Chapter 3

Synthesis, anti-microbial evaluation and *In Silico* studies of novel imidazole-naphthalene hybrids

3.1 Introduction

The imidazole moiety, a five-membered aromatic heterocycle with two nitrogen atoms, is crucial in medicinal chemistry since it is found in many physiologically active molecules.[117] The distinctive electron-rich configuration enables interactions with diverse enzymes and receptors via hydrogen bonding, π-π stacking, and coordination bonds, hence enhancing its extensive range of biological activities.[118] Imidazole derivatives are crucial components of several natural biomolecules, such as histidine, histamine, and purines, highlighting their vital function in physiological processes.[119] These chemicals have been thoroughly investigated for medicinal purposes, showing effectiveness in addressing disorders such as fungal infections,[120] hypertension,[121] inflammation,[122] cancer,[123] and parasite diseases.[124] The adaptability of the imidazole framework continues to motivate the creation of innovative pharmaceutical compounds with improved effectiveness and less toxicity [125]

The integration of polycyclic aromatic hydrocarbons, such as naphthalene, into bioactive heterocycles has become a significant approach for enhancing molecular stiffness, lipophilicity, and π-conjugation, which are frequently associated with improved pharmacokinetic and photophysical characteristics.[126] The naphthalene moiety, a fused bicyclic aromatic structure, is recognized for its planarity and extensive π-system, rendering it a significant structural element in the development of drugs with improved DNA intercalation, fluorescence, or enzyme inhibitory properties.[127] The amalgamation of imidazole with a naphthalene structure yields a hybrid system that integrates the multifaceted pharmacophore of imidazole with the aromatic complexity of naphthalene.[128] The structural variety obtained via substitution on the imidazole ring and the naphthalene unit enables precise modulation of physicochemical and biological aspects.[129]

Imidazole and naphthalene are regarded as important biologically active moieties with a variety of biological properties, such as antifungal (Clotrinazole, **1**),[130] general anesthetic (Etomidate, **2**),[131] antiviral (Hoechst 33342, **3**),[132] anticancer (Liarozole,

4),[133] antimicrobial (Nimorazole, **5**),[134] skin infection (Miconazole, **6**),[135] anticonvulsant (Nafimidone, **7**),[136] antitubercular (Bedaquiline, **8**)[137] (**Figure 1**), underscoring these frameworks' adaptability in drug creation.

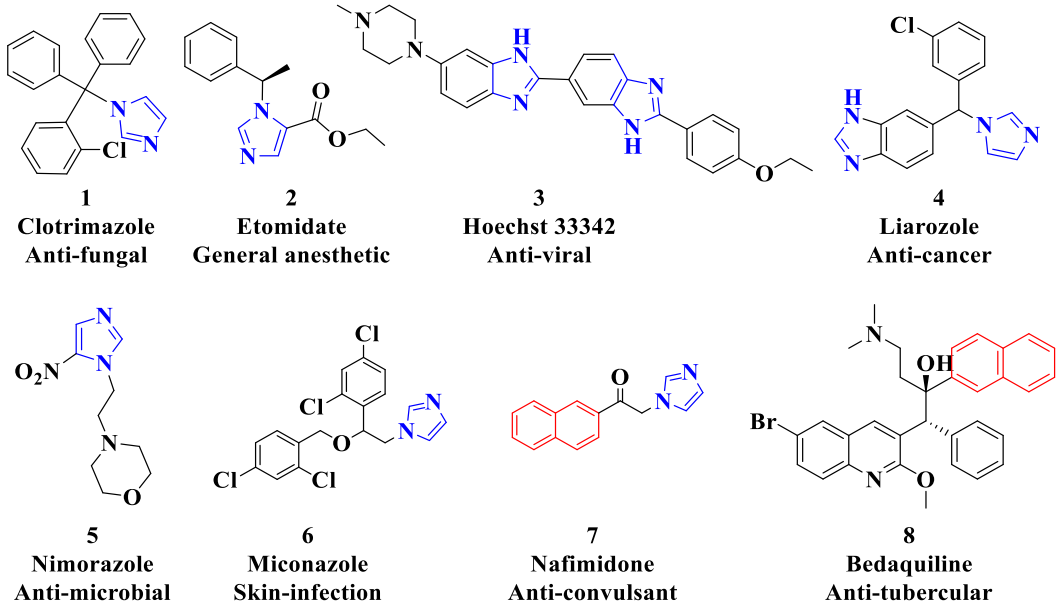


Figure 1: Marketed drugs containing imidazole and naphthalene motifs.

3.1.1 Synthetic methodologies for the substituted imidazole and naphthalene framework and their biological significance

The mitsunobu reaction was conducted with TPP, DIAD in MeOH on 4-methyl-1*H*-imidazole-5-carboxylate (**9**) to achieve methylation of the nitrogen in the imidazole molecule ethyl 1,4-dimethyl-1*H*-imidazole-5-carboxylate (**10**) (**Figure 2**).[138]

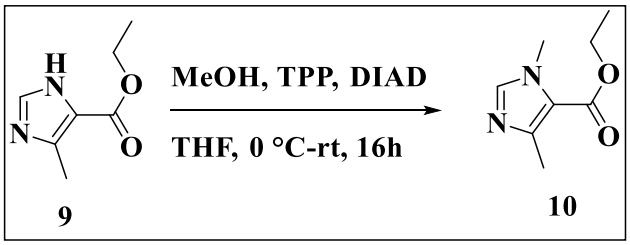


Figure 2

(1,4-Dimethyl-1*H*-imidazole-5-yl)methanol (**11**) was prepared by the reduction of ethyl 1,4-dimethyl-1*H*-imidazole-5-carboxylate (**10**) in the presence of lithium aluminium hydride in THF (**Figure 3**).[139]

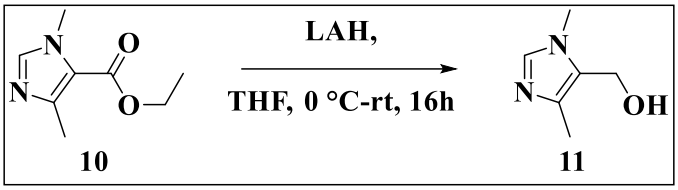


Figure 3

NaH was added to the 1,4-dimethyl-1*H*-imidazole-5-carboxylate (**10)** with dry DMF under nitrogen for the anoin generation and further 1-chloro-3-methylbut-2-ene (**12**) was added and reaction was stirred at 25 °C for 16h to get ethyl 4-methyl-1(3-methylbut-2-en-1-yl)-1*H*-imidazole-5-carboxylate (**13**) (**Figure 4**).[140]

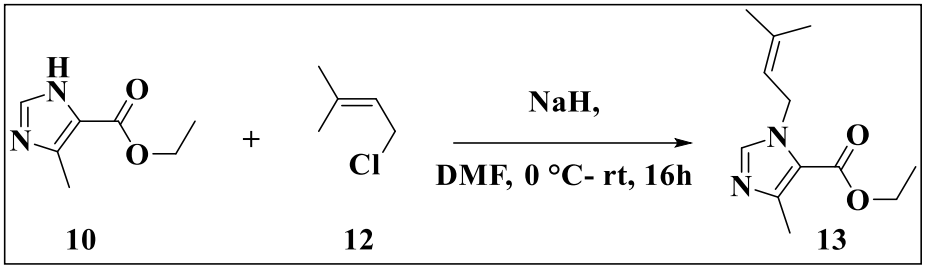


Figure 4

1-methyl-1*H*-imidazole-5-carboxylic acid (**14**) was reacted with HATU in DMF, DIPEA and 2-amino-7-methoxy-1*H*-benzo[*d*]imidazole-5-carboxamide derivatives (**15**) were and reaction was stirred for 5h at 25 °C to generate the derivatives of 7-methoxy-2(1-methyl-1*H*-imidazole-5-carboxamido)-1*H*-benzo[*d*]imidazole-5-carboxamide (**16**) (**Figure 5**).[141]

Figure 5

To a solution of 5-bromo-1-methyl-1*H*-imidazole (**17**) in DCM, anion was generated with ethyl magnesium bromide, *N*-methoxy-*N*-methylbenzamide (**18**) was added and reaction was stirred at 25 °C for 2h for generate (1-methyl-1*H*-imidazol-5-yl)(phenyl)methanone (**19**). (**Figure 6**).[142]

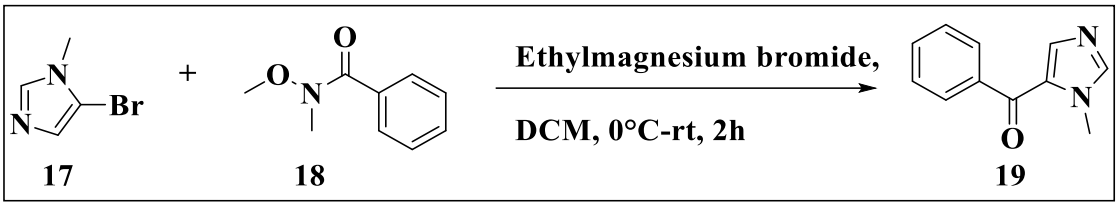


Figure 6

Suzuki reaction on methyl 2-bromo-1*H*-imidazole-5-carboxylate (**20**) with (2,4-dimethoxyphenyl)boronic acid (**21**) in presence of K_3PO_4 in toluene. Reaction was stirred for 15 min under nitrogen degassed and tetrakiss was added and reaction was stirred at 90 °C for 10h to get methyl 2-(2,4-dimethoxyphenyl)-1*H*-imidazole-5-carboxylate (**22**) (**Figure 7**).[143]

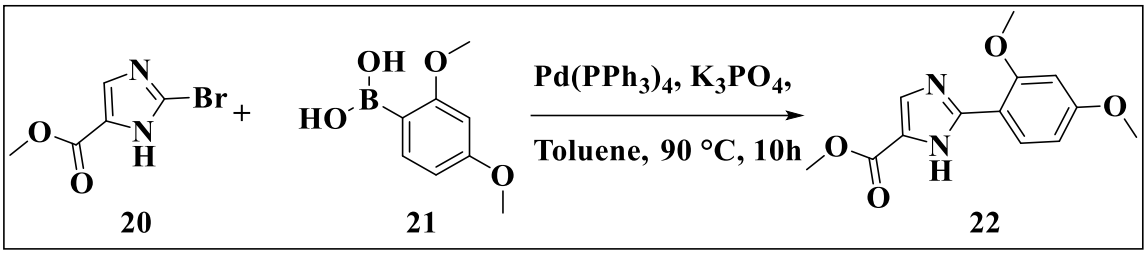


Figure 7

Some important imidazole derivatives having biological activity, such as antimicrobial (**23**),[144] antiinflammatory (**24**),[145] anti-neurodegenerative (**25**),[146] anti-convulsant (**26**),[147] anticancer (**27**),[148] antifungal (**28**),[149] angiotensin receptor blockers (**29**),[150] antihypertensive (**30**)[151] (**Figure 8**).

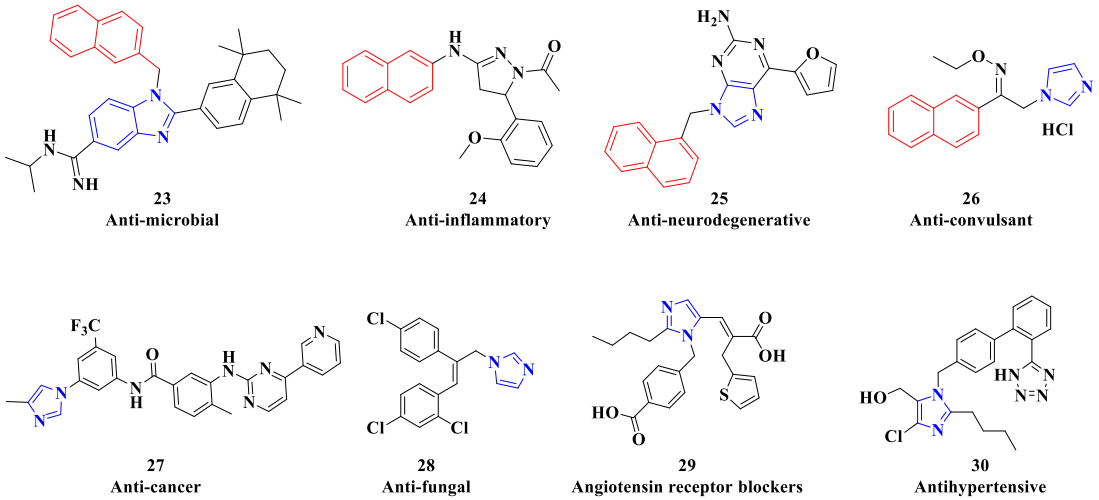
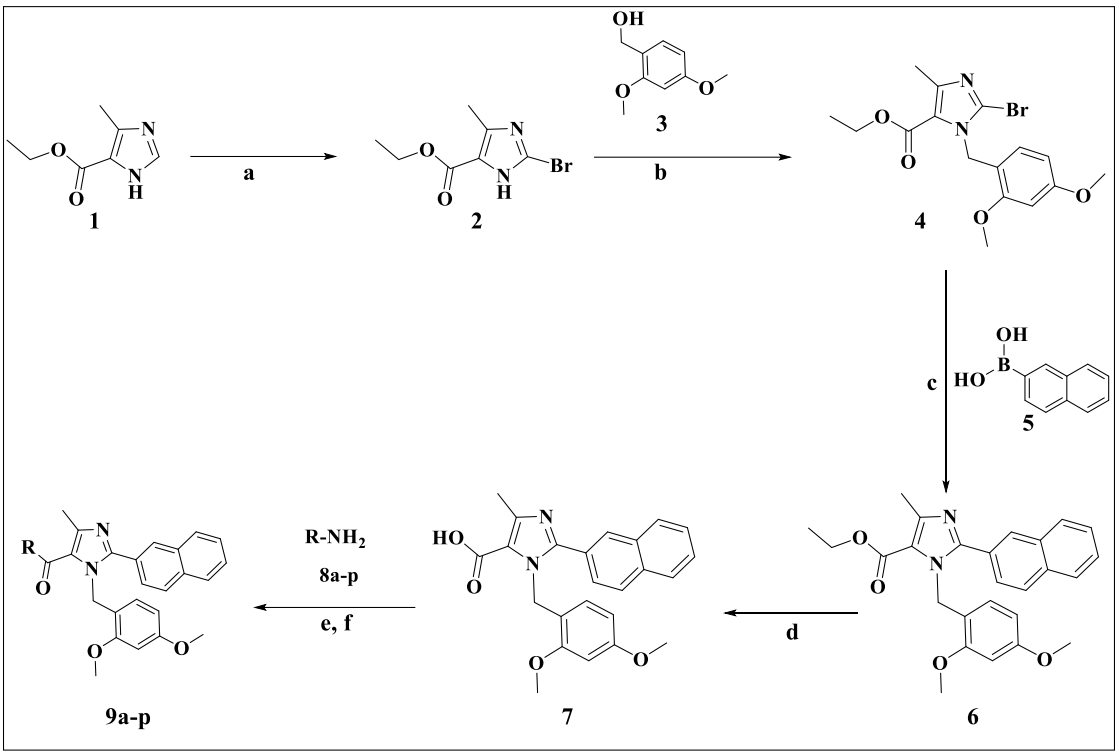


Figure 8: Important compounds containing imidazole and naphthalene motifs.

3.2 Results and Discussion

3.2.1 Chemistry

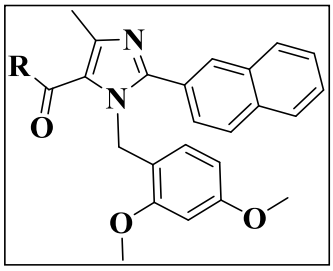
The synthesis of imidazole naphthalene hybrids with amide linkages (**9a-p**) was executed through a meticulously structured set of reactions aimed at modifying functional groups to investigate diverse chemical properties and possible therapeutic uses. The synthesis began with the bromination of ethyl 4-methyl-1*H*-imidazole-5-carboxylate (**1**) to produce ethyl 2-bromo-4-methyl-imidazole-5-carboxylate (**2**) with an 84% yield, validated by a 97% purity as determined by LC-MS analysis.[152] Compound **2** and (2,4-dimethoxyphenyl)methanol (**3**) were utilized to synthesize ethyl 2-bromo-1-(2,4-dimethoxybenzyl)-4-methyl-imidazole-5-carboxylate (**4**) using mitsunobu conditions, achieving a yield of 67%, which was corroborated by LC-MS analysis indicating 96% purity.[153] Compound **4** undergoes a suzuki coupling reaction with naphthalen-2-ylboronic acid (**5**), utilizing $PdCl_2$(dppf) as a catalyst in a 1,4-dioxane and water mixture at 100 °C, resulting in ethyl 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-1*H*-imidazole-5-carboxylate (**6**) with a yield of 68% and a purity of 99% as determined by LC-MS analysis.[154] The hydrolysis was conducted using a NaOH solution in methanol and water, yielding 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-1*H*-imidazole-5-carboxylic acid (**7**) with a 90% yield.[155] Compounds **9a-p** were produced by the acid-amine coupling of compound **7** with substituted amines (**8a-p**) under two distinct circumstances illustrated in Scheme 1.



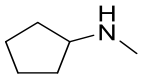
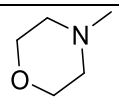
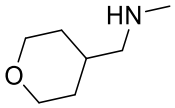
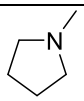
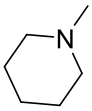
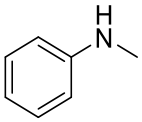
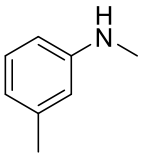
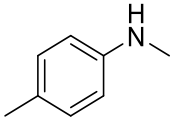
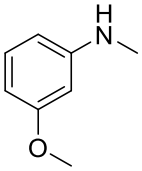
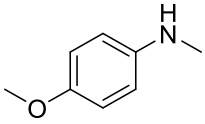
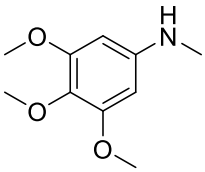
Reaction conditions: a) N-bromo succinimide (1.3 eq), Acetonitrile, 0 °C-rt, 3h**, b)** (2,4-dimethoxyphenyl)methanol (1.5 eq), Triphenylphosphine (1.6 eq), DIAD (1.6 eq), THF 0° C- rt 16h, **c)** 5 (1.5 eq), $PdCl_2$ (dppf) (0.05 eq), CS_2CO_3 (3.0 eq), 1,4-Dioxane:H_2O (2:1), 100° C, 3h, **d)** NaOH (3.0 eq), MeOH:H_2O (2:1), 60 °C, 16h.

Scheme 1: Synthesis of imidazole-naphthalene hybrid with amide linkage (**9a-p**).

Table 1: Physicochemical characteristics of the novel imidazole-naphthalene derivatives **9a-p**.



Compounds	R	Molecular Weight	Molecular Formula	Yield (%)	Melting Point (°C)
9a	-NH-CH_3	415.49	$C_{25}H_{25}N_3O_3$	87	162-165
9b	-N(CH_3)$_2$	429.52	$C_{26}H_{27}N_3O_3$	84	162-164
9c	-N-C_2H_5	429.52	$C_{26}H_{27}N_3O_3$	84	150-152
9d	-N-(C_2H_5)$_2$	457.57	$C_{28}H_{31}N_3O_3$	83	155-157

9e		469.59	$C_{29}H_{31}N_3O_3$	79	152-153
9f		471.56	$C_{28}H_{29}N_3O_4$	70	156-158
9g		499.61	$C_{30}H_{33}N_3O_4$	68	167-170
9h		441.53	$C_{27}H_{27}N_3O_3$	54	148-151
9i		455.56	$C_{28}H_{29}N_3O_3$	57	152-155
9j		469.59	$C_{29}H_{31}N_3O_3$	68	158-160
9k		477.56	$C_{30}H_{27}N_3O_3$	80	170-172
9l		491.59	$C_{31}H_{29}N_3O_3$	86	165-168
9m		491.59	$C_{31}H_{29}N_3O_3$	78	166-168
9n		507.59	$C_{31}H_{29}N_3O_4$	87	162-165
9o		507.59	$C_{31}H_{29}N_3O_4$	83	164-167
9p		567.64	$C_{26}H_{27}N_3O_3$	80	160-162

3.3 Antimicrobial activity

Using the nutrient agar disk diffusion technique, the antibacterial activity of all the newly synthesized hybrid imidazole-naphthalene derivatives with substituted amide (**9a-p**) was evaluated against gram-positive (*B. subtilis* ATCC6051/MTCC121, *S. aureus* ATCC12600/MTCC1430), gram-negative (*P. aeruginosa* ATCC10415/MTCC1934, *E. coli* ATCC9637/MTCC448) and fungal strains (*A. niger* ATCC 16888, *C. albicans* ATCC 10231). Chloramphenicol (30 µg/disc) and gentamicin (10 µg/disc) were used as the positive controls for antibacterial activity and nystatin as a positive control for antifungal activity while DMSO was used as a negative control, which did not influence microbial growth. Figure 3 & 4 illustrates the measured zones of inhibition (ZOI) for the produced compounds against each of the four microorganisms, compared with chloramphenicol the reference drug. Nutrient agar [composition (g/L): sodium chloride, 5.0; yeast extract, 10.0; peptone, 10.0 (pH 7.2)] was employed for assessment by the disc diffusion method.[156]

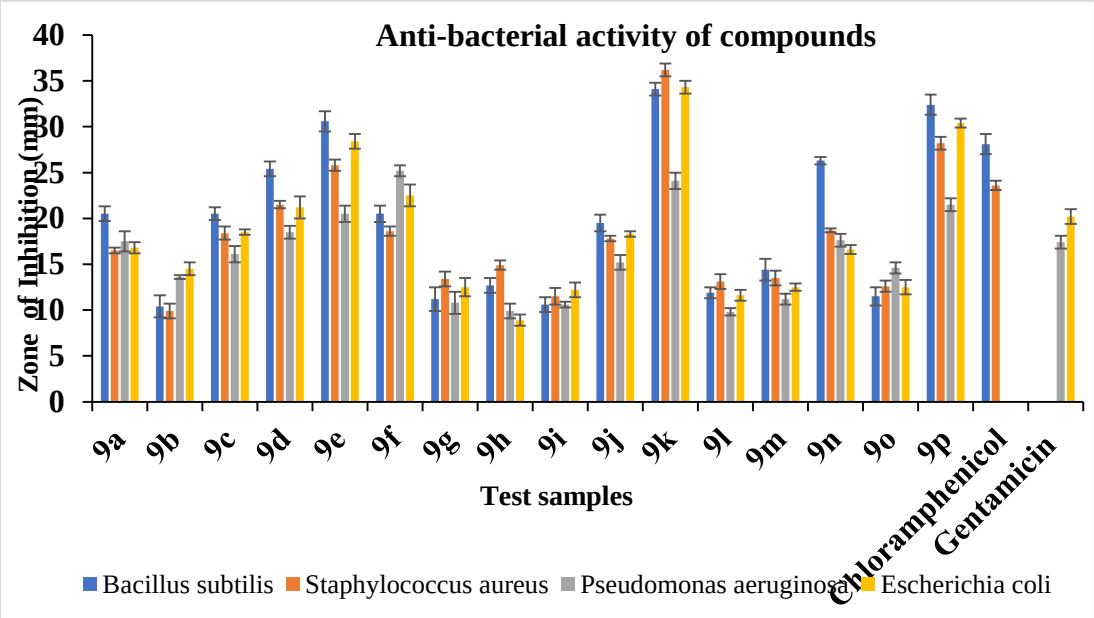


Figure 9: Graphical presentation of anti-bacterial activity data of newly synthesized imidazole-naphthalene hybrid with amide linkage **9a-p**.

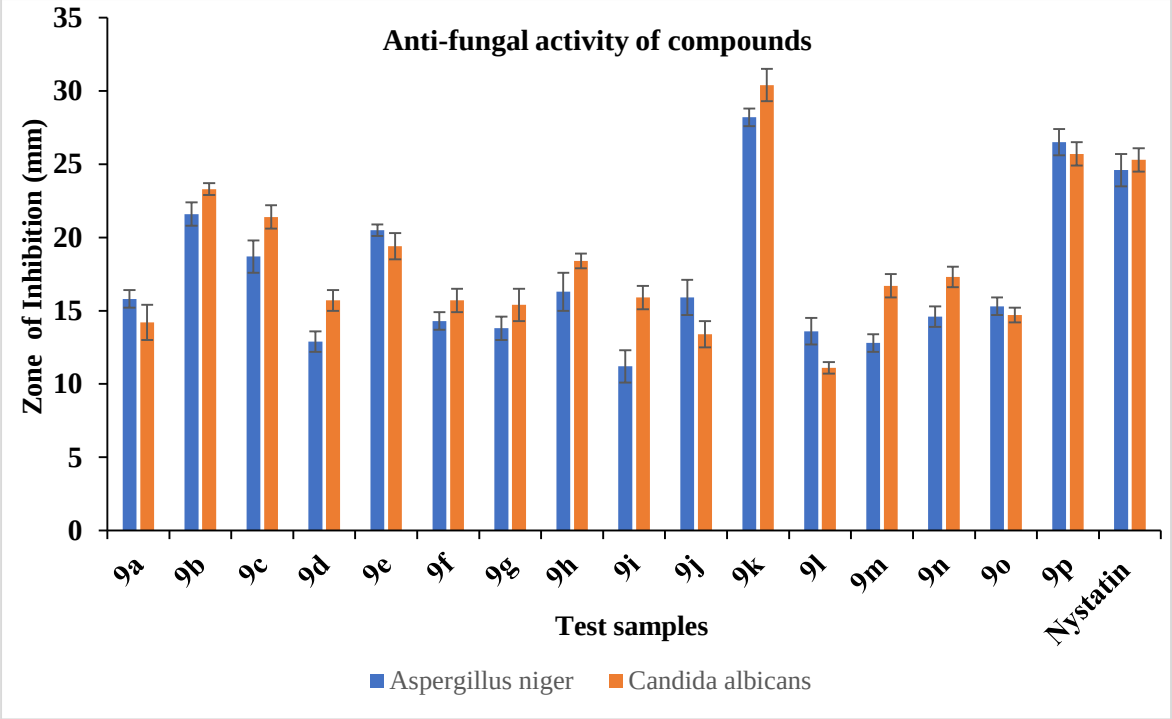


Figure 10: Graphical presentation of anti-fungal activity data of newly synthesized imidazole-naphthalene hybrid with amide linkage **9a-p**.

3.4 Structure-Activity Relationship (SAR)

In two gram-positive pathogens, *B. subtilis* (34.1 ± 0.7 mm) and *S. aureus* (36.2 ± 0.7 mm), compound **9k**, which has a para-position (N-Phenyl) substitution, demonstrated moderate to high antibacterial activity. Conversely, the traditional antibiotic chloramphenicol exhibited inhibition zones of 28.1 ± 1.1 mm and 23.6 ± 0.5 mm against the respective strains. Compound **9k** exhibited significant antibacterial efficacy against gram-negative organisms, with inhibition zones of 34.3 ± 0.7 mm for *E. coli* and 24.1 ± 0.9 mm for *P. aeruginosa*. In contrast, the poplar medicine gentamicin had lower inhibition zones of 17.4 ± 0.7 mm and 20.2 ± 0.8 mm. Compound **9b**, with -$N(CH_3)_2$, had the lowest antibacterial efficacy against both types of diseases. Moreover, compound **9k** demonstrated moderate to high antifungal efficacy against *A. niger* (28.2 ± 0.6 mm) and *C. albicans* (30.4 ± 1.1 mm), while the standard nystatin displayed activity against these pathogens of 24.6 ± 1.1 mm and 25.3 ± 0.5 mm, respectively.

3.5 Molecular Docking

The greatest performers, with the highest negative binding affinities in the collection, were compounds **9k** (-8.7 kcal/mol), **9p** (-8.4 kcal/mol), and **9e** (-8.5 kcal/mol),

according to the molecular docking study (Table 1). These compounds presumably derive advantages from strong hydrogen bonding networks, broad hydrophobic interactions, and supplementary stabilizing contacts, rendering them very intriguing candidates for antibacterial activity. Compounds of moderate strength, including **9j** (-8.0 kcal/mol), **9n** (-8.0 kcal/mol) and **9l** (-8.3 kcal/mol) have substantial binding stability and interaction potential. Compounds **9m** (-8.3 kcal/mol) and **9o** (-8.3 kcal/mol) belong to this group, signifying robust and persistent interactions with the protein binding pocket. Compounds with binding affinities between -7.8 and -7.9 kcal/mol, such as **9a**, **9f**, and **9g** exhibit a modest binding potential. Their interaction patterns are probably characterized by hydrophobic contacts, with a reduced number of hydrogen bonds or water-mediated interactions relative to the top achievers. Compounds **9b** (-7.4 kcal/mol) and **9d** (-7.3 kcal/mol) have comparatively diminished binding affinities, suggesting suboptimal interactions with the protein. The reference drug chloramphenicol demonstrates the binding affinity as -6.8 kcal/mol, indicating that all evaluated compounds had greater binding potential.

The interaction diagrams disclosed essential insights into their binding processes and confirmed their elevated binding affinities. Compound **9k**, exhibiting the highest binding affinity, establishes a strong network of contacts within the binding pocket. Significant hydrogen bonds are noted with residues like GLN_58, ARG_204, and ASP_17, with optimum bond distances of 2.93–3.92 Å. Furthermore, robust hydrophobic interactions with residues such as LYS_162 and VAL_149 substantially enhance its stability. Water-mediated interactions, exemplified by GLU_146, augment the flexibility and dynamic stability of the ligand inside the protein's active region. Likewise, compound **9p** demonstrates a similar albeit marginally less comprehensive interaction profile. It establishes hydrogen bonds with GLN_58 and ARG_204, which are essential residues for ligand stability. Hydrophobic interactions with LYS_162 and VAL_149 enhance its binding stability. The interaction network of **9p** is somewhat less diverse, exhibiting fewer water-mediated interactions. Compound **9k** is distinguished by its broader interaction network and enhanced binding affinity. These data substantiate the choice of **9k** as top candidates for further study, emphasizing their potential as antibacterial agents.

Table 2: Molecular docking results of the compounds **9a-p** against *E. coli* DNA gyrase B protein receptor (PDB: 4DUH).

Compounds	Binding affinity (kcal/mol)	Compounds	Binding affinity (kcal/mol)
9a	-7.9	**9i**	-7.7
9b	-7.4	**9j**	-8
9c	-7.8	**9k**	-8.7
9d	-7.3	**9l**	-8.3
9e	-8.4	**9m**	-8.3
9f	-7.9	**9n**	-8
9g	-7.8	**9o**	-8.3
9h	-7.7	**9p**	-8.5
Chloramphenicol	-6.8		

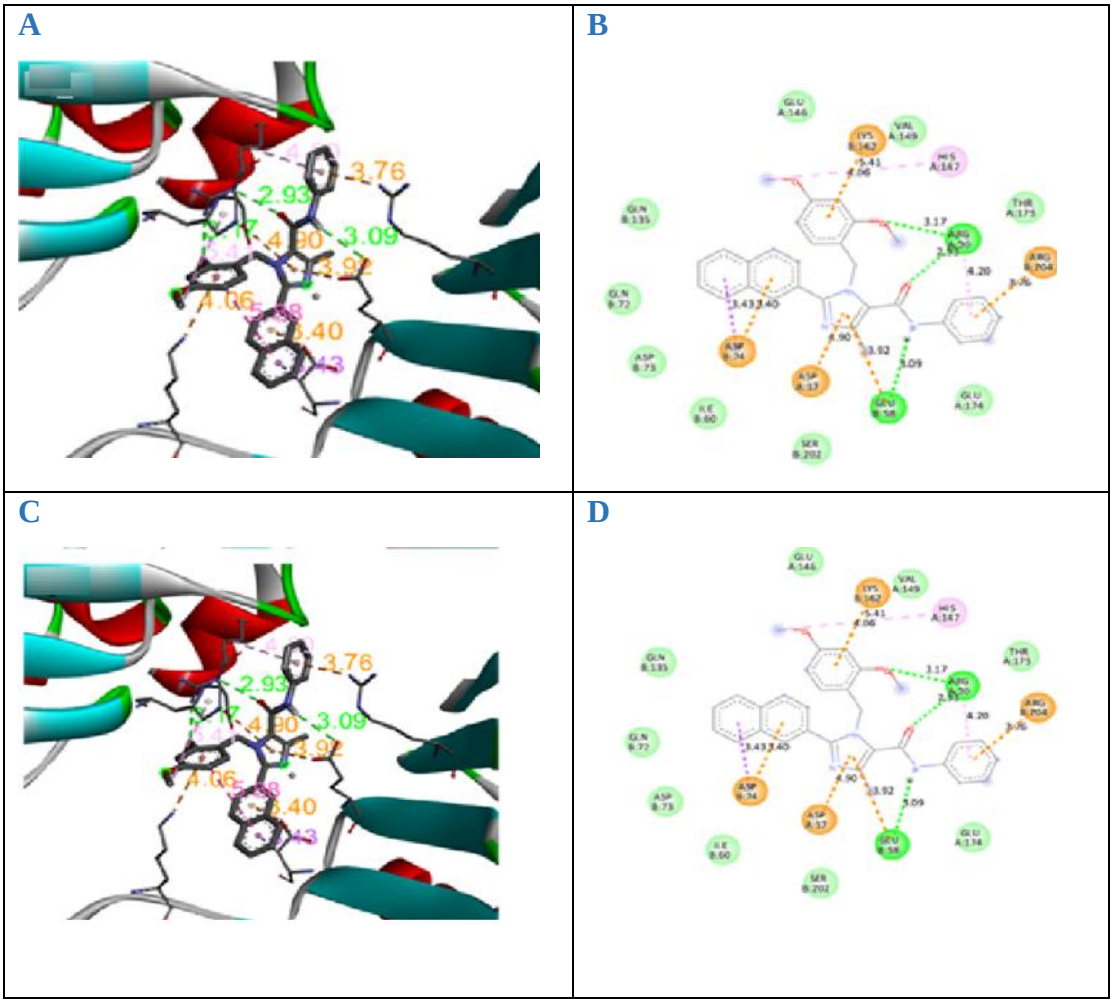


Figure 11: Docking pose of compound **9k** with 24 kDa domain of *E. coli* DNA gyrase. (**A**) Receptor-ligand interaction on a 2D diagram, (**B**) Receptor-ligand interaction on a 3D diagram. Docking pose of compound **9p** with 24 kDa domain of *E. coli* DNA gyrase. (**C**) Receptor-ligand interaction on a 2D diagram, (**D**) Receptor-ligand interaction on a 3D diagram.

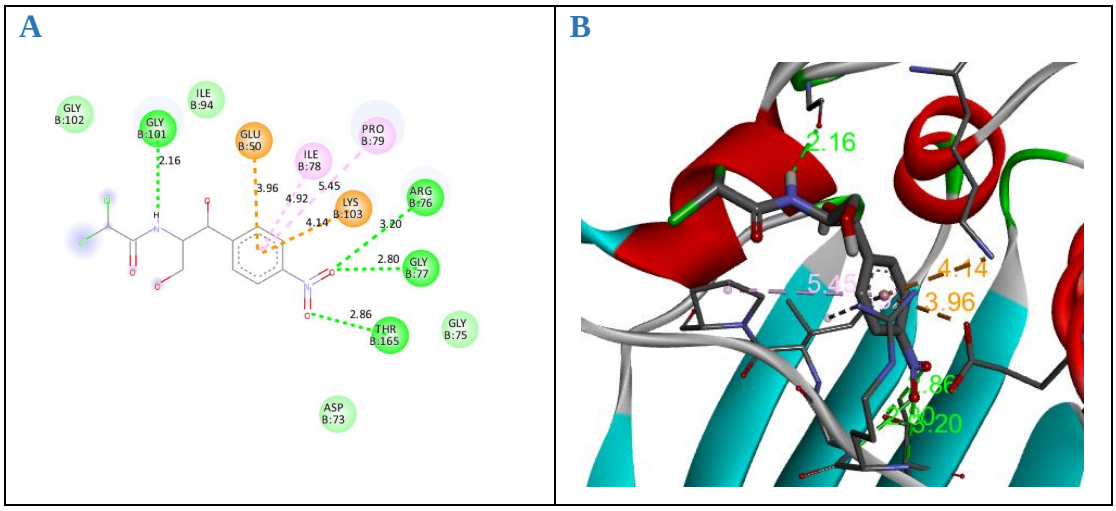


Figure 12: Docking pose of chloramphenicol with 24 kDa domain of *E. coli* DNA gyrase. (**A**) Receptor-ligand interaction on a 2D diagram, (**B**) Receptor-ligand interaction on a 3D diagram.

3.6 Molecular Dynamics Simulation Analysis

During the simulation, the dynamics and stability of the protein-ligand complex are thoroughly understood thanks to the molecular dynamic simulation. The most promising compound **9k**, based on antimicrobial activity and docking data, was selected for further validation. The RMSD graph illustrates the structural stability of the **9k**-4duh complex during the simulation (**Figure 13**). The protein RMSD stabilizes between 1.25 and 1.75 Å following an initial equilibration period of 10 to 15 ns, indicating the system's structural stability. The low RMSD value indicates that the protein maintains a stable structure throughout the simulation, exhibiting only slight oscillations, likely due to inherent dynamic motions. Conversely, compound **9k** has a more dynamic RMSD pattern. Initially, it demonstrates modest RMSD values (<1.0 Å), indicating stable binding inside the pocket. Transient spikes manifest between 40 and 80 ns, indicating conformational alterations or momentary instability. The compound **9k** ultimately stabilizes in a new binding conformation, as shown by its RMSD

plateauing at around 2.0–2.5 Å towards the conclusion of the simulation. The results indicate that compound **9k** remains attached to protein 4duh while experiencing adaptive conformational changes within the binding region. The RMSF analysis offers residue-specific insights about protein flexibility. Residues at the loop regions and terminal ends exhibit elevated RMSF values, particularly near residue indices ~75 and 175, indicating greater flexibility. Conversely, residues that constitute secondary structural components, such as alpha-helices and beta-sheets, have diminished RMSF values (<1.5 Å), thereby affirming their stiffness and stability. The stable core residues maintain the protein's structural integrity, whilst the flexible regions may facilitate ligand binding and enable dynamic interactions. The RMSF data underscore the equilibrium between stability and flexibility in the protein, which is essential for optimal ligand binding. The **9k**-4duh complex interaction histogram delineates the critical residues and interaction types that facilitate ligand stability. Hydrophobic interactions prevail, with residues including LEU_34, VAL_118, and PHE_104 making substantial contributions. These residues promote the ligand's robust and stable binding within the hydrophobic pocket. Hydrogen bonds, however few, are essential for specific stability, especially with residues such as GLU_190, which establishes constant polar contacts. Moreover, other polar interactions, including those with residues such as THR_174, enhance the hydrophobic interactions and further stabilize the ligand. The interaction data corresponds with the RMSF findings (**Figure 14**), as residues exhibiting moderate flexibility (e.g., LEU_34 and VAL_118) facilitate adaptation, whilst those with low RMSF values enhance the structural stability of the complex. Comprehensive investigations consistently validate a stable **9k**-4duh complex characterized by robust binding interactions. The protein preserves structural integrity, with flexibility concentrated in areas that improve ligand adaptation within the binding site. The ligand demonstrates early stability, temporary reorientation, and subsequent stabilization in a novel conformation, facilitated by predominant hydrophobic interactions and essential hydrogen bonds. The findings indicate the ligand's robust binding affinity and the system's overall stability during the simulation, rendering it a good option for antibacterial efficacy.

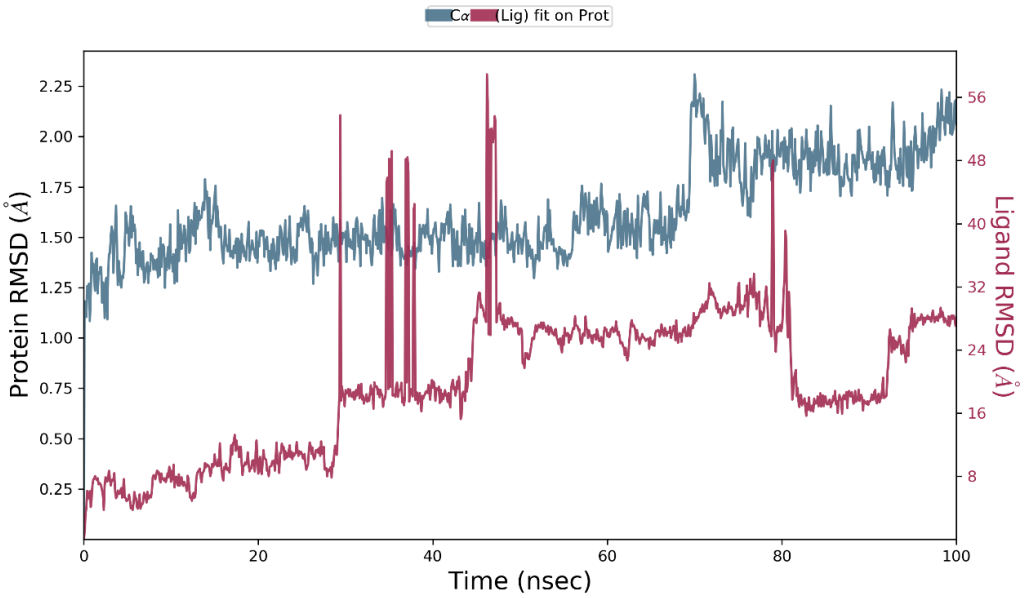


Figure 13: RMSD plot of compound **9k**-4DUH complex.

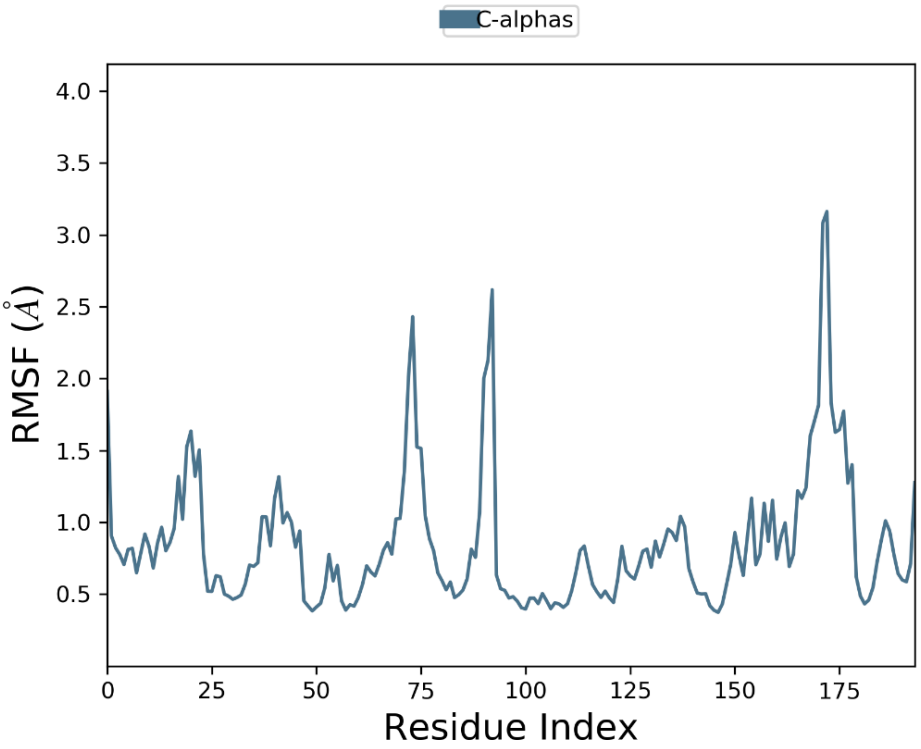


Figure 14: RMSF plot of compound **9k**-4DUH complex.

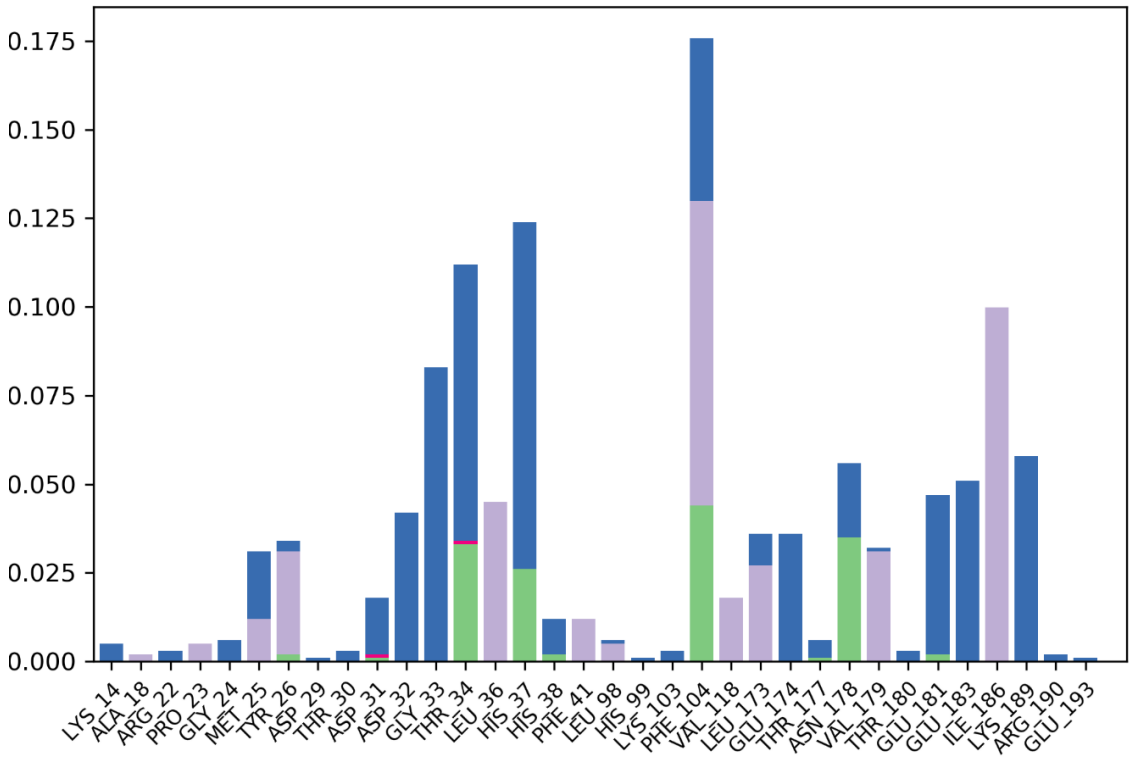
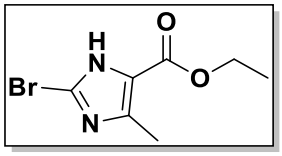


Figure 15: Interaction graph of compound **9k**-4DUH complex.

3.7 Experimental Section

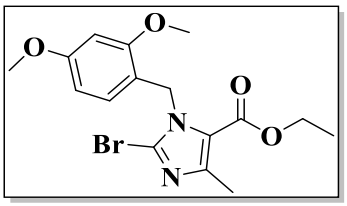
3.7.1 Chemistry

Synthesis of ethyl 2-bromo-4-methyl-1*H*-imidazole-5-carboxylate (2)



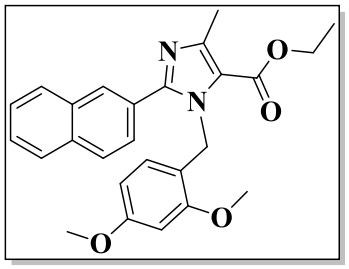
Compound ethyl 2-bromo-4-methyl-imidazole-5-carboxylate (**2**) was synthesized using previously reported method with yield 84%. mp: 151-154 °C. (Reported mp: 152-153 °C).[152]

Procedure for the synthesis of ethyl 2-bromo-1-(2,4-dimethoxybenzyl)-4-methyl-1*H*-imidazole-5-carboxylate (4)



To a solution of ethyl ethyl 2-bromo-4-methyl-1*H*-imidazole-5-carboxylate (**2**) (20 g, 85.81 mmol) in THF (110 mL) in 3-Neck RBF under nitrogen atmosphere, (2,4-dimethoxyphenyl)methanol (**3**) (21.64 g, 128.71 mmol) and triphenylphosphine (36 g, 137.29 mmol) were added and the reaction mixture was stirred at rt for 15 min, followed by the dropwise addition of diisopropyl azodicarboxylate (DIAD) (26.89 mL, 27.7 g, 137.29 mmol) at 0 °C and the reaction was stirred at 25 °C for 16h. After completion of the reaction, water was added to the reaction extracted with ethyl acetate (2 times). Combine organic layer was washed with a saturated brine solution to get crude product. Crude was purified by using flash chromatography (0-15% ethyl acetate in hexane) to give pale white solid as ethyl 2-bromo-1-(2,4-dimethoxybenzyl)-4-methyl-imidazole-5-carboxylate (**4**) 22 g, 67% yield.[153] mp: 145-147 °C. IR (KBr) ν_{max}/cm^{-1}: 3080 (aromatic-CH), 2905 (aliphatic-CH), 1697 (COO), 1613 (C=C), 1121 (C-N), 1023 (C-O). ^{1}H NMR (400 MHz, *DMSO-d*$_6$): δppm 6.47-6.43 (m, 2H, 2 x Ar-H), 6.38-6.36 (m, 1H, Ar-H), 5.49 (s, 2H, CH_2), 4.28-4.22 (q, *J* = 8Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.53 (s, 3H, CH_3 (methyl)), 1.33-1.28 (t, *J* = 12Hz, 3H (CH_3)). ^{13}C NMR (100 MHz, *DMSO-d*$_6$): 160.31, 159.96, 157.36, 148.49, 130.25, 126.93, 125.96, 121.77, 117.12, 103.91, 98.41, 77.35, 77.04, 76.72, 66.96, 60.49, 55.33, 46.35, 21.96, 15.89, 14.12. LC-MS (*m/z*): 96% $[M]^+$: 383, $[M+2]^+$: 385. Anal. Calcd. $C_{16}H_{19}BrN_2O_4$ (383.24): C, 50.14; H, 5.00; N, 7.31%. Found C, 50.12; H, 5.12; N, 7.40%.

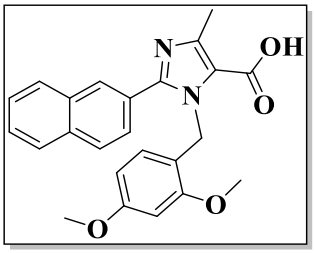
Procedure for synthesis of ethyl 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxylate (6)



To a solution of ethyl 2-bromo-1-(2,4-dimethoxybenzyl)-4-methyl-imidazole-5-carboxylate (**4**) (10 g, 26.09 mmol) in 1,4-dioxane (100 mL) and H_2O (50 mL) in 3 neck RBF, naphthalene-2-ylboronic acid (**5**) (6.73 g, 39.14 mmol) and CS_2CO_3 (25.45 g, 79.09 mmol) were added and the reaction mass was degassed with nitrogen for 15 min, after 15 min $PdCl_2$(dppf) (0.954 g, 1.30 mmol) was added and reaction was stirred at 100 °C for 3h. After completion of the reaction, cool it and water was added and extracted with ethyl acetate (3 times), collect organic and washed with brine (2 times)

and organic was dried over sodium sulphate to get crude product, crude was purified by column purification (0-60% ethylacetate in Hexane) to get Pure product off white solid as ethyl 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxylate (**6**) 7.7 g, 68% yield.[154] mp: 120-122 °C. IR (KBr) ν_{max}/cm^{-1}: 3078 (aromatic-CH), 2939 (aliphatic-CH), 1697 (COO), 1613 (C=C), 1120 (C-N), 1015 (C-O). ^{1}H NMR (400 MHz, *DMSO-d_6*): δppm 8.09-7.87 (m, 4H, Ar-H), 7.65- 7.57 (m, 3H, 3 x Ar-H), 6.52-6.40 (m, 3H, 3 x Ar-H)), 5.47 (s, 2H, CH_2), 4.18-4.17 (d, *J* = 5.6Hz, 2H, CH_2), 3.79-3.65 (m, 6H, 2 x OCH_3), 2.50 (s, 3H (merge with DMSO-d_6), CH_3 (methyl)), 1.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d_6*): 160.71, 160.28, 157.15, 151.28, 147.56, 233.26, 132.82, 128.87, 128.74, 128.57, 128.11, 127.70, 127.61, 127.31, 126.84, 126.38, 120.12, 118.54, 101.06, 98.68, 60.42, 55.77, 55.62, 45.38, 16.19, 14.42. LC-MS (*m/z*): 99% $[M+1]^+$: 431, $[M+2]^+$: 432. Anal. Calcd. $C_{26}H_{26}N_2O_4$ (430.50): C, 72.54; H, 6.09; N, 6.50%. Found C, 72.52; H, 6.11; N, 6.48%.

Procedure for synthesis of 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxylic acid (7)



To a solution of ethyl 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxylate (**6**) (7.7 g, 17.88 mmol) in methanol (70 mL) and H_2O (35 mL) in 3 neck RBF, NaOH (2.14 g, 53.64 mmol) and reaction was stirred at 60°C for 16 hours. After completion of the reaction, cool it and solvent was evaporated, water was added and 4-5 pH with diluted HCl to get solid precipitates filter it and solid compound was dried in vacuum, to get white solid as 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxylic acid (**7**) 6.5 g, 90% yield.[153] mp: 150-152°C. IR (KBr) ν_{max}/cm^{-1}: 3598 (OH), 3049 (aromatic-CH), 2929 (aliphatic-CH), 1686 (C=O), 1612 (C=C), 1121 (C-N), 1002 (C-O). ^{1}H NMR (400 MHz, *DMSO-d_6*): δppm 7.92-7.88 (m, 3H, 3 x Ar-H), 7.79-7.77 (m, 1H, Ar-H), 7.63-7.61 (m, 1H, Ar-H), 7.55-7.50 (m, 2H, 2 x Ar-H), 6.52 (s, 1H, Ar-H), 6.42 (s, 2H, 2 x Ar-H), 5.72 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.46 (s, 3H, CH_3 (methyl)). ^{13}C NMR (100 MHz, *DMSO-d_6*): 161.58, 160.57, 157.49, 133.76, 132.67, 129.74, 128.88, 128.23, 127.88, 127.60, 126.16, 121.29, 117.70, 105.16, 98.76, 55.82, 55.68, 45.72. LC-MS

(*m/z*): 99% $[M+1]^+$: 403. Anal. Calcd. $C_{24}H_{22}N_2O_4$ (402.45): C, 71.63; H, 5.51; N, 6.96%. Found C, 71.68; H, 5.48; N, 6.98%.

General procedure for the synthesis of imidazole-naphthalene hybrid compounds with amide linkage (9a-p)

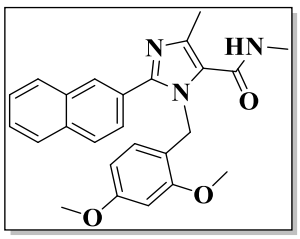
Procedure for compounds 9a-j

To a solution of 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxylic acid (**7**, 1 eq) in DMF (10 vol.), O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU) (1.5 eq) was added at 0°C under nitrogen atmosphere, and mixture was stirred for 30 min at 0°C, after 30 min corresponding aliphatic amine (**8a-j**) (2.0 eq) and DIPEA (2.5 eq) were added and the reaction was stirred at another 1hour at 25°C. Reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was quenched with cold water and extracted with ethyl acetate to get a crude product. Which was purified by reverse phase combi-flash (acetonitrile: 0.1% formic acid in water). The solvent was directly lyophilized to get pure final compounds **9a-j**.

Procedure for compounds 9k-p

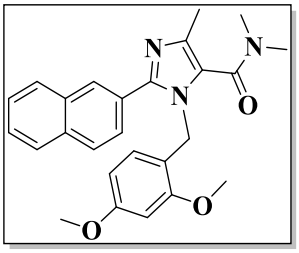
To a solution of 1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxylic acid (**7**, 1 eq) in DMF (10 vol.), 3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (EDC.HCl) (1.5 eq) was added at 0°C under a nitrogen atmosphere, and the mixture was stirred for 15 min at 0°C, after 15 min corresponding aromatic amine (**8k-p**) (1.2 eq) and (4-Dimethylaminopyridine) (DMAP) (0.5 eq) were added and the reaction was stirred at 50-55°C for 16 hours. The reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was quenched with cold water and extracted with ethyl acetate to get a crude product. Which was purified by reverse phase combi-flash (acetonitrile: 0.1% formic acid in water). The solvent was directly lyophilized to get pure final compounds **9k-p**.

1-(2,4-Dimethoxybenzyl)-*N*,4-dimethyl-2-(naphthalen-2-yl)-imidazole-5-carboxamide (9a)



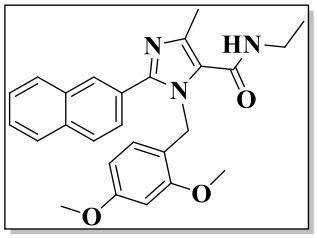
Compound **9a** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8a** (0.03 g, 0.98 mmol). White solid (0.180 g, 87% yield). mp: 162-165 °C. IR (KBr) ν_{max}/cm^{-1}: 3311 (NH), 3050 (aromatic-CH), 2916 (aliphatic-CH), 1629 (C=O-NH), 1612 (C=C), 1121 (C-N), 1032 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.05 (s, 1H), 8.01-7.90 (m, 3H), 7.66-7.63 (m, 1H), 7.62-7.56 (m, 2H), 6.78-6.75 (d, *J* = 12Hz, 1H), 6.44-6.34 (m, 2H), 5.41 (s, 2H), 3.73 (s, 3H), 3.48 (s, 3H), 2.84 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, *DMSO-d₆*): 163.50, 162.08, 160.45, 157.63, 148.74, 138.93, 133.11, 132.94, 128.67, 128.35, 128.08, 127.34, 127.13, 126.75, 125.64, 118.36, 104.84, 98.54, 55.60, 44.13, 26.34, 14.82. LC-MS (m/z): 97% $[M+1]^+$: 416, $[M+2]^+$: 417. Anal. Calcd. $C_{25}H_{25}N_3O_3$ (415.49): C, 72.27; H, 6.07; N, 10.11%. Found C, 72.20; H, 6.18; N, 10.19%.

1-(2,4-Dimethoxybenzyl)-*N*,*N*,4-trimethyl-2-(naphthalen-2-yl)-imidazole-5-carboxamide (9b)



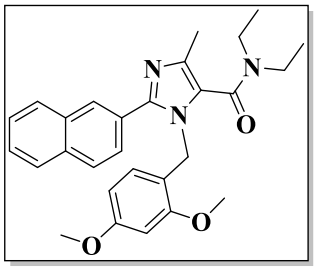
Compound **9b** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8b** (0.044 g, 0.98 mmol). White solid (0.180 g, 84% yield). mp: 162-164 °C. IR (KBr) ν_{max}/cm^{-1}: 3054 (aromatic-CH), 2955 (aliphatic-CH), 1586 (C=C), 1120 (C-N), 1039 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.18 (s, 1H, Ar-H), 8.08-8.06 (d, *J* = 8Hz, 1H, Ar-H), 8.03-7.98 (m, 2H, 2 x Ar-H), 7.78-7.76 (d, *J* = 8Hz, 1H, Ar-H), 7.64-7.59 (m, 2H, 2 x Ar-H), 7.01-6.98 (d, *J* = 12Hz, 1H, Ar-H), 6.47-6.41 (m, 2H, 2 x Ar-H), 4.89 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 2.93 (s, 3H, N-CH_3), 2.57 (s, 3H, N-CH_3), 2.20 (s, 3H, CH_3(methyl)). ^{13}C NMR (100 MHz, *DMSO-d₆*): 163.27, 160.91, 158.33, 149.13, 136.71, 133.11, 133.05, 129.92, 128.75, 128.60, 128.48, 128.37, 128.09, 127.28, 127.09, 126.95, 124.49, 117.51, 104.61, 98.72, 55.68, 44.84, 13.96. LC-MS (*m/z*): 100% $[M+1]^+$: 430, $[M+2]^+$: 431. Anal. Calcd. $C_{26}H_{27}N_3O_3$ (429.52): C, 72.71; H, 6.34; N, 9.78%. Found C, 72.65; H, 6.30; N, 9.82%.

1-(2,4-Dimethoxybenzyl)-*N*-ethyl-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxamide (9c)



Compound **9c** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8c** (0.044 g, 0.98 mmol). White solid (0.180 g, 84% yield). mp: 150-152 °C. IR (KBr) ν_{max}/cm^{-1}: 3315 (NH), 3058 (aromatic-CH), 2937 (aliphatic-CH), 1630 (C=O-NH), 1507 (C=C), 1135 (C-N), 1032 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.05-7.91 (m, 4H), 7.66-7.64 (d, *J* = 8Hz, 1H, Ar-H), 7.60-7.57 (m, 2H, 2 x Ar-H), 6.81-6.79 (d, *J* = 8Hz, 1H, Ar-H), 6.39-6.36 (m, 2H, 2 x Ar-H), 5.40 (s, 2H, CH_2), 3.86-3.75 (m, 5H, $OCH_3 + CH_2$), 3.48 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3 (methyl)), 1.16-1.12 (t, *J* = 8Hz, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d₆*): 161.34, 160.47, 157.70, 148.66, 138.88, 133.09, 132.94, 128.66, 128.54, 128.32, 128.28, 128.07, 127.30, 127.11, 126.79, 125.73, 118.29, 104.83, 98.50, 56.62, 55.54, 44.10, 34.03, 15.22, 14.78. LC-MS (*m/z*): 99% $[M+1]^+$: 430, $[M+2]^+$: 431. Anal. Calcd. $C_{26}H_{27}N_3O_3$ (429.52): C, 72.71; H, 6.34; N, 9.78%. Found C, 72.65; H, 6.30; N, 9.82%.

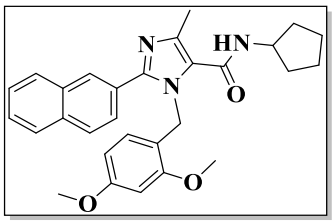
1-(2,4-Dimethoxybenzyl)-*N*,*N*-diethyl-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxamide (9d)



Compound **9d** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8d** (0.071 g, 0.98 mmol). Off white solid (0.190 g, 83% yield). mp: 155-157 °C. IR (KBr) ν_{max}/cm^{-1}: 3058 (aromatic-CH), 2929 (aliphatic-CH), 1619 (C=O-NH), 1541 (C=C), 1120 (C-N), 1039 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.16 (s, 1H, Ar-H), 8.06-8.03 (d, *J* = 12Hz, 1H, Ar-H), 7.99-7.96 (m, 2H, 2 x Ar-H), 7.76-7.74 (d, *J* = 8Hz, 1H), 7.61-7.59 (m, 2H, 2 x Ar-H), 6.98-6.96 (d, *J* = 8Hz, 1H, Ar-H), 6.45-6.41 (m, 2H, 2 x Ar-H), 5.30-5.24 (m, 2H, CH_2), 3.75 (s, 3H, O-CH_3), 3.52 (s, 3H, OCH_3), 3.27 (s, 2H, CH_2), 3.11 (s, 1H, CH), 2.22 (s, 3H,

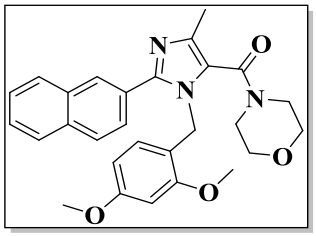
CH_3), 1.17 (s, 3H, CH_3), 0.80 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d₆*): 162.43, 160.82, 158.10, 148.67, 136.33, 133.09, 133.02, 129.30, 128.72, 128.58, 128.36, 128.07, 127.28, 127.08, 126.85, 124.72, 117.58, 104.98, 98.79, 55.74, 44.31, 14.09, 13.41. LC-MS (*m/z*): 96% $[M+1]^+$: 458, $[M+2]^+$: 459. Anal. Calcd. $C_{28}H_{31}N_3O_3$ (457.57): C, 73.50; H, 6.83; N, 9.18%. Found C, 73.61; H, 6.80; N, 9.12%.

***N*-Cyclopentyl-1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxamide (9e)**



Compound **9e** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol), and **8e** (0.083 g, 0.98 mmol). White solid (0.185 g, 79% yield). mp: 152-153 °C. IR (KBr) ν_{max}/cm^{-1}: 3326 (NH), 3056 (aromatic-CH), 2946 (aliphatic-CH), 1653 (C=O), 1507 (C=C), 1123 (C-N), 1030 (C-0). ^{1}H NMR (400MHz, *MeOD*): δppm 8.20 (s, 1H, Ar-H), 8.12-8.10 (d, *J* = 8Hz, 1H, Ar-H), 8.04-8.01 (m, 2H, 2 x Ar-H), 7.74-7.69 (m, 1H, Ar-H), 7.67-7.62 (m, 2H, 2 x Ar-H), 7.01-6.99 (d, *J* = 8Hz, 1H, Ar-H), 6.43-6.39 (m, 2H, 2 x 2Ar-H), 5.46 (s, 2H, CH_2), 4.25-4.18 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3), 2.00-1.93 (m, 2H, CH_2), 1.75-1.65 (m, 4H), 1.50-1.43 (m, 2H, CH + CH_3). ^{13}C NMR (100 MHz, *DMSO-d₆*): 161.02, 159.74, 158.29, 147.36, 135.54, 133.61, 132.79, 130.42, 129.42, 128.89, 128.82, 128.24, 128.07, 127.55, 126.51, 126.03, 116.71, 104.84, 98.56, 55.69, 55.48, 51.10, 45.05, 32.49, 23.91, 13.11. LC-MS (*m/z*): 98% $[M+1]^+$: 470, $[M+2]^+$: 471. Anal. Calcd. $C_{29}H_{31}N_3O_3$ (469.59): C, 74.18; H, 6.65; N, 8.95%. Found C, 74.21; H, 6.60; N, 8.90%.

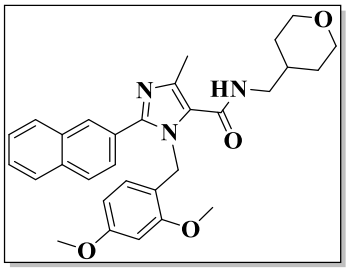
(1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazol-5-yl)(morpholino) methanone (9f)



Compound **9f** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol), and **8f** (0.085 g, 0.98 mmol). White solid

(0.165 g, 70% yield). mp: 156-158 °C. IR (KBr) ν_{max}/cm^{-1}: 3056 (aromatic-CH), 2931(aliphatic-CH), 1645 (C=O), 1550 (C=C), 1112 (C-N), 1023 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.40 (s, 1H, Ar-CH), 8.23-8.21 (d, *J* = 8Hz, 1H, Ar-CH), 8.14-8.06 (m, 2H, 2 x Ar-CH), 7.86-7.84 (d, *J* = 8Hz, 1H, Ar-CH), 7.76-7.69 (m, 2H, 2 x Ar-CH), 7.20-7.18 (d, *J* = 8Hz, 1H, Ar-CH), 6.58-6.46 (m, 2H, 2 x Ar-CH), 5.52-5.49 (m, 1H, CH), 5.35-5.31 (m, 1H, CH), 3.86- 3.78 (m, 4H, CH_3 + CH), 3.77-3.70 (m, 1H, CH), 3.55-3.48 (m, 6H, 2 x OCH_3), 3.40 (s, 1H, CH), 2.81 (s, 2H, CH_2), 2.36 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d₆*): 161.87, 159.28, 158.97, 147.06, 134.21, 132.66, 132.11, 131.24, 130.85, 129.38, 129.17, 128.89, 128.40, 127.97, 126.19, 123.71, 122.27, 114.88, 105.22, 99.13, 66.01, 55.96, 55.93, 46.63, 11.15. LC-MS (*m/z*): 100% $[M+1]^+$: 472, $[M+2]^+$: 473. Anal. Calcd. $C_{28}H_{29}N_3O_4$ (471.56): C, 71.32; H, 6.20; N, 8.91%. Found C, 71.28; H, 6.26; N, 8.82%.

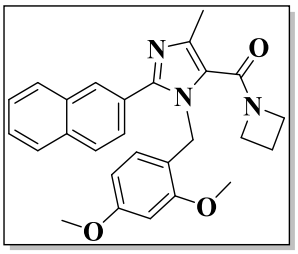
1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)-imidazole-5-carboxamide (9g)



Compound **9g** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8g** (0.113 g, 0.98 mmol). Off white solid (0.170 g, 68% yield). mp: 167-170 °C. IR (KBr) ν_{max}/cm^{-1}: 3293 (NH), 3050 (aromatic-CH), 2920 (aliphatic-CH), 1630 (C=O), 1541 (C=C), 1146 (C-N), 1030 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.07 (s, 1H, Ar-H), 8.05-7.88 (m, 3H, 3 x Ar-H), 7.66-7.64 (d, *J* = 8Hz, 1H, Ar-H), 7.62-7.55 (m, 2H, 2 x Ar-H), 6.74-6.72 (d, *J* = 8Hz, 1H, Ar-CH), 6.47-6.38 (m, 2H, 2 x Ar-CH), 5.41 (s, 2H, CH_2), 3.92-3.85 (m, 2H, CH_2), 3.81-3.75 (m, 4H, OCH_3 + H), 3.57 (s, 3H, OCH_3), 3.30 (s, 1H), 3.17-3.15 (d, *J* = 8Hz, 2H, CH_2), 2.41 (s, 3H, CH_3), 1.60 (s,1H), 1.50-1.47 (d, J=12Hz, 2H, CH_2), 1.27-1.17 (m, 2H, CH_2). ^{13}C NMR(100 MHz, *DMSO-d₆*): 161.69, 160.46, 157.66, 148.70, 138.87, 133.13, 132.97, 129.92, 128.67, 128.50, 128.38, 128.30, 128.24, 128.08, 127.32, 127.13, 126.95, 126.75, 125.70, 118.35, 104.86, 98.58, 67.24, 55.65, 55.63, 44.98, 44.08, 35.31, 30.90, 14.89. LC-MS (*m/z*): 100% $[M+1]^+$: 500, $[M+2]^+$: 500.

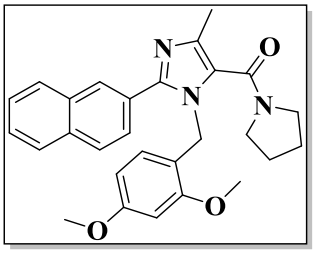
Anal. Calcd. $C_{30}H_{33}N_3O_4$ (499.61): C, 72.12; H, 6.66; N, 8.41%. Found C, 72.20; H, 6.60; N, 8.47%.

Azetidin-1-yl(1-(2,4-dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazol-5-yl)methanone (9h)



Compound **9h** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8h** (0.056 g, 0.98 mmol). Off-white solid (0.120 g, 54% yield). mp: 148-151 °C. IR (KBr) ν_{max}/cm^{-1}: 3032 (aromatic-CH), 2901 (aliphatic-CH), 1645 (C=O), 1507 (C=C), 1133 (C-N), 1030 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.38-8.37 (m, 1H, Ar-H), 8.22-8.20 (d, *J* = 8Hz, 1H, Ar-H), 8.13-8.06 (m, 2H, 2 x Ar-H), 7.85-7.83 (d, *J* = 8Hz, Ar-H), 7.75-7.68 (m, 2H, 2 x Ar-H), 7.13-7.11 (d, *J* = 8Hz, 1H, Ar-H), 6.53-6.49 (m, 1H, Ar-H), 6.46 (s, 1H, Ar-H), 5.50-5.40 (m, 2H, CH_2), 3.81-3.75 (m, 5H, OCH_3, CH_2), 3.50-3.46 (m, 3H, OCH_3), 2.93 (s, 2H, CH_2), 2.53 (s, 2H, CH_2), 2.36-2.32 (m, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d_6*): 161.85, 160.41, 158.95, 146.79, 134.12, 132.70, 131.94, 131.70, 130.66, 130.51, 129.30, 129.13, 128.77, 128.38, 127.91, 126.22, 124.85, 123.42, 114.84, 104.82, 98.89, 55.85, 46.51, 37.58, 34.74, 15.80, 11.09. LCMS (*m/z*): 97% $[M+1]^+$:442. Anal. Calcd. $C_{27}H_{27}N_3O_3$ (441.53): C, 73.45; H, 6.16; N, 9.52%. Found C, 73.42; H, 6.20; N, 9.61%.

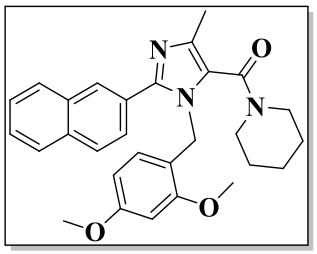
(1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazol-5-yl)(pyrrolidin-1-yl) methanone (9i)



Compound **9i** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8i** (0.07 g, 0.98 mmol). White solid (0.130 g, 57% yield). mp: 152-155 °C. IR (KBr) ν_{max}/cm^{-1}: 3058 (aromatic-CH), 2950 (aliphatic-CH), 1612 (C=O), 1507 (C=C), 1131 (C-N), 1030 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.28 (s, 1H, Ar-H), 8.15-8.13 (d, *J* = 8Hz, 1H, Ar-H), 8.11-8.06 (m, 1H,

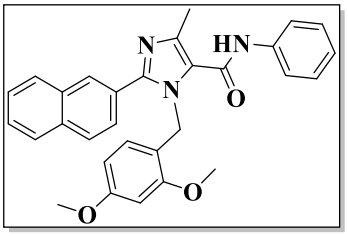
Ar-H), 8.04-8.02 (m, 1H, Ar-H), 7.82-7.80 (d, *J* = 8Hz, 1H, Ar-H), 7.69-7.63 (m, 2H, 2 x Ar-H), 7.14-7.12 (d, *J* = 8Hz, 1H, Ar-H), 6.50-6.46 (m, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 5.30 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.47 (s, 4H, OCH_3 + H), 3.44-3.41 (m, 2H, CH_2), 3.32 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.86-1.82 (m, 2H, CH_2). ^{13}C NMR (100 MHz, *DMSO-d₆*): 161.39, 160.36, 158.89, 147.97, 133.60, 132.90, 131.27, 129.59, 128.94, 128.79, 128.23, 127.97, 127.46, 126.72, 125.87, 116.34, 104.71, 98.81, 55.82, 55.75, 47.53, 45.87, 45.74, 25.43, 24.22, 12.83. LC-MS (*m/z*): 99% $[M+1]^+$= 456, $[M+2]^+$: 457. Anal. Calcd. $C_{28}H_{29}N_3O_3$ (455.56): C, 73.82; H, 6.42; N, 9.22%. Found C, 73.78; H, 6.34; N, 9.32%.

(1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-imidazol-5-yl)(piperidin-1-yl) methanone (9j)



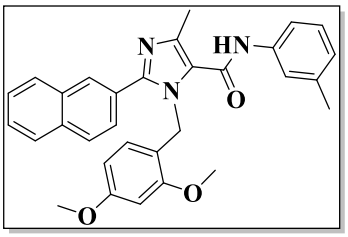
Compound **9j** was prepared from **7** (0.2 g, 0.49 mmol), HATU (0.280 g, 0.73 mmol) in DMF (4 mL), DIPEA (0.158 g, 1.22 mmol) and **8j** (0.083 g, 0.98 mmol). White solid (0.160 g, 68% yield). mp: 158-160°C. IR (KBr) ν_{max}/cm^{-1}: 3047 (aromatic-CH), 2937 (aliphatic-CH), 1612 (C=O), 1507 (C=C), 1129 (C-N), 1030 (C-O). ^{1}H NMR (400MHz, *MeOD*): δppm 8.29 (s, 1H, Ar-H), 8.15-8.13 (d, *J* = 8Hz, 1H, Ar-H), 8.10-8.02 (m, 2H, 2 x Ar-H), 7.82-7.79 (d, *J* = 12Hz, 1H, Ar-H), 7.70-7.63 (m, 2H, 2 x Ar-H), 7.12-7.10 (d, *J* = 8Hz, 1H, Ar-H), 6.52-6.49 (m, 1H, Ar-H), 6.44-6.43 (m, 1H, Ar-H), 5.45-5.25 (m, 2H, CH_2), 3.77 (s, 4H, OCH_3 + H), 3.49 (s, 3H, OCH_3), 3.38-3.24 (m, 2H, 2 x 1H), 2.95-2.93 (d, *J* = 8Hz, 1H), 2.28 (s, 3H, CH_3), 1.58-1.52 (m, 4H, CH_3+ H), 1.37 (s, 1H), 0.75 (s, 1H). ^{13}C NMR (100 MHz, *DMSO-d₆*): 161.43, 160.05, 158.90, 147.93, 113.67, 132.83, 131.23, 129.76, 128.96, 128.86, 128.25, 128.10, 127.54, 126.61, 125.53, 124.20, 116.24, 104.94, 99.10, 55.82, 45.66, 25.50, 24.22, 12.56. LC-MS (*m/z*): 99% $[M+1]^+$: 470, $[M+2]^+$: 471. Anal. Calcd. $C_{29}H_{31}N_3O_3$ (469.59): C, 74.18; H, 6.65; N, 8.95%. Found C, 74.12; H, 6.59; N, 9.03%.

1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-*N*-phenyl-imidazole-5 carboxamide (9k)



Compound **9k** was prepared from **7** (0.2 g, 0.49 mmol), EDC.HCl (0.142 g, 0.74 mmol) in DMF (4 mL), DMAP (0.03 g, 0.245 mmol) and **8k** (0.055 g, 0.59 mmol). White solid (0.190 g, 80% yield). mp: 170-172 °C. IR (KBr) ν_{max}/cm^{-1}: 3276 (NH), 3050 (aromatic-CH), 2935 (aliphatic-CH), 1653 (C=O), 1541 (C=C), 1121 (C-N), 1030 (C-O). ^{1}H NMR (400MHz, *DMSO-d$_6$*): δppm 10.12 (s, 1H), 8.13 (s, 1H), 8.03-7.95 (m, 3H), 7.72-7.63 (m, 3H), 7.60-7.56 (m, 2H), 7.35-7.31 (t, *J* = 8Hz, 2H), 7.10-7.07 (t, *J* = 8Hz, 1H), 6.65-6.63 (d, *J* = 8Hz, 1H), 6.41 (s, 1H), 6.31-6.28 (m, 1H), 5.45 (s, 2H), 3.65 (s, 3H), 3.44 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, *DMSO-d$_6$*): 160.63, 160.19, 157.86, 149.38, 140.39, 139.47, 133.21, 132.97, 129.18, 128.86, 128.74, 128.46, 128.13, 127.43, 127.19, 126.83, 125.79, 124.06, 120.22, 118.06, 104.90, 98.62, 55.64, 55.59, 44.22, 14.96. LC-MS (*m/z*): 97% $[M+1]^+$: 478. Anal. Calcd. $C_{30}H_{27}N_3O_3$ (477.56): C, 75.45; H, 5.70; N, 8.80%. Found C, 75.51; H, 5.58; N, 8.87%.

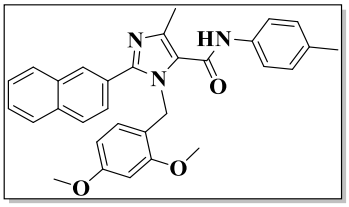
1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-*N*-(m-tolyl)-imidazole-5-carboxamide (9l)



Compound **9l** was prepared from **7** (0.2 g, 0.49 mmol), EDC.HCl (0.142 g, 0.74 mmol) in DMF (4 mL), DMAP (0.03 g, 0.245 mmol) and **8l** (0.063 g, 0.59 mmol). Off white solid (0.210 g, 86% yield). mp: 165-168 °C. IR (KBr) ν_{max}/cm^{-1}: 3293 (NH), 3052 (aromatic-CH), 2922 (aliphatic-CH), 1669 (C=O-NH), 1545 (C=C), 1123 (C-N), 1036 (C-O). ^{1}H NMR (400MHz, *DMSO-d$_6$*): δppm 10.05 (s, 1H, CONH), 8.13 (s, 1H, Ar-H), 8.03-7.94 (m, 3H, 3 x Ar-H), 7.72-7.70 (d, *J* = 8Hz, 1H, Ar-H), 7.60-7.59 (m, 2H, 2 x Ar-H), 7.51 (s, 1H, Ar-H), 7.46-7.44 (d, *J* = 8Hz, 1H, Ar-H), 7.24-7.20 (t, *J* = 8Hz, 1H, Ar-H), 6.92-6.91 (d, *J* = 4Hz, 1H, Ar-H), 6.65-6.63 (d, *J* = 8Hz, 1H, Ar-H), 6.44-

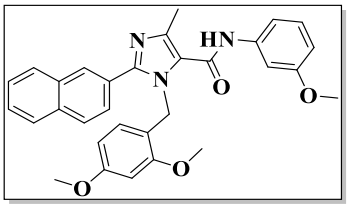
6.43 (d, *J* = 8Hz, 1H, Ar-H), 6.32-6.30 (d, *J* = 8Hz, 1H, Ar-H), 5.45 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d₆*): 160.58, 160.12, 157.80, 149.30, 140.32, 139.38, 138.33, 133.18, 132.95, 129.02, 128.77, 128.72, 128.44, 128.11, 127.42, 127.18, 126.80, 125.80, 124.74, 120.64, 118.05, 117.36, 104.86, 95.58, 55.62, 44.16, 21.67, 14.95. LC-MS (*m/z*): 100% $[M+1]^+$: 492, $[M+2]^+$: 493. Anal. Calcd. $C_{31}H_{29}N_3O_3$ (491.59): C, 75.74; H, 5.95; N, 8.55%. Found C, 75.69; H, 5.87; N, 8.62%.

1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-*N*-(p-tolyl)-1*H*-imidazole-5-carboxamide (9m)



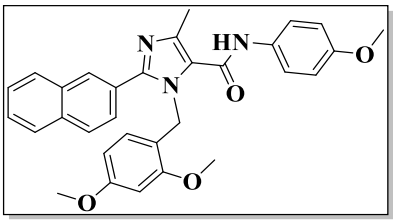
Compound **9m** was prepared from **7** (0.2 g, 0.49 mmol), EDC.HCl (0.142 g, 0.74 mmol) in DMF (4 mL), DMAP (0.03 g, 0.245 mmol) and **8m** (0.063 g, 0.59 mmol). Brown solid (0.190 g, 78% yield). mp: 166-168 °C. IR (KBr) ν_{max}/cm^{-1}: 3287 (NH), 3097 (aromatic-CH), 2922 (aliphatic-CH), 1669 (C=O-NH), 1535 (C=C), 1120 (C-N), 1036 (C-O). ^{1}H NMR (400MHz, *DMSO-d₆*): δppm 10.04 (s, 1H, CONH), 8.13 (s, 1H, Ar-H), 8.03-7.95 (m, 3H, 3 x Ar-H), 7.72-7.70 (d, *J* = 8Hz, 1H, Ar-H), 7.61-7.54 (m, 4H, 4 x Ar-H), 7.15-7.13 (d, *J* = 8Hz, 2H, 2 x Ar-H), 6.66-6.64 (d, *J* = 8Hz, 1H, Ar-H), 6.31 (s, 1H, Ar-H), 6.29-6.28 (d, *J* = 4Hz, 1H, Ar-H), 5.45 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d₆*): 160.59, 159.99, 157.85, 149.27, 140.14, 136.92, 133.17, 133.03, 132.96, 129.55, 128.88, 128.72, 128.45, 128.11, 127.41, 127.17, 126.82, 125.84, 120.17, 118.04, 104.82, 98.57, 70.24, 55.61, 55.55, 44.17, 20.96, 14.93. LC-MS (*m/z*): 100% $[M+1]^+$: 492. Anal. Calcd. $C_{31}H_{29}N_3O_3$ (491.59): C, 75.74; H, 5.95; N, 8.55%. Found C, 75.79; H, 5.89; N, 8.60%.

1-(2,4-Dimethoxybenzyl)-*N*-(3-methoxyphenyl)-4-methyl-2-(naphthalen-2-yl)-imidazole-5-carboxamide (9n)



Compound **9n** was prepared from **7** (0.2 g, 0.49 mmol), EDC.HCl (0.142 g, 0.74 mmol) in DMF (4 mL), DMAP (0.03 g, 0.245 mmol) and **8n** (0.072 g, 0.59 mmol). Yellow solid (0.220 g, 87% yield). mp: 162-165 °C. IR (KBr) ν_{max}/cm^{-1}: 3322 (NH), 3015 (aromatic-CH), 2926 (aliphatic-CH), 1638 (C=O-NH), 1541 (C=C), 1108 (C-N), 1034 (C-O). ^{1}H NMR (400MHz, *DMSO-d$_6$*): δppm 10.10 (s, 1H, CONH), 8.13 (s, 1H, Ar-H), 8.03-7.96 (m, 3H, 3 x Ar-H), 7.72-7.70 (d, *J* = 8Hz, 1H, Ar-H), 7.62-7.59 (m, 2H, 2 x Ar-H), 7.34 (s, 1H, Ar-H), 7.27-7.22 (m, 2H, 2 x Ar-H), 6.70-6.62 (m, 2H, 2 x Ar-H), 6.44 (s, 1H, Ar-H), 6.31-6.29 (d, *J* = 8Hz, 1H, Ar-H), 5.45 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d$_6$*): 160.63, 160.19, 160.00, 157.87, 149.42, 140.63, 140.46, 133.22, 132.97, 129.99, 128.83, 128.73, 128.45, 128.12, 127.43, 127.19, 126.81, 125.78, 118.06, 112.47, 109.46, 106.02, 104.91, 98.64, 55.64, 55.59, 55.52, 49.08, 44.20, 14.96. LC-MS (*m/z*): 100% $[M+1]^+$: 508, $[M+2]^+$: 509. Anal. Calcd. $C_{31}H_{29}N_3O_4$ (507.59): C, 73.35; H, 5.76; N, 8.28%. Found C, 73.27; H, 5.71; N, 8.14%.

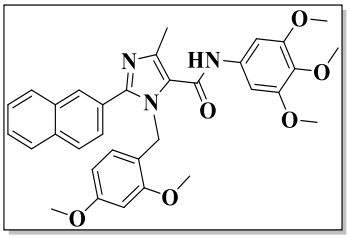
1-(2,4-Dimethoxybenzyl)-*N*-(4-methoxyphenyl)-4-methyl-2-(naphthalen-2-yl)-1*H*-imidazole-5-carboxamide (9o)



Compound **9o** was prepared from **7** (0.2 g, 0.49 mmol) and EDC.HCl (0.142 g, 0.74 mmol) in DMF (4 mL), DMAP (0.03 g, 0.245 mmol), **8o** (0.072 g, 0.59 mmol). Off white solid (0.210 g, 83% yield). mp: 164-167 °C. IR (KBr) ν_{max}/cm^{-1}: 3296 (NH), 3049 (aromatic-CH), 2925 (aliphatic-CH), 1640 (C=O-NH), 1507 (C=C), 1135 (C-N), 1034 (C-O). ^{1}H NMR (400MHz, *DMSO-d$_6$*): δppm 9.98 (s, 1H, CONH), 8.10 (s, 1H, Ar-H), 8.02-7.93 (m, 3H, 3 x Ar-H), 7.70-7.68 (d, *J* = 8Hz, 1H, Ar-H), 7.61-7.53 (m, 4H, 4 x Ar-H), 6.92-6.90 (d, *J* = 8Hz, 2H, 2 x Ar-H), 6.66-6.64 (d, *J* = 8Hz, 1H, Ar-H), 6.41 (s, 1H, Ar-H), 6.30-6.28 (d, *J* = 8Hz, 1H, Ar-H), 5.43 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d$_6$*): 160.61, 159.85, 157.86, 156.05, 149.19, 139.95, 133.19, 132.98, 132.54, 128.88, 128.72, 128.52, 128.43, 128.11, 127.39, 127.17, 126.84, 125.92, 121.83, 118.12, 114.36, 104.90, 98.61, 55.71, 55.64, 44.18, 14.92. LC-MS (*m/z*): 100% $[M+1]^+$:

508, $[M+2]^+$: 509. Anal. Calcd. $C_{31}H_{29}N_3O_4$ (507.59): C, 73.35; H, 5.76; N, 8.28%. Found C, 73.28; H, 5.80; N, 8.14%.

1-(2,4-Dimethoxybenzyl)-4-methyl-2-(naphthalen-2-yl)-*N*-(3,4,5-trimethoxyphenyl)-1*H*-imidazole-5-carboxamide (9p)



Compound **9p** was prepared from **7** (0.2 g, 0.49 mmol) and EDC.HCl (0.142 g, 0.74 mmol) in DMF (4 mL), DMAP (0.03 g, 0.245 mmol), **8p** (0.108 g, 0.59 mmol). Off white solid (0.225 g, 80% yield). mp: 160-162 °C. IR (KBr) ν_{max}/cm^{-1}: 3263 (NH), 3054 (aromatic-CH), 2929 (aliphatic-CH), 1636 (C=O-NH), 1507 (C=C), 1126 (C-N), 1026 (C-O). ^{1}H NMR (400MHz, *DMSO-d$_6$*): δppm 10.04 (s, 1H, CONH), 8.12 (s, 1H, Ar-H), 8.03-7.93 (m, 3H, 3 x Ar-H), 7.72-7.70 (d, *J* = 8Hz, 1H, Ar-H), 7.61-7.56 (m, 2H, 2 x Ar-H), 7.08 (s, 2H, 2 x Ar-H), 6.64-6.62 (d, *J* = 8Hz, 1H, Ar-H), 6.45 (s, 1H, Ar-H), 6.34-6.32 (d, *J* = 8Hz, 1H, Ar-H), 5.45 (s, 2H, CH_2), 3.76 (s, 6H, 2 x OCH_3), 3.69 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, *DMSO-d$_6$*): 160.60, 160.02, 157.79, 153.22, 149.33, 140.36, 135.59, 134.33, 133.21, 132.97, 128.72, 128.63, 128.44, 128.12, 127.43, 127.19, 126.77, 125.83, 118.12, 104.99, 98.66, 98.06. LC-MS (*m/z*): 100% $[M+1]^+$: 568, $[M+2]^+$: 569. Anal. Calcd. $C_{26}H_{27}N_3O_3$ (429.52): C, 69.83; H, 5.86; N, 7.40%. Found C, 69.79; H, 5.90; N, 7.48%.

3.7.2 Protocol of Antimicrobial Activity

The antibacterial and antifungal activity was evaluated against two gram-positive bacteria (*B. subtilis* and *S. aureus*), two gram-negative bacteria (*P. aeruginosa* and *E. coli*), and the common fungal pathogens *A. niger* and *C. albicans*. The inhibitory zone (mm) of nutritional agar composed of sodium chloride (5.0 gL^{-1}), beef extract (10.0 gL^{-1}), and peptone (10.0 gL^{-1}) was evaluated using the antibacterial and antifungal agents chloramphenicol (30 µg/disc), gentamicin (10 µg/disc), and nystatin (10 µg/disc), respectively. The medium was adjusted to a pH of 7.2 before sterilization.[157] The experimental results demonstrated that the examined compounds significantly inhibited all bacterial strains, with inhibition zones varying from 10 to 36 mm, and from 11 to 30

mm for fungal species. Compared to reference drugs, the synthesized compound demonstrated enhanced and more balanced action. The antibacterial efficacy of the examined compound was evaluated at a concentration of 10 µg/disc in DMSO.

3.7.3 Protocol of Molecular Docking Study

High-resolution crystal structures of *E. coli* DNA gyrase B (PDB: 4duh) was retrieved from the PDB database (https://www.rcsb.org/). To facilitate molecular docking, Discovery Studio Visualizer (v21.1.0) was employed to prepare the protein receptors by eliminating attached ligands and water molecules. This step ensured that the docking study remained unaffected. Furthermore, energy minimization with empirical force fields was performed to generate lower energy conformations for the proteins.[158] The molecular docking analysis utilized AutoDock (v4.2) virtual screening software, considering 4duh protein as macromolecules and the compounds as ligand molecules. The cubical grid box size was set at 72.77 × 47.35 × 62.99 for 4duh. Each compound underwent eight independent docking runs, and conformations were clustered based on a root mean square deviation (RMSD) value of less than 2.0 Å.[159] The choice of the optimal binding pose was based on the lowest free binding energy (in kcal/mol).[160] Discovery Studio Visualizer (v21.1.0) was employed to scrutinize molecular interactions.

3.7.4 Protocol of Molecular Dynamic Simulation

A molecular dynamics simulation lasting 100 nanoseconds was performed with Schrodinger LLC's Desmond program.[161-162] Before initiating MDS, protein-ligand docking was a crucial first step to ascertain the molecular positioning in the protein's active site. MDS, based on Newton's classical equation of motion, simulates atomic motions over time, providing insights into ligand-binding dynamics within a physiological context.[163] The ligand-receptor complex was pre-processed using maestro's protein preparation wizard, which included optimization, minimization, and the resolution of any missing residues as required. The system was then developed via the system builder tool. The models were relaxed prior to simulation, and trajectories were recorded for analysis at intervals of 100 ps.

3.8 Conclusion

A series of hybrid naphthalene-imidazole derivatives was synthesized and characterized using ^{1}H NMR, ^{13}C NMR, LC-MS, and IR spectroscopy. All produced compounds were assessed for their antibacterial characteristics. The majority of the newly synthesized compounds demonstrated exceptional antibacterial activity against both Gram-positive and Gram-negative infections. Among all the produced compounds, two, **9k** and **9p**, had significant antibacterial action, achieving the highest docking scores of -8.7 kJ/mol and -8.5 kJ/mol, respectively. Compounds **9e**, **9l**, and **9m** had significant or moderate antibacterial activity. Moreover, docking and molecular dynamics research have indicated that compound 9k may demonstrate antibacterial efficacy by inhibiting *E. coli* DNA gyrase.

3.9 Representative spectral data

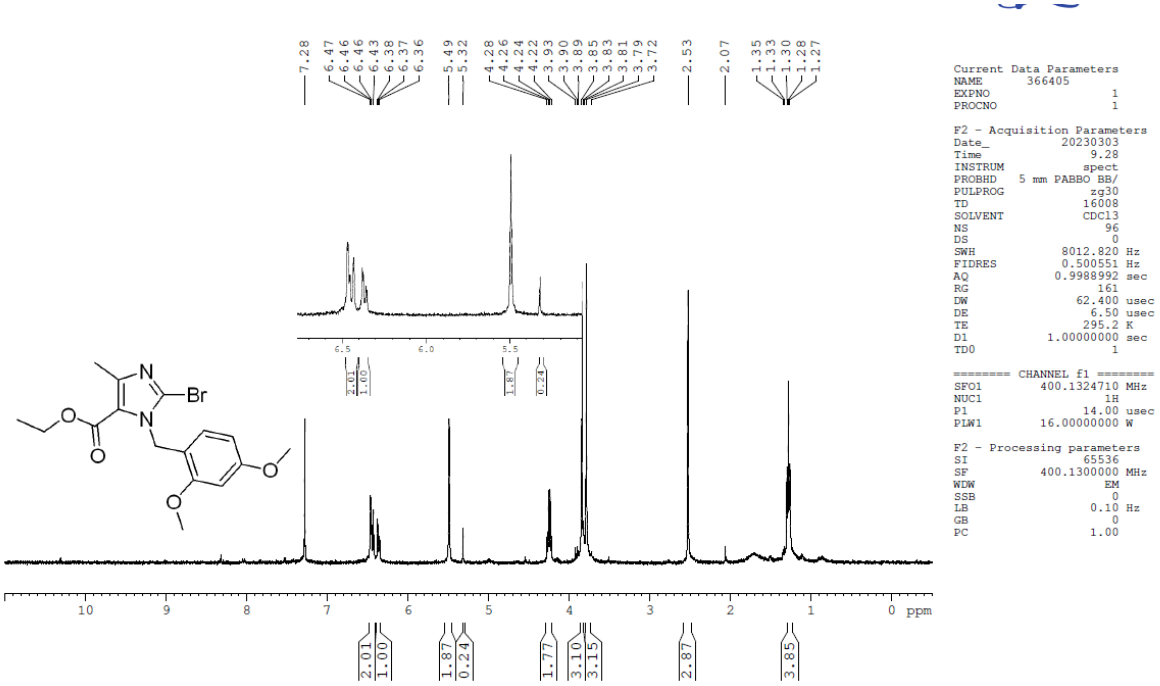


Figure 16: ^{1}H NMR of compound **4.**

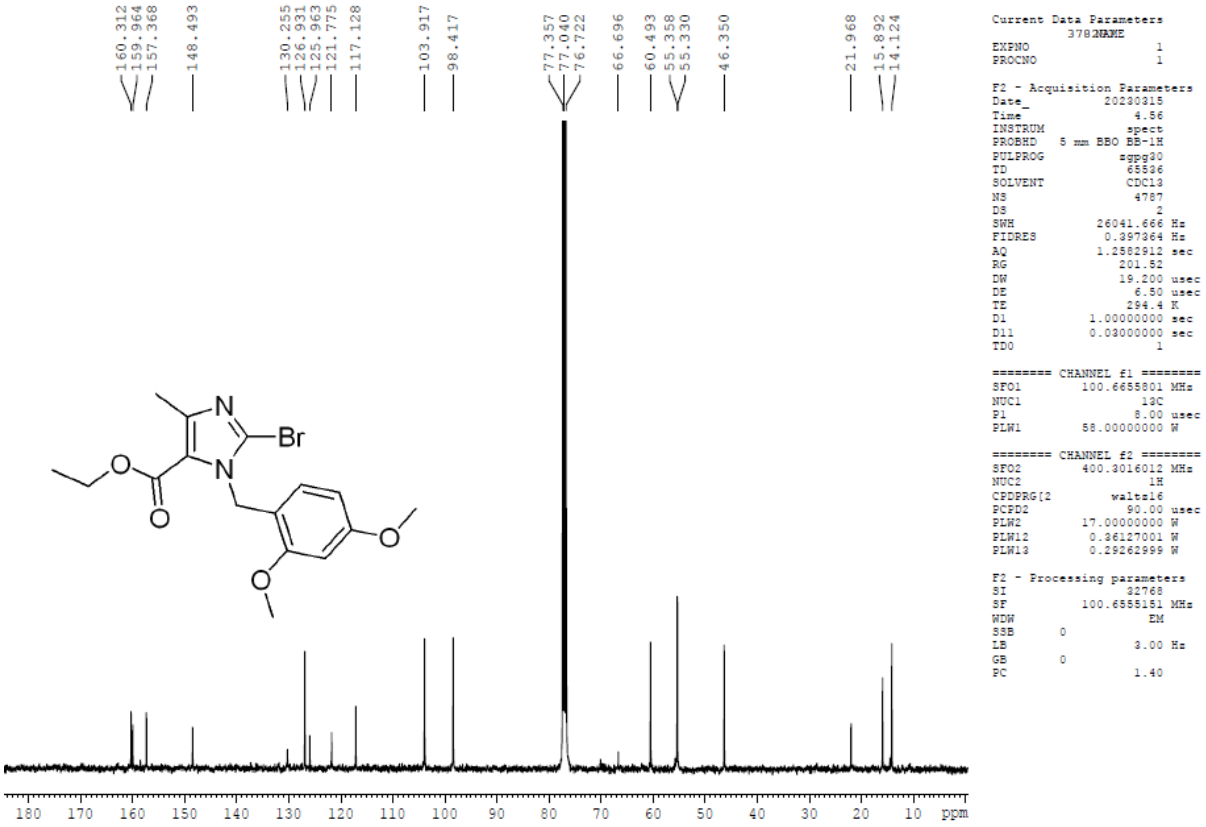
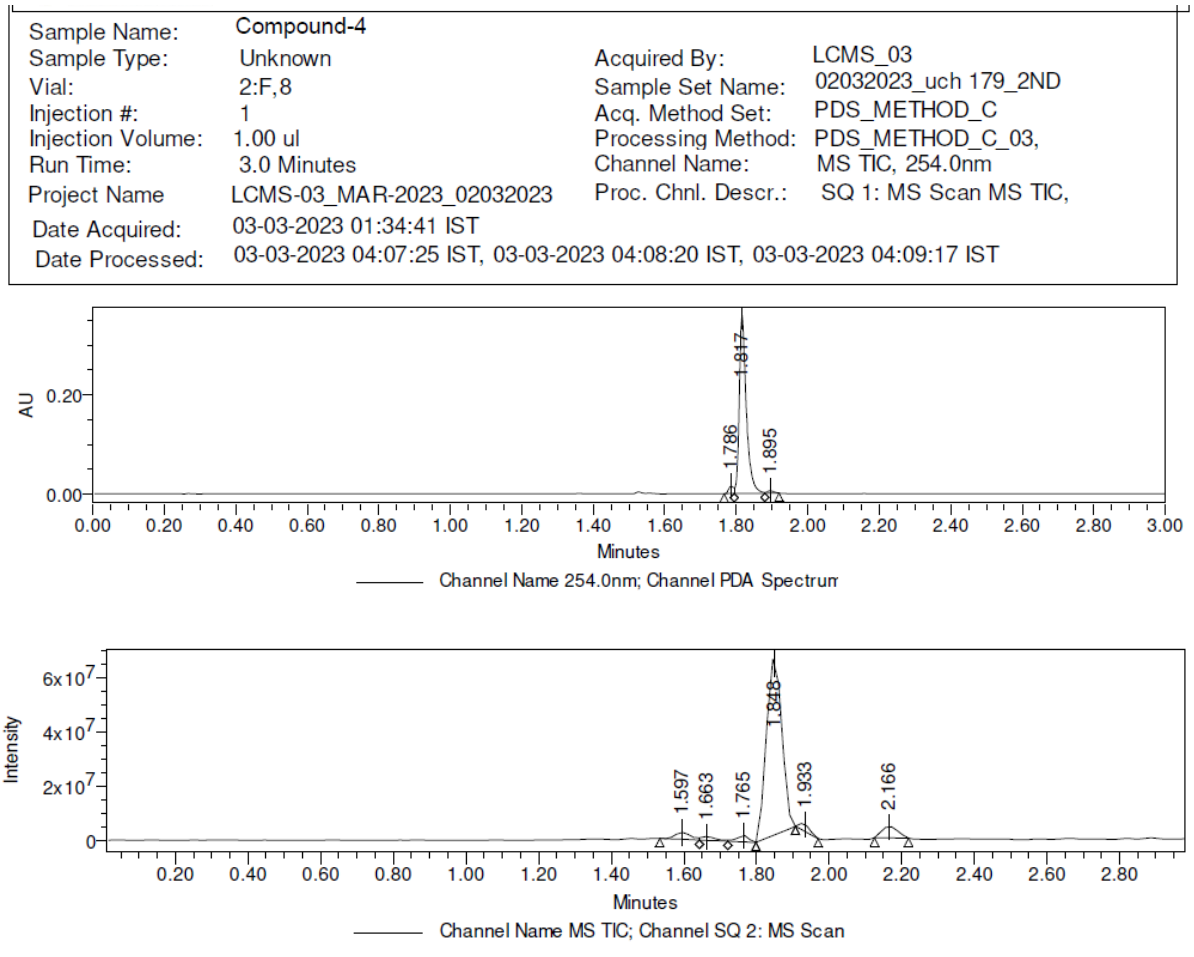
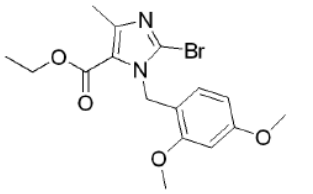


Figure 17: ^{13}C NMR of compound **4.**



Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.786		14775	14732	2.88	PDA Spectrum	254.0nm
2	1.817		357308	489479	95.84	PDA Spectrum	254.0nm
3	1.895		4941	6498	1.27	PDA Spectrum	254.0nm



Chemical Formula: $C_{16}H_{19}BrN_2O_4$
Molecular Weight: 383.24

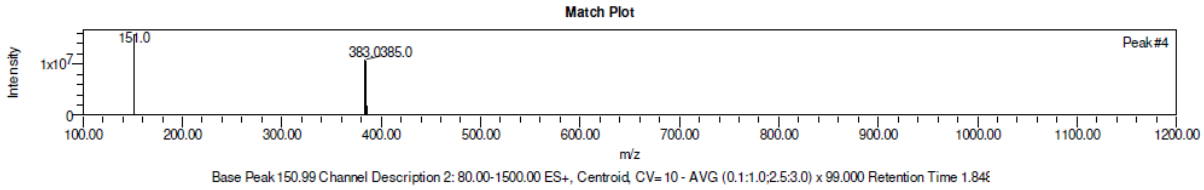


Figure 18: LC-MS of compound **4.**

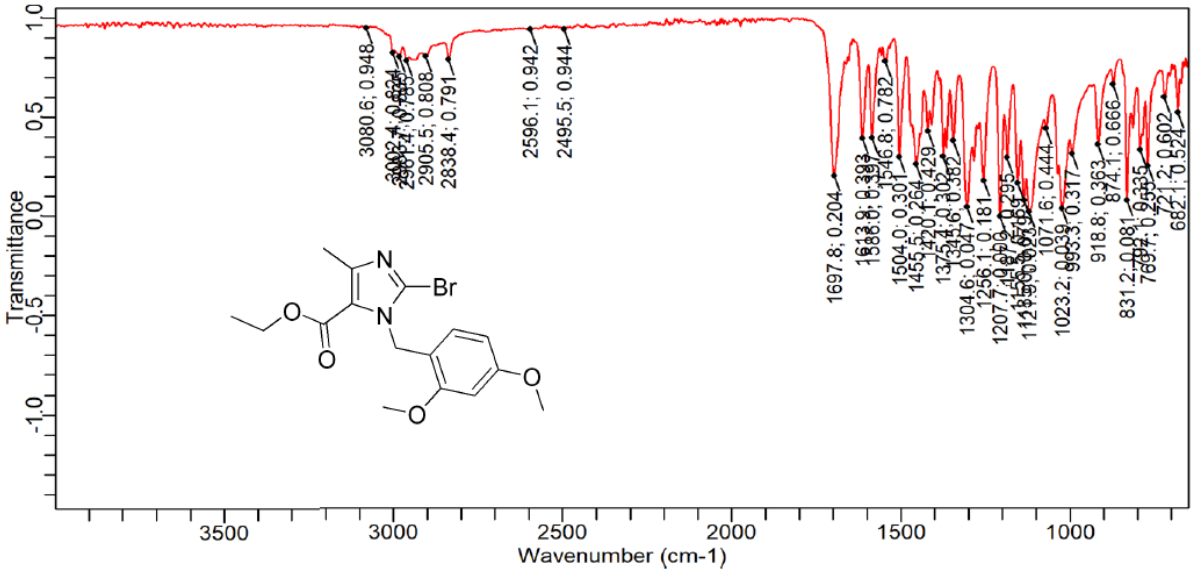


Figure 19: IR of compound **4.**

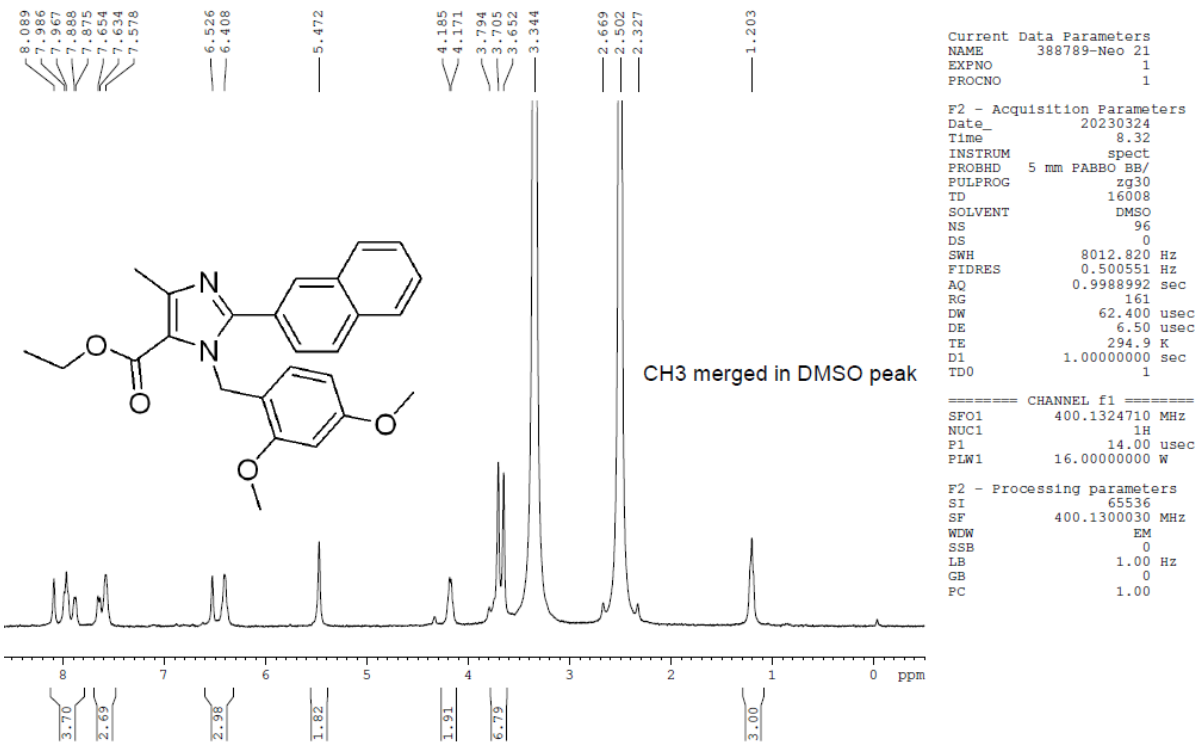


Figure 20: ^{1}H NMR of compound **6.**

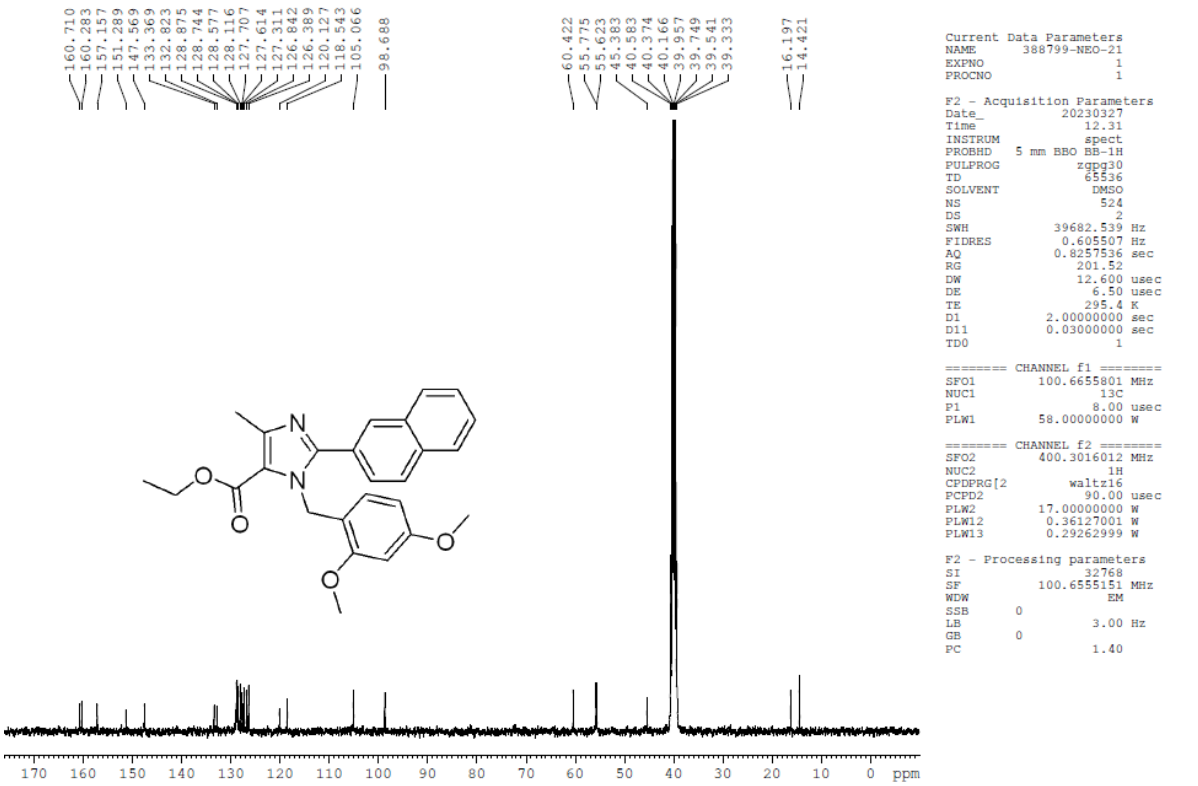
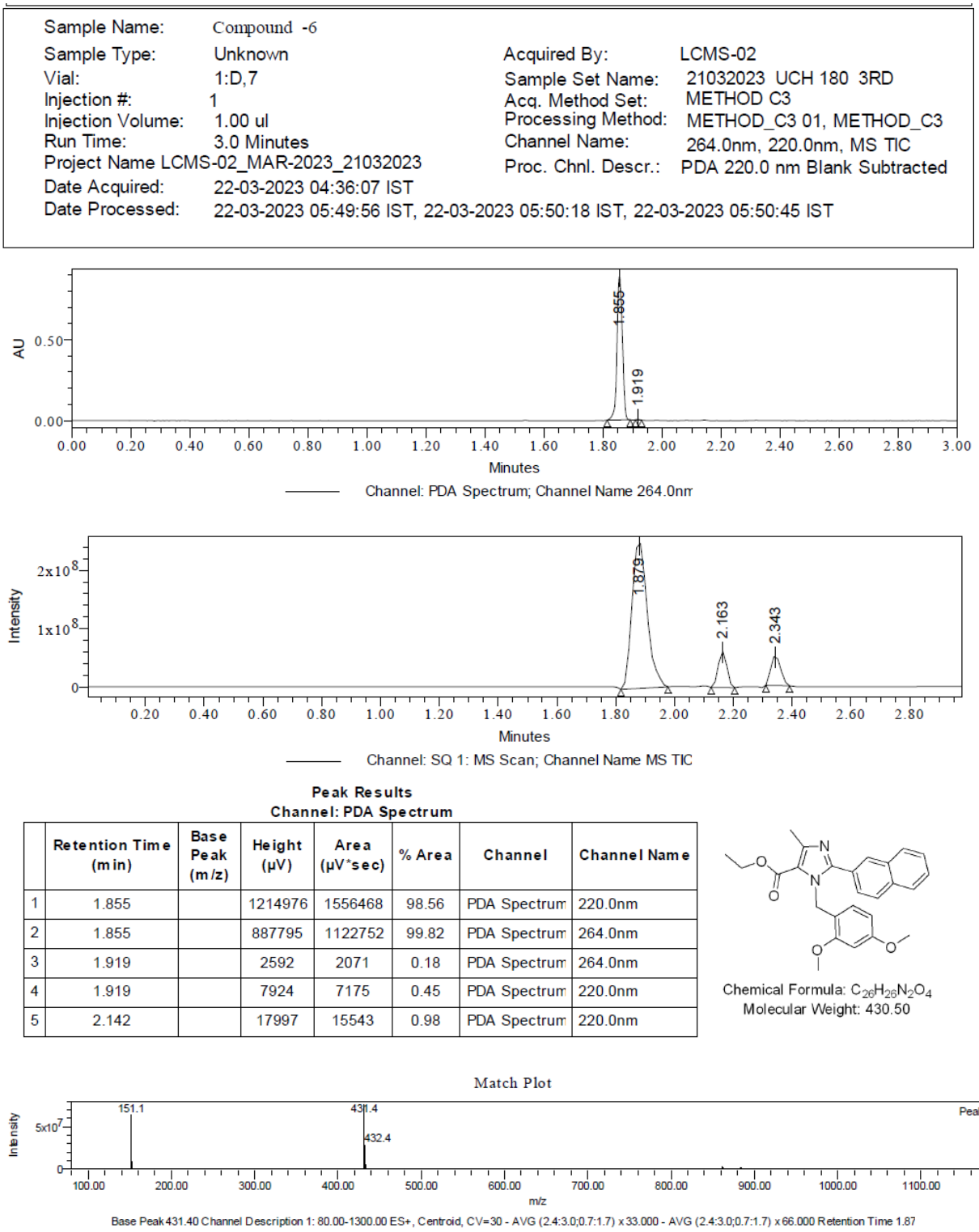


Figure 21: ^{13}C NMR of compound **6.**



Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.855		1214976	1556468	98.56	PDA Spectrum	220.0nm
2	1.855		887795	1122752	99.82	PDA Spectrum	264.0nm
3	1.919		2592	2071	0.18	PDA Spectrum	264.0nm
4	1.919		7924	7175	0.45	PDA Spectrum	220.0nm
5	2.142		17997	15543	0.98	PDA Spectrum	220.0nm

Figure 22: LC-MS of compound **6.**

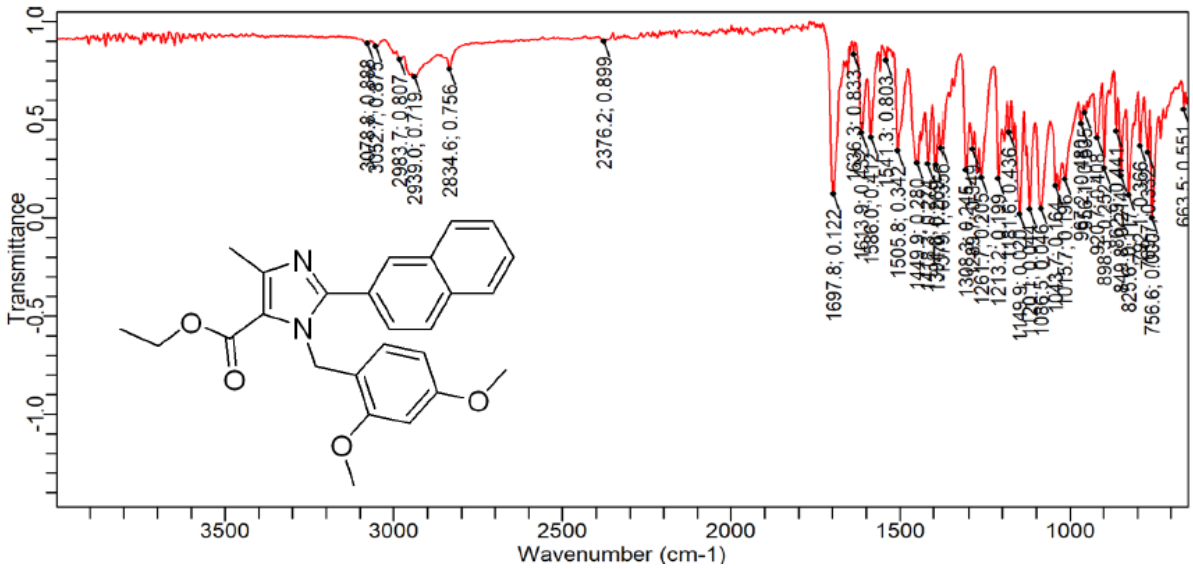


Figure 23: IR of compound **6.**

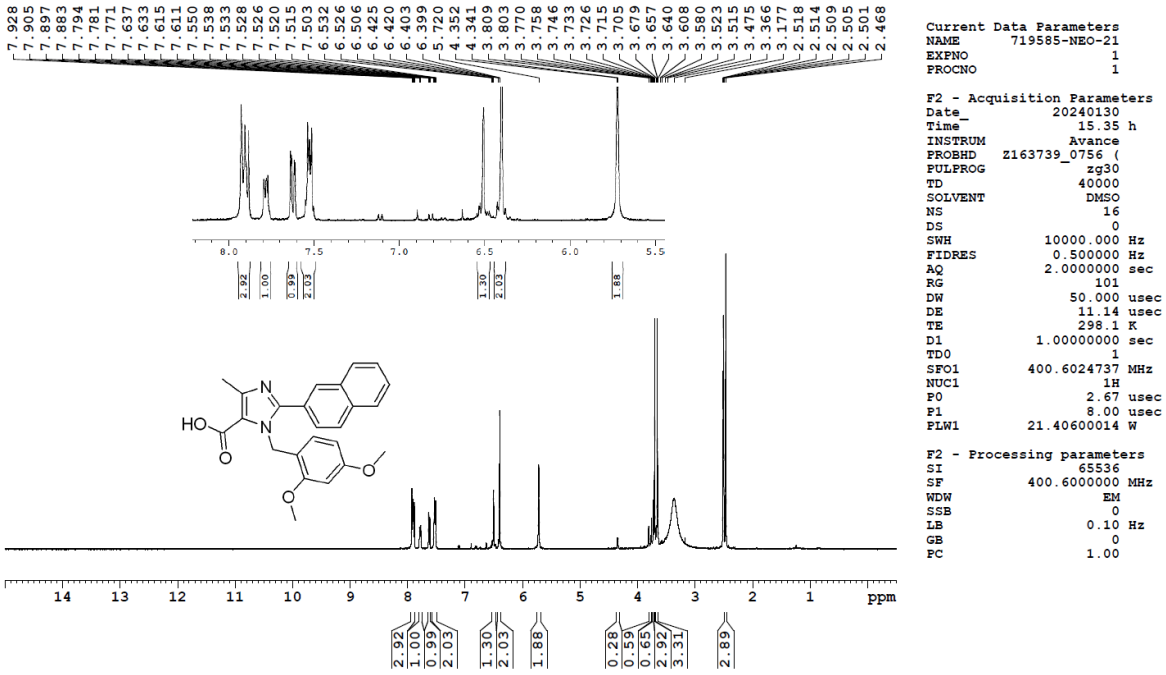


Figure 24: ^{1}H NMR of compound **7.**

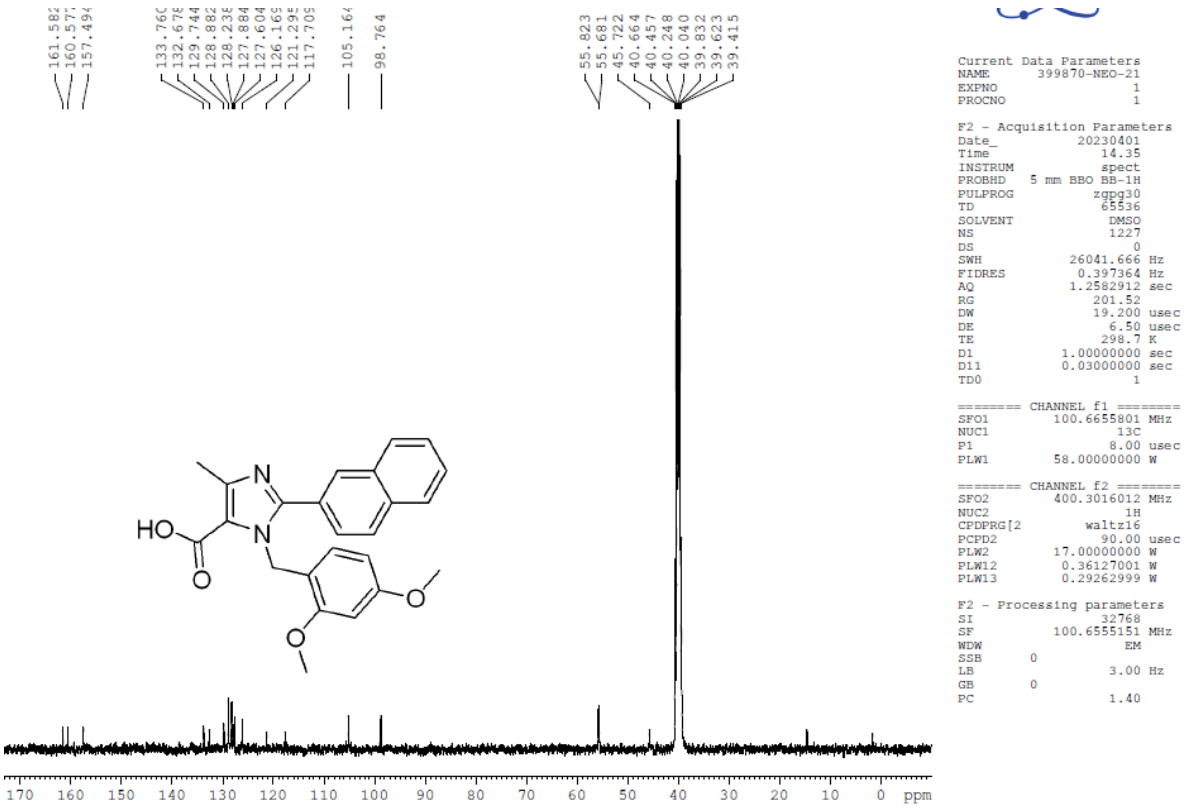
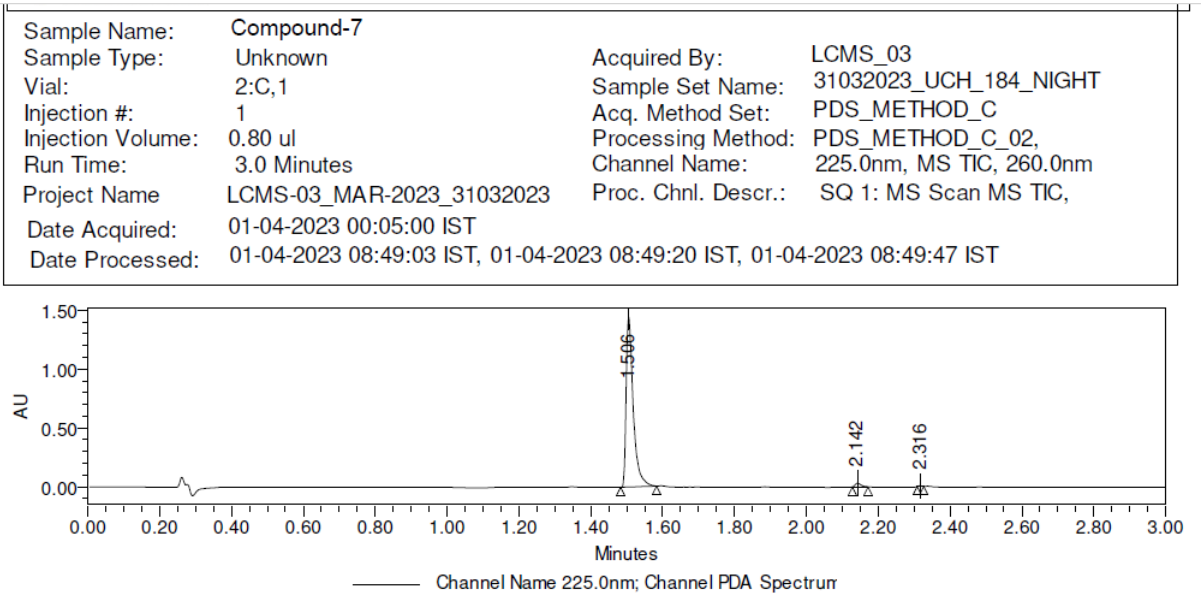
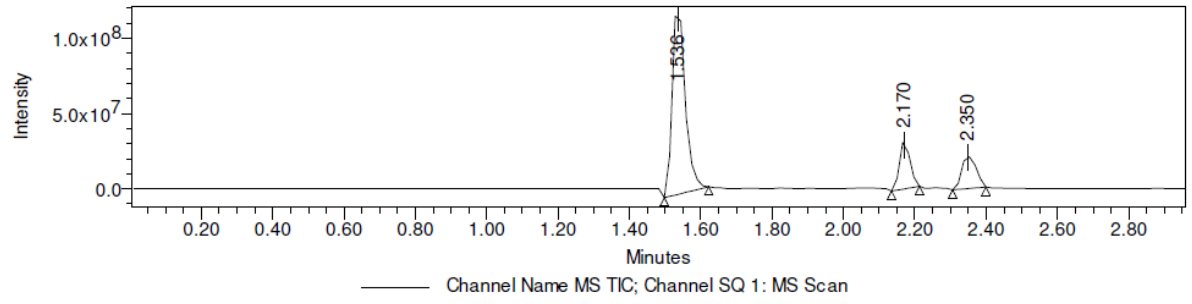


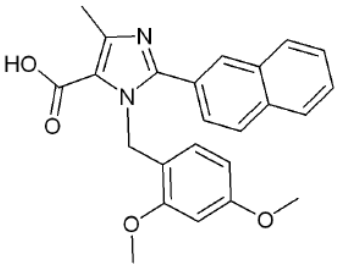
Figure 25: ^{13}C NMR of compound **7.**



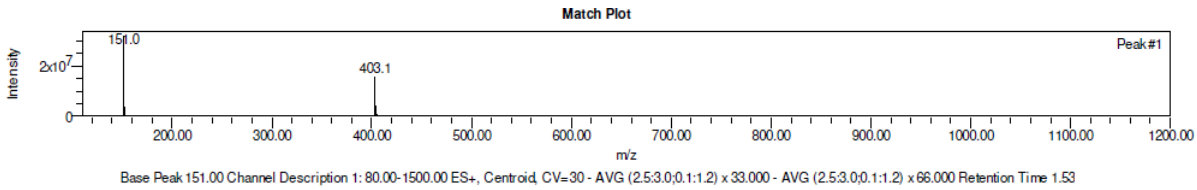


Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.347		6715	6273	0.37	PDA Spectrum	260.0nm
2	1.506		1270799	1668235	99.48	PDA Spectrum	260.0nm
3	1.506		1448179	1980191	98.10	PDA Spectrum	225.0nm
4	2.142		2614	2435	0.15	PDA Spectrum	260.0nm
5	2.142		31657	35251	1.75	PDA Spectrum	225.0nm
6	2.316		5043	3096	0.15	PDA Spectrum	225.0nm



Chemical Formula: $C_{24}H_{22}N_2O_4$
Molecular Weight: 402.45



Base Peak 151.00 Channel Description 1: 80.00-1500.00 ES+, Centroid, CV=30 - AVG (2.5:3.0;0.1:1.2) x 33.000 - AVG (2.5:3.0;0.1:1.2) x 66.000 Retention Time 1.53

Figure 26: LC-MS of compound **7.**

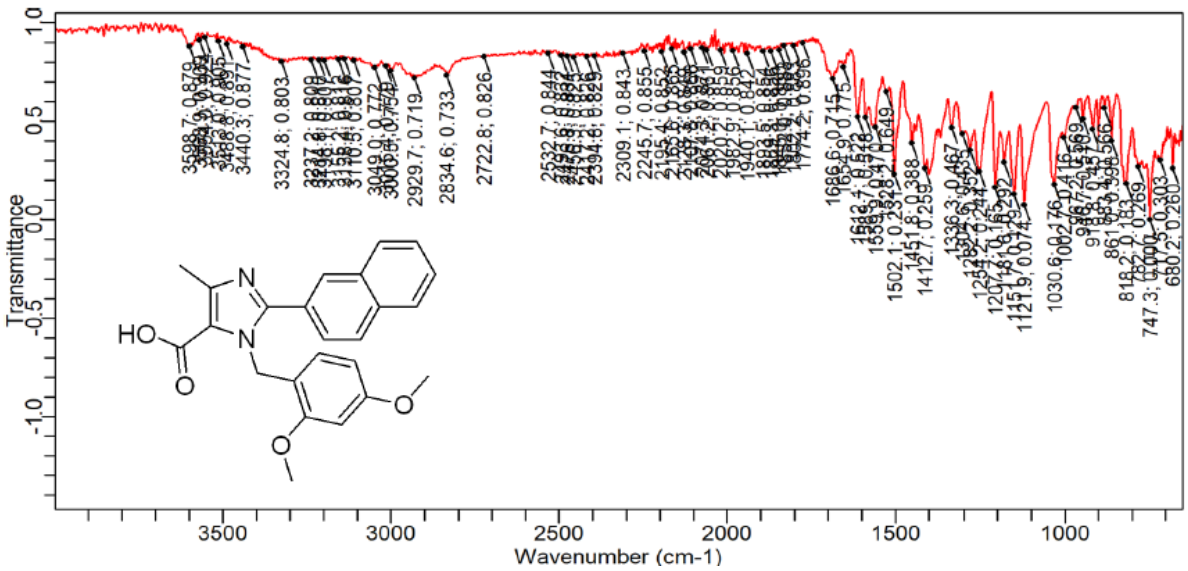


Figure 27: IR of compound **7.**

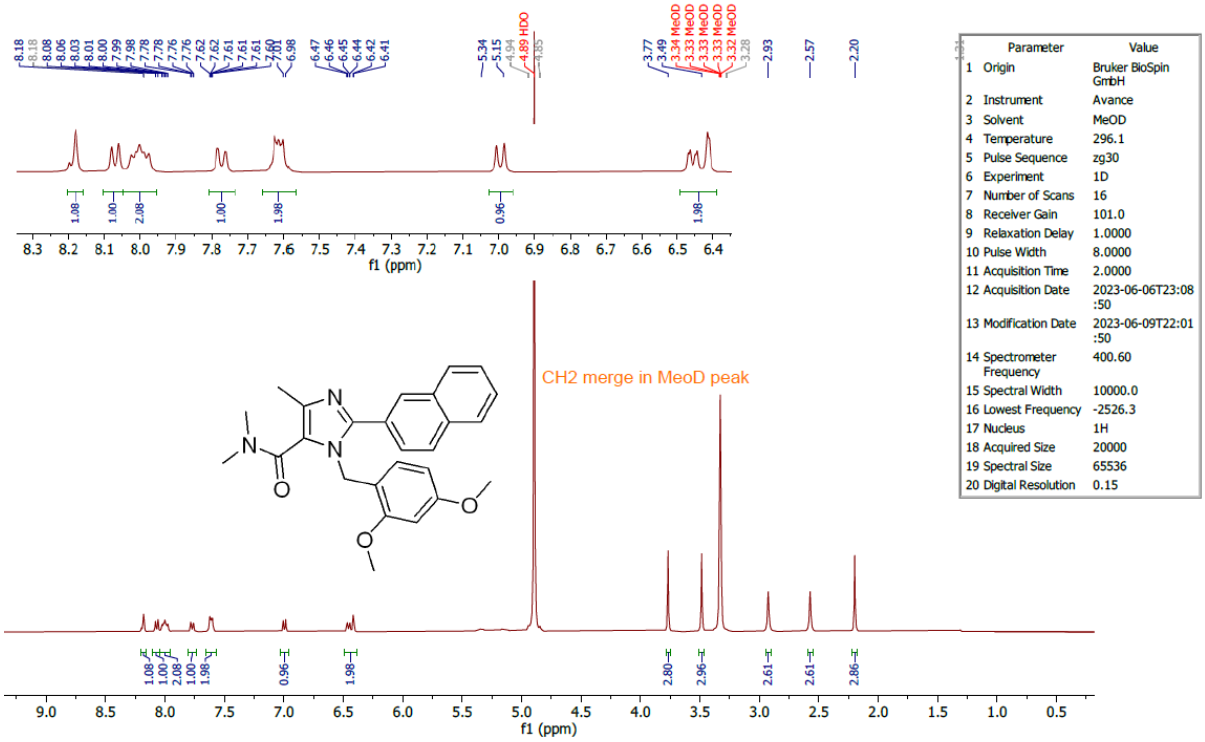


Figure 28: ^{1}H NMR of compound **9b.**

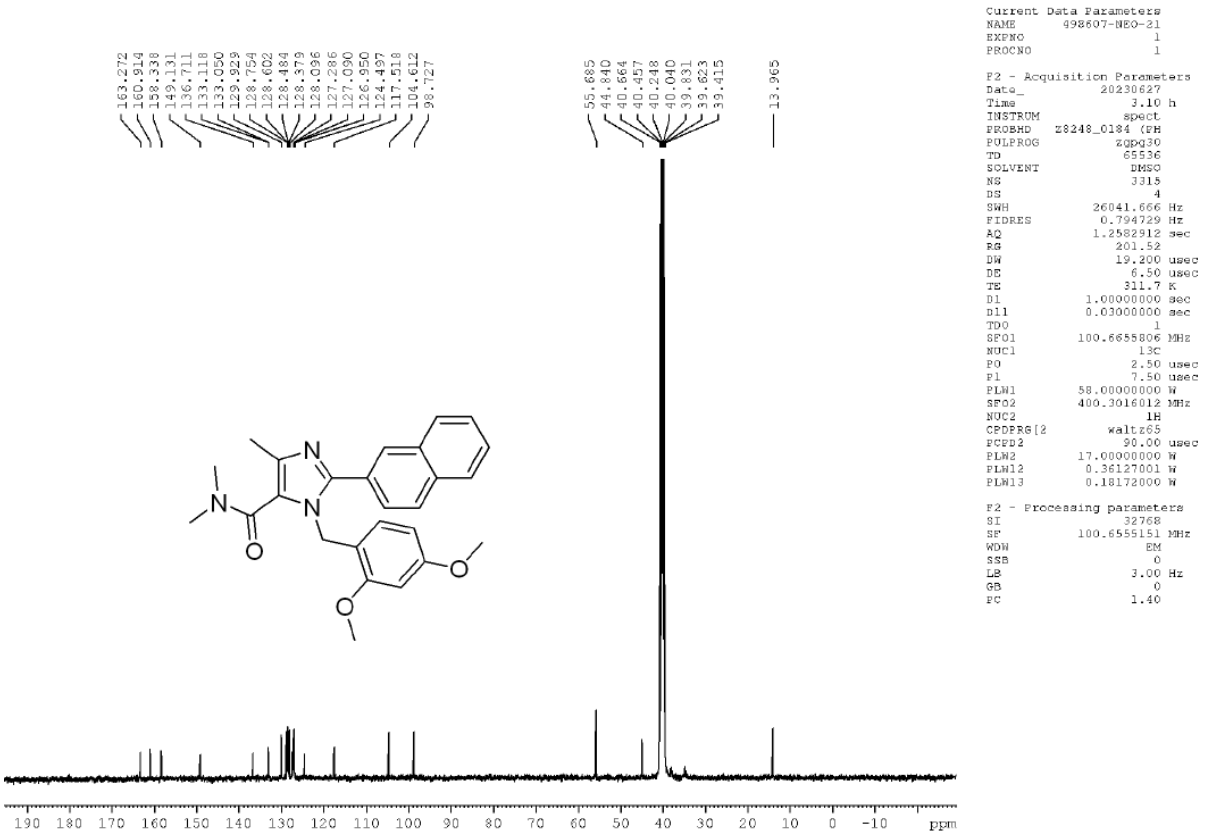


Figure 29: ^{13}C NMR of compound **9b.**

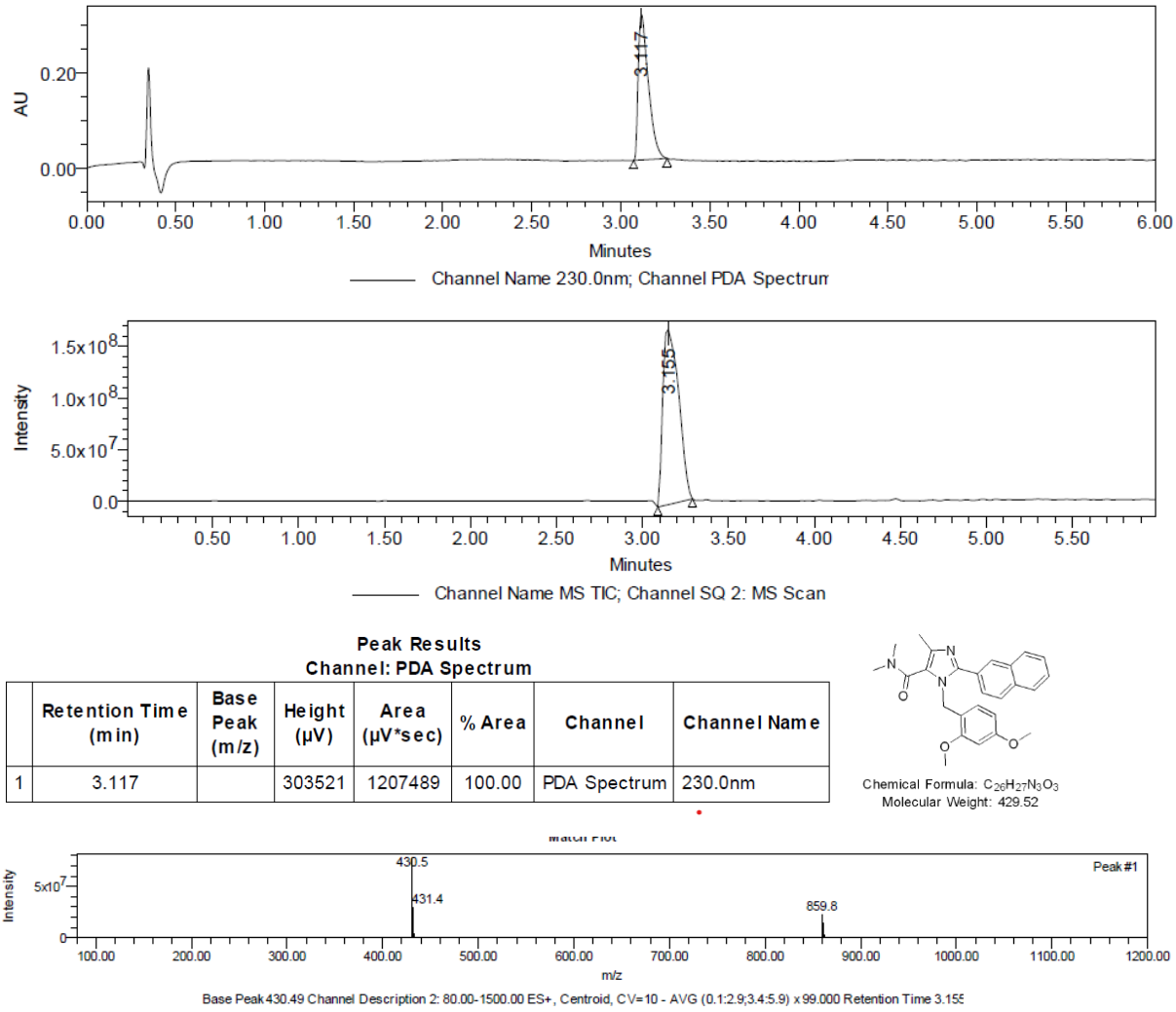


Figure 30: LC-MS of compound **9b.**

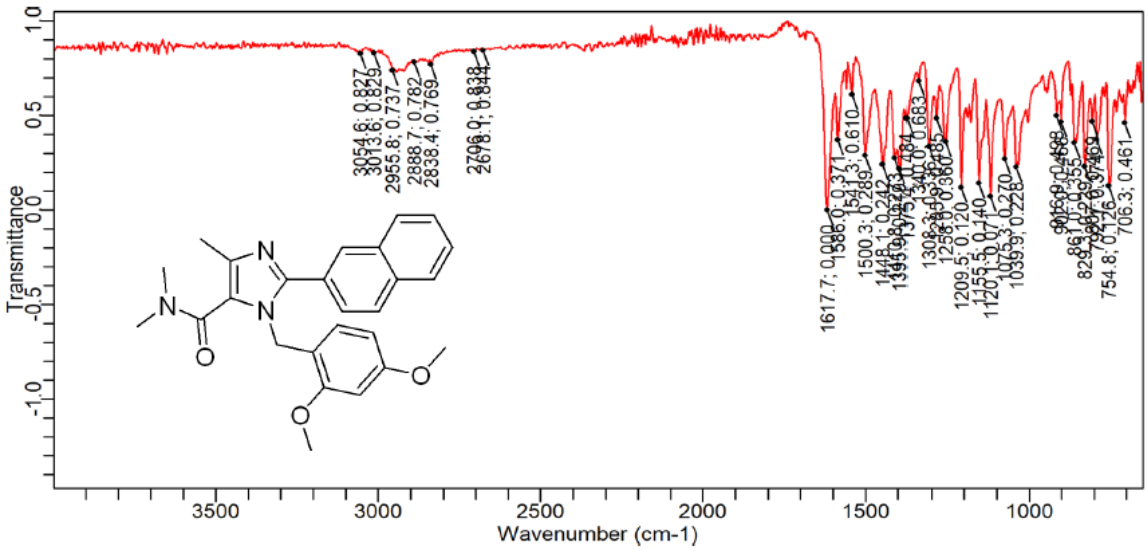


Figure 31: IR of compound **9b.**

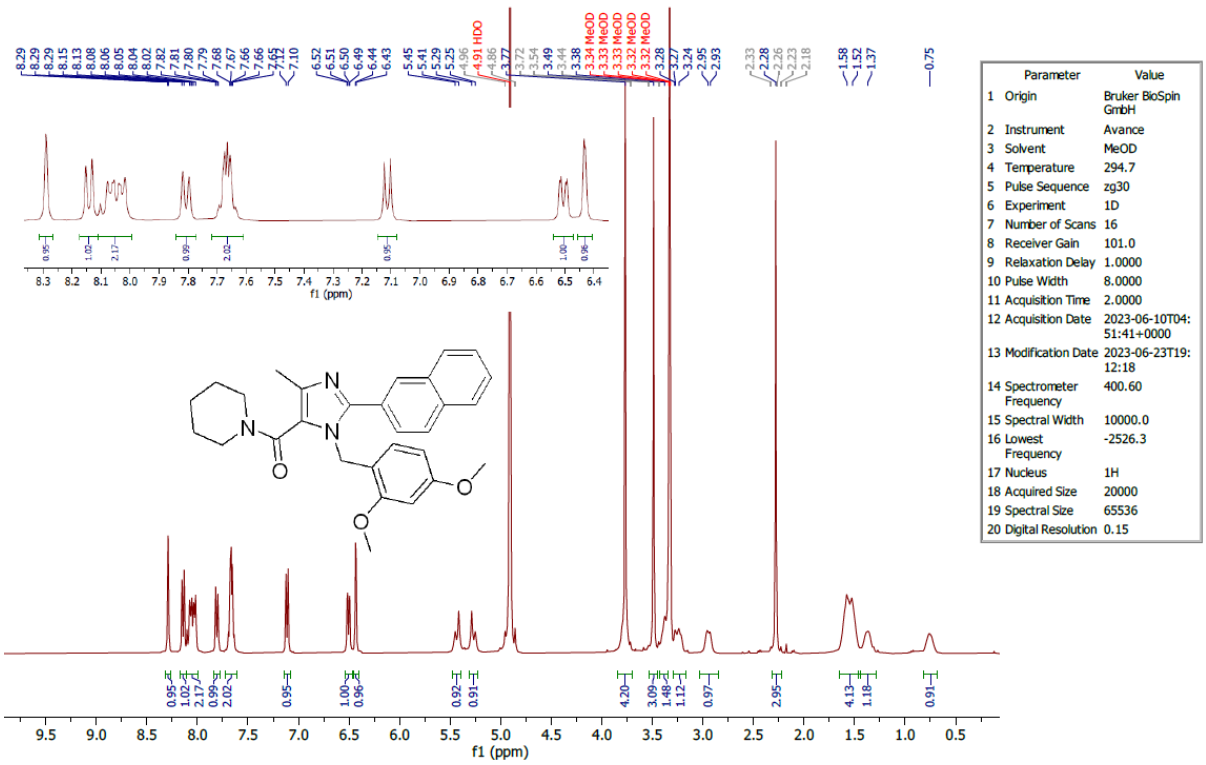


Figure 32: ^{1}H NMR of compound **9j.**

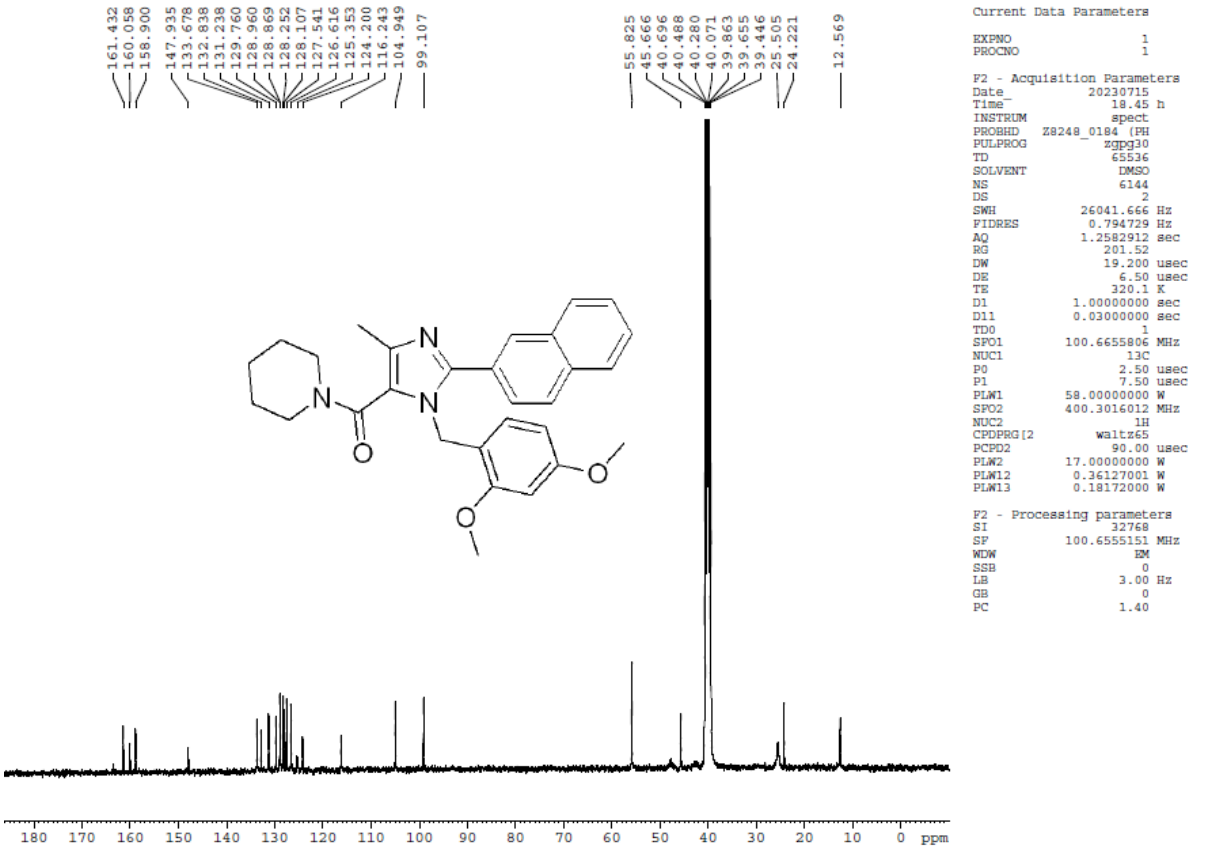
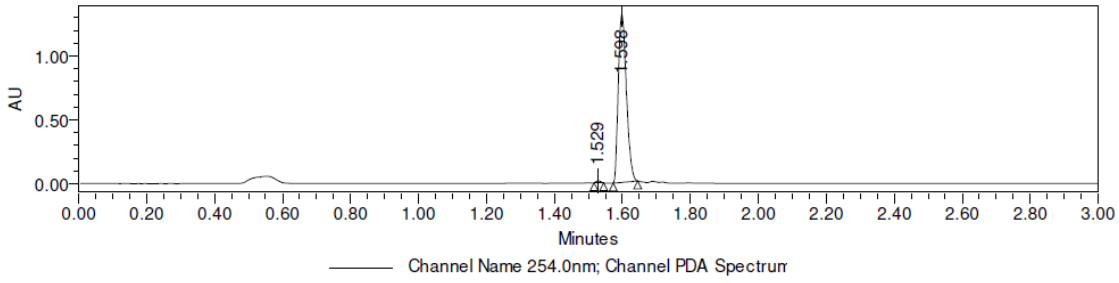
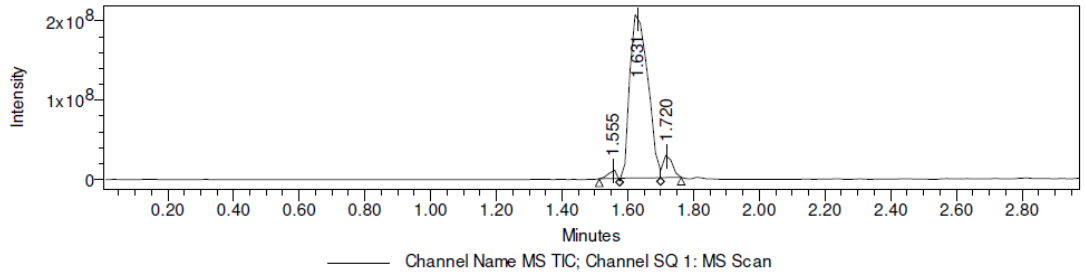


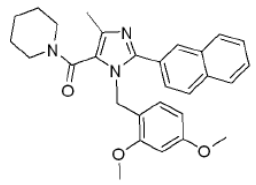
Figure 33: ^{13}C NMR of compound **9j.**





Peak Results
Channel: PDA Spectrum

	Retention Time (min)	Base Peak (m/z)	Height (µV)	Area (µV*sec)	% Area	Channel	Channel Name
1	1.529		21866	23930	1.07	PDA Spectrum	220.0nm
2	1.529		15371	14792	0.68	PDA Spectrum	254.0nm
3	1.598		1315747	2172825	99.32	PDA Spectrum	254.0nm
4	1.599		1180368	2205105	98.93	PDA Spectrum	220.0nm



Chemical Formula: $C_{29}H_{31}N_3O_3$
Molecular Weight: 469.59

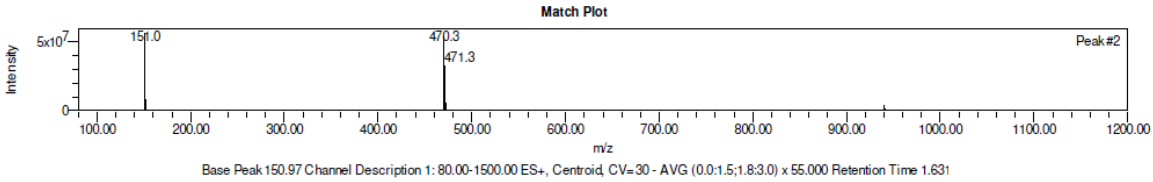


Figure 34: LC-MS of compound **9j.**

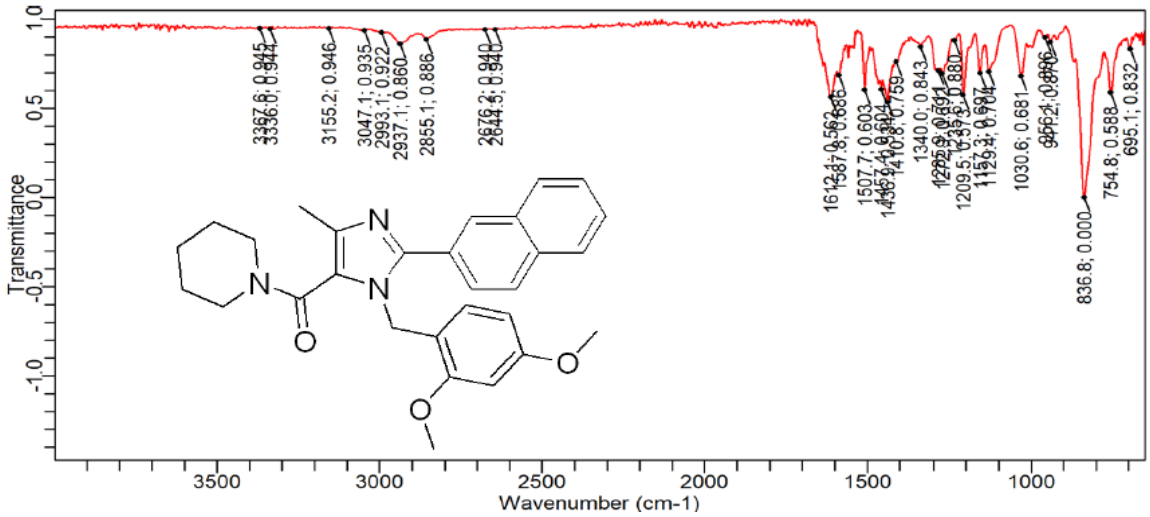


Figure 35: IR of compound **9j.**

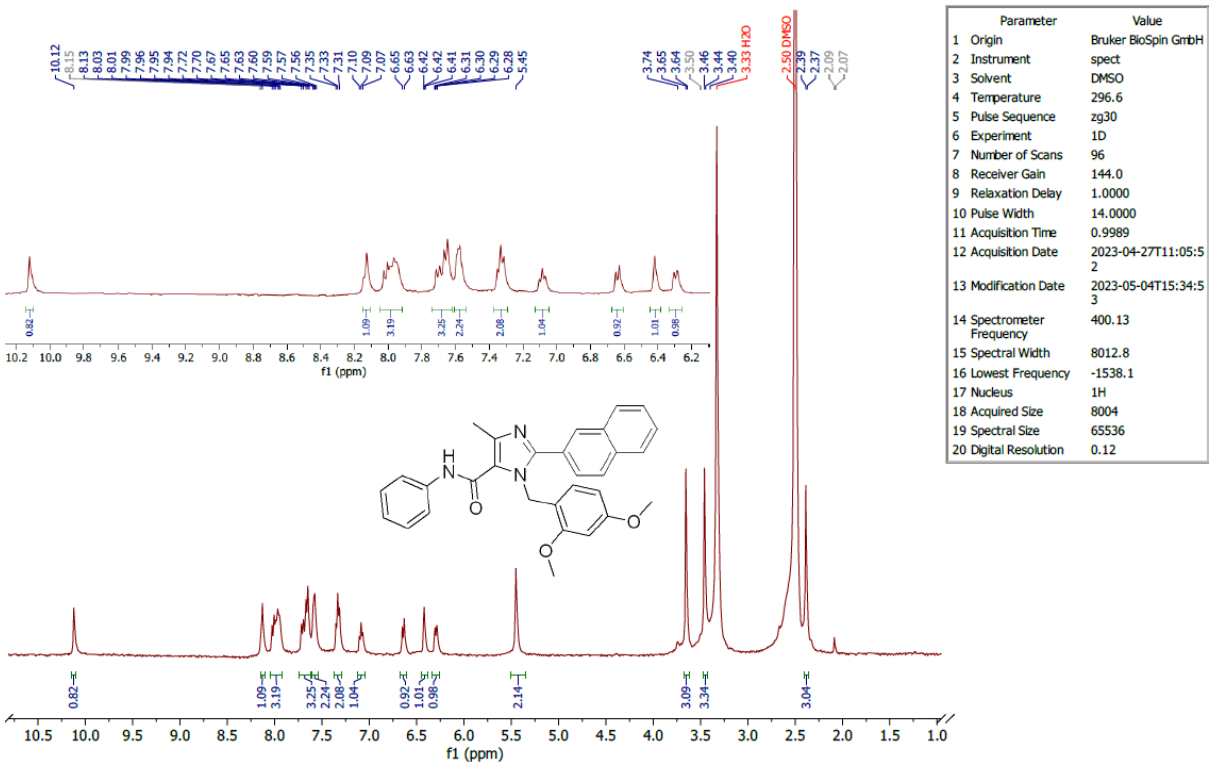


Figure 36: ^{1}H NMR of compound **9k.**

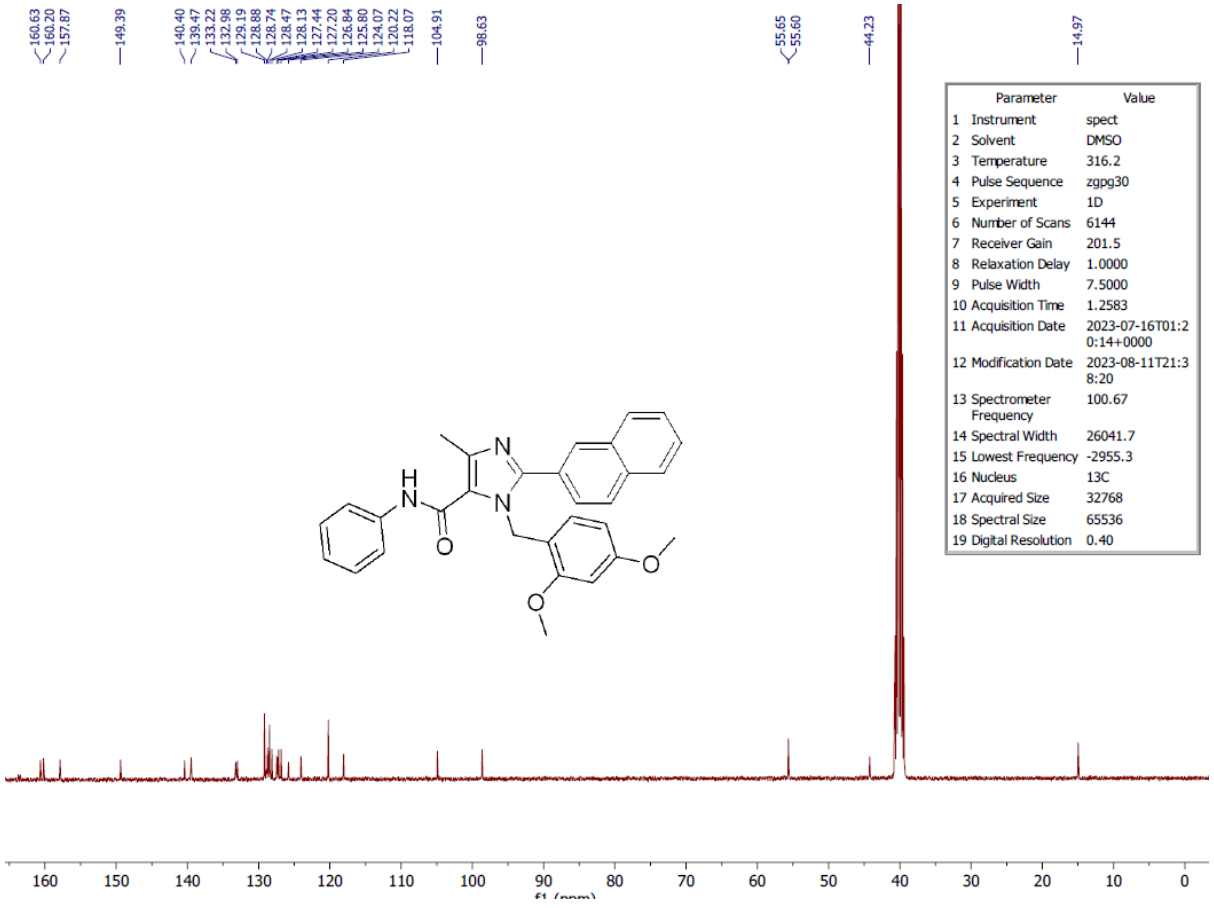
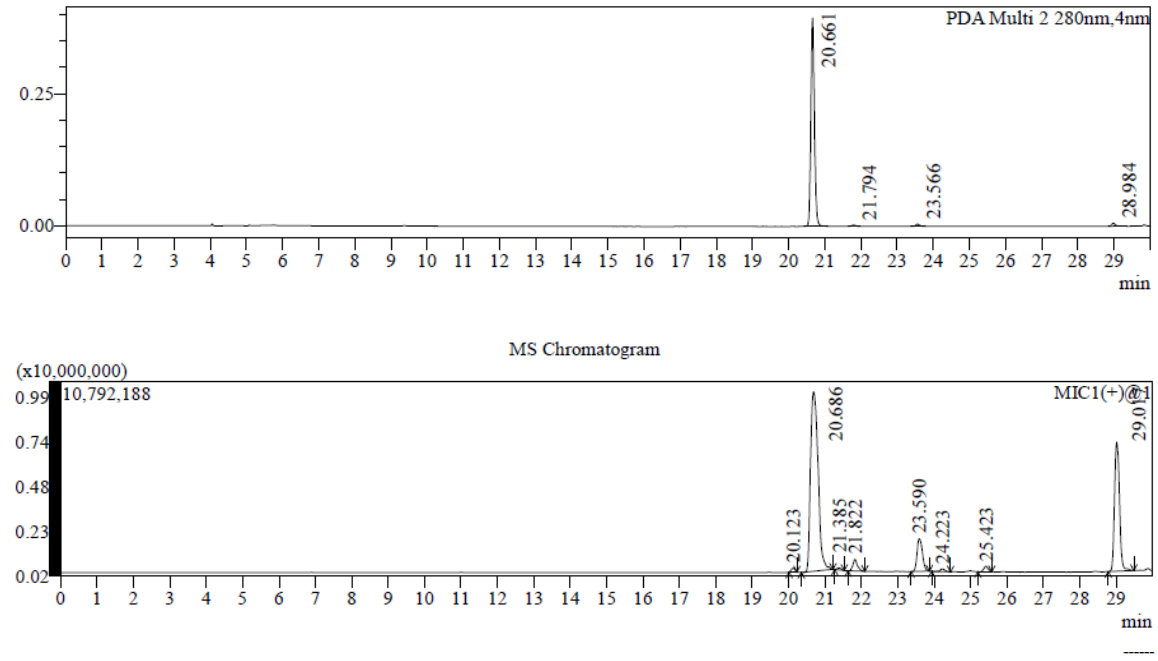


Figure 37: ^{13}C NMR of compound **9k.**



Peak Table

PDA Ch2 280nm

Peak#	Ret. Time	Area	Height	Area%
1	20.661	2645408	394911	96.991
2	21.794	15682	2177	0.575
3	23.566	29725	4050	1.090
4	28.984	36664	5519	1.344

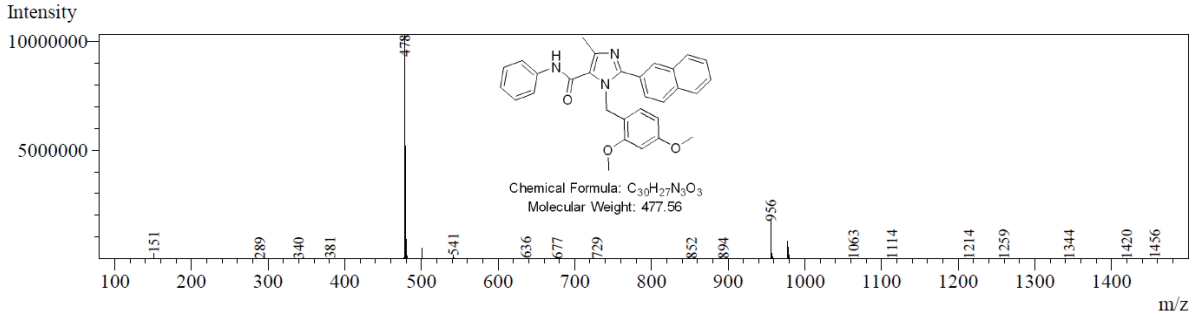


Figure 38: LC-MS of compound **9k.**

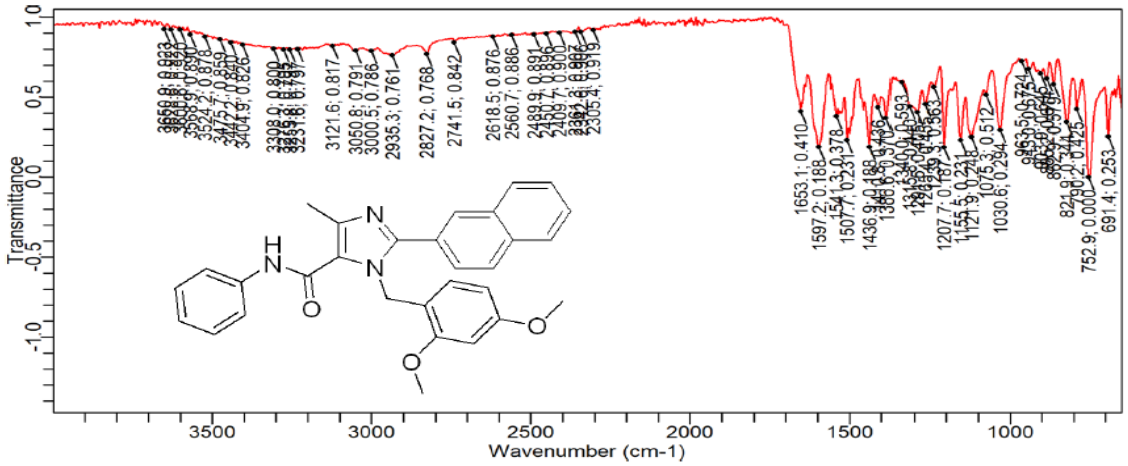
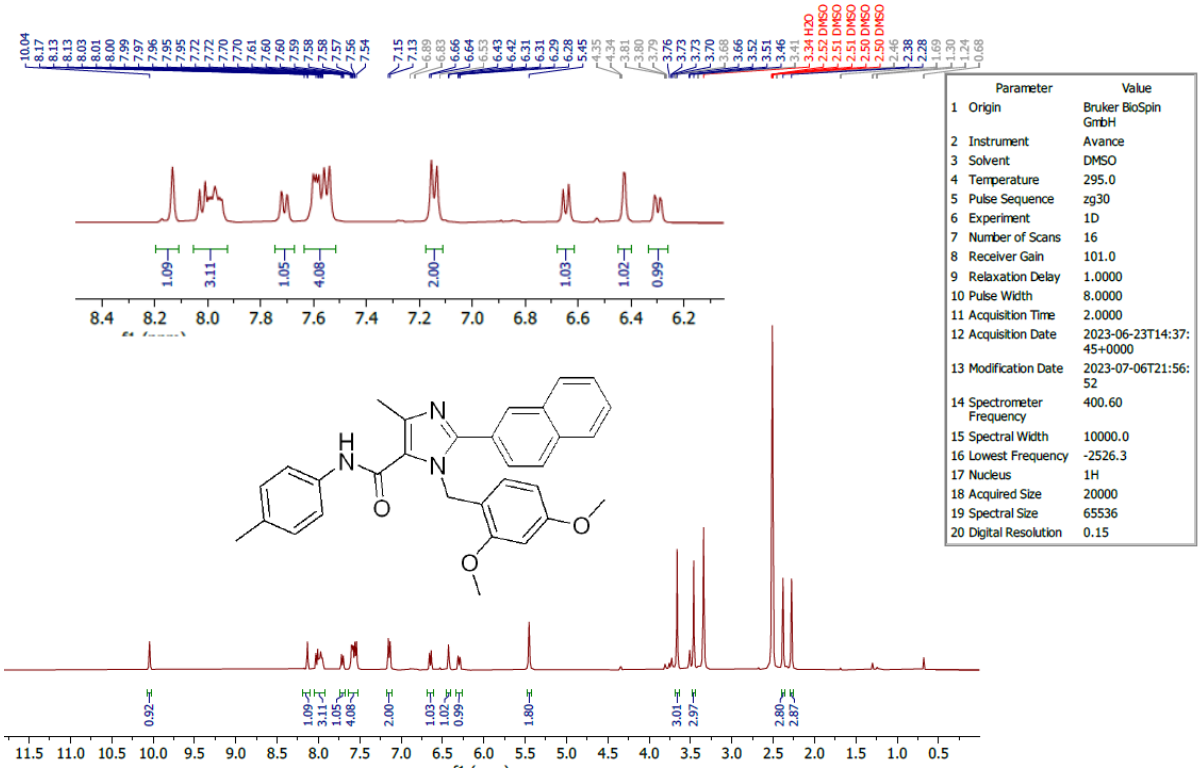
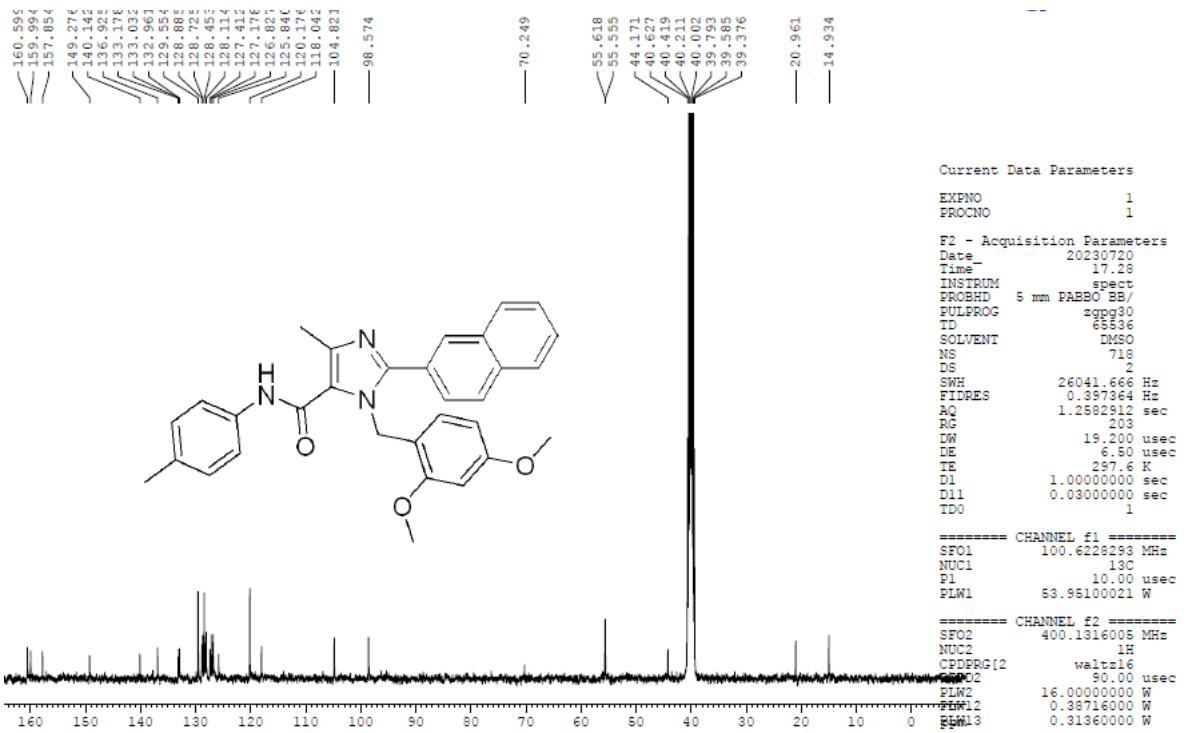


Figure 39: IR of compound **9k.**



	Parameter	Value
1	Origin	Bruker BioSpin GmbH
2	Instrument	Avance
3	Solvent	DMSO
4	Temperature	295.0
5	Pulse Sequence	zg30
6	Experiment	1D
7	Number of Scans	16
8	Receiver Gain	101.0
9	Relaxation Delay	1.0000
10	Pulse Width	8.0000
11	Acquisition Time	2.0000
12	Acquisition Date	2023-06-23T14:37:45+0000
13	Modification Date	2023-07-06T21:56:52
14	Spectrometer Frequency	400.60
15	Spectral Width	10000.0
16	Lowest Frequency	-2526.3
17	Nucleus	1H
18	Acquired Size	20000
19	Spectral Size	65536
20	Digital Resolution	0.15

Figure 40: ^{1}H NMR of compound **9m.**



```
Current Data Parameters

EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20230720
Time               17.28
INSTRUM             spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                   718
DS                     2
SWH            26041.666 Hz
FIDRES             0.397364 Hz
AQ                 1.2582912 sec
RG                   203
DW                19.200 usec
DE                 6.50 usec
TE                 297.6 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          100.6228293 MHz
NUC1                  13C
P1                 10.00 usec
PLW1          53.95100021 W

======== CHANNEL f2 ========
SFO2          400.1316005 MHz
NUC2                  1H
CPDPRG[2           waltz16
PCPD2              90.00 usec
PLW2          16.00000000 W
PLW12          0.38716000 W
PLW13          0.31360000 W
```

Figure 41: ^{13}C NMR of compound **9m.**

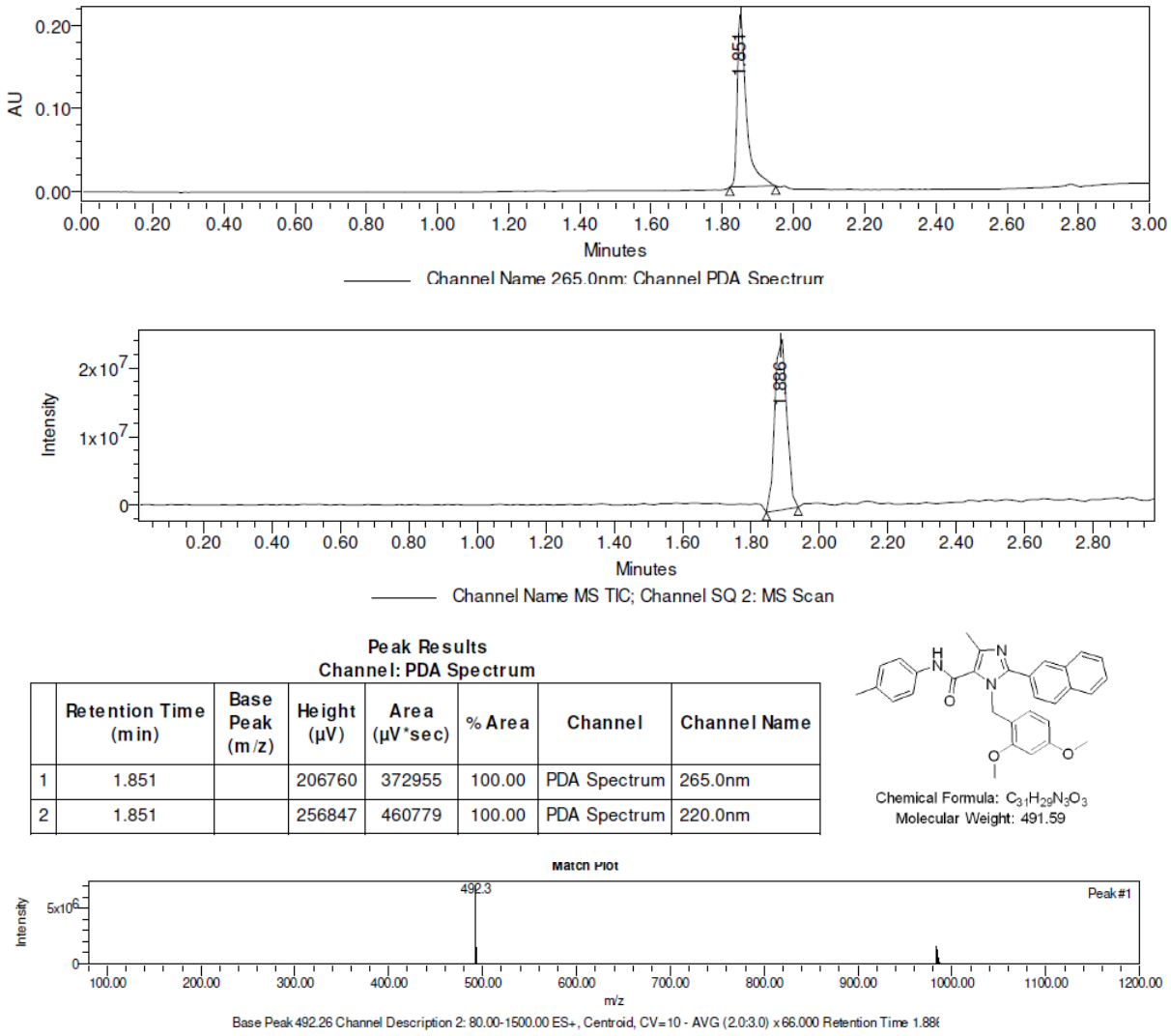


Figure 42: LC-MS of compound **9m.**

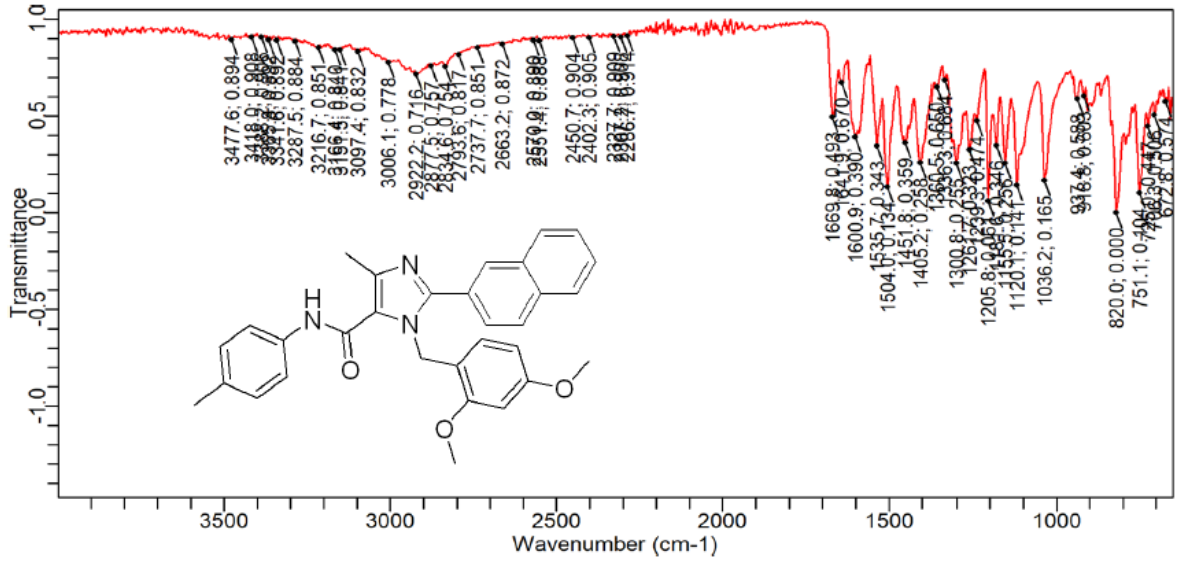


Figure 43: IR of compound **9m.**

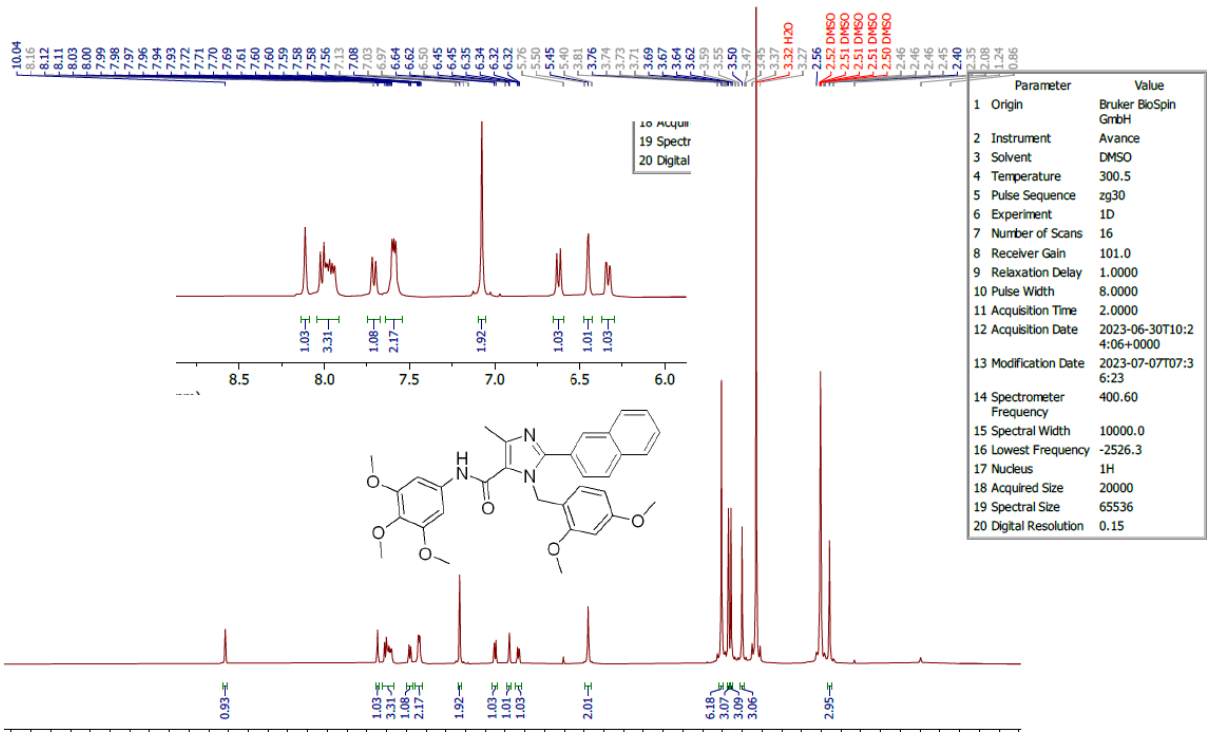


Figure 44: ^{1}H NMR of compound **9p.**

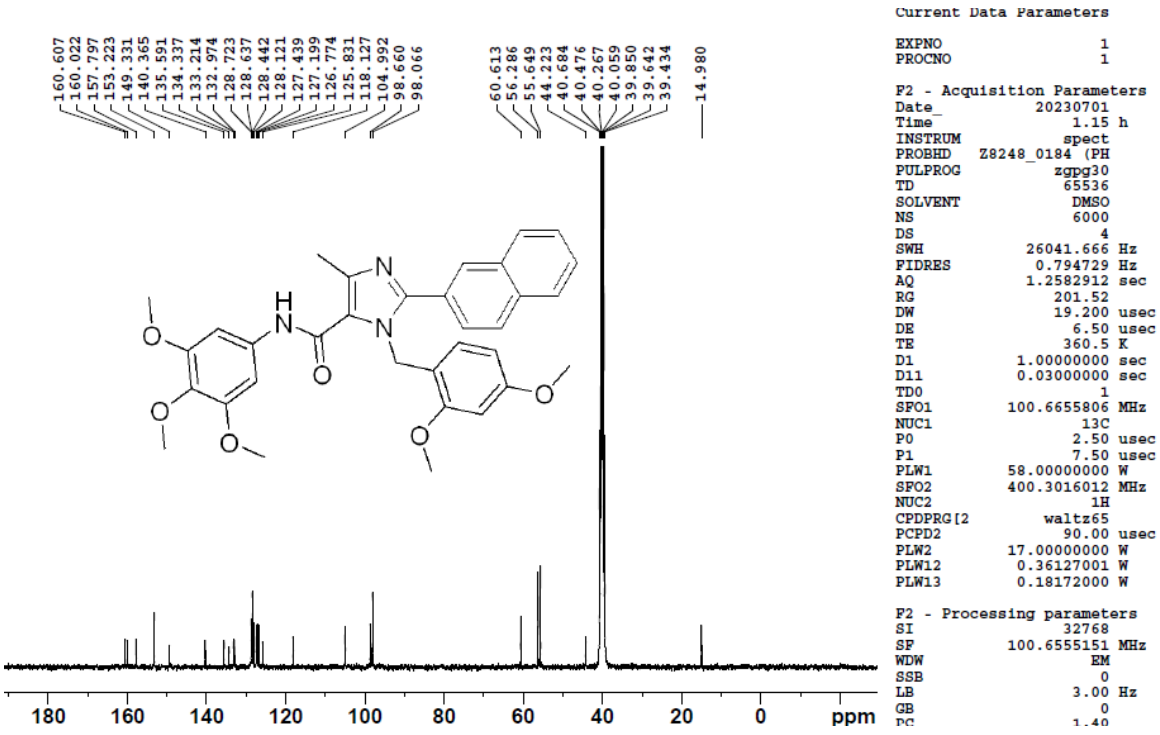


Figure 45: ^{13}C NMR of compound **9p.**

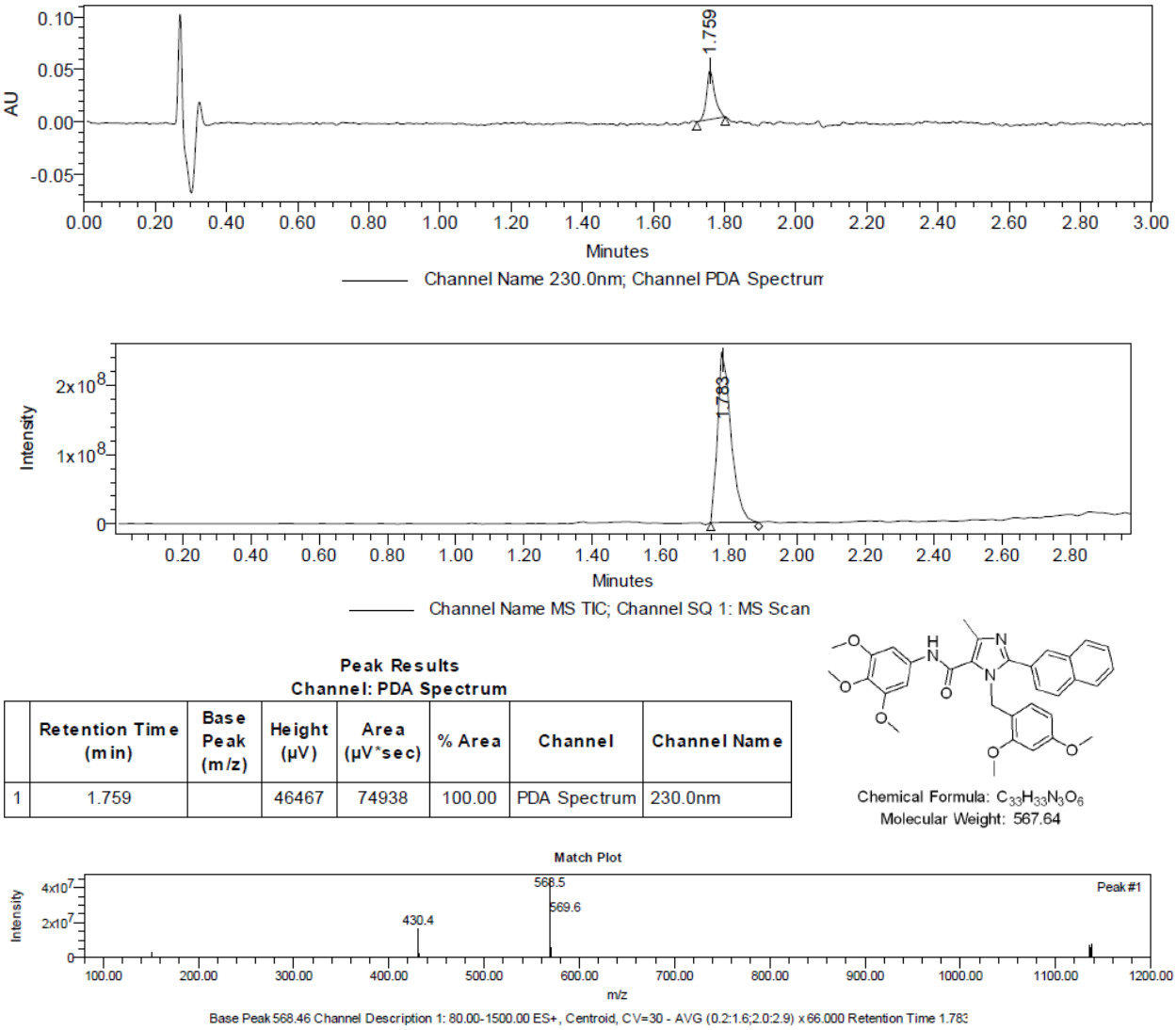


Figure 46: LC-MS of compound **9p.**

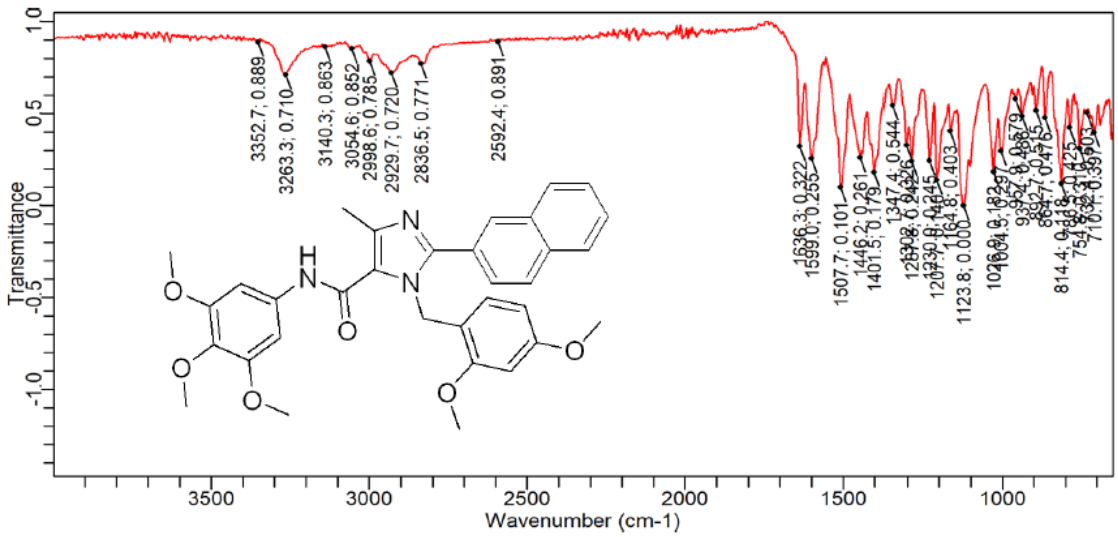


Figure 47: IR of compound **9p.**