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Calculated Infrared Spectral and Some Electronic Traits of Taurine Derivatives: A Novel Anti Zika Virus Agent

Munirah A Almessiere^{1,2}, Amira M Ali^{1,3}, Noha A Saleh^{1*}, Zhiyong Zhu⁴

¹Department of Physics, College of Science, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, 31441 Dammam, Saudi Arabia

²Department of Biophysics, Institute for Research & Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, P.O. Box 1982, 31441 Dammam, Saudi Arabia

³Faculty of Science, Physics Department, Al-Azhar University,  pt

⁴Supercomputing Laboratory (KSL), King Abdullah University of Science & Technology, Thuwal, Saudi Arabia

ABSTRACT

Distinctive electronic and spectral attributes of taurine derivatives are useful for designing a novel anti-Zika virus drug design and architecture. In this view, we introduced some exotic functional chemical compounds that may act as potential inhibitors of Zika virus attack via the NS3 protease which in turn responsible for virus replication inside the host cell. The proposed structures were derived from the natural compound taurine (already existed in the human body) which conjugated to tetra-peptide sequences for NS2A/NS2B junction. Optimization and infrared vibration analysis confirmed the validity of the structure. Electronic configuration was studied using B3LYP approach with 6-31G** basis set to evaluate each proposed compound. Infrared spectral analysis follows each optimization at the same level of method. The introduced compounds show more stability and reactivity than that for taurine. This indicates the important role of tetra-peptide sequences to increase the stability of suggested compounds and may give the compounds good inhibition activity against Zika virus NS3 protease. Computational studies were implemented on Shaheen supercomputer under operation of Gaussian 16 program.

Keywords: Electronic properties, Infrared spectra, Molecular modeling, NS3 protease inhibitor, Taurine, ZIKV.

INTRODUCTION

Being a new flavivirus, Zika virus (ZIKV) is presently considered as one of the most severe public health threats [1]. Amongst all the recently reported global infectious diseases, it ranked in the third position after the H1N1 flu and the Ebola virus [2,3]. Bite of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes are known to be the major reasons for the ZIKV transmission to humans [4]. Besides, non-vector-borne infection through perinatal [5] and sexual [6] transmission are the other routes. The symptoms for ZIKV infected patient include mild fever, skin rash, muscle and joint pain, and/or conjunctivitis [1,7].

Most importantly, ZIKV is also accountable for a rare disorder in the immune system wherein healthy nerve cells in the peripheral nervous system are attacked through congenital malformations and Guillain-Barre syndrome [7]. Pregnant women when exposed to ZIKV are under severe danger, leading to serious birth related defect of the newborn called microcephaly [8]. This defect is characterized by the cephalic perimeter shrinkage of the baby because of viral destruction of the neural cells. Thus, World Health Organization in early 2016 declared the ZIKV as a public health emergency [3].

Structurally, ZIKV is a single-stranded RNA virus with the genome of about 10.7 kb of positive polarity [9] which is translated into a polyprotein. This polyprotein is further cleaved into three structural proteins (capsid, precursor-membrane/membrane, and envelope) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [10,11]. The host cell invasion by ZIKV depends on the envelope protein that identifies the host receptor, followed by fusion between the virus and intracellular membranes [12], viral RNA translation and replication in the host cytoplasm, and eventual virion release. The NS3 and NS2B proteins reveal similar chymotrypsin-like fold as other flavivirus proteases [13]. The NS3 encloses a helicase and RNA tri-phosphatase domain that participate in viral replication at the C-terminus. Meanwhile, the NS3 at the N-terminus contains the sequences homologous to serine proteases that cleave the viral polyprotein through NS2B as a cofactor [14]. Therefore, the NS2B-NS3 protease can be the attractive candidate for antiviral target.

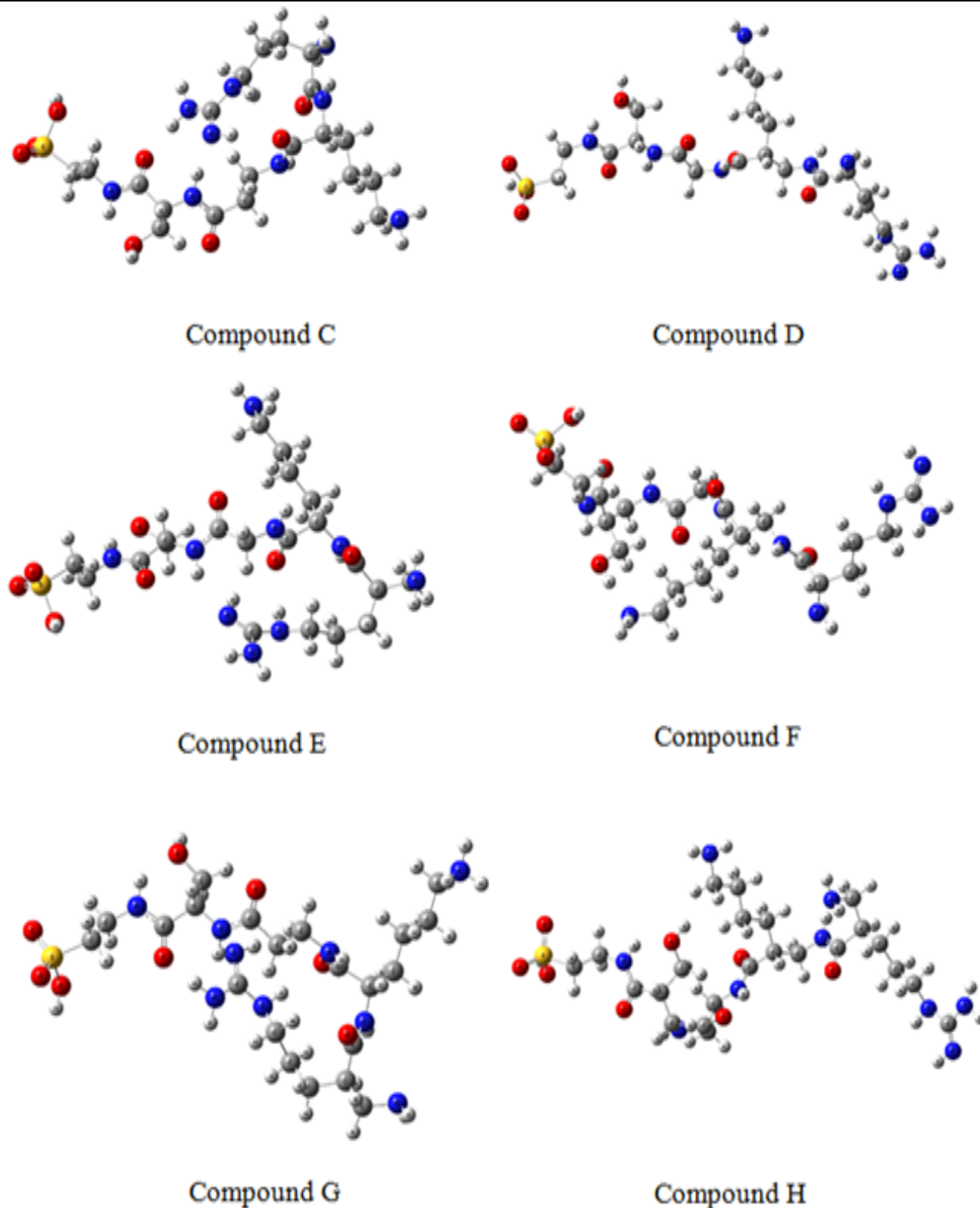


Figure 1: Optimized geometry of Taurine, natural substrate and other suggested compounds obtained using B3LYB/6-31G method. The occurrences of carbon (C), hydrogen (H), oxygen (O), nitrogen (N) and sulfur (S) atoms are indicated by respective gray, white, red, blue and yellow balls**

Electronic structure properties

Table 1 enlists the structure specific computed energies of the proposed compounds including the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), optical band gap (ΔE , signifying the energy difference between the HOMO and LUMO), and dipole moment. The total energy of the proposed compounds was observed to be below taurine and natural substrate. Besides, the value of ΔE for both the natural substrate and suggested inhibitors was lower compared to taurine. The achieved values of dipole moment revealed the polar (hydrophilic) character of these compounds. Distinctively, the dipole moment values were ranged from 3.4570 to 8.6526 Debye. The disclosure of such high dipole moment values clearly indicated the strong reactive nature of the proposed compounds. Such characteristics of the studied compounds were affirmed to be promising for strong interactions with other systems in the solution, suggesting their high solubility in the polar solutions (aqueous media) omnipresent in the biological systems.

Table 1: Calculated electronic structure properties of studied compounds obtained by B3LYP/6-31G** method

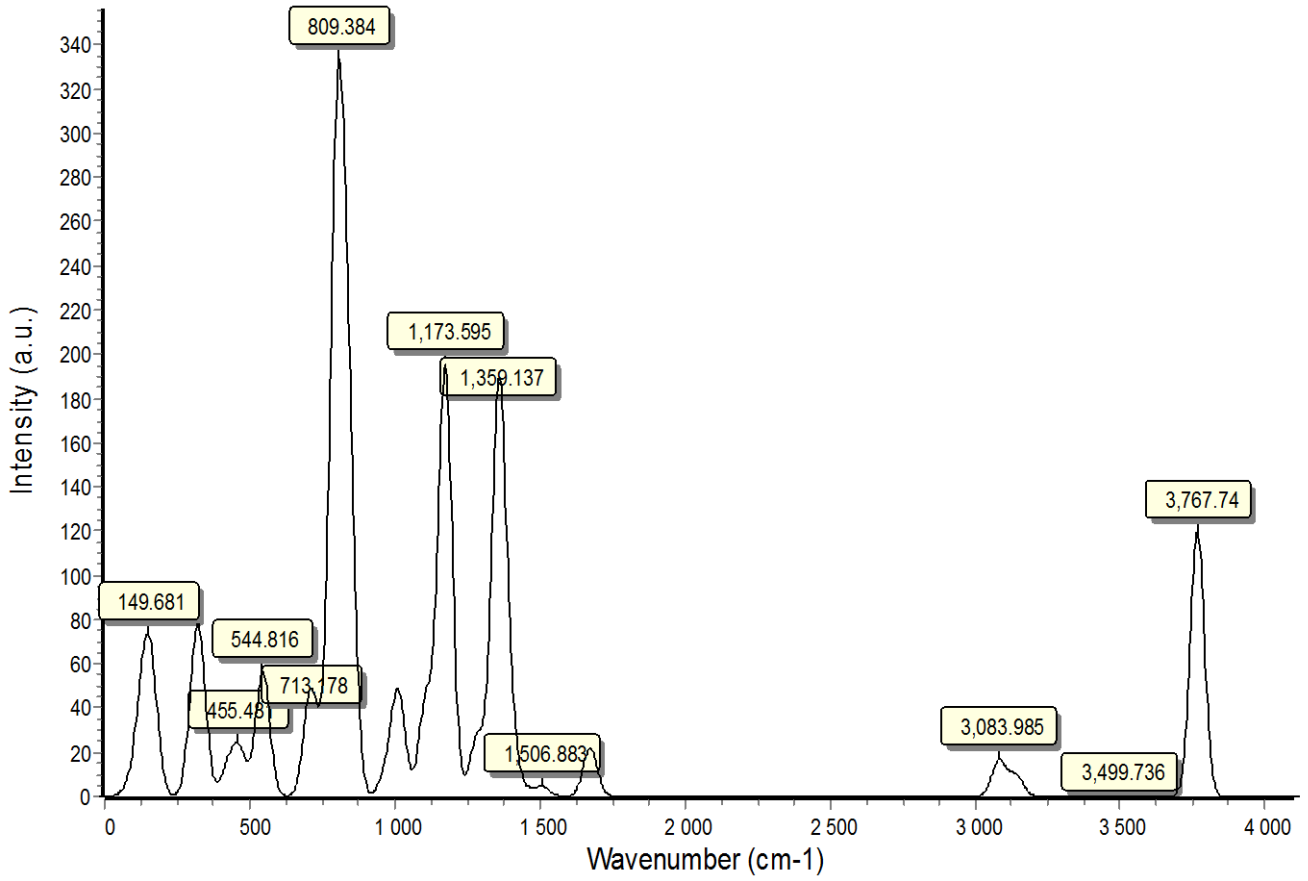
Compound	Composition	Total Energy (a.u.)	Dipole moment (Debye)	HOMO (a.u.)	LUMO (a.u.)	ΔE (a.u.)
Taurine	NH ₂ -CH ₂ -CH ₂ -SO ₂ -OH	-758.9794	3.4842	-0.2539	0.0276	0.2815
Substrate	Ser-Gly-Lys-Arg	-1557.7316	6.3308	-0.2108	0.0002	0.211
A	Taurine- Ser-Gly-Lys-Arg	-2240.3188	6.7914	-0.2205	0.0041	0.2246
B	Taurine-(β -Ser)-Gly-Lys-Arg	-2279.6426	5.8549	-0.2347	0.0014	0.2362
C	Taurine-Ser-(β -Gly)-Lys-Arg	-2279.6443	6.4701	-0.2196	0.0028	0.2224
D	Taurine-Ser-Gly-(β -Lys)-Arg	-2279.6261	7.5605	-0.2196	-0.0047	0.2149
E	Taurine-Ser-Gly-Lys-(β -Arg)	-2279.6354	6.3011	-0.2209	0.0028	0.2237
F	Taurine-(β -Ser)-Gly-(β -Lys)-Arg	-2318.9594	8.6513	-0.2221	0.0114	0.2335
G	Taurine-Ser-(β -Gly)-Lys-(β -Arg)	-2318.9539	8.6526	-0.2124	0.0067	0.2191
H	Taurine-(β -Ser)-(β -Gly)-(β -Lys)-(β -Arg)	-2397.5768	5.8638	-0.2148	0.0014	0.2162

Infrared spectral attributes

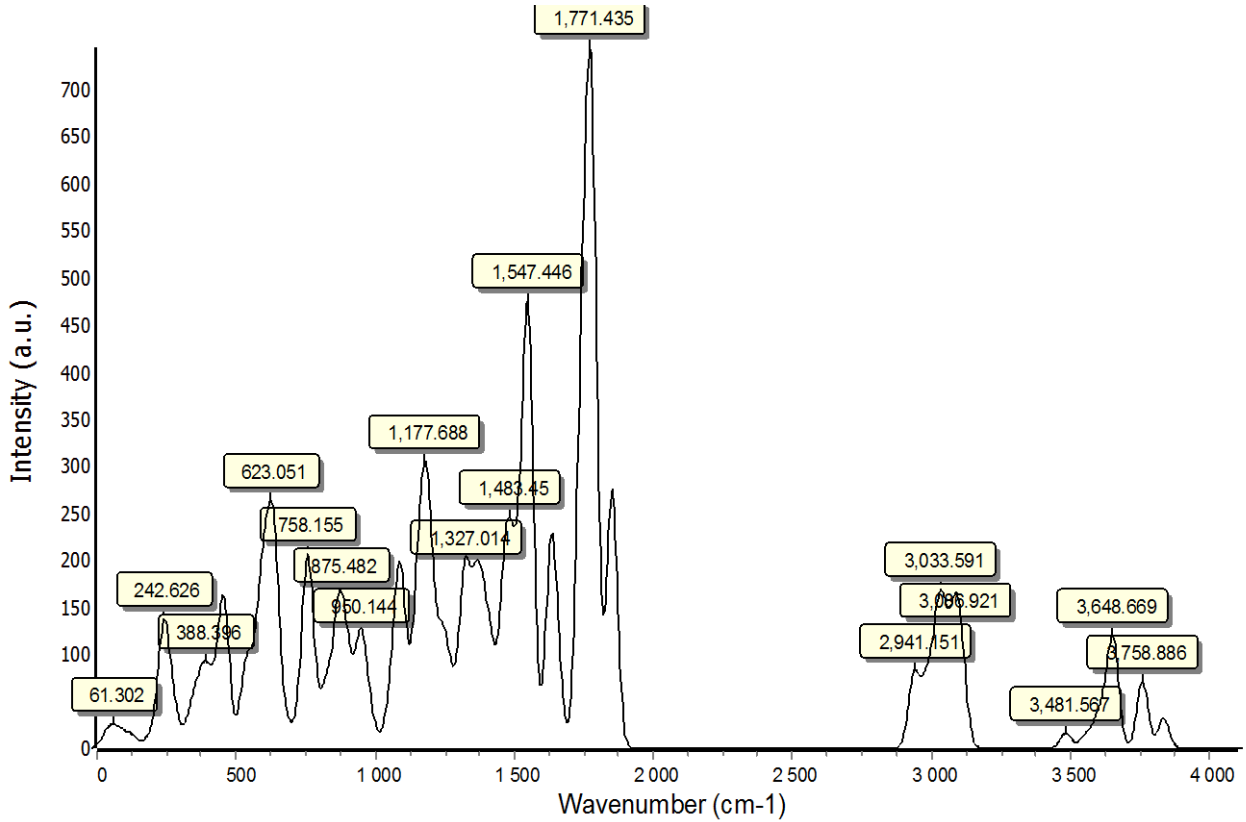
Figure 2 displays the calculated un-scaled infrared (IR) absorption spectra of all the studied compounds together with Gaussian broadening fit. The spectra were obtained using the optimized structure of each compound. IR spectral bands were categorized into two main domains such as the fingerprint region (800 to 1500 cm⁻¹) and the functional group region (1500 to 4000 cm⁻¹). Table 2 provides the structure dependent frequencies and intensities of the significant vibrational bands. The C-S-O asymmetric stretching vibrations of taurine was emerged at 802.68 cm⁻¹ (trans- form), which was assigned to the molecular conformation of a sulfur-containing molecule [34]. Conjugation of the both forms (alpha and beta) of substrate chain with taurine could result in vibrational peak shift towards higher energy, wherein the alpha-chain revealed higher energy shift than beta configuration. Moreover, the peak intensity of the C-S-O stretching vibration was reduced, indicating higher stabilization of the sulfur group. The S=O stretching vibration also exhibited similar trend with the lowest wavenumber for the taurine molecule and highest intensity. The amide I (C=O) peak disclosed a slight variation in the spectral profile among diverse groups with the highest value for the substrate group. Conversely, the amide II (C-N stretching and N-H bending) peak was varied among different groups with the lowest value detected for the substrate group.

Table 2: Calculated spectral band positions, intensities and the assignments of proposed compounds obtained via B3LYP/6-31G** method

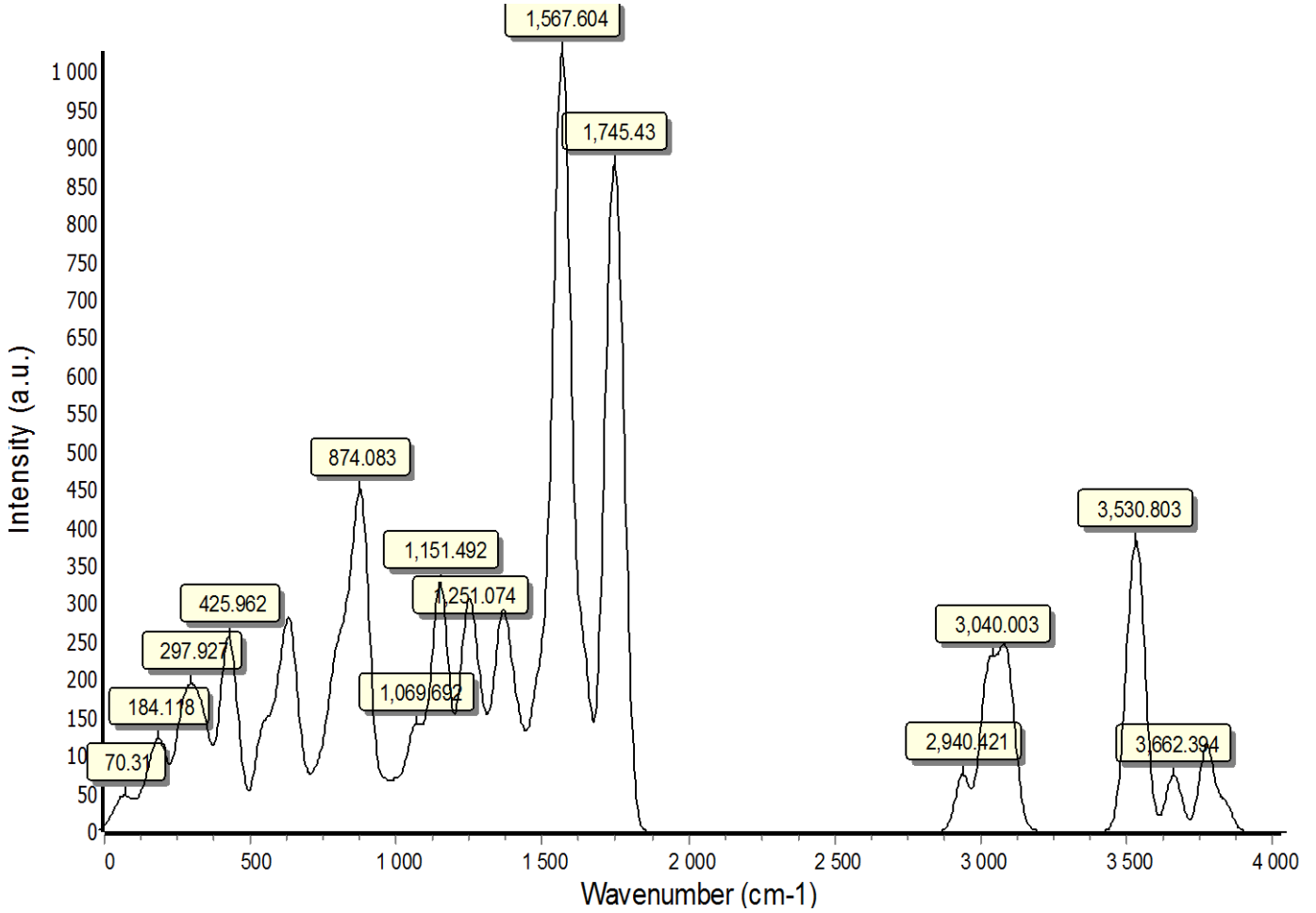
Compound	C-S-O Asymmetric		S=O		Amide II		Amide I		CH ₂ Symmetric		N-H		O-H	
	Freq. (cm ⁻¹)	Inten. (a.u.)	Freq. (cm ⁻¹)	Inten. (a.u.)	Freq. (cm ⁻¹)	Inten. (a.u.)	Freq. (cm ⁻¹)	Inten. (a.u.)	Freq. (cm ⁻¹)	Inten. (a.u.)	Freq. (cm ⁻¹)	Inten. (a.u.)	Freq. (cm ⁻¹)	Inten. (a.u.)
Taurine	802.68	285.01	1359.58	182.81	-	-	-	-	3081.16	15.33	3498.22	0.1	3766.29	119.83
Substrate	-	-	-	-	1554.78	184.79	1774.83	350.86	2936.13	75.24	3547.59	9.26	3758.16	71.14
A	831.99	140.6	1375.55	169.43	1574.69	593.88	1745.34	211.15	2938.8	74.29	3544.65	204.76	3773.04	114.22
B	826.16	28.42	1360.06	155.74	1593.77	268.54	1741.08	501.39	2976.83	79.95	3556.74	114.94	3765.16	114.93
C	830.58	172.96	1373.58	125.37	1597.58	397.34	1747.61	394.83	2938.14	76.04	3489.51	569.38	3771.73	113.3
D	822.23	119.8	1359.95	123.2	1592.14	227.83	1754.28	379.38	2943.91	70.32	3548.77	297.67	3763.25	122.37
E	831.63	141.51	1374.71	172.89	1575.6	591.74	1764.38	233.9	2937.88	77.87	3548.78	198.11	3772.91	114.37
F	822.66	112.14	1361.18	150.82	1598.74	260.07	1753.15	347.23	2999.91	50.85	3546.06	13.2378	3768.1	109.05
G	832.27	76.85	1372.56	154.29	1590.1	173.92	1744.9	302.2	2937.17	77.68	3572.27	165.02	3772.08	114.92
H	821.73	46.72	1360.04	153.16	1584.43	221.81	1744.66	427.41	2957.29	94.85	3535.72	213.26	3809.39	149.92



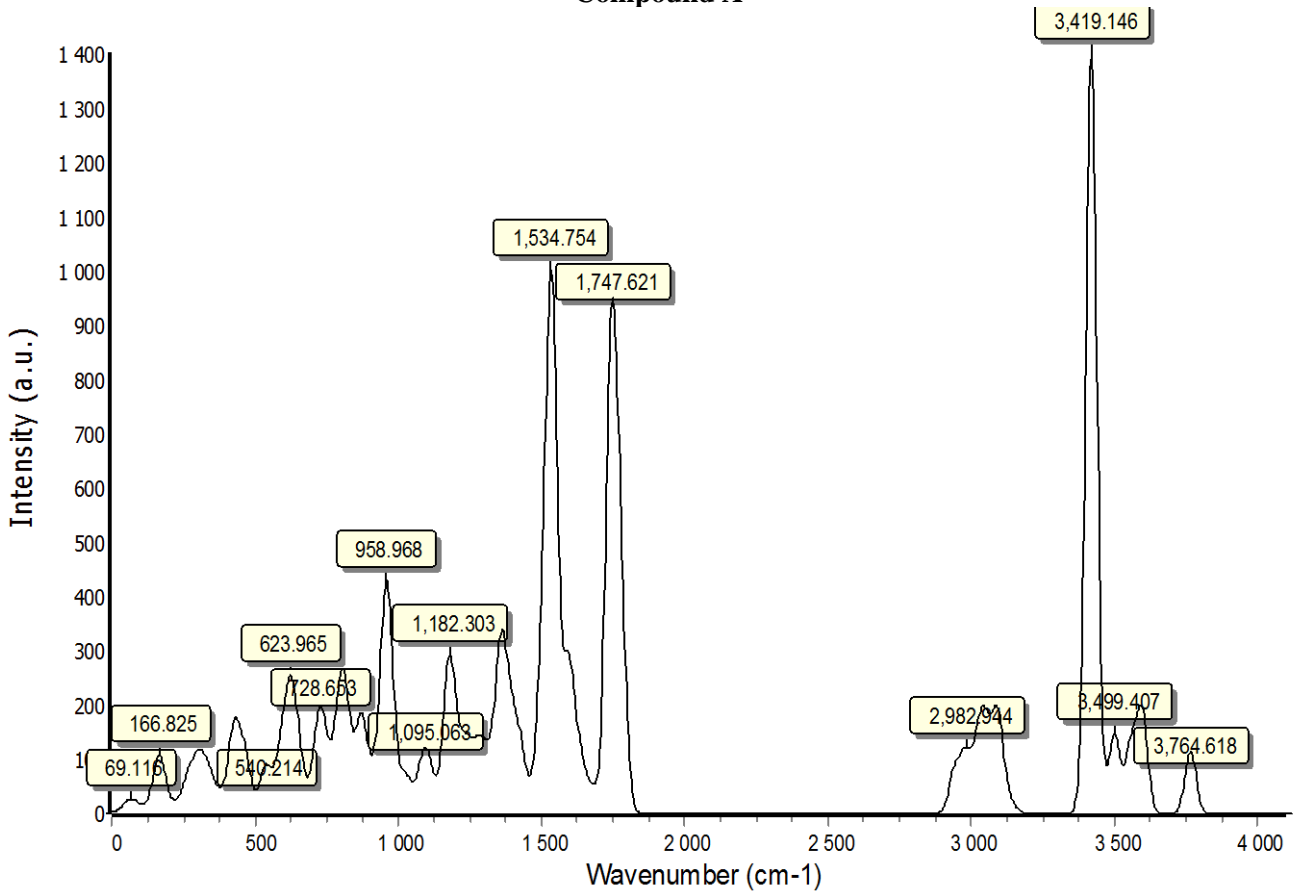
Taurine



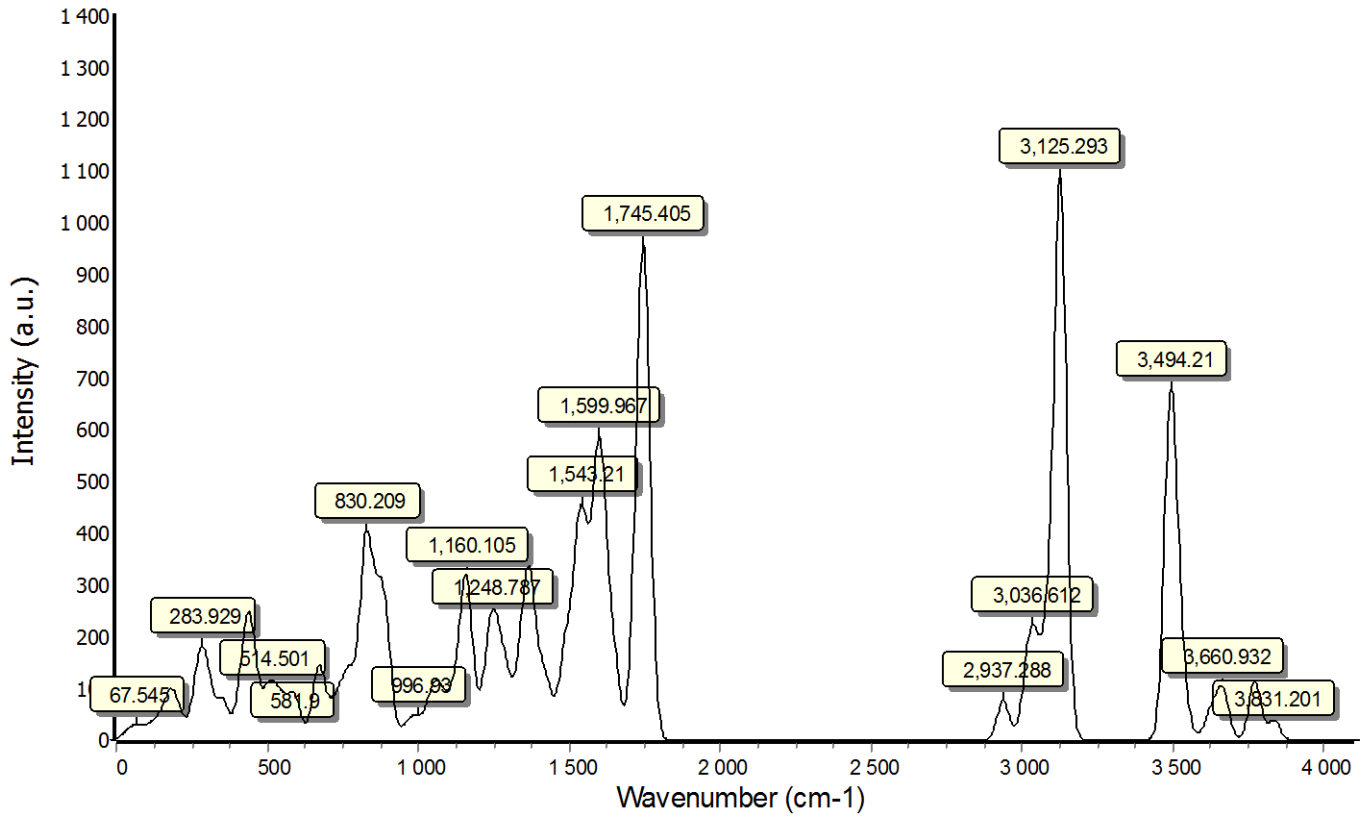
Natural substrate



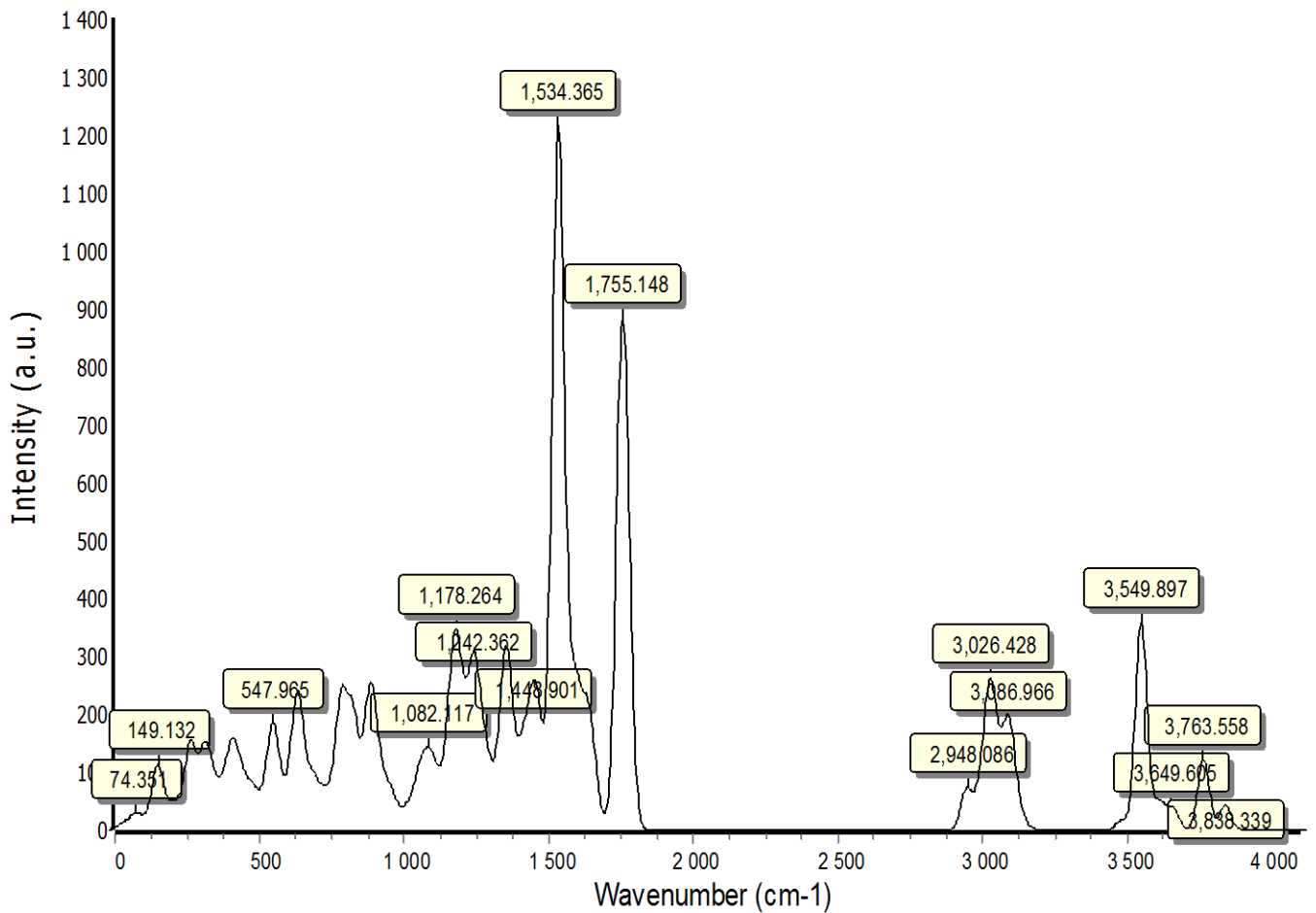
Compound A



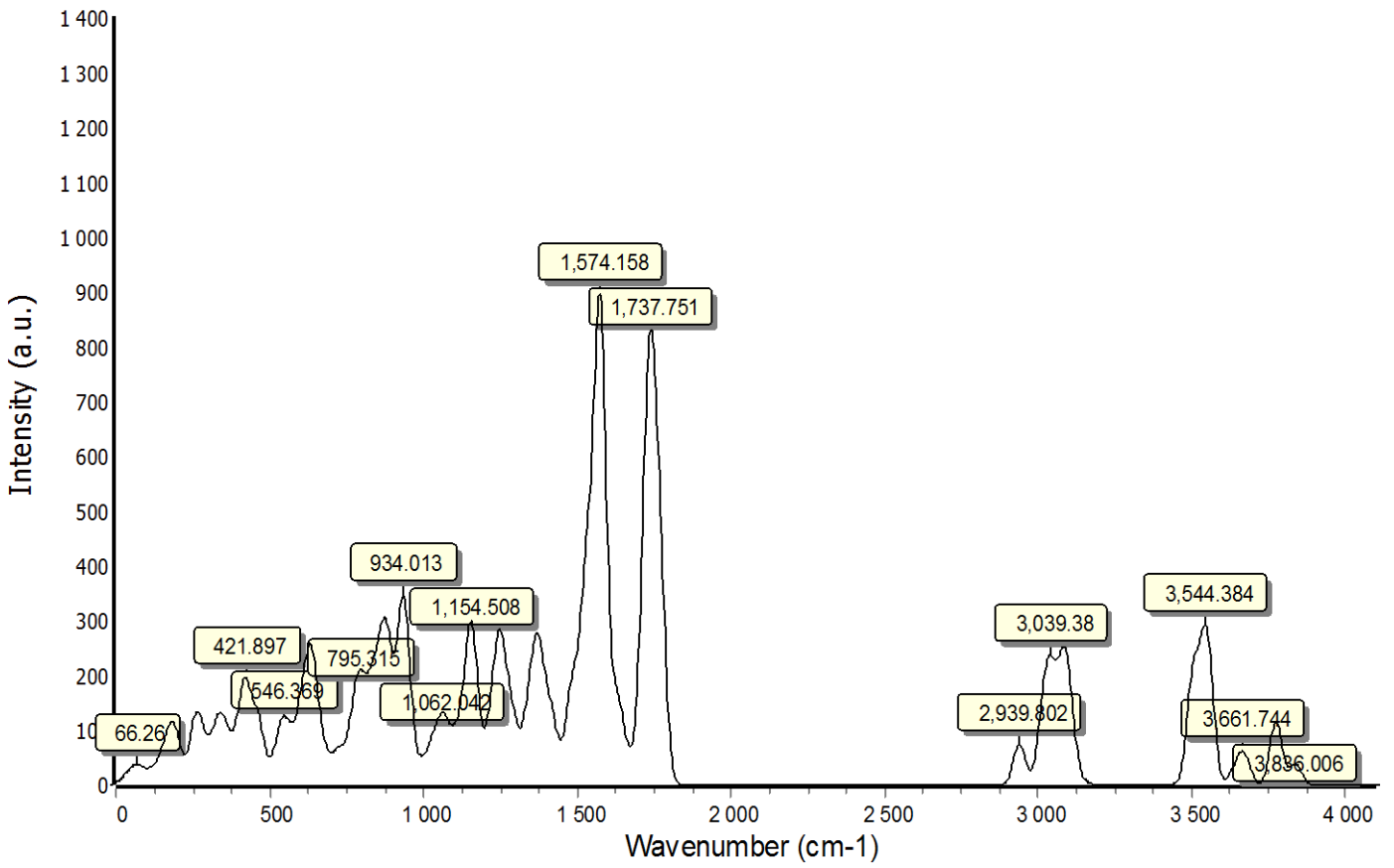
Compound B



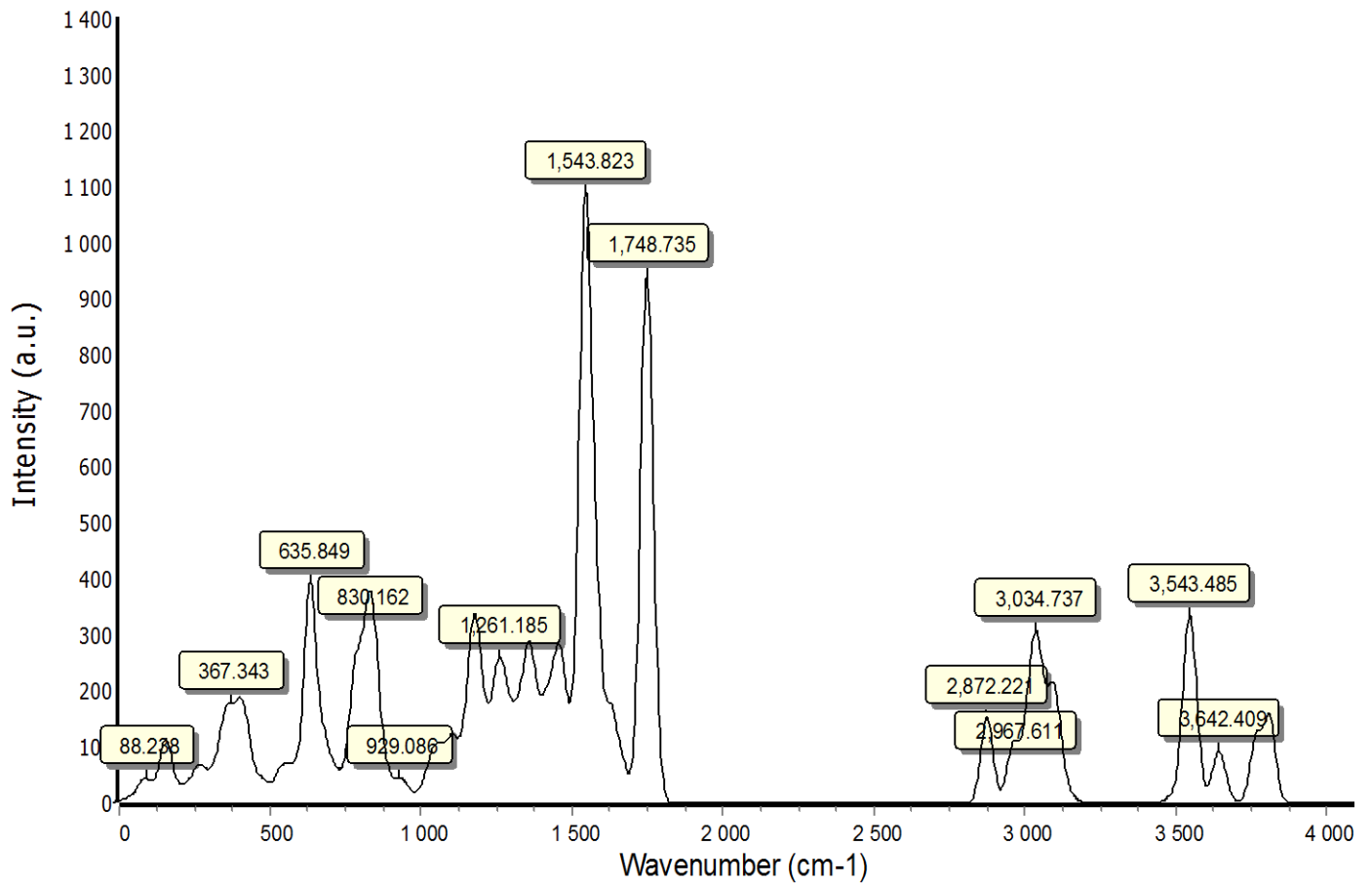
Compound C



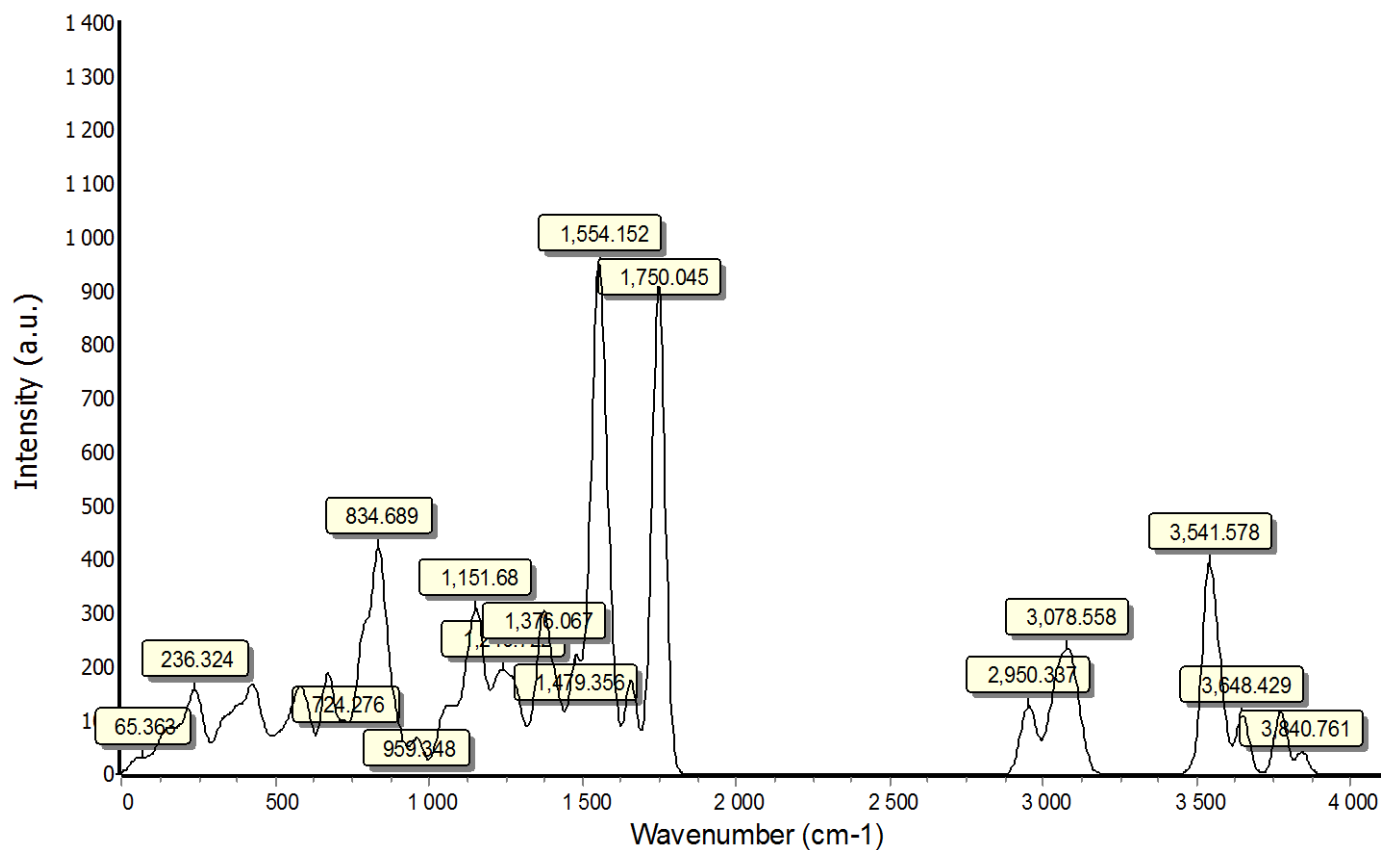
Compound D



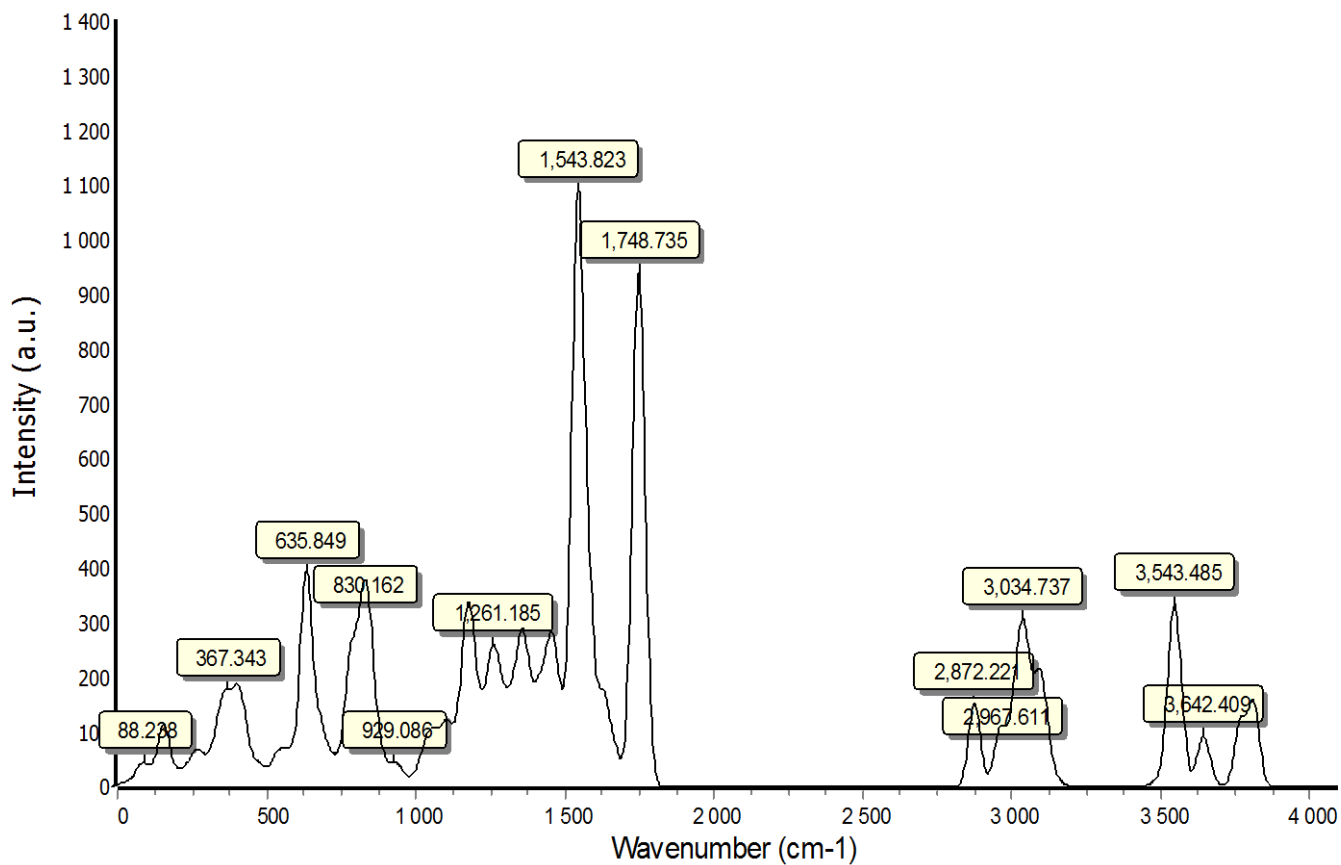
Compound E



Compound F



Compound G



Compound H

Figure 2: Calculated un-scaled infrared spectra together with Gaussian broadening fit achieved (Compounds A-H)

The predominant stretching vibration frequency for the O-H group was endorsed to the S-O-H linkage present in taurine (3766.29 cm^{-1}) and the C-O-H linkage in the substrate group (3758.16 cm^{-1}). The conjugation of taurine with the substrate was shown to enhance the stretching vibration frequency remarkably, especially for the taurine- β amino group which was originated from the secondary intra-molecular hydrogen bond in all groups. This revelation was supported by the observed reduction in the dipole moment value of the β -amino group. The N-H stretching was aroused from the peptide bond and R-group of both lysine and arginine, indicating some marked differences in the vibrational frequencies among various groups. The observed highest vibration frequency of sp^2 symmetric stretching of C-H bond for the taurine molecule was primarily attributed to its extreme stability, despite its lowest intensity that could arise from the contribution of reduced number of C-H bonds.

CONCLUSION

Electronic structures and IR spectra of candidate inhibitors, taurine, natural substrates and diverse compounds were computed using B3LYP/6-31G** molecular model simulation. The calculated electronic structure and IR spectra of taurine (a natural compound in the human body) revealed its effectiveness towards ZIKV-NS3 protease inhibitor. Upon conjugating taurine with natural substrate it was disclosed to compete with the ZIKV protease enzyme during the replication and maturation cycle of the virus. The studied compounds show more stability (low total energy) and more reactivity with surrounding system (high dipole moment and low ΔE) than that for taurine or natural substrate. This demonstrates the important role of conjugation between taurine and tetra-peptide sequences to increase the stability of suggested compounds and may give the compounds good inhibition activity against Zika virus NS3 protease. We demonstrated that the conjugation of taurine with a tetrapeptide substrate could produce a significant shift in the vibrational bands promising for anti ZIKV drug formulation. The molecular docking studies of the candidate inhibitors for further confirmation of the present findings and future anti- ZIKV drug development using taurine is worth undertaking.

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