Exploring Facile Synthesis and Cholinesterase Inhibiting Potential of Heteroaryl Substituted Imidazole Derivatives for the Treatment of Alzheimer's Disease

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1. ^{1}H NMR, ^{13}C NMR, FTIR, and EI-MS Spectra of Novel Imidazole Derivatives (5c-5j).

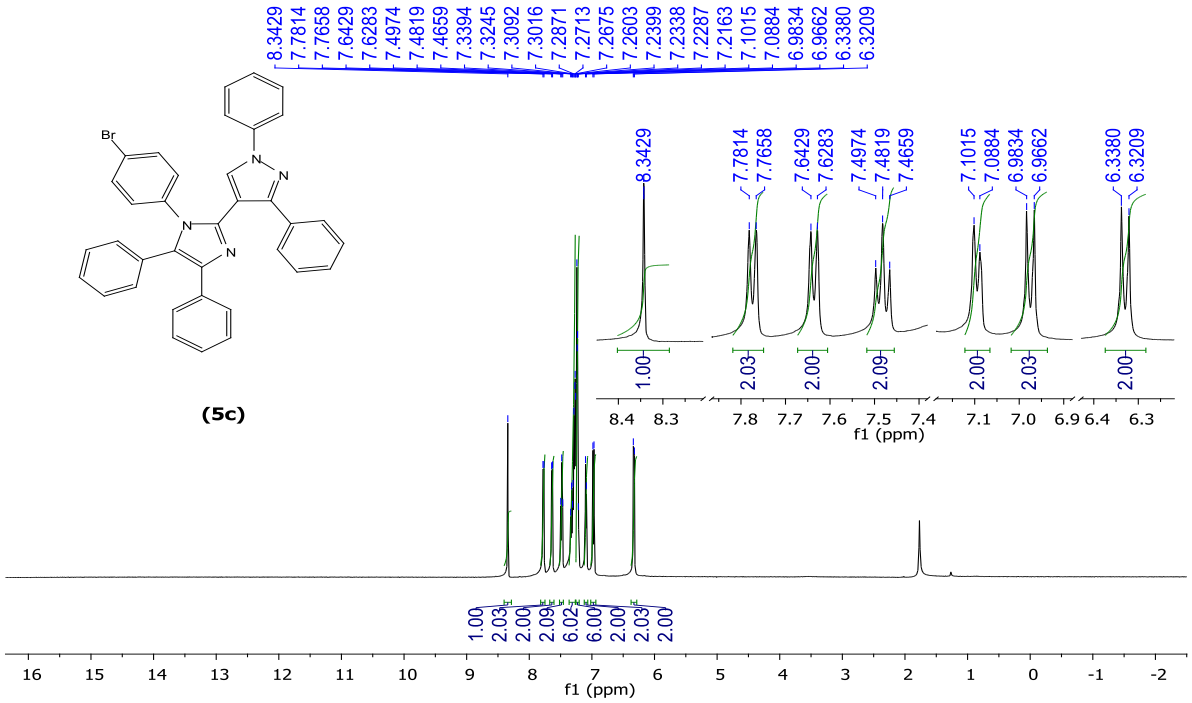


Figure-1S: ^{1}H NMR Spectrum of Compound **5c**.

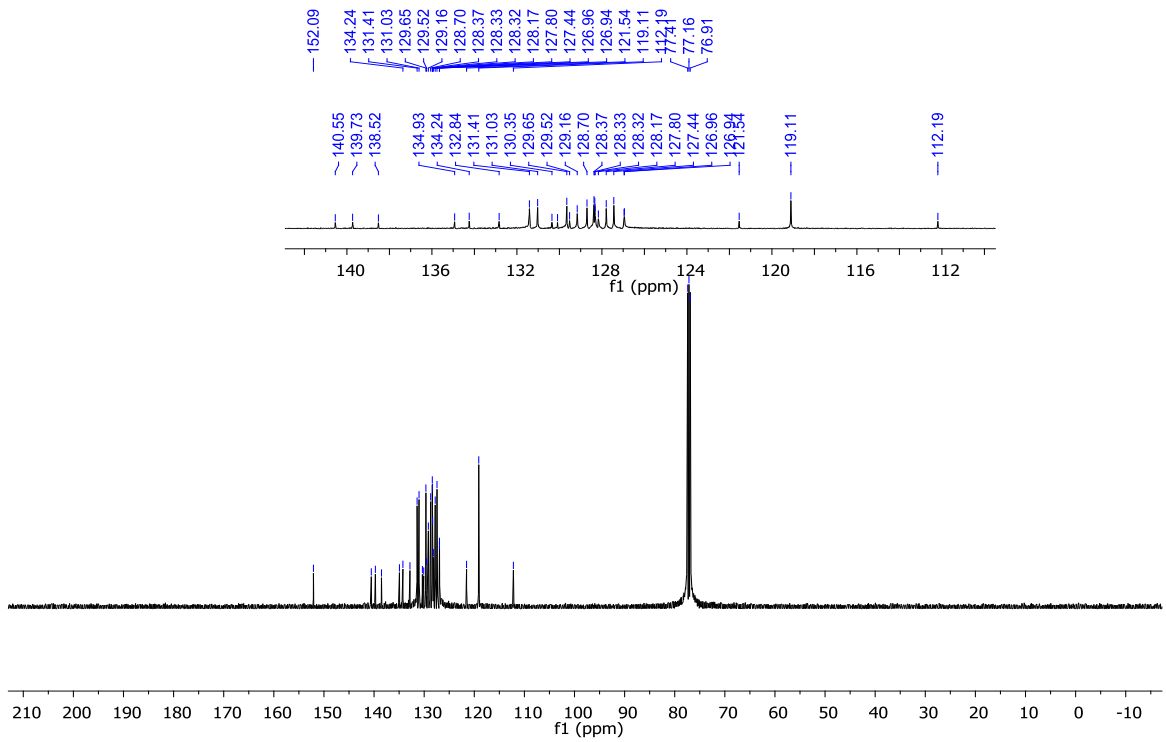


Figure-2S: ^{13}C NMR Spectrum of Compound **5c**.

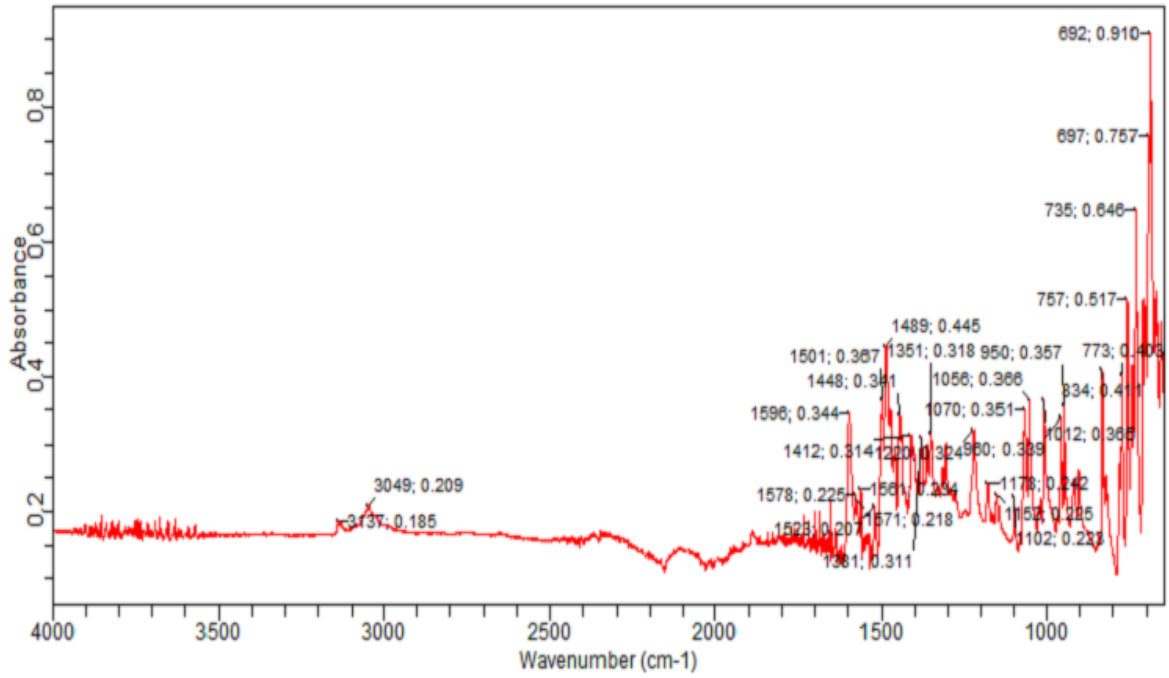


Figure-3S: FTIR Spectrum of Compound **5c**.

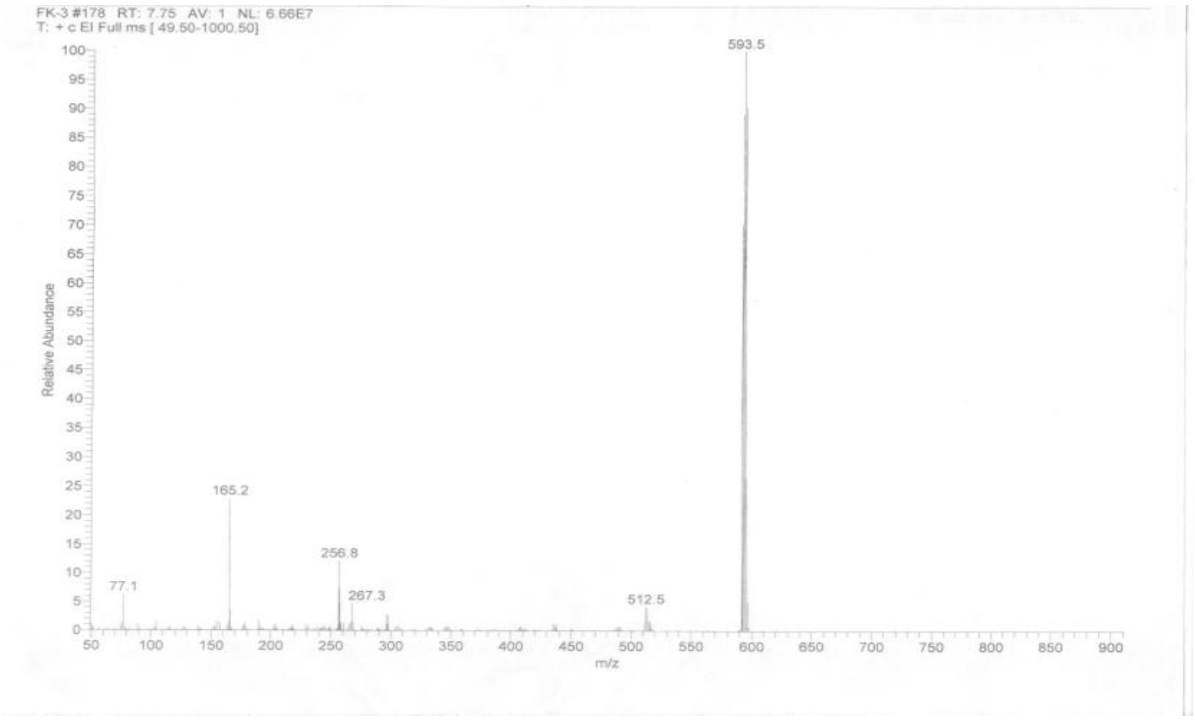


Figure-4S: EI-MS Spectrum of Compound **5c**.

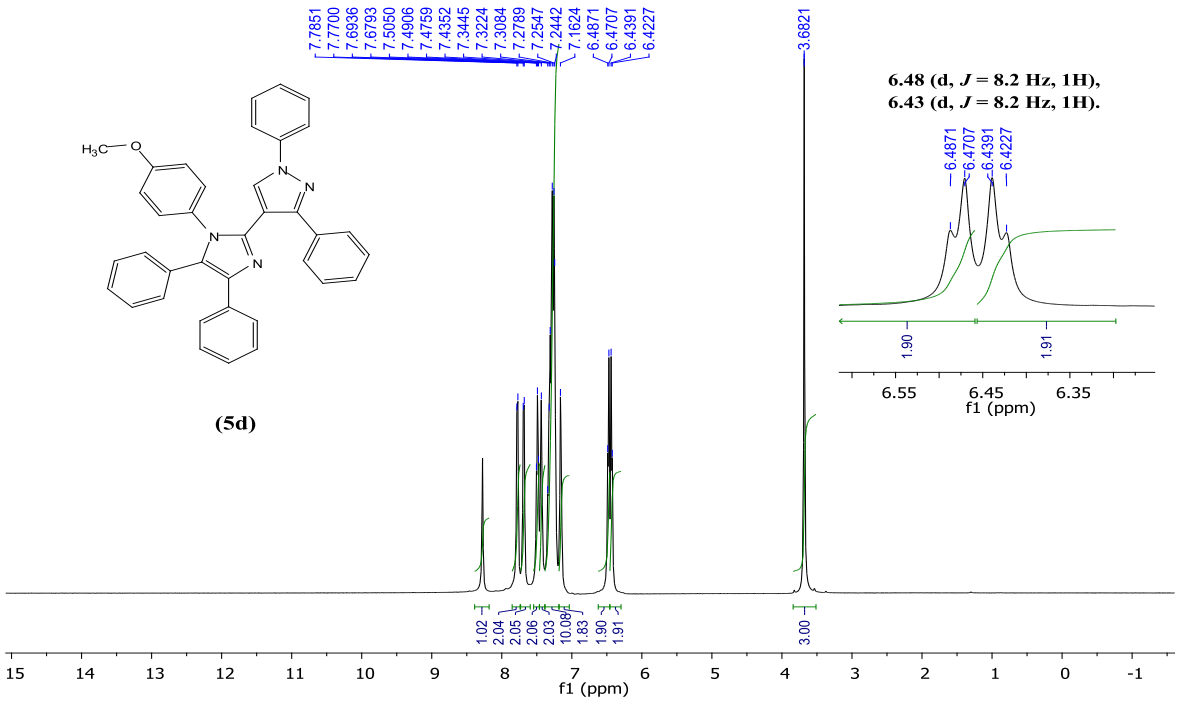


Figure-5S: ^{1}H NMR Spectrum of Compound **5d**.

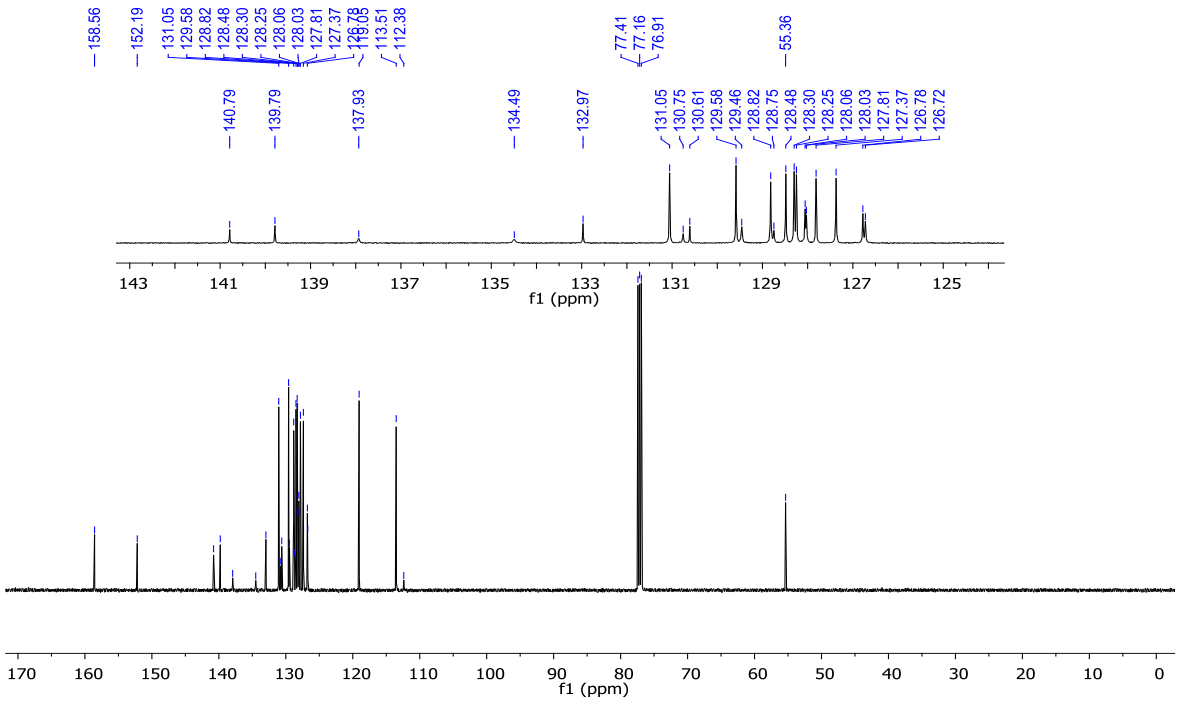


Figure-6S: ^{13}C NMR Spectrum of Compound **5d**.

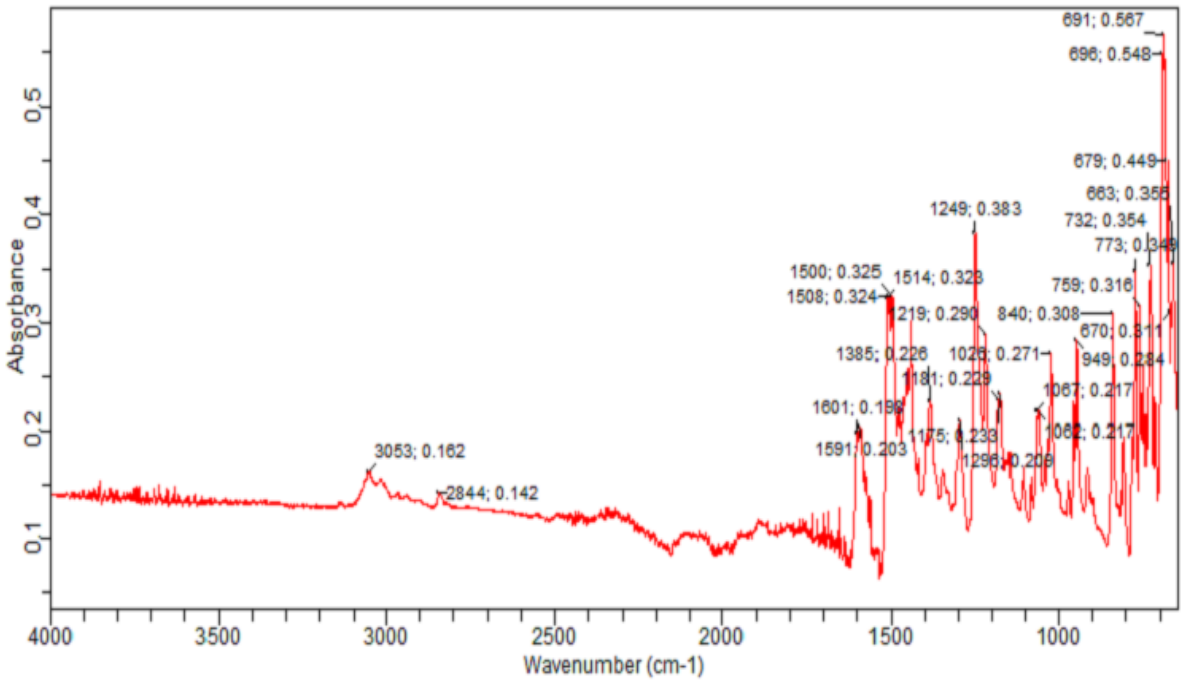


Figure-7S: FTIR Spectrum of Compound **5d**.

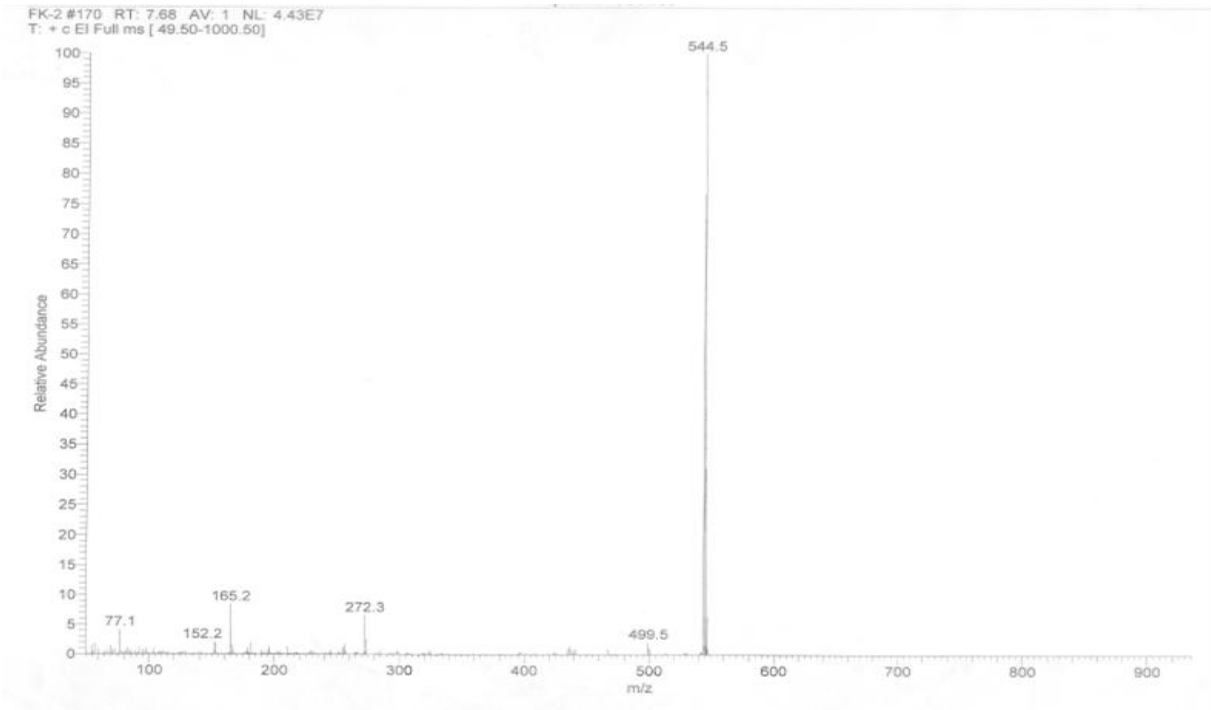


Figure-8S: EI-MS Spectrum of Compound **5d**.

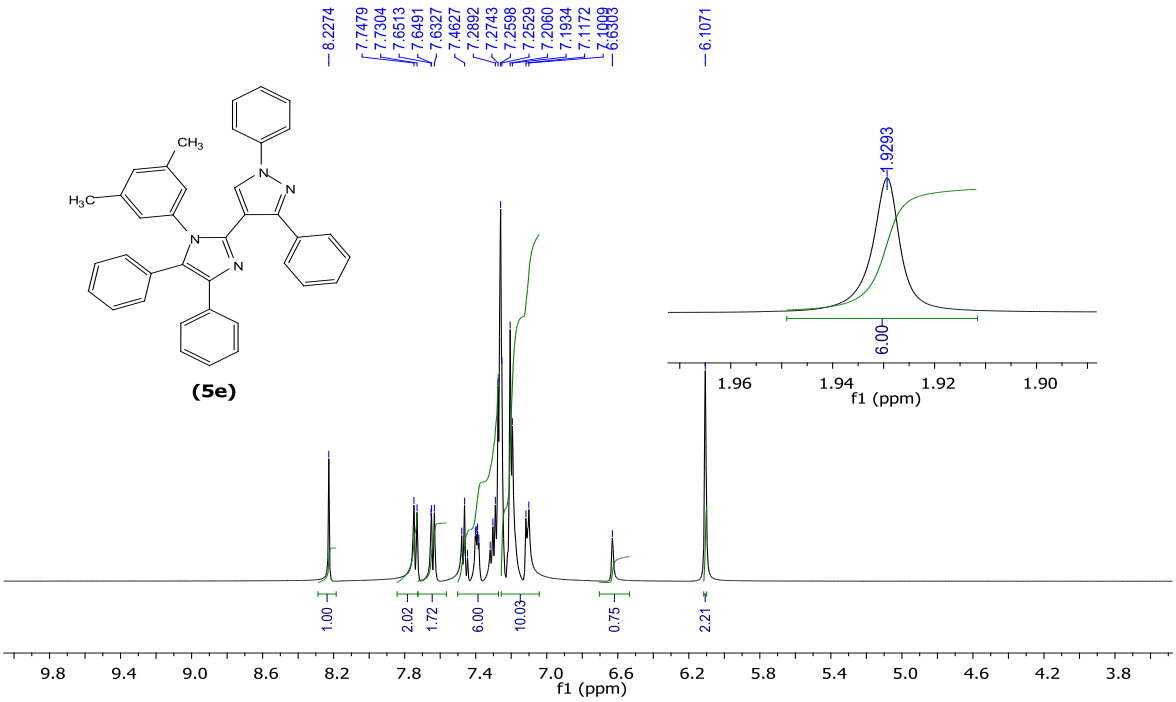


Figure-9S: ^{1}H NMR Spectrum of Compound **5e**.

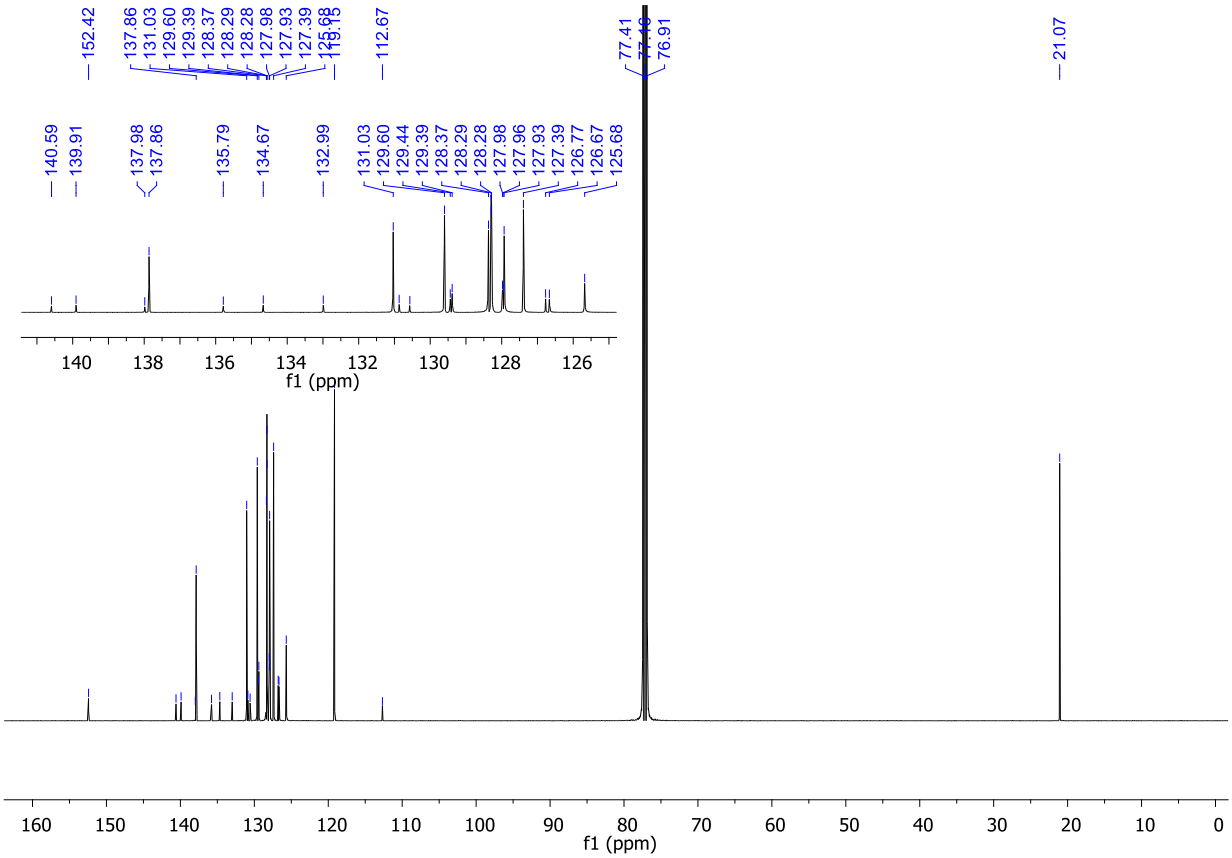


Figure-10S: ^{13}C NMR Spectrum of Compound **5e**.

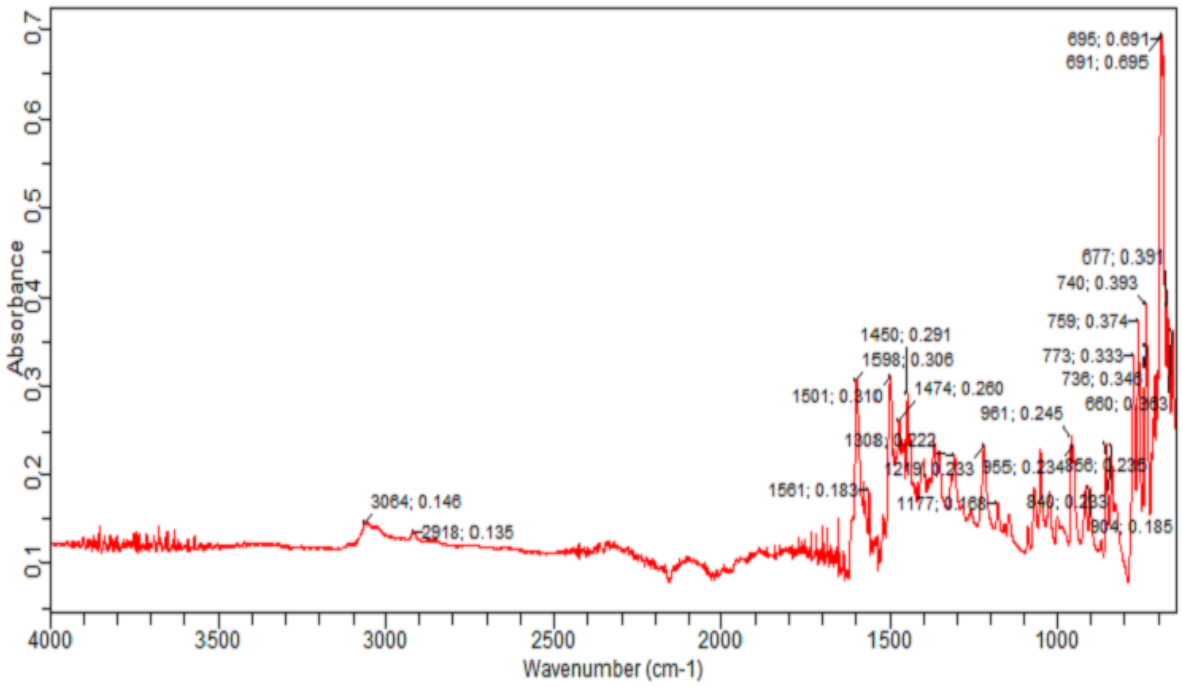


Figure-11S: FTIR Spectrum of Compound **5e**.

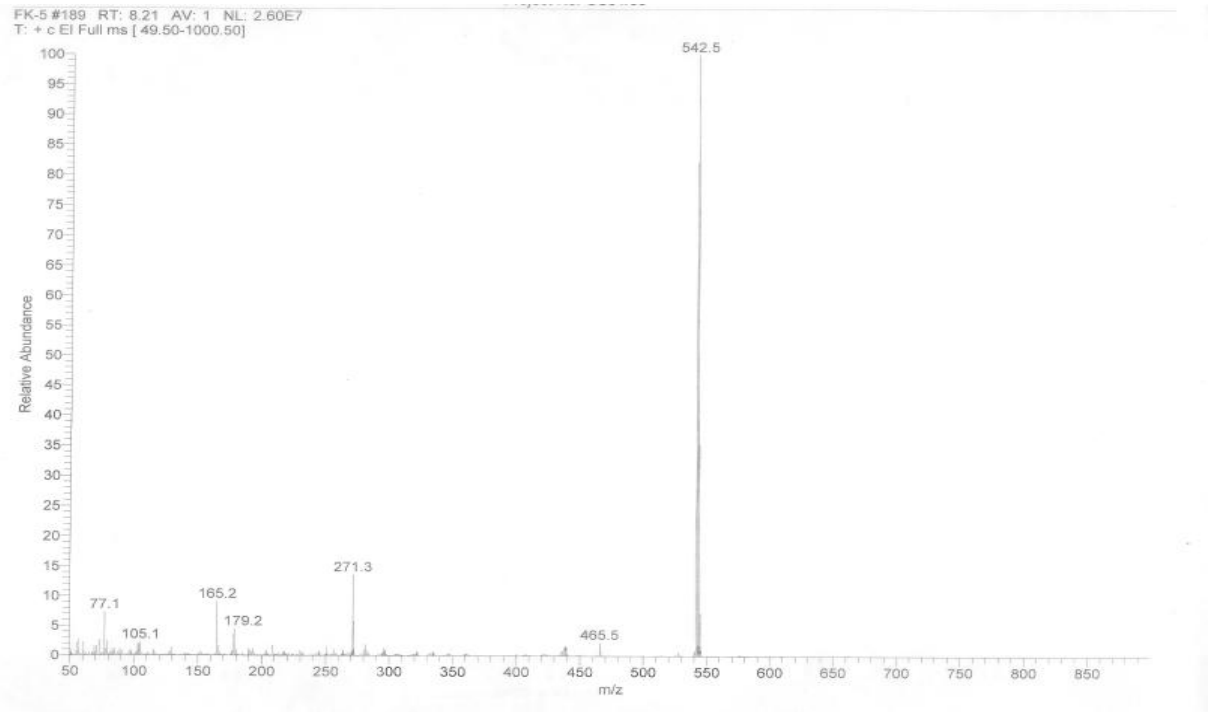


Figure-12S: EI-MS Spectrum of Compound **5e**.

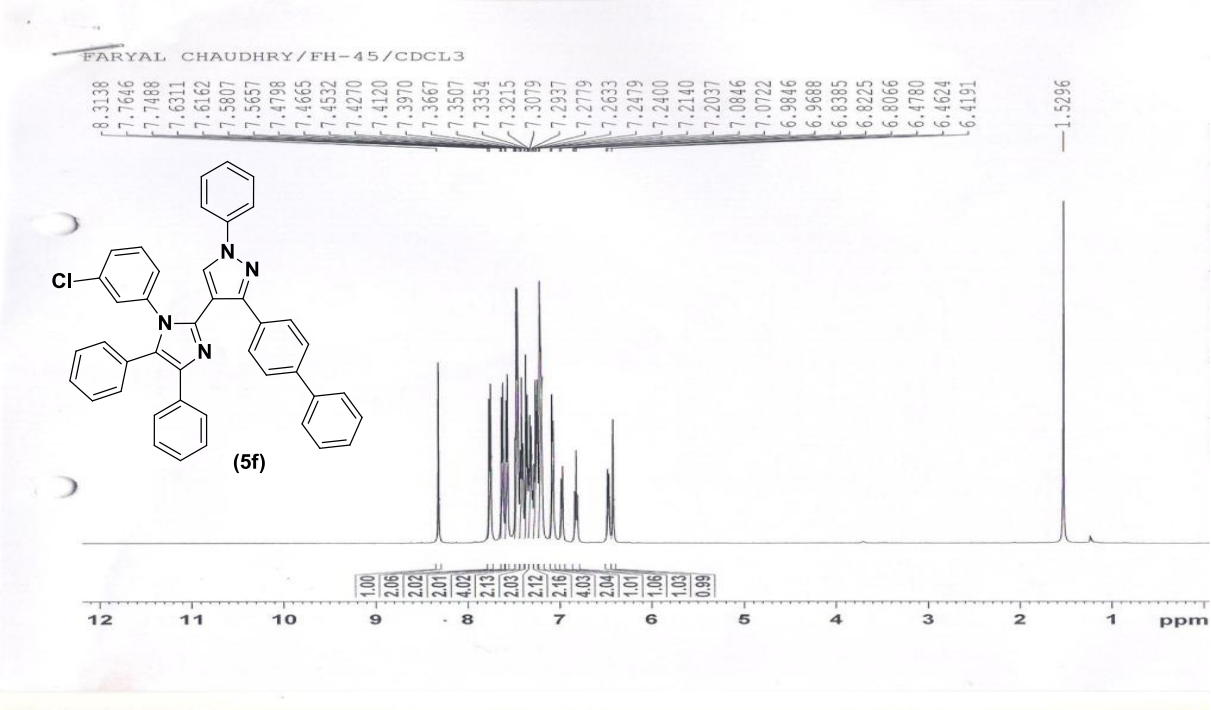


Figure-13S: ^{1}H NMR Spectrum of Compound **5f**.

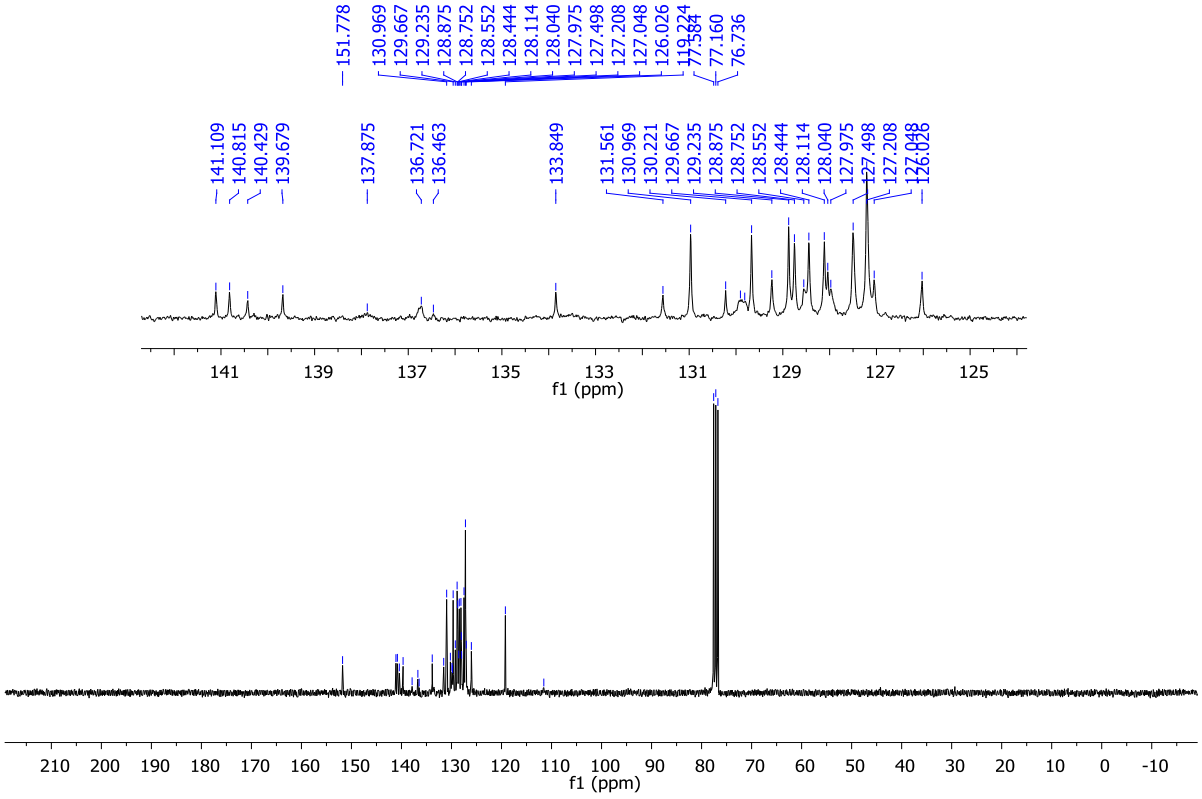


Figure-14S: ^{13}C NMR Spectrum of Compound **5f**.

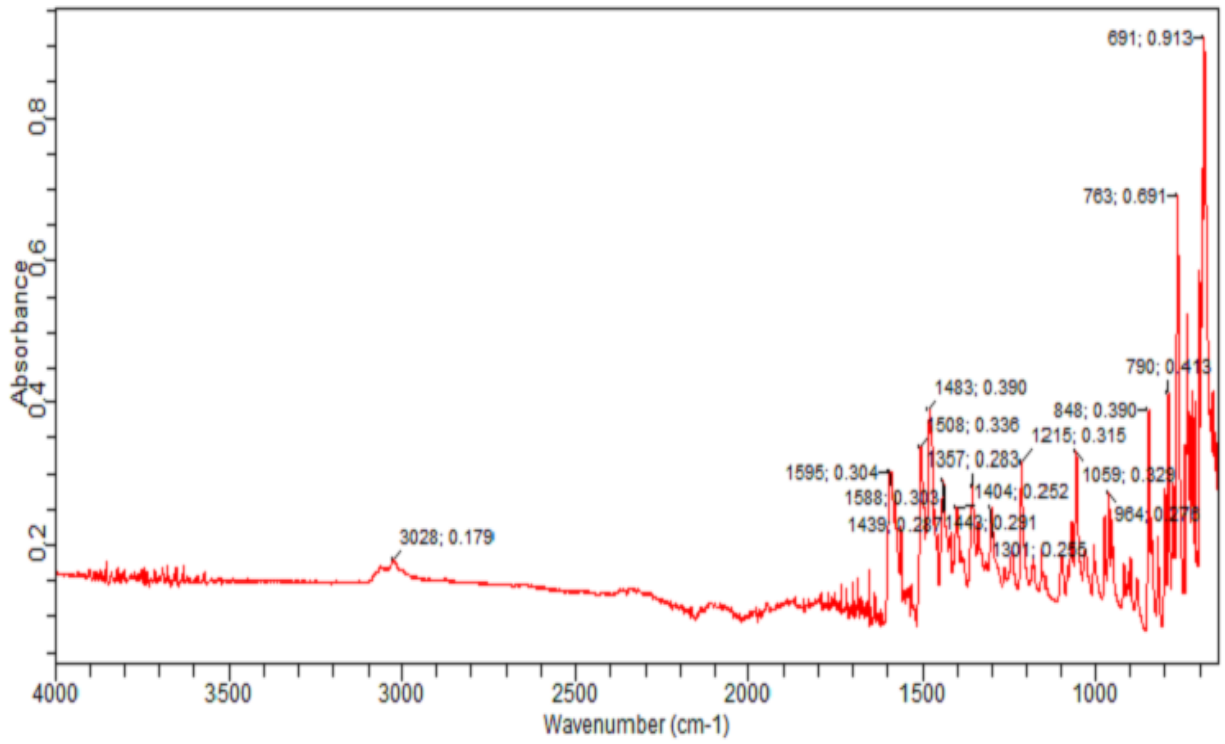


Figure-15S: FTIR Spectrum of Compound **5f**.

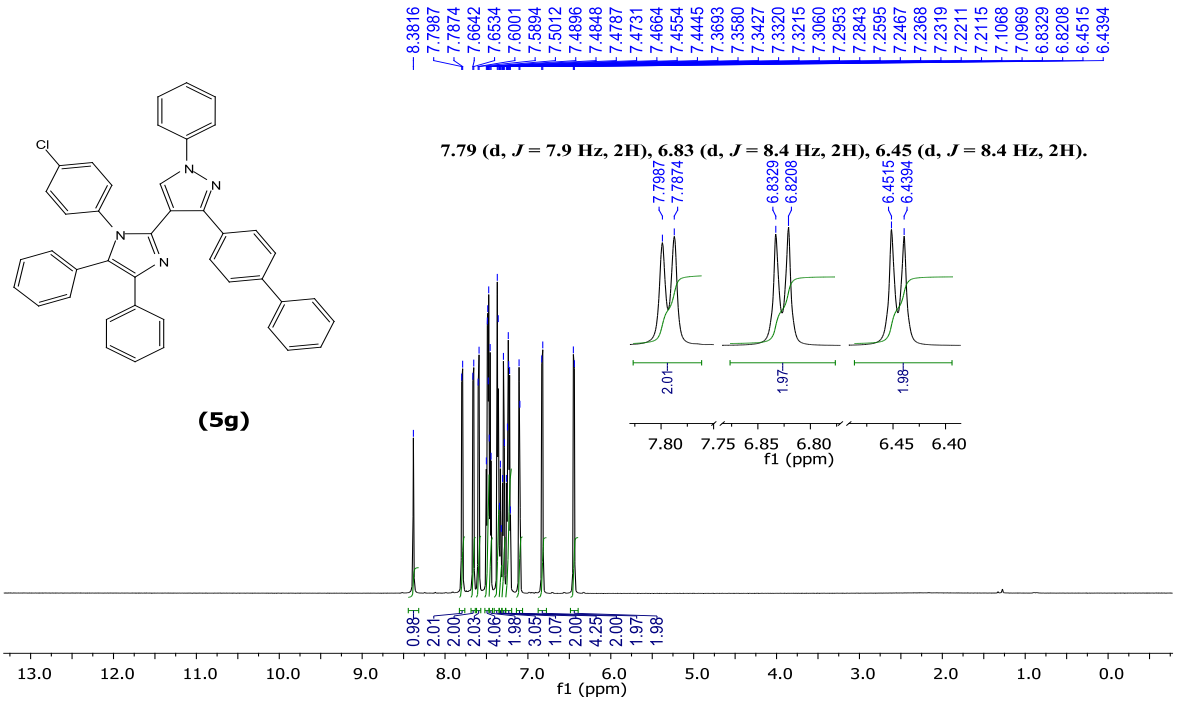


Figure-16S: ^{1}H NMR Spectrum of Compound **5g**.

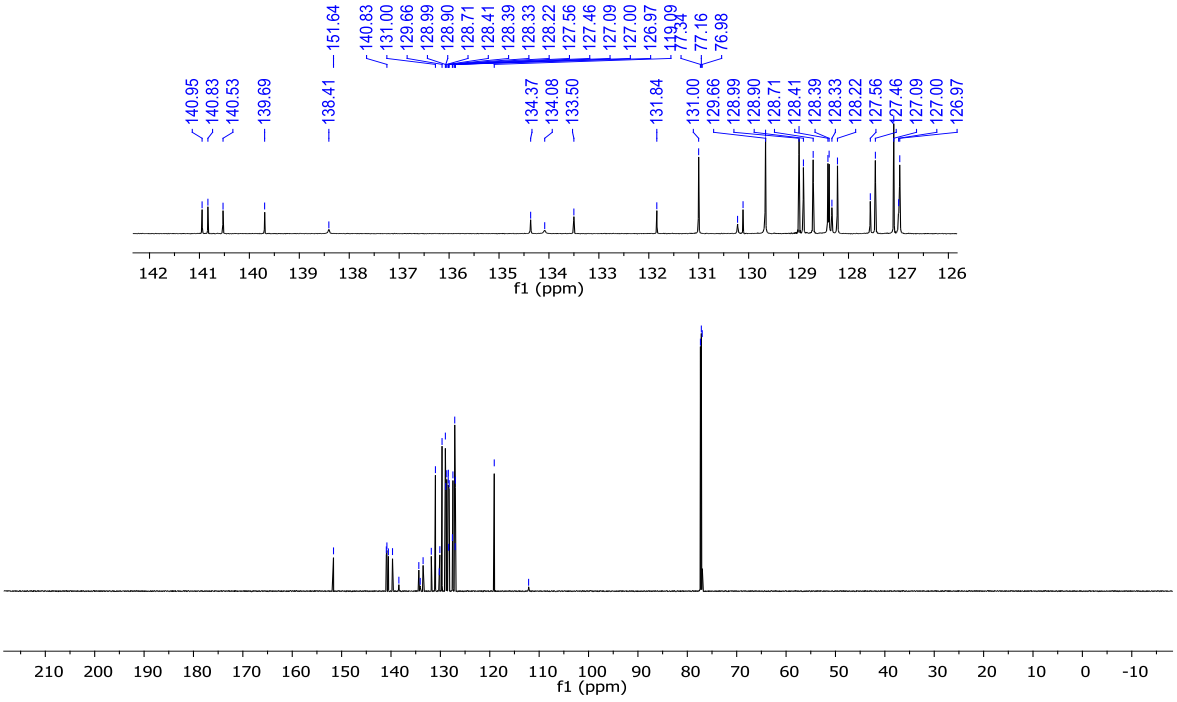


Figure-17S: ^{13}C NMR Spectrum of Compound **5g**.

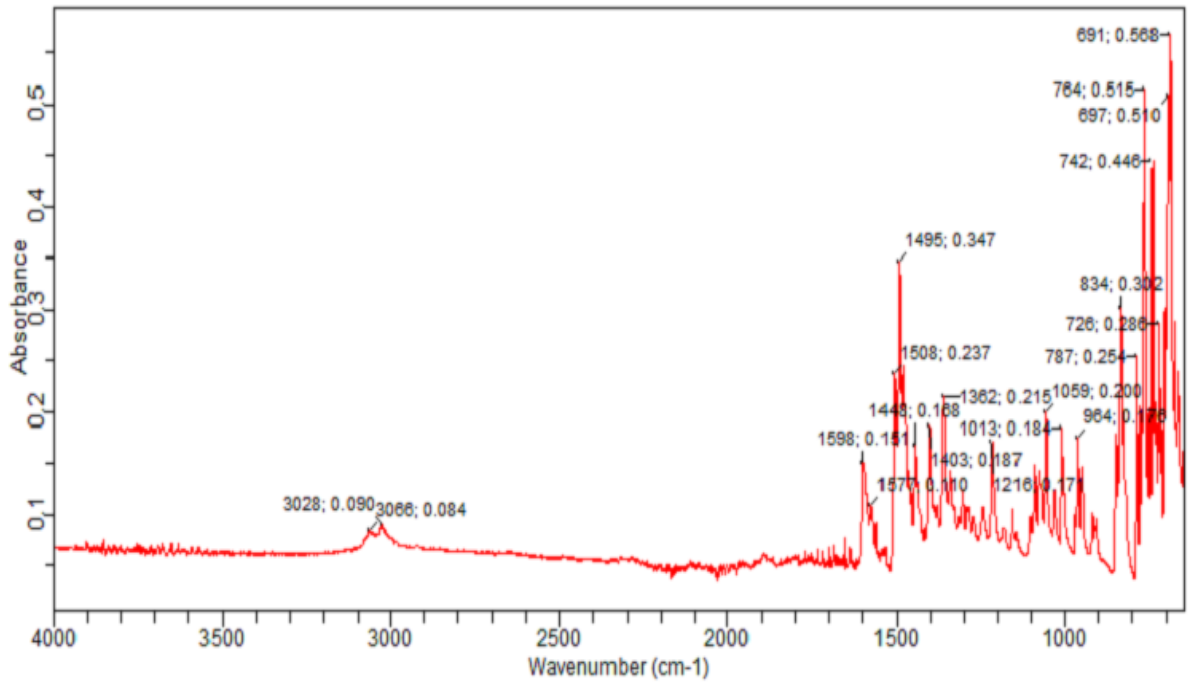


Figure-18S: FTIR Spectrum of Compound **5g**.

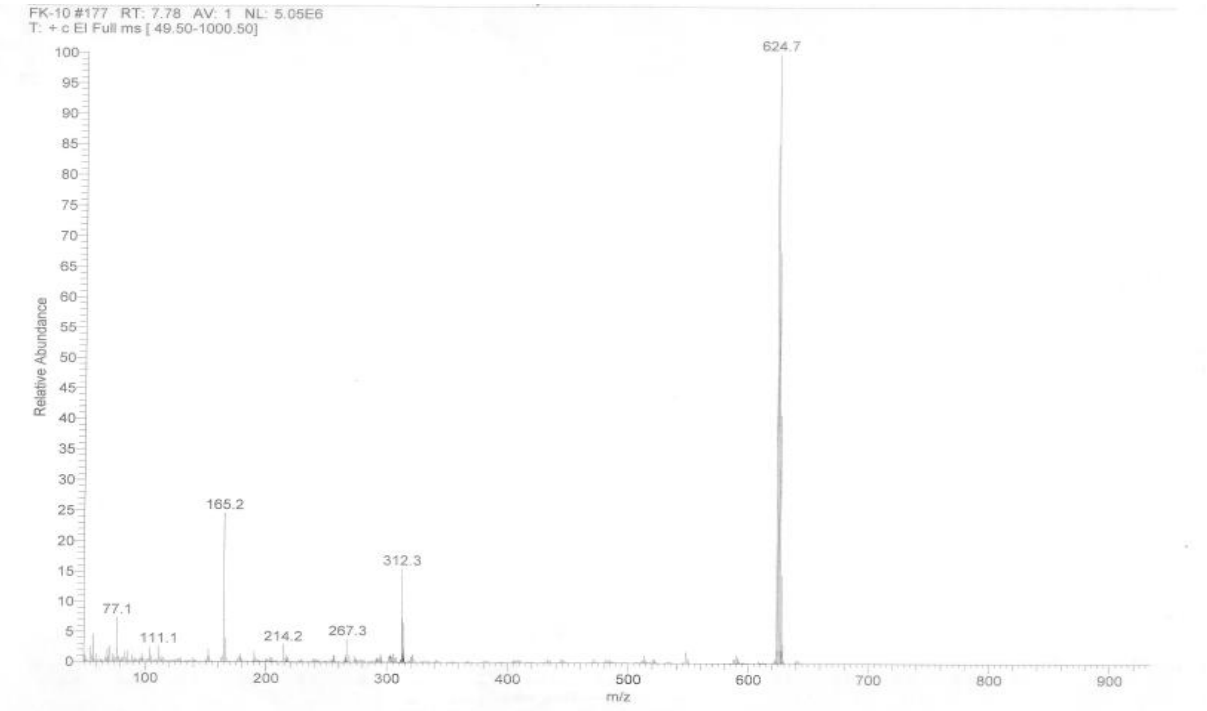


Figure-19S: EI-MS Spectrum of Compound **5g**.

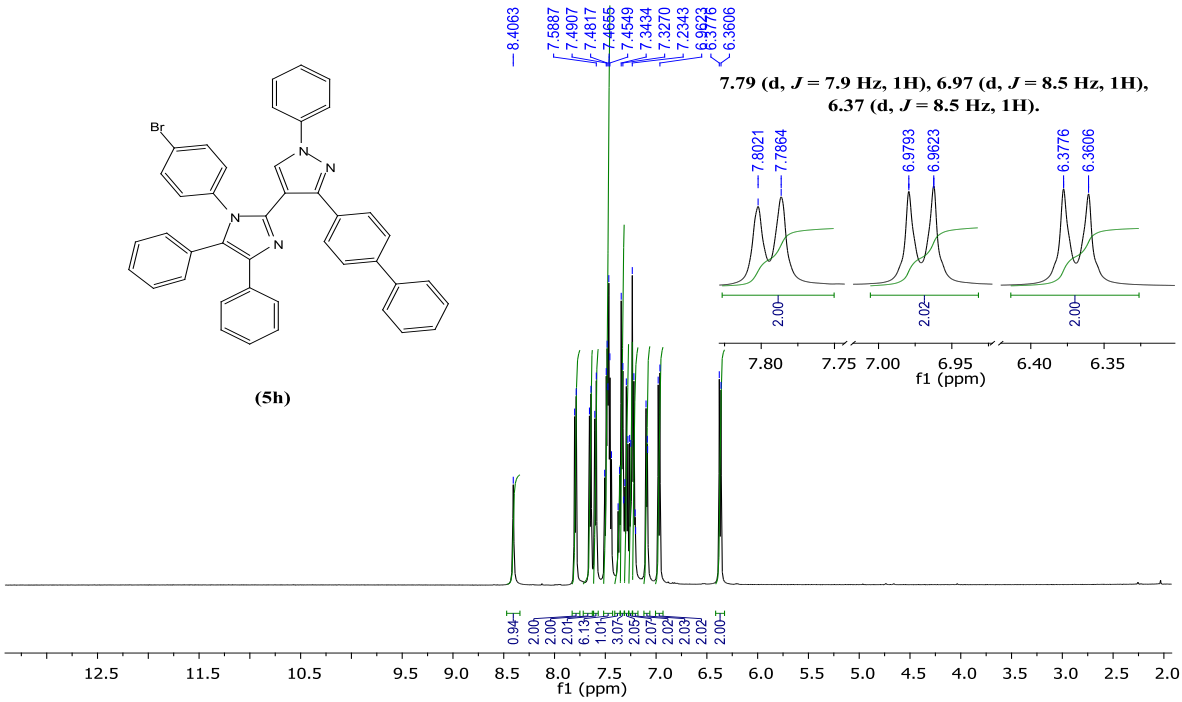


Figure-20S: ^{1}H NMR Spectrum of Compound **5h**.

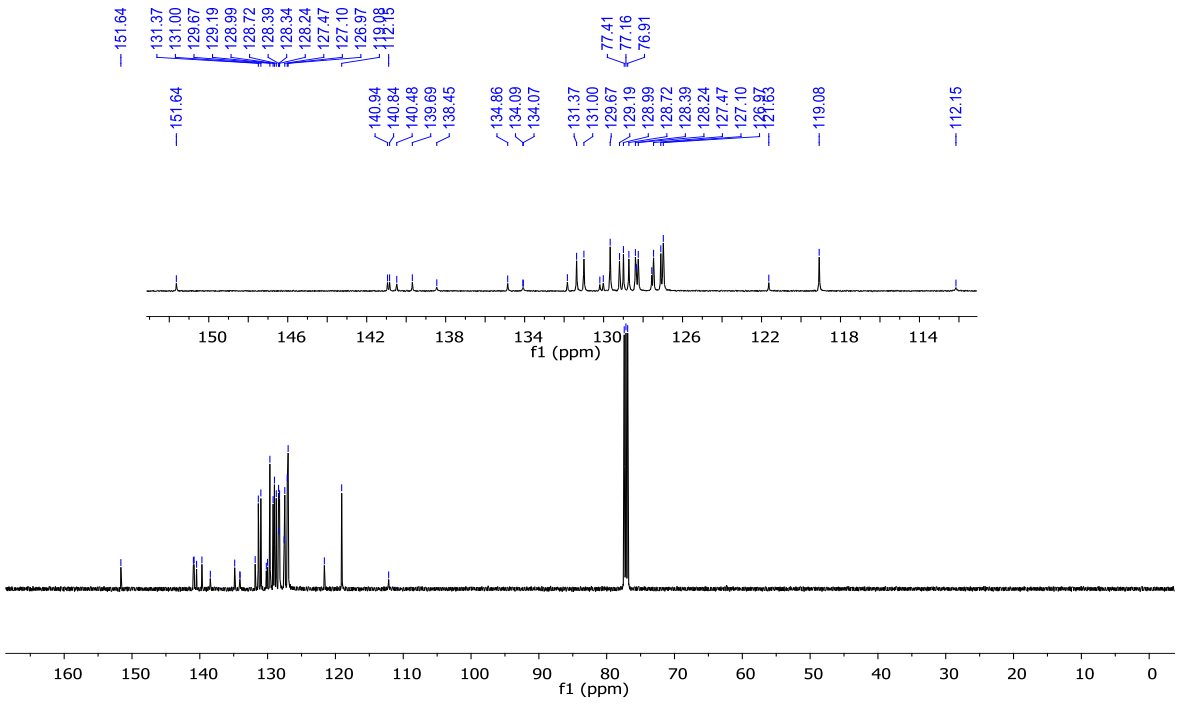


Figure-21S: ^{13}C NMR Spectrum of Compound **5h**.

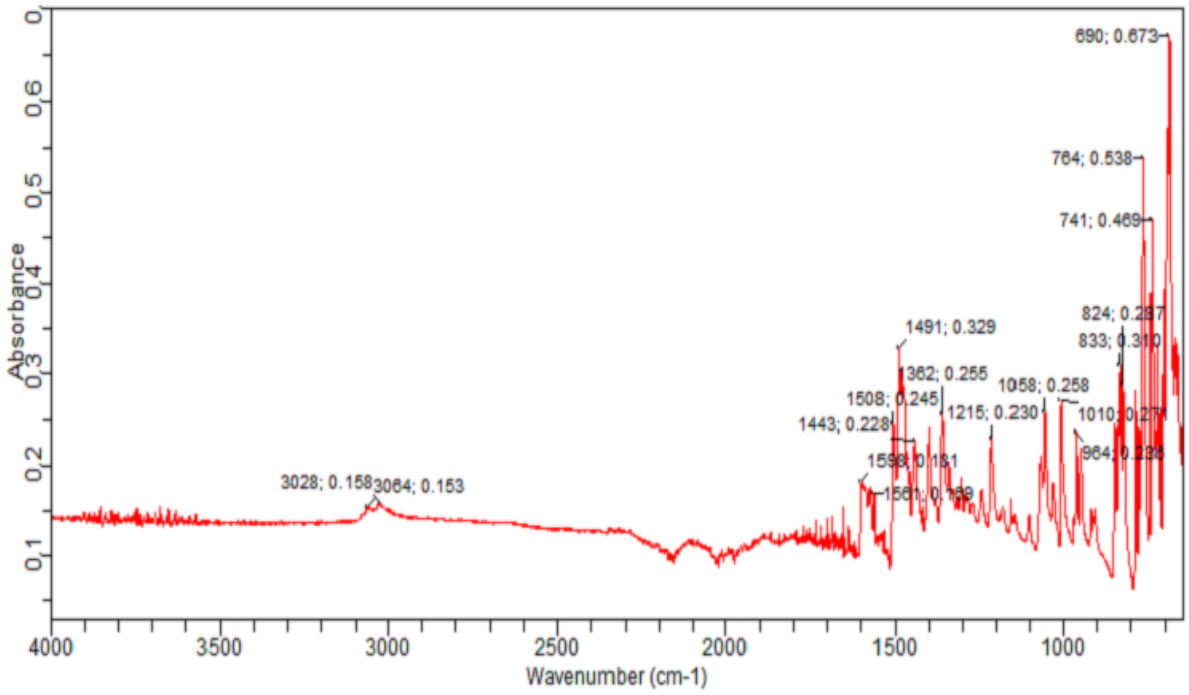


Figure-22S: FTIR Spectrum of Compound **5h**.

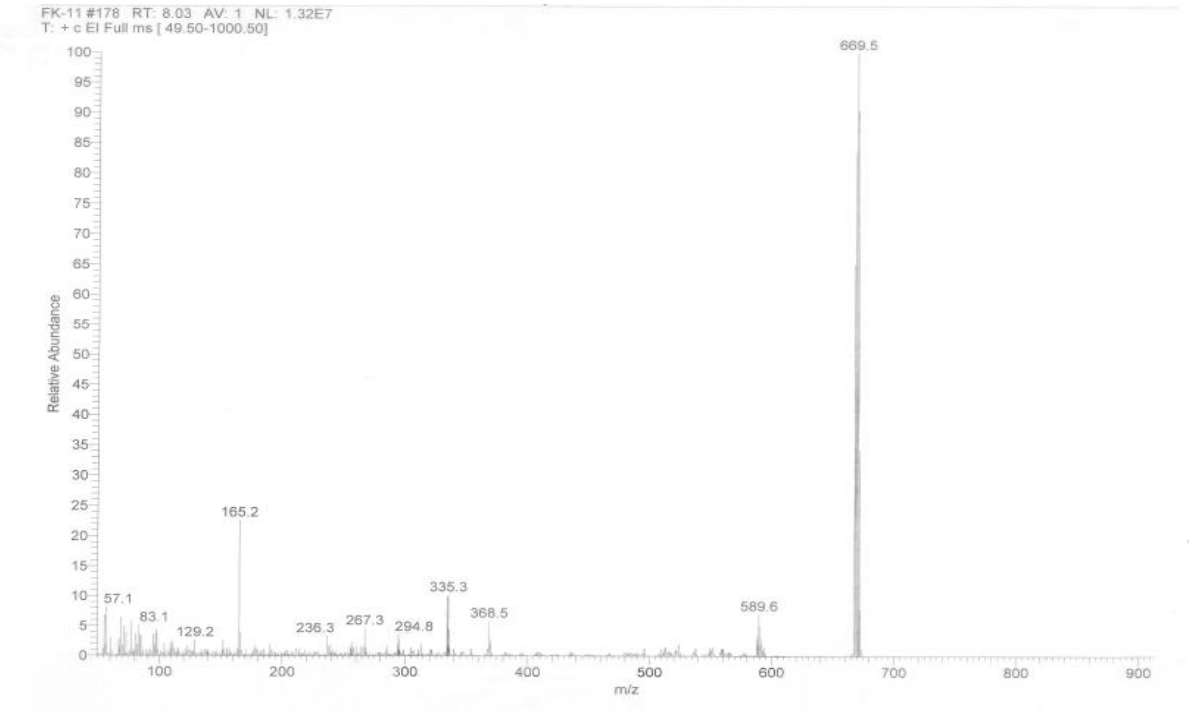


Figure-23S: EI-MS Spectrum of Compound **5h**.

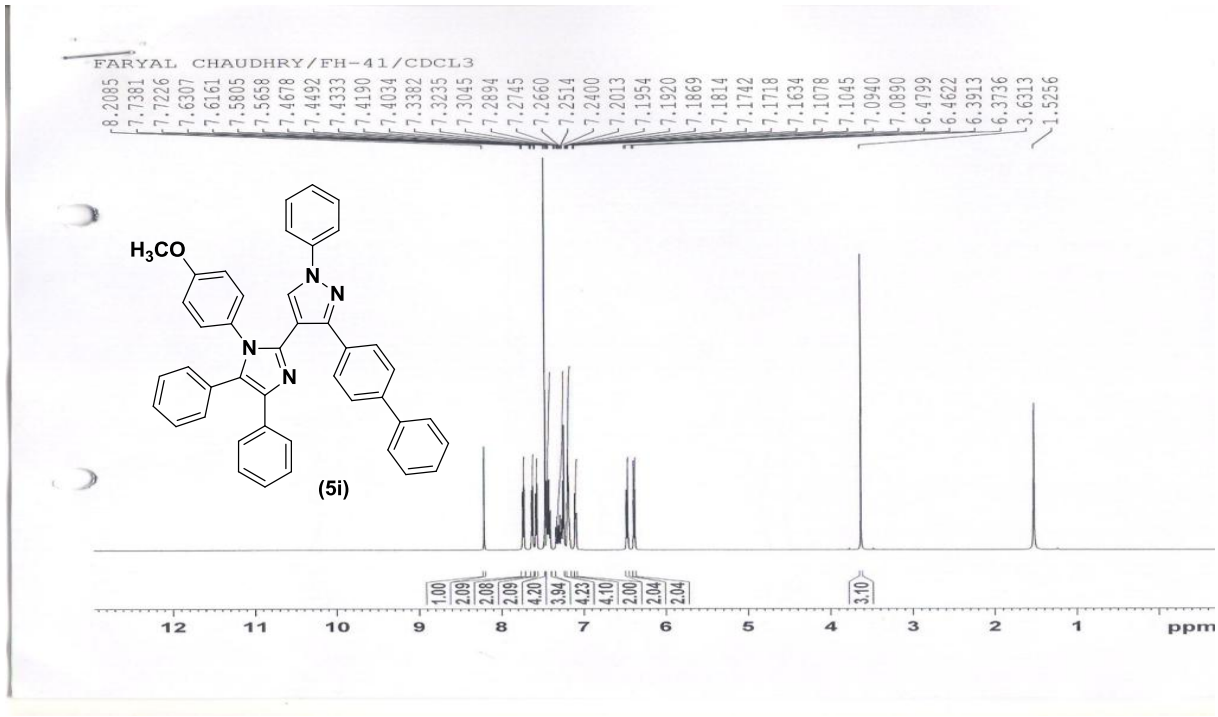


Figure-24S: ^{1}H NMR Spectrum of Compound **5i**.

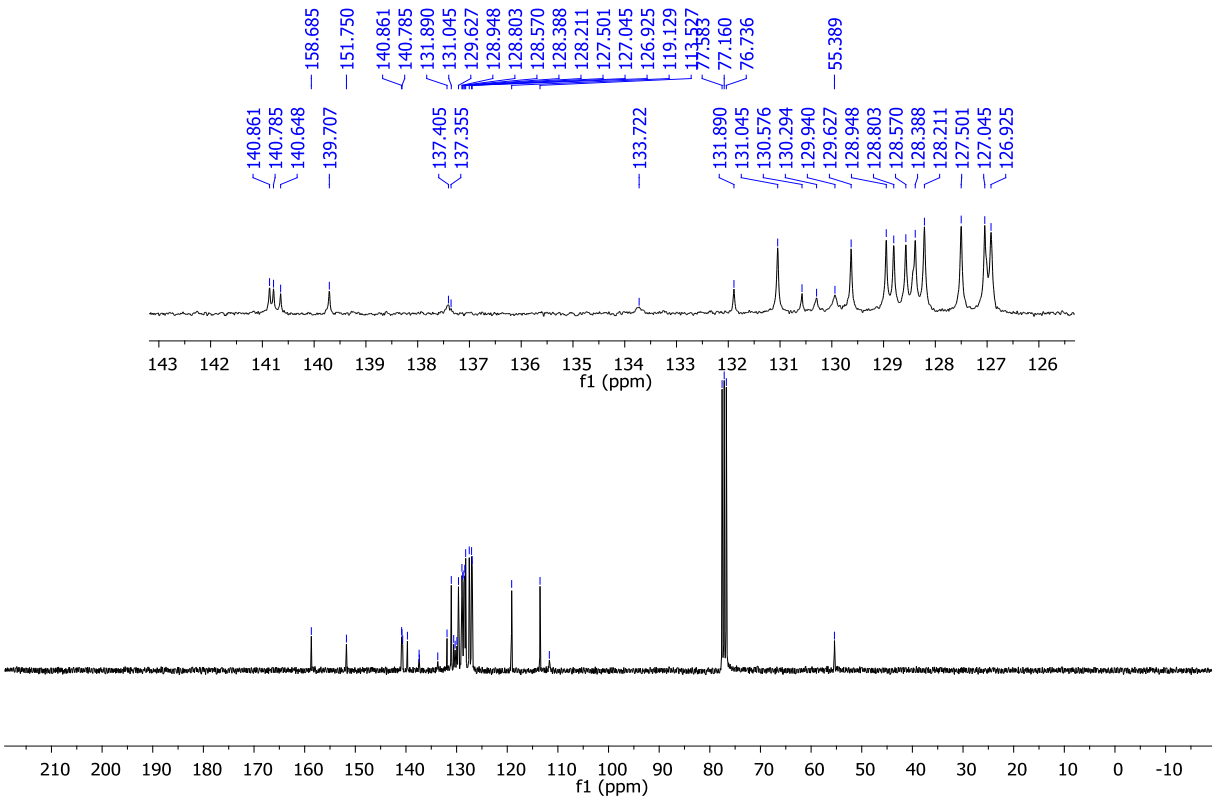


Figure-25S: ^{13}C NMR Spectrum of Compound **5i**.

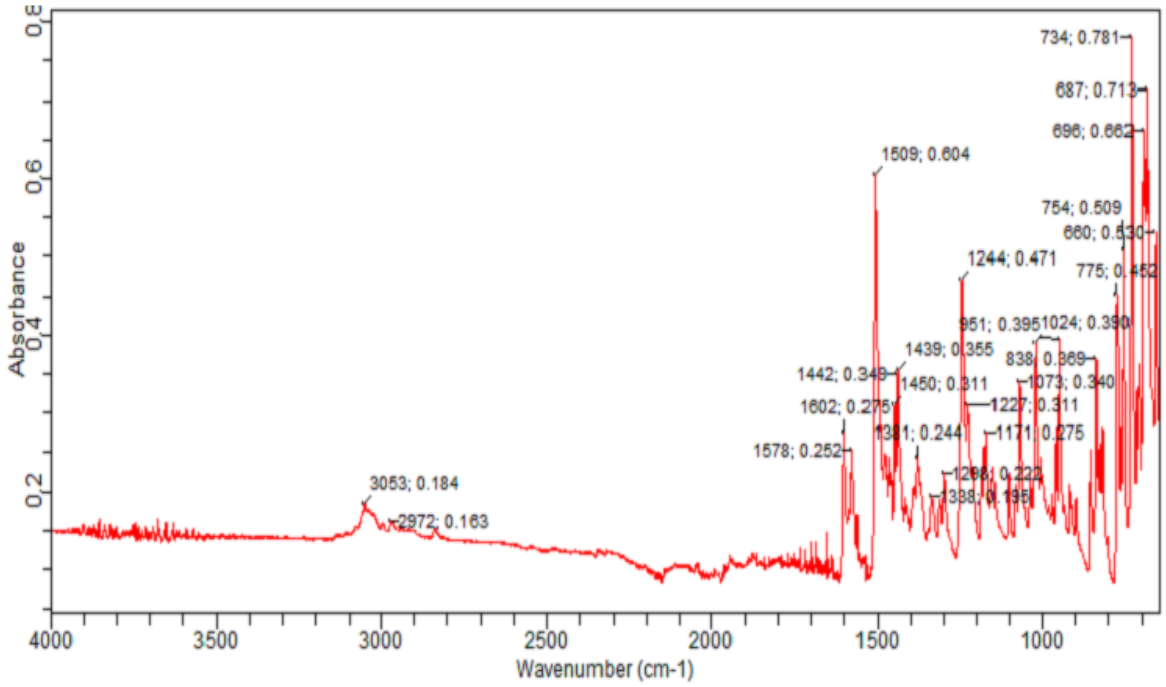


Figure-26S: FTIR Spectrum of Compound **5i**.

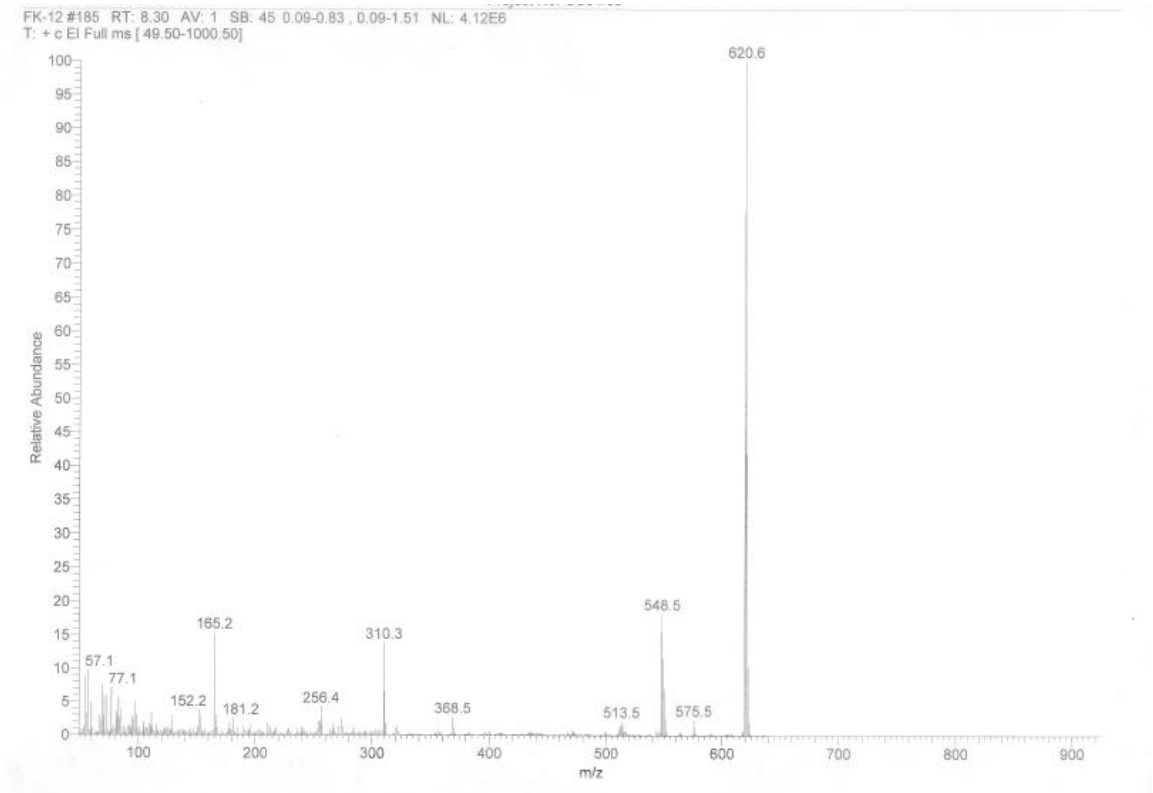


Figure-27S: EI-MS Spectrum of Compound **5i**.

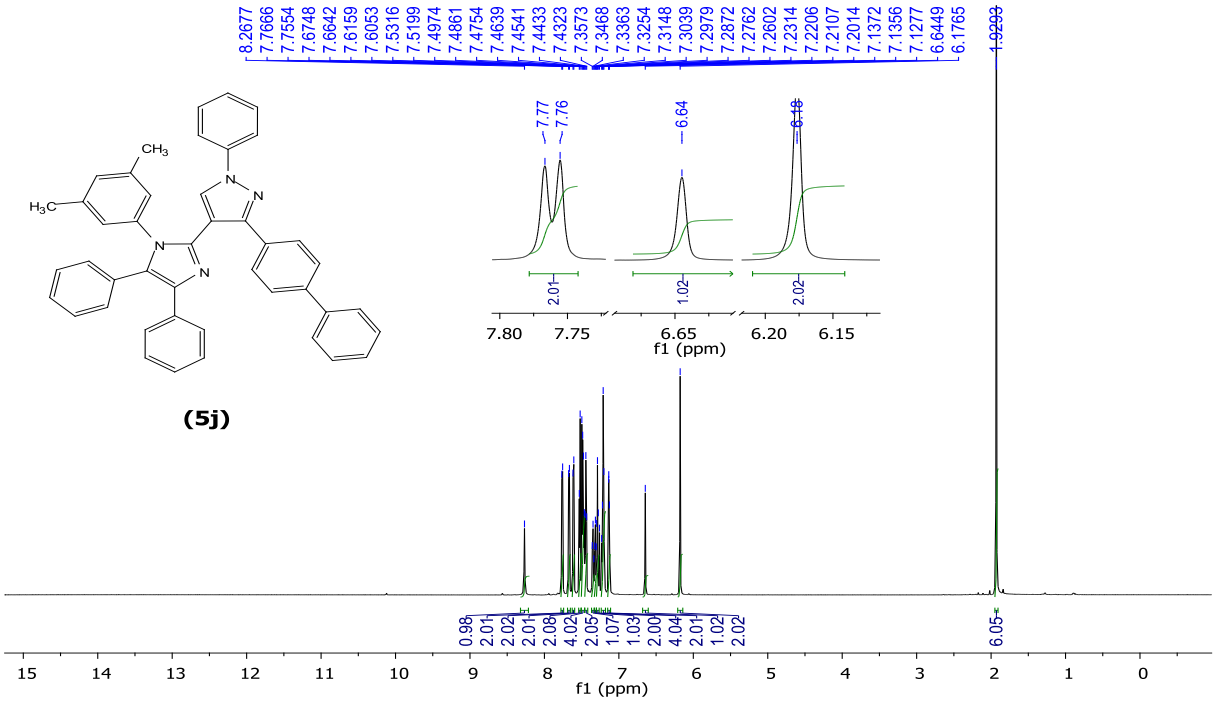


Figure-28S: ^{1}H NMR Spectrum of Compound **5j**.

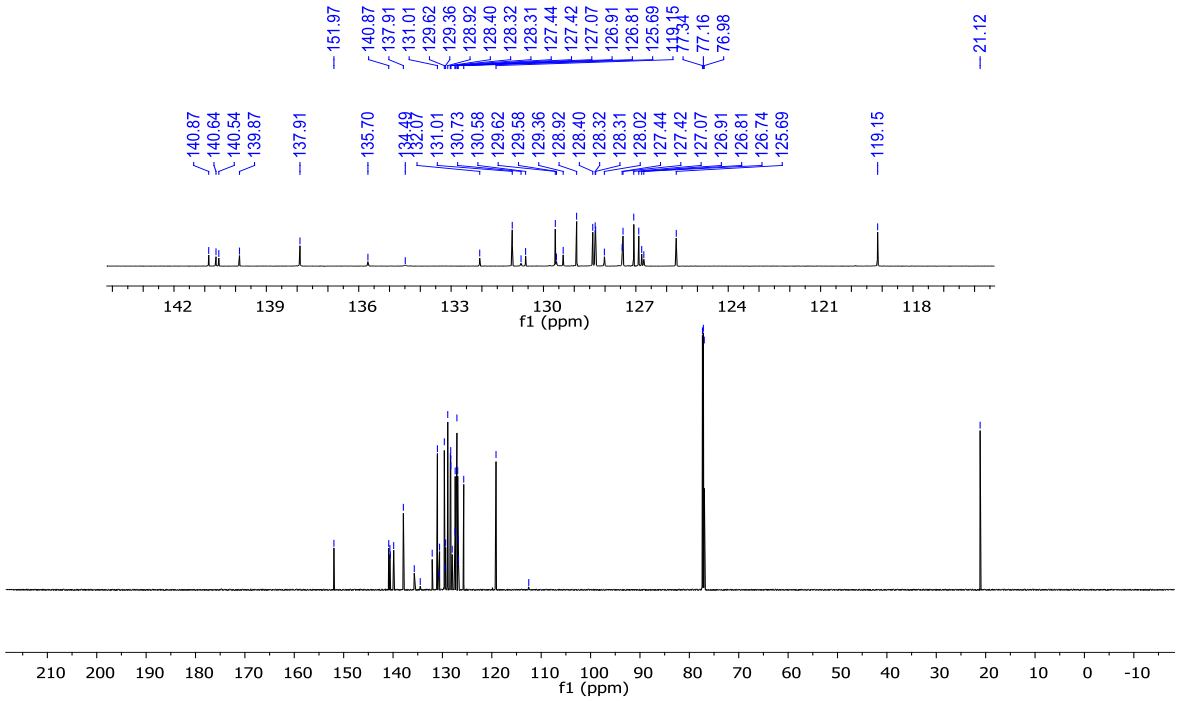


Figure-29S: ^{13}C NMR Spectrum of Compound **5j**.

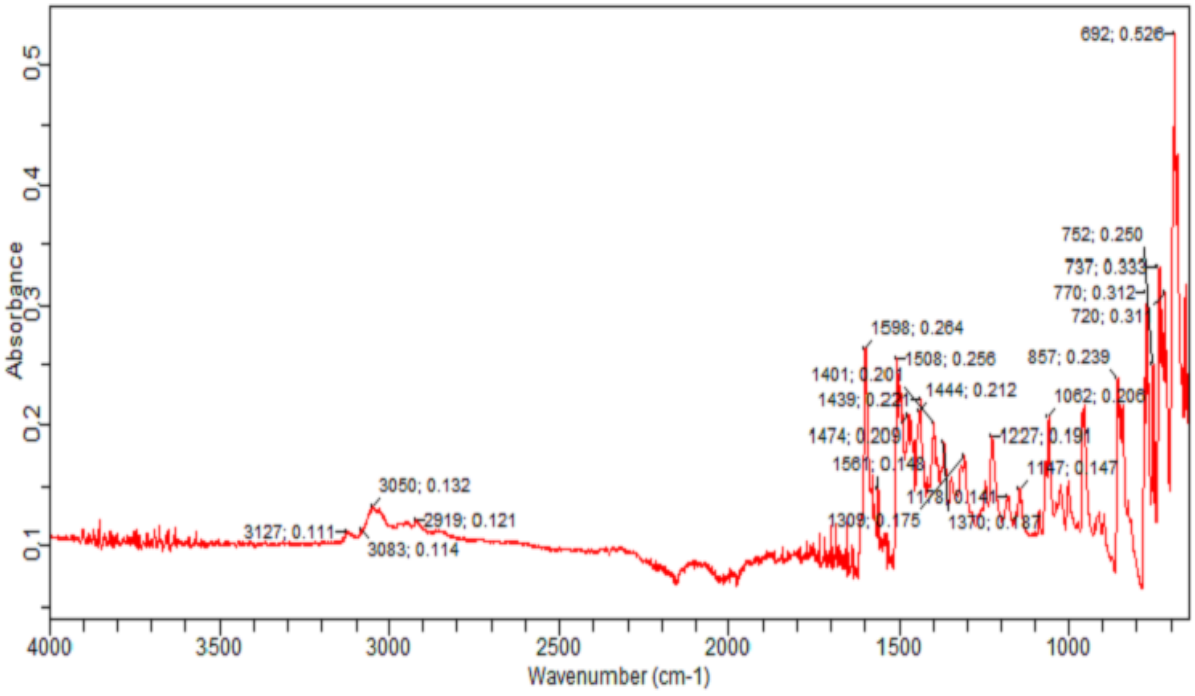


Figure-30S: FTIR Spectrum of Compound **5j**.

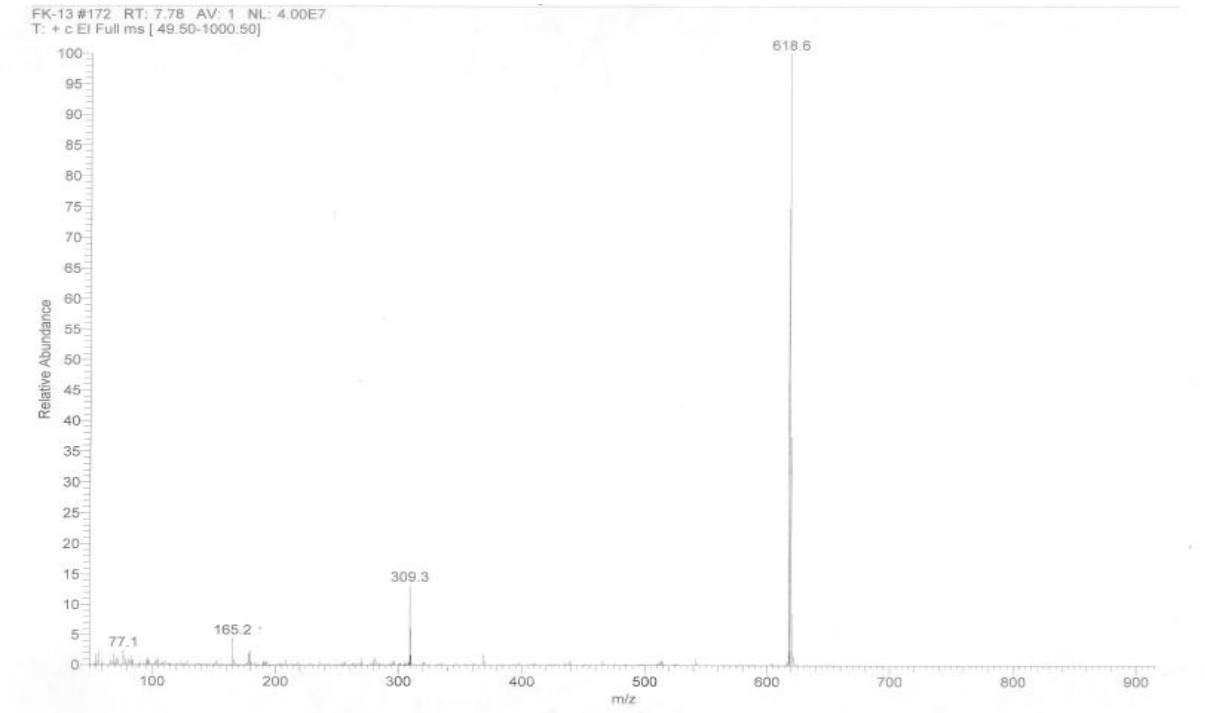


Figure-31S: EI-MS Spectrum of Compound **5j**.

2. Representative Graph for the Calculation of BChE IC_{50} Value for the Compound 5a.

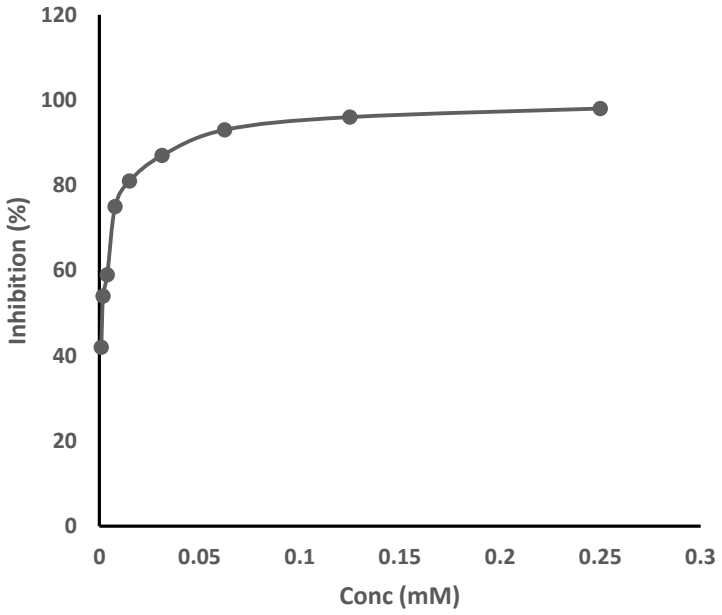
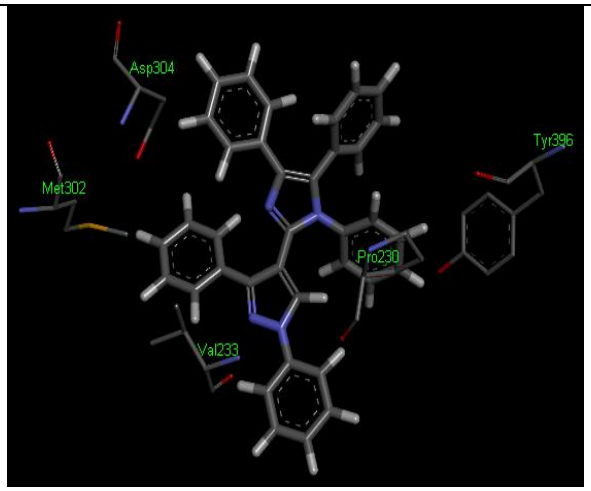
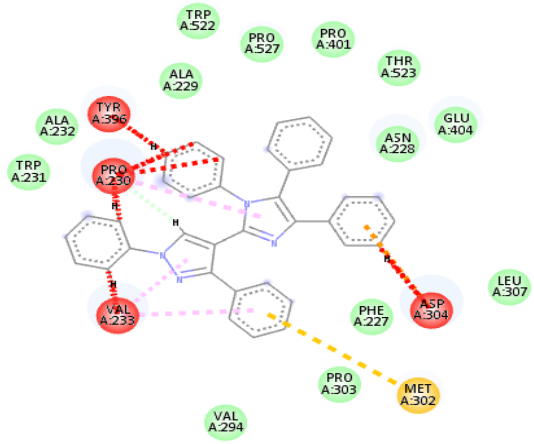
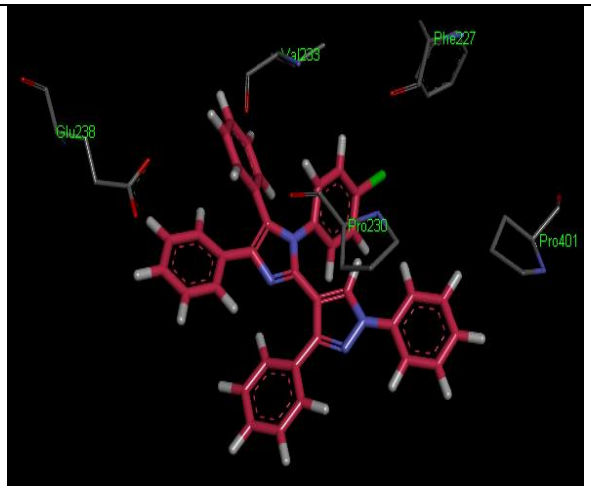
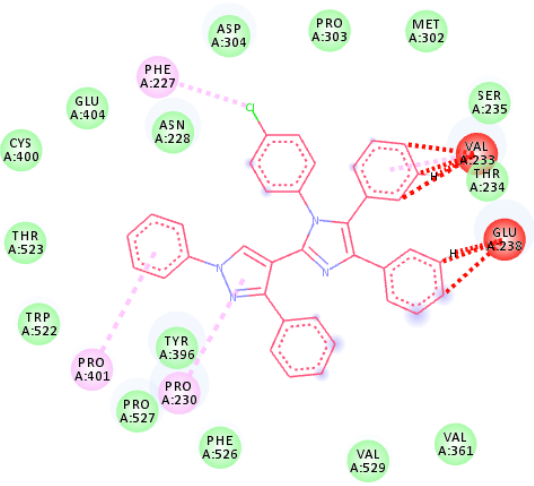
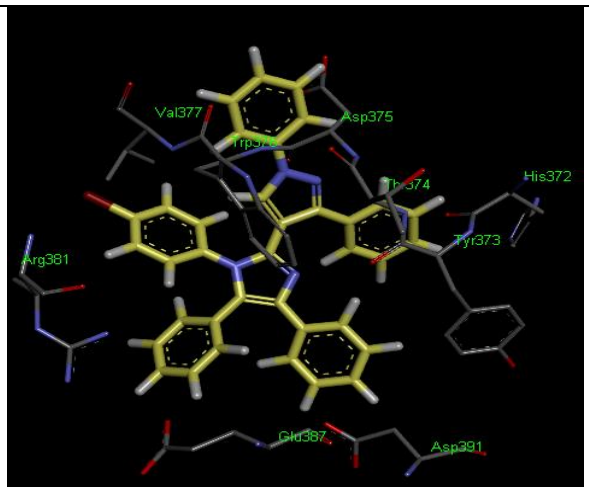
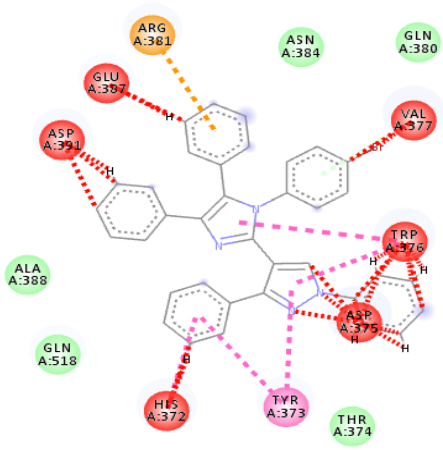
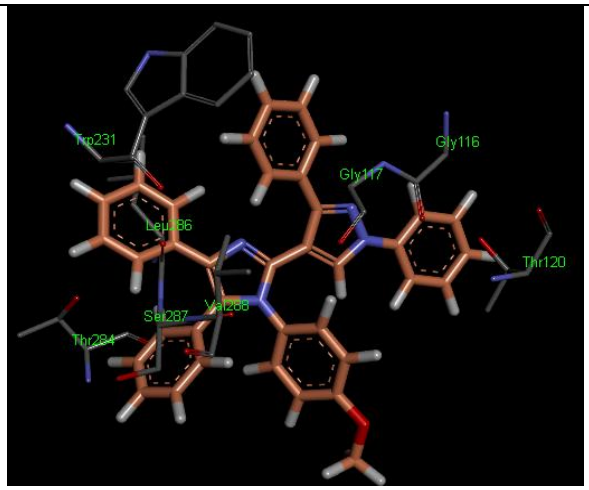
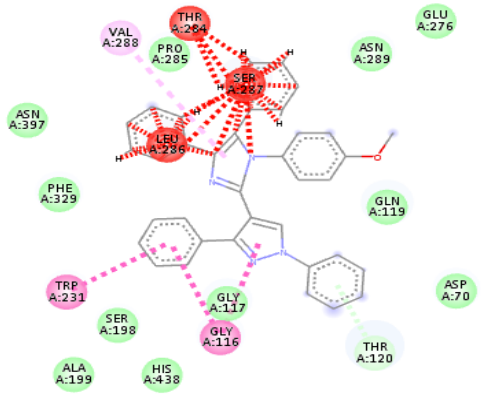
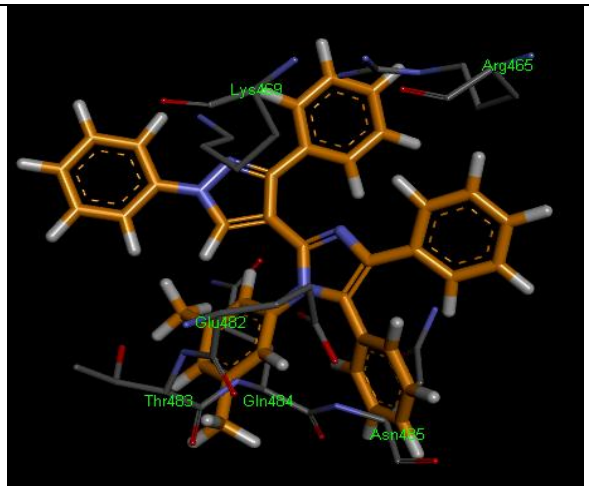
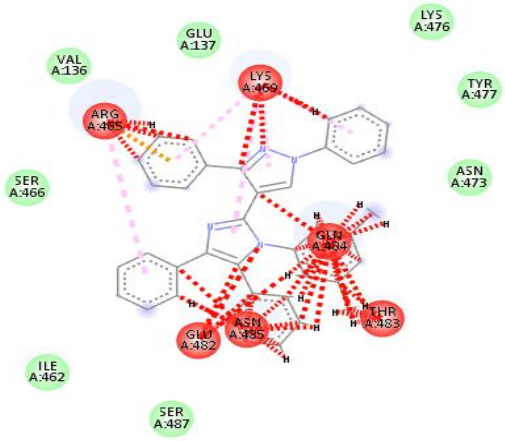


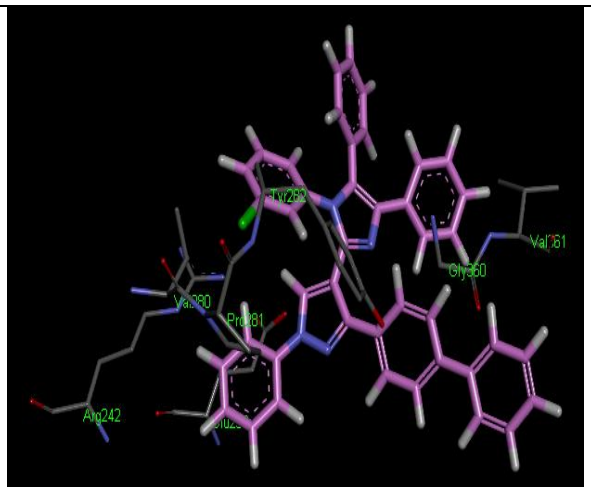
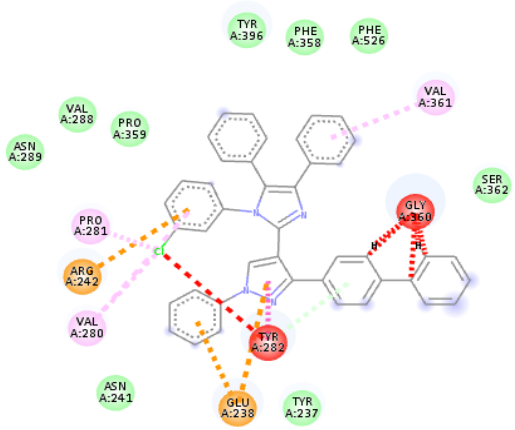
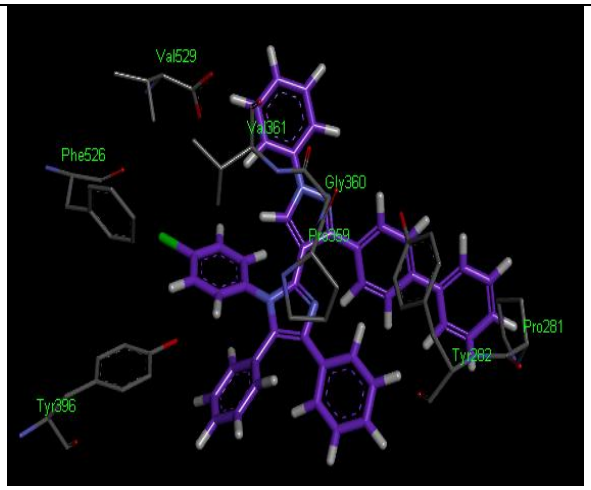
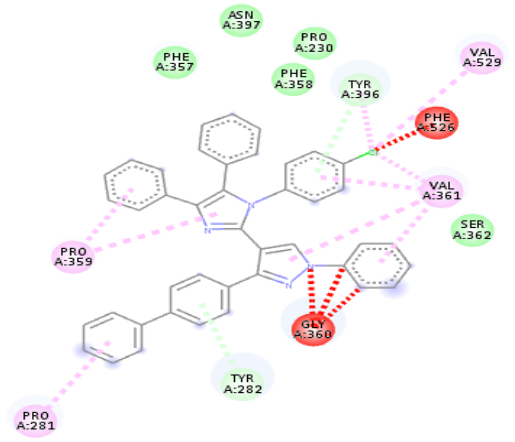
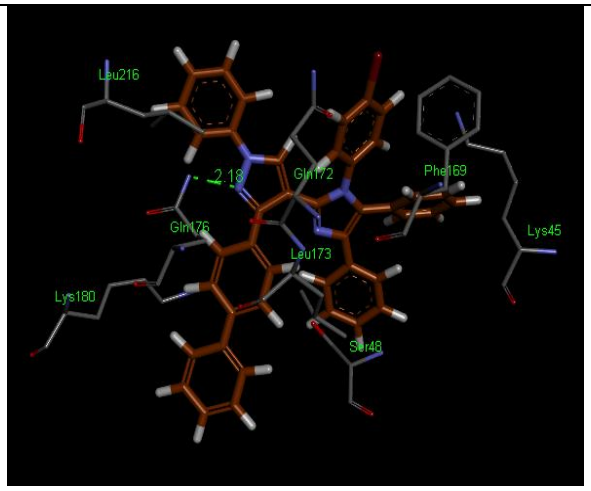
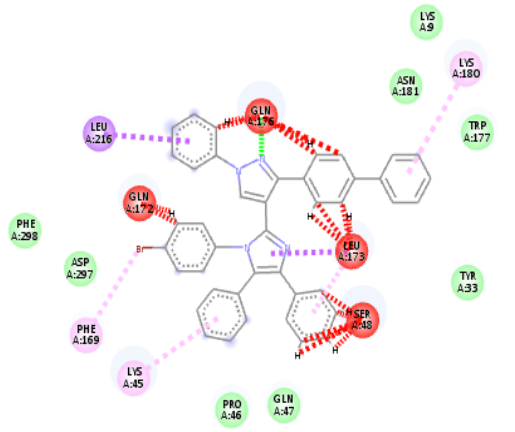
Figure-32S: A representative graph for the calculation of IC_{50} = 0.35 µM for the compound **5a**. IC_{50} value was computed by the Ez-Fit software as mentioned in the Methods section.

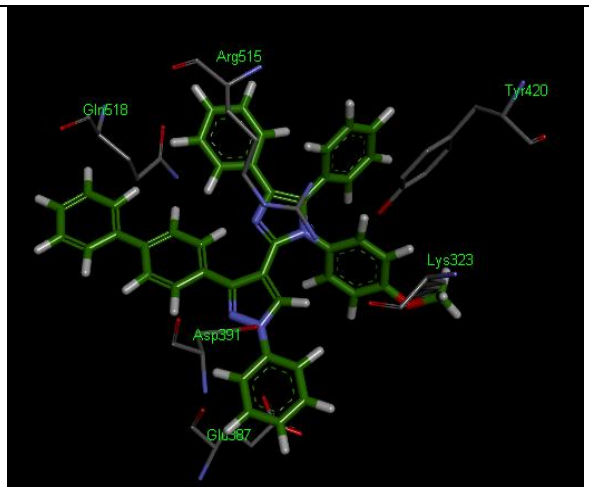
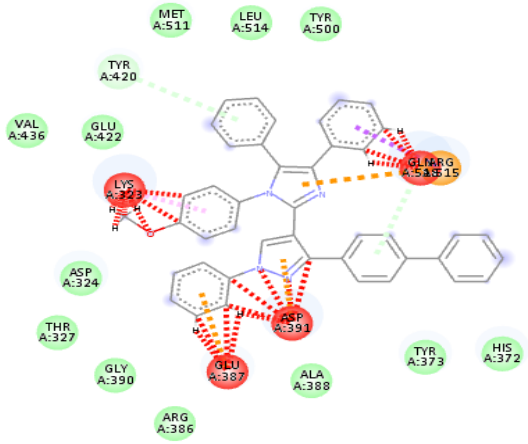
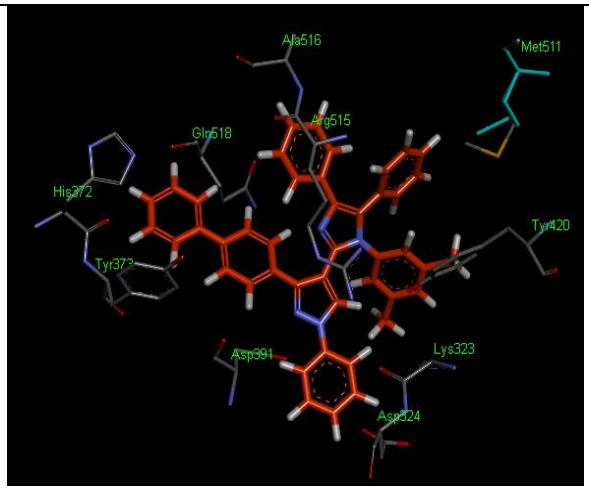
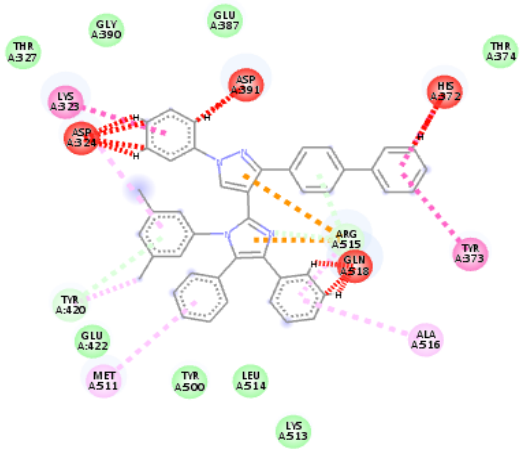
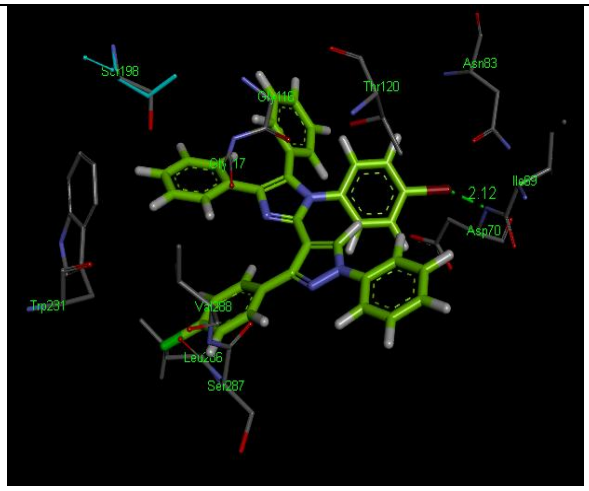
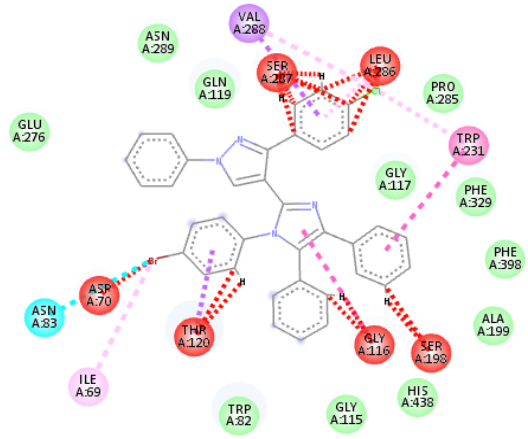
3. Representations of All Docked Ligands with Both AChE and BChE Enzymes (5a-5x).

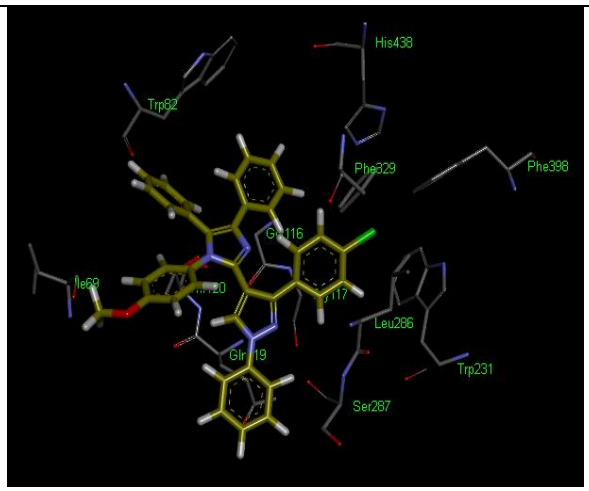
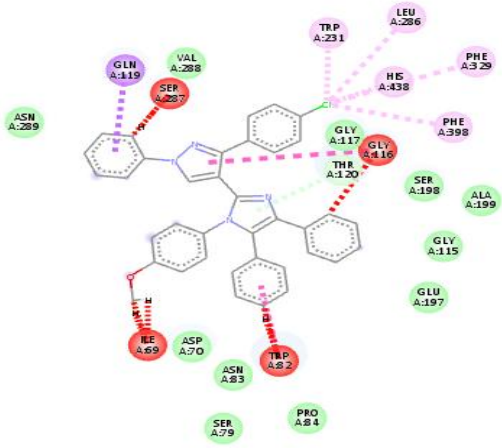
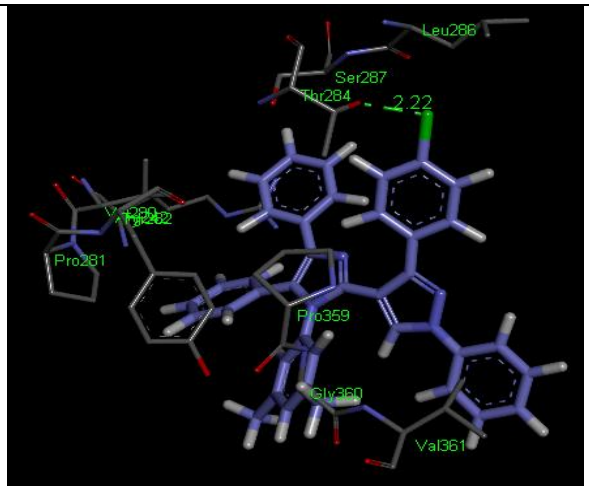
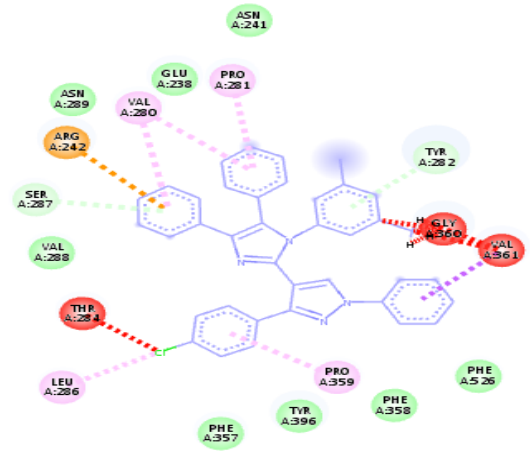
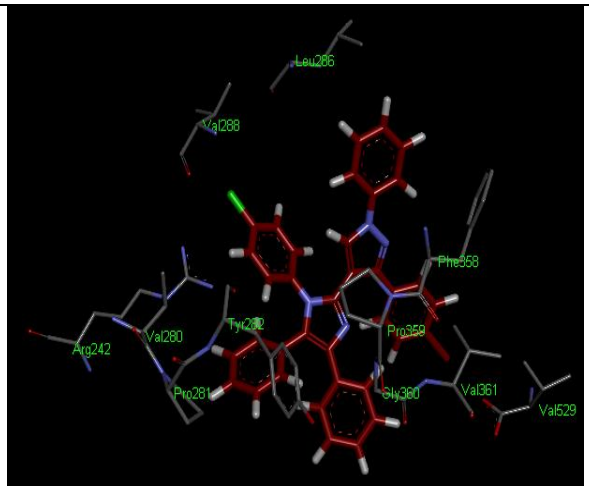
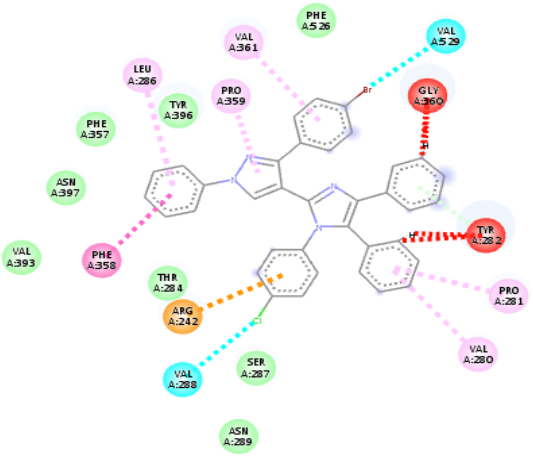
Table S1. 3D and 2D depictions of docked ligands (**5a-5x**); demonstrating H-bond (light green), unfavorable bump (red), π-cation (brown), π-alkyl (light pink), amide π-stack (pink) and π-π T-shaped (shocking pink) contacts inside a hotspot of the AChE (PDB ID: 4M0E).

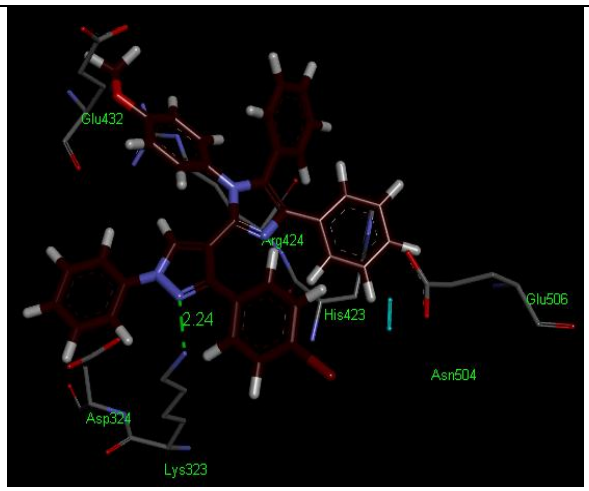
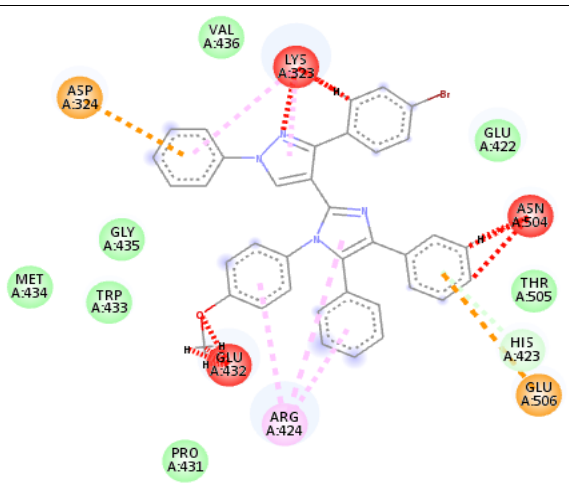
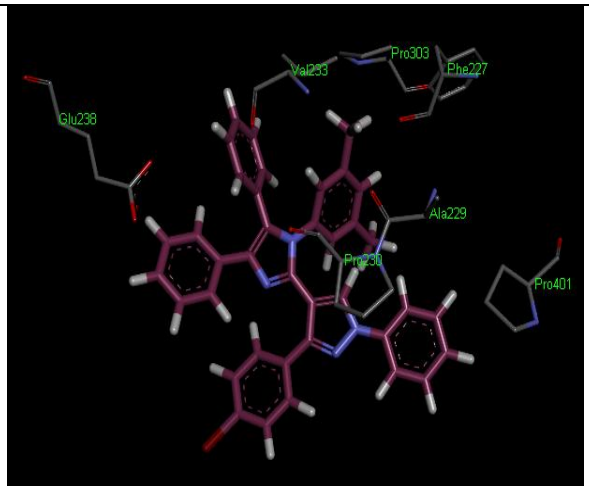
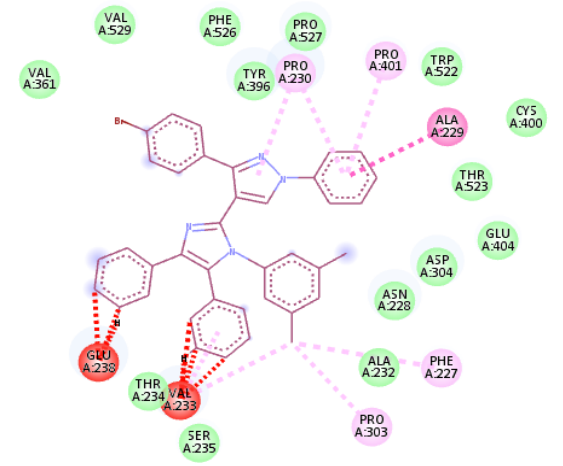
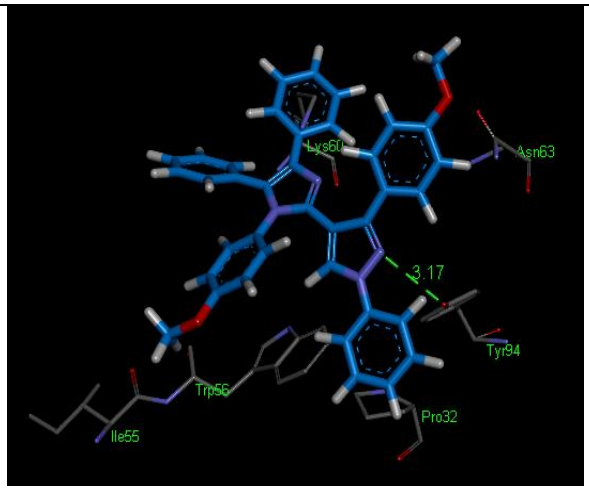
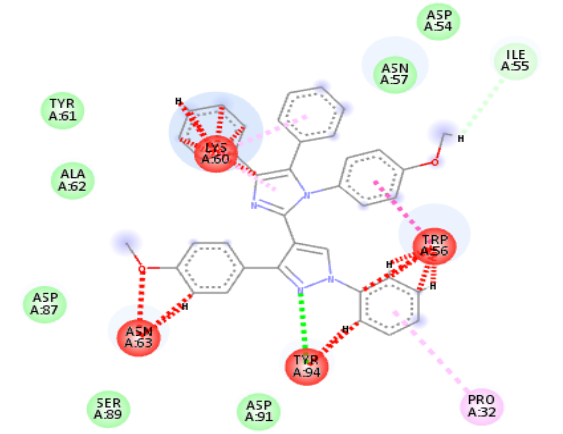
Compound	3D Binding Interaction Representation	2D Binding Interaction Representation
5a		
5b		

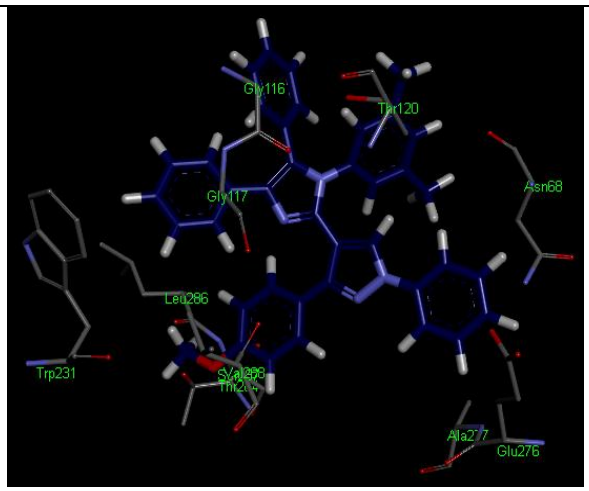
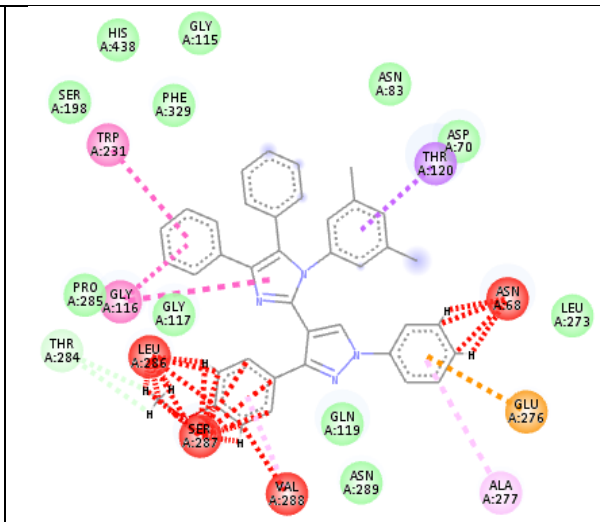
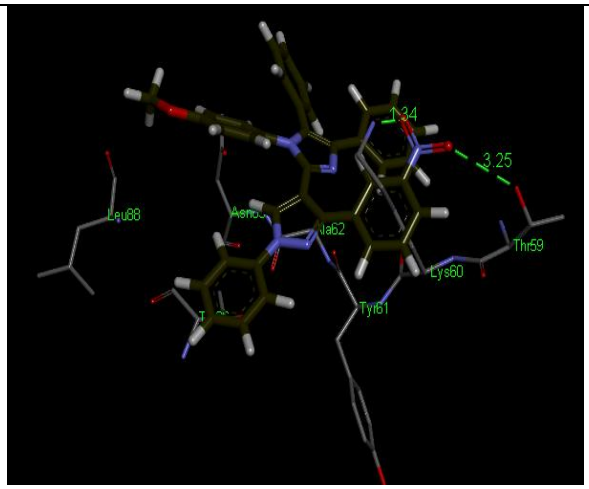
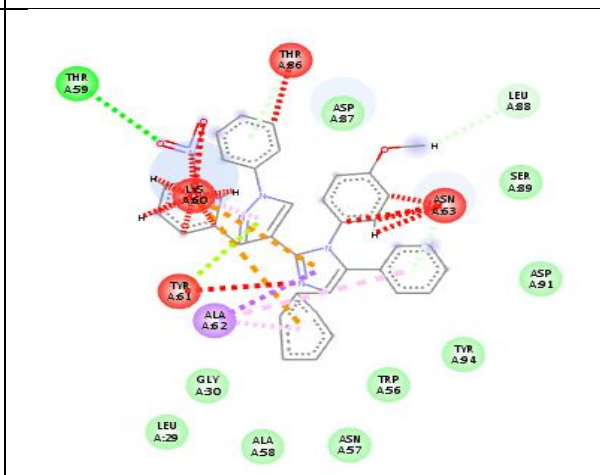
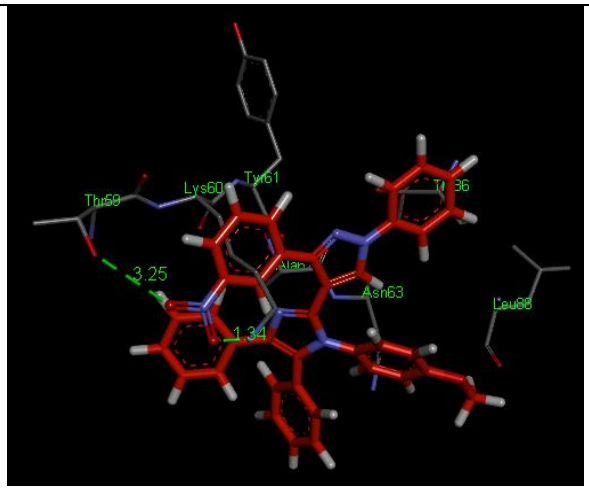
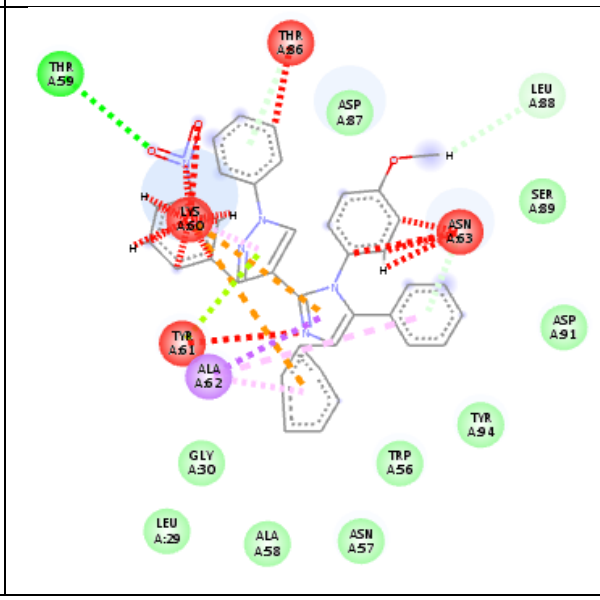
5c	 Val377 Asp375 His372 Tyr373 Arg381 Glu387 Asp391	 ARG A:381 ASN A:384 GLN A:380 GLU A:387 VAL A:377 ASP A:391 TRP A:376 ALA A:388 ASP A:375 GLN A:518 HIS A:372 TYR A:373 THR A:374
5d	 Trp231 Gly116 Gly117 Leu286 Thr120 Ser287 Val288 Thr284	 THR A:284 GLU A:276 VAL A:288 PRO A:285 ASN A:289 SER A:287 ASN A:397 LEU A:286 PHE A:329 GLN A:119 TRP A:231 GLY A:117 ASP A:70 SER A:198 GLY A:116 THR A:120 ALA A:199 HIS A:438
5e	 Arg465 Lys469 Glu482 Thr483 Gln484 Asn485	 LYS A:476 GLU A:137 VAL A:136 LYS A:469 TYR A:477 ARG A:465 SER A:466 ASN A:473 GLN A:484 THR A:483 ASN A:485 GLU A:482 ILE A:462 SER A:487

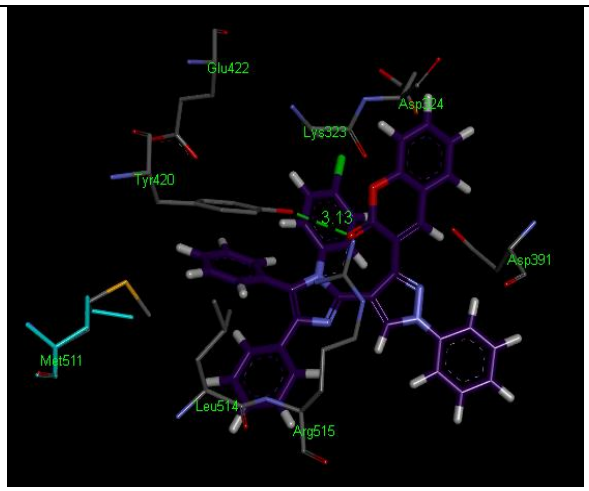
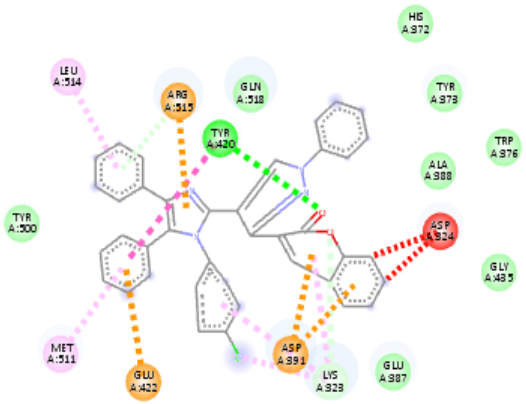
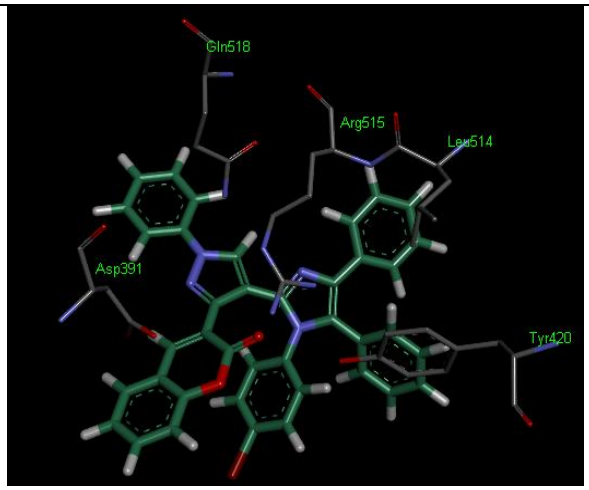
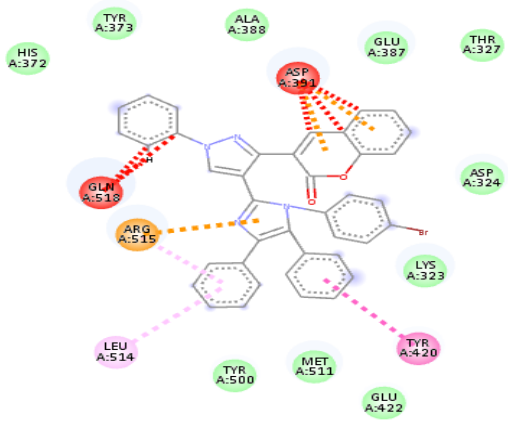
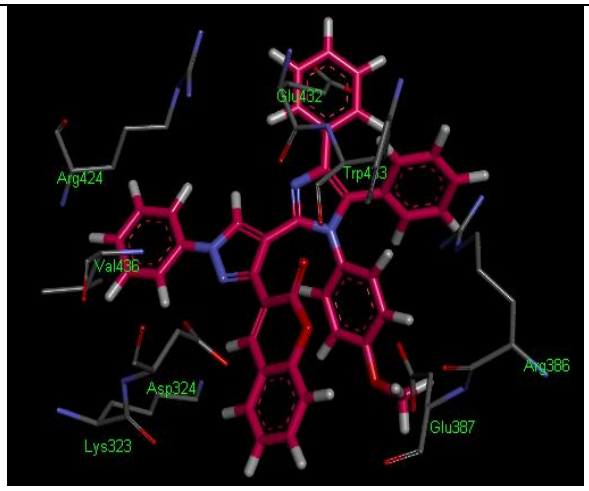
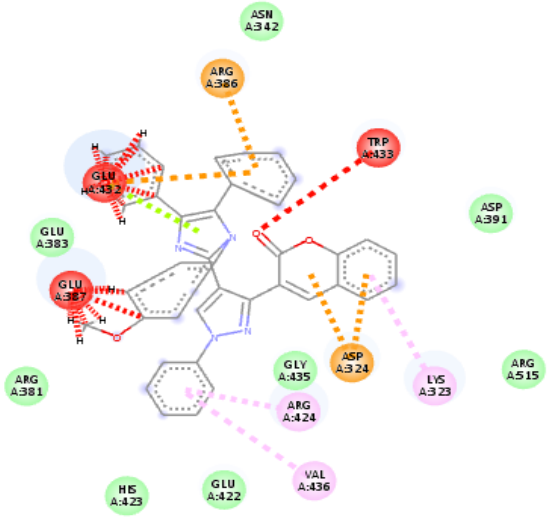
5f	 Tyr282 Val361 Gly360 Val290 Pro281 Arg242	 TYR A:396 PHE A:358 PHE A:526 VAL A:361 VAL A:288 PRO A:359 ASN A:289 SER A:362 GLY A:360 PRO A:281 ARG A:242 VAL A:280 TYR A:282 ASN A:241 GLU A:238 TYR A:237
5g	 Val529 Val361 Phe526 Gly360 Pro359 Pro281 Tyr282 Tyr396	 ASN A:397 PRO A:230 PHE A:357 VAL A:529 PHE A:358 TYR A:396 PHE A:526 VAL A:361 SER A:362 PRO A:359 GLY A:360 TYR A:282 PRO A:281
5h	 Leu216 2.18 Gln172 Phe169 Gln176 Lys45 Leu173 Lys180 Ser48	 LYS A:9 LYS A:180 ASN A:181 LEU A:216 GLN A:176 TRP A:177 GLN A:172 PHE A:298 LEU A:173 ASP A:297 TYR A:33 SER A:48 PHE A:169 LYS A:45 PRO A:46 GLN A:47

5i	 Arg515 Gln518 Tyr420 Lys323 Asp391 Glu387	 MET A:511 LEU A:514 TYR A:500 TYR A:420 VAL A:436 GLU A:422 LYS A:323 ASP A:324 THR A:327 ASP A:391 GLY A:390 GLU A:387 ALA A:388 ARG A:386 TYR A:373 HIS A:372
5j	 Ala516 Met511 Gln518 Arg515 His372 Tyr420 Tyr373 Asp391 Lys323 Asp324	 GLY A:390 GLU A:387 THR A:327 THR A:374 ASP A:391 LYS A:323 HIS A:372 ASP A:324 ARG A:515 GLN A:518 TYR A:373 TYR A:420 GLU A:422 ALA A:516 MET A:511 TYR A:500 LEU A:514 LYS A:513
5k	 Ser198 Asn83 Thr120 2.12 Ile69 Asp70 Trp231 Val288 Leu286 Ser287	 VAL A:288 ASN A:289 SER A:287 LEU A:286 GLN A:119 PRO A:285 GLU A:276 TRP A:231 GLY A:117 PHE A:329 PHE A:398 ASP A:70 ASN A:83 THR A:120 GLY A:116 SER A:198 ALA A:199 ILE A:69 HIS A:438 TRP A:82 GLY A:115

5l	 His438 Trp82 Phe329 Phe398 Gly116 Ile69 Thr120 Gly117 Leu286 Gln119 Trp231 Ser287	 LEU A:286 TRP A:231 GLN A:119 VAL A:288 PHE A:329 SER A:287 HIS A:438 ASN A:289 PHE A:398 GLY A:117 GLY A:116 THR A:120 SER A:198 ALA A:199 GLY A:115 GLU A:197 ILE A:69 ASP A:70 TRP A:82 ASN A:83 PRO A:84 SER A:79
5m	 Leu286 Ser287 Thr284 2.22 Pro281 Pro359 Gly360 Val361	 ASN A:241 GLU A:238 PRO A:281 ASN A:289 VAL A:280 ARG A:242 TYR A:282 SER A:287 GLY A:360 VAL A:361 VAL A:288 THR A:284 LEU A:286 PRO A:359 PHE A:526 PHE A:358 TYR A:396 PHE A:357
5n	 Leu286 Val288 Phe358 Tyr282 Arg242 Val280 Pro359 Pro281 Gly360 Val361 Val529	 PHE A:526 VAL A:361 VAL A:529 LEU A:286 PRO A:359 GLY A:360 TYR A:396 PHE A:357 ASN A:397 TYR A:282 VAL A:393 PHE A:358 THR A:284 PRO A:281 ARG A:242 VAL A:280 VAL A:288 SER A:287 ASN A:289

5o	 Glu432 Arg424 2.24 His423 Glu506 Asn504 Asp324 Lys323	 VAL A:436 LYS A:323 ASP A:324 GLU A:422 ASN A:504 GLY A:435 MET A:434 TRP A:433 THR A:505 HIS A:423 GLU A:432 GLU A:506 ARG A:424 PRO A:431
5p	 Pro303 Val233 Phe227 Glu238 Ala229 Pro230 Pro401	 VAL A:529 PHE A:526 PRO A:527 PRO A:401 TRP A:522 VAL A:361 TYR A:396 PRO A:230 CYS A:400 ALA A:229 THR A:523 GLU A:404 ASP A:304 ASN A:228 GLU A:238 ALA A:232 PHE A:227 THR A:234 VAL A:233 PRO A:303 SER A:235
5q	 Lys60 Asn63 3.17 Tyr94 Trp56 Pro32 Ile55	 ASP A:54 ILE A:55 ASN A:57 TYR A:61 LYS A:60 ALA A:62 TRP A:56 ASP A:87 ASN A:53 TYR A:94 SER A:89 ASP A:91 PRO A:32

5r	 Gly116 Thr120 Gly117 Asn68 Leu286 Trp231 Ala277 Glu276	 HIS A:438 GLY A:115 ASN A:83 SER A:198 PHE A:329 TRP A:231 ASP A:70 THR A:120 PRO A:285 GLY A:116 GLY A:117 ASN A:68 LEU A:273 THR A:284 LEU A:286 GLU A:276 GLN A:119 SER A:287 VAL A:288 ASN A:289 ALA A:277
5s	 1.34 3.25 Leu88 Asn63 Ala62 Thr59 Lys60 Tyr61	 THR A:86 THR A:59 ASP A:87 LEU A:88 SER A:89 LYS A:60 ASN A:63 TYR A:61 ASP A:91 ALA A:62 TYR A:94 GLY A:30 TRP A:56 LEU A:29 ALA A:58 ASN A:57
5t	 Thr59 Lys60 Tyr61 3.25 Asn63 Leu88 1.34	 THR A:86 THR A:59 ASP A:87 LEU A:88 SER A:89 LYS A:60 ASN A:63 TYR A:61 ASP A:91 ALA A:62 TYR A:94 GLY A:30 TRP A:56 LEU A:29 ALA A:58 ASN A:57

5u	 Glu422 Asp324 Lys323 Tyr420 3.13 Asp391 Met511 Leu514 Arg515	 HIS A:372 LEU A:514 ARG A:515 GLN A:518 TYR A:373 TYR A:420 TRP A:376 ALA A:388 TYR A:500 ASP A:324 GLY A:435 MET A:511 ASP A:391 LYS A:323 GLU A:387 GLU A:422
5v	 Gln518 Arg515 Leu514 Asp391 Tyr420	 TYR A:373 ALA A:388 HIS A:372 GLU A:387 THR A:327 ASP A:391 GLN A:518 ASP A:324 ARG A:515 LYS A:323 LEU A:514 TYR A:420 TYR A:500 MET A:511 GLU A:422
5w	 Glu432 Arg424 Trp433 Val436 Arg386 Asp324 Glu387 Lys323	 ASN A:342 ARG A:386 TRP A:433 GLU A:432 ASP A:391 GLU A:383 GLU A:387 ASP A:324 GLY A:435 ARG A:515 LYS A:323 ARG A:381 ARG A:424 VAL A:436 HIS A:423 GLU A:422

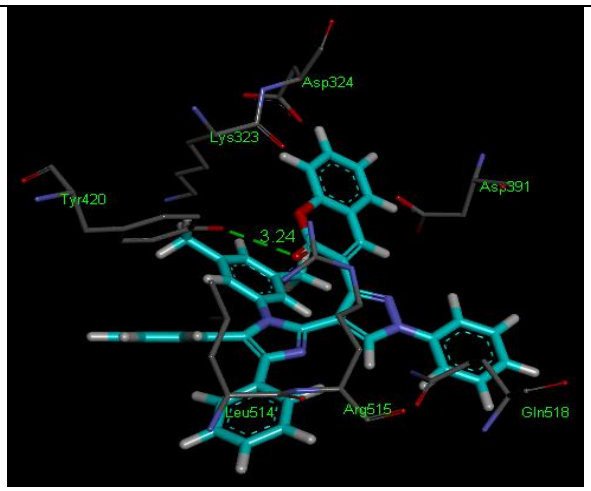
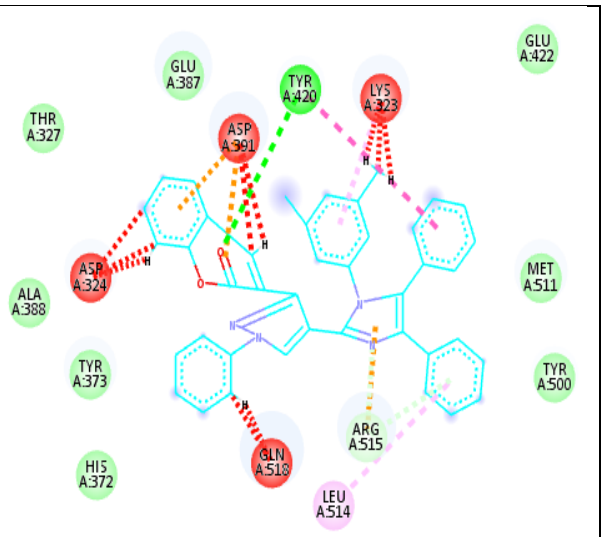
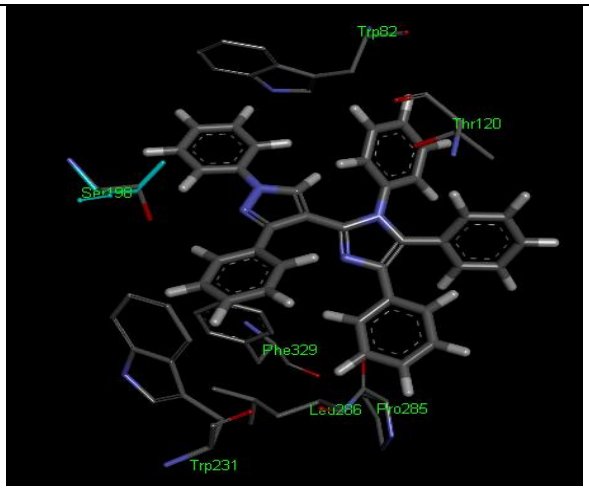
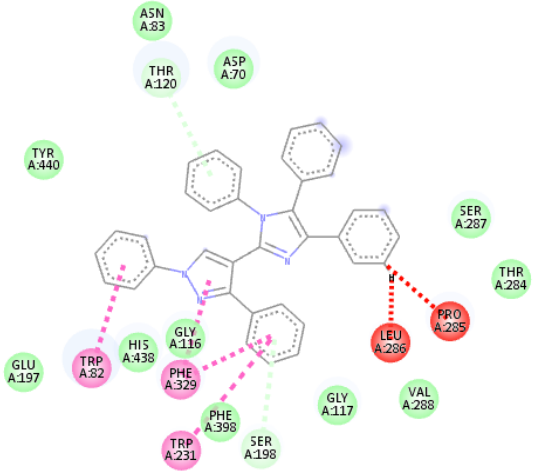
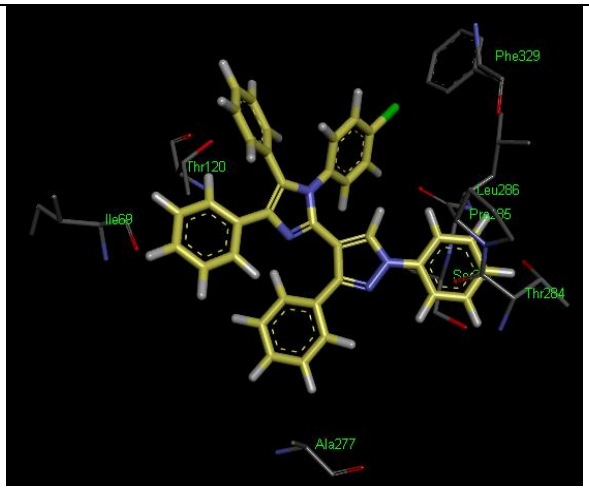
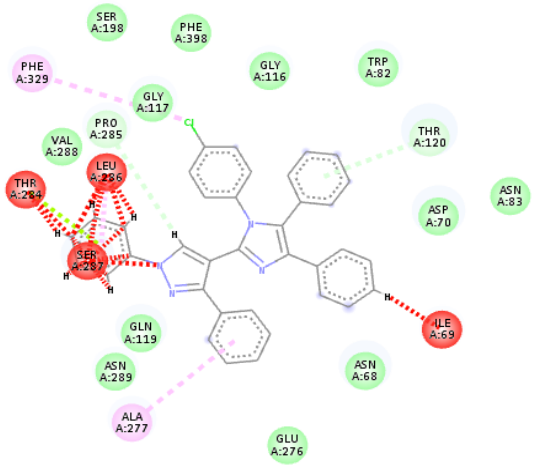
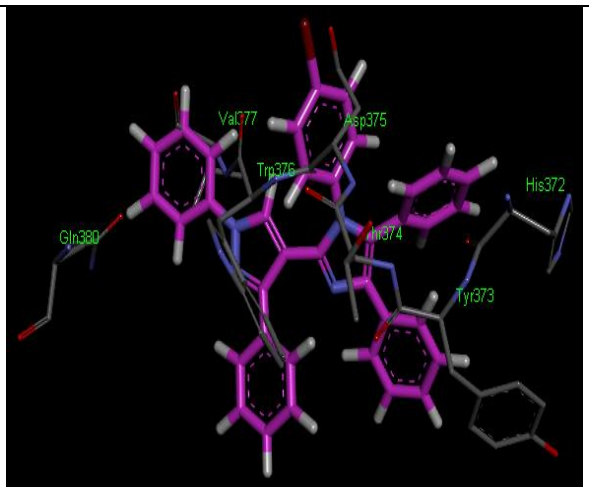
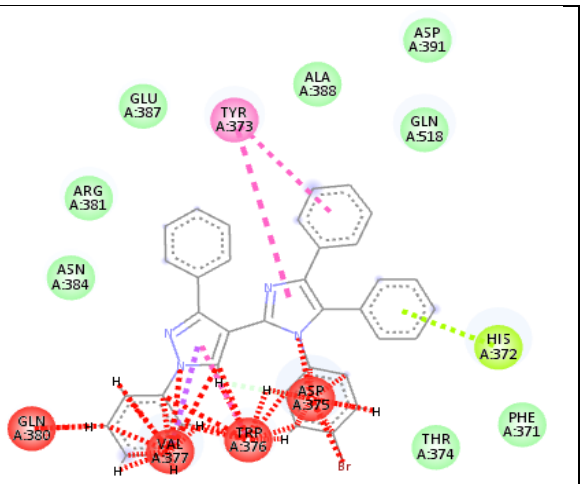
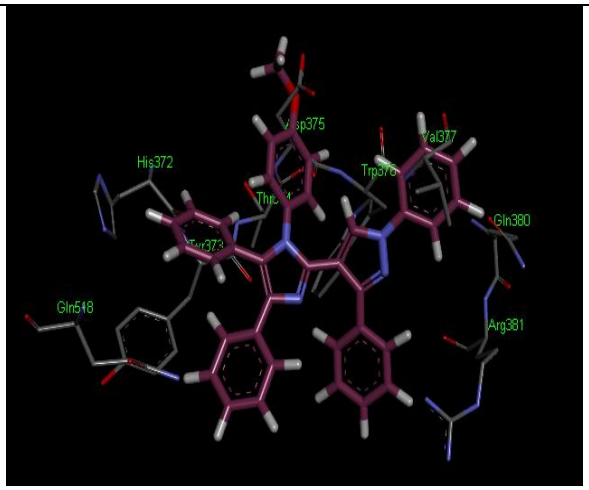
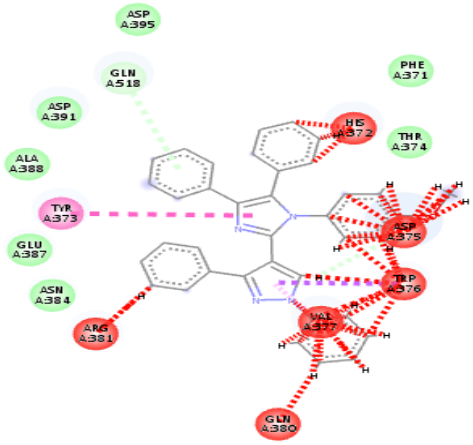
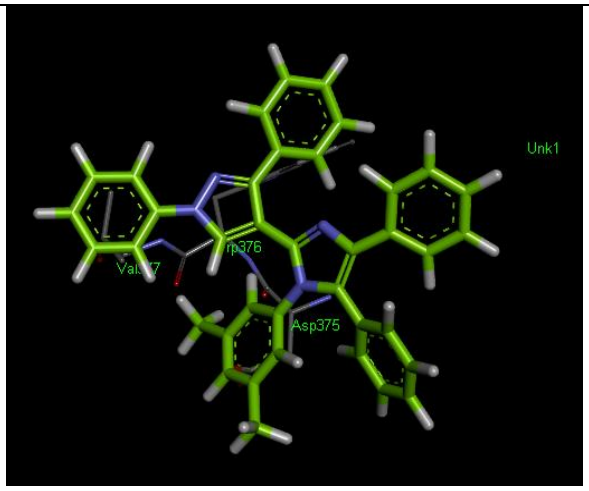
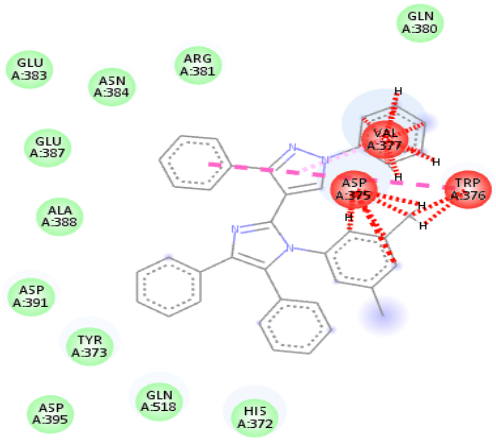
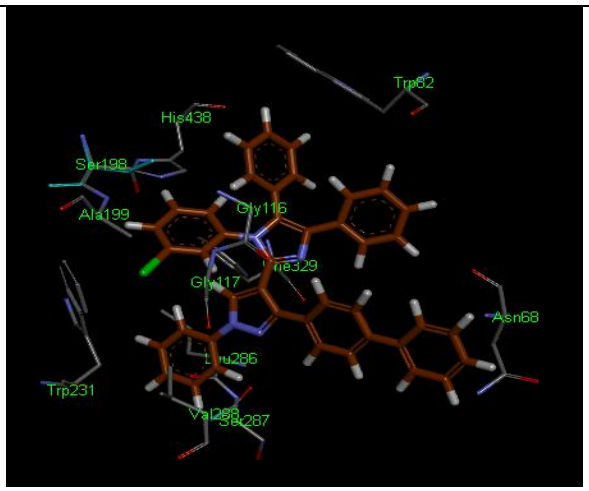
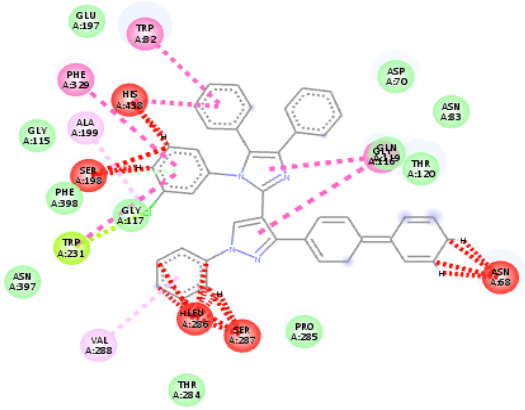
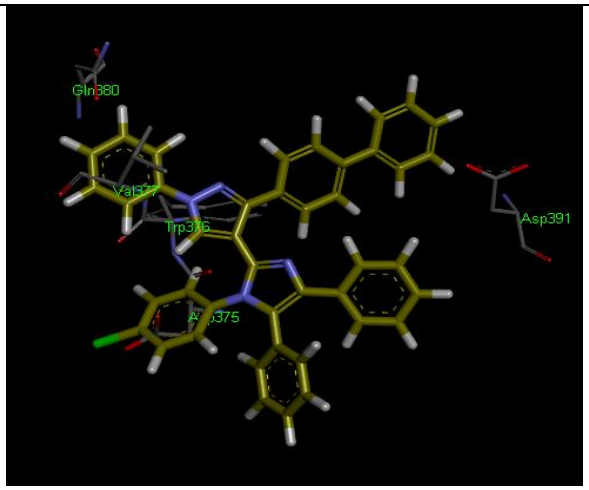
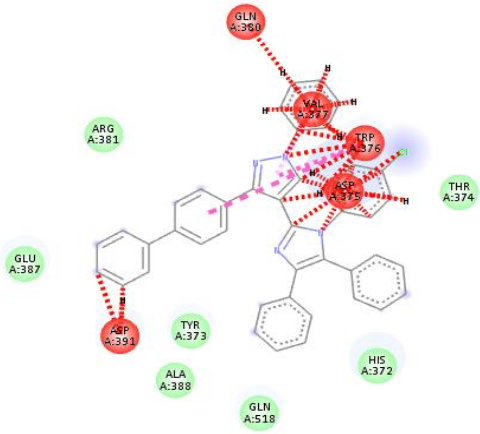
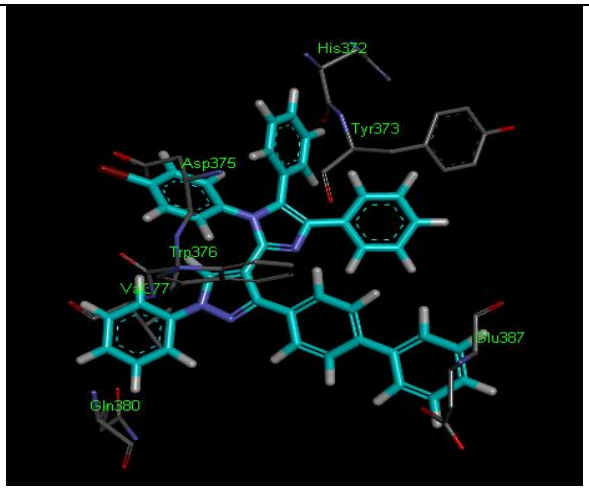
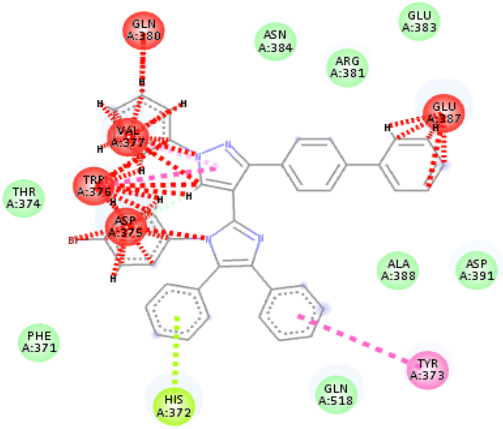
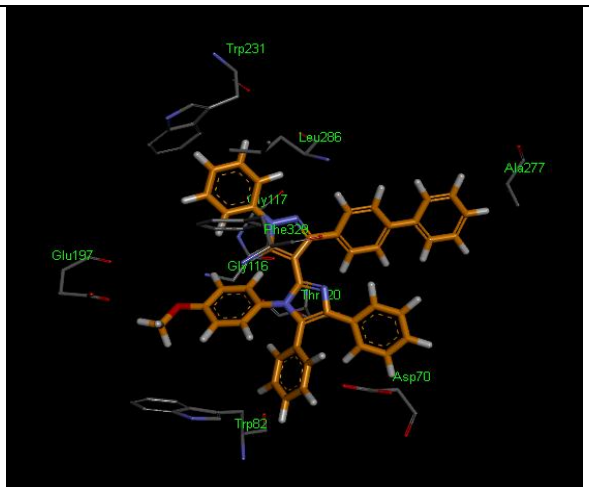
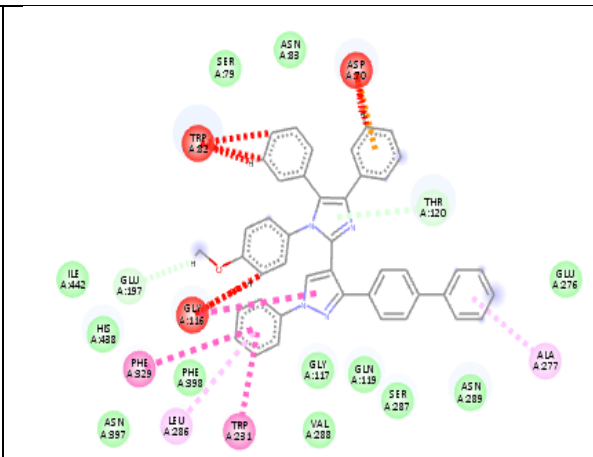
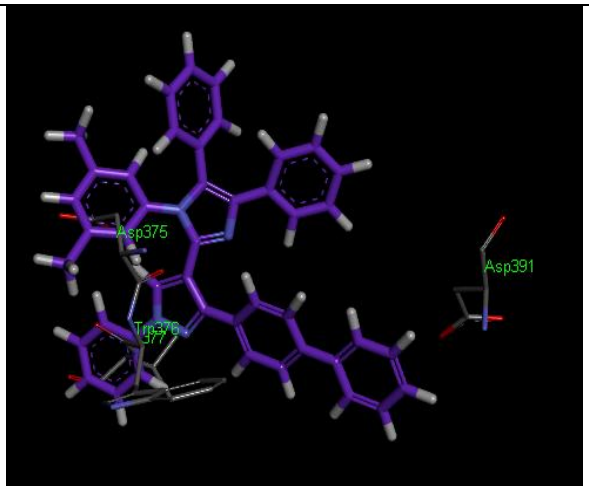
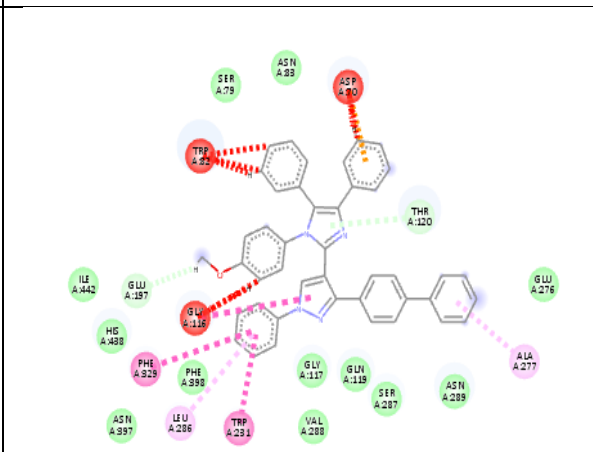
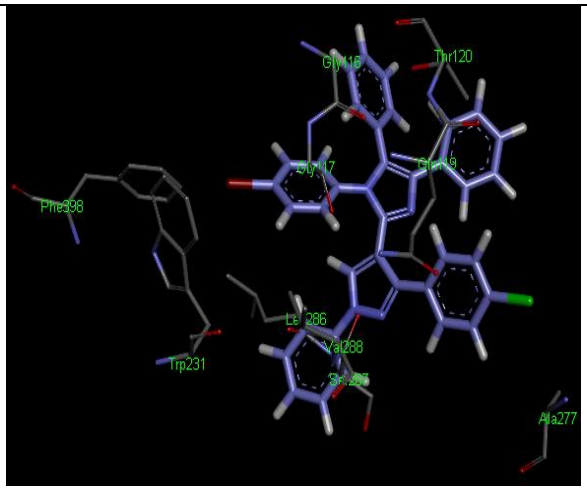
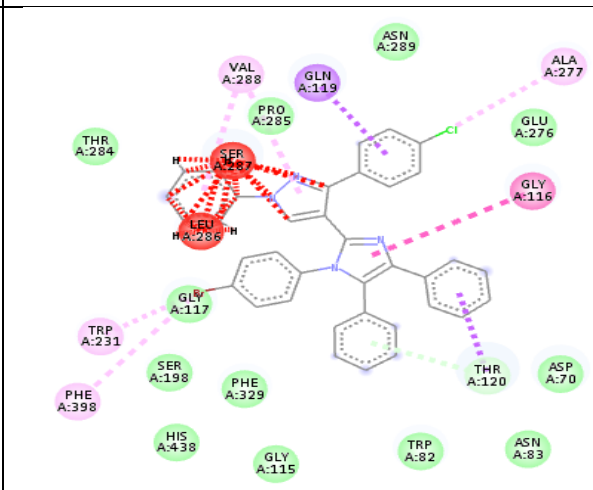
5x	 Asp324 Lys323 Tyr420 3.24 Asp391 Leu514 Arg515 Gln518	 GLU A:422 GLU A:387 TYR A:420 LYS A:323 THR A:327 ASP A:391 ASP A:324 ALA A:388 MET A:511 TYR A:373 TYR A:500 ARG A:515 GLN A:518 HIS A:372 LEU A:514

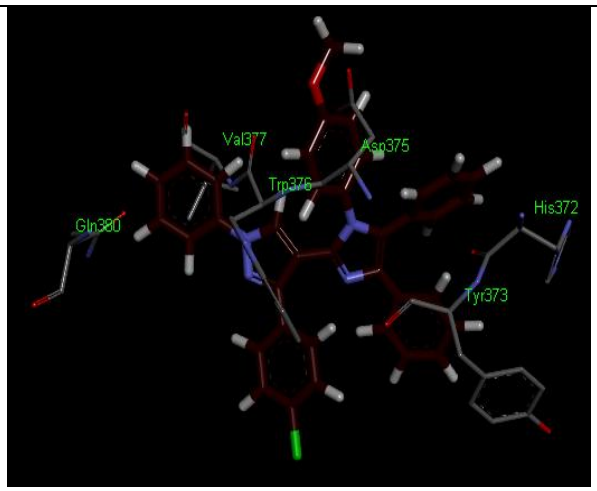
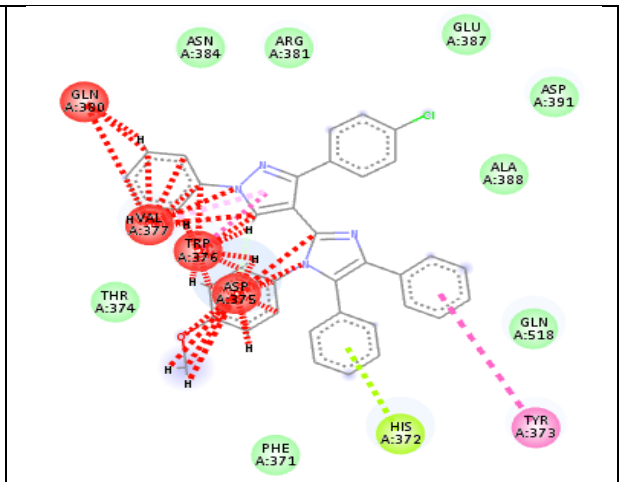
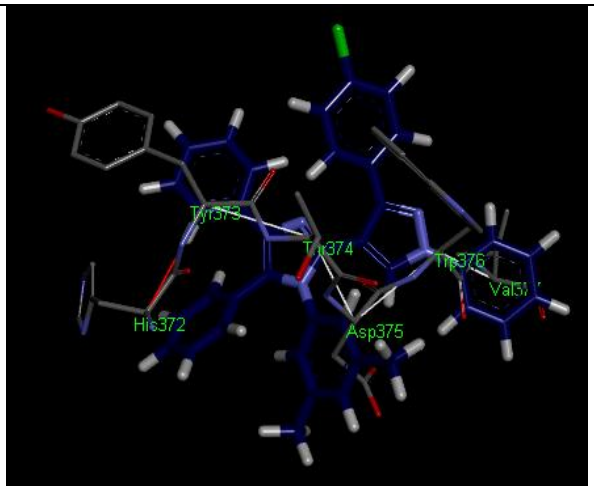
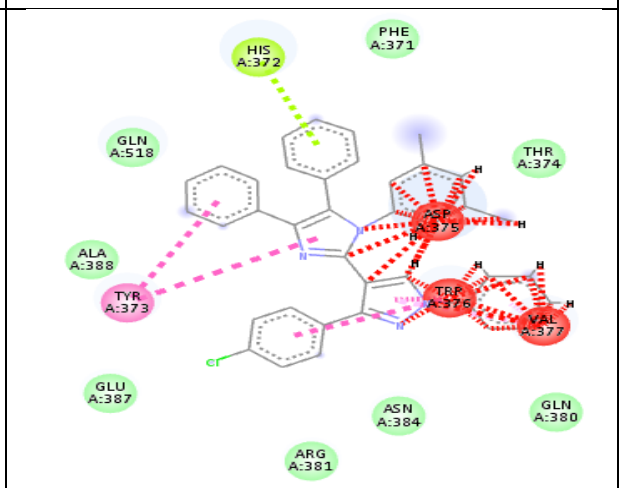
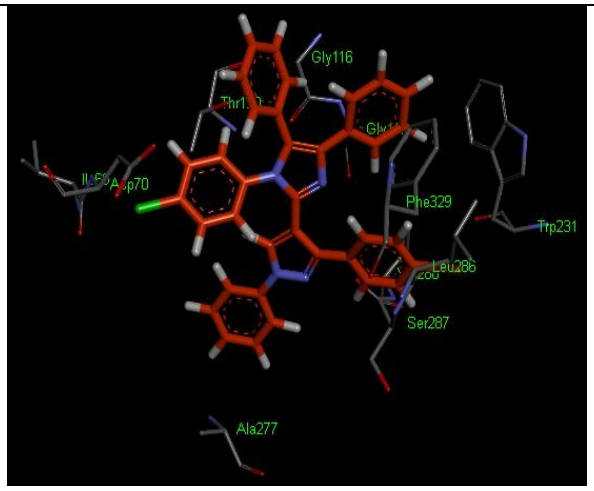
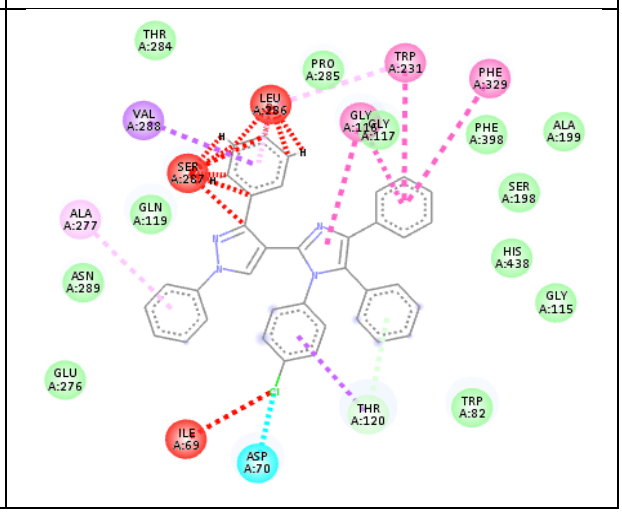
Table S2. 3D and 2D representations of docked ligands (**5a-5x**); demonstrating H-bond (light green), unfavorable bump (red), π-cation (brown), π-alkyl (light pink), amide π-stack (pink) and π-π T-shaped (shocking pink) contacts inside a binding pouch of the BChE (PDB ID: 4BDS).

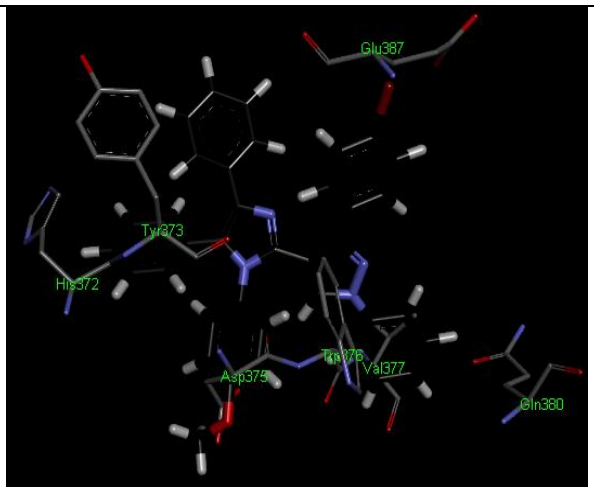
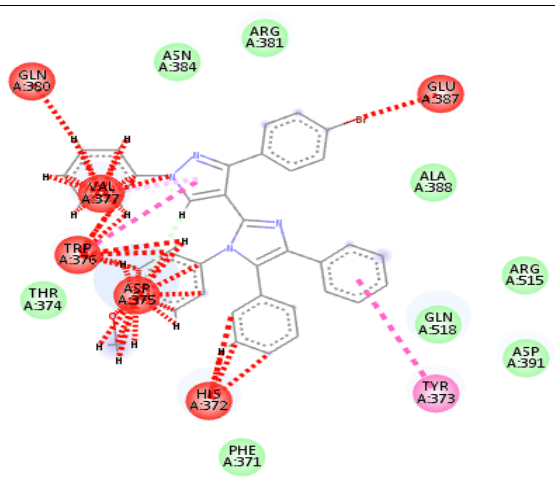
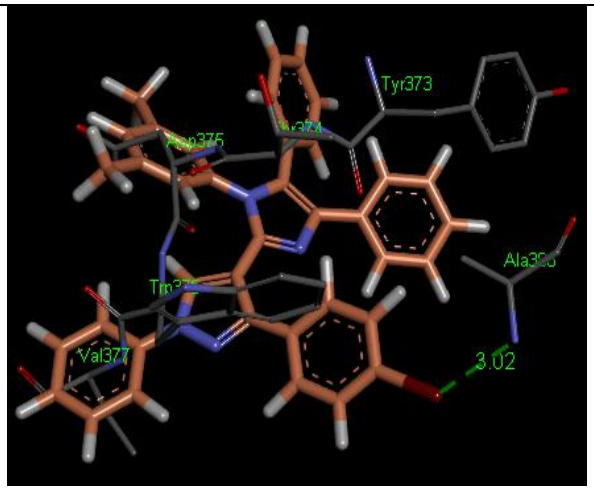
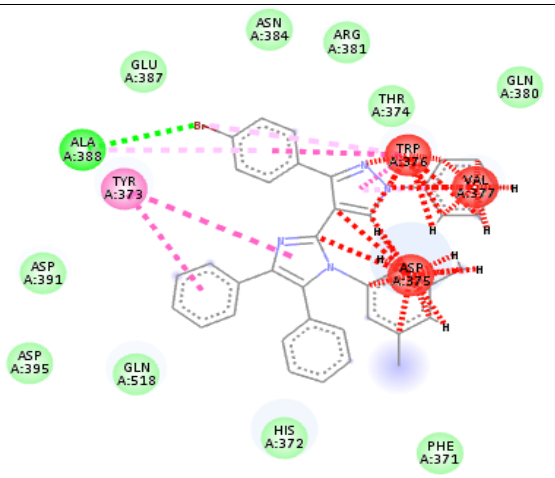
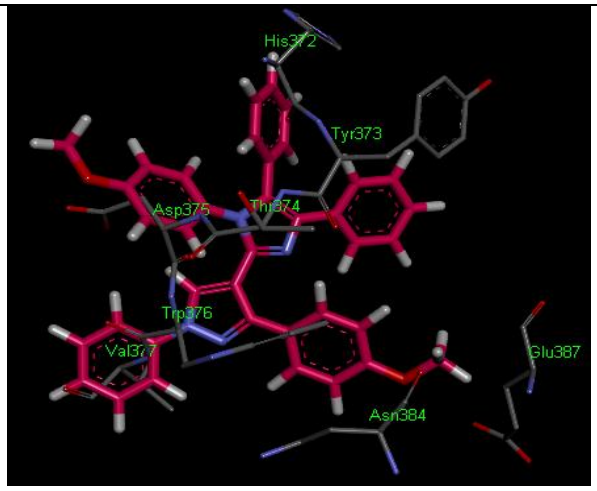
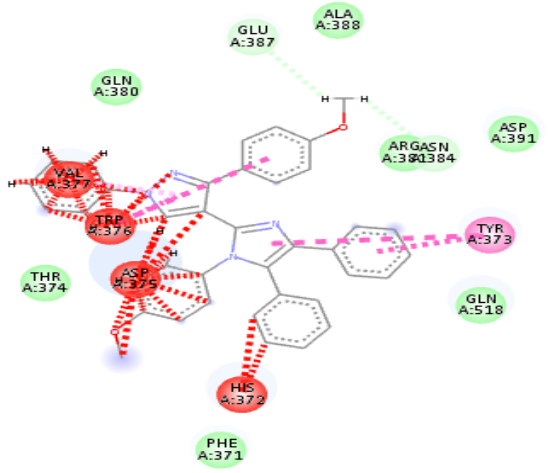
Compound	3D Binding Interaction Representation	2D Binding Interaction Representation
5a		
5b		

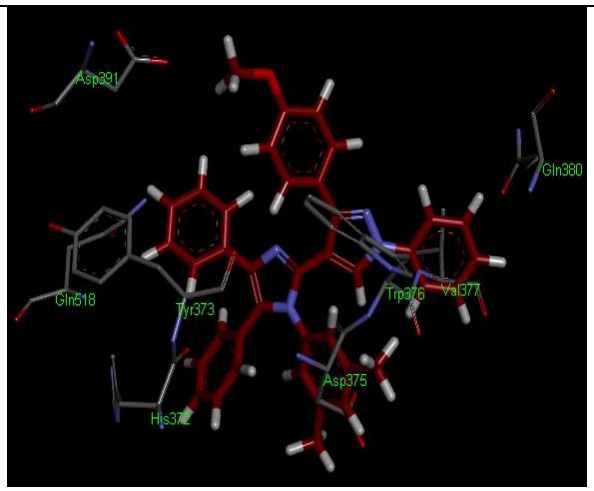
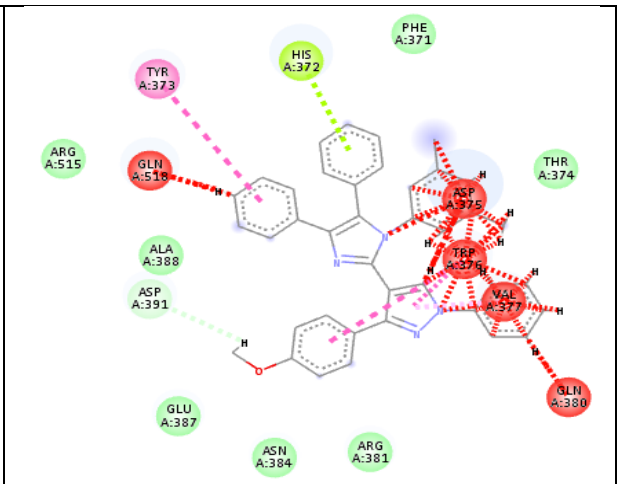
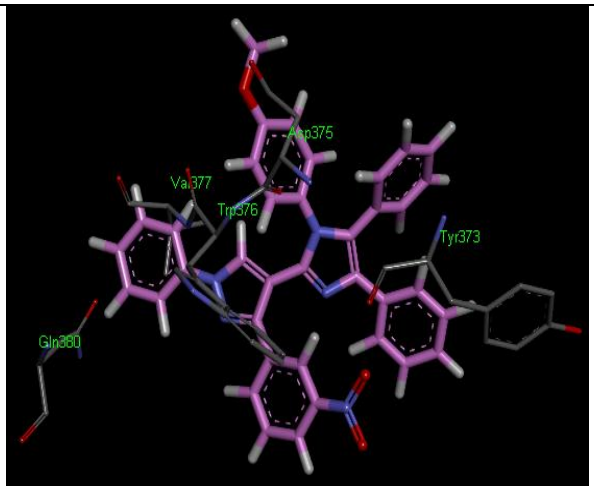
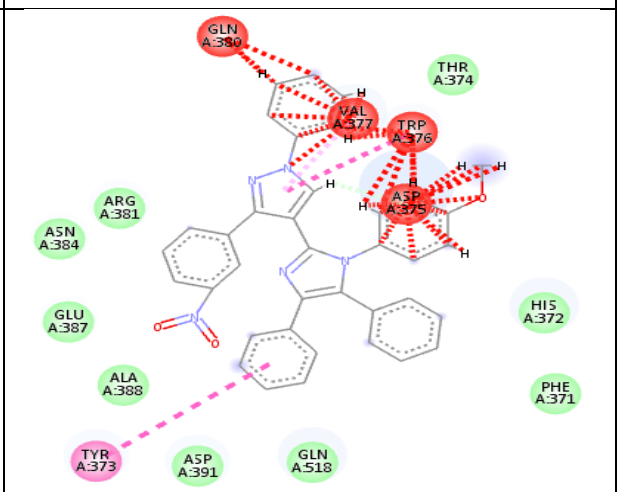
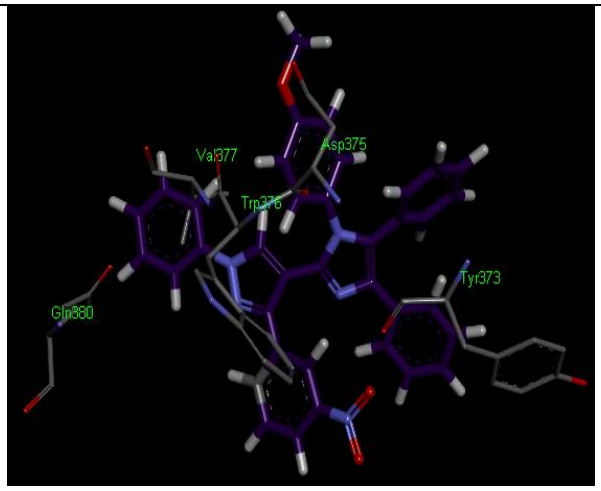
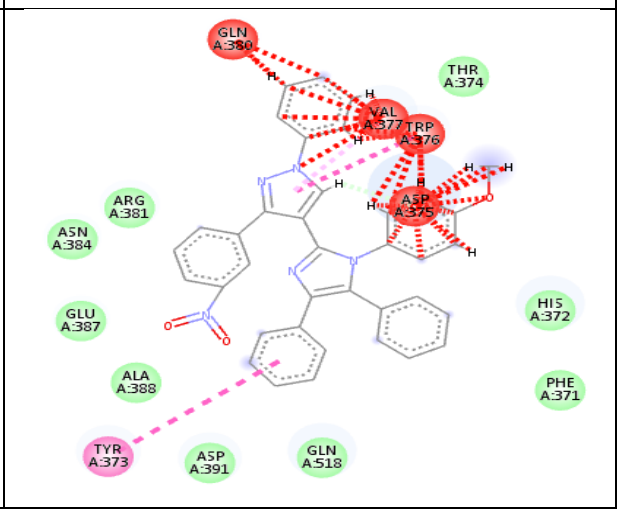
5c	 Val377 Asp375 Trp376 His372 Gln380 Tyr373	 ASP A:391 ALA A:388 GLU A:387 TYR A:373 GLN A:518 ARG A:381 ASN A:384 HIS A:372 ASP A:375 GLN A:380 TRP A:376 PHE A:371 VAL A:377 THR A:374
5d	 His372 Val377 Trp376 Gln380 Gln518 Arg381	 ASP A:395 GLN A:518 PHE A:371 ASP A:391 HIS A:372 THR A:374 ALA A:388 TYR A:373 ASP A:375 GLU A:387 TRP A:376 ASN A:384 VAL A:377 ARG A:381 GLN A:380
5e	 Unk1 Trp376 Asp375	 GLN A:380 GLU A:383 ARG A:381 ASN A:384 VAL A:377 GLU A:387 ASP A:375 TRP A:376 ALA A:388 ASP A:391 TYR A:373 GLN A:518 ASP A:395 HIS A:372

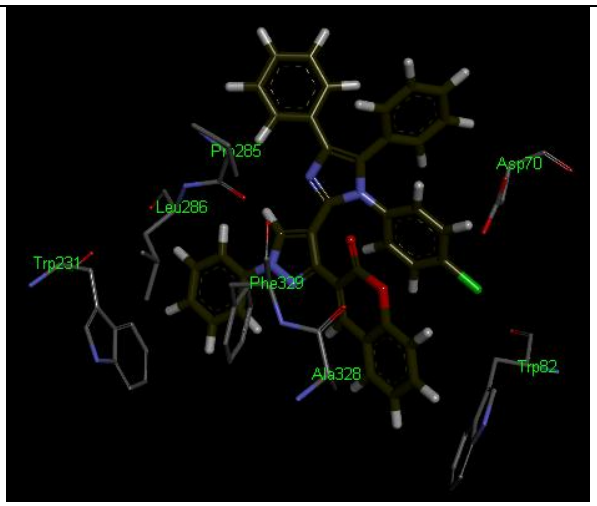
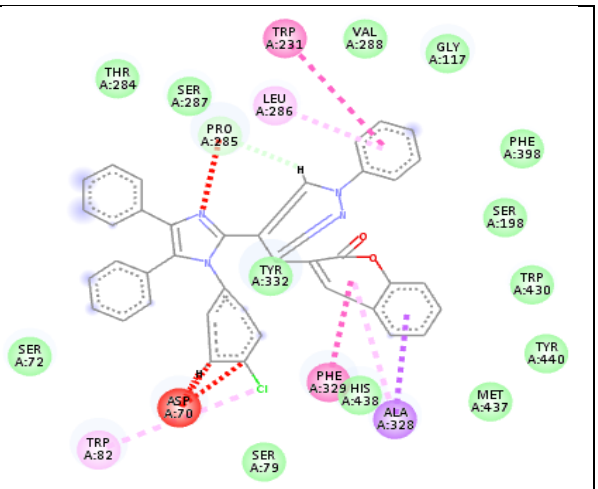
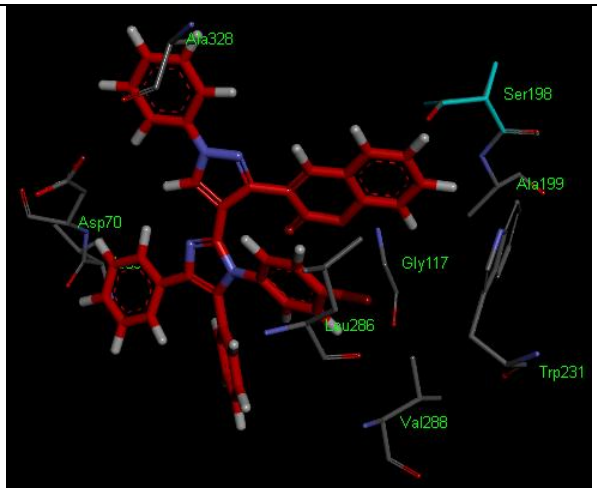
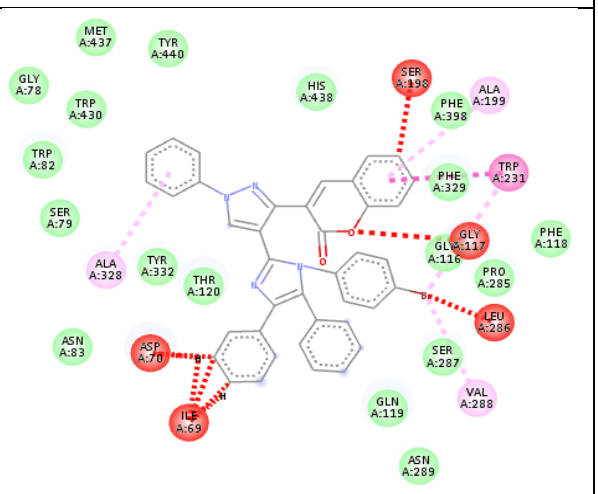
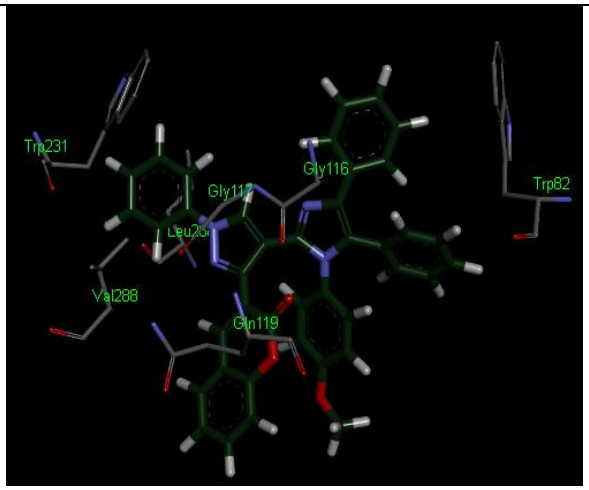
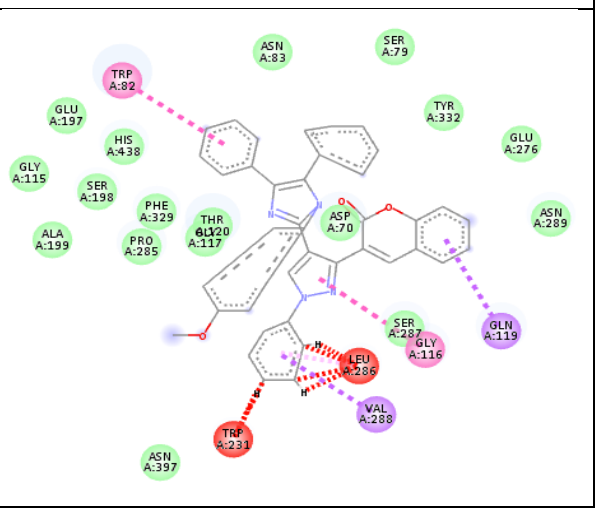
5f	 Trp62 His438 Ser198 Ala199 Gly116 Gly117 Asn68 Trp231	 GLU A:197 TRP A:62 PHE A:329 HIS A:438 ASP A:70 ASN A:68 GLY A:115 ALA A:199 SER A:198 PHE A:398 GLY A:117 TRP A:231 ASN A:397 HIS A:286 SER A:287 PRO A:285 VAL A:288 THR A:284
5g	 Gln380 Asp391	 GLN A:380 ARG A:381 TRP A:376 ASP A:375 THR A:374 GLU A:387 ASP A:391 TYR A:373 ALA A:388 HIS A:372 GLN A:518
5h	 His372 Tyr373 Asp375 Trp376 Glu387 Gln380	 GLN A:380 GLU A:383 ASN A:384 ARG A:381 GLU A:387 THR A:374 ASP A:375 ALA A:388 ASP A:391 PHE A:371 TYR A:373 HIS A:372 GLN A:518

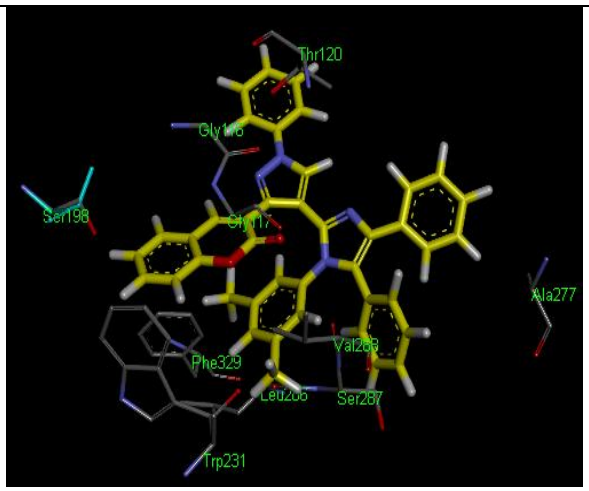
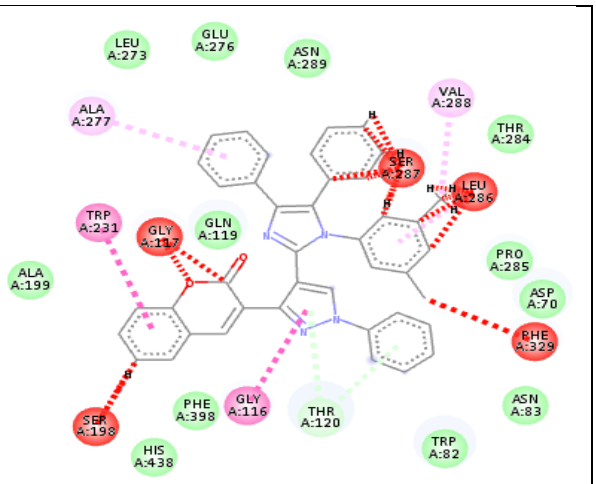
5i	 Trp231 Leu286 Ala277 Phe328 Glu197 Gly116 Asp70 Trp82	
5j	 Asp375 Asp391	
5k	 Thr120 Phe398 Trp231 Ala277	

5l	 Val377 Asp375 Trp376 Gln380 His372 Tyr373	 ASN A:384 ARG A:381 GLU A:387 GLN A:380 ASP A:391 ALA A:388 VAL A:377 TRP A:376 ASP A:375 THR A:374 GLN A:518 HIS A:372 TYR A:373 PHE A:371
5m	 Tyr373 Tyr374 Trp376 His372 Asp375	 HIS A:372 PHE A:371 GLN A:518 THR A:374 ASP A:375 ALA A:388 TYR A:373 TRP A:376 VAL A:377 GLU A:387 ASN A:384 GLN A:380 ARG A:381
5n	 Gly116 Phe329 Trp231 Leu286 Ser287 Ala277	 THR A:284 PRO A:285 TRP A:231 PHE A:329 LEU A:286 VAL A:288 GLY A:116 GLY A:117 PHE A:398 ALA A:199 SER A:287 SER A:198 ALA A:277 GLN A:119 HIS A:438 ASN A:289 GLY A:115 GLU A:276 TRP A:82 THR A:120 ILE A:69 ASP A:70

5o	 Glu387 Tyr373 His372 Asp375 Val377 Gln380	 ARG A:381 ASN A:384 GLN A:380 GLU A:387 ALA A:388 VAL A:377 TRP A:376 ASP A:375 THR A:374 ARG A:515 GLN A:518 ASP A:391 TYR A:373 HIS A:372 PHE A:371
5p	 Tyr373 Asp375 Val377 3.02	 ASN A:384 ARG A:381 GLU A:387 GLN A:380 THR A:374 ALA A:388 TRP A:376 TYR A:373 VAL A:377 ASP A:391 ASP A:375 ASP A:395 GLN A:518 HIS A:372 PHE A:371
5q	 His372 Tyr373 Asp375 Thr374 Trp376 Val377 Glu387 Asn384	 ALA A:388 GLU A:387 GLN A:380 ASP A:391 ARG A:384 VAL A:377 TRP A:376 TYR A:373 THR A:374 ASP A:375 GLN A:518 HIS A:372 PHE A:371

5r	 Asp391 Gln380 Gln518 Tyr373 Trp376 Val377 Asp375 His372	 PHE A:371 HIS A:372 TYR A:373 ARG A:515 GLN A:518 THR A:374 ASP A:375 ALA A:388 TRP A:376 ASP A:391 VAL A:377 GLN A:380 GLU A:387 ASN A:384 ARG A:381
5s	 Asp375 Val377 Trp376 Tyr373 Gln380	 GLN A:380 THR A:374 VAL A:377 TRP A:376 ASP A:375 ARG A:381 ASN A:384 HIS A:372 GLU A:387 ALA A:388 PHE A:371 TYR A:373 ASP A:391 GLN A:518
5t	 Val377 Asp375 Trp376 Tyr373 Gln380	 GLN A:380 THR A:374 VAL A:377 TRP A:376 ASP A:375 ARG A:381 ASN A:384 HIS A:372 GLU A:387 ALA A:388 PHE A:371 TYR A:373 ASP A:391 GLN A:518

5u	 Pro285 Asp70 Leu286 Trp231 Phe329 Ala328 Trp82	 TRP A:231 VAL A:288 GLY A:117 THR A:284 SER A:287 LEU A:286 PRO A:285 PHE A:398 SER A:198 TYR A:332 TRP A:430 SER A:72 TYR A:440 PHE A:329 HIS A:438 MET A:437 ASP A:70 ALA A:328 TRP A:82 SER A:79
5v	 Ala328 Ser198 Ala199 Asp70 Gly117 Leu286 Trp231 Val288	 MET A:437 TYR A:440 GLY A:78 SER A:198 HIS A:438 ALA A:199 TRP A:430 PHE A:398 TRP A:82 PHE A:329 TRP A:231 SER A:79 GLY A:117 PHE A:118 ALA A:328 TYR A:332 GLU A:116 THR A:120 PRO A:285 LEU A:286 ASN A:83 ASP A:70 SER A:287 VAL A:288 ILE A:69 GLN A:119 ASN A:289
5w	 Trp231 Gly116 Gly117 Trp82 Leu286 Val288 Gln119	 ASN A:83 SER A:79 TRP A:82 GLU A:197 TYR A:332 HIS A:438 GLU A:276 GLY A:115 SER A:198 PHE A:329 THR A:120 ASP A:70 ASN A:289 ALA A:199 PRO A:285 GLY A:117 SER A:287 GLN A:119 GLY A:116 LEU A:286 VAL A:288 TRP A:231 ASN A:397

5x	 Thr120 Gly118 Ser198 Gly117 Ala277 Val288 Phe329 Leu286 Ser287 Trp231	 LEU A:273 GLU A:276 ASN A:289 VAL A:288 ALA A:277 THR A:284 SER A:287 LEU A:286 TRP A:231 GLY A:117 GLN A:119 PRO A:285 ALA A:199 ASP A:70 PHE A:329 SER A:198 PHE A:398 GLY A:116 THR A:120 ASN A:83 HIS A:438 TRP A:82