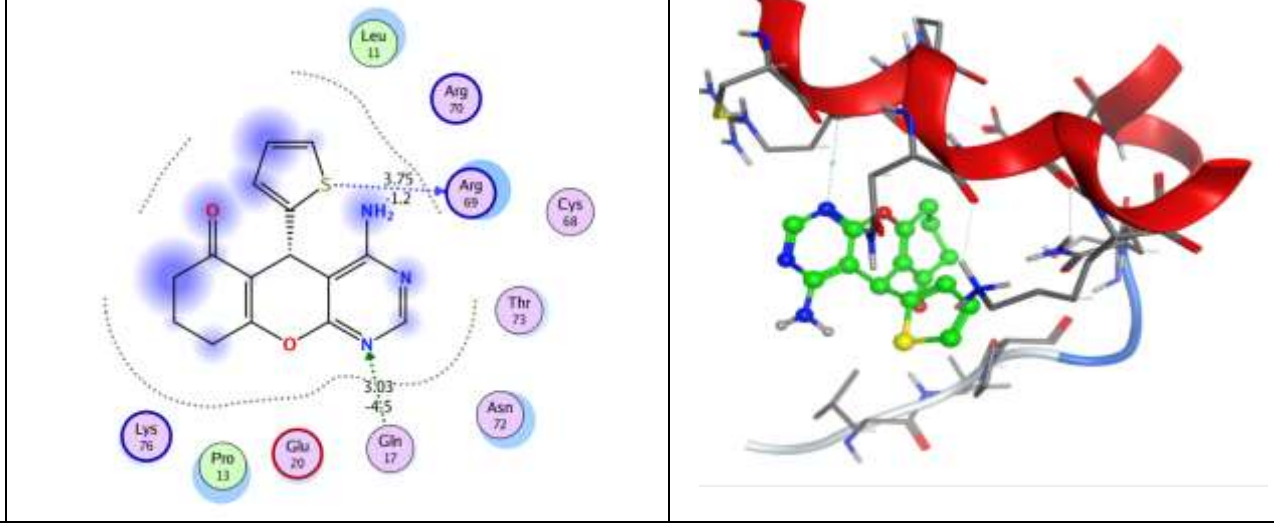
Compound **15** modeling configuration with HepG2-2JW2 shows two hydrogen bonds with Thr73 and Asn72. This compound recorded binding energy score of -5.59437 kcal/mol.

**17**




Compound **17** modelling configuration with HepG2-2JW2 protein possessed binding value of -5.59266 kcal/mol. This derivative (**17**) formed two binding interactions *via* hydrogen bonds of the cyano group that bended with both Gln17 and Thr73.

**18**




Compound **18** modeling configuration with HepG2-2JW2 shows two hydrogen bonding interteractions with Arg69 and Gln17 with binding energy score of -5.26642 kcal/mol.

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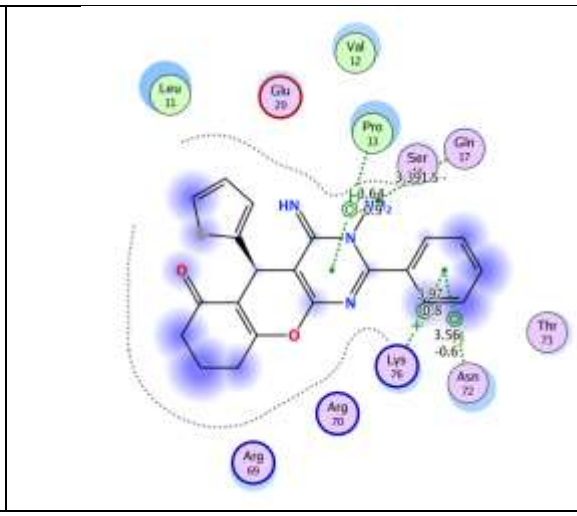
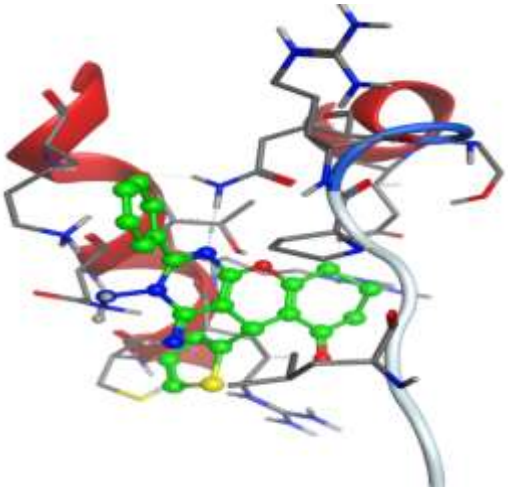
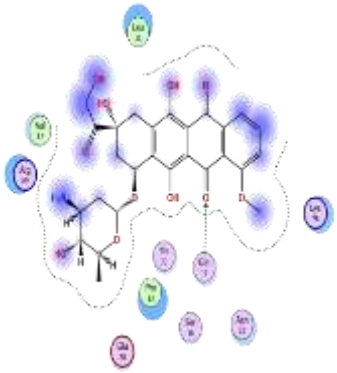
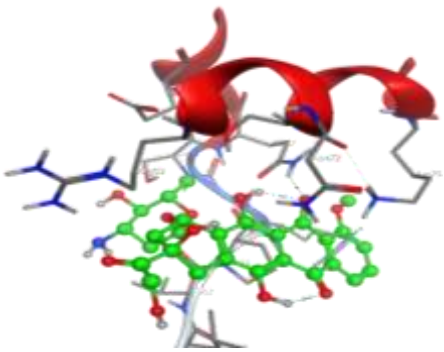
| **19** |  |  |
| Compound **19** formed three binding interactions *via* hydrophobic interactions: pyrimidine ring bended with Pro13, and phenyl ring bended with both Lys76 and Asn72. Besides, one hydrogen bond of amino group with Gln17. This derivative possessed the greatest activity with the lowest binding value (-5.95474 kcal/mol). | | |
| **Dox.** |  |  |
| Dox. exihibted one hydrogen bond with Gln17 with binding energy score of -6.6166 kcal/mol. | | |